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A New Approach to the Rapid Parallel Development of Four Neurokinin Antagonists. Part 3. Assembly of Neurokinin Antagonists

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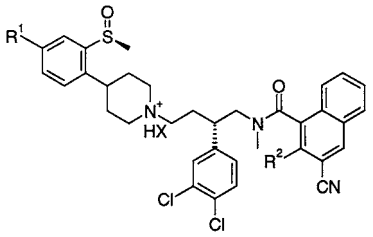
Abstract:

Four neurokinin antagonists were assembled using a rapid parallel development approach. Research Department processes were scaled up if process safety and robustness were not compromised. Using this approach, 1 kg of each compound was rapidly delivered for clinical trials.

Introduction

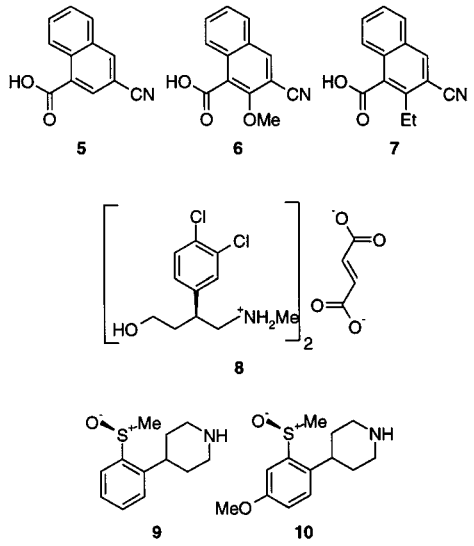
Zeneca Pharmaceuticals devised a rapid parallel development approach for the delivery of 1 kg of a compound for preliminary toxicity and clinical studies. This approach was applied to the preparation of a series of four neurokinin antagonists: ZD6021 **1**, ZD2249 **2**, ZD4979 **3**, and ZM374979 **4**.[1]



1 ($R^1 = R^2 = H$, X = Hydrogen Fumarate)
2 (R^1 = OMe, R^2 = H, X = Hydrogen Fumarate)
3 (R^1 = H, R^2 = OMe, X = Citrate)
4 (R^1 = H, R^2 = Et, X = Maleate)

The assembly of these neurokinin antagonists was undertaken from a number of advanced intermediates.[1] For this work, kilogram quantities of ZD6021 cyano acid **5**,[2,3] ZD4974 cyano acid **6**, and ZM374979 cyano acid **7**[4] were prepared, together with ZD6021 *N*-methylamine fumarate **8**, ZD7944 pip sulfoxide **9**, and ZD2249 methoxy sulfoxide **10**[5] (Figure 1). The preparation of a number of these molecules will be discussed in subsequent papers in this series.

This contribution describes the assembly of the four neurokinin antagonists from these advanced intermediates, using the rapid parallel development approach.



5 **6** **7** **8** **9** **10**

Figure 1.

Results and Discussion

The first transformation required in this sequence was the coupling of the cyano acids **5**−**7** to ZD6021 *N*-methylamine fumarate **8**, forming the corresponding amide alcohols **11**−**13**. ZD6021 *N*-methylamine fumarate **8** was converted to ZD6021 *N*-methylamine **14** by washing with aqueous sodium bicarbonate solution. The coupling was then achieved by activating the cyano acids **5**−**7** and reacting these with ZD6021 *N*-methylamine **14** (Scheme 1).

For ZD6021 amide alcohol **11**, the Discovery conditions involving the preparation of the ZD6021 acid chloride **15** were used. Thus, ZD6021 cyano acid **5** was reacted with oxalyl chloride, catalysed by DMF, affording the intermediate ZD6021 acid chloride **15** (Scheme 2), which was then further reacted with ZD6021 *N*-methylamine **14** to afford ZD6021 amide alcohol **11**. Concerns about gas evolution from the acid chloride formation led to a two-batch campaign, the first being run on a smaller scale (0.86 mol) to investigate the control of gas evolution during the reaction. In the event, control of gas evolution was not problematic, and the size of the reaction was increased to 2.43 mol for the second batch. The combined batches of product afforded 1.54 kg of crude ZD6021 amide alcohol **11** which was used without further purification in the subsequent stage.

This procedure, although effective at preparing ZD6021 amide alcohol **11**, raised concerns due to the potential production of carcinogenic dimethyl carbamyl chloride

(1) Moseley, J. D.; Moss, W. O. *Org. Process Res. Dev.* **2002**, *6*, 53−57.
(2) Moseley, J. D.; Moss, W. O.; Welham, M. J.; Ancell, C. L.; Banister, J.; Bowden, S. A.; Norton, G.; Young, M. J. *Org. Process Res. Dev.* **2002**, *6*, 58−66.
(3) Ashworth, I.; Bowden, M. C.; Dembofsky, B.; Levin, D.; Moss, W. O.; Robinson, E.; Szczur, N.; Virica, J. *Org. Process Res. Dev.* **2002**, *6*, 74−81.
(4) Parker, J. S.; Smith, N. A.; Welham, M. J.; Moss, W. O. *Org. Process Res. Dev.* Manuscript in preparation.
(5) Bowden, S. A.; Burke, J. N.; Gray, F.; McKown, S.; Moseley, J. D.; Moss, W. O.; Murray, P. M.; Welham, M. J. *Org. Process Res. Dev.* Manuscript in preparation.

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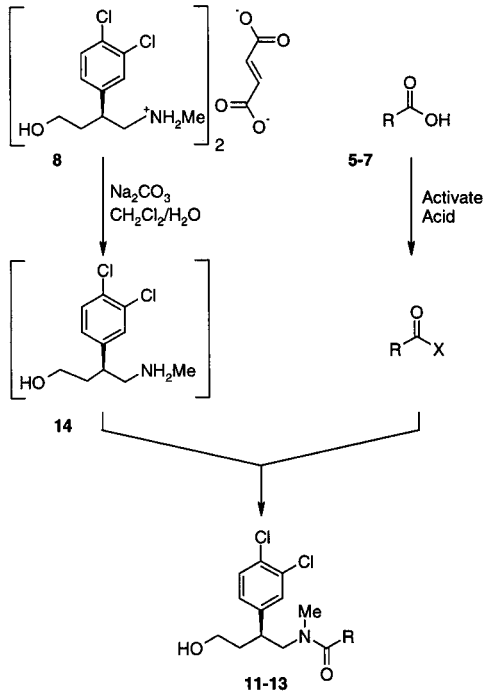
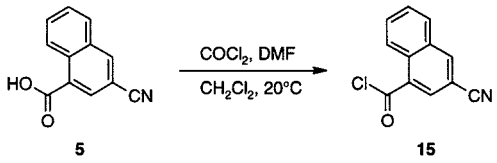
Scheme 1

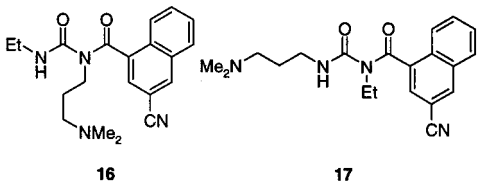


Scheme 2



(DMCC).[6] This concern led to investigations into the use of an EDCI coupling to effect this transformation for subsequent batches of ZD6021 amide alcohol **11**, which were being prepared for the second compound in the series, ZD2249 **2**.

Initial investigations involved the addition of ZD6021 *N*-methylamine **14** in dichloromethane to a stirred slurry of ZD6021 cyano acid **5**, EDCI, and triethylamine in dichloromethane.[7] This resulted in the formation of ZD6021 amide alcohol **11** (56%) but with the accompaniment of two impurities (27% and 7%). These were identified by LC−MS as the two possible *N*-acyl ureas, **16** and **17**, generated by rearrangement of the initially formed *O*-acyl urea.



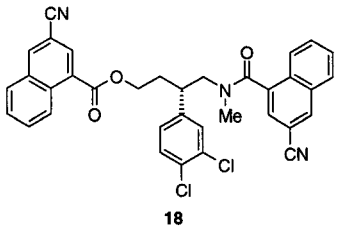
The amounts of these impurities could be reduced by the slow addition of a solution of EDCI to a solution of ZD6021 cyano acid **5** and ZD6021 *N*-methylamine **14**, with the addition of HOBt to the reaction mixture. This procedure was operated on a large scale, affording the required ZD6021 amide alcohol **11** with the impurities at low levels (1 and 0.5%, respectively).

(6) Levin, D. *Chem. Ind.* **1997**, 2; Levin, D. *Chem. Br.* **1997**, *33*, 20.
(7) Estenne, G.; Leclerc, G. *J. Heterocycl. Chem.* **1994**, *31*, 1121.

Table 1. **Values of parameters for selection of acid chloride formation**

catalyst	temperature (°C)	stoichiometry (mol equiv)
DMF	0	0.05
NMP	20	0.075
DMAP	40	0.01

However, on careful analysis of the crude product, a new impurity **18** was observed, which was slow-running on HPLC and thus had not been identified previously. This impurity, typically at a level of 10%, was shown to inhibit the crystallisation of the desired ZD6021 amide alcohol **11**; thus, work was undertaken to reduce the level of the impurity **18** in the crude product. Tituration of the crude, the use of cleaner input materials, and changing the order of addition and the amounts of the reagents were all investigated without significant effect. Eventually it was decided to hydrolyse the ester bond of the impurity, converting this material to ZD6021 amide alcohol **11**. Thus, treatment of an MTBE solution of the crude product with sodium hydroxide solution at 45 °C reduced the impurity level to 0.3% in 3 h. The crude material obtained after extraction of the hydrolysis reaction mixture was found to contain ZD6021 amide alcohol **11** at 88% strength. This material was successfully recrystallised from acetonitrile/water to afford 996 g of ZD6021 amide alcohol **11** at 90% strength. This represents a yield of 62%.



For delivery of the subsequent compounds in this series, and considering the problems identified during the previous preparations, it was decided to return to the preparation of acid chlorides to effect the coupling reaction to prepare amide alcohols **12** and **13**, for the preparation of ZD4974 **3** and ZM374979 **4**. Alternative reaction conditions were sought for this transformation, particularly focusing on changing the reaction catalyst from DMF to avoid the issue of DMCC. Factorial experimental design (FED) work was carried out to investigate this change, evaluating NMP and DMAP as alternative catalysts for the reaction. The parameters evaluated are shown in Table 1.

These parameters were evaluated in a nine-experiment Latin square factorial design as shown in Table 2.

As expected, DMF gave the best-quality product in the shortest reaction time. However, NMP at 40 °C gave comparable quality and yield, after a slightly longer reaction time, and this was selected as the catalyst for further reactions. The reaction stoichiometry and temperature were then further optimised using FED. The parameters evaluated are shown in Table 3.

Table 2. **Results of Latin square factorial design for selection of acid chloride formation**

experiment	catalyst	temp (°C)	stoichiometry (mol equiv)	corrected yield (%)	reaction time (h)
1	DMF	0	0.05	97.4	18
2	NMP	0	0.075	24.4	19
3	DMAP	0	0.10	4.3	18
4	DMF	20	0.075	97.5	1
5	NMP	20	0.10	91.4	19
6	DMAP	20	0.05	40.7	22
7	DMF	40	0.10	98.4	0.16
8	NMP	40	0.05	96.2	0.66
9	DMAP	40	0.075	96.2	6.5

Table 3. **Values of parameters for optimisation of acid chloride formation**

parameter	low level	high level
NMP charge	0.10 mol equiv	0.15 mol equiv
oxalyl chloride charge	1.0 mol equiv	1.1 mol equiv
temperature	30 °C	reflux

Table 4. **Results of fractional factorial design for optimisation of acid chloride formation**

expt	NMP charge	oxalyl chloride charge	temp	corrected yield (%)	reaction time (min)
1	−1	−1	−1	98.4	300
2	−1	1	1	97.6	80
3	1	−1	1	96.9	80
4	1	1	−1	98.3	300

Table 5. **Values of parameters for optimisation of amide formation**

parameter	low level	high level
N-methyl amine charge	1.0 mol equiv	1.1 mol equiv
addition time	30 min	60 min
addition temperature	10 °C	30 °C

These parameters were evaluated in a four-experiment fractional factorial design as shown in Table 4.

Temperature was shown to be the dominant parameter, with a slower reaction occurring at the lower temperature. However, the reaction was restricted to a maximum of 30 °C for manufacture, given concern for the hazard of gas evolution during charging of oxalyl chloride to the batch at reflux. The effect of the other factors was negligible; thus, the stoichiometry was fixed at 1.2 mol equiv oxalyl chloride and 0.1 mol equiv of NMP on the basis of trends.

As an extension to this work, it was decided to optimise the coupling reaction between the produced acid chlorides **19** and **20** and ZD6021 *N*-methylamine **14**. This also was achieved using FED studies, the parameters of which are shown in Table 5.

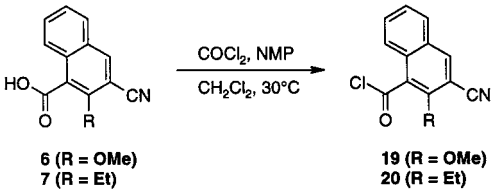
These parameters were evaluated in a four-experiment fractional factorial design as shown in Table 6.

With minimal difference between the results, the predicted best combination of 1.1 mol equiv ZD6021 *N*-methylamine **14** added over 30 min was selected for large-scale manufacture. The temperature effect was minimal and was set at ambient for convenience.

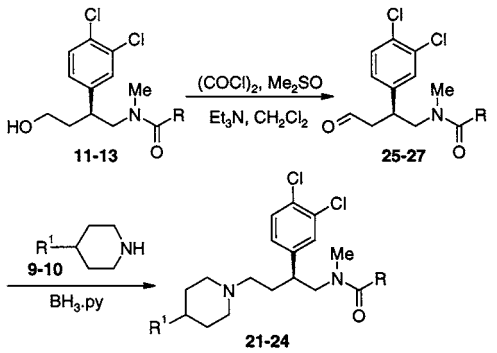
Table 6. **Results of fractional factorial design for optimisation of amide formation**

expt	*N*-methyl amine charge	addition time	addition temp	corrected yield (%)
1	−1	−1	−1	96.6
2	−1	1	1	95.6
3	1	−1	1	95.0
4	1	1	−1	96.5

Scheme 3



Scheme 4



These optimised conditions were utilised for the preparation of both ZD4974 amide alcohol **12** and ZD374979 amide alcohol **13** (Scheme 3). The crude ZD4974 amide alcohol **12** was purified by recrystallisation from tetrahydrofuran: isohexane, affording 3.67 kg of material with a typical strength of 96%, representing a 95% yield. Crude ZM374979 amide alcohol **13** (954 g) was manufactured and used without further purification in the subsequent stage.

The produced amide alcohols **11**−**13** now required coupling to the appropriate piperidine (**9** or **10**) to afford the crude products **21**−**24**. This was achieved by oxidation of the amide alcohols **11**−**13** to aldehydes **25**−**27**, followed by a reductive amination with appropriate piperidine (**9** or **10**) (Scheme 4).

The Discovery procedures for these transformations were investigated for the preparation of ZD6021 crude **21**.

Two initial concerns with the Discovery methodology were the need to conduct the Swern oxidation at low temperatures and containment of the dimethyl sulfide generated during the reaction. However, as appropriate equipment was available in the Macclesfield Large Scale Laboratory to address these concerns, it was decided to attempt scale-up of the process. The process utilised by Discovery involved the addition of DMSO to a solution of oxalyl chloride in dichloromethane at −78 °C. In practice, this led to the DMSO freezing on the side of the vessel; consequently, the procedure was modified to involve addition of DMSO as a

Table 7. **Values of parameters for optimisation of Swern oxidation**

parameter	low level	high level
oxalyl chloride/DMSO charge	1.5/3 mol equiv	3/6 mol equiv
amide alcohol addition time	10 min	60 min
hold time before Et_3N addition	30 min	60 min
Et_3N charge	4.5 mol equiv	7.5 mol equiv
Et_3N addition time	5 min	30 min

Table 8. **Results of fractional factorial design for optimisation of Swern oxidation**

expt	oxalyl chloride/ DMSO charge	amide alcohol addition time	hold time before Et_3N addition	Et_3N charge	Et_3N addition time	corrected yield (%)
1	−1	−1	−1	−1	−1	69.7
2	−1	−1	1	1	1	68.1
3	−1	1	−1	−1	1	64.0
4	−1	1	1	1	−1	69.7
5	1	−1	1	−1	1	73.0
6	1	−1	−1	1	−1	77.0
7	1	1	1	−1	−1	71.4
8	1	1	−1	1	1	70.0

solution in dichloromethane. The reaction was shown to operate well between −60 and −45 °C, but incomplete reaction was observed at −20 °C.

Due to concerns about the stability of the produced aldehyde, it was decided not to purify this material, using the crude product in the reductive amination stage. The reducing reagent was successfully changed from sodium cyanoborohydride used by Discovery, to the less toxic borane−pyridine. The reaction was first investigated in methanol but a competing side reaction occurred, thought to be the formation of the dimethyl acetal. To avoid this problem the reaction solvent was changed to dichloromethane.

With both stages for the formation of the ZD6021 crude **21** being conducted in dichloromethane, it was decided to investigate telescoping the two stages together. This procedure proved to be effective and was utilized for the delivery of 2.06 kg of ZD6021 crude **21**, with a yield of 76% achieved over the two steps from ZD6021 amide alcohol **11** and product strength of 68% (product contained 25% residual dichloromethane).

An analogous procedure was used for the delivery of 1.95 kg of ZD2249 crude **22**, with a yield of 79% achieved over the two steps from ZD6021 amide alcohol **11** and product strength of 75%.

For the preparation of ZD4974 crude **23**, extensive FED work was carried out to optimise and demonstrate the robustness of the oxidation. The parameters evaluated for the optimisation of oxidation stage are show in Table 7.

These parameters were evaluated in an eight-experiment fractional factorial design (resolution III) as shown in Table 8.

This work showed that high charges of oxalyl chloride, DMSO, and triethylamine provided the most effective reaction. Short addition times for the ZD4974 amide alcohol **12** and triethylamine were also beneficial to a lesser extent, but were more difficult to achieve on scale-up for a reaction requiring −60 °C.

Table 9. **Values of parameters for optimisation of reductive amination**

parameter	low level	high level
pip sulfoxide charge	0.9 equiv	1.1 equiv
CH_2Cl_2 charge for pip sulfoxide solution	0 vols	0.7 vols
water charge for pip sulfoxide solution	0 vols	0.7 vols
order of addition	aldehyde to pip sulfoxide (normal)	pip sulfoxide to aldehyde (inverse)
reaction temperature	22 °C	32 °C
hold time before borane−pyridine addition	0 h	1 h
borane−pyridine charge	0.8 equiv	1.2 equiv

The reductive amination was evaluated by a similar approach. The parameters evaluated for the optimisation of reductive amination stage are shown in Table 9. The addition of the water or dichloromethane was investigated to improve the solubility of the ZD7944 pip sulfoxide **9**.

These parameters were evaluated in a 16-experiment fractional factorial design (resolution III) using a Benchmate robot, as shown in Table 10

These results showed that ZD7944 pip sulfoxide **9** and the water charges were the most important parameters. A higher ZD7944 pip sulfoxide **9** charge gave improved conversion at the end of reaction. In contrast the presence of water was detrimental to the reaction.

The optimised conditions identified in these experiments were applied to the preparation of 3.67 kg of ZD4974 crude **23**, with a yield of 79% achieved over the two steps from ZD4974 amide alcohol **12**, and product strength of 85%.

These conditions were then applied, without modification, to the preparation of ZM374979 crude **24**, successfully producing 1.38 kg of product, with a yield of 87% achieved over the two steps from ZM374979 amine alcohol **13** and product strength of 82%.

The final step required for delivery of the final active pharmaceutical ingredients was a crystallisation of crude materials as amine salts. The purity target for these final stages was to produce material with strength greater than 95%.

For the crystallisation of ZD6021 hydrogen fumarate pure **1**, the Discovery recrystallisation conditions were used, involving dissolution in hot ethanol and the addition of fumaric acid. The purity of the material obtained from this stage was 90%, whereas Discovery had produced ZD6021 hydrogen fumarate pure **1** with a strength >98% using the same procedure.

The Discovery synthesis had made extensive use of chromatography and had produced ZD6021 crude **21** with strength of 98.7%. In contrast, the material produced by Development varied in strength from 65 to 75%, the material having been carried though five synthetic steps without crystallisation or chromatography.

Table 10. **Results of fractional factorial design for optimisation of reductive amination**

expt	pip sulfoxide	CH_2Cl_2 charge	water charge	order of addition	temp	hold time	borane−pyridine	solution conversion (%)
1	−1	−1	−1	−1	−1	−1	−1	77.8
2	−1	−1	−1	−1	1	1	1	64.0
3	−1	−1	1	1	−1	−1	1	35.3
4	−1	−1	1	1	1	1	−1	26.0
5	−1	1	−1	1	−1	1	−1	56.9
6	−1	1	−1	1	1	−1	1	64.4
7	−1	1	1	−1	−1	1	1	23.6
8	−1	1	1	−1	1	−1	−1	52.2
9	1	−1	−1	1	−1	1	1	80.9
10	1	−1	−1	1	1	−1	−1	85.1
11	1	−1	1	−1	−1	1	−1	22.1
12	1	−1	1	−1	1	−1	1	67.0
13	1	1	−1	−1	−1	−1	1	83.6
14	1	1	−1	−1	1	1	−1	80.1
15	1	1	1	1	−1	−1	−1	23.9
16	1	1	1	1	1	1	1	31.1

Thus, a further purification step was required, and a retreatment of semi-pure material was developed involving recrystallisation from an ethanol:water mixture. This procedure increased the strength of the material to 94.8%, which was judged to be of sufficient purity to use in toxicity trials. The retreatment yielded 980 g of ZD6021 hydrogen fumarate pure **1**, which represents a yield of 59%.

The learning from the preparation of ZD6021 hydrogen fumarate pure **1** was applied to the development of a process for ZD2249 hydrogen fumarate pure **2**. Extensive screening of crystallisation solvents showed that an ethanol:water mixture remained the most effective solvent system for this transformation, which would increase purity to ca. 92%. Retreatment of this material was considered, but due to low recoveries from the screening experiments it was decided to investigate the use of slurry washes. The use of hot aqueous ethanol washes were shown to give an increase in purity with low losses to liquors, as was the use of ethyl acetate washes. These techniques were combined, and the ZD2249 hydrogen fumarate pure **2** was crystallised from ethanol:water and then slurry-washed with hot ethanol and ethyl acetate, affording 950 g of product with a strength of 94.8%. As with ZD6021 hydrogen fumarate pure **1**, this material was considered to be of sufficient purity to use in toxicity trials. The yield for this stage was 75%.

The crystallisations of both ZD4974 citrate pure **3** and ZM374979 maleate pure **4** were complicated by the existence of atropisomerism in these molecules. The issue raised by the atropisomerism and the development work carried out on selective atropisomer crystallisation will be discussed in a subsequent paper.[4]

With the problems previously encountered with purification of both ZD6021 and ZD2249 hydrogen fumarate pures **1** and **2**, it was decided to purify ZD4974 and ZM374979 crudes **23** and **24** using flash column chromatography. Thus, ZD4974 crude **23** was purified by dry flash column chromatography, improving the purity to 97.3% with a 72% material recovery. This semi-pure material was crystallised as the citrate salt from hot ethanol, affording 1.22 kg of ZD4974 citrate pure **3**, with a strength of 97.3%. The citrate salt formation and crystallisation yield was 66%.

ZM374979 crude **24** was also purified by dry flash column chromatography, increasing the purity to 95.5% with a 75% material recovery (1.03 kg, mixture of four atropisomers). The semi-pure material was then crystallised as the maleate salt from hot methanol, affording 237 g of ZM374979 maleate pure **4** (single atropisomer), with a strength of 94.7%, which was judged to be of sufficient purity for toxicity trials. The maleate salt formation and crystallisation yield was 23%.

Conclusions

The use of the rapid parallel development approach allowed delivery of 1 kg of each of the neurokinin antagonists (ZM374979 as a mixture of atropisomers) providing a further example of the success of this approach.[1]

The key factors of robustness and safety remained the highest priorities during this work, robustness being demonstrated by extensive factorial experimental design work and the safety by adequate hazard evaluation.

As previously noted, the focus of this approach is on the short-term delivery of these compounds. For longer-term manufacture the use of a Swern oxidation would not be viable. However, for the manufacture of 1-kg quantities, the use of Research procedures, or a modification of these, has been successful in affording the necessary products within the scope of the rapid parallel development approach.

Experimental Section

General Procedures. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Inova 400 MHz spectrometer with chemical shifts given in ppm relative to TMS at $\delta = 0$. Electrospray (ES) mass spectra were determined on a Micromass Platform LC. The reaction mixtures and products were analysed by reverse phase HPLC on a Hewlett-Packard 1100 according to the following conditions: column, Waters Spherisorb S5ODS1, 250 mm × 4.6 mm i.d.; eluent, 560:440 acetonitrile:water with 0.1% v/v trifluoroacetic acid; flow rate, 1.0 mL/min; wavelength, 235 nm; injection volume, 5 μL, column temperature, 25 °C. HPLC purities were %w/w

against a standard of known strength as determined by ^{1}H NMR. 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).

Preparation of ZM374979 Amide Alcohol 13. A 250-mL round-bottomed flask was equipped with overhead stirrer, condenser, thermometer, and nitrogen inlet/outlet and then was purged with nitrogen for 10 min. ZM374979 cyano acid **7** (12.00 g, 53.3 mmol, 1.00 equiv) was then charged, followed by dichloromethane (120 mL). The resulting brown slurry was stirred, and NMP (0.51 mL, 5.33 mmol, 0.10 equiv) was charged in a single portion. The mixture was then heated to 30 °C and stirred at this temperature for 30 min. Oxalyl chloride (5.70 mL, 64.0 mmol, 1.20 equiv) was added over a 30-min period, during which time effervescence was observed. On completion of addition, the batch was held overnight at 30 °C, affording a dark brown solution; the reaction mixture was then cooled to ambient temperature. A 1000-mL round-bottomed flask was equipped with condenser, overhead stirrer, additions funnel, and thermometer. ZD6021 amine fumarate (17.95 g, 29.33 mmol, 0.55 equiv) was charged to this flask with sodium carbonate (16.96 g, 160.0 mmol, 3.00 equiv), dichloromethane (240 mL), and water (240 mL). This mixture was stirred at ambient temperature for 30 min, affording a biphasic system, with a white, cloudy, lower organic phase. The acid chloride solution was added dropwise over a 30-minute period and then the additions funnel was washed with dichloromethane (12 mL). The reaction mixture was stirred at ambient temperature for 2 h. Agitation was then stopped, and the layers were allowed to settle for 15 min. The lower organic phase was removed, dichloromethane (72 mL) was added, and the mixture was stirred for 15 min. Agitation was then stopped, and the layers were allowed to settle for 15 min. The lower organic phase was removed and combined with the other organic portions, the aqueous portion being discarded. The organic solution was recharged to the flask, and hydrochloric acid (1 M, aqueous, 96 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and sodium hydrogen carbonate solution (saturated, aqueous, 96 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and sodium chloride solution (saturated, aqueous, 96 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower organic phase was removed and the solvent removed using a rotary evaporator, affording a brown foam. This material was transferred to a vacuum oven at 40 °C and dried to a constant weight, affording ZM374979 amide alcohol **13** as a brown solid (25.00 g, 89% corrected for strength). HPLC purity 86.1%, t_R 12.7 min (single atropisomer); mp 131−132 °C; ^{1}H NMR (399.895 MHz, d_6-DMSO) 1.25 (3H, t, J = 7.4 Hz, $CH_2C\underline{H}_3$), 1.77−1.98 (2H, m, $Cl_2PhCHC\underline{H}_2CH_2$), 2.54−2.59 (3H, s, $NC\underline{H}_3$), 2.63−2.76 (1H, m, $C\underline{H}H'CH_3$), 2.80−2.93 (1H, m, $CH\underline{H}'CH_3$), 3.23−3.53 (4H, m, $Cl_2PhCHCH_2C\underline{H}_2$, $Cl_2PhC\underline{H}$ and $CH_3NC\underline{H}H'$), 4.51−4.65 (2H, m, $CH_3NCH\underline{H}'$ and $O\underline{H}$), 6.39 (1H, d, J = 8.5 Hz, ArH), 7.40 (1H, t, J = 7.4 Hz, ArH), 7.52 (1H, dd, J = 8.5, 1.8 Hz, ArH), 7.62−7.70 (1H, m, ArH), 7.72−7.81 (2H, m, ArH), 8.03−8.11 (1H, m, ArH), 8.63 (1H, s, ArH); MS (ES^+) 459 (8, MH^+, $^{37}Cl_2$), 457 (41, MH^+, $^{35}Cl^{37}Cl$), 455 (100, MH^+, $^{35}Cl_2$).

Preparation of ZM374979 Maleate Pure 4. A 1-L round-bottomed flask (previously oven-dried and cooled to ambient temperature under a nitrogen purge) was equipped with an overhead stirrer, a pressure-equalising additions funnel, and a nitrogen inlet/outlet; it was then purged with nitrogen for 10 min. Dichloromethane (125 mL) and oxalyl chloride (14.35 mL, 165 mmol, 3.00 equiv) were then charged to the flask. This solution was stirred and cooled to −70 °C, at which temperature it was held for 15 min. A solution of dimethyl sulfoxide (23.35 mL, 329 mmol, 6.00 equiv) in dichloromethane (45 mL) was charged to the additions funnel and then added dropwise at a rate such that the batch temperature was maintained below −65 °C. On completion of addition, the mixture was stirred at −70 °C for 30 min. A solution of ZM374979 amide alcohol **13** (25.00 g, 54.9 mmol, 1.00 equiv) in dimethyl sulfoxide (100 mL) and dichloromethane (137 mL) was charged to the additions funnel and then added dropwise at a rate such that the batch temperature was maintained below −60 °C. On completion of addition, the mixture was stirred at −70 °C for 30 min. Triethylamine (57.10 mL, 411.7 mmol, 7.50 equiv) was charged to the additions funnel and then added over a 5-min period, maintaining the reaction temperature below −60 °C. The reaction was stirred at −70 °C for 4 h and then warmed slowly to ambient temperature. Hydrochloric acid (1 M, aqueous, 275 mL) was added; the mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower, organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and hydrochloric acid (1 M, aqueous, 275 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower, organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and sodium hydrogen carbonate solution (saturated, aqueous, 275 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower, organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and sodium chloride solution (saturated, aqueous, 137 mL) and water (137 mL) were added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower organic phase was removed and retained, the aqueous phase being discarded. A 1-L round-bottomed flask was equipped with an overhead stirrer, a pressure-equalising additions funnel, and a nitrogen inlet/outlet. ZD7944 pip sulfoxide **9** (15.91 g, 71.4 mmol,

1.30 equiv) was charged to this vessel with methanol (100 mL). The mixture was stirred, and the solution of ZM374979 aldehyde **27** was added to the flask. The mixture was stirred for 15 min, and then borane−pyridine (5.55 mL, 54.9 mmol, 1.00 equiv) was added dropwise over a 30 min period. The reaction was stirred for 20 h, and then hydrochloric acid (1 M, aqueous, 275 mL) was added cautiously to the mixture. The mixture was stirred for 15 min a nd then left for 15 min for the layers to separate. The lower, organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and hydrochloric acid (1M, aqueous, 275 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower, organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and sodium hydrogen carbonate solution (saturated, aqueous, 275 mL) was added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower organic phase was removed and retained, the aqueous phase being discarded. The organic solution was recharged to the flask, and sodium chloride solution (saturated, aqueous, 137 mL) and water (137 mL) were added. The mixture was stirred for 15 min and then left for 15 min for the layers to separate. The lower, organic phase was removed and the solvent removed using a rotary evaporator, affording ZM374979 crude **24** as a brown foam (36.90 g, 93% corrected for strength). HPLC purity 91.7%, t_R 26.2 min (single atropisomer).

A 10-cm diameter sinter funnel (grade 3) was packed with silica (244.3 g, 12 times crude weight loading, depth 68 mm) slurried in 5% methanol in ethyl acetate. The solvent level was run down to the top of the silica. ZM374979 crude **24** (20.36 g, 30.85 mmol) was dissolved in 5% methanol in ethyl acetate (25 mL), and this solution was carefully applied onto the column by pipet. Quartz sand (20.4 g, 1 times crude weight loading) was carefully applied to the column, giving a level surface. Methanol (5%) in ethyl acetate (20 mL) was run down the side of the column to wet the sand, and then the column was filled with the same solvent, taking care not to disturb the surface of the sand. The column was eluted, collecting 100-mL fractions, ensuring that the solvent flow through that column was not too fast. When collected fractions contained only product spots by thin layer chromatography analysis (fraction 23), the eluent was changed to 5% methanol in dichloromethane. Elution was continued until no further product was detected in the collected fractions (fraction 40). The product fractions were combined, and the solvent was removed using a rotary evaporator, affording ZM374979 semi-pure as a yellow foam (14.11 g, 66% corrected for strength). HPLC purity 95.6%, t_R 26.2 min (single atropisomer).

A 50-mL round-bottomed flask was equipped with overhead stirrer, condenser, and thermometer. ZM374979 semi-pure (5.00 g, 7.58 mmol, 1.00 equiv) was charged with methanol (20 mL). The mixture was heated to 60 °C and then held at this temperature for 48 h. A 100-mL round-bottomed flask was equipped with overhead stirrer, condenser, and thermometer. A solution of maleic acid (0.89 g, 7.58 mmol, 1.00 equiv) in methanol (5 mL) was charged to this second flask, and this solution was heated to 40 °C. The solution of ZM374979 semi-pure was cooled to 40 °C and then transferred to the second flask via an in-line filter. The first flask was washed with methanol (15 mL), and this wash was transferred to the second flask via the in-line filter. The resulting solution was stirred at 40 °C for 1 h and then cooled to 23 °C over a 1-h period. The solution was stirred at 23 °C for 1 h, and then seed crystals of ZM374979 maleate pure **4** (0.5 mg, 6.0×10^{-4} mmol, 8.5×10^{-5} equiv) were added. The solution was then held for a further 24 h at 23 °C, after which time the mixture was a thick, white slurry. The product was then isolated by filtration, and the flask and cake were washed with methanol (5 mL). The solid was pulled dry using vacuum and then washed with methanol:isohexane (1:1, 5 mL). The solid was pulled dry using vacuum and then washed with isohexane (5 mL). The solid was pulled dry using vacuum and then transferred to a vacuum oven at 30 °C and dried to constant weight, affording ZM374979 maleate pure **4** as a white, crystalline solid (1.41 g, 23% corrected for strength). HPLC purity 94.7%, t_R 26.2 min (single atropisomer); mp 170−172 °C; ^{1}H NMR (399.895 MHz, d_6-DMSO, 80 °C) 1.23 (3H, t, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.86−2.18 (6H, m, MeSOPhCH($C\underline{H}_2$)$_2$ and Cl_2-PhCH$C\underline{H}_2CH_2$), 2.54 (3H, s, $NC\underline{H}_3$), 2.63−2.88 (6H, m, PhSO$C\underline{H}_3$, $C\underline{H}_2CH_3$ and MeSOPh$C\underline{H}$), 2.99−3.16 (4H, m, Cl_2PhCH$CH_2C\underline{H}_2$ and MeSOPhCH($CH_2C\underline{H}$H′)$_2$), 3.34−3.36 (1H, m, Cl_2Ph$C\underline{H}$), 3.44−3.51 (2H, m, MeSOPhCH(CH_2-C$\underline{H}$H′)$_2$), 3.58−3.63 (1H, m, $CH_3NC\underline{H}$H′), 4.66 (1H, t, J = 12.8 Hz, $CH_3NCH\underline{H}$′), 5.67−6.58 (1H, m, Ar$\underline{H}$), 7.36−7.44 (2H, m, Ar$\underline{H}$), 7.50−7.62 (4H, m, Ar$\underline{H}$), 7.71 (1H, d, J = 8.4 Hz, Ar$\underline{H}$), 7.77 (1H, s, Ar$\underline{H}$), 7.88 (1H, d, J = 7.6 Hz, Ar$\underline{H}$), 8.01 (1H, d, J = 8.0 Hz, Ar$\underline{H}$), 8.53 (1H, s, Ar$\underline{H}$); MS (ES$^+$) 664 (30, MH$^+$, $^{37}Cl_2$), 662 (65, MH$^+$, $^{35}Cl^{37}Cl$), 660 (100, MH$^+$, $^{35}Cl_2$).

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