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Discovery and optimization of indole and 7-azaindoles as Rho kinase (ROCK) inhibitors (Part-II)

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ABSTRACT

Therapeutic interventions with Rho kinase (ROCK) inhibitors may effectively treat several disorders such as hypertension, stroke, cancer, and glaucoma. Herein we disclose the optimization and biological evaluation of potent novel ROCK inhibitors based on substituted indole and 7-azaindole core scaffolds. Substitutions on the indole C3 position and on the indole NH and/or amide NH positions all yielded potent and selective ROCK inhibitors (**25**, **42**, and **50**). Improvement of aqueous solubility and tailoring of in vitro and in vivo DMPK properties could be achieved through these substitutions.

A downstream effector of the small GTPase Rho, Rho kinase (ROCK) is a serine–threonine kinase of the AGC-family that regulates vital cellular processes such as cell motility, size, division, differentiation, and contractility.[1–4] Two isoforms of ROCK have been identified—ROCK-I and -II that are highly homologous in their kinase domain (92% sequence identity).[2] Since ROCK inhibition can trigger cytoskeleton remodeling and reduce cellular contractility, it is generally believed that inhibition of ROCK can be of therapeutic value in diseases such as hypertension and glaucoma.[5–9]

In an earlier study (Part-I),[10] we reported a new series of potent ROCK inhibitors based on indole 2- and 3-carboxamides and their 7-azaindole analogs (inhibitors **1**–**4**, Fig. 1). While these unsubstituted ROCK inhibitors possess high enzyme and cell activity and good PKA selectivity, we believe that substitutions on the indole C3 position (for the 2-carboxamide series), and on the indole NH and/or amide NH positions will provide opportunities to perturb and fine tune the pharmaceutical properties, such as the aqueous solubility and the DMPK properties. Different applications could be then developed from these tailored properties. Our working model for the binding of these inhibitors with ROCK-II is shown in Figure 2 (also see the docking model in Part-I).[10] We surmised that additional substitutions might be tolerable based on this binding motif. For example, R^1 or R^2 on inhibitors **1**–**4** might engage in binding interactions with previously unexplored regions of the ATP-binding domain of ROCK-II, such as with Asp-176 or with the solvent. Exploration in these regions (R^1 and R^2) was thus undertaken by preparing analogs of inhibitors **1**–**4** using slight modifications in the synthetic routes previously developed.[10]

The general synthesis of di-substituted indole 2-carboxamides **9** and 7-azaindole-2-carboxamides **10** commenced from the corresponding carboxylic acids **5a** and **5b**[10] as illustrated in Scheme 1. HATU mediated amide coupling with various amines **6** followed by N-alkylation of the indole ring NH of **7a** and **7b** furnished the di-substituted indole/azaindole framework. Finally a Suzuki heteroarylation reaction with 1*H*-4-pyrazoleboronic acid pinacol ester (**8**) afforded the desired indoles **9** and **10**.

For the synthesis of di-substituted indole 3-carboxamides **14** and its 7-azaindole analogs **15**, the indole or 7-azaindole ring NH (N1) of the corresponding trifluoromethyl ketones[10] **11a** and **11b** were first alkylated with various alkyl halides **12**. A Suzuki coupling followed by hydrolysis under basic conditions gave the desired carboxylic acids. In the final step, amide formation with appropriate amines **6**, using HATU as the coupling reagent, gave the desired indole-3-carboxamide **14** and the corresponding 7-azaindole-3-carboxamide **15** (Scheme 2).

Taking advantage of the nucleophilicity of the C3 position of the indole nucleus, a Mannich reaction was used to access 3-substituted 2-indolecarboxamides by treating compounds **16a** and **16b** with formaldehyde and an appropriate amine in acetic acid. A Suzuki heteroarylation with pyrazole boronic ester **8** then furnished the target compound **17** (Scheme 3).

The effect of substituents R^1 and R^2 on the indole-2-carboxamides was first examined (Table 1).[11] As demonstrated by compounds

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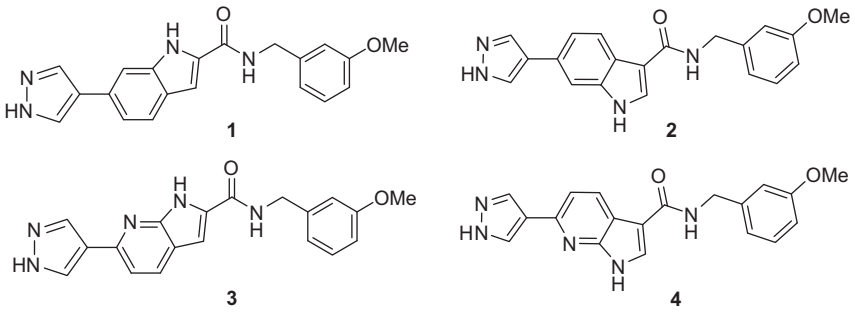


Figure 1. Lead indole and 7-azaindole ROCK inhibitors.

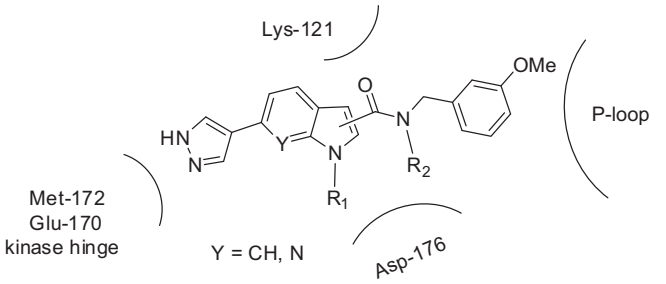
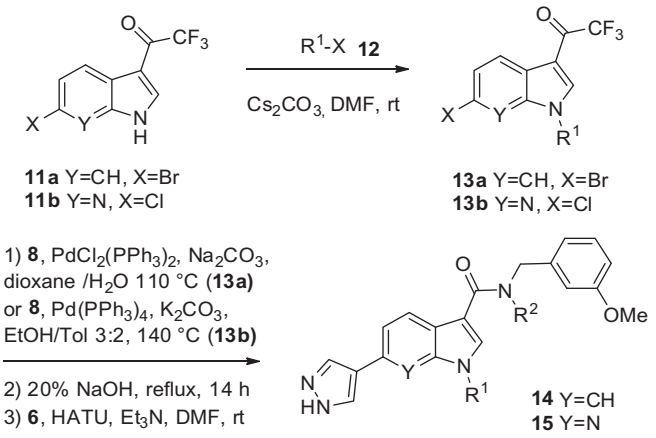


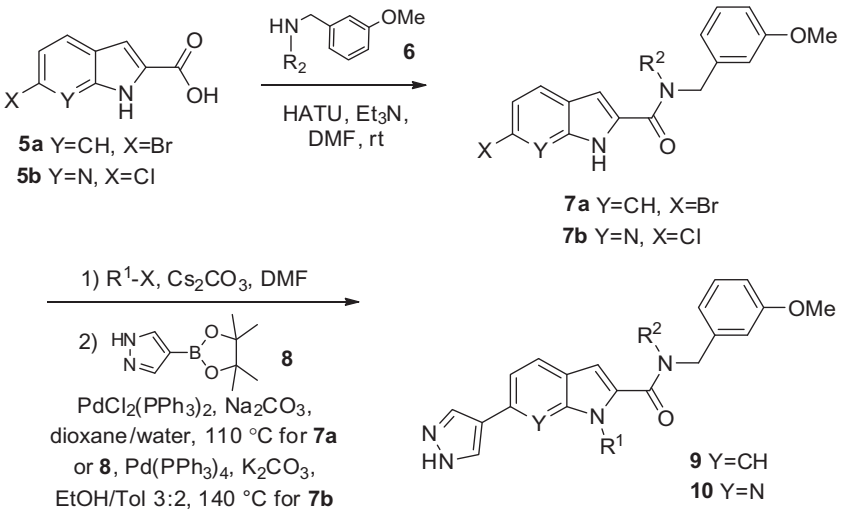
Figure 2. The indole/azaindole ROCK inhibitor scaffold and proposed interactions within the ROCK-II ATP-binding pocket.



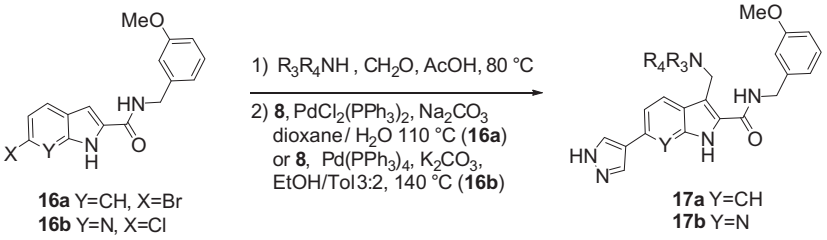
Scheme 2. A general route for the synthesis of 3-carboxamide indoles and 7-azaindoles.

18, **19**, **21**, and **22**, the N1 substitution of the indole nucleus was not tolerated by either ROCK isoforms with much reduced activity as compared to compound **1**. On the other hand, substitution on the amide NH (compounds **20**, **23, and 24**) maintained a good ROCK binding affinity. Nevertheless, R^2 substitution did not lead to improved selectivity for PKA nor did it improve ROCK potency.

A divergent trend of the substituent effect (relative to the indole series, Table 1) was observed for the isosteric 7-azaindole-2-carboxamide series. Similar to the indole 2-carboxamides, most substitutions at the amide NH (R^2) yielded potent ROCK inhibitors with good PKA selectivity (**32**–**34**). The same was true when a small methyl group was attached to the indole NH position (**25**). However, introduction of large groups without H-bonding capability, such as a methyl cyclopropyl or an aromatic group, at the indole NH position was not tolerated (**26** and **27**). Remarkably, in contrast to the analogous indole **19**, substitution by a larger group with H-bonding capability still gave potent (slightly reduced ROCK potency compared to **3** and **25**, though) compounds (**28** and **29**).[12] Compounds with substitutions at both R^1 and R^2 were found to have low affinity for both ROCK isoforms (**30** and **31**), and the one with a positively charged side chain (**30**) gave even lower ROCK activity. These results indicate that perhaps some azaindole 2-carboxamides can bind in an orientation somewhat different from the corresponding indole analogs.

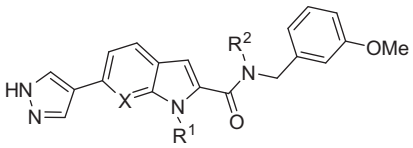


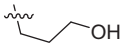
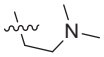
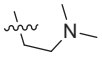
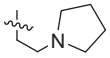
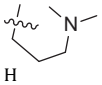
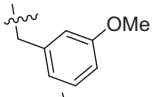
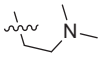
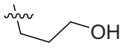
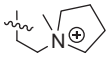
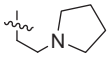
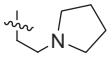
Scheme 1. A general route for the synthesis of 2-carboxamide indoles and 7-azaindoles.



Scheme 3. Synthesis of 3-aminomethyl-2-carboxamide indoles and 7-azaindoles.

Table 1
Effect of N-substitutions on indole and 7-azaindole-2-carboxamides



Compd	X	R^1	R^2	IC_{50}[a] (nM)		
				ROCK-II	ROCK-I	PKA
1	CH	H	H	2	19	6700
18	CH		H	24	88	1800
19	CH		H	310	710	>20,000
20	CH	H	Me	3	37	2800
21	CH	Me	Me	200	1,100	>20,000
22	CH		Me	2300	6900	>20,000
23	CH	H		11	62	1640
24	CH	H		10	46	1600
3	N	H	H	2	12	140
25	N	Me	H	<1	2	150
26	N		H	150	280	5000
27	N		H	4400	>20,000	Nd[b]
28	N		H	43	243	3670
29	N		H	24	88	5800
30	N	Me		1900	6600	3700
31	N	Me		220	1000	2200
32	N	H	Me	4	27	570
33	N	H		8	33	1700
34	N	H		18	121	>20,000

[a] Average of two or more measurements with derivations ⩽30%.
[b] Not determined.

We then turned our attention to the N-substitution effect on the 3-carboxamide inhibitors **2** and **4** (Table 2). The most important observation is that many substitutions at the indole NH position in both the indole and the 7-azaindole series were well tolerated. These substitutions include small or large groups with or without H-bonding capability (compounds **36**, **38**, **41**, **42**, **48**, and **49**).[13] Like that in the 2-carboxamide series, mono-substitution at the amide NH was always well tolerated and gave potent ROCK inhibitors (**35**, **45**–**47**). In contrast to the 2-carboxamide series, di-substitution at both the indole NH and the amide NH positions, with at least one of the substitutions being a small group such as a methyl group, still gave potent ROCK inhibitors (compounds **37**, **39, 40**, and **43**). However, di-substitution with two large groups yielded poor ROCK binding (compound **44**). Also noteworthy is that the

use of polar H-bonding side chains at either (but not both) position led to potent ROCK-II inhibitors with markedly reduced PKA activity (**39–43, 48, and 49**). For example, inhibitors **40** and **49**, both of which possess a tertiary amine side chain, were found to have much reduced affinity for PKA compared to that of compounds **2** and **4**, respectively.

The tolerance for large groups at the indole N1 position in 3-carboxamides contrasts remarkably with the absence of clearly positive effects for such N1 substitutions in the 2-carboxamide series (compare inhibitors **42**, **43** with **19**, **22**, for example). This divergence can be explained well by our docking studies (Fig. 2 in Part-I) that suggest that the binding conformation of 2-carboxamide indoles differ significantly from their 3-carboxamide analogs with a flipped orientation of the indole nucleus.[10] In indole 2-carboxamides, the indole NH is projected *away* from residue Asp-176 of ROCK-II and *toward* the inside of the binding pocket. In such an orientation, there is no space to accommodate a large alkyl group in that area. However, substitutions containing H-bonding capability at this position, such as those in compounds **28** and **29** in Table 1, might pick up some binding energy with the extra H-bonding interactions and thus still render ROCK affinity although the molecule conformation might be twisted. In the other orientation, predominant for most if not all 3-carboxamides, the indole NH is instead projected *towards* Asp-176 and to the solvent, where there is an open space to hold many different substitutions. Therefore, simple small or large groups (compounds **37** and **38**), or large groups containing H-bonding capability (compounds **41**–**43**, and **49**) are all well tolerated at this indole NH position.

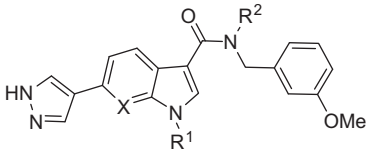
This binding hypothesis for 2-carboxamide indole/azaindole based ROCK inhibitors also suggests that adding a polar side chain of an appropriate length at the indole C3, rather than at the indole N1, would confer good ROCK potency. Additionally, such substitutions would change the inhibitor's physicochemical properties and thus have the potential to fine-tune the pharmaceutical profiles. This proposal was tested by preparing indole 2-carboxamides with polar groups added at the desired indole C3 position. As shown in Table 3, all polar side chain containing compounds (**50**–**55**) showed good ROCK-II potency. The morpholine analog **51** was found to have similar ROCK-II affinity as inhibitor **1** with improved selectivity over PKA (6000-fold). The *N*-methyl piperazine analog (**52**) and the homo-piperazine analog (**53**) gave even better ROCK potency although the PKA activity of **53** was increased as compared to **1**. Interestingly, these C3 substitutions slightly reduced both the ROCK activity and the selectivity against PKA in the 7-azaindole series although it still produced potent ROCK inhibitors (compounds **54** and **55** compared to compound **3**).

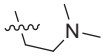
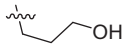
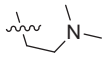
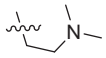
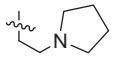
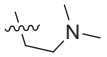
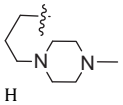
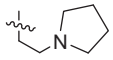
Some of the potent compounds from each indole and azaindole series were evaluated for their cell based activity. As shown in Table 4, all those compounds active in enzyme assays with IC_{50} values of <20 nM generally gave cell potency with IC_{50} values of less than ~200 nM in our cell-based myosin light chain bis-phosphorylation assays (ppMLC),[14] indicating that these compounds all possess good cell permeability.

To evaluate the drugability of these indole and azaindole based ROCK inhibitors, promising compounds from Tables 1–3 were also subjected to pharmacokinetic (DMPK) assays. The most important observation from the in vitro DMPK (Table 4) experiments was that any substitutions to the indole-2-carboxamide scaffold would reduce the CYP-450 enzyme inhibitions (compounds **20**, **23**, **25**, **50**–**53** compared to **1**) while the resulting compounds still remained a good human liver microsomal (HLM) stability (compounds **20**, **23**, **25**, **50**, and **53**). The exceptions were the morpholine analog **51** and *N*-methyl piperazine analog **52**. Remarkably, the dimethylamino analog **50** (also coded as **SR7309**) was very stable to human liver microsomes and had a low CYP-450 inhibition profile, which indicated that further investigations were warranted for this inhibitor considering its high ROCK potency (ROCK-II IC_{50} = 9 nM) and low PKA activity (PKA IC_{50} = 1500 nM). The most noticeable observation for the 7-azaindole-2-carboxamide ROCK inhibitors was that any substitutions on the C3 position, on the indole NH, and/or on the amide NH decreased the microsomal stability (compare compounds **28**, **32**–**34**, **54**, and **55** to compound **3**). On the other hand, no significant changes in CYP-450 inhibitions were observed for these substituted compounds with the exception of compound **32** which showed slightly increased inhibitions for CYP isoforms 1A2, 2C9, and 2D6. Nevertheless, none of these 7-azaindole-2-carboxamides gave significant CYP inhibitions.

The unsubstituted indole-2- and indole-3-carboxamide series were notorious for their high CYP inhibitions as demonstrated by data obtained for the lead compounds **1** and **2** (Table 4). Therefore, any structural modifications that can reduce these inhibitions, as seen in the 2-carboxamide series, will benefit the drugability of the indole-carboxamide based ROCK inhibitors. However, the substitution effect on the CYP-450 inhibitions is a little different in the indole-3-carboxamide series (**35**–**42**) from that in the indole-2-carboxamide series (**20**, **23**, and **25**). A methyl substitution on either or both the indole and the amide NH positions (**35**–**38**), or a phenyl substitution on the indole NH (**38**) did not significantly change this inhibition profile although the amide substitution

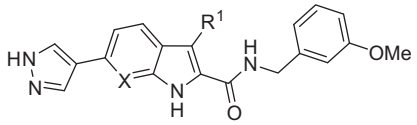
Table 2
Effect of N-substitutions on indole and 7-azaindole-3-carboxamides

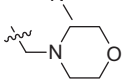
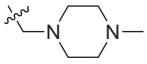
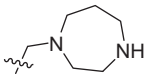
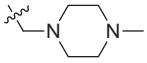
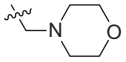


Compd	X	R^1	R^2	IC_{50}[a] (nM)		
				ROCK-II	ROCK-I	PKA
2	CH	H	H	<1	<1	510
35	CH	H	Me	2	19	4300
36	CH	Me	H	<1	<1	87
37	CH	Me	Me	<1	3	680
38	CH		H	5	21	Nd[b]
39	CH	Me		1	13	2810
40	CH	Me		1	9	2200
41	CH		H	1	3	900
42	CH		H	<1	5	7000
43	CH		Me	9	110	>20,000
44	CH			2800	8900	>20,000
45	N	H		6	30	>20,000
46	N	H	Et	19	76	5000
47	N	H		62	260	3700
48	N	Me	H	<1	<1	720
49	N		H	8	89	>20,000
4	N	H	H	2	11	8000

[a] Average of two or more measurements with derivations ⩽30%.
[b] Not determined.

Table 3
Effect of C3-substitutions on indole and 7-azaindole-2 carboxamides



Compd	X	R^1	IC_{50}[a] (nM)		
			ROCK-II	ROCK-I	PKA
1	CH	H	2	19	6700
50	CH		9	34	1500
51	CH		3	40	18,000
52	CH		<1	6	1300
53	CH		<1	8	385
3	N	H	2	12	8000
54	N		8	39	911
55	N		16	91	6100

[a] Average of two or more measurements with derivations ⩽30%.

(**35**) did reduce the 3A4 inhibition and the indole NH substitution did lower the 1A2 inhibition (**36**–**38**). On the other hand, substitutions with H-bonding capability (**39**–**42**) gave mixed results. When these substitutions were on the amide nitrogen (**39** and **40**), CYP inhibitions were greatly reduced, but when these substituents were on the indole nitrogen (**41** and **42**), CYP inhibitions were still high. Interestingly, compounds **41** and **42** were also the exception regarding effects of substitutions on the microsomal stability of these indole-3-carboxamide inhibitors. The half-life of **41** and **42** in human microsomes (HLM) was almost unchanged while that of all other compounds (**35**–**40**) was significantly reduced compared to compound **2**. In the 7-azaindole-3-carboxamide series, no clear trend was observed regarding the effect of substitutions on the microsomal stability and the inhibition for selected CYP isoforms (compounds **45**, **48**, and **49** compared to compound **4**).

A few lead ROCK inhibitors were also selected for in vivo pharmacokinetic studies (Table 5). The data for compound **3**, which have already been reported in Part-I (compound **21** in Part-I) are also listed in Table 5 for comparison. Data for compound **25** indicated that a simple methyl substitution to the indole nitrogen of the 7-azaindole-2-carboxamide scaffold did not affect much of the in vivo DMPK profile with only some reduction in AUC values. Compound **25**, which had an overall good pharmacokinetic profile, could be a good candidate for systemic applications by oral dosing. However, a cyclopropyl substitution on the amide nitrogen (**33**) significantly worsened the properties with a remarkable increase in clearance (Cl) and volume of distribution (V_{ss}), a reduction in half-life ($t_{1/2}$), and AUC values of both iv and po dosing, and a significant decrease in C_{max} of oral dosing. Similar to their unsubstituted analogs, compounds based on 3-carboxamides (**42** and **49**, for example) normally gave poor DMPK properties due to their generally short half-lives in liver microsomes. These compounds had high clearance (Cl) and volume of distribution (V_{ss}), low AUC and C_{max} values, and minimum oral bioavailability. The C3 morpholinomethyl substituted 7-zaindole-2-carboxamide **51**, again due to its low microsomal stability, also exhibited a pharmacokinetic profile with high clearance and very low oral absorbance. It was anticipated that many of these compounds would be rapidly cleared and would therefore be undesirable for systemic therapy.

Table 4
Cell activity and in vitro DMPK properties for selected compounds

Compd	ppMLC cell assays IC_{50}[a] (nM)	$t_{1/2}$ (min) HLM	CYP-450 inhibition at 10 μM (%)			
			1A2	2C9	2D6	3A4
1	28	80	42	87	81	87
20	70	46	−7	27	9	2
23	206	49	−2	65	78	59
25	25	68	1	76	48	40
3	Nd[b]	53	4	38	32	22
28	Nd[b]	17	26	46	55	65
32	25	24	32	83	52	27
33	Nd[b]	27	16	52	30	40
34	Nd[b]	21	12	26	52	43
2	4	25	87	97	51	72
35	Nd[b]	13	70	94	50	38
36	4	9	23	93	53	87
37	17	4	23	93	58	70
38	Nd[b]	10	36	96	76	93
39	53	14	4	28	31	31
40	34	8	3	62	52	36
41	Nd[b]	21	71	87	32	63
42	23	20	−6	91	53	70
4	Nd[b]	15	5	86	12	46
45	Nd[b]	9	−5	91	25	56
48	Nd[b]	13	−2	77	23	68
49	Nd[b]	21	9	51	69	44
50	Nd[b]	68	18	27	48	19
51	130	8	46	86	70	86
52	40	1	62	75	86	75
53	Nd[b]	50	41	53	81	51
54	Nd[b]	1	−15	−26	60	34
55	Nd[b]	4	7	9	28	46

[a] Average of two or more measurements with derivations ⩽30%.
[b] Not determined.

Table 5
In vivo pharmacokinetic profiles for selected inhibitors in rats[a]

Compd	Cl (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	AUC iv (μM ∗ h)	AUC po (μM ∗ h)	C_{max} po (nM)	Oral *F* (%)
25	4	0.5	1.8	11.5	7.9	1190	35
33	21	1.2	0.9	2.2	1.0	255	22
3	2	0.3	2.0	22.4	14.4	1800	32
42	42	3.2	1.2	1.0	0.02	0	1
49	114	10.0	1.5	0.3	0.0	0	0
51	32	2.0	1.4	1.2	0.0	0	0

[a] Data was generated from three determinations with derivations ⩽30%. Dosed at 1.0 mg/kg (iv) or 2.0 mg/kg (po).

However, local applications could be practical, for example, topical applications of some compounds could result in increased aqueous humor outflow and decreased intraocular pressure[8,9] as demonstrated in several of our studies for compounds based on other scaffolds developed in our laboratory.[15,16]

To demonstrate the improvement of aqueous solubility by these substitutions with polar side chains (or substitutions with H-bonding capability), two pairs of compounds (**1** vs **50** and **2** vs **40**) were subjected to solubility testing at both pH 5.5 and 7.4. Compounds **1** and **2** had low aqueous solubility at both pH values (⩽0.01 μM). In contrast, compounds **42** and **50** exhibited excellent aqueous solubility at pH 5.5 (⩾100 μM) mainly due to the tertiary amine moieties on their substitutions. In addition, compounds **42** and **50** still had fair to good solubility even at pH 7.4 (77 and 1.1 μM, respectively).

In conclusion, SAR studies demonstrated that incorporation of side-chains to the C3 position or to indole and/or amide nitrogen atoms of the indole carboxamide scaffolds still generated potent ROCK inhibitors with good selectivity against PKA. These substituents might affect the ROCK potency, PKA selectivity, and more importantly, they could modify the inhibitor's physicochemical properties, and in vitro and in vivo DMPK profiles, which is not easy to achieve in the original unsubstituted analogs. Several of our compounds have suitable properties which warrant further investigations to develop potential therapeutics, either for local or for systemic applications. For example, compounds **42** (also coded as **SR6781**), **49** (also coded as **SR9165**), and **51** (also coded as **SR7280**) might be good for nonsystemic local applications such as for the treatment of glaucoma. These compounds have much better aqueous solubility compared to their unsubstituted analogs due to the polar side chains. Their poor pharmacokinetic properties (high clearance and minimum oral absorbance) make these compounds suitable for local applications in order to diminish potential safety concerns. The overall best compound for systemic oral applications is compound **25** (also coded as **SR7583**). This compound has a low clearance, a low volume of distribution, a fair half-life, high AUC values, and a good bioavailability value in rat pharmacokinetic assays. In addition, compound **25** might possess higher brain penetration compared to its unsubstituted analog, which is very important for CNS applications. The specific brain penetration data together with in vivo studies for various applications of these compounds will be reported in due course.

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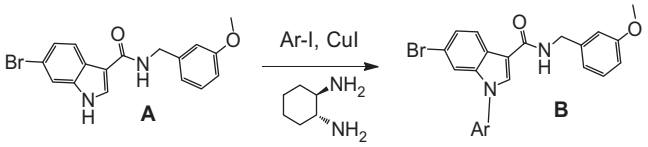
11. ROCK and PKA assays were performed as described in: (a) Schröter, T.; Minond, D.; Weiser, A.; Dao, C.; Habel, J.; Spicer, T.; Chase, P.; Baillargeon, P.; Scampavia, L.; Schürer, S. C.; Chung, C.; Mader, C.; Southern, M.; Tsinoremas, N.; LoGrasso, P.; Hodder, P. *J. Biomol. Screen.* **2008**, *13*, 17; (b) Chen, Y. T.; Vojkovsky, T.; Fang, X.; Pocas, J. R.; Grant, W.; Handy, A. M. W.; Schröter, T.; LoGrasso, P.; Bannister, T. D.; Feng, Y. *Med. Chem. Commun.* **2011**, *2*, 73.
12. In many instances compounds reported herein were also evaluated versus a selected panel of other kinases (e.g., MRCKα, p38, Akt, and JNK3,). No off-target activity <5 μM was seen.
13. The *N*-aryl indole **B** (e.g., compound **38** in Table 2) was synthesized by a copper-mediated coupling reaction:



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