Target Name	Dihydroorotate dehydrogenase
Target TTD ID	TTDS00059

Target Species	Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale
Chemical Type	Triazolopyrimidine derivatives
Mode of Action	Inhibitor
QSAR Model 1	$\mathrm{pIC50} = 7.95575 + 3.84989\langle \mathrm{B1_p} - 1.7\rangle - 1.28315 L_o - 0.99756\langle 0.633 - \mathrm{MR_p}\rangle + 0.744606\langle \mathrm{MR_m} - 0.605\rangle - 1.58856\langle 0.14 - \pi_m\rangle$ $n_{\mathrm{training}} = 22,\ R^2 = 0.872,\ R_a^2 = 0.859,\ F = 64.87\,(\mathrm{df}\,2,19),\ s = 0.266,\ \mathrm{PRESS} = 2.456,$ $Q^2 = 0.767,\ r^2_{\mathrm{m(LOO)}} = 0.740,\ n_{\mathrm{Test}} = 7,\ R^2_{\mathrm{pred}} = 0.767,\ r^2_{\mathrm{m(test)}} = 0.719,\ r^2_{\mathrm{m(overall)}} = 0.733.$
QSAR Model 2	$\mathrm{pIC50} = 7.47868 + 2.75262\langle \mathrm{B1_p} - 1.7\rangle - 2.22133\mathrm{B5_o} - 0.96816\langle 0.502 - \mathrm{MR_p}\rangle - 0.78873\langle 2.52 - \mathrm{B1_m}\rangle - 0.46286\langle 0.71 - \pi_p\rangle$ $n_{\mathrm{training}} = 22,\ R^2 = 0.849,\ R_a^2 = 0.833,\ F = 53.50\ (\mathrm{df}\,2,19),\ s = 0.289,\ \mathrm{PRESS} = 2.647,$ $Q^2 = 0.749,\ r^2_{\mathrm{m(LOO)}} = 0.711,\ n_{\mathrm{Test}} = 7,\ R^2_{\mathrm{pred}} = 0.824,\ r^2_{\mathrm{m(test)}} = 0.788,\ r^2_{\mathrm{m(overall)}} = 0.727.$
QSAR Model 3	$\mathrm{pIC50} = 3.9546 + 30.8661\langle \mathrm{Fo} - 0.846581\rangle - 0.1142\langle 75.893 - \mathrm{MolRef}\rangle - 0.0362\langle \mathrm{JursDPSA3} - 42.9235\rangle + 1.5690\mathrm{IursFPSA1} - 0.1898\,\mathrm{Log}P + 0.3697\langle 20.1604 - \mathrm{JursPPSA3}\rangle$ $n_{\mathrm{Training}} = 22.\ R^2 = 0.811.\ R_a^2 = 0.780.\ F = 25.74\,(\mathrm{df}\,3.18).\ s = 0.333,$ $\mathrm{PRESS} = 3.22,\ Q^2 = 0.695,\ r^2_{\mathrm{m(LOO)}} = 0.647,\ n_{\mathrm{Test}} = 7,\ R^2_{\mathrm{pred}} = 0.580,$ $r^2_{m(test)} = 0.450,\ r^2_{\mathrm{m(overall)}} = 0.618.$

QSAR Model 4	$pIC50 = 6.22659 + 2.52567\langle B1_p - 1.7\rangle - 0.524\langle 0.86 - \pi_p\rangle - 1.65359B1_o$ $- 0.02682\langle 226.01 - Vm\rangle$ $n_{Training} = 22, R^2 = 0.796, R_a^2 = 0.786, F = 78.27\ (df\ 1,20),\ s = 0.328,$ $PRESS = 2.741, Q^2 = 0.740,\ r^2_{m(LOO)} = 0.711,\ n_{Test} = 7, R^2_{pred} = 0.636,$ $r^2_{m(test)} = 0.567, r^2_{m(overall)} = 0.698.$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** The Sterimol width parameter B1 is defined as the smallest width along the Z axis. The positive regression coefficient of the spline term (B1p-1.7X) indicates that the numerical value of B1 of the para substituent of the phenyl ring should be greater than 1.7 for better DHODH inhibitory activity. The Sterimol length parameter L is defined as the maximum length along the X axis. The term L_o with negative regression coefficient indicates that to avoid detrimental interactions, the value of L should be less. Lo is the length of the substitutions at the ortho positions of the phenyl ring. The negative regression coefficient of the spline term (0.633-MR_p) indicates that molar refractivity has a negative impact in the para position of the phenyl ring when the value of MR is lower than 0.633. The positive regression coefficient of the spline term (MR_m-0.605) indicates that molar refractivity has a positive impact in the meta positions of the phenyl ring if the value of MR is higher than 0.605. The parameter π is the lipophilicity substitution constant which is a very important parameter in modeling studies. The positive regression coefficient of the spline term ($B1_p$-1.7) indicates that the numerical value of B1 for the para substituent of the phenyl ring should be greater than 1.7. The Sterimol width parameter B5 is defined as the maximum width (i.e. the maximum distance from X axis) of the substituent in the Z-Y plane (perpendicular to the X axis). The negative regression coefficient of the spline term (0.502-MR_p) indicates that molar refractivity has a negative impact in the para position of the phenyl ring when the value of MR is lower than 0.502. The negative regression coefficient of the spline term (2.52-$B1_m$) indicates that the numerical value of B1 of the meta substituents of the phenyl ring should be more than 2.52 for better DHODH inhibitory activity.

	The spline term (0.71-π_p) has a negative regression coefficient. The negative regression coefficient of the spline term indicates that the value of lipophilic substituent constant for the para substituent of the phenyl ring should be more than 0.71 for better DHODH inhibitory activity. MolRef is the atom type molar refractivity. The negative regression coefficient of the spline term (75.893-MolRef) indicates that for better DHODH inhibitory activity, the value of MolRef should be more than 75.893. JursDPSA_3 is difference in atomic charge weighted surface areas. JursFPSA_1 is fractional charged partial positive surface area. JursPPSA_3 is atomic charge weighted positive surface area. The positive regression coefficient of the spline term ($B1_p$-1.7) indicates that the numerical value of B1 at para substituent of the phenyl ring should be greater than 1.7. The spline term (0.86-π_p) has negative regression coefficient. The negative regression coefficient of the spline term indicates that the value of lipophilic substituent constants at the para position of the phenyl ring should be more than 0.86 for better DHODH inhibitory activity. Vm is a 3D spatial descriptor that defines the molecular volume inside the contact surface. The negative regression coefficient of the spline term (226.01-V_m) indicates that for better DHODH inhibitory activity.
Reference	Chemometric modeling, docking and in silico design of triazolopyrimidine-based dihydroorotate dehydrogenase inhibitors as antimalarials. *European Journal of Medicinal Chemistry* 45 (2010) 4645-4656