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Graphical Abstract

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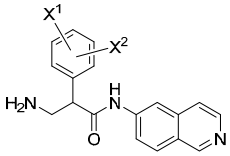

ROCK K_i = 0.2 nM-10.3 nM

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ABSTRACT

Inhibition of Rho kinase (ROCK) to improve fluid outflow through the trabecular meshwork and lower intraocular pressure is a strategy for the development of new anti-glaucoma agents. Alpha-aryl-beta-amino isoquinoline analogs were identified as potent ROCK inhibitors. Compounds that provided a longer duration of intraocular pressure reduction in Dutch Belted rabbits also inhibited norepinephrine transporter. Ester **60** improved bioavailability of its parent ROCK inhibitor, **29** (K_i = 0.2 nM) and demonstrated an effective and sustained IOP reduction for 24 h after dosing. From these studies, netarsudil (a.k.a.AR-13324) was discovered and is currently in clinical trials for the treatment of glaucoma and ocular hypertension.

One of the most common causes of blindness worldwide is glaucoma, a group of diseases characterized by progressive optic nerve damage. Elevated intraocular pressure (IOP) is a major risk factor for glaucoma and lowering of IOP is currently the only available treatment.[1] Common IOP-lowering therapies include beta-blockers (e.g. timolol)[2] and carbonic anhydrase inhibitors (e.g. dorzolamide)[3] which lower IOP by decreasing the production of aqueous humor by the ciliary body. Alpha agonists (e.g. brimonidine)[4] reduce IOP by decreasing aqueous humor production and increasing uveoscleral outflow. The most commonly prescribed medications, the prostaglandin F2α analogues (e.g. latanoprost)[5] reduce IOP by increasing aqueous humor outflow through the uveoscleral pathway. There are currently no medications that target the diseased trabecular outflow pathway in the eye, which is the underlying cause of elevated IOP in glaucoma.[6]

Over the last several years, Aerie has developed inhibitors of Rho kinase (ROCK) as a way to directly treat the diseased tissue of the trabecular meshwork and to lower IOP in patients with glaucoma.[7] The Rho kinases are serine/threonine protein kinases that exist as 2 isoforms, ROCK1 and ROCK2,[8] which are widely expressed in many tissues including the trabecular meshwork.[6-8] ROCK promotes the assembly of actin stress fibers and focal adhesions and regulates cell contraction and motility.[6]

Inhibition of ROCK by various inhibitors has demonstrated increased aqueous humor outflow through the trabecular meshwork with concomitant reduction of IOP in animal models including rabbit and monkey.[9] SNJ-1656 (also known as Y-39983) was the first ROCK inhibitor to demonstrate an IOP-lowering effect in human subjects.[10] Its IOP-lowering effect peaked at 4 hours after dosing and was no longer effective 24 hours after dosing. Recently, the ROCK inhibitor ripasudil (previously K-115), a fluorinated analog of fasudil, was approved in Japan as an adjunctive therapy for the treatment of glaucoma and ocular hypertension (Glanatek® 0.4%).[11] In a Phase 2 clinical study, ripasudil 0.4% demonstrated peak IOP reduction at two hours after dosing and required twice-daily dosing to maintain efficacy throughout the day.[12]

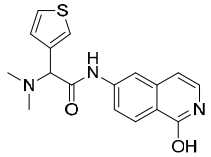


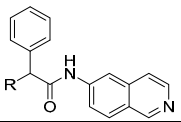
Figure 1. Structure of AR-12286

Aerie's Rho kinase program previously identified the amino isoquinoline amide AR-12286 as a potent ROCK inhibitor (K_i = 2.0 nM) that effectively lowered IOP in animal models and human subjects (Figure 1).[13] The goal of the present study was to discover ROCK inhibitors with a more durable IOP-lowering effect to allow once-daily dosing in patients. We describe the discovery of novel amino-isoquinoline amide ROCK inhibitors

that provide a longer duration of IOP-lowering effect in animal models than previous ROCK inhibitors. The most effective compounds were also found to have inhibitory activity against the norepinephrine transporter.

Table 1 summarizes the SAR derived from extending the amino alkyl arm of αaryl amino isoquinoline analogs. The αaryl αamino isoquinoline analog **2** displayed potent ROCK2 inhibition (K_i = 1.5 nM) but was less effective at disrupting focal adhesions and actin stress fibers in cell-based assays conducted with SV-40 transformed human trabecular meshwork cells[14] (HTM) and primary porcine trabecular meshwork cells[15] (PTM), respectively. Analogs including αaryl-βamino isoquinoline **3** and αaryl-γamino isoquinoline **6**, with extended alkyl-amino arms, displayed a significant improvement in both HTM and PTM assays. The βamino analog **3** was twice as potent against ROCK2 (K_i = 0.8 nM) relative to the α and γamino analogs **2** and **6,** respectively (K_i = 1.5 nM). Furthermore, the S-enantiomer **4** of the βamino analog **3** was 42 times more potent against ROCK2 than the R-enantiomer **5**.

Table 1.
Extension of the amino alkyl arm



Cpd	R	ROCK2[a] Ki nM	HTM[b] IC_{50} nM	PTM[c] IC_{50} nM
1/SNJ[d]	n.a.	2.3	278	243
2	NH_2	1.5	5609	2196
3	-CH_2NH_2	0.8	123	137
4	(S)-CH_2NH_2	0.4	47	179
5	(R)-CH_2NH_2	16	1216	1816
6	-$CH_2CH_2NH_2$	1.5	47	97

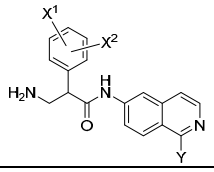
[a] ROCK2 enzyme inhibition assay.
[b,c] human (HTM) and porcine (PTM) trabecular meshwork cell assays; data represent average of at least duplicate runs.
[d] Reference ROCK inhibitor SNJ-1656
n.a. not applicable

Analogs **2, 3** and **6** were then compared to AR-12286 and SNJ-1656 (**1**) for their ability to lower IOP in Dutch Belted rabbits.[16] The compounds were dissolved in aqueous, buffered solutions (0.1% - 0.3%, pH-5-6.8) and the rabbits were dosed (1 drop, 30 μL) by topical ocular administration after the baseline (time 0) measurement of IOP and a second dose (0.1% - 0.3%, 1 drop, 30 μL) was given immediately after the 24 hour IOP measurement. IOP measurements were taken at 1, 2, 4, 8, and 24 hours after dosing each day. Each of the treated eyes was compared with its untreated contralateral control eye to determine the change in IOP (ΔIOP). On day 2, the maximum ΔIOP produced by AR-12286, 0.3% was -6.8 mmHg, $p<0.01$ at 2 hours post-dose and ΔIOP at 8 hours post-dose was -2.2 mmHg, $p<0.01$. SNJ-1656 (**1**), 0.3% produced a maximum **Δ**OP of -5.5 mmHg, $p<0.05$, at 2 hours post-dose on day 2 and a **Δ**OP at 8 hours post dose of -0.5 mmHg, $p=0.13$. In comparison, the αaryl βamino isoquinoline amide **3** at 0.2% produced a maximum **Δ**OP of -8.5 mmHg, $p< 0.01$ at 4 h post-dose on Day 2 and a sustained **Δ**OP at 8 h post-dose of -8.0 mmHg, $p<0.01$. Less effective reductions in IOP were observed for **2** (0.3%, max **Δ**OP = -2.3 mmHg, $p<0.05$, 2 h; **Δ**OP = 0 mmHg, 8 h) and **6** (0.3%, max **Δ**OP = -4.8 mmHg, $p<0.001$, 4 h; **Δ**OP = -3.1 mmHg $p<0.05$, 8h). Moderate conjunctival hyperemia and mild chemosis (swelling) were the only observed side effects of compound **3**.

The long duration of IOP lowering for **3** was a unique feature relative to the ROCK inhibitors AR-12286 and SNJ-1656, as well as other published ROCK inhibitors.[9-13] To screen for potential activity against other targets, **3** was tested against a panel of 79 human proteins including transmembrane receptors, transporters, channels, and CYTP450s (Eurofins PanLabs, Taipei, Taiwan).

For comparison, AR-12286 was screened against the same panel. When assayed at a concentration of 10 μM, **3** produced ≥70% inhibition against 5 proteins: norepinephrine transporter (NET), serotonin reuptake transporter (SERT), and CYP450 2C19, 2D6, and 3A4. AR-12286 had no activity against these proteins with the exception of CYP450 2D6 (67% inhibition). The inhibitory activity of **3** against NET and SERT was considered of interest since both adrenergic and serotonergic signaling are involved in IOP regulation,[17] and the adrenergic agonists epinephrine and brimonidine are in clinical use as IOP-lowering drugs for glaucoma.[18]Because of the potent and sustained efficacy of the αaryl βamino isoquinoline analog **3**, a continued SAR effort was further explored (Table 2). Substitution at the 4-position of the αaryl ring with both electron withdrawing and donating substituents resulted in better ROCK2, HTM and PTM activity compared with substitution at the 2 or 3 positions.

Table 2.
SAR of the αaryl βamino isoquinoline



Cpd	X1,X2	Y	ROCK2[a] K_i nM	HTM[b] IC_{50} nM	PTM[c] IC_{50} nM
7	H	OH	2.2	266	456
8	2-fluoro	H	1.0	139	260
9	3-fluoro	H	1.0	201	298
10	4-fluoro	H	1.0	102	175
11	4-fluoro	OH	2.0	219	247
12	3,4-difluoro	H	1.2	70	200
13	2-chloro	H	1.3	192	245
14	3-chloro	H	0.9	383	455
15	4-chloro	H	0.4	64	129
16	2,4-dichloro	H	0.8	208	414
17	2-methyl	H	1.0	90	200
18	3-methyl	H	3.3	324	511
19	4-methyl	H	0.4	39	84
20	3-OH	H	1.3	1721	459
21	4-OH	H	0.6	193	1015
22	3,4-OH	H	5.5	11002	5147
23	3-CH_3,4-OH	H	1.0	672	796
24	3-OCH_3, 4-OH	H	10.3	4239	2954
25	3-OCH_3	H	2.0	214	448
26	4-OCH_3	H	1.3	111	670
27	4-$OCH_2C_6H_5$	H	2.0	214	448
28	3-CH_2OH	H	3.0	248	1376
29	4-CH_2OH	H	0.2	48	485
30	3-CF_3	H	2.7	298	201
31	4-CF_3	H	1.8	493	152
32	αnaphthyl	H	1.0	4239	2954
33	βnaphthyl	H	0.7	193	1015

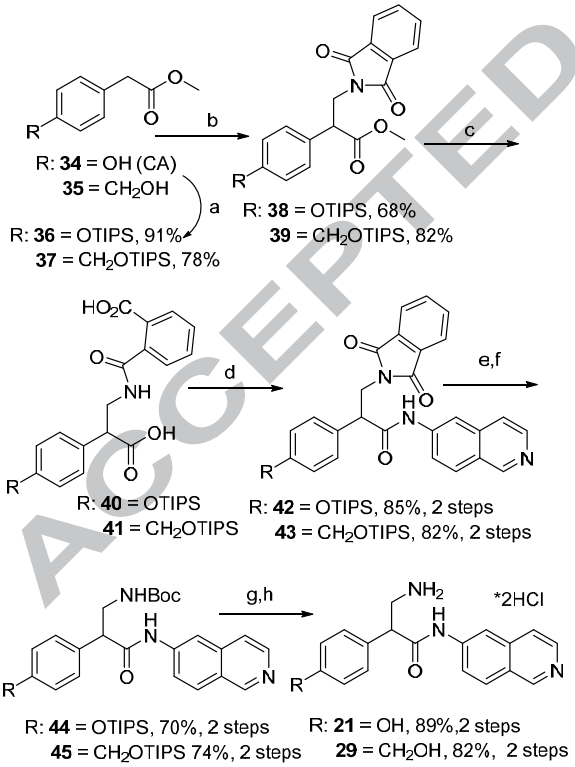
[a] enzyme inhibition data are an average of at least duplicate runs
[b,c] porcine and human trabecular meshwork cell assays; data represent average of at least duplicate runs

The most potent ROCK2 inhibitors (K_i <1nM) that were also effective in the HTM and PTM cells included 4-chlorophenyl **15**

(ROCK2 K_i = 0.4 nM), 4-methyl-phenyl **19** (ROCK2 K_i = 0.4 nM), 4-hydroxyl phenyl **21** (ROCK2 K_i = 0.6 nM), 4-hydroxylmethyl phenyl, **29** (ROCK2 K_i = 0.2 nM), and the β naphthyl analog, **33** (ROCK2 K_i = 0.7 nM). Also tested and compared with the 6-aminoisoquinoline (6-AIQ) parents **3** and **10** were the 1-hydroxy-6-aminoisoquinoline analogs **7** and **11** which were 2 times less potent in the ROCK2, PTM and HTM assays (Table 2).

These compounds were tested in Dutch Belted rabbits for their ability to lower IOP. Both 4-chloro and 4-methyl analogs **15** and **19** were dosed topically at 0.1% on day 1 and 0.3% on day 2. The βnaphthyl analog **33** was dosed at 0.1%. The 4-chloro analog **15** (max. **Δ**OP = -8.1 mmHg, p<0.01, 8 h, day 2), 4-methylated compound **19** (max. **Δ**OP = -9.6 mmHg, p<0.01, 8h, day 1) and αβnaphthyl analog **33** (max. **Δ**OP = -7.2 mmHg, p<0.05, 24h, day 1) produced significant maximum IOP reductions with moderate hyperemia and mild chemosis.

In an attempt to reduce the hyperemia and improve corneal penetration, esters were prepared of the most potent ROCK2 inhibitors, 4-hydroxyl phenyl **21** and 4-hydroxymethyl phenyl **29**. Topical ocular ester prodrugs with improved corneal penetration have been successfully developed previously for adrenergic agonists and prostaglandin analogues.[5a,17] The hydroxylated compounds **21** and **29** demonstrated sub-nanomolar potency against ROCK2 in vitro (Table 2) but did not lower IOP as well in Dutch Belted rabbits, with maximum **Δ**OPs of -1.5 mmHg, p<0.01 and -2.1 mmHg, p<0.05, respectively. This may be explained by their inability to penetrate the cornea. With three primary layers, consisting of the outer lipophilic epithelium, the thick hydrophilic stroma, and the inner endothelium, the cornea presents a strong resistance barrier which makes it a challenge to develop topical ophthalmic drugs.[19]

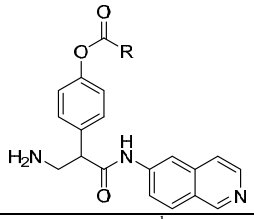


Scheme 1. Reagents and conditions: (a) TIPS-OTf, 2,6-lutidine, CH_2Cl_2; (b) LiHMDS, *N*-bromomethylphthalimide, THF, -78°C- 0°C; (c) LiOH*H_2O, THF-H_2O; (d) EDC, DMAP, 6-aminoisoquinoline; (e) NH_2NH_2, MeOH, reflux (f) Boc_2O, NEt_3, CH_2Cl_2; (g) TBAF, THF; (h) 4N HCl-dioxane, CH_2Cl_2, rt.

Both **21** and **29** as well as other analogs in Table 2 were synthesized following Scheme 1. Alternatively, some were prepared from commercially available *N*-Boc- α substituted phenyl amino acids which were coupled with 6-AIQ and deprotected. The methyl esters of the methyl 2-(4-hydroxyphenyl) acetate (**34**) and methyl 2-(4-(hydroxymethyl)phenyl) acetate (**35**) were TIPS protected using TIPS-OTf to give **36** (91%) and **37** (78%). Alkylation with *N*-(bromomethyl)phthalimide[20] gave **38** (68%) and **39** (82%). Hydrolysis of these methyl esters with lithium hydroxide also cleaved the imide ring to give the 2-carboxylbenzamides **40** and **41**. Using excess EDC, and coupling with 6-aminoisoquinoline provided isoquinoline amide analogs **42** (85% over 2 steps) and **43** (82% over 2 steps) with the cyclic imide intact. Aminolysis with hydrazine and Boc-protection gave the *N*-Boc amino isoquinoline amide analogs **44** (70% over 2 steps) and **45** (74% over 2 steps). Deprotection of the silyl protecting groups with TBAF gave *N*-Boc-protected phenol (**46**, 93%) and *N*-Boc protected benzyl alcohol (**47**, 92%). Final *N*-Boc deprotection with 4-N HCl- dioxane in CH_2Cl_2 gave **21** (96%) and **29** (89%).

Table 3.

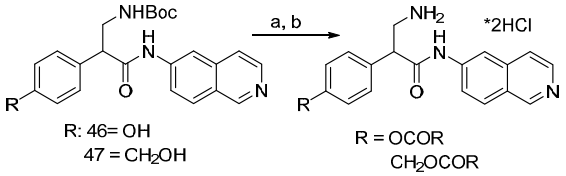
Esters of the α4-hydroxy phenyl βamino isoquinoline amide.



Cpd	R	ROCK2[a] K_i nM	HTM[b] XC_{50} nM	**Δ**OP[c] mmHg	Ave Irritat. Score[d]
48	$CH(CH_3)_2$	42	14	-6.5, 4 h -4.8, 8 h	0.8 c 0.8
49	$-C(CH_3)_3$	359	330	-5.9, 4 h -7.1, 8 h	1.8 c 1.5
50	C_6H_5	6.8	167	-7.8, 4 h -3.7, 8 h	0.9
51	$CH_2C_6H_5$	1.8	74	-6.0, 4 h -6.0, 8 h	0.4
52	2,4-dimethyl-C_6H_5	821	2459	-6.8, 4 h -6.5, 8 h	0.5
53	3,5-dimethyl C_6H_5	275	1250	-7.3, 4 h, -5.5, 8 h	0.5
54	3-pyridyl	4.8	832	-2.2, 4 h -0.3, 8 h	0.2
55	$-CH_2NH_2$	1	156	-1.1, 4 h -0.1, 8 h	0

[a] enzyme inhibition data are an average of at least duplicate runs.
[b] human trabecular meshwork cell assay; data represent average of at least duplicate runs.
[c] 0.1% compound dosed on day 1 and 0.3% dosed on day 2; IOP numbers from day 2;p =0.1-0.001.[d] average irritation score on Day 2, based on Draize method,
c = chemosis.

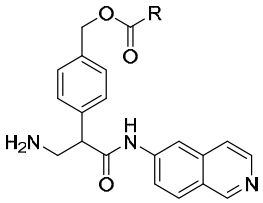
Esters of the 4-hydroxyl phenyl parent **46** and the 4-hydroxymethyl phenyl parent **47** were prepared with both hydrophilic and hydrophobic side chains following Scheme 2.



Scheme 2. Reagents and conditions: (a) EDC, DMAP, RCO_2H, pyridine; (b) 4N HCl-dioxane, CH_2Cl_2, rt.

Table 4.

Esters of the α4-hydroxymethyl phenyl βamino isoquinoline amide.



Cpd	R	ROCK 2[a] K_i nM	HTM[b] XC_{50} nM	ΔOP[c] mmHg	Ave Irritat Score[d]
56	$CH(CH_3)_2$	3.2	83	-7.3, 4 h -7.1, 8 h	1.0 c 0.5
57	$C(CH_3)_3$	21.8	424	-3.5, 4 h -8.1, 8 h	2.0 c 0.5
58	C_6H_5	1.7	72	-6.8, 4 h -9.7, 8 h	1.0
59	$CH_2C_6H_5$	0.8	118	-6.0, 4 h -6.0, 8 h	0.7
60	2,4-dimethyl C_6H_5	4.2	250	-6.3, 4 h -5.5, 8 h	0.4
61	3,5-dimethyl C_6H_5	0.9	65	-7.7, 4 h -9.7, 8 h	1.1
62	$(CH_2)_3CH_3$	1.6	44	-8.9, 4 h -5.4, 8 h	0.4
63	3-pyridyl[e]	0.7	65	-4.3, 4 h -1.8, 8 h	0.5
64	CH_2NMe[e]	ND	38	-2.1 4 h -1.3, 8 h	0 0

[a] enzyme inhibition data are an average of at least duplicate runs.
[b] human trabecular meshwork cell assay; data represent average of at least duplicate runs.
[c] 0.1% compound dosed on day 1 and 0.3% dosed on day 2; p =0.1-0.001.
[d] average irritation score on Day 2, based on Draize method, c = chemosis.
[e] dosed 0.08% on days 1 and 2.

The esters in both classes maintained ROCK2 and HTM activity, though the activity was less that of the respective parent compounds (Tables 3 and 4). These compounds were tested for IOP lowering in Dutch Belted rabbits at 0.1% on day one (1 drop, 30 μL) and the dose was increased to 0.3% on day 2. IOP measurements were taken at 1, 2, 4, 8, 24 hours after dosing each day. Irritation was scored according to the Draize scale[21] at each time point. To identify the optimal ester to carry forward, several criteria had to be met. The compound had to be dissolved and stable in a topical formulation. It also had to demonstrate a significant and sustained reduction in IOP with minimal hyperemia and no chemosis. The isopropyl and *tert*-butyl esters **48** and **49** in the 4-hydroxy phenyl class met the criteria for IOP lowering (**48**, Day 2 ΔOP = -6.5 mmHg, p<0.01, 4 h, **49,** ΔOP = -7.1 mmHg, p<0.001, 8 h), but moderate hyperemia and mild chemosis were observed at the higher dose level (0.3%) on day 2 (Table 3).

Improved irritation scores and effective IOP lowering were observed for the benzoate **50** (max ΔOP = -7.8 mmHg, p<0.01, 4 h), phenylacetate **51** (max ΔOP = -6.0 mmHg, p<0.001, 4 h) and the 2, 4-dimethylbenzoate **52** (max ΔOP = -6.8 mmHg, p<0.001, 4 h), on day 2, producing mild to moderate hyperemia and sustained reductions in IOP at 8 hours post-dose (Table 3). The more hydrophilic esters (**54, 55**) did not lower IOP as well and appeared to have a similar efficacy profile as the 4-hydroxyl phenyl parent **21**.

The esters in the 4-hydroxymethyl phenyl class typically exhibited more pronounced reductions in IOP than the 4-hydroxy phenyl esters (Table 4). The hydroxymethyl isopropyl **56** (max ΔOP = -7.3 mmHg, p<0.01, 4 h) and *tert*-butyl ester **57** (max ΔOP = -8.1 mmHg, p<0.01, 8 h) effectively reduced IOP at 0.3% on day 2, but also produced moderate hyperemia and mild chemosis. Benzoate ester **58** showed an impressive max IOP reduction of -9.7 mmHg, p<0.01, with no chemosis, but produced a relatively high hyperemia score. The 2,4-dimethyl benzoate analog **60** displayed a significant IOP reduction on day 2 of -6.3 mmHg, p<0.05, at 4 hours post-dose and a sustained IOP reduction of -5.5 mmHg, p<0.05, at 8 hours post-dose, and produced only mild hyperemia with no chemosis. Interestingly, the 3,5-dimethyl benzoate **61** also showed potent and sustained IOP lowering, but the hyperemia score was more than double the 2,4-dimethyl analog **60** at 0.3% on day 2. The more hydrophilic esters (**63**, **64**) did not produce the large reductions in IOP that were observed for the hydrophobicesters.

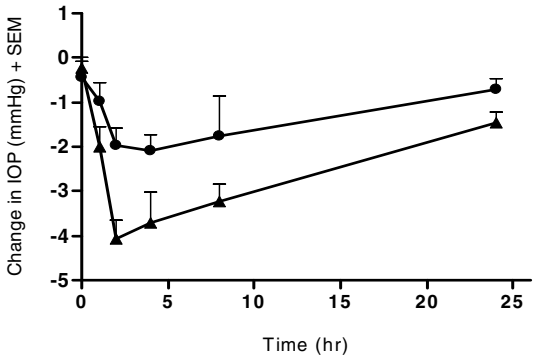


Figure 2. ΔIOP with **60** (▲ 0.1%) and parent alcohol **29** (• 0.1%). IOPs were measured in Dutch Belted rabbits. The rabbits were dosed (1 drop, 30 μL) after the baseline (time 0) measurements. Mean baseline IOP (on day 1, prior to dosing) in the study eye ranged from 21.1-24.4 mmHg. IOP measuremts were taken at 1, 2, 4, 8 and 24 hours after time 0. Each of the treated eyes was compared with its contralateral control eye to determine the change in IOP (ΔOP).

The 2,4-dimethyl benzoate **60** (0.1%) was compared directly with both the 4-hydroxymethyl phenyl parent **29** (0.1%) and ROCK inhibitor SNJ-1656 **1** (0.1%). As expected, **60** displayed improvement in IOP reduction compared to the 4-hydroxymethyl phenyl parent **29** (Figure 1). At the 2, 4, 8 and 24 h time points, **60** was 2, 1.6, 1.5, and 0.7 mmHg better than its parent alcohol **29.** Given that the ROCK2 inhibitory activity of **60** was 20-fold lower than the parent **29,** the superior IOP-lowering activity of **60** is likely due to improved corneal penetration and bioavailability.

60 (0.1%) also displayed much larger reductions in IOP at 8 hours (-3.2 mmHg) and 24 hours (-1.5 mmHg) post-dose than SNJ-1656 (**1**) 0.1% (8 h, -0.1 mmHg; 24 h, 0 mmHg, Figure 2). Given the similarity of this sustained IOP reduction to that observed for **3**, **60** was tested for inhibitory activity against NET and SERT (Eurofins PanLabs, Taipei, Taiwan). At 10 μM, the 2,4-dimethyl benzoate **60** demonstrated 96% inhibition of NET and 94% inhibition of SERT. In comparison, the 4-hydroxymethyl phenyl parent **29** demonstrated 48% and 39% inhibition of NET and SERT, respectively. **60** (500 nM) was also tested against a panel of 442 human protein kinases (DiscoverX, Fremont, CA). 11 Kinases were inhibited >90%, but only ROCK1 and ROCK2 (each 93% inhibition) and PKC (delta, 91%, and eta, 93% inhibition) have been identified as potential targets for lowering IOP. Similarly **29** (500 nM) inhibited 12 kinases >90 including ROCK1 and ROCK2 (100% inhibition each) and PKC (delta, 98%, epsilon, 93%, eta, 98% inhibition).

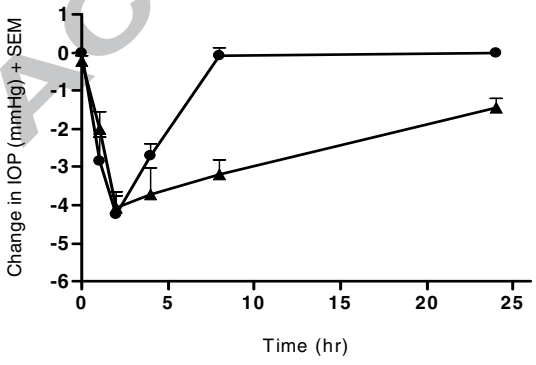


Figure 3. ΔIOP with **60** (▲ 0.1%) and SNJ-1656 (•0.1%). IOPs were measured in Dutch Belted rabbits. The rabbits were dosed (1 drop, 30 μL) after the baseline (time 0) measurements. Mean baseline IOP (on day 1, prior to dosing) in the study eye ranges from 24.2-25.5 mmHg. IOP measurements were taken at 1, 2, 4, 8 and 24 hours after time 0. Each of the treated eyes was compared with its contralateral control eye to determine the change in (ΔIOP.

In summary, compounds representing a new class of potent ROCK inhibitors have been developed that can be formulated and dosed as a topical eye drop, penetrate the cornea, and significantly lower IOP in a sustained manner. 2,4-Dimethyl benzoate **60** displayed improved bioavailability with minimum irritation in Dutch Belted rabbits. A sustained IOP reduction was observed for **60**, which appears to be a unique trait in this class, as compared to previously described classes of ROCK inhibitors. This sustained IOP reduction may be related to factors including corneal penetration, rate of hydrolysis by the corneal esterases, and the inhibition of norepinephrine transporter. Continued studies on **60** identified the *S*-enantiomer, netarsudil (a.k.a. AR-13324), as the active antipode (ROCK2 K_i= 2 nM).[22] Subsequently, netarsudil 0.02% was shown in two Phase II clinical trials to produce significant ΔIOPs that ranged from -5.7 to -6.3 mmHg after four weeks of dosing in patients with glaucoma and ocular hypertension.[23] Netarsudil was well tolerated, with trace to mild hyperemia being the most frequently reported adverse event.[23] Currently, netarsudil is in Phase III clinical trials for the treatment of open-angle glaucoma and ocular hypertension.

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