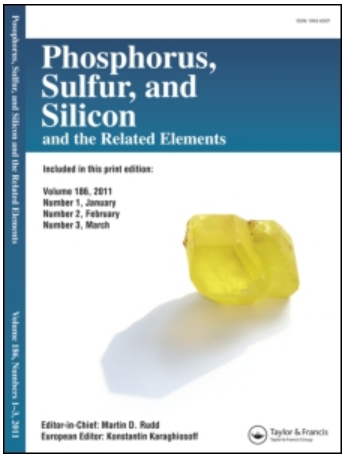

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Biological Activity of Some Novel Thieno[2,3-*b*]quinoline, Quinolino[3',2':4,5] thieno[3,2-*d*]pyrimidine and Pyrido[2',3':4,5] thieno[2,3-*b*]quinoline Derivatives

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To cite this Article El-Gaby, M. S. A. , Abdel-Gawad, S. M. , Ghorab, M. M. , Heiba, H. I. and Aly, H. M.(2006) 'Synthesis and Biological Activity of Some Novel Thieno[2,3-*b*]quinoline, Quinolino[3',2':4,5] thieno[3,2-*d*]pyrimidine and Pyrido[2',3':4,5] thieno[2,3-*b*]quinoline Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 2, 279 — 297

To link to this Article: DOI: 10.1080/104265090970322

URL: http://dx.doi.org/10.1080/104265090970322

Phosphorus, Sulfur, and Silicon, 181:279–297, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090970322

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Synthesis and Biological Activity of Some Novel Thieno[2,3-*b*]quinoline, Quinolino[3′,2′:4,5] thieno[3,2-*d*]pyrimidine and Pyrido[2′,3′:4,5] thieno[2,3-*b*]quinoline Derivatives

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*Thieno [2,3-*b*] quinoline derivative **5** was synthesized by the cycloalkylation of compound bi 3*a *with chloro acetonitrile. Interaction of compound **5** with formic acid, formamide, and thioacetamide furnished the corresponding quinolino[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivatives **7**, **8**, and **9**, respectively. Also, quinolinothienopyrimidine **11** was obtained in good yield by cyclization of compound **5** with phenyl isothiocyanate under reflux in pyridine. Triethyl orthoformate reacted with compound **5** to form the ethoxymethylene derivative **12**. Refluxing of **5** with acetic anhydride for a short time afforded acetamide derivative **16**, whereas when refluxed for a long time furnished the diacetyl derivative **17**. Fusion of compound **5** with urea and thiourea yielded the corresponding quinolinothienopyrimidines **19** and **20**, respectively. When compound **5** was reacted with urea in the presence of sodium ethoxide, the corresponding ureado derivative **18** was obtained.*

Received December 1, 2004; accepted February 15, 2005.

Many thanks are due to Prof. Dr. A. I. El-Batal, Department of Drug Radiation Research, National Centre for Radiation Research and Technology, Cairo, Egypt, for doing the antimicrobial activity of some of the synthesized compounds.

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*Treatment of **5** with sulfuric acid at r.t. furnished the novel thienoquinoline **6**, while on heating gave the acid derivative **21**. Pyrido [2′,3′: 4,5]thieno [2,3-*d*] quinoline **23–25** were synthesized by the interaction of **5** with ethyl cyanoacetate, benzylidenemalononitrile, and acetaldehyde/malononitrile, respectively. On preliminary screening, compounds **22** and **25** exhibited in vitro growth that was inhibitory activity against Saccharomyces Cerevisiae when compared with the standard fungicide Mycostatine. The structure of the biologically active compounds **22** and **25** remain unchanged when exposed to gamma irradiation up to 40 KGy.*

Keywords Quinoline; thieno[2,3-*b*]quinoline; condensed quinoline derivatives

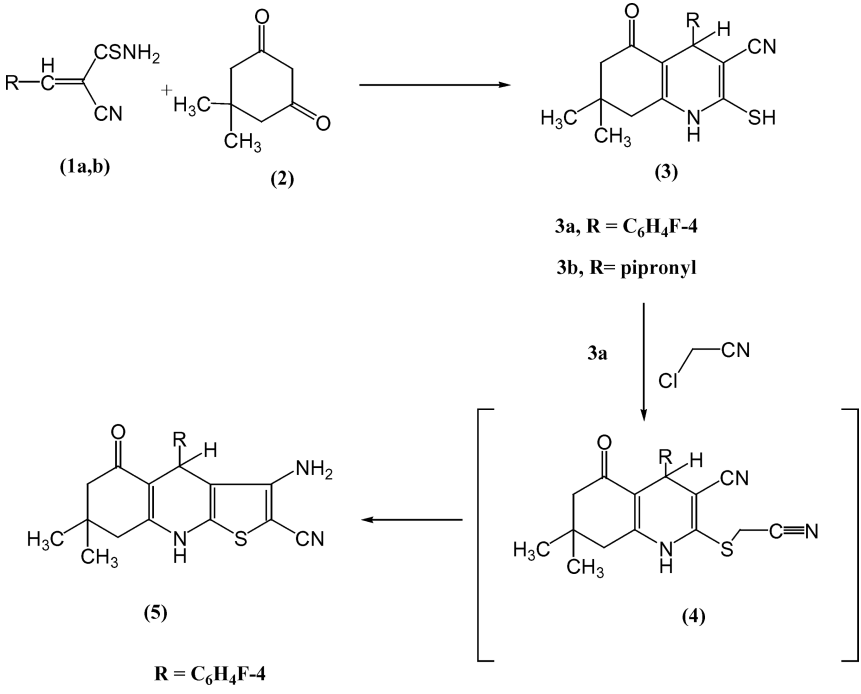
INTRODUCTION

Thieno [2,3-*b*] quinoline derivatives were reported to furnish interesting biological properties that show antimicrobial[1–3] and antibiotics[4] activities. In connection with our efforts to synthesize fused heterocycles[5–12] from readily available starting materials, we report here on the synthesis of some novel thieno[2,3-*b*]quinoline, quinolino[3′,2′:4,5]thieno[3,2-*d*] pyrimi-dine, and pyrido [2′,3′;4,5]thieno[2,3-*b*] quinoline derivatives in order to investigate the antimicrobial activity. In recent years considerable interest has been developed regarding the radiation sensitivity of various antibiotics[13–16] and synthetic biologically active heterocyclic compounds.[17–22] Studies, for the most part, have focused on the correlation between chemical structure and biological function. Generaly, data of these compounds indicates that even at a dose of 25 KGy, the radiosterilization may be feasible.[23,24]

CHEMISTRY

The starting materials **3a**, **b** were synthesized by cyclocondensation[25] of (4-flourophenyl and/or 4-pipronyl) methylenecyanothioacetamide **1a**, **b** with dimedone **2**. The structure of **3a**, **b** was established through microanalyses, IR, ^{1}H NMR, and mass spectral data. The IR spectrum of **3a** showed bands at 3300 (NH), 3050 (CH arom.), 2930 (CH aliph.), 2200 (C≡N), 1670 (C=O), and 1630 cm^{-1} (C=N). Its ^{1}H NMR spectrum (in DMSO-d_6) exhibited signals at δ 0.9, 1.1 [2s, 6H, 2CH_3], 2.2, 2.3 [2s, 4H, 2CH_2], 4.5 [s,1H, pyridine CH], 7.0–7.5 [m, 4H, Ar-H], and 10.0 [s, 1H, NH]. Mass spectrum of **3a** showed a molecular ion peak m/z at 328 (M^+, 54.30%), 327 (M-1, 29.23%), and 326 (M-2, 84.10%) with a base peak at 83, and other significant peaks appeard at 270 (80.0%), 244 (4.51%), 210 (23.08%), 182 (40.0%), and 95 (89.23 %). IR spectrum of compound **3b** revealed bands at 4380 (NH), 3100 (CH arom.), 2940 (CH aliph.), 2200 (C≡N), 1650 (C=O), and 1580 cm^{-1} (C=N). ^{1}H NMR

spectrum of (**3b** in DMSO-d_6) exhibited signals at δ 1.5, 1.6 [2s, 6H, $2CH_3$], 2.1, 2.5 [2s, 4H, $2CH_2$], 4.5 [hump, 2H, pyridine CH + NH], 6.1 [s, 1H, O—CH_2—O], and 7.0–7.5 [m, 3H, Ar-H]. Its mass spectrum showed a molecular ion peak m/z at 352 (M-2, 4.88%), with a base peak at 296, and other significant peaks appeared at 266 (27.53%), 238 (21.25%), 178 (18.82%), 135 (44.60%), and 55 (93.73%). Cycloalkylation of compound **3a** with chloroacetonitrile in the presence of sodium ethoxide in ethanol under reflux yielded the novel thieno [2,3-*b*]-quinoline derivative **5** in good yield. The structure of compound **5** was characterized by analytical and spectral data. The IR spectrum of **5** showed bands at 3470, 3340, 3200 (NH, NH_2), 2950 (CH aliph.), 2200 (C≡N), 1640 (C=O), and 1600 cm^{-1} (C=N). ^1H NMR spectrum of (**5** in DMSO-d_6) revealed signals at δ 0.9, 1.1 [2s, 6H, $2CH_3$], 2.2, 2.5 [2s, 4H, $2CH_2$], 5.0 [s, 1H, pyridine CH], 6.2 [s, 2H, NH_2], 6.9–7.4 [m, 4H, Ar-H], and 10.3 [s,1H, NH]. The formation of thienoquinoline **5** is assumed to proceed through the initial alkylation to form (**4**) followed by an intramolecular cyclization and tautomerization to yield **5** (Scheme 1).

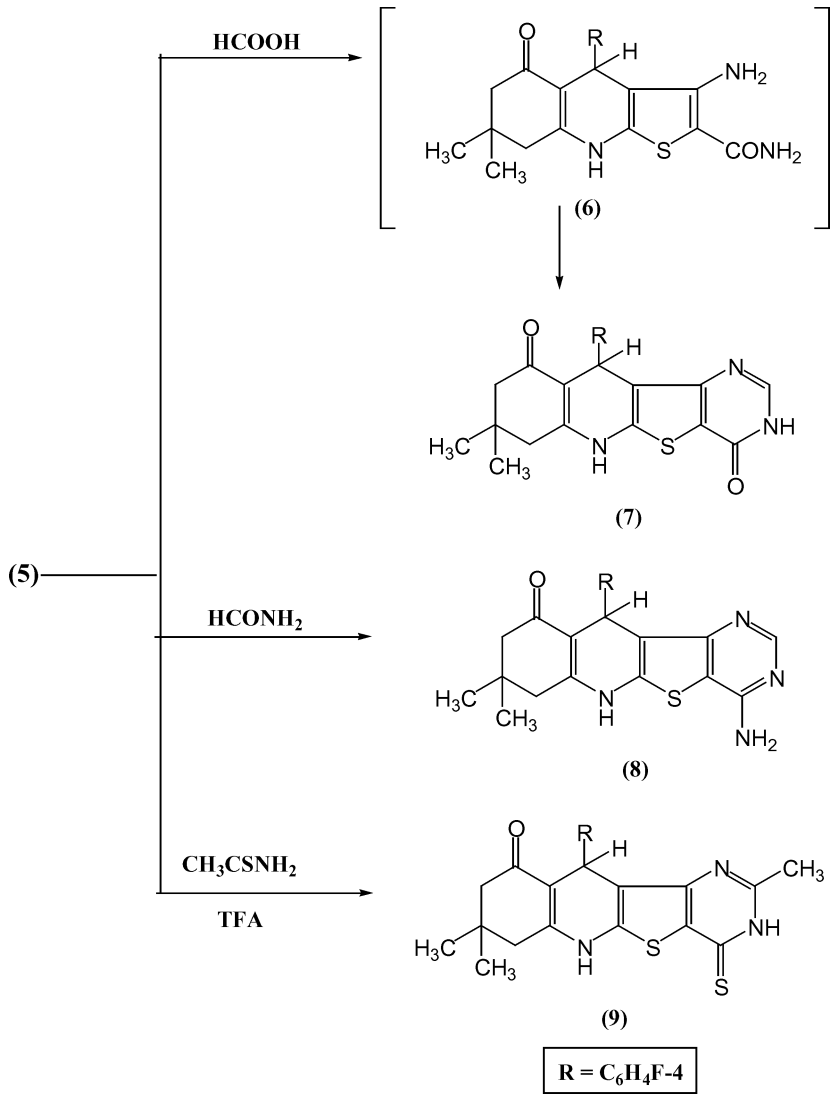


SCHEME 1

Heteroaromatic orthoaminocarbonitriles are versatile intermediates, which have been extensively utilized in the synthesis of condensed heterocyclic compounds.[26,27] Thus, the refluxing of **5** with formic acid afforded the quinolino[3′,2′:4,5]thieno[3,2-*d*] pyrimidine derivative **7**. The IR spectrum of compound **7** showed bands at 3200 (NH), 2940 (CH aliph.), 1680, 1660 (2C=O), and 1640 cm^{-1} (C=N). The mass spectrum of **7** exhibited a molecular ion peak m/z at 395 (M^+, 22.0 %), 396 (M + 1, 5.34%), 397 (M + 2, 18.41%), and 398 (M + 3, 6.52%), with a base peak at 393 and other significant peaks appeared at 337 (85.40%), 300 (44.8%), 254 (24.42%), 183 (10.80%), 109 (18.21%), and 83 (13.71%).

The formation of compound **7** is assumed to proceed via the amide formation[28] **6** followed by an intramolecular cyclization with formic acid to furnish **7** (Scheme 2).

Also, compound **5** was cyclocondensed with formamide under reflux and afforded the quinolinothienopyrimidine **8**. The IR spectrum of **8** showed bands at 3300, 3200 (br, NH, NH_2), 2930 (CH aliph.), and 1670 cm^{-1} (C=O). Its ^1H NMR spectrum in (DMSO-d_6) revealed signals at δ 1.1, 1.2 [2s, 6H, $2CH_3$], 2.1, 2.4 [2s, 4H, $2CH_2$], 4.6 [s, 1H, pyridine CH], 7.0–7.8 [m, 6H, Ar-H + NH_2], 8.3 [s, 1H, CH pyrimidine], and 10.2 [s, 1H, NH]. Cyclocondensation of compound **5** with thioacetamide under reflux in trifluoroacetic acid[29] produced the novel quinolinothienopyrimidine **9** in a high yield. The IR spectrum of **9** showed bands at 3390, 3200 (2NH), 2930 (CH aliph.), 1640 (C=O), 1600 (C=N), and 1290 cm^{-1} (C=S). Mass spectrum of compound **9** revealed a molecular ion peak m/z 425 (M^+, 53.22%) and 424 (M-1, 17.80%) with a base peak at 95, and other significant peaks appeared at 340 (28.33%), 330 (88.53%), 300 (27.47%), and 75 (44.21%). Compound **5** was treated with phenyl isothiocyanate under reflux in pyridine to give the corresponding condensed pyrimidinethione **11**. Its IR spectrum showed bands at 3220, 3180 (NH), and 3100 (CH arom.), 1650 (C=O), 1600 (C=N), and 1310 cm^{-1} (C=S). Mass spectrum of **11** exhibited a molecular ion peak m/z at 501 (M-1, 41.48%) together with a base peak at 107, and other significant peaks appeared at 252 (35.20%), 213 (55.88%), 202 (44.12%), 118 (41.48%), and 98 (55.88%). The formation of **11** was assumed to proceed via the thiourea intermediate **10** followed by the intramolecular cyclization at the adjcent cyano function group to form **11**. Refluxing of compound **5** with triethylorthoformate in the presence of acetic anhydride yielded the ethoxymethyleneamino derivative **12**. The IR spectrum of **12** showed bands at 3280 (NH), 2950 (CH aliph.), 2210 (C≡N), 1680(C=O), and 1620 cm^{-1} (C=N), the ^1H NMR spectrum of (**12** in DMSO-d_6) revealed signals at δ 0.9, 1.2 [2s, 6H, $2CH_3$], 1.8 [t, 3H, CH_3 ethyl], 1.9, 2.1 [2s, 4H, $2CH_2$], 4.1 [s, 1H, pyridine CH], 5.1 [q, 2H, CH_2 ethyl], 6.2 [s, 1H, N=CH], 7.0–7.4 [m, 4H, Ar-H], and 9.9

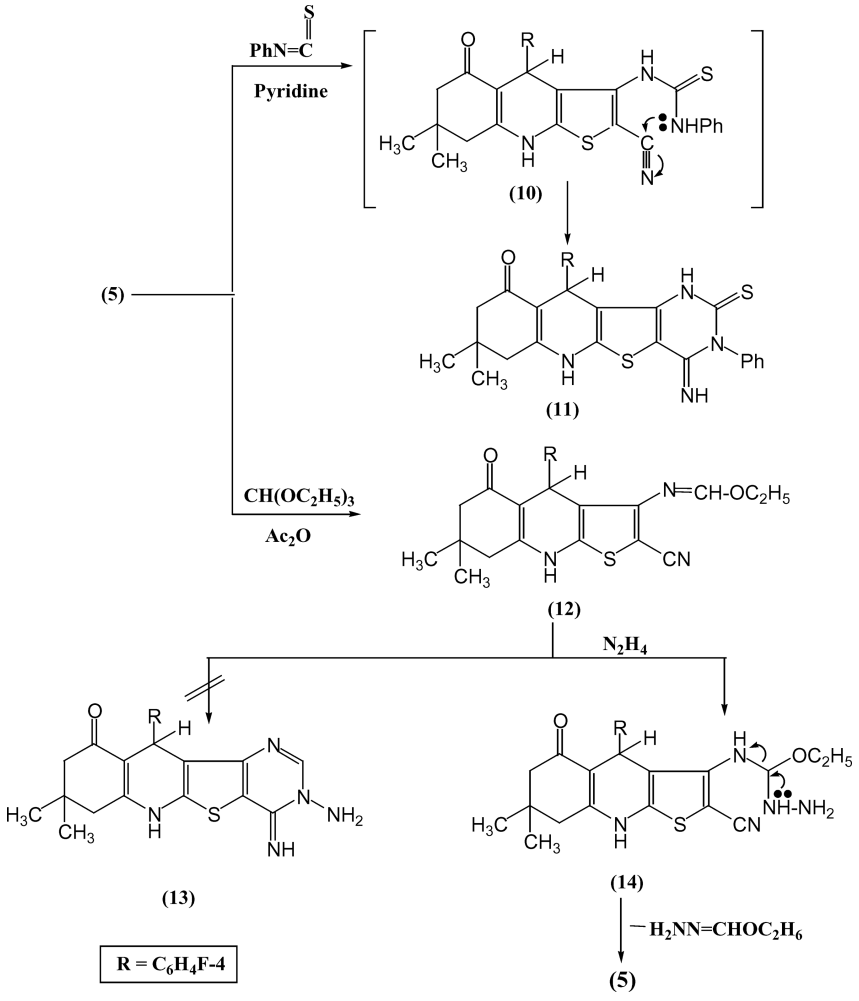


SCHEME 2

[s,1H, NH]. When compound **12** was treated with hydrazine hydrate in benzene at r.t., the enaminonitrile **5** was recovered (m.p., m.m.p., and TLC). The expected pyrimidine **13** formation was ruled out on the basis of analytical and spectral data. The formation of **5** from the reaction of **12**with hydrazine hydrate was assumed to proceed via the addition

of hydrazine at the imino function group to form the intermediate **14**, followed by the elimination of ethyl formate hydrazone[30] (Scheme 3).

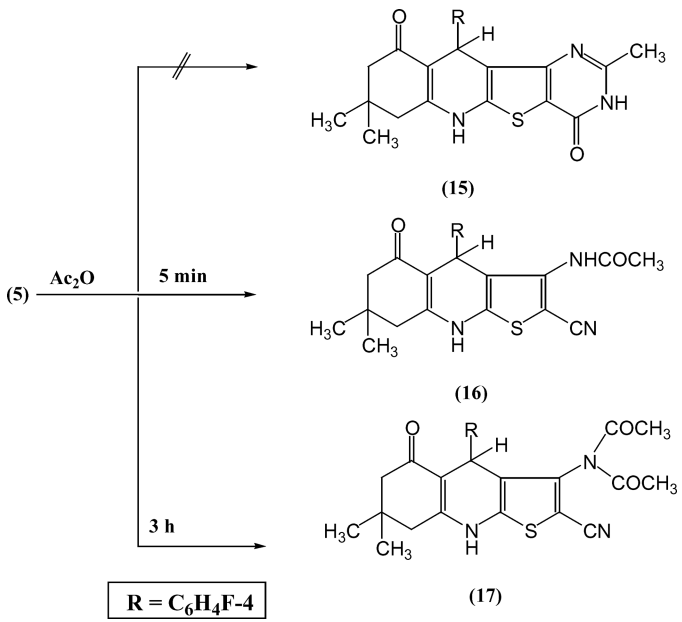
Attempts to synthesize the pyrimidine derivative **15** from compound **5** and acetic anhydride failed. Thus, the acetamide derivative **16** was achieved by the refluxing of **5** with acetic anhydride for 5 min on the basis of analytical and spectral data. Its IR spectrum showed the presence of (NH) at 3480 and 3350 (CH aliph.) at 2940, (C≡N) function group at 2200 and (2C=O) at 1660 and 1630 cm^{-1}. The ^1H NMR; spectrum of **16** revealed signals at δ 0.9, 1.1 [2s, 6H, $2CH_3$], 2.1, 2.3 [2s, 4H,



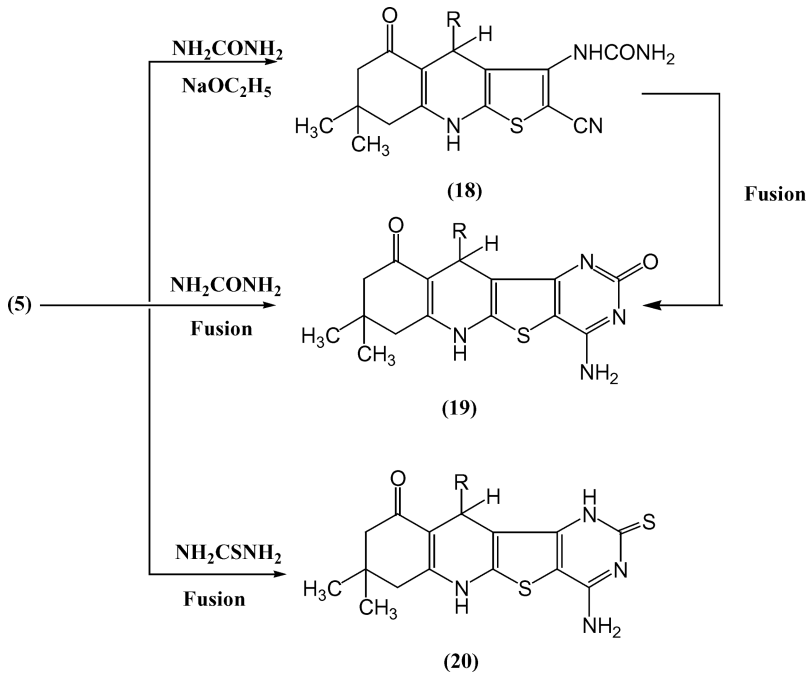
SCHEME 3

$2CH_2$], 2.6 [s, 3H, $COCH_3$], 4.9 [s, 1H, pyridine CH], 6.9–7.4 [m, 4H, A-B system, Ar-H], and 10.2 [s, 2H, 2NH] (Scheme 4). Also, diacetyl derivative **17** was obtained by the refluxing of compound **5** in acetic anhydride for a long time. The IR spectrum revealed bands at 3250 (NH), 2950 (CH aliph.), 2200 (C≡N), 1710, 1700, and 1670 (3C=O), and 1610 cm^{-1} (C=N). The ^1H NMR spectrum of (**17** in DMSO-d_6) showed signals at δ 0.9, 1.1 [2s, 6H, $2CH_3$], 2.0, 2.1 [2s, 4H, $2CH_2$], 2.4, 2.6 [2s, 6H, $2COCH_3$], 4.8 [s, 1H, pyridine CH], and 7.0–7.5 [m, 5H, Ar-H + NH].

When compound **5** was allowed to react with urea in the presence of sodium ethoxide in ethanol, a product of the molecular formula $C_{21}H_{19}N_4O_2SF$ formed via the elimination of ammonia. Based on the presence of CN absorption in the IR spectrum. Its IR spectrum showed bands at 3490, 3320, 3200 (NH, NH_2), 2940 (CH aliph.), 2200 (C≡N), 1660, and 1620 (2C=O). The mass spectrum of compound **18** exhibited a molecular ion peak m/z at 410 (M^+, 33.11%), with a base peak at 272, and other significant peaks appeared at 387 (31.78%) 368 (22.30%), 342 (53.38%), 282 (35.81%), 188 (28.38%), 170 (85.14%), 136 (50.88%), 88 (8.08%), and 76 (81.08%) (Scheme 5). While fusion of compound **5** with urea furnished the condensed pyrimidine **19**. Its IR spectrum exhibited



SCHEME 4



SCHEME 5

the disappearance of a band characteristic for the carbonitrile function group and presence of bands at 3480, 3400, 3200 (NH, NH_2), 3100 (CH arom.), 1730, 1710 (2C=O), and 1600 cm^{-1} (C=N). The mass spectrum of **19** revealed a molecular ion peak m/z at 408 (M-2, 73.33%), with a base peak at 330 and other significant peaks appeard at 379 (58.87%), 309 (88.87%), 272 (73.33%), 102 (50.22%), 71 (43.33%). Also the structure of compound **19** was proved via another synthetic route through the fusion of compound **18** at a high temperature. The formation of compound **19** was assumed to proceed through the elimination of ammonia followed by intramolecular cyclization at the cyano group and tautomerization to yield **19**. In a similar manner compound **5** was cyclized with thiourea under the condition of fusion to yield thiopyrimidine derivative **20**. Its IR spectrum showed bands at 3360, 3340, 3185 (NH,NH_2), 2950 (CH aliph.), 1640 (C=O), 1610 (C=N), and 1240 cm^{-1} (C=S). The mass spectrum of compound **20** revealed a molecular ion peak m/z at 392 (M-H_2S, 8.54%) with a base peak at 126, and other significant peaks appeared at 313 (8.21%), 257(8.35%), 207 (17.24%), 88 (12.20%), and 76 (28.70%).

The treatment of compound **5** with sulfuric acid at r.t. furnished the novel carboxamide derivative **6**, via partially the hydrolysis of the

cyano function group, while the complete hydrolysis of the cyano group occured when compound **5** was refluxing in sulfuric acid to give the corresponding acid derivative **21**. The IR spectrum of **6** showed bands at 3480, 3310, 3190 (NH, NH_2), 2950, 2820 (CH aliph.), 1650 (2C=O), and 1600 cm^{-1} (C=N). Its ^1H NMR spectrum in (DMSO-d_6) revealed signals at δ 0.9, 1.1 [2s, 6H, $2CH_3$], 2.0–2.2 [2s, 4H, $2CH_2$], 3.7 [s, 5H, $2NH_2$ + Pyridine CH], and 7.0–7.6 [m, 5H, Ar-H +NH]. The mass spectrum of **6** exhibited a molecular ion peak m/z at 385 (M^+, 7.58%) with a base peak at 109, and other significant peaks appeared at 368 (57.05%), 328 (18.0%), 286 (24.03%), 277 (8.21%), 188 (7.20%), 164 (70.47%), and 83 (99.48%). The IR spectrum of compound **21** revealed bands at 3400–3300 (NH—NH_2), 3500–3000 (br, OH), 1690 (2C=O), and 590 cm^{-1} (C=N). The mass spectrum of compound **21** exhibited a molecular ion peak m/z at 386 (M^+, 2.71%) and 387 (M + 1, 0.83%) with a base peak at 113, and other significant peaks appeared at 341 (5.57%), 271 (2.70%), 229 (5.70%), 198 (7.81%), 149 (18.88%), and 69 (38.85%). Also compound **6** was obtained via the reaction of compound **3a** with chloroacetamide in methanol in the presence of sodium methoxide. The corresponding condensed pyrimidine **7** was also obtained by the refluxing of **6** with formic acid. When compound **5** was refluxed with hydroxylamine in ethanol in the presence of sodium ethoxide, it gave the pyrazolothienoquinoline derivative **22**. Compound **22** is assumed to be formed through the addition of the amino group of hydroxylamine to the cyano function group followed by intramolecular cyclization by the elimination of water. The IR spectrum of **22** showed bands at 3490, 3330, 3215 (NH, NH_2), 2930, 2820 (CH aliph.), 1640 (C=O), and 1610 cm^{-1} (C=N). The mass spectrum of compound **22** exhibited a molecular ion peak m/z at 382 (M^+, 13.87%) with a base peak at 55 and other significant peaks appeared at 365 (27.31%), 309 (12.18%), 281 (10.50%), 170 (11.34%), and 95 (20.57%). The reaction of **5** with ethyl cyanoacetate in dimethylformamide in the presence of a few drops of piperidine under reflux yielded the corresponding pyridothienoquinoline derivative **23**. The formation of compound **23** is assumed to take place via the elimination of ethanol followed by an intramolecular cyclization at the cyano function group and tautomerization to yield **23**. IR spectrum of **23** showed bands at 3400, 3360, 3190 (NH,NH_2), 2930 (CH aliph.), 2220 (C≡N), 1670, 1620 (2C=O), and 1600 cm^{-1} (C=N) ^1H NMR spectrum of (**23** in DMSO-d_6) revealed signals at δ 1.1, 1.3 [2s, 6H, $2CH_3$], 2.2 [s, 4H, $2CH_2$], 4.2 [s,1H, pyridine CH], 6.8–7.5 [m, 6H, Ar-H + NH_2], and 8.3 [s, 2H, 2NH]. Compound **5** was cyclocondensed with benzylidenemalononitrile in ethanol in the presence of a catalytic amount of piperidine under reflux and provided the corresponding pyridothienoquinoline derivative **24**. IR spectrum of **24** showed bands at 3490, 3320, 3200 (NH, NH_2),

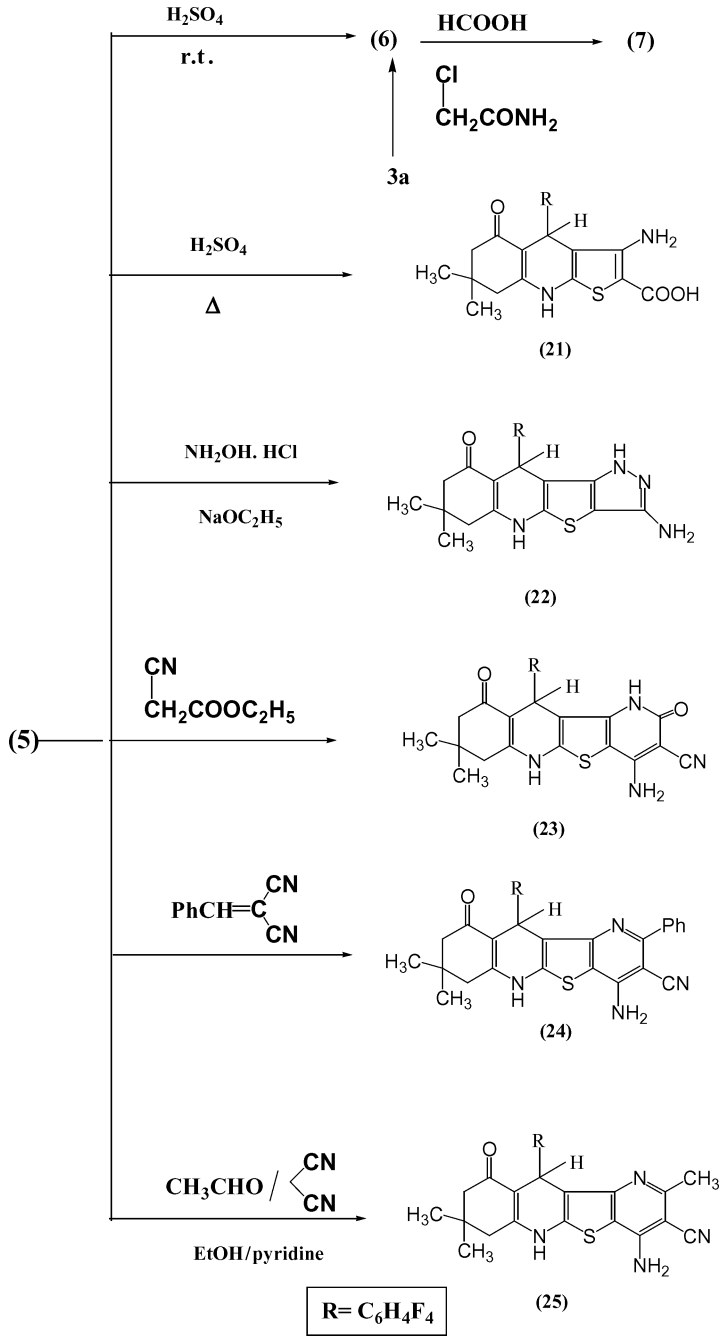
2950, 2840 (CH aliph), 2200 (C≡N), 1670 (C=O), and 1600 cm^{-1} (C=N). The ^1H NMR spectrum of (**24** in DMSO-d_6) revealed signals at δ 1.2, 1.3 [2s, 6H, $2CH_3$], 2.4, 2.5 [2s, 4H, $2CH_2$], 4.5 [s, 1H, pyridine CH], 6.1 [s, 2H, NH_2], 7.0–7.6 [m, 9H, Ar-H], and 7.9 [s,1H, NH]. The formation of compound **24** can be explained on the basis of an initial Michael addition of the amino function group in compound **5** to double the bond of benzylidinemalononitrile followed by intramolecular cyclization, which loses hydrogen cyanide and tautomerization to give **24** (Scheme 6). Finally compound **25** was obtained also in good yield via the reaction of **5** with acetaldehyde and malononitrile in refluxing ethanol containing pyridine. The IR spectrum of compound **25** showed bands at 3480, 3360, 3220 (NH, NH_2), 2930, 2870 (CH aliph.), 2195 (C≡N), 1625 (C=O), and 1600 cm^{-1} (C=N). The mass spectrum of **25** revealed a molecular ion peak m/z at 430 (M^+-2, 12.88%) with a base peak at 101, and other significant peaks appeared at 385 (22.14%), 352 (80.0%), 325 (45.0%), 266 (58.57%), 194 (57.88%), 125 (89.20%), and 83 (0.71%).

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. ^1H 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 the HP Model MS-5988. Elemental analyses were carried out at the microanalytical laboratories of the Faculty of Science, Cairo University, Cairo, Egypt. The samples were irradiated with gamma radiation (^{60}Co) at the National Center for Radiation Research and Technology. A powder sample was irradiated at r.t. condition in polycarbonate vials at a dose rate (10 KGy/h). UV spectra were recorded using an ATI unicam. UV is AURORA SCAN. Physical data is collected in Table 1.

4-(4-Fluoro-phenyl)-2-mercapto-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile 3a and 4-Benzo[1,3]-dioxo-5-yl-2-mercapto-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile 3b

A mixture of **1a**, **b** (0.01 mole) and dimedone (0.01 mole) in ethanol containing few drops of pipredine was heated under reflux for 4 h. The solid obtained was recrystalized from ethanol to give **3a**, **b**, respectively.



SCHEME 6

3-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-thieno [2,3-*b*]quinoline-2-carbonitrile (5)

A mixture of compound **3a** (0.01 mole), chloroacetonitrile (0.01 mole), and sodium ethoxide (0.01 mole) in absolute ethanol (50 mL) was heated under reflux for 2 h. The solid product, which was produced on heating, was collected and recrystallized from ethanol to give **5**.

3-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-thieno[2,3-*b*]quinoline-2-carboxylic acid amide (6)

Method A

A sample of compound **5** (0.01 mole) was dissolved in conc. sulfuric acid (10 mL) and stirred at r.t. for 2 h. The reaction mixture was diluted with ice-cold water and neutralized with ammonium hydroxide. The resulting precipitate was collect by filtration and recrystallized from ethanol to give **6**.

Method B

A mixture of compound **3a** (0.01 mole), sodium methoxide (0.01 mole), and chloroacetamide (0.01 mole) in (50 mL) methanol was refluxed for 2 h. The reaction mixture then cooled and poured into cold water (60 mL) and acidified with HCl. The solid product was collected and recrystallized from ethanol to give **6**.

8,8-Dimethyl-11-(4-fluorophenyl)-4,7,8,9,10,11-hexahydro-4,10-dioxo-quinolino [3′,2′:4,5]thieno[3,2-*d*]pyrimidine (7)

A mixture of compound **5** (0.01 mole) and formic acid (10 mL) was heated under reflux for 24 h. After cooling the precipitate was filtered and recrystallized from dioxane to give **7**.

4-Amino-8,8-dimethyl-11-(4-fluorophenyl)-7,8,9,10,11-pentahydro-10-oxo-quinolino[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (8)

Compound **5** (0.01 mole) in formamide (10 mL) was heated under reflux for 24 h and left to cool. The crystalline product thus formed was filtered, washed with ether, and recrystallized from dioxane to give **8**.

2,8,8-Trimethyl-11-(4-fluorophenyl)-4,7,8,9,10,11-hexahydro-4-thioxo-10-oxo-quinolino[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (9)

A mixture of compound **5** (0.01 mole), thioacetamide (0.01 mole), and trifluoroacetic acid (5 mL) was heated for 24 h on a steam bath. The

mixture was cooled and then poured into excess of ice and water. The solid obtained was recrystallized from acetic acid to give **9**.

8,8-Dimethyl-4-(4-fluorophenyl)-3-phenyl-2,4,7,8,9,10,11-heptahydro-2-thioxo-4-imino-10-oxo-quinolino[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (11)

A mixture of compound **5** (0.01 mole) and phenyl isothiocyanate (0.01 mole) in pyridine (15 mL) was refluxed for 6 h. The reaction mixture was cooled and diluted with water and the resulting solid was recrystallized from DMF-ethanol to give **11**.

N-[2-Cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-thieno[2,3-*b*]quinolin-3-yl]-formimidic Acid Ethyl Ester (12)

A mixture of compound **5** (0.01 mole), triethyl orthoformate (3 mL), and acetic anhydrid (10 mL) was heated under reflux for 4 h and then allowed to cool. The product was collected and recrystallized from ethanol to give **12**.

N-[2-Cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo- 4,5,6,7,8,9-hexahydro-thieno[2,3-*b*]quinolin-3-yl]-acetamide (16)

A solution of compound **5** (0.01 mole) in acetic anhydride (10 mL) was heated for 5 min. After cooling the solid that was separated was recrystallized from ethanol to give **16**.

N-Acetyl-*N*- [2-cyano-4-(fluorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-thieno[2,3-*b*]quinolin-3-yl]-acetamide (17)

A solution of compound **5** (0.01 mole) in acetic anhydride (15 mL) was refluxed for 3 h. After cooling the solid product thus formed was collected and recrystallized from ethanol to give **17**.

[2-Cyano-4-fluorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-thieno[2,3-*b*]quinolin-3-yl]-urea (18)

To a solution of sodium ethoxide (prepared from 0.5 g of sodium and 50 mL of absolute ethanol), compound **5** (0.01 mole), and urea (0.01 mole) were added. The reaction mixture was refluxed for 6 h and then concentrated in vacuo. On cooling and neutralizing with HCl, a solid

formed, which was collected by filtration, washed with water, and recrystallized from ethanol to give **18**.

4-Amino-2,8,8-trimethyl-11-(4-fluorophenyl)-2,7,8,9,10,11-hexahydro-2,10-dioxo-quinolino[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine (19) and 4-amino-8,8-dimethyl-11-(4-fluorophenyl)-2,7,8,9,10,11-hexahydro-2-thioxo-10-oxo-quinolino-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (20)

Method A

General procedure. A mixture of compound **5** (0.01 mole) and urea or thiourea (0.01 mole) was heated on an oil bath at 180°C for 2 h. On cooling the product solidified, which was recrystallized from DMF-ethanol to give **19** or **20**, respectively.

Method B

A sample of compound **18** was heated on an oil bath at 180°C for 2 h, and then allowed to cool; the resulting solid was recrystallized from DMF-ethanol to give **19**.

3-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-thieno[2,3-*b*]quinoline-2-carboxylic Acid (21)

A solution of compound **5** in conc. sulfuric acid (10 mL) was heated under reflux for 20 min. The obtained solid was recrystallized from dioxane to give **21**.

3-Amino-7,7-dimethyl-10-(4-fluorophenyl)-6,7,8,9,10-penta-hydro-9-oxo -pyrazolo[3′,4′: 4,5]thieno[2,3-*b*]quinoline (22)

A mixture of compound **5** (0.01 mole), hydroxylamine hydrochloride (0.012 mole), and sodium ethoxide (0.01 mole) in ethanol (50 mL) was heated under reflux for 3 h, was allowed to cool, and poured into cold water (60 mL). The solid product was collected and recrystallized from dioxane to give **22**.

4-Amino-8,8-dimethyl-11-(4-fluorophenyl)-2,7,8,9,10,11-hexahydro-2,10-dioxo- pyrido[2′,3′:4,5] thieno [2,3-*b*]-quinolin-3-carbonitrile (23)

A mixture of compound **5** (0.01 mole), ethyl cyanoacetate (0.01 mole) and piperidine (0.5 mL) in dimethylformamide (10 mL) was heated under

reflux for 3 h.The solid product was collected and recrystallized from ethanol to give **23**.

4-Amino-8,8-dimethyl-11-(4-fluorophenyl)-2-phenyl-7,8,9,10, 11-pentahy-dro-10-oxo-pyrido[2′,3′:4,5] thieno[2,3-*b*]quinolin-3-carbonitrile (24)

A mixture of compound **5** (0.01 mole), benzylidenemalononitrile (0.01 mole) and piperidine (0.01 mole) in ethanol (50 mL) was heated under reflux for 2 h, allowed to cool, and poured into ice/H_2O and acidified with HCl. The solid product was collected and recrystallized from dioxane to give **24**.

4-Amino-2,8,8-trimethyl-11-(4-fluorophenyl)-6,7,8,9,10,11-hexahydro-10-oxo-pyrido[2′,3′:4,5]thieno[2,3-*b*]quinolin-3-carbonitrile (25)

A solution of equimolar amounts of acetaldehyde and malononitrile (0.01 mole) in absolute ethanol (50 mL) was added to a suspension of appropriate enaminonitrile **5** (0.01 mole) in absolute ethanol (20 mL) and pyridine (0.5 mL). The reaction mixture was heated under reflux for 4 h. The solvent was then evaporated under reduced pressure and the solid product was recrystallized from dioxane to give **25**.

ANTIMICROBIAL ACTIVITY

Seventeen 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.[31] 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 h of incubation at 30°C for bacteria and 48 h of incubation at 28°C for fungi. The diameter of inhibition zone (mm) was measured (Table II).

Ofloxacin and SXT in a concentration (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 II). The pyrazolothieno-quinoline having fluorophenyl, free amino group

TABLE I Physical and Analytical Data of the Synthesized Compounds

Compound no.	Yield %	M.P. °C	Mol. formula (mol-wt)	Analysis % required/(found) C	H	N
3a	86	157–158	$C_{18}H_{17}N_2OSF$	65.85	5.18	8.54
			(328)	65.60	4.80	8.70
3b	81	226–228	$C_{19}H_{18}N_2O_3S$	64.41	5.08	7.91
			(354)	64.70	5.20	8.20
5	78	263–264	$C_{20}H_{18}N_3OSF$	65.40	4.90	11.44
			(367)	65.10	4.70	11.20
6	57	231–233	$C_{20}H_{20}N_3O_2SF$	62.33	5.19	7.27
			(385)	62.60	5.50	7.50
7	75	219–221	$C_{21}H_{18}N_3O_2SF$	63.80	4.56	10.63
			(395)	63.60	4.80	10.90
8	76	> 350	$C_{21}H_{19}N_4OSF$	63.96	4.82	14.21
			(394)	63.70	4.60	14.50
9	81	242–244	$C_{22}H_{20}N_3OS_2F$	62.12	4.71	9.88
			(425)	62.30	4.40	9.60
11	64	146–147	$C_{27}H_{23}N_4OS_2F$	64.54	4.58	11.16
			(502)	64.20	4.20	11.50
12	71	208–210	$C_{23}H_{22}N_3O_2SF$	65.25	5.20	9.93
			(423)	65.50	5.40	9.60
16	68	314–316	$C_{22}H_{20}N_3O_2SF$	64.55	4.89	10.27
			(409)	64.80	4.60	10.50
17	61	123–125	$C_{24}H_{22}N_3O_3SF$	63.86	4.88	9.31
			(451)	63.70	4.60	9.50
18	76	293–295	$C_{21}H_{19}N_4O_2SF$	61.46	4.63	13.66
			(410)	61.20	4.90	13.80
19	59	> 350	$C_{21}H_{19}N_4O_2SF$	61.46	4.63	13.66
			(410)	61.30	4.80	13.40
20	63	> 350	$C_{21}H_{19}N_4OS_2F$	59.15	4.46	13.15
			(426)	59.50	4.70	13.50
21	59	> 350	$C_{20}H_{19}N_2O_3SF$	62.18	4.92	7.25
			(386)	62.50	4.70	7.10
22	76	199–201	$C_{20}H_{19}N_4OSF$	62.83	4.97	14.66
			(382)	63.10	4.60	14.50
23	64	> 350	$C_{23}H_{19}N_4O_2SF$	63.59	4.38	12.90
			(434)	63.90	4.10	12.60
24	66	138–140	$C_{29}H_{23}N_4OSF$	70.45	4.66	11.34
			(494)	70.10	4.40	11.10
25	71	311–313	$C_{24}H_{21}N_4OSF$	66.67	4.86	12.96
			(432)	66.40	4.50	13.30

22 and pyridothienoquinoline containing fluorophenyl, cyano and free amino moieties **25** were found to be the most active compounds against *Saccharomyces cerrevisiae*, whereas compounds **11**, **17**, and **23** exhibited a moderate activity against *Staphylococcus aurous*(29213).

TABLE II Antimicrobial Activity of the Newly Synthesized Compounds

Compound no.	*Staphylococcus aureus* (29213)	*Escherichia coli* (ATCC 25922)	*Saccharomyces* cerevisiae
3a	+	+	0
5b	0	0	0
6	+	+	0
8	0	0	0
9	+	0	0
11	++	0	0
12	0	0	++
16	+	+	0
17	++	0	0
18	+	+	0
19	+	0	0
20	+	+	0
21	+	+	0
22	0	+	++++
23	+	+	0
24	++	+	0
25	0	+	+++
Ofloxacin (Tarivid)[a]	++++	+++	0
SXT[a]	++++	+++	0
Mycostatine[b]	0	0	+++
DMF	0	0	0

[a]Ofloxacin and SXT 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.

From these results it can be concluded that the biologically active compounds **22** and **25** (MIC values were <50 μg/mL) are nearly as active as the standard fungicide 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 **22** and **25** after irradiation. These compounds in a 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

TABLE III UV and Visible Data of the Biologically Active Compounds Before and After Gamma Irradiation

Compound no.	Dose (KGy) control	Conc. (mol)	$\lambda_{max}(1)$	Abs. (O.D.)	$\lambda_{max}(2)$	Abs. (O.D.)
			299	1.120	370	0.740
22	5	5×10^{-5}	299	1.126	370	0.752
	10		299	1.128	370	0.751
	15		299	1.127	370	0.763
	20		299	1.130	370	0.801
	25		299	1.134	370	0.769
	30		299	1.132	370	0.764
	40		299	1.136	370	0.770
			268	0.843	369	1.942
25	5	5×10^{-5}	268	0.880	369	1.950
	10		268	0.889	369	1.956
	15		268	0.891	369	1.963
	20		268	0.895	369	1.968
	25		268	0.899	369	1.980
	30		268	0.890	369	1.974
	40		268	0.896	369	1.979

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 III).

The results showed that the biologically active compounds **22** and **25** remain radioresistant, retaining their structures unchanged up to 40 KGy (Table III).

Further, TLC analyses (R_f) were made on precoated silica gel G sheets IB-F and were detected by the use of a UV lamp at 254 nm. The R_f values of the unirradiated compounds **22** and **25** were 0.31 and 0.22, 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 radiosterilization of these compounds in dry form by gamma irradiation may prove to be applicable.

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