Bioorganic & Medicinal Chemistry Letters 19 (2009) 5209–5213

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Optimization of the aminopyridopyrazinones class of PDE5 inhibitors: Discovery of 3-[(*trans*-4-hydroxycyclohexyl)amino]-7-(6-methoxypyridin-3-yl)-1-(2-propoxyethyl)pyrido[3,4-*b*]pyrazin-2(1*H*)-one

Robert O. Hughes [a,*], John K. Walker [a], D. Joseph Rogier [a], Steve E. Heasley [a], Rhadika M. Blevis-Bal [a], Alan G. Benson [a], E. Jon Jacobsen [a], Jerry W. Cubbage [a], Yvette M. Fobian [a], Dafydd R. Owen [b], John N. Freskos [a], John M. Molyneaux [a], David L. Brown [a], Brad A. Acker [a], Todd M. Maddux [a], Mike B. Tollefson [a], Joseph B. Moon [a], Brent V. Mischke [a], Jeanne M. Rumsey [a], Yi Zheng [a], Alan MacInnes [a], Brian R. Bond [a], Ying Yu [a]

[a] *Pfizer Global Research and Development, Chesterfield Parkway West, St. Louis, MO 63017, USA*
[b] *Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK*

ARTICLE INFO

Article history:
Received 22 June 2009
Accepted 6 July 2009
Available online 10 July 2009

Keywords:
PDE5
Aminopyrazinone
Pharmacokinetics

ABSTRACT

We describe efforts to improve the pharmacokinetic profile of the aminopyridopyrazinone class of PDE5 inhibitors. These efforts led to the discovery of 3-[(*trans*-4-hydroxycyclohexyl)amino]-7-(6-methoxypyridin-3-yl)-1-(2-propoxyethyl)pyrido[3,4-*b*]pyrazin-2(1*H*)-one, a potent and selective inhibitor of PDE5 with an excellent PK profile.

Phosphodiesterase type 5 (PDE5), which specifically hydrolyzes cGMP to the inactive metabolite 5′-GMP, is expressed in vascular smooth muscle cells. Evidence gained with known specific inhibitors of PDE5 has demonstrated that inhibition of this enzyme increased cGMP levels, leading to vascular relaxation and reduction of systemic blood pressure.[1]

As part of our program directed toward the synthesis of long acting PDE5 inhibitors, we explored the potential of the aminopyridopyrazinone class. Our laboratories have previously reported on the elaboration of a lead identified during a screen of the Pfizer compound collection[2] and the systematic modification of the core ring structure to improve potency and physical chemical properties.[3] This work led to the discovery of compounds such as aminopyrazinones **1** and **2** (Fig. 1) which possessed excellent potency against PDE5 and good selectively over closely related PDE isoforms, in particular PDE6. These compounds, however, suffered from an undesired pharmacokinetic (PK) profile which precluded further development. Specifically, in the rat, southern pyridine **1** had a clearance which exceeded liver blood flow and an effective half-life ($T_{1/2}$) of 1.8 h, while southeastern pyridine **2** had a clearance of 33 mL/min/kg and a short $T_{1/2}$ of 0.8 h. As we sought compounds suitable for once-a-day dosing in human,[4] we focused our efforts on improving the PK profile of this series of compounds without sacrificing the excellent potency and selectivity. Described herein, these efforts, culminated in the discovery of 3-[(*trans*-4-hydroxycyclohexyl)amino]-7-(6-methoxypyridin-3-yl)-1-(2-propoxyethyl)pyrido[3,4-*b*]pyrazin-2(1*H*)-one, a potent and selective inhibitor of PDE5 with an excellent preclinical PK profile that should translate into an attractive human PK profile.

As summarized in Figure 1, our early efforts to define the structure–activity (SAR) and structure–property relationships (SPR) of the aminopyridopyrazinones had identified several important features: (1) the combination of methoxypyridyl and *n*-propyloxy groups generally offered the optimal balance between PDE5 potency, selectivity over PDE6, solubility and metabolic stability;[2] (2) the southern and southeastern pyridine isomers were preferred in terms of PDE5 potency with the southern pyridyl isomer often displayed improved solubility relative to the other core ring systems;[3] and (3) the southwestern substituent pointed toward solvent and was capable of accommodating a broad range of polar functionality. For these reasons, we decided to focus our efforts to improve the PK profile of this series on further optimization of the southwest (SW) substituent. At the outset, we anticipated that compounds with reduced lipophilicity would also possess increased metabolic stability and reduced clearance in vivo.[5]

* Corresponding author. Tel.: +1 636 247 9303.
E-mail address: robert.o.hughes@pfizer.com (R.O. Hughes).

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doi:10.1016/j.bmcl.2009.07.019

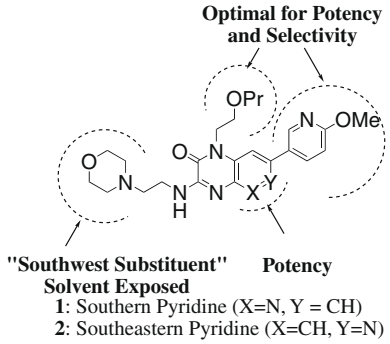
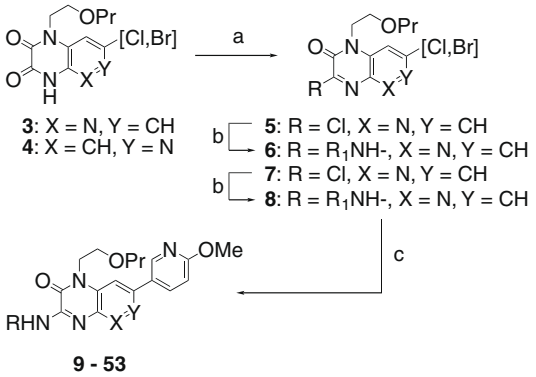


Figure 1. Structures of **1** and **2** and an overview of some of the key features of the SAR and SPR.

In addition to uncovering several key trends in the SAR/SPR of the aminopyridopyrazinones, previous work to understand the PK/PD relationship for this series of compounds had demonstrated that steady-state concentrations of approximately 10 × PDE5 IC_{50} were required for maximum efficacy in in vivo models of blood pressuring lowering. This put selectivity over other PDE isoforms at a premium and we required at least 100-fold selectivity. In the case of the aminopyridopyrazinones, we focused on maintaining selectivity over PDE6 as this was the most challenging to achieve.[6]

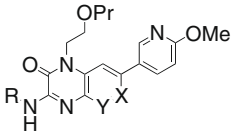
The synthesis of compounds **1, 2,** and **9–53** is illustrated in Scheme 1. The construction of elaborated aminopyridopyrazinones commenced with the previously described[2,3] diones **3** and **4**. Treatment of these diones with oxalyl chloride in the presence of a catalytic amount of DMF afforded the activated chloroimidates **5** and **7**, which were typically reacted directly with the required amines to give the desired aminopyrazinones (**6** and **8**) in good yield. Amines that were not readily commercially available were synthesized using standard methods. Finally, a Suzuki reaction between the chloro or bromo aminopyrazinones (**6** and **8**) and 6-methoxypyridin-3-ylboronic acid gave the final analogs **1**,**2** and **9–53** in good overall yield.

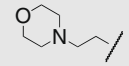
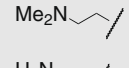
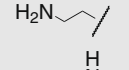
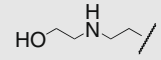
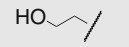
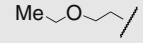
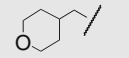
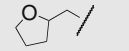
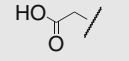
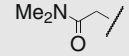
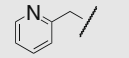
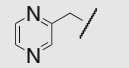
As our goal was to define which portion of chemical space offered the most attractive starting point based on potency and selectivity data in addition to having the potential for improved PK (e.g., reduced polarity and/or metabolic soft spots), we examined a wide variety of groups such as amines, alcohols, ethers, acids, amides and heteroaromatics to determine which were tolerated. Gratifyingly, all of the newly synthesized compounds (Table 1) demonstrated excellent potency against PDE5. Although directed toward solvent, this region of the molecule was able to



Scheme 1. Synthesis of aminopyridopyrazinones **1**, **2** and **9–53**. Reagents and conditions: (a) $(COCl)_2$, DMF(cat), CH_2Cl_2, rt, 30 min, ~80%; (b) aminoethylmorpholine, Et_3N, CH_2Cl_2, rt, 1 h, 50–90%; (c) 6-methoxypyridin-3-ylboronic acid, $(Ph_3P)_4P$ (10 mol %), Na_2CO_3, 1,4-dioxane–EtOH, 100 °C, 2 h, 50–85%.

Table 1
Initial survey of southwest SAR



Compound	Core	R-group	PDE5[a]	PDE6[b]
1	S		0.34	61.8
2	SE		0.07	11.3
9	S		4.00	1590
10	SE		0.78	261
11	S		16.3	>2000
12	SE		0.25	1210
13	SE		1.10	272
14	S		1.17	114
15	SE		0.90	26.3
16	S		0.17	57.4
17	SE		0.11	9.3
18	S		0.14	31.4
19[c]	SE		0.05	8.6
20	S		2.95	576
21	SE		1.05	45.5
22	S		2.59	398
23	SE		0.68	86.6
24	S		0.36	34.5
25	SE		0.04	10.8
26	S		0.28	23.6
27	SE		0.06	4.7

[a] PDE5 IC_{50} (nM).
[b] PDE6 IC_{50} (nM).
[c] Racemic.

significantly affect the overall potency and selectivity profile of the compound. PDE5 potencies were found to cover 2-orders of magnitude (IC_{50} = 0.05–16 nM) and PDE6 selectivities[7] spanned a 30-fold range from 30-fold to >4700-fold. For all the pairs (southern and southeastern pyridyl isomers) of compounds shown in Table 1 the southeastern isomers were always more potent; however, the southern isomers were less potent on PDE6.[8] Finally, as the lipophilicity of the compounds increased the selectivity over PDE6 also tended to increase.

Amines more basic than morpholines **1** and **2**, such as **9** - **12** and aminohydroxy compound **13**, were, with the exception of **11** well tolerated. These basic compounds also retained greater than 100-fold selectivity over PDE6. Alcohols **14** and **15** retained potency at PDE5, but the PDE6 selectivity for southeastern analog **15** was somewhat eroded (30-fold). Incorporation of ethers, such as in **16**–**19**, afforded analogs with exceptional potency. In general, placement of more lipophilic groups in the southwest tended to impart greater PDE5 potency. Compounds **17** and **19**, although possessing a high PDE6/PDE5 ratio, were very potent on PDE6 (IC_{50} = 9.3 nM and 8.6 nM, respectively). Carboxylic acids **20** and **21** were also well tolerated (PDE5 IC_{50} = 2.95 and 1.05 nM, respectively). Again southeastern isomer, **21**, was only moderately

selective over PDE6 (43-fold). Incorporation of *N*,*N* dimethyl glycine-amide units to give analogs such **22** and **23** yielded potent and selective analogs.

Similar to the ethers, installation of heteroaromatic groups (**24**–**27**) afforded compounds with excellent potencies against PDE5 and increased potency on PDE6.

As a wide variety of southwestern substituents met our requirements in terms of both potency and selectivity, we turned our attention to the evaluation of the effect of these changes on the PK profile. To prioritize our efforts, we first screened these compounds in an acute in vivo model of hypertension in spontaneously hypertensive rats (SHR).[9] Specifically, telemeterized rats were dosed at 10 mpk by oral gavage and the effect on blood pressure was monitored.[10] Compounds which demonstrated a robust response in this model were further evaluated.[11] Table 2 summarizes data from the SHR model and rat PK parameters for representative compounds from Table 1. Typically, the performance of compounds in the SHR model was found to be qualitatively predictive of the rat PK properties giving us confidence in the utility of this model for the rapid screening of compounds. For instance, compounds **13** and **18** with short duration of action in the SHR model also possessed relatively poor PK profiles which, significantly, were not improved relative to **1** or **2**. Based on the data from these studies, we elected to initially focus our attention on the further elaboration of the glycine-amides (**22** and **23**). Importantly, this sub-series of compounds was among the most polar examined and was expected to be more likely to demonstrate improved PK properties.

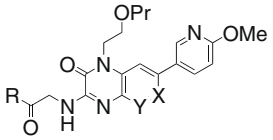
Table 3 summarizes our efforts to expand the SAR around the glycine-amide derivatives **22** and **23**. Analogous to the trend we noted in our initial scan of the southwest pocket SAR, more lipophilic compounds tended to be among the most potent and selective analogs. For instance, pyrolidine derivative **32** possessed a PDE5 IC_{50} = 0.08 nM and was 480-fold selective over PDE6. Potential desmethyl metabolites of **22** and **23**, **28**–**31**, retained a similar potency and selectivity profile to the parent compounds. From the point of view of further improving the PK of this series, we were encouraged to find that more polar amides such as 4-hydroxypiperidine **33** (IC_{50} = 0.13 nM), morpholino (**34**, IC_{50} = 1.17 nM, **35** IC_{50} = 0.15 nM) were well tolerated. Finally, alkyl piperazine derivatives (**37**–**40**) were potent and selective while the underivatized piperazine, **36**, suffered from a decreased selectivity over PDE6 (60-fold).

Table 2
Selected data from acute SHR model of hypertension and rat PK

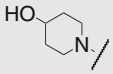
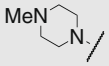
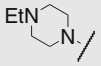
Compound	clog *P*	SHR[a]	Cl[b]	%*F*[c]
2	3.1	+	33	*ND*[d]
13	2.0	+	170	53
14	1.9	+	*ND*	*ND*
15	2.1	–	*ND*	*ND*
16	3.1	–	*ND*	*ND*
18	2.9	++	30	15
19	3.4	++	52	*ND*
21	2.4	–	*ND*	*ND*
22	2.0	+++	33	46
23	2.2	+++	27	52
25	2.8	++	21.9	54
26	2.2	++	*ND*	*ND*

[a] Duration of effect in the SHR model following a single 10 mpk oral dose. – = inactive; + → +++ qualitative assessment of the robustness of response; this score factors in duration of action and magnitude of response.
[b,c] IV: 2 mpk (n = 3) vehicle: 70% PEG400/20% 0.05 M citrate buffer/10% ethanol, pH 5; PO: 2 mpk (n = 3) vehicle: 0.5% methylcellulose/0.1% Tween 80 in 50 mM citric acid, pH 5; Cl = mL/min/kg; %*F* = oral bioavailability.
[d] Not determined.

Table 3
PDE5 and PDE6 potency of glycine-amide derivatives (**22**–**40**)



X = CH, Y = N: Core = Southern
X = N, Y = CH: Core = Southeastern

Compound	Core	R-group	PDE5[a]	PDE6[b]
28	S		2.59	398
29	SE		0.68	86.6
30	S		0.43	115
31	SE		0.07	15.2
22	S		0.78	131
23	SE		0.19	36.7
32	SE		0.08	39.5
33	SE		0.13	24.6
34	S		1.17	114
35	SE		0.15	16.1
36	SE		1.65	100
37	S		0.32	80.2
38	SE		0.07	14.7
39	S		0.38	98.9
40	SE		0.13	55.9

[a] PDE5 IC_{50} (nM).
[b] PDE6 IC_{50} (nM).

Again, we utilized the SHR acute in vivo screen to rapidly evaluate compounds (data not shown) and followed up on attractive compounds identified in these studies by collecting rat and dog PK data. Table 4 summarizes selected PK parameters for the most promising glycine-amide derivatives. Simple methyl glycine-amides such as *N*-methyl amide, **30**, or *N*,*N*-dimethylamides, **22** and **23**, displayed low to moderate clearance in both the rat and dog. Metabolite ID studies in both rat and human microsomal systems confirmed that N-demethylation of the glycine-amide side chain of **23** was the significant route of clearance. As was previously noted these metabolites retained similar potency and selectivity profiles[12] to the parent and possessed similar PK profiles. The likely formation of long-lived active metabolites dampened our enthusiasm for the simple glycine-amides such as **22**, **23** and **28**–**31**. Cyclic amides, less likely to form active metabolites, such as **33**, **34** and **35** had a similar PK profile to the simple amides. In general, incorporation of small alkyl or polar groups led to a decrease in clearance relative to **1** or **2** and a commensurate reduction in the volume of distribution (V_d) yielding compounds with no net improvement in the effective half-life. In an attempt to alter the Cl and V_d relationship which we observed with the neutral amides, we examined the somewhat basic *N*-ethyl-piperazinylamide **40**.[13] In both rat and dog, **40** possessed a higher V_d than neutral amides; although this compound still lacked the overall profile enhancement which we sought.

As our examination of the glycine-amide sub-series failed to yield compounds which significantly improved PK over amides **22** and **23**, we sought an alternate sub-series. Upon re-examination

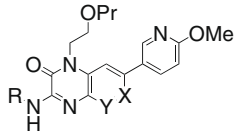
Table 4
Rat and dog pharmacokinetic parameters for select glycine-amide derivatives

Compound	Species	V_d[a]	Cl[b]	$T_{1/2}$[c]	%F[d]
22	Rat	1.1	33	0.6	46
22	Dog	1.2	9.4	2.1	32
23	Rat	0.9	27.0	0.6	52
23	Dog	0.4	1.8	4.3	30
30	Rat	1.0	19.5	0.8	39
30	Dog	1.3	8.8	2.4	52
33	Rat	1.0	10.5	1.7	52
34	Rat	0.8	18.0	0.8	51
34	Dog	0.9	16.7	0.9	32
35	Rat	0.5	9.1	0.8	35
35	Dog	1.2	5.3	3.9	32
40	Dog	8.0	37.0	3.5	15
40	Rat	2.3	28.0	1.4	61

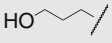
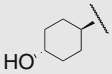
[a,b,c,d] IV: 2 mpk ($n = 3$) vehicle: 70% PEG400/20% 0.05 M citrate buffer/10%ethanol, pH 5; PO: 2 mpk ($n = 3$) vehicle: 0.5% methylcellulose/0.1% Tween 80 in 50 mM citric acid, pH 5; V_d = volume of distribution (L/kg); Cl = clearance (mL/min/kg); %F = oral bioavailability.

of the compounds classes shown in Table 1, we determined that alcohols, represented by **14** and **15**, might be an attractive starting point for further refinement. Neither **14** nor **15** were particularly efficacious in the SHR model. However, we speculated that the primary alcohol motif in **14** and **15** may be the site of rapid phase II metabolism resulting in poor PK and non-durable efficacy. We reasoned that increasing the branching proximal to the alcohol would reduce the rate of this route of metabolism. Furthermore, as previously noted, slight increases in the lipophilicity of the southwestern substituent often led to increases in PDE6 selectivity (a liability of **15**). Accordingly, we synthesized several analogs with increased branching, which we anticipated would improve the overall profile of **14** and **15**. Table 5 shows the PDE5 and PDE6 potency data for a series of straight chain and branched alcohols. We were encouraged to find that homologation of the side chain, for example propyl derivatives **41** and **42,** improved the PDE6 selectivity.[14] Gratifyingly, methyl branching either proximal (**43–46**) or distal (**47–50**) to the alcohol conferred both excellent potency and improved selectivity relative to the straight chain analogs. Among the set of compounds **43–50**, the secondary alcohols were more selective over PDE6. Incorporation of ethyl branching as in **51** afforded a potent and selective compound. Constraint of the southwest side chain into a cyclohexane ring system provided the exquisitely potent (IC_{50} = 0.05 nM) **53** and the somewhat less potent southern pyridyl isomer **52** (IC_{50} = 0.32 nM).

Table 5
PDE5 and PDE6 potency data for the alcohol sub-series



X = CH, Y = N: Core = Southern
X = N, Y = CH: Core = Southeastern

Compound	Core	R-group	PDE5[a]	PDE6[b]
14	S		1.17	114
15	SE		0.90	26.3
41	S		0.71	124
42	SE		0.26	13.8
43	S		0.34	51.8
44	SE		0.09	15.3
45	S		0.54	49.7
46	SE		0.10	15.1
47	S		0.88	63.2
48	SE		0.14	17.7
49	S		0.55	68.2
50	SE		0.24	17.9
51	SE		0.25	23.2
52	S		0.32	15.3
53	SE		0.05	9.8

[a] PDE5 IC_{50} (nM).
[b] PDE6 IC_{50} (nM).

Table 6
Rat and dog pharmacokinetic parameters for select glycine-amide derivatives

Compound	Species	V_d[a]	Cl[b]	$T_{1/2}$[c]	%F[d]
42	Rat	1.2	28.0	0.7	52
44	Rat	1.0	13.8	1.3	42
44	Dog	4.3	17.8	4.1	38
51	Rat	2.4	22.6	1.8	61
53	Rat	1.4	5.5	4.1	50
53	Dog	3.7	3.5	17.6	75

[a,b,c,d] IV: 2 mpk ($n = 3$) vehicle: 70% PEG400/20% 0.05 M citrate buffer/10%ethanol, pH 5; PO: 2 mpk ($n = 3$) vehicle: 0.5% methylcellulose/0.1% Tween 80 in 50 mM citric acid, pH 5; V_d = volume of distribution (L/kg); Cl = clearance (mL/min/kg); %F = oral bioavailability.

Table 6 shows selected PK data for compounds from the alcohol sub-series. In the rat, linear alcohol **42** demonstrated moderate clearance (28 mL/min/kg) with a volume of distribution (V_d, 1.1 L/kg) resulting in a short overall half-life. Encouragingly, the isomeric secondary alcohol, **44**, displayed significantly improved clearance in the rat. Branching beta to the alcohol, **51**, was not as effective as alpha branching and resulted in a slight reduction in clearance and an increase in V_d. Finally, cyclohexanol derivative, **53**, possessed low clearance in both rat and dog. Indeed, **53** displayed fivefold lower clearance in the rat relative to **42** while maintaining a similar V_d; in the dog the clearance was further reduced (3.5 mL/min/kg) and a $T_{1/2}$ = 17 h realized.

As summarized in Table 7, examination of the unbound volume of distribution (V_{du}) and unbound clearance (Cl_u)[15] for compounds **42**, **44** and **53** sheds further light on the underlying reasons for the improvement observed. The threefold increase in V_{du} determined for **53** is consistent with the higher lipophilicity of this compound. The decrease in Cl_u for **53** may be due to increased steric encumbrance near the alcohol and/or a reduction is rotable bonds.

Due to the excellent potency and PK profile of cyclohexanol **53**, it was selected for further evaluation. Keeping with our expectations, **53** was exquisitely selective against a complete panel of PDE isoforms.[16,17] Additionally, as shown in Figure 2, a 3 mpk oral dose of **53** in the SHR model resulted in robust efficacy lasting greater than 24 h. A more detailed evaluation of the PK/PD relationships for this compound coupled with allometric projections of human PK suggested a clinically efficacious dose of one mg once per day.

Table 7
Alcohol PK profile

Compound	V_{du}[a]	Cl_u[b]	RotBonds	Clog P
42	31	730	11	2.5
44	35	500	10	2.4
53	100	400	9	2.8

[a] Unbound volume of distribution (L/kg).
[b] Unbound clearance (mL/min/kg).

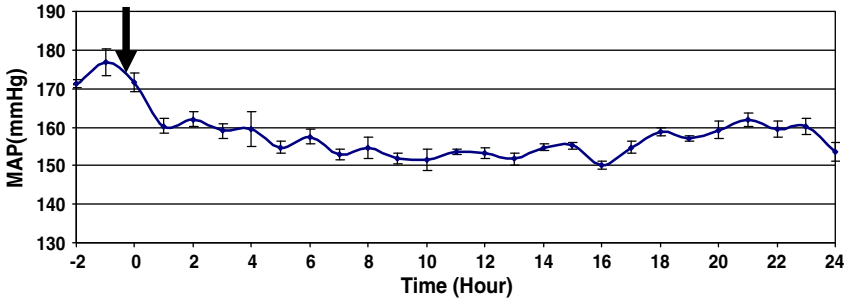


Figure 2. Effect of compound **53** on blood pressure following a 3 mpk oral dose.

In summary we have described the optimization of the PK profile of the aminopyrazinone class of PDE5 inhibitors. These efforts have focused on both amide and alcohol derived compounds and resulted in the discovery of **53**, 3-[(*trans*-4-hydroxycyclohexyl)amino]-7-(6-methoxypyridin-3-yl)-1-(2-propoxyethyl)pyrido[3,4-*b*]pyrazin-2(1*H*)-one, which has excellent PK properties and >24 h efficacy in the SHR model following a single dose.

References and notes

1. See for instance: Wolk, R.; Smith, W. B.; Neutal, J. M.; Rubino, J.; Xuan, D.; Mancuso, J.; Gilbert, J.; Pressler, M. L. *Hypertension* **2009**, *53*, 1091.
2. Owen, D. R.; Walker, J. K.; Jacobsen, E. J.; Freskos, J. N.; Hughes, R. O.; Brown, D. L.; Bell, A. S.; Brown, D. G.; Phillips, C.; Mischke, B. V.; Molyneaux, J. M.; Fobian, Y. F.; Heasley, S. E.; Moon, J. B.; Stallings, W. C.; Rogier, D. J.; Fox, D. A.; Plamer, M. J.; Ringer, T.; Rodriquez-Lens, M.; Cubbage, J. W.; Blevis, R. M.; Benson, A. G.; Acker, B. A.; Maddux, T. M.; Tollefson, M. B.; Bond, B. R.; MacInnes, A.; Yu, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4088.
3. Hughes, R. O.; Walker, J. K.; Cubbage, J. W.; Fobian, Y. M.; Rogier, D. J.; Heasley, S. E.; Blevis-Bal, R. M.; Benson, A. G.; Owen, D. R.; Jacobsen, E. J.; Freskos, J. N.; Molyneaux, J. M.; Brown, D. L.; Stallings, W. C.; Acker, B. A.; Maddux, T. M.; Tollefson, M. B.; Williams, J. M.; Moon, J. B.; Mischke, B. V.; Rumsey, J. M.; Zheng, Y.; MacInnes, A.; Bond, B. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4092.
4. To help define the goal of our early efforts, we anticipated that a $T_{1/2}$ (in rat) of 3–4 h would likely translate into a once-a-day profile in man: Hosea, N. A.; Collard, W. T.; Cole, S.; Maurer, T. S.; Fang, R. X.; Jones, H.; Kaker, S. M.; Nakai, Y.; Smith, B. J.; Webster, R.; Beaumont, K. *J. Clin. Pharm.* **2009**, *49*, 513.
5. Van de Waterbeemd, H.; Smith, D. A.; Jones, B. C. *J. Comput. Aided Mol. Des.* **2001**, *15*, 239.
6. *For compound* **2**: PDE11 IC_{50} = 346 nM (4900-fold), PDE1A, 1B, 1C, 2, 3A, 3B, 4A, 4B, 4C, 4D, 7A, 7B, 8A, 8B, 9 IC_{50} >2000 nM (>28,000-fold).
7. PDE6 IC_{50}/PDE5 IC_{50}.
8. This is a general trend. Over a larger set of compounds than is shown in Table 1 the southeastern isomers is approximately 6-times more potent than the southern isomer; Over the same set of compounds the southern isomer is roughly threefold less potent against PDE6.
9. The Pfizer Institutional Animal Care and Use Committee reviewed and approved the animal use in these studies. The animal care and use program is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International.
10. See Ref. 3 for details of the SHR study.
11. Select compounds were found to be equipotent on rat and human versions of PDE5.
12. Additional metabolism resulted in cleavage of the propoxy group from the ethylpropoxy side chain and the methoxy group from the methoxy pyridyl moiety. The resultant compounds lost significant potency against PDE5 and PDE6.
13. Van de Waterbeemd, H.; Smith, D. A.; Beaumont, K.; Walker, D. K. *J. Med. Chem.* **2001**, *44*, 1313.
14. Compound **14** → 41: 97-fold → 174-fold PDE6 selectivity; **15** → **42**: 30-fold → 53-fold PDE6 selectivity.
15. Calculated utilizing the parameters determined from the rat PK experiments and ppb.
16. PDE11 IC_{50} = 64.1 nM (1300-fold), PDE4B IC_{50} = 290 nM (5950-fold), PDE4D IC_{50} = 1210 nM (24,800-fold), PDE1A, 1B, 1C, 2, 3A, 3B, 4A, 4C, 7A, 7B, 8A, 8B, 9 IC_{50} >2000 nM (>41,000-fold).
17. The compound was negative in both micro Ames and micronucleus assays. In addition, compound 53 possessed excellent flux in CACO2 model of permeability (A→B 34×10^{-6} cm/s) and was determined not to be a PGP substrate.