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Mini Review

Discovery of Atropisomer PH-797804 as a Potent, Selective and Efficacious P38 MAP Kinase Inhibitor as Clinical Candidate

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Abstract

PH-797804 is a diarylpyridinone inhibitor of p38α mitogen activated protein (MAP) kinase derived from a racemic mixture as the more potent atropisomer. Systematic structural modifications to the HTS lead led to the identification of the racemate as potential candidate. Molecular modeling predicted that the two isomers should differ in their binding affinity to p38α kinase, whereas the atropic S isomer (aS) binds favorably, the opposite aR isomer incurs significant steric interferences with the p38α kinase. Extensive pharmacological characterization corroborates that PH-797804 carries most activity in vitro and in vivo, and possess high level of specificity across the broad human kinase genome. It is under clinical development for the treatment of several inflammatory diseases.

ABBREVIATION

MAP: Mitogen Activated Protein; RA: Rheumatoid Arthritis; TNF-A: Tumor Necrosis Factor-A; DFT: Density Functional Theory.

The p38 mitogen activated protein (MAP) kinase is a widely prosecuted therapeutic target that has resulted in the discovery of a variety of inhibitor classes with diverse molecular architecture [1]. This enzyme plays a pivotal role in the MAP kinase signal transduction pathway regulating the production and downstream signaling of inflammatory cytokines such as TNF-α and IL-1β and IL-6 [2]. Modulation of p38 by ATP competitive small molecules has led to the generation of a variety of novel p38 inhibitors as potential therapeutics for the treatment of inflammatory conditions including Crohn's disease, chronic obstructive pulmonary disease (COPD), psoriasis, and rheumatoid arthritis (RA) [3]. Several of the p38 kinase inhibitors have advanced into human clinical trials, and our own efforts have led to the identification of a novel pharmacophore PH-797804 (Figure 1) as a clinical candidate for RA [4-7].

This novel series of highly potent and selective p38 mitogen activated protein (MAP) kinase inhibitors was developed originating from a substituted *N*-aryl-6-pyridinone scaffold. First proposed by molecular modeling, PH-797804 is the more potent atropisomer (aS) of a racemic pair [4]. Due to steric constraints imposed by the pyridinone carbonyl and the 6,6'-methyl substituents, the rotation around the connecting bond of the pyridinone and the N-phenyl ring is restricted. Density functional theory predicted a remarkably high rotational energy barrier of >30 kcal/mol, corresponding to a half life of 111 years of racemic inter conversion under ambient conditions. This gives rise to discrete conformational spaces of N-phenyl pyridinone group and as a result two atropic isomers that do not inter convert under ambient conditions. Molecular modeling predicted that the two isomers should differ in their binding affinity to p38α kinase, whereas the atropic S isomer (aS) binds favorably, the opposite aR isomer incurs significant steric interferences with the p38α kinase. Subsequently chiral chromatography identified and separated the two isomers. Upon chiral separation and small molecule X-ray diffraction experiment, it was confirmed that the more potent atropisomer (PH-797804) is the aS isomer of the racemic pair.IC_{50} values from the p38α enzyme assay confirmed that PH-797804 is 16nM, whereas the off-isomer PH797805 is more than 100-fold less potent (IC_{50}: 1800 nM). In human whole blood, a cellular system thatmimics the physiological in vivo milieu, LPS stimulated TNF-α and IL-1β production were measured. MAP kinase modulated cytokine production in whole blood was inhibited with comparable 26 fold differences in IC_{50} values by PH-797804 (85nM) and PH-797805 (4600nM). Taking into account inhibitor-protein binding in the whole blood, the cellular potency of PH-797804 correlates well with its inhibition of recombinant enzyme activity.

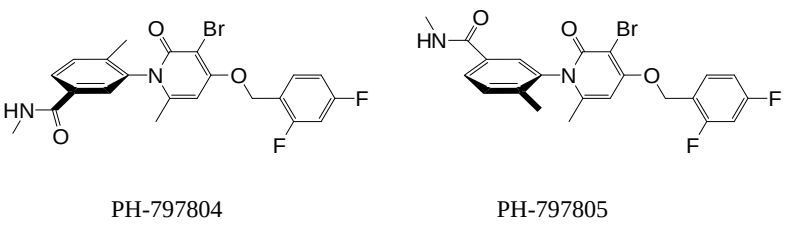

Figure 1 PH-797804 and PH-797805 are the atropisomers of a racemic pair.

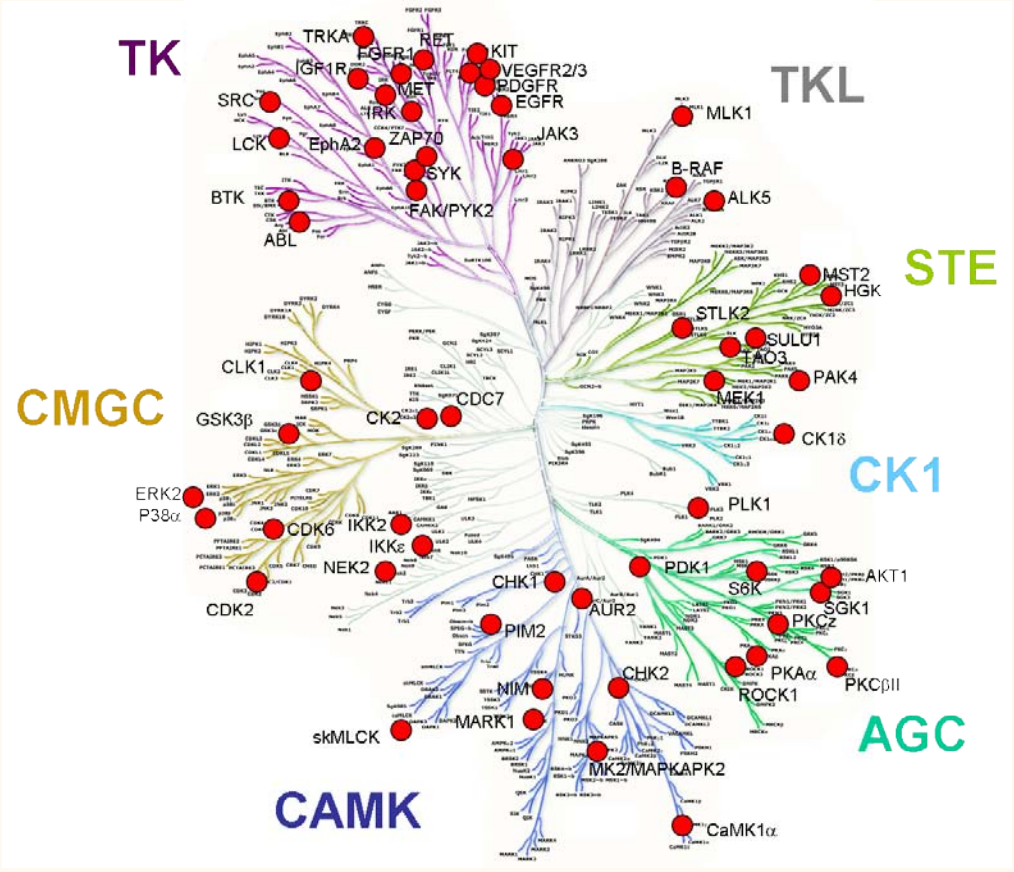

Figure 2 Kinase selectivity screens contain representative members from broad kinase families.

The pyridinoneclass of compounds exhibits exceptional selectivity for p38 MAP kinase versus other kinases due to a unique binding mode involving a dual H bond motif, engaging the backbones of Met109 and Gly110 residues, with a flipped peptide conformation of Gly110 from its apo state [4,8].The backbone flip occurs in p38α due to the presence of the glycine in the hinge region, which has no side chain and consequently has sufficient conformational flexibility to induce a peptide flip (Amgen has also observed a glycine flip. Ramanchandran diagram indicates the flipped backbone conformation is unavailable to other amino acids that bear a side chain. In the human kinome, only p38α, p38β and Myt-1 contain the corresponding glycine and a threonine at the gatekeeper position, which provides a structural rationale for the observed high level of selectivity [6]. p38β kinase is the closest structural homolog to p38α, sharing 75% overall sequence identity, and even higher in the ATP binding site (close to 90%). In general p38 α and β kinase inhibition parallels with each other. Myt-1 is a mixed serine/threonine and tyrosine kinase upstream of CDKs. Its kinase domain is merely 23% identical to p38α in primary structure. Cross reactivity is not anticipated for PH-797804 due to the remote evolutionary relationship between Myt-1 and p38α kinase. This is confirmed by a marginal Myt-1 inhibition of 14% at 10 μM concentration. PH-797804 was further tested against several kinase screening panels for its off-target activities. The kinase selectivity panels contain large number of targets covering diverse kinase families, as indicated by the broad distribution over the kinase dendrogram (Figure 2). Over a hundred kinases have been screened, and PH-797804 was found completely selective with no off target signal. The selectivity windows are greater than 500 fold compared with the primary target p38α kinase. In cellular assays PH-797804 demonstrated superior potency and selectivity consistent with biochemical measurements.

The dose response analysis demonstrate disparate efficacy for the two atropisomers in the acute in vivo model. LPS- induced TNF-α production in rats allowed evaluation of oral efficacy for inhibition of an acute inflammatory response [9]. Treatment of rats with PH-797804 resulted in dose dependent inhibition of LPS-induced TNF-α production, yielding an ED_{80} value of 0.3 mg/kg. In comparison the ED_{80} for PH-797805 is greater than 10 mg/kg. PH-797804 and PH-797805 have essentially the same pharmacokinetic properties (95% remaining in the rat metabolic stability assay), hence the difference observed in vivo can be primarily attributed to translation from their in vitro activities. The ability to suppress chronic inflammation was evaluated in an inflammatory arthritis model in rats induced by streptococcal cell wall (SCW) extract. The SCW model is characterized by an acute phase of inflammation from day 1 today 5, followed by a more severe and chronic phase of bone destruction that occurs from day 10 to day 21. A role for TNF-α and IL-1β in the chronic phase has been demonstrated with neutralizing TNF-α and IL-1 antibodies. PH-797804 was highly effective in attenuating SCW-induced inflammation. Untreated control rats exhibited profound joint inflammation from day 10 to day 21. PH-797804 treatment resulted in dose dependent inhibition of paw swelling when administered daily with an ED_{50} of 0.186 mg/kg. In comparison, PH-797805 required a daily dose of about 40 mg/kg to produce the half maximal efficacy. The potency and efficacy demonstrated by PH-797804 is consistent with that expected from a viable human drug candidate given the appropriate safety profile.

Numerous competitor p38 kinase inhibitors have been reported to show anti inflammatory efficacy in Phase IIa studies of psoriasis and rheumatoid arthritis over the years, but their development has been terminated by the dose limiting side effects of liver enzyme elevation and skin rash. By contrast, PH-797804 is differentiated from previous p38 kinase inhibitors by being generally safe and well tolerated in healthy volunteers, and more importantly, in patients with a relatively low incidence of liver enzyme elevations (<0.5%) and skin rash (<10%). These observations are on the basis of five Phase I studies, as well as three proof of concept studies in rheumatoid arthritis, post herpetic neuralgia and COPD. Efficacy has been achieved in moderate to severe COPD patients in a proof of concept study. The authors should mention the rebound effect observed in Phase II clinical trials observed with the p38 inhibitors pamapimod (Arthritis and Rheumatology 2009, 60, 335) and with SCIO-469 (ACR 2008).

REFERENCES

1. Saklatvala J. The p38 MAP kinase pathway as a therapeutic target in inflammatory disease, Curr Opin Pharmacol. 2004; 4: 372-377.
2. Adams JL, Badger AM, Kumar S, Lee JC. p38 MAP kinase: molecular target for the inhibition of pro inflammatory cytokines. Prog Med Chem. 2001; 38: 1-60.
3. Kumar S, Boehm J, Lee JC. p38 MAP kinases: key signalling molecules as therapeutic targets for inflammatory diseases. Nat Rev Drug Discov. 2003; 2: 717-726.
4. Xing L, Shieh HS, Selness SR., Devraj RV, Walker JK, Devadas B, et al. Structural bioinformatics based prediction of exceptional selectivity of p38 MAP kinase inhibitor PH-797804, Biochemistry 2009; 48: 6402-6411.
5. Selness SR, Devraj RV, Monahan JB, Boehm TL, Walker JK, Devadas B, et al. Discovery of N-substituted pyridinones as potent and selective inhibitors of p38 kinase, Bioorg Med Chem Lett. 2009; 19, 5851-5856.
6. Selness SR, Devraj RV, Devadas B, Walker JK, Boehm TL, Durley RC, et al. Discovery of PH-797804, a highly selective and potent inhibitor of p38 MAP kinase, Bioorg Med Chem Lett. 2011; 21: 4066-4071.
7. Selness SR, Boehm TL, Walker JK, Devadas B, Durley RC, Kurumbail R, et al. Design, synthesis and activity of a potent, selective series of N-aryl pyridinone inhibitors of p38 kinase. Bioorg Med Chem Lett. 2011; 21: 4059-4065.
8. Xing L, Devadas B, Devraj RV, Selness SR, Shieh H, Walker JK, et.al. Discovery and characterization of atropisomer PH-797804, a p38 MAP kinase inhibitor, as a clinical drug candidate. Chem MedChem. 2012; 7: 273-280.
9. Hope HR, Anderson GD, Burnette BL, Compton RP, Devraj RV, Hirsch JL, Keith RH, et al. Anti inflammatory properties of a novel N-phenyl pyridinone inhibitor of p38 mitogen activated protein kinase: preclinical to clinical translation, The Journal of pharmacology and experimental therapeutics. 2009; 331: 882-895.

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