Bioorganic & Medicinal Chemistry Letters 21 (2011) 1588–1592

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The discovery of potent and long-acting oral factor Xa inhibitors with tetrahydroisoquinoline and benzazepine P4 motifs

Nigel S. Watson [a], Carl Adams [a], David Belton [a], David Brown [a], Cynthia L. Burns-Kurtis [b], Laiq Chaudry [a], Chuen Chan [a], Máire A. Convery [a], David E. Davies [a], Anne M. Exall [a], John D. Harling [a], Stephanie Irvine [a], Wendy R. Irving [a], Savvas Kleanthous [a], Iain M. McLay [a], Anthony J. Pateman [a], Angela N. Patikis [a], Theresa J. Roethke [b], Stefan Senger [a], Gary J. Stelman [b], John R. Toomey [b], Robert I. West [a], Caroline Whittaker [a], Ping Zhou [a], Robert J. Young [a,*]

[a] GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom
[b] GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, United States

ARTICLE INFO

Article history:
Received 17 December 2010
Revised 26 January 2011
Accepted 27 January 2011
Available online 2 February 2011

Keywords:
Factor Xa
Oral inhibitors
Property based design
Structure based design
P450 inhibition

ABSTRACT

The discovery and evaluation of potent and long-acting oral sulfonamidopyrrolidin-2-one factor Xa inhibitors with tetrahydroisoquinoline and benzazepine P4 motifs are described. Unexpected selectivity issues versus tissue plasminogen activator in the former series were addressed in the later, delivering a robust candidate for progression towards clinical studies.

The licensing of the first anticoagulants targeting selective inhibitors of specific enzymes, such as factor Xa (fXa), in the blood coagulation cascade has been achieved in a highly competitive and challenging environment, which has exacting requirements to achieve potency, selectivity, safety and oral efficacy.[1] In the accompanying paper,[2] the synthesis and evaluation of fXa inhibitors with the sulfonamidopyrrolidin-2-one template containing the constrained indane and phenyl pyrrolidine motifs (Fig. 1; **2**A and **2**B) are described, the latter of which delivered a series of candidate quality molecules that addressed the time-dependant inhibition (TDI) of Cyp3A4 seen in our previously reported α-methyl benzylamine (αMBA) series,[3] exemplified by **1**. This approach to address TDI is developed further in this communication through the rational design, synthesis and evaluation of molecules constrained by fusion of the benzylic motif into a tetrahydroisoquinoline (THIQ) ring (**2**C or **3** $m = n = 1$). This strategy was extended into the isomeric 7-THIQ structure (**3** $m = 2$, $n = 0$) and into the homologous tetrahydro-2-benzazepine (BAZ) ring system (**3** $m = 1$, $n = 2$). Consolidated learnings within the programme gave high confidence that these molecules would display excellent physical characteristics, which were predicted to result in compounds suitable for progression as long acting oral anticoagulants.

The requisite 6- and 7-amino 2-*N*-Boc-THIQ building blocks were commercially available. 6-amino-5-fluoro-2-*N*-Boc-THIQ **4** was accessed via 6-amino-5-fluoro isoquinolinone **5**, itself constructed using a modified Bischler–Napieralski procedure from 2-(3,4-difluorophenyl)ethyl amine **6** (Scheme 1). Similarly 2-(4-fluorophenyl)ethyl amine **7** was converted via 6-nitro-7-fluoro-2-*N*- trifluoracetyl-THIQ **8** into the isomeric 7-fluoro intermediate **9**. 7-Amino-2-*N*-Boc-BAZ (**10**, X = H) was accessed via a literature route[4] from 6-amino tetralone (**11**, X = H), with modified protecting groups. The same chemistry on 6-amino-5-fluoro-tetralone (**11**, X = F), itself constructed from 1-bromo-2,3-difluorobenzene (**12**) via Sonogashira coupling, hydrogenation, oxidation and cyclisation, furnished 2-*N*-Boc-7-amino-6-fluoro-2-benzazepine (**10**, X = F).

These building blocks were converted into the target compounds, in homochiral form,[5] via the established generic route outlined in Scheme 2.[6] Accordingly, key orthogonally protected intermediates **13** were prepared by construction of the pyrrolidin-2-one from Cbz-methionine; ensuing hydrogenolysis followed by sulfonylation and deprotection furnished the desired test compounds **14**.

* Corresponding author. Tel.: +44 1438 768372.
E-mail address: Rob.J.Young@gsk.com (R.J. Young).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.01.129

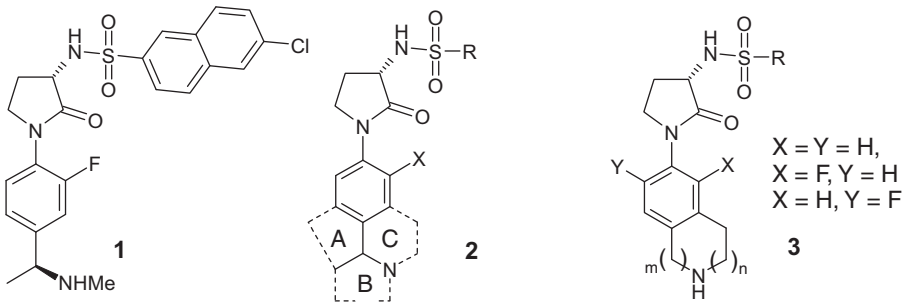
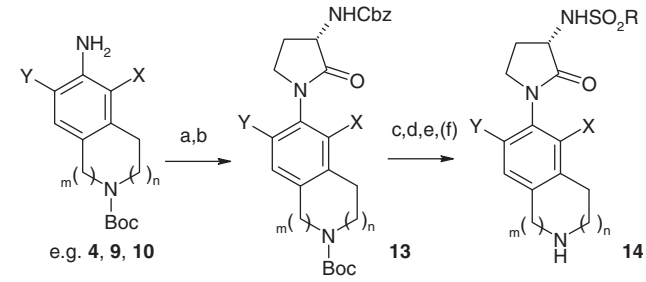


Figure 1. αMBA **1**, constraining strategies **2** and generic 6-THIQ ($m = 1$, $n = 1$), 7-THIQ ($m = 2$, $n = 0$) and BAZ ($m = 1$, $n = 2$) **3** structures described.

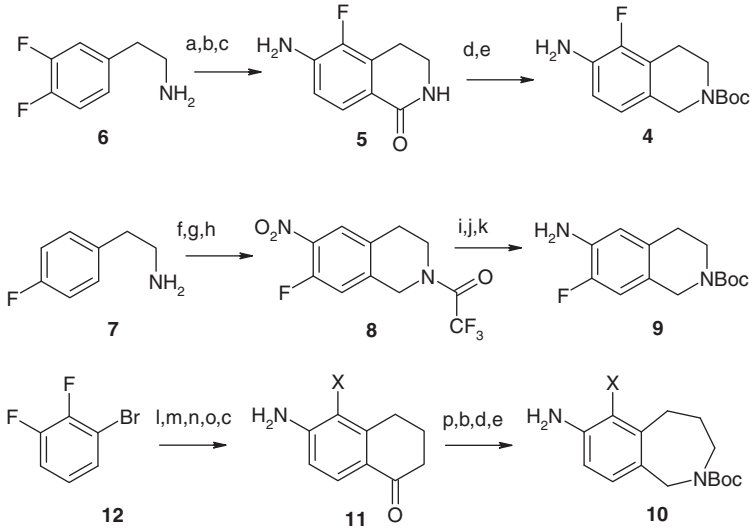
The evaluation of the 6-THIQ series (**15**–**19**) gave very gratifying results, providing compounds with low nM fXa potency,[7] which translated, as expected, into good levels of anticoagulant activity (Prothrombin Time, PT assay),[8] even with relatively more lipophilic P1 motifs (Table 1).[9] The isomeric 7-substituted series (**20**–**22**) showed generally more modest intrinsic and plasma-based activities. The potency of the 6-substituted series was rationalised by an interaction of the protonated distal nitrogen with the backbone carbonyl of Glu97 (akin to that seen in the αMBA series) and X-ray structural analysis of **17** bound into fXa supported this rationale (vide infra); this interaction appeared not to be feasible in the 7-substitued analogues in modelling studies.[10]

The rat pharmacokinetic profiles[11] for members of the 6-THIQ series were also very encouraging, showing long half lives but variable oral bioavailability (Table 2); most notably the more lipophilic 6-chloronaphthyl (6ClNap) analogue **17**, possessed a volume driven extended half-life and acceptable bioavailability. *N*-Methyl analogue **15** possessed a much shorter half-life, which is consistent with findings in related in-house series[2,3] for tertiary versus secondary amino compounds. Disappointingly, poor oral exposure was achieved with the potent 6-indolyl analogues **18** and **19**.

Addition of a 5- or 7-fluoro THIQ substituent was designed to reduce the basicity of the THIQ nitrogen (calculations suggested that 5-F or 7-F would reduce the pKa by about a log unit, from the measured value of 9.3 for **16**–**19**), and thus modulate physical properties, with potential impact on derived PK parameters. These compounds (Table 3) were found to be essentially equipotent to the des-fluoro analogues in both activity assays; the PK profiles were also broadly similar (Table 2), though a trend to lower volumes and lower clearance was apparent. These data also reinforced observations in the accompanying paper that the 6-indolyl P1 motifs gave attractive intravenous PK profiles, but very poor oral bioavailability, even if it was at least quantifiable for the fluorinated analogues **25** and **28**.

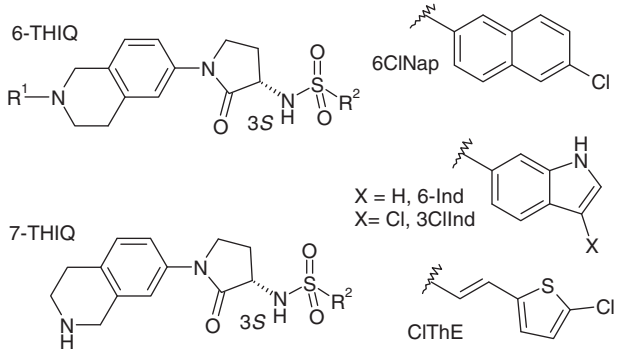


Scheme 2. Reagents and conditions with representative yields: (a) Cbz-Met-OH, HATU, DIPEA, DCM, rt, 65–95%; (b) MeI, MeCN, rt, then Cs_2CO_3, MeCN, 60 °C, 70%; (c) H_2, $Pd(OH)_2$–C, EtOH, rt, quant.; (d) RSO_2Cl, pyridine, MeCN, rt, 80–95%; (e) HCl, MeOH, rt, 95%; (f) for *N*-TIPS-protected indole-P1; Et_4NF, THF, rt 90%.



Scheme 1. Reagents and conditions with representative yields: (a) MeOC(=O)Cl, pyridine, DCM, 0 °C, 85%; (b) PPA, P_2O_5, 120 °C, 20%; (c) NH_3, MeOH, 160 °C autoclave, 80%; (d) BH_3, THF, Δ, 90%; (e) Boc_2O, DCM or dioxane, rt, 80%; (f) TFAA, DCM, Et_3N, −5 to 0 °C, 96%; (g) $(H_2CO)_n$, concd H_2SO_4, AcOH, rt, 77%; (h) $NaNO_3$; concd H_2SO_4, 0 to 5 °C, 45%; (i) aq HCl, MeOH, Δ, 95; (j) Boc_2O, Et_3N, dioxane, rt, 76%; (k) H_2, Pd–C, EtOH, rt, quant. (l) $(Ph_3P)_2PdCl_2$, CuI, 3 butyn-1-ol, Me_2NH, 65 °C, quant.; (m) H_2, 50 psi, $Pd(OH)_2$-C, EtOH, rt, quant.; (n) pyridinium dichromate, DMF, rt, 65%; (o) $MeSO_3H$, P_2O_5, rt, 65%; (p) $H_2NOH{\cdot}HCl$, NH_4OAc, aq EtOH, 95%.

Table 1
fXa inhibitory activities,[7] anticoagulant potency[8] and physical descriptors[9] for compounds **1** and **15–22**, with P1 structures and abbreviations



Entry	R^2	R^1	THIQ	fXa (K_i, nM)	1.5 × PT (μM)	*c* log $D_{7.4}$	MW	cmr
1	6ClNap	—	—	2	7.0	1.6	476	12.5
15	ClThE	Me	6–	1	3.2	1	452	11.8
16	ClThE	H	6–	0.6	0.9	0.4	438	11.4
17	6ClNap	H	6–	1	4.2	0.6	456	12.3
18	3ClInd	H	6–	1	1.1	0.4	445	11.7
19	6-Ind	H	6–	nd	1.3	−0.5	411	11.2
20	ClThE	H	7–	8	8.8	1.1	438	11.4
21	6ClNap	H	7–	10	12.5	1.3	456	12.3
22	3ClInd	H	7–	15	8.4	1	445	11.7

Table 2
Rat DMPK parameters[11] for THIQs in Tables 1 and 3

Entry	R^2	THIQ sub	Cl_p[a] (mL/min/kg)	$T_{1/2}$[b] (h)	V_{ss}[c] (L/kg)	F[d] (%)
1	6ClNap	—	1.6	18	2.4	>10
15	ClThE	H(Me)	26	0.4	0.7	33
17	6ClNap	H	4.0	11	3.6	24
24		5F	2.1	6.7	2.4	nd
27		7F	1.7	7.5	1.0	28
16	ClThE	H	3.0	3.5	0.9	nd
23		5F	3.0	3.3	0.9	68
26		7F	1.4	4.9	0.5	43
18	3ClInd	H	7.7	6.3	2.9	<1
25		5F	2.7	7.8	1.5	7
28		7F	1.3	6.2	0.5	6
19	6-Ind	H	12.0	6.1	4.1	<1

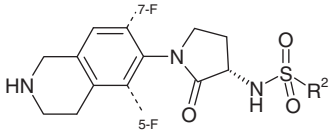
[a] Cl_p, plasma clearance expressed as mL/min/kg.
[b] $T_{1/2}$, half-life of the test compound expressed in hours.
[c] V_{ss}, steady state volume of distribution expressed as L/kg.
[d] *F*, oral bioavailability expressed as percentage.

A crystal structure of **24** soaked into fXa (Fig. 2)[12] showed the predicted binding mode and was almost identical to that established for the des-fluoro analogue **17**. The THIQ nitrogen atom is located 3.0 Å from the backbone carbonyl of Glu97, with two water molecules mediating hydrogen bonds to the likely protonated form, with a further relay to Lys96. The distance from the 5-fluorine to the pyrrolidin-2-one carbonyl carbon was 2.65 Å, consistent with a probable F···C=O interaction,[13] even if it apparently made no significant contribution towards increasing potency.

Most importantly for this series, no significant TDI of Cyp450 isoforms was observed with **15**, **17**, **21** and **24**;[14] thus lending support to the hypothesis that a putative dihydroisoquinoline metabolite might act as a metabolic sink.[15] However, in spite of their highly encouraging profiles the series was discontinued due to relatively potent inhibition of tissue plasminogen activator (tPA), one of the critical screens in our selectivity panel of trypsin-like serine proteases (Table 4). It was noted that the *N*-methyl compound **15** did show much weaker activity against tPA, suggesting that modest changes to the P4 motif could enhance selectivity. A gridding and partitioning (GAP) analysis of all available tPA data on compounds incorporating P4 variations within the sulfonamidopyrrolidin-2-one series predicted that the ring expansion from THIQ to BAZ might reduce tPA activity.

In the BAZ series, excellent levels of potency and anticoagulant activity were retained, with 6-fluorinated analogues showing a similar activity profile (Table 5). However, our property based

Table 3
fXa inhibitory activities,[7] anticoagulant potency[8] and physical descriptors[9] for THIQ compounds **16–18** and their fluorinated analogues **23–28**



R^2	5-H, 7-H				5-F, 7-H				5-H, 7-F			
	#	fXa (K_i, nM)	1.5 × PT (μM)	*c* log $D_{7.4}$	#	fXa (Ki, nM)	1.5 × PT (μM)	*c* log $D_{7.4}$	#	fXa (K_i, nM)	1.5 × PT (μM)	*c* log $D_{7.4}$
ClThE	**16**	0.6	0.9	0.4	**23**	0.6	0.8	1.6	**26**	2	1.2	1.4
6ClNap	**17**	1	4.2	0.6	**24**	1.3	4.2	1.8	**27**	3	7.4	1.7
3ClInd	**18**	1	1.1	0.4	**25**	2	1.7	1.5	**28**	1	1.3	1.4

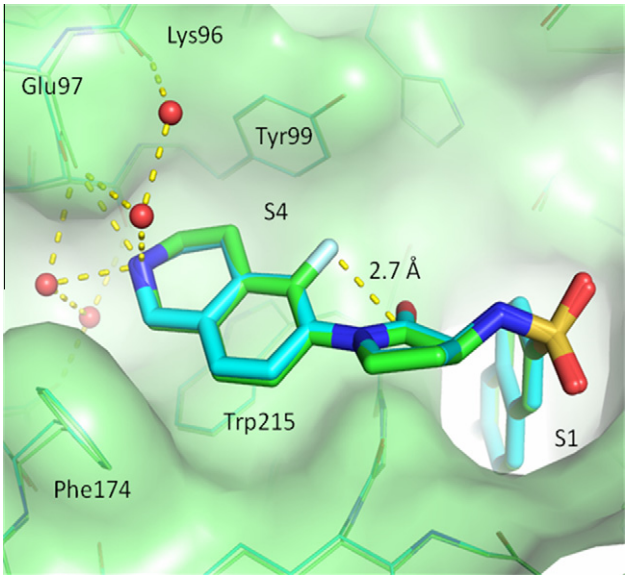


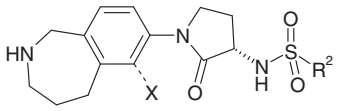
Figure 2. Overlay of the X-ray crystal structures of **17** and **24** bound into fXa, showing contacts and water mediated hydrogen bondsin the S4 pocket and the proximity of the 5-F···C=O interaction.

Table 4
Selectivity data versus a panel of trypsin-like serine proteases, expressed as fold selectivity by ratio of K_i values

Entry	Thrombin	tPA	Kallikrein	APC	Plasmin	Trypsin
15	4000	800	40	>25,000	10,000	>10,000
16	3200	25	160	>25,000	5000	>25,000
23	1300	8	20	>8000	800	>10,000
26	2500	130	320	>25,000	800	>25,000
29	1000	1000	100	>25,000	20,000	>25,000

tPA = tissue plasminogen activator.
APC = activated protein C.

Table 5
fXa inhibitory activities,[7] anticoagulant potency[8] and physical descriptors[9] for BAZ compounds **29**–**33**



Entry	R^2	X	fXa (K_i nM)	1.5 × PT (μM)	*c* log $D_{7.4}$	MW	cmr
29	ClThE	H	1	0.9	1.2	452	11.8
30	6ClNap	H	0.8	3.0	1.4	470	12.7
31	3ClInd	H	0.8	1.2	1	459	12.2
32	ClThE	F	1.3	1.1	1.9	470	11.9
33	6ClNap	F	0.8	4.3	2.1	488	12.8

design models had suggested that the increased hydrophobicity and aromatic ring count[16] would limit oral bioavailability in combination with the lipophilic 6ClNap P1 motif, which was indeed observed (Table 6). However, the overall potency and DMPK profiles of (*E*)-2-(5-chloro-2-thienyl)ethenesulfonamide **29** were strongly supportive of further progression; allometric scaling was indicative of once daily dosing in humans,[17] whilst appreciable selectivity was achieved (Table 4) and the risk of Cyp3A4 TDI was effectively discharged.[18] No significant risks with this P1 motif have been indicated during the continued progression of our first clinical candidate GW813893.[19]

Table 6
Rat DMPK parameters[11] for BAZs **29** and **30**

Entry	P1	Cl_p[a] (mL/min/kg)	$T_{1/2}$[b] (h)	V_{ss}[c] (L/kg)	F[d] (%)
29	ClThE	7.8	4.4	2.6	45
30	6ClNap	6.8	9.7	5.5	10

a, b, c, d as Table 2.

In conclusion, the discovery of potent, orally bioavailable, inhibitors of blood coagulation factor Xa with long half lives has been described, rationally addressing Cyp3A4 TDI and unexpected serine protease selectivity issues. These BAZ inhibitors and the phenylpyrrolidine series described in the accompanying paper[2] were the culmination of an extensive programme driven by structure and property based design, in which key interactions were exploited, molecular size/hydrophobicity minimised and aromaticity reduced. The chemical space occupied by the majority of marketed oral drugs can be represented by the median values[20] *c* log *P* 3.2, *c* log $D_{7.4}$ 0.8 and MW 420; corresponding values for **29** are *c* log *P* 3.2, *c* log $D_{7.4}$ 1.2, MW 452 and for the equivalent phenylpyrrolidine[2] 3.4, 1.1, 470 (respectively). Further data on the progression of these molecules will be reported in due course.

Acknowledgements

We gratefully acknowledge the numerous individuals, across many disciplines, who contributed to the successful discovery phase of the fXa programme.

References and notes

1. (a) Sobieraj-Teague, M.; O'Donnell, M.; Eikelboom, J. *Semin. Thromb. Hemost.* **2009**, *35*, 515; (b) Pinto, D. J. P.; Smallheer, J. M.; Cheney, D. L.; Knabb, R. M.; Wexler, R. R. *J. Med. Chem.* **2010**, *53*, 6243.
2. Young, R. J.; Adams, C.; Blows, M.; Brown, D.; Burns-Kurtis, C. L.; Chan, C.; Chaudry, L.; Convery, M. A.; Davies, D. E.; Exall, A. M.; Foster, G.; Harling, J. D.; Hortense, E.; Irvine, S.; Irving, W. R.; Jackson, S.; Kleanthous, S.; Pateman, A. J.; Patikis, A. N.; Roethka, T. J.; Senger, S.; Stelman, G. J.; Toomey, J. R.; West, R. I.; Whittaker, C.; Zhou, P.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, preceding paper.
3. Kleanthous, S.; Borthwick, A. D.; Brown, D.; Burns-Kurtis, C. L.; Campbell, M.; Chan, C.; Chaudry, L.; Clarte, M. O.; Convery, M. A.; Harling, J. D.; Hortense, E.; Irving, W. R.; Irvine, S.; Pateman, A. J.; Patikis, A. N.; Pinto, I. L.; Pollard, D. R.; Roethka, T. J.; Senger, S.; Shah, G. P.; Stelman, G. J.; Toomey, J. R.; Watson, N. S.; West, R. I.; Whittaker, C.; Zhou, P.; Young, R. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 618.
4. Johnson, P. D.; Aristoff, P. A.; Zurenko, G. E.; Schaadt, R. D.; Yagi, B. H.; Ford, C. W.; Hamel, J. C.; Stapert, D.; Moerman, J. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4197.
5. Compound **15** was produced using the trimethylaluminium methodology described in Ref. 3, with, by analogy, likely >80% ee. ^{19}F NMR of Mosher amides of intermediate amines formed by hydrogenolysis of the variations on generic structure **13** produced using the Methioine route indicated that these transformations generated homochiral compounds.
6. (a) Harling, J. D.; Watson, N. S.; Young, R. J. WO108709 A1 **2006**; (b) Camus, L.; Chudasama, R.; Day, C. J.; Deshmukh, D.; Gleason, J. G.; Harling, J. D.; Lee, C. -P.; Saklatvala, P.; Senger, S.; Vallance, S.; Watson, J.; Watson, N. S.; Young, R. J.; Yuan, B. WO 059952 A2 **2007**.
7. Factor Xa inhibitory activities were determined using Rhodamine 110, bis-(CBZ-glycylglycyl)-L-arginine amide as the fluorogenic substrate; details are described in Ref. 19a.
8. Anticoagulant activities were determined in the prothrombin time (PT) assay; see Ref. 19a, expressed as the concentration required to extend the control coagulation time by 50% (1.5 × PT).
9. Hydrophobicity predictions, expressed as *c* log $D_{7.4}$, were all re-calculated using Advanced Chemistry Development software v11.0 to ensure consistency in this paper; calculated molecular refractivity (cmr) values were derived from Daylight software v4.9.
10. Docking studies were undertaken using QXP/FLO, ThistleSoft Inc.: Colebrook, C. T.; McMartin, C.; Bohacek, R. S. *J. Comput. Aided Mol. Des.* **1997**, *11*, 333.
11. Pharmacokinetics measured in male Sprague–Dawley rats following intravenous and oral administration. The formulation used for both iv and po dosing was a 5:95% (v/v) mixture of DMSO and 50:50 PEG-200/sterile water. Serial blood samples were collected into heparinised containers at various time-points and blood centrifuged to yield plasma. These studies used at least three animals for each (iv/po) leg.

12. The structure for **24** was refined at 1.9 Å (overall R_{merge} is 0.049) in Refmac5 to a final R factor of 0.186 and R_{free} of 0.229 using procedures described in Ref. 19a. Co-ordinates are deposited in the protein data bank with code 2y7x.
13. This is consistent with the observation we have previously noted, Young, R. J.; Borthwick, A. D.; Brown, D.; Burns-Kurtis, C. L.; Campbell, M.; Chan, C.; Charbaut, M.; Chung, C.-w.; Convery, M. A.; Kelly, H. A.; King, N. P.; Kleanthous, S.; Mason, A. M.; Pateman, A. J.; Patikis, A. N.; Pinto, I. L.; Pollard, D. R.; Senger, S.; Shah, G. P.; Toomey, J. R.; Watson, N. S.; Weston, H. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 23; An intermolecular C–F···C═O interaction has been suggested when fluorine atoms are located within the range of 3–4 Å Olsen, J. A.; Banner, D. W.; Seiler, P.; Obst Sander, U.; D'Arcy, A.; Stihle, M.; Müller, K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2507.
14. Time dependant inhibition of Cyp3A4 was not observed for compounds **15**, **17**, **21** and **24** in the Biodynamics (www.biodynamics.co.uk) assays described in the accompanying paper.[2]
15. (a) Kalgutkar, A. S.; Gardner, I.; Obach, R. S.; Shaffer, C. L.; Callegari, E.; Henne, K. R.; Mutlib, A. E.; Dalvie, D. K.; Lee, J. S.; Nakai, Y.; O'Donnell, J. P.; Boer, J.; Harriman, S. P. *Curr. Drug Metab.* **2005**, *6*, 161; (b) Kalgutkar, A. S.; Obach, R. S.; Maurer, T. S. *Curr. Drug Metab.* **2007**, *8*, 407.
16. The recognition of an additive contribution of hydrophobicity plus number of aromatic rings in impacting solubility was noted in Hill, A. P.; Young, R. J. *Drug Discovery Today*, **2010**, *15*, 648; this observation also holds for, inter alia, %HSA binding, permeation and intrinsic clearance, to be published shortly in Young, R. J.; Green, D. V. S.; Luscombe, C. N.; Hill, A. P. *Drug Discovery Today*, **2011** invited submission, manuscript under review.
17. In vitro hepatocyte metabolism data suggested that rat was the best predictor of likely human disposition; based on the rat PK data reported herein and other species (to be reported in due course), allometric scaling supported likely once daily human dosing.
18. Time dependent inhibition (TDI) of **29** versus CYP isoforms was investigated using the two assays described in the accompanying paper.[2] In house, **29** did not demonstrate TDI of CYP3A4 in the 7BQ assay, over a concentration range of 0.33–100 μM. However apparent concentration-dependent TDI of CYP3A4 activity was observed in the CYP3A4 DEF assay with approximately twofold shift at 50 μM (2.5 times the IC_{50}). In the Biodynamics assay TDI against 3A4 (DEF and BFC) was not observed. No TDI was observed with the other CYP isoforms.
19. (a) Chan, C.; Borthwick, A. D.; Brown, D.; Burns-Kurtis, C. L.; Campbell, M.; Chaudry, L.; Chung, C.-W.; Convery, M. A.; Hamblin, J. N.; Johnstone, L.; Kelly, H. A.; Kleanthous, S.; Patikis, A.; Patel, C.; Pateman, A. J.; Senger, S.; Shah, G. P.; Toomey, J. R.; Watson, N. S.; Weston, H. E.; Whitworth, C.; Young, R. J.; Zhou, P. *J. Med. Chem.* **2007**, *50*, 1546–1557; (b) Abboud, M. A.; Needle, S. J.; Burns-Kurtis, C. L.; Valocik, R. E.; Koster, P. F.; Amour, A. J.; Chan, C.; Brown, D.; Chaudry, L.; Zhou, P.; Patikis, A.; Patel, C.; Pateman, A. J.; Young, R. J.; Watson, N. S.; Toomey, J. R. *J. Cardiovasc. Pharmacol.* **2008**, *52*, 66.
20. (a) Gleeson, M. P. *J. Med. Chem.* **2008**, *51*, 817; (b) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discov.* **2007**, *6*, 881.