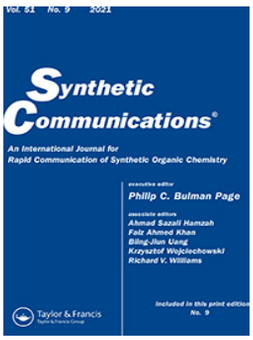

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Synthesis and biological activity evaluation of some new mixed azines appended tetrahydro-1,2,4-triazines

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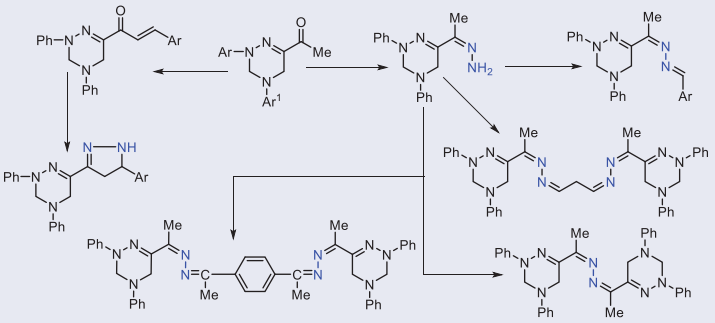
ABSTRACT

A series of 6-acetyl-2,4-diaryl-2,3,4,5-tetrahydro-1,2,4-triazines (**2a–2f**) was synthesized by double Mannich reaction of the hydrazone **1a** or **1b** with formaldehyde and the appropriate amine. A similar reaction of **1a** with the appropriate diamine afforded the *bis*(tetrahydro-triazines) **3a–b**, and **4a–b**. Whereas, the 6-cinnamoyl derivatives **5a-c** were obtained by the reaction of **2a** with the appropriate aldehyde. The hydrazone **7**, derived from **2a**, was treated with the appropriate aldehyde or ketone to afford the mixed azines **8–12** and **13–16**. The biological activity, antibacterial, antifungal and antioxidants of the most newly synthesized compounds of these derivatives were screened. Compounds **2b**, **3a** and **7** revealed the best results against all screened biological activity

GRAPHICAL ABSTRACT



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Introduction

The chemistry of 1,2,4-triazines and related compounds have been the subject of wide interest, due to their wide range of biological and pharmacological activities. The literature dealing with the chemistry and pharmacological activities of 1,2,4-triazines has been reviewed.[1–3] 1,2,4-Triazines have several biological activities such as anticancer,[3–6] cytotoxic,[7,8] antimicrobial,[9,10] antifungal,[11] anti-inflammatory and analgesic,[12] antimalarial,[13] antibacterial[14–16] and antidiabetics.[17]

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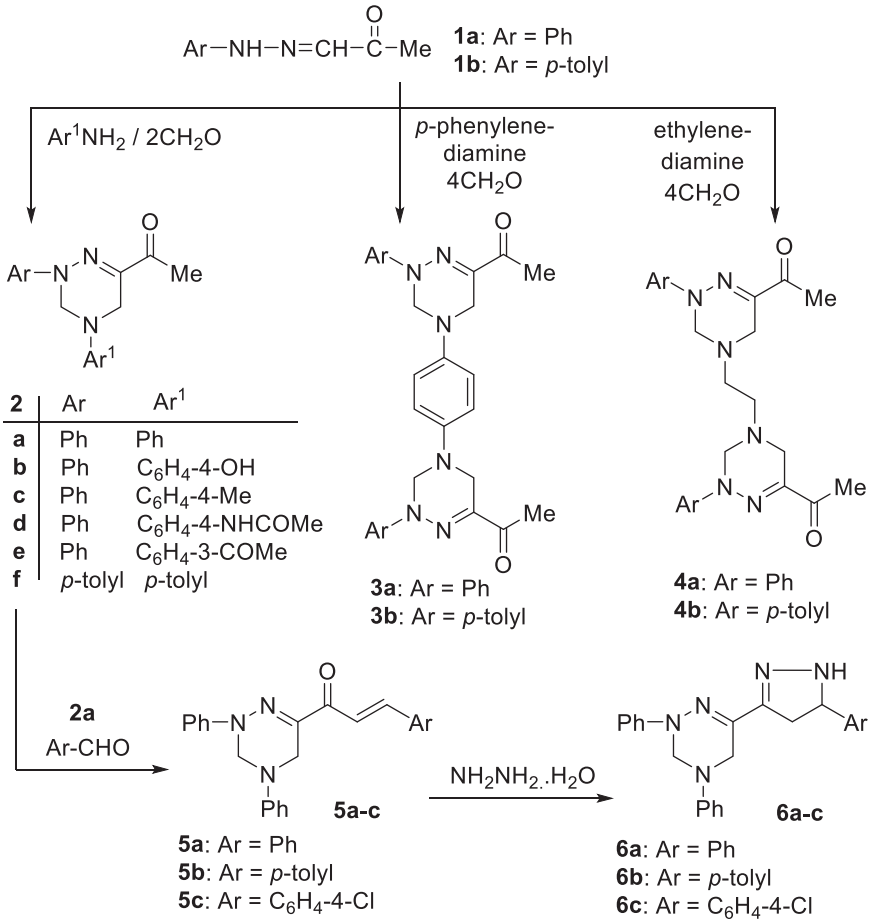


Scheme 1. Synthesis of 6-acetyl- and 6-cinnamoyl-2,4-diaryl-tetrahydro-1,2,4-triazines and bis(tetrahydro-1,2,4-triazines).

On the other hand, azines and mixed azines are receiving attention due to their antibacterial and antifungal,[18–20] antimalarial,[21] cytotoxic[22–24] and antioxidant[25] activity. In addition, a number of azines have also been used as ligands.[26–28]

However, a limited number of azines and mixed azines incorporated into heterocyclic systems are reported in the literature.[29] In view of this, and in connection with our studies in this area,[29] the synthesis of some new 6-acetyl tetrahydro-1,2,4-triazines and their conversion into mixed azines was investigated.

Results and discussion

A series of 6-acetyl-2,4-diaryl-2,3,4,5-tetrahydro-1,2,4-triazines (**2a–f**) was prepared by a double Mannich reaction of pyruvaldehyde phenylhydrazone (**1a**)[30] or pyruvaldehyde *p*-tolylhydrazone (**1b**) with formaldehyde and the appropriate aromatic amine, according to an earlier report[31] (Scheme 1). Compounds **2b–f** are reported for the first time by this study. Confirmatory evidence for the structures of compounds **2–4** is provided by analytical and spectral data. The main characteristic features of the ^{1}H NMR and ^{13}C NMR spectrum

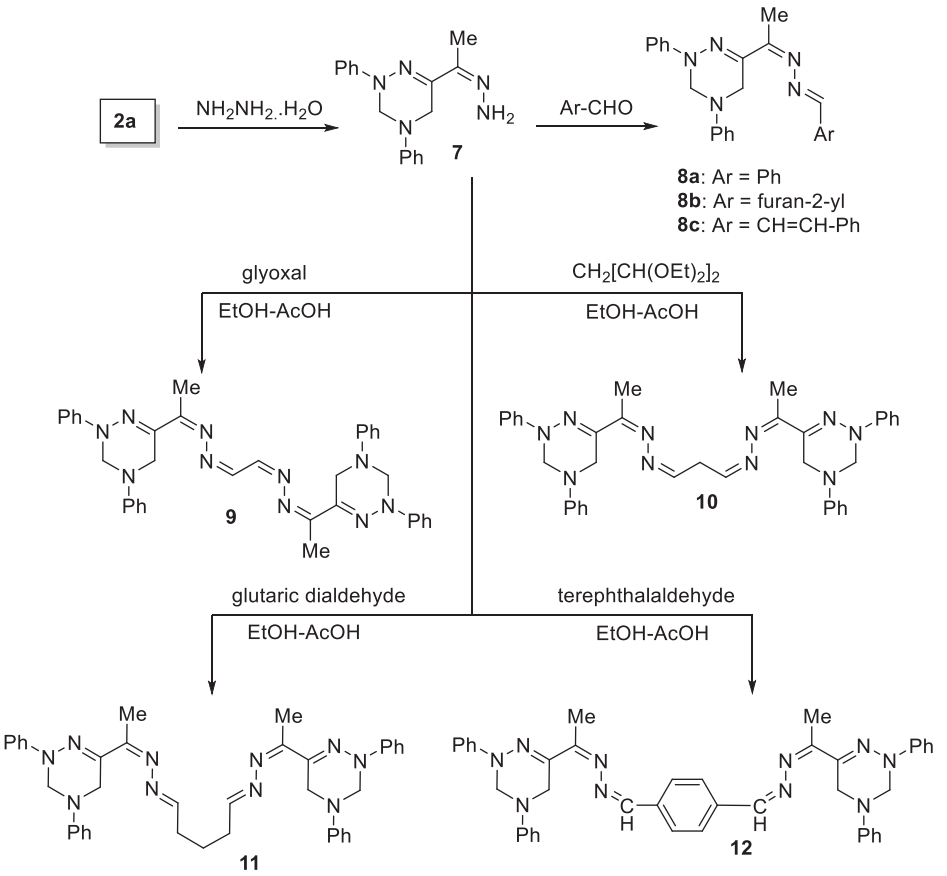
of these compounds are the presence of signals assignable to (3-H_2) and (5-H_2) of triazine moiety. The structure of **2d**, as an example, was elucidated by its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum assigned in addition to representative signals at δ 6.94–7.42 ppm for 9 Ar-H and –NH protons, four singlet signals at δ 2.16, 2.46, 4.26 and 5.07 ppm characteristic for two methyl and two methylene groups, respectively. Furthermore, the ^{13}C NMR spectrum showed signals for two methyl groups at 23.6 and 24.3 ppm, while the methylene groups of the triazine ring appeared at 45.7 and 62.2 ppm.

This reaction was developed by treating **1a** or **1b** with formaldehyde and *p*-phenylenediamine in molar ratio (2:4:1) to afford the 4,4′-*p*-phenylenebis-(6-acetyl-2-aryl-2,3,4,5-tetrahydro-1,2,4-triazines) (**3a** and **3b**), respectively (Scheme 1). A similar reaction of **1a** or **1b** with ethylenediamine and formaldehyde gave 1,2-bis(6-acetyl-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-4-yl)ethane (**4a**) and the 2-(*p*-tolyl) analogue (**4b**), respectively. Confirmatory evidence for the structures of compounds **3** and **4** is provided by analytical and spectral data. For example, the ^{1}H NMR spectrum of compound **4a** exhibited four singlets at 2.43, 2.71, 3.65 and 4.58 ppm assignable to CH_3 and CH_2 protons. The ^{13}C NMR spectrum also confirmed the structure of **4a** through the appearance of signals at 23.5, 46.06, 51.4 and 64.6 ppm related to CH_3 and CH_2 carbons.

On the other hand, the synthesis of 6-cinnamoyl-2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (**5a**) and its derivatives **5b–c**, has been achieved by the base catalyzed condensation of **2a** with appropriate aromatic aldehyde (Scheme 1). The formation of the chalcone type compounds **5a–c**, incorporating tetrahydro-1,2,4-triazine moiety, is of biological interest because a variety of chalcones have been reported to exhibit multifarious pharmacological effects, including antibacterial,[32,33] anti-tumor,[34–36] antifungal,[37] and anti-inflammatory.[38–40] In addition, compounds **5a–c** are used as precursors for the synthesis of the pyrazoline/tetrahydro-1,2,4-triazine hybrids **6a–c**, by treating with hydrazine hydrate. The analytical and spectral data of compounds **5a–c** and **6a–c** are consistent with their structures. For example, the IR spectra of the pyrazoline derivatives **6a–c** exhibited disappearance of the carbonyl (C=O) peak at 1650 cm^{-1} and appearance of –NH stretching vibration in the region of 3307 cm^{-1} revealed the formation of pyrazolines. In the ^{1}H NMR spectrum of **6b**, the 4-H_a, 4-H_b and 5-H protons of the pyrazoline ring exhibited doublets of doublets at δ 3.060–3.124 ppm, 4-H_a, δ 3.46–3.53 ppm, 4-H_b and δ 4.85–4.89 ppm, 5-H, respectively. Additionally, the ^{13}C NMR of compound **6b** showed signals at 39.9, 61.6 and 148.4 distinguishing for C4, C5 and C=N of the pyrazoline ring, along with signals at 21.1, 46.6 and 63.4 for CH_3- and two methylene groups of triazine ring.

The condensation of **2a** with hydrazine hydrate afforded 6-(1-hydrazonoethyl)-2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (**7**)[41] which reacts with the appropriate aromatic aldehyde namely, benzaldehyde, furfural, and cinnamaldehyde, in refluxing ethanol, to afford, in each case, a sole product, identified as mixed unsymmetrical azines **8a–c** as depicted in (Scheme 2).

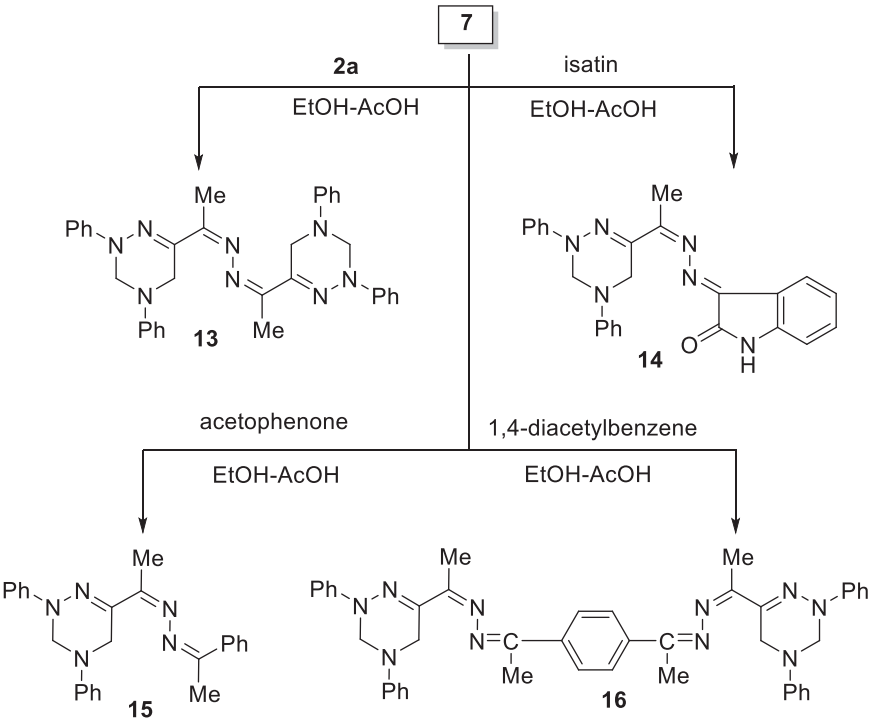
Elemental analyses and spectral data (FT-IR, ^{1}H and MS) confirmed the structure of the products. The FT-IR spectrum of azine **8c**, as a representative example, showed strong absorption bands at 1625 and 1593 cm^{-1} due to C=N and C=C functions, respectively. Its ^{1}H-NMR spectrum revealed, in addition to expected aromatic signals, three singlet signals at δ 2.41, 4.51, 5.13 ppm assignable to the protons of methyl and



Scheme 2. Synthesis of mixed azines **8a–c** and bis(azines) **9–12**.

two methylene groups of triazine ring, respectively. In addition, the mass spectrum of **8c** revealed a molecular ion peak at *m/z* 407 (M^+) corresponding to a molecular formula ($C_{26}H_{25}N_5$)

In addition, the reaction of the hydrazone **7** with the appropriate dialdehyde, could be valuable in the synthesis of mixed *bis*(azines) incorporating two tetrahydro-1,2,4-triazine moieties. In view of this, **7** was treated with glyoxal, malonaldehyde diethyl acetal, and glutaric dialdehyde to give 1,2-*bis*((1-(2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)ethylidene)hydrazono)ethane (**9**), 1,3-*bis*((1-(2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)ethylidene)hydrazono)propane (**10**) and 1,5-*bis*((1-(2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)ethylidene)hydrazono)pentane (**11**), respectively. A similar reaction of **7** with terephthaldehyde afforded the mixed *bis*(azine) **12**. The structures of the synthesized compounds were elucidated by spectral data. In the ^{1}H NMR spectra of the symmetrical *bis*-azine **9**, the protons of two methylene groups give singlet signals at δ 4.52, 5.12 ppm assignable to the protons of four methylene groups. Furthermore, a singlet signal at 2.23 ppm for CH_3 protons and the chemical shift observed at 8.18 ppm as a singlet is assigned to the protons of the imine group (CH = N). The ^{1}H NMR spectral data of the new *bis*-azine **9** was also supported by its ^{13}C-NMR spectrum.



Scheme 3. Synthesis of the azines **13–16**.

The chemical shift observed at 12.2, 46.4, 61.8 and 158.0 ppm are attributed to methyl, methylene groups of triazine moiety and the imine carbons respectively.

On the other hand, the synthesis of the symmetrical *bis*(azine) **13** has been achieved by the reaction of **7** with **2a**. Compound **13** was identified by analytical and spectral data. Its ^{1}H-NMR spectrum showed, in addition to expected aromatic signals, three singlet signals at δ 2.20, 4.54, 5.13 ppm assignable to the protons of methyl and two methylene groups of triazine ring, respectively. In addition, its ^{13}C NMR spectrum displayed two characteristic peaks for two imine carbons at δ 157.5 ppm (Scheme 3).

In connection with this study, treatment of the hydrazone **7** with ketones, namely isatin, acetophenone and 1,4-diacetylbenzene led to the formation of the mixed azines **14**, **15** and **16**, respectively (Scheme 3). The mass spectra of the latter products showed, in each case, the molecular ion peak. The ^{1}H NMR spectrum of the symmetrical azine **16** revealed four singlet signals at δ 2.27, 2.37, 4.55, and 5.13 ppm characteristic for four methyl and four methylene groups.

Biological activity

Most of the newly synthesized tetrahydro-1,2,4-triazine derivatives were subjected to biological screening. The results shown in Tables 1–3 indicate that most of the newly synthesized tetrahydro-1,2,4-triazine derivatives revealed excellent to good activities as, antibacterial, antifungal and antioxidant activities compared with Ampicillin, Colitrimazole and (*L*)-Ascorbic acid as references.

Table 1. Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* bacteria.

	Diameter of inhibition zone (mm)		% Activity index	
Compound number	*E. coli* (mg/mL)	*S. aureus* (mg/mL)	*E. coli* (mg/mL)	*S. aureus* (mg/mL)
2b	20	23	76.9	95.8
2c	10	18	38.5	75.0
2d	9	15	34.6	62.5
2e	13	17	50.0	70.8
2f	9	14	34.6	58.3
3a	18	21	69.2	87.5
3b	11	17	42.3	70.8
4a	6	10	23.1	41.7
4b	7	11	26.9	45.8
7	14	20	53.8	83.3
8a	4	9	15.4	37.5
8b	NA	2	—	8.3
8c	NA	NA	—	—
9	2	4	7.7	16.7
10	2	5	7.7	20.8
11	8	13	30.8	54.2
12	4	7	15.4	29.2
13	NA	2	—	8.3
15	NA	2	—	8.3
16	3	6	11.5	25.0
Ampicillin	26	24	100	100

Antimicrobial activity

The results shown in Table 1 indicate that most of the synthesized compounds have low activities against the standard chemotherapeutics, whereas compound **2b** exhibited good activities against *Escherichia coli*, compounds **2e**, **3a**, and **7** showed moderate activities against *Escherichia coli*. Furthermore, compounds **2b**, **3a**, and **7** exhibited excellent activities against *Staphylococcus aureus*, compounds **2c**, **2e**, and **3b** showed good activities against *Staphylococcus aureus*.

On the other hand, from the results indicated in Table 2, compounds **2b**, **3a**, and **7** showed excellent activities against fungi *Candida albicans*. Whereas, compounds **2c**, **2d**, **2e**, **3b**, and **11** exhibited good activity against *Candida albicans* Therefore, the presence of tetrahydro-1,2,4-triazine moiety in the synthesized compounds possess a good activity against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*.

Antioxidant screening for [ABTS]

Most of the synthesized triazines are tested as antioxidant agents. As shown in Table 3, most of these compounds showed different antioxidant activity. Although Compounds **2b** and **3a** and **7** exhibited excellent antioxidant activity, other tested compounds showed moderate antioxidant activity

Conclusion

In the present work, various derivatives of tetrahydro-1,2,4-triazines, 6-cinnamoyl-2,4-diaryl-tetrahydro-1,2,4-triazines and mixed azines were synthesized. All the newly

Table 2. Antifungal activity against *Candida albicans* fungi.

Compound number	Diameter of inhibition zone (mm)	% Activity index
2b	25	92.6
2c	21	77.8
2d	15	55.5
2e	16	59.2
2f	12	44.4
3a	23	85.2
3b	16	59.2
4a	9	33.3
4b	10	37.0
7	24	88.9
8a	7	25.9
8b	NA	—
8c	NA	—
9	3	11.1
10	4	14.8
11	14	51.8
12	6	22.2
13	NA	—
15	2	7.4
16	5	18.5
Clotrimazole	27	100

Table 3. Antioxidant activity by ABTS method.

Compounds	Samples absorbance	% inhibition
ABTS control	0.520	0
Ascorbic-acid	0.060	88.3%
2b	0.061	87.9%
2c	0.270	46.5%
2d	0.317	37.2%
2e	0.295	41.6%
2f	0.325	35.6%
3a	0.071	85.9%
3b	0.315	37.6%
4a	0.351	30.5%
4b	0.350	30.7%
7	0.068	86.5%
8a	0.359	28.9%
8b	0.383	24.1%
8c	0.392	22.4%
9	0.376	25.5%
10	0.370	26.7%
11	0.321	36.4%
12	0.360	28.7%
13	0.390	22.8%
15	0.382	24.3%
16	0.364	27.9%

synthesized products were screened against antimicrobial and antioxidant activities, compounds **2b**, **3a**, and **7** have the highest activity.

Experimental

All melting points were measured on a Gallenkamp electric melting point apparatus (Sanyo Gallenkamp, Southborough, UK) and were uncorrected. Elemental microanalyses were carried out on a Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany)

at the Microanalytical Unit, Al-Azhar University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer (Mattson Instruments, Inc., Madison, WI, USA). The ^{1}H NMR data were obtained in $CDCl_3$ solution on a Varian XL 400 MHz instrument (Varian, Inc., CA, USA) and a Jeol Resonance apparatus (500 MHz), using TMS as internal standard. Chemical shifts are reported in ppm (δ) downfield from internal TMS. The ^{13}C NMR data were obtained in $CDCl_3$ solution on a Jeol Resonance apparatus (125 MHz), using TMS as internal standard. Chemical shifts are reported in ppm (δ). The mass spectra were recorded on a GC-MS QP–1000 EX Shimadzu instrument (Shimadzu, Tokyo, Japan). The course of the reaction and the purity of the synthesized compounds were monitored by TLC using EM science silica gel coated plates, 0.25 nm, 60 GF 254 (Merck, Darmstadt, Germany) with visualization by irradiation with an ultraviolet lamp.

Synthesis of 6-acetyl-2,4-diaryl-2,3,4,5-tetrahydro-1,2,4-triazines (2a–2e)

General procedure

A mixture of pyruvaldehyde phenylhydrazone (**1a**) (0.53 g, 3.3 mmol), the appropriate primary aromatic amine (3.3 mmol) and formalin 37% (0.54 mL, 6.6 mmol) in ethanol (20 mL) was refluxed on water bath for 2 h. The product obtained by cooling filtered and crystallized from ethanol to give compounds **2a–e**.

6-Acetyl-2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (2a). Yield 60%, (yellow needles), mp 119–121 °C (119–121 °C[31]). ^{1}H NMR ($CDCl_3$): $\delta = 2.21$ (s, 3H, CH_3), 4.51 (s, 2H, N-CH_2-C), 5.11 (s, 2H, N-CH_2-N), 6.95–7.42 ppm (m, 10H, Ar-*H*)

6-Acetyl-4-(4-hydroxyphenyl)-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine (2b). Yield 73%, (yellow needles), mp 180–182 °C; IR (KBr): $\nu = 3473$ (OH), 1651 (C=O), 1575, 1507, 1272, 1308, 1201, 817, 753, 692, 558 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.44$ (s, 3H, CH_3), 4.17 (s, 2H, N-CH_2-C), 4.99 (s, 2H, N-CH_2-N), 6.72–7.41 ppm (m, 9H, Ar-*H* and O*H*); MS (EI, 70 eV): *m/z* (%) = 297 (1) $[M+2]^+$, 296 (2) $[M+1]^+$, 295 (5) $[M]^+$, 294 (36) $[M-1]^+$, 283 (56), 218 (1) [M – Ph]$^+$, 97 (21), 85 (21), 83 (31), 82 (39), 81 (21), 77 (100) [Ph]$^+$, 76 (59), 70 (44), 69 (43), 57 (35), 55 (50). *Anal.* Calcd for $C_{17}H_{17}N_3O_2$ (295.34): Calcd C 69.14, H 5.80, N 14.23. Found C 69.28, H 5.98, N 14.30.

6-Acetyl-4-(p-tolyl)-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine (2c). Yield 60%, (yellow peels), mp 122–123 °C; IR (KBr): $\nu = 1654$ (C = O), 1597, 1552, 1503, 1263, 1138, 881, 752, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.29$ (s, 3H, COCH_3), 2.47 (s, 3H, Ar-CH_3), 4.26 (s, 2H, N-CH_2-C), 5.06 (s, 2H, N-CH_2-N), 6.88–7.45 ppm (m, 9H, Ar-*H*); MS (EI, 70 eV): *m/z* (%) = 294 (7) $[M+1]^+$, 293 (21) $[M]^+$, 288 (100), 283 (47), 278 (30) [M – Me]$^+$, 264 (49), 216 (6) [M – Ph], 104 (73), 77 (9) [Ph]$^+$, 51 (22). *Anal.* Calcd for $C_{18}H_{19}N_3O$ (293.37): Calcd C 73.69, H 6.53, N 14.32. Found C 73.52, H 6.35, N 14.30.

Microbiological procedure for the activity study

Antimicrobial the antibacterial activity of the synthesized compounds was tested against gram-positive bacteria (*Staphylococcus aureus*) and gram-negative bacteria (*Escherichia*

coli). The antifungal activity of the compounds was tested against one fungus (*Candida albicans*). A solution of each compound in DMSO with concentration 1 mg/mL was prepared and a solution separately paper disks of Whatman filter paper were prepared with standard size (5 cm) were cut and sterilized in an autoclave. The paper disks soaked in the desired concentration of the complex solution were placed aseptically in the petri dishes containing nutrient agar media (agar 20 g + beef extract 3 g + peptone 5 g) seeded with *Staphylococcus aureus, E. coli and Candida albicans.* The petri dishes were incubated at 36 °C and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic ampicillin and antifungal colitrimazole was also recorded using the same procedure as above at the same concentration and solvents. The % activity index for the compound was calculated by the formula as under:

$$\%\text{Activity Index} = \text{Zone of inhibition by test compound (diameter)}/\text{Zone of inhibition by stander (diameter)}.$$

Antioxidant screening using 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS). The antioxidant screening of the examined compounds was determined in vitro using the technique prescribed in the literature.[42] The inhibition for each derivative was calculated using the following mathematical equation.

$$\%\text{Inhibition} = [\text{Abs (control)} - \text{Abs (test)}/\text{Abs (control)}] \times 100$$

Full experimental details and spectroscopic data ^{1}H NMR for compounds **2b–2f–16**, ^{13}C NMR for compounds **2d, 4a, 6b, 6c, 9** and **13** can be found *via* the Supplementary Content section of this article's Web page.

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