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Synthesis and evaluation of some new fluorinated hydroquinazoline derivatives as antifungal agents

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Abstract

The key intermediate octahydroquinazoline (**1**) was obtained in one pot synthesis by a modification of the Biginelli reaction. Compound **1** was allowed to react with phenacyl bromide and bromomalononitrile to furnish thiazolo[2,3-*b*]quinazoline **3** and **12**, respectively. Interaction of compound **12** with formamide, formic acid and phenyl isothiocyanate yielded the corresponding pyrimidino[4′,5′:4,5]thiazolo[2,3-*b*] quinazolines **13**, **14** and **17**, respectively. The structure of the synthesized compounds were elucidated by elemental analyses and spectroscopic analyses. Some of the prepared compounds were tested for their antifungal activity in comparison with tioconazole as a reference fungicide.

Keywords: Quinazolines; Thiazoloquinazolines; Pyrimidinothiazoloquinazolines and antifungal activity

1. Introduction

Quinazoline and its synthetic analogues have been found to exhibit a broad spectrum as biologically active compounds. Quinazolines, in particular, as antimicrobial agents has attracted a special interest [1–5]. In the meantime, many thiazole derivatives are known to exhibit antifungal activity [6–11]. It was, therefore, thought worthwhile to incorporate the thiazole, pyrimidinothiazole and triazinothiazole moieties with the hydroquinazoline nucleus in one molecule to evaluate their effect as anticipated active antifungal compounds.

2. Chemistry

4-(4′-Fluorophenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5 -one (**1**) was obtained by a modification of the Biginelli reaction [12] employing a three component system comprising 1,3-cyclohexanedione with 4-fluorobenzaldehyde and thiourea (Scheme 1).

The phenacylthio derivative **2** was prepared via reaction of compound **1** with phenacyl bromide in anhydrous acetone/K_2CO_3,which was cyclized by a simple acid cyclodehydration in 98% H_2SO_4 to give compound **3**. The thiazoloquinazoline derivative **3** was obtained also in one step via reaction of **1** with phenacyl bromide in boiling ethanol (Scheme 2). When compound **1** was treated with $POCl_3$/DMF at room temperature (r.t.) [8], intermediate **4** was readily formed, which upon hydrolysis gave the formyl derivative **5**. Condensation of compound **5** with malononitrile caused cyclization to give thiazinoquinazoline derivative **6**.

Refluxing of compound **1** with acetic anhydride leads to the formation of corresponding 3-acetyl derivative **7**. The site of acetylation in **7** was supported by ^{1}H NMR spectrum. The signal for C4 proton collapsed from a doublet in compound **1** to a singlet in compound **7**. Reaction of compound **1** with methyl iodide in acetone in the presence of anhydrous K_2CO_3 produced compound **8**, instead of the expected product **9**. This result was proved using ^{1}H NMR data, which showed two singlets at 2.9 and 3.1 ppm due to SCH_3 and N_3-methyl protons [13]. Compound **1** reacted with acrylonitrile to give the 3-(2-cyanoethyl) derivative **10** rather than **11**, which is in agreement with previous works [14]. This is

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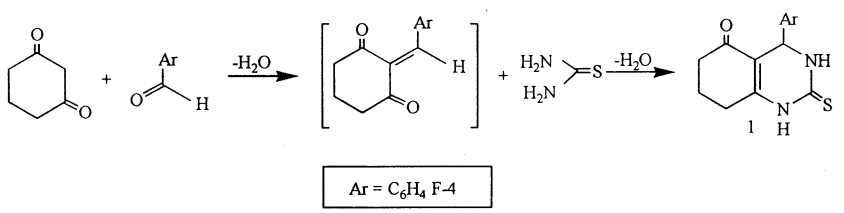
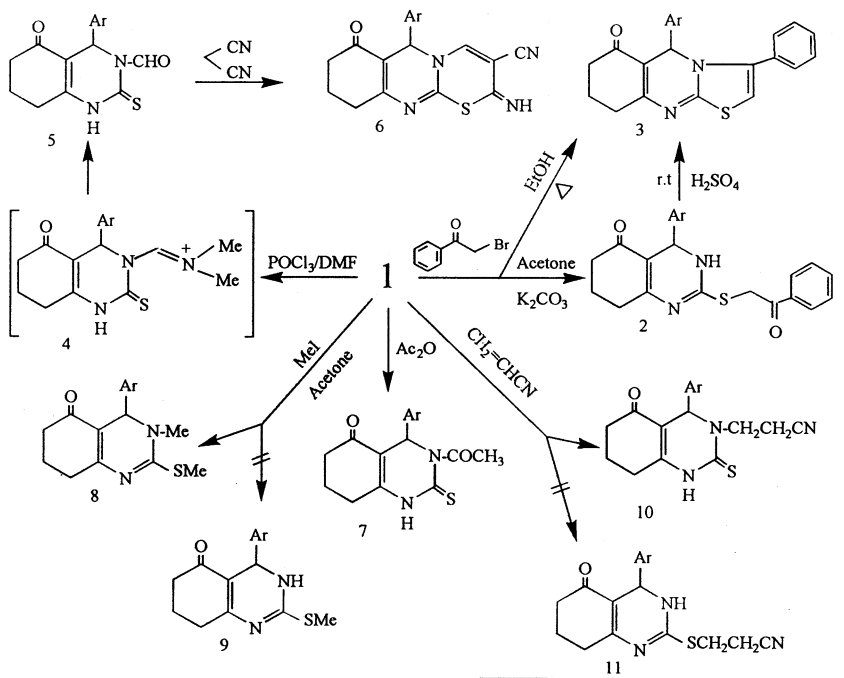
also approved by ^{1}H NMR which revealed a signal for C4 proton converted from a doublet in compound **1** to a singlet in compound **10** due to N_3-cyanoethylation. When a solution of **1** in ethanolic potassium hydroxide was treated with cold bromomalononitrile, 3-amino-2-cyano - 5 - (4′ - fluorophenyl) - 5,6,7,8,9-pentahydrothiazolo[2,3-*b*]quinazolin-6-one (**12**) was obtained in good yield (Scheme 3). The reaction of compound **12** with formamide gave pyrimidinothiazoloquinazoline (**13**). Compound **12** gave characteristic reactions for enaminonitriles. Thus, when **12** was heated under reflux with formic acid it gave pyrimidinothiazolo-quinazoline derivative **14**. Interaction of **12** with malononitrile in ethanol in presence of piperidine furnished the corresponding pyridothiazolo-quinazoline derivative **15**. Compound **12** reacted with hydroxylamine hydrochloride in boiling ethanolic sodium ethoxide [15] to give pyrazolothiazoloquinazoline derivative **16**, its IR spectrum showed the absence of (C≡N) band and presence of (NH, NH_2) bands. Compound **12** was reacted with phenyl isothiocyanate in pyridine to give 4-amino-3-phenyl-11-(4-fluorophenyl)-2-thioxo-2,7,8,9,10,11-hexahydroquinazolin-10-one (**17**). In addition compound **12** reacted with acetic anhydride, for which two products **18** and **19** seemed possible. Structure **19** was ruled out due to presence of (C≡N) band in the IR spectrum.

Compound **12** when stirred with concentrated H_2SO_4 at r.t. [16] for 2 h, afforded 3-amino-2-carboxamido derivative **20**. The formation of the amide **20** was confirmed by IR, which showed the disappearance of the cyano (C≡N) group and exhibited a carbonyl stretch at 1650 cm^{-1} along with characteristic amino (NH_2) and carboxamido ($CONH_2$) bands at 3410, 3320, 3250, 3180 cm^{-1} (Scheme 4).

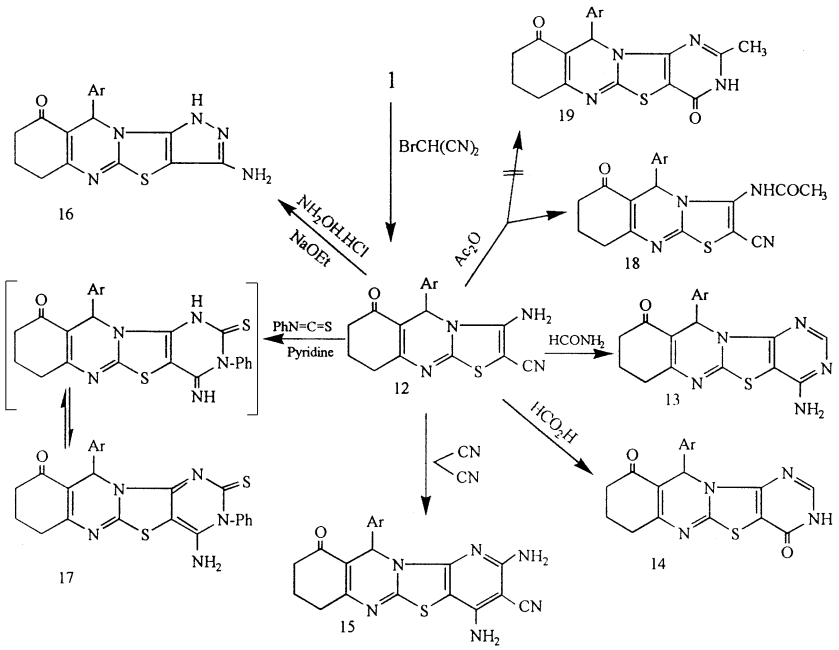
Condensation of compound **20** with acetic anhydride furnished the corresponding 2-methyl-11-(4′-fluorophenyl) - 3,4,7,8,9,10,11 - heptahydroquinazolin - 4,10-dione (**19**). Heating compound **20** with formamide yielded the pyrimidinothiazolo-quinazoline (**14**). Interaction of compound **20** with thionyl chloride yielded the thiadiazinothiazoloquinazoline derivative **21**.



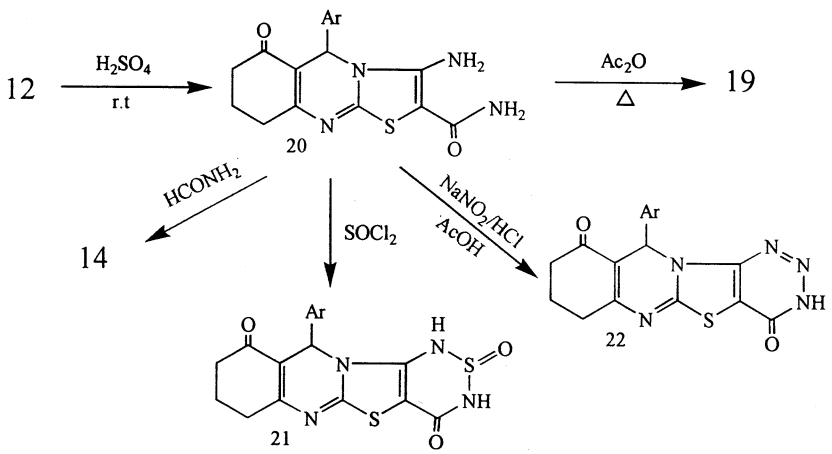
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

Finally, reaction of compound **20** with nitrous acid gave the triazinothiazoloquinazoline derivative **22**.

3. Experimental

All melting points are uncorrected and were determined on a Stuart melting point apparatus. IR spectra (cm^{-1}) were recorded on a Pye-Unicam spectrophotometer type 1200 using KBr Wafer technique. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Chemical shifts were expressed in δ (ppm) values. Mass spectra were run using HP Model: MS-5988. Elemental analysis were determined using Perkin–Elmer 240 C Microanalyser.

*3.1. 4-(4′-Fluorophenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (**1**)*

A mixture of thiourea (0.005 mol), 4-fluorobenzaldehyde (0.005 mol), 1,3-cyclohexanedione (0.007 mol), abs. C_2H_5OH (20 ml) and 37% HCl (4 drops) was heated under reflux for 3 h and the reaction solution was allowed to cool, filtered off and crystallized from C_2H_5OH to give **1** (Table 1).

*3.2. 4-(4′-Fluorophenyl)2-(phenacylthio)-3,4,5,6,7,8-hexahydroquinazolin-5-one (**2**)*

A solution of **1** (0.005 mol), phenacyl bromide (0.005 mol) in anhydrous acetone in presence of (1 g) anhydrous K_2CO_3 was refluxed for 10 h. The reaction

Table 1
Physical and spectral data of the synthesized compounds **1**–**22**

Compd no.	M.p. (°C) yield (%)	Molecular formula (Mol. Wt)	Elemental analyses calculated/found			IR ν (cm^{-1})	^{1}H NMR δ (ppm) (DMSO-d_6)
			C%	H%	N%		
1 [a]	276–278 81	$C_{14}H_{13}N_2OSF$ (276.31)	60.85 60.50	4.73 4.90	10.13 10.40	3280, 3200 (2NH), 1700 (C=O), 1500, 1220 (C=S)	1.8–2.5 (6H, m, CH_2-6, CH_2-7, CH_2-8), 5.2 (1H, d, H-4), 7.2–7.8 (4H, m, arom); 9.7 (1H, s, N_1-H), 10.7 (1H, s, N_3-H).
2	104–106 69	$C_{22}H_{19}N_2O_2SF$ (394.44)	66.99 67.20	4.85 4.60	7.10 7.40	3410 (NH), 1710, 1655 (2C=O), 1600 (C=N)	1.4–2.6 (6H, m, CH_2-6, CH_2-7, CH_2-8), 4.2 (2H, s, SCH_2), 5.2 (1H, d, H-4), 7.2–7.8 (9H, m, arom), 9.8 (1H, s, N_3-H).
3	235–237 58	$C_{22}H_{17}N_2OSF$ (376.43)	70.19 70.50	4.54 4.70	7.44 7.10	1650 (C=O), 1600 (C=N).	1.7–2.7 (6H, m, CH_2-7, CH_2-8, CH_2-9), 6.4 (1H, s, H-5), 7.1–7.6 (9H, m, arom), 8.1 (1H, s, H-2)
5	129–131 71	$C_{15}H_{13}N_2O_2SF$ (304.32)	59.20 59.40	4.30 4.60	9.20 9.30	3250 (NH), 1700, 1650 (2C=O), 1520, 1240 (C=S)	1.6–2.6 (6H, m, CH_2-6, CH_2-7, CH_2-8), 6.6 (1H, s, H-4), 7.0–7.6 (4H, m, arom), 8.3 (1H, s, CHO), 9.4 (1H, s, N_1-H).
6	167–169 64	$C_{18}H_{13}N_4OSF$ (352.37)	61.35 61.10	3.71 3.50	15.89 15.60	3320 (NH), 2220 (C≡N), 1655 (C=O), 1600 (C=N)	
7	210–212 66	$C_{16}H_{15}N_2O_2SF$ (318.35)	60.36 60.10	4.74 4.50	8.79 8.60	3200 (NH), 1730, 1680 (2C=O), 1510, 1250 (C=S)	1.8–2.6 (6H, m, CH_2-6, CH_2-7, CH_2-8), 2.7 (3H, s, $COCH_3$), 6.4 (1H, s, H-4), 7.0–7.4 (4H, m, arom), 11.9 (1H, s, N_1-H)
8	>300 53	$C_{16}H_{17}N_2OSF$ (304.36)	63.14 63.30	5.62 5.40	9.20 9.50	1660 (C=O), 1600 (C=N)	1.6–2.5 (6H, m, CH_2-6, CH_2-7, CH_2-8), 2.9 (3H, s, SCH_3), 3.1 (3H, s, N-CH_3), 6.7 (1H, s, H-4), 7.0–7.4 (4H, m, arom).
10	260–262 49	$C_{17}H_{16}N_3OSF$ (329.37)	61.99 61.70	4.89 4.60	12.75 12.50	3260 (NH), 2950 (CH aliph), 2240 (C≡N), 1640 (C=O), 1540, 1210 (C=S)	1.4–2.5 (6H, m, CH_2-6, CH_2-7, CH_2-8), 4.2 (2H, t, CH_2CN), 5.2 (2H, t, N-CH_2), 6.2 (1H, s, H-4), 7.0–7.6 (4H, m, arom), 9.8 (1H, s, N_1-H).
12 [a]	235–237 92	$C_{17}H_{13}N_4OSF$ (340.36)	59.99 60.20	3.84 3.60	16.46 16.20	3300, 3180 (NH_2), 2200 (C≡N), 1650 (C=O)	1.6–2.5 (6H, m, CH_2-7, CH_2-8, CH_2-8, CH_2-9); 5.7 (2H, s, NH_2), 6.4 (1H, s, H-4), 7.1–7.6 (4H, m, arom).
13	>300 78	$C_{18}H_{14}N_5OSF$ (367.38)	58.84 58.60	3.83 3.90	19.06 19.30	3310, 3170 (NH_2), 1690 (C=O), 1600 (C=N)	1.4–2.6 (6H, m, CH_2-7, CH_2-8, CH_2-9); 5.7 (2H, s, NH_2), 6.6 (1H, s, H-11), 7.1–7.6 (4H, m, arom), 8.3 (1H, s, H-2).
14	252–254 68	$C_{18}H_{13}N_4O_2SF$ (368.37)	58.69 58.90	3.55 3.30	15.20 15.50	3280, (NH), 1695, 1650 (2C=O), 1600 (C=N)	1.6–2.6 (6H, m, CH_2-7, CH_2-8, CH_2-9); 6.5 (1H, s, H-11), 7.2–7.6 (4H, m, arom), 8.2 (1H, s, H-2), 9.6 (1H, s, NH).
15	287–289 66	$C_{20}H_{15}N_6OSF$ (406.42)	59.10 59.30	3.71 3.40	20.67 20.40	3400, 3320, 3270, 3190 ($2NH_2$), 2200 (C≡N), 1600 (C=N)	
16	>300 53	$C_{17}H_{14}N_5OSF$ (355.37)	57.45 57.10	3.96 3.60	19.70 19.80	3415, 3260, 3200 (NH, NH_2), 1600 (C=O), 1610 (C=N)	1.5–2.6 (6H, m, CH_2-6, CH_2-7, CH_2-8); 5.6 (2H, s, NH_2), 6.8 (1H, s, H-10), 7.1–7.6 (4H, m, arom), 9.4 (1H, s, NH).
17	152–154 68	$C_{24}H_{18}N_5OS_2F$ (475.54)	60.61 60.30	3.81 3.70	14.72 14.40	3250, 3210 (NH_2), 1660 (C=O), 1600 (C=N)	1.4–2.5 (6H, m, CH_2-7, CH_2-8, CH_2-9); 5.7 (2H, s, NH_2), 6.8 (1H, s, H-11), 7.2–7.9 (9H, m, arom)
18	>300 59	$C_{19}H_{15}N_4O_2SF$ (382.39)	59.67 59.80	3.95 3.70	14.65 14.50	3360, (NH), 2930 (CH aliph), 2210 (C≡N), 1710, 1670 (2C=O), 1605 (C=N)	1.3–2.4 (6H, m, CH_2-7, CH_2-8, CH_2-9); 2.6 (3H, s, $COCH_3$), 6.5 (1H, s, H-5), 7.0–7.6 (4H, m, arom), 9.1 (1H, s, NH)
19	150–152 76	$C_{19}H_{15}N_4O_2SF$ (382.39)	59.67 59.40	3.95 3.60	14.65 14.90	3340 (NH), 1700, 1600 (2C=O), 1610 (C=N)	1.4–2.5 (6H, m, CH_2-7, CH_2-8, CH_2-9); 2.2 (3H, s, CH_3), 6.5 (1H, s, H-11), 7.1–7.7 (4H, m, arom), 9.3 (1H, s, NH)
20	274–276 81	$C_{17}H_{15}N_4O_2SF$ (358.37)	56.97 56.70	4.21 4.40	15.63 15.90	3410, 3320, 3250, 3180 ($2NH_2$), 1660, 1650 (2C=O), 1600 (C=N)	
21 [a]	>300 62	$C_{17}H_{13}N_4O_3S_2F$ (404.42)	50.48 50.20	3.23 3.10	13.85 13.50	3360, 3280 (2NH), 1720, 1690 (2C=O), 1610 (C=N)	
22 [a]	>300 51	$C_{17}H_{12}N_5O_2SF$ (369.36)	55.28 55.10	3.27 3.50	18.95 18.70	3290 (NH), 1695, 1670 (2C=O), 1610 (C=N)	

[a] MS: m/z (%) for compound **1**: 276 (57.82, M^+, 277 (12.57, M+1), 278 (3.34, M+2), 122 (100); **12**: 340 (3.65, M^+), 341 (0.85, M+1), 25 g (100); 21: 404 (9.14, M^+), 157 (100); 22: 369 (6.05, M^+), 69 (100).

mixture was concentrated under reduced pressure. The separated solid was filtered off and crystallized from C_2H_5OH to give **2**.

*3.3. 3-Phenyl-5-(4-fluorophenyl)-5,6,7,8,9-pentahydrothiazolo[2,3-b]quinazolin-6-one (**3**)*

3.3.1. Method A

A suspension of **2** (0.005 mol) in 98% H_2SO_4 (5 ml) was stirred for 2 h, then left at r.t. overnight. The solid formed, pouring the clear solution in ice-water (100 ml) under stirring, was collected, washed with water, dried and crystallized from dioxane to give **3**.

3.3.2. Method B

To a solution of **1** (0.005 mol) in abs. C_2H_5OH (50 ml), was added phenacyl bromide (0.005 mol). The resulting mixture was refluxed for 24 h and the obtained solid was crystallized from dioxane to give **3**.

*3.4. 3-Formyl-4-(4′-fluorophenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazoline-5-one (**5**)*

To a solution of **1** (0.005 mol) in dry DMF (30 ml); $POCl_3$ (0.009 mol) was added under stirring in an-ice-bath. Stirring was continued at r.t. for another 15 min and then the solution was poured into ice-water, filtered, dried and crystallized from C_2H_5OH to give **5**.

*3.5. 2-Imino-3-cyano-6-(4′-fluorophenyl)-6,7,8,9,10-pentahydro[1,3]thiazino[2,3-b]quinazolin-7-one (**6**)*

To a solution of **5** (0.005 mol) in C_2H_5OH (25 ml), malononitrile (0.005 mol), and triethylamine (0.5 ml) were added; the mixture was refluxed for 6 h. Then the reaction mixture was cooled and the solid obtained was crystallized from C_2H_5OH to give **6**.

*3.6. 3-Acetyl-4-(4′-fluorophenyl)-2-thioxo-1,2,3,4,5,6,7,8-octahydroquinazolin-5-one (**7**)*

To a solution of **1** (0.005 mol) in Ac_2O (30 ml) was refluxed for 2 h. The separated product was filtered off and crystallized from C_2H_5OH to give **7**.

*3.7. 2,3-Dimethyl-4-(4′-fluoropheny)-3,4,5,6,7,8,-hexahydroquinazolin-5-one (**8**)*

A mixture of **1** (0.005 mol) and methyl iodide (0.005 mol) in acetone (50 ml) in presence of (1 g) anhydrous K_2CO_3 was refluxed for 24 h. The obtained solid was crystallized from C_2H_5OH to give **8**.

*3.8. 3-(2-Cyanoethyl)-4-(4′-fluorophenyl)-2-thioxo-1,2,3,4,5,6,7,8,-octahydroquinazolin-5-one (**10**)*

A mixture of **1** (0.005 mol) and acrylonitrile (0.005 mol) in pyridine (20 ml) was refluxed for 4 h. Then it was cooled and poured into an ice–HCl mixture. The separated solid was filtered off, washed with H_2O, dried and crystallized from C_2H_5OH to give **10**.

*3.9. 3-Amino-2-cyano-5-(4′-fluorophenyl)-5,6,7,8,9-pentahydrothiazolo[2,3-b]-quinazolin-6-one (**12**)*

Compound **1** (0.005 mol) was dissolved in an aqueous solution of KOH (0.005 mol). The solution was stirred at r.t., subsequently a solution of bromomalononitrile (0.005 mol) in ethanol was added dropwise over a period of 30 min. The reaction mixture was stirred for a further 2 h at r.t. and the resulting precipitate was collected by filtration, washed with water several times and dried. The crude product was crystallized from C_2H_5OH to give **12**.

*3.10. 4-Amino-11-(4′-fluorophenyl)- 7,8,9,10,11-pentahydropyrimidino[4′,5′:4,5]-thiazolo[2,3-b]-quinazolin-10-one (**13**)*

A solution of **12** (0.005 mol) in formamide (20 ml) was refluxed for 6 h. The reaction mixture was cooled, diluted with water and the resulting precipitate was collected by filtration and crystallized from C_2H_5OH to give **13**.

*3.11. 11-(4′-fluorophenyl)-3,4,7,8,9,10,11-heptahydropyrimidino[4′,5′:4,5]thiazolo[2,3-b]-quinazolin-4,10-dione (**14**)*

3.11.1. Method A

A solution of **12** (0.005 mol) in formic acid (10 ml), was refluxed for 4 h. The solid obtained was crystallized from C_2H_5OH to give **14**.

3.11.2. Method B

A solution of **20** (0.005 mol) in formamide (20 ml) was refluxed for 8 h. The obtained solid was crystallized from C_2H_5OH to give **14**.

*3.12. 2,4-Diamino-3-cyano-11-(4-fluorophenyl)-7,8,9,10,11-pentahydropyrido[2′,3′:4,5]thiazolo[2,3-b]-quinazolin]-10-one (**15**)*

A suspension of **12** (0.005 mol) in C_2H_5OH (20 ml) containing a catalytic amount of triethylamine was treated with malononitrile (0.005 mol). The reaction mixture was refluxed for 10 h. The separated solid was filtered off and crystallized from dioxane to give **15**.

*3.13. 3-Amino-10-(4-fluorophenyl)-1,6,7,8,9,10-hexahydropyrazolo[3′,4′:4,5]-thiazolo[2,3-b]-quinazolin-9-one (**16**)*

A solution of **12** (0.005 mol), hydroxylamine hydrochloride (0.005 mol) and sodium ethoxide (0.005 mol) in abs C_2H_5OH (50 ml) was refluxed for 8 h. The separated solid was filtered and crystallized from C_2H_5OH to give **16**.

*3.14. 4-Amino-3-phenyl-2-thioxo-11-(4′-fluorophenyl)-2,3,7,8,9,10,11-heptahydropyrimidino[4′,5′:4,5]-thiazolo[2,3-b]quinazolin-10-one (**17**)*

A mixture of **12** (0.005 mol), phenyl isothiocyanate (0.005 mol) and pyridine (20 ml) was refluxed for 6 h. The reaction mixture was cooled, diluted with water and resulting solid was crystallized from dioxane to give **17**.

*3.15. 3-Acetylamino-2-cyano-5-(4′-fluorophenyl)-5,6,7,8,9-pentahydrothiazolo-[2,3-b]quinazolin-6-one (**18**)*

A solution of **12** (0.005 mol) in Ac_2O (10 ml) was refluxed for 2 h. The obtained solid was crystallized from C_2H_3OH to give **18**.

*3.16. 2-Methyl-11-(4′-fluorophenyl)-3,4,7,8,9,10,11-heptahydropyrimidino[4′,5′:4,5]thiazolo[2,3-b]-quinazolin-4,10-dione (**19**)*

A solution of **20** (0.005 mol) in Ac_2O (20 ml) was refluxed for 6 h. The obtained solid was crystallized from C_2H_5OH to give **19**.

*3.17. 3-Amino-2-carboxamido-5-(4′-fluorophenyl)-5,6,7,8,9-pentahydrothiazolo[2,3-b]quinazolin-6-one (**20**)*

Compound **12** (0.005 mol) was dissolved in conc. H_2SO_4 (20 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 collected by filtration, dried and crystallized from C_2H_3OH to give **20**.

*3.18. 11-(4′-fluorophenyl)-2-sulfoxido-1,3,4,7,8,9,11-heptahydro[1,2,6]thiadiazino[4′,5′:4,5]-thiazolo[2,3-b]quinazolin-4,10-dione (**21**)*

A solution of **20** (0.005 mol) in thionyl chloride (10 ml) was refluxed for 4 h. The obtained solid was crystallized from C_2H_5OH to give **21**.

*3.19. 11-(4′-fluorophenyl)-3,4,7,8,9,10,11-heptahydro[1,2,3]triazino[4,5′:4,5]-thiazolo[2,3-b]-quinazolin-4,10-dione (**22**)*

To a stirred suspension of **20** (0.005 ml) in a mixture of acetic acid (8 ml) and water (4 ml) a solution of sodium nitrite (0.005 mol) in water (6 ml) was added dropwise at 0°C. The mixture was left in the refrigerator for 12 h and the precipitate was collected by filtration and crystallized from C_2H_5OH to give **22**.

4. Antifungal activity

Most of the newly synthesized compounds were tested for their antifungal activity against four species of fungi namely, *Aspergillus ochraceus* Wilhelm (AUCC-230), *Penicillium chrysogenum* Thom (AUCC-530), *Aspergillus flavus* Link (AUCC-164) and *Candida albicans* Robin Berkho (AUCC- 1720), using the hole cupplate agar diffusion method [17].

The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1000 μg/ml concentration. The fungi cultures were maintained on Czapek's Dox agar medium. Dimethylformamide showed no inhibition zones. The minimum inhibitory concentration (MIC) of the active compounds were measured using the serial dilution method. Five dilutions from the stock solution in DMF equivalent to 100, 50, 40, 25 and 20 μg/ml, respectively were used. The fungicide Trosyd (Tioconazole) was used as a reference to evaluate the potency of the tested compounds. Zone diameter of inhibition (mm) were measured in at the end of an incubation period of 48 h at 28°C. The results are illustrated in Table 2, compounds **3** and **14**, were found to be the more active compounds, nearly as Trosyd, against *Aspergillus ochraceus* and *Aspergillus flavus* (MIC values 40 μg/ml). On the other hand compounds **10**, **12**, **14**, **19** (MIC values 40 μg/ml) and **17**, **21** (MIC values 50 μg/ml) possess high activity, nearly as Trosyd, against *Penicillium Chrysogenum*, while only compound **12** (MIC values 40 μg/ml), exhibited a high activity, nearly as Trosyd, against *Candida albicans*.

5. Discussion and conclusions

From the biological assay it was found that compounds containing both the quinazoline and the pyrimidinothiazole moieties (**13**, **14**, **17**, **19**) were found to be the most active compounds against *Aspergillus ochraceus*, *Penicillium Chrysogenum* and *Aspergillus flavus* compared to Trosyd, while compounds containing both the quinazoline and thiazole moieties (**3**, **12**) were found to be the most active compounds against

Table 2
Antifungal activity of some quinazoline derivatives

Compd. no.	*Aspergillus ochraceus* Wilhelm (AUCC-230)		*Penicillium chrysogenum* Thom (AUCC-530)		*Aspergillus flavus* Link (AUCC-164)		*Candida albicans* (Robin) Berkho (AUCC-1720)	
	Diameter (mm)	MIC (μg/ml)	Diameter (mm)	MIC (μg/ml)	Diameter (mm)	MIC (μg/ml)	Diameter (mm)	MIC (μg/ml)
1	12		10		8		8	
2	18		20		16		18	
3	30	40	18		30	40	20	
5	12		18		10		8	
8	12		20		14		18	
10	20		30	40	20		20	
12	18		30	40	20		30	40
13	20		20		28	50	18	
14	30	40	30	40	30	40	18	
17	18		28	50	18		18	
18	18		16		18		18	
19	18		30	40	16		18	
21	18		28	50	18		16	
22	8		12		8		8	
Trosyd [a]	30		30		32		34	

[a] Manufactured by Pfizer-Egypt, S.A.E., Cairo, A.R.E. under authority of Pfizer INC., USA.

Candida albicans, compared to Trosyd. Quinazoline derivatives (**2**, **5**, **8**) showed a moderate activity against *Penicillum chrysogenum* with exception of compound **10** containing the cyanoethyl group which showed high activity compared to Trosyd.

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