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Synthesis of new annulated pyridazine derivatives and studying their antioxidant and antimicrobial activities

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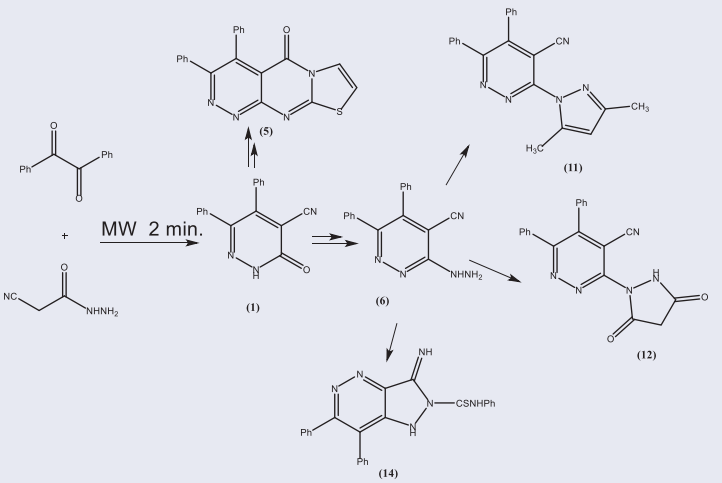
ABSTRACT

Benzil was reacted with cyanoacetohydrazide under microwave irradiation to give 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonitrile **1** which used as starting material for the synthesis of new heterocyclic compounds. Chlorination of pyridazinone **1** with $POCl_3$ afforded the chloro-pyridazine derivative **3**, which then condensed with 2-aminothiazole or hydrazine hydrate to produce 3,4-diphenyl-5H-thiazolo[3′,2′:1,2]pyrimido[4,5-c]pyridazin-5-one **5** or 3-hydrazinyl-5,6-diphenylpyridazine-4-carbonitrile **6**, respectively. *New* Schiff bases were obtained by condensation reactions of compound **6** with different aldehydes. On the other hand, compound **6** reacted with different carbon electrophiles naming acetyl acetone, diethyl malonate, and phenyl isothiocyanate producing *new* pyarazolo-pyridazine derivatives **11**, **12**, and **14**, respectively. Chemical structures of all newly synthesized compounds were confirmed on the basis of spectral data and had been screened for antimicrobial and antioxidant activity.

GRAPHICAL ABSTRACT



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Introduction

Pyridazine derivatives attract considerable research due to their structures stability and pharmacological activities.[1,2] Many of pyridazine derivatives possess analgesics, insecticidal,[3] fungicidal,[4,5] cardiotonic,[6] and bactericidal[7] activities. Also, other five-membered heterocyclic compounds such as pyrazole, triazole, tetrazole, and thiodiazole have been used in medicinal chemistry[8–10] due to their important biological activities. Such as anti-inflammatory,[11,12] antifungal,[13] herbicidal,[14] insecticidal,[15] antitumor, anti-HCV,[16] and antiviral activities.[17]

Pyrazole is a very important constituent in drug development. Over the years, growing interest has been paid to pyrazole derivatives due to their importance in agrochemical, pharmaceutical, and chemical industries.[18,19] Pyrazole derivatives showing significant bioactivities[19,20] such as anti-inflammatory,[21] anticonvulsant,[22] anticancer,[23] and antifungal behavior.[24]

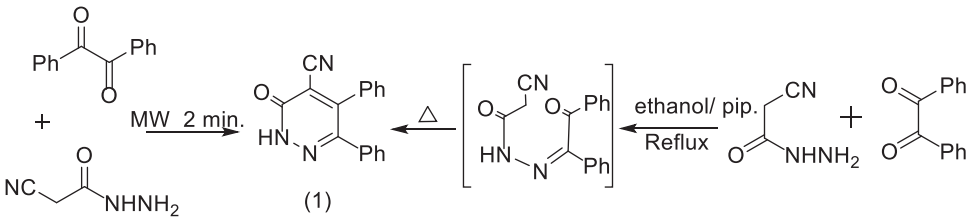
On the basis of this view, our work was aimed to synthesis some new heterocyclic system annulated with pyridazine ring as a central moiety to improve their biological activity.

Results and discussion

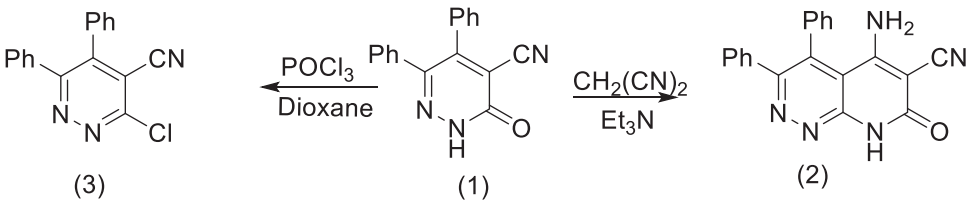
Chemistry

Green synthesis of 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonitrile (**1**) was achieved by reacting equimolar amounts of benzil and cyanoacetohydrazide under microwave irradiation for 2 min. It was found to be identical in all respects with which prepared under conventional thermal method.[25] However, the microwave irradiation method gave better yield and needs short reaction time (Scheme 1).

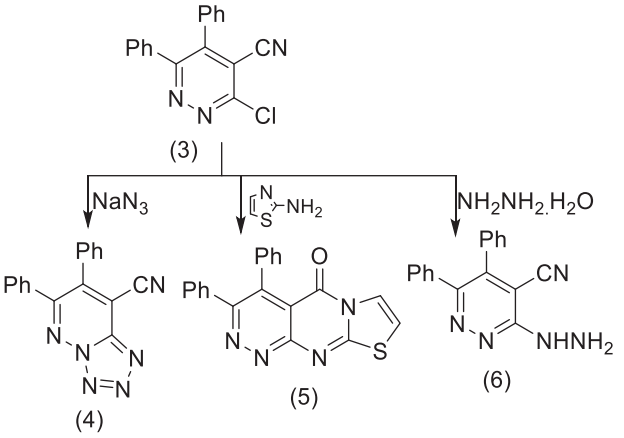
Refluxing of the pyridazinone **1** with malononitrile in ethanol and in the presence of tri-ethylamine as a base gave 5-amino-7-oxo-3,4-diphenyl-7,8-dihydropyrido[2,3-c]pyridazine-6-carbonitrile (**2**) (cf. Scheme 2).



Scheme 1. Synthesis of pyridazin-6-one **1** using microwave irradiation or conventional thermal reflux.



Scheme 2. Reactions of pyridazinone **1** with malononitrile or $POCl_3$.



Scheme 3. Reaction of chloropyridazine **3** with different N-nucleophile.

The structure of compound **2** was evidenced from its spectral data. The IR spectrum showed absorptions characteristic for NH, CN, and C=O groups.

^{1}H NMR spectrum exhibited two broad singlet signals attributable to protons of NH and NH_2 groups as well as multiplet signals for aromatic protons. Further evidence was gained from its mass spectrum that revealed its molecular ion peak together with some important peaks (cf. "Experimental" section).

On the other hand, treatment of compound **1** with $POCl_3$ in refluxed dioxane produced 3,4-diphenyl-5-cyano-6-chloro-pyridazine (**3**).[26] The IR spectrum of compound **3** was devoid of any absorption for carbonyl group but it showed a band for CN group (cf. Scheme 2).

Chloropyridazine **3** was utilized as synthons for some annulated systems by reacting with some nitrogen nucleophiles.

Heating of chloropyridazine **3** with sodium azide afforded the fused tetrazolo-pyridazine derivative **4** (cf. Scheme 3).

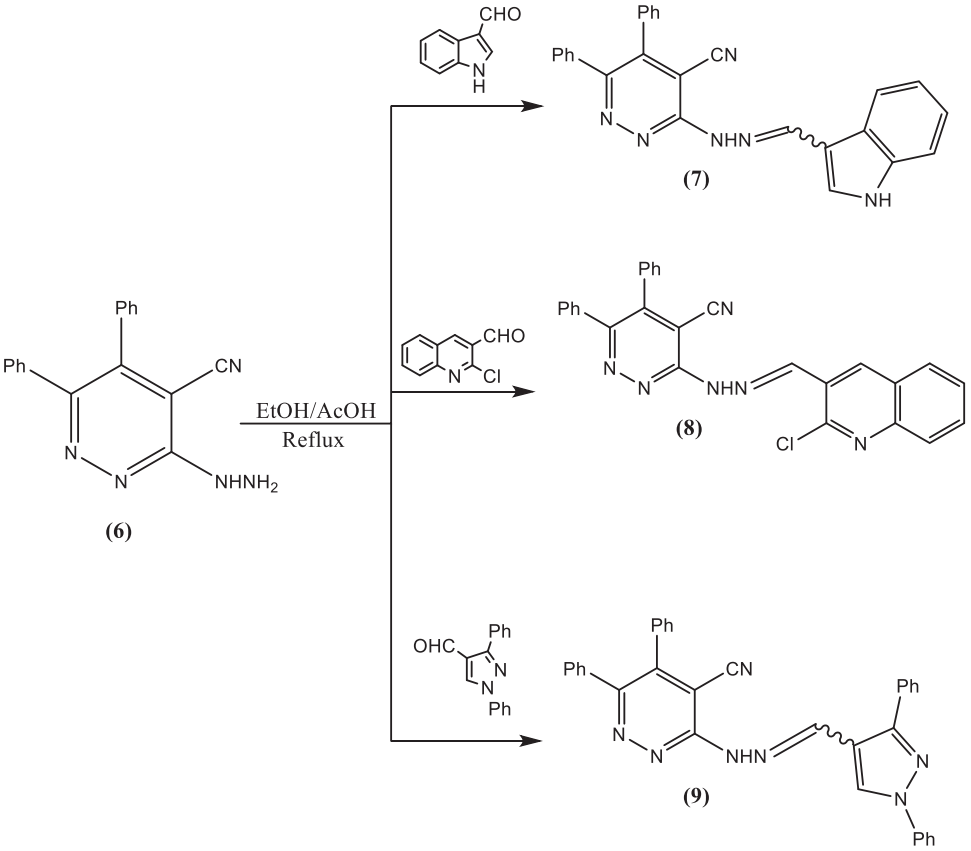
The structure of **4** was substantiated from its IR spectrum that exhibited absorption bands corresponding to C=N, N=N and CN groups. Further proof for the assigned structure of compound **4** was achieved from its mass spectrum, which revealed the correct molecular ion peak and some of the abundant peaks (cf. "Experimental" section).

Refluxing of compound **3** with 2-aminothiazole in *n*-butanol yielded 3,4-diphenyl-5H-thiazolo[3′,2′:1,2]pyrimido[4,5-c]pyridazin-5-one (**5**). The absence of any absorption corresponding to CN group in its IR spectrum was in accordance with the complete cyclization which afforded the three-fused heterocyclic ring (cf. Scheme 3). Moreover, its ^{1}H NMR spectrum was in a good agreement with proposed structure, where it was devoid of any signals for NH protons in the downfield region. Further proof for the assigned structure of compound (**5**) is gained from its mass spectrum (cf. "Experimental" section).

On the other hand, treatment of chloropyridazine **3** with hydrazine hydrate in refluxing ethanol furnished 3-hydrazinyl-5,6-diphenylpyridazine-4-carbonitrile (**6**).

The structure of compound **6** was inferred from its IR spectrum that showed absorptions characteristic for NH, NH_2, and CN groups.

^{1}H NMR spectrum was in accordance with the proposed structure as it displayed two broad singlet signals for NH and NH_2 protons which were exchanged on deuteration.



Scheme 4. Synthesis of some new Schiff bases from hydrazinyl-pyridazine 6.

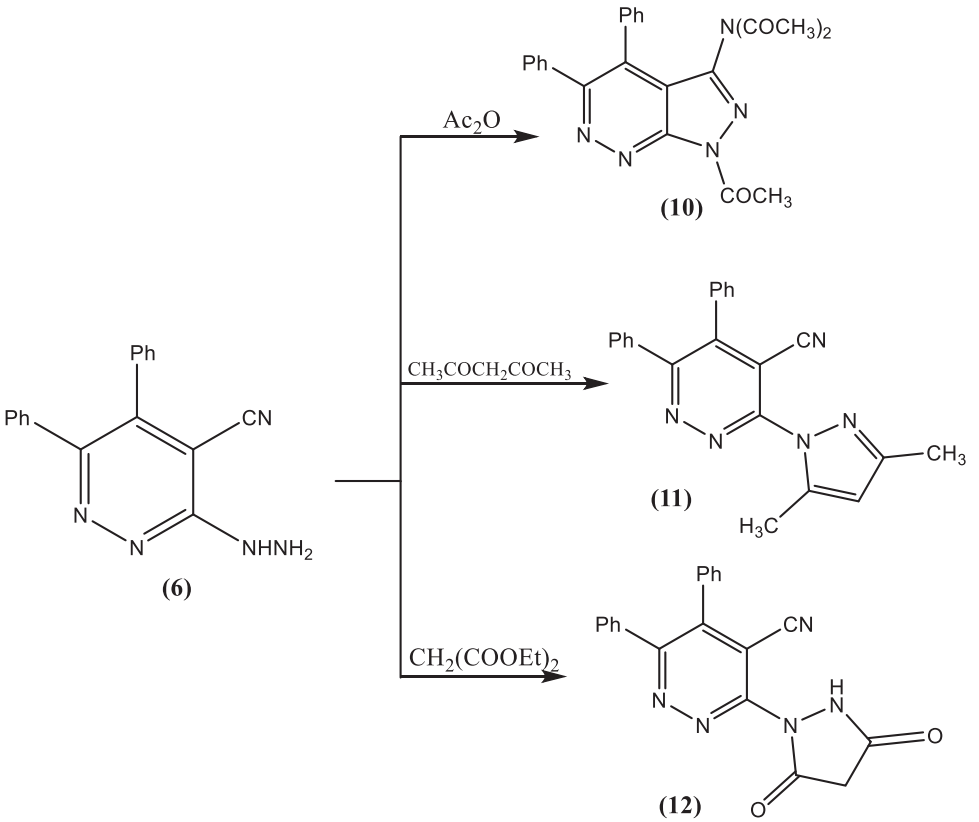
Further evidence was gained from its EIMS spectrum as it showed the correct molecular ion peak and some other important peaks (cf. "Experimental" section).

Treatment of hydrazinyl-pyridazine **6** with different heterocyclic aldehydes namely indole-3-carbaldehyde, 2-chloro-quinoline-3-carboxaldehyde and 1,3-diphenyl pyrazole-4-carbaldehyde in refluxing ethanol and few drops of acetic acid glacial afforded new Schiff base compounds **7**, **8**, and **9**, respectively (cf. Scheme 4).

IR spectra of compounds **7–9** showed absorption bands correlated to NH, C=N, and CN groups. Further support for the assigned structures was gained from ^{1}H NMR spectra which exhibited extra exchangeable broad singlet signals for NH protons in compounds **7**, **9** as well as the imino methine CH=N protons that suggest their existence as mixtures of Syn/Anti stereoisomers in equal ratio.

Mass spectra of compounds **7–9** supported the suggested structures as they displayed the molecular ion peaks and other some important peaks (cf. "Experimental" section).

Heating of the hydrazinyl derivative **6** with acetic anhydride yielded the fused pyrazolo-pyridazine derivative **10** (cf. Scheme 5). The structure of compound **10** was established from its spectral data. Its IR spectrum revealed strong absorption bands at 1747, 1732 cm^{-1} characteristic for the coupling pattern for the carbonyl groups. The ^{1}H NMR spectrum didn't show any signals corresponding to NH protons, instead, it showed three singlet signals for CH_3 groups.



Scheme 5. Reactions of hydrazinyl derivative 6 with different carbon electrophiles.

The suggested structure got further support from its mass spectrum as it revealed its molecular ion peak and other important peaks (cf. "Experimental" section).

Further synthesis of new heterocyclic compounds was achieved by the reactions of hydrazinyl derivative **6** with different carbon electrophiles such as acetyl acetone or diethyl malonate (cf. Scheme 5).

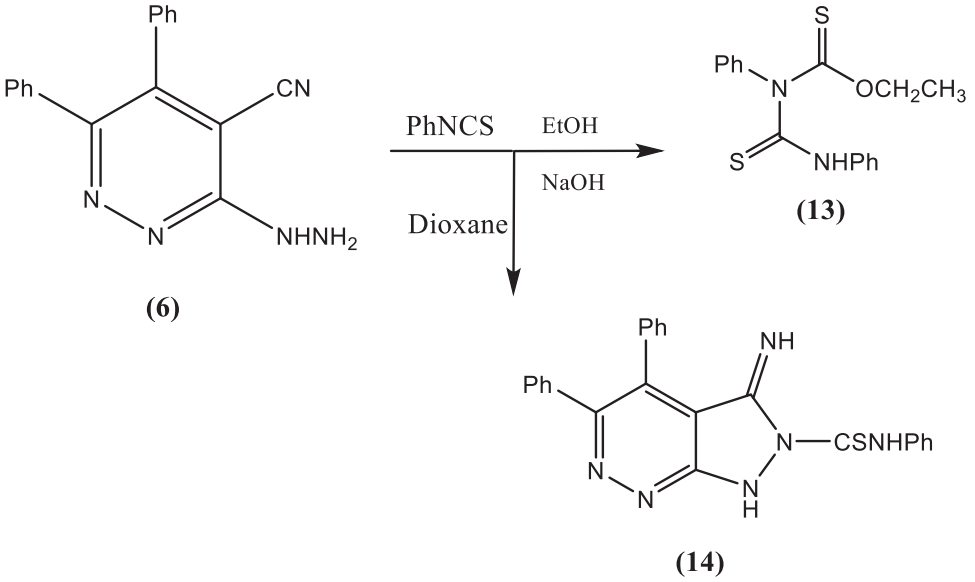
Refluxing an ethanolic solution of compound **6** with acetyl acetone in the presence of few drops of glacial acetic acid gave the pyrazolyl pyridazine derivative **11** (cf. Scheme 5).

The structure of compound **11** was established from its spectral data. Its IR spectrum was devoid from any absorptions characteristic for NH groups, but it showed bands for CN and C = N groups. Moreover, the ^{1}H NMR spectrum revealed two singlet signals for protons of two CH_3 groups, as well as multiplet signals correlated to the aromatic and CH = protons(cf. "Experimental" section).

Mass spectrum of compound **11** showed its molecular ion peak and other abundant peaks corresponding with its structure.

Heating equimolar amounts of compound **6** and diethyl malonate in refluxing dioxane afforded 3-(3,5-dioxopyrazolidin-1-yl)-5,6-diphenylpyridazine-4-carbonitrile (**12**) in a good yield.

Infrared spectrum of compound **12** exhibited absorption bands correlated to CN, NH, and CO groups. Further support for the structure of compound **12** was gained



Scheme 6. Reaction of hydrazinyl derivative **6** with phenylisothiocyanate in different media

from its ^{1}H NMR spectrum which showed one singlet signal for protons of CH_2 group and another broad singlet in the downfield region for NH proton which collapsed rapidly on deuteration. Moreover, EIMS spectrum of compound **12** displayed the correct molecular ion peak together with some abundant peaks (cf. "Experimental" section).

Further synthesis was achieved by reacting of the hydrazinyl derivative **6** with phenyl isothiocyanate in refluxing ethanol and a catalytic amount of sodium hydroxide that furnished the carbamothioate derivative **13**. However, on doing the same reaction in refluxing dioxane, it gave the fused pyrazolopyridazine derivative **14** (cf. Scheme 7).

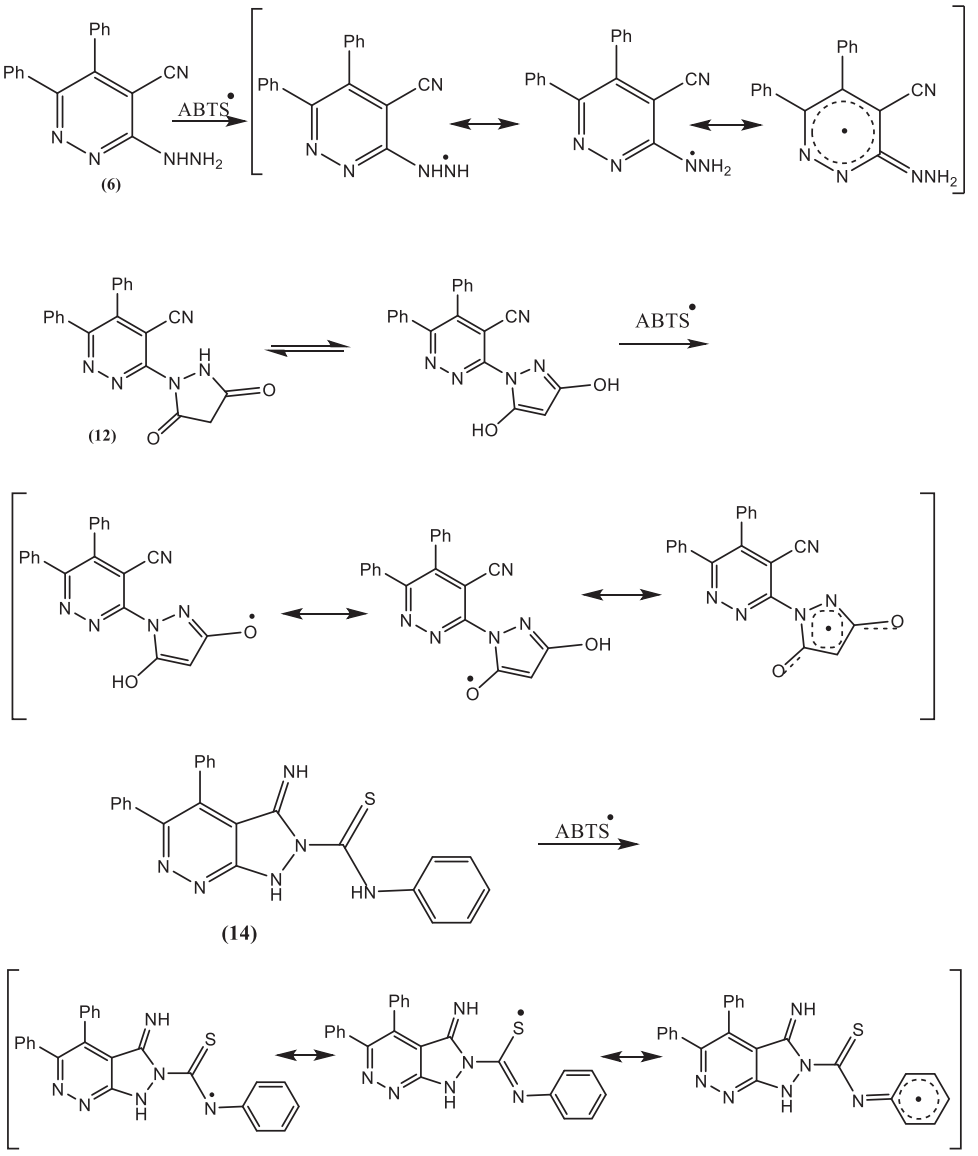
The structures of compounds **13** and **14** were evidenced by studying their analytical as well as spectral data. Their IR spectra showed bands for NH and C=S groups. Moreover, their ^{1}H NMR spectra were in accordance with the suggested structures (cf. "Experimental" section). Their EIMS spectra supported their structures as they displayed their correct molecular ion peaks beside other important peaks (cf. "Experimental" section).

It is observed that the hydrazinyl pyridazine **6** has no role in the formation of compound **13**, however, phenylisothiocyanate underwent dimerization followed by concurrent ring opening by one molecule of ethanol (Scheme 6).

Pharmacology

Anti-microbial activity

The newly synthesized compounds were evaluated for antimicrobial activity against gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*). The anti-fungal activities of the new compounds were tested against (*Candida albicans*).



Scheme 7. The proposed mechanism for the reactivity of compounds **6**, **12**, and **14** towards ABTS radical.

All compounds dissolved in DMSO (1 mg/ml), paper discs of Whatman filter paper were prepared with standard size (5 cm), cut and sterilized in an autoclave. The paper discs 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 *S. aureus*, *E. coli*, and *C. albicans*. The petri dishes were incubated at 36 °C and the inhibition zones were recorded after 24 h of incubation.[27]

Each treatment was replicated three times. The antibacterial activity of a common standard Ciprofloxacin as high antibiotic drugs and antifungal Clotrimazole was also recorded using the same procedure as above at the same concentration and solvents.

Table 1. Diameter of inhibition zone (mm) and percentage activity index results for the newly synthesized compounds as antibacterial and antifungal activity.

		E. coli (mg/ml)		*S. aureus* (mg/ml)		*C. albicans* (mg/ml)	
No.	Compound	Diameter of inhibition zone (mm)	Percentage activity index	Diameter of inhibition zone (mm)	Percentage activity index	Diameter of inhibition zone (mm)	Percentage activity index
1	**2**	NA	–	8	33.3	10	37.0
2	**4**	NA	–	NA	–	3	11.1
3	**5**	2	7.7	7	29.2	7	25.9
4	**6**	12	46.1	19	79.2	17	63.0
5	**7**	7	26.9	13	54.2	12	44.4
6	**8**	5	19.2	10	41.7	8	29.6
7	**9**	9	34.6	16	66.7	14	51.8
8	**10**	4	15.4	5	20.8	5	18.5
–	**11**	NA	–	NA	–	NA	–
10	**12**	10	38.5	18	75.0	17	63.0
11	**14**	7	26.9	11	45.8	15	55.5
Ciprofloxacin		26	100	24	100	NA	–
Colitrimazole		NA	–	NA	–	27	100

The percentage activity index for the complex was calculated by the formula:

$$\text{Percentage activity index} = \frac{\text{zone of inhibition by test compound (diameter)}}{\text{zone of inhibition by standard (diameter)}} \times 100$$

The result of the study showed that compounds **6**, **9**, and **12** have highest activity against bacteria and fungi. Compounds **7** and **8** exhibit moderate activity against gram-negative bacteria and fungi, and low activity against gram-positive activity. Compound **14** has high activity against fungi and moderate antibacterial activity. Compound **2** has no activity against gram-positive bacteria. However it exhibits moderate activity against fungi and gram-negative bacteria. Compounds **4**, **5**, and **10** showed low antimicrobial activity (cf. Table 1).

Antioxidant activity

Antioxidant chemical compounds have significant importance for inhibition of oxidation process for therapeutic process "in activating the immune response, in preventing the clotting of blood vessels, and in many other metabolic processes."[28–30]

Antioxidant activity can be detected by different mechanisms, such as hydrogen atom transfer (HAT), single electron transfer (ET), or others.

In our present work, the newly synthesized compounds were tested as antioxidant activity by using the ABTS method.[31] The results of the study showed that compounds **6**, **7**, **9**, **12**, and **14** exhibit high antioxidant activity comparable with the standard antioxidant Ascorbic acid. Compounds **2** and **8** have moderate activity, while compounds **3**, **5**, **10**, and **11** have low antioxidant activity (cf. Table 2 and Figure 1).

Structure-activity relationship (SAR)

The results obtained from antimicrobial and antioxidant activity of the newly prepared heterocyclic compounds can explicate the *structure-activity relationships* as follow:

Table 2. Antioxidant activity using ABTS method for the newly synthesized compounds.

No.	Method Compounds	ABTS Abs (control) − Abs (test)/Abs (control) × 100	
		Absorbance of samples	% inhibition
	Control of ABTS	0.518	0
*	**Ascorbic acid**	0.058	88.8
1	**2**	0.316	39.0
2	**4**	0.384	25.9
3	**5**	0.353	31.8
4	**6**	0.201	61.2
5	**7**	0.250	51.7
6	**8**	0.328	36.7
7	**9**	0.232	55.2
8	**10**	0.372	28.2
9	**11**	0.407	21.4
10	**12**	0.193	62.7
11	**14**	0.229	55.8

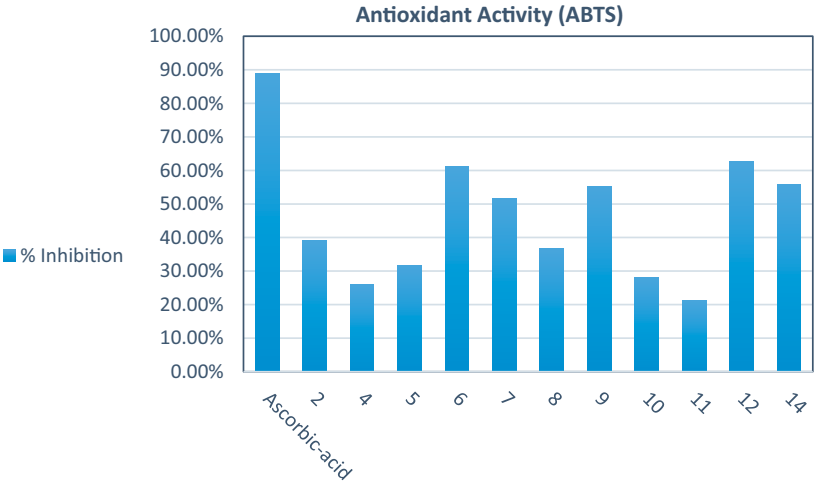


Figure 1. Antioxidant activity (% inhibition) for tested compound against standard ascorbic acid.

- The basic moiety of pyridazine responsible for the broad activity against different bacteria and fungi.
- Hydrazinyl derivative **6** is the most potent active compound as antimicrobial due to the presence of free amino group with high electron density that increases the reactivity towards the enzyme.
- The presence of hydrazinyl, dioxypyrazolidine, and thioamide moieties, in compounds **6**, **12**, and **14**, respectively revealed their highest antioxidant activity that detects the stabilization of free radicals of nitrogen or oxygen atoms as shown in (Scheme 7).
- The prepared Schiff base **9** showed the highest antimicrobial and antioxidant activity comparable to the other two Schiff bases **7** and **8**. This result affirms that the pyrazole moiety is more active than quinolone and indole rings.

Conclusion

New pyridazine, fused pyridazine, and Schiff bases were synthesized starting from benzil and cyanoacetohydrazide under green chemistry using microwave irradiation. Most of

the new compounds possess significant biological activity when tested as antimicrobial and antioxidant.

Experimental

All melting points are uncorrected and were measured on a Gallenkamp electric melting point apparatus. The IR spectra were recorded using potassium bromide disks on an FTIR Thermo Electron Nicolet 7600 (USA) IR spectrometer at the Central Laboratory of Faculty of Science, Ain Shams University. ^{1}H NMR spectra were run at 300 MHz on a GEMINI 300 BB NMR spectrometer using tetramethylsilane as internal standard in deuterated dimethyl sulfoxide (DMSO-d_6) at Faculty of Pharmacy, Ain Shams University. The mass spectra were recorded on Shimadzu GCMSQP 1000EX mass spectrometer operating at 70 eV and the elemental analyses at the Micro Analytical Center of Al-Azhar University. TLC was performed on Merck Kiesel gel 60 F254 aluminum-backed plates. The spots were detected by UV irradiation at 254–365 nm.

3-Oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonitrile (1)

Method [A]: Microwave radiation

Equimolar amounts of benzil and cyanoacetohydrazide in ethanol and drops of piperidine were irradiated in microwave oven for 2 min. The reaction mixture was cooled at room temperature and then treated with water. The solid product formed was filtered off, dried and recrystallized from ethanol to give compound (**1**) (Yield: 94%).

Method [B]: Thermal reflux

A mixture of benzil (0.01 mol) and cyanoacetohydrazide (0.01 mol) in boiling ethanol (20 ml) and drops of piperidine was refluxed for 3 h, the solvent was distilled off and then poured onto water and HCl. The solid formed was filtered off and recrystallized from ethanol (Yield: 85%); off-white crystals; m.p. 264–266 °C (lit. m.p. 260–261 °C) [25]; IR (KBr) (υ, cm^{-1}): 3194 (NH), 3064 (CH_{arom}), 2230 (CN), 1665 (CO).

5-Amino-7-oxo-3, 4-diphenyl-7,8-dihydropyrido [2, 3-c] pyridazine-6-carbonitrile (2)

A mixture of pyridazinone **1** (0.01 mol) and malononitrile (0.01 mol) was refluxed in boiling ethanol (25 ml) and drops of trimethylamine for 6 h. The solid product formed while cooling at room temperature was filtered off and recrystallized from ethanol to give compound **2** (Yield 71%); brown crystals; m.p. 240–242 °C; IR (KBr) (υ, cm^{-1}): 3333 (NH), 3245, 3194 (NH_2), 3063 (CH_{arom}), 2215 (CN), 1659 (CO); ^{1}H NMR (DMSO-d_6) δ: 4.10 (br.s, 2H, NH_2, exchangeable), 7.08–7.48 (m, 10H, ArH), 14.00 (br.s, 1H, NH, exchangeable); MS (70 eV) m/z (%): 339 (M^+, 6), 323 (3), 315 (4), 296 (4), 273 (68), 262 (4), 245 (12), 94 (16), 77 (36).

Anal. calcd. for $C_{20}H_{13}N_5O$ (339.11): C, 70.79; H, 3.86; N, 20.64. Found: C, 70.48; H, 4.06; N, 20.28.

3-Chloro-5,6-diphenylpyridazine-4-carbonitrile (3)

A mixture of pyridazinone **1** (0.5 g) and phosphurs oxychloride (10 ml) in dioxane (20 ml) was heated under reflux for 8 h. The reaction mixture cooled at room temperature and poured gradually onto ice/water. The solid formed was filtered off and recrystallized from diluted ethanol to give compound **3** (Yield 59%); off-white crystals; m.p. 195–196 °C (lit. m.p. 201 °C).[25]

Full experimental detail, ^{1}H NMR spectra, Mass, IR and elemental analysis. This material can be found via the "Supplementary Content" section of this article's webpage.

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