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Structure–Activity Relationship of a Novel Class of Naphthyl Amide K_{ATP} Channel Openers

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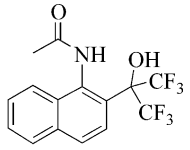
Abstract—We have discovered a novel series of *N*-[2-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-naphthalen-1-yl] amides that are potent openers of K_{ATP} channels and investigated structure–activity relationships (SAR) around the 1,2-disubstituted naphthyl core. A-151892, a prototype compound of this series, was found to be a potent and efficacious potassium channel opener in vitro in transfected Kir6.2/SUR2B cells and pig bladder strips. Additionally, A-151892 was found to selectively inhibit unstable bladder contractions in vivo in an obstructed rat model of myogenic bladder function

Potassium channels play a vital role in the regulation of cellular excitability. They are involved in the maintenance of resting membrane potential, in addition to controlling repolarization of the action potential. Opening of K_{ATP} channels results in an efflux of potassium ions from the cell and an accompanying reduction in membrane potential (hyperpolarization) that restricts calcium entry through L-type calcium channels thereby dampening cellular excitability. There has been widespread interest in exploring K_{ATP} openers as therapeutic agents in the treatment of bladder overactivity, a condition associated, in part, with the hyperexcitability of diseased bladder smooth muscle.[1]

A number of structurally distinct series of K_{ATP} openers have been described.[2] Among these the benzopyran cromakalim,[3] tertiary carbinol ZD 6169,[4] dihydropyridines ZM 244085[5] and A-278637,[6] and the squarate WAY-151616,[7] have been reported to activate the bladder K_{ATP} channel in vitro and to inhibit bladder function in vivo.

Naphthyl amide **1** was identified as a potent K_{ATP} channel opener by a $^{86}Rb^+$ efflux assay. In this article we wish to present the synthesis and SAR studies that were conducted on this new series of naphthyl amide K_{ATP} channel openers.[8]



1: A-151892

The synthesis of the 2-substituted 1-aminonaphthalene core was accomplished using an electrophilic α-alkylation reaction as depicted in Scheme 1. A mixture of 1-aminonaphthalene **2**, hexafluoroacetone trihydrate and a catalytic quantity of *p*-toluenesulfonic acid was heated at 170 °C in a sealed vessel.[9] The resulting bis-(trifluoromethyl) carbinol **3** was purified by recrystallization.

A number of *N*-acylation methods were explored. Heating **3** with an anhydride at 140 °C (Method A) or treatment with an acid chloride and pyridine (Method B) were the optimal routes to naphthyl amide **4**. A

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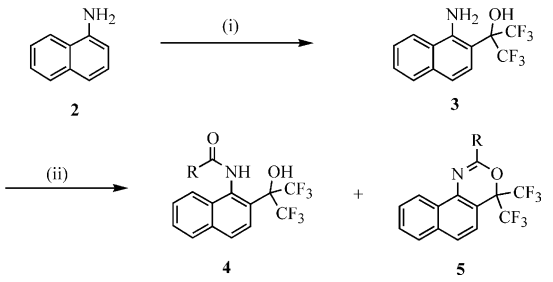


Scheme 1. Reagents and conditions: (i) $(CF_3)_2CO{\cdot}3H_2O$, *p*-TSA, 170 °C; (ii) Method A-$(RCO)_2O$, 140 °C. Method B–RCOCl, pyridine.

frequently observed by-product was the tricyclic **5** (0–25%) which was readily separated by recrystallization or chromatography on silica gel.

SAR studies were conducted by varying the R substituent of **4**. A wide range of alkyl, aryl and heterocyclic analogues were accessed by the methodology shown in Scheme 1. The tricyclic oxazines **5** were inactive. The reaction of **3** with the appropriate isocyanates was used to prepare ureas **21** and **22**. The carbamate **23** was synthesized by reaction of **3** with isopropylchloroformate.

Examples of naphthyl-substituted analogues were also studied. The 5- and 6-hydroxy analogues (**53** and **54**) were prepared from the corresponding substituted 1-aminonaphthalenes by the route shown in Scheme 1. Competitive alkylation α to the –OH group necessitated separation of the regioisomeric products by chromatography on silica gel before acylation. The 4-bromo compound **55** was accessed by selective bromination of **1** using bromine/sodium acetate.

Compounds were evaluated for potassium channel opening activity using Ltk cells stably transfected with Kir6.2/SUR2B exon 17.[10] Functional activity at potassium channels was measured by evaluating changes in membrane potential using DIBAC dye in a 96-well cell-based kinetic assay system, Fluorometric Imaging Plate Reader (FLIPR). Changes in fluorescence were measured by comparison to the effect elicited by P1075 (a potent KCO[11]). The maximal response of each compound, expressed as % relative to P1075, was equal to or above 80%. The observed effects were reversed by glyburide, confirming a K_{ATP} mechanism.

A selection of the more potent compounds was also evaluated in vitro using tissue strips obtained from Landrace pig bladders.[12] Tissues were stimulated by a low-frequency (0.05 Hz) current that produced a stable twitch response. P1075 completely eliminated the stimulated twitch response in a dose-dependant fashion. The maximal efficacy of each compound was expressed in comparison to P1075.

Table 1 summarizes the effects of varying aliphatic substitution of the amide. Alkyl chains were found to be optimal at methyl **1** and ethyl **6**, with -branching reducing potency by 400-fold. Unsaturation in the alkyl

Table 1. SAR of the aliphatic substitution of **4**

Compd	Method of preparation	R	Kir6.2/SUR2B EC_{50} (μM)
1	A	CH_3	0.018[b]
6	A	CH_2CH_3	0.015[a]
7	B	$CH(CH_3)_2$	6.63[a]
8	B	$CH_2CH_2CH_3$	0.131[a]
9	B	$CH(CH_3)CH_2CH_3$	1.77
10	A	$CH(CH_2CH_3)_2$	4.34
11	A	$CHC(CH_3)_2$	0.046[a]
12	A	$CHCHCH_3$	0.072[a]
13	B	$CH(CH_3)CH_2CH_2CH_3$	>10
14	B	$CH_2CH_2CH(CH_3)_2$	0.049[a]
15	B	cC_3H_5	0.751
16	B	cC_4H_7	0.045 [a]
17	B	cC_5H_9	0.495
18	B	CH_2-cC_5H_9	0.081[a]
19	B	CH_2OCH_3	0.213[a]
20	B	CH_2CH_2Ph	1.75
21	B	$NH(CH_2)_5CH_2Cl$	4.84
22	B	NH-4-Cl-Ph	0.276
23	B	$OCH(CH_3)_2$	1.16

Values are the mean of two experiments, unless otherwise indicated.
[a]Values are the mean of three experiments.
[b]Values are the mean of six experiments.

chain was tolerated (**12**) as was the introduction of an ether moiety (**19**). A series of cycloalkyl ring sizes was examined with the cyclobutyl **16** the most potent example. Conversion of the amide to urea **22** retained significant activity, but changing to carbamate **23** led to loss of activity.

Replacing the aliphatic with aromatic groups generated some highly potent analogues (Table 2). *Para* and *meta* aromatic substitution was optimal with ortho groups 20 to 400-fold less active. A general trend observed was for higher potency with smaller substituents.

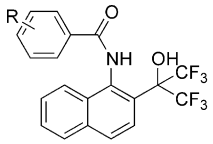
A selection of heterocyclic amide analogues was also studied. (Table 3). Introduction of furyl **47**, oxazole **48** or thiophene **51** groups gave very potent analogues. Tolerance of a basic pyridyl moiety was also observed.

Substitution of the naphthyl core of **1** led to considerable decreases in potency (Table 4).

The most potent compounds were also evaluated for their K_{ATP} activity in pig bladder strips. These results are summarized in Table 5. Twelve analogues were found to be more active than cromakalim.

Compound **1** was also evaluated in an in vivo model of overactive bladder (Table 6). Cystometry was performed using anesthetized male Sprague–Dawley rats with bladder hypertrophy and exhibiting unstable bladder contractions due to intravesical outflow obstruction.[13] Administration[14] of **1** produced a dose dependent inhibition of unstable contractions with an EC_{35} of 30 nmol/kg. A reduction in mean arterial pressure was observed with an ED_{10} of 50 nmol/kg. Literature standards were found to be less potent (WAY-133537 3-fold and ZD-6169 40-fold) and of comparable selectivity.

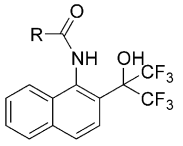
Table 2. SAR of the aromatic substitution

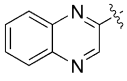
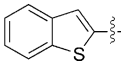


Compd	Method of preparation	R	Kir6.2/SUR2B EC_{50} (μM)
24	B	H	0.044[a]
25	B	2-Cl	2.04[b]
26	B	2-CH_3	5.55[a]
27	B	3-F	0.044
28	B	3-Cl	0.098[b]
29	B	3-Br	0.080[b]
30	B	3-CH_3	0.023[a]
31	B	3-CF_3	0.084[a]
32	B	3-CN	0.012[a]
33	B	3-NO_2	0.117[a]
34	B	3-OCH_3	0.185[a]
35	B	4-F	0.070[a]
36	B	4-Cl	0.057[b]
37	B	4-Br	0.047[b]
38	B	4-I	0.154[b]
39	B	4-CH_3	0.076[b]
40	B	4-CF_3	0.160[b]
41	B	4-OCH_3	0.417[b]
42	B	4-OCF_3	>10[a]
43	B	4-Ph	>10[a]
44	B	2,3-Cl	>10[b]
45	B	3,4-Cl	0.194[b]
46	B	3,5-Cl	0.306[b]

[a]Values are the mean of two experiments, unless otherwise indicated.
[b]Values are the mean of three experiments.

Table 3. SAR of the heterocyclic substitution

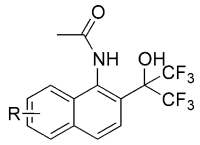


Compd	Method of preparation	R	Kir6.2/SUR2B EC_{50} (μM)
47	B		0.009[b]
48	B		0.024[b]
49	B		0.060[b]
50	B		0.317[b]
51	B		0.012[b]
52	B		>10[a]

[a]Values are the mean of two experiments, unless otherwise indicated.
[b]Values are the mean of three experiments.

In summary, we have identified naphthyl amides as a structurally novel class of K_{ATP} channel openers. A concise synthetic route was developed which allowed rapid analysis of the optimal amide substitution, exploration of pharmacophore modifications and probing of the steric tolerance around the naphthyl core. The lead compound of the series was demonstrated to be both potent in in vitro cell and bladder strip functional assays, and highly efficacious in a rat model of bladder overactivity.

Table 4. SAR of naphthyl substitution



Compd	Method of preparation	R	Kir6.2/SUR2B EC_{50} (μM)
53	A	6-OH	2.22
54	A	5-OH	0.137
55	A	4-Br	5.31

Values are the mean of two experiments.

Table 5. Functional K_{ATP} activity in isolated bladder strips

Compd	Efficacy (%P1075)	pEC_{50}
(−) Cromakalim	95	6.34±0.16
1	87	7.02±0.13
6	96	8.05±0.22
8	92	6.15±0.16
11	96	6.26±0.13
12	96	7.31±0.09
15	100	6.90±0.53
16	97	7.09±0.32
19	93	6.69±0.10
28	84	6.07±0.05
30	97	7.28±0.16
32	96	6.43±0.16
33	99	6.37±0.16
36	99	6.41±0.19
47	96	6.74±0.24
48	97	6.52±0.19
49	97	6.21±0.09

Values are the mean of four or more experiments.

Table 6. Anesthetized obstructed rat model of bladder overactivity

Compd	AUC ED_{35}[a] (μmol/kg iv)	MAP ED_{10}[b] (μmol/kg iv)	Selectivity MAP/AUC
1	0.030±0.009	0.05±0.01	1.7
WAY-133537	0.10±0.02	0.12±0.02	1.2
ZD-6169	1.4±0.4	1.5±0.2	1.1

[a]Concentration required to give a 35% inhibition of unstable contractions.
[b]Concentration required to give a 10% reduction in mean arterial pressure.

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14. Compounds dissolved in a solution containing equal parts of a hydroxypropyl-beta-cyclodextrin solution (100 g/200 mL) and sterile water, and dosed in a volume of 1 mL/kg, warmed to body temperature before injection, and administered slowly over 2 min.