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The Synthesis and Activity *in vitro* of a Series of 5-Amino-8-methoxyquinolones

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Abstract: A series of 1-cyclopropyl-5-amino-6-fluoro-8-methoxyquinoline-3-carboxylic acids have been prepared and evaluated for antibacterial activity *in vitro.*

Keywords: Quinolone, synthesis, antibacterial activity.

Since Lesher's discovery of nalidixic acid in 1962, a tremendous amount of synthetic effort has been channeled into the synthesis of quinolone antibacterial agents[1]. These research efforts have been rewarded by very significant improvements in antibacterial potency as well as *in vivo* efficacy. In 1995, Sanchez *et al.*[2] reported that series of (5-amino-)8-methoxyquinolones had antibacterial activity against Gram-positive, Gram-negative, and anaerobic bacteria equivalent to the most active 8-substituted compounds (8-F and 8-Cl). There was also a concomitant reduction in several of the potential side effects (*i.e.*, phototoxicity and clonogenicity) compared to the most active quinolones with classic substitution at C-8. In their research, side chains of C-7 position were only substitute piperazine, pyrrolidine and piperidine as usual, so our interest was directed to the synthesis a series of 5-amino-8-methoxyquinolones that have novel side chain[3~4] and their antibacterial activity.

Scheme 1

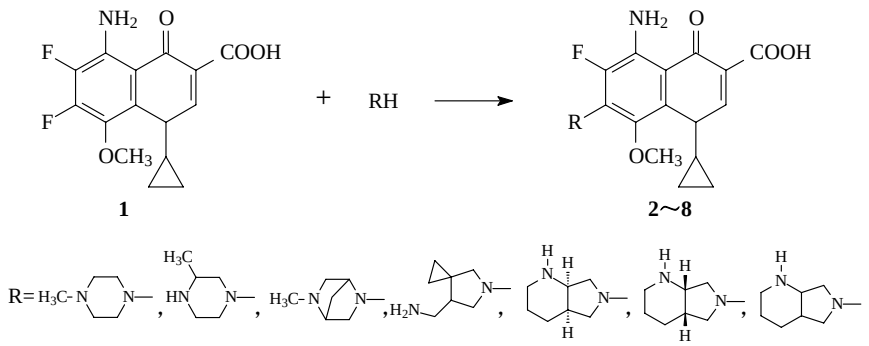

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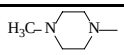
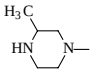
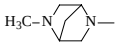
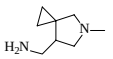
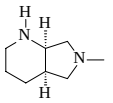
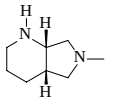
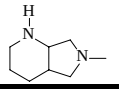
Table 1 ^{1}H NMR and HR-MS data of target compounds

Entry	R	^{1}H NMR (CF_3COOD, δ ppm),	HR-MS *m/z*
2		1.00-1.31 (m, 4H), 3.09 (s, 3H), 3.33-3.97 (m, 11H), 4.24 (m, 1H), 9.11 (s, 1H)	Calcd: 390.170334, Found: 390.171200
3		1.00-1.46 (m, 7H), 3.80-3.97 (m, 10H), 4.26(m, 1H), 9.12 (s, 1H)	Calcd: 390.170334, Found: 390.171239
4		0.93-1.42 (m, 4H), 2.43-2.57 (s, 2H), 3.08 (s, 3H), 3.64 (s, 3H), 3.26-5.04 (m, 7H), 9.10 (s, 1H)	Calcd: 402.170334, Found: 402.169586
5		0.78-1.39 (m, 8H), 2.38 (br, 1H), 3.63 (s, 3H), 3.17-4.37 (m, 7H) 8.92 (s, 1H)	Calcd: 416.185984, Found: 416.187194
6		($CDCl_3$) 0.72-1.02 (m, 4H), 1.55-1.81 (m, 4H), 2.34(br, 1H), 2.69-3.10(m, 2H), 3.44(s, 3H), 3.46-4.05 (m, 6H), 6.34 (br, 2H), 8.62 (s, 1H)	Calcd: 416.185984, Found: 416.187308
7		($CDCl_3$) 0.72-1.00 (m, 4H), 1.65-1.80 (m, 4H), 2.31 (br, 1H), 2.44-3.20 (m, 2H), 3.21 (s, 3H), 3.46-4.02 (m, 6H), 6.34 (br, 2H), 8.62(s, 1H)	Calcd: 416.185984, Found: 416.185257
8		($CDCl_3$) 0.72-1.24 (m, 4H), 1.63-1.82 (m, 4H), 2.42 (br, 1H), 2.76-3.19 (m, 2H), 3.46 (s, 3H), 3.57-4.04 (m, 6H), 6.34 (br, 2H), 8.61(s, 1H)	Calcd: 416.185984, Found: 416.185949

The coupling reactions of the novel side chains with 5-amino-8-methoxyquinolone substrates according to well-established literature procedures (**Scheme 1**)[2].

In total, we have synthesized seven new target compounds. The structures of these compounds were confirmed by ^{1}H NMR and HR-MS (data shown in **Table 1**).

Antibacterial Activity

Table 2 The antibacterial activity *in vitro* of target compounds

Strains	MIC (μg/ml)								
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
S. pneumonias 70	0.12	0.06	0.25	0.002	0.01	0.002	0.01	2	0.06
S. pneumonias 9798	0.12	0.06	0.03	0.005	0.01	0.005	0.01	1	0.12
S. pyogenes A12	0.12	0.06	0.03	0.01	0.03	0.005	0.03	0.5	0.25
S. aureus 9616	0.25	0.01	1	0.005	0.5	0.005	0.03	0.25	0.12
S. epidermidis 26069	0.06	0.01	0.12	0.005	0.01	0.002	0.01	0.5	0.06
S. epidermidis 9726	0.5	0.01	0.5	0.005	0.03	0.005	1	1	0.12
E. Coli ATCC 25922	0.5	0.005	2	0.01	1	0.005	1	0.03	0.01
E. Coli 834	0.06	0.06	0.12	0.01	1	0.01	1	0.03	0.03
P. aeruginosa ATCC 27853	4	0.5	4	1	4	1	4	0.5	1
*K. pneumoniae*14	0.005	0.005	0.5	0.01	1	0.005	0.01	0.01	0.03
S. typhi H901	0.5	0.12	1	0.03	0.25	0.12	0.12	0.12	0.25
S. macescens 932	0.25	0.12	1	0.25	1	0.12	0.5	0.06	0.25

Using ciprofloxcin **9** and gatifloxacin **10** as contrast, we tested the antibacterial activity *in vitro* of the target compounds with some clinical separated pathogens, quality control strains and standard strains. The target compounds **2-8** were tested MICs using double dilution method. The results were shown in **Table 2**.

Compound **3** has activity equivalent to gatifloxacin *vs* Gram-positive and Gram-negative organisms, compounds **5** and **7** are more active than gatifloxacin *vs* Gram-positive and Gram-negative organisms. All seven compounds, while more active than ciprofloxcin *vs* Gram-positive organisms, were equipotent against Gram-negative organisms. On the basis of these results, compounds **5** and **7** were selected as candidates for further evaluation.

Acknowledgments

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References

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