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5-Lipoxygenase-activating protein inhibitors. Part 2: 3-{5-((*S*)-1-Acetyl-2,3-dihydro-1*H*-indol-2-ylmethoxy)-3-*tert*-butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-1*H*-indol-2-yl}-2,2-dimethyl-propionic acid (AM679)—A potent FLAP inhibitor

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ABSTRACT

A series of potent 5-lipoxygenase-activating protein (FLAP) inhibitors are herein described. SAR studies focused on the discovery of novel alicyclic moieties appended to an indole core to optimize potency, physical properties and off-target activities. Subsequent SAR on the N-benzyl substituent of the indole led to the discovery of compound **39** (AM679) which showed potent inhibition of leukotrienes in human blood and in a rodent bronchoalvelolar lavage (BAL) challenge model.

5-Lipoxygenase-activating protein (FLAP) works in concert with 5-lipoxygenase (5-LO) to convert membrane derived arachidonic acid to the pro-inflammatory mediator leukotriene epoxide LTA_4.[1] This is rapidly converted to either LTB_4 by LTA_4 hydrolase or LTC_4 through reaction with LTC_4 synthase (Fig. 1). LTB_4 binds to the GPCRs BLT1 and BLT2 eliciting neutrophil and eosinophil chemotaxis and subsequent activation of downstream inflammatory responses. LTC_4 is further converted to LTD_4 and LTE_4, and collectively these three are termed cysteinyl leukotrienes (CysLTs). CysLTs are responsible for bronchoconstriction, airway edema and hypersecretion of mucus via binding to their GPCRs $CysLT_1$ and $CysLT_2$, however the role of the $CysLT_2$ receptor remains unclear.[2] Recent research also indicates the existence of other CysLT receptors, namely GPR17,[3] P2Y12R,[4] and $CysLT_E$.[5] Zyflo™, a marketed 5-LO inhibitor, ablates the production of both LTB_4 and the CysLTs but is not widely prescribed due to poor pharmacokinetic parameters and a low but significant incidence of hepatotoxicity.[6] $CysLT_1$ antagonists are also used clinically for the treatment of asthma, the most widely prescribed of which is Singulair™. Inhibition of the FLAP protein is therefore an attractive target as it would prevent the biosynthesis of both LTB_4 and CysLTs and as such prove a valuable therapy for asthma and other diseases where LT involvement is implicated.

MK-591 **1** and DG031 **2** (formerly known as BAYX1005) are both FLAP inhibitors that have progressed to clinical trials in human (see Fig. 2).[7] The former is an inhibitor of CYP450 (IC_{50}'s 3A4 = 5.2 μM, 2C9 = 0.5 μM), is poorly bioavailable as a crystalline sodium salt and showed an incidence of mild maculopapular rash

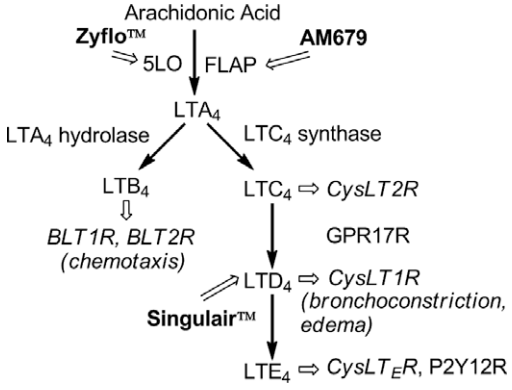

Figure 1. The arachidonic acid/leukotriene pathway. Zyflo™ is a marketed 5-LO inhibitor. Singulair™ is a marketed $CysLT_1$ receptor antagonist.

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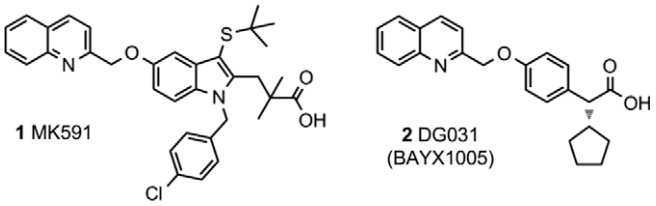
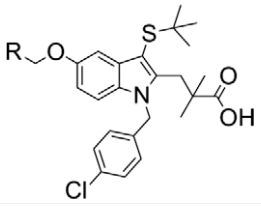
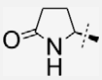
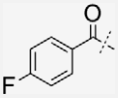
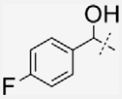
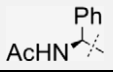


Figure 2. MK-591 and BAY X1005, published FLAP inhibitors.

in humans.[8] The latter, DG031 is only a weak inhibitor of FLAP (IC_{50} inhibition of LTB_4 ~6 μM in calcium ionophore challenged human whole blood).[9]

Table 1
In vitro IC_{50} assay results for compounds **4**–**13**[a]



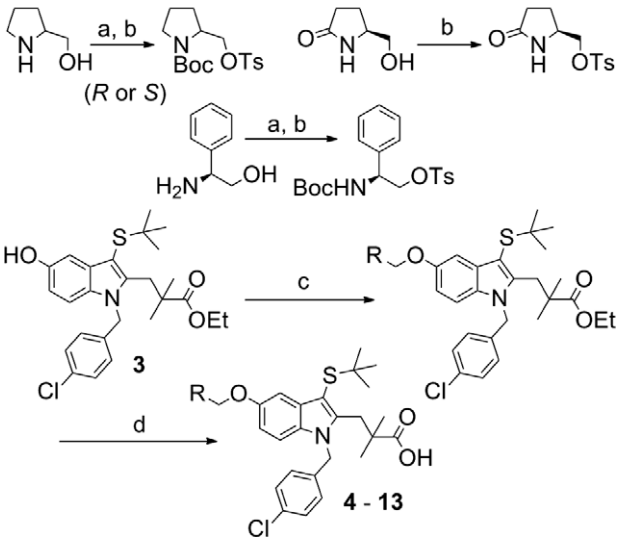
No.	R	FLAP binding (nM)	hLA (nM)	hWB (nM)
4		1114	29	17,221*
5		1805	193	67,753
6		>10,000	2781	ND
7		6	16	403#
8		441	30	4299
9		616	108	9024*
10		38	28	2141&
11		13	769	11,831
12		19	7	469
13		581	72	23,111*

[a] FLAP binding and hLA (human leukocyte) data are the average of $n \geqslant 3$. Unless otherwise noted. hWB data is the average of two experiments ($n = 2$, each expt. averages two donors).
* $n = 1$.
& $n = 3$.
# $n = 72$.

There are currently no FLAP protein inhibitors on the market, therefore we directed our efforts at addressing the weaknesses of previous FLAP inhibitors by identifying novel, potent compounds devoid of major CYP liabilities with good pharmacokinetic parameters. The quinoline moiety is a known pharmacophore for the FLAP protein and only limited SAR studies have focused on replacement of this entity.[10] This functional group has also been implicated as a moiety susceptible to bioactivation and covalent labeling.[11] We initiated our SAR studies by replacing this pharmacophore with a variety of alicyclic groups (Table 1). All compounds were screened in a FLAP binding assay using human polymorphonuclear leukocyte (PMN) derived membranes, a human leukocyte assay (hLA) whereby LTB_4 produced in these cells is measured after calcium ionophore challenge and finally, to ascertain the degree of shift in the presence of blood proteins, compounds were tested in a human whole blood (hWB) assay to measure the inhibition of LTB_4 production following ionophore challenge after 15 min incubation.[12]

Compounds were prepared from the indole–phenol **3**[13] through reaction with the appropriate alkylating reagent (Scheme 1). Carboxylic acids **4** and **5** derive from alkylation of **3** with the tosylate of either enantiomer of *N*-Boc-2-hydroxymethylpyrrolidine and subsequent hydrolysis of the hindered ethyl ester. Deprotection of the Boc group (4 N HCl in dioxane) afforded the free amine **6**. Acylation (acetic anhydride, Hunig's base) afforded the acetylated product **7** or alternate reaction with methanesulfonylchloride gave the sulfone **8.** Compound **9** was prepared in a similar fashion from the tosylate of 5-hydroxymethyl-pyrrolidin-2-one. Alkylation of **3** with 2-chloro-4′-fluoroacetophenone under similar conditions with subsequent hydrolysis of the ester yielded **11**. The corresponding racemic alcohol **12** arose from $NaBH_4$ reduction of **11**. The amide **10** was synthesized using 2-bromoacetamide as the electrophile. Benzylic acetamide **13** was prepared from reacting **3** with the tosylate of Boc-protected phenylglycinol, deprotection of the Boc group (4 N HCl in dioxane), acetylation of the amine (Ac_2O, Hunigs base) and subsequent ester hydrolysis.

Of the initial compounds prepared, the (*S*)-stereochemistry proved the more active (the *R*-isomers of **6, 7, 8**, and **9** were also less potent than their (*S*)-counterparts, data not shown). The simple amide **10** showed reasonable FLAP binding and hLA potency but shifted to 2.1 μM in the human blood assay. The *N*-acetylpyrrolidine



Scheme 1. Reagents and conditions: (a) Boc_2O, CH_2Cl_2; (b) TsCl, pyridine; (c) alkylating agent, Cs_2CO_3, DMF or MeCN, 60 °C; (d) $LiOH{\cdot}H_2O$, MeOH/THF/H_2O (1:1:1), 60 °C.

7 showed excellent potency in all three assays, especially in hWB (IC_{50} = 403 nM). However, **7** showed significant inhibition of CYP3A4 (64% @ 10 μM) and 2C9 (93% @ 10 μM), indicating a potential for drug–drug interaction. Pharmacokinetic parameters in rat were also poor, characterized by low bioavailability, moderate clearance and low AUC (10 mg/kg po as sodium carboxylate salt: F = 10%, Cl = 20 mL/min/kg, AUC = 1.2 h μg/mL).

Maintaining the more potent (*S*)-stereochemistry, a small number of alkyl amide derivatives were prepared (Table 2). Synthesis of these was accomplished through reaction of the ethyl ester of **6** with the appropriate acyl chloride under standard conditions and subsequent ester hydrolysis (Scheme 2).

Increasing the steric bulk of the amide had a detrimental effect on the overall potency of the compounds, the smaller methyl **7** and ethyl **14** amides showing the greatest potency in all three in vitro assays. Subsequent to the completion of this work, X-ray crystal data of the FLAP protein was published indicating a restricted binding pocket for the quinoline moiety of **1**.[14] This correlates well with our findings that increased steric size of the alicyclic group reduces potency against FLAP. However, all these derivatives still possessed significant inhibition of CYP3A4 and 2C9 (data not shown).

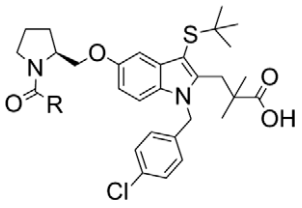
With a potent alicyclic substituent identified in the *N*-acylpyrrolidine **7**, incorporation of a fused phenyl to the pyrrolidine structure (indoline) was anticipated to improve potency due to it more closely mimicking the planar structure of quinoline and thereby increasing binding affinity to the FLAP protein (Table 3). This was prepared in analogous fashion reacting the tosylate of *N*-Boc-protected (*S*)-indoline-2-methanol with the indole–phenol **3** to afford **18** and subsequent deprotection and acylation to give **19** and **20**, respectively (Scheme 3).

The N-acylated indoline **20** showed excellent activity in all three in vitro assays, most notably hWB (IC_{50} = 169 nM). Unfortunately, pharmacokinetic parameters were similar to its pyrrolidine counterpart **7**, with low bioavailability, moderate clearance and low Cmax in rat (10 mg/kg as sodium carboxylate salt: F = 11%, Cl = 25 mL/min/kg, C_{max} = 270 nM). CYP inhibition also worsened against 3A4 (80% @ 10 μM) and 2C9 (96% @ 10 μM). The (*R*)-Boc-enantiomer **21** again proved less active than the (*S*)-enantiomer as in the prior pyrrolidine derivatives vide infra.

Removal of the *t*-butylthio group using $AlCl_3$ and H_2O in dichloromethane allowed the preparation of a variety of acyl and alkyl substituents at the 3-position of the indole.[15] Acylation with a variety of acyl chlorides under Friedel–Crafts type conditions and the subsequent reduction with $NaBH_4$ in TFA/dichloromethane (Scheme 4) afforded the derivatives shown (Table 4). The sulfoxide **29** and sulfone **30** were also prepared through sequential reaction of 1 equiv of *m*-CPBA in dichloromethane with the thiane **20**.

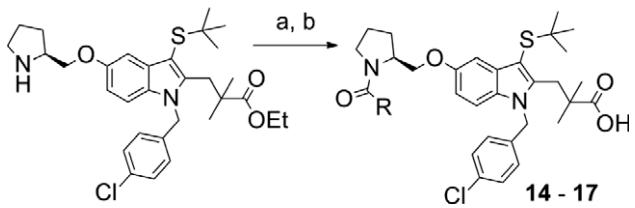
Removal of the *t*-butylthio group significantly reduced the potency against FLAP (**22**, FLAP binding IC_{50} = 218 nm). Acyl groups with substituents alpha to the carbonyl (**23, 24**) also reduced activity. However, the *t*-butylacetyl derivative **25** showed good potency in binding and hLA with a reasonable blood shift (hWB IC_{50} = 521 nM). Due to the more polar nature of the vinylogous acyl unit we anticipated an improvement in solubility and potentially bioavailability. However, upon oral dosing of the sodium salt of **25** (10 mg/kg in rat), it showed low bioavailability (F = 7%) and low C_{max} (190 nM). Removal of the carbonyl group yielded compounds **26**, **27**, and **28** with good in vitro potencies but activity against CYP3A4 and 2C9 remained (>80% @ 10 μM). The racemic sulfoxide **29** loses a significant degree of potency which is regained

Table 2
In vitro IC_{50} data for compounds **14**–**17**[a]



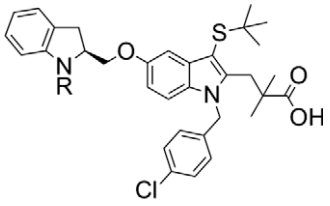
No.	R	FLAP binding (nM)	hLA (nM)	hWB (nM)
7	Me	6	16	403[#]
14	Et	4	1.5	307[*]
15		50	8.0	885
16		186	51	5663
17		1345	110	22,270

[a] FLAP binding and hLA data are the average of $n \geqslant 3$. Unless otherwise noted hWB data is the average of two experiments (n = 2, each expt. averages two donors).
[*] n = 1.
[#] n = 72.



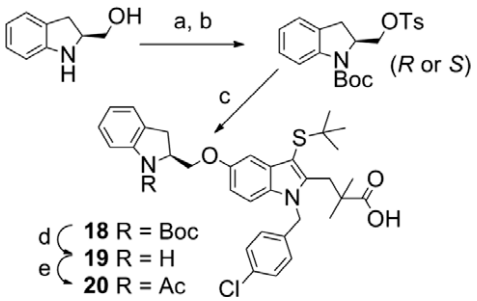
Scheme 2. Reagents and conditions: (a) acyl chloride, diisopropylethylamine, CH_2Cl_2; (b) LiOH·H_2O, MeOH, THF, H_2O (1:1:1), 60 °C.

Table 3
In vitro IC_{50} data for indolines **18**–**21**[a]

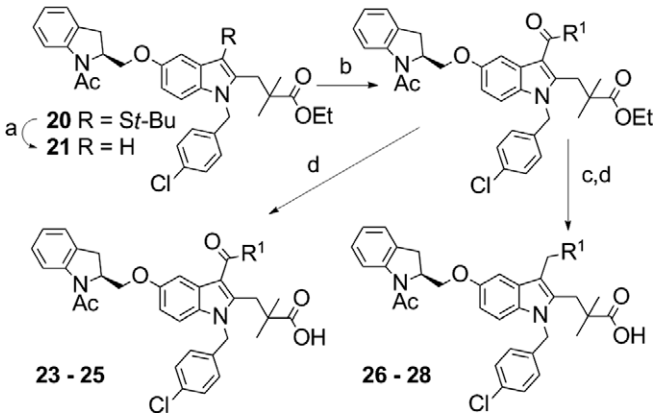


No.	R	FLAP binding (nM)	hLA (nM)	hWB (nM)
18	Boc	1100	106	ND
19	H	85	4.1	1431
20	Ac	1.4	0.5	169[&]
21[*]	(*R*)-Boc	>10,000	102	12,254

[a] FLAP binding and hLA data are the average of $n \geqslant 3$. Unless otherwise noted hWB data is the average of 1 experiment using two different donors.
[&] n = 3.
[*] Compound **21** was derived from alkylation of **3** with the toslyate of *N*-Boc-protected (*R*)-indoline-2-methanol.

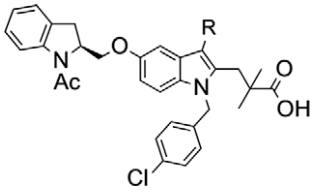


Scheme 3. Reagents and conditions: (a) Boc_2O, CH_2Cl_2; (b) TsCl, Et_3N, CH_2Cl_2; (c) **3**, Cs_2CO_3, MeCN, 60 °C; (d) 4 N HCl, dioxane; (e) Ac_2O, diisopropylethylamine, CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) $AlCl_3$ (4 equiv), H_2O (3 equiv), DCM, 0 °C to rt; (b) R^1COCl, $AlCl_3$, DCE, 80 °C; (c) $NaBH_4$, TFA, DCM (1:1), 0 °C to rt; d) $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (1:1:1), 60 °C.

Table 4
SAR at the 3-position of the indole: in vitro IC_{50} data for compounds **22**–**30**[a]



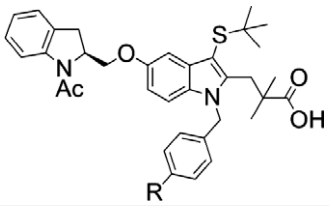
No.	R	FLAP binding (nM)	hLA (nM)	hWB (nM)
22	H	218	12.9	31,518
23		20.6	20.6	4901
24		>10,000	263	63,105
25		19	1.3	521
26		35	0.5	200
27		15.2	1.5	428
28		4.7	4.2	405
29	S(O)*t*-Bu	74	335	23,154
30	SO_2t-Bu	4.5	19	1744[&]

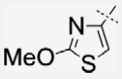
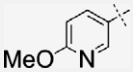
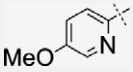
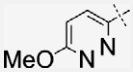
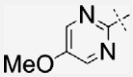
[a] FLAP binding and hLA data are the average of $n \geqslant 3$. Unless otherwise noted hWB data is the average of one experiment using two different donors.
[&] $n = 2$.

in the sulfone **30** albeit with a greater degree of shift in the presence of human blood proteins compared to the parent thiane **20** (120-fold hWB vs FLAP binding for **30** compared to 387-fold vs FLAP binding for **20**).

During our studies in another structurally similar series of FLAP inhibitors,[13] replacement of the chloro substituent on the phenyl ring greatly reduced their CYP inhibition activity. We therefore prepared derivatives of the indoline **20** by replacing the 4-chlorobenzyl unit with a similar series of heteroaromatic biaryls (Table 5). This was accomplished in several ways (Scheme 5). All but

Table 5
In vitro $IC_{50's}$ of biaryl indoline derivatives **34**–**39** (AM679)[a]



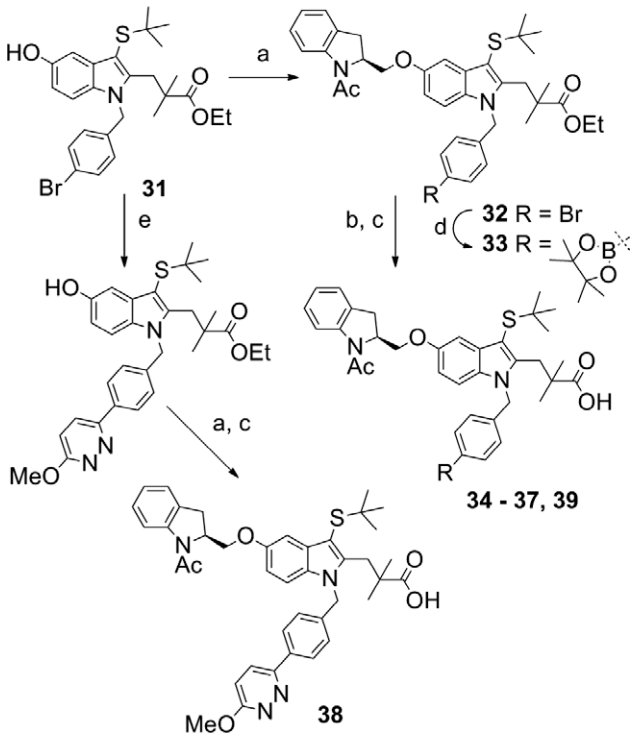
No.	R	FLAP binding (nM)	hLA (nM)	hWB (nM)
34		1.7	0.5	235
35		2.5	0.6	573
36		9.3	1.8	276[*]
37		3.8	0.5	373
38		3.2	12.6	1109[&]
39		2.2	0.6	154[%]

[a] FLAP binding and hLA data is the average of $n \geqslant 3$. Unless otherwise noted hWB data is the average of one experiment using two different donors.
[&] $n = 2$.
[*] $n = 3$.
[%] $n = 4$.

one of these compounds **35**, were prepared from the common intermediate shown. Alkylation of the bromo-phenol **31** with the indoline-tosylate vide infra, deprotection and acylation afforded the benzylbromide **32**. This could then be reacted with the required heteroaryl boronic acid or boronate ester under standard Suzuki reaction conditions ($Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 80 °C) to afford the desired compounds after subsequent hydrolysis of the ethyl ester. Alternatively, **32** was converted to the pinacolato-boron derivative **33** and reacted through Suzuki coupling with the appropriate halogenated heteroaryl compound followed by ester hydrolysis. In the case of compound **39**, 2-chloro-5-fluoropyrimidine was used as the Suzuki reaction coupling partner and prolonged ester hydrolysis in the presence of methanol lead to the displacement of the arylfluoride to yield the methoxypyrimidine **39**. Compound **38** was prepared through Suzuki reaction of the bromo-phenol **31** first, then alkylation of the resulting phenol as previously described.

All of the biaryl compounds **34** to **39** showed excellent in vitro inhibition against FLAP. Of particular note was compound **39** with an excellent hWB IC_{50} potency of 154 nM. This compound also showed an improved CYP inhibition profile (IC_{50} 3A4 = 16.7 μM, 2C9 = 3.7 μM, 2D6 >30 μM), no time dependent inhibition against CYP3A4 (0.003 min^{-1} vs 0.057 min^{-1} for troleandomycin control @ 10 μM) and no CYP3A4 induction.[†] The pharmacokinetic properties of **39** had also significantly improved over the chlorobenzyl

[†] Time-dependent inhibition (TDI) measures a compounds ability to irreversibly bind to the CYP enzyme and hence reduce its metabolic activity and the induction assay measures a compounds ability to induce the activity of the CYP enzyme.



Scheme 5. Reagents and conditions: (a) (i) ethyl (*S*)-2-(toluene-4-sulfonyloxymethyl)-2,3-dihydro-indole-1-carboxylate, Cs_2CO_3, MeCN or DMF, heat; (ii) 4 N HCl in dioxane, CH_2Cl_2; (iii) Ac_2O, diisopropylethylamine, DCM; (b) K_2CO_3, DME, H_2O, $Pd(PPh_3)_4$ (cat.), 85 °C, heteroarylboronate (from **32**) or halogeno-heteroaryl (from **33**); c) LiOH·H_2O, THF/MeOH/H_2O (1:1:1), 60 °C; (d) bis(pinacolato)diboron, $Pd(dppf)Cl_2·CH_2Cl_2$ (cat.), KOAc, *p*-dioxane, 85 °C; (e) 3-bromo-6-methoxypyridazine, K_2CO_3, DME, H_2O, $Pd(PPh_3)_4$ (cat.), 85 °C.

derivative **20**, showing reasonable bioavailability, low clearance and improved AUC (10 mg/kg sodium carboxylate salt in rat po $F = 29\%$, Cl = 11 mL/min/kg, $C_{max} = 1.6$ μM, AUC = 4.6 h μg/mL, $T_{½} = 6.8$ h). Compound **39** (AM679) was profiled in a rodent bronchoalveolar lavage (BAL) model to measure its ability to inhibit production of leukotrienes in vivo.[16] Oral administration of **39** (10 mg/kg as the sodium carboxylate salt) 4 h prior to ionophore challenge reduced LTB_4 and CysLT levels in the rodent lung lavage fluid by 98% and 87%, respectively, with corresponding average rodent plasma levels of 605 nM (3 h post dose, rat blood LTB_4 $IC_{50} = 125$ nM). Dose response studies showed an ED_{50} of 0.8 and 1.4 mg/kg in rat for LTB_4 and CysLT, respectively. When dosed at 3 mg/kg po 16 h prior to ionophore challenge, significant inhibition of leukotrienes was still evident (77% and 45% inhibition of LTB_4 and CysLT, respectively) indicating a sustained pharmacodynamic effect as average plasma levels at this time point were measured at 4 nM.

Incubation of **39** in the hWB assay for an extended time period (5 h) indicated an increase in potency against LTB_4 production in human blood ($IC_{50} = 53$ nM [$n = 6$, where each n is the average of two donors]).[17] This time-dependent increase also occurs in rat blood as compound **39** shows an IC_{50} of 9 nM when assayed after incubation in rat blood for 4 h. This equilibrium potency in rat blood helps explain the aforementioned extended pharmacodynamic effect in the rat BAL model, where the measured 16 h plasma levels correlate well with the 4 h IC_{50}. Indoline **39** was further profiled in a murine ocular model of respiratory syncytial virus (RSV) due to its excellent in vitro parameters and solubility profile (~10 mg/mL as the sodium salt in water or 0.03 mg/mL in 0.9% saline, a vehicle suitable for the RSV study) the successful results of which have recently published.[18]

In conclusion, we have discovered a series of potent FLAP inhibitors, the best of which possesses a novel N-acylated-(*S*)-indoline group that shows excellent potency at inhibiting LTB_4 in human blood (**39,** AM679, 5 h $IC_{50} = 53$ nM), reduced CYP inhibitory activity compared to **1** and shows excellent leukotriene inhibition in several in vivo models. Further investigation of the use of **39** in disease states where leukotrienes are implicated is ongoing.

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