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# Eco-friendly and Regiospecific synthesis of Novel (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide Derivatives

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**Abstract**: The Ultrasonic (US) technique is used in the present work as an eco-friendly method for the synthesis of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide derivatives. A simple and efficient method has been described for the alkylation of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**). Besides the IR and NMR spectra, the regioselectivity of the *N*-alkylation is chemically achieved. Furthermore, fusion of sodium salt of **1** with ethyl bromide in DMF as solvent using ultrasound irradiation as a source of power afforded (1,3-diethyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**9**).
**Keywords:** Ultrasonic technique, Eco-friendly, Cyanoguanidinophenytoin, Regioselectivity, Alkylation.

## 1. Introduction

Nowadays, there is mounting interest in the development of clean technologies to replace conventional methods involving reducing pollution, waste-to-energy, long reaction times, and tedious purification steps. This greener method, such as the ultrasound technique, is crucial to reduce the negative impact of traditional methods [1, 2]. Applying the ultrasound (US) technique reduces the reaction time and unwanted side reactions while improving the product yield. Hence, the ultrasound technique is a green chemistry technique that is quicker and healthier than traditional methods. On the other hand, imidazoles have the greatest interest in studying their biological and pharmacological activities, such as; anti-malarial [3], anti-cancer [4], anti-microbial [5, 6], antiepileptic [7] anti-tubercular [8], anti-viral [9], anti-diabetic [10], anti-histaminic [11, 12], and anti-parasitic [13, 14]. Nowadays, many imidazoles are used as drugs in the treatment of various cancer diseases, such as dacarbazine, zoledronic acid, mercaptopurine, azathioprine, and nilotinib [15], (**Fig. 1**).

From all mentioned above and in continuation of our previous works [16 - 29], the present work was concerned with the preparation of a novel series of (*N*-alkylated-4,4-diphenylimidazolidin-2-ylidene)cyanamide and its Mannich base derivatives using the ultrasonic technique as an eco-friendly method. For these purposes, we used (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) (*see* **Scheme 1**) as the starting material, which was previously prepared as described in the reported procedure [30].

## 2. Results and discussion

The Ultrasonic (US) technique is used in the present work as an eco-friendly method for the synthesis of (4,4-diphenylimidazolidin-2-ylidene)cyanamide derivatives. A simple and efficient method has been described for the alkylation of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**). Thus, the reaction of its sodium salt with alkyl halides in DMF using ultrasound irradiation as a source of power was studied (Method A). The outputs of (1-alkyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamides **2-5** were obtained in about three hours of irradiation (**Scheme 1**), and the results are summarized in **Table 1**.

Excellent yields of products **2-5** were obtained (85–90%), and troubles due to energy consumption and toxic solvents were averted. Also, the same products **2-5** were obtained in good yields using the traditional method under reflux conditions (75–83%) (Method B). From **Table 1**, it is intelligible that using the US method is an effective and spotless method that is outstanding to the conventional method and gives products with excellent yields in a lower time.

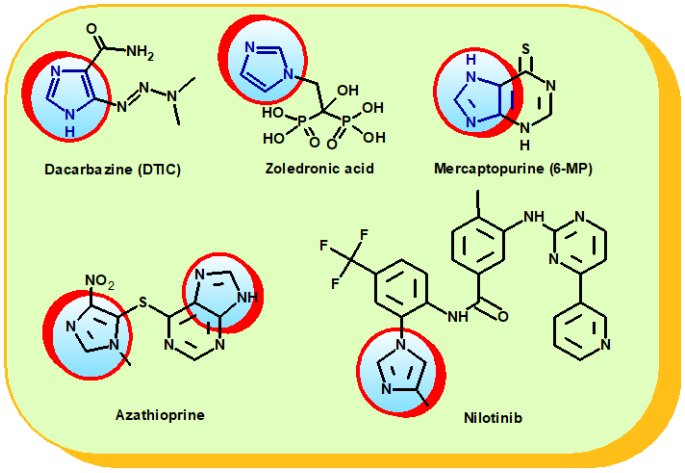
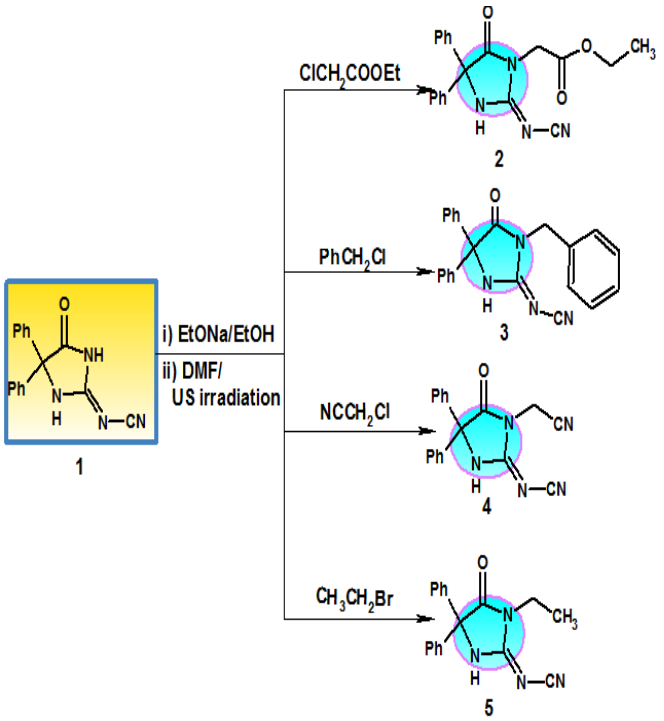
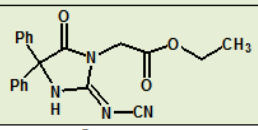
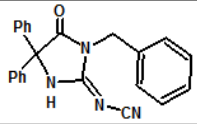
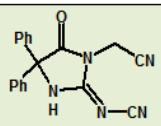
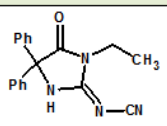



**Fig. 1**: Chemical structures of some imidazole-based anticancer marketing drugs.



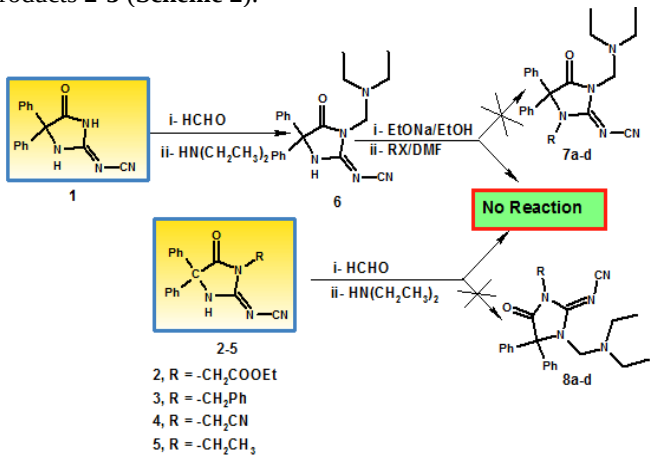

**Scheme 1:** *N*-Alkylation of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide **1**.

**Table 1**: Reaction times and yields of products **2-5** under US and traditional conditions.

| product | Chemical Structure | US irradiation | | Conventional method | |
|---|---|---|---|---|---|
| | | Method A | | Method B | |
| | | Reaction Time (h) | Yield (%) | Reaction Time (h) | Yield (%) |
| 2 |  | 2:75 | 84 | 7 | |
| 3 |  | 3 | 83 | 7 | |
| 4 |  | 2:66 | 85 | 7 | |
| 5 |  | 2:50 | 90 | 6 | |

The chemical structures of the newly formed *N*-alkylation products **2-5** were confirmed by their spectral IR, $^{1}$H, $^{13}$C NMR, DEPT-135, and elemental analyses. The IR spectrum of compound **2** displayed bands at 3274 cm$^{-1}$ for the NH group, 3074, 3027 cm$^{-1}$ for CH-from., 2982, 2918, 2848 cm$^{-1}$ for CH-aliph., 2199 cm$^{-1}$ for cyano group, and 1745 cm$^{-1}$ for carbonyl group. Its $^{1}$H-NMR spectrum showed the following signals: triplet and quartet signals at $\delta$ 1.17-1.21 and 4.15-4.21 ppm are represented to methyl and methylene protons, respectively, with coupling constant $J$ = 7 Hz; two singlet signals at $\delta$ 4.40 and 11.44 ppm correspond to protons of *N*-$CH_2$ and NH groups, respectively; while protons of the two symmetrical phenyl groups are represented as multiplet signals in the aromatic region at $\delta$ 7.37-7.49 ppm. Its $^{13}$C NMR spectrum showed the appearance of seven signals at $\delta$ 127.5, 129.2, 129.3, 138.2, 159.4, 167.1, and 173.1 ppm assigned to $sp^2$-carbons; a signal at $\delta$ 114.7 ppm is due to *sp*-carbon of cyano group; and three signals at $\delta$ 14.3, 41.1, and 62.1 ppm assigned to carbons of methyl, *N*-$CH_2$, and *O*-$CH_2$ groups, respectively; while a signal of quaternary $sp^3$-carbon appears at $\delta$ 72.2 ppm (disappeared with *DEPT-135*).

From previous results, it turns out that there is regioselectivity for the *N*-alkylation reaction of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) at NH-1 instead of NH-3. Besides the IR and NMR spectra, the regioselectivity of the *N*-alkylation is chemically achieved. Mannich reaction involves the imino alkylation of an NH proton next to a carbonyl (C=O) or thioxo (C=S) groups using formaldehyde with primary and/or secondary amines as reagents. Thus, here in this work, we prepared Mannich base **6** *via* the reaction of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) with formaldehyde and diethyl amine, but all our attempts for the alkylation of Mannich base **6** by different alkyl halides namely: ethyl chloroacetate, chloroacetonitrile, or ethyl bromide were failed. Also, all our attempts at applying a Mannich reaction to products **2-5** failed, i.e., the alkylation took place at the NH-1, and hence they can't undergo a Mannich reaction on the NH-3, **Scheme 2**. All these results confirm the regiospecific *N*-alkylation of the starting compound (**1**) and the chemical structures of products **2-5** (**Scheme 2**).

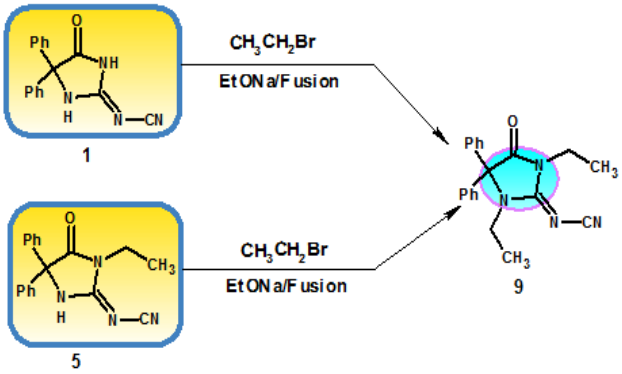



**Scheme 2:** Confirmation of the regiospecific of *N*-alkylation of imidazole **1**.

Furthermore, fusion of sodium salt of imidazole **1** with ethyl bromide in a few mL of DMF using ultrasound irradiation as a source of power afforded (1,3-diethyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**9**) (**Scheme 3**). The same product **9** was also synthesized in a conservative yield *via* fusion of (1-ethyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**5**) with ethyl bromide in the same condition (**Scheme 3**).

The chemical structure of compound **9** was proven by its

spectral IR, $^{1}H$, $^{13}C$, HMBC NMR, and elemental analyses. Its IR spectrum showed characteristic absorption bands at 3061, 3028 $cm^{-1}$ (CH-arom.); 2973, 2934, and 2904 $cm^{-1}$ (CH-aliph.); 2190 $cm^{-1}$ (C≡N); and 1751 $cm^{-1}$ (C=O) $cm^{-1}$. Its $^{1}H$-NMR spectrum showed two signals at $\delta$ 0.49 and 1.17 ppm representing two $CH_3$ protons; a singlet signal at 3.76 ppm representing for two $CH_2$ protons; and multiple signal at $\delta$ 7.27-7.50 ppm corresponding to ten aromatic protons. Its $^{13}C$ NMR spectrum showed the presence of eight signals at $\delta$ 127.3, 128.6, 129.1, 129.6, 129.9, 136.1, 155.1, and 172.9 ppm assigned to $sp^2$–aromatic, C=O and C=N carbons; signal at $\delta$ 114.2 ppm due to *sp*-carbon of cyano group; and two signals at $\delta$ 13.7 and 14.5 ppm assigned to carbons of two methyl groups; two signals at $\delta$ 35.9 and 38.7 ppm assigned to carbons of two methylene groups, while a signal of quaternary $sp^3$–carbon at position C-4 appeared at $\delta$ 76.5 ppm.




**Scheme 3:** Green synthesis of (1,3-diethyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (9).

## 3. Conclusion

Concisely, we used a simple eco-friendly, and efficient method for alkylation of starting compound **1** *via* the reaction of compound **1** with different alkyl halides. Besides the IR and NMR spectra, the regioselectivity of the *N*-alkylation is chemically achieved. Furthermore, fusion of sodium salt of compound **1** with ethyl bromide in a few mL of DMF using ultrasound irradiation as a source of power afforded (1,3-die thyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**9**).

## 4. Experimental

### 4.1. General procedure for the synthesis of compounds 2-5

#### 4.1.1. Method A (ultrasonic irradiation):

A mixture of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) **[30]** (0.01 mol, 2.76 g), alkyl halide (0.01 mol), and EtONa (0.02 mol) was dissolved in 10 mL DMF in a closed vessel and exposed to US irradiation for about 3 hours at 50 °C in a sonicator. After completion of the reaction (monitored with TLC), the reaction mixture was then cooled to room temperature and poured into cold water. The formed precipitate was collected by filtration, washed with distilled water, dried, and recrystallized from ethanol.

#### 4.1.2. Method B (Conventional method)

A mixture of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) [30] (0.01 mol, 2.76 g) and an appropriate alkyl halide (0.01 mol), namely: ethyl chloroacetate (1.22 g), benzyl chloride (1.26 g), 2-chloroacetonitrile (0.76 g), and bromoethane (1.09 g) was refluxed in DMF in the presence of EtONa for about 3 hrs. After completion of the reaction (monitored with TLC), the reaction mixture was then cooled to room temperature and poured into cold water. The formed precipitate was collected by filtration, washed with distilled water, dried, and recrystallized from ethanol.

**Ethyl [(2-(cyanoimino)-5-oxo-4,4-diphenylimidazolidin-1-yl]acetate (2)**

M.p. 228-230 °C; FT-IR $\upsilon_{max}$ 3274 (NH), 3027 ($CH_{arom.}$), 2982, 2918, 2848 ($CH_{aliph.}$), 2199 (C≡N), 1745 (C=O) $cm^{-1}$; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.17-1.21 (t, $J$ = 7 Hz, 3H, $CH_3$), 4.15-4.21 (q, $J$ = 7 Hz, 2H, $CH_2$), 4.40 (s, 2H, $CH_2$), 7.37-7.49 (m, 10H, $CH_{arom.}$), 11.44 (s, 1H, NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 14.3 (unchangeable with DEPT-135), 41.1(exchangeable with DEPT-135), 62.1 (exchangeable with DEPT-135), 72.2, 114.7, 127.5, 129.2, 129.3, 138.2, 159.4, 167.1, 173.1 ppm; Anal. Calcd./Found for $C_{20}H_{18}N_4O_3$ (362.39): C, 66.29/ 66.35; H, 5.01/5.15; N, 15.46/15.38.

***N*-(1-Benzyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (3)**

M.p. 195-197°C; FT-IR $\upsilon_{max}$ 3669 (NH), 3092 ($CH_{arom.}$), 2903 ($CH_{aliph.}$), 2198 (C≡N), 1745 (C=O) $cm^{-1}$; $^{1}H$ NMR (400 MHz, DMSO-$d_6$):$\delta$ 4.77 (s, 2H, $CH_2$), 7.25-7.44 (m, 15H, $CH_{arom.}$), 11.41 (s, 1H, NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 43.3 (exchangeable with DEPT-135), 71.9, 114.9, 127.3, 127.8, 128.3, 129.2, 135.9, 138.4, 159.9, 173.3 ppm. Anal. Calcd./Found for $C_{23}H_{18}N_4O$ (366.42): C, 75.39/ 75.45; H, 4.95/4.74; N, 15.29/15.43 %.

***N*-[1-(Cyanomethyl)-5-oxo-4,4-diphenylimidazolidin-2-ylidene]cyanamide (4)**

M.p. 230-232°C; FT-IR $\upsilon_{max}$ 3412 (NH), 3023 ($CH_{arom.}$), 2897 ($CH_{aliph.}$), 2206 (C≡N), 1770 (C=O) $cm^{-1}$; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): δ 4.77 (s, 2H, $CH_2$), 7.34-7.49 (m, 10H, $CH_{arom.}$), 11.73 (s, 1H, NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 28.2 (exchangeable with DEPT-135), 72.3, 114.3, 115.1, 127.4, 129.3, 129.4, 137.9, 158.2, 172.1 ppm. Anal. Calcd./Found for $C_{18}H_{13}N_5O$ (315.34): C, 68.56/68.66; H, 4.16/4.07; N, 22.21/22.32 %.

***N*-(1-Ethyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (5)**

M.p. 220°C. FT-IR $\upsilon_{max}$ 3372 (NH), 3047 ($CH_{arom.}$), 2987, 2969, 2903, ($CH_{aliph.}$), 2194 (C≡N), 1757 (C=O) $cm^{-1}$; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.14-1.15 (t, $J$ = 6 Hz, 3H, $CH_3$), 3.58- 3.60 (q, $J$ = 6. Hz, 2H, $CH_2$), 7.33-7.45 (m, 10H, $CH_{arom.}$), 11.26 (s, 1H, NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 13.2, 35.2, 71.7, 115.1, 127.4, 129.2, 138.5, 159.9, 173.2 ppm. Anal. Calcd/Found. for $C_{18}H_{16}N_4O$ (304.35): C, 71.04/71.21; H, 5.30/5.55; N, 18.41/18.72 %.

### 4.2. Synthesis of *N*-(1-((diethylamino)methyl)-5-oxo-4,4-

**diphenylimidazolidin-2-ylidene)cyanamide (6):**

A solution of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) (0.01 mol, 2.76 g) and formaldehyde (0.2 mL, 0.03 mol) was stirred in 40 mL EtOH for 40 min, then the diethylamine (0.01 mol, 0.73 g) was added, and the reaction mixture was stirred for 2h. The separated solid was filtered and crystallized from ethanol. Yield 83 %, m.p: 290 °C. FT-IR $\upsilon_{max}$ 3171 (NH), 3029 ($CH_{arom.}$), 2938, 2863 ($CH_{aliph.}$), 2178 (C≡N), 1705 (C=O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.16 (m, 6H, $2CH_3$), 2.94 (m, 4H, $2CH_2$), 4.13 (br.s, 2H, $CH_2$), 7.36-7.24 (m, 10H, $CH_{arom.}$), 8.83 (br. s, 1H, NH) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 186.15, 175.36, 142.39, 128.38, 127.45, 127.25, 120.34, 73.10, 41.83 (exchangeable with DEPT-135), 11.48 ppm (unchangeable with DEPT-135). Anal. Calcd/Found. for $C_{21}H_{23}N_5O$ (361.44): C, 69.78/69.59; H, 6.4/6.371; N, 19.38/19.41 %.

### 4.3. Synthesis of *N*-(1,3-diethyl-5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (9)

#### 4.3.1. Method A

A mixture of (5-oxo-4,4-diphenylimidazolidin-2-ylidene)cyanamide (**1**) (0.01 mol, 2.76 g), bromoethane (10 mL), and sodium ethoxide (0.025 mol, 1.7 g), and 5 mL DMF was placed in a closed vessel and exposed to US irradiation for 5 hrs at 50 °C in a sonicator. After completion of the reaction (monitored with TLC), the reaction mixture was then cooled to room temperature and poured into cold water. The formed precipitate was collected by filtration, washed with distilled water, dried, and recrystallized from ethanol.

#### 4.3.2. Method B

A mixture of *N*-[1-(cyanomethyl)-5-oxo-4,4-diphenylimidazolidin-2-ylidene]cyanamide (**4**) (0.01 mol, 3.15 g), bromoethane (7 mL), and sodium ethoxide (0.025 mol, 1.7 g), and 5 ml DMF was placed in a closed vessel and exposed to US irradiation for 5 hrs at 50 °C in a sonicator. After completion of the reaction (monitored with TLC), the reaction mixture was then cooled to room temperature and poured into cold water. The formed precipitate was collected by filtration, washed with distilled water, dried, and recrystallized from ethanol.

Yield (59% **method A**, 64% **method B**), m.p: 128-130 °C. FT-IR $\upsilon_{max}$ 3061 ($CH_{arom.}$), 2973, 2934, 2904 ($CH_{aliph.}$), 2190 (C≡N), 1751 (C=O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.49 (2, 3H, $CH_3$), 1.17 (s, 3H, $CH_3$), 3.74-3.76 (d, $J$ = 5.0 Hz, 4H, $2CH_2$), 7.27-7.50 (m, 10H, $CH_{arom.}$) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 13.7, 14.4, 35.9, 38.7, 76.5, 114.2, 127.3, 128.6, 129.1, 129.6, 129.9, 136.1, 155.1, 172.9 ppm. Anal. Calcd./Found for $C_{20}H_{20}N_4O$ (332.41): C, 72.27/72.37; H, 6.06/5.97; N, 16.86/16.91 %.

## CRediT authorship contribution statement:

"Conceptualization, Amr H. Moustafa and Amer A. Amer; methodology, Doaa H. Ahmed; software, Amr H. Moustafa; validation, Amr H. Moustafa, Amer A. Amer and Doaa H. Ahmed; formal analysis, Doaa H. Ahmed; investigation, Amr H. Moustafa and Amer A. Amer; resources, Doaa H. Ahmed; Amr H. Moustafa; writing—original draft preparation, Amer A. Amer; writing—review and editing, Amr H. Moustafa; visualization, Amer A. Amer; supervision, Amr H. Moustafa; project administration, Amer A. Amer; funding acquisition, Doaa H. Ahmed. All authors have read and agreed to the published version of the manuscript."

## Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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