SUPPORTING INFORMATION

Discovery and optimization of thiazolidinyl- and pyrrolidinyl- derivatives as inhaled PDE4 inhibitors for respiratory diseases

Laura Carzaniga, Amari Gabriele, Andrea Rizzi, Carmelida Capaldi, Renato De Fanti, Eleonora Ghidini, Gino Villetti, Chiara Carnini, Nadia Moretto, Fabrizio Facchinetti, Paola Caruso, Gessica Marchini, Loredana Battipaglia, Riccardo Patacchini, Valentina Cenacchi, Roberta Volta, Francesco Amadei, Alice Pappani, Silvia Capacchi, Valentina Bagnacani, Maurizio Delcanale, Paola Puccini, Silvia Catinella, Maurizio Civelli and Elisabetta Armani**

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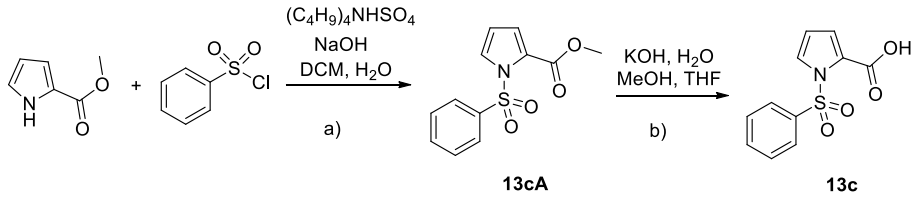
1. Preparation of not commercially available acids 13c, 13d

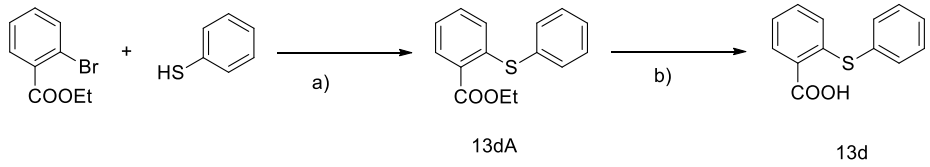
1.1: Synthesis of acid 13c



Step a): synthesis of methyl 1-(phenylsulfonyl)-1H-pyrrole-2-carboxylate (13cA). To a mixture of methyl 1H-pyrrole-2-carboxylate (1 g, 7.99 mmol), tetrabutylammonium hydrogen sulfate (0.271 g, 0.799 mmol) and NaOH (2.88 g, 71.9 mmol) in water (5 ml) and DCM (40 ml) under vigorous stirring, a solution of benzenesulfonyl chloride (1.794 ml, 13.99 mmol) in DCM (5 ml) was added drop-wise over 10 minutes at RT. The reaction was stirred at the RT for 3 h. The mixture was diluted with water (50 ml) and DCM (100 ml), the organics were separated, washed with brine (50 ml) and dried over sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel column (petroleum ether/acetone 8/2) to afford 1.448 g of **(13cA)** (yield 68%). MS/ESI$^+$ 287.9 $[MNa]^+$.

Step b): synthesis of 1-(phenylsulfonyl)-1H-pyrrole-2-carboxylic acid (13c). To a solution of methyl 1-(phenylsulfonyl)-1H-pyrrole-2-carboxylate **(13cA)** (500 mg, 1.885 mmol) in MeOH (7 ml) and THF (7 ml) cooled to 0°C, aqueous 1N KOH (2.827 ml, 2.83 mmol) was added drop-wise and the resulting mixture was stirred at RT for 24 h. The mixture was poured into ice-water and washed with DCM. The aqueous phase was acidified with 37% HCl (pH=2) and extracted with DCM. The organic layer was dried over sodium sulfate, filtered and evaporated to afford a mixture of compound **(13c).** This mixture was used as such in the next step. (MS/ESI$^+$ 252.0 $[MH]^+$) and methyl 1H-pyrrole-2-carboxylate (MS/ESI$^+$ 126.0 $[MH]^+$) (234 mg, ratio about 3/7).

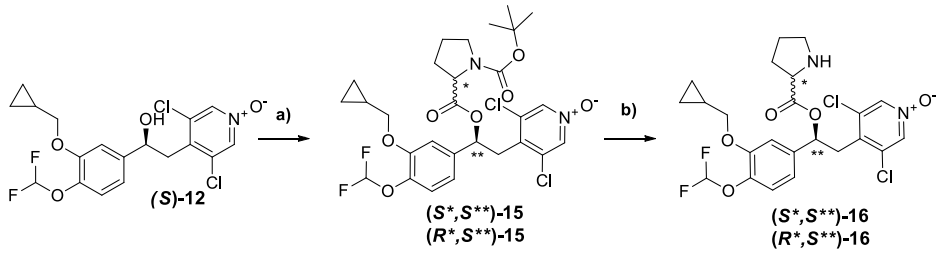
1.2: Synthesis of acid 13d



Step a): synthesis of ethyl 2-(phenylthio)benzoate (13dA). Ethyl 2-bromobenzoate (347 µL, 2.183 mmol), benzenethiol (224 µL, 2.183 mmol) were dissolved in dry DMF (4 ml) and Cu_2O (468 mg, 3.27 mmol) was added. The reaction mixture was heated at 150°C overnight and almost complete conversion was noticed. The solid was filtered off and the filtrate was treated with water (50 ml) and extracted with AcOEt (150 ml). The organic phase was washed several times with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a residue that was purified by flash chromatography on silica gel eluting with petroleum ether/DCM 95/5 to give ethyl 2-(phenylthio)benzoate **13dA** (550 mg, 2.129 mmol, 98% yield) as a colourless oil. MS/ESI$^+$ 259.34 $[MH]^+$

Step b): synthesis of 2-(phenylthio)benzoic acid (13d). Ethyl 2-(phenylthio)benzoate **13dA** (708 mg, 2.74 mmol) was dissolved in EtOH (40 ml) and 1 M aqueous NaOH (4.10 mL, 4.10 mmol) was added. The reaction mixture was stirred at RT over three days and complete conversion was noticed. The mixture was portioned between ethyl acetate and 1N HCl. The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to afford 2-(phenylthio)benzoic acid **13d** (620 mg, 2.69 mmol, 98% yield) as white solid that was used for the next steps without any further purification. MS/ESI$^+$ 231.04 $[MH]^+$

2. Preparation of Intermediates 15 and 16



Step a): Synthesis of 4-((*S*)-2-((*S*)-1-(tert-butoxycarbonyl)pyrrolidine-2-carbonyloxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-ethyl)-3,5-dichloropyridine 1-oxide (*S*,S*)-15.**

(*S*)-3,5-dichloro-4-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl) pyridine 1-oxide (*S*)-**12** (550 mg, 1.309 mmol), (*S*)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (282 mg, 1.309 mmol), EDC (251 mg, 1.309 mmol) and DMAP (160 mg, 1.309 mmol) were dissolved in DMF (5 mL). The reaction was stirred at rt for 48 h to achieve completion. After that time, the reaction was quenched with HCl 1M and extracted with EtOAc. The organic extract was washed with HCl 1M (x3) and with K_2CO_3 5% (x3) before being dried over Na_2SO_4 and concentrated under vacuum to yield 800 mg of desired product (1.29 mmol, 98% yield). *m/z* 617.16 $[MH]^+$

Synthesis of 4-((*S*)-2-(((*R*)-1-(tert-butoxycarbonyl)pyrrolidine-2-carbonyl)oxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*R*,S*)-15.**

Compound (*R**,*S***)-**15** was synthesized following the same procedure as for compound (*S**,*S***)-**15**: (*S*)-3,5-dichloro-4-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl) pyridine 1-oxide (*S*)-12 (300 mg, 0.714 mmol), (*R*)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (154 mg, mmol), EDC (137 mg, 0.714 mmol), DMAP (87 mg, 0.714 mmol), DMF (5 mL), rt for 48h, 300 mg of desired product (0.486 mmol, yield 68%). *m/z* 617.16 $[MH]^+$

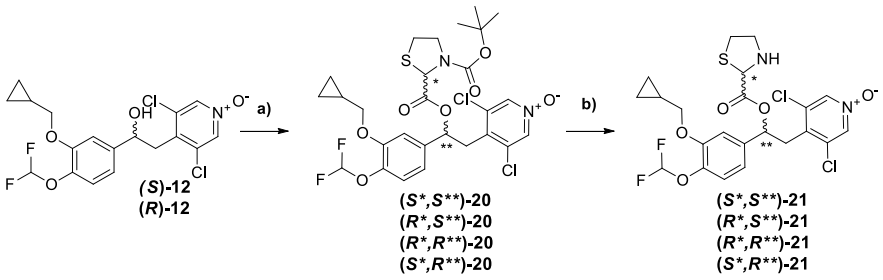
Synthesis of 3,5-dichloro-4-((*S*)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-((*S*)-pyrrolidine-2-carbonyloxy)ethyl)-pyridine 1-oxide (*S*,S*)-16.**

4-((*S*)-2-((*S*)-1-(tert-butoxycarbonyl)pyrrolidine-2-carbonyloxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S*,S***)-**15** (300 mg, 0.486 mmol) was dissolved in HCl/Dioxane (4M, 2 mL) and stirred at rt for 8 h. After that time, the solvent was removed under reduced pressure and dried in a vacuum oven overnight to yield (*S*,S***)-**16** as an hydrochloride salt (200 mg, 0.39 mmol, 80% yield). *m/z* 517.2 $[MH]^+$; t_R= 3.75 min (Method A). When (*S*,S***)-**16** was used as free base, (*S*,S***)-**16** hydrochloride underwent a basic work-up with aqueous $NaHCO_3$ 5% and ethyl acetate.

Synthesis of 3,5-dichloro-4-((*S*)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-(((*R*)-pyrrolidine-2-carbonyl)oxy)ethyl)pyridine 1-oxide, (*R*,S*)-16.**

(*R*,S***)-**15** (200mg, 0.324 mmol) was dissolved in HCl/Dioxane (4M, 5 mL) and stirred at rt for 8 h. After that time, the reaction was quenched with aq K_2CO_3 and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to yield (*R*,S***)-**16** (120 mg; 71.6 % yield). *m/z* 517.16 [MH] +

3. Preparation of Intermediates 20 and 21



Step a): Synthesis of 4-((*S*)-2-(((*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carbonyl)oxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S*,S*)-20**

(*S*)-3,5-dichloro-4-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl) pyridine 1-oxide (*S*)-**12** (40 g, 95 mmol), (*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carboxylic acid (33.3g, 143 mmol), EDC (73g, 381 mmol) and DMAP (13.9 g, 114 mmol) were dissolved in DMF (556 mL). The

reaction was stirred at rt for 2 h to achieve completion. After that time, the reaction was poured onto water (8 Liter), the solid filtered off and dissolved with DCM (1.2 Liter), washed with water before being dried over Na_2SO_4 and concentrated under vacuum to yield 60.5 mg of desired product (quantitative yield) . *m/z* 635.2 $[H]^+$. LC-MS t_R min 4.34/4.37; Diastereomeric Ratio= 5/95 (Method B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (s, 2 H), 7.18 (d, *J*=7.9 Hz, 1 H), 7.05 - 7.12 (m, 2 H), 6.96 (dd, *J*=8.4, 1.8 Hz, 1 H), 5.93 (m, 1 H), 5.06 - 5.23 (m, 1 H), 3.91 (d, *J*=7.1 Hz, 2 H), 3.68 (m, 2 H), 3.42 (dd, *J*=14.1, 9.7 Hz, 1 H), 3.25 (m, 1 H), 3.01 - 3.17 (m, 1 H), 2.97 (td, *J*=7.1, 4.0 Hz, 1 H), 1.05 - 1.45 (m, 10 H), 0.52 - 0.61 (m, 2 H), 0.25 - 0.41 (m, 2 H)

Compounds (*S*,R***)- **20,** (*R*,R***)- **20,** (*R*,S***)- **20** were synthesized following the same procedure starting from the corresponding alcohols (*S*)-**12** or (*R*)-**12.**

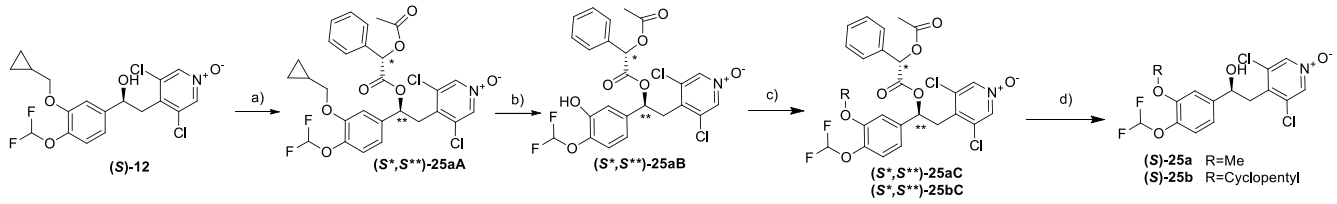
Step b: Synthesis of 3,5-dichloro-4-((*S*)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-(((*S*)-thiazolidine-2-carbonyl)oxy)ethyl)pyridine 1-oxide (*S*,S*)-21**

To a solution of 4-((*S*)-2-(((*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carbonyl)oxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S*,S***)- **20** (70 g, 110 mmol) in AcOEt (620 mL), HCl/AcOEt (5.72M, 400 mL) was added and the mixture stirred at rt for 20 min . After that time, the hydrochloride salt, which spontaneously precipitates from the reaction mixture, was filtered at room temperature to yield 52 grams of (*S*,S***)-**21** as an hydrochloride salt (yield 83%). *m/z* 535.2 $[MH]^+$. LC-MS t_R min 3.26; Diastereomeric Ratio= >99:1 (Method B). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 8.57 (s, 2 H), 7.19 (d, J=7.94 Hz, 1 H), 7.12 (d, J=1.76 Hz, 1 H), 7.08 (t, J=75.00 Hz, 1 H), 6.93 - 7.00 (m, 1 H), 5.89 - 5.98 (m, 1 H), 5.12 (s, 1 H), 3.91 (d, J=7.06 Hz, 2 H), 3.37 - 3.47 (m, 1 H), 3.10 - 3.31 (m, 3 H), 2.77 - 2.93 (m, 2 H), 1.05 - 1.36 (m, 1 H), 0.51 - 0.63 (m, 2 H), 0.34 (d, J=4.85 Hz, 2 H). Alternatively NaHCO3 5% is added to the reaction mixture till basic pH and the two phases separated. The organic phase was dired over Na_2SO_4, evaporated in vacuo to afford

(*S,*S***)-21** as a free base.

Compounds (*S**,*R***)-**21**, (*R**,*R***)-**21,** (*R**,*S***)-**21** were synthesized following the same procedure starting from the corresponding Boc-protected intermediates *(S*,R**)*-**20,** (*R**,*R***)-**20,** (*R**,*S***)-**20.**

4. Preparation of intermediates (*S*)-25a-b



Step a): synthesis of 4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(3-(cyclopropyl-methoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S,*S***)-25aA.**

A mixture of (*S*)-2-acetoxy-2-phenylacetic acid (0.924 g, 4.76 mmol), (*S*)-3,5-dichloro-4-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl)pyridine 1-oxide (*S*)-**12** (1.0 g, 2.380 mmol), EDC (0.684 g, 3.57 mmol) and DMAP (0.436 g, 3.57 mmol) in DCM (150 ml) was stirred at RT for 24 hrs. More (*S*)-2-acetoxy-2-phenylacetic acid (0.350 g, 1.802 mmol), EDC (0.456 g, 2.380 mmol) and DMAP (0.300g, 2.456 mmol) were added and the stirring was continued for 3 hrs to complete conversion. The reaction mixture was washed twice with aqueous 1N HCl and then with aqueous 1M K_2CO_3; the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was triturated with iPrOH (30 ml) and filtered to afford 1.27 g of (*S**,*S***)-**25aA** (89% yield). MS/ESI$^+$ 596.18 $[MH]^+$

Step b): synthesis of 4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S,*S***)-25aB**

4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S**,*S***)-**25aA** (1.27 g, 2.129 mmol) was

treated with trifluoroacetic acid (15 ml, 195 mmol) and the resulting solution was stirred at RT for 20 hrs. The reaction mixture was diluted with DCM and washed twice with water; the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography on silica gel (DCM/EtOAc = 3:2 to 1:1). The mixed fractions were combined and triturated with a mixture of iPr_2O/Et_2O (10:1). The collected solid was then combined to pure fractions from chromatography to afford 1.08 g of (*S**,*S***)-**25aB** (94% yield); MS/ESI$^+$ 542.11 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.56 (s, 2 H), 7.27 - 7.50 (m, 5 H), 6.98 (d, 1 H), 6.81 (d, 1 H), 7.00 (t, 1 H), 6.54 (dd, 1 H), 5.89 (dd, 1 H), 5.84 (s, 1 H), 3.40 (dd, 1 H), 3.18 (dd, 1 H), 2.13 (s, 3 H)

Step c): synthesis of 4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(4-(difluoromethoxy)-3-methoxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S*,S*)-25aC**

A suspension of 4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S**,*S***)-**25aB** (1.080 g, 1.991 mmol), methyl iodide (0.162 ml, 2.59 mmol) and potassium carbonate (0.550 g, 3.98 mmol) in CH_3CN (40 ml) was vigorously stirred at RT for 20 hrs. The reaction mixture was partitioned between DCM and water and the organic layer was dried over Na_2SO_4. The solvent was removed under vacuum to afford 0.984 g of (*S**,*S***)-**25aC** (89% yield) that was used without further purification. MS/ESI$^+$ 556.17 $[MH]^+$.

Synthesis of 4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S*,S*)-25bC**

(*S**,*S***)-**25bC** was prepared following an analogous procedure as for (*S**,*S***)-**25aC**, from 4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S**,*S***)-**25aB** (1.2 g, 2.2 mmol), bromocyclopentane (0.47 ml, 4.43 mmol), potassium carbonate (0.61 g, 4.43 mmol), CH_3CN (70 ml), RT, 18 hrs. The reaction mixture was partitioned between AcOEt and water and the organic layer was dried over Na_2SO_4. The solvent was removed under

vacuum to afford 1.3 g of (*S**,*S***)-**25bC** (97% yield). MS/ESI$^+$ 612.17 $[MH]^+$.

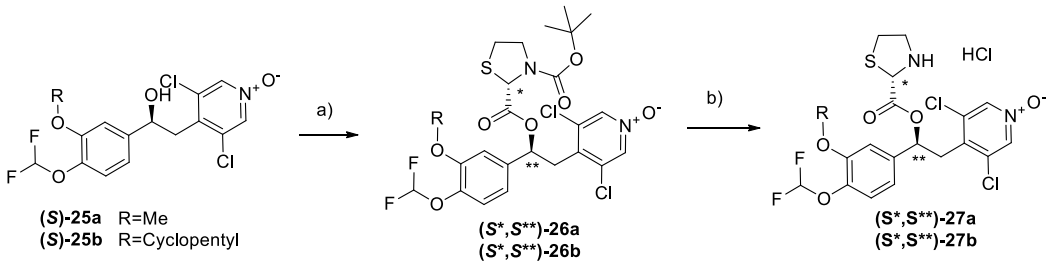
Step d): synthesis of (*S*)-3,5-dichloro-4-(2-(4-(difluoromethoxy)-3-methoxyphenyl)-2-hydroxyethyl)pyridine 1-oxide (*S*)-25a

4-((*S*)-2-((*S*)-2-acetoxy-2-phenylacetoxy)-2-(4-(difluoromethoxy)-3-methoxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S**,*S***)-**25aC** (984 mg, 1.769 mmol) was dissolved in a mixture of MeOH (50 ml) and DCM (10 ml). Aqueous sat. $NaHCO_3$ solution (10 ml, 11.00 mmol) was added and the resulting suspension was stirred at RT for 2 hrs. The reaction mixture was partitioned between water and DCM; the organic layer was dried over Na_2SO_4 and evaporated to dryness to afford the desired compound (650 mg, 1.71 mmol, 97% yield). MS/ESI$^+$ 380.17 $[MH]^+$.

Synthesis of (*S*)-3,5-dichloro-4-(2-(3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl)pyridine 1-oxide (*S*)-25b

(*S*)-**25b** was prepared following an analogous procedure as for (*S*)-**25a**, from (*S**,*S***)-**24bC**(1.31 g, 2.15 mmol), MeOH (70 ml) and aqueous sat. $NaHCO_3$ solution (20 ml, 22 mmol), RT, 2 hrs. 470 mg of (*S*)-**25b** (50% yield). MS/ESI$^+$ 434.26 $[MH]^+$.

5. **Preparation of Intermediates** (*S**,*S***)-**26a-b** and (*S**,*S***)-**27a-b**



Step a): synthesis of 4-((*S*)-2-((*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carbonyloxy)-2-(4-(difluoromethoxy)-3-methoxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S,*S***)-26a.**

A solution of (*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carboxylic acid (479 mg, 2.052 mmol), (*S*)-3,5-dichloro-4-(2-(4-(difluoromethoxy)-3-methoxyphenyl)-2-hydroxyethyl)pyridine 1-oxide (*S*)-**25a**(650

mg, 1.710 mmol), EDC (492 mg, 2.56 mmol) and DMAP (313 mg, 2.56 mmol) in DCM (60 mL) was stirred at rt for 3 h. The reaction mixture was diluted with DCM and washed twice with aqueous 1N HCl; the organic layer was dried over Na_2SO_4 and evaporated to dryness to afford 1.017 g of (*S**,*S***)-**26a** (quantitative yield). *m/z* 595.24 $[MH]^+$. The resulting compound was used without further characterization.

Synthesis of 4-((*S*)-2-(((*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carbonyl)oxy)-2-(3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S,*S***)-26b.**

(*S**,*S***)-**26b** was prepared following an analogous procedure as for (*S**,*S***)-**26a** from (*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carboxylic acid (278 mg, 1.19 mmol), (*S*)-3,5-dichloro-4-(2-(3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl)pyridine 1-oxide (*S*)-**25b** (345 mg, 0.79 mmol), EDC (457 mg, 2.38 mmol), DMAP (146 mg, 1.19 mmol), DCM (8 mL), rt, 3 h. 502 mg of **26b** (97%yield). *m/z* 649.5 $[MH]^+$. The resulting compound was used without further characterization.

Step b: synthesis of 3,5-dichloro-4-((*S*)-2-(4-(difluoromethoxy)-3-methoxyphenyl)-2-((*S*)-thiazolidine-2-carbonyloxy)ethyl)pyridine 1-oxide hydrochloride (*S,*S***)-27a.**

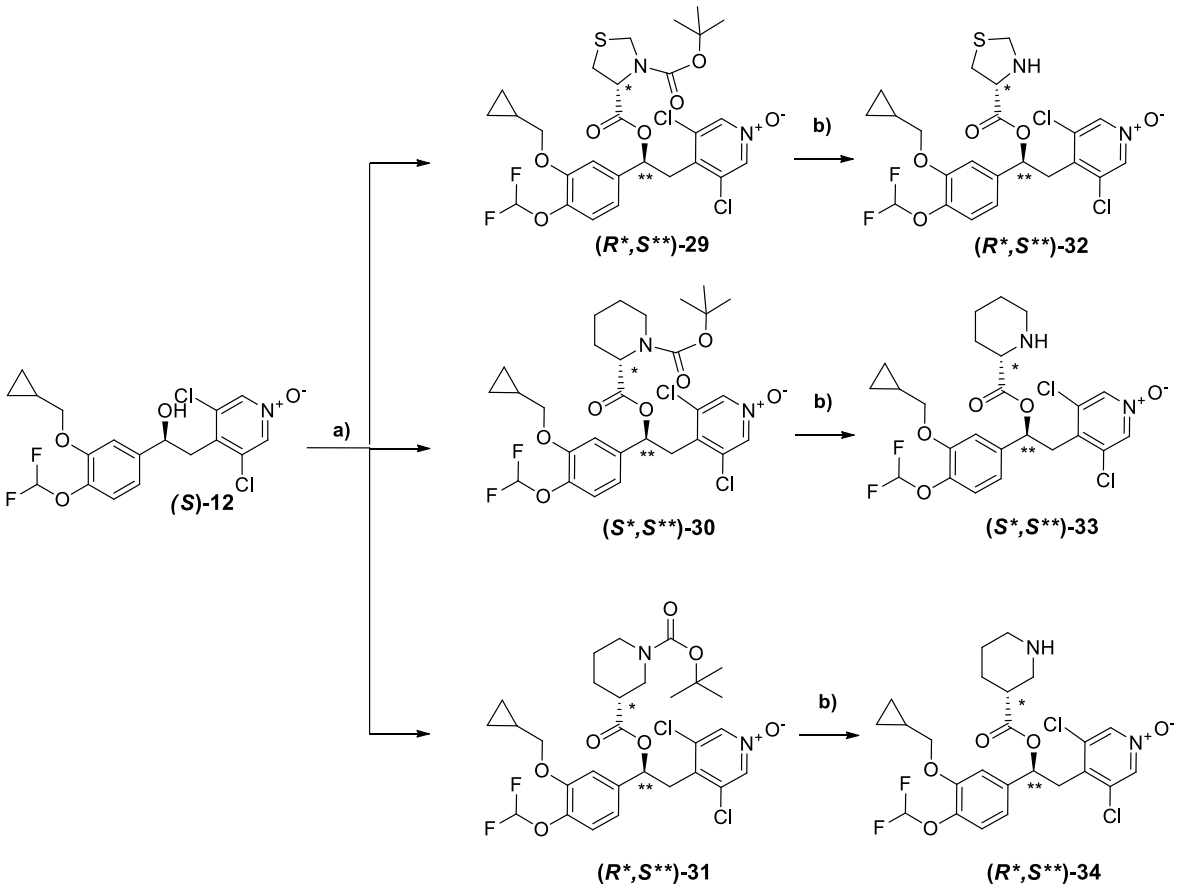
To a solution of 4-((*S*)-2-((*S*)-3-(tert-butoxycarbonyl)thiazolidine-2-carbonyloxy)-2-(4-(difluoromethoxy)-3-methoxyphenyl)ethyl)-3,5-dichloropyridine 1-oxide (*S**,*S***)-**26a**(1.017 g, 1.710 mmol) in EtOAc (10 mL) cooled at 0°C, HCl, 4M solution in EtOAc (10 mL, 40.0 mmol) was added and the resulting mixture was stirred at rt for 2 h. More HCl, 4M solution in EtOAc (10 mL, 40.0 mmol) was added and the solution was stirred at 0°C for additional 2 h to reach complete conversion. The solution was concentrated to 10 mL under reduced pressure, then iPr_2O (20 mL) was added and the product precipitated as a sticky gummy solid. The solid was allowed to settle down and the solvent was removed by aspiration. The residue was dried in vacuo at rt to afford 0.890 g of (*S**,*S***)-**27a** (1.674 mmol, 97% yield), which underwent next step without any additional purification. *m/z* 494.97 [MH].

The resulting compound was used without further characterization.

Synthesis of 3,5-dichloro-4-((*S*)-2-(3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl)-2-(((*S*)-thiazolidine-2-carbonyl)oxy)ethyl)pyridine 1-oxide hydrochloride (*S*,S*)-27b.**

(*S**,*S***)-**27b** was prepared following an analogous procedure as for (*S**,*S***)-**27a** from (*S**,*S***)-**26b** (502 mg, 0.77 mmol), EtOAc (6 mL), HCl 4.5M in AcOEt (6.088 mL, 27.4 mmol) rt, 3 h. 390 mg of (*S**,*S***)-**27b** (86% yield). *m/z* 549.5 $[MH]^+$.

6. Preparation of Intermediates 29, 30, 31, 32, 33 and 34.



Step a): synthesis of 4-((*S*)-2-(((*R*)-3-(tert-butoxycarbonyl)thiazolidine-4-carbonyl)oxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*R*,S*)-29**

(*S*)-3,5-dichloro-4-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-hydroxyethyl) pyridine 1-oxide (*S*)-**12** (550 mg, 1.309 mmol), (*R*)-3-(tert-butoxycarbonyl)thiazolidine-4-carboxylic acid (250 mg,

1.07 mmol), EDC (411 mg, 2.14 mmol) and DMAP (105 mg, 0.86 mmol) were dissolved in DMF (5 mL). The reaction was stirred at rt for 3 h to achieve completion. After that time, the reaction was quenched with HCl 1M and extracted with EtOAc. The organic extract was washed with HCl 1M (x3) and with K_2CO_3 5% (x3) before being dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by preparative HPLC (Method 1) to afford 320 mg of (*R*,S***)-**29** (70% yield); *m/z* 634.1 $[MH]^+$. The resulting compound was used without further characterization.

Compounds **30** and **31** were synthesized following the same protocol described for **29** starting from corresponding alcohol (*S*)-**12.**

Step b): synthesis of 3,5-dichloro-4-((*S*)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-(((*R*)-thiazolidine-4-carbonyl)oxy)ethyl)pyridine 1-oxide (*R*,S*)-32**

4-((*S*)-2-(((*R*)-3-(tert-butoxycarbonyl)thiazolidine-4-carbonyl)oxy)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)ethyl)-3,5-dichloropyridine 1-oxide (*R*,S***)-**29** (320 mg, 0.50 mmol) was dissolved in HCl/Dioxane 4M (5 mL) and stirred at rt for 2 h. After that time, $NaHCO_3$ sat. sol. was added till pH=8 and the acqueous phase extracted with AcOEt to yield 250 mg of (*R*,S***)-**32** as a free base (yield 93%). *m/z* 535.2 $[MH]^+$. LC-MS t_R min 3.19; Diastereomeric Ratio= 99:1(Method B). $[\alpha_D]$ = -45.77(c =0.48; $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.56 (s, 2 H), 7.18 (d, J=7.94 Hz, 1 H), 7.04 - 7.13 (m, 2 H), 6.97 (dd, J=8.16, 1.54 Hz, 1 H), 5.88 - 6.03 (m, 1 H), 3.97 - 4.15 (m, 3 H), 3.90 (d, J=7.06 Hz, 2 H), 3.43 (dd, J=14.11, 9.26 Hz, 1 H), 3.24 (dd, J=14.11, 4.85 Hz, 1 H), 3.08 (dd, J=10.14, 7.06 Hz, 1 H), 2.80 (dd, J=10.14, 5.73 Hz, 1 H), 1.14 - 1.28 (m, 1 H), 0.48 - 0.67 (m, 2 H), 0.26 - 0.46 (m, 2 H).

Compounds **33** and **34** were synthesized following the same protocol described for **32** starting from corresponding Boc-protected intermediates **30** and **31**.

7. Summary of Crystallographic Data of the *h*PDE4Bcat-UCR in complex with the inhibitor

(*S,*S***)-18e.**

Data Collection

X-ray source	I04-1, Diamond Light Source, Didcot (UK)
Wavelength (Å)	0.92
Detector	Pilatus 2M – Dectris Ltd.
Space group	$P2_12_12_1$
Unit cell parameters	
a (Å)	55.27
b (Å)	55.73
c (Å)	225.56
Resolution range (Å)	29.61 - 1.51 (1.55 - 1.51)[a]
Total observations	544788 (8392)
Number of unique reflections ($I \geq 0$)	85681 (2246)
Completeness (%)	77.7 (28.3)
Multiplicity	6.4 (3.7)
$<I/\sigma (I)>$	22.4 (2.6)
R_{merge}[b]	0.046 (0.467)
R_{pim}[b]	0.041 (0.149)
R_{meas}[b]	0.019 (0.276)
$CC_{1/2}$	0.999 (0.791)

Refinement Statistics

Resolution range (Å)	29.61 - 1.60 (1.64 - 1.60) [a]
Number of reflections ($F_o \geq 0$)	76169
R_{all}[c]	0.185
R_{work}[c]	0.184 (0.255)
R_{free}[d]	0.211 (0.294)

Number of atoms

Non-hydrogen protein	5434
Non-hydrogen waters	165
Non-hydrogen **CHD_4** ligands	96
Cations (Mg^{2+}, Zn^{2+})	4
R.m.s.d bond lengths/bond angles (Å, °)[e]	0.02 / 1.9
Ramachandran plot (%) favored/allowed regions (%)[f]	98.4 / 99.7

Average Temperature Factors (Å^2)

Protein	22.6
Water	27.0
CHD_4 ligands	19.6
Cations (Mg^{2+}, Zn^{2+})	11.4
R.m.s.d. ΔB (Å^2)[g]	1.95

[a] Number in parentheses refer to the highest resolution shell.

[b] $R_{merge} = \sum_{\mathbf{h}}\sum_i \left| I_{\mathbf{h}i} - \langle I_{\mathbf{h}} \rangle \right| / \sum_{\mathbf{h}}\sum_i I_{\mathbf{h}i}$, with $I_{\mathbf{h}}$ is the *i*th measurement of reflection **h**, and $\langle I_{\mathbf{h}} \rangle$ is the (weighted) average of all symmetry-related or replicate observations of the unique reflection **h**. The summations include all "n" observed reflections; $R_{pim} = \sum_{\mathbf{h}} (1/n-1)^{1/2} \sum_i \left| I_{\mathbf{h}i} - \langle I_{\mathbf{h}} \rangle \right| / \sum_{\mathbf{h}}\sum_i I_{\mathbf{h}i}$; $R_{meas} = \sum_{\mathbf{h}} (n/n-1)^{1/2} \sum_i \left| I_{\mathbf{h}i} - \langle I_{\mathbf{h}} \rangle \right| / \sum_{\mathbf{h}}\sum_i I_{\mathbf{h}i}$
[c] $R_{work} = \sum_{\mathbf{h}} \left| F_o \right| - \left| F_c \right| / \sum_{\mathbf{h}} \left| F_o \right|$, where $\left| F_o \right|$ and $\left| F_c \right|$ are the observed and calculated structure factor amplitudes for reflection h. The summation is extended over all unique reflections to the specified resolution.
[d] R_{free}, R factor calculated using 4027 randomly chosen reflections (5%) set aside from all stages of refinement.
[e] Stereochemical criteria are those of Engh and Huber.[1]
[f] The reliability of the protein structure has been assessed using the MolProbity package.[2] There were 2 outliers (phi, psi): A 541 Ser (112.9°, -26.5°) and B 547 Asp (-49.8°, -74.7°)
[g] R.m.s.d ΔB is the r.m.s. deviation of the B factor of bonded atoms (all atoms).[3]

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