

AstraZeneca	AZD5904
Mechanism of Action	Myeloperoxidase (MPO) inhibitor https://www.ncbi.nlm.nih.gov/gene/4353
Overview	AZD5904 is a potent (IC ₅₀ of 140 nM), irreversible inhibitor of human MPO with similar potency in mouse and rat. It is 10- to 19-fold selective compared to the closely related lactoperoxidase and thyroid peroxidase; >70-fold to a broad panel of other enzymes, ion channels, and receptors. In isolated human neutrophils, 1 μM inhibited PMA-stimulated HOCl by >90%. In rats, a plasma concentration of ~5 μM decreased the <i>in vivo</i> formation of glutathione sulphonamide (a product of the reaction of HOCl with glutathione) from <i>in situ</i> zymosan activated peritoneum neutrophils.
Safety/Tolerability	AZD5904 has been administered orally to healthy volunteers in single doses of up to 1200mg (1400mg with extended release, ER, formulation) and multiple doses of up to 325mg TID (600mg BID for 10 days with ER formulation). In total, 181 subjects have been dosed in five Phase 1 studies. No overtly drug-related adverse event has been identified, although a minimal effect on free P-Thyroxin (T4) and free P-Triiodothyronine (T3) could not be ruled out in the first multiple ascending dose study. Preclinical studies of up to 12 months duration have been performed.
Additional Information	Via both standard (TID) and extended release (BID) oral formulations, 300mg yielded blood concentrations of ~30 μM peak, ~4 μM trough, and 12 – 16 μM C _{avg} . The main route of clearance is renal, possibly via active transport. Plasma protein binding is 44%. In vitro studies indicate CYP2C19 inhibition and P-gp substrate as well as low BBB penetration.
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of foetal toxicity. The inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk benefit and the use of appropriate highly effective contraception. AZD5904 is renally cleared, thus, requiring caution and PK monitoring if dosed to subjects with impaired renal function. Proposals related to male infertility will not be considered.
Clinical Trials	
Additional Characteristics: CNS penetrance	AZD5904 has low CNS penetration and, thus, is probably not suitable for a CNS indication.
Publications	http://www.jbc.org/content/286/43/37578.full