ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 6, pp. 1246–1255. © Pleiades Publishing, Ltd., 2017.

Synthesis and Antimicrobial Activity of Novel Fused [1,2,4]Triazino[5,6-*b*]indole Derivatives[1]

A. G. Al Osaimi[a], R. S. Ali[a,b]*, H. A. Saad[a,c], and M. R. El Sayed Aly[a,d]

[a] *Chemistry Department, Faculty of Science, Taif University, Taif, 21974 Kingdom of Saudi Arabia*
**e-mail: raniaelatar2010@gmail.com*

[b] *Department of Basic Science, Faculty of Industrial Education, Helwan University, Cairo, Egypt*

[c] *Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt*

[d] *Chemistry Department, Faculty of Applied Science, Port Said University, Port Said, Egypt*

Received January 24, 2017

Abstract—Synthesis of new fused systems of triazino[5,6-*b*]indole starting with preparation of 3-amino[1,2,4]-triazino[5,6-*b*]indole **1** by reaction of isatin with 2-aminoguanidinium carbonate in boiling acetic acid is presented [1]. Intermediate compound **1** reacted with aldehyde, ethyl chloroformate, triethyl orthoformate, and ninhydrine and gave new heterotetracyclic nitrogen systems, such as 3-(N^2-guanidinylimino)indole-2(1*H*)-one **2**, 3-(*N*-ethoxycarbonylamino)-4*H*-[1,2,4]triazino[5,6-*b*]indole **3**, 3-(*N*-ethoxymethyleneamino)-4*H*-[1,2,4]-triazino[5,6-*b*]indole **4**, 3-(hydrazinothiocarbonylamino)-4*H*-[1,2,4]triazino[5,6-*b*]indole **5,** respectively. *N*-(1,3-dioxoindene-2-ylidene)-4*H*-[1,2,4]triazino[5,6-*b*]indol-3-amine **6** was synthesized by reaction of compound **1** with aldehyde, ethyl chloroformate, triethyl orthoformate, and ninhydrine. New fused indole systems, pyrimido[2',1':3,4][1,2,4]triazino[5,6-*b*]indol-3(4*H*)-one **8**, **9**, **11**, **12** and 1*H*-imidazo[2',1':3,4][1,2,4]triazino-[5,6-*b*]indol-2(3*H*)-one **10,** were synthesized in the reaction of the intermediate **1** with bifunctional compounds. Structures of the products were elucidated from their elemental analysis and spectral data (IR, ^{1}H and ^{13}C NMR and mass spectra). Antimicrobial activity of some synthesized compounds was tested.

Keywords: imidazo[2',1':3,4][1,2,4]triazino[5,6-*b*]indole, [1,2,4]triazino[5,6-*b*]indol-3-amine, pyrimido[2',1':3,4]-[1,2,4]triazino[5,6-*b*]indole, biological activity

DOI: 10.1134/S1070363217060202

INTRODUCTION

Various derivatives of 5*H*-1,2,4-triazino[5,6-*b*]-indoles demonstrate a broad spectrum of antiparasitic, antifungal, antibacterial, and antihypertensive activities [2–4]. Considerable attention has been drawn to the synthesis of several condensed heterocyclic systems derived from triazines and triazoles [5, 6].

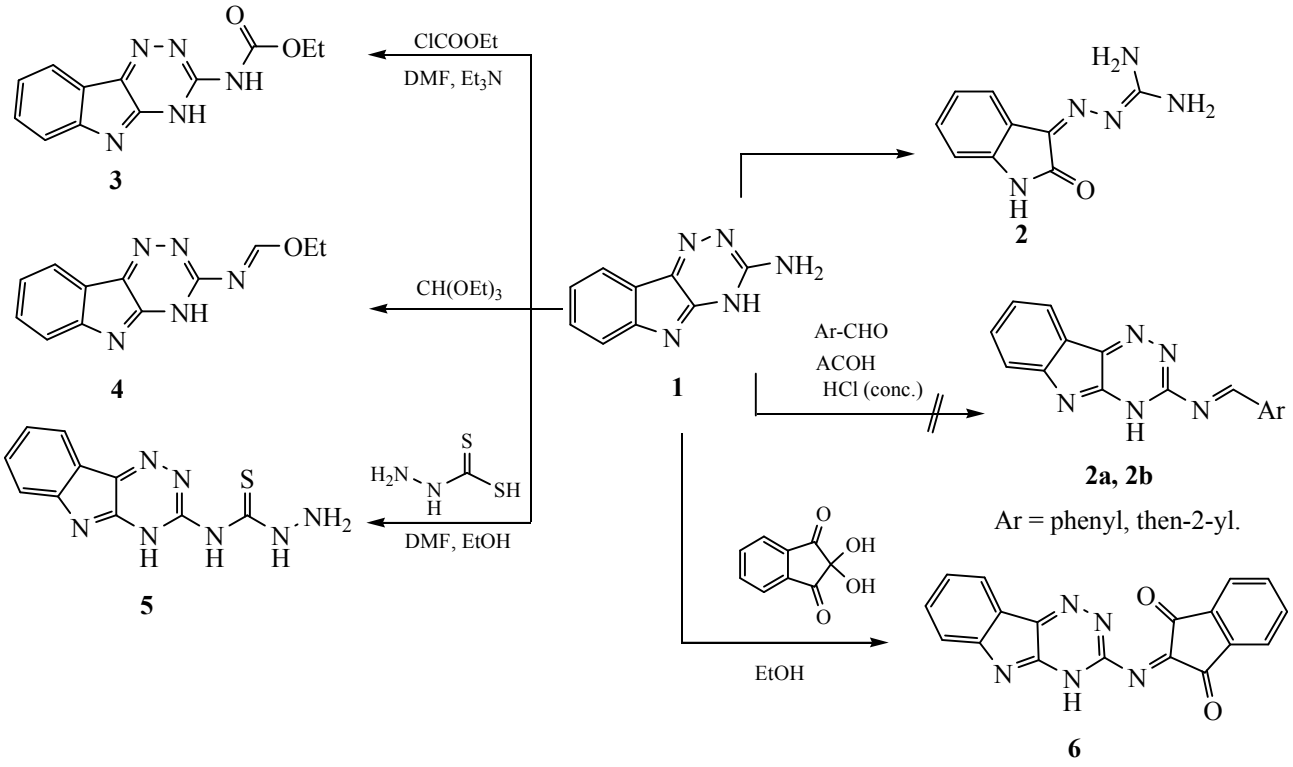
Isatin has been used for the synthesis of fused indole derivatives, such as, thiadiazinoindole [7], Tris-indolobenzene [8], indoloquinazoline [9], indolothiazoles [10], pyrazinoindole [11], and 1,2,4-triazinoindole derivatives [12, 13]. In the course of developing our previous study we synthesized new products with superior biological activities [14, 15]. Earlier we had synthesized some triazino[5,6-*b*]indole derivatives and used those as starting materials for the synthesis of numerous fused triazino[5,6-*b*]indole derivatives with moderate to high antimicrobial activity [16]. Herein we report synthesis of a series of new triazino[5,6-*b*]indole derivatives based on 3-amino-[1,2,4]triazino[5,6-*b*]indole **1.** The latter was synthesized by a reaction of isatin with 2-aminoguanidinium carbonate [1] (Scheme 1).

Reaction of **1** with benzaldehyde or thiophene-2-carbaldehyde in acidic medium led to formation of 3-(N^2-guanidinylimino)indol-2(1*H*)-one **2** instead of the expected Schiff bases. In IR spectrum of compound **2** were recorded bands at 1656 and 3369–3119 cm^{-1} attributed to C=O$_{stretching}$ and amino groups, respectively. ^{1}H NMR spectrum contained two signals at 8.54 and 12.51 ppm belonging to two NH_2 and one NH groups. Signal of the tautomeric OH group was recorded at 11.37 ppm.

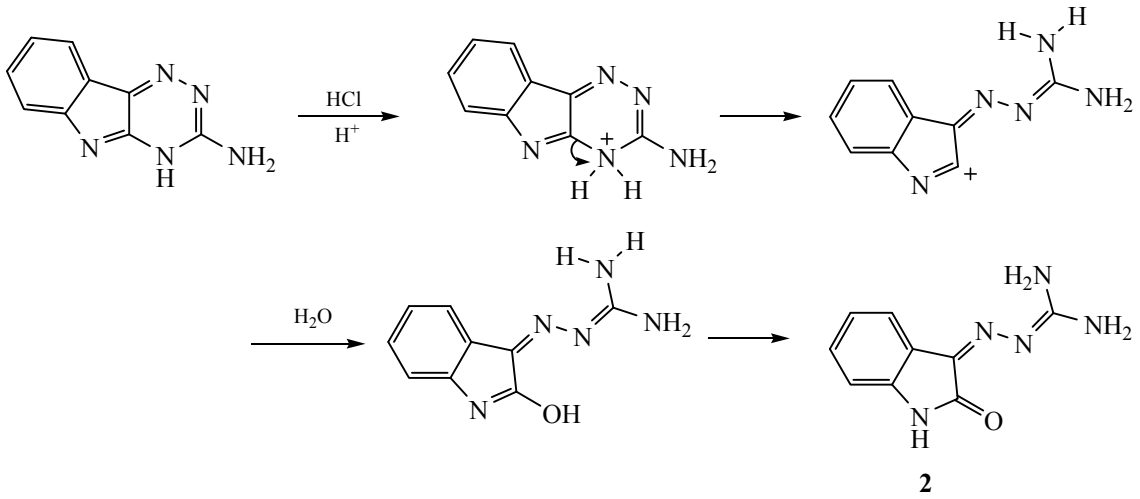
A plausible mechanism probably includes fast protonation of triazine ring with HCl instead of the

[1] The text was submitted by the authors in English.

Scheme 1.



Scheme 2.



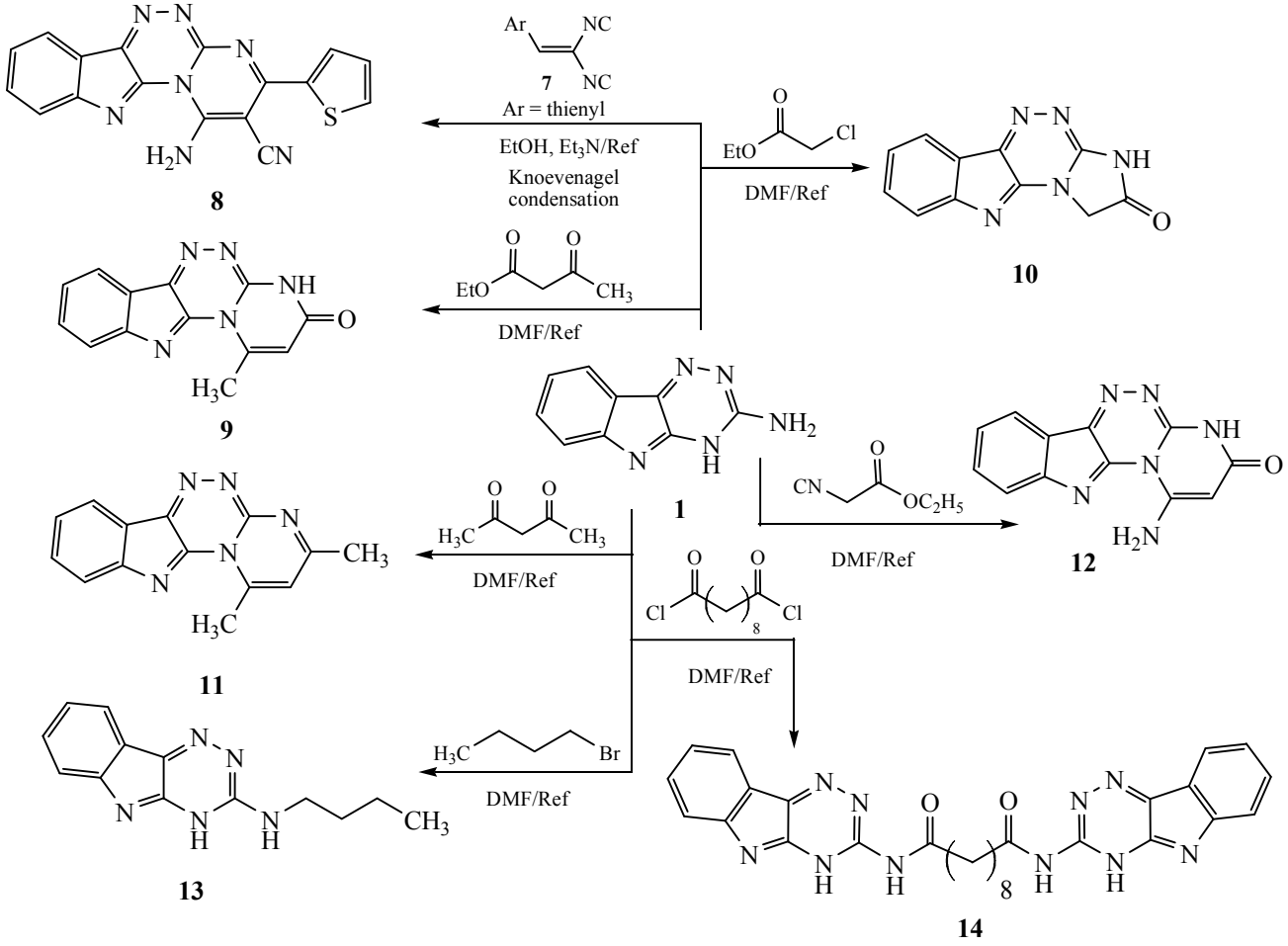
nucleophilic attack of the amino group on aldehyde molecule followed by ring opening and hydrolysis (Scheme 2).

3-Substituted [1,2,4]triazino[5,6-*b*]indoles **3–5** were accumulated in the reaction of compound **1** with ethyl chloroformate, triethyl orthoformate and thioformic acid hydrazide (Scheme 1). Structures of the products were confirmed by spectral data.

Derivatives of indane demonstrate wide range of biological activities such as antimicrobial, anti-inflammatory, and antagonistic inhibition [17, 18].

Compound **1** reacted with ninhydrin in refluxed ethanol to give *N*-(1,3-dioxo-indene-2-ylidene)-4*H*-[1,2,4]triazino[5,6-*b*]indol-3-amine **6**. IR spectrum of compound **6** demonstrated bands at 3231 cm^{-1} (NH) and 1709–1685 cm^{-1} (two $C{=}O_{sym}$) that indicated

Scheme 3. Some reaction of 3-amino[1,2,4]triazino[5,6-*b*]indole (**1**).



formation of the Schiff base with the NH_2 group. ^1H NMR of compound **6** demonstrated disappearance of the NH_2 group signal of 3-aminotriazine with appearance of the phenyl group of ninhydrin signals. ^{13}C NMR demonstrated signals of two C=O groups at 159.1 and 160.4 ppm.

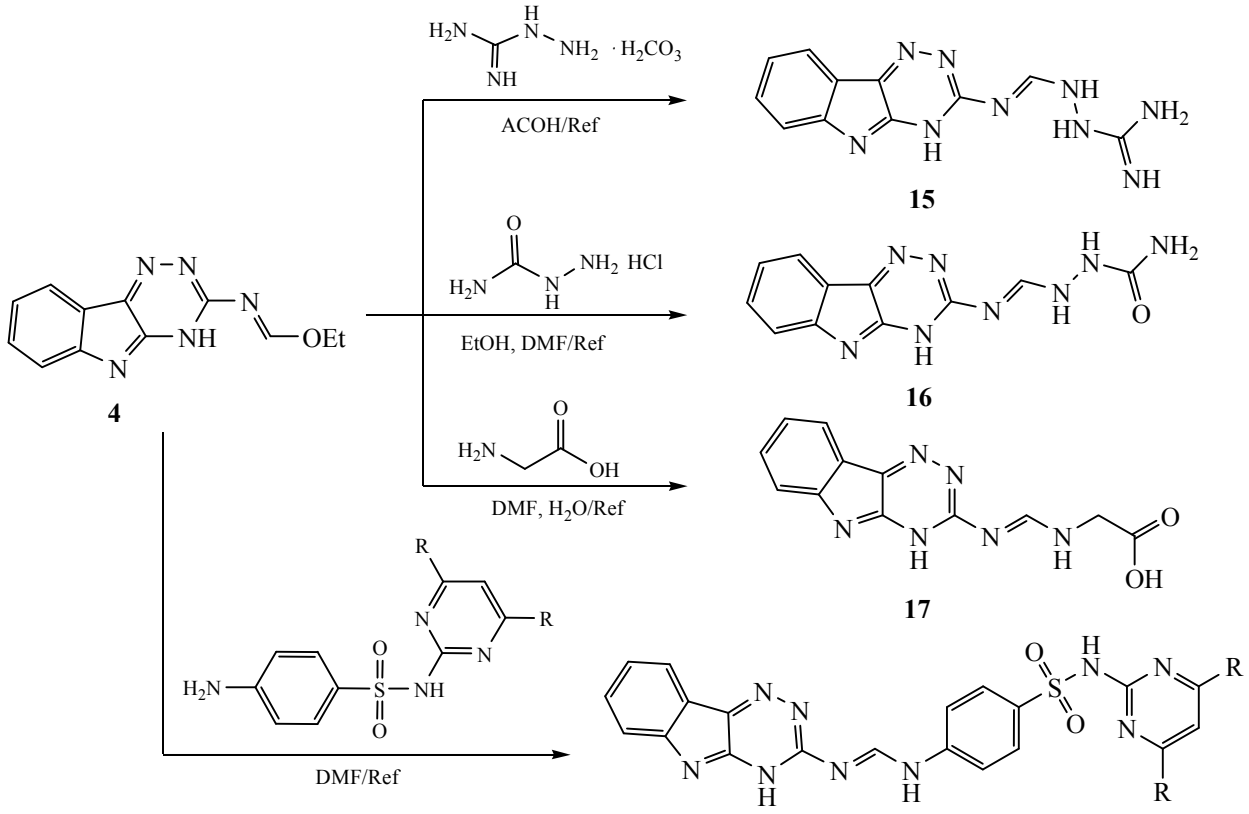
Fused heterocyclic nuclei exhibit enhanced pharmacological activities compared with the parent nucleus [19].

The polycyclic fused system was formed in the reaction of 3-amino[1,2,4]triazino[5,6-*b*]indole **1** with malononitrile and 2-thiophenaldehyde according to the Knoevenagel condensation that led to 1-amino-3-(2-thienyl)pyrimido[2',1':3,4][1,2,4]triazino[5,6-*b*]indole-2-carbonitrile **8** (Scheme 3). IR spectrum of compound **8** demonstrated two characteristic bands at 3350 and 2209 cm^{-1} attributed to the NH_2 and CN groups respectively. ^1H NMR recorded the characteristic signals of thiophene ring at 7.29, 7.93, and 8.20 ppm attributed to the C_4, C_3, and C_5 atoms of the thiophene ring, respectively. Mass spectra measured the molecular ion peak $[M]^+$ at *m/z* 343.

Different azoles and/or azines fused with the compound **1** were synthesized in its reactions with such bifunctional carbonyl compounds as ethyl acetoacetate, ethyl chloroacetate, acetylacetone, and ethyl cyanoacetate in boiling DMF. The reactions led to formation of 1-methylpyrimido[2',1':3,4][1,2,4]triazino-[5,6-*b*]indol-3(4*H*)-one **9,** 1*H*-imidazo[2',1':3,4][1,2,4]-triazino[5,6-*b*]indol-2(3*H*)-one **10**, 1,3-dimethylpyrimido[2',1':3,4][1,2,4]triazino-[5,6-*b*]indole **11,** and 1-aminopyrimido[2',1':3,4][1,2,4]triazino[5,6-*b*]indol-3-(4*H*)-one **12**, respectively (Scheme 3).

Targeting enhancement of biological activity of the compound **1,** it was introduced in the reaction with 1-butuylbromide and/or sebacoyl chloride. Reaction of

Scheme 4. Formation of some isolated derivatives of 3-amino[1,2,4]triazino[5,6-*b*]indole (**1**).



R = H (**a**), CH_3 (**b**).

compound **1** with butuylbromide and/or sebacoyl chloride in boiling DMF gave 3-butylamino-4*H*-[1,2,4]-triazino[5,6-*b*]indole **13** and N^1,N^{10}-di(4*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)decanediamide **14**, respectively.

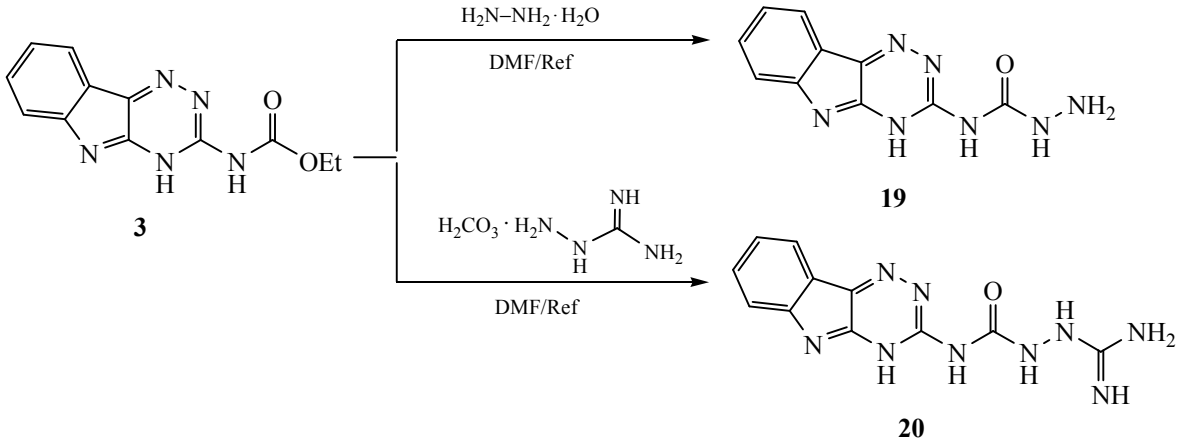
Reactions of the compound **4** with amines (Scheme 4) such as 2-aminoganidinium hydrocarbonate, semicarbazide hydrochloride, glycine, and sulfur containing drugs (sulfadiazine and sulfadimidine) gave 2-[(4*H*-[1,2,4]-triazino[5,6-*b*]indol-3-ylimino)methyl]hydrazine-carboximidamide **15,** 2-[(4*H*-[1,2,4]Triazino[5,6-*b*]indol-3-ylimino)methyl]hydrazine-carboxamide **16,** 2-[(4*H*-[1,2,4]triazino-[5,6-*b*]indol-3-ylimino)methyl]glycine **17**, *N*-pyrimidin-2-yl-4-{[(4*H*-[1,2,4]triazino[5,6-*b*]-indol-3-ylimino)methyl]amino}benzenesulfonamide **18a** and *N*-(4,6-dimethylpyrimidin-2-yl)-4-{[(4*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylimino)methyl]amino}benzenesulfonamide **18b**, respectively.

Structures of **18a** and **18b** were elucidated from appearance of two methyl groups signals in ^{1}H and ^{13}C NMR spectra of compound **18b** (2.72 and 23.60 ppm) and disappearance of the NH_2 group band in IR spectra of both compounds.

Compound **3** reacted with hydrazine hydrate and 2-aminoganidinium hydrocarbonate in boiling DMF to yield *N*-(4*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)hydrazine-carboxamide **19** and 2-[amino(imino)methyl]-*N*-4*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylhydrazinecarboxamide **20,** respectively (Scheme 5).

Antimicrobial activity. Antimicrobial activity of the synthesized compounds was tested *in vitro* against four microorganisms, namely, *Escherichia. coli* ATCC 11775, *Pseudomonas. Aeruginosa* (G^- bacteria), *Staphylococcus aureus* ATTC 12600, *Bacillus subtilis,* (G^+ bacteria), also, tested *in vitro* against *Aspergillus flavus* Link (filamentous fungi) and *Candida. albicans* ATCC 7102 (yeast). Screening was carried out according to the Kirby–Bauer disc diffusion method at concentration of 4.0 mM of the test compounds in DMSO, which was used as a solvent and negative control as well [20].

Scheme 5. Synthesis of some 3-substituted-[1,2,4]triazino[5,6-*b*]indol derivatives.



The accumulated data (see the table) demonstrated that the compounds were tolerant to the fungal species. No compounds exhibited inhibition zones toward *C. albicans* but compounds **19,** that demonstrated moderate activity towards *A. flavus* probably due to the presence of semicarbazide moiety as a substituent in the main triazinoindole nucleus.

In contrast, most tested compounds demonstrated moderate activity towards the studied bacterial strains.

Antibacterial screening for the synthesized compounds

Sample	Inhibition zone diameter (mm/mg sample)					
	Bacillus subtilis (G^+ bacteria)	*Escherichia coli* (G^- bacteria)	*Pseudomonas. Aeruginosa* (G^- bacteria)	*Staphylococcus aureus* (G^+ bacteria)	*Aspergillus flavus*	*Candida albicans*
2a	11.0	11.0	11.0	11.0	0.0	0.0
2b	10.0	9.0	9.0	11.0	0.0	0.0
4	9.0	0.0	0.0	9.0	0.0	0.0
6	12.0	12.0	12.0	13.0	0.0	0.0
8	0.0	0.0	0.0	0.0	0.0	0.0
9	0.0	0.0	0.0	0.0	0.0	0.0
14	15.0	14.0	14.0	16.0	0.0	0.0
15	0.0	0.0	0.0	0.0	0.0	0.0
16	0.0	0.0	0.0	0.0	0.0	0.0
17	0.0	0.0	0.0	0.0	0.0	0.0
18a	0.0	10.0	10.0	15.0	0.0	0.0
18b	0.0	0.0	0.0	0.0	0.0	0.0
19	11.0	14.0	14.0	15.0	10.0	0.0
20	9.0	9.0	9.0	10.0	0.0	0.0
Ampicillin antibacterial agent	20.0	22.0	17.0	18.0	0.0	0.0
Amphotericin B antifungal agent	0.0	0.0	0.0	0.0	17.0	19.0
Control: DMSO	0.0	0.0	0.0	0.0	0.0	0.0

Compounds **2a, 2b, 6, 14, 18a, 19,** and **20** demonstrated antimicrobial activity towards all bacteria strains. In case of triazinoindole moiety containing the group N=CH–NH or pyrimidinotriazinoindole system containing the NHC=O or NH_2 groups in combination with the CN group the products became inactive towards all bacterial strains. The presence of the sulfur group in a product was not necessary to make it biologically active. The compound **18a** was active towards all bacterial strains, in contrast, **18b** demonstrated no activity.

The compound **4** demonstrated activity towards G^+ bacteria but was inactive towards G^- bacteria which could be due to the presence of the N=CH-OEt group in the triazinoindole ring. The compound **9** demonstrated no activity against *Aspergillus flavus* which could be may be attributed to the presence of the semicarbazide group in the triazinoindole moiety. All synthesized compounds were inactive towards *Candida albicans.*

EXPERIMENTAL

All chemicals were purchased from Sigma (USA). The melting points were measured on a digital Electrothermal IA 9100 instruments. IR spectra were recorded on an ATR-Alpha FT-IR Spectrophotometer in the range of 400–4000 cm^{-1}. ^1H and ^{13}C NMR spectra were measured on a Bruker AC-600 Spectrometer in DMSO-d_6 using TMS as an internal standard. Mass spectra and elemental analyses were performed at the Micro-analytical Center, Cairo University. Progress of the reactions was monitored by TLC.

3-(*N*"-Guanidinylimino)indole-2(1*H*)-one (2). A mixture of **1** (0.19 g, 1 mmol) with an appropriate aldehyde (1 mmol) in glacial acetic acid (10 mL) and hydrochloric acid (0.5 mL) was stirred under reflux for 5 h. The mixture was cooled down to room temperature and the precipitate formed was filtered off and crystallized from ethanol as yellow powder. Yield 20%, mp 270–273°C. IR spectrum, ν, cm^{-1}: 3369–3119 ($2NH_2$, NH), 1656 (C=O), 1623 (C=N). ^1H NMR spectrum, δ, ppm: 6.95 d [1H, Ar-H(C_6) J = 7.6 Hz], 7.07 d.d [1H, ArH(C_7)], 7.36 d.d [1H, Ar-H(C_8)], 7.70 d [1H, Ar-H(C_9), J = 7.2 Hz], 8.54 s (4H, $2NH_2$), 11.37 s (1H, tautomeric O$\underline{H}_{indole}$), 12.51 s (1H, N$\underline{H}_{indole}$). ^{13}C NMR spectrum, δ, ppm: 111.9, 116.6, 123.6, 123.7, 133.7, 146.9, 158.2, 158.9, 166.7. Found, %: C 53.14; H 4.42; N 34.46. $C_9H_9N_5O$. Calculated, %: C 53.20; H 4.46; N 34.47.

3-(*N*-Ethoxycarbonylamino)-4*H*-[1,2,4]triazino-[5,6-*b*]indole (3). A mixture of 1 (0.19 g, 1 mmol) with ethyl chloroformate (0.11 mL, 1 mmol) in DMF (10 mL) and TEA (3 drops) was stirred under reflux for 4 h. The mixture was cooled down to room temperature and the precipitate was filtered off and crystallized from ethanol to give the brown product. Yield 40%, mp 260–263°C. IR spectrum, ν, cm^{-1}: 3389–3211 (2NH), 1715 (C=O), 1616 (C=N). ^1H NMR spectrum, δ, ppm: 1.15 t (3H, CH_3), 4.25 q (2H, CH_2), 6.93 d [1H, Ar-H(C_6) J = 8.0 Hz], 7.10 d.d [1H, ArH(C_7)], 7.37 d.d [1H, Ar-H(C_8)], 7.62 d [1H, Ar-H (C_9), J = 7.2 Hz], 11.32 s (1H, N$\underline{H}_{triazine}$), 13.01 s (1H, N$\underline{H}$C=O). ^{13}C NMR spectrum, δ, ppm: 14.50 (CH_3), 61.91 (CH_2), 116.9, 119.5, 121.8, 125.8, 132.5, 146.9, 150.8, 157.5, 158.3 and 162.0 (Ar, C=C, C=N and C=O). Found, %: C 55.98; H 4.23; N 27.17. $C_{12}H_{11}N_5O_2$. Calculated, %: C 56.03; H 4.31; N 27.22. MS m/z (I_{rel}, %): 257 (1.9), 236 (2.0), 222 (1.5), 198 (1.4), 184 (2.1), 176 (2.0), 132 (2.2), 129 (2.2), 80 (66.9), 64 (100), 63 (2.0).

3-(*N*-Ethoxymethyleneamino)-4*H*-[1,2,4]triazino-[5,6-*b*]indole (4). A mixture of **1** (0.19 g, 1 mmol) with triethyl orthoformate (10 mL) was stirred under reflux for 4 h. The mixture was cooled down to room temperature and the precipitate was filtered off and crystallized from ethanol to give the yellow product. Yield 43%, mp 250–252°C. IR spectrum, ν, cm^{-1}: 3 428(NH), 1613 (C=N). ^1H NMR spectrum, δ, ppm: 1.14 t (3H, CH_3, J = 7.2 Hz), 3.58 q (2H, CH_2, J = 7.2 Hz), 6.27 s (1H, CH=N), 7.20 d.d [1H, Ar-H(C_7)], 7.39 d [1H, ArH(C_6), J = 7.6 Hz], 7.43 d.d [1H, Ar-H (C_8)], 7.70 d [1H, Ar-H(C_9), J = 7.2 Hz], 12.74 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 13.70 (CH_3), 63.12 (CH_2), 117.7, 120.2, 121.8, 126.2, 132.4, 143.9, 156.2, 159.1 160.4 and 165.7 (Ar, C–O, C=C, C=N and C=O). Found, %: C 59.69; H 4.58; N 29.02.1.24. $C_{12}H_{11}N_5O$. Calculated, %: C 59.74; H 4.60; N 29.03.

3-(Hydrazinothiocarbonylamino)-4*H*-[1,2,4]-triazino[5,6-*b*]indole (5). A mixture of **1** (0.19 g, 1 mmol) with thioformaic acid hydrazid (0.11 g, 1 mmol) in ethanol/DMF (10:3 mL) was stirred under reflux for 10 h. The mixture was cooled down to room temperature and the precipitate was filtered off and crystallized from ethanol to give yellow powder. Yield 57%, mp 260–262°C. IR spectrum, ν, cm^{-1}: 3422 strong (NH_2 and NH), 1623 (C=N). ^1H NMR spectrum, δ, ppm: 5.64 s (2H, NH_2), 6.93 d [1H, Ar-H (C_6) J = 8 Hz], 7.06 d.d [1H, ArH(C_7)], 7.32 d.d [1H, Ar-H(C_8)], 7.50 d [1H, Ar-H(C_9), J = 7.2 Hz], 11.22 s

(1H, N<u>H</u>NH$_2$), 12.85 s (1H, N<u>H</u>$_{triazine}$), 13.31 s (1H, N<u>H</u>–C=S). ^{13}C NMR spectrum, δ, ppm: 111.0, 119.9, 120.1, 122.5, 130.7, 133.9, 141.4, 148.1, 163.1 and 165.4. Found, %: C 46.29; H 3.48; N 37.77; S 12.34. $C_{16}H_9N_7S$. Calculated, %: C 46.32; H 3.50; N 37.81; S 12.37. MS *m/z* (I_{rel}, %): 259 (0.73), 244 (0.87), 227 (0.61), 221 (0.96), 207 (0.73), 194 (0.68), 177 (1.02), 158 (0.67), 145 (0.83), 130 (0.76), 125 (0.82), 80 (36.79), 64 (100).

***N*-(1,3-Dioxoindene-2-ylidene)-4*H*-[1,2,4]triazino-[5,6-*b*]indol-3-amine (6).** A mixture of **1** (0.19 g, 1 mmol) with ninhydrin (0.18 g, 1 mmol) in ethanol (7 mL) was stirred under reflux for 2 h. Yellow precipitate was filtered off while hot and recrystallized from ethanol. Yield 40%, mp 240–244°C. IR spectrum, ν, cm^{-1}: 3231 (NH), 1709–1685 (2C=O), 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 6.71 d [2H, phenyl-H(C_a), *J* = 5.6 Hz], 7.11 d [2H, phenyl-H(C_b), *J* = 8.0 Hz] 7.62 d [1H, Ar-H(C_6), *J* = 7.8 Hz], 7.68 d.d [1H, ArH(C_7)], 7.76 d [1H, ArH(C_9), *J* = 7.6 Hz], 7.88 d.d [1H, Ar-H(C_8)], 10.17 s (1H, N<u>H</u>$_{triazine}$). ^{13}C NMR spectrum, δ, ppm: 117.7, 120.8, 121.5, 125.6, 126.3, 132.4, 136.6, 139.4, 143.9, 148.2, 150.7, 155.8, 157.4, 159.1, 160.4. Found, %: C 65.97; H 2.70; N 21.32. $C_{18}H_9N_5O_2$. Calculated, %: C 66.05; H 2.77; N 21.40.

1-Amino-3-(2-thienyl)pyrimido[2',1':3,4][1,2,4]-triazino[5,6-*b*]indole-2-carbonitrile (8). A mixture of **1** (0.19 g, 1mmol) with malononitrile (0.66 g, 1 mmol), thiophenaldehyde (0.11 g, 1mmol) and drops of TEA in ethanol (10 mL) was stirred under reflux for 3 h. The mixture was cooled down to room temperature, the precipitate was filtered off and crystallized from ethanol to give orange crystals. Yield 57%, mp >300°C. IR spectrum, ν, cm^{-1}: 3350 (NH_2), 2209 (CN), 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 6.36 s (2H, NH_2), 6.94 d [1H, Ar-H(C_6), *J* = 8 Hz], 7.09 d.d [1H, ArH (C_7)], 7.29 d.d→t (1H, thiophene-$H_{b,}$), 7.31 d.d [1H, Ar-H(C_8)], 7.49 d [1H, Ar-H(C_9), *J* = 7.2 Hz], 7.93 d (1H, *J* = 1.2 Hz, thiophene-H_c), 8.20 d (1H, *J* = 1.2 Hz, thiophene-H_a). ^{13}C NMR spectrum, δ, ppm: 111.6, 117.4, 120.6, 120.6, 123.0, 124.6, 129.3, 130.1, 131.3, 133.1, 134.6, 140.4, 142.2, 158.8, 161.4, 163.6, 165.9. Found, %: C 59.42; H 2.62; N 28.50; S 9.27. $C_{17}H_9N_7S$. Calculated, %: C 59.46; H 2.64; N 28.55; S 9.34. MS *m/z* (I_{rel}, %): 343 (49.11), 226 (18.06), 211 (8.71), 200 (2.75), 185 (5.57), 171 (3.62), 161 (4.49), 145 (12.69), 130 (9.42), 118 (30.27), 104 (22.02), 90 (17.48), 80 (24.62), 64 (100).

1-Methylpyrimido[2',1':3,4][1,2,4]triazino[5,6-*b*]-indol-3(4*H*)-one (9). A mixture of **1** (0.19 g, 1 mmol) with ethyl acetoacetate (0.13 g, 1 mmol) in DMF (7 mL) was stirred under reflux for 3 h. The mixture was cooled down to room temperature and the precipitate was filtered off and crystallized from ethanol to give yellow powder. Yield 68%, mp 260–262°C. IR spectrum, ν, cm^{-1}: 3145 (NH), 1649 (C=O amide), 1623 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 5,87 s (1H, $CH_{pyrimidine}$), 6.92 d [1H, Ar-H (C_6) *J* = 8 Hz], 7.07 d.d [1H, ArH(C_7)], 7.31 d.d [1H, Ar-H(C_8)], 7.73 d [1H, Ar-H(C_9), *J* = 7.2 Hz], 12.31 s (1H, N<u>H</u>–C=O). ^{13}C NMR spectrum, δ, ppm: 22.09, 104.6, 110.1, 120.1, 121.0, 122.3, 122.4, 129.6, 130.7, 133.3, 141.6, 155.5, 162.8. Found, %: C 62.09; H 3.62; N 27.82. $C_{13}H_9N_5O$. Calculated, %: C 62.15; H 3.61; N 27.87. MS *m/z* (I_{rel}, %): 251 (0.71), 249 (1.43), 238 (0.94), 223 (1.57), 209 (0.88), 185 (44.71), 176 (0.75), 157 (10.50), 140 (1.15), 129 (19.79), 115 (6.91), 103 (44.11), 88 (11.61), 80 (34.45), 64 (100).

1*H*-Imidazo[2',1':3,4][1,2,4]triazino[5,6-*b*]indol-2(3*H*)-one (10). A mixture of **1** (0.19 g, 1 mmol) with ethyl chloroacetate (0.12 g, 1 mmol) in DMF (10 mL) was stirred under reflux for 6 h. The mixture was cooled down and poured into ice-cold water. The precipitate was filtered off and washed with 10 mL of ethanol to give dark yellow product. Yield 60%, mp > 300°C. IR spectrum, ν, cm^{-1}: 3278 (NH), 1650 (C=O), 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.61 s (2H, CH_2), 6.94 d [1H, Ar-H(C_6), *J* = 8 Hz], 7.09 d.d [1H, ArH(C_7)], 7.29 d.d→t (1H, thiophene-$H_{b,}$), 7.31 d.d [1H, Ar-H(C_8)], 7.49 d [1H, Ar-H(C_9), *J* = 7.2 Hz], 10.20 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 51.01 (CH_2), 115.3, 119.0, 121.7, 125.6, 132.8, 139.6, 155.7, 157.9, 160.0 and 165.4. Found, %: C 58.60; H 3.08; N 31.00. $C_{11}H_7N_5O$. Calculated, %: C 58.67; H 3.13; N 31.10. MS *m/z* (I_{rel}, %): 225 (0.95), 196 (0.92), 173 (1.14), 162 (1.21), 152 (1.25), 140 (1.37), 116 (1.08), 103 (1.12), 95 (1.14), 80 (21.67), 64 (100).

1,3-Dimethylpyrimido[2',1':3,4][1,2,4]triazino-[5,6-*b*]indole (11). A mixture of **1** (0.19 g, 1 mmol) with acetyl acetone (0.3 g, 1 mmol) in DMF (7 mL) was stirred under reflux for 3 h. The mixture was cooled down and poured into ice-cold water. The precipitate was filtered off and washed with 10 mL ethanol then 10 mL of diethyl ether to give yellow powder. Yield 70%, mp 264–266°C. IR spectrum, ν, cm^{-1}: 1618 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.38 s (6H, 2CH_3), 6.89 s (1H, $CH_{pyrimidine}$), 6.93 d [1H, Ar-H (C_6) *J* = 8.0 Hz], 7.06 d.d [1H, ArH(C_7)], 7.29 d.d [1H, Ar-H(C_8)], 7.55 d [1H, Ar-H(C_9), *J* = 7.2 Hz]. Found, %: C 67.43; H 4.44; N 28.07. $C_{14}H_{11}N_5$. Calculated, %: C 67.46; H 4.45; N 28.10.

1-Aminopyrimido[2',1':3,4][1,2,4]triazino[5,6-*b*]-indol-3-(4*H*)-one (12). A mixture of **1** (0.19 g, 1 mmol) with ethyl cyanoacetate (0.13 g, 1 mmol) in DMF (7 mL) was stirred unpon reflux for 3 h. The mixture was cooled down and poured into ice-cold water. The precipitate was filtered off and crystallized from ethanol to give red crystals. Yield 50%, mp 254–256°C. IR spectrum, ν, cm^{-1}: 3310 (NH_2), 3185 (NH), 1643 (C=O), 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 5.87 s (1H, C=CH), 6.95 s (2H, NH_2), 7.25 d.d [1H, ArH(C_7)], 7.39 d [1H, Ar-H(C_6), J = 8 Hz], 7.45 d.d [1H, Ar-H(C_8)], 8.07 d [1H, Ar-H(C_9), J = 7.6 Hz], 11.78 s (1H, NH). Found, %: C 57.09; H 3.15; N 33.29. $C_{12}H_8N_6O$. Calculated, %: C 57.14; H 3.20; N 33.32. MS *m/z* (I_{rel}, %): 251 (0.19), 227 (0.44), 213 (0.27), 201(0.16), 185 (100), 169 (0.12), 157 (65.95), 142 (0.89), 129 (25.44), 115 (9.01), 103 (57.43), 88 (12.69), 76 (14.98), 64 (7.63).

3-Butylamino-4*H*-[1,2,4]triazino[5,6-*b*]indole (13). A mixture of **1** (0.19 g, 1 mmol) with 1-butylbromide (0.14 g, 1 mmol) in DMF (7 mL) was stirred under reflux for 6 h. The mixture was cooled down and poured into ice-cold water. The precipitate was filtered off and crystallized from ethanol to give yellow powder. Yield 10%, mp 159–162°C. IR spectrum, ν, cm^{-1}: 3382–3178 (2NH), 1613 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.24 t (3H, CH_3), 1.46 m (2H, CH_2), 2.16 m (2H, CH_2), 3.76 t (2H, NHC$\underline{H}_2$), 6.96 d [1H, Ar-H(C_6), J = 7.6 Hz], 7.39 d.d [1H, ArH(C_7)], 7.36 d.d [1H, Ar-H(C_8)], 7.62 d [1H, Ar-H(C_9), J = 7.6 Hz], 11.79 s (1H, N$\underline{H}_{triazine}$), 13.01 s (1H, N$\underline{H}$). ^{13}C NMR spectrum, δ, ppm: 25.94, 26.05, 28.70, 30.99 (CH_3 and $3CH_2$), 116.4, 118.4, 120.3, 124.4, 130.8 (C=C, C_{9a}, C_9, C_8, C_6, C_7), 143.2 (N=C_{4a}–N), 156.0 (N=C_{9b}–C), 157.8 (C=C_{5a}–N), 166.3 (C_3), 168.6 (C=O). Found, %: C 64.66; H 6.24; N 28.98. $C_{13}H_{15}N_5$. Calculated, %: C 64.71; H 6.27; N 29.02. MS *m/z* (I_{rel}, %): 241 (0.79), 240 (1.23), 226 (2.47), 220 (0.97), 207 (0.96), 185 (1.40), 174 (0.79), 157 (1.41), 155 (1.00), 129 (1.07), 118 (1.30), 103 (2.27), 97 (1.59), 80 (41.85), 64 (100).

***N*^{1},*N*^{10}-Di(4*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)-decanediamide (14).** A mixture of **1** (0.19 g, 1 mmol) with sebacoyl chloride (0.24 g, 0.21 mL, 1 mmol) and drops of TEA in DMF (15 mL) was refluxed for 6 h. The reaction mixture was cooled down to room temperature and poured onto ice. The precipitate was filtered off and recrystallized from ethanol to give **14** as orange crystals. Yield 57%, mp >280°C. IR spectrum, ν, cm^{-1}: 3234–3070 (2NH), 1653 (C=O), 1611 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.24 m (4H, $2CH_2$), 1.46 t (4H, $2CH_2$), 2.16 m (4H, $2CH_2$), 3.33 t (4H, 2COC$\underline{H}_2$), 7.25 d.d [1H, ArH(C_7)], 7.39 d [1H, Ar-H(C_6), J = 8 Hz], 7.46 d.d [1H, Ar-H(C_8)], 8.07 d [1H, Ar-H(C_9), J = 7.6 Hz], 8.60 s (1H, CON$\underline{H}$), 11.79 s (1H, N$\underline{H}_{triazine}$). ^{13}C NMR spectrum, δ, ppm: 25.94, 26.05, 28.70, 30.99 ($4CH_2$), 116.4, 118.4, 120.3, 124.4, 130.8 (C=C, C_{9a}, C_9, C_8, C_6, C_7), 143.2 (N=C_{4a}-N), 156.0 (N=C_{9b}–C), 157.8 (C=C_{5a}–N), 166.3 (C_3) and 168.6 (C=O). Found, %: C 62.61; H 5.20; N 26.04.5. $C_{28}H_{28}N_{10}O_2$. Calculated, %: C 62.67; H 5.26; N 26.10.

2-[(4*H*-[1,2,4]Triazino[5,6-*b*]indol-3-ylimino)-methyl]hydrazine-carboximidamide (15). A mixture of **4** (0.24 g, 1 mmol) with aminoguanidinium hydrocarbonate (0.136 g, 1 mmol) in glacial acetic acid (10 mL) was stirred under reflux for 3 h. Yellow precipitate was filtered while hot and recrystallized from ethanol. Yield 42%, mp 300°C. IR spectrum, ν, cm^{-1}: 3444 (NH_2), 3201–3079 (4NH), 1655 (C=N). ^{1}H NMR spectrum, δ, ppm: 5.87 s (2H, NH_2), 6.95 d [1H, Ar-H(C_6), J = 8.0 Hz], 7.10 d.d [1H, ArH(C_7)], 7.36 d.d [1H, Ar-H(C_8)], 7.62 d [1H, Ar-H(C_9), J = 7.6 Hz], 8.70 s (1H, HC=N), 10.13 s (2H, 2NH), 11.30 s (1H, N$\underline{H}_{triazine}$), 13.01 s (1H, N$\underline{H}$). ^{13}C NMR spectrum, δ, ppm: 117.7, 120.4, 121.8, 126.2, 132.4 (C=C, C_{9a}, C_9, C_8, C_6, C_7), 143.2 (C_{4a}), 156.7 (N=$\underline{CH}$–N), 159.1 (C_{5a}), 160.4 (C_{9b}), 160.9 (NH–C=NH) and 161.3 (C_3). Found, %: C 49.12; H 4.07; N 46.75. $C_{11}H_{11}N_9$. Calculated, %: C 49.07; H 4.12; N 46.82. MS *m/z* (I_{rel}, %): 269 (0.96), 256 (1.07), 246 (1.25), 229 (1.20), 218 (1.40), 203 (1.35), 192 (1.59), 169 (1.61), 157 (1.01), 151 (1.61), 127 (1.90), 119 (1.81), 111 (2.20), 80 (48.38), 64 (100).

2-[(4*H*-[1,2,4]Triazino[5,6-*b*]indol-3-ylimino)-methyl]hydrazine-carboxamide (16). Mixture of **4** (0.24 g, 1 mmol) with semicabazide HCl (0.11 g, 1 mmol) in ethanol/DMF (10 : 2 mL) was stirred under reflux for 5 h. Yellow precipitate was filtered off while hot and recrystallized from ethanol. Yield 50%, mp 271–273°C. IR spectrum, ν, cm^{-1}: 3415 (NH_2), 3190 (NH), 1691 (C=O), 1617 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.51 s (2H, NH_2), 6.43 s (1H, N=CH), 6.95 d [1H, Ar-H(C_6) J = 8 Hz], 7.09 d.d [1H, ArH(C_7)], 7.36 d.d [1H, Ar-H(C_8)], 7.61 d [1H, Ar-H(C_9), J = 7.2 Hz], 8.70 s (1H, N$\underline{H}$–C=O), 11.31 s (1H, NH–N$\underline{H}$–C=O), 12.99 s (1H, N$\underline{H}_{triazine}$). Found, %: C 48.85; H 3.70; N 41.44. $C_{11}H_{10}N_8O$. Calculated, %: C 48.89; H 3.73; N 41.46. MS *m/z* (I_{rel}, %): 270 (0.62), 269 (1.29), 260 (0.76), 240 (6.16), 225 (10.15), 213 (0.70), 197 (0.88), 185 (3.60), 171 (0.66), 157 (3.17), 145 (1.15), 131

(2.13), 118 (2.49), 103 (5.91), 90 (2.84), 80 (27.69), 64 (100).

***N*-[(4*H*-[1,2,4]Triazino[5,6-*b*]indol-3-ylimino)-methyl]glycine (17).** Mixture of compound **4** (0.24 g, 1 mmol) with glycine (0.075 g, 1 mmol) in DMF/ H_2O mixture (7 : 1 mL) was stirred under reflux for 4 h. Yellow precipitate was filtered while hot and recrystallized from ethanol. Yield 80%, mp ≥ 300°C. IR spectrum, ν, cm^{-1}: 3429 (OH), 3152–3072 (2NH), 1702 (C=O), 1622 (C=N). ^{1}H NMR spectrum, δ, ppm: 4.31 s (2H, CH_2), 6.48 s (1H, N=CH), 6.95 d [1H, Ar-H(C_6) J = 8 Hz], 7.09 d.d [1H, ArH(C_7)], 7.36 d.d [1H, Ar-H(C_8)], 7.62 d [1H, Ar-H(C_9), J = 7.2 Hz], 8.70 s (1H, NH–CH_2), 11.30 (N<u>H</u>$_{triazine}$), 12.99 s (1H, OH). Found, %: C 53.31; H 3.68; N 31.04. $C_{12}H_{10}N_6O_2$. Calculated, %: C 53.33; H 3.73; N 31.10. MS *m/z* (I_{rel}, %): 270 (0.96), 269 (0.96), 256 (1.22), 246 (1.25), 229 (1.20), 203 (1.35), 192 (1.59), 185 (1.11), 169 (1.61), 157 (1.01), 151 (1.61), 127 (1.90), 119 (1.81), 110 (1.59), 85 (4.10), 80 (48.38), 64 (100).

Compounds 18a and 18b *(general procedure).* Mixture of compound **4** (0.24 g, 1 mmol) with the appropriate sulfur containing drug (1 mmol) in DMF (10 mL) was stirred under reflux for 4 h. The mixture was cooled down to room temperature and the precipitate was filtered off and crystallized from ethanol.

***N*-Pyrimidin-2-yl-4-{[(4*H*-[1,2,4]triazino[5,6-*b*]-indol-3-ylimino)methyl]amino}benzenesulfonamide (18a)**. Yellow powder, yield 54%, mp 240–242°C. IR spectrum, ν, cm^{-1}: 3294–3151 (3NH), 1643 (C=N). ^{1}H NMR spectrum, δ, ppm: 5.98 s (1H, N=C<u>H</u>–NH), 6.46 d (2H, benzene H(C_2, C_6), J = 8.4 Hz], 6.93 d [2H, benzene H(C_3, C_5), J = 7.2 Hz], 6.95 d [1H, indole-H(C_6), J = 8.0 Hz], 7.00 s (1H, N=CH–N<u>H</u>), 7.09 d.d [1H, indole-H (C_7)], 7.36 d.d [1H, indole-H (C_8)], 7.59 d [1H, indole-H(C_9), J = 7.6 Hz], 8.46 t (1H, pyridine ring C_3), 8.69 d (2H, pyridine ring C_2,C_4), 11.30 s (1H, N<u>H</u>$_{triazine}$), 12.99 s (1H, SO_2N<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 108.9, 117.7, 120.2, 121.1, 121.8, 126.2, 129.6, 132.4, 137.3, 143.8, 143.9, 148.4, 151.2, 154.8, 157.2, 159.1, 160.4. Found, %: C 53.89; H 3.31; N 28.25; S 7.16. $C_{20}H_{15}N_9O_2S$. Calculated, %: C 53.93; H 3.39; N 28.30; S 7.20.

***N*-(4,6-Dimethylpyrimidin-2-yl)-4-{[(4*H*-[1,2,4]-triazino[5,6-*b*]indol-3-ylimino)methyl]amino}benzenesulfonamide (18b).** Orange yellow powder, yield 20%, mp >300°C. IR spectrum, ν, cm^{-1}: 3283–3219 (3NH), 1648 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.72 s (6H, $2CH_3$), 5.93 s (1H, N=C<u>H</u>–NH), 6.45 d (2H, benzene H(C_2, C_6), J = 8.4 Hz], 6.91 d (2H, benzene H(C_3, C_5), J = 7.2 Hz], 6.95 d [1H, indole-H(C_6), J = 8.0 Hz], 7.01 s [1H, N=CH–N<u>H</u>], 7.11 d.d [1H, indole-H(C_7)], 7.37 d.d [1H, indole-H(C_8)], 7.61 d [1H, indole-H(C_9), J = 7.6 Hz], 8.40 s (1H, pyridine ring C_3), 11.32 s (1H, N<u>H</u>$_{triazine}$), 13.00 s (1H, SO_2N<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 23.60 ($2CH_3$), 108.7, 117.7, 120.2, 121.1, 121.8, 126.2, 129.6, 132.4, 137.4, 143.8, 143.9, 151.2, 151.3, 154.8, 159.1, 160.4, 167.8. Found, %: C 55.72; H 3.97; N 26.55; S 6.74. $C_{22}H_{19}N_9O_2S$. Calculated, %: C 55.80; H 4.04; N 26.62; S 6.77.

***N*-(4*H*-[1,2,4]Triazino[5,6-*b*]indol-3-yl)hydrazine-carboxamide (19).** Mixture of compound **3** (0.5g, 2 mmol) with hydrazine hydrate (0.1 g, 2 mmol) in DMF (20 mL) was stirred under reflux for 1 h. Yellow precipitate was filtered off while hot and recrystallized from benzene. Yield 70%, mp 236–238°C. IR spectrum, ν, cm^{-1}: 3421 (NH_2), 3382–3178 (3NH), 1654 (C=O), 1623 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.23 s (2H, NH_2), 6.84 d [1H, Ar-H(C_6) J = 7.6 Hz], 6.94 d.d [1H, ArH(C_7)], 7.12 d.d [1H, Ar-H(C_8)], 7.34 d [1H, Ar-H(C_9), J = 7.6 Hz], 9.51 s (1H, NHCON<u>H</u>NH_2), 10.50 s (1H, N<u>H</u>CONHNH_2), 10.67 s (1H, N<u>H</u>$_{triazine}$). Found, %: C 49.32; H 3.68; N 40.25.$C_{10}H_9N_7O$ (243.22). Calculated, %: C 49.38; H 3.73; N 40.31. MS *m/z* (I_{rel}, %): 243 (33.04), 228 (18.27), 215 (31.37), 210 (21.64), 200 (19.80), 186 (2.65), 171 (2.93), 159 (24.11), 145 (12.58), 131 (100), 118 (48.34), 103 (95.62), 90 (30.34), 76 (34.20), 64 (57.84).

2-[Amino(imino)methyl]-*N*-4*H*-[1,2,4]triazino-[5,6-*b*]indol-3-ylhydrazine-carboxamide (20). Mixture of compound **3** (0.5 g, 2 mmol) with amino-guanidinium hydrocarbonate (0.13 g, 2 mmol) in DMF (20 mL) was stirred under reflux for 1 h. Yellow precipitate formed was filtered off while hot and recrystallized from ethanol. Yield 65%, mp 145–148°C. IR spectrum, ν, cm^{-1}: 3400 (NH_2), 3271–3163 (5NH), 1657 (C=O), 1618 (C=N). ^{1}H NMR spectrum, δ, ppm: 6.23 s (2H, NH_2), 6.83 d [1H, Ar-H(C_6) J = 7.6 Hz], 6.95 d.d [1H, ArH(C_7)], 7.13 d.d [1H, Ar-H(C_8)], 7.37 d [1H, Ar-H(C_9), J = 7.6 Hz), 7.84 s (1H, C=NH), 9.51 s (1H, NHCONHN<u>H</u>NH_2), 10.50 s (1H, N<u>H</u>CONHNHNH_2), 10.67 s (1H, NHCON<u>H</u>NHNH_2), 11.30 s (1H, N<u>H</u>$_{triazine}$). ^{13}C NMR spectrum, δ, ppm: 116.9, 119.2, 121.8, 125.7, 132.4, 146.2, 155.3, 157.6, 158.3, 160.4 and 164.1. Found, %: C 46.27; H 3.87; N 44.10. $C_{11}H_{11}N_9O$. Calculated, %: C 46.31; H 3.89; N 44.19. MS *m/z* (I_{rel}, %): 285 (0.98), 280 (0.87), 263 (0.98), 241 (0.85), 228 (1.33), 218 (1.18), 201 (3.38), 193 (0.74), 185 (49.45), 171 (1.11), 157 (45.18), 145

(1.53), 130 (13.40), 114 (100), 103 (49.63), 99 (61.81), 88 (11.49), 72 (41.99), 59 (29.58).

Antimicrobial activity. *In vitro* antimicrobial activity of the synthesized compounds was determined using the modified Kirby–Bauer disc diffusion method [20]. Ampicillin and amphotericin B were used as bacterial and fungal positive controls, respectively, and DMSO was used as solvent and negative control as well. Six microbial species were considered, namely, *E. coli* (G^- bacteria), *P. aeruginosa* (G^- bacteria), *S. aureus* (G^+ bacteria), *B. subtilis* (G^+ bacteria), *A. flavus* (filamentous fungi), and *C. albicans* (yeast).

Briefly, 100 mL of the test organism were grown in 10 mL of fresh media until they reached a count of 108 cells/mL for bacteria and 105 cells/mL for fungi. Approximately 100 μL of the microbial suspension was spread onto Muller-Hinton agar plates. Paper discs (Scleicher and Schull, Spain) with a diameter of 8.0 mm were impregnated by 10 mL of the test compound (4.0 mM), and the controls were treated similarly. The plates were incubated for 48 h at 35–37°C for bacterial strains, 25°C for *A. flavus* and 30°C for *C. albicans*. Inhibition zone diameters were measured with slipping calipers.

CONCLUSIONS

Several fused derivatives of [1,2,4]triazino[5,6-*b*]-indole were synthesized from 3-amino-[1,2,4]triazino-[5,6-*b*]indole **1**. *In vitro* antimicrobial screening of this series revealed that the compounds were moderately active against *Candida albicans* and inactive against *Aspergillus flavus* fungal strains. *However,* derivative **19** showed moderate activity against *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis*.

REFERENCES

1. Tomchin, A.B., Uryupoy, O.Yu., and Smirnov, A.V., *Pharm. Chem. J.*, 1997, vol. 31(12), p. 6. doi 10.1007/BF02464248
2. Ram, V.J., *Arch. Pharm*., 1980, vol. 313, p. 108. doi 10.1002/ardp.19803130203
3. Gladych, J.M.Z., Hornby, R., Hunt, J.H., Jack, D., Boyle, J.J., Ferlauto, R.J., Haff, R.F., Kormendy, C.G., Stanfield, F.J., and Steward, R.C., *J. Med. Chem*., 1972, vol. 15, p. 277. doi 10.1021/jm00273a017
4. Ali, R.S., Al Harthi, R.R., Saad, H.A., and Amin, M.A., *Russ. J. Gen. Chem*., 2016, vol. 86, p. 2906. doi 10.1134/S1070363216120598
5. Yahia Nasser Mabkhot, Y.N., Alatibi, F., El-Sayed, N.N.E., Kheder, N.A., and Al-Showiman, S.S., *Molecules*, 2016, vol. 21, p. 1036. doi 10.3390/molecules21081036
6. Voskoboynik, O.Y., Kovalenko, S.I., Okovytyy, S.I., Shishkina, S.V., *J. Heterocyclic Chem*., 2017, vol. 54, p. 2038. doi 10.1002/jhet.2801
7. Deokar, H., Chaskar, J., and Chaskar, A., *J. Heterocyclic. Chem.,* 2014, vol. 51, p. 719. doi 10.1002/jhet.1761
8. Bergman, J. and Eklund, N., *Tetrahedron*, 1980, vol. 36, p. 1445. doi 10.1016/0040-4020(80)85060-5
9. Cornforth, J.W., Hitchcock, P.B., and Rozos, P., *J. Chem. Soc. Perkin Trans. 1*, 1996, p. 2787. doi 10.1039/P19960002787
10. Abdel-Wahab, B.F. and Mohamed, H.A., *Phosphorus, Sulfur Silicon Relat. Elem*., 2016, vol. 191, p. 1199. doi org/10.1080/10426507.2016.1160242.
11. Rothkopf, H.W., Wohrle, D., Muller, R., and KoBmehl, G., *Chem. Ber*., 1975, vol. 108, p. 875. doi 10.1002/cber.19751080320
12. Abdel-Rahman, R.M., El-Gendy, Z., and Fawzy, M.M., *Asian J. Chem*., 1992, vol. 4(2), p. 364.
13. Abdel-Rahman, R.M., Fawzy, M.M., and El-Gendy, Z., *Asian J. Chem*., vol. 1992, 4(3), p. 534.
14. Saad, H.A., Youssef, M.M., and Mosselhi, A.M., *Molecules*, 2011, vol. 16(6), p. 4937. doi 10.3390/molecules16064937
15. Saad, H.A., *Curr. Org. Synth*., 2012, vol. 9(4), p. 573. doi 10.2174/157017912802651447
16. Amin, M.A. and Saad, H.A., *Curr. Org. Synth*., 2016, vol. 13, p. 116. doi 10.2174/1570179412666150511224828
17. Mahendran, S., Badami, S., Ravi, S., Thippeswamy, B.S., and Veerapur, V.P., *Pharm. Chem. J*., 2011, vol. 45, p. 547. doi 10.1007/s11094-011-0676-x
18. Lakshmi, N.V., Sivakumar, P.M., Muralidharan, D., Doble, M., and Perumal, P.T., *RSC Adv*., 2013, no. 3, p. 496. doi 10.1039/C2RA01215D
19. Abdel-Rahman, R.M., Makkia, M.S.T., Alib, T.E.S., and Ibrahim, M.A., *Eur. J. Chem*., 2010, no. 1, p. 236. doi 10.5155/eurjchem.1.3.236-245.54
20. Bauer, A.M., Kirby, W.M., Sherris, C., and Turck, M., *Am. J. Clin. Path*., 1966, vol. 45, p. 493.