Synthesis and Antimicrobial Activity of 1,3,4-Oxadiazole-2(3H)-thione and Azidomethanone Derivatives Based on Quinoline-4-carbohydrazide Derivatives

Mansoura I. Mohamed,* Nadia G. Kandile, and Howida T. Zaky

Department of Chemistry, Faculty of Women, Ain Shams University, Heliopolis, 11757 Cairo, Egypt
*E-mail: mansouraismail@yahoo.com
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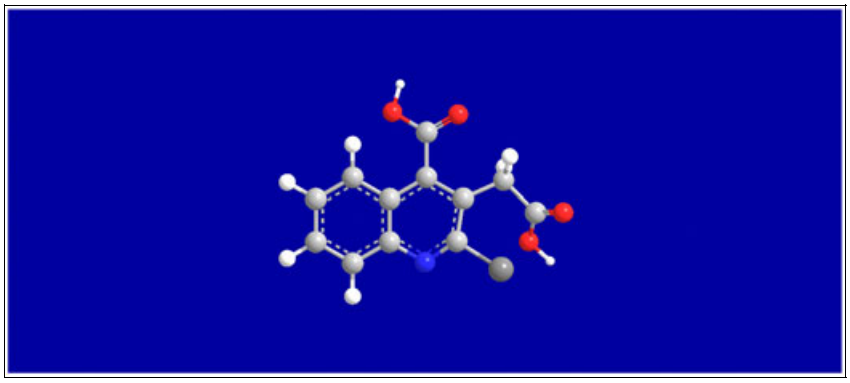

A new series compounds of quinoline derivatives were synthesized by reaction of 3-(carboxymethyl)-2-arylquinoline-4-carboxylic acids **1a–c** with different nucleophiles. The structures of the new compounds were elucidated on the basis of FTIR, ^{1}H-NMR, ^{13}C-NMR spectral data, GC/MS, and chemical analysis. Investigation of antimicrobial activity of all new compounds was evaluated using a broth dilution technique in terms of minimal inhibitory concentration count against four pathogenic bacteria and two pathogenic fungi. Most of the new compounds were significantly active against bacteria and fungi.

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INTRODUCTION

The quinoline nucleus is an important heterocyclic structure found in many synthetic and natural occurring products with a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, anti-obesity, and anti-inflammatory [1–8], which can be well illustrated by the large number of commercially available drugs containing the quinoline nucleus.

Recently, a number of new quinoline derivatives with excellent antitumor activity have been reported [9–21]. Among them, 6,7-disubstituted-4-phenoxyquinoline derivatives, which inhibit c-Met kinase, have attracted our attention.

In particular, the acridine family includes derivatives of many pharmacologically significant compounds such as actinomycin-D, daunomycin, adriamycin, and some of which show the significant bioactivity of inhibiting topoisomerase enzyme [22–24]. As one type of acridine compound, the 6,7-dihydrodibenzo*[b,j]* phenanthroline derivatives may be of interesting biomedical use. The Pfitzinger reaction [25,26] is probably a shortcut to obtain these derivatives, yet there are few successful examples synthesized using 1,3-diketones and isatins via this reaction up to date, during our investigation of synthetic methodologies [27–29].

Quinoline derivatives are versatile biodynamic agents both from synthetic and natural origin. Rebamipide (2-(4-chlorobenzoylamino)-3-[2-(1H)-quinolinon-4-yl] propionic acid) (1, Fig. 1) is a quinoline-derived compound acting as efficient anti-gastric ulcer agent, the protective effect of rebamipide is not only because of stimulating endogenous prostaglandin in gastric mucosa but also because of inhibiting oxygen-derived free radicals production. The quinoline derivative 4-(arylamino)quinoline (2, Fig. 1) inhibited the gastric (Hþ/Kþ)-ATPase, the enzyme responsible for the secretion of acid into the gastric lumen. Consequently, several research groups have synthesized quinoline-based derivatives [including AU-461 (3, Fig. 1) and AS-2646] as potential anti-ulcer agents [30].

The Pfitzinger reaction of isatins with α-methylidene carbonyl compounds is used widely for the synthesis of physiologically active derivatives of substituted quinoline-4-carboxylic acids [25,26,31–34]. Herein, we report a simple one-pot synthesis of quinoline-4-carboxylic acid derivatives by an improved Pfitzinger reaction of isatins with β-aroylpropionic acid and catalysts in aqueous medium [35].

RESULTS AND DISCUSSION

The synthesis of the target compounds was carried out as outlined in Schemes 1 and 2. The versatile Pfitzinger

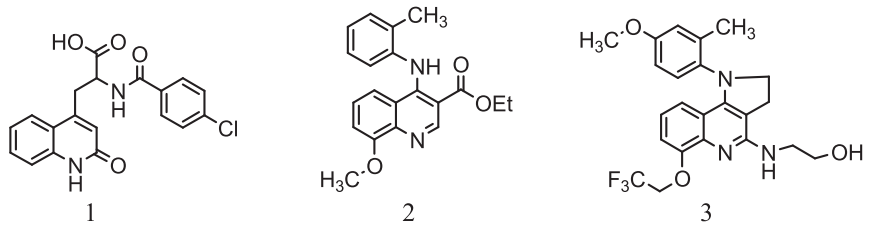
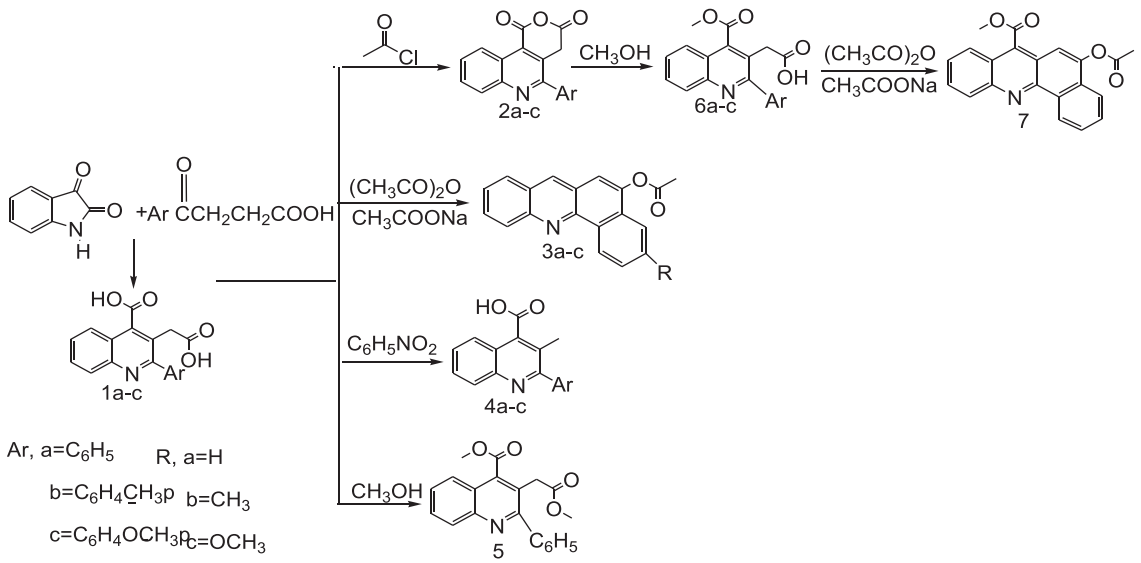
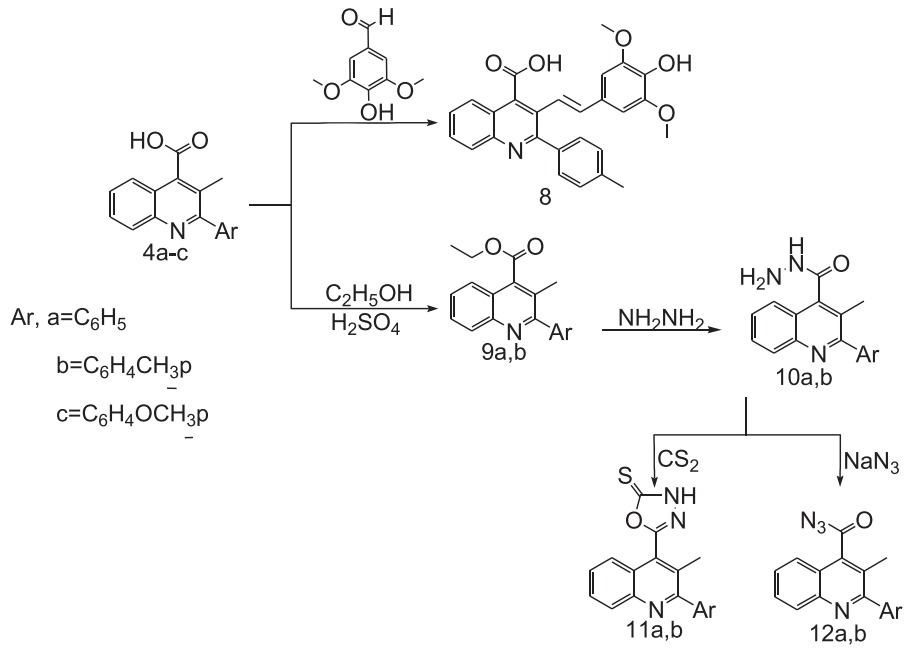


Figure 1. Quinoline derivatives showing anti-ulcer activity.

Scheme 1



Scheme 2



reaction [25,35] was utilized to synthesize the 3-(carboxymethyl)-2-arylquinoline-4-carboxylic acids **1a–c** by reaction of isatin (indolin-2,3-dione) with β-aroylpropionic acids under basic conditions as described in Scheme 1.

Treatment of compounds **1a–c** with different nucleophilic reagents such as acetyl chloride and methyl alcohol afforded 3-(carboxymethyl)-2-arylquinoline-4-carboxylic acid anhydrides **2a–c** and half esters 2-[(4-methoxycarbonyl)-2-arylquinolin-3-yl] acetic acids **6a–c**, respectively. These structures were established by FTIR, ^{1}H-NMR, ^{13}C-NMR, mass spectral, and analytical data. The ^{1}H-NMR spectrum of compound 2[(4-methoxycarbonyl)-2-(4-methylphenyl) quinolin-3-yl] acetic acid **6b** showed bands at δ 11.12 (s, 1H, OH of COOH), 8.95–7.15 (m, 8H, 2Ar-H), 3.88 (s, 3H, $COOCH_3$), 3.49 (s, 2H, CH_2 of CH_2COOH), and 2.35 (s, 3H, CH_3 of CH_3-Ar) ppm. The ^{13}C-NMR spectrum of compound **6b** showed bands at δ 174.3, 166.2, 166.0, 151.4, 145.6, 136.3, 133.4, 129.3, 129.2, 128.7, 127.6, 127.4, 125.9, 123.8, 51.5, 35.2.

Cyclization of 2-[(4-methoxycarbonyl)-2-phenylquinolin-3-yl] acetic acid **6a** with fused sodium acetate in the presence of acetic anhydride gave 5-acetoxymethylbenzo [c] acridine-7-carboxylic acid **7**. However, 3-(carboxymethyl)-2-arylquinoline-4-carboxylic acids **1a–c** were reacted with fused sodium acetate in the presence of acetic anhydride and yielded 3-alkylbenzo[c]acridin-5-yl acetates **3a–c**. These structures were confirmed by FTIR, ^{1}H-NMR, mass spectral, and analytical data. The ^{1}H-NMR spectrum of compound 3-methoxybenzo[c]acridin-5-yl acetate **3c** showed bands at δ 7.82–7.12 (m, 8H, 3Ar-H), 5.78 (s, 1H, CH), 3.73 (s, 3H, OCH_3 of CH_3O-Ar), and 2.08 (s, 3H, CH_3 of $COCH_3$) ppm. Accordingly, the products 3-methyl-2-arylquinoline-4-carboxylic acids **4a–c** were obtained by the reaction of **1a–c** with nitrobenzene. Moreover, the reaction of **1a** with methyl alcohol (2 mole) gave the corresponding methyl-3-(2-methoxy-2-oxoethyl)-2- phenylquinoline-4-carboxylate **5**. This structure was assigned by FTIR, ^{1}H-NMR, mass spectral, and analytical data. ^{1}H-NMR spectrum of compound **5** showed bands at δ 7.86–7.11 (m, 9H, 2Ar-H), 3.88 (s, 3H, CH_3 of $COOCH_3$), 3.79 (s, 2H, CH_2 of CH_2COOCH_3), and 3.27 (s, 3H, CH_3 of CH_2COOCH_3) ppm as described in Scheme 1.

Fusion of 3-methyl-2-(p-tolyl)quinoline-4-carboxylic acid **4b** with 3,5-dimethoxy-4-hydroxybenzaldehyde above their melting point afforded 3-(4-hydroxy-3,5-dimethoxystyryl)-2-(4-methylphenyl)quinolin-4-carboxylic acid **8**. Esterification of **4a**,**b** by their reaction with ethyl alcohol in the presence of a few drops of conc. H_2SO_4 gave ethyl-3-methyl-2-arylquinoline-4-carboxylates **9a**,**b**. The structures 3-methyl-2-phenylquinoline-4-carbohydrazide **10a** and 3-methyl-2-(4-methylphenyl)quinoline-4-carbohydrazide **10b** were confirmed by reaction of **9a**,**b** with hydrazine hydrate in ethyl alcohol. The ^{1}H-NMR spectrum of 3-methyl-2-(4-methylphenyl)quinoline-4-carbohydrazide **10b** showed bands at δ 10.00 (t, 1H, NH of $NHNH_2$), 8.89 (d, 2H, NH_2 of $NHNH_2$), 7.54–6.87 (m, 8H, 2Ar-H), 2.87 (s, 3H, CH_3 of CH_3-Ar), and 2.53 (s, 3H, CH_3) ppm. As indicated in Scheme 2, the title compounds named 5-(3-methyl-2-phenylquinolin-4-yl)-1,3,4-oxadiazole-2(3H)-thione **11a**, 5-[3-methyl-2-(p-tolyl)quinolin-4-yl]-1,3,4-oxadiazole-2(3H)-thione **11b**, (3-methyl-2-phenylquinolin-4-yl)azidomethanone **12a**, and [3-methyl-2-(p-tolyl)quinolin-4-yl]azidomethanone **12b** were prepared via reaction of **10a**,**b** with carbon disulfide and sodium azide, respectively. The ^{1}H-NMR spectrum of 5-(3-methyl-2-phenylquinolin-4-yl)-1,3,4-oxadiazole-2(3H)-thione **11a** showed bands at δ 10.12 (s, 1H, NH), 7.21–6.99 (m, 9H, 2Ar-H), and 2.55 (s, 3H, CH_3) ppm. The structure of **11b** was supported by its analytical and spectral data. The IR spectrum shows disappearance of absorption of NH_2 group of the hydrazide. The structure of **12a** was supported by its analytical and spectral data. The IR spectrum shows disappearance of absorption of NH_2 group of hydrazide, and the appearance of absorption peaks for N_3 group for azide. The ^{1}H-NMR spectrum of [3-methyl-2-(p-tolyl) quinolin-4-yl]azidomethanone **12b** showed bands at δ 8.12–7.15 (m, 8H, 2Ar-H), 2.75 (s, 3H, CH_3 of CH_3-Ar), and 2.32 (s, 3H, CH_3) ppm. The synthetic route used to synthesize these compounds is outlined in Scheme 2.

CONCLUSION

A number of 2-arylquinoline derivatives were synthesized and evaluated for antimicrobial activities against four antibacterial such as *E. coli* (ATCC-25922) and *K. pneumoniae*; Gram-positive *S. aureus* (ATCC-25923) and *S. epidermidis*; and two antifungal such as *C. albicans* and *A. fumigatus*. The investigation of the antimicrobial revealed that all the synthesized compounds showed strong *in vitro* antibacterial and moderate *in vitro* antifungal activities. The susceptibility of the microorganisms to the compounds on the basis of measuring the inhibition zone diameters varied according to the stains used, but globally, the highest inhibition zone diameters were recorded for compounds **6b**, **10b**, and **11b**. Compounds **1c**, **4c**, and **8** had no antifungal effect, while compounds **1a**, **1c**, **2a**, **2c**, **3c**, **4c**, **6a**, and **8** were completely inactive against *A. fumigatus* only.

EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp instrument (General Scientific Instrument Services Inc., London).

Infrared spectra were measured on a Perkin-Elmer spectrophotometer model 1430 (Perkin Elmer, Waltham , MA) using potassium bromide pellets, and frequencies are reported in cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR were measured on Varian Gemini-300 MHz spectrophotometer,

and chemical shifts (δ) are in ppm. The mass spectra (*m/z*) values were measured on mass spectrophotometer HP model GC MS-QPL000EX (Shimadzu) at 70 eV. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. Antimicrobial activity evaluations were carried out at the Basic Science Department, Faculty of Applied Medical Science, October 6 University, October City, Egypt.

Preparation of 3-(carboxymethyl)-2-arylquinoline-4-carboxylic acids 1a,b [35],c. β-aroylpropionic acid (0.04 mole) was added to a solution of isatin (0.04 mole) in 33% ethanolic potassium hydroxide solution (100 mL) and refluxed for about 12 h. The solution after cooling was acidified by dilute hydrochloric acid then made just alkaline with potassium hydroxide solution and finally acidified with aqueous acetic acid.

The precipitate was collected and crystallized from ethyl alcohol to give **1a–c**.

3-(Carboxymethyl)-2-phenylquinoline-4-carboxylic acid 1a. Pale yellow solid, yield 65%, mp 277°C; IR (KBr pellet): 3424, 3398 for (OH of COOH) group; 1670, 1664 for (C=O); and 1580 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.32–11.21 (s, 2H, 2OH of 2COOH), 8.08–7.18 (m, 9H, 2Ar-H), and 3.49 (s, 2H, CH_2) ppm. *Anal.* Calcd for $C_{18}H_{13}NO_4$ (307.29): C, 70.35; H, 4.26; N, 4.56. Found: C, 70.80; H, 4.40; N, 4.50. MS (*m/z*): 307 M^+.

3-(Carboxymethyl)-2-(4-methylphenyl)quinoline-4-carboxylic acid 1b. Pale yellow solid, yield 62%, mp 264°C; IR (KBr pellet): 3446, 3434 for (OH of COOH) group, 1668, 1658 for C=O, and 1579 for C=N cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.05–10.86 (s, 2H, 2OH of 2COOH), 7.88–7.08 (m, 8H, 2Ar-H), 3.29 (s, 2H, CH_2), and 2.67 (s, 3H, CH_3 of CH_3-Ar) ppm. ^{13}C-NMR (DMSO, 300 MHz) δ 174.3, 169.4, 165.0, 150.8, 145.9, 137.0, 133.3, 132.5, 129.6, 127.9, 127.5, 127.4, 124.5, 122.5, 35.2, 24.3. *Anal.* Calcd for $C_{19}H_{15}NO_4$ (321.32): C, 71.02; H, 4.71; N, 4.36. Found: C, 71.12; H, 5.30; N, 4.40. MS (*m/z*): 321 M^+.

3-(Carboxymethyl)-2-(4-methoxyphenyl)quinoline-4-carboxylic acid 1c. Pale yellow solid, yield 60%, mp 260–261°C; IR (KBr pellet): 3434, 3386 for (OH of COOH) group; 1663, 1652 for (C=O); and 1608 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 10.99-10.52 (s, 2H, 2OH of 2COOH), 8.00-6.99 (m, 8H, 2Ar-H), 3.55 (s, 2H, CH_2), and 3.21 (s, 3H, OCH_3 of CH_3O-Ar) ppm. *Anal.* Calcd for $C_{19}H_{15}NO_5$ (337.32): C, 67.65; H, 4.48; N, 4.15. Found: C, 67.40; H, 4.30; N, 4.50. MS (*m/z*): 340 M^++2.

Preparation of 3-(carboxymethyl)-2-arylquinoline-4-carboxylic acid anhydrides 2a,b [35],c. A mixture of **1a–c** (0.01 mole) and acetyl chloride (10 mL) was heated under reflux for 3 h. The reaction mixture after cooling was filtered and crystallized from benzene to give **2a–c**.

3-(Carboxymethyl)-2-phenylquinoline-4-carboxylic acid anhydride 2a. Yellow solid, yield 66%, mp 170°C; IR (KBr pellet):1807, 1750 for (C=O) and 1629 for (C=N) cm^{-1}.^{1}H-NMR (DMSO, 300 MHz) δ 7.99–7.00 (m, 9H, 2Ar-H) and 3.55 (s, 2H, CH_2) ppm. *Anal.* Calcd for $C_{18}H_{11}NO_3$ (289.28): N, 4.84. Found: N, 5.10. MS (*m/z*): 288 $M^+ - 1$.

3-(Carboxymethyl)-2-(4-methylphenyl)quinoline-4-carboxylic acid anhydride 2b. Yellow solid, yield 94%, mp 170–171°C; IR (KBr pellet): 1798, 1729 for (C=O) and 1605 for (C=N) cm^{-1}.^{1}H-NMR (DMSO, 300 MHz) δ 8.00–6.99 (m, 8H, 2Ar-H), 3.43 (s, 2H, CH_2), and 2.45 (s, 3H, CH_3 of CH_3-Ar) ppm. *Anal.* Calcd for $C_{19}H_{13}NO_3$ (303.31): C, 75.23; H, 4.32; N, 4.62. Found: C, 75.60; H, 4.30; N, 4.80. MS (*m/z*): 303 M^+.

3-(Carboxymethyl)-2-(4-methoxyphenyl)quinoline-4-carboxylic acid anhydride 2c. Yellow solid, yield 85%, mp 198°C; IR (KBr pellet): 1797, 1732 for (C=O) and 1607 for (C=N) cm^{-1}.^{1}H-NMR (DMSO, 300 MHz) δ 7.89–7.11 (m, 8H, 2Ar-H), 3.29 (s, 2H, CH_2), and 3.04 (s, 3H, OCH_3 of CH_3O-Ar) ppm. ^{13}C-NMR (DMSO, 300 MHz) δ 166.0, 165.0, 159.3, 150.8, 149.5, 145.9, 132.5, 128.6, 128.0, 127.9, 127.4, 124.5, 122.5, 114.8, 55.9, 32.0. *Anal.* Calcd for $C_{19}H_{13}NO_4$ (319.31): C, 71.46; H, 4.10; N, 4.39. Found: C, 71.70; H, 4.30; N, 4.60. MS (*m/z*): 319 M^+.

Preparation of 3-alkylbenzo [c]acridin-5-yl acetates 3a,b [35],c. A mixture of **1a–c** (0.02 mole), fused sodium acetate (2 g) and acetic anhydride (25 mL) was refluxed for 5 h. The excess acetic anhydride was evaporated under reduced pressure, and water was added. The solid formed was treated with ether. The ether insoluble fraction was crystallized from benzene to give **3a–c**.

Benzo[c]acridin-5-yl acetate 3a. Pale yellow solid, yield 47%, mp 300°C; IR (KBr pellet): 1729 for (C=O) and 1554 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 7.87–7.12 (m, 9H, 3Ar-H), 5.99 (s, 1H, CH), and 2.34 (s, 3H, CH_3 of $COCH_3$) ppm. *Anal.* Calcd for $C_{19}H_{13}NO_2$ (287.30): C, 79.43; H, 4.56; N, 4.88. Found: C, 79.90; H, 4.10; N, 4.50. MS (*m/z*): 287 M^+.

3-Methylbenzo[c]acridin-5-yl acetate 3b. Pale yellow solid, yield 48%, mp 312°C; IR (KBr pellet): 1727 for (C=O) and 1555 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 7.86–7.02 (m, 8H, 3Ar-H), 6.00 (s, 1H, CH), 3.08 (s, 3H, CH_3 of $COCH_3$), and 2.46 (s, 3H, CH_3 of CH_3-Ar) ppm. ^{13}C-NMR (DMSO, 300 MHz) δ 169.0, 150.3, 148.8, 146.9, 136.4, 135.3, 134.5, 129.9, 129.0, 128.5, 128.3, 128.0, 127.3, 127.2, 127.0, 121.3, 118.5, 24.7, 20.3. *Anal.* Calcd for $C_{20}H_{15}NO_2$ (301.33): C, 79.71; H, 5.02; N, 4.65. Found: C, 79.70; H, 5.00; N, 4.90. MS (*m/z*): 301 M^+.

3-Methoxybenzo[c]acridin-5-yl acetate 3c. Pale yellow solid, yield 48%, mp > 312°C; IR (KBr pellet): 1726 for (C=O) and 1605 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 7.82–7.12 (m, 8H, 3Ar-H), 5.78 (s, 1H, CH), 3.73 (s, 3H, OCH_3 of CH_3O-Ar), and 2.08 (s, 3H, CH_3 of $COCH_3$) ppm. *Anal.* Calcd for $C_{20}H_{15}NO_3$ (317.33): C, 75.69; H, 4.76; N, 4.41. Found: C, 75.70; H, 4.76; N, 4.70. MS (*m/z*): 316 $M^+ - 1$.

Preparation of 3-methyl-2-arylquinoline-4-carboxylic acids 4a,b [35],c. A mixture of **1a–c** (1 g) was refluxed in nitrobenzene (20 mL) for 1 h. The solid product separated on cooling at room temperature was filtered off and crystallized from benzene to give **4a–c**.

3-Methyl-2-phenylquinoline-4-carboxylic acid 4a. Pale green solid, yield 50%, mp 299°C; IR (KBr pellet): 3425 for (OH of carboxylic acid), 1675 for (C=O), and 1617 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.00 (s, 1H, OH of COOH), 7.78–7.02 (m, 9H, 2Ar-H), and 2.32 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{17}H_{13}NO_2$ (263.28): C, 77.55; H, 4.98; N, 5.32. Found: C, 77.90; H, 5.40; N, 5.00. MS (*m/z*): 264 $M^+ + 1$.

3-Methyl-2-(4-methylphenyl)quinoline-4-carboxylic acid 4b. Pale green solid, yield 62%, mp 295–296°C; IR (KBr pellet): 3425 for (OH of carboxylic acid), 1680 for (C=O), and 1614 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 10.98 (s, 1H, OH of COOH), 7.89–7.22 (m, 8H, 2Ar-H), 3.35 (s, 3H, CH_3 of CH_3-Ar), and 2.32 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{18}H_{15}NO_2$ (277.31): C, 77.96; H, 5.45; N, 5.05. Found: C, 77.90; H, 5.40; N, 5.00. MS (*m/z*): 278 $M^+ + 1$.

3-Methyl-2-(4-methoxyphenyl) quinoline-4-carboxylic acid 4c. Pale green solid, yield 50%, mp 290–291°C; IR (KBr pellet): 3426 for (OH of carboxylic acid), 1662 for (C=O), and 1607 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.02 (s, 1H, OH of COOH), 8.21–7.12 (m, 8H, 2Ar-H), 3.75 (s, 3H, OCH_3 of CH_3O-Ar), and 2.33 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO, 300 MHz) δ 169.4, 165.0, 159.3, 150.8, 145.9, 132.0, 128.6, 128.0, 127.9, 127.4, 124.5, 122.5, 114.8, 55.9, 11.3. *Anal.* Calcd for $C_{18}H_{15}NO_3$ (293.31): C, 73.70; H, 5.15; N, 4.77. Found: C, 73.90; H, 5.40; N, 5.00. MS (*m/z*): 293 M^+.

Preparation of methyl-3-(2-methoxy-2-oxoethyl)-2-phenylquinoline-4-carboxylate 5. A mixture of **1a** (0.01 mole) was refluxed in methyl alcohol (0.02 mole) for 3 h. The reaction mixture was evaporated under reduced pressure, and the solid product was filtered off and crystallized from benzene to give **5**.

Methyl-3-(2-methoxy-2-oxoethyl)-2-phenylquinoline-4-carboxylate 5. Pale yellow solid, yield 55%, mp 102°C; IR (KBr pellet): 1736–1720 for (C=O) and 1617 for (C=N) cm^{-1}.^{1}H-NMR (DMSO, 300 MHz) δ 7.86–7.11 (m, 9H, 2Ar-H), 3.88 (s, 3H, CH_3 of $COOCH_3$), 3.79 (s, 2H, CH_2 of CH_2COOCH_3), and 3.67 (s, 3H, CH_3 of CH_2COOCH_3) ppm. *Anal.* Calcd for $C_{20}H_{17}NO_4$ (335.35): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.90; H, 5.40; N, 4.52. MS (*m/z*): 336 M^+.

Preparation of 2-[(4-methoxycarbonyl)-2-arylquinolin-3-yl] acetic acids 6a–c. A mixture of **2a–c** (0.01 mole) was refluxed in methyl alcohol (0.01 mole) for 3 h. The reaction mixture was evaporated under reduced pressure, and the solid product was filtered off and crystallized from benzene to give **6a-c**.

2[(4-Methoxycarbonyl)-2-phenylquinolin-3-yl] acetic acid 6a. Pale yellow solid, yield 70%, mp 150–152°C; IR (KBr pellet): 3426 for (OH of carboxylic acid), 1730 for (C=O of ester), 1692 for (C=O of acid), and 1651 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.00 (s, 1H, OH of COOH), 7.99–7.27 (m, 9H, 2Ar-H), 3.88 (s, 3H, CH_3 of $COOCH_3$), and 3.49 (s, 2H, CH_2 of CH_2COOCH) ppm. *Anal.* Calcd for $C_{19}H_{15}NO_4$ (321.32): C, 71.02; H, 4.71; N, 4.36. Found: C, 70.92; H, 4.58; N, 4.54. MS (*m/z*): 323 $M^+ + 2$.

2[(4-Methoxycarbonyl)-2-(4-methylphenyl)quinolin-3-yl] acetic acid 6b. Pale yellow solid, yield 65%, mp 135–137°C; IR (KBr pellet): 3389 for (OH of carboxylic acid), 1726 for (C=O of ester), 1686 for (C=O of acid), and 1632 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.12 (s, 1H, OH of COOH), 8.95–7.15 (m, 8H, 2Ar-H), 3.88 (s, 3H, $COOCH_3$), 3.49 (s, 2H, CH_2 of CH_2COOH), and 2.35 (s, 3H, CH_3 of CH_3-Ar) ppm. ^{13}C-NMR (DMSO, 300 MHz) δ 174.3, 166.2, 166.0, 151.4, 145.6, 136.3, 133.4, 129.3, 129.2, 128.7, 127.6, 127.4, 125.9, 123.8, 51.5, 35.2. *Anal.* Calcd for $C_{20}H_{17}NO_4$ (335.35): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.42; H, 4.88; N, 4.54. MS (*m/z*): 336 $M^+ + 1$.

2[(4-Methoxycarbonyl)-2-(4-methoxyphenyl)quinolin-3-yl] acetic acid 6c. Pale yellow solid, yield 65%, mp 143–145°C; IR (KBr pellet): 3377 for (OH of carboxylic acid), 1716 for (C=O of ester), 1686 for (C=O of acid), and 1620 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.6 (s, 1H, OH of COOH), 8.15–7.01 (m, 8H, 2Ar-H), 3.67 (s, 3H, $COOCH_3$), 3.59 (s, 2H, CH_2 of CH_2COOH), and 3.43 (s, 3H, OCH_3 of CH_3O-Ar) ppm. *Anal.* Calcd for $C_{20}H_{17}NO_5$ (351.35): C, 68.36; H, 4.88; N, 3.99. Found: C, 68.42; H, 4.86; N, 4.14. MS (*m/z*): 351 M^+.

Preparation of 5-acetoxymethylbenzo[c]acridine-7-carboxylic acid 7. A mixture of **6a** (0.02 mole), fused sodium acetate (2 g) and acetic anhydride (25 mL) was refluxed for 5 h. The excess acetic anhydride was evaporated under reduced pressure, and water was added. The solid formed was crystallized from benzene to give **7**.

5-Acetoxymethylbenzo[c]acridine-7-carboxylic acid 7. Yellow solid, yield 45%, mp 135–137°C; IR (KBr pellet): 1730–1689 for (C=O) and 1620 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 8.05–7.21 (m, 9H, 3Ar-H), 3.51 (s, 3H, CH_3 of $COOCH_3$), and 2.49 (s, 3H, CH_3 of $OCOCH_3$) ppm. *Anal.* Calcd for $C_{21}H_{15}NO_4$ (345.34): C, 73.03; H, 4.38; N, 4.06. Found: C, 73.23; H, 4.58; N, 4.23. MS (*m/z*): 345 M^+.

Preparation of 3-(4-hydroxy-3,5-dimethoxystyryl)-2-(4-methylphenyl)quinolin-4-carboxylic acid 8. Fusion of **4b** (0.01 mole) with 3, 5-dimethoxy-4-hydroxybenzaldehyde (0.01 mole) for 2 h above their melting point. The solid product obtained was crystallized from benzene to give **8**.

3-(4-Hydroxy-3,5-dimethoxystyryl)-2-(4-methylphenyl)quinolin-4-carboxylic acid 8. Pale yellow solid, yield 56%, mp

270–272°C; IR (KBr pellet): 3440 for (OH of carboxylic acid), 3133 for (OH of phenol), 1675 for (C=O), and 1602 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 11.00 (s, 1H, OH of COOH), 8.13–7.02 (m, 10H, 3Ar-H), 5.99–5.67 (d, 2H, CH=CH), 5.21 (s, 1H, OH), 3.78–3.53 (s, 6H, 2OCH_3 of 2CH_3O-Ar), and 2.35 (s, 3H, CH_3 of CH_3-Ar) ppm. *Anal.* Calcd for $C_{27}H_{23}NO_5$ (441.46): C, 73.45; H, 5.25; N, 3.17. Found: C, 73.65; H, 5.03; N, 3.42. MS (*m/z*): 439 $M^+ - 2$.

Preparation of ethyl-3-methyl-2-arylquinoline-4-carboxy lates 9a,b. A mixture of **4a**,**b** (0.01 mole) was refluxed in ethyl alcohol in the presence of a few drops of conc. sulfuric acid for 3 h. The reaction mixture was evaporated under reduced pressure, and the solid product was washed with water, filtered off, and crystallized from benzene to give **9a**,**b**.

Ethyl-3-methyl-2-phenylquinoline-4-carboxylate 9a. Pale yellow solid, yield 78%, mp 176–178°C; IR (KBr pellet): 1712 for (C=O of ester) and 1607 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 7.99–7.05 (m, 9H, 2Ar-H), 3.53 (q, 2H, CH_2 of –CH_2CH_3), 2.76 (t, 3H, CH_3 of –CH_2CH_3), and 2.35 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{19}H_{17}NO_2$ (291.34): C, 78.32; H, 5.88; N, 4.81. Found: C, 78.62; H, 5.91; N, 5.00. MS (*m/z*): 291 M^+.

Ethyl-3-methyl-2-(4-methylphenyl)quinoline-4-carboxylate 9b. Pale yellow solid, yield 80%, mp 150–152°C; IR (KBr pellet): 1725 for (C=O of ester) and 1600 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 7.75– 6.98 (m, 8H, 2Ar-H), 3.76 (q, 2H, CH_2 of –CH_2CH_3), 2.88 (t, 3H, CH_3 of –CH_2CH_3), 2.52 (s, 3H, CH_3), and 2.26 (s, 3H, CH_3 of CH_3-Ar) ppm. ^{13}C-NMR (DMSO, 300 MHz) δ 166.2, 166.0, 151.4, 145.6, 137.0, 133.4, 133.3, 129.6, 129.3, 129.2, 128.7, 127.5, 125.9, 123.8, 60.9, 24.3, 14.1, 11.3. *Anal.* Calcd for $C_{20}H_{19}NO_2$ (305.37): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.54; H, 6.78; N, 4.83. MS (*m/z*): 305 M^+.

Preparation of 3-methyl-2-arylquinoline-4-carbohydrazides 10a,b. A mixture of **9a**,**b** (0.01 mole) and hydrazine hydrate (0.02 mole) was refluxed in ethyl alcohol (20 mL) for 3 h. The reaction mixture was evaporated under reduced pressure. After cooling, the resulting solid was filtered, dried, and recrystallized from benzene to give **10a**,**b**.

3-Methyl-2-phenylquinoline-4-carbohydrazide 10a. Pale brown solid, yield 56%, mp 302°C; IR (KBr pellet): 3360 for (NH), 3215–3198 for (NH_2), 1665 for (C=O), and 1607 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 10.43 (t, 1H, NH of $NHNH_2$), 9.10 (d, 2H, NH_2 of $NHNH_2$), 7.22–6.69 (m, 9H, 2Ar-H), and 2.35 (s, 3H,

Table 1

Antimicrobial activity of compounds **1a** to **12b**.

	Inhibition zone diameter (mm)					
Compounds (50 μg/mL)	*Escherichia coli*	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Aspergillus fumigatus*	*Candida albicans*
1a	19	14	16	15	Negative	13
1b	21	15	18	16	11	14
1c	21	13	18	15	Negative	Negative
2a	20	15	18	16	Negative	12
2b	23	14	19	16	12	15
2c	19	13	16	16	Negative	11
3a	18	13	14	13	11	14
3b	21	13	18	15	12	14
3c	20	14	17	16	Negative	14
4b	20	13	19	14	10	12
4c	20	14	18	14	Negative	Negative
5	17	13	14	13	10	15
6a	18	15	15	13	Negative	12
6b	24	16	20	15	12	15
7	21	13	16	16	11	12
8	21	13	18	14	Negative	Negative
9a	19	13	17	16	11	13
9b	21	14	19	14	12	15
10b	28	16	21	19	15	17
11a	21	15	19	17	10	12
11b	25	16	20	16	14	16
12a	21	15	18	16	11	12
12b	21	16	20	14	10	14
Tetracycline (30 μg/mL)	27	22	25	25	—	—
Fluconazole (10 μg/mL)	—	—	—	—	21	24

Negative, no inhibition up to 100 μg/well.

CH_3) ppm. *Anal.* Calcd $C_{17}H_{15}N_3O$ (277.32): C, 73.62; H, 5.45; N, 15.16; Found: C, 73.99; H, 5.45; N, 14.98. MS (*m/z*): 277 M^+.

3-Methyl-2-(4-methylphenyl)quinoline-4-carbohydrazide 10b. Pale brown solid, yield 60%, mp 220°C; IR (KBr pellet) 3343 for (NH), 3210–3185 for (NH_2), 1676 for (C=O), and 1602 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 10.00 (t, 1H, NH of $NHNH_2$), 8.89 (d, 2H, NH_2 of $NHNH_2$), 7.54–6.87 (m, 8H, 2Ar-H), 2.87 (s, 3H, CH_3 of CH_3-Ar), and 2.53 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{18}H_{17}N_3O$ (291.35): C, 74.20; H, 5.88; N, 14.43. Found: C, 73.85; H, 5.92; N, 14.76. MS (*m/z*): 291 M^+.

Preparation of 5-(3-methyl-2-arylquinolin-4-yl)-1,3,4-oxa diazole-2(3H)-thione 11a,b. A mixture of **10a,b** with carbon disulfide was refluxing in dry pyridine for 5 h, the reaction mixture was evaporated under reduced pressure, treated with dil. HCl and was washed with water. The solid product formed was crystallized with benzene to give **11a,b**.

5-(3-Methyl-2-phenylquinolin-4-yl)-1,3,4-oxadiazole-2(3H)-thione 11a. Yellow solid, yield 55%, mp 278°C; IR (KBr pellet): 3356 for NH, 1659 for (C–O), 1613–1604 for (2C=N), and 1252 for (C=S) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 10.12 (s, 1H, NH), 7.21–6.99 (m, 9H, 2Ar-H), and 2.55 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{18}H_{13}N_3OS$ (319.31): C, 67.70; H, 4.10; N, 13.16. Found: C, 67.65; H, 4.53; N, 13.42. MS (*m/z*): 318 $M^+ - 1$.

5-(3-Methyl-2-(4-methylphenyl)quinolin-4-yl)-1,3,4-oxadiazole-2(3H)-thione 11b. Pale yellow solid, yield 56%, mp 282–284°C; IR (KBr pellet): 3396 for NH, 1647 for (C–O), 1600–1594 for (2C=N), and 1252 for (C=S) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 9.87 (s, 1H, NH), 7.57–6.83 (m, 8H, 2Ar-H), 2.72 (s, 3H, CH_3 of CH_3-Ar), and 2.47 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{19}H_{15}N_3OS$ (333.34): N, 12.61; S, 9.60. Found: N, 13.00; S, 9.31. MS (*m/z*): 333 M^+.

Preparation of (3-methyl-2-arylquinolin-4-yl)azidomethanone 12a,b. To a cooled solution of 3-methyl-2-arylquinoline carbohydrazides **10a,b** (0.01 mole) in 1.25 N HCl (20 mL) was added sodium nitrite solution (0.01 mole) at 0–5°C for 30 min with stirring. The reaction mixture was kept for 2 h at room temperature, diluted with water, and filtered. The solid product obtained was dried and crystallized from benzene to give **12a,b**.

(3-Methyl-2-phenylquinolin-4-yl)azidomethanone 12a. Yellow solid, yield 60%, mp 320°C; IR (KBr pellet): 2053 for (N_3), 1675 for (C=O) and 1603 for (C=N) cm^{-1}. *Anal.* Calcd for $C_{17}H_{12}N_4O$ (288.31): C, 70.82; H, 4.20; N, 19.44. Found: C, 71.02; H, 4.26; N, 19.85. MS (*m/z*): 287 $M^+ - 1$.

(3-Methyl-2-(4-methylphenyl)quinolin-4-yl)azidomethanone 12b. Yellow solid, yield 60%, mp 308–309°C; IR (KBr pellet): 2038 for (N_3 azide), 1653 for (C=O), and 1607 for (C=N) cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ 8.12–7.15 (m, 8H, 2Ar-H), 2.75 (s, 3H, CH_3 of CH_3-Ar), and

Table 2

MIC (μg/mL) results of compounds **1a** to **12b**.

Compounds	MIC values (μg/mL)					
	Escherichia coli	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Aspergillus fumigatus*	*Candida albicans*
1a	10	15	15	15	—	15
1b	15	15	15	15	20	15
1c	10	20	10	10	—	—
2a	10	15	10	10	—	15
2b	5	15	15	15	15	15
2c	15	20	15	15	—	10
3a	15	20	15	15	15	15
3b	15	15	15	15	15	15
3c	15	20	15	15	—	10
4b	15	15	15	15	20	20
4c	15	15	10	15	—	—
5	15	20	15	15	20	15
6a	15	15	15	15	—	20
6b	10	10	10	10	15	15
7	10	10	10	10	20	20
8	10	10	10	10	—	—
9a	15	15	15	15	20	20
9b	10	10	10	10	15	15
10b	5	5	5	5	10	10
11a	15	15	15	15	20	20
11b	5	10	5	10	10	10
12a	15	15	15	15	20	20
12b	10	10	10	10	15	15

MIC, minimum inhibitory concentration.

2.32 (s, 3H, CH_3) ppm. *Anal.* Calcd for $C_{18}H_{14}N_4O$ (302.34): C, 71.50; H, 4.67; N, 18.54. Found: C, 71.75; H, 4.89; N, 18.82. MS (*m/z*): 302 M^+.

Biological activity evaluation. The synthesized compounds were screened for their antibacterial and antifungal activities using the agar well diffusion technique [36]. The microorganisms (reference and clinical isolates) used include Gram-negative *Escherichia coli* (ATCC-25922) and *Klebsiella pneumoniae*; Gram-positive *Staphylococcus aureus* (ATCC-25923) and *Staphylococcus epidermidis*; and *Candida albicans* and *Aspergillus fumigatus*.

For the antibacterial assay, a standard inoculum (105 CFU/mL) was distributed on the surface of sterile nutrient agar plates by a sterile glass spreader. While for the antifungal assay, a loopful of a particular fungal strain was transferred to a 3-mL saline to obtain a suspension of the corresponding species, 0.1 mL of the spore suspension was distributed on the surface of sterile Sabouraud dextrose agar plats.

A 6-mm diameter well was punched in the agar media and filled with 100 µL of (500 µg/mL in DMSO) the tested chemical compounds previously sterilized through 0.45 sterile membrane filter [37]. The plates were kept at room temperature for 1 h and then incubated at 37°C for 24 h for bacteria and 30°C for 4 days for fungi. The antimicrobial activities were evaluated by measuring the inhibition zone diameters. Commercial antibiotic discs were used as positive reference standard to determine the sensitivity of the strains; see Table 1.

Determination of minimum inhibitory concentration of the synthesized compounds. Compounds inhibiting the growth of one or more of the aforementioned microorganisms were further tested for their minimum inhibitory concentration (MIC) and were determined by the broth dilution technique [38]. The nutrient broth and the yeast extract broth media, which contained 1 mL of different concentrations of the tested compounds (5, 10, 15, 20, 25 µg/mL), were inoculated with the microbial strains, the bacterial cultures were incubated for 24 h at 37°C, while the fungal ones were incubated at 30°C for 48 h. The growth was monitored spectrophotometrically. The lowest concentration required to arrest the microbial growth was regarded as MICs and is given in Table 2. The investigation of the antimicrobial screening data in Table 1 revealed that all the synthesized compounds showed strong *in vitro* antibacterial and moderate *in vitro* antifungal activities. The susceptibility of the microorganisms to the compounds on the basis of measuring the inhibition zone diameters varied according to the stains used, but globally, the greatest inhibition zone diameters were recorded for compounds **6b**, **10b**, and **11b**. Compounds **1c**, **4c**, and **8** have no antifungal effect, while compounds **1a**, **1c**, **2a**, **2c**, **3c**, **4c**, **6a**, and **8** were completely inactive against *A. fumigatus* only.

Minimum inhibitory concentration is defined as the lowest concentration of an antimicrobial that will inhibit visible growth after definite period of incubation [39]. It is considered a standard for determining the susceptibility of microorganisms to different compounds.

The microdilution assay gave MIC values ranging from 5 to 25 µg/mL. From Table 2, it was found that MICs for the bacterial strains were ranging from 5 to 20 µg/mL, while that for the fungal strains were ranging from 10 to 20 µg/mL. Compound **10b** was found to have a broad antimicrobial spectrum with MIC 5 µg/mL for bacteria and 10 µg/mL for fungi.

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DECLARATION OF INTEREST

The authors confirm that this article contents has no conflict of interest.

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