Synthesis and Antimycobacterial Evaluation on Arylsulfonyl and Arylcarbonyl Derivatives of Ofloxacin

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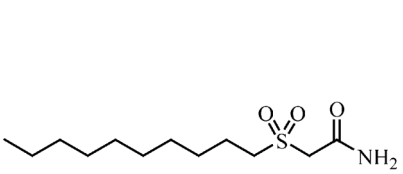
Four ofloxacin derivatives **3**, **5**, **6**, and **11** were found to exhibit > 90 % inhibition on the growth of *M. tuberculosis* at a concentration of 6.25 μg/mL. Compounds **3**, **5** and **11** have also exhibited a broad spectrum of antibacterial activities while 8-fluoro-3-methyl-9-[4-(4-nitrophenylsulfonyl)piperazin-1-yl)-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (**6**), which exhibited potent activity against the growth of TB with the MIC of 2.23 μg/mL and a selectivity index (SI) of > 14.80, was inactive against the growth of G(+)- and G(-)-bacteria. Selective anti-TB activity was achieved by the introduction of an arylsulfonyl group at C-7 piperazin-4-yl of *N*-demethyl ofloxacin. Compound **6** is species-specific, exhibiting no significant activity against the growth of bacterial species other than *M. tuberculosis*, which implied the possibility of developing new specific anti-TB drug candidates without inducing cross resistance with other currently used antibacterial drugs. Structural optimization of **6** is on-going.

Keywords: Fluoroquinolone; Antimycobacterial activity; Ofloxacin derivatives.

INTRODUCTION

The drugs currently used for the treatment of tuberculosis (TB) infection are streptomycin, isoniazid, ethambutol, pyrazinamide, and rifampicin.[1] However, the current TB treatment regimens, although highly effective, are far from idea. Recently, the emergence of multi-drug resistant tuberculosis (MDRTB)[2,3] has caused an urgent need in search of alternative chemotherapeutics for *Mycobacterium tuberculosis* infection. Several fluoroquinolone antibacterial drugs were examined as potential chemotherapeutics for *M. tuberculosis* infection.[4-10] A number of newer fluoroquinolone derivatives have been synthesized and evaluated for their anti-TB activity.[11-15] However, the optimization of the fluoroquinolones against TB infection has not been thoroughly explored especially the optimum substituent at the C-7 position which has a great impact on potency, antibacterial spectrum, solubility, and pharmacokinetics, has not been precisely defined.

Over the past few years, we were particularly interested in the synthesis and evaluation of fluoroquinolons for their antibacterial and anticancer activities.[16-22] Since the antibacterial mechanism of these fluoroquinolones is unique and absolutely different from the currently used anti-TB drugs, it will become a very important anti-TB drug candidate if proved to be active against the growth of *M. tuberculosis*. Therefore, we have synthesized and evaluated certain hybrid compounds for anti-TB evaluation.[21] To continue our search for more potent anti-TB agents, we report herein synthesis and evaluation of ofloxacin derivatives with an arylsulfonyl group substituented at C-7 piperazine moiety on the ground that a number of sulfonylated derivatives such as *1*[23] and *2*[24] exhibited significant anti-TB



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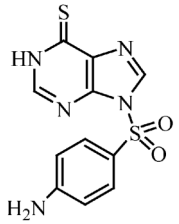

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activities. The bio-isosteric arylcarbonyl counterparts of arylsulfonyl ofloxacin derivatives were also synthesized for evaluation.

RESULTS AND DISCUSSION

Synthesis

Preparation of ofloxacin derivatives with arylsulfonyl and arylcarbonyl substituents at C-7 piperazine moiety is depicted in the Scheme I. Treatment of *N*-demethyl ofloxacin (**3**) with substituted benzenesulfonyl chloride or benzoyl chloride in the presence of K_2CO_3 afforded benzenesulfonyl derivatives **4-7** and their bio-isosteric benzoyl isomers **8-11**, respectively.

Biological activities

Primary screening is conducted against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay to determine the actual minimum inhibitory concentration (MIC) using the Microplate Alamar Blue Assay (MABA).[25] The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. Concurrent with the determination of MICs, compounds are screened by serial dilutions to assess cytotoxicity (IC_{50}) to a VERO cell. After 72 h exposure, viability is assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 Non-radioactive Cell Proliferation Assay and the results are summarized in Table 1. 8-Fluoro-3-methyl-9-[4-(4-nitrophenylsulfonyl)piperazin-1-yl)-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (**6**),[26] with 4-nitro group substituted at benzenesulfonyl moiety, exhibited 96% inhibition on the growth of *M. tuberculosis* at a concentration of 6.25 μg/mL, which was comparable to the positive *N*-demethyl ofloxacin **3** (99%) and its 4-fluoro counterpart **5** (92%) but was more active than its 4-methoxy counterpart **7** (62%). These results implied that the electron-withdrawing groups, NO_2 and F, enhanced while the electron-donating group, MeO, decreased anti-TB activity. However, the above structure-activity relationships can not be applied to their bio-isosteric benzoyl derivatives in which **9** (4-F, 64%) and **10** (4-NO_2, 73%), bearing electron-withdrawing groups, exhibited only marginal activity while **11** (4-OMe, 94%) was much more potent. The cytotoxicity (IC_{50}) against mammalian VERO cells as well as the selectivity index (SI), defined as IC_{50}/MIC, for compounds **3**, **5**, **6**, and **11** were also determined. Compounds with an SI of > 10 are of interest for further development as potential anti-TB agents. Results indicated that compounds **3**, **5**, and **6** exhibited significant activities against the growth of *M. tuberculosis* with MIC values of 1.58, 1.83, and 2.23 μg/mL respectively. Compounds **3** and **6** have also exhibited SI values of greater than 20.89 and 14.80 respec-

Scheme I

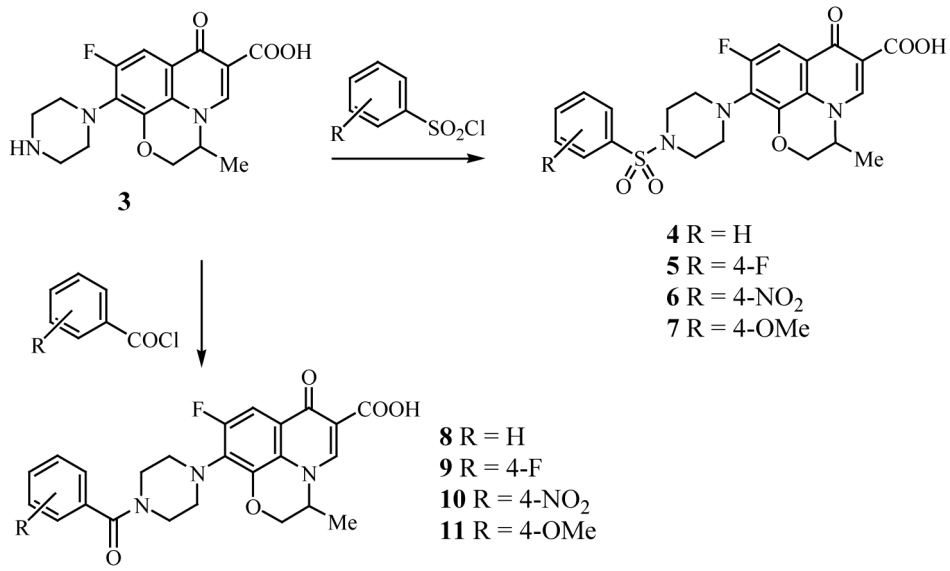
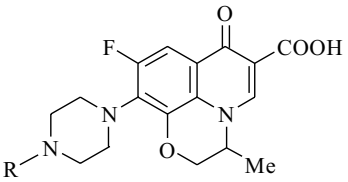


Table 1. Anti-*Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) activity of ofloxacin derivatives



	R	% Inhibition at 6.25 μg/mL	MIC (μg/mL)	IC_{50} (μg/mL)	SI (IC_{50}/MIC)
3	H	99	1.58	> 33	> 20.89
4	SO_2Ph	66	nd[a]	nd	nd
5	SO_2Ph-4-F	92	1.81	16.60	9.16
6	SO_2Ph-4-NO_2	96	2.23	> 33	> 14.80
7	SO_2Ph-4-OMe	62	nd	nd	nd
8	CO-Ph	86	nd	nd	nd
9	COPh-4-F	64	nd	nd	nd
10	COPh-4-NO_2	73	nd	nd	nd
11	COPh-4-OMe	94	> 6.25	> 10	nd

[a] Not determined.

tively.

The zone of inhibition in diameter at a concentration 100 μg/mL of each tested agent was determined by the disk diffusion (Kirby-Bauer) methods[27,28] and the results are summarized in Table 2. The positive *N*-demethyl ofloxacin (**3**) exhibited a broad spectrum of antibacterial activity. However, its arylsulfonyl derivatives such as compounds **4** and **7** were much less active while compound **6** was inactive. With exception of **9**, the antibacterial activity of all the arylcarbonyl derivatives **8**, **10**, and **11** were very active and

Table 2. Antimicrobial activity of ofloxacin derivatives

	Ec[a]	Pa	Ef	Sp	Spn	Sa	Sa-a	Sa-b	Sa-c	Ml-a	Ml-b	Ms
3	26[b]	20	17	24	24	20	23	24	22	24	28	40
4	N[c]	N	N	N	+/-	16	15	14	15	9	N	N
5	22	N	16.5	20	20	25	24	30	22	22	22	35
6	N	N	N	11	N	9	+/-	11	7.5	N	N	N
7	14	N	9	12	15	16.5	13	13	12	8	8	+/-
8	22	15	16	22	25	22	28	27	33	29	27	52
9	15	N	7.5	14	8	14	16	17	12	9	8	+/-
10	24	12	15	21	25	24	30	27	32	25	30	47
11	24	14	15	21	24	22	26	23	29	22	23	50

[a] Ec, *Escherichia coli*; Pa, *Pseudomonas aeruginosa*; Ef, *Enterococcus faecalis*; Sp, *Streptococcus pyogenes*; Spn, *Streptococcus pneumoniae*; Sa, *Staphylococcus aureus*; Sa-a, *Staphylococcus aureus* (ATCC12692) resistant to novobiocin; Sa-b, *Staphylococcus aureus* (ATCC12715) resistant to tetracycline; Sa-c, *Staphylococcus aureus* (ATCC14154) resistant to tetracycline, penicillin, streptomycin, and erythromycin, sensitive to carbomycin, neomycin, chloramphenicol, and novobiocin; Ef-s, *Enterococcus faecalis* (vancomycin resistant strain, clinical isolated); Ml-a, *Micrococcus luteus* (ATCC10240A) resistant to dihydrostreptomycin sulfate and streptomycin; Ml-b.

[b] Diameter of the zone of inhibition (in mm), each compound was tested at concentration of 100 μg/mL.

[c] No inhibition.

comparable to that of **3**.

EXPERIMENTAL PART

1. General

All reactions were monitored by TLC on silica gel 60 F-254 plates purchased from EM Laboratories, Inc. and were detected by UV light at 254 nm. All flash column chromatographic separations were performed using silica gel (Merck 60 230-400 mesh). Melting points were determined on an Electrothermal IA9100 melting point apparatus and are uncorrected. UV Spectra (λ_{max} (log ε) in nm) were recorded on a Shimadzu UV-Visible UV-160A spectrophotometer. IR Spectra (cm^{-1}): Perkin-Elmer System-2000 infrared spectrophotometer. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 spectrometer or Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer, and results were within ± 0.4% of calculated values. Electrospray ionization mass spectra (ESI MS or HRMS (ESI)) were recorded on Bruker APEX II FT-MS.

2. Syntheses

General Procedure for the Synthesis of *N*-Benzoyl or *N*-Phenylsulfonyl Ofloxacins

A mixture of *N*-demethyl ofloxacin (1 mmol), K_2CO_3 (0.28 g, 2 mmol), KI (70 mg), and corresponding phenylsulfonyl chlorides or benzoyl chlorides (4 mmol) in dry DMF (8 mL) was heated at 80 °C (monitored until the reactant disappeared by TLC). Evaporation of the solvent gave a residue, which was participated into biphasic mixture of saturated $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic extracts were washed with H_2O (50 mL × 2) and brine (50 mL × 1), dried over Na_2SO_4, filtered, and concentrated in a vacuum. The crude product was purified by flash column chromatography and/or crystallization.

8-Fluoro-3-methyl-6-oxo-9-[4-(phenylsulfonyl)piperazin-1-yl]-2,3-dihydro-6*H*-1-oxo-3a-aza-phenalene-5-carboxylic acid (4)[26]

Compound **4** was obtained by FC (MeOH/DCM = 1:100) and recrystallized from EtOH to give 0.39 g (79% yield) as a white powder. Mp 279-280 °C. UV λ_{max} nm (log ε): 230 (4.20), 297 (4.50) in MeOH. IR ν_{max} cm^{-1}: 1171, 1458, 1525, 1620, 1713 in KBr. ^1H-NMR (DMSO-d_6): 1.41 (d, 3H, J = 6.8 Hz, 2-CH_3), 3.03, 3.34 (m, 8H, 9-piperazinyl-H), 4.31, 4.53 (AB, 2H, J = 11.6 Hz, 2H-C(1)), 4.90 (q, 1H, J = 6.8 Hz, 1H-C(2)), 7.56 (d, 1H, J = 12.0 Hz, 1H-C(7)), 7.69 (m, 2H, Ar-H), 7.79 (m, 3H, Ar-H), 8.96 (s, 1H, 1H-C(4)), 15.12 (br s, COOH). ESI MS *m/z*: 488 $(M + H)^+$.

8-Fluoro-9-[4-(4-fluorophenylsulfonyl)piperazin-1-yl)-3-methyl-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (5)

Compound **5** was obtained by recrystallization from EtOH to give 0.38 g (76% yield) as a white powder. Mp 245-246 °C. UV λ_{max} nm (log ε): 230 (4.32), 294 (4.62) in MeOH. IR ν_{max} cm^{-1}: 1158, 1472, 1522, 1617, 1718 in KBr. ^1H-NMR (DMSO-d_6): 1.41 (d, 3H, J = 6.4 Hz, 2-CH_3), 3.04, 3.35 (m, 8H, 9-piperazinyl-H), 4.32, 4.53 (AB, 2H, J = 10.4 Hz, 2H-C(1)), 4.91 (m, 1H, 1H-C(2)), 7.56 (m, 3H, Ar-H and 1H-C(7)), 7.87 (m, 2H, Ar-H), 8.97 (s, 1H, 1H-C(4)), 15.12 (br s, COOH). *Anal.* Calc. for $C_{23}H_{21}F_2N_3O_6S$: C 54.65, H 4.19, N 8.31; found: C 54.48, H 4.36, N 7.32. ESI MS *m/z*: 506 $(M + H)^+$.

8-Fluoro-3-methyl-9-[4-(4-nitrophenylsulfonyl)piperazin-1-yl)-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (6)[26]

Compound **6** was obtained by FC (MeOH/DCM = 1:50) and recrystallized from EtOH to give 0.38 g (71% yield) as a pale yellow powder. Mp 286-287 °C. UV λ_{max} nm (log ε): 296 (4.54) in MeOH. IR ν_{max} cm^{-1}: 1167, 1351, 1469, 1529, 1620, 1712 in KBr. ^1H-NMR (DMSO-d_6): 1.41 (d, 3H, J = 6.4 Hz, 2-CH_3), 3.12, 3.37 (m, 8H, 9-piperazinyl-H), 4.31, 4.52 (AB, 2H, J = 12.0 Hz, 2H-C(1)), 4.89 (q, 1H, J = 6.4 Hz, 1H-C(2)), 7.55 (d, 1H, J = 12.0 Hz, 1H-C(7)), 8.07 (m, 2H, Ar-H), 8.47 (m, 2H, Ar-H), 8.97 (s, 1H, 1H-C(4)), 15.11 (br s, COOH). *Anal.* Calc. for $C_{23}H_{21}FN_4O_8S{\cdot}1.0\ H_2O$: C 50.18, H 4.21, N 10.18; found: C 50.47, H 4.03, N 9.80. ESI MS *m/z*: 533 $(M + H)^+$.

8-Fluoro-9-[4-(4-methoxyphenylsulfonyl)piperazin-1-yl]-3-methyl-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (7)

Compound **7** was obtained by recrystallization from EtOH, to give 0.42 g (82% yield) as a white powder. Mp 245-246 °C. UV λ_{max} nm (log ε): 238 (4.44), 296 (4.58) in MeOH. IR ν_{max} cm^{-1}: 1160, 1463, 1525, 1620, 1716 in KBr. ^1H-NMR (DMSO-d_6): 1.40 (d, 3H, J = 6.8 Hz, 2-CH_3),

2.99, 3.34 (m, 8H, 9-piperazinyl-H), 3.88 (s, 3H, OCH_3), 4.32, 4.53 (AB, 2H, J = 11.2 Hz, 2H-C(1)), 4.89 (q, 1H, J = 6.8 Hz, 1H-C(2)), 7.20 (m, 2H, Ar-H), 7.55 (d, 1H, J = 12.4 Hz, 1H-C(7)), 7.72 (m, 2H, Ar-H), 8.96 (s, 1H, 1H-C(4)), 15.12 (br s, COOH). *Anal.* Calc. for $C_{24}H_{24}FN_3O_7S\cdot 0.4\ H_2O$: C 54.94, H 4.76, N 8.01; found: C 54.91, H 4.75, N 7.99. ESI MS *m/z*: 518 $(M + H)^+$. HRMS (ESI): Calcd for $C_{24}H_{25}FN_3O_7S$: 518.1397; found: 518.1398.

9-(4-Benzoylpiperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (8)

Compound **8** was obtained by FC (MeOH/DCM = 1:100) and recrystallized from EtOH, to give 0.38 g (85% yield) as a white powder. Mp 223-225 °C. UV λ_{max} nm (log ε): 297 (4.44) in MeOH. IR ν_{max} cm^{-1}: 1475, 1620, 1706 in KBr. ^{1}H-NMR (DMSO-d_6): 1.45 (d, 3H, J = 6.0 Hz, 2-CH_3), 3.36-3.53 (m, 8H, 9-piperazinyl-H), 4.39, 4.60 (AB, 2H, J = 11.2 Hz, 2H-C(1)), 4.93 (q, 1H, J = 6.0 Hz, 1H-C(2)), 7.50-7.67 (m, 3Ar-H and 1H-C(7)), 7.92-7.97 (m, 2Ar-H), 8.98 (s, 1H, 1H-C(4)), 15.11 (br s, COOH). *Anal.* Calc. for $C_{24}H_{22}FN_3O_5\cdot 0.3\ H_2O$: C 63.10, H 4.99, N 9.20; found: C 63.14, H 5.16, N 9.18. ESI MS *m/z*: 452 $(M + H)^+$. HRMS (ESI): Calcd for $C_{24}H_{23}FN_3O_5$: 452.1622; found: 452.1619.

8-Fluoro-9-[4-(4-fluorobenzoyl)piperazin-1-yl]-3-methyl-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (9)

Compound **9** was obtained by FC (MeOH/DCM = 1:50) and recrystallized from EtOH, to give 0.34 g (72% yield) as a white powder. Mp 270-272 °C. UV λ_{max} nm (log ε): 232 (4.28), 297 (4.56) in MeOH. IR ν_{max} cm^{-1}: 1467, 1619, 1727 in KBr. ^{1}H-NMR (DMSO-d_6): 1.45 (d, 3H, J = 6.8 Hz, 2-CH_3), 3.49, 3.74 (m, 8H, 9-piperazinyl-H), 4.38, 4.60 (AB, 2H, J = 10.4 Hz, 2H-C(1)), 4.93 (q, 1H, J = 6.8 Hz, 1H-C(2)), 7.30 (m, 2H, Ar-H), 7.53 (m, 2Ar-H), 7.60 (d, 1H, J = 12.4 Hz, 1H-C(7)), 8.99 (s, 1H, 1H-C(4)), 15.18 (br s, COOH). *Anal.* Calc. for $C_{24}H_{21}F_2N_3O_5$: C 61.41, H 4.51, N 8.95; found: C 61.16, H 4.70, N 8.72. ESI MS *m/z*: 470 $(M + H)^+$. HRMS (ESI): Calcd for $C_{24}H_{22}F_2N_3O_5$: 470.1527; found: 470.1525.

8-Fluoro-3-methyl-9-[4-(4-nitrobenzoyl)piperazin-1-yl]-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (10)

Compound **10** was obtained by recrystallization from EtOH to give 0.34 g (68% yield) as a yellow powder. Mp 258 °C (dec). UV λ_{max} nm (log ε): 213 (4.33), 296 (4.57) in MeOH. IR ν_{max} cm^{-1}: 1467, 1619, 1727 in KBr. ^{1}H-NMR (DMSO-d_6): 1.54 (d, 3H, J = 6.8 Hz, 2-CH_3), 3.32, 3.61 (m, 8H, 9-piperazinyl-H), 4.48, 4.69 (AB, 2H, J = 11.6 Hz, 2H-C(1)), 5.02 (q, 1H, J = 6.8 Hz, 1H-C(2)), 7.70 (d, 1H, J = 12.4 Hz, 1H-C(7)), 8.22 (m, 2H, Ar-H), 8.42 (m, 2Ar-H), 9.07 (s, 1H, 1H-C(4)), 15.16 (br s, COOH). *Anal.* Calc. for $C_{24}H_{21}FN_4O_7\cdot 0.3\ H_2O$: C 57.44, H 4.34, N 11.16; found: C 57.13, H 4.52, N 11.09. ESI MS *m/z*: 497 $(M + H)^+$.

8-Fluoro-3-methyl-9-[4-(4-methoxybenzoyl)piperazin-1-yl]-6-oxo-2,3-dihydro-6*H*-1-oxo-3a-azaphenalene-5-carboxylic acid (11)

Compound **11** was obtained by recrystallization from EtOH, to give 0.39 g (82% yield) as a yellow powder. Mp 256-258 °C. UV λ_{max} nm (log ε): 221 (3.96), 297 (4.82) in MeOH. IR ν_{max} cm^{-1}: 1458, 1619, 1721 in KBr. ^{1}H-NMR ($CDCl_3$): 1.61 (d, 3H, J = 6.4 Hz, 2-CH_3), 3.38, 3.78 (m, 8H, 9-piperazinyl-H), 3.85 (s, 3H, OCH_3), 4.39-4.56 (M, 3H, 2H-C(1) and 1H-C(2)), 6.95 (m, 2H, Ar-H), 7.43 (m, 2H, Ar-H), 7.74 (d, 1H, J = 12.0 Hz, 1H-C(7)), 8.64 (s, 1H, 1H-C(4)), 14.91 (br s, COOH). *Anal.* Calc. for $C_{25}H_{24}FN_3O_6\cdot 0.2\ H_2O$: C 61.90, H 5.07, N 8.66; found: C 61.83, H 5.29, N 8.57. ESI MS *m/z*: 482 $(M + H)^+$. HRMS (ESI): Calcd for $C_{25}H_{25}FN_3O_6$: 482.1727; found: 482.1725.

3. Anti-mycobacterium activity

Primary screening is conducted against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay to determine the actual minimum inhibitory concentration (MIC) using the Microplate Alamar Blue Assay (MABA).[25] The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. Concurrent with the determination of MICs, compounds are screened by serial dilutions to assess cytotoxicity (IC_{50}) to a VERO cells. After 72 h exposure, viability is assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 Non-radioactive Cell Proliferation Assay.

4. Antimicrobial assays

Disk diffusion (Kirby-Bauer) is one of the most commonly used antimicrobial susceptibility testing (AST) methods among diagnostic laboratories. This method is a well-established procedure for which there are accepted standards including those endorsed by the National Committee for Clinical Laboratory Standards (NCCLS).[27,28]

Growth inhibitory activity of the target compounds was tested against five strains (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Entercocus* species, *Streptococcus pyrogenes*, and *Streptoccus pneumoniae*). These microorganisms were provided from the Microbiology Laboratory Culture Collection, Department of pathology, Tri-service General Hospital, Taipei, Taiwan. The bacteria were first incubated at 37 ± 0.1 °C for 24 h in nutrient broth (Difco). The standard NCCLS disk diffusion test was performed on each bacteria strain using unsupplemented Mueller-Hinton agar (Becton Dickinson Microbiology System, Cocleysville, Md) and standard 10-μg gentamicin dis, 10-μg penicillin disk and 30-μg vancomycin (Becton Dickinson). With the Bauer-Kirby method, an activity growing broth culture is diluted until the turbidity matches that of a MacFarland 0.5 $BaSO_4$ standard (ca. 10^8 colony-forming units [CPU]/mL), 15 mL of mueller hinton agar (MHA, Oxoid) and sabouraud dextrose agar (SDA) (sterilized in a flask and cooled to 40-50 °C) were homogenously distributed onto the sterilized petri dishes. Sterilized blank paper discs 6 mm in diameter were saturated with 80-μg of tested compounds per disc, then placed onto the agar plates which had previously been inoculated with the above organisms. Standard paper discs treated with gentamycin, penicillin and vancomycin-saturated antibiotics were used as postive controls. Following incubation for 16 to 18 h at 37 ± 0.1 °C, inhibition zones appearing around the discs were measured and recorded in mm.

CONCLUSION

In summary, the positive *N*-demethyl ofloxacin (**3**) exhibited a broad spectrum of antibacterial activity including the growth inhibition of *M. tuberculosis* while compound **6** exhibited a potent activity against the growth of TB but was inactive against the growth of G(+)- and G(-)-bacteria. Selective anti-TB activity was achieved by the introduction of an arylsulfonyl group at C-7 piperazin-4-yl of *N*-demethyl ofloxacin. These results implied compound **6** could be a potential lead for further development of new specific anti-TB drug candidates without inducing cross resistance with other currently used antibacterial drugs.

ACKNOWLEDGEMENTS

Financial support of this work by the National Science Council of the Republic of China is gratefully acknowledged. We also thank National Center for High-Performance Computing for providing computer resources and chemical database services. Antimycobacterial data were provided by Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) through a research and development contract with the US National Institute of Allergy and Infectious Diseases.

Received August 28, 2008.

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