Identification of chemical features linked to thyroperoxidase inhibition

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Disruption of maternal serum thyroid hormone (TH) adversely affects fetal neurodevelopment. Therefore, assay development within the US EPA ToxCast program is ongoing to enable screening for chemicals that may disrupt TH, in support of the Endocrine Disruption Screening Program (EDSP21). The AUR-TPO assay was recently developed to screen >1,000 ToxCast chemicals for potential thyroperoxidase (TPO) inhibition activity. TPO is critical for TH synthesis and is a known target of thyroid-disrupting chemicals. The bioactivity results from the AUR-TPO assay were used to identify chemical substructures associated with *in vitro* TPO inhibition. Substructure profiles were generated for each chemical in the ToxCast test set using the publicly-available ToxPrint 2.0 chemotypes. Chemotypes enriched among the putative TPO inhibitors were identified using a cumulative hypergeometric probability ($p < 0.01$). Of the total 729 chemotypes evaluated, 31 were overrepresented among TPO inhibitors. Examination of those 31 chemotypes revealed four basic pharmacophores that accounted for 70% of the ToxCast chemicals active in the AUR-TPO assay: aromatic alcohols, aromatic amines, thiocarbonyls and phosphothioates. Chemico-structural analysis of AUR-TPO screening results enabled the identification of chemical features that likely drive TPO inhibition in the AUR-TPO assay. This highlights the potential to identify thyroid-disrupting chemicals *in silico* using structural alerts identified by chemotype analysis and confirmed by *in vitro* testing. The pharmacophores identified using this approach also offer key insights into mechanisms of TPO inhibition, which should strengthen the development of predictive tools. *This abstract does not necessarily reflect the policy of the US EPA.*