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Design, synthesis and antibacterial activity evaluation of moxifloxacin-amide-1,2,3-triazole-isatin hybrids

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ABSTRACT

In this work, a series of novel moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** were designed and synthesized. The *in vitro* antibacterial activity against a panel of clinically important Gram-positive and Gram-negative bacteria including drug-resistant pathogens was also evaluated. All hybrids showed considerable activity against the tested pathogens with MIC values of ≤0.03 to 128 μg/mL, and some of them such as hybrids **7e**, **7g** and **7j** were comparable to or better than the parent moxifloxacin (MIC: ≤0.03–8 μg/mL). Moreover, hybrids **7e**, **7g** and **7j** also demonstrated low cytotoxicity towards CHO cells. However, the *in vivo* pharmacokinetic profiles of these three hybrids were generally far inferior to the parent moxifloxacin. The structure-activity relationship and structure-cytotoxicity relationship were also studied and discussed which may help with the identification of new chemical entities as potent antibacterial agents.

1. Introduction

Bacterial infections are very common both in hospital and in community settings, and they are responsible for a main cause of morbidity and mortality throughout the world [1–4]. Antibiotics can either kill or inhibit the growth of pathogens and they represent effective weapons for fighting bacterial infections [5,6]. Unfortunately, bacteria have already developed resistance to almost all antibiotics due to the long-term use even abuse of antibiotics [7,8]. Roughly 700,000 drug-resistant bacterial infection related deaths occur every year, and the number may increase to 10 million in 2050 if there are no effective solutions [9,10]. Novel antibacterial agents might be a useful tool to control the bacterial infection.

Moxifloxacin, the fourth generation of quinolone antibiotics, can act with bacteria by binding DNA gyrase and topoisomerase IV [11]. Moxifloxacin possesses broad-spectrum antimicrobial activity and has been used widely to treat various bacterial infections such as pneumonia, conjunctivitis, endocarditis, tuberculosis, and sinusitis in clinics [12,13]. However, bacteria also developed resistance to moxifloxacin. Moreover, serious adverse effects like irreversible peripheral neuropathy [14], hepatitis [15], Stevens-Johnson syndrome [16] and phototoxicity reactions [17] may occur as a result of moxifloxacin treatment. To overcome the drug-resistance and reduce the adverse effects, modification and optimization of moxifloxacin are necessary.

Isatin and 1,2,3-triazole possess diverse pharmacological properties such as anticancer [18,19], antitubercular [20,21], antiviral [22,23], and antibacterial [24,25] activities because these heterocycles can serve as a useful tool to manipulate lipophilicity, polarity, and hydrogen bonding capacity of molecules, consequently improving pharmacological, pharmacokinetic, toxicological, and physicochemical properties of drug candidates and the ultimate drugs [26]. Obviously, isatin and 1,2,3-triazole derivatives occupy an important position in the development of new drugs.

Fluoroquinolone-1,2,3-triazole-isatin hybrids including moxifloxacin-1,2,3-triazole-isatin **1** (Fig. 1) tethered with various alkyl linkers demonstrated considerable antimicrobial activity [27–35]. The structure-activity relationship (SAR) and structure-cytotoxicity relationship demonstrated that the linker between the fluoroquinolone and 1,2,3-triazole fragments as well as substituents on the isatin moiety influenced the activity significantly for fluoroquinolone-1,2,3-triazole-isatin hybrids [27–30]. Substituents at C-3 position of isatin motif could control the lipophilicity of the hybrids, while substituents at the phenyl ring demonstrated the electronic effect which was closely correlated with the biological activity [31–35]. Introduction of amide onto the C-7 position of fluoroquinolone framework could boost up the biological activity when compared with the parent compounds, so amide may be

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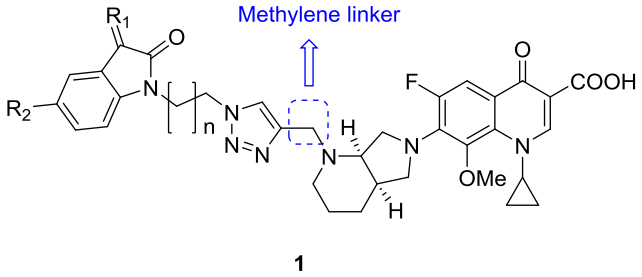

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Fig. 1. Chemical structures of alkyl tethered moxifloxacin-1,2,3-triazole-isatin hybrids **1**.

an excellent linker between the fluoroquinolone and 1,2,3-triazole moieties [36–38].

In this work, a series of novel moxifloxacin-amide-1,2,3-triazole-isatin hybrids were designed, synthesized and evaluated for their *in vitro* antibacterial activity against a panel of Gram-positive and Gram-negative bacteria including drug-resistant pathogens. The design strategy was depicted in Fig. 2.

2. Results and discussion

All moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** were synthesized by the route depicted in Scheme 1. Treatment of 2-bromoacetic acid **1** with sodium azide yielded 2-azidoacetic acid **2**, which was then reacted with dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS), giving succinimidyl ester **3** [39]. Condensation of moxifloxacin with succinimidyl ester **3** with triethylamine (TEA) as base generated 2-azidoacetyl moxifloxacin **4**. Alkylation of isatin/5-fluoroisatin/5-methylisatin/7-fluoroisatin **5a-d** with propargyl bromide provided *N*-propargyl isatin intermediates **6a-d** [30,31]. Cyclization of 2-azidoacetyl moxifloxacin **4** and *N*-propargyl isatin intermediates **6a-d** in presence of $Cu(OAc)_2$ provided the desired acetyl tethered moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-d** [40]. Finally, condensations of **7a-d** with methoxylamine hydrochloride or ethoxylamine hydrochloride with sodium bicarbonate as base gave acetyl tethered moxifloxacin-amide-1,2,3-triazole-isatin-oxime hybrids **7e-l**.

The chemical structures and yields of the synthesized moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** were listed in Table 1. The yields were in a range of 19% to 66%, and hybrids with carbonyl and methyloxime groups at C-3 position of isatin moiety showed higher yields than the corresponding ethyloxime analogs which may be attributed to the steric effect.

The antibacterial activity of the synthesized moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** against Gram-positive and Gram-negative bacteria was investigated, and the minimum inhibitory concentration (MIC) values were listed in Tables 2 and 3, respectively.

All hybrids **7a-l** (MIC: 0.06–128 μg/mL) showed considerable antibacterial activity against the tested six Gram-positive organisms including drug-resistant MRSE and MRSA strains, and the activities of some hybrids among **7a-l** were comparable to or more potent than those of the parent moxifloxacin (MIC: 0.06–8 μg/mL) and the reference vancomycin (MIC: 0.5–16 μg/mL) against certain strains. The SAR indicated the substituents at R_1 position had great influence on the activity, and electron-donating methyl was more favorable than electron-withdrawing fluoro. The position of substituents on the phenyl ring also had a profound effect on the antibacterial activity, and hybrids with substituents at C-5 positions were more potent than the corresponding C-7 position substituted analogs. Compared with unsubstituted analogs, introduction of methyloxime (R_2 position) at C-3 position of isatin moiety could enhance the activity to some extent, while ethyloxime was harmful to the activity generally. The most active hybrid **7g** (MIC: 0.06–16 μg/mL) was no inferior to the parent moxifloxacin (MIC: 0.06–8 μg/mL) against all tested Gram-positive pathogens and it was 2–16 times more potent than moxifloxacin and vancomycin against MSSE, 2- and 8-fold more active than moxifloxacin against drug-resistant MRSE and MRSA strains.

From Table 3, it can be seen that the majority of hybrids **7a-l** exhibited excellent activities against *E. coli* ESBLs(−), *E. coli* ESBLs(+), *K. pneumoniae* ESBLs(+), *K. pneumonia* ESBLs(−), *E. cloacae*, *E. aerogenes*, *P. rettgeri*, and *Proteus vulgaris* with MIC < 1 μg/mL, and moderate activities against *P. aeruginosa* and *A. coacetious* with MIC of 0.5–16 μg/mL. All of them were more potent than vancomycin (MIC: > 128 μg/mL), and five of them **7e**, **7g**, **7i**, **7j** and **7k** with MIC ≤ 1 μg/mL were comparable to or superior to the parent moxifloxacin (MIC: ≤0.03–0.5 μg/mL) against all tested Gram-negative strains. In general, incorporation of oximes onto the C-3 position of isatin fragment increased the activity, and ethyloxime > methyloxime ≈ ketone. Electron-withdrawing fluoro at C-5 position of isatin could boost up the activity, while methyl reduced the activity when compared to the unsubstituted analogs. Movement of fluoro to C-7 position led to great loss of activity, suggesting the position also influenced the activity remarkedly.

In general, isatin structural scaffold could act as potent DNA gyrase and FtsZ inhibitors, while moxifloxacin could bind DNA gyrase and topoisomerase IV [41,42]. Thus, the hybrids might have the potential to exert multiply action mechanisms, and possess the activity against drug-resistant strains. The action mechanisms of the hybrids are being under investigated, and the results will be reported soon.

It could be observed from Table 4 that all hybrids also displayed acceptable toxicological profiles with CC_{50} ranging from 8 to 64 μg/mL against CHO cells, but they were more toxic than the parent moxifloxacin (CC_{50}: > 128 μg/mL). The structure-cytotoxicity relationship study revealed that introduction of either electron-donating or electron-withdrawing groups at C-5 or C-7 position could increase the

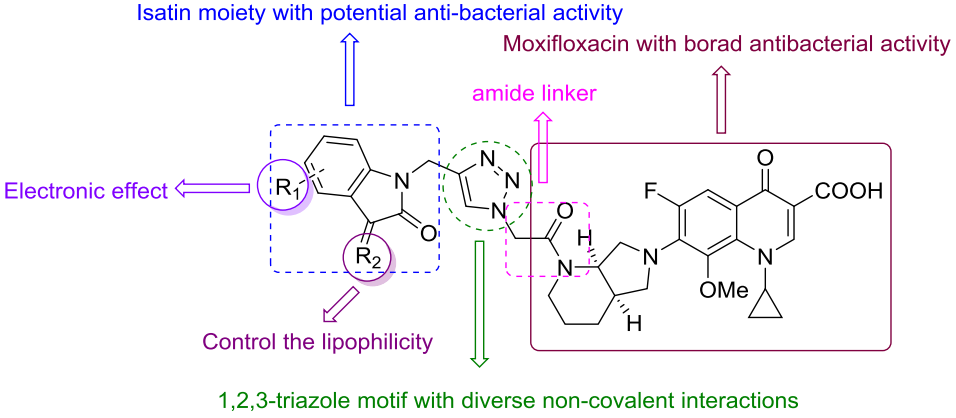
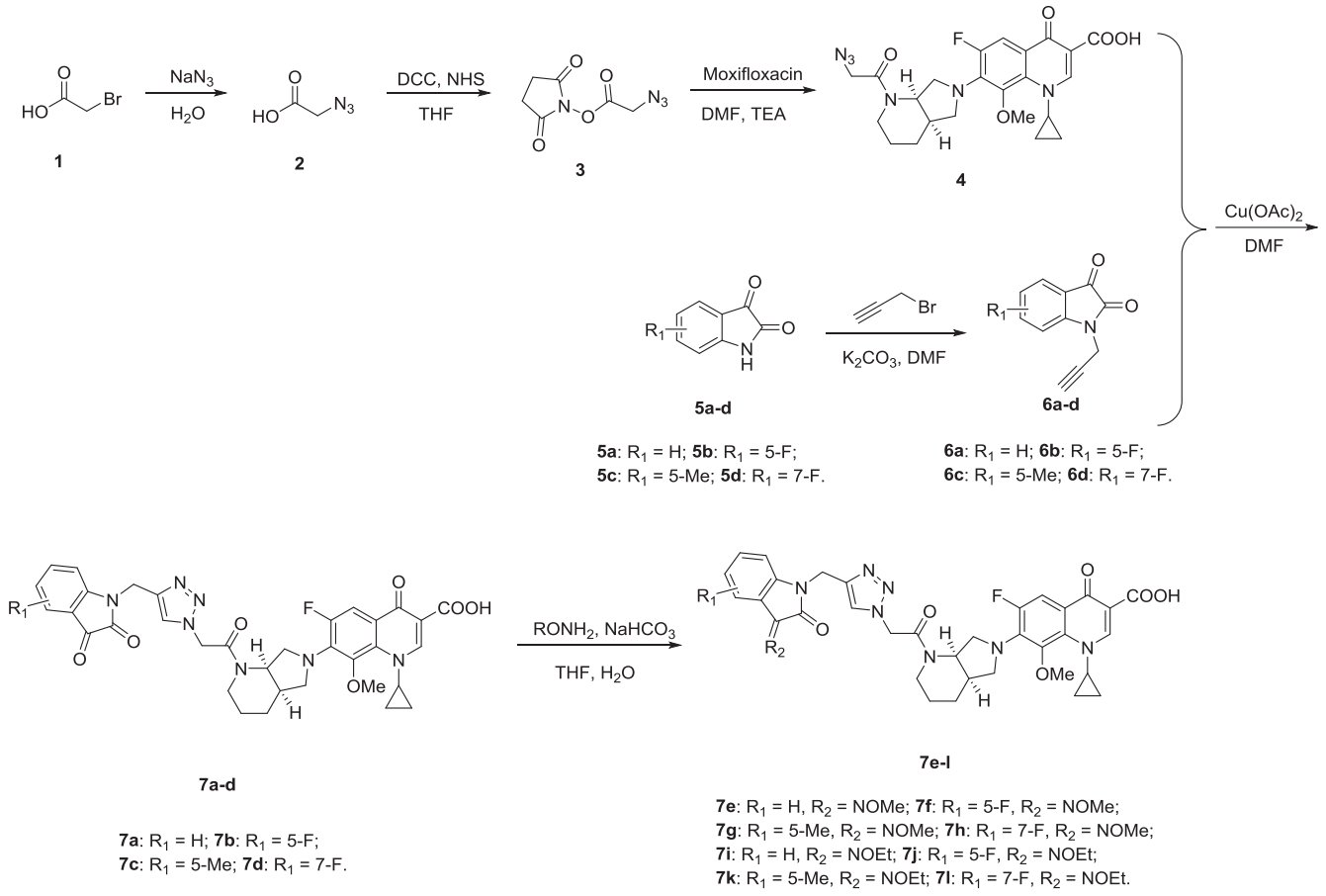
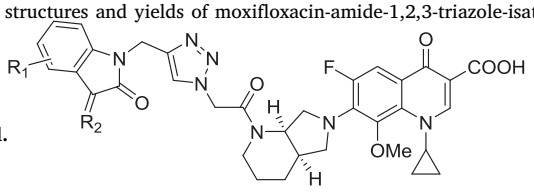


Fig. 2. Design strategy for moxifloxacin-amide-1,2,3-triazole-isatin hybrids.



Scheme 1. Synthesis of moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l.**

Table 1
Chemical structures and yields of moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l.**



7a-l

Compound	R_1	R_2	Yield (%)
7a	H	O	44%
7b	5-F	O	52%
7c	5-Me	O	39%
7d	7-F	O	34%
7e	H	NOMe	57%
7f	5-F	NOMe	43%
7g	5-Me	NOMe	66%
7h	7-F	NOMe	31%
7i	H	NOEt	35%
7j	5-F	NOEt	27%
7k	5-Me	NOEt	38%
7l	7-F	NOEt	19%

Table 2
In vitro antibacterial activity of acetyl tethered moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** against Gram-positive strains.

Compd.	MIC (μg/mL)					
	MSSE	MRSE	MSSA	MRSA	E.fa.	E.fm.
7a	0.5	4	1	1	8	16
7b	1	8	2	2	16	16
7c	0.25	8	1	2	4	32
7d	2	8	2	8	32	128
7e	0.125	2	0.5	16	8	8
7f	0.125	4	0.125	2	8	16
7g	0.06	1	0.125	1	4	16
7h	0.5	4	2	32	16	32
7i	0.5	16	2	8	32	64
7j	1	16	2	2	32	32
7k	1	8	1	2	8	32
7l	4	32	4	16	16	16
Moxifloxacin	0.125	2	0.06	8	0.5	8
Vancomycin	1	0.5	0.5	1	1	16

Abbreviations: MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; E.fa., *Enterococcus faecalis*; E.fm., *Enterococcus faecium*.

cytotoxicity, and installation of ethyloxime or methyloxime at C-3 position of isatin moiety could not improve toxicological profile when compared with unsubstituted analogs.

Three hybrids **7e**, **7g** and **7j** with promising activity against Gram-positive or Gram-negative pathogens and low cytotoxicity towards CHO cells were selected for further *in vivo* pharmacokinetic investigation in mice (100 mg/kg, subcutaneous injection/s.c. administration), and the results were presented in Table 5.

From Table 5, the *in vivo* pharmacokinetic profiles of the selected hybrids **7e**, **7g** and **7j** were worse than those of the parent moxifloxacin in terms of the peak concentration (C_{max}), the time to reach peak concentration (T_{max}) and the area under the curve ($AUC_{0\text{-}inf}$), and this may be attributed to the existence of 1,2,3-triazole and amide functional groups led to poor solubility and bioavailability. However, the

Table 3
In vitro antibacterial activity of moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** against Gram-negative strains.

Compd.	MIC (μg/mL)									
	E.co.1	E.co.2	K.p.1	K.p.2	P.a.	A.c.	E.c.	E.a.	P.r.	P.v.
7a	≤0.03	≤0.03	≤0.03	0.25	1	1	≤0.03	0.12	≤0.03	≤0.03
7b	≤0.03	≤0.03	≤0.03	1	2	1	0.12	0.12	≤0.03	≤0.03
7c	0.03	0.06	0.06	1	2	1	0.5	0.25	≤0.03	≤0.03
7d	0.12	0.5	0.12	8	8	2	4	1	≤0.03	≤0.03
7e	≤0.03	≤0.03	≤0.03	0.5	1	0.5	≤0.03	0.06	≤0.03	≤0.03
7f	≤0.03	≤0.03	0.03	1	4	0.5	0.12	0.25	≤0.03	≤0.03
7g	0.06	0.12	0.06	2	4	1	0.25	0.12	≤0.03	≤0.03
7h	0.12	0.25	0.12	8	16	1	8	1	0.12	0.06
7i	≤0.03	≤0.03	≤0.03	0.5	0.5	1	≤0.03	0.12	≤0.03	≤0.03
7j	≤0.03	≤0.03	≤0.03	0.5	1	0.5	0.12	0.12	≤0.03	≤0.03
7k	≤0.03	≤0.03	0.03	1	1	1	0.25	0.5	0.03	0.06
7l	0.06	0.06	012	4	4	2	4	0.5	≤0.03	≤0.03
Moxifloxacin	≤0.03	≤0.03	≤0.03	0.5	0.25	0.125	≤0.03	0.06	≤0.03	≤0.03
Vancomycin	> 128	> 128	> 128	> 128	> 128	> 128	> 128	> 128	> 128	> 128

Abbreviations: E.co.1, *Escherichia coli* ESBLs(−); E.co.2, *Escherichia coli* ESBLs(+); K.p.1, *Klebsiella pneumoniae* ESBLs(+); K.p.2, *Klebsiella pneumonia* ESBLs(−); P.a., *Pseudomonas aeruginosa*; A.c., *Acinetobactercal coacetious*; E.c., *Enterobacter cloacae*; E.a., *Enterobacter aerogenes*; P.r., *Providentia rettgeri*; P.v., *Proteus vulgaris*; ESBLs (+): Extended spectrum beta-lactamases (ESBLs).

Table 4
In vitro cytotoxicity of moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l** towards CHO cells.

Compound	CC_{50} (μg/mL)
7a	64
7b	16
7c	32
7d	8
7e	64
7f	64
7g	32
7h	16
7i	16
7j	8
7k	32
7l	16
Moxifloxacin	> 128

Table 5
The *in vivo* pharmacokinetic values of hybrids **7e**, **7g**, **7j** and moxifloxacin in mice.

Compd.	Pharmacokinetics (s.c.)			
	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (min)	$AUC_{0\text{-inf}}$ (ng h/mL)
7e	798	3.8	48	2138
7g	3247	3.1	39	6435
7j	1398	4.3	52	3269
Moxifloxacin	10,783	2.6	27	19,243

C_{max}: the peak concentration; $t_{1/2}$: half-life.
T_{max}: the time to reach peak concentration; AUC: the area under the curve.

half-life ($t_{1/2}$) of the hybrids was longer than that of moxifloxacin.

3. Conclusions

In summary, twelve moxifloxacin-amide-1,2,3-triazole-isatin hybrids **7a-l**, were prepared and their *in vitro* antibacterial activity against clinically important Gram-positive and Gram-negative pathogens including drug-resistant strains was assessed in this work. The majority of the synthesized hybrids showed considerable *in vitro* activity against both drug-sensitive and drug-resistant strains, and acceptable cytotoxicity towards CHO cells. In particular, three hybrids **7e**, **7g** and **7j**, which were comparable to or better than the parent moxifloxacin against Gram-positive or Gram-negative pathogens, also demonstrated low cytotoxicity towards CHO cells. However, the *in vivo* pharmacokinetic profiles of these three hybrids were generally no superior to moxifloxacin.

The SAR and structure-cytotoxicity relationship were summarized in Fig. 3, and the enriched SAR and structure-cytotoxicity relationship may help global efforts for identification of new chemical entities as potent antibacterial agents with low toxicity.

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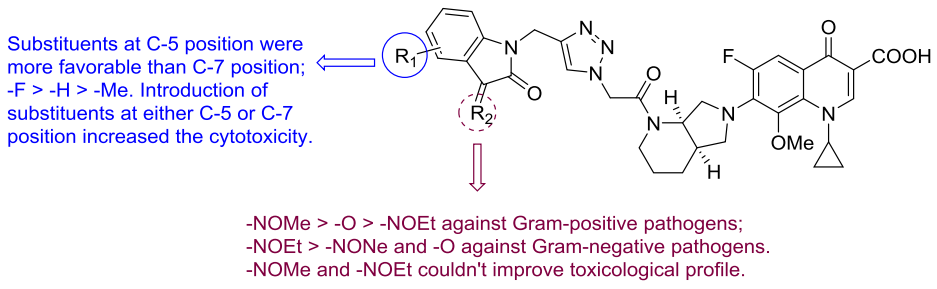

Fig. 3. The antibacterial SAR and structure-cytotoxicity relationship of moxifloxacin-amide-1,2,3-triazole-isatin hybrids.

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