Bioorganic & Medicinal Chemistry Letters 20 (2010) 3511–3514

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of a series of indan carboxylic acid glycogen phosphorylase inhibitors

Stuart N. L. Bennett, Andrew D. Campbell, Andrew Hancock, Craig Johnstone, Peter W. Kenny, Adrian Pickup, Alleyn T. Plowright *, Nidhal Selmi, Iain Simpson, Andy Stocker, David P. Whalley, Paul R. O. Whittamore

AstraZeneca, Medicinal Chemistry, Cardiovascular and Gastrointestinal Research Area, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

ARTICLE INFO

Article history:
Received 9 April 2010
Revised 28 April 2010
Accepted 29 April 2010
Available online 5 May 2010

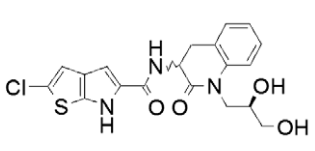
Keywords:
Glycogen phosphorylase
Antidiabetic agent
Type 2 diabetes
Design criteria
Physicochemical properties

ABSTRACT

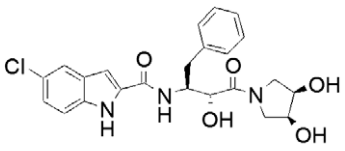
A series of carboxylic acid glycogen phosphorylase inhibitors, which have potential as oral antidiabetic agents, is described. Defining and applying simple physicochemical design criteria was used to assess the opportunity and to focus synthetic efforts on compounds with the greatest probability of success. The study led to compound **17**, which exhibits a good balance of properties including potent inhibition of recombinant human liver glycogen phosphorylase in vitro, a good DMPK profile including excellent bioavailability and low clearance and good in vivo activity in a glucagon challenge model of diabetes in Zucker rats.

Type 2 diabetes is a complex disease caused by defects in both the action and secretion of insulin, leading to fasting hyperglycaemia and vascular complications. It has become one of the leading causes of death and affects over 150 million people worldwide, with its prevalence expected to double by the year 2025.[1] Current therapies do not achieve adequate glycaemic control,[2] hence there is a need for new, effective pharmacological agents.

Glycogen phosphorylase (GP) catalyses the breakdown of glycogen to glucose-1-P. In the liver this is metabolised further to glucose which is then secreted into the bloodstream. One approach to reducing hyperglycaemia in Type 2 diabetes is to seek to restore normal net hepatic glucose balance by inhibition of hepatic GP.[3] The more active phosphorylated form (GPa) of the enzyme is a homodimer having an inhibitory allosteric binding site at the dimer interface for which synthetic ligands have been described previously by us,[4] and others,[5] including ingliforib (CP368296)[5f] which has undergone phase II clinical evaluation.



AstraZeneca[4]



Ingliforib (CP368296)[5(f)]

During the course of our research into GPa inhibitors and our search for the optimal biological profile we aimed to develop a complementary series of compounds with a different pharmacokinetic and physical property profile to that described previously.[4] One way this could be achieved was via introduction of an acid functionality into the molecule. This would give the opportunity to enhance the solubility profile of the series whilst varying the DMPK (drug metabolism and pharmacokinetic) parameters, particularly clearance and volume of distribution, to help identify the optimal biological profile. Preliminary docking studies suggested there was an opportunity to introduce a carboxylic acid moiety whilst maintaining or even enhancing potency. Whilst the idea of introducing an acid functionality was appealing we were fully aware of the potential issues of poor oral absorption and high plasma protein binding leading to low free plasma exposure after oral dosing, which we knew would be detrimental to achieving the desired in vivo effect.[6]

In order to achieve the required free plasma exposure after oral dosing it was clear that the physicochemical properties of the molecules would need to be balanced to achieve the required oral absorption and clearance (leading ultimately to good oral bioavailability) and plasma protein binding. Therefore, prior to embarking on the synthesis of compounds, we wanted to understand if there was an area of physicochemical property space that could be targeted with this acidic series that could give the best chance of achieving the required balance of properties. An early assessment of feasibility was achieved by analysing in house AstraZeneca data on compounds containing carboxylic acids across a range of projects and chemical classes. Based on these known compounds this

* Corresponding author at present address: AstraZeneca, CVGI Medicinal Chemistry, Pepparedsleden 1, Mölndal 43183, Sweden. Tel.: +46 31 7761572; fax: +44 31 7763868.
E-mail address: alleyn.plowright@astrazeneca.com (A.T. Plowright).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.04.147

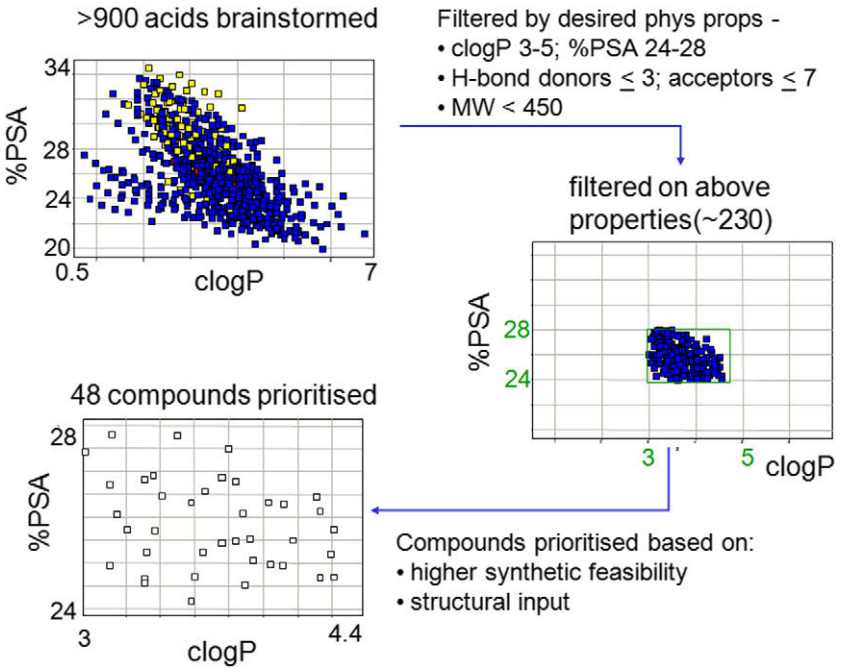


Figure 1. Design process from brainstorm to selection for synthesis.

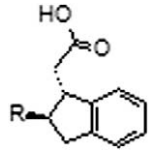
analysis revealed an area of physicochemical property space where it looked as if this balance could be achieved (*c*log *P* 3–5; hydrogen bond donors ⩽3; hydrogen bond acceptors ⩽7; %polar surface area (%PSA) 24–28% (PSA defined as the sum of surfaces of polar atoms in a molecule) and molecular weight <450). We then aimed to target this area of physicochemical property space in the design of novel acidic compounds and avoid investing time synthesising compounds where the probability of achieving the desired profile would be very low.

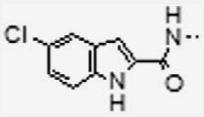
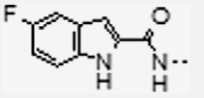
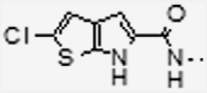
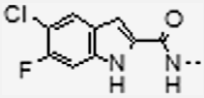
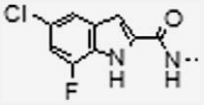
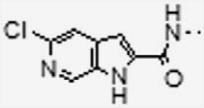
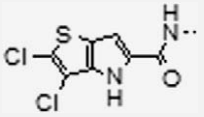
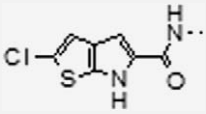
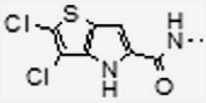
A brainstorm led to over 900 new ideas of acidic compounds being enumerated by the project team and a virtual library of compounds was built and their physicochemical properties calculated (Fig. 1). The above physicochemical property criteria were then applied to these virtual compounds to reduce the number of ideas to those that we believed would have the greatest chance of meeting the requirements of the project. This filtration left 230 potential compounds for synthesis. Each of these compounds was then assessed based on the feasibility for chemical synthesis and docking studies into the known x-ray structure of the human enzyme.[4,7] This left 48 compounds that were prioritised for synthesis.

Gratifyingly the initial compounds synthesised proved to be potent inhibitors of recombinant human liver glycogen phosphorylase as shown in Table 1.[8,9] For example, the acetic acid derivative, **1**, had an IC_{50} of 57 nM. The left hand side chain was varied with a set of substituted indoles and heterocyclic indole isosteres and showed a positive relationship with lipophilicity (determined by *c*log *P*). The most potent compound identified was **7** (IC_{50} = 18 nM) containing a dichlorothienopyrrole side chain.[4b] All attempts to reduce the lipophilicity of the left hand side heterocycle led to a reduction in activity (e.g., the azo-indole derivative **6**). There was a marked difference in the activity of the enantiomers of the indan ring. The data generated clearly showed the most active enantiomer had the (1*R*,2*R*) configuration as shown with the enantiomeric pairs (examples **3** and **8**, and **7** and **9**). As hoped the compounds all have excellent solubility in the millimolar range (data not shown[10]) and importantly, as predicted by the design criteria, most compounds have excellent oral plasma exposure and high bioavailability in the rat, ranging from 41–88% after dosing 5 mg/kg orally (po) and 2 mg/kg intravenously (iv). For example, the most potent compound **7** had good oral bioavailability of 65% in the rat. The one exception was azo-indole **6** with an extra H-bond acceptor in the compound compared with the other derivatives. However, despite these compounds meeting the design criteria, they were more protein bound than expected (compounds in Table 1 ranged from 0.01% to 0.12% free in rat plasma).[11]

Compounds with variation in the acidic side chain could also be designed to meet the design criteria in an attempt to further enhance potency whilst reducing protein binding. The results for the dichlorothienopyrrole sub-series are shown in Table 2. Differing substitution was well tolerated providing potent inhibitors of GPa with IC_{50} 20–60 nM. For example, the acetic acid side chain could be extended to a propionic (**10**) or butanoic acid (**11**) and maintain good potency with IC_{50} values ~50 nM. Introduction of heteroatoms was also tolerated. For example, the oxy-acetic acid side chain **12** had excellent potency as did both the thioacetic acid and sulfonyl containing side chains (**14** and **15**, respectively). Substitution on the α-carbon of the side chain could also be tolerated as exemplified by the α-methoxyethyl substituted acetic acid **17**. Interestingly, just as the stereochemistry of the indan ring was critical, the stereochemistry of the substituent on the side chain was also very important for potency. For example, for the pair of diastereoisomers **17** and **18** there was a 10-fold difference in potency. However, varying the side chain gave a wider spread of oral bioavailability compared to what was observed with varying the left hand side heterocycle. Varying the side chain explored a broader range of physicochemical properties and hence the design criteria were tested more thoroughly leading to a wider spread. Compounds with just carbon-containing side chains (e.g., **10** and **11**) maintained the very high oral bioavailability, whilst introduction of heteroatoms gave a broader range of bioavailability. Compound **13** showed a heteroatom could be introduced into the acid side chain and still maintain good oral exposure. In comparison **12** and **15** had very poor rat bioavailability. For both, this can most likely be explained by poor oral absorption as a result of; for **12**, an increased acidity of the acid functionality and for **15**, the fact the sulfone functionality causes the physicochemical properties

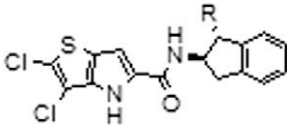
Table 1
Acetic acid derivative SAR

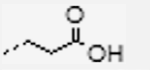
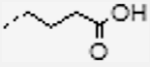
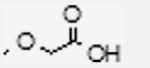
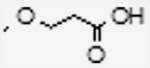
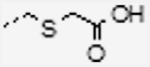
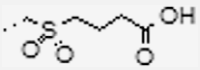
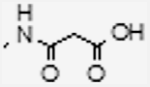
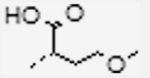
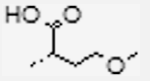


Compound	R	Enzyme inhibition[a] IC_{50}[b] (nM)	clog *P*	Rat oral bioavailability (%)
1		57	3.9	77
2		160	3.4	88
3		40	3.6	41
4		76	4.1	65
5		52	4.1	41
6		260	3.2	11
7		18	4.4	65
8[c]		1200	3.6	—
9[c]		1500	4.4	—

[a] Using recombinant human liver GPa: glucose-1-phosphate production from glycogen monitored by a multienzyme coupled assay.[7]
[b] $n = 3$, unless otherwise stated.
[c] Compounds **8** and **9** have the (1*S*,2*S*)-enantiomeric configuration. Compounds **1**–**7** have the (1*R*,2*R*) configuration.

Table 2
Variation of the acid side chain



Compound	R	Enzyme inhibition[a] IC_{50}[b] (nM)	clog *P*	Rat oral bioavailability (%)
10		56	4.4	80
11		54	4.9	118
12		30	4.3	5
13		59	4.5	55
14		40	4.8	23
15		42	4.0	2
16		56	4.0	2
17[c]		17	4.7	150
18[c]		170	4.7	65

[a] Using recombinant human liver GPa: glucose-1-phosphate production from glycogen monitored by a multienzyme coupled assay.[2]
[b] $n = 3$, unless otherwise stated.
[c] Compounds **17** and **18** are individual diastereomers. The configuration of the asymmetric centre in the α-position of the carboxylic acid is not known.

to lie at the upper end of the design criteria regarding %PSA (25.4) and above the upper limit of molecular weight (515). When both the greater acidity of the acid group and the higher %PSA are combined it is no surprise that **16** had very low oral bioavailability (pK_a 2.5, %PSA 28.5). Combining these observations in the α-substituted acetic acid derivatives, such as **17**, allowed us to meet the design criteria and also not affect the pK_a of the acid group and subsequently maintain excellent oral bioavailability. These compounds were still highly protein bound but some reduction in protein binding was achieved. For example, **15** was 0.3% free in rat plasma.

Once a larger dataset on acid compounds from our own series was available, the data was reanalysed to increase the specificity of the design criteria to guide design within this specific series of compounds. The analysis revealed this series had a narrower window of physicochemical properties to be able to achieve good oral exposure (as measured by area under the concentration–time curve after oral dosing to rats) compared to the original data set of broader chemical structures. As an example Figure 2 shows the plot of total area under the curve after oral dosing in the rat normalised to a 1 mg/kg oral dose versus %PSA. The plot shows that all compounds with a normalised area under the curve of greater than 15 μM/h have a %PSA less than 24.5. This is at the lower end of our original design criteria. The redefined criteria are hence more stringent than before leaving a very narrow window to maintain high oral exposure and modify other properties. For example, as all three H-bond donors in compound **17** are required for binding there was no scope to introduce a further H-bond donor to try to reduce plasma protein binding and maintain good oral bioavailability.

Compounds **7** and **17** had the best overall profile with excellent potency, high rat bioavailability, low clearance and low volume of distribution as shown in Table 3. Furthermore both compounds showed no inhibition of the hERG encoded potassium channel[12] (IC_{50} >30 μM) and no activity against a panel of cytochrome P450 isoforms (1A2, 2C9, 2C19, 2D6, 3A4; <50% inhibition at 10 μM).

Compound **17** was taken forward to test in a glucagon challenge model of diabetes in Zucker rats.[13] In this model administration of glucagon increases hepatic glucose output through cAMP mediated activation of GP. Compounds were dosed orally to between four and six animals in each group (basal blood glucose was around 5–6 mM) and did not affect pre-glucagon challenge blood glucose at doses which inhibited the glucagon response. When dosed at 17 μmol/kg (dose volume 5 mL/kg) 45 min prior to the glucagon,

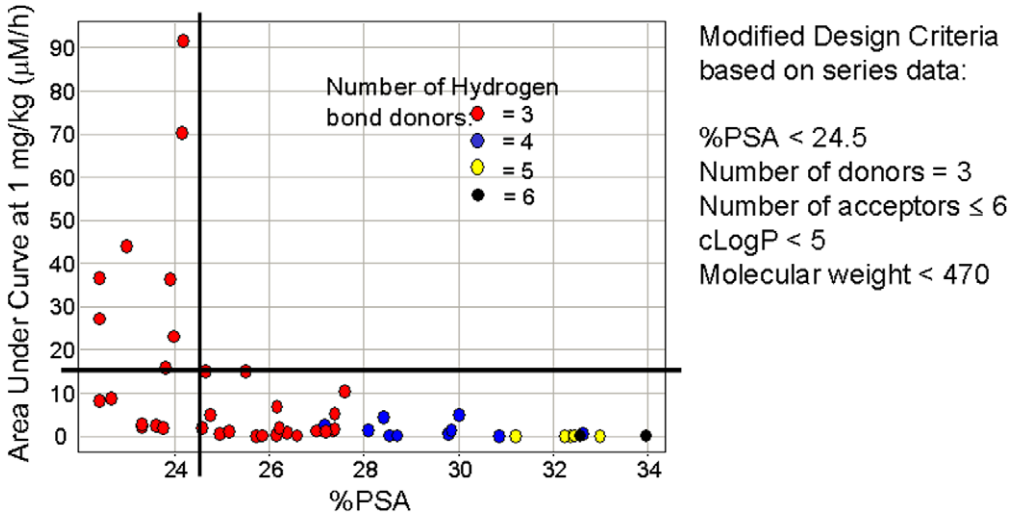


Figure 2. Area under curve (μM/h) normalised to a 1 mg/kg oral dose in the rat versus %PSA.

Table 3
Pharmacokinetic data for compounds **7** and **17**

Compound	Clearance (mL/min/kg)	Volume of distribution (L/kg)	Oral half life, $t_{½}$ (h)	Oral bioavailability (%)
7	0.23	0.2	8	65
17	0.40	0.2	7	118

Compounds dosed at 4.3–4.9 μmol/kg (iv) and 11–12.2 μmol/kg (po) to male AP Wistar rats.

17 caused a 50% lowering of the induced glucose increase, measured 90 min after the compound dose.

In conclusion, a novel series of acidic glycogen phosphorylase inhibitors is described leading to compound **17**. Compound **17** exhibits a good balance of properties including potent inhibition of recombinant human liver glycogen phosphorylase (GPa) in vitro, a good DMPK profile including excellent bioavailability and low clearance and good in vivo activity in a glucagon challenge model of diabetes in Zucker rats. Defining and applying simple physicochemical design criteria to assess the opportunity within a new series and to focus synthetic efforts on compounds with the greatest probability of success were also described.

Acknowledgements

Thanks to Sue Freeman, Simon Poucher, Gemma Boardman, Julie Bartlett, Joanne Teague and Sue Loxham for the bioscience testing and Jack Allen, Clare Hammond and Clare Wilson for DMPK testing.

References and notes

1. Gershell, L. *Nat. Rev. Drug. Disc.* **2005**, *4*, 367.
2. Krentz, A. J.; Bailey, C. J. *Drugs* **2005**, *65*, 385.
3. Treadway, J. L.; Mendys, P.; Hoover, D. J. *Expert Opin. Invest. Drugs* **2001**, *10*, 439.
4. (a) Birch, A. M.; Kenny, P. W.; Oikonomakos, N. G.; Otterbein, L.; Schofield, P.; Whittamore, P. R. O.; Whalley, D. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 394; (b) Whittamore, P. R. O.; Addie, M. S.; Bennett, S. N. L.; Birch, A. M.; Butters, M.; Godfrey, L.; Kenny, P. W.; Morley, A. D.; Murray, P. M.; Oikonomakos, N. G.; Otterbein, L. R.; Pannifer, A. D.; Parker, J. S.; Readman, K.; Siedlecki, P. S.; Schofield, P.; Stocker, A.; Taylor, M. J.; Townsend, L. A.; Whalley, D. P.; Whitehouse, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5567.
5. (a) Chen, L.; Li, H.; Liu, J.; Zhang, L.; Liu, H.; Jiang, H. *Bioorg. Med. Chem.* **2007**, *15*, 6763; (b) Thomson, S. A.; Banker, P.; Bickett, D. M.; Boucheron, J. A.; Carter, H. L.; Clancy, D. C.; Cooper, J. P.; Dickerson, S. H.; Garrido, D. M.; Nolte, R. T.; Peat, A. J.; Scheckler, L. R.; Sparks, S. M.; Tavares, F. X.; Wang, L.; Wang, T. Y.; Weiel, J. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1177; (c) Hoover, D. J.; Lefkowitz-Snow, S.; Burgess-Henry, J. L.; Martin, J. H.; Armento, S. J.; Stock, A. I.; McPherson, R. K.; Genereux, P. E.; Gibbs, E. M.; Treadway, J. L. *J. Med. Chem.* **1998**, *41*, 2934; (d) Klabunde, T.; Wendt, K. U.; Kadereit, D.; Brachvogel, V.; Burger, H.-J.; Herling, A. W.; Oikonomakos, N. G.; Kosmopoulou, M. N.; Schmoll, D.; Sarubbi, E.; von Roedern, E.; Schönafinger, K.; Defossa, E. *J. Med. Chem.* **2005**, *48*, 6178; (e) Henke, B. R.; Sparks, S. M. *Mini-Rev. Med. Chem.* **2006**, *6*, 845; (f) Tracey, W. R.; Treadway, J. L.; Magee, W. P.; Sutt, J. C.; McPherson, R. K.; Levy, C. B.; Wilder, D. E.; Yu, L. J.; Chen, Y.; Shanker, R. M.; Mutchler, A. K.; Smith, A. H.; Flynn, D. M.; Knight, D. R. *Am. J. Physiol. Heart Circ. Physiol.* **2004**, *286*, H1177; (g) Somsák, L.; Czifrák, K.; Tóth, M.; Bokor, É.; Chrysina, E. D.; Alexacou, K.-M.; Hayes, J. M.; Tiraidis, C.; Lazoura, E.; Leonidis, D. D.; Zographos, S. E.; Oikonomakos, N. G. *Curr. Med. Chem.* **2008**, *15*, 2933. and references therein.
6. Yu, L. J.; Chen, Y.; Treadway, J. L.; McPherson, R. K.; McCoid, S. C.; Gibbs, E. M.; Hoover, D. J. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 1230.
7. Lin, K.; Rath, V. L.; Dai, S. C.; Fletterick, R. J.; Hwang, P. K. *Science* **1996**, *273*, 1539.
8. (a) The compounds described herein were prepared by methods included in, or analogous to, those described in (a) PCT Int. App. WO2006082400, 2006.; (b) PCT Int. App. WO2006082401, 2006.
9. For in vitro assay experimental conditions, see: Bartlett, J. B.; Freeman, S.; Kenny, P. W.; Morley, A. D.; Whittamore, P. R. O. PCT Int. App. WO200220530, 2002.
10. As measured in 0.1 M phosphate at pH 7.4 following 24 h of agitation.
11. Plasma protein binding was determined using the equilibrium dialysis technique at 37 °C, analysing by generic LC/UV/MS.
12. Redfern, W.; Carlsson, L.; Davis, A. S.; Lynch, W. G.; MacKenzie, I.; Palethorpe, S.; Siegl, P. K. S.; Strang, I.; Sullivan, A. T.; Wallis, R.; Camm, A. J.; Hammond, T. G. *Cardiovasc. Res.* **2003**, *58*, 32.
13. Loxham, S. J. G.; Teague, J.; Poucher, S. M.; De Schoolmeester, J.; Turnbull, A. V.; Carey, F. *J. Pharmacol. Toxicol. Methods* **2007**, *55*, 71.