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3-Thio-quinolinone maxi-K openers for the treatment of erectile dysfunction

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Abstract—A series of Maxi-K openers for the treatment of erectile dysfunction based on the 3-thio-quinolinone core is described. Significant levels of channel opening (up to 550% of control) are seen in transfected oocytes. Functional activity in rabbit corpus cavernosum tissue strips confirms the potential to effect therapy for ED, the effect being maximal for the 3-amino-2-hydroxy thiol side chain.

1. Introduction

Maxi-K, or BK, potassium channels are large-conductance voltage- and calcium-activated potassium channels.[1] These trans-membrane proteins are composed of a homo-tetrameric assembly of α-subunits, which form the channel, and may be co-assembled with β-subunits.[2] They are distributed in many types of excitable cells, including those of neurons, cardiac cells, and smooth muscle.[3] The physiology of penile erection involves the increased inflow of blood into the corpus cavernosum via the relaxation of the helicine arterioles and trabecular smooth muscle.[4] Openers of the maxi-K channel may lead to membrane hyperpolarization, augment the relaxation of this tissue, and hence provide a novel therapy for erectile dysfunction.[5]

2. Design and synthesis

The 4-aryl quinolinone core previously investigated in these laboratories[6] provided a template of active maxi-K openers from which to further optimize. Placing a sulfur atom at the 3-position would provide a handle that would facilitate facile incorporation of pendant alkyl

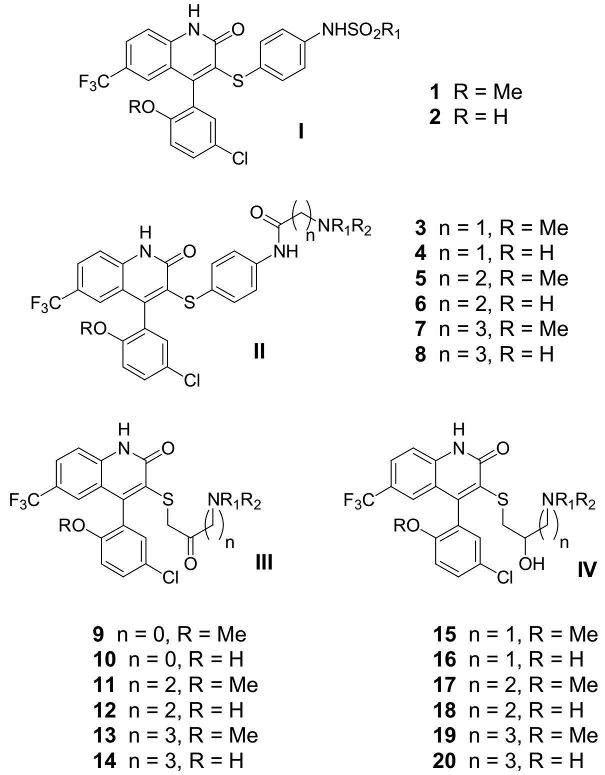

Figure 1. Maxi-K openers for erectile dysfunction.

Keywords: Maxi-K; BK; Potassium channels; Erectile dysfunction.

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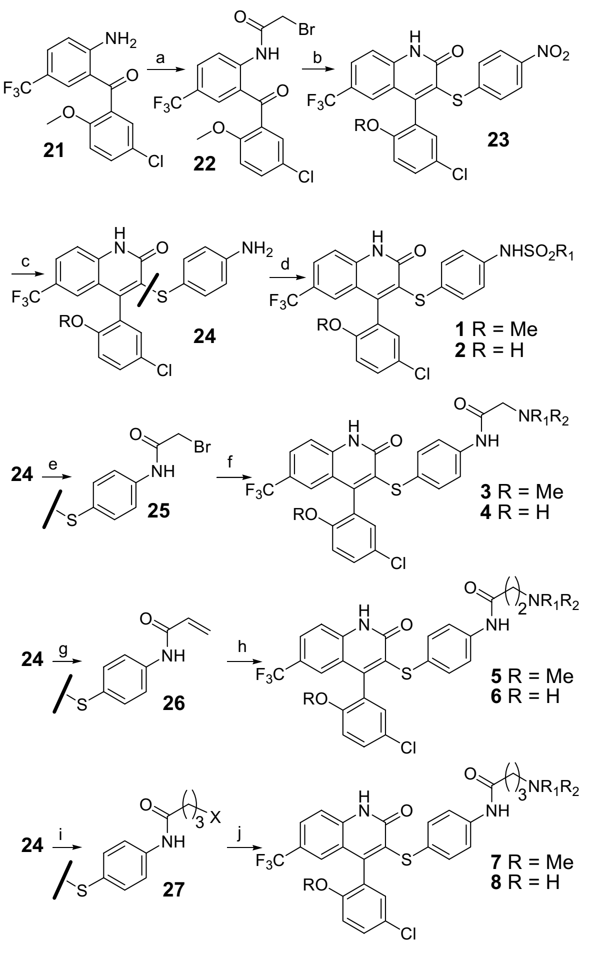
moieties. Additional functionality, such as the sulfonamides and amines described in this paper, offer an opportunity to investigate the PK properties of these modifications. Target structures are depicted in Figure 1.

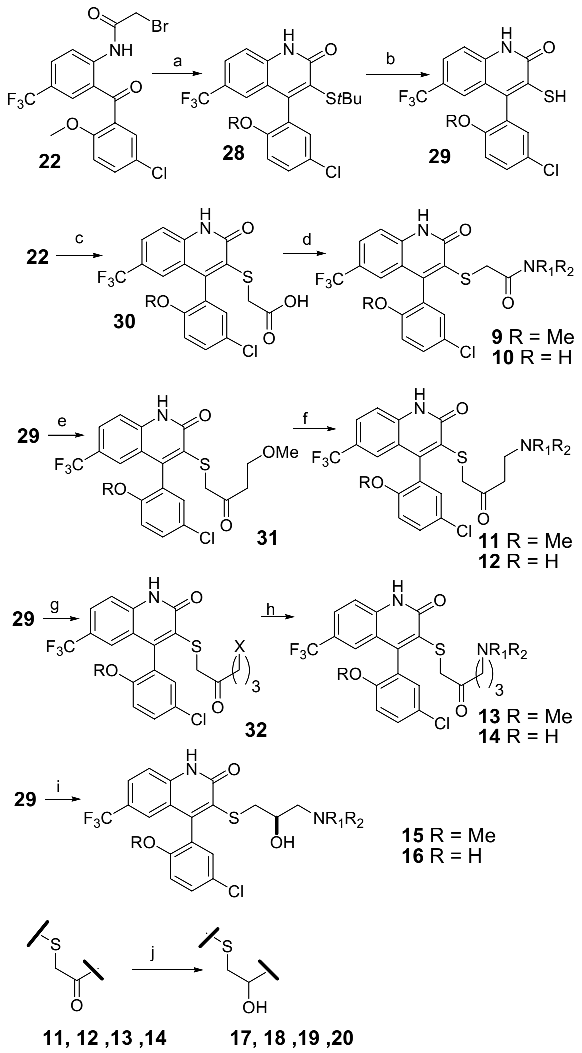
Starting from the previously reported benzophenone **21**,[7] acylation with bromoacetyl bromide proceeded smoothly to provide intermediate **22** (Scheme 1). Cleavage of the methyl group under the action of boron tribromide at this stage proved to be optimal in terms of yield, and so the phenol and methyl ether series diverged at this point. Displacement of the bromide with sodium *p*-nitro thiophenolate, and subsequent intramolecular Knoevenagel condensation provided the S-3 quinolinone **23**, which was then reduced to the corresponding aniline **24**. Sulfonamides were easily prepared by reaction with the appropriate sulfonyl chlorides. Likewise, amide formation from **24** proceeded without incident to provide amides **25**–**27**. It should be noted that in no instance was ester formation on the phenol observed.



Scheme 1. Reagents and conditions: (a) bromoacetyl bromide, CH_2Cl_2, 0 °C; (b) 4-nitrothiophenol, NaH, THF; (c) $SnCl_2$, EtOH, reflux; (d) RSO_2Cl, pyridine, 80 °C; (e) bromoacetyl bromide, CH_2Cl_2, 0 °C; (f) HNR_1R_2, Na_2CO_3, CH_3CN; (g) acryloyl chloride, Et_3N, CH_3CN; (h) HNR_1R_2, MeOH; (i) 4-chlorobutyryl chloride, Et_3N, CH_3CN; (j) HNR_1R_2, NaI, DMF, 70 °C.

Final halide displacement (**25**, **27**) or Michael addition (**26**) with various amines provided an array of targets.

Truncation of the aryl amide moiety and replacement by a methyl group allowed us to consider additional analogs with lower molecular weight. By varying the tether length distal to the H-bond acceptor, we could optimize the placement of the ionizable group. Reaction of bromoacetamide **22** with 2-methyl-2-propanethiolate (Scheme 2) followed by cyclization and deprotection (TFA) provided thiol **29**. Reaction of **22** under basic conditions with methyl thioglycolate, followed by condensation under the action of potassium *tert*-butoxide and saponification provided acid **30**, again with no reaction evident on the phenol. Standard amide coupling technology provided the series of amides **9** and **10**.



Scheme 2. Reagents and conditions: (a) 2-methyl-2-propanethiol, NaH, 0 °C to rt; (b) TFA, reflux; (c) (i) methyl thioglycolate, NaH, THF, (ii) KOtBu, THF, reflux, (iii) 10 N NaOH, THF; (d) HNR_1R_2, EDC, THF; (e) 1-bromo-4-methoxybutan-2-one, K_2CO_3, EtOH; (f) HNR_1R_2, K_2CO_3, THF, EtOH; (g) 5-bromo-1-chloropentan-2-one, K_2CO_3, EtOH; (h) HNR_1R_2, THF; (i) epichlorohydrin, HNR_1R_2, 80 °C, then **29**, K_2CO_3, EtOH, 80 °C; (j) $NaBH_3CN$, EtOH.

Initial synthesis of the β-amino ketones **11** and **12** was achieved by the reaction of **29** with the pre-formed bromomethyl aminoethyl ketone salts. These salts were made by forming methyl aminoethyl ketones (either by Michael addition to methyl vinyl ketone or by Mannich reaction) followed by bromination with pyridine·HBr·Br_2 in HBr/HOAc. This route suffered, however, by the serial nature of the synthesis, and not

Table 1. Percent Maxi-K channel opening observed by voltage-clamp in transfected oocyte cells for compounds **1**–**20**[9]

Compds	R_1	R_2	Maxi-K opening (% of control) at 20 μM in oocytes[a]
1a	CF_3		235 ± 18.7
1b	NMe_2		114 ± 4.7 (5 μM)
1c	*n*-Pr		95 ± 7.3 (5 μM)
2a	CF_3		277 ± 17.3
2b	NMe_2		222 ± 8.3 (5 μM)
2c	*n*-Pr		255 ± 11.8 (5 μM)
2d	CH_2CF_3		170 ± 8.1
2e	Et		296 ± 32.2 (10 μM)
2f	$(CH_2)_3$morpholine		354 ± 19.8
4a	Pyrrolidine		291 ± 17.2
4b	Morpholine		296 ± 16.3 (10 μM)
4c	*N*-Methylpiperazine		246 ± 11.4
4d	4-Dimethylaminopiperidine		292 ± 22.7
4e	4-Piperidinylpiperidine		283 ± 22.6
4f	2-Pyridinylpiperazine		116 ± 3.8 (5 μM)
4g	Me	$(CH_2)_2NMe_2$	231 ± 8.2
6a	Pyrrolidine		264 ± 19.8
6b	Morpholine		453 ± 39.6
6c	*N*-Methylpiperazine		474 ± 14.4
6d	4-Piperidinylpiperidine		255 ± 25.0
6e	2-Pyridinylpiperazine		169 ± 12.2 (10 μM)
6f	Me	$(CH_2)_2NMe_2$	489 ± 20.9
8a	Pyrrolidine		280 ± 22.6
8b	4-Piperidinylpiperidine		268 ± 20.3
8c	2-Pyridinylpiperazine		197 ± 12.5 (10 μM)
10a	*N*-Methylpiperazine		422 ± 38.8
10b	4-Dimethylaminopiperidine		286 ± 15.7
10c	*N*-(2-Hydroxyethyl)piperazine		151 ± 8.7
10d	*N*-(2-(2-Hydroxyethoxy)ethyl)piperazine		205 ± 16.1
10e	Isonipecotamide		203 ± 14.8
10f	*N*-(Ethoxycarbonylmethyl)piperazine		281 ± 16.9
12a	Pyrrolidine		335 ± 28.3
12b	*N*-Methylpiperazine		550 ± 117.4[b]
12c	*N*-(2-Hydroxyethyl)piperazine		241 ± 7.3
12d	Piperidine		199 ± 11.2
12e	4-Hydroxypiperidine		235 ± 7.8[c]
12f	Me	$(CH_2)_3NMe_2$	178 ± 7.4
14a	4-Piperidinylpiperidine		298 ± 24.9
14b	Acetylpiperazine		284 ± 18.3
14c	3-Methylpiperidine		271 ± 19.6
14d	4-Methylpiperidine		213 ± 17.2
14e	Me	*N*-Methylpyrrolid-3-yl	226 ± 15.2
15a	*N*-Methylpiperazine		163 ± 4.5
15b	Acetylpiperazine		192 ± 7.4
15c	Thiomorpholine		97 ± 5.5
15d	4-Methylpiperidine		115 ± 6.2
15e	4-Hydroxypiperidine		125 ± 4.9
15f	*N*-(2-Hydroxyethyl)piperazine		150 ± 5.9
15g	(2-Pyrimidyl)piperazine		80 ± 8.4 (5 μM)
16a	Et	Et	192 ± 10.8
16b	Pyrrolidine		192 ± 8.3
16c	Morpholine		292 ± 24.9
16d	Thiomorpholine		319 ± 24.0
16e	*N*-(2-Hydroxyethyl)piperazine		287 ± 24.0
16f	*N*-(2-(Dimethylamino)ethyl)piperazine		113 ± 6.3
16g	Me	$(CH_2)_3NMe_2$	214 ± 6.4
18a	*N*-Methylpiperazine		515 ± 66.3

[a] Alternative testing concentration given in parentheses, $n \geqslant 5$.

[b] $n = 3$.

[c] $n = 4$.

least of all by the necessity of high-purity crystalline salts for successful reaction. A solution in the form of a β-methoxy ketone provided a common intermediate for high-throughput synthesis of β-amino ketones. In the event, reaction of **29** with 1-bromo-4-methoxybutan-2-one under basic conditions provided intermediate **31**, which upon exposure to the desired amine and K_2CO_3 in ethanol underwent a retro-Michael elimination/Michael addition to provide the desired amines. The γ-amino ketones **13** and **14** were obtained in straightforward fashion by reaction of **29** with 5-bromo-1-chloro-pentan-2-one, followed by amine displacement in THF. The amino alcohols **15** and **16** were prepared directly from thiol **29** by adding the thiol to pre-mixed epichlorohydrin and the desired amine. While exposure of ketones **11–14** to $NaBH_4$ produced over-reduced products, the action of $NaBH_3CN$ cleanly produced the analogous alcohol products **17–20**.

3. Results and discussion

Initial investigation by voltage-clamp techniques[8] in human Maxi-K cRNA microinjected oocytes of the compounds synthesized revealed many general trends in the SAR. First, the series of phenols were universally more active than the corresponding methyl ethers (Table 1, compare **1** vs **2** and **15** vs **16**). Secondly, robust levels of activity were maintained in compounds of structure **II** (**4**, **6**, **8**), even though the length of the spacer varied from 1 to 3 carbons. A similar consistency of activity was observed within compounds of type **III** (**10**, **12**, **14**). Additionally, this insensitivity to tether length was conserved even when chemotypes **II** and **III** are compared. Compounds **II** and **III** differ by replacing the phenyl group and adjoining NH moiety in series **II** with a single methylene group. The difference in S–C(O) distance as well as the difference in the electronics of ketones **11–14** and amides **3–8** had little effect on activity. The side chain also influenced the activity of the quinolinones. Simple aminoalkyl S-3 quinolinones, for example, were devoid of activity (data not shown). Similar to the ketones and amides of type **III**, the alcohols of type **IV** (**16**, **18**, **20**) were active regardless of spacer length. Good to excellent activity was observed for these alcohols, the additional possible H-bond donating property was not detrimental to their utility.

Several amines potently opened maxi-K channels when incorporated into the molecules. Among them, *N*-methyl piperazine and other diamines such as *N*,*N*′,*N*′-trimethylethylenediamine and 4-piperidinylpiperidine were the best. Morpholine and pyrrolidine also often exemplified robust levels of activity.

Evaluation of pertinent compounds in a secondary assay was accomplished by noting the degree of relaxation of pre-constricted strips of rabbit corpus cavernosum. In many cases (Table 2), potent channel opening did not translate into tissue relaxation in the preparations. This may be due to tissue-penetration issues for some compounds, or may be due to a difference in the channels expressed in the oocytes versus the naturally occurring channels. Of the compounds, which were active in the tissue strip assay, the aniline-based amides **4e**, **6e**, and **8c** demonstrated modest levels of activity. These compounds have a diamine structure in common. The activity of ketones **12** and **14** did not translate well into the strips, but amides **10a–f** did provide tissue relaxing properties, with the isonipecotamide based amide **10e** having exemplary activity. Amino alcohols **16a–e** provided a rich class of active maxi-K openers with tissue relaxing activity. Simple amines (diethylamine, morpholine, thiomorpholine) as well as derivatized piperazines were all robustly active. The confluence of a H-bond acceptor and a remote amino group on the side chain of these compounds is a consistent feature among the most potent maxi-K openers presented in this paper, and is hypothesized to be responsible for the activity observed.

Table 2. Percent relaxation of phenylephrine-contracted rabbit corpus cavernosum tissue strips (drug concentration 10 μM)[9,10]

Compounds	Percent relaxation of tissue strips (%)
1a	21
2a	32
2f	35
4a	28
4b	34[a]
4c	19
4d	19[a]
4e	45[a]
4f	17[a]
4g	16
6a	35
6b	22
6c	30
6d	23[a]
6e	37[a]
6f	29
8a	36
8b	28[a]
8c	37
10a	14
10b	35
10c	22
10d	17
10e	67
10f	19
12a	30
16a	57
16c	49
16d	48
16e	44

[a] $n = 2$.

3-Thio-quinolinones provide a platform on which is built potent openers of the maxi-K channel in vitro as well as in tissue preparations. The in vivo characterization of these compounds will be disclosed in due course.

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9. For comparison, 4-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyethyl)-6-(trifluoromethyl)quinolin-2(1H)-one was measured to have a 378% ± 35 increase over control in oocytes, and a 83.7% ± 11.0 inhibition of force in rabbit corpus cavernosum (compd **11b** in Hewawasam, P.; Fan, W.; Ding, M.; Flint, K.; Cook, D.; Goggins, G. D.; Myers, R. A.; Gribkoff, V. K.; Boissard, C. G.; Dworetzky, S. I.; Starrett, J. E.; Lodge, N. J. *J. Med. Chem.* **2003**, *46*, 2819–2822.
10. *n*'s were typically 3–4; if needed, additional *n*'s were added such that SEM's were less than 10% of the reported value.