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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, antibacterial, antifungal, and immunomodulating activities of gatifloxacin derivatives

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Abstract Gatifloxacin is a synthetic broad-spectrum fluorquinolone antibacterial agent with a 3-methylpiperazinyl-side chain at position 7 and a methoxy group at position 8 of the quinolone ring. In the present study different analogues of gatifloxacin were prepared; the piperazinyl ring was chosen as the center of reaction for synthesizing this series of derivatives. The structures of these derivatives were established using spectroscopic techniques such as IR, ^{1}H NMR, and EIMS. In vitro antibacterial and antifungal activities were evaluated by disc diffusion method and these derivatives were compared with in-use fluoroquinolones like gatifloxacin, sparfloxacin, and gemifloxacin. Derivative A proved very potent against Gram-negative organisms, especially *Pseudomonas aeruginosa, Shigella flexeneri*, and *Klebseilla pneumoniae*, and derivatives **A–C** exhibited good antifungal activity compared to in-use quinolones. In addition, gatifloxacin and derivatives were investigated for immunomodulating activities. Derivative **B** has good anti-inflammatory activity, with $IC_{50} < 12.5$ μg/ml.

Keywords Gatifloxacin · Derivatives · Immunomodulatory activity · Antibacterial activity · Antifungal activity

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Introduction

Fluoroquinolone (Scheme 1) is a class of synthetic antibacterial agents that offer a broad spectrum of activity (Scheld, 1989; Keiser and Burri, 2001; Emami *et al.*, 2006) and exert their effect by inhibition of two type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV (Hoshino *et al.*, 1994). Structure–activity relationship studies discovered that N1, C2–H, C3-carboxylic acid, C4-carbonyl, C6–F, and C7-piperazine are essential or beneficial for antibacterial activity. The type of substituent at the C-7 position of quinolones is closely associated with their properties, such as the antibacterial spectrum, especially to include Gram-negative organisms such as *Pseudomonas aeruginosa* (Bryskier and Chantot, 1995; Drusano *et al.*, 1989), and bioavailability (Domagala *et al.*, 1988; Walsh, 2003; Ronald and Low, 2003); however,; this group also increases CNS toxicity, which can be reduced by adding a methyl or ethyl group to the piperazine ring or by a bulky subsitituent on N-1 (Bryskier and Chantot, 1995; Drusano *et al.*, 1989).

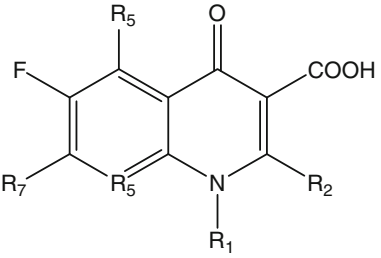
Gatifloxacin is a fourth-generation broad-spectrum fluorquinolone also reported to have an inhibitory effect on the production of inflammatory cytokines by macrophages/monocytes and, particularly, suppresses bacterial infection-induced inflammation (Tokushige *et al.*, 2003; Kenneth, 2007; Deborah and Virginia, 1999; Bailly *et al.*, 1990). The present work describes the synthesis of new derivatives of gatifloxacin and biological activities like antibacterial, antifungal, and immuno-modulating activities of these derivatives. We have focused on introducing new functional groups to the piperzinyl ring in gatifloxacin.

Experimental

Materials and methods

Triethylamine, acetic anhydride, anhydrous pyridine, anhydrous tetrahydrofuran, capryloyl oil, and benzoyl chloride were procured from Merck (Germany). Gatifloxacin (98.67%) was kindly gifted by Barrett Hodgson Pakistan. IR and ^{1}H-NMR spectra were recorded on a Prestige-21 Shimadzu FTIR (KBr) and Bruker AMX (400 MHz), respectively. Chemical shifts are reported as parts per million (ppm) using tetramethyl silane (TMS) as an internal standard. Mass spectra were

Scheme 1 Fluoroquinolone



recorded on a MAT312 Mass spectrometer (Jeol, Tokyo) operating at 70 eV by electron ionization technique (EI MS). Luminol (3-aminophthalhydrazine) was purchased from Researched Organics; Hanks balance salts solution (HBSS), from Sigma (Germany); lymphocyte separation medium (LSM), from MP Biomedicals, Inc. (Germany); and Zymson-A (*Saccharomoyces cerevisiae* origin) and phorbol 12-myristate 13-acetate (PMA), from Fluka (Bio Chemika). Chemiluminescence and T-cell proliferation assay were performed using a Luminoskan RS (Finland) B-scintillation counter (1211 LKB Wallac).

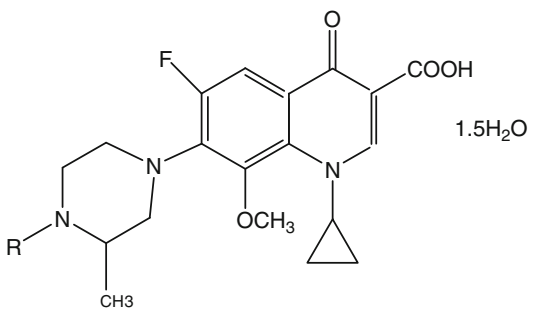
Synthesis of 7-(4-acetyl-3-methylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**A**; Scheme 2)

Gatifloxacin, 2.48 mmol or 1.0 g, was dissolved in anhydrous pyridine (15 ml) in a 100-ml round-bottomed flask, with continuous stirring, and to this, acetic anhydride (0.054 ml) was added. The mixture was stirred continuously till completion of the reaction (4–5 h), which was checked by thin-layer chromatography (TLC). Excess solvent was removed under reduced pressure on a rotary evaporator, and the residue was suspended in water and extracted with ethyl acetate (8 ml × 3). Yield, 74%; m.p., 148°C (dec.). IR (KBr) *v*max: 1249 (CF), 1337 (C–N), 1715 sharp (C=O), 1217 and 3421 (OH). ^{1}H NMR (MeOD, 400 MHz) δ: 2.4 (s, 2H), 3.6 (s, 2H), 2.0 (s, 1H, CH_3), and 3.6 (s, OCH_3). Formula: $C_{21}H_{24}FN_3O_5$. EI-MS m/z: 417.1 $[M]^+$, 374 (M-C_2H_3O), and 346 (M-C_2H_3O–CO).

Synthesis of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-4-octanoylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**B**; Scheme 2)

Gatifloxacin, 1.0 g (2.48 mmol), was dissolved in anhydrous tetrahydrofuran (30 ml) in a 100-ml round-bottom flask, with continuous stirring; to this was added triethylamine (0.62 ml) and caproyl chloride (0.77 ml), which was prepared by continous stirring of caproyl oil with thionyl chloride at room temprature. The resultant mixture was refluxed in a sand bath for 5 h, and the progress of the reaction was monitored by TLC. After completion of the reaction excess solvent was removed under reduced pressure on a rotary evaporator and the residue was

Scheme 2 R = H (gatifloxacin); $COCH_3$ (**A**); COC_7H_{15} (**B**); COC_6H_5 (**C**)



suspended in water and extracted with ethyl acetate (10 ml × 4). Yield, 70%; m.p., 76°C. IR (KBr) *v*max: 1124 (CF), 1384 (C–N), 1762 sharp (C=O), and 3461 (OH). ^{1}H NMR (MeOD, 400 MHz) δ: 2.3 (s, 1H), 2.05 (s, 2H), 1.6 (s, 1H), 1.2 (m, 2H), and 0.83 (s, CH_3). Formula: $C_{27}H_{36}FN_3O_5$. EI-MS m/z: 501.1 $[M]^+$. 456 (M-COOH) and 415 (M-COOH–C_3H_5).

Synthesis of 7-(4-benzoyl-3-methylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**C**; Scheme 2)

Gatifloxacin, 1.0 g (3.01 mmol), was dissolved in anhydrous tetrahydrofuran (30 ml) in a 100-ml round-bottom flask, with continuous stirring, and to this triethylamin (0.629 ml) and benzoyl chloride (0.268 ml) were added. The reaction mixture was refluxed in a sand bath for 8–9 h, and the progress of the reaction was monitored by TLC. Yield, 63%; m.p., 129°C; IR (KBr): 1210 (CF), 1251 (C–N), 1720 sharp (C=O), 1298 (C–O), 3462 (OH), and 3048 (CH aromatic). ^{1}H NMR (MeOD, 400 MHz) δ: 3.5 (s, 3H), 3.3–3.2 (s, 2H), 7.5–7.4 (m, phenyl). Formula: $C_{26}H_{26}FN_3O_3$. EI-MS m/z: 479 $[M]^+$. Peak add at 434 and 329 for fragments $C_{25}H_{25}FN_3O_3$ and $C_{18}H_{20}FN_3O_2$, respectively.

Antibacterial and antifungal activity

Test bacteria and fungi

Gram-positive and Gram-negative microorganisms, i.e., the bacteria *Citrobacter* species, *Escherichia coli*, *Bacillus subtilius*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi*, *Proteus mirabilis*, *Klebsiella pneumonia*, *Shigella flexneri*, and *Mycobacterium lutus* and the fungi *Trichophyton rubrum*, *Candida albicans*, *Fusarium solani*, and *Sacchromyces cerevisiae* were isolated from clinical samples. These were purified and identified according to WHO (2003) and stored at 4°C.

Antibiotic susceptibility testing

Antibacterial and antifungal activity was evaluated by paper disc diffusion method (Kabir *et al.*, 2005; National Committee for Clinical Laboratory Standards, 1993). The antibacterial discs (diameter, 6 mm) were prepared at home at concentrations of 5, 10, 20 and 40 μg/ml and applied to each of the culture plates previously seeded with the 0.5 McFarland turbidity cultures of the test bacteria. These culture plates were then incubated at 37°C for 18–24 h and for 7 days for antifungal activity. Antimicrobial activity was determined by calculating the percentage zone of inhibition (ZOI) taking gatifloxacin as a standard (100%). For each compound, three replicate trials were conducted against each organism: mean percentage ZOI (%ZOI), linear coefficient (R^2), and percentage relative standard deviation (%RSD) were calculated by an Excel-based program.

Chemiluminescence assay

Luminol-enhanced chemiluminescence assay was performed as reported by Helfand *et al.* (1982) and Haklar *et al.*, 2001): 25 µl of diluted whole blood (1:50 dilution in sterile $HBSS^{2+}$) was incubated with 25 µl of serially diluted drug with concentration ranges between 6.25 and 100 µg/ml. Control wells received $HBSS^{2+}$ and cells but no drug. Tests were performed in white 96-well plates, which were incubated at 37°C for 30 min in the thermostat chamber of a luminometer. After incubation a 25 µl of luminol (7×10^5 M) and 25 µl of serum opsonized zymosan (SOZ) were added to each well except 'A,' which served as a blank, and $HBSS^{2+}$ was added to each well to obtain a 200-µl volume per well. Phagocytosis kinetic studies were monitored with the luminometer for 50 min in the repeated-scan mode. Peak and total integral chemiluminescence readings are expressed as relative light units.

T-Cell proliferation assay

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized venous blood of healthy humans by Ficoll-Hypaque gradient centrifugation. Fifty microliters of 5% complete RPMI was added to each well of a sterile 96-well plate in a sterile environment using a safety cabinet, followed by sample drugs having concentrations between 3.125 and 50 µg/ml, with adjustment to a final volume of 0.3 ml. Well A contained only 5% complete RPMI to be used as control. Fifty microliters of PBMCs (1 × 106/ml) was added in a suspension of 5% complete RPMI to each well except the blank, followed by the addition of 50 µl of PHA except for the negative control and blank, and the volume of each well was made up to 0.2 ml with 5% complete RPMI. The mixture was incubated for 72 h in a CO_2 incubator at 37°C. After incubation 25 µl of thymidine was added to each well except the blank and the plate was again incubated in the CO_2 incubator at 37°C for 18 h. Cells were harvested onto a glass-fiber filter (Cambridge Technology, USA) using a cell harvester (SKATRON A.S.; Flow Laboratories, Norway). Tritiated thymidine incorporation into cells was measured with a liquid scintillation counter. Results were recorded after 120 s, as counts per minute.

Results and discussion

Chemistry

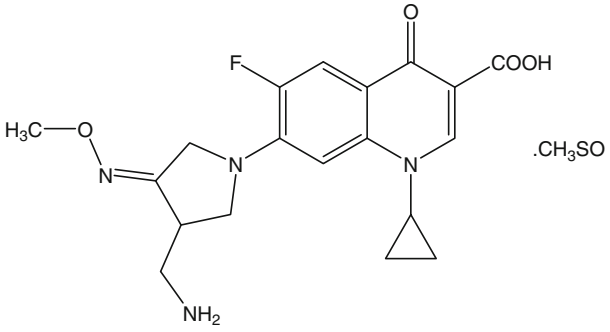
All gatifloxacin analogues synthesized had high yields. Infrared spectra of all synthesized compounds showed easily distinguishable amide stretching at 1,729–1,720 cm^{-1}along with a peak at 1,610–1,575 cm^{-1} due to the keto carboxylic group (Yong *et al.*, 2004). Furthermore, the absence of free NH stretching between 3,300 and 3,200 confirmed that the reaction had taken place at N4 of the piperazine ring and amides of gatifloxacin were formed. A sharp multiplet at 7.4 ppm (for the phenyl proton) in ^1H NMR spectra of compound **C** (Scheme 2) confirmed the structure of the compound; similarly, ^1H NMR spectra of compound **B** indicate a side alkyl chain

at N4 of the piperzinyl ring. The appearance of a CH_3 singlet at 2.0 ppm in ^{1}H NMR spectra of compound **A** provided conformational structural information. Furthermore, M-C_2H_3O fragment ion peaks appeared at m/z values of 374 in mass spectra of synthesized compound **A**, confirming its assigned structure. All compounds gave satisfactory elemental analysis. IR ^{1}H NMR and E1-MS spectra were consistent with the assigned structures as discussed under Experimental.

Biological activities

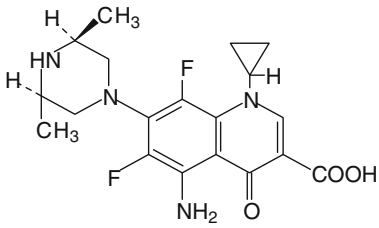
Gram-negative bacteria have lipid-rich cell walls and lipophilicity is an important consideration in the design of novel analogues (de Almeida *et al*., 2007; Jensen *et al*., 1996). The synthesized compound **A**, with modified lipophilicity, has better activity than that of the present fluorquinolones, i.e., gatifloxacin, gemifloxacin mesylate (**3**; Scheme 3), and sparfloxacin (**4**; Scheme 4). Compound **A** exhibits 125% activity against methicillin-resistant *Staphylococcus aureus* (MRSA; a troublesome organism that rapidly became resistant not only to methicillin but also to other β-lactam antibiotics, and the causative agent of most nosocomial and skin allergen infections), which is higher that of any other derivative or in-use quinolone, i.e., sparfloxacin, gemifloxacin, and gatifloxacin (77%, 70%, and 100%, respectively). This is probably due to an acetyl group at the piperazinyl ring of compound **A**, as gatifloxacin already has a methoxy group at the C-8 position, which is responsible for its enhanced activity toward Gram-positive organisms. It also shows higher activity against *P. aeruginosa* (150%), *K. pneumoniae* (158%), *E. coli* (134%), *S. typhi* (113%), and *S. flexneri* (151%). Compound **A** is superior to gatifloxacin, gemifloxacin, and sparfloxacin for all Gram-negative organisms. This is an important finding, and after supplementary in vivo activities to evaluate its safety this compound can be a lead molecule for therapeutic purposes, as *E. coli, P. aeruginosa, S. typhi, P. mirabilis, K. pneumonia*, and *S. flexneri* are responsible for death-causing infections (Nakajima *et al*., 1995. However, the intrinsic susceptibility of *P. mirabilis* to compound **A** was lower than that to the above three marketed antibiotics.

Compounds **B** and **C** also exhibit moderate to good activity (76–104%) against all Gram-positive and Gram-negative organisms, much better than that of sparfloxacin and gemifloxacin. We previously synthesized similar derivatives of ciprofloxacin



Scheme 3 Gemifloxacin

Scheme 4 Sparfloxacin



that proved less effective than the parent molecule (Siddiqui *et al*., 2007). Antibacterial activities of all compounds were in good linear relationship to their concentrations, i.e., linear coefficients (R^2) were in the range of 0.769–0.999, with ignorable variations (%RSD <2). It was found that all gatifloxacin derivatives showed excellent activity against *Trichophyton rubrums* and *Fusarium solani*, in most cases 50–100% that of gatifloxacin. The antifungal activity of most of the derivatives against *Candida albicans* is similar to that gatifloxacin. Results showed (Tables 1, 2) that these compounds are more suitable for immune-compromised patients, as they posses broad-spectrum antibacterial activity and antifungal activity. Combination therapy with available antifungal drugs and quinolone antibiotics yields additive to synergistic activity over the antifungal drugs used alone (Nakajima *et al*., 1995; Shen and Fostel, 1994).

Luminol-enhanced chemiluminesence assay was performed as described by Helfand *et al*. (1982) and Haklar *et al.* (2001). The luminol probe is capable of detecting the level of reactive oxygen species (ROS) to study the effect of these derivatives on oxidative burst. Luminol is characterized by its ability to enter the cell and react with intracellular ROS (Dahlgren and Briheim, 1985). Percentage inhibition was calculated as 100 = 100 [(CL count in presence of compound/CL count in absence of compound) × 100] by an Excel-based program. Preliminary screening results of whole blood showed that compound **B** showed 74.1–96.1% inhibition ($IC_{50} < 12.5$ μg/ml), while gatifloxacin showed 19.7–84.7% inhibition ($IC_{50} = 31 \pm 6.5$ μg/ml). Compounds **A** and **C** have no considerable inhibitory activity (Table 3). The sensitivity of gatifloxacin and its derivatives to nonproliferative and proliferative responses of the mitogen phytohemagglutinin (PHA) and mitogen-induced proliferation of T lymphocytes were evaluated. Proliferative response of mitogens was monitored at concentrations of 3.12, 12.5, and 50 μg/ml. The results revealed that neither gatifloxacin nor any of its derivative has immunosuppressive activity (Table 4).

Conclusion

The best substitution at N4 of the piperazinyl ring is an acetyl group, which increases antibacterial activity against Gram-negative organisms and retains the original activity of the compounds against Gram-positive organisms. Additionally, all N4-substituted gatifloxacin derivatives exhibited encouraging antifungal activity. The data presented here indicate that an N4-substituted piperazinyl on the quinolone

Table 1 In vitro antibacterial activity of the drugs against selected strains

Compound	Compound disc content (μg/ml)			R^2	Mean %ZOI	Mean %RSD	Compound disc content (μg/ml)			R^2	Mean %ZOI	Mean %RSD
	5-mm ZOI	10-mm ZOI	20-mm ZOI				5-mm ZOI	10-mm ZOI	20-mm ZOI			
	Hofmanni bacterium						*Bacillus subtilis*					
A	8	12	16	0.999	99	0.05	11	15	17	0.86	100	0.06
B	7	11	14	0.993	88	1.05	10	11	13	0.99	80.2	0.09
C	6	12	14	0.923	86	0.95	12	15	18	0.96	104	1.19
DMSO	–	–	–	–	–	–	–	–	–	–	–	–
GTX	8	13	15	0.824	100	0.50	11	15	17	0.86	100	0.02
SPR	11	13	14	0.964	110	0.87	12	13	15	0.99	94.6	1.23
GMX	5	7	8	0.860	56.6	1.23	5	7	8	0.86	46.3	1.05
	Citrobacterium						Methylene—resistant *Staph. aureus*					
A	17	21	24	0.92	98.9	0.32	14	21	24	0.835	124	1.76
B	08	10	15	0.99	51.5	2.31	07	14	16	0.769	76.7	1.52
C	08	10	12	0.96	47.6	1.23	09	14	19	0.964	87.4	1.21
DMSO	–	–	–	–	–	–	–	–	–	–	–	–
GTX	15	23	26	0.81	100	0.23	13	16	18	0.999	100	1.05
SPR	8	9	10	0.96	42.73	1.48	11	12	13	0.964	77.2	1.03
GMX	7	9	11	0.96	42.83	1.36	9	10	14	0.979	69.8	1.23
	Pseudomonas aeruginosa						*Escherichia coli*					
A	11	17	24	0.978	150.1	1.67	10	17	22	0.920	134.8	1.33
B	8	10	11	0.862	78.57	1.02	8	10	14	0.999	90.78	0.25
C	10	12	18	0.991	117.9	0.97	8	16	19	0.813	117.3	0.24
DMSO	–	–	–	–	–	–	–	–	–	–	–	–
GTX	8	12	14	0.862	100	0.98	7.5	12	17	0.975	100	1.31

Table 1 continued

Compound	Compound disc content (μg/ml)			R^2	Mean %ZOI	Mean %RSD	Compound disc content (μg/ml)			R^2	Mean %ZOI	Mean %RSD
	5-mm ZOI	10-mm ZOI	20-mm ZOI				5-mm ZOI	10-mm ZOI	20-mm ZOI			
SPR	11	13	15	0.964	117.6	1.24	9	11	14	0.994	98.01	0.24
GMX	8	9	10	0.964	75.0	0.96	7	9	10	0.862	75.72	1.28
	Shigella flexneri						*Klebsiella pneumoniae*					
A	19	22	24	0.910	151	1.01	16	23	25	0.769	158	1.67
B	12	15	20	0.998	105	0.94	13	14	18	0.979	113	1.41
C	11	13	14	0.862	88.1	1.25	8	14	21	0.978	99.8	1.37
DMSO	–	–	–	–	–		–	–	–	–	–	–
GTX	9	16	23	0.964	100	0.15	9	14	19	0.964	100	0.33
SPR	9	11	13	0.964	75.1	1.11	10	13	16	0.964	96.1	1.28
GMX	7	8	13	0.969	61.4	1.54	10	11	12	0.964	84.2	0.25
	Shigella typhi						*Proteus mirabilis*					
A	9	16	22	0.946	113	0.99	9	10	12	0.999	76.6	1.54
B	8	10	18	0.98	87.5	0.55	11	12	14	0.999	92.0	1.23
C	8	9	15	0.96	80.2	0.025	9	11	12	0.862	78.8	1.11
DMSO	–	–	–	–	–	–	–	–	–	–	–	–
GTX	8	13	21	0.99	100	0.25	9	15	19	0.91	100	0.44
SPR	9	10	15	0.96	87.0	1.16	10	12	15	0.994	90.0	0.23
GMX	8	9	12	0.99	75.5	0.85	10	11	12	0.81	82.5	0.33

ZOI zone of inhibition, *GTX* gatifloxacin, *GMX* gemifloxacin, *SPR* sparfloxacin

Table 2 In vitro antifungal activity of the drugs against selected strains

Compound	Compound disc content (μg/ml)		Mean %ZOI	Mean %RSD
	20-mm ZOI	40-mm ZOI		
Trichophyton rubrum				
A	28	34	239	0.65
B	16	17	127	1.01
C	21	27	185	1.69
DMSO	–	–	–	–
GTX	12	14	100	1.25
SPR	20	24	169	1.32
Candida albicans				
A	16	19	206	1.03
B	16	21	218	2.05
C	10	14	141	2.03
DMSO	–	–	–	–
GTX	8	9	100	0.02
SPR	13	17	176	0.09
Fusarium solani				
A	13	15	93.3	1.87
B	14	19	110	1.61
C	17	19	120	0.99
DMSO	–	–	–	–
GTX	12	18	100	0.37
SPR	10	11	70	0.87
Saccharomyces cerevisiae				
A	0	0	0	0
B	0	0	0	0
C	0	0	0	0
DMSO	–	–	–	–
GTX	0	0	0	0
SPR	0	0	0	0

ZOI zone of inhibition, *GTX* gatifloxacin, *GMX* gemifloxacin, *SPR* sparfloxacin

Table 3 Screening of gatifloxacin and its derivatives using whole blood for chemiluminescene activity

Compound	Reading (RLU × 1000)			% inhibition			$IC_{50} \pm SD$
	100 μg/ml	50 μg/ml	12.5 μg/ml	100 μg/ml	50 μg/ml	12.5 μg/ml	
A	485.6	495.2	482.4	−15.1	−17.4	−14.3	>100 ± 0.0
B	16.3	45.7	109.3	96.1	89.2	74.1	<12.5 ± 0.0
C	358.6	375.1	443.3	15.0	11.1	−5.1	>100 ± 0.0
GTX	471.9	1047.6	2475.5	84.7	66.0	19.7	31 ± 6.5

RLU relative light units

Table 4 Screening of gatifloxacin and its synthesized derivatives for their immune modulating inhibitory properties, using whole blood

Compound	Reading (cpm × 1000)			% inhibition			$IC_{50} \pm SD$
	50 μg/ml	12.5 μg/ml	3.12 μg/ml	50 μg/ml	12.5 μg/ml	3.12 μg/ml	
A	29,751.8	26,503.8	24,101.2	−52.30	−35.70	−23.40	>50 ± 0.0
B	20,881.2	27,642.0	31,144.1	−6.90	−41.50	−59.50	>50 ± 0.0
C	20,881.2	27,642.0	31,144.1	−6.90	−41.50	−59.50	>50 ± 0.0
GTX	24,450.9	38,657.7	33,427.3	−25.20	−97.90	−71.10	>50 ± 0.0
Control		34,246.4					

ring also greatly influences the oxidative burst activity, in addition to the antibacterial activity. The caproyl OC_7H_{15} increases activity (% inhibition, 74.1–96.1%; $IC_{50} < 12.5$ μg/ml), while an acetyl or benzoyl group at the same position decreases activity. However, further mechanism-based studies are required for better understanding of the mechanism of action of gatifloxacin derivatives on the immune response.

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