Preprint Title	An improved, scalable synthesis of Notum inhibitor LP-922056 using 1-chloro-1,2-benziodoxol-3-one as a superior electrophilic chlorinating agent
Authors	Nicky J. Willis, Elliott D. Bayle, George Papageorgiou, David Steadman, Benjamin N. Aktinson, William Mahy and Paul V. Fish
Publication Date	16 Jul 2019
Article Type	Full Research Paper
Supporting Information File 1	SI File 1.doc; 675.5 KB
Supporting Information File 2	SI File 2.csv; 1.3 KB
ORCID® iDs	George Papageorgiou - https://orcid.org/0000-0002-8960-5836; David Steadman - https://orcid.org/0000-0003-4271-5525; Benjamin N. Aktinson - https://orcid.org/0000-0001-5511-9859; Paul V. Fish - https://orcid.org/0000-0002-2117-2173

An improved, scalable synthesis of Notum inhibitor LP-922056 using 1-chloro-1,2-benziodoxol-3-one as a superior electrophilic chlorinating agent

Nicky J. Willis,[1] Elliott D. Bayle,[1,2] George Papageorgiou,[2] David Steadman,[1] Benjamin N. Atkinson,[1] William Mahy[1] and Paul V. Fish* [1,2]

[1] Alzheimer's Research UK UCL Drug Discovery Institute, The Cruciform Building, University College London, Gower Street, London WC1E 6BT, UK.

[2] The Francis Crick Institute, 1 Midland Road, Kings Cross, London NW1 1AT, UK.

Email: p.fish@ucl.ac.uk

*Corresponding author

Abstract

Background: The carboxylesterase Notum has been shown to act as a key negative regulator of the Wnt signalling pathway by mediating the depalmitoleoylation of Wnt proteins. LP-922056 (**1**) is an orally active inhibitor of Notum. We are investigating the role of Notum in modulating Wnt signalling in the central nervous system and wished to establish if **1** would serve as a peripherally restricted control. An accessible and improved synthetic route would allow **1** to become more readily available as a chemical tool to explore the fundamental biology of Notum and build target validation to underpin new drug discovery programs.

Results: An improved, scalable synthesis of **1** is reported. Key modifications include: (1) the introduction of the C7-cyclopropyl group was most effectively achieved with a Suzuki–Miyaura cross-coupling reaction with MIDA-boronate **11** (**5** → **6**); and (2) C6 chlorination was performed with 1–chloro-1,2-benziodoxol-3-one (**12**) (**6** → **7**) as a mild selective electrophilic chlorination agent. This 7-step route has been reliably performed on large scale to produce multigram quantities of **1** in good efficiency and high purity. Pharmacokinetic studies in mouse showed CNS penetration of **1** is very low with brain:plasma concentration ratio of just 0.01. A small library of amides **17** were prepared from acid **1** to explore if **1** could be modified to deliver a CNS penetrant tool by capping off the acid as an amide. Although significant Notum inhibition activity could be achieved, none of these amides demonstrated the required combination of metabolic stability along with cell permeability without evidence of P-gp mediated efflux.

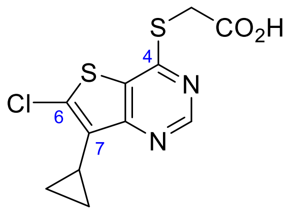
Conclusion: Mouse pharmacokinetic studies demonstrate that **1** is unsuitable for use in models of disease where brain penetration is an essential requirement of the compound but would be an ideal peripherally restricted control. These data will contribute to the understanding of drug levels of **1** to overlay with appropriate *in vivo* efficacy endpoints, i.e. the PK-PD relationship. The identification of a suitable analogue of **1** (or **17**) which combines Notum inhibition with CNS penetration would be a valuable chemical probe for investigating the role of Notum in disease models.

Keywords

brain penetration; 1-chloro-1,2-benziodoxol-3-one; electrophilic chlorination; LP-922056; Notum inhibitor.

Introduction

The Wnt signalling pathway has been shown to regulate crucial aspects of cell fate determination, organogenesis, cell migration and polarity [1]. Importantly, compromised Wnt signalling has been implicated in the perturbation of synaptic integrity and function in Alzheimer's disease (AD) [2]. Palmitoleoylation of Wnt proteins is required for efficient binding to Frizzled receptors and the subsequent signal transduction. The carboxylesterase Notum has been shown to act as a key negative regulator of the Wnt signalling pathway by specifically mediating the depalmitoleoylation of Wnt proteins [3,4].



LP-922056 (**1**)

LP-922056 (**1**) is an orally active inhibitor of Notum recently reported by Lexicon Pharmaceuticals [5,6]. Their research with **1** has shown that Notum is a potential drug target for stimulating bone formation and treating osteoporosis [7]. However, although **1** demonstrates low plasma clearance, the structure contains an essential carboxylic acid and acids tend to have low passive brain penetration [8-12]. We are investigating the role of Notum in modulating Wnt signalling in the central nervous system (CNS) [13] and wished to establish if **1** would serve as a peripherally restricted control compound. Hence, we required a synthetic route to **1** that could be reliably and safely performed on large scale.

A synthesis of **1** has been published in the patent literature [6], although many of the experimental procedures are described in terms of 'general procedures' which do not seem to work well when applied to **1** which contains function groups sensitive to certain reagents employed (*vide infra*). An improved synthetic route should allow **1** to become more readily available as a chemical tool to explore the fundamental biology of Notum and build target validation to underpin new drug discovery programs for non-CNS disease.

Results and Discussion

Improved synthesis of 1

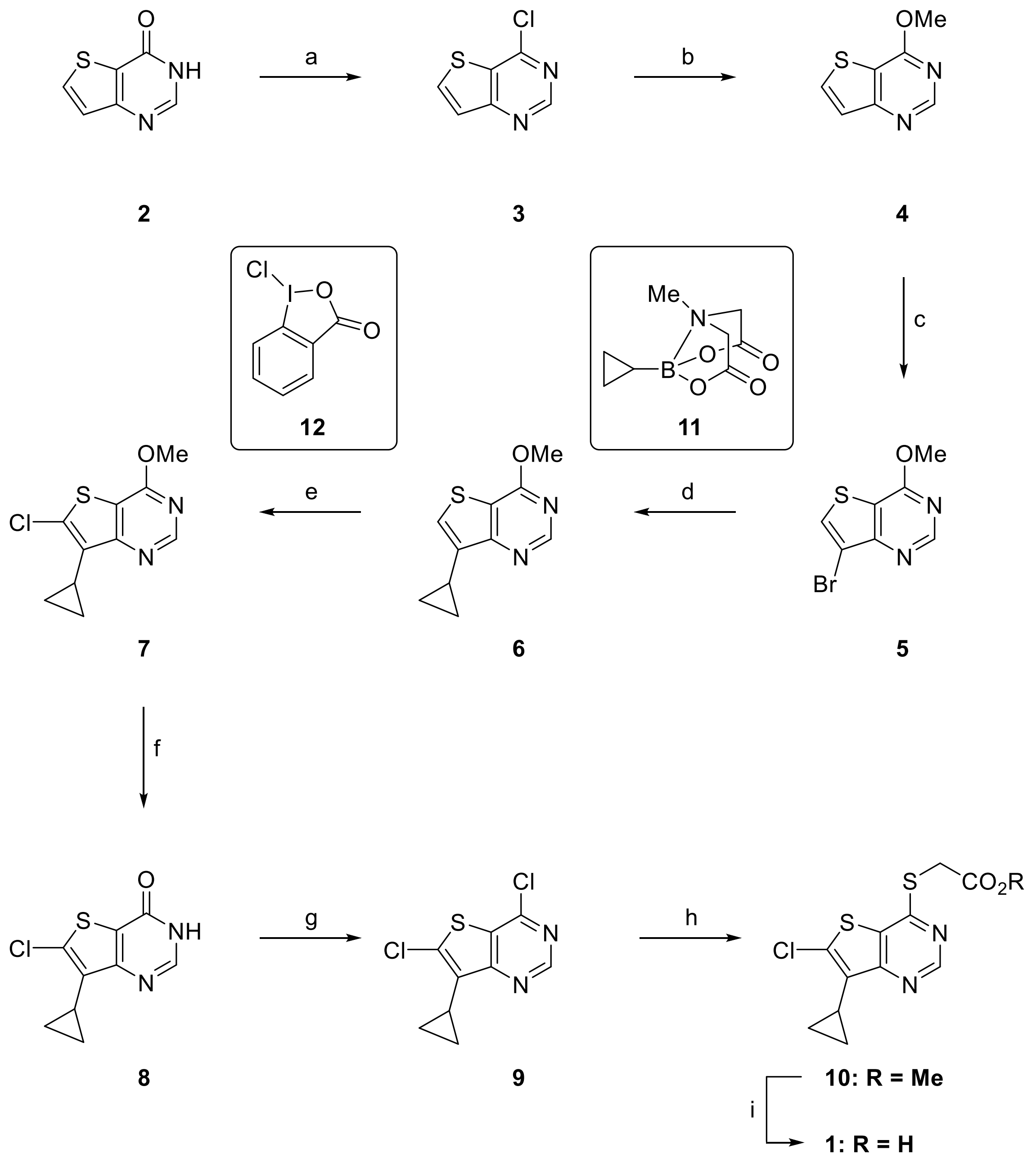
Our first complete synthesis of **1** is presented in Scheme 1 (see Supporting Information for experimental procedures and characterisation data (File 1)). This 8-step sequence starts with 4-chlorothieno[3,2-

d]pyrimidine (**3**), which is readily available from commercial suppliers, and generally follows published procedures [5,6] but with key modifications to increase yields/selectivities and significantly improve ease of purification of key intermediates. Our modifications include: (1) the introduction of the C7-cyclopropyl group was most effectively achieved with a Suzuki–Miyaura cross-coupling reaction with MIDA-boronate **11** (**5** → **6**); and (2) C6 chlorination was performed with 1‒chloro-1,2-benziodoxol-3-one (**12**) (**6** → **7**) as a mild selective electrophilic chlorination agent.

4-Chlorothieno[3,2-d]pyrimidine (**3**) was either purchased or prepared from thieno[3,2-d]pyrimidin-4(*3H*)-one (**2**) by C4 chlorination with oxalyl chloride/DMF following the method of Mitchell *et al.* [14]. Treatment of **3** with NaOMe displaced the C4-Cl to give **4** in good yield as described by Atherall *et al*. [15]. Thieno[3,2-d]pyrimidine (**4**) is now suitably functionalised for introduction of the C7-cyclopropyl, C6-chloro and elaboration of the thioaceteic acid at C4.

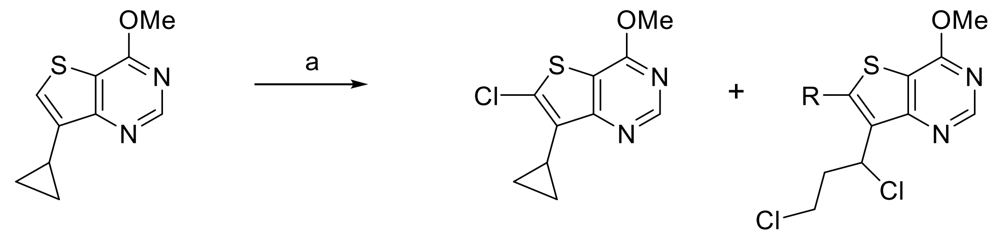
Electrophilic bromination at C7 with *N*-bromosuccinamide gave **5** as the major regioisomer reproducibly on 100 mmol scale in modest yield (41-48 %). This proved to be the least efficient step in our sequence and justified further optimisation (*vide infra*). Suzuki-Miyaura cross-coupling of bromide **5** with cyclopropylboronic acid (2.5 equiv.) produced **6** in good yield (62-89 %) but the product required extensive chromatographic purification. We reasoned that switching from the boronic acid (*c*-PrB(OH)$_2$) to the corresponding MIDA-boronate **11** would improve the quality of the reagent and slow release of the active boron species during the course of the reaction would allow us to reduce the number of molar equivalents required to improve conversion [16]. Palladium mediated cross-coupling of **5** with **11** (1.5 equiv.) gave **6** in reproducibly high yield (ca. 95 %) when performed on gram scale. However, when performed on larger scale (9.3 g), the reaction stalled after ca. 90 % conversion and addition of extra catalyst Pd[(PPh$_3$)$_2$Cl$_2$] and/or **11** failed to drive the reaction to completion. We found the most efficient way to complete the reaction conversion was to isolate the crude product (mostly **6**) and subject this material to a repeat reaction; this procedure gave **6** in good yield 95 % and simplified purification.

With multigram quantities of **6** in hand, attention was turned to the C6 chlorination step. Unfortunately, despite this reaction being reported in the literature, there were no experimental details for this specific transformation as only a 'general procedure' was described [6]. Our attempts to use this procedure with *N*-chlorosuccinimide (NCS) as the chlorinating agent gave poor yields of the desired product **7** (ca. 15-32 %) due to competing ring opening reactions of the 7-cyclopropyl group (Scheme 2). Clearly, a better procedure was required.



Scheme 1. Synthesis of **LP-922056** (**1**). Reagents and conditions:[a] (a) $(COCl)_2$ (3.3 equiv.), DMF, CH_2Cl_2, 55 °C , 16 h, 63-78 %; (b) NaOMe (5 equiv.), 1,4-dioxane, 0 °C then rt, 16 h, 92-93 %; (c) NBS (1.1 equiv.), AcOH-MeCN (1:100), 85 °C, 16 h, 41-48 %; (d) **11** (1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), K_3PO_4 (6 equiv), PhMe-H_2O (3:1, 0.25 M), 100 °C, 12 h, 94-95 %; (e) 1-Chloro-1,2-benziodoxol-3-one (**12**) (1.5 equiv.), DMF, 50 °C, 16 h, 77-94 %; (f) HCl (12 M)(40 equiv.), 70 °C, 16 h; (g) $POCl_3$ (20 equiv.), 90 °C, 16 h, 81 % over 2 steps; (h) $HSCH_2CO_2Me$ (**13**)(1.2 equiv.), NEt_3 (2.1 equiv.), MeOH, 0 °C to rt, 16 h, 84 %; (i) NaOH (1 M) (2 equiv.), THF, 0 °C, 1 h, then HCl (1 M), 0 °C, 30 min, 98 %. [a] These reactions have been performed several times but have not been systematically optimised. Yields are the ranges obtained from repeated reactions. DMF, *N,N*-dimethylformamide; NBS, *N*-bromosuccinimide; THF, tetrahydrofuran.

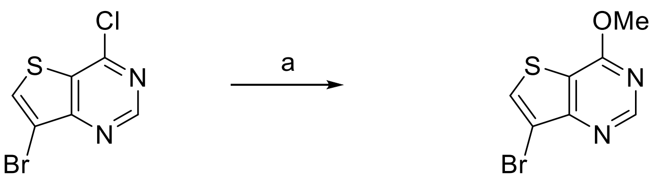
A large number of electrophilic chlorinating reagents for the direct chlorination of aromatic rings have been reported [17]. Recently, Xue *et al.* described the electrophilic chlorination of arenes and heterocycles by 1‒chloro-1,2-benziodoxol-3-one (**12**) [18,19]. The hypervalent iodine(III) reagent **12** is reported to be a mild and effective reagent for the chlorination of nitrogen containing heterocycles which is easy to prepare and air- and moisture-stable. The scope of published substrates includes chlorination of 7*H*-pyrrolo[2,3-d]pyrimidines and we wished to see if we could extend the scope to include sulphur containing heterocycles such as thieno[3,2-d]pyrimidines (e.g. **6**). It was also important to explore if **12** would efficiently chlorinate **6** at the less activated C6 position in the presence of the C7 cyclopropyl group.



Scheme 2. Chlorination of **6** with *N*-chlorosuccinimide (NCS). Reagents and conditions: (a) NCS (1.2 equiv.), AcOH, 55 °C, 7 h, 15-32 %.

Treatment of **6** with **12** (1.5 equiv.) in DMF at 50 ^{o}C for 16-24 h gave the desired chloro product **7** in 77-94 % isolated yield. Analysis of the crude reaction mixtures showed only trace amounts of cyclopropyl ring opened products such as **14**/**15** as detectible by LCMS. Hence, **12** proved to be a far superior reagent, when compared to NCS, for the C6 chlorination of thieno[3,2-d]pyrimidine **6** (i.e. **6** → **7**).

Completion of our synthesis of **1** followed established procedures although it proved expedient to carry material through several of these later steps without the need for extensive purification beyond a simple work-up procedure (**7** → **8** → **9**). Activation of C4 was accomplished by a two-step procedure of acid hydrolysis of the C4-OMe of **7** to give thieno[3,2-*d*]pyrimidin-4(3*H*)-one **8**, followed by chlorination with $POCl_3$ to give **9**. Finally, nucleophilic displacement of the C4-Cl of **9** by methyl thioglycolate (**13**) gave ester **10** which was hydrolysed with NaOH to afford **1**. This route has been reliably performed on large scale to produce multigram quantities of **1** in good efficiency (total yield over 8-steps from **3**: 18-26 %) and high purity (> 99 %).



Scheme 3. Improved synthesis of **5**. Reagents and conditions: (a) NaOMe (5 equiv.), 1,4-dioxane, 0 °C then rt, 16 h, 84 %.

A shorter synthesis was then developed by accessing bromide **5** by an alternative route. The low-yielding C7 bromination of **4** with NBS to give **5** as described above (Scheme 2, step c) was avoided by starting with 7-bromo-4-chlorothieno[3,2-d]pyrimidine (**16**) which is readily available from commercial suppliers. Treatment of **16** with NaOMe displaced the C4-Cl to give **5** in good yield on 10 g scale (Scheme 3). Even though **16** is somewhat more expensive than **2** or **3** per unit cost (by ca. 5-fold), this updated route shortens the sequence to just 7 steps and improves the overall yield to 40-50 % from **16**.

Mouse pharmacokinetics for 1.

Assessment of **1** in mouse liver microsomes (MLM) showed excellent metabolic stability (Cl_i 1.0 μL/min/mg protein) which predicts for low clearance *in vivo*. Binding to mouse plasma proteins (mPPB) was very high with percent unbound drug (f_u) of just 0.1 %; this mPPB value can be used to calculate free drug concentrations from measured drug levels in plasma taken during *in vivo* experiments. The high mPPB is entirely consistent with the physicochemical properties of **1** as a lipophilic acid (m.w. 300; cLog P 3.1; cpK_a 3.1).

Pharmacokinetic (PK) data for **1** was generated *in vivo* in mouse to evaluate brain penetration (Table 1; Figure 1) (see Supporting Information Tables S1-S3 (File 1)). The route of administration and dose were selected to most closely match relevant published mouse disease model studies [5,7]. Following single oral dose (p.o.) of 10 mg/kg, plasma exposure was high and plasma clearance was low relative to liver blood flow resulting in a plasma elimination half-life of 8.8 hours. The plasma parameters from these mouse PK experiments (C_{max} and AUC) are consistent with published preclinical PK data [5].

Table 1. Mouse pharmacokinetic data for **1**; oral (p.o.) dose at 10 mg/kg.[a]		
PK Parameter	Plasma	Brain
$T_{1/2}$	8.8 h	7.1 h
T_{max}	2.0 h	2.0 h
C_{max}	35,400 ng/mL	500 ng/g
$AUC_{0\text{-}t}$	303,000 h.ng/mL	3,700 h.ng/g
$AUC_{0\text{-}\infty}$	354,000 h.ng/mL	4,080 h.ng/g

[a] Male fed CD1 mouse; suspension formulation in 0.1% Tween80 in water; n = 3 per time point; terminal blood and brain levels measured at seven time points: 0.17, 0.50, 1, 2, 5, 7.5 and 24 h.

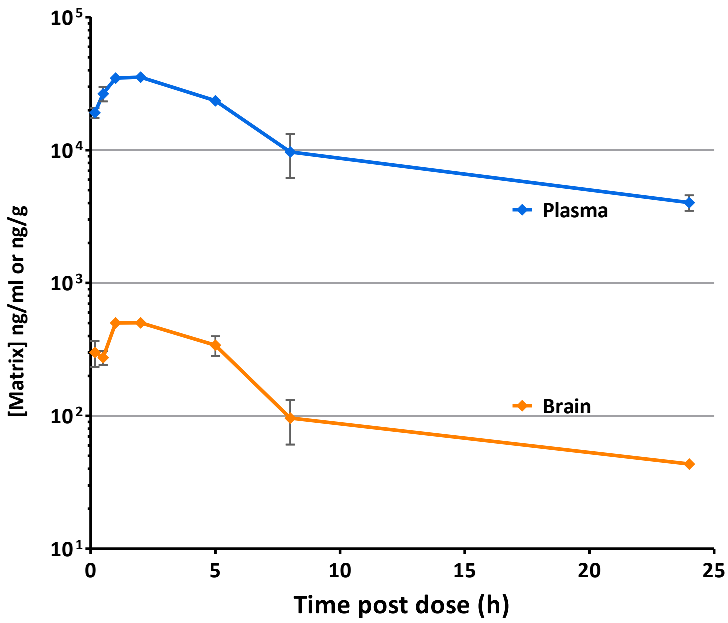
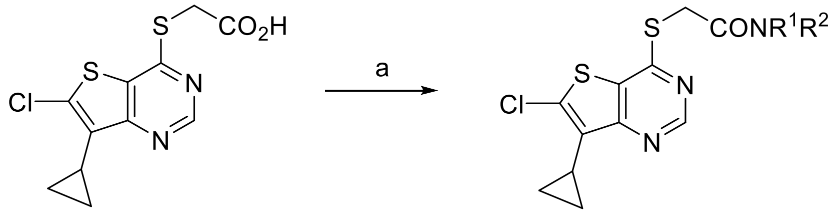


Figure 1. Concentrations of **1** in mouse following oral administration (p.o.) at 10 mg/kg.

CNS penetration of **1** is very low with brain:plasma concentration ratios ~0.01 at all time points measured and also 0.01 based on $AUC_{(0\rightarrow inf)}$. At this level of exposure, a significant proportion of the compound detected in brain samples is likely to have arisen from residual blood in the brain tissue.

Amide analogues of 1 to explore CNS penetration and future opportunities

With a peripherally restricted control in hand, we elected to explore if **1** could be modified to deliver a CNS penetrant tool by capping off the acid as an amide. A small library of amides **17** were prepared from acid **1** by activation with HBTU and then subsequent reaction with the amine **18** (Scheme 4). Although significant Notum inhibition activity could be achieved (IC_{50} <100 nM), none of these specific amides demonstrated the required combination of sufficient MLM stability along with cell permeability as measured by transit performance across a MDCK-MDR1 monolayer without evidence of P-gp mediated efflux.



1 **17a-r**: 18 examples

Scheme 4. Preparation of amides **17**. Representative reagents and conditions:[a] (a) HBTU (1.1 equiv.), iPr_2NEt (2.5 equiv.), DMF, rt, 15 min; then amine **18** (1.05 equiv.). [a] These reactions were performed once for each amide and have not been optimised. DMF, *N,N*-dimethylformamide; HBTU, *O*-(1*H*-Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate.

This collection of data for amides **17a-r** is shared as 'open data' to assist others in evaluating these results with the objective of solving this challenge (see Supporting Information Table S4 (Files 1 and 2)). Our own efforts took us to an alternative chemotype [20].

The use of selective small molecule inhibitors as chemical probes to investigate the relationship between the target and disease is significantly enhanced when two structurally orthogonal chemical probes are employed. Two different chemotypes which share the same primary pharmacology are likely to offer the advantage of a different secondary pharmacology fingerprint profile and so help identify any off-target effects in cellular assays. Hence, the identification of a suitable analogue of **1** (or **17**) which combines Notum inhibition with CNS penetration would be a valuable chemical probe for investigating the role of Notum in disease models.

Conclusion

An improved, scalable synthesis of Notum inhibitor **1** is reported. Key modifications include: (1) the introduction of the C7-cyclopropyl group was most effectively achieved with a Suzuki–Miyaura cross-coupling reaction with MIDA-boronate **11** (**5** → **6**); and (2) C6 chlorination was performed with 1–chloro-1,2-benziodoxol-3-one (**12**) (**6** → **7**) as a mild selective electrophilic chlorination agent. This 7-step route has been reliably performed on large scale to produce multigram quantities of **1** in good efficiency.

Pharmacokinetic studies in mouse showed CNS penetration of **1** is very low with brain:plasma concentration ratio of just 0.01 based on $AUC_{(0\rightarrow inf)}$. Hence, **1** is unsuitable for use in models of disease where brain penetration is an essential requirement of the compound but would be an ideal peripherally restricted control. These data will contribute to the understanding of drug levels of **1** to overlay with appropriate *in vivo* efficacy endpoints, i.e. the PK-PD relationship. The full PK data set is presented and shared as 'open data'. This complete data set (along with others) will also assist with the creation of improved predictive pharmacokinetic models.

A small library of amides **17** were prepared from acid **1** to explore if **1** could be modified to deliver a CNS penetrant tool by capping off the acid as an amide. Although significant Notum inhibition activity could be achieved, none of these amides demonstrated the required combination of metabolic stability along with cell permeability without evidence of P-gp mediated efflux. The identification of a suitable analogue of **1** which combines Notum inhibition with CNS penetration would be a valuable chemical probe for investigating the role of Notum in disease models. This collection of data for amides **17a-r** is shared as 'open data' to assist others in evaluating these results with the objective of solving this challenge.

Supporting Information

Supporting information: (1) experimental procedures and characterisation data for **3**-**10** and **1**; (2) mouse PK data which includes: study design summary; plasma concentrations; brain concentrations; (3) Notum IC_{50}s (nM), MLM Cl_i (μL/min/mg protein) and MDCK-MDR1 AB/BA P_{app} (x10^6 cm/s) for **17a-r**.

Supporting Information File 1:

File Name: SI File 1.pdf

File Format: PDF

Title: Experimental Section, Mouse Pharmacokinetics, Profiles of Amides

Supporting Information File 2:

File Name: SI File 2.csv

File Format: CSV

Title: Profiles of Amides

Acknowledgments

This work was supported by Alzheimer's Research UK (ARUK) and The Francis Crick Institute. The ARUK UCL Drug Discovery Institute is core funded by Alzheimer's Research UK (520909). The Francis Crick

Institute receives its core funding from Cancer Research UK (FC001002), the UK Medical Research Council (FC001002), and the Wellcome Trust (FC001002).

We thank our colleagues Sarah Frew, Amy Monaghan, Fiona Jeganathan and Magda Bictash of the ARUK UCL DDI Screening and Pharmacology team for Notum inhibition data. We thank Abil Aliev and Kersti Karu at the UCL Department of Chemistry for spectroscopic and analytical services. Mouse PK studies were performed by Pharmidex (London, UK) and ADME studies reported in this work were performed by GVK Biosciences (Hyderabad, India) and Cyprotex (Macclesfield, UK).

References

1. Komiya, Y.; Habas, R. *Organogenesis* **2008**, *4*, 68-75.
2. (a) Liu, C.-C.; Tsai, C.-W.; Deak, F.; Rogers, J.; Penuliar,M.; Sung, Y. M.; Maher, J. N.; Fu, Y.; Li, X.; Xu, H.; Estus, S.; Hoe, H.-S.; Fryer, J. D.; Kanekiyo, T.; Bu, G. *Neuron* **2014**, *84*, 63-77; (b) Palomer, E.; Buechler, J.; Salinas, P. C. *Front. Cell. Neurosci.* **2019**, *13*, 227.
3. Kakugawa, S.; Langton, P. F.; Zebisch, M.; Howell, S. A.; Chang, T.-H.; Liu, Y.; Feizi, T.;Bineva, G.; O'Reilly, N.; Snijders, A. P.; Jones, E. Y.; Vincent, J. P. *Nature* **2015**, *519*, 187-192.
4. Zhang, X.; Cheong, S.-M.; Amado, N. G.; Reis, A. H.; MacDonald, B. T.; Zebisch, M.; Jones, E. Y.; Abreu, J. G.; He, X. *Dev Cell*. **2015**, *32*, 719-730.
5. Tarver Jr., J. E.; Pabba, P. K.; Barbosa, J.; Han, Q.; Gardyan, M. W.; Brommage, R.; Thompson, A. Y.; Schmidt, J. E.; Wilson, A. G.; Hei, W.; Lombardo, V. K.; Carson, K. G. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1525-1528.
6. Barbosa, J.; Carson, K. G.; Gardyan, M. W.; He, W.; Lombardo, V.; Pabba, P.; Tarver Jr., J. Inhibitors of Notum pectinacylesterase and methods of their use. US Patent 0,065,200, March 15, 2012.
7. Brommage, R.; Liu, J.; Vogel, P.; Mseeh, F.; Thompson, A. Y.; Potter, D. G.; Shadoan, M. K.; Hansen, G. M.; Jeter-Jones, S.; Cui, J.; Bright, D.; Bardenhagen, J. P.; Doree, D. D.; Movérare-Skrtic, S.; Nilsson, K. H.; Henning, P.; Lerner, U. H.; Ohlsson, C.; Sands, A. T.; Tarver, J. E.; Powell, D. R.; Zambrowicz, B.; Liu, Q. *Bone Research* **2019**, *7*, 2.
8. Manallack, D. T. *Perspect. Medicin. Chem.* **2007**, *1*, 25-38.
9. Wager, T. T.; Chandrasekaran, R. Y.; Hou, X.; Troutman, M. D.; Verhoest, P. R.; Villalobos, A.; Will, Y. *ACS Chem Neurosci.* **2010**, *1*, 420-34.
10. Manallack , D. T.; Prankerd, R. J.; Oprea, E.; Chambers, D. K. *Chem. Soc. Rev.* **2013**, *42*, 485-496.
11. Charifson, P. S.; Walters, W. P. *J. Med. Chem.* **2014**, *57*, 9701-9717.
12. Di, L.; Rong, H.; Feng, B. *J. Med. Chem.* **2013**, *56*, 2-12.

13. Atkinson, B. N.; Steadman, D.; Zhao, Y.; Sipthorp, J.; Vecchia, L.; Ruza, R. R.; Jeganathan, F.; Lines, G.; Frew, S.; Monaghan, A.; Kjaer, S.; Bictash, M.; Jones, E. Y.; Fish, P. V. *Med. Chem. Comm.* In press, DOI: 10.1039/C9MD00096H.
14. Mitchell, I. S.; Spencer, K. L.; Stengel, P.; Han, Y.; Kallan, N. C.; Munson, M.; Vigers, G. P. A.; Blake, J.; Piscopio, A.; Josey, J.; Miller, S.; Xiao, D.; International Patent 2005/051304, June 9, 2005.
15. Atheral, J. F.; Hough, T. L.; Lindell, S. D.; O'Mahony, M. J.; Parsons, J. H.; Saville-Stones, E. A. Fungicides. US Patent 6,432,964, August 13, 2002.
16. Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.
17. For a recent summary of electrophilic chlorination approaches, see: Rogers, D. A; Bensalah, A. T; Alvaro Tomas Espinosa, A. T.; Hoerr, J. L.; Refai, F. H.; Pitzel, A. K.; Alvarado, J. J.; Lamar, A. L.; *Org. Lett*., **2019**, *21*, 4229-4233.
18. Wang, M.; Zhang, Y.; Wang, T.; Wang, C.; Xue, D.; Xiao, J. *Org. Lett.* **2016**, *18*, 1976-1979.
19. Matousek, V.; Pietrasiak, E.; Schwenk, R.; Togni, A. *J. Org. Chem.* **2013**, *78*, 6763-6768.
20. Fish, P. V. Development of Potent, Selective, CNS Penetrant Small Molecule Inhibitors of Notum to Potentiate Wnt Signalling. Presented at EFMC: XXVth International Symposium on Medicinal Chemistry; 2-6th September 2018; Ljubljana, Slovenia.