Monitor

Monitor provides an insight into the latest developments in the pharmaceutical and biotechnology industries. ***Chemistry*** examines and summarises recent presentations and publications in medicinal chemistry in the form of expert overviews of their biological and chemical significance, while ***Profiles*** provides commentaries on promising lines of research, new molecular targets and technologies. ***Biology*** reports on new significant breakthroughs in the field of biology and their relevance to drug discovery. ***Business*** reports on the latest patents and collaborations, and ***People*** provides information on the most recent personnel changes within the drug discovery industry.

Chemistry

Molecules

Phenylpropanoic acids activators of PPAR α

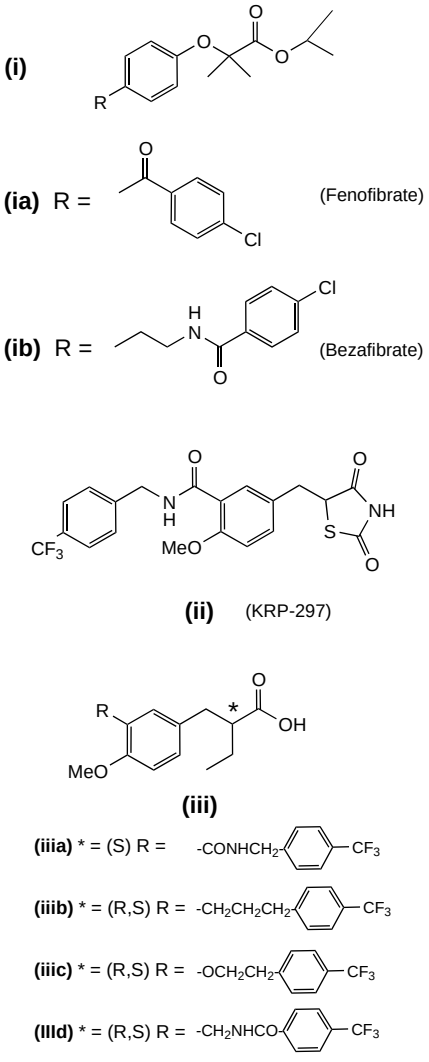
Peroxisome proliferator activated receptors (PPARs) are a family of ligand-activated transcription factors belonging to the nuclear receptor gene superfamily. Upon binding to the agonist, these receptors heterodimerize with the 9-cis retinoic acid receptor (RXR); the heterodimer thus interacts with DNA, turning on the transcription of target genes.

Three subtypes of PPARs have been isolated to date: PPARα, PPARγ and PPARδ. X-ray crystal structures show that all these receptors have a common Y-shaped binding pocket; in addition, PPARγ and PPARα have an extra binding area. Most of the small molecules that bind PPAR receptors have an acidic moiety [1,2]. PPARγ is central to the regulation of adipocyte differentiation, which in turn leads to the expression of other genes involved in glucose and lipid homeostasis; thiazolidinedione antidiabetic drugs act as PPARγ agonists. The biological function of PPARδ is not clear; there are some reports indicating that PPARδ agonists could be useful for the treatment of dyslipidemia and other pathologies.

PPARα has an important role in lipid metabolism, acting as a dietary fat sensor by upregulating lipid metabolism in the presence of fatty acids, which are presumed to be their natural ligands. The antihyperlipidemic drugs of the fibrate class (clofibrate, fenofibrate **ia**, bezafibrate **ib**) work through their agonist activity on PPARα [1]. However, the affinity of the fibrates is weak and the PPAR subtype-selectivity is poor [2]. Therefore, there is a strong effort for the identification of more potent and selective PPARα activators for the treatment of altered lipid homeostasis.

Kyorin Pharmaceuticals (http://www.kyorin-pharma.co.jp/eg/) identified KRP297 (**ii**) as a lead [3], which structurally belongs to the glitazones (thiazolidinedione insulin sentitizers) and is able to activate both PPARα and PPARγ isoforms with low selectivity. An intense effort was undertaken to modify the three key regions of KRP297: the acidic head part (the thiazolidinedione moiety) the linker and the hydrophobic tail (the trifluoromethylphenyl moiety).

Replacement of the thiazolidine-2,4-dione ring of KRP297 with another acidic functionality, the carboxy group, usually used in fibrates, improved the potency and selectivity for the PPARα subtype. Thus, among the compounds synthesized, **iiia** was developed, which was a more potent PPARα transactivation activator, with higher selectivity for PPARα over other PPAR isoforms compared with classical fibrates (EC_{50} in μM for the transactivation of human receptors transfected into Chinese Hamster Ovary K1 cells: PPARα = 0.040, PPARγ = 0.40, PPARδ = 3.6) [3]. When **iiia** was adminstered to normal rats at 3 mg kg^{-1}, it decreased serum levels of triglycerides, free fatty acids and cholesterol by >20%. This compound, at 30 mg kg^{-1},



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showed an activity comparable with that obtained with the same dose of bezafibrate **ib**. However, **iiia** was more potent than bezafibrate at the same dose in lowering the hepatic levels of triglycerides and total cholesterol to fructose-fed fatty-liver rats [3].

In addition, experiments were conducted on this compound to assess the species-dependent PPAR transactivation activity; **iiia** was 100-fold and 30-fold less potent on rat and dog PPARα, respectively, than on human PPARα [3], as a result of differences in amino acid composition at the active site [4].

Manipulation of the linker led to compounds **iiib** and **iiic**, which were moderately potent dual activators of PPARα and PPARδ. They showed about 10-fold less potency for PPARα compared with **iiia**, but are more potent as PPARδ activators. Compound **iiid**, a dual activator of PPARα and PPARδ (EC_{50} μM for the transactivation assay: PPARα = 0.040, PPARγ >10, PPARδ = 0.12), could be of potential value as a substance capable of modulating cholesterol metabolism.

1 Sternbach, D.D. (2003) Modulators of peroxisome proliferator-activated receptors (PPARs). *Ann. Rep. In Med. Chem.* 38, 71–80

2 Willson, T.M. *et al.* (2000) The PPARs: from orphan receptors to drug discovery. *J. Med. Chem.* 43, 527–550

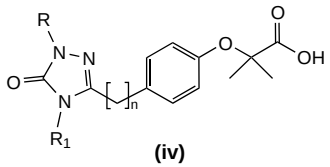
3 Nomura, M. *et al.* (2003) Design, synthesis and evaluation of substituted phenylpropanoic acid derivatives as human peroxisome proliferator activated receptor activators. Discovery of potent and human peroxisome proliferator activated receptor α subtype selective activators. *J. Med. Chem.* 46, 3581–3599

4 Miyachi, H. *et al.* (2003) Analysis of the critical structural determinant(s) of species-selective peroxisome proliferator-activated receptor a (PPARα)-activation by phenylpropanoic acid-type PPARα agonists. *Bioorg. Med. Chem. Lett.* 13, 3145–3149

Triazolone derivatives activators of PPARα

Scientists at Lilly (http://www.lilly.com) discovered a new lead compound by screening with a triazolone core tethered to the acidic head found in fenofibrate **ia** (compound **iva**) [5]. The analog **ivb** exerted micromolar activity (EC_{50}) on both human PPARα and PPARγ receptors, comparable to **iva**. By contrast, a 450-fold increase in PPARα agonist activity was observed by extending the linker to three carbons (**ivc** versus **ivb**); at the same time, the compound retains selectivity over PPARγ and PPARδ.

The affinity and the activity is dependent on R (the activity and the affinity were lost on all the three receptors when R = H), therefore, this residue was modified in several ways; substituent effects of R1 were less pronounced. Among the synthesized compounds, **ivd** was found to be potent and selective, with an EC_{50} (μM) for PPARα = 0.042, for PPARγ and PPARδ activity <20% at 10 μM). The compound was also tested *in vivo* on human apo-AI transgenic mice for its ability to alter serum triglyceride and HDL-cholesterol levels and was found to be 2–3 orders of magnitude more potent than fenofibrate **ia**. This compound had a good oral bioavailability and an acceptable safety profile and was selected (LY 518674) for clinical studies [5].



(iv)

(iva) R = 3-methoxybenzyl; R1 = 1-hexyl; n = 2

(ivb) R = 4-methoxybenzyl; R1 = 1-propyl; n = 3

(ivc) R = 4-methoxybenzyl; R1 = 1-propyl; n = 3

(ivd) R = 4-methoxybenzyl; R1 = H; n = 3

5 Xu, Y. *et al.* (2003) Design, synthesis of a potent and selective triazolone-based peroxisome proliferator activated receptor α agonist. *J. Med. Chem.* 46, 5121–5124

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Medicinal chemistry

Integration of silicon into the building blocks of life

Amino acids and the peptides derived from them are essential in biological pathways. As a result, the synthesis of new amino acid building blocks has been an active area of research for many decades. Silicon is a natural bio-isostere of carbon that medicinal chemists are now using in drug discovery.

Although some methods for the preparation of silyl amino acids (in which silicon is attached directly to the amino acid back-bone) have been described previously, they have been limited to the production of racemic mixtures or mixtures of diastereomers.

Sieburth *et al.* [6] have now described the enantioselective synthesis of alpha-silyl amino acids through a reverse-aza-Brook rearrangement. This involves the intramolecular transfer of a silicon group from nitrogen to carbon (of compound **i**) in the presence of a strong base and a chiral amine, (–)-sparteine. The transformation occurs in up to 95% enantiomeric excess leading to virtually enantiopure material **(ii)**. Furthermore, it has been demonstrated that the product from this reaction can be taken forward to the silyl amino acid **(iii)** and incorporated into a peptide without any loss in chiral purity.

Sparteine is only commercially available in the (–)-form. However, a recent report has described the synthesis of a surrogate of (+)-sparteine [7], which should allow access to the opposite enantiomers of the silyl amino acid described above.

The amino acids described within this paper could be used in a host of biochemistry and medicinal chemistry projects. However, before this new method can be applied widely, the key asymmetric aza-Brook reaction needs further investigation. Currently, it only works well with a tert-butyldimethylsilyl group and reactions with substrates that incorporate other silyl substituents have not yet provided acceptable yields.

Once this caveat has been addressed, the silyl amino acid building blocks produced by this new reaction could find increasing widespread use.

6 Sieburth, S.M. *et al.* (2003) Enantioselective alpha-silyl amino acid synthesis by reverse-aza-Brook rearrangement. *Org. Lett.* 5, 4677–4679

7 Dearden, M.J. *et al.* (2002) A readily-accessible (+)-sparteine surrogate. *J. Am. Chem. Soc.* 124, 11870–11871

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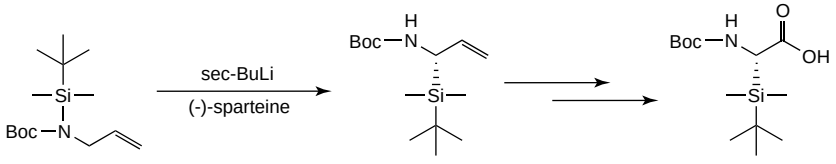

(i) **(ii)** **(iii)**