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Synthesis and antifungal activity of novel pyrano[2′,3′:4,5]thiazolo[2,3-*b*]quinazolines, pyrido[2′,3′:4,5]thiazolo[2,3-*b*]quinazolines and pyrazolo[2′,3′:4,5]thiazolo[2,3-*b*]quinazolines

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Abstract

The starting materials thiazolo[2,3-*b*]quinazolines (**5a**,**b**) were obtained in one pot synthesis by treating octahydroquinazoline (**2**) with chloroacetic acid and aromatic aldehydes. Thiazoloquinazoline (**5**) was reacted with $CH_2(CN)_2$/piperidine and $CH_2(CN)_2$/NaOH (CH_3OH), to furnish pyrano[2′,3′:4,5]thiazolo[2,3-*b*]quinazolines (**6a**,**b**) and pyrido[2′,3′:4,5]thiazolo[2,3-*b*]quinazoline (**7**), respectively. Refluxing of **5a** with NH_2CSNH_2/KOH and hydrazines in ethanol furnished the corresponding, [1,3]thiazino-[4′5′:4,5]thiazolo[2,3-*b*]quinazoline (**10**) and pyrazolo[3′,4′:4,5]thiazolo[2,3-*b*]quinazolines (**11a**,**b**), respectively. Antifungal activity was shown for some of the synthesized compounds.

Keywords: Thiazoloquinazolines; Pyranothiazoloquinazoline; Antifungal activity

1. Introduction

Quinazolines are reported to have a broad spectrum of biological activities. Some are endowed with antimicrobial [1], antimalarial [2], anticonvulsant [3], antidepressant [4], antihistamine [5], stimulant [4], anticancer [6] and antiinflammatory properties [7]. On the other hand, some thiazole derivatives also have various biological properties like antimicrobial [8], anthelmintic [9], immunorestoration [10] and antineoplastic [11]. These observations prompted us to synthesize heterocyclic compounds containing a thiazolo[2,3-*b*]quinazoline moiety fused with pyrane, pyridine and pyrazole to evaluate the antifungal activity of them.

2. Chemistry

The octahydroquinazoline **2** was synthesized by acid-catalysed condensation of 1,3-cyclohexanedione (**1**), *p*-fluorobenzaldehyde and thiourea in ethanol, by a modification of the Biginelli reaction [12]. The structure of **2** was confirmed by spectral data and elemental analysis. The IR spectrum of **2** show absorption bands at 3280, 3200 cm^{-1} (secondary amino group), 1700 cm^{-1} (C=O) and 1500,1220 cm^{-1} (C=S; amide II and amide I). The CH-4 proton in the ^1H NMR spectrum exhibited signal at 5.2 ppm region doublets. Also, two downfield one proton singlets at 9.72 and 10.67 ppm regions were assigned to the N_1–H and N_3–H protons of the octahydroquinazoline structure. The mass spectrum of **2** exhibited a molecular ion peak at m/z 276 (57.82%) together with a base peak at m/z 122. The fragmentation pattern of compound **2** is illustrated in Scheme 2. Quinazoline **2** can be considered as a cyclic thiourea derivative and therefore can react with chloroacetic acid as dielectrophiles in acetic acid/acetic

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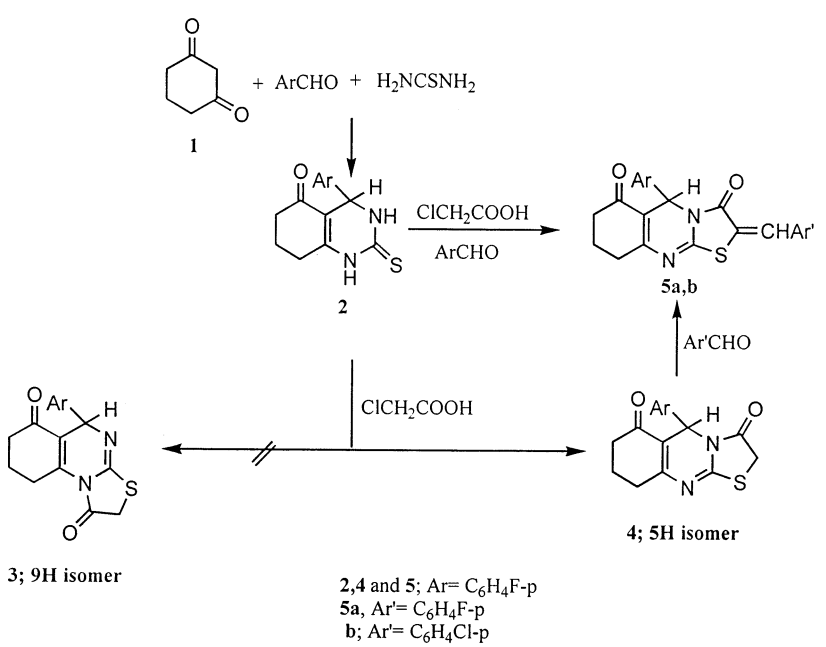
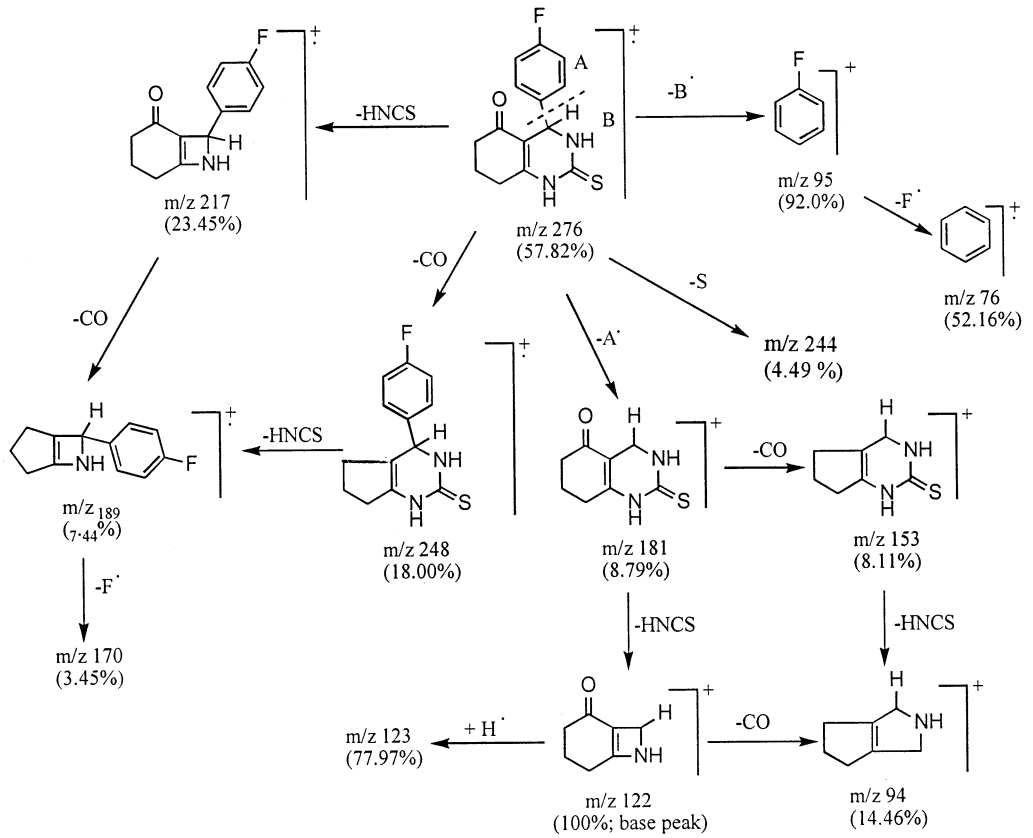
anhydride in the presence of fused sodium acetate to yield thiazoloquinazoline. Theoretically, two isomeric cyclization products (**3**, 9H isomer; and **4**, 5H isomer) may be expected. The ^{1}H NMR spectrum exhibited the downfield of the thiazoloquinazoline H-5 in compound **4** (5H isomer) compared to the octahydroquinazoline H-4, which appeared at δ 6.00 ppm, indicate that a 5H condensation product was obtained [13]. Refluxing of **4** with aromatic aldehydes in acetic acid/sodium acetate furnished 2-arylmethylene derivatives **5a**,**b**. Syntheses of 2-arylmethylene derivatives (**5a**,**b**) were achieved in a single step by treating octahydroquinazoline (**2**) with chloroacetic acid and aromatic aldehydes in the presence of sodium acetate, acetic acid and acetic anhydride (Scheme 1).

Because of their α,β-unsaturated ketone moiety, thiazoloquinazolines (**5**) are convenient starting materials for the synthesis of fused thiazoloquinazolines. Thus, refluxing of equimolar amounts of 2-arylmethylenes (**5a**,**b**) with malononitrile in the presence of ethanol and piperidine furnished the corresponding pyrano-[2′,3′:4,5]thiazolo[2,3-*b*]quinazolines (**6a**,**b**). The structure of **6** was established on the basis of analytical and spectral data. Thus, the appearance of NH_2, C≡N and C=O absorption bands in the IR spectra of the reaction products corroborated the assigned structure **6**. Also, ^{1}H NMR spectrum of compound **6a** exhibited a peak at δ 3.9 ppm and this could be attributed to pyran-4H. The formation of **6** may proceed [14] via the initial addition of malononitrile to exocyclic bond in **5** to yield an acyclic intermediate, which may cyclize into final product **6** (Scheme 3). When the reaction of 2-arylmethylene (**5a**) with malononitrile was carried out in methanol and sodium hydroxide, the pyrido[2′,3′:4,5]-thiazolo[2,3-*b*]quinazoline (**7**) was formed, as established from their elemental analysis and spectral data. IR spectrum of **7** revealed the presence of C≡N and C=O function and ^{1}H NMR showed, in addition to the aromatic signals, a methoxy signal at δ 4.0 ppm. A suggested mechanism for the formation of **6** is given in Scheme 4. In the presence of sodium hydroxide, the initially formed pyran **6** undergoes ring opening and subsequent pyridine ring formation, the pyridine nitrogen being derived from the 2-amino group [15]. Also, the pyrido[2′,3′:4,5]thiazolo[2,3-*b*]quinazoline (**8**) was obtained through interaction of **5a** with malononitrile in the presence of ammonium acetate [14].

Refluxing of 2-arylmethylene (**5a**) with cyanothioacetamide in ethanol containing sodium ethoxide furnished pyrido[2′,3′:4,5]thiazolo[2,3-*b*]quinazoline (**9**). The study was also extended to investigate the behaviour of 2-arylmethylene against thiourea in the presence of base. Thus, the [1,3]thiazino[4′,5′:4,5]-thiazolo[2,3-*b*]quinazoline (**10**) was synthesized by refluxing of 2-aryl-methylene (**5a**) with thiourea in the presence of potassium hydroxide [16]. It was reported that [17], pyrazolines could be synthesized through interaction of α,β-unsaturated carbonyl compounds with hydrazines. Thus, when α,β-unsaturated ketone **5a** was treated with hydrazine or phenylhydrazine in ethanol yielded the respective pyrazolo[3′,4′:4,5]-thiazolo[2,3-*b*]quinazolines (**11a**,**b**) (Scheme 5).



Scheme 1.



Scheme 2. Fragmentation pattern of compound **2**.

3. Experimental

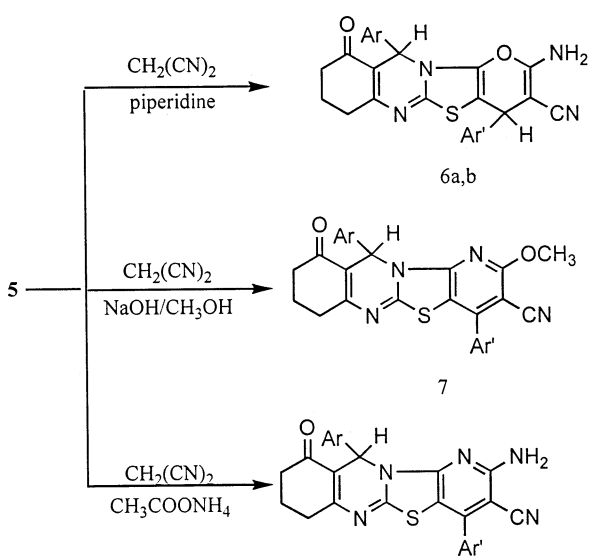
All melting points are uncorrected. IR spectra were recorded on a Shimadzu-440 IR spectrophotometer using the KBr technique (Shimadzu, Japan). ^{1}H NMR spectra were measured on a Varian EM-360-90 MHz spectrophotometer (Varian, UK) using TMS as an internal standard. The mass spectra were performed by a Shimadzu-GC-MS-QP 100 EX (Shimadzu, Japan). Elemental analyses were carried out by the Microanalytical Research Centre, Faculty of Science, Cairo University. Characteristics of the prepared compounds are given in Table 1, analytical results for C, H, N were within $\pm 0.1\%$ of the calculated values. The spectral data are shown in Table 2.

3.1. 4-(4-Fluorophenyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-thione (2)

A mixture of 1,3-cyclohexanedione (**1**) (0.01 mol), *p*-fluorobenzaldehyde (0.01 mol), thiourea (0.01 mol), absolute ethanol (20 ml) and 36% HCl (3 ml) as heated under reflux for an 4 h and the reaction mixture was allowed to cool. The product, which appeared as a precipitate, was filtered off and washed with ethanol (Table 1).

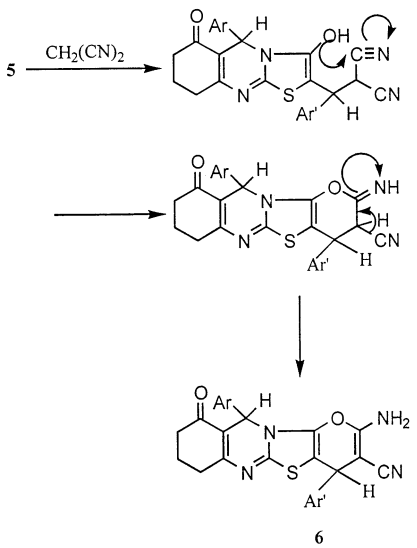
3.2. 4-(4-Fluorophenyl)-3,6-dioxo-2,3,6,7,8,9-hexahydro-5H-thiazolo[2,3-b]quinazoline (4)

A mixture of **2** (0.01 mol), chloroacetic acid (0.01 mol), acetic anhydride (10 ml) in acetic acid (20 ml) was

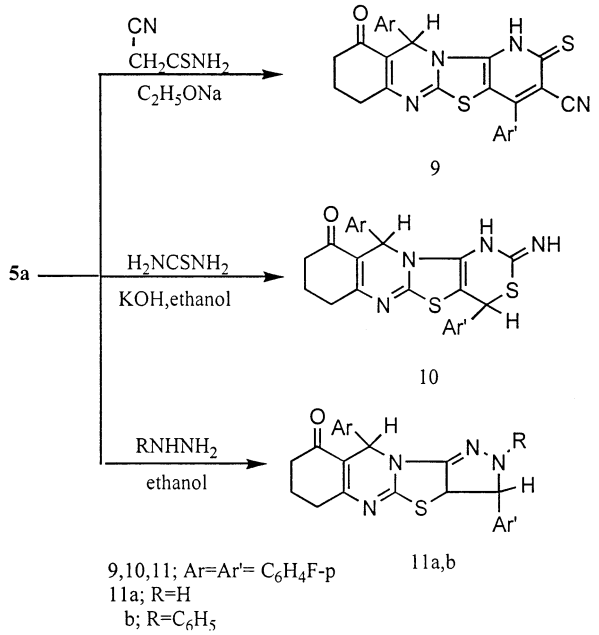


6a, **7** and **8** Ar= Ar'=C_6H_4F-p
6b, Ar= C_6H_4F-p, Ar'= C_6H_4Cl-p

Scheme 3.



Scheme 4.



Scheme 5.

refluxed for 4 h. The solid obtained was recrystallized from proper solvent to give **4** (Table 1).

*3.3. 2-(4-Substituted phenyl)-5-(4-fluorophenyl)-3,6-dioxo-2,3,6,7,8,9-hexahydro-5H-thiazolo[2,3-b]-quinazoline (**5a**,**b**)*

3.3.1. Method 1

A mixture of **4** (0.01 mol), required aromatic aldehydes (0.01 mol) in acetic acid (20 ml) in the presence of fused sodium acetate (0.5 g) was refluxed for 2 h. The solid obtained was recrystallized from proper solvent to give **5a**,**b** (Table 1).

3.3.2. Method 2

A mixture of **2** (0.01 mol), chloroacetic acid (0.01 mol), required aromatic aldehydes (0.01 mol) in acetic anhydride (10 ml) and acetic acid (20 ml) in the presence of fused sodium acetate (0.5 g) was refluxed for 2 h. The solid obtained was recrystallized from proper solvent to give **5a**,**b**.

*3.4. 2-Amino-3-cyano-4-(4-substituted phenyl)-11-(4-fluorophenyl)-10-oxo-7,8,9,10-tetrahydro-4H,11H-pyrano[2′,3′:4,5]thiazolo[2,3-b]quinazolines (**6a**,**b**)*

A mixture of **5a** or **5b** (0.01 mol), malononitrile (0.01 mol) in absolute ethanol (30 ml) containing piperidine (0.5 ml) was refluxed for 3 h. The solid obtained recrystallized from proper solvent to give **6a**,**b**.

*3.5. 2-Methoxy-3-cyano-4,11-bis-(4-fluorophenyl)-7,-8,9,10-tetrahydro-11H-pyrido[2′,3′:4,5]thiazolo[2,3-b]-quinazoline (**7**)*

A mixture of **5a** (0.01 mol) and malononitrile (0.01 mol) were dissolved in methanol (25 ml). Crushed sodium hydroxide (0.2 g) was added and the reaction mixture was stirred under reflux for 10 h. The precipitated product was filtered, washed with water and recrystallized from proper solvent to give **7** (Table 1).

*3.6. 2-Amino-3-cyano-4,11-bis-(4-fluorophenyl)-7,8,9,10-tetrahydro-11H-pyrido[2′,3′:4,5]thiazolo[2,3-b]-quinazolin (**8**)*

A mixture of **5a** (0.01 mol), malononitrile (0.01 mol) and ammonium acetate (1 gm) in absolute ethanol (30 ml)

Table 1
Analytical data for the synthesized compounds

Comp.	Solvent crystal	Yield (%)	M.p. (°C)	Molecular formula (M_w)
2	ethanol	84	275–277	$C_{14}H_{13}FN_2OS$ (276)
4	acetic acid	90	224–225	$C_{16}H_{13}FN_2O_2S$ (316)
5a	acetic acid	78	230–232	$C_{23}H_{16}F_2N_2O_2S$ (422)
5b	acetic acid	76	235–236	$C_{23}H_{16}ClFN_2O_2S$ (438.5)
6a	ethanol	60	236–238	$C_{26}H_{18}F_2N_4O_2S$ (488)
6b	ethanol	64	185–186	$C_{26}H_{18}ClFN_4O_2S$ (504.5)
7	ethanol	53	108–110	$C_{27}H_{18}F_2N_4O_2S$ (500)
8	ethanol	80	125–126	$C_{26}H_{17}F_2N_5OS$ (485)
9	ethanol	60	>300	$C_{26}H_{16}F_2N_4OS_2$ (502)
10	dioxane	60	220–222	$C_{24}H_{18}F_2N_4OS_2$ (480)
11a	dioxane	73	272–274	$C_{23}H_{18}F_2N_4OS$ (436)
11b	dioxane	78	282–281	$C_{29}H_{22}F_2N_4OS$ (512)

Table 2
Spectral data for the synthesized compounds

Comp.	IR (KBr)	^{1}H NMR (δ ppm) (in DMSO-d_6)
2	3280, 3200 cm^{-1} (NH); 1700 cm^{-1} (C=O); 1500,1220 cm^{-1} (–C=S; amide II and amide I)	1.8–2.5 (6H, m, CH_2-6, CH_2-7, CH_2-8); 5.2 (1H, d, CH-4); 7.2–7.8 (4H, m, Ar–H); 9.72 (1H, s, N_1–H; exchangeable), 10.72 (1H, s, N_3–H; exchangeable)
4	1690, 1680 cm^{-1} (2C=O)	1.9–2.57 (6H, m, CH_2-7, CH_2-8,CH_2-9); 3.40 (2H, s, CH_2-2); 6.00(1H, s, CH-5), 7.41–7.85 (4H, m, Ar–H)
5a	2950 cm^{-1} (CH-aliphatic); 1710 cm^{-1} (C=O); 1660 cm^{-1} (C=O; thiazole ring)	
5b	2900 cm^{-1} (CH-aliphatic); 1708 cm^{-1} (C=O); 1680 cm^{-1} (C=O)	1.7–2.60 (6H, m, CH_2-7, CH_2-8, CH_2-9); 6.00 (1H, s, CH-4); 7.15–8.0 (9H, m, Ar–H+CH-2)
6a	3450, 3350 cm^{-1} (NH_2); 2950 cm^{-1} (CH-aliphatic); 2205 cm^{-1}(C≡N); 1700 cm^{-1} (C=O)	1.65–2.58 (m, 6H, CH_2-7, CH_2-8, CH_2-9); 3.00 (2H, s, NH_2; exchangeable); 3.9 (1H, s, CH-4);6.1 (1H, s, CH-11); 7.10–7.7 (8H, m, Ar–H)
6b	3400, 3450 cm^{-1} (NH_2); 2900 cm^{-1} (CH-aliphatic); 2200 cm^{-1} (C≡N); 1680 cm^{-1} (C=O)	
7	2980 cm^{-1} (CH-aliphatic); 2200 cm^{-1} (C≡N); 1680 cm^{-1} (C=O)	1.80–2.57 (6H, m, CH_2-7, CH_2-8, CH_2-9); 4.0 (3H, s, OCH_3), 5.7 (1H, s, CH-11); 7.0–7.7 (8H, m, Ar–H)
8	3336, 3217 cm^{-1} (NH_2); 3069 cm^{-1} (CH-aromatic); 2945 cm^{-1} (CH-aliphatic); 2208 cm^{-1} (C≡N); 1664 cm^{-1} (C=O)	1.70–2.41 (6H, m, CH_2-7, CH_2-8, CH_2-9); 4.10 (2H, s, NH_2; exchangeable), 6.10 (1H, s, CH-11), 7.1–7.81 (8H, m, Ar–H)
9	3415 cm^{-1} (NH); 2910 cm^{-1} (CH-aliphatic); 2217 cm^{-1} (C≡N); 1665 cm^{-1} (C=O)	1.62–2.50 (6H, m, CH_2-7, CH_2-8, CH_2-9); 6.00 (1H, s, CH-11); 7.20–7.90 (8H, m, Ar–H); 9.4 (1H, s, NH; exchangeable)
10	3400, 3300 cm^{-1} (2NH); 2900 cm^{-1} (CH-aliphatic); 1700 cm^{-1} (C=O)	1.9–2.51 (6H, m, CH_2-7, CH_2-8, CH_2-9); 5.1 (1H, s, CH-4); 5.5 (1H, s, CH-11); 7.0–7.6 (8H, m, Ar–H); 8.9 (1H, s, NH; exchangeable), 9.8 (1H, s, NH; exchangeable)
11a	3353 cm^{-1} (NH); 3060 cm^{-1} (CH-aromatic); 2941 cm^{-1} (CH-aliphatic);1671 cm^{-1} (C=O)	
11b	3051 cm^{-1} (CH-aromatic); 2922 cm^{-1} (CH-aliphatic); 1668 cm^{-1} (C=O)	

and the reaction mixture was refluxed for 3 h. The solid product was filtered off and recrystallized from proper solvent to give **8** (Table 1).

*3.7. 3-Cyano-4,11-bis-(4-fluorophenyl)-1,2,7,8,9,10-hexahydro-11H-pyrido[2′,3′,4,5]-thiazolo[2,3-b]quinazolin-2-thione (**9**)*

A mixture of compound **5a** (0.01 mol), cyanothioacetamide (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (30 ml) was refluxed for 2 h. The product formed was collected and recrystallized from proper solvent to give **9** (Table 1).

*3.8. 4,11-Bis(4-fluorophenyl)-1,2,7,8,9,10-hexahydro-2-imino-4H,11H-[1,3]-thiazino[4′,5′:4,5]thiazolo[2,3-b]-quinazoline (**10**)*

A mixture of **5a** (0.01 mol), thiourea (0.01 mol) and potassium hydroxide (0.02 mol) was refluxed in ethanol for 2 h. On cooling it was acidified with dilute HCl. The resulting solid product was washed with water and recrystallized from proper solvent to give **10** (Table 1).

*3.9. Pyrazolo[3′,4′:4,5]thiazolo[2,3-b]quinazolines (**11a**,**b**)*

A solution of **5a** (0.01 mol), and hydrazine hydrate or phenyl hydrazine (0.02 mol) in absolute ethanol (50 ml) was refluxed for 3 h. It was then cooled and the resulting solid was recrystallized from proper solvent to give **11a**,**b** (Table 1).

Mass spectrum of **11a** exhibited a molecular ion peak at m/z 436 (3.56%) together with a base peak at m/z 57. Other significant peaks were observed at m/z: 414 (3.37%), 387 (5.1%), 353 (7.89%), 285 (7.89%), 285 (18.86%), 237 (15.5%), 209 (10.39%), 170 (12.9%), 138 (23.29), 9.9 (20.21%) and 71 (40.90).

3.10. Antifungal activity

The search for antifungal activity was carried out by the microbiology laboratory at the Faculty of Science, Al-Azhar University, Cairo, Egypt.

Some 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 disc diffusion method [18,19].

The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1% concentration. Filter paper discs (Whatman No. 3 filter paper, 5 mm diameter) were saturated with this former solution. The saturated filter paper discs were placed on

Table 3
Antifungal activity of the synthesized compounds [a]

Comp.	*Aspergillus ochraceus* Wilhelm (AUCC-230)	*Penicillium chrysogenum* Thom (AUCC-530)	*Aspergillus flavus* Link (AUCC-164)	*Candida albicans* (Robin) Berkho (AUCC-1720)
4	+	+++	+	+
5b	++	+++	++	+++
6b	++	+++	++	+++
7	++	+	++	++
8	+++	++	++	++
10	+	+	+	+
11	+	+	+	+
Trosyd [b]	++++	++++	++++	++++

[a] +, 1–1.5 cm; ++, 1.6–2 cm; +++, 2.1–3 cm; ++++, >3 cm.
[b] Manufactured by Pfizer-Egypt, S.A.E., Cairo, A.R.E. under authority of Pfizer Inc., USA.

the surface of solidified Czapek's Dox agar dishes seeded by the test fungi. The inhibition zones were measured in millimetres at the end of an incubation period of 48 h at 28°C. The results are shown Table 3.

The minimal inhibitory concentration (MIC) values for the biological active compounds **4**, **5b**, **6b** and **8** were determined by the serial dilution method [20]. Trosyd (Tioconazole) was used as a reference drugs to evaluate the potency of the tested compounds.

4. Antifungal activity

The results (Table 3) showed that compounds **4**, **5b** and **6b** possess high activity against *Penicillium chrysogenum* Thom (AUCC-530) (MIC 100 μg ml^{-1}); compound **8** showed a high activity against *Aspergillus ochraceus* Wilhelm (AUCC-230). Also, compounds **5b** and **6b** revealed the high activity against *Candida albicans* (Robin) Berkho (AUCC-1720). MIC values for the biological active compounds **4**, **5b**, **6b** and **8** were 100 μg ml^{-1}, all these compounds are less active than reference drug (Trosyd).

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