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Reaction of hydrazonoyl halides 49 1: Synthesis and antimicrobial activity of some new pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one, tetrazino[3,2-*b*]quinazolin-5-one, pyrimidino[1,2-*b*]1,2,4,5-tetrazin-5-one and triazolo[4,3-*a*]pyrimidine derivatives

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Reaction of hydrazonoyl halides 49 [1]: Synthesis and antimicrobial activity of some new pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one, tetrazino[3,2-*b*]quinazolin-5-one, pyrimidino[1,2-*b*]1,2,4,5-tetrazin-5-one and triazolo[4,3-*a*]pyrimidine derivatives

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Pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one, tetrazino[3,2-*b*]quinazolin-5-one, pyrimidino[1,2-*b*]1,2,4,5-tetrazin-5-one and triazolo[4,3-*a*]pyrimidine derivatives were synthesized from *C*-(4-methyl-2-phenyl)thiazol-5-oyl-*N*-phenyl-hydrazonoyl bromide and different pyrimidine-2-thiones. New compounds had their structures confirmed by elemental and spectral analysis and were screened antimicrobial activity.

Keywords: Hydrazonoyl halides; Triazolo[4,3-*a*]pyrimidine; Pyrimidino[1,2-*b*]tetrazine; Tetrazino[3,2-*b*]quinazoline

1. Introduction

As part of our continued interest in biologically active heterocycles, we note pyrimidotetrazines have been reported as antiviral agents [2, 3] and triazolopyrimidines possess a wide variety of biological activities. For instance, they exhibit in vivo activity against the amastigate stage of leishmania donovani [4, 5], have cardiovascular activity [6–8], are active against Aspergillus and Pencicillium species [9], and have been tested as bioregulator agents [10]. In this report, we disclose a general and facile synthesis of these heterocycles and their biological activity.

2. Results and discussion

Treatment of *C*-(4-methyl-2-phenyl)thiazol-5-oyl–*N*-phenylhydrazonoyl bromide (**1**) with 2,3,5,6,7,8-hexahydro-3-amino-2-thioxo[*b*]benzothieno[2,3-*d*]pyrimidin-4(1H)-one (**2**) or its

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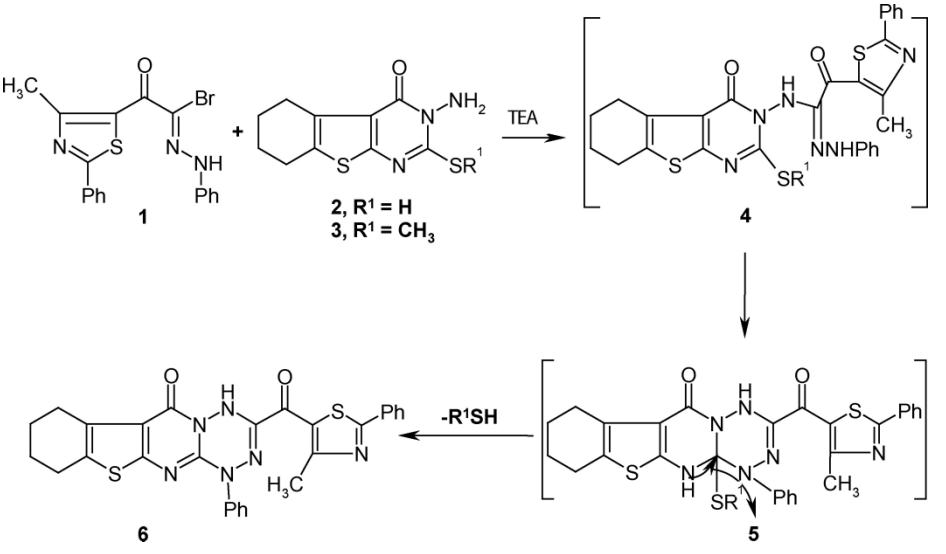
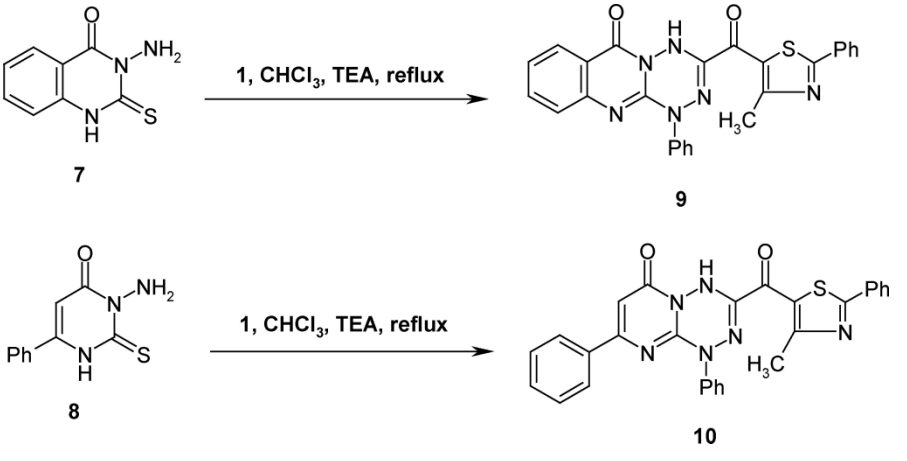
methylthio derivative **3** in refluxing chloroform (ethanol) containing triethylamine to give 1,4,7,8,9,10-hexahydro-6H-[*b*]benzothieno[2′,3′:4,5]pyrimido[1,2-*b*][1,2,4,5] tetrazin-6-one derivative **6** (scheme 1). Compound **6** gave satisfactory elemental analysis and spectral data.



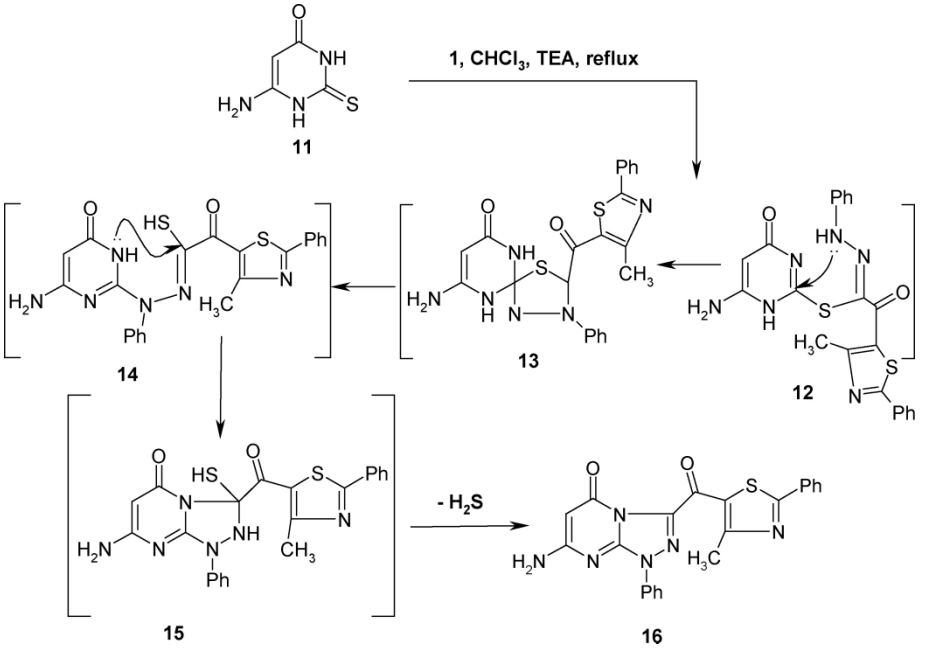
SCHEME 1

We propose initial acylation of the hydrazide amine with **1** to give **4**, followed by ring closure to tetrazine **5** and elimination of either H_2S or MeSH to account for the formation of **6** (scheme 1). Similar treatment of 3-amino-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (**7**) and 3-amino-6-phenyl-2-thioxo-2,3-dihyro-1*H*-pyrimidine-4-one (**8**) with **1** afforded compounds **9** and **10** respectively in good yield (scheme 2).



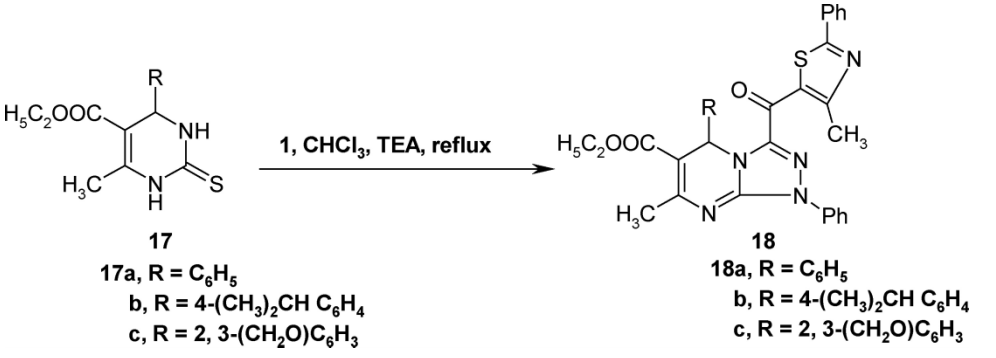
SCHEME 2

Treatment of reagent **1** with compounds lacking hydrazide functionality gave rise to a different reaction, which yielded a single regioselective product. Thus reaction of **1** with 6-amino-2-thiouracil (**11**) gave compound **16** cleanly in good yield (scheme 3). Mechanistically we explain the production of this compound by initial 1,3-addition to give thiohydrazonate ester **12**, which undergo a *Smiles* rearrangement to the thiohydrazide **14** via intermediate **13**. The latter was cyclized with concurrent elimination of hydrogen sulfide to give the product **16**. The proposed structure is in agreement with elemental and spectral data.



SCHEME 3

Similar treatment of **1** with alkyl 4-methyl-6-substituted-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate **17a–c** and triethylamine in boiling chloroform gave triazolino[4,3–*a*]pyrimidines **18a–c**, respectively (scheme 4).



SCHEME 4

3. Antimicrobial activity

The biological activity of these compounds against gram positive and gram negative bacteria as well as fungi was determined by filter paper and hole plate method [11], using amplicillin and tetracycline as controls and is shown in table 1.

4. Experimental

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of the Cairo University. Compounds **1** [12], **2** [13], **3** [13], **7** [14], **8** [15], **11** [16, 17], **17a–c** [18] were prepared as previously reported.

4.1 *Synthesis of benzothieno[2′,3′:4,5]pyrimido[1,2-b][1,2,4,5]tetrazin-6-one (6), tetrazino[3,2-b]quinazolin-5-one (9), pyrimidino[1,2-b]1,2,4,5-tetrazin-5-one (10), 1,2,4-triazoloino[4,3-a]pyrimidin-4-one (16) and triazolino[4,3-a]pyrimidines (18a–c)*

4.1.1 General procedure. Equimolar amounts of hydrazonoyl bromide **1** (2.0 g, 5 mmol), the appropriate pyrimidine-2-thione derivatives (**2**, **3**, **7**, **8**, **11** or **17a–c**; 5 mmol each) and triethylamine (0.75 mL, 5 mmol) were dissolved in chloroform (20 mL) and refluxed for 10 h. The reactions were concentrated in vacuo ($CHCl_3$ reactions were then triturated with EtOH), the residual solids were collected and recrystallized from the indicated solvents to give the products described.

4.1.2 1,4,7,8,9,10-Hexahydro-6H-[b]benzothieno[2′,3′:4,5]pyrimido[1,2-*b*][1,2,4,5]-tetrazin-6-one derivative (6). Yield 77%; mp. 235–237 °C, (Dioxan-EtOH), orange crystals; IR (KBr) (cm^{-1}): 3290 (NH) and 1680 (CO). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.84–1.85

Table 1. Response of various microorganisms to some synthesized compounds in vitro (culture)

Microorganism/ Compound no.	*Staphylococcus albus* (G^+)	*Streptococcus faecalis* (G^+)	*Bacillus subtilis* (G^+)	*Echerichia coli* (G^+)	*Aspergills flvus (Fungus)*	*Candida albicans (Fungus)*
Amplicillin/ Tetracycline	34R/27	37/31	33/30	39/34	0.0/0.0	20/37
6	18	13	16	17	0.0	15
9	17	13	14	14	0.0	14
10	17	14	13	16	0.0	13
16	16	15	12	15	0.0	13
18a	14	16	13	18	0.0	13
18b	13	15	14	17	0.0	14

R: Repellent action (not complete inhibition).
Values show zone of inhibition in mm. Diameter of the inhibition zones were: high (11–15 mm), moderate (6–10 mm), slight (1–5 mm), negative (0).

(m, 4H, $2CH_2$), 2.67 (s, 3H, CH_3), 2.89–2.96 (m, 4H, $2CH_2$), 7.35–8.02 (m, 10H, ArH's) and 9.52 (br., s, 1H, NH). ^{13}C NMR, δ (ppm): 14.6 (CH_3), 16.9 (CH_2), 17.7 (CH_2), 19.8 (CH_2), 19.9 (CH_2), 113.4 (thiazole, C-5), 118.5, 121.4, 121.9, 123.6, 123.9, 125.9, 126.3, 127.4, 127.5, 134.6, 139.1, 146.7, 161.2 (CO), 168.6 (CO). m/z 538 (100%) [M^+], 336 (31%) [M^- $C_{11}H_8NOS^+$], 202 (23%) [$C_{11}H_8NSO^+$], 174 [$C_{10}H_8NS^+$], 105 (4%) [$C_6H_5N_2^+$], 92 (3%) [$C_6H_6N^+$], 77 (19%) [$C_6H_5^+$]. Elemental analysis (%) for **6** $C_{28}H_{22}N_6O_2S_2$, calcd.: C 62.44, H 4.12, N 15.60, S 11.91; Found: C 62.20, H 4.00, N 15.82, S 12.15.

4.1.3 3-(4-Methyl-2-phenyl)thiazol-5-oyl-1-phenyl-4a-hydro-4H-1,2,4,5-tetrazino [3,2-*b*]quinazolin-5-one (9). Yield 79%; mp. 264–266 °C (Dioxan-EtOH), reddish orange crystals; IR (KBr) (cm^{-1}): 3292 (NH) and 1685 (CO). ^{1}H NMR ($CDCl_3$), δ (ppm): 2.90 (s, 3H, CH_3), 7.33–8.02 (m, 14H, ArH's) and 9.49 (br., s, 1H, NH). ^{13}C NMR (δ ppm): 14.6 (CH_3), 114.2 (thiazole C-5), 119.0, 120.4, 121.0, 121.5, 121.9, 122.0, 123.5, 123.9, 126.4, 127.5, 129.4, 134.8, 138.3, 150.1, 161.3. m/z 478 (100%) [M^+], 304 (9%) [$C_{15}H_{10}N_5O^+$], 202 (25%) [$C_{11}H_8NOS^+$], 174 (20%) [$C_{10}H_8NS^+$], 104, (7%) [$C_7H_4O^+$], 77 (17%) [$C_6H_5^+$]. Elemental analysis (%) for **9** $C_{26}H_{18}N_6O_2S$, calcd.: C 65.26, H 3.79, N 17.56, S 6.70; Found: C 65.10, H 3.80, N 17.65, S 6.60.

4.1.4 3-(4-Methyl-2-phenyl)thiazol-5-oyl-1,7-diphenyl-4a-hydro-4H-pyrimidino[1,2-*b*]-1,2,4,5-tetrazin-5-one (10). Yield 80%; mp.255–257 °C (Dioxan-EtOH), orange crystals; IR (KBr) (cm^{-1}): 3300 (NH) and 1690 (CO). ^{1}H NMR ($CDCl_3$), δ (ppm): 2.90 (s, 3H, CH_3), 6.68 (s, 1H, pyrimidine C-5), 7.36–8.03 (m, 15H, ArH's) and 9.43 (br., s, 1H, NH). ^{13}C NMR (δ ppm): 14.2 (CH_3), 100.7 (pyrimidine C-5), 100.8 (thiazole C-5), 100.9, 103.3, 120.8, 123.7, 126.6, 126.8, 128.7, 129.5, 130.7, 131.8, 159.0 (CO), 164.1 (CO); m/z 505 (100%) [M^+], 504 (99%) [M-1], 302 (3%) [$C_{17}H_{12}NOS^+$], 202 (71%) [$C_{11}H_8NOS^+$], 174 (26%) [$C_{10}H_8NS^+$], 104 (10%) [$C_7H_4O^+$], 77 (22%) [$C_6H_5^+$]. Elemental analysis (%) for **10** $C_{28}H_{20}N_6O_2S$, calcd.: C 66.65, H 4.00, N 16.66, S 6.32; Found: C 66.50, H 3.90, N 16.55, S 6.50.

4.1.5 6-Amino-3-(4-methyl-2-phenyl)thiazol-5-oyl-1-phenyl1-3a-hydro-1,2,4-triazoloino[4,3-*a*]pyrimidin-4-one (16). Yield 85%; mp. 253–254 °C, (Dioxan-EtOH), yellow crystals; IR (KBr) (cm^{-1}): 3380, 3321 (NH_2), 3036, 2965 (CH) and 1684 (CO). ^{1}H NMR ($CDCl_3$), δ (ppm): 2.66 (s, 3H, CH_3), 4.91 (s, 1H, pyrimidine C-5), 6.92 (s, br., 2H, NH_2) and 7.21–8.12 (m, 10H, ArH's). ^{13}C NMR: δ 14.3 (CH_3), 105.2 (pyrimidine C-5), 110.5 (thiazole C-2), 115.7, 121.6, 122.0, 123.9, 124.2, 127.2, 161.8 (CO). Elemental analysis (%) for **16** $C_{22}H_{16}N_6O_2S$, calcd.: C 61.67, H 3.76, N 19.61, S 7.48; Found: C 61.50, H 3.92, N 19.45, S 7.65.

4.1.6 Ethyl 7-methyl-3-(4-methyl-2-phenyl)thiazol-5-yl-1,5-diphenyl[1,2,4]triazolo [4,3-*a*]pyrimidine-6-carboxylate (18a). Yield 81%; mp. 117–120 °C, (EtOH), yellow crystals; IR (KBr) (cm^{-1}): 1705 (CO ester), 1655 (CO conjugated) and 1618 (C=N). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.23–1.30 (t, J = 6.7 Hz, 3H, OCH_2CH_3), 1.71 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.14–4.21 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.49 (s, 1H, pyrimidine C-5) and 7.26–8.04 (m, 15H, ArH's). Elemental analysis (%) for **18a** $C_{32}H_{27}N_5O_3S$, calcd.: C 68.43, H 4.85, N 12.47, S 5.71; Found: C 68.10, H 4.60, N 12.60, S 5.89.

4.1.7 Ethyl (4-isopropylphenyl)-7-methyl-3-(4-methyl-2-phenyl)thiazol-5-yl-5-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carboxylate (18b). Yield 77%; mp. 172–175 °C, (EtOH), yellow crystals; IR (KBr) (cm^{-1}): 1708 (CO ester), 1675 (CO conjugated) and 1624 (C=N). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20–1.25 (d, J = 6.5 Hz, 6H, $(CH_3)_2CH-$), 1.29–1.32 (d, J = 7.0 Hz), 6H, $(CH_3)_2$, 1.33–1.35 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.71 (s, 3H, CH_3), 2.47 (s, 1H, CH_3), 2.96 (sept, 1H, J = 7.0 Hz, $(CH_3)_2CH-$), 3.92–3.96 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 4.49 (s, 1H, pyrimidine C-5), 7.16–8.08 (m, 14H, ArH's). Elemental analysis (%) for **18b** $C_{35}H_{33}N_5O_3S$, calcd.: C 69.63, H 5.51, N 11.60, S 5.31; Found: C 69.35, H 5.40, N 11.90, S 5.54.

4.1.8 Ethyl 5-benzo[1,3]dioxol-4-yl-7-methyl-3-(4-methyl-2-phenyl)thiazol-5-yl-5-phe-nyl-[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carboxylate (18c). Yield 70%; mp. 125–127 °C, (EtOH), yellow crystals; IR (KBr) (cm^{-1}): 1697 (CO ester), 1637 (CO conjugated) and 1608 (C=N). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20–1.32 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.71 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.19–4.23 (q, 2H, J = 7.6 Hz, OCH_2CH_3), 4.55 (s, 1H, pyrimidine C-5), 5.90 (s, 2H, CH_2) and 7.13–8.05 (m, 13H, ArH's). Elemental analysis (%) for **18c** $C_{33}H_{27}N_5O_5S$, calcd: C 65.44, H 4.49, N 11.56, S 5.29; Found: C 65.26, H 4.50, N 11.88, S 5.60.

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