Accepted Manuscript

Route scouting and optimization of a potent sulfoximine-based inverse agonist of RORγt

Guillaume Lafitte, Veronique Parnet, Romain Pierre, Catherine Raffin, Rodolphe Vatinel, Branislav Musicki, Loic Tomas, Claire Bouix-Peter, Gilles Ouvry, Sebastien Daver, Jean-Marie Arlabosse, Jean-Guy Boiteau, Thibaud Gerfaud, Craig S. Harris

PII: S0040-4020(18)31025-1

DOI: 10.1016/j.tet.2018.08.043

Reference: TET 29763

To appear in: *Tetrahedron*

Received Date: 11 July 2018

Revised Date: 16 August 2018

Accepted Date: 23 August 2018

Please cite this article as: Lafitte G, Parnet V, Pierre R, Raffin C, Vatinel R, Musicki B, Tomas L, Bouix-Peter C, Ouvry G, Daver S, Arlabosse J-M, Boiteau J-G, Gerfaud T, Harris CS, Route scouting and optimization of a potent sulfoximine-based inverse agonist of RORγt, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.08.043.

Graphical Abstract

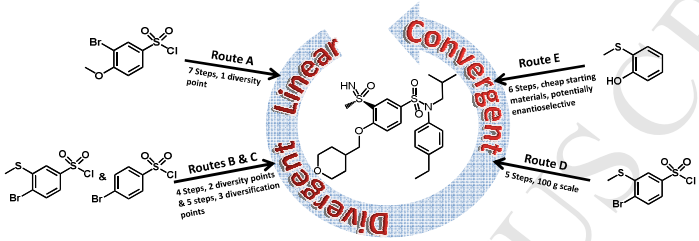
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Route scouting and optimization of a potent sulfoximine-based inverse agonist of RORγt

Leave this area blank for abstract info.

Guillaume Lafitte, Veronique Parnet, Romain Pierre, Catherine Raffin, Rudolphe Vatinel, Branislav Musicki, Loic Tomas, Claire Bouix-Peter, Gilles Ouvry, Sebastien Daver, Jean-Marie Arlabosse, Jean-Guy Boiteau, Thibaud Gerfaud, Craig S. Harris

Nestlé Skin Health R&D, 2400 Route de Colles, 06410 Biot, France



Tetrahedron
journal homepage: www.elsevier.com

Route scouting and optimization of a potent sulfoximine-based inverse agonist of RORγt

Guillaume Lafitte, Veronique Parnet, Romain Pierre, Catherine Raffin, Rodolphe Vatinel, Branislav Musicki, Loic Tomas, Claire Bouix-Peter, Gilles Ouvry, Sebastien Daver, Jean-Marie Arlabosse, Jean-Guy Boiteau, Thibaud Gerfaud*, Craig S. Harris*

Nestlé Skin Health R&D, 2400 Route de Colles, 06410 Biot, France

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
RORγt inverse agonist
Psoriasis
Sulfoximine
S_NAr
Route scouting

ABSTRACT

During our research looking for novel inverse agonists of RORγt, we identified a potent sulfoximine-based modulator as one of our pre-clinical candidates for the topical treatment for psoriasis. Herein, we describe the various routes we evaluated during the lead generation and optimization phases and the final route chosen for scale-up to deliver the first 100 g of API.

* Corresponding author. Tel.: +33 4 93 95 70 42; fax: +33 4 93 95 70 71; e-mail: craig.harris@galderma.com

* Corresponding author. Tel.: +33 4 92 38 30 87; fax: +33 4 93 95 70 71; e-mail: thibaud.gerfaud@galderma.com

1. Introduction

Psoriasis is a chronic autoimmune disease characterized by thick, red and scaly lesions that affects 2% of the population worldwide.[1] Psoriasis, among other autoimmune diseases, is believed to be caused by pro-inflammatory cytokines IL-17 produced by differentiated pathogenic T-helper 17 cells (TH-17).[2] With a direct impact on the IL-17 pathway, RORγ is a highly sought after target for the treatment of autoimmune disease and in particular of psoriasis.[2] Proof of concept was achieved with Vitae's VTP43742 and several molecules have now followed suit in clinic.[3]

In recent communications, we described the design and synthesis of a novel class of bis(aryl) sulfonamide-based RORγt inverse agonists.[4-5] During our SAR (structure-activity relationship) and SPR (structure-property relationship) investigation, sulfoximine **1** was identified as a key molecule to target. The sulfoximine motif has attracted much attention in drug discovery with kinase inhibitors *Roniciclib*, *Atuveciclib* (BAY 1143572) and *Ceralasertib* (AZD 6738) under clinical evaluation.[6] In our specific case, the sulfoximine residue, a recognized alcohol bioisostere,[5,7] was identified as part of a broader exploration to introduce hydrophilicity to one of GSK's lead compounds (Figure 1).[8] Retrosynthetic analysis of **1** drove us to consider 2 approaches: 1) a linear, convergent route whereby the sulfoximine would be introduced at the end of the sequence preceded by sulfonamide coupling from commercially-available sulfonyl chloride **6** and aniline **5** followed by aryl methyl ether deprotection, alkylation and Pd-catalysed thioether formation; and 2) a much more appealing divergent route allowing variation of the key vector of interest at the end of the route *via* S_NAr or PGM (platinum group metal) catalysis preceded by sulfoximine formation, sulfonamide coupling requiring access to unknown sulfonyl chloride **9** that we anticipated to be achievable through a 4-step approach starting from **10**.

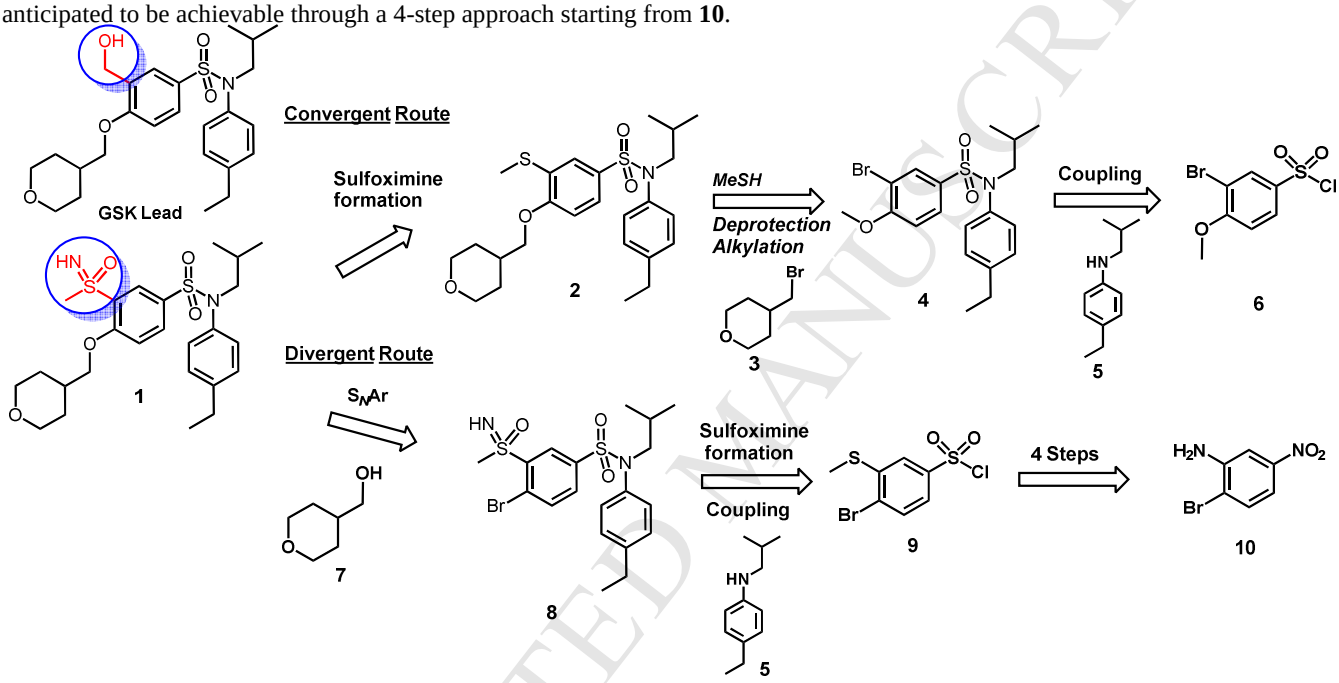
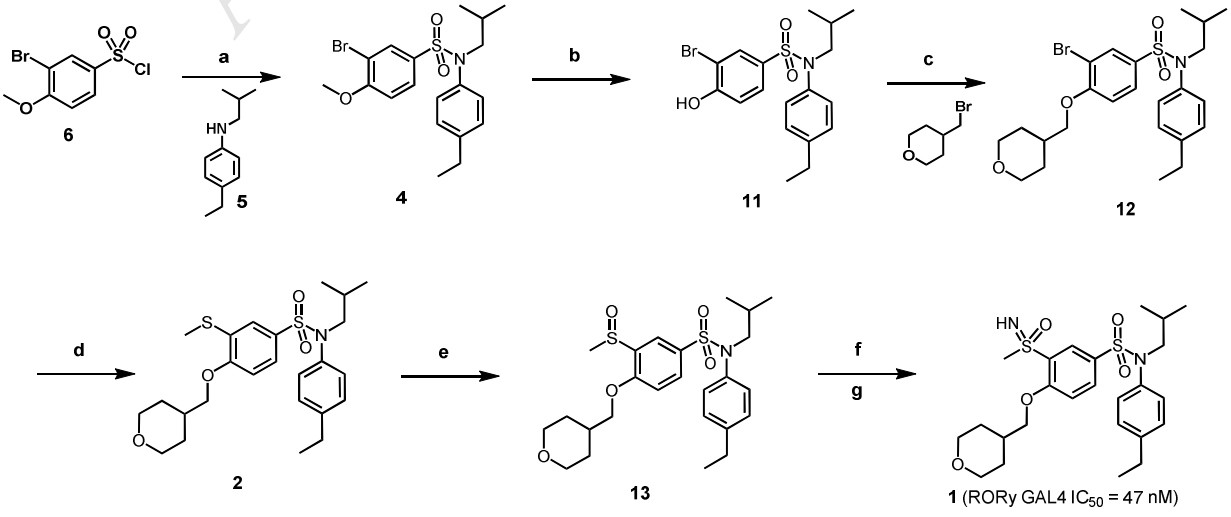


Figure 1. Retrosynthetic analysis of racemic sulfoximine target **1**

2. Results and discussion

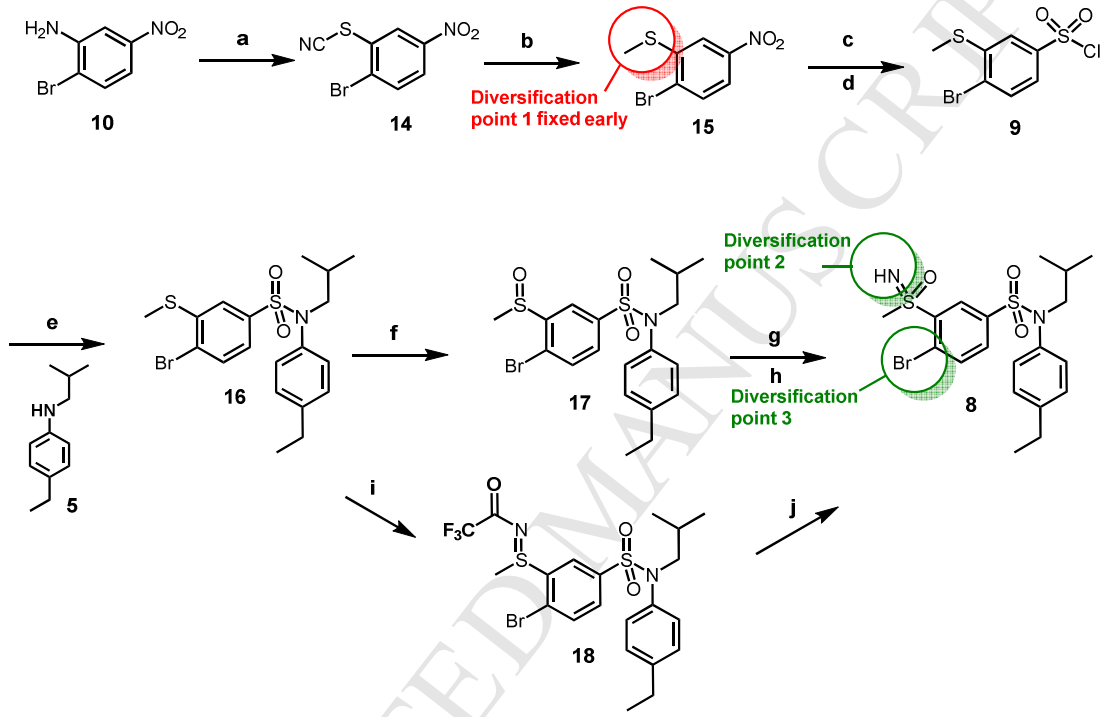
2.1. Medicinal chemistry: vector exploration

Our first successful route to **1** focused on a linear convergent approach starting from commercially-available 3-bromo-4-methoxybenzenesulfonyl chloride (**6**). Coupling with aniline **5** afforded **4** followed by revelation of the phenol moiety through dealkylation of the aryl methyl ether using thiophenolate to afford **11**.[9] Alkylation of phenol derivative **11** with 4-(bromomethyl)tetrahydro-2*H*-pyran afforded **12**. Transformation to thioether **2** was achieved in a respectable 67% isolated yield using palladium catalysis.[10] Finally, transformation to sulfoximine **1** was achieved *via* first transformation to sulfoxide **13** followed by rhodium-catalyzed sulfoximine formation using trifluoroacetamide as the imine source as described by Bolm and co-workers (Scheme 1).[11]

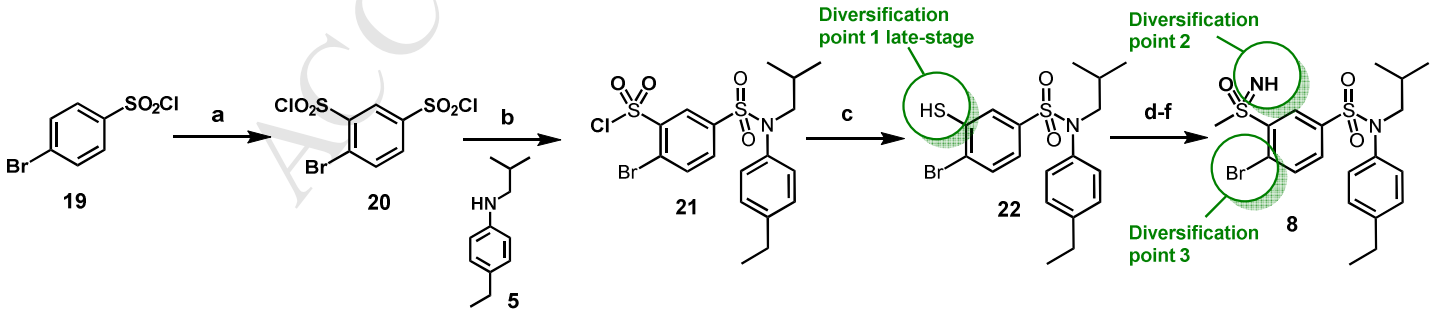


Scheme 1. Route A: First route to our racemic sulfoximine target **1**. Reagents and conditions: a) pyridine, THF, r.t., 65%; b) thiophenol, Cs_2CO_3, DMF, 100 °C, 80%; c) Cs_2CO_3, DMF, 80 °C, 87%; d) Pd_2dba_3, Xantphos, CH_3SNa, DIPEA, 1,4-dioxane, r.t., 67%; e) mCPBA, DCM, r.t., 63%; f) Trifluoroacetamide, $Rh_2(OAc)_2$, MgO, $PhI(OAc)_2$, DCM, 40 °C; g) K_2CO_3, MeOH, r.t., 30%

Encouraged by the *in vitro* activity of racemic **1**,[5] we decided to focus on building our SAR knowledge by exploring the vector from C-4 (diversification point 3) and assessing the activity of the individual enantiomers. To prepare our key sulfonyl chloride building block (**9**),[12] we targeted 2-bromo-5-nitroaniline (**10**) as the starting material. Formation of thiocyanate **14** through diazotisation[13] followed by reduction[14] and *in situ* alkylation of the thiol moiety with dimethylsulfate[15] afforded thioether **15**. Reduction, followed by a second diazotisation step[16] afforded our key sulfonyl chloride building block **9** which was in turn coupled with aniline **5** to afford sulfonamide **16**. Unfortunately, from sulfoxide **17**, we achieved a very poor conversion to sulfoximine **8** employing the rhodium catalyzed methodology[11] that we used previously which could be explained by the presence of the bromine atom that both lowers nucleophilicity of the thioether moiety compared to sulfoxide **13** and creates considerable steric hindrance. However, inversion of the steps, by formation of sulfilimine **18** followed by oxidation[17] and cleavage of the trifluoroacetamide moiety afforded an acceptable overall yield of our key library precursor **8** with two orthogonal diversification points (Scheme 2).



Scheme 2. Route B: Route to sulfoximine building block **8**. Reagents and conditions: a) $NaNO_2$, KSCN, CuSCN, 0 °C-r.t., 2 h, 63%; b) NaOH (aq), $NaBH_4$, Me_2SO_4, 2 h, 84%; c) Fe(s), NH_4Cl, MeOH-H_2O (2:1), reflux, 2 h, 53%; d) $NaNO_2$, SO_2 in AcOH, $CuCl_2$, -10 °C-r.t., 46%; e) pyridine, THF, r.t., 16 h, 78%; f) mCPBA, DCM, r.t., 30 min., 75%; g) trifluoroacetamide, $Rh_2(OAc)_2$, MgO, $PhI(OAc)_2$, DCM, r.t., 48 h; h) K_2CO_3, MeOH, r.t., 11%; i) NaH, trifluoroacetamide, 1,3-dibromo-5,5-dimethylhydantoin, THF, 0 °C-r.t., 2 h, 73%; j) K_2CO_3, mCPBA, 0 °C-r.t., 16 h, 54%.



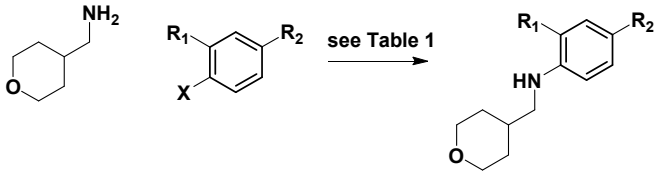
Scheme 3. Route C: Alternative unoptimized route to sulfoximine building block **8**. Reagents and conditions: a) $ClSO_3H$, 0 °C-150 °C, 6 h, 78%; b) pyridine, THF, r.t., 16 h, 80%; c) PPh_3, toluene, 90 °C, 10 min. quant.; d) MeI, K_2CO_3, DMF, r.t., 20 min., 64%; e) NaH, trifluoroacetamide, 1,3-dibromo-5,5-dimethylhydantoin, THF, 0 °C-r.t., 2 h, 73%; f) K_2CO_3, mCPBA, 0 °C-r.t., 16 h, 54%

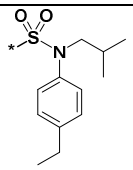
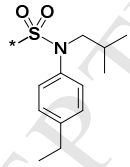
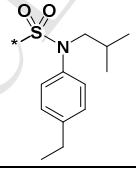
While our route to our sulfoximine building block **8** furnished the project with gram quantities of **8**, the sequence was very long with two sensitive Sandmeyer steps to control and afforded an overall yield of just 13% to sulfonyl chloride **9** and 4% to **8**. Moreover, the alkyl group of the sulfoximine moiety (diversification point 1) was fixed early on in the sequence thus limiting diversity (Scheme 2).

Going forwards in the project, we explored a safer, quicker and more versatile route starting from commercially-available 4-bromobenzenesulfonyl chloride (**19**) whereby the key step concerned the differentiation of bis(sulfonylchloride) intermediate **20** to access **21** (Scheme 3). Briefly, careful chlorosulfonylation afforded **20** in excellent yield that can also be prepared directly from bromobenzene.[7] Despite the generally surprising absence of literature supporting the differentiation of the two chlorosulfonyl groups of **20**, we envisioned that the steric hindrance of the C-2 bromine atom and our hindered secondary aniline motif should increase our chances of obtaining **21** with high regioselectivity. To our delight, through careful dropwise addition of aniline **5** to **20**, the desired sulfonamide regioisomer **21** was obtained in 80% isolated yield with only traces of the undesired regioisomer. From here, reduction of **21** to the versatile and stable thiophenol intermediate **22** was achieved in quantitative yield using triphenylphosphine[18] permitting late stage variation of the alkyl vector of the sulfoximine moiety (diversification point 1). To complete the sequence, we employed the sulfoximine protocol described in Scheme 2 and were able to prepare **8** in a much improved overall yield of 15% over 6 steps (Scheme 3).

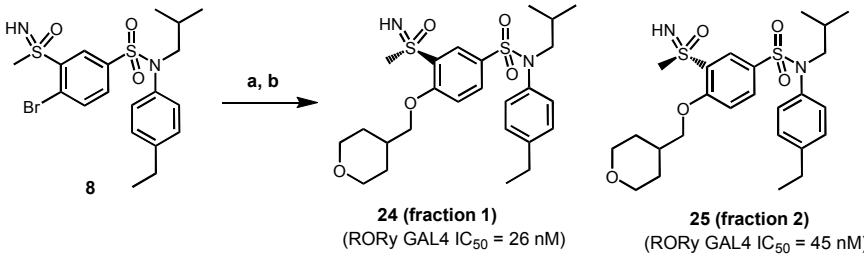
With these routes in hand, we gained access to larger quantities of intermediate **8** to study SARs from C-4. Although S_NAr reactions on haloarenes with unprotected sulfoximines at the *ortho* position have not yet been reported and there is only one reference at the *para* position with a fluorine atom as the leaving group,[19] we preferred to explore the S_NAr option first owing to the ease of preparing large libraries compared to palladium or copper catalyzed processes.[20] From our model experiments using an excess of (tetrahydro-2*H*-pyran-4-yl)methanamine as the nucleophile, product was observed using the most reactive *p*-fluoro derivative albeit in poor yield and conversion (entry 1). While we also expected a very poor reaction with bromide substrate having a deactivating SMe group at C-3 (entry 2), we were surprised to observe only trace amounts of substituted product with an unprotected sulfoximine group at C-3 (entry 3). However and to our delight, using intermediate **8** as the substrate, the desired product **23** was afforded in 93% isolated yield at just room temperature (entry 4, Table 1).

Table 1. S_NAr trials on **8** and related structural motifs



Entry	Compound	X	R_1	R_2	Conditions	Yield %
1[a]	-	F	H		70 °C, 3 d	45
2[b]	-	Br	MeS-*		150 °C	traces
3[b]	-	Br	MeNH(O)S-*	H	180 °C	traces
4[b]	**23**	Br	MeNH(O)S-*		r.t.	93%

[a] a 3-fold of excess of amine in DMF (5 volumes) was used; [b] amine used as solvent



Scheme 4. Preparation of enantiomers of **1**. Reagents and conditions: a) (tetrahydro-2*H*-pyran-4-yl)methanol, NaH, DMF, r.t., 16 h, 84%; b) a solution of 20 mg / mL was purified by stack-injection using SFC chromatography to afford **24** (35.4%) and **25** (37.3%)

Using **8** as our diversification point, we prepared a very large library of final compounds through S_NAr reaction with alcohol, amine and thiol based nucleophiles in order to thoroughly explore the SARs from vector C-4 while retaining the sulfoximine motif in place. However, despite the large number of final compounds evaluated (>100 final compounds), no improvement over our original hit was made. Going forwards in the program, we decided to exploit this strategy to prepare **1** in large quantity in order to separate the enantiomers and compare their individual activity *in vitro* and *in vivo*. From this head-to-head property evaluation, the only significant difference observed between the first eluting fraction (**24**) and the second eluting fraction (**25**) was in potency.[5] Enantiomer **24** was ~2 fold more potent, therefore, we selected **24** for chemical development with no knowledge of its absolute configuration (Scheme 4).

2.2. Chemical development of the clinical candidate

In order to start early formulation activities and pursue the biological evaluation of the candidate, larger quantities of drug substance were required. At that point it became critical to determine its chirality (Figure 2). Isolation of the least active enantiomer (**25**) by chiral HPLC followed by salt formation with (1*R*)-(−)-10-camphorsulfonic acid[21] allowed for single crystal X-Ray diffraction and attribution of the *R* configuration to the sulfoximine stereocenter. Chiral resolution of the racemate with chiral sulfonic acids was attempted but was unsuccessful.

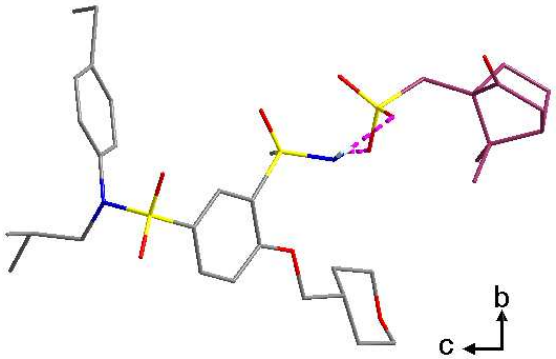
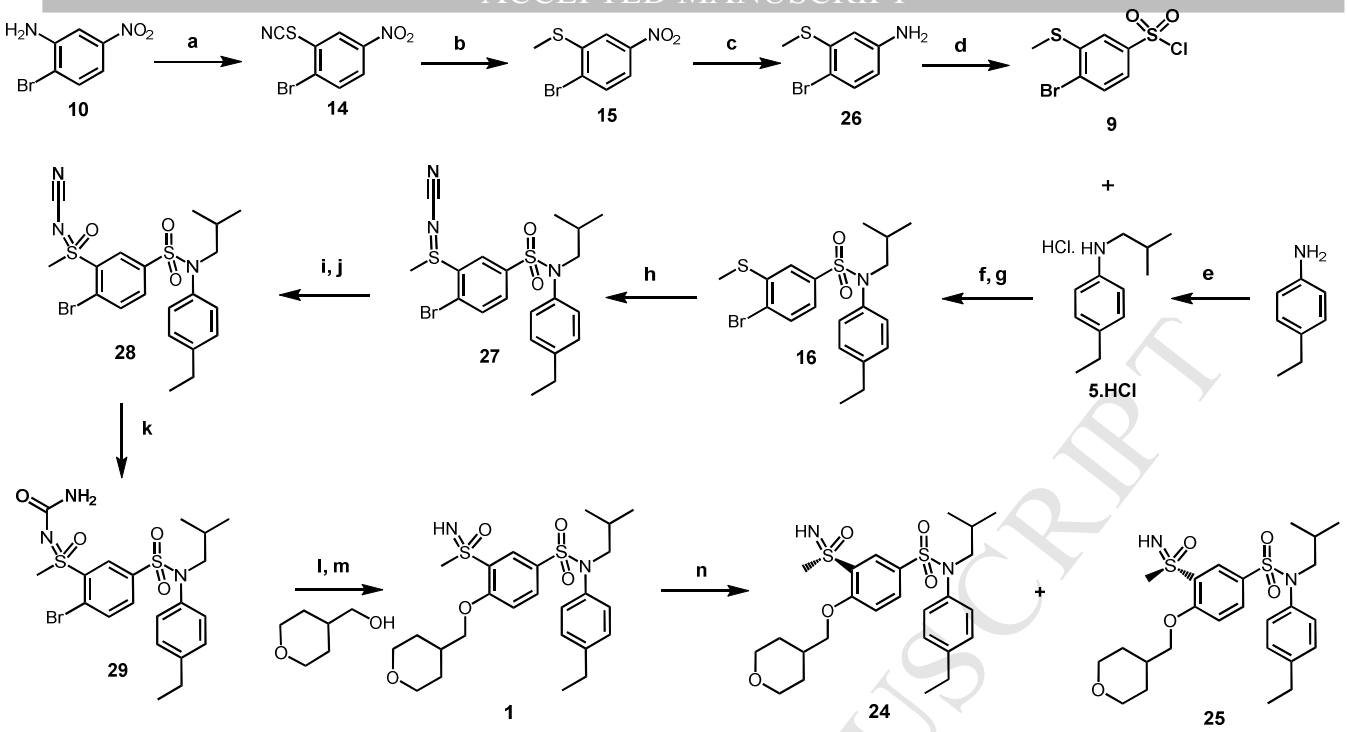


Figure 2. X-Ray of least active enantiomer **25.camphorsulfonate**

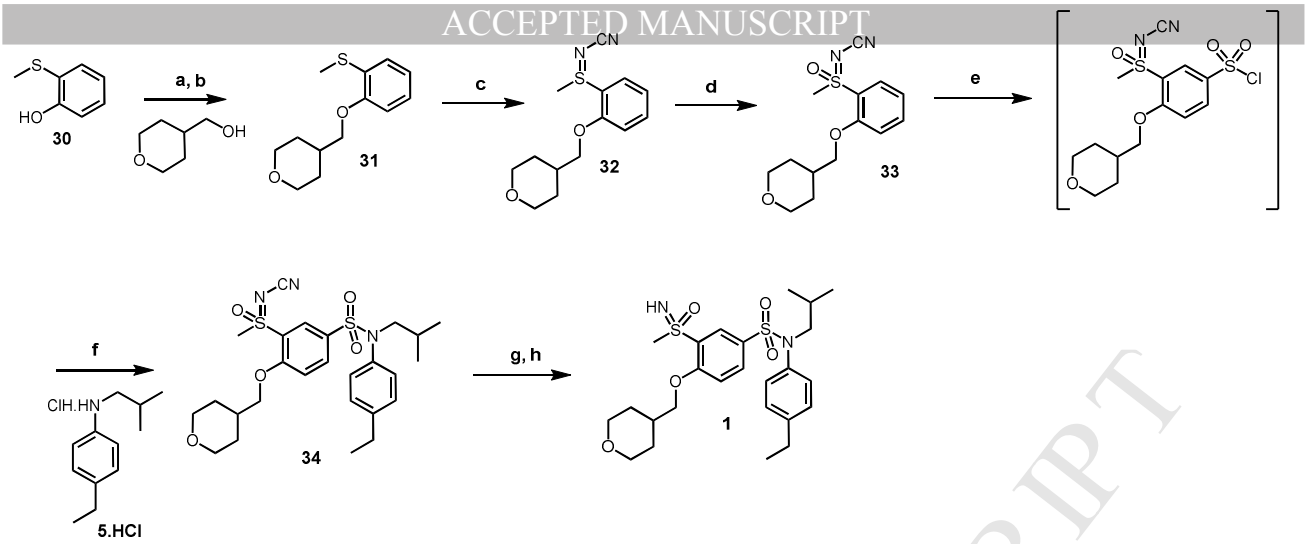
Route A was not really appealing for several reasons: **6** and 4-(bromomethyl)tetrahydropyran (**3**) are not commercially available on large scale, use of thiophenol and sodium methanethiolate is not preferred on scale and final sulfoximine installation was low yielding. To meet the project's timelines, early stage process development activities were initiated to ensure a smooth scale-up of second generation route B. Scale-up of the first steps proved complicated: conversion of **10** to **14** involved energetic intermediates and purification of **14** was difficult, rendering chromatography impossible to overcome. On scale the reaction was not robust with important batch to batch yield variations. Thiocyanate reduction and alkylation scaled up smoothly but involved toxic reagents. Nitro reduction followed by the second diazotization was also cumbersome involving once again highly energetic intermediates along with lack of robustness. Several campaigns at 100 g scale were necessary to furnish ultimately 500 g of **9**.

Most of our efforts were turned toward the last steps of the synthesis focusing mainly on the improvement of intermediate isolation and purification and on a robust and scalable introduction of the sulfoximine moiety. Aniline **5** is not commercially available on large scale and was prepared by reductive amination and isolated in high yield and purity as a hydrochloride salt. From **5.HCl**, a convenient coupling process with **9** was devised. The 2 solids were suspended in acetonitrile at 50 °C and coupling occurred smoothly upon DIPEA (*N*,*N*-diisopropylethylamine) addition. After addition of 1N aqueous HCl, the product crystallized out and was collected by filtration before being recrystallized (wet) in pure *i*-PrOH. **16** was obtained in good yield and high purity at >300 g scale. Sulfoximine formation was challenging on large scale. Formation of trifluoroacetyl sulfilimine **18** could be scaled up with minimal modifications (NaH replaced with safer *n*-HexLi) but concomitant sulfoxide formation (15-18% depending on batches) could not be avoided. Recrystallization from iPrOH:water was necessary to eliminate this impurity, reducing the overall yield to 71% at 50 g scale. Further oxidation of the trifluoroacetyl sulfilimine to the corresponding sulfoximine was not an easy task. Among all oxidants tested (mCPBA, H_2O_2, Oxone, $KMnO_4$, NaOCl, $RuCl_3$…), only Ru based oxidation systems were able to deliver the sulfoximine as the major product. However, high amounts of $RuCl_3$ (up to 30 mol%) and 4 to 6 equivalents of co-oxidant were required, with conversion stalling at ~70%. This prompted us to investigate other sulfilimines and preliminary experiments rapidly showed that oxidation of cyanosulfilimine to cyanosulfoximine were much cleaner and higher yielding.[22] Ru based oxidation systems were once again affording the best reaction profiles and after complete optimization of the 2 steps, a convenient and scalable access to the cyanosulfoximine **27** was devised (Scheme 5). **16** was converted to the cyanosulfilimine **27** using cyanamide with NBS as oxidant and potassium *tert*-butoxide as base in a THF-MeOH mixture. **27** crystallized out of the reaction mixture upon addition of an aqueous sodium metabisulfite solution and was easily isolated in high yield and high purity (89% yield, >97% purity at 500g scale). Oxidation of **27** to cyanosulfoximine **28** was performed in a DCM-MeCN-water mixture with $RuCl_3$ (2 mol%) and periodic acid as a co-oxidant. Complete conversion was reached within two hours and after workup and solvent switch to a mixture of *i*PrOH-DIE-acetone, cyanosulfoximine **28** crystallized and was isolated in 82% yield and >96% purity at 500 g scale. For a more efficient process, remaining steps (cyano moiety hydrolysis and S_NAr) were combined. Upon treatment with TFA in wet DCM,[23] crude cyanosulfilimine **27** was converted to the crystalline and easily isolated urea **29**. Concomitant urea hydrolysis and S_NAr were achieved by treating the crude urea with 4-(hydroxymethyl)tetrahydropyran and cesium carbonate in 1,4-dioxane under reflux. After completion of the reaction and base filtration, the final product **1** was crystallized out of the reaction mixture as a tosylate salt, enabling a very efficient impurity purging. Free-basing was achieved readily from 2-methyltetrahydrofuran/aq. NaOH and after a solvent switch to acetone-TBME, **1** was crystallized and isolated in good yield and high purity (72% yield, >98% purity, 400 g scale).



Scheme 5. Route D: Optimized route to deliver 100 g of **24**. Reagents and conditions: a) $NaNO_2$, KSCN, CuSCN, 0 °C-r.t., 2 h, 50%; b) NaOH (aq), $NaBH_4$, Me_2SO_4, 2 h, 50%; c) Fe(s), NH_4Cl, MeOH-H_2O (2:1), reflux, 2 h, 82%; d) $NaNO_2$, SO_2 in AcOH, $CuCl_2$, -10 °C-r.t., 30%; e) Isobutyraldehyde, $NaBH(OAc)_3$, TBME, 23°C, 18 h then 3M HCl in CPME, 75%; f) DIPEA, MeCN then 1N HCl; g) *i*PrOH, 89% over 2 steps; h) Cyanamide, NBS, *t*-BuOK, MeOH-THF (2:1), 89%; i) $RuCl_3$ (1.5 mol%), H_5IO_6, DCM-MeCN-H_2O (2:2:1); j) *i*PrOH, acetone, DIE, 93% over 2 steps; k) TFA, DCM-H_2O (40:1), 85%; l) Cs_2CO_3, 1,4-dioxane, reflux, 24 h then p-TsOH, acetone; m) NaOH (aq), 2-methyltetrahydrofuran-H_2O, 70%; n) chiral HPLC, chiralpack AD

While scaling up this route, the search for a more viable approach for larger scale production was pursued. We focused on the following criteria: 1) shorter sequence; 2) readily available and cheap starting materials; and 3) possible earlier separation of the enantiomers. Route C, involving the two chlorosulfonyl group differentiation (Scheme 3) was briefly explored but while well suited for small scale production, the anticipated low stability of **20** and the harsh reaction conditions of its formation were not suitable for large scale production.[24] A good compromise was found using the synthetic pathway described in Scheme 6 and demonstrated on mg scale. 2-Hydroxythioanisole (**30**), a cheap and readily available compound,[25] can be reacted with 4-(hydroxymethyl)tetrahydropyran under Mitsunobu conditions to deliver **31** in high yield. Conducting the reaction in toluene with DEAD/PPh_3 as the activating agent allowed easy removal of all by-products without chromatography: Ph_3PO was removed by addition of $MgCl_2$ to the reaction mixture triggering the formation of an insoluble $MgCl_2$-Ph_3PO complex[26] and reduced DEAD could be removed by crystallization upon heptane addition. Cyanosulfilimine formation using the previously optimized conditions worked in 55% yield after crystallization albeit on small scale. Oxidation of **32** to the corresponding cyanosulfoximine under Ru catalysis worked well, furnishing **33** in 40% yield (not optimized). When **33** was treated with chlorosulfonic acid, a clean and fully regioselective chlorosulfonylation at C5 took place. The crude sulfonylchloride was directly engaged in a coupling step with **5.HCl** delivering **34** in 40% yield over 2 steps. Access to **1** could then be completed by converting cyanosulfoximine into the corresponding trifluoroacetamide using TFAA followed by hydrolysis with K_2CO_3 in MeOH. A lot of development work still remains to optimize and ensure complete robustness but this novel approach reduces the longest linear sequence to only 6 steps and circumvents the use of expensive starting materials. It also offers interesting possibilities such as earlier enantiomers separation by chiral HPLC on cyanosulfoximine **33** or a possible enantioselective version by conducting a chiral oxidation of sulfide **31** to the corresponding sulfoxide followed by imination using Bolm's method.[11]



Scheme 6. Route E: Last generation route towards racemic **1**. Reagents and conditions: a) PPh_3, DEAD, toluene; b) $MgCl_2$, heptane-toluene, 92% over 2 steps; c) Cyanamide, NBS, *t*-BuOK, MeOH-THF (2:1), 55%; d) $RuCl_3$ (1.5 mol%), H_5IO_6, DCM-MeCN-H_2O (2:2:1), 40%; e) HSO_3Cl, DCM, 0°C; f) DIPEA, DCM, 40% over 2 steps; g) TFAA, DCM; h) K_2CO_3, MeOH, 75%.

3. Conclusion

In conclusion, we have developed five novel racemic routes (A,B,C,D and E) to a potent sulfoximine-based RORγt inverse agonist. For exploratory medicinal chemistry, diversity-orientated routes B and C were particularly appealing as they facilitated late stage variation, particularly from our key exploratory vector C-4 but also from *S* and *N* of the sulfoximine moiety.[5] Out of the three routes explored during the medicinal chemistry phase, Route B was retained and further optimised to deliver the first 100 g of our lead candidate **24**. Further route scouting led to the discovery of Route E, a much more efficient and convergent 6-step route offering potential avenues to develop an enantioselective approach that is under investigation in our laboratories.

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded on a BRUKER Biospin AVANCE 400 spectrometer. Chemical shifts are reported as δ values downfield from internal TMS in appropriate organic solutions. The abbreviations used for explaining the multiplicities were as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass (ESI HRMS) was recorded on a Thermofisher Q Exactive™ Hybrid Quadrupole-Orbitrap™ Mass Spectrometer. The relative purity and the mass of the products were confirmed by UPLC-MS (220 nm to 420 nm) on a Waters acquity uplc photodiode array detector system using the following conditions: Column, BEH C18 50*2.1 mm; 1.8 µm; Solvent A, water 0.1% formic acid or water ammonium carbonate 2 g/l; Solvent B, CH_3CN; flow rate, 0.8 ml/min; run time, 2.2 min; gradient, from 5 to 95% solvent B; mass detector, Waters SQ detector. For route D, in process controls were performed using the previously described HPLC-MS conditions and relative purity was assessed by HPLC on an Agilent system using the following parameters: column Acquity BEH C18 1.7 µm 2.1*150 mm, flow rate= 0.8 mL/min, 14.0 min runs, solvent system: MeCN+0.1% HCOOH, H_2O +0.1% HCOOH, gradient: 10% to 35% MeCN from 0 to 10 min, and 35% to 95% from 10 to 14 min. All compounds for routes A, B and C were purified by LC/MS on a waters Autopurification system using the following conditions unless otherwise stated: Column, Xbridge C18 150*30mm, 5µm; Solvent A, water 0.1% formic acid or water ammonium carbonate 2 g/l; Solvent B, CH_3CN; flow rate, 50 ml/min; run time, 10 or 15 min; with adapted isocratic elution mode; mass detector, Waters ZQ detector. Enantiomeric purity was determined by chiral SFC under the following conditions: column: IA 5µm x 4.6 x 250mm; flow rate= 4.0 mL/min; co-solvent: EtOH 35%; isocratic conditions.

4.2. Route A: First route to racemic sulfoximine target 1

*4.2.1. 4-Ethyl-N-isobutylaniline (**5**)*

To a stirred solution of 4-ethylaniline (94.8 mL, 0.76 mol), was added *iso*-butyraldehyde (63.3 mL, 0.69 mol) in THF (1.0 L) and the reaction mixture was stirred at 2-methyltetrahydrofuran temperature for 30 minutes, cooled to 0 °C and $NaBH(OAc)_3$ (162 g, 0.76 mol) was added portionwise while keeping the temperature below 25 °C. The reaction mixture was stirred at room temperature for 16 h, quenched with water (100 mL) and extracted with EtOAc (2 x 200 mL). The organic phases were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated to dryness to afford a pale brown residue. The residue was purified by flash chromatography eluting with heptane-DCM (0-100%) to afford the title compound (**5**, 111 g, 90%) as a pale orange oil: UPLC-MS (t_R=1.10 min, purity=100%), ESI *m/z* 179.20 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 0.91 (d, *J*=6.6 Hz, 6H), 1.10 (t, *J*=7.6 Hz, 3H), 1.80 (m, 1H), 2.42 (q, *J*=7.6 Hz, 2H), 2.77 (dd, *J*=6.7, 5.5 Hz, 2H), 5.35 (t, *J*=5.7 Hz, 1H), 6.40 – 6.56 (m, 2H), 6.77 – 7.01 (m, 2H).

*4.2.2. 3-Bromo-N-(4-ethylphenyl)-N-isobutyl-4-methoxy-benzenesulfonamide (**4**)*

3-Bromo-4-methoxy-benzenesulfonyl chloride (4.83 g, 16.9 mmol) was added portionwise to a stirred solution of 4-ethyl-*N*-isobutylaniline (**5**, 3.00 g, 16.9 mmol) and pyridine (8.19 mL, 102 mmol) in THF (60 mL). The reaction mixture was stirred at r.t. for 5 h, quenched with water (10 mL) and extracted with EtOAc (2 x 30 mL). The organic phases were combined, washed with 1.0 M HCl (aq) (10 ml), brine (10 mL), dried over $MgSO_4$

and concentrated to dryness to afford an orange residue. The crude product was purified by flash chromatography eluting with heptane-EtOAc (0-20%) to afford the title compound (4.69 g, 65%) as a white solid: UPLC-MS (t_R=1.51 min, purity=100%), ESI *m/z* 426.10 / 429.08 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, *J*=2.2 Hz, 1H), 7.50 (dd, *J*=8.6, 2.2 Hz, 1H), 7.23 – 7.11 (m, 2H), 7.02 – 6.95 (m, 2H), 6.92 (d, *J*=8.6 Hz, 1H), 3.98 (s, 3H), 3.30 (d, *J*=7.4 Hz, 2H), 2.67 (q, *J*=7.6 Hz, 2H), 1.69 – 1.56 (m, 1H), 1.26 (t, *J*=7.6 Hz, 3H), 0.93 (d, *J*=6.7 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8, 143.6, 136.5, 131.7, 130.6, 128.9, 128.3, 112.8, 110.9, 57.1, 57.0, 27.7, 26.4, 19.7, 15.4.

*4.2.3. 3-Bromo-N-(4-ethylphenyl)-4-hydroxy-N-isobutyl-benzenesulfonamide (**11**)*

To a stirred suspension of 3-bromo-*N*-(4-ethyl-phenyl)-*N*-isobutyl-4-methoxy-benzenesulfonamide (**4**, 5.0 g, 11.7 mmol) and Cs_2CO_3 (4.58 g, 14.1 mmol) in DMF (100 mL) , was added thiophenol (1.32 mL, 12.9 mmol). The reaction mixture was stirred at 100 °C, treated with a saturated aqueous solution of sodium sulfite and dlitued with EtOAc (100 mL). The reaction mixture was extracted with EtOAc (2 x 100 ml) and the organic phases were combined, washed with water (2 x 50 mL), dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography eluting with heptane-EtOAc (0-80%) to afford the title compound (3.87 g, 80%) as a white solid: UPLC-MS (t_R=1.36 min, purity = 100%), ESI *m/z* 413.96 / 415.82 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (br s, 1H), 7.49 (d, *J*=2.3 Hz, 1H), 7.37 (dd, *J*=8.6, 2.3 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.06 (d, *J*=8.6 Hz, 1H), 7.01 – 6.92 (m, 2H), 3.28 (d, *J*=7.3 Hz, 2H), 2.60 (p, *J*=7.6 Hz, 2H), 1.40 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.84 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.2, 143.5, 136.6, 132.1, 129.0, 128.3, 116.4, 109.4, 57.1, 27.8, 26.4, 19.7, 15.4.

*4.2.4. 3-Bromo-N-(4-ethylphenyl)-N-isobutyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (**12**)*

To a stirred suspension of 3-bromo-*N*-(4-ethyl-phenyl)-4-hydroxy-*N*-isobutyl-benzenesulfonamide (**11**, 2.20 g, 5.34 mmol) and Cs_2CO_3 (3.48 g, 10.7 mmol) in DMF (44 mL), was added 4-(bromomethyl)tetrahydropyran (1.15 g, 6.40 mmol). The reaction mixture was stirred at 80 °C for 16 h, cooled to r.t. and quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 50 mL) and the organic phases were combined, washed with a saturated solution of sodium carbonate, brine, dried over $MgSO_4$ and concentrated to dryness. The residue was triturated with heptane and the solid obtained was collected by filtration and dried to a constant weight in a vacuum oven at 40 °C to afford the title compound (2.36 g, 87%) as a white solid: UPLC-MS (t_R=1.52 min, purity=100%), ESI *m/z* 510.11 / 512.11 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*=2.3 Hz, 1H), 7.46 (dd, *J*=8.6, 2.3 Hz, 1H), 7.21 – 7.09 (m, 2H), 7.04 – 6.93 (m, 2H), 6.87 (d, *J*=8.6 Hz, 1H), 4.07 (ddd, *J*=11.6, 5.0, 1.8 Hz, 2H), 3.94 (d, *J* = 6.4 Hz, 2H), 3.50 (td, *J*=11.6, 2.1 Hz, 2H), 3.29 (d, *J*=7.3 Hz, 2H), 2.67 (q, *J*=7.6 Hz, 2H), 2.19 (m, 1H), 1.83 (m, 2H), 1.67 – 1.49 (m, 2H), 1.26 (t, *J*=7.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 6H).

*4.2.5. N-(4-Ethylphenyl)-N-isobutyl-3-(methylthio)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (**2**)*

To a stirred solution of 3-bromo-*N*-(4-ethyl-phenyl)-*N*-isobutyl-4-(tetrahydro-pyran-4-ylmethoxy)-benzenesulfonamide (**12**, 2.35 g, 4.60 mmol), DIPEA (2.38 mL, 13.8 mmol), bis(dibenzylidene-acetone)palladium (0) (0.53 g, 0.92 mmol) and sodium methanethiolate (0.35 g, 5.06 mmol) in 1,4-dioxane (23.5 mL) purged with argon, was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.21 g, 0.37 mmol). The reaction mixture was heated at 90 °C for 16 h, cooled to r.t. and divided between water (10 mL) and EtOAc (50 mL). The organic phase was collected, washed with brine (2 x 5 mL), dried ($MgSO_4$) and concentrated to dryness. The residue was purified by flash chromatography eluting with heptane-EtOAc (0-30%) to afford the title compound (1.75 g, 59%) as a pale yellow solid: UPLC-MS (t_R=1.48 min, purity=100%), ESI *m/z* 478.23 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J*=8.5, 2.2 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.93 – 6.86 (m, 2H), 6.73 (d, *J*=8.5 Hz, 1H), 4.01 – 3.90 (m, 2H), 3.86 (d, *J*=6.4 Hz, 2H), 3.40 (m, 2H), 3.18 (dd, *J*=7.3, 5.3 Hz, 2H), 2.56 (q, *J*=7.6 Hz, 2H), 2.16 (s, 3H), 1.73 (m, 2H), 1.49 (overlapping s and m, 3H), 1.30 – 1.02 (m, 3H), 0.83 (d, *J*=6.8, 6H).

*4.2.6. N-(4-Ethylphenyl)-N-isobutyl-3-(methylsulfinyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (**13**)*

To a stirred solution of *N*-(4-ethyl-phenyl)-*N*-isobutyl-3-methylsulfanyl-4-(tetrahydro-pyran-4-ylmethoxy)-benzene-sulfonamide (500 mg 0.73 mmol) in DCM (7.0 mL) at 0 °C, was added mCPBA (131 mg, 0.59 mmol). The reaction mixture was stirred at r.t. for 30 minutes, quenched with a 10% (w/v) aqueous solution of $Na_2S_2O_3$ and extracted with DCM (20 mL). The organic phases were washed with 0.1 M NaOH (aq), brine, dried over $MgSO_4$ and concentrated to dryness. The residue obtained was purified by flash chromatography eluting with heptane-EtOAc (0-100%) to afford the title compound (235 mg, 65%) as a white solid: UPLC-MS (t_R=1.32 min, purity=100%), ESI *m/z* 494.22 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 – 7.59 (m, 2H), 7.34 (d, *J*=8.5 Hz, 1H), 7.26 – 7.11 (d, *J*=8.4 Hz, 2H), 7.01 – 6.89 (d, *J*=8.4 Hz, 2H), 4.18 – 3.97 (m, 2H), 3.90 (ddd, *J*=11.6, 4.6, 1.9 Hz, 2H), 3.32 (m, 2H), 2.74 (s, 3H), 2.60 (q, *J*=7.6 Hz, 2H), 2.05 (m, 1H), 1.65 (m, 2H), 1.51 – 1.26 (m, 3H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (t, *J*=6.8 Hz, 6H).

*4.2.7. N-(4-Ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (**1**)*

To a stirred solution of *N*-(4-Ethylphenyl)-*N*-isobutyl-3-(methylsulfinyl)-4-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzene-sulfonamide (230 mg, 0.47 mmol) in DCM (11.5 mL) purged with argon, was added 2,2,2-trifluoroacetamide (132 mg, 1.16 mmol), rhodium(II) acetate dimer (30.9 mg, 70 µmol), magnesium oxide (93.9 mg, 2.33 mmol) and iodobenzene diacetate (285 mg, 0.89 mmol). The reaction mixture was stirred at r.t. for 16 h, filtered through a pad of Celite® and concentrated to dryness. The residue was dissolved in MeOH (11.5 mL) and K_2CO_3 (322 mg, 2.33 mmol) was added and the reaction mixture was stirred for 30 minutes. Water (2.5 mL) was added and the reaction mixture was extracted with EtOAc (2 x 20 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography eluting with DCM-MeOH (0-5%) to afford the title compound (91.4 mg, 39%) as a white solid: UPLC-MS (t_R=1.33 min, purity=100%), ESI *m/z* 509.33 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J*=2.4 Hz, 1H), 7.67 (dd, *J*=8.8, 2.4 Hz, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 7.21 (d, *J*=8.4 Hz, 2H), 7.01 (d, *J*=8.4 Hz, 2H), 4.41 (s, 1H), 4.11 (m, 2H), 3.96 – 3.83 (m, 2H), 3.39-3.24 (m, 4H), 3.19 (s, 3H), 2.61 (q, *J*=7.6 Hz, 2H), 2.21 – 2.02 (m, 1H), 1.83 – 1.66 (m, 2H), 1.58 – 1.27 (m, 3H), 1.18 (t, *J*=7.6 Hz, 3H), 0.86 – 0.84 (d, *J*=6.4 Hz, 6H); HRMS:

$(M+H)^+$ calculated for $C_{25}H_{36}N_2O_5S_2$ 509.20656; found 509.21724.

4.3. Route B: Route to building block 8

*4.3.1. 1-Bromo-4-nitro-2-thiocyanatobenzene (**14**)*

2-Bromo-5-nitroaniline (**10**, 470 g, 2.19 mol) and 6N HCl (4 L) were stirred at r.t. until a homogeneous paste was obtained. Sodium nitrite (167.4 g, 2.42 mol) dissolved in H_2O (300 mL) was added dropwise to the paste at 0 °C under an inert atmosphere. After the addition was complete, the mixture was stirred for an additional hour at 0 °C then added portionwise to a solution of KSCN (295 g, 3.03 mol) and CuSCN (259 g, 2.13 mol) in water (1.50 L) at r.t. over a period of 2 hours and the reaction mixture was stirred overnight. The resulting suspension was filtered and the solid was washed with DCM (3 x 500 mL). The filtrate was recuperated and washed with DCM (1000 mL) and the combined organic extracts were washed with water (200 mL) and dried over $MgSO_4$ and concentrated to dryness to afford the title compound (352 g, 63%) as a yellow solid that was used without further purification: MS ESI *m/z* no ion detected; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.24 (d, *J*=8.4 Hz, 2H), 7.88 (d, *J*=8.4 Hz Hz, 1H).

*4.3.2. (2-Bromo-5-nitrophenyl)(methyl)sulfane (**15**)*

NaOH (55.4 g, 1.39 mol) was dissolved in a mixture of water (660 mL) and methanol (3400 mL). 1-Bromo-4-nitro-2-thiocyanatobenzene (**41**, 352 g, 1.36 mol) was added under stirring. After 30 minutes, the reaction mixture was cooled to 0-5 °C and sodium borohydride (25.7 g, 0.68 mol) was added and the reaction mixture was stirred for a further 30 minutes in an ice bath. Me_2SO_4 (176 g, 1.40 mol) was added dropwise and the resulting mixture was stirred for 30 minutes then at r.t. for 30 minutes. The volatiles were removed and water was added to the reaction mixture and the product was extracted in diethyl ether (2.00 L). The extract was washed twice with water (100 mL), dried over $MgSO_4$ and concentrated to dryness to afford the title compound (283 g, 84%, purity 65%) that was used in the following step without further purification: MS ESI *m/z* no ion detected; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.82 (d, *J*=8.4 Hz, 2H), 7.69 (d, *J*=8.4 Hz, 1H).

4.3.3. 4-Bromo-3-(methylthio)aniline

Fe (291 g, 5.20 mol) and NH_4Cl (223 g, 4.16 mol) were added to a solution of (2-bromo-5-nitrophenyl)(methyl)sulfane (258 g, 1.04 mol) in a mixture of CH_3OH-H_2O (2.00 L-1.00 L). The reaction mixture was heated at refluxed for 2 hours, the suspension was filtered, concentrated and the residue was extracted with EtOAc (3 x 1.00 L). The organic layers were combined, dried over $MgSO_4$, concentrated and purified by flash chromatography eluting with DCM-MeOH (0-5%) to afford the title compound as a pale brown solid (120 g, 53 %): MS ESI *m/z* 217 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.8 Hz, 1H), 6.45 (s, 1H), 6.34 (m, 1H), 3.70 (br s, 2H), 2.43 (s, 3H).

*4.3.4. 4-Bromo-3-(methylthio)benzenesulfonyl chloride (**9**)*

To a solution of concentrated HCl (300 mL) diluted with H_2O (160 mL) was added 4-bromo-3-(methylthio)aniline (100 g, 0.46 mol) and the mixture was cooled to -10 ° C. A solution of $NaNO_2$ (34.8 g, 0.51 mol) in H_2O (60 mL) was added and the resulting slurry was stirred at -10 °C for 20 minutes then poured into a freshly prepared chilled saturated solution of SO_2 in AcOH (1000 mL). A solution of $CuCl_2$ (25.9 g, 0.19 mol) in H_2O (60 mL) was added and the reaction mixture was allowed to warm to r.t. and stirred for 2 hours. The reaction mixture was extracted with EtOAc (500 mL). The extract was washed brine, dried over Na_2SO_4, concentrated to dryness and purified by flash chromatography eluting with heptane-EtOAc (0-10%) to afford the title compound (63 g, 46%) as a white solid: UPLC-MS (t_R=1.02 min, purity=100%), ESI *m/z* 281.03 / 282.96 (M(-Cl)+OH)-H)$^-$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 1H), 7.62 (m, 2H), 2.57 (s, 3H), ^{13}C NMR (101 MHz, DMSO) δ 148.2, 139.6, 132.6, 123.6, 122.5, 121.2, 15.4. HRMS: $(M-H)^-$ calculated for $C_7H_6BrClO_2S_2$ 298.8681; found 280.8952 (M(-Cl)+OH)-H)$^-$.

*4.3.5. 4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(methylthio)-benzenesulfonamide (**16**)*

To a stirred solution of 4-ethyl-*N*-isobutylaniline (**5**, 5.58 g, 31.5 mmol) and pyridine (15.3 mL, 189 mmol) in THF (190 mL) at r.t., was added 4-bromo-3-(methylthio)benzenesulfonyl chloride (**9**, 10.0 g, 31.5 mmol) in THF (47.5 mL) over 10 minutes. The reaction mixture was stirred for 16 h at r.t. Water (5 mL) was added and the reaction mixture was extracted with EtOAc (2 x 200 mL). The organic phases were combined, washed with a saturated aqueous solution of NH_4Cl, brine, dried over $MgSO_4$ and concentrated to dryness to afford the title compound (12.9 g, 92%) as a pale yellow solid that was used without further purification: UPLC-MS (t_R=1.53 min, purity=100%), ESI *m/z* 443.95 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, *J*=8.2 Hz, 1H), 7.26 (dd, *J*=8.2, 2.0 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 7.06 – 7.00 (d, *J*=8.2 Hz, 2H), 6.98 (d, *J*=2.0 Hz, 1H), 3.47 – 3.16 (m, 3H), 2.61 (q, *J*=7.6 Hz, 2H), 2.32 (s, 3H), 1.43 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.2, 141.6, 137.8, 136.6, 132.8, 131.2, 128.7, 128.5, 128.4, 128.3, 125.8, 124.9, 123.9, 123.6, 58.3, 57.9, 41.8, 28.4, 26.8, 26.7, 19.8, 15.4, 15.3; HRMS: $(M+H)^+$ calculated for $C_6H_3BrCl_2O_4S_2$ 442.0431; found 442.0503.

*4.3.6. 4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(methylsulfinyl)-benzenesulfonamide (**17**)*

To a stirred solution of 4-bromo-*N*-(4-ethylphenyl)-*N*-isobutyl-3-(methylthio)-benzenesulfonamide (**16**, 1.00 g 2.26 mmol) in DCM (20 mL) at 0 °C, was added mCPBA (0.46 g, 2.03 mmol). The reaction mixture was stirred at r.t. for 30 minutes, treated with a 10% w/v aqueous solution of $Na_2S_2O_3$ and extracted with DCM (100 mL). The organic phase was washed with 0.1 M NaOH (aq), brine, dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography eluting with heptane-EtOAc (0-100%) to afford the title compound (784 mg, 76%) as a white solid: LCMS (t_R = 1.35 min, purity = 100%), ESI *m/z* 460.04 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, *J*=8.2 Hz, 1H), 7.74 (d, *J*=2.3 Hz, 1H), 7.66 (dd, *J*=8.2, 2.3 Hz, 1H), 7.20 (d, *J*=8.2 Hz, 2H), 7.01 (d, *J*=8.2 Hz, 2H), 3.44 – 3.20 (m, 2H), 2.79 (s, 3H), 2.60 (p, *J*=7.6 Hz, 2H), 1.43 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.86 (overlapping d, *J*=6.6 Hz, 6H).

*4.3.7. (E)-N-((2-bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ^4-sulfaneylidene)-2,2,2-trifluoroacetamide (**18**)*

A solution of 4-bromo-*N*-(4-ethylphenyl)-*N*-isobutyl-3-(methylsulfinyl)-benzenesulfonamide (12.0 g, 27.1 mmol) and 2,2,2-trifluoroacetamide (4.60 g, 40.7 mmol) in THF (24 mL) was added to a suspension of 60% NaH (0.98 g, 24.4 mmol) in

THF (60 mL) at 0-5 °C over 10 minutes. Next, a solution of 1,3-dibromo-5,5-dimethylhydantoin (11.6 g, 40.7 mmol) in THF (24 mL) was added while maintaining the temperature at 0-5 °C. The reaction mixture was allowed to warm to r.t. and stirred for 2 h, quenched with a 10% w/v aqueous solution of citric acid (5 mL) and extracted with EtOAc (2 x 100 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was triturated in a mixture of isopropyl ether and the solid was collected by filtration and dried to a constant weight to afford the title compound (11.0 g, 73%) as a white solid: UPLC-MS (t_R=1.40 min, purity=100%), ESI *m/z* 553.07 / 554.97 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, *J*=8.4 Hz, 1H), 7.79 (d, *J*=2.2 Hz, 1H), 7.68 (dd, *J*=8.4, 2.2 Hz, 1H), 7.28 – 7.13 (d, *J*=8.4 Hz, 2H), 7.05 – 6.85 (d, *J*=8.4 Hz, 2H), 3.38 – 3.26 (m, 2H), 3.21 (dd, *J*=12.9, 6.6 Hz, 1H), 3.13 (s, 3H), 2.60 (q, *J*=7.6 Hz, 2H), 1.51 – 1.33 (m, 1H), 1.17 (t, *J*=7.6 Hz, 5H), 0.83 (2 d, *J*=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 177.4, 144.6, 140.8, 135.7, 134.3, 132.8, 128.8, 128.3, 126.4, 126.2, 58.5, 33.5, 28.3, 26.7, 25.0, 19.6, 15.1.

*4.3.8. 4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (**8**)*

Potassium carbonate (8.24 g, 59.6 mmol) was added to (*E*)-*N*-((2-bromo-5-(*N*-(4-ethylphenyl)-*N*-isobutylsulfamoyl)phenyl)-(methyl)-λ^4-sulfaneylidene)-2,2,2-trifluoroacetamide (**18**, 11.0 g, 19.9 mmol) in MeOH (110 mL) at 0 °C, followed by mCPBA (6.68 g, 29.8 mmol) while maintaining a temperature of 0-5 °C. The reaction mixture was allowed to warm to r.t. and was stirred for 16 h. Water (5 mL) was added and the reaction mixture was extracted with EtOAc (2 x 100 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was triturated with isopropyl ether and the solid was collected by filtration and dried to a constant weight to afford the title compound (**8**, 5.07 g, 54%) as a white solid: UPLC-MS (t_R =1.35 min, purity=100%), ESI *m/z* 473.01 / 475.01 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J*=2.4 Hz, 1H), 8.06 (d, *J*=8.3 Hz, 1H), 7.61 (dd, *J*=8.3, 2.4 Hz, 1H), 7.29 – 7.14 (d, *J*=8.3 Hz, 2H), 7.09 – 6.95 (d, *J*=8.3 Hz, 2H), 4.73 (d, *J*=1.6 Hz, 1H), 3.33 (m, 2H), 3.26 (s, 3H), 2.61 (q, *J*=7.6 Hz, 2H), 1.44 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.86 (2 d, *J*=6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 144.2, 140.3, 136.6, 128.5, 128.4, 126.3, 122.4, 110.2, 67.3, 58.1, 48.7, 34.2, 30.6, 28.4, 26.8, 19.9, 15.3. HRMS: $(M+H)^+$ calculated for $C_{19}H_{25}BrN_2O_3S_2$ 473.04899; found 473.05634.

4.4. Route C: Alternative route to sulfoximine building block 8

*4.4.1. 4-Bromobenzene-1,3-disulfonyl dichloride (**20**)*

A mixture of 4-bromobenzene sulfonyl chloride (**19**, 50.0 g, 197 mmol) and chlorosulfonic acid (260 mL, 3.91 mol) was stirred for 6 h at 150 °C. The reaction mixture was poured slowly in a 1.5 L bath of ice-water [CAUTION: Strongly exothermic]. The reaction mixture was extracted with DCM (500 mL and 200 mL) and the organic phases were combined, dried over $MgSO_4$ and concetrated to dryness. The solid was suspended in a mixture of EtOAc-heptane (1:10, 330 mL) and the resulting grey precipitate was collected by filtration and dried to a constant weight to afford the title compound (**20**, 54.0 g, 78%) as a grey solid: UPLC-MS (t_R =1.26 min, purity=98%), ESI *m/z* 332.78 / 334.73 $(M-(Cl+OH)H)^-$; ^{1}H NMR ($CDCl_3$) δ 8.81 (d, *J*=2.0 Hz, 1H), 8.18 (d, *J*=2.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.32, 143.90, 138.26, 132.85, 129.04, 129.01. HRMS: $(M-H)^-$ calculated for $C_6H_3BrCl_2O_4S_2$ 350.8033; found 332.8320 $(M-(Cl+OH)-H)^-$.

*4.4.2. 2-Bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-benzenesulfonyl chloride (**21**)*

A solution of 4-ethyl-*N*-isobutylaniline (**5**, 0.43 g, 2.17 mmol) and pyridine (180 µL, 2.23 mmol) in THF (11.0 mL) at 0 °C was added dropwise a solution of 4-bromobenzene-1,3-disulfonyl dichloride (**20**, 1.00 g, 2.17 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at r.t. for 20 h, quenched with 1.0 M HCl (aq) (1 mL) and extracted with EtOAc (30 mL). The organic phase was washed with water (2 x 5 mL), dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography eluting with heptane-EtOAc (0-20%) to afford the title compound (**21**, 0.86 g, 80%) as an off-white solid: UPLC-MS (t_R=1.49 min, purity=92%), ESI *m/z* 474.00 / 476.98 $(M-(Cl+OH)H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, *J*=2.3 Hz, 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.28 (dd, *J*=8.3, 2.3 Hz, 1H), 7.21 (d, *J*=8.4 Hz, 2H), 7.01 (d, *J*=8.4 Hz, 2H), 3.31 (d, *J*=7.2 Hz, 2H), 2.61 (q, *J*=7.6 Hz, 2H), 1.42 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (d, *J*=6.7 Hz, 6H).

*4.4.3. 4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-mercapto-benzenesulfonamide (**22**)*

A solution of 2-bromo-5-(*N*-(4-ethylphenyl)-*N*-isobutylsulfamoyl)benzenesulfonyl chloride (1.50 g, 3.03 mmol) in toluene (6.00 mL) was added dropwise to a stirred solution of triphenylphosphine (2.39 g, 9.09 mmol) in toluene (15.0 mL) and the reaction mixture was heated at 90 °C for 2 h, cooled to r.t. and concentrated to dryness to afford the title compound (4.30 g, (contaminated with excess triphenylphospshine and triphenylphosphine oxide) as a white solid that was used directly in the next step without further purification: UP-LCMS (t_R=1.51 min, purity=89%), ESI^- *m/z* 426.01 / 428.01 $(M-H)^-$.

*4.4.4. 4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(methylthio)-benzenesulfonamide (**16**)*

To a stirred solution of 4-bromo-*N*-(4-ethylphenyl)-*N*-isobutyl-3-mercaptobenzenesulfonamide (**22**, 1.20 g, 2.80 mmol, 1.00 eq.) in DMF (12 mL) at r.t. was added K_2CO_3 (0.43 g, 3.08 mmol) followed by iodomethane (0.26 mL, 4.20 mmol). The reaction mixture was stirred at r.t. for 20 minutes and water (5 mL) was added. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the organic phases were combined, washed with brine (3 x 5 mL) and concentrated to dryness. The residue was purified by flash chromatography eluting with heptane-EtOAc (0-10%) to afford the title compound (0.79 g, 64%) as a white solid: UPLC-MS (t_R=1.53 min, purity=100%), ESI *m/z* 441.85 / 443.90 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 7.83 (d, *J*=8.3 Hz, 1H), 7.26 (dd, *J*=8.3, 2.1 Hz, 1H), 7.24 (d, *J*=8.3 Hz, 2H), 7.05 (d, *J*=8.3 Hz, 2H), 6.99 (d, *J*=2.1 Hz, 1H), 3.30 (m, 2H), 2.61 (q, *J*=7.6 Hz, 2H), 2.32 (s, 3H), 1.44 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (d, *J*=6.7 Hz, 6H).

4.5. Exploration of C-4 vector by S_NAr

*4.5.1. N-(4-Ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (**1**)*

NaH (60% dispersion in mineral oil, 0.51 g, 12.7 mmol) was added portionwise to (tetrahydropyran-4-yl)methanol (1.08 g, 9.29 mmol) in DMF (80 mL) at 0 °C followed by 4-bromo-*N*-(4-ethylphenyl)-*N*-isobutyl-3-(*S*-methylsulfonimidoyl)benzene-sulfonamide (4.00 g, 8.45 mmol). The reaction mixture was allowed to warm to r.t. and stirred overnight. Water (5 mL) was added and the reaction mixture was extracted with EtOAc (2 x

100 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography eluting with DCM-MeOH (0-5%) to afford the title compound (**1**, 3.63 g, 84%) as a white solid: UPLC-MS (t_R=1.32 min, purity=100%), ESI *m/z* 510.16 $(M+H)^+$; NMR analyses were identical to **1**.

*4.5.2. (S)-N-(4-Ethylphenyl)-N-isobutyl-3-(S-methylsulfon-imidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzene-sulfonamide (**24**) and (R)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfon-imidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzene-sulfonamide (**25**)*

A solution of **1 (**2.60 g, 5.11 mmol) in a mixture of MeOH-MeCN-DCM (52 mL:52 mL:13 mL) was purified by stack injections using SFC at 20 mg / mL (PIC Solution Preparative SFC; column: Chiralpak IA, 5 µM x 4.6 x 250 mm; eluent: 65% CO_2 / 35% *iso*-propanol; flow rate, 4 mL / min.; 100 Bar) to afford **24** as the first eluting fraction (0.92 g, 35.4%): (t_R=2.49 min, purity=100%), $[\alpha]_D^{20}$ = +0.6° (c = 2 g/L, EtOH); and **25** as the second eluting fraction (0.97 g, 37.3%): (t_R=5.31 min, purity=100%), $[\alpha]_D^{20}$ = -0.6° (c = 2 g/L, EtOH).

*4.5.3. (5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)(methyl)(oxo)-l6-sulfaniminium ((1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate (**25.camphorsulfonate**)*

To a solution of **25** (from elution fraction 2) (0.50 g, 0.9 mmol) in DCM (3.0 mL) at 23 °C was added a solution of (1*R*)-(−)-10-camphorsulfonic acid (228 mg, 0.9 mmol) in DCM (3.0 mL). The solution was stirred at 23 °C for 24 h and evaporated to dryness to yield a white solid. In a 20 mL vial, the solid was suspended in 10 mL of acetonitrile and 5 mL of DCM were added until complete dissolution occurred. The vial was then sealed and the screw cap perforated with a needle. The vial was then allowed to settle for several days at 23°C while large needle shape crystals slowly formed. Crystals of **25.camphorsulfonate** were collected by filtration, dried under vacuum and used as such for single crystal X-Ray analysis. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, *J* = 2.5 Hz, 1H), 7.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 4.27 – 4.12 (m, 2H), 3.96 – 3.87 (m, 2H), 3.70 (s, 3H), 3.37 (td, *J* = 11.7, 2.2 Hz, 2H), 3.30 (dd, *J* = 7.3, 3.8 Hz, 2H), 2.89 (d, *J* = 14.7 Hz, 1H), 2.73 – 2.56 (m, 3H), 2.39 (d, *J* = 14.7 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.20 – 2.09 (m, 1H), 1.94 (t, *J* = 4.6 Hz, 1H), 1.90 – 1.61 (m, 5H), 1.51 – 1.24 (m, 6H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.05 (s, 3H), 0.86 (dd, *J* = 6.6, 3.6 Hz, 6H), 0.75 (s, 3H)

*4.5.4. N-(4-Ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (**23**)*

A solution of 4-bromo-*N*-(4-ethylphenyl)-*N*-isobutyl-3-(*S*-methylsulfonimidoyl)benzene-sulfonamide (**8**, 15.0 mg, 30 µmol) in (tetrahydro-2*H*-pyran-4-yl)methanamine (11.3 µl, 0.10 mmol) was stirred overnight and purified directly by mass-triggered preparative LC/MS to afford the title compound (**23**, 15.0 mg, 93%) as a white solid: UPLC-MS (t_R=1.30 min, purity=100%), ESI *m/z* 509.33 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.84 (t, *J*=5.5 Hz, 1H), 7.70 (d, *J*=2.3 Hz, 1H), 7.50 (d, *J*=9.0 Hz, 1H), 7.20 (d, *J*=8.1 Hz, 2H), 7.00 (d, *J*=7.9 Hz, 2H), 6.95 (d, *J*=8.9 Hz, 1H), 4.74 (s, 1H), 3.89 (dd, *J*=11.6, 4.0 Hz, 2H), 3.24 (dd, *J*=7.4, 3.3 Hz, 2H), 3.17 (q, *J*=6.8 Hz, 2H), 3.01 (s, 3H), 2.61 (q, *J*=7.4 Hz, 2H), 1.87 (s, 1H), 1.66 (d, *J*=13.3 Hz, 2H), 1.46 – 1.37 (m, 1H), 1.28 (dd, *J*=14.5, 10.3 Hz, 2H), 1.18 (t, *J*=7.7 Hz, 3H), 0.84 (d, *J*=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) *δ* 169.87, 144.21, 140.34, 136.64, 133.38, 128.47, 128.42, 126.28, 123.19, 122.40, 110.15, 77.32, 77.21, 77.01, 76.69, 67.29, 58.07, 48.74, 34.18, 30.59, 28.41, 26.79, 19.86, 15.26.

4.6. Route D: Optimized route to deliver 100 g of 24

*4.6.1. 4-Ethyl-N-isobutylaniline hydrochloride (**5.HCl**)*

In a 15 L double jacketed reactor 4-ethylaniline (442 mL, 3.56 mol, 1.00 eq.) and isobutyraldehyde (324 mL, 3.56 mol, 1.00 eq.) were charged at 23 °C followed by *tert*-butylmethylether (4.50 L). Reaction mixture turned to a deep red solution. This solution was stirred at 23 °C for 1 h and then cooled to 15 °C. At this temperature solid sodium triacetoxyborohydride (1.13 Kg, 5.34 mol, 1.50 eq.) was added portionwise (~200 g per portions) over 1 hour. An exotherm was observed after each addition and the internal temperature was kept below 25 °C between each addition. After the last addition the reaction mixture was allowed to warm to 23 °C and stirred at this temperature for 18 h. LC/MS analysis after this time revealed complete conversion. To the reaction medium was added water (2.50 L) (no exotherm or gaz evolution was observed) and the mixture was stirred at 23 °C for 15 minutes. Phases were separated and the aqueous layer was discarded. The organic layer was washed with water (2.50 L). The reactor was cleaned and the organic layer re-charged. To this solution was added at 23 °C 3M HCl in cyclopentylmethylether (1.40 L, 3.00 M, 4.27 mol, 1.20 eq.). Crystallization occurred rapidly and the suspension was stirred for 2 h at 23 °C. The solid was collected by filtration and the cake washed with TBME (2 x 1.00 L) collected and dried under vacuum at 45 °C for 18 h to afford the title compound (575 g, 75% yield) as a white crystalline solid: mp = 147 °C; UPLC-MS (t_R=1.11 min, purity=100%), ESI *m/z* 179.1 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 11.21 (s, 2H), 7.48 (d, *J*=8.5 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 3.01 (t, 2H), 2.59 (q, *J*=7.6 Hz, 2H), 2.09 (m, 1H), 1.17 (t, *J*=7.6 Hz, 3H), 0.98 (d, *J*=6.7 Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 143.9, 135.0, 129.1, 122.6, 57.8, 27.7, 25.3, 20.2, 15.6.

*4.6.2. 4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(methylthio)-benzenesulfonamide (**16**)*

In a 15 L double jacketed reactor was introduced 4-ethyl-*N*-isobutylaniline hydrochloride (183 g, 0.86 mol, 1.05 eq.) followed by a suspension of 4-bromo-3-(methylthio)benzene-1-sulfonyl chloride **9** (260 g, 0.82 mol, 1.00 eq.) in acetonitrile (1.73 L). The reaction mixture was warmed up to 50 °C and *N*,*N*-diisopropylethylamine (352 ml, 2.05 mmol, 2.50 eq.) was added slowly. An exotherm was observed upon addition with internal temperature rising to 60 °C. The reaction mixture turned to a solution and was stirred at 50 °C for 3 h. LC/MS analysis after this time revealed complete conversion with less than 3% of starting material remaining. The reaction mixture was warmed up to 70 °C and slowly was added 1N aqueous HCl (1.70 L). A precipitate formed rapidly. The suspension was stirred at 50 °C for 30 minutes and allowed to cool down to 23°C over 1 h. The solid was collected by filtration, washed with water and dried on the filter for 2 h with a flux of N_2. The crude wet solid was charged in the clean reactor and isopropanol (3.70 L) was added. The suspension was warmed to 80 °C and turned to a solution. The solution was stirred under reflux for 15 minutes and allowed to cool down to 23 °C slowly over 4 h. The solid was collected by filtration, washed with 1.00 L of *i*PrOH and dried under vacuum at 45 °C to afford the title compound (320 g, 88% yield) as a beige solid: mp = 114 °C; HPLC-MS (t_R=11.9 min, purity=98.9%), ESI *m/z* 443.5 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.83 (d, *J*=8.3 Hz, 1H), 7.26 (dd, *J*=8.3, 2.2 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 7.03 (d, *J*=8.2 Hz, 2H), 6.98 (d,

J=2.0 Hz, 1H), 3.35 – 3.28 (m, 2H), 2.61 (q, *J*=7.6 Hz, 2H), 2.32 (s, 3H), 1.43 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 143.6, 141.3, 137.5, 136.2, 133.2, 128.3, 128.1, 125.0, 124.0, 122.9, 56.8, 27.6, 26.3, 19.5, 15.3, 14.5.

*4.6.3. 4-Bromo-3-(N-cyano-S-methylsulfinimidoyl)-N-(4-ethylphenyl)-N-isobutylbenzenesulfonamide (**27**)*

In a 15 L double jacketed reactor were charged **16** (540 g, 1.22 mol, 1.00 eq.) and potassium *tert*-butoxide (164 g, 1.46 mol, 1.20 eq.) followed by THF (2.70 L) and methanol (4.80 L). At 23 °C was added a solution of cyanamide (66.7 g, 1.59 mol, 1.30 eq.) in methanol (540 mL). No exotherm was observed. Solid *N*-bromosuccinimide (326 g, 1.83 mol, 1.50 eq.) was added portionwise over 30 min. (a slight exotherm from 23 to 26 °C was observed). A yellow precipitate formed rapidly and the suspension was stirred for 18 h at 23 °C. LC/MS analysis after this time revealed complete conversion. The reaction mixture was diluted with 3.5 L of 5% aqueous $Na_2S_2O_5$ solution. The suspension turned white (slight exotherm observed) and was cooled down to 5 °C. The solid was collected by filtration, washed with 1.0 L of water and dried under high vacuum at 45 °C for 36 h to afford the title compound (525 g, 89% yield) as a white solid: mp = 191 °C; HPLC-MS (t_R=9.3 min, purity=97.1%), ESI *m/z* 504.0 $(M+Na)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J*=8.3 Hz, 1H), 7.89 (d, *J*=2.2 Hz, 1H), 7.75 (dd, *J*=8.3, 2.2 Hz, 1H), 7.24 (d, *J*=8.3 Hz, 2H), 7.03 (d, *J*=8.3 Hz, 2H), 3.37 – 3.28 (m, 2H), 3.09 (s, 3H), 2.61 (q, *J*=7.6 Hz, 2H), 1.43 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.86 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 144.0, 138.7, 138.7, 136.0, 135.2, 132.2, 128.7, 128.3, 126.2, 125.3, 119.7, 57.4, 35.8, 27.7, 26.4, 19.6, 15.3; HRMS: $(M+H)^+$ calculated for $C_{20}H_{24}BrN_3O_2S_2$ 482.04933; found 482.05649.

*4.6.4. 4-Bromo-3-(N-cyano-S-methylsulfonimidoyl)-N-(4-ethyl-phenyl)-N-isobutylbenzenesulfonamide (**28**)*

In a 15 L double jacketed reactor was charged **27** (483 g, 1.00 mol, 1.00 eq.) followed by dichloromethane (1.93 L) and acetonitrile (1.93 L). To this solution was added ruthenium(III) chloride hydrate (3.39 g, 0.02 mol, 0.02 eq.) followed by a solution of periodic acid (274 g, 1.20 mol, 1.20 eq.) in water (966 mL). The black suspension was stirred at 23 °C for 1 h. HPLC analysis after this time revealed 6% remaining starting material. Extra periodic acid (12.0 g, 0.05 mol, 0.05 eq) was added (solid) and stirring was pursued for 1 h. LCMS analysis after this time revealed complete conversion. Water (2.00 L) was added to the solution and layers were separated. The aqueous layer was extracted with DCM (1.00 L) and the combined organic layers were charged in the reactor. A solution of sodium metabisulfite (300 g, 1.58 mol, 1.58 eq.) in 3.00 L of water was added. Biphasic mixture was stirred vigorously for 15 minutes (color changed from dark-brown to yellow) and phases were separated. The aqueous layer was extracted with 500 mL of dichloromethane. Combined organic layers were charged in the reactor, washed with 1.00 L of water and filtered to remove mechanical impurities. The reactor was cleaned and the filtrate was charged and distilled to a residual volume of 2.00 L. 3.00 L of *i*PrOH were added and distillation was pursued to a residual volume of 2.00 L. 3.00 L of *i*PrOH were added and distillation was pursued to a residual volume of 2.00 L. 3.80 L of diisopropylether were slowly added to the reaction mixture at 80 °C followed by acetone (300 mL) to solubilize crusts. The solution was then allowed to cool down to 23 °C over 48 h while a white solid crystallized. The solid was collected by filtration and the cake washed with 2 x 500 mL of diisopropylether. The solid was dried under vacuum at 45 °C for 18 h to afford the title compound (408 g, 82 %, 96.1 HPLC A% purity) as a beige solid: mp = 167°C; HPLC-MS (t_R =9.7 min, purity=96.1%), ESI *m/z* 498.1 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, *J*=8.0 Hz, 1H), 7.98 – 7.90 (m, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 6.99 (d, *J*=8.4 Hz, 2H), 3.89 (s, 3H), 3.44 – 3.21 (m, 2H), 2.61 (q, *J*=7.5 Hz, 2H), 1.45 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 0.84 (d, *J*=6.6 Hz, 3H), ^{13}C NMR (101 MHz, DMSO) δ 144.2, 137.9, 137.9, 136.3, 135.7, 134.4, 130.2, 128.8, 128.3, 125.5, 111.0, 57.5, 40.9, 27.8, 26.4, 19.6, 19.6, 15.4. HRMS: $(M+H)^+$ calculated for $C_{20}H_{24}BrN_3O_3S_2$ 498.04424; found 498.05118.

*4.6.5. 4-Bromo-3-(N-carbamoyl-S-methylsulfonimidoyl)-N-(4-ethylphenyl)-N-isobutylbenzenesulfonamide (**29**)*

In a 10 L double jacketed reactor was introduced **28** (445 g, 0.89 mol, 1.00 eq.) followed by dichloromethane (1.30 L) and water (32.1 ml, 1.79 mol, 2.00 eq.). To this solution was added slowly at 23 °C trifluoroacetic acid (2.2 L) (no exotherm was observed). The solution turned dark brown and was stirred at 23 °C for 20 h. LC/MS analysis after this time revealed complete conversion. The solution was cooled down to 0 °C and water (4.0 L) was added slowly, keeping the internal temperature below 25 °C. Then dichloromethane (1.0 L) was added and phases were separated. The aqueous layer was extracted with dichloromethane (1.0 L) and discarded. The combined organic layers were washed with water (2 x 1.0 L). Phases were separated and the organic layer (slurry) was recharged in the reactor. 1.5 L of dichloromethane were distilled off and then 3.0 L of *i*PrOH followed by 1.0 L of water were added. The suspension was stirred at 23 °C for 1 h and the solid collected by filtration and dried under vacuum at 45 °C for 18 h to afford the title compound (327 g, 71% yield): mp = 211 °C; HPLC-MS (t_R=7.7 min, purity=97.6%), ESI *m/z* 515.1 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J*=8.1 Hz, 1H), 8.07 (d, *J*=2.1 Hz, 1H), 7.70 (dd, *J*=8.3, 2.3 Hz, 1H), 7.21 (d, *J*=8.4 Hz, 2H), 7.01 (d, *J*=8.3 Hz, 2H), 6.51 (s, 1H), 6.16 (s, 1H), 3.45 (s, 3H), 3.29 (d, *J*=7.3 Hz, 2H), 2.61 (q, *J*=7.5 Hz, 2H), 1.43 (m, 1H), 1.18 (t, *J*=7.6 Hz, 3H), 0.87 (d, *J*=2.5 Hz, 3H), 0.85 (d, *J*=2.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 159.8, 143.9, 140.8, 137.7, 136.5, 136.0, 132.2, 130.1, 128.7, 128.4, 124.2, 57.6, 40.8, 27.7, 26.4, 19.6, 15.3; HRMS: $(M+H)^+$ calculated for $C_{20}H_{26}BrN_3O_4S_2$ 516.05481; found 516.06201.

*4.6.6. (S)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methyl-sulfonim-idoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzene-sulfonamide (**24**)*

In a 4 L double jacketed reactor were charged **29** (405 g, 0.73 mol, 1.00 eq.) and cesium carbonate (831 g, 2.55 mol, 3.50 eq.) followed by a solution of 4-(hydroxymethyl)tetrahydropyran (339 g, 2.92 mol, 4.00 eq.) in 1,4-dioxane (2.63 L). This suspension was warmed to reflux (105 °C) and 1.4 L of 1,4-dioxane were distilled off in 7 h. Distillation was stopped after this time and the suspension stirred at 100 °C for 24 h. LC/MS analysis after this time revealed complete conversion. The reaction mixture was cooled down to 80 °C and cesium carbonate was removed by filtration. The solid was rinse with 2 x 500 mL of acetone. The filtrate was charged in the clean reactor and heated to 60 °C to yield a clear dark mixture. To this solution was added a solution of *p*-toluenesulfonic acid monohydrate (166 g, 0.88 mol, 1.20 eq.) in acetone (750 mL). A solid formed rapidly and the suspension was allowed to cool down to 23 °C over 48 h. The solid was collected by filtration, washed with 500 mL of acetone and dried overnight under vacuum to yield a beige solid

(386 g). This solid was charged in the clean reactor and suspended in 2-methyltetrahydrofuran (3.0 L). The suspension was warmed to 50 °C and half of a solution of sodium hydroxide (117 g, 2.92 mol, 4.00 eq.) in water (1.5 L) was added. When complete solubility was reached, phases were separated at 50 °C. The organic layer was washed with the second half of the NaOH solution and finally with 500 mL of water. The mixture was then warmed to reflux and 2-methyltetrahydrofuran was distilled off to a final volume of 200 mL. *tert*-butylmethylether (1.0 L) was added slowly to the hot reaction mixture followed by acetone (830 mL) keeping the internal temperature above 50 °C to ensure full solubility. Then 2.30 L of *tert*-butylmethylether were slowly added and the solution stirred for 45 min under reflux. The solution was allowed to cool to 23 °C over 18 h. The suspension was then cooled to 5 °C and stirred at this temperature for 2 h. The solid was collected by filtration at 5 °C and dried under vacuum at 45 °C for 24 h to afford **1** (racemate, 279 g, 70% yield, 98.5 HPLC A% purity) as a white solid. **Chiral separation**: Enantiomer separation was performed by our partner Kyrapharm on 250 g of the racemate under the following conditions: Stationnary phase = CHIRALPACK AD, semi-automated Prochrom LC200 apparatus, 200 mm DAC column packed at 100 bars. 17 injections were performed using EtOH as the eluent with a 40 L/h flow rate. Fractions containing the desired enantiomer was evaporated to dryness under reduced pressure to afford the title compound (121 g) as a white solid: mp = 155°C; LC/MS (t_R=1.61 min), HPLC-MS (t_R=7.9 min, purity=99.6%), ESI *m/z* 509.2 $(M+H)^+$; Chiral SFC (t_R=2.4 min, purity=99.9% ee); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J*=2.5 Hz, 1H), 7.67 (dd, *J*=8.8, 2.5 Hz, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 7.20 (d, *J*=8.0 Hz, 2H), 7.00 (d, *J*=8.0 Hz, 2H), 4.58 (br s, 1H), 4.10 (dt, *J*=11.8, 5.8 Hz, 2H), 3.90 (dd, *J*=11.0, 4.1 Hz, 2H), 3.44 – 3.21 (m, 4H), 3.20 (s, 3H), 2.61 (q, *J*=7.6 Hz, 2H), 2.17 – 2.03 (m, 1H), 1.73 (d, *J*=9.9 Hz, 2H), 1.41 (q, *J*=11.0, 9.7 Hz, 3H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (dd, *J*=6.6, 4.4 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.0, 143.5, 136.4, 133.6, 132.1, 129.2, 128.5, 128.5, 128.3, 114.1, 73.8, 66.7, 57.2, 43.7, 34.4, 29.1, 29.1, 27.7, 26.4, 19.6, 15.3.

4.7. Route E: Last generation route to 1

*4.7.1. 4-((2-(Methylthio)phenoxy)methyl)tetrahydro-2H-pyran (**31**)*

In a 1 L flask was charged triphenylphosphine (112 g, 0.43 mol, 1.20 eq.), 4-(hydroxymethyl)tetrahydropyran (45.6 g, 0.39 mol, 1.10 eq.) and 2-methylsulfanyl-phenol (50 g, 0.36 mol, 1.00 eq.) in toluene (500 mL). The reaction mixture was warmed to 50 °C. At this temperature was added slowly diethyl azodicarboxylate (170 g, 0.39 mol, 1.10 eq.) (40% w/w solution in toluene). An exotherm was observed upon addition and the temperature of the reaction mixture was kept below 65 °C. The reaction mixture was stirred overnight at 23 °C. LC/MS analysis after this time revealed complete conversion. The slurry was warmed to 50-60 °C and magnesium chloride (74.7 g, 0.78 mol, 2.20 eq.) (70 microns from Aldrich) was added. Stirring was pursued for 1 h. The reaction mixture was cooled to 23 °C and filtered. The cake was washed with 50 mL of toluene. To the filtrate was added 500 mL of heptane and stirring was pursued for 2 h at 23 °C. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was triturated in 500 mL of a 8:2 heptane/toluene mixture. A solid formed and was removed by filtration. The filtrate was evaporated to dryness to yield and orange oil. This oil was triturated in 250 mL of heptane and crystallized rapidly as a white solid. Trituration was pursued for 1 h at 23 °C and the solid collected by filtration to afford the title compound (78.0 g, 92% yield) as a white solid: UPLC-MS (t_R=1.66 min), ESI *m/z* 239.3.2 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 – 7.05 (m, 2H), 7.03 – 6.86 (m, 2H), 3.93 – 3.81 (m, 4H), 3.34 (td, *J*=11.7, 2.2 Hz, 2H), 2.36 (s, 3H), 2.07 – 1.88 (m, 1H), 1.70 (ddd, *J*=12.9, 4.1, 2.0 Hz, 2H), 1.38 (dtd, *J*=13.3, 11.8, 4.5 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ 154.7, 127.2, 125.4, 124.8, 121.2, 111.3, 72.5, 66.8, 34.7, 29.3, 13.3; HRMS: $(M+H)^+$ calculated for $C_{13}H_{18}O_2S$ 239.10275; found 239.10994 $(M+H)^+$.

*4.7.2. N-(Methyl(2-((tetrahydro-2H-pyran-4-yl)methoxy)-phenyl)-λ4-sulfaneylidene)cyanamide (**32**)*

To a stirred solution of **31** (30.0 g, 0.13 mol, 1.00 eq.) and potassium *tert*-butoxide (16.9 g, 0.15 mol, 1.20 eq.) in THF (210 mL) at 23 °C was added a solution of cyanamide (6.88 g, 0.16 mol, 1.30 eq.) in methanol (90.0 mL). No significant exotherm was observed. Solid *N*-bromosuccinimide (33.6 g, 0.19 mol, 1.50 eq.) was added portionwise. An exotherm was observed after each addition, total addition time of 30 minutes with internal temperature rising to 45 °C. LC/MS analysis after 10 minutes revealed complete conversion. The reaction mixture was diluted with 10% $Na_2S_2O_5$ (200 mL) and evaporated under reduced pressure to remove the organic solvents. The aqueous layer was extracted with 2-methyltetrahydrofuran (2 x 200 mL) and the combined organic layers were dried and evaporated to dryness to yield an orange liquid which was further purified by chromatography eluting with DCM-EtOAc (0-30%) to afford the title compound (19.1 g, 54% yield) as a white crystalline solid: UPLC-MS (t_R=1.15 min,), ESI *m/z* 279.0 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (dd, *J*=7.9, 1.6 Hz, 1H), 7.65 (ddd, *J*=8.6, 7.4, 1.6 Hz, 1H), 7.34 – 7.26 (m, 2H), 4.10 – 3.99 (m, 2H), 3.95 – 3.85 (m, 2H), 3.37 (dd, *J*=11.8, 2.2 Hz, 2H), 3.05 (s, 3H), 2.14 – 1.99 (m, 1H), 1.76 – 1.62 (m, 2H), 1.47 – 1.28 (m, 2H).

*4.7.3. N-(Methyl(oxo)(2-((tetrahydro-2H-pyran-4-yl)methoxy)-phenyl)-λ6-sulfaneylidene)cyanamide (**33**)*

To a stirred solution of **32** (11.0 g, 0.04 mol, 1.00 eq.) and ruthenium(III) chloride hydrate (267 mg, 1.18 mmol, 0.03 eq.) in acetonitrile (110 mL) and dichloromethane (44 mL) at 23 °C was added a solution of periodic acid (9.91 g, 0.04 mol, 1.10 eq.) in water (44.0 mL). LC/MS analysis after 1 h revealed complete conversion. The reaction was quenched by addition of 10% $Na_2S_2O_5$ and diluted with DCM. Phases were separated and the aqueous layer washed with DCM. Combined organic layers were washed with 10% $Na_2S_2O_5$, dried and evaporated to dryness to yield a brown oil. The oil was purified by flash chromatography on SiO_2 eluting with DCM-EtOAc (0-30%) to afford the title compound (4.75 g, 40 %) as a white crystalline solid: UPLC-MS (t_R=1.18 min), ESI *m/z* 295.0 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, *J*=8.0, 1.7 Hz, 1H), 7.85 (ddd, *J*=9.0, 7.3, 1.8 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.29 (td, *J*=7.8, 0.9 Hz, 1H), 4.12 (ddd, *J*=39.6, 9.4, 6.3 Hz, 2H), 3.90 (ddd, *J*=11.2, 4.5, 1.9 Hz, 2H), 3.67 (s, 3H), 3.43 – 3.31 (m, 2H), 2.20 – 2.05 (m, 1H), 1.83 – 1.62 (m, 2H), 1.51 – 1.27 (m, 2H).

*4.7.4. 3-(N-Cyano-S-methylsulfonimidoyl)-N-(4-ethylphenyl)-N-isobutyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzene-sulfonamide (**34**)*

To **33** (300 mg, 1.02 mmol, 1.00 eq.) at 10 °C was added pure chlorosulfonic acid (1.36 mL, 20.0 mmol, 20.0 eq.) and the solution was stirred at 23 °C. LCMS analysis after 1.5 h (pyrrolidine quench) revealed complete conversion. The reaction mixture was slowly poured over ice and extracted with DCM.

Phases were separated and the organic layer was washed with water, dried and evaporated to dryness. The white solid obtained was dissolved in DCM (6.0 mL) and *N*,*N*-diisopropylethylamine (0.53 mL, 3.05 mol, 3.00 eq.) was added followed by 4-ethyl-*N*-isobutylaniline hydrochloride (240 mg, 1.12 mol, 1.10 eq.). The reaction mixture was stirred at 23 °C for 18 h. HPLC analysis after 18 h (pyrrolidine quench) revealed complete conversion. The reaction mixture was diluted with 1N HCl and phases were separated. The organic layer was washed with sat. aqueous $NaHCO_3$, brine, dried and evaporated to dryness. The orange solid was purified was purified by flash chromatography on SiO_2 eluting with DCM-EtOAc (0-50%) to afford the title compound (220 mg, 40% yield) as a white solid: UPLC-MS (t_R=1.69 min), ESI *m/z* 534.3 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (dd, *J*=8.8, 2.4 Hz, 1H), 7.74 (d, *J*=2.3 Hz, 1H), 7.64 (d, *J*=9.0 Hz, 1H), 7.22 (d, *J*=8.3 Hz, 2H), 6.96 (d, *J*=8.3 Hz, 2H), 4.32 – 4.12 (m, 2H), 3.91 (ddd, *J*=11.3, 4.5, 1.9 Hz, 2H), 3.72 (s, 3H), 3.41 – 3.36 (m, 2H), 3.42 – 3.17 (m, 2H), 2.61 (q, *J*=7.6 Hz, 2H), 2.22 – 2.08 (m, 1H), 1.84 – 1.63 (m, 2H), 1.51 – 1.33 (m, 3H), 1.18 (t, *J*=7.6 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H), 0.84 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 159.2, 143.9, 136.3, 136.2, 129.7, 129.6, 128.7, 128.3, 123.0, 115.4, 111.7, 74.8, 66.6, 57.4, 41.5, 34.2, 29.1, 28.8, 27.8, 26.4, 19.7, 19.6, 15.4.

*4.7.5. N-(4-Ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzene-sulfonamide (**1**)*

To **34** (200 mg, 0.37 mmol, 1.00 eq.) in DCM (3 ml) was added trifluoroacetic anhydride (83.0 mg, 0.39 mmol, 1.05 eq.) and the solution was stirred at 23 °C for 2 h. HPLC analysis after 2 h revealed complete conversion to the intermediate trifluoroacetamide. The reaction mixture was quenched with water (0.50 mL) and evaporated to dryness. The residue was dissolved in MeOH (3 mL) and K_2CO_3 (100 mg, 0.74 mmol, 2.00 eq.) was added. The suspension was stirred at 23 °C for 1 h. LC/MS analysis after 1 h revealed complete conversion. The reaction mixture was diluted with water (5.0 mL) and a white solid precipitated. The solid was collected by filtration to afford the title compound (173 mg, 92% yield) as a white solid: UPLC-MS (t_R=1.61 min, purity=97.2%), ESI *m/z* 509.2 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J*=2.5 Hz, 1H), 7.67 (dd, *J*=8.8, 2.5 Hz, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 7.20 (d, *J*=8.0 Hz, 2H), 7.00 (d, *J*=8.0 Hz, 2H), 4.58 (br, 1H), 4.10 (dt, *J*=11.8, 5.8 Hz, 2H), 3.90 (dd, *J*=11.0, 4.1 Hz, 2H), 3.44 – 3.21 (m, 4H), 3.20 (s, 3H), 2.61 (q, *J*=7.6 Hz, 2H), 2.17 – 2.03 (m, 1H), 1.73 (d, *J*=9.9 Hz, 2H), 1.41 (q, *J*=11.0, 9.7 Hz, 3H), 1.18 (t, *J*=7.6 Hz, 3H), 0.85 (dd, *J*=6.6, 4.4 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.0, 143.5, 136.4, 133.6, 132.1, 129.2, 128.5, 128.5, 128.3, 114.1, 73.8, 66.7, 57.2, 43.7, 34.4, 29.1, 29.1, 27.7, 26.4, 19.6, 15.3.

Acknowledgments

The authors would like to acknowledge the support of our CRO partners, in particular, Santai Labs for supplying building block **9** on large-scale. Grégoire Mouis and Ghizlane El-Bazbouz are gratefully acknowledged for their help with the purification of a selection of these compounds. Prof. Gérard Coquerel is acknowledged for the absolute configuration elucidation of compound **25**.

Supporting information

The structural elucidation of compound **25** (1*R*)-(−)-10-camphorsulfonic acid salt as well as LCMS chromatograms and NMR spectra for a majority of compounds described in this paper are included at no extra charge.

References and notes

1. a) Greb, J. E.; Goldminz, A. M.; Elder, J. T.; Lebwohl, M. G.; Gladman, D. D.; Wu, J. J.; Mehta, N. N.; Finlay, A. Y.; Gottlieb, A. B. *Nat. Rev. Disease Primers* **2016**, *2*, 1-17.
2. a) Kojetin, D. J.; Burris T. *Nat. Rev. Drug Discov.* **2014**,*13*,197–216; b) Banerjee, D.; Zhao, L.; Wu, L.; Palanichamy, A.; Ergun, A.; Peng, L.; Quigley, S.; Hamann, S.; Dunstan, R.; Cullen, P.; Allaire; N.; Guertin, K.; Wang, T.; Chao, J.; Loh, C.; Fontenot, J. D. *Immunology* **2016**, *147*, 399–413; c) Cyr, P.; Bronner, S. M.; Crawford, J.J. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4387–4393 and references cited therein.
3. http://ir.vitaepharma.com/phoenix.zhtml?c=219654&p=irol-newsArticle&ID=2149044
4. Ouvry, G.; Atrux-Tallau, N.; Bihl, F.; Bondu, A.; Bouix-Peter, C.; Carlavan, I.; Christin, O.; Cuadrado, M.-J.; Defoin-Platel, C.; Deret, S.; Duvert, D.; Feret, C.; Forissier, M.; Fournier, J.-F.; Froude, D.; Hacini-Rachinel, F.; Harris, C. S.; Hervouet, C.; Huguet, H.; Lafitte, G.; Luzy, A.-P.; Musicki, B.; Orfila, D.; Ozello, B.; Pascau, C.; Pascau, J.; Parnet, V.; Peluchon, G.; Pierre, R.; Piwnica, D.; Raffin, C.; Rossio, P.; Spiesse, D.; Taquet, N.; Thoreau, E.; Vatinel, R.; Vial, E.; Hennequin, L. F. *ChemMedChem* **2018**, *13*, 321-337.
5. Ouvry, G.; Bihl, F. ; Bouix-Peter, C. ; Christin, O. ; Defoin-Platel, C. ; Deret, S. ; Feret, C. ; Froude, D. ; Hacini-Rachinel, F. ; Harris, C. S. ; Hervouet, C. ; Lafitte, G. ; Luzy, A-P. ; Musicki, B. ; Orfila, D. ; Parnet, V. ; Pascau, C.; Pascau, J.; Pierre, R. ; Raffin, C. ; Rossio, P. ; Spiesse, D. ; Taquet, N. ; Thoreau, E.; Vatinel, R.; Vial, E.; Hennequin, L. F. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1269-1273.
6. a) Lücking, U. *Angew. Chem. Int. Ed Engl.* **2013**, *52*, 9399-9340; b) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. *Eur. J. Med. Chem.* **2017** *126*, 225-245; c) Sirvent, J.A; Lücking, U. *ChemMedChem* **2017**, *12*, 487-501; Zenzola, M.; Doran, R.; Degennaro, L.; Luisi R.; Bull, J.A. *Ang. Chem. Int. Ed Engl.* **2016**, *55*,7203-7207.
7. Raza, A.; Sham, Y. Y.; Vince, R. *Bioorg. Med. Chem. Lett.* **2008,** *18*, 5406-5410.
8. a) Birault, V.; Campbell, A. J.; Harrison, S. A.; Le, J.; Shukla, L. WO2013/160418, 31 Oct, 2013; b) Birault, V.; Campbell, A. J.; Harrison, S.; Le, J. WO2015/061515, 30 Apr, 2015. GSK's lead compound is suspected to be GSK2981278.
9. Chakraborti, A. K.; Nayak, M. K.; Sharma, L. *J. Org. Chem.* **2002**, *67*, 1776–1780.
10. Mispelaere-Canivet, C.; Spindler, J-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253-5259.
11. Okamura, H.; Bolm, C. *Org. Lett.*, **2004**, *6*, 1305–1307.
12. Porte, A. M.; Caggiano, T. J.; Diamantidis, G.; Hauze, D. B.; Harrison, B. L.; Hoke, M.; Kreft, A.; Kubrak, D. M.; Mann, C. W.; Mayer, S.; Morris, K. M. U.S. Pat. Appl. Publ., 20070249722,
13. Park, K. K.; Lee, J. H. *Bull. Kor. Chem. Soc.* **2008,** *29*, 2502-2504.
14. Ramadas, K.; Srinivasan, N. *Synth. Commun.* **1992**, *22*, 3189-3195.
15. Deprez, P.; Jary, H.; Temal, T. PCT Int. Appl., 2007060026.
16. Choong, I. C.; Lew, W.; Lee, D.; Pham, P.; Burdett, M. T.; Lam, J. W.; Wiesmann, C.; Luong, T. N.; Fahr, B.; DeLano, W. L.; McDowell, R. S.; Allen, D. A.; Erlanson, D. A.; Gordon, E. M.; O'Brien, T. *J. Med. Chem.* **2002**, *45*, 5005-5022.
17. Gries, J.; Krueger, J. *Synlett* **2014**, *25*, 1831-1834.
18. Bellale, E. V.; Chaudhari, M. K.; Akamanchi, K. G. *Synthesis* **2009**, *19*, 3211-3213.
19. a) Dixon, D. D.; Grina, J.; Josey, J. A.; Rizzi, J. P.; Schlachter, S. T.; Wallace, E. M.; Wang, B.; Wehn, P.; Xu, R.; Yang, H. PCT Int. Appl., 2015035223; b) Luecking, U.; Siemeister, G.; Bader, B. PCT Int. Appl., 2007079982.
20. a) Heinrich, T.; Zenke, F.; Rohdich, F.; Friese-Hamim, M.; Hahn, D. PCT Int. Appl., 2016020031; b) Schulze, V.; Kosemund, D.; Wengner, A. M.; Siemeister, G.; Stoeckigt, D.; Lienau, P.; Schirok, H.; Briem, H. PCT Int. Appl., 2012143329.
21. See the supporting information for the synthesis of **25.camphorsulfonate**
22. a) Mancheño, O. G.; Bolm, C. *Org. Lett.* **2007**, *9*, 2951-2954; b) Mancheño, O. G.; Bistri, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 3809-3811.
23. Addition of a small amount of water to DCM ensure a reproducible hydrolysis time on scale
24. Double chlorosulfonylation was achieved at 150°C with a highly exothermic quench limiting its throughput on larger scale

25. ~500€ per mol from Aldrich
26. Isola, A. M.; Klintz R.; Koser S.; Watts J.P.; Muenster P.; Holman N. J. Tometzki G. B. Patent CA2222854, 1998