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Synthesis, Characterization, and Biological Activities of Novel Schiff Bases Derived from 3-acetyl-4-hydroxy-2h-chromen-2-one and 5-(4-ethoxy/ halo substituted phenyl)-1,3,4-oxadiazol-2-amine

Jadhav R.L., Ubale S.B.
Department of Chemistry, Swa. Sawarkar College, Beed, Maharashtra, India

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ABSTRACT

Five novel Schiff base ligands (5a-e) were synthesized by condensing 3-acetyl-4-hydroxy-2H-chromen-2-one with 5-(4-ethoxy/ halo substituted phenyl)-1, 3, 4-oxadiazol-2-amine. Their structures were confirmed using different methods like elemental analysis, infrared spectra, 1H and 13C NMR, and mass spectroscopy. The antibacterial and antifungal activity of the synthesized compounds was studied against selected bacterial cultures; gram- negative E. coli, S. typhi and gram-positive S. aureus, B. subtilis. It was observed that all the compounds except 5a showed strong antibacterial effects against these bacteria, similar to penicillin, which is a standard antibacterial drug, because they contain halogen elements. Furthermore, they underwent testing against fungi like A. niger, P. chrysogenum, F. moniliforme and A. flavus, employing the poison plate method. Compound 5a had moderate antifungal activity compared to 5b-e. Compounds 5b-e showed excellent antifungal activity, similar to Griseofulvin, a standard antifungal drug. In brief, it may be concluded that antimicrobial activity may be attributed to the presence of both the Coumarin and oxadiazole moiety in the molecule.

Keywords : Coumarin, 3-acetyl-4-hydroychromen-2-one, 5-(4-ethoxy/ halo substituted phenyl)-1, 3, 4-oxadiazol-2-amine, Schiff bases and biological activity

I. INTRODUCTION

Schiff bases carry the azomethine functional group (-C=N-), which has predictable implications in the medicinal and pharmaceutical fields due to its applications in organic synthesis. They are versatile organic intermediates with a wide range of biological activities, including antibacterial and antifungal [1,2], analgesic effects [3], anti-inflammatory [4], anti-mycobacterial activity [5], anti-tuberculosis potential [6], anti-cancer properties [7], and anti-convulsant effect [8,9].

On the other hand, compounds containing coumarin derivatives hold great importance in medicinal applications. Numerous research papers have reported on the antibacterial, antiviral, anti-HIV, anticoagulant, and cytotoxic properties of coumarin derivatives [10-18]. In addition to this, they find applications as perfumes, cosmetics, dyes, herbicides and food additives [19, 20].

Among the isomers of oxadiazole, 1, 3, 4-oxadiazole is a versatile pilot nucleus for designing probable bioactive agents [21]. The oxadiazole nucleus has been recognized as an essential part in the synthesis of heterocyclic compounds exhibiting promising pharmacological properties. A wide range of therapeutic applications for oxadiazole derivatives has been explored in the literature, including anticancer [22-25], antitubercular [26, 27], antibacterial [27], antifungal [28], anti-HIV [29], anti-inflammatory [30], and insecticidal [31] activities. Due to the enhanced hydrolytic and metabolic stability of the oxadiazole ring, which has been frequently experimentally validated, this structural motif plays a significant role in pharmaceutical manufacturing [32]. Consequently, 1, 3, 4-oxadiazole moiety has become a target for several drug discovery programs, encompassing analgesic, antibacterial, anti-inflammatory, anti-malarial, antidepressant agents, hyperglycemic agents, fungicidal agents, and others [33,34]. As a result, derivatives of coumarin and oxadiazole have garnered increasing attention for their broad range of biological and pharmacological activities.

The literature review demonstrates that there has been significant research work on Schiff bases resulting from the reaction of 3-acetyl-4-hydroxy-2H-chromen-2-one with substituted anilines and hydrazones [35-37]. However, there has been relatively little work executed on Schiff bases derived from 3-acetyl-4-hydroxychromen-2-one and heterocyclic amines [38]. In the present paper, we report the synthesis of novel Schiff bases obtained from 3-acetyl-4-hydroxy-chromen-2-one and 5-(4-substitutedphenyl)-1,3,4-oxadiazol-2-amine. The incorporation of these two key structural motifs aims to impart enhanced biological activities to the resulting compounds. The synthesis and characterization of these Schiff bases are crucial steps towards exploring their potential pharmacological applications. The synthesized compounds were characterized and their biological activity was assessed against different selected cultures of bacterial and fungi.

II. METHODS AND MATERIAL

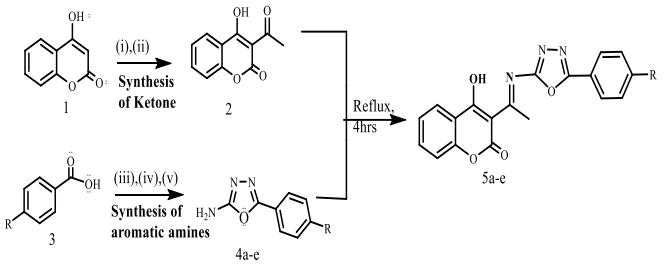
Chemicals and Instrumentations: All the chemicals and solvents utilized were of AR Grade and purchased from SD fine chemicals and E Merk. The purity of these compounds was confirmed through TLC, and melting points were determined using an open capillary tube and uncorrected. IR (KBr, cm^{-1}) spectra were recorded using a Shimadzu FTIR-8300 spectrophotometer with $CHCl_3$ as solvent. The ^{1}HNMR (300 MHz) and ^{13}CNMR (300 MHz) spectra were acquired using a Brucker Avance DPX-250 spectrometer in $CDCl_3$, with TMS serving as internal standard. The δ scale is used to denote the chemical shift values. Mass spectra were obtained using a Finnigan Mat LCQ mass spectrometer with methanol as mobile phase. The synthesized Schiff bases were subjected to screening against different bacterial species using the Agar cup method and against fungal species using the poison plate method.

Procedure for the synthesis of 3-acetyl-4-hydroxychromen-2-one (2): The mixture containing 4-hydroxy-chromen-2-one (4g, 24.7 mmoles) dissolved in 16 mL acetic acid, along with 7.5 mL phosphorous oxychloride, was subjected to reflux for 30 minutes. After cooling, the resulting precipitate was recrystallized using ethanol. This process yielded 4.64g (92%) of 3-acetyl-4-hydroxy-chromen-2-one (2), which presented as white needle-shaped crystals with melting point of 134-136^{0}C. Notably, the

observed melting point closely matched the literature values [35-41].

General method of synthesis of 5-(4-substitutedphenyl)-1, 3, 4-oxadiazol-2-amine (4a-e): The procedure described in reference [42-44] was followed with appropriate adjustments to synthesize these aromatic primary amines. To elaborate, a mixture comprising 1 mole of p-substituted benzoic acid and 1 mole of semicarbazide (0.455g) was dissolved in 5 mL of phosphorous oxychloride and subjected to reflux for a duration of 50 minutes. After completing the reflux, the reaction mixture was allowed to cool down to room temperature. After that, 5 mL of water was carefully poured in. Then, the mixture was reflux again for 4-5 hours. It was filtered while still hot, and the solid was washed with warm water. The filtrate was made basic with saturated potassium hydroxide. The solid that formed was filtered out and purified by dissolving it in ethanol and letting it crystallize again.

General procedure for the synthesis of novel Schiff bases (5a-e): In Fig: 1 Scheme, synthesized the novel Schiff bases, (3-(1-((5-(4-ethoxy/ halo substituted phenyl)-1,3,4-oxadiazol-2-yl) imino) ethyl)-4-hydroxy-2H-chromen-2-one) as: An equimolar mixture of 3-acetyl-4-hydroxy-chromen-2-one and 5-(4-hsubsttutedphenyl)-1,3,4-oxadiazol-2-amine was dissolved in ethanol and subjected to reflux for a duration of 4 hours. After cooling, the resulting product was isolated through crystallization using appropriate solvents. The purity of the Schiff bases was assessed using TLC, melting point determination (m. p.), and elemental analysis. Further characterization was performed through IR spectroscopy, ^{1}HNMR, ^{13}CNMR, and mass spectral studies.



(i) Acetic acid, (ii) Phosphoryl trichloride ($POCl_3$), (iii) Semicarbazide, (iv) $POCl_3$, (v) KOH
R=(a)-OC_2H_5,(b)-F, (c)-Cl, (d) -Br, (e) -I

Fig.1: Scheme outlining the synthesis of novel Schiff's Bases (5a-e)

Biological Activity: Antimicrobial testing is useful for new drug development, epidemiology, and therapy. Novel Schiff bases are screened along with pure drugs to assess their potential as antimicrobial agents through in vitro examination.

Anti-bacterial Evaluation:

The antibacterial activity assessment was carried out utilizing the agar cup-plate method as described in references [45-46]. Nutrient agar (Himedia) was prepared and sterilized in an autoclave at 15 Psi for 15 minutes to ensure aseptic conditions. After it cooled down, it was inoculated with inoculated bacteria, including *Escherichia coli, Salmonella typhi Staphylococcus aureus,* and *Bacillus subtilis.* Each kind of bacterium was dispensed onto a Petri dish. Wells of experiments were established by employing 10mm corks, into which 1% ethanolic Schiff bases were introduced in each cup, while controls contained ethanol in certain instances. Furthermore, a 100µl solution of penicillin in 0.1% ethanol was applied onto the seeded nutrient agar surface as the positive control. Plates were refrigerated for 15 minutes, and then inoculated at 37 ^{0}C for 24 hours. A zone reader tool used for zone inhibition and it measured in millimeters. Finally, we recorded our findings in a table-3.

Antifungal Evaluation:

The antifungal activity was evaluated using the Poison plate method [45-46]. The Potato Dextrose Agar made from Himedia just right and then put it in an autoclave at 10 Psi for 15 minutes to sterilize it. After sterilization, the Schiff base was introduced into

the sterile medium under sterile surroundings, reaching a concentration of 1%. A dish containing ethanol was prepared to serve as the negative control. Another plate with 1% Griseofulvin the standard reference plate was set up as the positive control. The selected fungal cultures *Aspergillus niger, Penicillium chrysogenum, Fusarium moniliform,* and *Aspergillus flavus* were allowed to grow on a slant for a time period of 48 hours with the intention of rich sporulation. Subsequently, added a 5 mL aqueous solution containing Tween 80 (at a ratio 1:100) to the slant. Then, spores were carefully collected using a Nichrome wire loop to make a suspension. The fungal suspension was then inoculated onto the organized plates using the compound, with the help of a Nichrome wire loop. After incubation, the plates were observed for fungal growth, recorded as reduced (+), moderate (++) and absent (-) indicating antifungal activity shown in table-4.

III.RESULTS AND DISCUSSION

5a: MF $C_{21}H_{17}N_3O_5$; colour-White, yield 65%, m.p.248-252°C, elemental analysis: (C) %obs.64.45 (64.45), (H) % obs.4.38(cal.4.38), (N) %10.74 (10.74), (O) % obs.20.44 (20.44); Infrared (IR) Spectrum (in KBr, cm^{-1}) The stretching frequency at 3498 cm^{-1} for broad phenolic (—O—H),1710 cm^{-1} (>C=O) of lactone, 1616 cm^{-1} (>C=N) of imine, 1602 cm^{-1} (>C=N-) of oxadiazol ring, 1273, 1081 (C-O-C) of oxadiazol, 1565, 1506 and 1476 cm^{-1} for (>C=C<), 1374 cm^{-1} for (>C—O) and 1224 cm^{-1} for (enolic —O—H), 803 Aromatic ring C-H out of plane deformation (para disubstituted benzene). ^{1}HNMR ($CDCl_3$) (300 MHz): The peak at δ2.15 (S, 3H, –CH_3 imine), 4.8 (q, CH_2) and 1.70 (T, CH_3) C_2H_5 group of p-ethoxy phenyl ring; 7.58-7.36 (Ar—H of ligand), 8.07 and 7.20 (dd of p-ethoxy phenyl moiety);14.69(bs, S, 1H, O—H). ^{13}CNMR ($CDCl_3$) (300 MHz): [The δ value at 86.92 for C^3, 120.68-114.78 for aromatic carbons, 156.11 for C^9 carbon, 158.98 for lactone carbon, 168.89 for C^4 carbon] of coumarin moiety. The δ value 21.67 (imine-CH_3 carbon), and 175.92 for imine carbon. The peak at 182.12 for 1,3,4-oxadiazol ring carbon, 125.63-133.88 for aromatic carbons of p-ethoxy phenyl ring bonded to C^2 of 1,3,4-oxadiazol ring and 159.12 for p-substituted -carbon; 64.2 for -CH_2 and 15.8 for -CH_3 carbon of p-ethoxy phenyl ring. Mass Spectra $[M+1]^+$392.10.

5b: MF$C_{19}H_{12}FN_3O_4$; colour- white, yield 75%, m.p.222-224°C, elemental analysis: (C) % 62.47 (62.47), (H) % 3.31(3.31), (N) %10.74(10.74), (O) %17.52 (17.52), (X) % 5.20 (5.20). IR: The stretching frequency at 3500 cm^{-1} for broad phenolic (—O—H), 1712 cm^{-1} (>C=O) of lactone, 1610 cm^{-1} (>C=N) of imine, 1604 cm^{-1} (>C=N-) of oxadiazol ring, 1272, 1071 (C-O-C) of oxadiazol, 1549, 1496 and 1476 cm^{-1} for (>C=C<), 1360 cm^{-1} for (>C—O) and 1214 cm^{-1} for (enolic —O—H), 799cm^{-1} aromatic ring C-H out of plane deformation (p-disubstituted phenyl ring). ^{1}HNMR: The peak at δ2.14 (S, 3H, –CH_3 imine), 8.04-7.66 (Ar—H of ligand), 7.62 and 7.44 (dd of p-Fluorophenyl moiety),14.75(bs, S, 1H, O—H). ^{13}CNMR: [The δ value at δ 80.38 for C^3, 130.29-115.28 for aromatic carbons, 155.54 for C^9 carbon, 163.26 for lactone carbon, 170.12 for C^4 carbon] of coumarin moiety, δ 20.46 (imine-CH_3 carbon), and 178.22 for imine carbon. 171.57 for 1,3,4-oxadiazol ring carbon, 135.42-129.32 for aromatic carbons of 4-chlorophenyl ring bonded to C^2 of 1,3,4-oxadiazol ring. Mass $[M+1]^+$366.24.

5c: MF$C_{19}H_{12}ClN_3O_4$; colour-white; yield 74 %, m. p. -237-239 °C, elemental analysis: (C) % 58.98 (59.78), (H) % 3.10 (3.17), (N) %10.84 (11.01), (O) % 16.26 (16.76), (X) % 9.12 (9.29). IR: The stretching frequency at 3506 cm^{-1} for broad phenolic (—O—H), 1715 cm^{-1} for (>C=O) of lactone,1612 cm^{-1} for (>C=N) of imine, 1600 cm^{-1} for (>C=N-) of oxadiazol ring, 1278, 1078 cm^{-1} for (C-O-C) of oxadiazol,1558 and 1473 cm^{-1} for (>C=C<), 1375 cm^{-1} for (>C—O) and, 1216 cm^{-1} for (enolic —O—H), 807 aromatic ring C-H out of plane deformation (p-disubstituted phenyl ring).

^{1}HNMR: The peak at δ2.18 (S, 3H, imine─CH_3), 7.84-7.39 (Ar─H of ligand), 7.48 and 7.24 (dd of p-chlorophenyl moiety), 14.72 (bs, S, 1H, O─H). ^{13}CNMR: [The δ value at 82.48 for C^3, 126.29-116.71 for aromatic carbons, 154.30 for C^9 carbon, 162.12 for lactone carbon, 168.12 for C^4 carbon] of coumarin moiety. δ 20.34 (imine- CH_3 carbon), and 176.19 for imine carbon. 172.62 for 1,3,4-oxadiazol ring carbon, 127.03-135.69 for aromatic carbons of 4-chlorophenyl ring bonded to C^2 of 1,3,4-oxadiazol ring. Mass [M+1]$^+$382.33.

5d: MF $C_{19}H_{12}BrN_3O_4$; colour- Pale yellow; yield 82%, m. p.- 250-252 °C, elemental analysis: (C) % 52.94 (53.54), (H) % 2.42 (2.84), (N) % 9.57 (9.86), (O) % 14.78 (15.01), (X) % 18.25 (18.75). IR: The stretching frequency at 3510 cm^{-1} for broad phenolic (─O─H), 1718 cm^{-1} for (>C=O) of lactone,1620 cm^{-1} for (>C=N) of imine,1595 cm^{-1} for (>C=N-) of oxadiazol ring, 1272, 1080 cm^{-1} for(C-O-C) of oxadiazol, 1582 and 1477 cm^{-1} aromatic (>C=C<), 1368 cm^{-1} for (>C─O) and 1219 cm^{-1} for (enolic ─O─H), 804 aromatic ring C-H out of plane deformation (para disubstituted phenyl ring).^{1}HNMR: The peak at 2.16 (S, 3H, imine ─CH_3), 7.80-7.42 (Ar─H of ligand), 7.36 and 7.14 (dd of para bromo phenyl moiety) 14.78 (bs, S, 1H, O─H). ^{13}CNMR: [The δ value at 76.68 for C^3, 130.29-115.92 for aromatic carbons, 156.10 for C^9 carbon, 158.92 for lactone carbon, 167.98 for C^4 carbon] of coumarin moiety. δ20.22 (imine-CH_3 carbon), and 175.96 for imine carbon. 171.89 for 1,3,4-oxadiazol ring carbon, 129.00-136.64 for aromatic carbons of 4-bromophenyl ring bonded to C^2 of 1,3,4-oxadiazol ring. Mass [M+1]$^+$426.24.

5e: MF $C_{19}H_{12}BrN_3O_4$; colour- yellow; yield 70%, m. p.- 269-271°C, elemental analysis: (C) % 47.96 (48.22), (H) % 2.36 (2.56), (N) % 8.54 (8.88), (O) % 13.32 (13.52), (X) % 26.65 (26.82). IR: The stretching frequency at 3498 cm^{-1} for broad phenolic (─O─H), 1714 cm^{-1} for (>C=O) of lactone, 1609 cm^{-1} for (>C=N) of imine, 1596 (>C=N-) of oxadiazol ring, 1267, 1082 cm^{-1} for (C-O-C) of oxadiazol, 1573, 1464 cm^{-1} for aromatic (>C=C<), 1370 cm^{-1} for (>C─O) and 1227 cm^{-1} for (enolic ─O─H), 800 cm^{-1} for aromatic ring C-H out of plane deformation (p-disubstituted phenyl ring). ^{1}HNMR: The peak at 2.20 (S, 3H, imine ─CH_3), 7.92-7.32 (Ar─H of ligand), 7.40 and 7.22 (dd of para iodo phenyl moiety) 14.79 (bs, S, 1H, O─H). ^{13}CNMR: [The δ value at 80.28 for C^3, 132.02-118.44 for aromatic carbons, 159.50 for C^9 carbon, 160.92 for lactone carbon, 171.74 for C^4 carbon] of coumarin moiety. δ20.34 (imine- CH_3 carbon), and 176.77 for imine carbon. 172.08 for 1,3,4-oxadiazol ring carbon, 131.07-137.84 for aromatic carbons of 4-iodophenyl ring bonded to C^2 of 1,3,4-oxadiazol ring. Mass [M+1]$^+$474.23.

Table-3: Anti-Bacterial activity

Compound	Bacterial strain zone of inhibition (Diameter in mm)			
	E. coli	*S. typhi*	*S. aureus*	*B. subtilis*
Penicillin	25	19	20	15
5(a)	20	17	16	12
5(b)	24	20	21	15
5(c)	27	20	23	17
5(d)	26	18	22	18
5(e)	25	19	21	16

Table-4: Anti-fungal activity

Compound	**Fungi strain zone of inhibition**			
	A. niger	*P. chrysogenum*	*F. moniliform*	*A. flavus*
Griseofulvin	-	-	-	-
5(a)	++	++	++	++
5(b)	-	-	-	-
5(c)	-	-	-	-
5(d)	-	-	-	-
5(e)	-	-	-	-

A. Chemistry: All the reactions for synthesis of novel Schiff bases were carried out under conventional methods (Fig:1 Scheme). In first step, the intermediate compound (2 and 4a-e) was synthesized, recrystallized in ethanol and purity was checked by TLC. The reaction progress was monitored throughout by using TLC. Increase in refluxing time did not get better the yield of product. The characterizations of these intermediates were carried out and were found similar to literature values. The Schiff bases, 3-(1-((5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl) imino) ethyl)-4-hydroxy-2H-chromen-2-one (5a-e) were synthesized and m. p., elemental analysis and their purity was checked by TLC. All of these synthesized compounds are established by studying usual IR, ^{1}HNMR, ^{13}CNMR and mass spectral interpretations.

B. IR: The significant band observed in IR spectra of the compounds 5a-e having high intensity band at 1620-1609 cm^{-1}, is assigned for ν(C=N) vibration, suggesting the formation of Schiff base. The assignment of hydrogen bonded –OH in the Schiff bases shown a broad weak band around 3500 cm^{-1}. The band appeared at 1582-1477 cm^{-1} is assigned to the arrangement of ν(C=C) of the aromatic ring. A high intensity band in the region 1372 cm^{-1} is assigned to phenolic ν(C-O) vibration and 1710-1718 cm^{-1} for lactone carbonyl [29]. Also, specific bands found around 1375-1360 cm^{-1}, for (ν>C-O) and 1227-1214 cm^{-1}, for enolic (-OH); these findings give us important information about how compounds 5a-e are built and how they move.

C. ^{1}H-NMR: The Schiff bases ^{1}H-NMR were observed in DMSO. The peaks between δ2.20-2.14 ppm belong to the (S, 3H, imine –CH_3) part. There are also peaks from δ8.4 to 7.32 ppm for the aromatic -H of the ligand. A δ value ranging from 7.62 to 7.44 ppm, with doublets for 4H, confirms para substitution. The phenolic –OH group shows a singlet at 14.79-14.69 ppm. Additionally, in 5a, there is a quadrate at δ 4.8 for CH_2 and a triplet at δ 1.70 for the CH_3 group, which are from the ethoxy of the p-ethoxy phenyl ring. The value 4.8 for 2H indicates the CH_2 group adjacent to the CH_3 group, which is shown as a triplet at 1.70 ppm.

D. ^{13}CNMR and Mass spectra: The ^{13}CNMR peak between 158.92-163.26 ppm confirmed the presence of lactone carbon, and the peak between 175.92-178.22 ppm for the imine carbon. The peaks at about 125.63-137.84 for aromatic carbons of para-substituted phenyl ring bonded to C^2 of 1,3,4-oxadiazol ring and the δ value at 76.68-86.92 for C^3. Additionally, in 5a compound 64.2 for -CH_2 and 15.8 for -CH_3 carbon of p-ethoxy group attached para position on phenyl ring. The peaks at about 182.12-171.57 ppm due to presence of the carbon atom of oxadiazole ring. Assignment giving to other peaks observed in ^{1}HNMR, ^{13}CNMR spectra, and also molecular ion peaks in mass spectra justifies the structures of compounds 5a-e.

E. Biological activity: The tested compounds (5a-e) were examined in the lab to see how they affect bacteria like *E. coli, S. typhi, S. aureus,* and *B. subtilis* using the Agar cup method. The results are in Table-3. All the compounds except 5a showed strong antibacterial effects against these bacteria, even better than penicillin, which is a standard antibacterial drug, because they contain halogen elements. They were also tested against fungi like *A. niger, P. chrysogenum, F. moniliforme,* and *A. flavus* using the poison plate method, with results shown in Table-4. Compound 5a had moderate antifungal activity compared to 5b-e. Compounds 5b-e showed excellent antifungal activity, similar to Griseofulvin, a standard antifungal drug. In brief, it may be concluded that antimicrobial activity may be due to the presence of coumarin and oxadiazole moiety in the molecule.

IV. CONCLUSION

Coumarin incorporated 1,3,4-thiadiazole moiety containing Schiff bases showed sensible to powerful activity against bacterial and fungal species. The activity of synthesized Schiff bases may inhibit further growth of microbe's cell wall formation. The phenolic hydroxyl group present in the molecule may enhance the penetration through some of the specialized channels present in gram negative bacteria. Therefore halogen substituted compounds are more significant than non-halogenated compounds in these synthesized Schiff bases. All these compounds with electron withdrawing groups on aromatic ring showed extensive activity as antifungal agents. These findings highlight the promising potential of utilizing coumarin-incorporated 1,3,4-oxadiazole Schiff bases as effective agents combating microbial infections.

Conflicts of interest: There are no conflicts of interest.

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