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Synthesis and antifungal activity of furo[2,3-*f*]quinolin-5-ols

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ABSTRACT

Furo[2,3-*f*]quinolin-5-ol derivatives were synthesized and tested for in vitro antifungal activity against *Candida, Aspergillus* species, and *Cryptococcus neoformans*. Among them tested, many furo[2,3-*f*]quinolin-5-ols showed good antifungal activity. The results suggest that furo[2,3-*f*]quinolin-5-ols would be promising antifungal agents.

Benzofuran scaffolds **1** have potent biological properties including antifungal activity[1,2] as well as antibacterial[3,4] (Fig. 1). A benzofuran derivative, a novel myristoyltransferase inhibitor, has been reported as antifungal agent.[1,2] *N*-Myristoyltransferase has been proven to be essential for the viability of fungi, including medically important pathogenic fungi, *Candida albicans*[5] and *Cryptococcus neoformans*[6] making it a possible target for the development of antifungal agents with a novel mode of action.

In our previous Letters,[7] benzofuran-5-ol scaffolds **2** have demonstrated potent antifungal activity against pathogenic fungi (Fig. 1). We speculated that incorporation of a heterocyclic ring to the benzofuran-5-ol skeleton would change the physicochemical properties and lead to a new pharmacophore furo[2,3-*f*]quinolin-5-ols **3** with a different biological profile from benzofuran-5-ol scaffolds **2**. Furo[2,3-*f*]quinolin-5-ols **3** could metabolize to 5,8-quinolinedione derivatives with a quinonoid structure in fungi (Fig. 1). Quinonoid compounds display potent biological properties including antifungal, antimalarial, and antibacterial activity.[8] We assumed that furo[2,3-*f*]quinolin-5-ols **3** could have similar biological activities with those of quinonoid compounds. There have been a few reports[9,10] on furo[2,3-*f*]quinoline derivatives that exhibit cytotoxic activity against cancer cell lines. The antifungal activity of compounds **3** has not been reported to the best of our knowledge. The presence of aryl, thio, amino group, or halogen atoms on quinonoid compounds significantly affects their antifungal activity.[11] A variety of furo[2,3-*f*]quinolin-5-ols with different substituents could exhibit the biological activities through different actions and sometimes improve upon the activities.

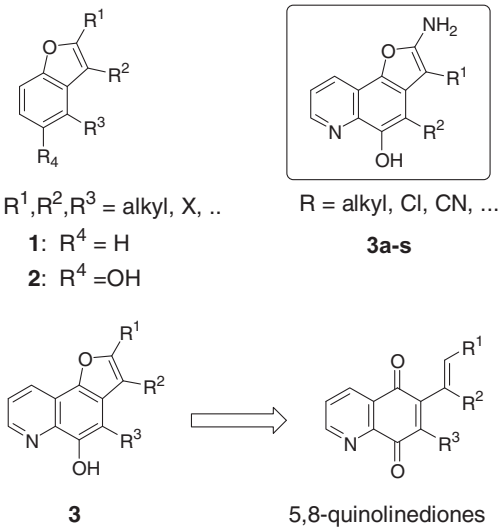

Figure 1. Benzofuran scaffolds and furo[2,3-*f*]quinolin-5-ol derivatives.

Based on this speculation, furo[2,3-*f*]quinolin-5-ols **3a–s** with various substituents were designed and synthesized to elucidate their contribution to the antifungal activity (Scheme 1). The in vitro antifungal activity of compounds **3a–s** against pathogenic fungi was determined by the twofold broth dilution method. Additional data for antifungal activity of 5-aminoquinolin-8-ol (**7**) and 7-methyl-8-nitroquinoline (**8**) are provided.

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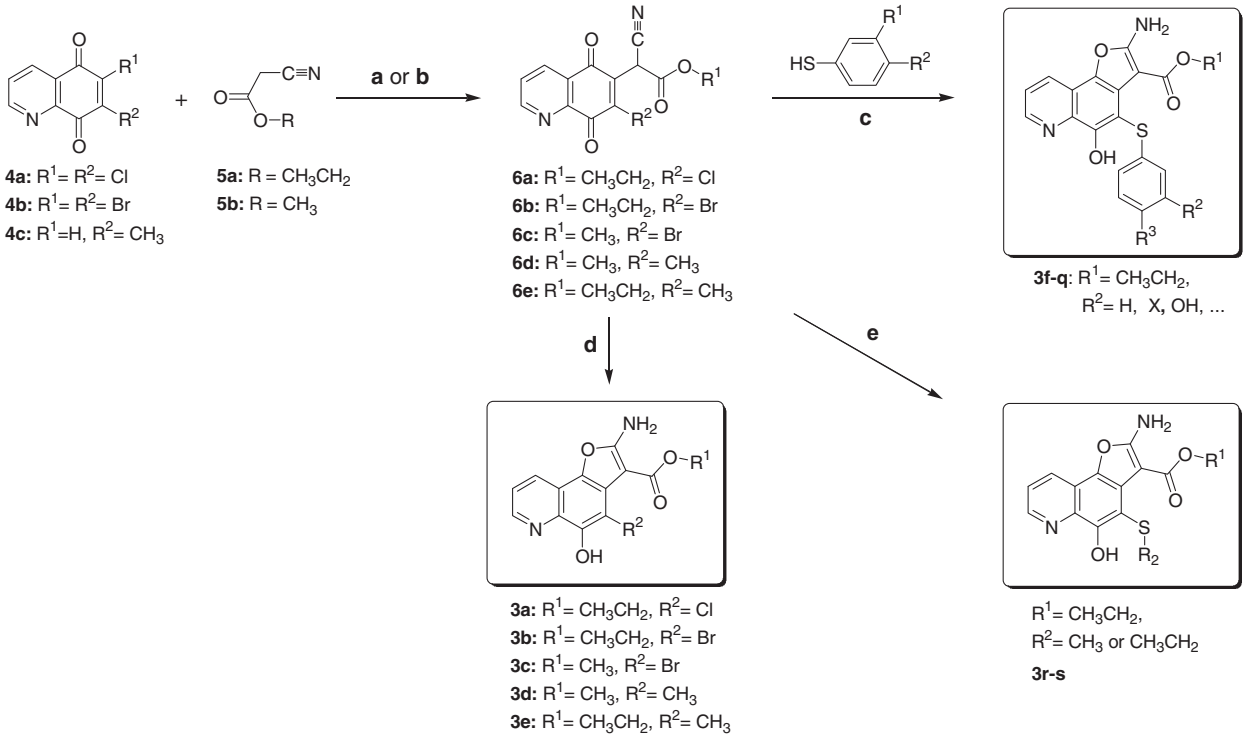


Scheme 1. Synthesis of furo[2,3-*f*]quinolin-5-ol derivatives. Reagents and conditions: (a) **5a** for **6a**, **6b**, or **6e**/NH_4OH/$CeCl_3$ (0.1 equiv)/EtOH/rt/10 min/47–61%; (b) **5b** for **6c** or **6d**/NH_4OH/$CeCl_3$ (0.1 equiv)/EtOH/rt/10 min/40–55%; (c) **6a**/ arylthiol **9** (1 equiv)/EtOH/reflux/5 h/60–86%; (d) **6a**–**e**/ hydrazine hydrate (1 equiv)/EtOH/reflux/2 h/42–72%; (e) **6a**/alkylthiol (1 equiv)/EtOH/reflux/5 h/63–81%.

Methods for the synthesis of furo[2,3-*f*]quinolin-5-ols **3a–s** are shown in Scheme 1 and Table 1. The 6,7-dichloro-5,8-quinolinedione (**4a**),[12] 6,7-dibromo-5,8-quinolinedione (**4b**),[13] and 7-methyl-5,8-quinolinedione (**4c**) were prepared from commercially available 5-aminoquinolin-8-ol (**7**) and 7-methyl-8-nitroquinoline (**8**) according to the known method.

Alkyl 2-(7-halo-5,8-dioxo-5,8-dihydroquinolin-6-yl)-2-cyanoacetates **6a–e** were synthesized by regioselective nucleophilic substitution or addition of compound **4a**, **4b**, or **4c** with 1 equiv of methyl- or ethylcyanoacetate (**5a** or **5b**) and 0.1 equiv of $CeCl_3$ in the presence of NH_4OH according to the reported method[14,15] with minor modification. The mechanism of formation of compounds **6** was cited in Ref. 16.

When the equivalent amount of each compound **6a–e** and hydrazine hydrate were mixed in EtOH and refluxed for 2 h, furo[2,3-*f*]quinolin-5-ols **3a–e** were formed. 2-Amino-4-arylthio-5-hydroxyfuro[2,3-*f*]quinolines **3f–q** were synthesized by nucleophilic substitution and cyclization of compound **6a** with appropriate arylthiols **9** in EtOH. To a solution of compound **6a** in EtOH, 1 equiv of arylthiol was added. The mixture was refluxed for 5 h and concentrated in vacuo. Purification of residual crude product by column chromatography yielded compounds **3f–q**. Most of these reactions went as expected and had overall high yields of 60–86%.

In a similar manner, 4-alkylthio-5-hydroxyfuro[2,3-*f*]quinolines **3r–s** were synthesized by cyclization of compound **6a** with 1 equiv of methyl- or ethylthiol in EtOH.

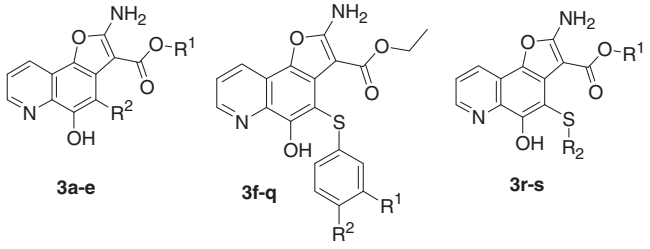
The mechanism for the formation of compounds **6** involves Michael-type addition of the anion of compounds **5** to quinones **4** followed by subsequent dechlorination.[7] The substitution of compounds **6** with nucleophilic thiols resulted in the formation of aromatic hydroquinone system as intermediates and subsequent cyclization to compounds **3**. The substitution was similar to the formation of stable aromatic hydroquinone system by the substitution of thiols on quinones.[17] The mechanism of formation of compounds **3** by the cyclization was cited in Ref. 16.

The synthesized furo[2,3-*f*]quinolin-5-ols **3a–s**, compound **7**, and **8** were tested in vitro for their growth inhibitory activity against pathogenic fungi using the standard method.[18] The MIC (minimum inhibitory concentration) values were determined by comparison with fluconazole and 5-fluorocytosine as standard agents.

As indicated in Table 1, many of furo[2,3-*f*]quinolin-5-ols **3a–s** showed potent antifungal activity against all tested fungi. Actually, the activity of compounds **3h**, **3i**, and **3k** was superior or comparable to those of 5-fluorocytosine against fungi. The compounds **3h**, **3i**, and **3k** completely inhibited the growth of all against *Candida* and *Aspergillus* species tested at the MIC level of 0.8–3.2 μg/mL. Many of furo[2,3-*f*]quinolin-5-ols **3a–s** also showed potent antifungal activity against *Candida krusei*, *C. neoformans*, and *Aspergillus* species. Actually, the activity of compounds **3j** or **3q** were superior or comparable to those of 5-fluorocytosine against *C. krusei* or *C. neoformans*.

Generally, the 4-arylthio-furo[2,3-*f*]quinolin-5-ols scaffolds **3f–q** exhibited the greatest activity, indicating a correlation that may offer insight into the mode of action of these compounds. In contrast, furo[2,3-*f*]quinolin-5-ols **3a–e** and 4-alkylthio-moieties of compounds **3r–s** did not show significant antifungal activity against tested fungi, although they exhibited good activity against *C. neoformans* and *Aspergillus flavus*. 4-Alkylthio-moieties of compounds **3r–s** did not improve their antifungal activity in comparison to 4-arylthio-compounds **3f–q**. The structure–activity relationship may not exist between properties of substituents (R^1, R^2: H, Me, Et, X, ...) for the 4-arylthio moieties of compounds **3f–q** and alkyl substituents for the compounds **3a–e** and **3r–s**. In addition, the 5-aminoquinolin-8-ol (**7**) and 7-methyl-8-nitroquinoline (**8**) exhibited no or poor, if any, antifungal activity. Thus, furo[2,3-*f*]quinolin-5-ols moiety is important for the antifungal activity.

Table 1
Structures and antifungal activity for furo[2,3-*f*]quinolin-5-ols



Compound	R^1	R^2	MIC[a] (μg/mL)					
			C. albicans [b]	*C. tropicalis*	*C. krusei*	*C. neoformans*	*A. niger*	*A. flavus*
3a	CH_3CH_2	Cl	>50.0	50.0	6.3	25.0	>50.0	>50.0
3b	CH_3CH_2	Br	12.5	6.3	6.3	25.0	6.3	6.3
3c	CH_3	Br	50.0	6.3	25.0	12.5	25.0	25.0
3d	CH_3	CH_3	0.8	6.3	25.0	25.0	12.5	3.2
3e	CH_3CH_2	CH_3	6.3	25.0	25.0	12.5	>50.0	12.5
3f	F	H	50.0	50.0	50.0	50.0	25.0	12.5
3g	H	F	50.0	50.0	50.0	50.0	50.0	6.3
3h	H	Br	1.6	0.8	1.6	25.0	1.6	0.8
3i	H	Cl	0.8	0.8	1.6	25.0	3.2	3.2
3j	H	H	3.2	1.6	3.2	25.0	3.2	3.2
3k	F	F	0.8	1.6	1.6	50.0	1.6	1.6
3l	CH_3	H	12.5	25.0	25.0	3.2	25.0	12.5
3m	CH_3	CH_3	25.0	12.5	25.0	12.5	12.5	6.3
3n	H	OH	12.5	6.3	25.0	12.5	3.2	25.0
3o	H	CH_3O	6.3	6.3	6.3	25.0	3.2	12.5
3p	H	CH_3	6.3	12.5	50.0	12.5	3.2	50.0
3q	Cl	H	6.3	12.5	6.3	1.6	3.2	12.5
3r	CH_3CH_2	CH_3	12.5	12.5	50.0	6.3	50.0	50.0
3s	CH_3CH_2	CH_3CH_2	50.0	25.0	>50.0	>50.0	25.0	6.3
7	—	—	50.0	50.0	>50.0	>50.0	50.0	>50.0
8	—	—	>50.0	>50.0	>50.0	50.0	>50.0	>50.0
Fluconazole	—	—	50.0	6.3	12.5	6.3	12.5	25.0
5-Fluorocytosine	—	—	3.2	3.2	3.2	6.3	3.2	1.6

[a] The MIC value was defined as the lowest concentration of the antifungal agent. MIC values were read after one day for *Candida* species and *Cryptococcus neoformans,* and two days for *Aspergillus* species in 37 °C. The inoculum sizes contained approximately 1×10^5 cells/mL. Culture media tested were the modified Sabouraud dextrose broth (Difco Lab.). The final concentration of antifungal agents was between 0.2 and 50.0 μg/mL.

[b] Fungi tested: *Candida albicans* Berkout KCCM 50235, *C. tropicalis* Berkout KCCM 50662, *C. krusei* Berkout KCCM 11655, *Cryptococcus neoformans* KCCM 50564, *Aspergillus niger* KCTC 1231, and *Aspergillus flavus* KCCM 11899.

In conclusion, 4-arylthio-furo[2,3-*f*]quinolin-5-ol scaffolds **3f–q** were synthesized by cyclization of compounds **4** with 1 equiv of appropriate arylthiols **9**. Furo[2,3-*f*]quinolin-5-ols **3a–e** were synthesized by cyclization of compounds **4** with hydrazine. 4-Alkylthio-furo[2,3-*f*]quinolin-5-ols **3r–s** were synthesized by cyclization of compound **6a** with 1 equiv of alkylthiols in EtOH. Most of these reactions went as expected and had overall high yields. We have identified a lead compound that has antifungal activity by screening of our furo[2,3-*f*]quinolin-5-ols **3a–s**. Among them tested, many of furo[2,3-*f*]quinolin-5-ols showed potent antifungal activity. The results suggest that furo[2,3-*f*]quinolin-5-ol scaffolds would be promising leads for the development of antifungal agents. Moreover, the results should encourage the synthesis of furo[2,3-*f*]quinolin-5-ol analogs for improving antifungal properties.

Acknowledgments

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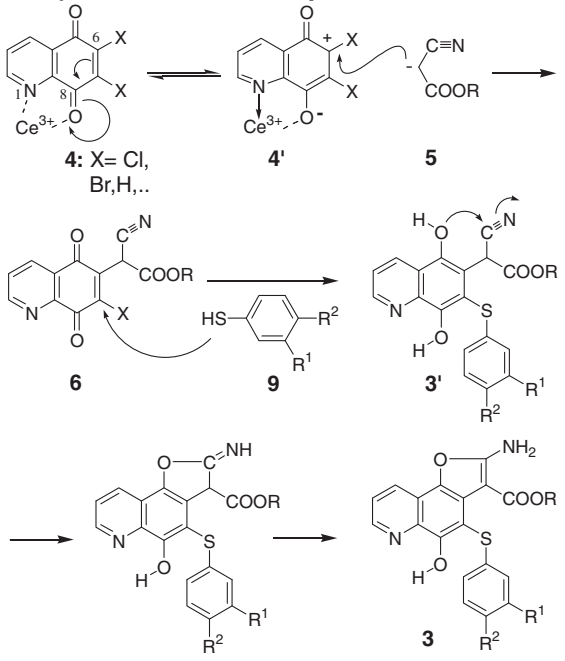
16. Compounds **6** were formed by regioselective nucleophilic substitution or addition of compounds **4** with 1 equiv of alkylcyanoacetates **5** and 0.1 equiv of $CeCl_3$ in the presence of NH_4OH. As results of catalytic action of Ce^{3+} ions, the substitution or addition in compounds **4** gave mainly 6-substituted products **6**.

The regioselectivity should be originated from the selective increment of the electrophilicity of 6-position in compounds **4** by the formation of Ce(III) chelate between carbonyl oxygen at 8-position and nitrogen at 1-position. The catalysis by Ce^{3+} ions is understood from the intermediate **4′**. The 6-substituted products **6** were formed by a Michael-type addition of the anion of alkylcyanoacetates **5** to **4′**. These substitutions or additions were similar to the regioselective reaction of arylamines on 5,8-quinolinedione in the presence of Ce(III).[15] The substitution of **6** with nucleophilic thiols **9** resulted in the formation of aromatic hydroquinone system[7,17] as intermediates **3'** and subsequent cyclization to compounds **3**. The mechanism of cyclization was similar to the formation of furo[2,3-*f*]quinolin-5-ols[9,10] by cyclization of *N*,*N*'-dimethylhydrazone on 5,8-quinolinedione and naphthofuranol[19] by cyclization of acetylacetone on 1,4-naphthoquinone. Most of these reactions went as expected. The products **3** were separated by silica gel column chromatography. Purity of products **3** was determined both by to TLC and GC. The results showed that a single compound was contained in each product. TLC was performed on precoated silica gel (60G 254, Merck) using $CHCl_3$ for solvent. The compounds were detected under UV light (254 nm). The purity of products was also verified by GC (Hewlett Packard 5890A, HP-5 capillary column at 260 °C, N_2, 17 mL/mim as carrier gas, FID). The compounds **3** were identified by ^1H NMR, ^{13}C NMR, or Mass spectra.



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