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Synthesis of novel tetrahydroisoquinoline bronchodilators

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Dedicated to the memory of Salo Gronowitz

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ABSTRACT

The synthesis and bronchorelaxing effects of a series of novel tetrahydroisoquinoline amides are described. The compounds were evaluated for their ability to relax LTD4 contracted isolated human small airways ex-vivo. Several compounds demonstrated highly efficacious bronchorelaxing properties. Cinnamide 71 was selected for further studies and constitutes a promising candidate as a novel bronchorelaxing agent for the treatment of pulmonary disorders.

Bronchodilators, alone or in combination with anti-inflammatory agents, are the mainstay of asthma and COPD therapies. Currently used bronchodilators, β_2-agonists and anti-cholinergics, rely on two pharmacological principles; stimulation of adrenergic receptors and blockade of muscarinic receptors to acetylcholine activation, respectively. In the treatment of severe (refractory) asthma and COPD there is an increased awareness of the role that the small (peripheral or distal) airways play in these diseases.[1] Improvements in pulmonary function and health status have been closely linked to the relaxation of the small airways.[2] However, current treatments have not been optimized to target the small airways.[3] Improving the bronchodilatory response in the small, peripheral airways can be achieved through optimizing delivery or addressing new targets/pathways. The use of ultrafine formulations of β_2-agonist/steroid treatments in limited trials suggest that this might lead to improved outcomes.[4] Conversely, we[5] and others[6] have demonstrated that β_2-agonists have a reduced efficacy in relaxing contracted small airways compared to larger airways suggesting the need of finding novel mechanisms and optimizing compounds that can lead to the efficacious relaxation of the small airways. New principles of smooth muscle relaxation should therefore be viewed as a possible strategy for finding improved asthma and COPD therapies.[7] In this context it is important to realize that there are differences between large and small airways just as there are differences in pulmonary physiology and pharmacology between species. Finding novel compounds that can relax human small airways should thus focus on studying human small airways to the largest extent.

We recently described capsazepine (**1**) and related capsazepinoid compounds (e.g., **2**) as constituting a novel class of bronchodilators (Fig. 1).[5,8] We now wish to describe the further development of this class of compounds and the improvement of their drug-like properties.

Wanting to avoid the thiourea moiety present in most of the previous compounds,[8] we followed up on the fact that the previously described amide **3** was roughly equipotent to thiourea **2**.[8d] We also focused on the improvement of physical–chemical properties to allow a lung selective action following inhaled administration.

A series of (hetero)aromatic amide derivatives were therefore prepared to evaluate for their bronchorelaxing properties ex-vivo using isolated human small airways.

Previous work had established the crucial role of the 4,7-dichloro-5,6-dihydroxy tetrahydroisoquinoline core structure for obtaining good bronchorelaxing properties so this was retained throughout this study.[8c] The desired butanoyl amides were prepared by coupling the tetrahydroisoquinoline scaffold with the corresponding acids.

The necessary carboxylic acids, depicted in Scheme 1, were synthesized via Negishi couplings between the corresponding aryl halides **4–11** and 4-ethoxy-4-oxobutylzinc bromide using PEPPSI-IPr as catalyst.[9] Attempts using $Pd(PPh_3)_4$ gave lower yields.[10] Hydrolysis of the resulting esters **12–19** gave the desired acids **20–27**.

3,5-Disubstituted 2-pyridyl butanoic acids, **33–36**, shown in Scheme 2 were synthesized from 2,3-dichloro-5-(trifluoromethyl)-pyridine. A regioselective Negishi coupling yielded the desired isomer (**29**) as the major product. Suzuki couplings of **29** with

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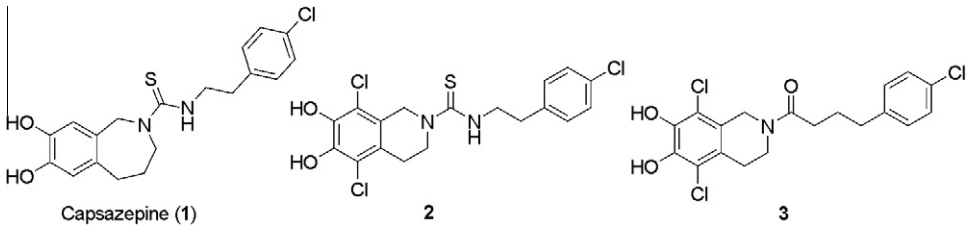
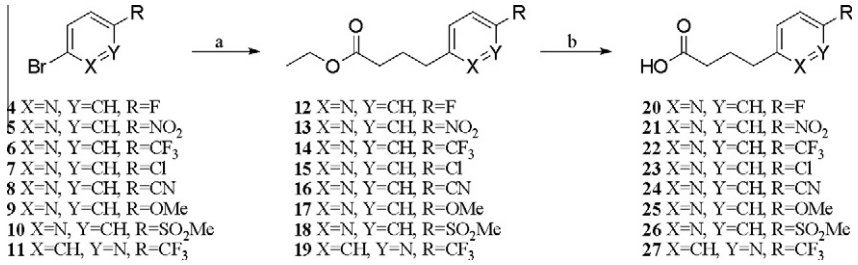
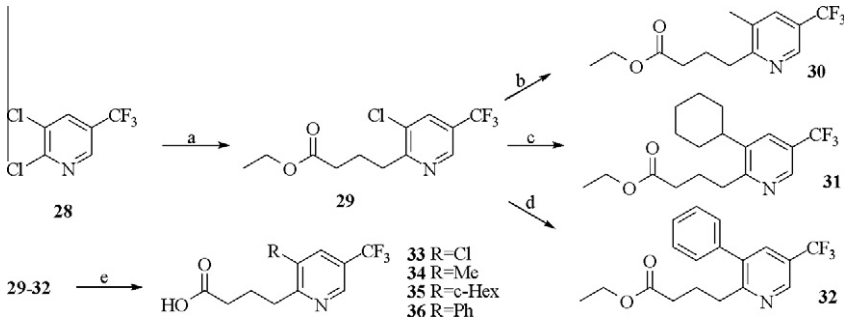


Figure 1.



Scheme 1. Reagents and conditions: (a) For **4**–**9** and **11**; 4-ethoxy-4-oxobutylzinc bromide, PEPPSI-Ipr, THF, rt, 48 h, yields >80%. For **10**; 4-ethoxy-4-oxobutylzinc bromide, $Pd(Ph_3P)_4$, THF, rt, 48 h; (b) NaOH (1 N aq), EtOH/THF (1:1).



Scheme 2. Reagents and conditions: (a) 4-ethoxy-4-oxobutylzinc bromide, PEPPSI-Ipr, THF, rt, 56%; (b) trimethyl boroxine, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene(1,4-naphthoquinone)palladium(0) dimer, CsF, 1,2-dimethoxyethane, microwave, 100 °C, 45 min, 64%; (c) cyclohexylzinc bromide, PEPPSI-Ipr, THF, rt, 40 h, 27%; (d) phenyl boronic acid, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene(1,4-naphthoquinone)palladium(0) dimer, CsF, 1,2-dimethoxyethane, microwave, 100 °C, 45 min, 80%; (e) NaOH (1 N aq), EtOH/THF (1:1).

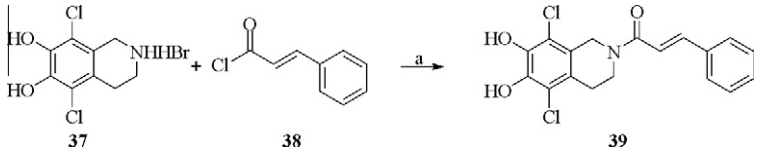
trimethylboroxine[11] and phenylboronic acid yielded esters **30** and **32** respectively, while a Negishi coupling with cyclohexylzinc bromide yielded **31**. Finally, the esters were hydrolyzed to the corresponding carboxylic acids.

In attempt to vary the length and flexibility of the linker, cinnamide **39** was prepared by coupling of **37**[8c] and cinnamoyl chloride (Scheme 3). The cinnamide **39** displayed bronchorelaxing properties similar to butanamide **3** (vide infra) so a series of cinnamides were also prepared.

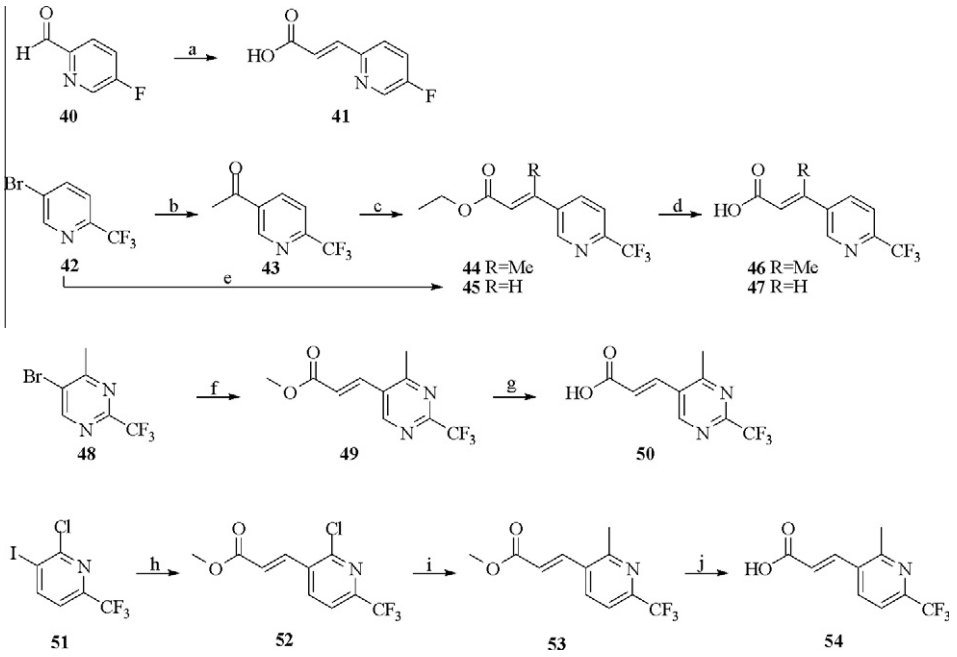
The synthesis of cinnamic acid derivatives is outlined in Scheme 4. Knoevenagel condensation using aldehyde **40** and malonic acid yielded acid **41**.[12] A halogen lithium exchange of compound **42** followed by acylation using *N*,*N*-dimethylacetamide gave acetylpyridine **43**. Subsequent Horner–Wadsworth–Emmons reaction between **43** and triethylphosphonoacetate[13] yielded compound **44** which was hydrolyzed to acid **46**. Carboxylic acids **47** and **50** were synthesized from 5-bromo-2-(trifluoromethyl)pyridine (**42**) and 5-bromo-4-methyl-2-(trifluoromethyl)pyrimidine (**48**) via Heck reactions[11,14] followed by hydrolysis. Finally, trisubstituted pyridine carboxylic acid **54** was synthesized from 2-chloro-3-iodo-6-(trifluoromethyl)pyridine (**51**) by a Heck reaction to introduce the acryl moiety followed by a Suzuki coupling with trimethylboroxine to introduce the methyl group in the 2-position.[15]

The target amides were prepared using one of the procedures shown in Scheme 5. Compounds **68** and **69** were prepared from commercially available (*E*)-3-(pyridin-3-yl)acrylic acid and 4-methoxycinnamic acid, respectively.

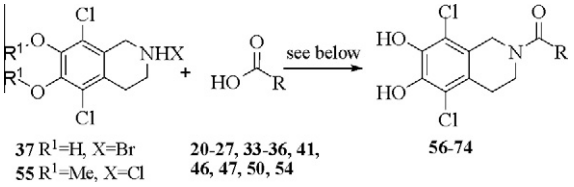
It was previously established that dichlorination of the dihydroxy tetrahydroisoquinoline moiety greatly increased the bronchorelaxing potency within the capsazepinoid series.[8c] To further



Scheme 3. Reagents and conditions: (a) Et_3N, DMF, rt, 16 h, 40%.



Scheme 4. Reagents and conditions: (a) Malonic acid, pyridine, piperidine, 115 °C, 2 h, 45%; (b) *sec*-BuLi, *N*,*N*-dimethylaminoacetamide, Et_2O, −78 °C, 1 h, then rt 16 h, 54%; (c) Triethyl phosphonoacetate, NaH, THF, 0 °C, 30 min, reflux, 125 °C, 6 h, 100%; (d) NaOH (1 N aq), EtOH–THF (1:1), 75%; (e) ethyl acrylate, $Pd(OAc)_2$, DABCO, K_2CO_3, 125 °C, 12 h, 97%; (f) methyl acrylate, $P(OCH_3)_3$, $Pd(OAc)_2$, Et_3N, DMF, 110 °C, 1.5 h, 72%. (g) NaOH (1 N aq), MeOH, 65%; (h) methyl acrylate, $Pd(OAc)_2$, DABCO, K_2CO_3, DMF, 120 °C, 4 h, 67%; (i) trimethyl boroxine, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 110 °C, 24 h, 82%; (j) NaOH (1 N aq), MeOH, 40 °C, 2 h, 100%.



Scheme 5. Reagents and conditions: Procedure A: (i) **55**, EDC·HCl, HOBt, DMAP, Cs_2CO_3, DMF, rt, 48 h; (ii) BBr_3, CH_2Cl_2, 0 °C, 1 h, rt, 18 h; (iii) MeOH, $NaHCO_3$, rt, 30 min. Procedure B: **37**, EDC·HCl, HOBt, DMAP, Cs_2CO_3, DMF, rt, 48 h. Procedure C: (i) CDI, EtOAC, reflux, 1 h. (ii) **37**, HOBt, reflux, 3 h.

investigate this phenomenon the dimethyl-, difluoro- and bis-fused benzotetrahydrofuran analogues were prepared to see if lipophilic, electronic or other factors were responsible for the increase in potency.

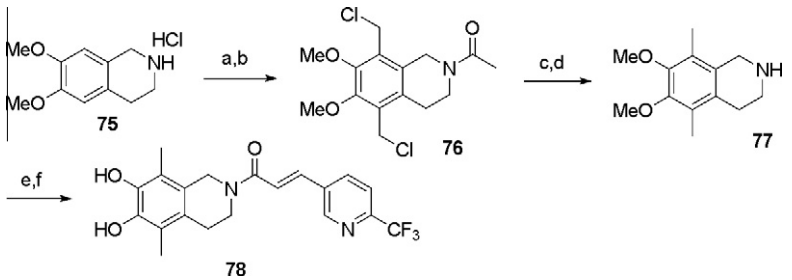
The dimethylated tetrahydroisoquinoline analogue **78** was prepared by a halomethylation procedure (Scheme 6). Thus, commercially available **75** was acetylated and treated with 2-methoxyacetylchloride to obtain bis-benzyl chloride **76**.[16] Reductive substitution with sodium cyanoborohydride followed by alkaline hydrolysis afforded the desired amine **77**.

This amine was then coupled with **47** to obtain the dimethylated analogue **78**.

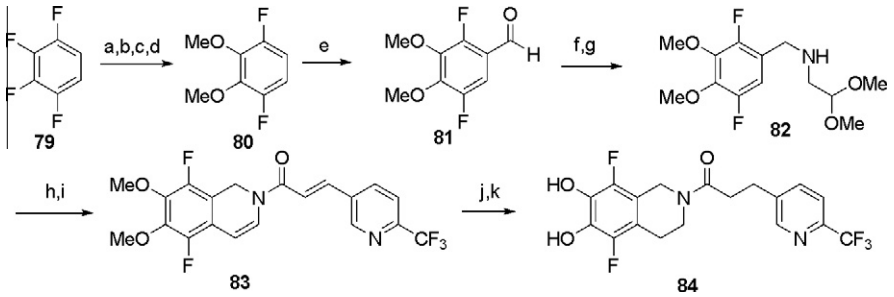
Difluorinated catechols are relatively scarce and derivative **84** proved to be a more challenging target (Scheme 7). Difluorodimethoxybenzene **80** was obtained from tetrafluorobenzene **79**.[17] Formylation was then performed with dichloromethyl methyl ether.[18] Reductive amination of **81** gave **82**. This amine was coupled with acid **47** and then cyclized under acidic conditions to give dihydroisoquinoline **83**.[19] Palladium-catalyzed transfer-hydrogenation, unfortunately which also led to reduction of the cinnamide moiety, followed by demethylation afforded compound **84**.

The bis-fused dihydrofuran analogue **89** was prepared using a bis-lithiation/Parham cyclization strategy (Scheme 8).[20] 6,7-Dihydroxy-tetrahydroisoquinoline **85** was brominated and protected using Boc-anhydride. Di-alkylation and chlorination yielded cyclization precursor **87**. Rapid addition of *n*-BuLi at 0 °C gave the doubly fused tetrahydrobenzodifuran **88**. Deprotection and coupling afforded the desired compound **89**.

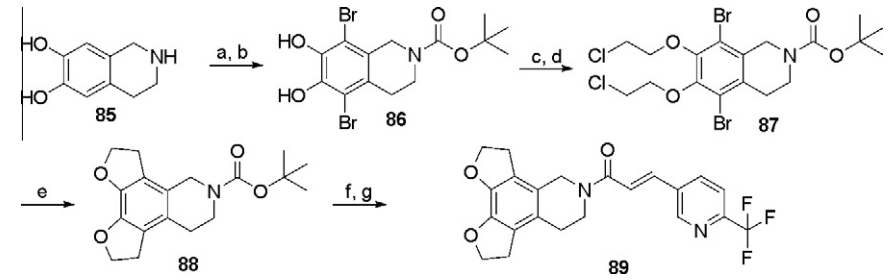
All compounds were tested for their bronchorelaxing properties on isolated human small airways (inner diameter <2.0 mm) using a procedure and apparatus previously described.[5,8] The measure of bronchorelaxing efficacy is given as percentage remaining contraction (%RC) which is defined as the quote of the remaining contrac-



Scheme 6. Reagents and conditions: (a) AcCl, Et_3N, CH_2Cl_2, rt, 0.5 h; (b) 2-methoxyacetylchloride, $SnCl_4$, CH_3NO_2, rt, 24 h, 14% (over 2 steps); (c) $NaCNBH_3$, DMF, 100 °C, 16 h; (d) NaOH, H_2O, dioxane, reflux, 21 h, 42% (over 2 steps); (e) **47**, PyBrOP, DMAP, THF, rt, 2.5 h, 87%; (f) BBr_3, CH_2Cl_2, 0 °C then rt, 3.5 h, reflux 1.5 h, 93%.



Scheme 7. Reagents and conditions: (a) NaOH, ethyleneglycol, 180 °C, 24 h, 58%; (b) Cs_2CO_3, DMF, 160 °C, 17 h, 45%; (c) $AlCl_3$, toluene, 110 °C, 4 h, quant; (d) Me_2SO_4, K_2CO_3, acetone, reflux, 3 h, 47%; (e) $MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 °C, 30 min, rt, 2 h; (f) 2,2-dimethoxyethanamine, benzene, reflux, 16 h, 72% (over 2 steps); (g) $NaBH_4$, MeOH, 0 °C, 0.5 h, 81%; (h) **47**, EDC·HCl, HOBt, DMF, rt, 2 h, 73%; (i) $AlCl_3$, 1,2-dichloroethane, rt, 10 min, 33%; (j) Pd/C, HCO_2NH_4, MeOH, rt, 3 h, 17%; (k) BBr_3, CH_2Cl_2, 0 °C, 1 h, 49%.



Scheme 8. Reagents conditions: (a) Br_2, AcOH, rt, 16 h, 80%; (b) $(Boc)_2O$, Et_3N THF/H_2O (6:1), rt, 2 h, 92%; (c) 2-chloroethanol, NaOH, EtOH/H_2O, reflux, 4 h, 6%; (d) PPh_3, CCl_4, reflux, 3 h, 41%; (e) *n*-BuLi, THF, 0 °C, 15 min, 47%; (f) TFA, $CHCl_3$, rt, 1 h, 77%; (g) **47**, EDC·HCl, HOBt, DMF, rt, 16 h, 32%.

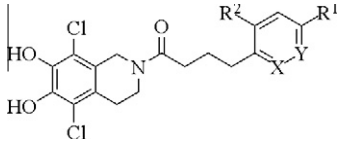
tion in the presence of the test item at a given concentration (usually 10 μM) and the maximum contraction evoked by the contractile agent (LTD_4) in the absence of test item.

In the butanoyl amide series changing a phenyl for a pyridyl, preferably a 2-pyridyl, did not affect the potency (cf. **3** and **59**, Table 1). However, changing the phenyl for a heteroaromatic ring had a pronounced effect on the in vitro metabolism. The in vitro disappearances and metabolic profiles of **3** and **56** were determined using human liver homogenate incubations. Compound **56** showed a rapid disappearance as determined by LC/UV and gave a single major metabolite (99%) compared to **3** which gave rise to multiple metabolites. This major metabolite was identified as a glucuronide.

Small lipophilic *ortho* substituent combined with a trifluoromethyl group in the *para* position improved the potency as witnessed by compounds **64** and **65** (–Cl and Me, respectively). Larger *ortho* substituents (e.g., **66** and **67**) decreased or did not improve potency. Larger, polar groups in the *para* position were not tolerated as witnessed by the loss of potency of the sulfone analogue **62**.

The SAR of the cinnamides followed the same trend with a *para* trifluoromethyl group improving potency (cf. **68** and **72**, Table 2). 3-Pyridyls were the preferred heteroaromatics, being slightly more potent than the corresponding pyrimidine (cf. **73** and **74**). *ortho* Substitution with a small lipophilic group (**74**) did not significantly

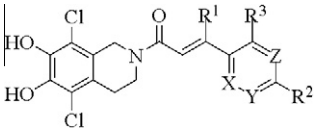
Table 1
Butanoyl amides



Compound	R^1	R^2	X	Y	Coupling procedure	% RC[a] 10 μM	% RC[a] 1 μM
3	Cl	H	CH	CH	Ref[8d]	16	80
56	F	H	N	CH	**A**	25	89
57	NO_2	H	N	CH	**A**	33	74
58	CF_3	H	N	CH	**A**	19	72
59	Cl	H	N	CH	**A**	15	85
60	CN	H	N	CH	**A**	34	86
61	OMe	H	N	CH	**A**	31	96
62	SO_2Me	H	N	CH	**A**	72	99
63	CF_3	H	CH	N	**B**	26	93
64	CF_3	Cl	N	CH	**A**	5	61
65	CF_3	Me	N	CH	**B**	7	67
66	CF_3	cHex	N	CH	**B**	77	nd[b]
67	CF_3	Ph	N	CH	**B**	38	90

[a] Percentage remaining contraction at the indicated concentration in the presence of test compound and LTD_4 compared to the maximum contraction caused by LTD_4.
[b] Not determined.

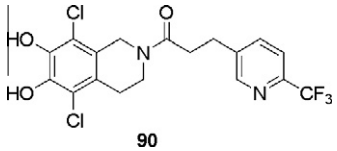
Table 2
Cinnamides



Compound	R^1	R^2	R^3	X	Y	Z	Coupling procedure	% RC [a] (10 μM)	% RC [a] (1 μM)
39	H	H	H	CH	CH	CH	Scheme 3	41	83
68	H	H	H	CH	N	CH	**A**	44	100
69	H	OH	H	CH	CH	CH	**A**	32	nd[b]
70	H	F	H	N	CH	CH	**A**	24	nd[b]
71	Me	CF_3	H	CH	N	CH	**A**	7	74
72	H	CF_3	H	CH	N	CH	**C**	6	87
73	H	CF_3	Me	CH	N	N	**C**	18	88
74	H	CF_3	Me	CH	CH	N	**B**	9	71

[a] Percentage remaining contraction at the indicated concentration in the presence of test compound and LTD_4 compared to the maximum contraction caused by LTD_4 alone.
[b] Not determined.

Table 3



90

Compound	% RC[a] 10 μM
90[b]	29
84	85
78	75
89	91

[a] Percentage remaining contraction at the indicated concentration in the presence of test compound and LTD_4 compared to the maximum contraction caused by LTD_4.

[b] Prepared by catalytic transfer hydrogenation of **72**.

improve the potency as seen in the butanoyl amide series. However, substitution of the cinnamide moiety was allowed (**71**).

Finally the role of dichlorination was evaluated. As can be seen in Table 3 only the di-chlorinated analogue **90** displayed retained potency. Neither di-fluorination nor di-methylation provided active compounds (**84** and **78**, respectively). Although chlorine has an inductive effect, intramolecular hydrogen bonding plays a dominant role in lowering the p*K*a of chlorophenols.[21] We suggest that the role of the chlorine atoms is to provide intramolecular hydrogen bonding to the hydroxyl groups, lowering the p*K*a of both hydroxyl groups and providing a partial dianion character. This is partially verified by the difluorinated analogue as it has been experimentally demonstrated that fluorine provides a much smaller hydrogen bond in *ortho*-halogenated phenols.[22] If the hydrogen bonding only improved the bidentate binding capability of the catechol it was believed that the bis-dihydrofuran derivative **89** would show activity, which was not the case.

Compound **71**[23] was further evaluated and characterized as a potential drug candidate. The EC_{50} was determined to 2.27 μM and the maximum functional efficacy to 98% in the ex-vivo assay. Further pharmacological studies using isolated human small airways revealed that 10 μM **71** gave 93%, 97% and 82% relaxation of acetylcholine, histamine and a combination, "cocktail", of LTD_4, acetylcholine and histamine induced contractions, respectively. This demonstrates that **71** act as a fully functional antagonist against contractile agents.

Compound **71** has moderate aqueous solubility (18 μM) with a measured log $D_{7.4}$ of 3.5. The compound is stable in plasma but rapidly metabolized through phase II mechanisms in human hepatocytes in the presence of co-factors (in vitro). Half-life in vivo was estimated to 0.02 h. Metabolites arising from glucuronidation and sulfatation were identified as the main metabolites and **71** showed very similar in vitro metabolic profiles in both rat and dog.

In vivo pharmacokinetic studies in rats following intratracheal administration showed that **71** was detectable in the lung up to 24 h post dosing but not in plasma after 2 h. At all time points higher levels of **71** were measured in the lung compared to plasma suggesting that **71** has a suitable profile for selective pulmonary delivery with low systemic exposure.

Interestingly, **71** also displayed relevant anti-inflammatory properties. LTB_4 and MCP-1 production in LPS stimulated human peripheral mononuclear blood cells was significantly inhibited by **71** at 10 μM.

The combination of the demonstrated relaxing effects on contracted human small airways (ex-vivo), anti-inflammatory properties and lung selective pharmacokinetics makes **71** a very suitable candidate for further development towards the treatment of pulmonary diseases such as COPD and asthma.

References and notes

1. (a) Contoli, M.; Bousquet, J.; Fabbri, L. M.; Magnussen, H.; Rabe, K. F.; Siafakas, N. M.; Hamid, Q.; Kraft, M. *Allergy* **2010**, *65*, 141; (b) Sturton, G.; Persson, C.; Barnes, P. J. *Trends Pharmacol. Sci.* **2008**, *29*, 340.
2. (a) Takeda, T.; Oga, T.; Niimi, A.; Matsumoto, H.; Ito, I.; Yamaguchi, M.; Matsuoka, H.; Jinnai, M.; Otsuka, K.; Oguma, T.; Nakaji, H.; Chin, K.; Mishima, M. *Respiration* **2009**. doi:10.1159/000242113; (b) Hasegawa, M.; Makita, H.; Nasuhara, Y.; Odajima, N.; Nagai, K.; Ito, Y.; Betsuyaku, T.; Nishimura, M. *Thorax* **2009**, *64*, 332.
3. Janssen, L. J.; Killian, K. *Respir. Res.* **2006**, *7*, 123.
4. Huchon, G.; Magnussen, H.; Chuchalin, A.; Dymek, L.; Gonod, F. B.; Bousquet, J. *Respir. Med.* **2009**, *103*, 41.
5. Skogvall, S.; Dalence-Guzmán, M. F.; Berglund, M.; Svensson, K.; Mesic, A.; Jönsson, P.; Persson, C. G. A.; Sterner, O. *Pulm. Pharmacol. Ther.* **2008**, *21*, 125.
6. (a) Finney, M. J.; Karlsson, J. A.; Persson, C. G. *Br. J. Pharmacol.* **1985**, *85*, 29; (b) Wagner, E. M.; Bleecker, E. R.; Permutt, S.; Liu, M. C. *Am. J. Respir. Crit. Care Med.* **1998**, *157*, 447.
7. Baroffio, M.; Emanuele, C.; Brusasco, V. *Ther. Adv. Respir. Dis.* **2008**, *2*, 129.
8. (a) Skogvall, S.; Berglund, M.; Dalence-Guzmán, M. F.; Svensson, K.; Jönsson, P.; Persson, C. G. A.; Sterner, O. *Pulm. Pharmacol. Ther.* **2007**, *20*, 273; (b) Dalence-Guzmán, M. F.; Berglund, M.; Skogvall, S.; Sterner, O. *Bioorg. Med. Chem.* **2008**, *16*, 2499; (c) Berglund, M.; Dalence-Guzmán, M. F.; Skogvall, S.; Sterner, O. *Bioorg. Med. Chem.* **2008**, *16*, 2513; (d) Berglund, M.; Dalence-Guzmán, M. F.; Skogvall, S.; Sterner, O. *Bioorg. Med. Chem.* **2008**, *16*, 2529.
9. Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749.
10. Blommaert, A.; Turcaud, S.; Anne, C.; Roques, B. P. *Bioorg. Med. Chem.* **2004**, *12*, 3055.
11. Kwok, T. J.; Virgilio, J. A. *Org. Process. Res. Dev.* **2005**, *9*, 694.
12. Hynd, G.; Ray, N. C.; Finch, H.; Middlemiss, D.; Cramp, M. C.; Blaney, P. M.; Williams, K.; Griffon, Y.; Harrison, T. K.; Crackett, P. PCT Int. Appl. WO 2006136859 A2, 2006.
13. Srikrishna, A.; Satyanarayana, G.; Prasad, M. R. *Synth. Commun.* **2005**, *35*, 1687.
14. For compound **9** see Li, J.-H.; Wang, D.-P.; Xie, Y.-X. *Synthesis* **2005**, *13*, 2193.
15. Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. **2000**, *41*, 6237.
16. McKillop, A.; Madjdabadi, F. A.; Long, D. A. *Tetrahedron Lett.* **1983**, *24*, 1933.
17. Ladd, D. L.; Weinstock, J. *J. Org. Chem* **1981**, *46*, 203.
18. Adejare, A.; Gusovsky, F.; Padgett, W.; Creveling, C. R.; Daly, J. W.; Kirk, K. L. *J. Med. Chem.* **1988**, *31*, 1972.
19. Perchonock, C. D.; Lantos, I.; Finkelstein, J. A.; Holden, K. G. *J. Org. Chem.* **1980**, *45*, 1950.
20. (a) Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1996**, *39*, 2953; (b) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184.
21. Han, J.; Deming, R. L.; Tao, F.-M. *J. Phys. Chem. A* **2004**, *108*, 7736.
22. Bourassa-Bataille, H.; Sauvageau, P.; Sandorfy, C. *Can. J. Chem.* **1963**, *41*, 2240.
23. ^{1}H NMR (CD_3OD) rotameric mixture δ 8.92 (maj) (d, J = 2.0 Hz, 1H) 8.88 (min) (d, J = 1.6 Hz, 1H) 8.21 (maj) (dd, J = 2.0, 8.4 Hz, 1H) 8.17 (min) (dd, J = 2.0, 8.4 Hz, 1H) 7.84 (d, J = 8.4 Hz, 1H) 6.72 (maj) (br s, 1H) 6.70 (min) (br s, 1H) 4.72 (maj) (s, 2H) 4.66 (min) (s, 2H) 3.91 (min) (t, J = 6.0 Hz, 2H) 3.82 (maj) (t, J = 6.0 Hz, 2H) 2.87–2.82 (m, 2H) 2.29 (maj) (d, J = 1.2 Hz, 3H) 2.19 (min) (d, J = 1.0 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 164.2, 149.9, 146.3 (q), 141.9, 141.6, 136.9, 136.7, 136.6, 134.3, 123.6, 123.0, 122.9, 120.8, 119, 6, 117.7, 48.6, 42.6, 42.2, 27.4. HRMS (ESI) calc. for $C_{19}H_{16}Cl_2F_3N_2O_3$ [M+H] 447.0490, found 447.0374.