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Kepner-Tregoe Decision Analysis as a Tool To Aid Route Selection. Part 3. Application to a Back-Up Series of Compounds in the PDK Project

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Abstract:

Kepner-Tregoe Decision Analysis was used to rank 22 potential routes to a back-up series of compounds in the PDK project. The ten highest scoring routes were evaluated practically, affording four new synthetic sequences for preparing the target compounds.

Introduction

The use of Kepner-Tregoe Decision Analysis (KTDA) to help prioritise synthetic routes has been described in a previous paper in this series.[1] Following on from the lead compound in the PDK project, AZD7545,[2] a back-up series of compounds was identified for the treatment of type II diabetes (Figure 1).

The back-up series bears some similarities to AZD7545, the most important being the presence of the same chiral amide group. The back-up compounds are also anilines with a *p*-sulfone and an *o*-chlorine; however, the sulfones were changed to simple alkyl and a piperazine unit was introduced in the *meta* position.

The medicinal chemistry synthetic route was a seven-step synthesis starting from 2,3,4-trifluoronitrobenzene (Scheme 1 shows the preparation of AZM574670). The 2-fluorine of the starting material was selectively displaced using ammonia in a sealed tube, and then the 4-fluorine was substituted using the appropriate alkyl thiol. The amino group was converted to a chloro using a Sandmeyer reaction, and the nitro group was reduced. The chiral amine portion of the molecule was then introduced using the original conditions developed for AZD7545. Finally the sulfide was oxidised to the afford the sulfone, and the appropriate piperazine was introduced using an S_NAr reaction to afford the target molecules. All four possible piperazines were commercially available, and sourcing these molecules on scale was not considered to be an issue.

When the project was received into Process Research and Development, this route was evaluated for potential long-term manufacture, allowing identification of the key issues. The most significant of the two issues identified was that the third step of the synthesis is a diazotization, and following a hazard evaluation of this reaction, it was decided that it would not be safe for further scale-up using standard processing equipment. The other major issue was that the starting material was extremely expensive, and using this compound would push the cost of the final API well beyond the cost of goods target.

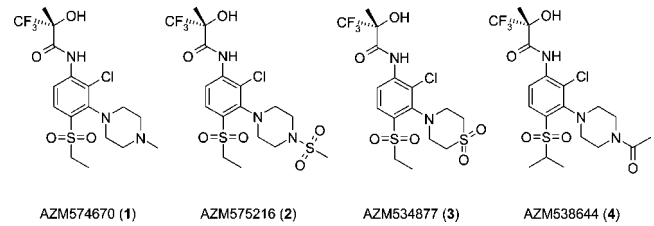
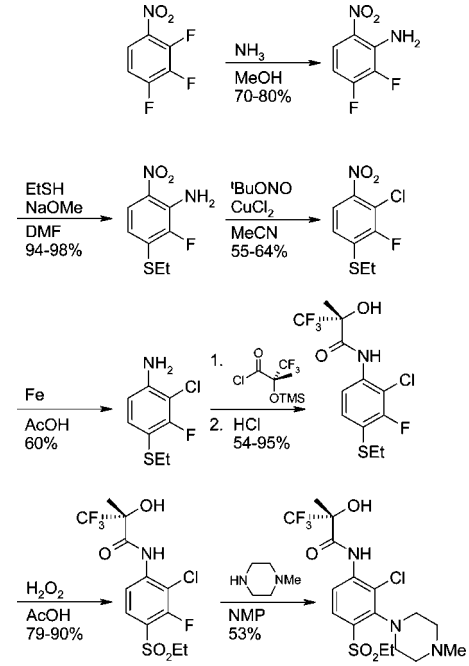


Figure 1. **PDK back-up compounds.**

Scheme 1. **Medicinal Chemistry route**



Having determined that a new synthesis would be required, a search for alternative routes was started. The preparation of 1,2,3,4-tetrasubstituted aromatic rings is a challenging synthetic problem, and following extensive literature searching, 21 new routes were proposed by scientists across the department.

The use of Kepner-Tregoe Decision Analysis was then introduced to compare the ideas, allowing prioritisation of routes and development of a work plan.

Kepner-Tregoe Decision Analysis

Decision Statement. Following discussions by the project team, the following decision statement was agreed upon: "To identify routes for the long-term manufacture of the drug candidates, the bond-forming reactions of which will be used for delivery of the first campaign, paying particular attention to safety, health and environmental issues. Any new routes

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(1) Parker, J. S.; Moseley, J. D. *Org. Process Res. Dev.* **2008**, *12*, 1041–1043.

(2) Moseley, J. D.; Brown, D.; Firkin, C.; Jenkin, S.; Patel, B.; Snape, E. *Org. Process Res. Dev.* **2008**, *12*, 1044–1059.

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should have the flexibility to deliver any of the candidates under consideration."

The statement clarifies that the objective is to identify routes that could be used for long-term manufacture and that whichever route was selected, the intention would be to use transformations identified to deliver the first campaign.

Develop Objectives. The list of possible factors was reviewed,[1] and the following were selected:

- Safety, health and environment were obvious factors to include, particularly as they were identified in the decision statement.
- Intellectual property was included, as any new route would need to have freedom to operate if outside the scope of the medicinal chemistry patent.
- Accommodation of any difficult steps needed to be considered.
- Raw material costs were important, as starting material costs made the medicinal chemistry route too expensive. Additionally, any proposed starting materials needed to be available to purchase in bulk.
- Feasibility of any proposed chemistry needed to be considered.
- Number of steps, with a reduction from the seven steps used in the medicinal chemistry route desired.
- Number of steps to key step was included, as with limited resource it was unlikely that it would be possible to evaluate all of the routes proposed. Thus, working through the options as quickly as possible by tackling key reactions, the maximum number of routes could be evaluated.
- Flexibility was included as the project had yet to choose a single compound, and thus routes allowing delivery of all four compounds were required.

Identify Musts and Wants. The factors selected in the Develop Objects section were considered and divided into Musts (Table 1) and Wants (Table 2). It was decided that flexibility was both a Must and a Want, as it was essential that a route could deliver any of the three compounds under consideration but also desirable that the route introduced the variability (piperazine and/or alkyl sulfone) late in the synthesis, allowing preparation of common intermediates while the short list was being narrowed to one compound.

Table 1. **Musts**

factor	Must
safety	have no safety issues that would prevent large-scale manufacture
health	have no health issues that would prevent large-scale manufacture
environment	not use stoichiometric heavy metals
raw materials	use raw materials that are available to purchase on a large scale
intellectual property	have no patent or freedom to operate issues
flexibility	allow delivery any of the compounds
raw material costs	meet raw material cost targets The cost of goods for the compounds was known to be an issue. The exact raw material cost target was unknown at the start of the route selection work, so this factor remained in the Decision Analysis calculations, but no routes were eliminated due to high raw material costs unless the cost equaled or exceed that for the medicinal chemistry route.

Table 2. **Wants**

factor	Want
accommodation	routes with no difficult reactions (e.g., low temperature steps, exothermic reactions, etc)
feasibility	well precedented chemistry
number of steps	minimum number of steps
flexibility	to be able to deliver any of the compounds by introducing the variable portions late in the synthesis
no. of steps to key step	a minimum number of steps to key step

Weigh the Wants. The relative importance of the Wants was considered, and feasibility, number of steps and number of steps to key step were selected as the most important. It was hoped that these represented a balance between how likely the route was to work (feasibility) and how quickly the route could be evaluated (number of steps to key step) against the benefits of reducing the length of the route (number of steps). Accommodation was considered to be the next most important Want, scoring 7, with flexibility being less important, scoring 4 (Table 3).

Table 3. **Weighting for Wants**

Want	weighting
accommodation	7
feasibility	10
number of steps	10
flexibility	4
number of steps to key step	10

Generate Alternatives. A request for ideas was issued across the Global Process Research and Development department, resulting in 21 alternative routes to the target compounds. With these alternatives in hand the process of scoring, ordering and selecting new routes for evaluation could begin.

Screen Alternatives through the Musts. A data table (Table 4) was generated to analyse the suggested routes (routes being displayed by name of starting material, then by route name), and the alternatives were screened against the Musts.[3] Routes passing Musts were scored 1; those failing to meet the objective scored 0. The majority of failures were due to high raw material costs, including the medicinal chemistry route and a number of variants using the same starting material. Some other routes failed for not being flexible enough to deliver all the candidates under consideration. Multiplying the scores together gives a final score of 1 (route passes all Musts) or 0 (route fails at least one Must), giving a go/no go decision for each route to proceed to scoring against the Wants.

Compare Alternatives against the Wants. A scoring system for the Wants was now developed to allow the routes to be evaluated (Table 5):

- Accommodation. It was decided to consider the final three steps of any route (those most likely to be conducted in-house in the future), scoring 10 for any routes with no perceived problems. Three points would be deducted for any "problem" steps.

(3) Details of the highest scoring 10 routes are included in this paper. Details of lower scoring routes and those not passing the Musts are provided in Supporting Information.

Table 4. **Decision Analysis data table**

		Musts								Wants							
starting material	route title	safety	health	environment	raw materials	intellectual property	flexibility	raw material costs	go/ no go	accommodation, 7[a]	feasibility, 10[a]	no. of steps, 10[a]	flexibility, 4[a]	steps to key step, 10[a]	total score	rank	route
1-chloro-2,6-difluorobenzene	sulfonylation route	1	1	1	1	1	1	1	1	10	8	9	5	9	350	1	A
2,3-dichlorotoluene	Hoffmann	1	1	1	1	1	1	1	1	10	6	8	5	10	330	2	B
2,3-difluoro-6-nitrophenol	phenol activation and elimination	1	1	1	1	1	1	1	1	10	8	7	5	8	320	3	C
3,4-difluoronitrobenzene	thiol displacement	1	1	1	1	1	1	1	1	10	6	7	5	9	310	4	D
2,4-difluorothiophenol	2,4-difluorothiophenol	1	1	1	1	1	1	1	1	10	6	7	5	9	310	4	E
2,3,4-trichloronitrobenzene	sulfone displacement	1	1	1	1	1	1	1	1	10	6	9	5	7	310	4	F
2,3-dichloroaniline	diethyl disulphide	1	1	1	1	1	1	1	1	10	6	9	5	7	310	4	G
3,4-difluoronitrobenzene	sulfone displacement	1	1	1	1	1	1	1	1	10	4	8	5	9	300	8	H
2,4-dichloronitrobenzene	thiol displacement/ bromination	1	1	1	1	1	1	1	1	10	4	7	5	8	280	9	I
2,3-dichloroaniline	thiocyanation	1	1	1	1	1	1	1	1	10	6	7	5	5	270	10	J
3-aminophenol	diethyl disulphide	1	1	1	1	1	1	1	1	10	4	5	5	7	250		
3-aminophenol	thiocyanation	1	1	1	1	1	1	1	1	10	4	6	0	5	220		
4-nitrobenzenesulfonylchloride		1	1	1	1	1	1	1	1	10	4	7	0	5	230		
3,4-difluoronitrobenzene	late chlorination	1	1	1	1	1	1	1	1	10	4	3	5	5	210		
2,3 difluoro-6-nitroaniline	med chem route	0	1	1	1	1	1	0	0	7	10	6	5	10	329		
2,3 difluoro-6-nitroaniline	avoiding diazotisation	1	1	1	1	1	1	0	0								
2,3 difluoro-6-nitroaniline	sulphinic acid variation	1	1	1	1	1	1	0	0								
3,4-dichlorothiophenol	Br_2 S_EAr + Pd cross-coupling	1	1	1	1	1	1	0	0								
2,4-dianiline sulfonic acid	diamine differentiation	1	1	1	1	1	0	1	0								
2,4-dinitrohalobenzene	diamine differentiation	1	1	1	1	1	0	1	0								
2-chloro-3-nitroaniline		1	1	1	1	1	1	0	0								
2-chloro-3-fluorothiophenol		1	1	1	0	1	1	0	0								

[a] Weighting.

Table 5. **Scoring system for Wants**

want	scoring system
accommodation	consider final 3 steps score 10 −3 for any "problem" steps (sulfide to sulfone oxidation considered to be a problem step)
feasibility	score 10 for exact literature or AstraZeneca precedent score 8 for close literature precedent score 6 for a "better than even chance" score 4 for significant doubts, but some precedent score 2 for "one obscure paper suggests this is possible"
number of steps	score 10 for 3 steps score 9 for 4 steps score 8 for 5 steps score 7 for 6 steps score 6 for 7 steps score 5 for 8 steps score 4 for 9 steps score 3 for 10 steps score 2 for 11 steps score 1 for 12 steps score 0 for >12 steps
flexibility	score 10 if both heterocycle and sulfur introduced in last 3 steps score 5 if only heterocycle introduced in last 3 steps score 0 if neither heterocycle or sulfur introduced in last 3 steps
number of steps to key step	score 10 for first step score 9 for second step score 8 for third step score 7 for fourth step score 6 for fifth step score 5 for sixth step score 4 for seventh step score 3 for eighth step score 2 for ninth step score 1 for 10th step score 0 for >10th step

- Feasibility. The feasibility of the transformations was considered an extremely important factor in comparing the routes. The highest scoring routes would be any in which all the transformations had been demonstrated, and of the 22 routes proposed, only the medicinal chemistry route fulfilled this criteria. Thus, the other routes were scored against literature or in-house precedence (Table 5), with those that appeared to be reasonably feasible scoring highly and those with more speculative ideas scoring lower.
- Number of steps. Reducing the number of steps is a key aim in looking for an alternative route. It was initially hoped that it would be possible to identify a three-step route to the target compounds, and a score of 10 was offered for any route that achieved this. On receiving the alternative routes, the shortest option was four steps, which scored 9 (it was decided not adjust the scoring for the lack of three-step routes), and as the number of steps increased, the score decreased.
- Flexibility. Flexibility had been selected as a Want as it was hoped that it would be possible to find a route where the piperazine and sulfone fragments were introduced at a late stage, allowing the early preparation of an advanced intermediate which could be used to deliver any of the possible drug candidates. Of the two fragments, late introduction of the piperazine section was seen the more important, as this fragment was the more complex. Thus, any route that introduced both fragments in the final three steps scored 10, if the piperazine was introduced in the final three steps, the route scored 5 and if neither fragment was introduced in the final three steps the route scored 0.
- Number of steps to key step. Number of steps to key step measured how quickly it would be possible to look at the critical transformations in each route, either eliminating the route if the transformation did not work or increasing the feasibility of the route if the transformation did work. Routes where the key step was the first step (thus could be evaluated quickly) were scored 10, with the score decreasing the further through the route that the key step lay. With the scoring system

completed, all routes were scored against the Wants (Table 5), and the scores multiplied by the weight of the Want, giving a total score for each route. The routes were then ranked by total score, the highest scoring 360, the lowest scoring 189.

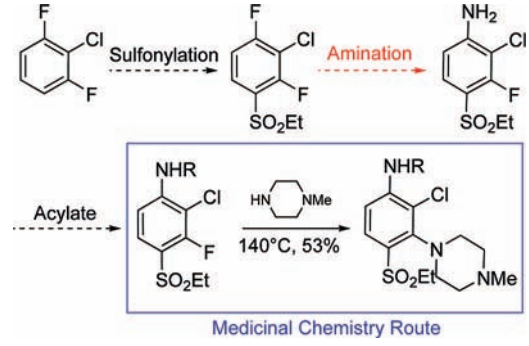
Identify Adverse Consequences. The top scoring routes were assessed in the light of the decision-making process, and no issues that would adversely affect the investigation of these routes were identified.

Make the Best Balanced Choice. The decision analysis procedure produced an ordered list of 14 routes that had the potential to deliver the drug candidates (Table 4). With limited amount of time and resource available, it was decided to investigate the top 10 routes (those scoring 249 or above), and work started initially focusing on the highest scoring routes.

Results and Discussion

The investigations into each of the 10 highest scoring routes are discussed below. For each proposed route, a scheme (for the synthesis of AZM574670) is given covering the type of chemistry required for each transformation. Additionally the Key Step in each scheme is marked in red. The chemistry that had been demonstrated previously (medicinal chemistry route) is shown in blue boxes. A table providing comments on how the route was evaluated against the Wants is available in the Appendix.

Route A



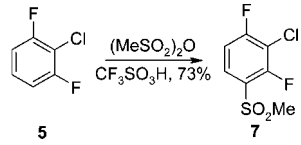
The highest scoring route, Route A (see Table A), is a four-step route starting from 1-chloro-2,6-difluoro-benzene (**5**). This

material is initially sulfonylated *ortho* to the fluorine (either fluorine as the molecule is symmetrical). The key step is then selectively displacing the fluorine *para* to the alkylsulfone group with an ammonia source. For this amination reaction, it was hoped that the bulk of the alkylsulfone group would shield the *o*-fluorine, improving the selectivity for substitution of the *p*-fluorine. If this reaction was successful, the sequence could be completed by acylating the aniline and introducing the piperazine using an S_NAr reaction.

The sulfonylation reaction was investigated using standard conditions from the literature.[4] Thus, 1-chloro-2,6-difluoro-benzene (**5**) was reacted with ethanesulfonyl chloride, catalysed by aluminium trichloride. Initial studies used nitrobenzene as the solvent, but when no conversion was observed, the reaction was conducted without solvent at 100 °C. Slow consumption of the starting material was observed using these conditions, affording a mixture of products including small amounts of the required 2-chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**), as well as mono- and bis-chlorination of the starting material.

In an attempt to avoid the chlorination of the starting material, it was decide to investigate the use of the corresponding fluoride in the reaction.[5] Ethanesulfonyl fluoride is not commercially available, but methanesulfonyl fluoride can be purchased and was used to investigate this approach. Also investigated at this time was the use of sulfonic anhydrides catalysed by trifluoromethanesulfonic acid.[6] Ethanesulfonic anhydride is not commercially available, but methanesulfonic anhydride could be purchased. Both these reactions were successful in producing 2-chloro-1,3-difluoro-4-(methylsulfonyl)benzene (**7**), and the procedure using the sulfonic anhydride was chosen for further development (Scheme 2) as it was simpler to handle the reagents and waste products.

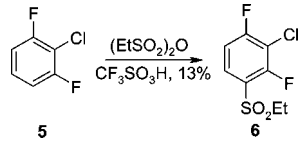
Scheme 2



5 **7**

Having identified suitable methodology for the sulfonylation reaction, ethanesulfonic anhydride was prepared[7] and reacted with 1-chloro-2,6-difluoro-benzene (**5**) to afford 2-chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**) (Scheme 3). The yield of the reaction was disappointing compared to the equivalent reaction with methanesulfonic anhydride, but enough material was prepared to continue with the route investigation.

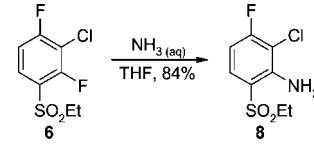
Scheme 3



5 **6**

The key step of the synthesis was then investigated, looking to substitute the *p*-fluorine to afford the required aniline. Reacting 2-chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**) with aqueous ammonia in organic solvents gave exclusive substitution at the *o*-fluorine, affording 2-chloro-3-(ethylsulfonyl)-6-fluoroaniline (**8**) (Scheme 4), with no evidence of any substitution at the *p*-fluorine.

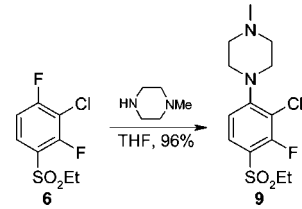
Scheme 4



6 **8**

With such good selectivity for substitution at the *o*-fluorine, it was decided to introduce the *N*-methyl piperazine group first, and then investigate the conversion of the *p*-fluorine to an amino group. However, reacting 2-chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**) with *N*-methyl piperazine in THF gave exclusive substitution at the *p*-fluorine affording 1-(2-chloro-4-(ethylsulfonyl)-3-fluorophenyl)-4-methylpiperazine (**9**) (Scheme 5), with no substitution at the *o*-fluorine.

Scheme 5



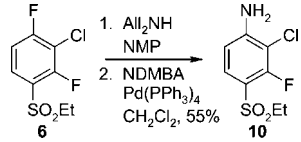
6 **9**

The two reactions showed that it was possible to get selective reaction at both the *o*- and *p*-fluorines, but the regioselectivity with ammonia and *N*-methyl piperazine was opposite to that required. To get around this problem, it was decided to identify an ammonia surrogate that would give the required regioselectivity at the *p*-fluorine and could then be converted to the required aniline. Work started looking at primary amines, but benzylamine, benzhydrylamine and *tert*-butylamine all reacted exclusively at the *o*-fluorine, and no reaction was observed with tritylamine. Attention then changed to looking at secondary amines, as *N*-methyl piperazine (a secondary amine) had given exclusive reaction at the *p*-fluorine. No reaction was observed with dibenzylamine, 1:1 *ortho*:*para* selectively was observed with diallylamine and 2:5 *ortho*:*para* selectivity with isoindoline. The selectivity with isoindoline was the most promising, and this reaction was probed further in an attempt to improve the regioselectivity. Increasing the polarity of the solvent was found to improve selectivity for *para*-substitution, with 1:160 *ortho*:*para* selectively in NMP and 1:50 *ortho*:*para* selectively in MeOH. Although good selectivity was observed, it was decided not to pursue this approach as the removal of the isoindoline group is known to be challenging,[8] and the

(4) Truce, W. E.; Vriesen, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 5032–5036.
(5) Hyatt, J. A.; White, A. W. *Synthesis* **1984**, 214–217.
(6) Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I. *Chem. Lett.* **1988**, 395–398.
(7) Field, L.; Settlage, P. H. *J. Am. Chem. Soc.* **1954**, *76*, 1222–1225.

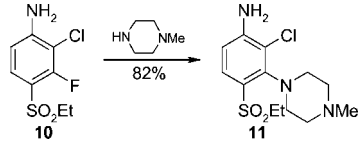
presence of a chlorine atom on the molecule was likely to further complicate this. Thus attention refocused on the use of diallylamine. Changing the solvent to NMP and keeping the temperature low gave 1:40 *ortho*:*para* selectively. The allyl groups could then be removed using palladium (0)-catalyzed deallylation[9] to afford the required 2-chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) (Scheme 6).

Scheme 6



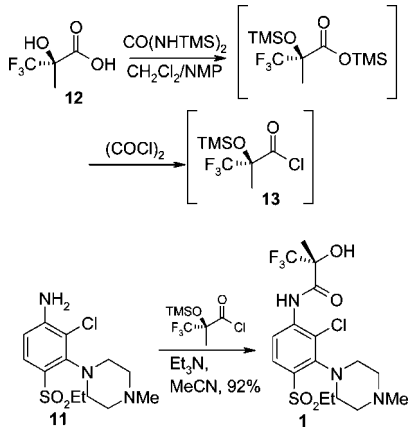
Having obtained the required intermediate, it was decided to reverse the order of the final two steps, introducing the chiral amine portion as the final step. Thus, 2-chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) was reacted with *N*-methyl piperazine, affording 2-chloro-3-(4-methylpiperazin-1-yl)-4-(ethylsulfonyl)-aniline (**11**) (Scheme 7).

Scheme 7



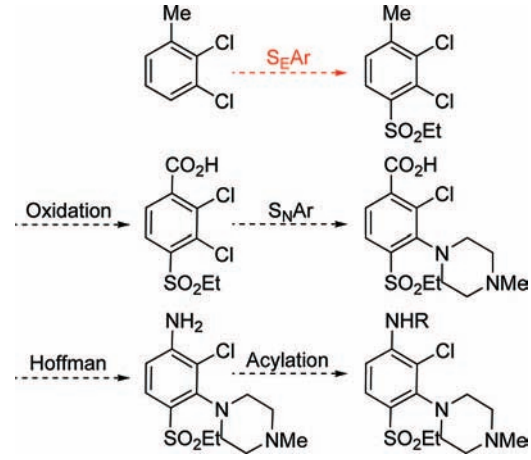
The final step, introduction of the chiral amide portion of the molecule, was achieved using the original conditions developed for the preparation of AZD7545.[2] (*R*)-3,3,3-Trifluoro-2-hydroxy-2-methyl-propionic acid (**12**) was doubly protected with trimethylsilyl groups and then converted to (*S*)-3,3,3-trifluoro-2-methyl-2-trimethylsilanyloxy-propionyl chloride (**13**) using oxalyl chloride. This acid chloride was then reacted with 2-chloro-3-(4-methylpiperazin-1-yl)-4-(ethylsulfonyl)aniline (**11**) (Scheme 8), affording AZM574670 (**1**) and completing the first new route to the drug candidates.

Scheme 8



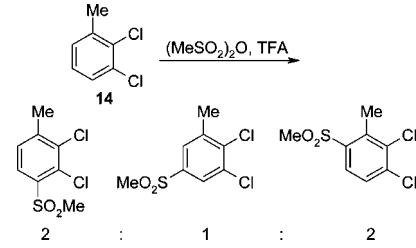
(8) Hou, D-R.; Hsieh, Y-D; Hsieh, Y-W. *Tetrahedron Lett.* **2005**, *46*, 5927–5929.

Route B



The route with the second highest score, Route B (see Table B), was one step longer than Route A but scored highly due to the key step being the first in the sequence, as well having precedented chemistry. Starting with 2,3-dichlorotoluene (**14**), the sulfone group is introduced using electrophilic aromatic substitution chemistry. The methyl group is then oxidised, and the piperazine is introduced by nucleophilic aromatic substitution of chlorine.[10] Finally, a Hoffman reaction converts the carboxylic acid group to an amine, which can be acylated to afford the required product.

Scheme 9

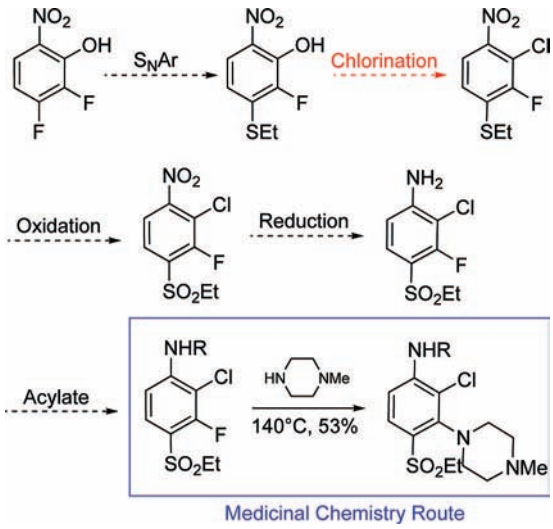


Workstarted looking at the key electrophilic aromatic substitution reaction, chemistry that was also under investigation for Route A. In Route B, regioselectivity was necessary to set up the correct substitution pattern on the aromatic ring, and thus sulfonylation *para* to the methyl group was required. It was hoped that the *ortho/para* directing effect of both the methyl group and the 3-chloride would provide some selectivity at the 4-position and that it would be possible to purify the product from any regioisomeric byproduct. The reaction was initially investigated using ethane sulfonyl chloride catalysed by aluminium trichloride in benzotrifluoride. The procedure produced a complicated mixture of products, and it was decided to change to using the sulfonylation conditions successfully demonstrated in Route A. Reacting 2,3-dichlorotoluene (**14**) with methanesulfonic anhydride in the presence of trifluoromethanesulfonic acid cleanly produced three products in a ratio of 2:1:2. Analysis of these products identified them as the 4-, 5- and 6-sulfones (Scheme 9) with substitution dominating at the 4- and 6-positions.

With no selectivity for 4-sulfonylation observed in the key reaction, it was decided to halt work on Route B.

(9) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109–6113.
(10) Feit, P. W.; Tvaermose Nielsen, O. B. *J. Med. Chem.* **1976**, *19*, 402–406.

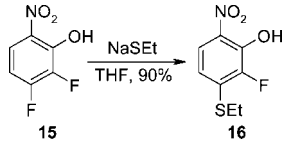
Route C



Route C (see also Table C) represented the closest route to the original medicinal chemistry route, with the aniline being replaced with the equivalent phenol. The phenol had the advantage of being less than 25% of the cost of aniline and removed the hazardous diazotisation step from the route.

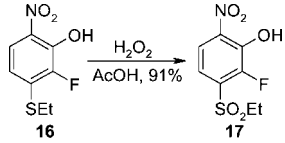
The first step on the route was completed by reacting the sodium salt of ethanethiol with 2,3-difluoro-6-nitrophenol (**15**), affording 3-(ethylthio)-2-fluoro-6-nitrophenol (**16**) in a 90% yield (Scheme 10).

Scheme 10



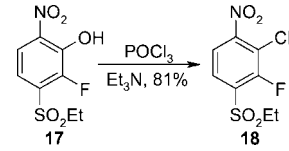
Chlorination of this molecule was investigated using phosphorus oxychloride and a variety of bases;[11] however, no reaction was observed. A further review of the literature suggested that the presence of electron-withdrawing groups on the aromatic ring is important to allow the reaction to proceed. Thus, it was decided to reverse the order of steps 2 and 3, first oxidising the sulfide to the sulfone to reduce the electron density of the aromatic ring, and then investigate the chlorination. 3-(Ethylthio)-2-fluoro-6-nitrophenol (**16**) was oxidised to 3-(ethylsulfonyl)-2-fluoro-6-nitrophenol (**17**), using the conditions developed for AZD7545[2] (Scheme 11).

Scheme 11



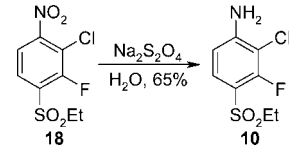
The chlorination was investigated again using phosphorus oxychloride and a variety of bases, which identified triethylamine as the best base for the reaction, affording 2-chloro-4-(ethanesulfonyl)-3-fluoro-1-nitrobenzene (**18**) in an 81% yield (Scheme 12).

Scheme 12



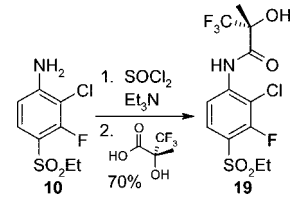
Two steps remained to link Route C with the medicinal chemistry route, the first of which was reduction of the nitro-group to an aniline. Hydrogenation was considered, but with the aromatic halogens present, it was decided to investigate alternative methodologies. Sodium hydrosulfite was successfully used as a reducing agent,[12] affording 2-chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) (Scheme 13).

Scheme 13



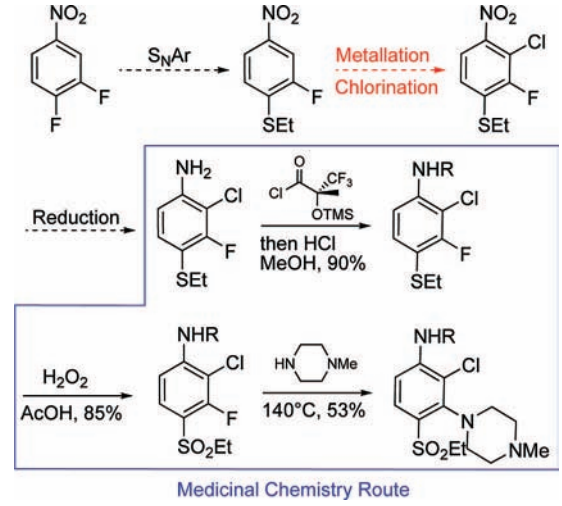
Finally, this compound was acylated using the conditions developed for AZD7545,[2] affording (2*R*)-*N*-[2-chloro-4-(ethylsulfonyl)-3-fluorophenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**19**) (Scheme 14) and thus linking into the medicinal chemistry route.

Scheme 14



Completion of this synthetic sequence represented a second alternative route to the drug candidates.

Route D

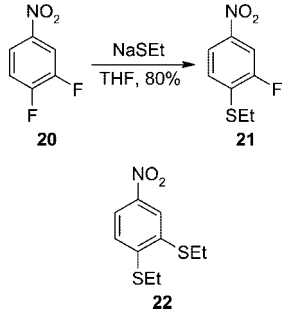


The key step in Route D (see Table D) is metalation of the aromatic ring, followed by chlorination using an electrophilic chloride source, such as NCS. Fluorine has been shown to be a powerful *ortho* director of lithiation,[13] and it was anticipated that the fluorine in the 3-position would direct lithiation to the 2-position.

(11) Sbarskii, V. L.; Shutov, G. M.; Zhilin, V. F.; Chirkova, R. G.; Orlova, E. Y. *J. Org. Chem. USSR. (Eng. Transl.)* **1971**, *7*, 303–307.
(12) Antolini, L. *J. Heterocycl. Chem.* **1992**, *29*, 1449–1455.

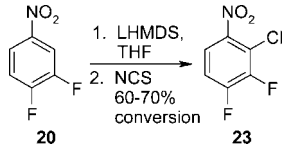
The first step on Route D was based on the chemistry reported by Suggs,[14] displacing the 1-fluorine of 1,2-difluoro-4-nitrobenzene (**20**) using the sodium salt of ethanethiol and affording 1-(ethylthio)-2-fluoro-4-nitrobenzene (**21**) (Scheme 15). The major impurity observed in the reaction was the formation of the bisthioether (**22**).

Scheme 15



The metalation/chlorination of both 1,2-difluoro-4-nitrobenzene (**20**) and 1-(ethylthio)-2-fluoro-4-nitrobenzene (**21**) was then investigated using *s*-BuLi and NCS. The reaction afforded a mixture of compounds, including a significant amount of starting material, and analysis suggested that metalation was taking place at various locations on the aromatic ring, as well as addition of butyl groups. It was thus decided to investigate the metalation/chlorination reaction stepwise, first looking at the extent and location of the lithiation and then examining the chlorination. The lithiation reaction was investigated using LDA and LHMDS, followed by quenching with acetic acid-*d*, with the incorporation of deuterium (determined by ^{1}H and ^{2}D NMR) measuring the extent and location of deprotonation. LDA proved to be too strongly basic, causing decomposition of both 1,2-difluoro-4-nitrobenzene (**20**) and 1-(ethylthio)-2-fluoro-4-nitrobenzene (**21**). LHMDS was effective at lithiating 1-(ethylthio)-2-fluoro-4-nitrobenzene (**21**), with the majority of deuteration being observed at the 3-position (54% deuteration); however, deuteration was also observed at the 5-position (22% deuteration) and to a lesser extent at the 6-position (9% deuteration). The most effective combination of base and substrate was LHMDS and 1,2-difluoro-4-nitrobenzene (**20**), where deuteration was observed exclusively at the 3-position (50% deuteration), with no decomposition of the starting material. The use of these conditions, then quenching the lithiated aromatic with NCS, afforded a 60−70% conversion to 2-chloro-3,4-difluoro-1-nitrobenzene (**23**) (Scheme 16). Purification of the product proved to be challenging, with separation by flash column chromatography difficult due to the similar polarity of the remaining starting material and product. However, with care, 20−30% of the required product could be isolated for use in further transformations.

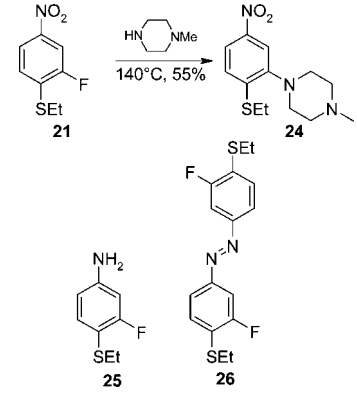
Scheme 16



(13) Gilday, J. P.; Negri, J. T.; Widdowson, D. A. *Tetrahedron* **1989**, *45*, 4605–4618.
(14) Farmer, J. D.; Rudnicki, S. M.; Suggs, J. W. *Tetrahedron Lett.* **1988**, *29*, 5105–5108.

With the difficulties separating product from remaining starting material, it was decided to investigate alterative substrates for the metalation/chlorination reaction. The intention was to find a substrate that would give complete chlorination, avoiding the problems of separation of chlorinated and nonchlorinated compounds. It was reasoned that introduction of the *N*-methyl piperazine group at the 2-position may provide some chelation to the lithium base, providing more effective lithiation of the aromatic. Thus, it was decided to investigate the displacement of the remaining fluorine on 1-(ethylthio)-2-fluoro-4-nitrobenzene (**21**). This approach would introduce the *N*-methyl piperazine group earlier than planned but, if successfully metallated/chlorinated, would afford a molecule with the correct heteroatoms in the 1−4 positions at an early stage. Displacement of the fluorine was found to proceed using conditions similar to those used on the medicinal chemistry route, stirring the starting material in neat *N*-methyl piperazine for 24 h at 140 °C (Scheme 17). The majority of the starting material was consumed, but significant amounts of impurities were generated in the reaction, including aniline (**25**) (4%) and azo compound (**26**) (20%). However, the required product could be easily separated using flash column chromatography affording 1-[2-(ethylthio)-5-nitrophenyl]-4-methylpiperazine (**24**) in a 55% yield.

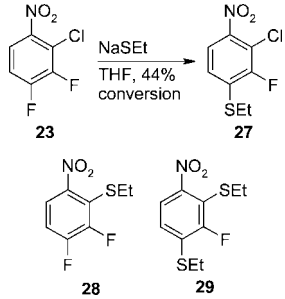
Scheme 17



As before, the metalation/chlorination of 1-[2-(ethylthio)-5-nitrophenyl]-4-methylpiperazine (**24**) was investigated in a stepwise manner, using *s*-BuLi, LDA and LHMDS followed by a deuterium quench to probe the extent and location of lithiation. With *s*-BuLi, extensive decomposition of the starting material was observed, forming a mixture of unknown products. No deuterium incorporation was observed using LDA or LHMDS, suggesting that substrate was not undergoing any lithiation using these bases.

The limited success in investigating the metalation/chlorination approach focused the work onto the successful conversion of 1,2-difluoro-4-nitrobenzene (**20**) to 2-chloro-3,4-difluoro-1-nitrobenzene (**23**), and it was decided to progress the product of this reaction through the required transformations to link into the medicinal chemistry route. Thus, the displacement of the 4-fluorine of 2-chloro-3,4-difluoro-1-nitrobenzene (**23**) using sodium ethanethiolate was investigated. Conversion of the starting material to 2-chloro-4-(ethylthio)-3-fluoro-1-nitrobenzene (**27**) was observed (44%, Scheme 18), but the final reaction mixture also contained thioether (**28**) (14%), formed by displacement of the 2-chlorine rather than the 4-fluorine and bisthioether (**29**) (16%), as well as residual starting material (**23**) (7%).

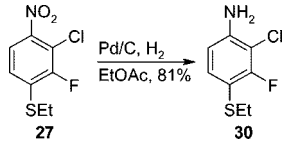
Scheme 18



As with previous compounds on this route, purification of the product by flash column chromatography was challenging due to the similar polarity of the impurities, and only 26% of the required 2-chloro-4-(ethylthio)-3-fluoro-1-nitrobenzene (**27**) was isolated.

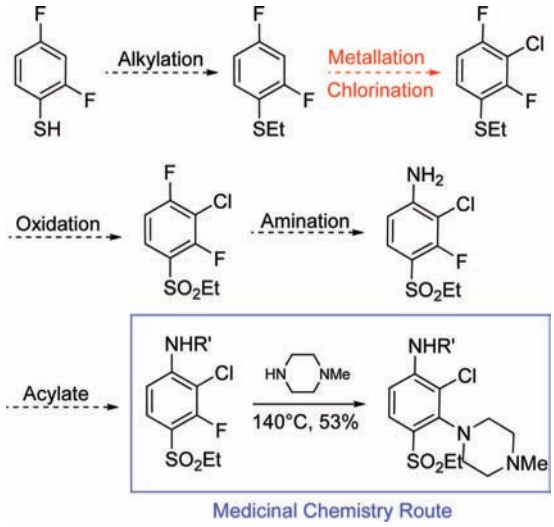
Completing work on the route, the nitro-group was reduced to an amino-group using hydrogenation. A catalyst was sourced from Johnson-Matthey for the reduction of aromatic nitro-groups in the presence of aromatic chlorides, and this successfully converted 2-chloro-4-(ethylthio)-3-fluoro-1-nitrobenzene (**27**) to 2-chloro-4-(ethylthio)-3-fluoroaniline (**30**) (Scheme 19).

Scheme 19



This final conversion linked Route D to the medicinal chemistry route, formally providing a third route to the drug candidates.

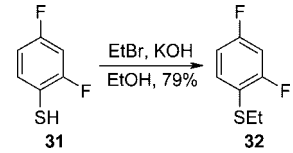
Route E



Route E has a key step similar to that of Route D but starts from 2,4-difluorothiophenol (**31**), affording a substrate with two *ortho* directing fluorines.[13] The key metalation/chlorination step was examined at the same time as those for Route D (see also Table E).

2,4-Difluorothiophenol (**31**) was alkylated with bromoethane,[15] affording 1-(ethylthio)-2,4-difluorobenzene (**32**) in a 79% yield (Scheme 20).

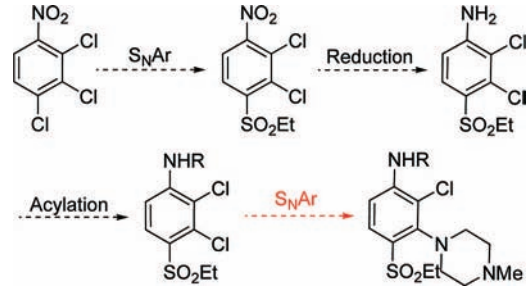
Scheme 20



As with the substrates on Route D, it was decide to initially investigate the extent and location of lithiation, and thus 1-(ethylthio)-2,4-difluorobenzene (**32**) was reacted with LDA and LHMDS, followed by quenching with acetic acid-*d*. LDA was found to deprotonate exclusively at the 3-position (30% deuteration), with no decomposition of the starting material. No deprotonation was observed using LHMDS.

As the lithiation of 1-(ethylthio)-2,4-difluorobenzene (**32**) was not as extensive as that of 1,2-difluoro-4-nitrobenzene (**20**) evaluated for Route D (30% vs 50%), it was decided to pursue the lithiation/chlorination of the later substrate, thus halting work on Route E.

Route F



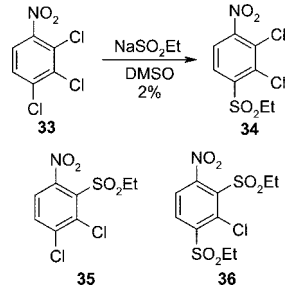
Route F was another four-step route, with two S_NAr reactions introducing the alkylsulfone and the heterocycle. The key step in the sequence was the second S_NAr reaction (fourth step), as this involved the displacement of a chlorine atom. The equivalent reaction, displacing a fluorine atom, had been demonstrated as part of the medicinal chemistry route, but the lower reactivity of the chlorine[16] made it essential to investigate this transformation (see also Table F).

The first step of the route was investigated using sodium ethanesulfinate[17] and 1,2,3-trichloro-4-nitrobenzene (**33**) based on conditions from the literature.[18] No significant reaction was observed in ethanol and THF, but slow consumption of the starting material was noted in DMSO and DMF at 130 °C. Analysis of the reaction in DMSO after 24 h showed that the majority of the starting material remained (86%), with a small amount of the required 2,3-dichloro-1-(ethylsulfonyl)-4-nitrobenzene (**34**) present (2%, Scheme 21). The analysis also detected small amounts of 1,2-dichloro-3-(ethylsulfonyl)-4-nitrobenzene (**35**, 2%), 2-dichloro-1,3-bis(ethylsulfonyl)-4-nitrobenzene (**36**, 2%) and other sulfonylated species.

On reflection, this result is not particularly surprising, as introduction of the first ethylsulfonyl group further activates the ring towards nucleophilic aromatic substitution, promoting

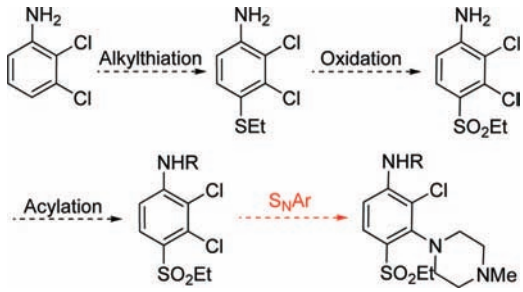
(15) Wnuk, S. F.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4757–4760.
(16) Smith, M. B.; March, J. *Advanced Organic Chemistry*; Wiley Interscience: New York, 2001; Chapter 13.
(17) Bearlocher,; F, J.; Baerlocher, M. O.; Chaulk, C. L.; Langler, R. F.; MacQuarrie, S. L. *Aust. J. Chem.* **2000**, *53*, 399–402.

Scheme 21



the introduction of further ethylsulfonyl groups. With the lack of selectivity and poor conversion for the first step, it was decided to stop work on Route F.

Route G

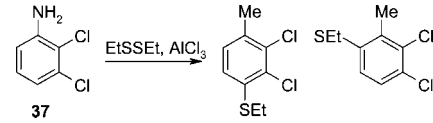


Route G shows similarities to Route F, both having four steps and with the same final two transformations. Route G differs from Route F with aniline nitrogen starting at the correct oxidation state and the sulfur being oxidised in the second step, whereas Route F has the sulfur at the correct oxidation state with the nitrogen being reduced in the second step. As with Route F, there were concerns about the displacements of the chlorine, and thus the fourth step was considered to be the key step (see also Table G). A similar issue to that encountered in Route B was also present, with regioselectivity being required in the first-step alkylthiation.

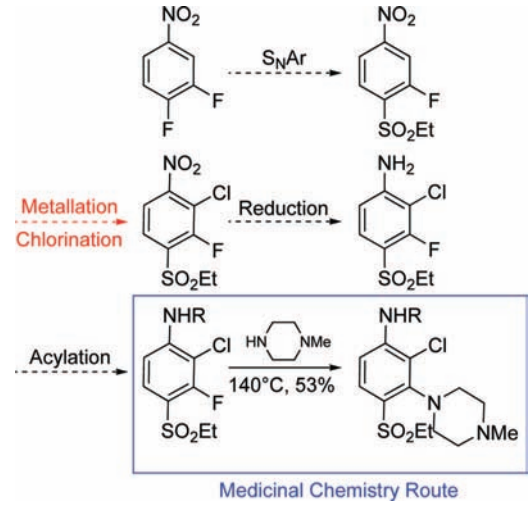
The alkylthiation chemistry is known in the literature, but only moderate selectivity is seen between the positions *ortho* and *para* to the aniline nitrogen.[19] With the presence of the two additional chlorines, it was hoped that better selectivity would be observed *para* to the amino-group. The alkylthiation reaction of 2,3-dichloroaniline (**37**) was investigated using standard conditions and resulted in a number of new products. Analysis of these showed that alkylthiation had occurred extensively at the 4- and 6-positions (Scheme 22), as well some dialkylthiation.

With the lack of selectivity for the 4-thiol and the anticipated difficulty in separating the regioisomers, it was decided to stop work on the route.

Scheme 22



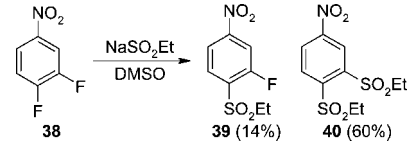
Route H



Route H pursues a strategy similar to that of Route D, with the key step involving the metalation/chlorination of the aromatic ring. The route is made one step shorter than Route D by introduction of the sulfur substituent at the correct oxidation state. However, the route was viewed as having poorer feasibility, as the acidic protons on the alkyl group of the sulfone were likely to interfere with the metalation/chlorination step (see also Table H).

The first step of the route was investigated at the same time as the equivalent first step on Route F, using sodium ethanesulfinate to displace the halogen *para* to the nitro-group. As with route F, no significant reaction was observed in ethanol and THF, and slow consumption of the starting material was noted in DMSO and DMF at 130 °C. Further investigation of the reaction in DMSO, increasing the amount of the sodium ethanesulfinate (1 equiv to 5 equiv), resulted in the consumption of the majority of the starting 1,2-difluoro-4-nitrobenzene (**38**), affording the required 1-(ethylsulfonyl)-2-fluoro-4-nitrobenzene (**39**), but with a larger amounts of the bisulphone (**40**)(Scheme 23).

Scheme 23



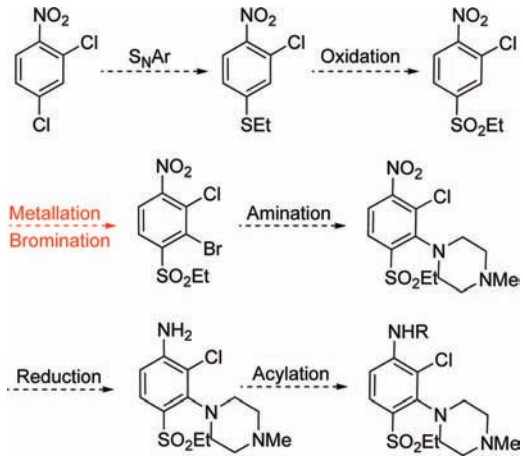
Analogous to the first reaction on Route F, the introduction of the first ethylsulfonyl group further activates the ring towards nucleophilic aromatic substitution, promoting the introduction of the second ethylsulfonyl group. As fluorine is a better leaving group than chlorine, the reaction proceeds to give significant amounts of both the mono- and bisulfones, whereas in Route F, only small amounts of sulfonylated products are observed.

(18) (a) Li, J. J.; Norton, M. B.; Reinhard, E. J.; Anderson, G. D.; Gregory, S. A.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Zhang, Y.; Zweifel, B. S.; Reitz, D. B. *J. Med. Chem.* **1996**, *39*, 1846–1856. (b) Dack, K. N.; Dickinson, R. P.; Long, C. J.; Steele, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2061–2066. (c) Lacour, J.; Monchaud, D.; Bernardinelli, G.; Favarger, F. *Org. Lett.* **2001**, *3*, 1407–1410.

(19) Ranken, P. F.; McKinnie, B. G. *J. Org. Chem.* **1989**, *54*, 2985–2988.

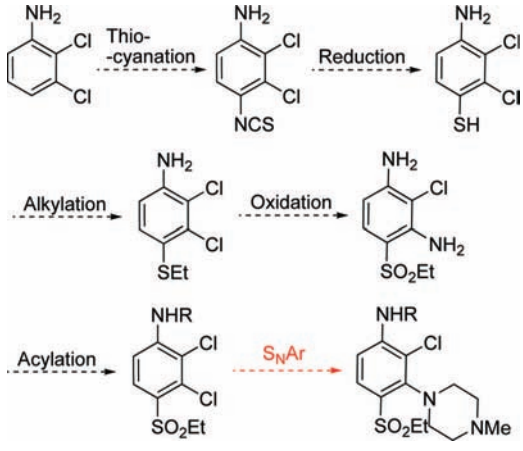
The lack of selectivity observed in the first step of Route H halted work on this approach.

Route I



Route I bears a number of similarities to Route D, with the key step being the metalation of the aromatic ring, followed by halogenation. Work on Routes D and E had been completed at the time of starting work on Route I, and the experience gained on the key transformation of these two reactions was considered. With the difficultly of regioselective metalation of the aromatic substrate in Routes D and E and also without any *ortho*-directing fluorides present, it was felt unlikely that it would be possible to get regioselective bromination in the key step of Route I. Thus the feasibility score for the route was changed from 4 to 2, reducing the total score and ranking of Route I. For this reason it was decided not start work on Route I (see also Table I), transferring the available effort onto Route J.

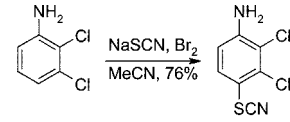
Route J



The final sequence evaluated as part of the route selection was Route J. The final three steps in this route were identical to those in Route G, but three steps were required to introduce the thioethyl substrate, whereas only one step was required in Route G. It was felt that the thiocyanation, reduction and alkylation sequence was well precedented, as the same chemistry had been used for the preparation of AZD7545.[2] However, as with Routes F and G, the key step in the sequence was seen to the be the displacement of chloride by the nitrogen heterocycle, and as the last transformation in the six-step sequence, Route J scored poorly on number of steps to key step (see Table J).

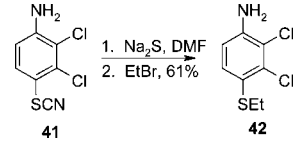
Studies on the route started with the thiocyanation reaction of 2,3-dichloroaniline (**37**). These reactions are well precedented to give substitution *para* to the nitrogen of anilines, and using the AZD7545 conditions, the correct regioisomer was obtained in a 76% yield (Scheme 24), with no trace of any *ortho* substitution.

Scheme 24



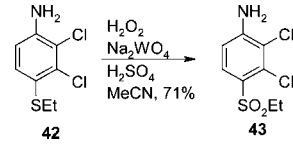
The obtained 4-amino-2,3-dichlorophenyl thiocyanate (**41**) was then reduced and alkylated in a one-pot procedure using sodium sulfide and bromoethane, affording 2,3-dichloro-4-(ethylthio)aniline (**42**) (Scheme 25).

Scheme 25



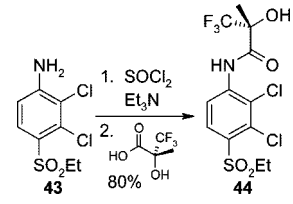
Oxidation of the sulfur was achieved using hydrogen peroxide/sodium tungstate, affording 2,3-dichloro-4-(ethylsulfonyl)aniline (**43**) (Scheme 26).

Scheme 26



The acylation to introduce the chiral amide portion was completed using the AZD7545 conditions,[2] affording (2*R*)-*N*-[2,3-dichloro-4-(ethylsulfonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**44**) (Scheme 27).

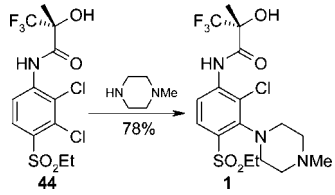
Scheme 27



Finally, the key nucleophilic aromatic substitution of the 3-chlorine was investigated, using the medicinal chemistry conditions for the displacement of the equivalent fluorine. The reaction was successful, affording AZM574670 (**1**) in a 78% yield (Scheme 28).

The completion of this sequence represented the fourth new route to the drug candidates and marked the end of the experimental work on the project.

Scheme 28



Data Review. The completion of the synthetic work provided an opportunity to reassess all the routes against the Wants that had been selected, showing how the proven routes measured up against each other (Table 6).

All routes now score 10 for feasibility, as all the steps had been demonstrated. Additionally Route A had changed from 4 to 5 steps, decreasing the number of steps score from 9 to 8.

A revaluation of the routes against the Decision Statement clearly showed that Route D was not suitable for long-term manufacture as the yields and selectivity of the first two reactions are poor, as well as the first step requiring low temperatures. The other routes all had potential, and the relative merits of each needed to be considered.

A further review of the Wants used to prioritise the evaluation of routes showed that on completion of synthetic work, both feasibility and steps to key step were no longer relevant (the former scoring 10 for all routes and the latter not being applicable as all the key steps had been proven). Accommodation and flexibility did not provide any differentiation between the routes, as the same score was obtained for each route. This left number of steps, which is an important factor for choosing between proven routes, as it implicitly contains elements of throughput, yield and cost. Thus a simple method of choosing an appropriate route for manufacture involved measuring the number of steps, which gave Route A as the preferred route, as it has the smallest number of steps.

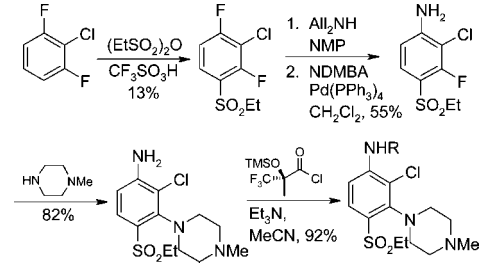
An alternative approach (which was not conducted due to termination of the project) would be to conduct a new Kepner-Tregoe Decision Analysis session to compare the proven routes, using a set of criteria based on the fact that detailed information was available for all the transformations. Factors such as overall yield and robustness, as well as number of steps, could be used to provide a more considered comparison of the proven routes.

Conclusions

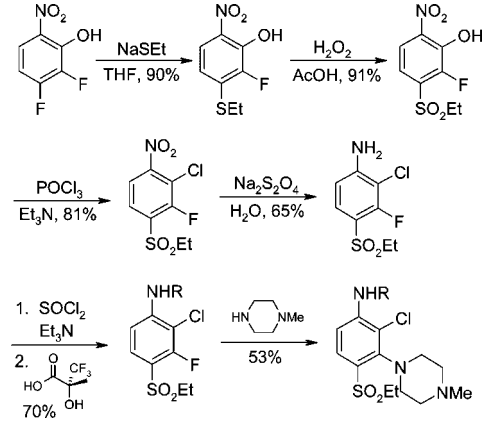
The investigation into the 10 highest scoring routes afforded four new alternatives to the drug candidates: Route A (1-chloro-2,6-difluorobenzene/sulfonylation route, Scheme 29), Route C (2,3-difluoro-6-nitrophenol/phenol activation and elimination, Scheme 30), Route D (3,4-difluoronitrobenzene/thiol displacement, Scheme 31) and Route J (2,3-dichloroaniline/thiocyanation, Scheme 32).

A further evaluation of the Wants used to prioritise the routes suggests that Route A would be preferred route for manufacture. A more through comparison of the proven routes could be completed using Kepner-Tregoe Decision Analysis, incorporating additional factors that had been measured during the experimental evaluation.

Scheme 29



Scheme 30



Scheme 31

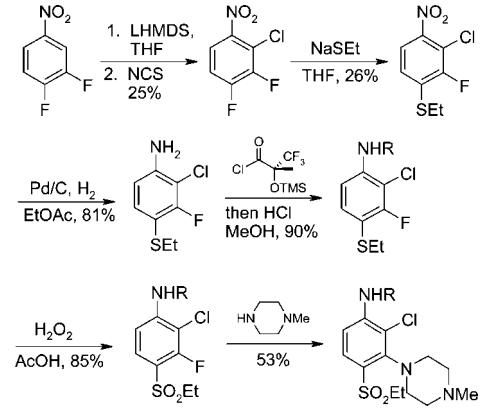
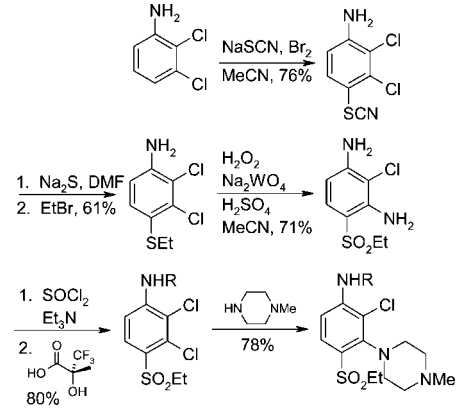


Table 6. Final Decision Analysis data table

	Wants					
route title	accommodation, 7[a]	feasibility, 10[a]	no. of steps, 10[a]	flexibility, 4[a]	steps to key step, 10[a]	total score
Route A	10	10	8	5	9	360
Route C	10	10	7	5	8	340
Route D	10	10	7	5	9	350
Route J	10	10	7	5	5	310

[a] Weighting.

Scheme 32



Disappointingly at this stage in the exercise, the project was terminated because of adverse toxicology results for all of the compounds, and the selection of a single route for long-term manufacture was never completed. However, this has provided an opportunity to publish the work conducted in this area using Kepner-Tregoe Decision Analysis, providing an extensive example of how such a technique can be used to aid route selection.

Experimental Section

General Procedures. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian Inova 400 MHz spectrometer with chemical shifts given in ppm, using internal standards (^{1}H and ^{13}C) and external standards (^{19}F). The reaction mixtures and products were analysed by gas chromatography on a Hewlett-Packard 6890 according to the following conditions: injector, 250 °C; split ratio, 25:1; column, Agilent HP-5, 5% phenyl methyl siloxane, Capillary 30 m × 320 μm × 1.00 mm nominal; pressure, 80 kPa, make-up, nitrogen; temperature program, 50−0−10−280−7; detector, 250 °C. GC purities are quoted as normalized area %. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography was carried out by standard procedures using Merck Kieselgel 60 (230−400 mesh).

Route A. *Preparation of 2-Chloro-1,3-difluoro-4-(methylsulfonyl)benzene (**7**).* Methanesulfonic anhydride (23.46 g, 134.7 mmol, 2.00 equiv) was charged to a 100 mL flask with trifluoromethanesulfonic acid (0.596 mL, 6.73 mmol, 0.10 equiv), and the mixture heated to 70 °C. 1-Chloro-2,6-difluorobenzene (**5**) (10.00 g, 67.4 mmol, 1.00 equiv, t_R 3.1 min) was added over 2 min, and the mixture then placed in an oil bath at 130 °C for 21 h. The reaction was then cooled to 55 °C, and water (50 mL) was added (note: addition is exothermic), followed by ethyl acetate (50 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (25 mL). The organic extracts were combined and washed with aqueous sodium hydrogen carbonate solution (saturated, 2 × 50 mL) and aqueous sodium chloride solution (saturated, 25 mL), and the solvent was removed in vacuo, affording 2-chloro-1,3-difluoro-4-(methylsulfonyl)benzene (**7**) as a brown solid (11.08 g, 73%). GC purity 59%; t_R 12.1 min; δ_H (400 MHz, d_6-DMSO) 7.89 (m, 1H), 7.57 (m 1H), 3.38 (s, 3H); δ_C (100 MHz, d_6-DMSO) 161.30 (dd, J = 256.3, 3.1 Hz), 155.54 (dd, J = 257.0, 3.8 Hz), 128.87 (d, J = 10.7 Hz), 126.05 (dd, J = 14.6, 3.8 Hz), 113.19 (dd, J = 21.5, 3.8 Hz), 110.55 (t, J = 21.5 Hz), 43.68 (d, J = 2.3 Hz); δ_F (376 MHz, d_6-DMSO) −103.24 (m), −108.21 (m); MS (EI^+) 226/228 (M^+).

*Preparation of 2-Chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**).* Ethanesulfonic anhydride (1.36 g, 6.73 mmol, 2.00 equiv) was charged to a small reaction tube with trifluoromethanesulfonic acid (0.60 mL, 6.73 mmol, 2.00 equiv), and the mixture was heated to 70 °C. 1-Chloro-2,6-difluorobenzene (**5**) (0.50 g, 3.37 mmol, 1.00 equiv, t_R 3.1 min) was added in a single portion, and the mixture then placed in an oil bath at 130 °C for 18 h. The reaction was then cooled to 55 °C, and water (10 mL) was added (note: addition is exothermic), followed by ethyl acetate (10 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (10 mL). The organic extracts were combined and washed with aqueous sodium hydrogen carbonate solution (saturated, 10 mL), water (10 mL) and aqueous sodium chloride solution (saturated, 10 mL), and the solvent was removed in vacuo, affording a dark brown oil which was purified by flash column chromatography, affording 2-chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**) as a pale brown solid (109 mg, 13%). GC purity 100%; t_R 13.0 min; δ_H (400 MHz, $CDCl_3$) 7.89 (m, 1H), 7.21 (m, 1H), 3.34 (q, J = 7.4 Hz, 2H), 1.33 (t, J = 7.4 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 162.39 (dd, J = 260.3, 3.1 Hz), 156.51 (dd, J = 258.7, 3.8 Hz), 129.39 (d, J = 10.0 Hz), 123.80 (d, J = 16.1 Hz), 123.86 (d, J = 4.4 Hz), 112.49 (dd, J = 22.3, 3.8 Hz), 112.01 (d, J = 21.9 Hz), 50.16 (d, J = 2.3 Hz), 6.98; δ_F (376 MHz, $CDCl_3$) −101.79 (m), −106.99 (m); MS (CI^+) 226/228 (MH^+).

*Preparation of 2-Chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**).* 2-Chloro-1,3-difluoro-4-(ethylsulfonyl)benzene (**6**) (366.0 mg, 1.52 mmol, 1.00 equiv) was charged to a small reaction tube with diallylamine (0.75 mL, 6.08 mmol, 4.00 equiv) and *N*- methylpyrrolidone (3.6 mL). The tube contents were stirred at ambient temperature for 7 days. The reaction mixture was partitioned between *N*-butyl acetate (20 mL) and water (20 mL). The layers were separated, and the organic portion was washed with water (20 mL). The organic solution was dried over magnesium sulfate and filtered, and the solvent was removed in vacuo, affording a yellow oil. The oil was redissolved in dichloromethane (2 mL), and this solution was added to a small reaction tube containing palladium(II) acetate (6.95 mg, 0.31 mmol, 0.02 equiv), triphenylphosphine (32.5 mg, 0.124 mmol, 0.08 equiv) and dichloromethane (2 mL) under a nitrogen atmosphere. *N*,*N*-Dimethylbarbituric acid (1.21 g, 7.74 mmol, 5.00 equiv) was added in a single portion, and the mixture was stirred at 45 °C for 4 days. The solvent was then removed in vacuo, and the orange oil partitioned between ethyl acetate (20 mL) and saturated

aqueous sodium hydrogen carbonate solution (10 mL). The layers were separated, the organic portion was dried over magnesium sulfate and filtered, and the solvent was removed in vacuo, affording an orange oil which was purified by flash column chromatography (eluent 50% EtOAc in isohexane), affording 2-chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) as pale yellow solid (198 mg, 55%). GC purity 99%; t_R 18.8 min; mp 113.5−114.5 °C; υ_{max} cm^{-1} 3456, 3634, 1301, 1132; δ_H (400 MHz, d_6-DMSO) 1.08 (t, J = 7.3 Hz, 3H), 3.22 (q, J = 7.3 Hz, 2H), 6.67 (d, J = 9.0 Hz, 1H), 6.72 (s, 2H), 7.37 (dd, J = 8.3, 9.0 Hz, 1H); δ_C (100 MHz, d_6-DMSO) 7.12, 49.84, 103.72 (d, J = 19.9 Hz), 109.29 (d, J = 2.3 Hz), 111.67 (d, J = 14.6 Hz), 128.89 (d, J = 1.5 Hz), 151.90 (d, J = 3.1 Hz), 155.98 (d, J = 250.9 Hz); MS (EI^+) 238/240 (M^+).

*Preparation of 2-Chloro-3-(4-methylpiperazin-1-yl)-4-(ethylsulfonyl)aniline (**11**).* 2-Chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) (50.0 mg, 0.210 mmol, 1.0 equiv) was charged to a small reaction tube with 1-methylpiperazine (1.00 mL, 9.00 mmol, 42.8 equiv). The tube was sealed, and the mixture was stirred at 130 °C for 16 h. The solvent was then removed in vacuo, and the brown oil was partitioned between ethyl acetate (5 mL) and saturated aqueous sodium hydrogen carbonate solution (5 mL). The layers were separated, the organic portion was dried over magnesium sulfate and filtered, and the solvent was removed in vacuo, affording 2-chloro-3-(4-methylpiperazin-1-yl)-4-(ethylsulfonyl)aniline (**11**) as a yellow solid (55 mg, 82%). GC purity 100%; t_R 24.6 min; δ_H (400 MHz, $CDCl_3$) 7.77 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 4.58 (br s, 2H), 3.83 (m, 2H), 3.47 (q, J = 7.5 Hz, 2H), 2.85 (m, 4H), 2.36 (s, 3H), 2.31 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 149.27, 148.21, 130.18, 127.15, 120.22, 111.75, 55.32, 49.00, 48.62, 46.46, 7.47; MS (ES^+) 318/320 (MH^+).

*Preparation of (2R)-N-[2-Chloro-4-(ethylsulfonyl)-3-(4-methylpiperazin-1-yl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**1**).* (*R*)-3,3,3-Trifluoro-2-hydroxy-2-methylpropionic acid (**12**) (876 mg, 5.54 mmol) was dissolved in dichloromethane (12.75 mL) and dimethylformamide (21.3 μL). 1,3-Bis(trimethylsilyl)urea (1.42 g, 6.93 mmol) was added portionwise, followed by dichloromethane (12.75 mL), and the mixture was stirred at ambient temperature for 24 h. The mixture was then filtered, and the collected solid was washed with dichloromethane (2 × 5.8 mL). Oxalyl chloride (696.24 mg, 5.49 mmol) in dichloromethane (2 mL) was added to the filtrate over 1 h, and the mixture was stirred at ambient temperature for 24 h. Finally, the reaction solution was filtered to remove the remaining urea byproducts, affording (*S*)-3,3,3-trifluoro-2-methyl-2-trimethylsilanyloxy-propionyl chloride (**13**) as a solution in dichloromethane. 2-Chloro-3-(4-methylpiperazin-1-yl)-4-(ethylsulfonyl)aniline (**11**) (73.6 mg, 0.24 mmol) was dissolved in dichloromethane (1 mL), and a portion of the previously prepared (*S*)-3,3,3-trifluoro-2-methyl-2-trimethylsilanyloxy-propionyl chloride (**13**) solution in dichloromethane (2.4 mL) was added in a single portion, followed by triethylamine (69.7 mg, 0.69 mmol). The mixture was stirred at ambient temperature for 90 min, and then aqueous hydrochloric acid (2 M, 5 mL) was added, and the mixture was stirred for a further 30 min. The layers were separated, and the organic portion further extracted with aqueous hydrochloric acid (2 M, 5 mL). The combined aqueous extracts were basified with aqueous sodium hydroxide solution (2 M, 20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracted were dried over magnesium sulfate and filtered, and the solvent was removed in vacuo, affording (2*R*)-*N*-[2-chloro-4-(ethylsulfonyl)-3-(4-methylpiperazin-1-yl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**1**) as a cream solid (101 mg, 92%) GC purity 95%; t_R 28.7 min; δ_H (400 MHz, $CDCl_3$) 9.90 (s, 1H), 8.61 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 4.04 (m, 1H), 3.89 (m, 1H), 3.46 (q, J = 7.3 Hz, 2H), 2.97 (m, 4H), 2.48 (m, 5H), 1.75 (s, 3H), 1.28 (t, J = 7.4 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 167.23, 146.69, 140.05, 134.08, 130.39, 125.41, 124.30 (q, J = 286.4 Hz), 118.06, 75.75 (q, J = 28.4 Hz), 55.17, 49.09, 47.89, 47.57, 46.05, 20.38, 7.37; MS (ES^+) 458/460 (MH^+).

Route C. *Preparation of 3-(Ethylthio)-2-fluoro-6-nitrophenol (**16**).* To a suspension of sodium ethanethiolate (5.00 g, 2.83 equiv, 47.6 mmol) in tetrahydrofuran (25 mL) at 0 °C, under a nitrogen atmosphere was added a solution of 2,3-difluoro-6-nitrophenol (**15**) (3.00 g, 1.00 equiv, 16.8 mmol) in tetrahydrofuran (25 mL) over 5 min to give a brown slurry. The mixture was stirred at room temperature overnight. The mixture was then partitioned between ethyl acetate (50 mL), aqueous hydrochloric acid (1 M, 50 mL) and aqueous sodium chloride solution (saturated, 50 mL). The layers were separated, and the organic layer was washed with aqueous sodium chloride solution (saturated, 2 × 15 mL), dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo, affording a brown solid, which was purified by flash column chromatography (eluent 10% EtOAc in isohexane) affording 3-(ethylthio)-2-fluoro-6-nitrophenol (**16**) as an orange oil (2.05 g, 90%). GC purity 90%; t_R 14.5 min; mp (crude) 70.5−71.5 °C; υ_{max} cm^{-1} 3231, 1512, 1204, 1143; δ_H (400 MHz, d_6-DMSO) 1.29 (t, J = 7.3 Hz, 3H), 3.11 (q, J = 7.3 Hz, 2H), 7.00 (dd, J = 6.9, 9.2 Hz, 1H), 7.79 (dd, J = 1.8, 9.2 Hz, 1H), 11.14 (s, 1H); δ_C (100 MHz, d_6-DMSO) 13.78, 24.42, 115.50, 120.54 (d, J = 3.1 Hz), 133.68 (d, J = 14.6 Hz), 134.76 (d, J = 3.1 Hz), 141.26 (d, J = 16.9 Hz), 148.24 (d, J = 239.4 Hz); MS (EI^+) 217 (M^+).

*Preparation of 3-(Ethylsulfonyl)-2-fluoro-6-nitrophenol (**17**).* To a solution of 1-(ethylthio)-2-fluoro-4-nitrobenzene (**16**) (2.10 g, 1.00 equiv, 9.66 mmol) in acetic acid (20 mL) was added aqueous hydrogen peroxide solution (27.5%, 3.00 mL, 2.74 equiv, 26.9 mmol) in acetic acid (10 mL). The mixture was heated to 75 °C, causing a slight darkening of the solution. After stirring for 3 h, the reaction was allowed to cool to ambient temperature. Sodium metabisulfite (1.50 g, 7.70 mmol) in water (20 mL) was added dropwise to quench excess peroxide/peracid, the absence of which was confirmed by the use of peroxide test strips. The solution was partitioned between ethyl acetate (200 mL) and water (250 mL). The layers were separated, the organic layer was washed with water (2 × 100 mL), dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo, affording 3-(ethylsulfonyl)-2-fluoro-6-nitrophenol (**17**) as a yellow solid (2.23 g, 93%). GC purity 97%; t_R 16.6 min;

mp 110.5−111.5 °C; υ_{max} cm^{-1} 3279, 3066, 1538, 1320, 1221, 1129; δ_H (400 MHz, d_6-DMSO) 1.14 (t, J = 7.4 Hz, 3H), 3.43 (q, J = 7.4 Hz, 2H), 7.34 (dd, J = 6.3, 8.8 Hz, 1H), 7.88 (dd, J = 1.7, 8.8 Hz, 1H); δ_C (100 MHz, d_6-DMSO) 6.72, 49.43, 117.92, 120.32 (d, J = 3.8 Hz), 129.99 (d, J = 13.0 Hz), 141.56 (d, J = 17.6 Hz), 142.63, 149.94 (d, J = 253.2 Hz); MS (EI$^+$) 248 (M$^+$).

*Preparation of 2-Chloro-4-(ethanesulfonyl)-3-fluoro-1-nitrobenzene (**18**).* 3-(Ethylsulfonyl)-2-fluoro-6-nitrophenol (**17**) (500 mg, 1.00 equiv, 2.00 mmol) was charged to a N_2-purged vessel fitted with a water scrubber. Phosphorus oxychloride (10.0 mL, 52.5 equiv, 105.0 mmol) was then added to form a yellow solution. Triethylamine (0.85 mL, 3.00 equiv, 6.01 mmol) was added dropwise, affording an orange suspension. The reaction mixture was then heated to 105 °C and stirred for 60 h. The reaction mixture was then diluted by addition of toluene (25 mL) and added dropwise into ice-cooled water (150 mL) to quench excess phosphorus oxychloride. Toluene (175 mL) was added, the layers were separated, the organic layer was washed with water (2 × 100 mL) and aqueous sodium hydroxide solution (2 M, 100 mL), dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo, affording 2-chloro-4-(ethanesulfonyl)-3-fluoro-1-nitrobenzene (**18**) as a colourless solid (431 mg, 81%). GC purity 83%; t_R 16.9 min; mp 106.5−108.0 °C; υ_{max} cm^{-1} 3096, 1537, 1316, 1143; δ_H (400 MHz, d_6-DMSO) 1.19 (t, J = 7.3 Hz, 3H), 3.53 (q, J = 7.3 Hz, 2H), 8.05 (dd, J = 6.8, 8.6 Hz, 1H), 8.20 (dd, J = 1.0, 8.6 = Hz, 1H); δ_C (100 MHz, d_6-DMSO) 6.71, 49.57, 116.21 (d, J = 22.9 Hz), 121.43 (d, J = 4.6 Hz), 129.84, 130.47 (d, J = 16.2 Hz), 152.81 (d, J = 254.5 Hz), 156.66; MS (EI$^+$) 267/269 (M$^+$).

*Preparation of 2-Chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**).* To a suspension of 2-chloro-4-(ethanesulfonyl)-3-fluoro-1-nitrobenzene (**18**) (600 mg, 1.00 equiv, 2.25 mmol) in water (15 mL) was added sodium hydrosulfite (1.40 g, 3.02 equiv, 6.80 mmol). The reaction mixture was then heated to 75 °C and stirred for 90 min. Aqueous hydrochloric acid (32%, 2.9 mL) was added dropwise to the mixture, and precipitation of the product was allowed to occur over 3 h by stirring the mixture at ambient temperature; the mixture was then cooled to 0 °C for 1 h to promote further precipitation. The reaction mixture was adjusted to pH 7 by addition of aqueous sodium hydrogen carbonate (saturated, 25 mL), and the product was isolated by filtration, washed with water (4 × 10 mL), and dried in a stream of air affording 2-chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) as colourless crystals (348 mg, 65%).

*Preparation of (2R)-N-[2-Chloro-4-(ethylsulfonyl)-3-fluorophenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**19**).* To a solution of 2-chloro-4-(ethylsulfonyl)-3-fluoroaniline (**10**) (100 mg, 1.00 equiv, 0.42 mmol) in acetonitrile (1.5 mL) at 45 °C was added triethylamine (32 μL, 1.17 equiv, 0.49 mmol) in acetonitrile (0.2 mL). Thionyl chloride (63 μL, 2.02 equiv, 0.85 mmol) in acetonitrile (0.2 mL) was then added dropwise causing a darkening of the reaction solution. After 2 h, heating was stopped, and the vessel was allowed to cool to ambient temperature. A solution of (2*R*)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (80 mg, 1.21 equiv, 0.51 mmol) in acetonitrile (0.3 mL) was added, and the reaction was stirred at ambient temperature overnight. The reaction was quenched by dropwise addition of water (20 mL) and then further diluted with ethyl acetate (20 mL). The layers were separated, the organic layer was washed with water (10 mL) and aqueous sodium hydrogen carbonate solution (saturated, 2 × 10 mL), dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo, affording (2*R*)-*N*-[2-chloro-4-(ethylsulfonyl)-3-fluorophenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**19**) as a pale yellow solid (111 mg, 70%). GC purity 96%; t_R 20.6 min; mp 146.5−148 °C; υ_{max} cm^{-1} 3456, 3316, 1692, 1155, 1100; δ_H (400 MHz, d_6-DMSO) 1.12 (t, J = 7.4 Hz, 3H), 1.60 (s, 3H), 3.40 (q, J = 7.4 Hz, 2H), 7.83 (dd, J = 8.3, 9.0 Hz, 1H), 8.08 (s, 1H), 8.14 (d, J = 9.0 Hz, 1H), 9.99 (s, 1H); δ_C (100 MHz, d_6-DMSO) 6.86, 19.41, 49.61, 74.99 (q, J = 27.9 Hz), 113.49 (d, J = 21.7 Hz), 117.49 (d, J = 3.8 Hz), 122.77 (d, J = 20.0 Hz), 129.20, 140.42, 154.83 (d, J = 254.5 Hz), 167.49; MS (EI$^+$) 376/378 (M$^+$).

Route D. *Preparation of 2-Chloro-3,4-difluoro-1-nitrobenzene (**23**).* 1,2-Difluoro-4-nitrobenzene (**20**) (12.00 g, 75.4 mmol, 1.00 equiv, t_R 5.4 min) was dissolved in tetrahydrofuran (100 mL) and cooled in a dry ice/acetone bath to −78 °C (internal reaction temperature −74 °C). Lithium hexamethyldisilazide (1.0 M in THF, 75.4 mL, 74.5 mmol, 1.00 equiv) was added dropwise over 80 min, turning the colourless solution dark orange. Stirring was then continued for a further 21/2 h. *N*-Chlorosuccinamide (10.07 g, 75.4 mmol, 1.00 equiv) in tetrahydrofuran (200 mL) was added dropwise over 100 min, turning the reaction mixture first dark burgundy, then back to dark orange. The mixture was then allowed to warm to ambient temperature overnight, forming a light brown, cloudy solution. The reaction solvent was removed in vacuo, affording a brown solid, which was partitioned between ethyl acetate (400 mL) and aqueous hydrochloric acid (1 M, 400 mL). The layers were separated, and the organic layer was washed with aqueous sodium hydrogen carbonate solution (saturated, 400 mL), water (400 mL) and aqueous sodium chloride solution (saturated, 400 mL), affording a clear, orange solution. The solvent was removed from this solution in vacuo, affording a brown oil which was purified by flash column chromatography (250 g silica, eluent 1% EtOAc in isohexane) affording 2-chloro-3,4-difluoro-1-nitrobenzene (**23**) as a yellow oil (3.96 g, 27%). GC purity 87%; t_R 7.9 min; δ_H (400 MHz, $CDCl_3$) 7.28 (m, 1H), 7.82 (ddd, J = 9.4, 4.7, 2.2 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 113.94 (dd, J = 22.0, 2.0 Hz), 115.43 (d, J = 19.2 Hz), 121.23, 144.19, 147.86 (dd, J = 253.0, 14.0 Hz), 147.86 (dd, J = 260.0, 13.0 Hz); δ_F (376 MHz, $CDCl_3$) −125.27 (ddd, J = 20.4, 7.9, 4.7 Hz), −131.31 (m); MS (EI$^+$) 193 (M$^+$).

*Preparation of 1-(Ethylthio)-2-fluoro-4-nitrobenzene (**21**).* 1,2-Difluoro-4-nitrobenzene (**20**) (10.00 g, 62.8 mmol, 1.00 equiv) was dissolved in tetrahydrofuran (100 mL), and the mixture was sparged with nitrogen for 10 min. Sodium ethanethiolate (80% purity, 6.61 g, 62.8 mmol, 1.00 equiv) was added portionwise (Note: addition is exothermic), following which the mixture was sparged with nitrogen for 10 min. The mixture was then heated at reflux for 1 h, affording a dark brown solution. The reaction mixture was then cooled, diluted with ethyl acetate (150 mL), and washed with aqueous sodium hydroxide solution (1 M, 2 × 100 mL), aqueous hydrochloric

acid solution (1 M, 100 mL), aqueous sodium hydrogen carbonate solution (saturated, 100 mL) and aqueous sodium chloride solution (saturated, 100 mL). The solvent was then removed from the dark brown solution in vacuo, affording a brown solid which was purified by flash column chromatography (250 g silica, eluent 5% EtOAc in isohexane) affording 1-(ethylthio)-2-fluoro-4-nitrobenzene (**21**) as an orange oil (10.12 g, 80%). GC purity 90%; t_R 13.0 min; δ_H (400 MHz, $CDCl_3$) 1.41 (t, J = 7.4 Hz, 3H), 3.06 (q, J = 7.3 Hz, 2H), 7.35 (t, J = 7.9 Hz, 1H), 7.89 (dd, J = 9.6, 2.2 Hz, 1H), 8.00 (m, 1H); δ_C (100 MHz, $CDCl_3$) 16.46, 25.54 (d, J = 2.3 Hz), 110.67 (d, J = 26.9 Hz), 117.90 (d, J = 19.0 Hz), 119.59 (d, J = 3.1 Hz), 126.87 (d, J = 3.1 Hz), 135.44 (d, J = 16.9 Hz), 158.52 (d, J = 248.6 Hz); δ_F (376 MHz, $CDCl_3$) −108.45 (m); MS (EI^+) 201 (M^+).

*Preparation of 1-[2-(Ethylthio)-5-nitrophenyl]-4-methylpiperazine (**24**).* 1-(Ethylthio)-2-fluoro-4-nitrobenzene (**20**) (10.00 g, 49.7 mmol, 1.00 equiv) was dissolved in 1-methyl piperazine (50.0 mL, 0.45mol, 9.06 equiv), and the mixture was heated slowly to reflux. The mixture was stirred at reflux for 24 h, cooled to ambient temperature, diluted with ethyl acetate (250 mL), and washed with water (3 × 250 mL). The solvent was then removed from the dark brown solution in vacuo, affording a dark brown solid which was purified by flash column chromatography (250 g silica, eluent 2% MeOH in CH_2Cl_2), affording 1-[2-(ethylthio)-5-nitrophenyl]-4-methylpiperazine (**24**) as dark brown oil (7.30 g, 52%). GC purity 100%; t_R 21.4 min; δ_H (400 MHz, $CDCl_3$) 1.43 (t, J = 7.4 Hz, 3H), 2.38 (s, 3H), 2.62 (br s, 4H), 2.99 (q, J = 7.4 Hz, 2H), 3.05 (br s, 4H), 7.20 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 2.3 Hz, 1H), 7.92 (dd, J = 8.7, 2.6 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 13.22, 25.15, 46.05, 51.27, 55.13, 114.40, 119.12, 123.86, 144.38, 145.15, 149.60; MS (EI^+) 281 (M^+).

*Preparation of 2-Chloro-4-(ethylthio)-3-fluoro-1-nitrobenzene (**27**).* 2-Chloro-3,4-difluoro-1-nitrobenzene (**23**) (2.00 g, 10.3 mmol, 1.00 equiv) was dissolved in tetrahydrofuran (100 mL), and the mixture was sparged with nitrogen for 10 min. Sodium ethanethiolate (80% purity, 1.09 g, 10.3 mmol, 1.00 equiv) was added in a single portion, following which the mixture was sparged with nitrogen for 10 min. The mixture was then heated at reflux for 1 h, affording a dark brown solution. The reaction mixture was then cooled, and the solvent was removed in vacuo, affording a dark brown oil. This material was dissolved in ethyl acetate (100 mL) and washed with aqueous sodium hydroxide solution (1 M, 100 mL), aqueous hydrochloric acid solution (1 M, 100 mL), aqueous sodium hydrogen carbonate solution (saturated, 100 mL) and aqueous sodium chloride solution (saturated, 100 mL). The solvent was then removed from the dark brown solution in vacuo, affording a brown oil, which was purified by flash column chromatography (100 g silica, eluent 2% EtOAc in isohexane) affording 2-chloro-4-(ethylthio)-3-fluoro-1-nitrobenzene (**27**) as an orange oil (639 mg, 26%). GC purity 73%; t_R 15.0 min; δ_H (400 MHz, $CDCl_3$) 1.41 (t, J = 7.1 Hz, 3H), 3.05 (q, J = 7.4 Hz, 2H), 7.24 (m, 1H), 7.77 (dd, J = 8.7, 1.5 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 13.64, 25.84 (d, J = 2.3 Hz), 120.10 (d, J = 3.8 Hz), 121.04 (d, J = 3.8 Hz), 124.44 (d, J = 3.1 Hz), 125.32 (d, J = 3.8 Hz), 134.21, 155.23 (d, J = 248.8 Hz); δ_F (376 MHz, $CDCl_3$) −107.28 (d, J = 6.3 Hz); MS (EI^+) 193/195 (M^+).

*Preparation of 2-Chloro-4-(ethylthio)-3-fluoroaniline (**30**).* 2-Chloro-4-(ethylthio)-3-fluoro-1-nitrobenzene (**27**) (55.0 mg, 0.23 mmol, 1.00 equiv) was dissolved in ethyl acetate (1.5 mL) and acetic acid (0.1 mL). Platinum on carbon (JM Pt 117, 5% w/w, 16.0 mg) was added, and the mixture was stirred at 50 °C under 1barG hydrogen for 18 h. The reaction mixture was then cooled and filtered to remove the catalyst. The solvent was then removed from the orange solution in vacuo, affording 2-chloro-4-(ethylthio)-3-fluoroaniline (**30**) as a red oil (39.0 mg, 81%). GC purity 99%; t_R 14.1 min; δ_H (400 MHz, $CDCl_3$) 1.41 (t, J = 7.3 Hz, 3H), 3.05 (q, J = 7.4 Hz, 2H), 4.24 (br s, 2H), 7.24 (m, 1H), 7.77 (dd, J = 8.7, 1.5 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 13.67, 25.88 (d, J = 2.3 Hz), 111.39 (d, J = 3.0 Hz), 121.03 (d, J = 3.8 Hz), 124.48 (d, J = 3.1 Hz), 133.93 (d, J = 2.0 Hz), 134.19 (d, J = 18.0 Hz), 155.32 (d, J = 248.0 Hz); δ_F (376 MHz, $CDCl_3$) −107.16 (d, J = 7.9 Hz); MS (ES^+) 206 (M^+).

Route E. *Preparation of 1-(Ethylthio)-2,4-difluorobenzene (**32**).* 2,4-Difluorobenzenethiol (**31**) (1.00 g, 6.84 mmol, 1.00 equiv, t_R 4.0 min) was dissolved in ethanol (5 mL) under a nitrogen atmosphere. Potassium hydroxide (0.426 g, 7.52 mmol, 1.10 equiv) added, and after stirring for 5 min the solid had completely dissolved. The mixture was stirred for 20 min, then ethyl bromide (0.77 mL, 10.3 mmol, 1.50 equiv) was added in a single portion, and the mixture was stirred at ambient temperature for a further 3.5 h. Aqueous sodium hydroxide solution (2 M, 4 mL) was then added to destroy any remaining ethyl bromide, and the ethanol removed in vacuo. The remaining aqueous solution was extracted with dichloromethane (2 × 10 mL), and the combined extracts washed with water (10 mL), dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo, affording 1-(ethylthio)-2,4-difluorobenzene (**31**) as a pale yellow oil (0.90 g, 79%). GC purity 98%; t_R 6.5 min; δ_H (400 MHz, $CDCl_3$) 1.25 (t, J = 7.3 Hz, 3H), 2.86 (q, J = 7.3 Hz, 2H), 6.84 (m, 2H), 7.39 (dd, J = 15.0, 8.1 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 14.46, 28.36 (d, J = 1.5 Hz), 104.30 (t, J = 26.6 Hz), 111.62 (dd, J = 3.3, 20.1 Hz), 118.14 (d, J = 3.8, 18.4 Hz), 134.51 (d, J = 3.1, 9.2 Hz), 162.91 (ddd, J = 10.7, 25.7, 249.2 Hz); δ_F (376 MHz, $CDCl_3$) −104.70 (m), −111.33 (m); MS (EI^+) 174 (M^+).

Route J. *Preparation of 4-Amino-2,3-dichlorophenyl Thiocyanate (**41**).* 2,3-Dichloroaniline (**37**) (20.00 g, 123.4 mmol, 1.00 equiv) and sodium thiocyanate (20.01 g, 246.9 mmol, 2.00 equiv) were slurried in acetonitrile (200 mL). The mixture was cooled to 0 °C and bromine (19.73 g, 123.4 mmol, 1.00 equiv) in acetonitrile (60 mL) was added over 1.5 h. A solution of sodium hydrogen carbonate (10.37 g, 123.4 mmol, 1.00 equiv) in water (400 mL) was then added over 30 min. The precipitated product was stirred at ambient temperature and then isolated by filtration. The filter cake was washed with water (2 × 200 mL) and then dried in vacuum oven at 40 °C, affording 4-amino-2,3-dichlorophenyl thiocyanate (**41**) as a white solid (22.00 g, 76%). GC purity 81%; t_R 17.4 min; δ_H (400 MHz, d_6-DMSO) 7.51 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.40 (s, 2H); δ_C (100 MHz, d_6-DMSO) 149.13, 135.63, 134.36, 116.07, 113.88, 111.54, 106.15.

*Preparation of 2,3-Dichloro-4-(ethylthio)aniline (**42**).* Sodium sulfide (13.01 g, 166.6 mmol, 1.80 equiv) was slurried in dimethylformamide (60 mL), and the mixture was heated to 60 °C. 4-Amino-2,3-dichlorophenyl thiocyanate (**41**) (15.00 g, 92.6 mmol, 1.00 equiv) in dimethylformamide (52.5 mL) was added over 10 min, turning the green/blue slurry orange. The mixture was stirred at 60 °C for 30 min, then bromoethane (10.59 g, 97.2 mmol, 1.05 equiv) in dimethylformamide (15.0 mL) was added over 10 min, and the mixture was stirred for a further 3 h. Water (375 mL) was added to the reaction, and the resultant aqueous solution extracted with methyl *tert*-butyl ether (2 × 600 mL). The organic extracts were combined and washed with water (2 × 600 mL), and the solvent was removed in vacuo, affording 2,3-dichloro-4-(ethylthio)aniline (**42**) as a yellow oil (12.15 g, 61%). GC purity 97%; t_R 16.3 min; δ_H (400 MHz, $CDCl_3$) 7.18 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 4.16 (br s, 2H), 2.84 (q, J = 7.3 Hz, 2H), 1.24 (t, J = 7.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 143.54, 135.37, 131.60, 123.42, 118.36, 113.48, 28.68, 14.20; MS (EI^+) 222/224/226 (M^+).

*Preparation of 2,3-Dichloro-4-(ethylsulfonyl)aniline (**43**).* 2,3-Dichloro-4-(ethylthio)aniline (**42**) (11.00 g, 49.5 mmol, 1.00 equiv) was dissolved in acetonitrile (95 mL). Sodium tungstate dihydrate (1.47 g, 4.46 mmol, 0.10 equiv) was added, followed by sulfuric acid (1.46 g, 14.9 mmol, 0.30 equiv) and hydrogen peroxide solution (25% in water, 20.2 mL, 148.6 mmol, 3.0 equiv). The mixture was stirred at ambient temperature for 18 h, at which time water (220 mL) was added, causing the precipitation of a brown solid. The solid was collected by filtration, washed with water (2 × 50 mL), and dried in a vacuum oven at 50 °C, affording 2,3-dichloro-4-(ethylsulfonyl)aniline (**43**) as a brown solid (12.60 g, 71%). GC purity 97%; t_R 20.5 min; δ_H (400 MHz, $CDCl_3$) 7.78 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 4.85 (br s, 2H), 3.38 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 148.85, 132.17, 130.74, 124.72, 118.82, 111.83, 48.80, 7.31; MS (EI^+) 253/255/257 (M^+).

*Preparation of (2R)-N-[2,3-Dichloro-4-(ethylsulfonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**44**).* 2,3-Dichloro-4-(ethylsulfonyl)aniline (**43**) (8.50 g, 33.4 mmol, 1.00 equiv) was dissolved in acetonitrile (42.5 mL). Triethylamine (4.90 mL, 35.1 mmol, 1.10 equiv) was added in a single portion, followed by thionyl chloride (2.56 mL, 35.1 mmol, 1.10 equiv). (^2R)-3,3,3-Trifluoro-2-hydroxy-2-methylpropanoic acid (6.08 g, 38.5 mmol, 1.15 equiv) in acetonitrile (17.0 mL) was added dropwise, and the mixture was stirred at ambient temperature for 18 h. The reaction mixture was then partitioned between aqueous hydrochloric acid solution (0.5M, 170 mL) and dichloromethane (170 mL). The organic layer was separated, and the solvent was removed in vacuo, affording a dark brown oil. This material was triturated with isohexane (200 mL), affording a brown solid, which was isolated by filtration, washed with isohexane (2 × 50 mL) and dried in a vacuum oven at 50 °C, affording (2*R*)-*N*-[2,3-dichloro-4-(ethylsulfonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**44**) as a brown solid (10.50 g, 80%). δ_H (400 MHz, $CDCl_3$) 9.53 (br s, 1H), 8.61 (d, J = 9.0 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 4.09 (s, 1H), 3.43 (q, J = 7.4 Hz, 2H), 1.78 (s, 3H), 1.28 (t, J = 7.4 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 166.56, 139.56, 132.27, 131.66, 130.86, 124.36, 123.63 (q, J = 287.0 Hz), 118.03, 76.11 (q, J = 29.8 Hz), 48.72, 20.30, 7.12; δ_F (376 MHz, $CDCl_3$) −80.11; MS (CI^+) 394/396/398 (MH^+).

*Preparation of (2R)-N-[2-Chloro-4-(ethylsulfonyl)-3-(4-methylpiperazin-1-yl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**1**).* (2*R*)-*N*-[2,3-Dichloro-4-(ethylsulfonyl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**44**) (100 mg, 0.25 mmol, 1.00 equiv) was dissolved in *N*-methyl piperazine (0.25 g, 2.50 mmol, 10.0 equiv), and the mixture was heated at 140 °C for 5 h. The reaction mixture was cooled, diluted with dichloromethane (20 mL), and washed with water (4 × 50 mL). Isohexane (100 mL) was added to the organic solution, and the resultant solid collected by filtration and dried in a vacuum oven at 40 °C, affording (2*R*)-*N*-[2-chloro-4-(ethylsulfonyl)-3-(4-methylpiperazin-1-yl)phenyl]-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide (**1**) as a cream solid (112 mg, 78%).

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Appendix

Each table included below provides comments on how each route as shown in the text was evaluated against the Wants.

Table A

Wants	Comments
Accommodation	None
Feasibility	
Number of Steps	4
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	2nd Step

Table B

Wants	Comments
Accommodation	None
Feasibility	Sulfonylation and chlorine displacement both precedented
Number of Steps	5
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	1st step

Table C

Wants	Comments
Accommodation	None
Feasibility	Reasonable precedent for chlorination
Number of Steps	6
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	2nd step

Table D

Wants	Comments
Accommodation	None
Feasibility	*ortho* lithiation precedented, but not many examples
Number of Steps	6
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	2nd step

Table E

Wants	Comments
Accommodation	None
Feasibility	*ortho* lithiation precedented, but not many examples
Number of Steps	6
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	2nd step

Table F

Wants	Comments
Accommodation	None
Feasibility	Questions about displacement of chlorine by heterocycle
Number of Steps	4
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	4th step

Table G

Wants	Comments
Accommodation	None
Feasibility	Questions about displacement of chlorine by heterocycle
Number of Steps	4
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	4th step

Table H

Wants	Comments
Accommodation	None
Feasibility	Questions about metallation with Sulfone present
Number of Steps	5
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	2nd step

Table I

Wants	Comments
Accommodation	None
Feasibility	Poor precedent for bromination
Number of Steps	6
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	3rd step

Table J

Wants	Comments
Accommodation	None
Feasibility	Questions about displacement of chlorine by heterocycle
Number of Steps	6
Flexibility	Early alkyl sulfur introduction
Number of Steps to Key Step	6th step

Supporting Information Available

Details of lower scoring routes and those not passing the Musts. This material is available free of charge via the Internet at http://pubs.acs.org.

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