Regular Article

Synthesis, Antimicrobial and Anti-inflammatory Activity of Some New Benzoxazinone and Quinazolinone Candidates

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Benzoxazinones and quinazolinones have a wide spectrum of biological activity. In this paper we focused on studying the antimicrobial and anti-inflammatory activities of some newly synthesized benzoxazinone and quinazolinone derivatives. Thus we prepared 2-[α -benzoylamino-2-phenyl-4-oxo-4,5-dihydro-1H-benzoxazin-3-yl]-6,8-dibromo-3,1-benzoxazin-4(1H)-one **2 which underwent a reaction with primary and secondary amines, and hydrazine hydrate to give compounds **3**, **4** and **5**, respectively. Treatment of **2** with hydroxylamine hydrochloride, formamide and/or NaN₃/AcOH afforded compounds **7**, **8**, **11** and **12**, respectively. Also, compound **2** reacted with maleic anhydride, aromatic hydrocarbons and/or active methylene compounds to produce compounds **13**, **15a–c** and **16**, respectively. Most of the newly synthesized compounds showed significant antimicrobial and anti-inflammatory activities comparable to ampicillin, mycostatine and indomethacin positive controls.**

Key words benzoxazinone; quinazolinone; imidazole; tetrazole; antimicrobial; anti-inflammatory

Heterocycles containing benzoxazinone and quinazolinone moieties have great importance in medicinal chemistry. They are of considerable interest on account of the diverse range of biological properties such as antimicrobial, herbicidal, anti-inflammatory, anticancer, antibacterial, antifungal, central nervous system (CNS), antimalarial, antitumor, and adenosine receptor antagonistic activities.^{1–14} In continuation of our interest in the synthesis of some of heterocyclic nitrogen compounds having biological and pharmacological activities,^{15–25} and through our program^{26–29} aiming to explore the chemical reactivity of the oxazinone moiety present in 4(*H*)-3,1-benzoxazin-4-one derivatives, we have decided to synthesize a series of novel 3-substituted quinazolin-4(3*H*)-one, with two bromine atoms in the benzene ring using 2-[α -benzoylamino-2-phenyl-4-oxo-4,5-dihydro-1H-benzoxazin-3-yl]-6,8-dibromo-3,1-benzoxazin-4(*H*)-one (**2**) as a versatile starting material. Compound **2** was subjected for the reaction with some nitrogen nucleophiles and other reactions. The structures of the newly synthesized compounds were elucidated through their IR, ¹H-NMR, ¹³C-NMR and mass spectroscopic data. The new products showed remarkable antibacterial, antifungal and anti-inflammatory activities upon screening for biological activity tests.

Results and Discussion

Chemistry *N*-[α -Benzoylamino-2-phenyl-4-oxo-4,5-dihydro-1H-benzoxazin-3-yl]-3,5-dibromoanthranilic acid (**1**) was synthesized in a good yield by the treatment of a solution of 3,5-dibromoanthranilic acid (0.01 mol) in pyridine with equimolecular amount of 2-phenyl-4-(phenyl methylene)-5(4*H*)-oxazolone. The structure of compound **1** was confirmed by elemental analysis and spectral data (Experimental). On refluxing the acid **1** with acetic

anhydride, the title compound **2** was obtained in 59% yield as a result of ring closure (Chart 1). Structure of 4(*H*)-3,1-benzoxazin-4-one derivative **2** was elucidated from its analytical data, IR (showed $\nu_{C=O}$ at 1749 cm⁻¹ which is characteristic for the benzoxazinone moiety) and ¹H-NMR spectrum which displayed peaks at δ 6.71 for CH=, 7.28–7.77 (10, Ar-H), 8.20, 8.37 (2s, 2H, Ar-H benzoxazinone), 10.22 exchangeable with D₂O for NH. The ¹³C-NMR spectrum contained 14 signals; the most important, at δ 118.10, 120.30 and 161.60, 163.40 ppm for (C=C) and (2C=O). Its mass spectrum displayed the expected molecular ion peaks at *m/z* 526 (4.8%), 528 (10.1%) and 530 (5.1%).

When compound **2** was heated with primary amines such as aniline, *t*-butyl amine, benzyl amine and/or phenyl hydrazine in boiling ethanol, afforded the corresponding *N*-[α -benzoylamino-2-phenyl-4-oxo-4,5-dihydro-1H-benzoxazin-3-yl]-3,5-dibromoanthranilic acid amides and hydrazide **3a–d**, respectively. Similarly, secondary amines (piperidine and/or morpholine) reacted with **2** yielding *N*-[α -benzoylamino-2-phenyl-4-oxo-4,5-dihydro-1H-benzoxazin-3-yl]-3,5-dibromoanthranilic acid piperidide and morpholide **4a** and **b** respectively (Chart 1). Analytical and spectral data for **3a–d** and **4a, b** were in agreement with the proposed structures (Experimental).

On the other hand, hydrazinolysis of **2** with hydrazine hydrate in refluxing *n*-butanol gave the 3-aminoquinazolinone derivative **5**. The IR spectrum showed three bands at 3429, 3230 and 3110 cm⁻¹, corresponding to the NH₂ and NH groups. Also, the ¹H-NMR spectrum indicated the presence of a broad singlet peak at δ 4.86 ppm integrated for two exchangeable protons (NH₂ group). Its mass spectrum gave the molecular ion peaks at *m/z* 540 (8.6%), 528 (17.7%) and 5530 (9.1%). When compound **5** was subjected to condensation with benzaldehyde in boiling ethanol, Schiff's base **6** was obtained. Similarly, hydroxyl amine hydrochloride reacted with **2** producing the 3-hydroxyquinazolinone derivative **7** (Chart 2). Fusion of the benzoxazinone **2** with ammonium acetate

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Chart 1. Synthetic Routs of Compounds 1–4

Chart 2. Synthetic Routs of Compounds 5–12

afforded the quinazolin-4-one derivative **8**, which was also obtained by refluxing **2** in excess formamide. The existence of compound **8** in the lactam–lactim tautomeric equilibrium was proved through its reaction with acetic anhydride where it underwent *N*-acetylation (through the lactam form) to give compound **9**, but, it upon alkylation with ethyl chloroacetate the ester **10** was formed (through the lactim form) (Chart 2). The ¹H-NMR spectra of compounds **9** and **10** showed sig-

nals at δ 2.23 ppm for three protons corresponding to CH₃–C=O, 1.25–1.34 (t, *J*=6.5 Hz, 3H, CH₃–CH₂–), 4.14–4.27 (q, *J*=6.6 Hz, 2H, –OCH₂CH₃), which indicated the presence of the acetyl group in compound **9** and the ester group in compound **10**, respectively. Treatment of compound **2** with hydrazoic acid³⁰⁾ (sodium azide in acetic acid) gave a mixture of the tetrazole derivative **11** and the benzimidazolone derivative **12**, respectively (Chart 2).

Chart 3. Formation of Compound 11

Chart 4. Formation of Compound 12

Chart 5. Synthesis of Compounds 13–16

Formation of compounds **11** and **12** could be visualized as shown in Charts 3 and 4.

An interesting result was obtained when compound **2** was boiled with maleic anhydride in xylene, which afforded the Diels–Alder adduct **13**, which was hydrolyzed with alcoholic NaOH to give the diacid **14**. The investigation was further extended to explore the reactivity of the benzoxazin-4-one **2** towards aromatic hydrocarbons under Friedel–Crafts reaction conditions. Thus, when compound **2** was reacted with benzene, toluene and/or cumene in the presence of anhydrous AlCl_3 , aromatic ketones **15a–c** were obtained, respectively (Chart 5). The reaction proceeded *via* ring opening and the structures of the formed compounds were elucidated from their spectral data. Finally, the reaction of **2** with compounds containing an active methylene group was also investigated. Thus, treatment of compound **2** with diethyl malonate and/or ethyl acetoacetate in refluxing pyridine produced the ethyl acetate derivatives **16** as a sole product in both cases (Chart 5). The reaction took place *via* heterocyclic ring opening as a result of attack of the carbanion from the active methylene

compounds. The proposed structure was indicated by its $^1\text{H-NMR}$ spectrum which displayed signals at δ 1.23–1.32 (t, $J=6.5\text{ Hz}$, 3H, $\text{CH}_3\text{--CH}_2\text{--}$), 3.75 (s, 2H, $\text{CH}_2\text{--C=O}$), 4.24–4.35 (q, $J=6.6\text{ Hz}$, 2H, $\text{--OCH}_2\text{CH}_3$), which indicated the presence of the $\text{COCH}_2\text{COOC}_2\text{H}_5$ group. Also, the IR spectrum showed a peak at 1715 cm^{-1} corresponding to $\nu_{\text{C=O}}$ of the ester group, analytical and spectral data for compounds **15** and **16** confirmed their chemical structures.

Biological Activity

Antimicrobial Activity

All of the new synthesized compounds were screened for *in vitro* antibacterial and antifungal activities. The microorganisms used were *Serratia marcescens*, *Proteus merabitis* (Gram-negative bacteria), *Staphylococcus aureus*, *Bacillus cereus* (Gram-negative bacteria), *Aspergillus ochraceus* WILHELM and *Penicillium chrysogenum* THOM (fungi). The standard drugs used were ampicillin and mycostatine, following the agar diffusion technique.³¹⁾ The antimicrobial activity results are shown in Table 1. The antimicrobial activity results revealed that most of the tested compounds have moderate to

Table 1. Antimicrobial Activity of the Synthesized Compounds

Compd. no.	Antibacterial activity				Antifungal activity	
	Gram-positive		Gram-negative		<i>Aspergillus ochraceus</i> WILHELM	<i>Penicillium chrysogenum</i> THOM
	<i>Staphylococcus aureus</i>	<i>Bacillus cereus</i>	<i>Serratia marcescens</i>	<i>Proteus merabilis</i>		
2	24	22	21	22	20	22
3a	26	18	10	12	9	11
3b	7	9	8	11	12	13
3c	13	12	6	9	4	3
3d	6	9	7	10	3	5
4	12	11	4	3	7	8
5	30	28	27	25	14	11
6	29	30	27	28	24	22
7	26	30	28	29	19	21
8	29	27	25	30	14	14
9	14	14	11	12	3	5
10	28	28	27	29	24	26
11	2	5	4	3	5	4
12	3	2	5	4	3	3
13	21	24	23	27	22	26
14	23	22	26	22	19	17
15a	11	12	15	14	7	9
15b	9	7	11	13	12	8
15c	4	6	3	5	8	7
16	10	9	14	12	14	13
Ampicilin	34	33	31	32	—	—
Mycostatine	—	—	—	—	31	32

The width of the zone of inhibition indicates the potency of antibacterial activity; (0) no antimicrobial activity; the diameter of zones equal to 2–5 mm, weak reactivity; 6–14 mm, moderate activity; 15–30 mm, high activity and very high activity with the diameter of the zones (more than 30 mm).

Table 2. Minimum Inhibitory Concentration (MIC) of the Most Potent Compounds

Compd. no.	MIC ($\mu\text{g/mL}$)			
	<i>Staphylococcus aureus</i>	<i>Bacillus cereus</i>	<i>Serratia marcescens</i>	<i>Proteus merabilis</i>
5	20	20	20	25
6	20	20	20	20
7	25	20	20	20
8	20	20	25	20
10	20	20	20	20

high activity. Minimum inhibitory concentration (MIC) of the most potent compounds are listed in Table 2.

Carrageenan-Induced Rat Paw Edema (Anti-inflammatory)

Carrageenan-induced edema is a nonspecific inflammation resulting from a complex of diverse mediators. Since edemas of this type are highly sensitive to non steroidal anti-inflammatory drugs (NSAIDs), carrageenan has been accepted as a useful agent for studying new anti-inflammatory drugs. This model reliably predicts anti-inflammatory efficacy of the NSAIDs, and during the second phase it detects compounds which are anti-inflammatory agents as a result of inhibition of prostaglandin amplification. The method developed by Winter *et al.*³²⁾ was employed. Values, which are listed in Table 3, were expressed as the mean $\pm$ standard error (S.E.). Comparisons between means were carried out using one way ANOVA followed by Tukey multiple comparisons test. The results, listed in Table 3, revealed that some of the tested compounds

have higher efficacy than indomethacin.

Experimental

Chemistry Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded in KBr disks on a PerkinElmer, Inc. System 2000 Fourier transform (FT)-IR spectrophotometer (ν in cm^{-1}) and ^1H -NMR spectra on a DPX 300MHz Bruker FT-NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm) and coupling constant (J) values are given in Hz using tetramethyl silane (TMS) as internal standard and CDCl_3 or $\text{DMSO}-d_6$ as solvents. Elemental analysis was performed on a Perkin-Elmer 2400C, H, N analyzer. Elemental analysis indicated that the calculated and observed values were within the acceptable limits ($\pm 0.4\%$). The progress of reactions and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60F₂₅₄) (3 $\times$ 8 cm) and spots were located by Ultraviolet chamber. All the chemicals were obtained from Aldrich; all the solvents used were of commercial grade only. The antibacterial and anti-inflammatory were evaluated in Biochemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt.

Synthesis of 2-(2-Benzamido-3-phenylacrylamido)-3,5-dibromobenzoic Acid (1) A mixture of 3,5-dibromoanthranilic acid (0.01 mol, 2.95 g) and 4-benzylidene-2-phenyl-oxazole-5-one (0.01 mol, 2.49 g) in pyridine (30 mL) was stirred for one hour at room temperature. The precipitated solid was filtered off, washed with water, dried and crystallized from ethanol to give compound 1. Yellow solid, mp: 176–178°C, yield: 4.52 g (83%); IR, ν cm^{-1} : 3432, 3314 (br) (NH, OH),

Table 3. Rat Paw Edema and Percentage of Edema Inhibition

Compd. no.	Rat paw edema				% Edema inhibition			
	1 h	2 h	3 h	4 h	1 h	2 h	3 h	4 h
Control	117±9	137±12	152±12	132±14	-	-	-	-
Indomethacin	49±4	36.8±4	19.5±2.9	7.2±0.1	58.11	73.13	87.17	94.54
2	58±13	46±6	33±6	17±6	50.42	66.42	78.29	87.12
3a	40±6	45±3	22±8	18±2	65.81	67.15	85.52	86.36
3b	41±8	46±7	36±7	21±9	64.95	66.42	76.31	84.09
3c	39±3.2	46.1±2	27±2.5	19.3±1.4	66.66	66.35	82.23	85.38
3d	38±3.9	32±1.6	24±1.7	20±1.7	67.52	76.64	84.21	84.84
4	44±4	34±4	19±3	10±4	62.39	75.18	87.5	92.42
5	62±3	72±7	51±8	19±6	47.00	47.44	66.44	85.60
6	66±6	70±7	50±7	39±5	43.58	48.90	67.32	70.45
7	56±11	66±10	44±15	12±6	52.13	51.82	71.05	90.90
8	60±4	45±4	20±2	11±1	48.71	67.15	86.84	91.66
9	65±6	52±2	37±3	13±4	44.44	62.04	75.65	90.15
10	62±4.3	43±4	22±3	13±1	47.00	68.61	85.52	90.15
11	52±10	67±11	46±14	32±13	55.55	51.09	69.73	75.75
12	51±9	40±5	23±6	16±4	56.41	70.80	84.86	87.87
13	64±5	45±4	20±2	11±1	45.29	67.15	86.84	91.66
14	64±4	50±4	34±4	12±2	45.29	63.50	77.63	90.90
15a	42.7±3.9	47.9±2.7	29.1±3.0	18.1±1.8	63.50	65.03	80.85	86.28
15b	43±2.6	30±1.6	23±1.5	19±1.9	63.24	78.10	84.86	85.60
15c	40±10	47±12	34±9	15±7	65.81	65.69	77.63	88.63
16	48±12	44±7	31±6	15±4	58.97	67.88	79.60	88.63

1696, 1669, 1653 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 6.82 (s, 1H, CH=), 7.31–7.82 (m, 10, Ar-H two phenyl groups), 8.18, 8.34 (2s, 2H, Ar-H), 10.49 (brs, 2H, NH, D₂O exchangeable), 12.32 (brs, 1H, OH, D₂O exchangeable); ¹³C-NMR (DMSO-*d*₆) δ ppm: 118.2, 120.6, 122.7, 124.1, 125.0, 126.6, 127.3, 128.8, 132.6, 134.3, 141.7 (aromatic+*sp*²-C), 162.3, 166.1, 169.3 (CO); MS: *m/z*: 544 M⁺ (4.2%), 546 (9.6%), 548 (5.1%), 500 (M–CO₂ 43%), 502 (73.4%) and 504 (36.3%). *Anal.* Calcd for C₂₃H₁₆Br₂N₂O₄ (544): C, 50.74; H, 2.94; N, 5.15. Found: C, 51.11; H, 3.26; N, 5.44.

Synthesis of *N*-(1-(6,8-Dibromo-4-oxo-4*H*-benzo[*d*][1,3]-oxazin-2-yl)-2-phenylvinyl)benzamide (2**)** A solution of **1** (0.01 mol, 5.44g) in a freshly distilled acetic anhydride (30 mL) was refluxed for one hour. The excess acetic anhydride was removed in a rotatory evaporator. The solid obtained was washed with cold dilute sodium carbonate solution (20%, 3×50 mL) then with water (3×50 mL). The solid was collected by filtration, dried and recrystallized to furnish compound **2**. Pale yellow solid, mp: 124–126°C (from Light petroleum (L.P.), bp 100–120°C), yield: 3.11 g (59%); IR, ν cm^{−1}: 3421, 3303 (NH), 1749, 1676 (C=O), 1590 (C=N); ¹H-NMR (DMSO-*d*₆) δ ppm: 6.71 (s, 1H, CH=), 7.28–7.77 (m, 10, Ar-H two phenyl groups), 8.20, 8.37 (2s, 2H, Ar-H benzoxazinone), 10.22 (brs, 1H, NH, D₂O exchangeable); ¹³C-NMR (DMSO-*d*₆) δ ppm: 118.2, 120.6, 121.7, 123.1, 125.3, 126.6, 127.3, 128.8, 129.2, 131.4, 132.3, 134.2, 141.7, 143.1, 145.6 (aromatic+*sp*²-C), 161.3, 163.4 (CO); MS: *m/z*: 526 M⁺ (4.8%), 528 (10.1%), 530 (5.1%), 482 (M–CO₂ 22.6%), 484 (44.6%) and 486 (19.8%). *Anal.* Calcd for C₂₃H₁₄Br₂N₂O₃ (526): C, 52.47; H, 2.66; N, 5.32. Found: C, 52.11; H, 3.02; N, 5.68.

Synthesis of 2-(2-Benzamido-3-phenylacrylamido)-3,5-dibromo-*N*-substitutedbenzamide (3a–c**) and *N*-(3-(2,4-Dibromo-6-(2-phenylhydrazinecarbonyl)phenylamino)-3-**

oxo-1-phenylprop-1-en-2-yl)benzamide (3d**)** In 30 mL of ethyl alcohol, a mixture of **2** (0.01 mol, 5.26 g) and amines (0.01 mol), namely aniline, *t*-butyl amine, benzyl amine and/or phenyl hydrazine, was refluxed for 3 h. The solid precipitated upon cooling was filtered off and recrystallized from suitable solvent to afford compounds **3a–d**, respectively.

Compound **3a**

Yellow solid, mp: 196–198°C (from ethanol), yield: 4.7 g (76%); IR, ν cm^{−1}: 3385–3230 (NH), 1674, 1659, 1645 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 6.68 (s, 1H, CH=), 7.22–7.71 (m, 15, Ar-H three phenyl groups), 8.16, 8.33 (2s, 2H, Ar-H, C4, C6), 9.28 (s, 1H, NH, D₂O exchangeable), 10.66 (brs, 2H, NH, D₂O exchangeable); ¹³C-NMR (DMSO-*d*₆) δ ppm: 118.4, 119.2, 120.3, 121.2, 122.1, 123.4, 125.3, 126.2, 127.3, 127.9, 128.8, 129.2, 131.2, 132.3, 134.2, 135.6, 138.4, 139.5, 140.3 (aromatic+*sp*²-C), 163.3, 164.6, 166.6 (CO); MS: *m/z*: 619 M⁺ (7.8%), 621 (16.1%), 623 (8.4%), M–CONHPh 499 (18.8%), 501 (34.5%) and 503 (16.9%). *Anal.* Calcd for C₂₉H₂₁Br₂N₃O₃ (619): C, 56.22; H, 3.39; N, 6.78. Found: C, 56.56; H, 3.61; N, 6.43.

Compound **3b**

Yellow solid, mp: 184–186°C (from ethanol), yield: 4.7 g (76%); IR, ν cm^{−1}: 3372–3214 (NH), 1671, 1655, 1640 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 1.32 (s, 9H, *t*-Bu), 6.59 (s, 1H, CH=), 7.29–7.81 (brm, 10, Ar-H), 8.14, 8.34 (2s, 2H, Ar-H, C4, C6), 9.06 (s, 1H, NH, D₂O exchangeable), 10.61 (brs, 2H, NH, D₂O exchangeable). *Anal.* Calcd for C₂₇H₂₅Br₂N₃O₃ (599): C, 54.09; H, 4.17; N, 7.01. Found: C, 54.42; H, 4.44; N, 6.74.

Compound **3c**

mp: 135–137°C (from benzene), yield: 4.49 g (71%); IR, ν cm^{−1}: 3334–3202 (NH), 1672, 1658, 1643 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 4.83 (d, 2H, CH₂), 6.62 (s, 1H, CH=), 7.26–7.76 (brm, 15, Ar-H), 8.18, 8.35 (2s, 2H, Ar-H, C4, C6),

8.94 (s, 1H, NH, D₂O exchangeable), 10.69 (brs, 2H, NH, D₂O exchangeable). *Anal.* Calcd for C₃₀H₂₅Br₂N₃O₃ (633): C, 56.87; H, 3.63; N, 6.64. Found: C, 57.13; H, 3.88; N, 6.92.

N-(3-(2,4-Dibromo-6-(2-phenylhydrazinecarbonyl)-phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (**3d**)

mp: 182–184°C (from acetic acid), yield: 4.69 g (74%); IR, ν cm⁻¹: 3350–3242 (NH), 1677, 1660, 1646 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 6.71 (s, 1H, CH=), 7.30–7.80 (m, 15, Ar-H), 8.16, 8.34 (2s, 2H, Ar-H, C3, C5), 9.12 (s, 1H, NH, D₂O exchangeable), 9.39 (s, 1H, NH, D₂O exchangeable), 10.51 (brs, 2H, NH, D₂O exchangeable). *Anal.* Calcd for C₂₉H₂₂Br₂N₄O₃ (634): C, 54.89; H, 3.47; N, 8.83. Found: C, 54.55; H, 3.31; N, 8.56.

Synthesis of Benzamide Derivatives (4a, b) Compound **2** (0.01 mol, 5.26 g) was refluxed in 50 mL of ethanol with piperidine and/or morpholine (0.01 mol) for 3 h. The excess alcohol was removed in a rotatory evaporator. The solid obtained was recrystallized from a suitable solvent to give compounds **4a** and **b**.

N-(3-(2,4-Dibromo-6-(morpholine-4-carbonyl)-phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (**4a**)

mp: 159–161°C (from ethanol), yield: 3.80 g (62%); IR, ν cm⁻¹: 3321, 3179 (NH), 1675, 1658, 1641 (C=O); ¹H-NMR (CDCl₃) δ ppm: 2.98 (br, 4H), 3.46 (br, 4H), 6.44 (s, 1H, CH=), 7.27–7.82 (m, 10, Ar-H), 8.21, 8.41 (2s, 2H, Ar-H, C3, C5), 9.88 (brs, 2H, NH, D₂O exchangeable). *Anal.* Calcd for C₂₇H₂₃Br₂N₃O₄ (613): C, 52.85; H, 3.75; N, 6.85. Found: C, 52.57; H, 4.01; N, 7.12.

N-(3-(2,4-Dibromo-6-(piperidine-4-carbonyl)phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (**4b**)

mp: 172–174°C (from ethanol), yield: 4.10 g (67%); IR, ν cm⁻¹: 3312, 3183 (NH), 1678, 1663, 1649 (C=O); ¹H-NMR (CDCl₃) δ ppm: 1.68–3.54 (brm, 10H, piperidine ring), 6.54 (s, 1H, CH=), 7.33–7.79 (m, 10, Ar-H), 8.20, 8.39 (2s, 2H, Ar-H, C3, C5), 9.79 (brs, 2H, NH, D₂O exchangeable). *Anal.* Calcd for C₂₈H₂₅Br₂N₃O₃ (611): C, 54.99; H, 4.09; N, 6.87. Found: C, 54.66; H, 3.88; N, 6.56.

Synthesis of *N*-(1-(3-Amino-6,8-dibromo-4-oxo-3,4-dihydroquinazolin-2-yl)-2-phenylvinyl)benzamide (5) A solution of **2** (0.01 mol, 5.26 g) and hydrazine hydrate (0.05 mol, 80%) in 50 mL *n*-butanol was refluxed for 12 h. The excess solvent was evaporated under vacuum. The solid deposited was recrystallized to give compound **5**. mp: 110–112°C (from L.P., 60–80°C), yield: 2.81 g (52%); IR, ν cm⁻¹: 3429–3230, 3110 (NH₂, NH), 1678, 1654 (C=O); ¹H-NMR (CDCl₃) δ ppm: 4.86 (brs, 2H, NH₂, D₂O exchangeable), 6.32 (s, 1H, CH=), 7.22–7.74 (m, 10, Ar-H), 8.13, 8.30 (2s, 2H, Ar-H, quinazolinone), 9.13 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (DMSO-*d*₆) δ ppm: 118.2, 119.7, 121.2, 122.4, 123.6, 125.3, 126.2, 127.4, 127.9, 128.6, 131.2, 133.3, 134.2, 135.6, 138.4, 139.5, 140.2 (aromatic+*sp*²-C), 161.3 (pyrimidine C-2), 162.6, 164.5 (CO); MS: *m/z*: 619 M⁺ (10.1%), 621 (18.9%) and 623 (9.4%). *Anal.* Calcd for C₂₉H₂₁Br₂N₃O₃ (619): C, 56.22; H, 3.39. *Anal.* Calcd for C₂₃H₁₆Br₂N₄O₂ (540): C, 51.11; H, 2.96; N, 10.37. Found: C, 51.44; H, 3.28; N, 10.67.

Synthesis of *N*-(1-(3-Benzylideneamino)-6,8-dibromo-4-oxo-3,4-dihydroquinazolin-2-yl)-2-phenylvinyl)benzamide (6) A mixture of **5** (0.01 mol, 5.4 g) and benzaldehyde (0.01 mol) in 60 mL of ethanol, containing a few drops of piperidine as a catalyst, was refluxed for 3 h. The solid separated out upon cooling was filtered off and recrystallized

to produce compound **6**. mp: 184–186°C (from benzene), yield: 3.58 g (57%); IR, ν cm⁻¹: 3281 (NH), 1672, 1651 (C=O); ¹H-NMR (CDCl₃) δ ppm: 6.23 (s, 1 H, CH=), 7.27–7.69 (m, 15, Ar-H), 8.13, 8.28 (2s, 2H, Ar-H, quinazolinone), 8.79 (s, 1H, N=CH), 9.33 (s, 1H, NH, D₂O exchangeable). *Anal.* Calcd for C₃₀H₂₀Br₂N₄O₂ (628): C, 57.32; H, 3.18; N, 8.91. Found: C, 57.57; H, 3.48; N, 9.29.

Synthesis of *N*-(1-(6,8-Dibromo-3-hydroxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-phenylvinyl)benzamide (7) A solution of **2** (0.01 mol, 5.26 g) and hydroxylamine hydrochloride (0.015 mol, 1.05 g) in 50 mL ethanol containing 30 mL pyridine was refluxed for 3 h. The solid separated after cooling was filtered off, washed with ethanol (30 mL), dried and crystallized to give compound **7**. mp: above 240°C (from ethanol), yield: 3.30 g (61%); IR, ν cm⁻¹: broad 3404–3244 (OH, NH), 1671, 1650 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 6.52 (s, 1H, CH=), 7.29–7.78 (m, 10, Ar-H), 8.19, 8.37 (2s, 2H, Ar-H, quinazolinone), 9.44 (s, 1H, NH, D₂O exchangeable), 10.22 (brs, 1H, OH, D₂O exchangeable); ¹³C-NMR (DMSO-*d*₆) δ ppm: 118.1, 119.8, 121.3, 122.4, 123.6, 125.1, 126.2, 127.4, 127.7, 128.6, 131.2, 133.4, 134.2, 135.6, 138.2, 139.5, 140.2 (aromatic+*sp*²-C), 162.1 (pyrimidine C-2), 162.6, 164.5 (CO); MS: *m/z*: 541 M⁺ (14.1%), 543 (27.9%) and 545 (13.4%). *Anal.* Calcd for C₂₃H₁₅Br₂N₃O₃ (541): C, 51.02; H, 2.77; N, 7.76. Found: C, 51.37; H, 3.01; N, 8.00.

Synthesis of *N*-(1-(6,8-Dibromo-4-oxo-3,4-dihydroquinazolin-2-yl)-2-phenylvinyl)benzamide (8) Compound **2** (0.01 mol, 5.26 g) was fused with excess formamide (5 mL) and/or ammonium acetate (2 g) in an oil bath at 190°C for 2 h. The solid product obtained was washed with water (3×50 mL), dried and crystallized to furnish compound **8**. mp: above 240°C (from ethanol), yield: 3.15 g (60%); IR, ν cm⁻¹: 3362, 3281 (NH), 1677, 1657 (C=O); ¹H-NMR (DMSO-*d*₆) δ ppm: 6.66 (s, 1H, CH=), 7.35–7.81 (m, 10, Ar-H), 8.17, 8.36 (2s, 2H, Ar-H, quinazolinone), 8.82 (s, 1H, NH, quinazolinone ring, D₂O exchangeable), 10.05 (brs, 1H, NH, D₂O exchangeable). *Anal.* Calcd for C₂₃H₁₅Br₂N₃O₂ (525): C, 52.57; H, 2.85; N, 8.00. Found: C, 52.86; H, 3.22; N, 7.70.

Synthesis of *N*-(1-(3-Acetyl-6,8-dibromo-4-oxo-3,4-dihydroquinazolin-2-yl)-2-phenylvinyl)benzamide (9) A solution of **8** (0.01 mol, 5.25 g) in 30 mL acetic anhydride was refluxed for 6 h. The reaction mixture was then allowed to stand at room temperature for 2 h. The separated solid product was washed with water (4×100 mL), dried and crystallized to afford compound **9**. mp: 130–132°C (from L.P., 100–120°C), yield: 3.74 g (66%); IR, ν cm⁻¹: 3281 (NH), 1679, 1663, 1649 (C=O); ¹H-NMR (CDCl₃) δ ppm: 2.23 (s, 3H, CH₃-C=O), 6.48 (s, 1H, CH=), 7.24–7.73 (m, 10, Ar-H), 8.18, 8.35 (2s, 2H, Ar-H, quinazolinone), 9.91 (brs, 1H, NH, D₂O exchangeable). *Anal.* Calcd for C₂₅H₁₇Br₂N₃O₃ (567): C, 52.91; H, 3.00; N, 7.41. Found: C, 53.23; H, 3.31; N, 7.77.

Synthesis of Ethyl 2-(2-(1-Benzamido-2-phenylvinyl)-6,8-dibromoquinazolin-4-yloxy)acetate (10) To a mixture of **8** (0.01 mol, 5.25 g) and ethyl chloroacetate (0.04 mol, 4.9 g) in dry acetone (50 mL), anhydrous potassium carbonate (0.05 mol, 6.9 g) was added and refluxed on a water-bath for 20 h. The reaction mixture was washed with water (3×100 mL). The organic material was extracted with ether (2×100 mL) and left for slow evaporation. The solid obtained was crystallized to furnish **10** as pale yellow crystals, mp: 185–187°C (from ethanol), yield: 4.52 g (74%); IR, ν cm⁻¹: 3281, 3193 (NH),

1733, 1659 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.25–1.34 (t, $J=6.5\text{ Hz}$, 3H, $\text{CH}_3\text{--CH}_2\text{--}$), 4.14–4.27 (q, $J=6.6\text{ Hz}$, 2H, $\text{--OCH}_2\text{CH}_3$), 4.78 (s, 2H, $\text{O--CH}_2\text{--C=O}$), 6.53 (s, 1H, CH=), 7.26–7.75 (m, 10, Ar-H), 8.19, 8.38 (2s, 2H, Ar-H, quinazolone), 10.05 (brs, 1H, NH, D_2O exchangeable). *Anal.* Calcd for $\text{C}_{27}\text{H}_{21}\text{Br}_2\text{N}_3\text{O}_4$ (611): C, 53.03; H, 3.44; N, 6.87. Found: C, 52.72; H, 3.22; N, 7.19.

Synthesis of 2-(5-(1-Benzamido-2-phenylvinyl)-1H-tetrazol-1-yl)-3,5-dibromobenzoic Acid (11) and N-(3-(5,7-Dibromo-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (12) Sodium azide (0.016 mol, 1.04 g) was dissolved in minimal amount of water and added to a solution of **2** (0.01 mol, 5.26 g) in 15 mL glacial acetic acid. The reaction mixture was refluxed for 4 h and left to cool. The solid deposited was collected by filtration, dried and underwent fractional crystallization where compound **12** obtained from L.P., 40–60°C and compound **11** from ethanol.

2-(5-(1-Benzamido-2-phenylvinyl)-1H-tetrazol-1-yl)-3,5-dibromobenzoic Acid (11)

mp: above 240°C (from ethanol), yield: 1.99 g (35%); IR, $\nu\text{ cm}^{-1}$: 3445, 3293 (OH, NH), 1694, 1662 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 6.48 (s, 1H, CH=), 7.23–7.79 (m, 10, Ar-H), 8.16, 8.37 (2s, 2H, Ar-H), 9.92 (brs, 1H, NH, D_2O exchangeable), 11.12 (s, 1H, --COOH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 110.1, 120.8, 121.5, 122.7, 123.6, 125.3, 126.2, 127.4, 127.7, 128.6, 131.3, 133.4, 134.5, 135.6, 138.0, 139.5, 140.0 (aromatic+ sp^2 -C), 146.1 (tetrazol C), 162.6, 170.3 (CO); MS: m/z : 569 M^+ (16.1%), 571 (33.1%) and 573 (15.4%). *Anal.* Calcd for $\text{C}_{23}\text{H}_{15}\text{Br}_2\text{N}_5\text{O}_3$ (569): C, 48.51; H, 2.64; N, 12.30. Found: C, 48.83; H, 3.00; N, 11.99.

N-(3-(5,7-Dibromo-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (12)

mp: 102–104°C (from L.P., 40–60°C), yield: 1.57 g (29%); IR, $\nu\text{ cm}^{-1}$: 3308, 3279 (NH), 1723, 1678, 1657 (C=O); $^1\text{H-NMR}$ (CDCl_3) δ ppm: 6.38 (s, 1H, CH=), 7.24–7.80 (m, 10, Ar-H), 8.15, 8.39 (2s, 2H, Ar-H), 9.81 (brs, 1H, NH, D_2O exchangeable), 10.18 (s, 1H, NH, D_2O exchangeable); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 118.2, 120.5, 121.6, 123.1, 125.6, 126.3, 126.8, 127.3, 128.4, 129.3, 131.4, 132.3, 134.6, 134.9 (aromatic+ sp^2 -C), 157.3, 161.3, 163.4 (CO); MS: m/z : 541 M^+ (5.6%), 543 (10.3%) and 545 (5.1%). *Anal.* Calcd for $\text{C}_{23}\text{H}_{15}\text{Br}_2\text{N}_3\text{O}_3$ (541): C, 51.02; H, 2.77; N, 7.76. Found: C, 51.33; H, 3.06; N, 8.08.

Synthesis of 4-Benzamido-8,10-dibromo-6-oxo-3-phenyl-1,2,3,6-tetrahydro-benzo[d]pyrido-[2,1-b][1,3]oxazine-1,2-dicarboxylic Acid Anhydride (13) Maleic anhydride (0.01 mol, 0.98 g) and compound **2** (0.01 mol, 5.26 g) were dissolved in 50 mL dry xylene and the reaction mixture was refluxed for 20 h. The solvent was removed by rotatory evaporator. The solid obtained was washed with cold dilute sodium carbonate solution, followed by water (3×100 mL), dried and crystallized from a suitable solvent to afford **13**. mp: 183–185°C (from L.P., 100–120°C), yield: 3.37 g (54%); IR, $\nu\text{ cm}^{-1}$: 3246 (NH), 1772, 1739, 1653 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 4.43–4.59 (m, 3H, pyridine ring), 7.28–7.83 (m, 10, Ar-H), 8.15, 8.35 (2s, 2H, Ar-H, quinazolone), 9.77 (brs, 1H, NH, D_2O exchangeable); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 27.3, 38.1, 61.0 (sp^3 -C), 95.0, 107.3, 108.7, 110.5, 118.2, 122.7, 123.1, 124.0, 128.6, 129.0, 131.8, 135.6, 137.3, 147.7 (aromatic+ sp^2 -C), 165.3, 168.1, 169.3 (CO); MS: m/z : 624 M^+ (11.6%), 626 (21.3%) and 628 (10.1%). *Anal.* Calcd for $\text{C}_{27}\text{H}_{16}\text{Br}_2\text{N}_2\text{O}_6$ (624):

C, 51.92; H, 2.56; N, 4.49. Found: C, 51.66; H, 2.80; N, 4.20.

Synthesis of 4-Benzamido-8,10-dibromo-6-oxo-3-phenyl-1,2,3,6-tetrahydrobenzo[d]pyrido-[2,1-b][1,3]oxazine-1,2-dicarboxylic Acid (14) A suspension of **13** (0.005 mol, 3.12 g) in ethanolic sodium hydroxide solution (30 mL, 10%) was refluxed for 2 h, filtered while hot. The filtrate was acidified with ice–HCl mixture and the precipitate obtained was collected by filtration, washed with water (3×100), dried and crystallized from suitable solvent to furnish the diacid **14**. mp: 225–227°C (from ethanol), yield: 2.60 g (81%); IR, $\nu\text{ cm}^{-1}$: broad 3451–2783, (OH, NH), 1764–1651 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 4.21–4.36 (m, 3H, pyridine ring) 7.24–7.80 (m, 10, Ar-H), 8.12, 8.31 (2s, 2H, Ar-H, quinazolone), 9.86 (brs, 1H, NH, D_2O exchangeable), 11.24, 11.53 (s, 2H, --2COOH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 26.3, 39.4, 60.0 (sp^3 -C), 93.1, 111.5, 115.6, 120.5, 121.4, 122.3, 122.7, 123.1, 125.0, 127.6, 128.2, 129.0, 131.8, 132.4, 135.6, 137.3, 147.6 (aromatic+ sp^2 -C), 161.3, 168.1, 173.3 (CO); MS: m/z : 642 M^+ (5.1%), 644 (9.3%) and 646 (5.0%). *Anal.* Calcd for $\text{C}_{27}\text{H}_{18}\text{Br}_2\text{N}_2\text{O}_7$ (642): C, 50.47; H, 2.80; N, 4.36. Found: C, 50.11; H, 3.09; N, 4.00.

Synthesis of N-(3-(2-Benzoyl-4,6-dibromophenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (15a), N-(3-(2,4-Dibromo-6-(4-methylbenzoyl)phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (15b) and N-(3-(2,4-Dibromo-6-(4-isopropylbenzoyl)phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (15c) A solution of **2** (0.01 mol, 5.26 g) in dry aromatic hydrocarbons (100 mL, namely benzene, toluene and/or cumene) was added gradually to a cold suspension of anhydrous aluminium chloride (0.04 mol, 5.34 g) in excess of the same hydrocarbon with continuous stirring. The temperature of the reaction mixture was not allowed to rise above 60°C. After the addition complete, the reaction mixture was heated on a water bath (at 60°C) for 10 h, then poured into hydrochloric acid containing crushed ice. The separated solid product was filtered off and crystallized from a suitable solvent to give compounds **15a–c**, respectively.

N-(3-(2-Benzoyl-4,6-dibromophenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (15a)

mp: 192–194°C (from benzene), yield: 5.01 g (83%); IR, $\nu\text{ cm}^{-1}$: 3404, 3333 (NH), 1688, 1668, 1644 (C=O). *Anal.* Calcd for $\text{C}_{29}\text{H}_{20}\text{Br}_2\text{N}_2\text{O}_3$ (604): C, 50.47; H, 2.80; N, 4.36. Found: C, 50.11; H, 3.09; N, 4.00.

N-(3-(2,4-Dibromo-6-(4-methylbenzoyl)phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (15b)

mp: 221–223°C (from benzene), yield: 5.13 g (83%); IR, $\nu\text{ cm}^{-1}$: 3421, 3318 (NH), 1691, 1665, 1642 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.77 (s, 3H, CH_3), 6.56 (s, 1H, CH=), 7.29–7.73 (m, 14, Ar-H), 8.13, 8.27 (2s, 2H, Ar-H, quinazolone), 9.89 (brs, 2H, 2NH, D_2O exchangeable); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 22.3 (sp^3 -C), 119.5, 120.6, 122.6, 123.1, 124.2, 125.3, 126.6, 127.3, 128.8, 129.2, 131.4, 132.3, 135.7, 134.2, 141.7, 142.1, 142.5 (aromatic+ sp^2 -C), 161.3, 163.4 (CO); MS: m/z : 618 M^+ (4.8%), 620 (10.3%) and 622 (3.7%). *Anal.* Calcd for $\text{C}_{30}\text{H}_{22}\text{Br}_2\text{N}_2\text{O}_3$ (618): C, 58.25; H, 3.56; N, 4.53. Found: C, 58.01; H, 3.33; N, 4.31.

N-(3-(2,4-Dibromo-6-(4-isopropylbenzoyl)phenylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (15c)

mp: 212–214°C (from benzene), yield: 4.91 g (76%); IR, $\nu\text{ cm}^{-1}$: 3412, 3309 (NH), 1686, 1663, 1645 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.18 (d, 6H, 2 CH_3), 4.13–4.27 (m, 1H,

CH), 6.43 (s, 1H, CH=), 7.31–7.79 (m, 12, Ar-H), 8.18, 8.35 (2s, 2H, Ar-H, quinazolone), 9.83 (br_s, 2H, 2NH, D₂O exchangeable). *Anal.* Calcd for C₃₂H₂₆Br₂N₂O₃ (646): C, 59.44; H, 4.02; N, 4.33. Found: C, 59.08; H, 3.77; N, 4.06.

Synthesis of Ethyl 3-(2-(2-Benzamido-3-phenylacrylamido)-3,5-dibromophenyl)-3-oxo-propanoate (16) A mixture of **2** (0.01 mol, 5.26 g) and diethyl malonate and/or ethyl acetoacetate (0.03 mol) in dry pyridine (50 mL) was refluxed for 12 h. The reaction mixture was poured into ice-cold dilute hydrochloric acid, and the precipitated products were filtered off and recrystallized from benzene to give the same product **16**. mp: 175–177°C (from benzene), yield: 5.13 g (83%); IR, ν cm⁻¹: 3421, 3318 (NH), 1736, 1689, 1656, 1642 (C=O); ¹H-NMR (CDCl₃) δ ppm: 1.23–1.32 (t, J =6.5 Hz, 3H, CH₃–CH₂–), 3.75 (s, 2H, CH₂–C=O), 4.24–4.35 (q, J =6.6 Hz, 2H, –OCH₂CH₃), 6.48 (s, 1H, CH=), 7.20–7.72 (m, 12, Ar-H), 8.14, 8.32 (2s, 2H, Ar-H, quinazolone), 10.11 (brs, 2H, 2NH, D₂O exchangeable); ¹³C-NMR (DMSO-*d*₆) δ ppm: 15.3, 44.6, 59.1 (*sp*³-C), 118.5, 119.6, 120.5, 121.6, 122.3, 122.7, 123.4, 126.6, 127.6, 128.2, 129.0, 131.7, 132.4, 135.6, 137.3, 142.4 (aromatic+*sp*²-C), 161.6, 168.1, 170.3, 189.2 (CO); MS: *m/z*: 614 M⁺ (2.3%), 616 (3.9%) and 618 (1.8%). *Anal.* Calcd for C₂₇H₂₂Br₂N₂O₅ (614): C, 52.77; H, 3.58; N, 4.56. Found: C, 53.03; H, 3.31; N, 4.88.

Pharmacological Assay

Antimicrobial Activity

One milligram of each compound was dissolved in dimethyl sulfoxide (DMSO, 1 mL) then made up to 10 mL with sterile water to give a concentration of 100 µg/mL. The bacteria were maintained on nutrient agar media. The agar media was incubated with the different tested microorganisms. After 24–48 h of incubation at 37°C, DMSO showed no inhibition zones. The diameters of the inhibition zones of the tested compounds were measured.

Anti-inflammatory Activity

Albino Wistar rats of either sex (130–150 g) were divided into various groups of six animals each. Animals were deprived of food for 12 h prior to experiment and only water was given *ad-libitum*. First group was used as a control group and received 1 mL of 20% (v/v) DMSO solution; the second group received indomethacin orally (10 mg/kg) dissolved in 20% (v/v) DMSO solution. Other groups received DMSO solution of test compounds at a dose of 100 mg/kg orally. One hour after the administration of the tested compounds, carrageenan suspension (0.1 mL of 1% (w/v) suspension in 0.9% saline solution) was injected into the sub-planter region of left hind paw of animals. Immediately, the paw volume was measured initial paw volume using plethysmometer (UGO Basile 21025 Comerio, Italy) before carrageenan injection. Thereafter, the paw volume was measured after 1, 2, 3 and 4 h after carrageenan administration. The difference between initial and subsequent readings gave the change in edema volume for the corresponding time. Edema volume of control (V_c) and treated (V_t) animals were used to calculate percentage (%) of edema volume and edema inhibition by using following formula:

$$\% \text{ Edema volume} = 100 \times (V_t / V_c)$$

$$\% \text{ Inhibition} = [1 - (V_t / V_c)] \times 100$$

Conclusion

In present study, we have synthesized some new ben-

zoxazinones and quinazolinones using *N*-(1-(6,8-dibromo-4-oxo-4*H*-benzo[*d*][1,3]-oxazin-2-yl)-2-phenylvinyl)benzamide as starting material. The newly synthesized compounds were screened for different bacterial and fungal strains and against Carrageenan-induced rat paw edema. Most of the synthesized compounds showed moderate to high antimicrobial and anti-inflammatory activities.

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Conflict of Interest The authors declare no conflict of interest.

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