Target Name	Topoisomerase II
Target TTD ID	TTDS00080

Target Species	Human
Chemical Type	Benzimidazole derivatives
Mode of Action	Inhibitor
QSAR Model 1	$\log 1/C = 3.28(\pm 0.60)\mathrm{MgVol} - 4.59(\pm 1.76)$ $n = 7, \quad r^2 = 0.975, \quad s = 0.180, \quad q^2 = 0.963$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** C log *P*, calculated octanol/water partition coefficient; σ_x^+, substituents ability to delocalize a positive charge; *I*, indicator variable given for the presence (=1) of 10-OCH2O-11; MR_9, molar refractivity; *n*, number of data points; r^2 is the goodness of fit; *s*, standard deviation; q^2, goodness of prediction. MR is the molar refractivity and defined by the Lorentz–Lorenz equation: $$MR = n^2 - \frac{1}{n^2} + 2(MW/\delta)$$ where *n* = refractive index, δ = density, *MW* = molecular weight. CMR is the calculated molar refractivity. Molar refractivity (MR) has a strong correlation with the molecular polarizability. NVE (number of valence electrons) is a parameter that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule. Electronic parameters: σ, σ^-, σ^+, and σ^* that account for specific electronic effects of substituents on a parent molecule. MgVol is the molar volume calculated by using the method of McGowan. I is an indicator variable that takes the value of 1 or 0 for structural features and cannot be defined by the normal parameters. *n* is the number of data points, *r* is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness

	of prediction and s is the standard deviation.
Reference	Understanding topoisomerase I and II in terms of QSAR. *Bioorganic & Medicinal Chemistry* 13 (2005) 1059–1067

Target Species	Human
Chemical Type	1,4-naphthoquinone derivatives
Mode of Action	Inhibitor
QSAR Model 1	$\log 1/C = -52.4(\pm 26.8)\mathrm{MgVol} + 10.39(\pm 5.45) \times \mathrm{MgVol}^2 + 67.4(\pm 32.8)$ $n = 7, \quad r^2 = 0.897, \quad s = 0.334, \quad q^2 = 0.630, \quad \text{optimum MgVol} = 2.52(2.46\text{–}2.63)$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** C log *P*, calculated octanol/water partition coefficient; σ_x^+, substituents ability to delocalize a positive charge; *I*, indicator variable given for the presence (=1) of 10-OCH2O-11; MR_9, molar refractivity; *n*, number of data points; r^2 is the goodness of fit; *s*, standard deviation; q^2, goodness of prediction. MR is the molar refractivity and defined by the Lorentz–Lorenz equation: $$MR = n^2 - \frac{1}{n^2} + 2(MW/\delta)$$ where *n* = refractive index, δ = density, *MW* = molecular weight. CMR is the calculated molar refractivity. Molar refractivity (MR) has a strong correlation with the molecular polarizability. NVE (number of valence electrons) is a parameter that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule. Electronic parameters: σ, σ^-, σ^+, and σ^* that account for specific electronic effects of substituents on a parent molecule. MgVol is the molar volume calculated by using the method of McGowan. I is an indicator variable that takes the value of 1 or 0 for structural features and cannot be defined by the normal parameters. *n* is the number of data points, *r* is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction and s is the standard deviation.

Reference	Understanding topoisomerase I and II in terms of QSAR. *Bioorganic & Medicinal Chemistry* 13 (2005) 1059–1067

Target Species	Human
Chemical Type	Quinolone derivatives
Mode of Action	Inhibitor
QSAR Model 1	$\log 1/C = -0.57(\pm 0.43)\sigma^{-} + 1.31(\pm 0.32)I + 5.06(\pm 0.20)$ $n = 16, \quad r^2 = 0.912, \quad s = 0.263, \quad q^2 = 0.865$
QSAR Model 2	$\log 1/C = 2.63(\pm 1.31)\mathrm{CMR} - 12.07(\pm 9.95)$ $n = 5, \quad r^2 = 0.932, \quad s = 0.339, \quad q^2 = 0.845$
QSAR Model 3	$\log 1/C = 12.38(\pm 4.11)\mathrm{CMR} - 0.65(\pm 0.22)\mathrm{CMR}^2 - 0.91(\pm 0.21)I - 57.63(\pm 19.51)$ $n = 18, \quad r^2 = 0.901, \quad s = 0.167, \quad q^2 = 0.847, \quad \text{optimum CMR} = 9.48(9.35\text{–}9.60)$
QSAR Model 4	$\log 1/C = -2.33(\pm 1.01)\mathrm{C}\log P - 1.33(\pm 0.88)$ $n = 6, \quad r^2 = 0.910, \quad s = 0.281, \quad q^2 = 0.800$

Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** *I*, presence of OH at X; *n*, number of data points; r^2 is the goodness of fit; *s*, standard deviation; q^2, goodness of prediction; CMR, calculated molar refractivity; C log *P*, calculated octanol/water partition coefficient; σ_x^+, substituents ability to delocalize a positive charge; *I*, indicator variable given for the presence (=1) of 10-OCH2O-11; MR_9, molar refractivity; *n*, number of data points; r^2 is the goodness of fit; *s*, standard deviation; q^2, goodness of prediction. MR is the molar refractivity and defined by the Lorentz–Lorenz equation: $$MR = n^2 - \frac{1}{n^2} + 2(MW/\delta)$$ where *n* = refractive index, δ = density, *MW* = molecular weight. CMR is the calculated molar refractivity. Molar refractivity (MR) has a strong correlation with the molecular polarizability. NVE (number of valence electrons) is a parameter that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule. Electronic parameters: σ, σ^-, σ^+, and σ^* that account for specific electronic effects of substituents on a parent molecule. MgVol is the molar volume calculated by using the method of McGowan. I is an indicator variable that takes the value of 1 or 0 for structural features and cannot be defined by the normal parameters. *n* is the number of data points, *r* is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction and s is the standard deviation.
Reference	Understanding topoisomerase I and II in terms of QSAR. *Bioorganic & Medicinal Chemistry* 13 (2005) 1059–1067

Target Species	Human
Chemical Type	Fused heterocycles
Mode of Action	Inhibitor
QSAR Model 1	$\log 1/C = -0.57(\pm 0.15)\mathrm{C}\log P - 0.02(\pm 0.005) \times \mathrm{NVE} + 8.02(\pm 1.08)$ $n = 13, \quad r^2 = 0.874, \quad s = 0.215, \quad q^2 = 0.781$

QSAR Model 2	$\log 1/C = 1.04(\pm 0.27)\mathrm{CMR} - 1.58(\pm 0.40) \times \log(\beta \times 10^{\mathrm{CMR}} + 1) - 3.24(\pm 1.93)$ $n = 11, \quad r^2 = 0.926, \quad s = 0.156, \quad q^2 = 0.902, \quad \text{optimum CMR} = 8.48,$ $\log \beta = -8.20$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** *I*, presence of OH at X; *n*, number of data points; r^2 is the goodness of fit; *s*, standard deviation; q^2, goodness of prediction; CMR, calculated molar refractivity; C log *P*, calculated octanol/water partition coefficient; σ_x^+, substituents ability to delocalize a positive charge; *I*, indicator variable given for the presence (=1) of 10-OCH2O-11; MR_9, molar refractivity; *n*, number of data points; r^2 is the goodness of fit; *s*, standard deviation; q^2, goodness of prediction. MR is the molar refractivity and defined by the Lorentz–Lorenz equation: $$MR = n^2 - \frac{1}{n^2} + 2(MW/\delta)$$ where *n* = refractive index, δ = density, *MW* = molecular weight. CMR is the calculated molar refractivity. Molar refractivity (MR) has a strong correlation with the molecular polarizability. NVE (number of valence electrons) is a parameter that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule. Electronic parameters: σ, σ^-, σ^+, and σ^* that account for specific electronic effects of substituents on a parent molecule. MgVol is the molar volume calculated by using the method of McGowan. I is an indicator variable that takes the value of 1 or 0 for structural features and cannot be defined by the normal parameters. *n* is the number of data points, *r* is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction and s is the standard deviation.
Reference	Understanding topoisomerase I and II in terms of QSAR. *Bioorganic & Medicinal Chemistry* 13 (2005) 1059–1067

Target Species	Human
Chemical Type	Benzophenazines
Mode of	Dual Inhibitor toward Topoisomerase I/II

Action	
QSAR Model 1	$-\log(IC_{50}) = -0.79(\pm0.12)\cdot \text{Mor07m} - 1.19(\pm0.25)\cdot \text{Mor11m} + 3.80(\pm0.52)\cdot \text{Mor16m} + 10.13(\pm2.00)\cdot \text{Mor12v} - 2.15(\pm0.62)\cdot \text{Mor26v} - 0.28(\pm0.06)\cdot \text{Mor03e} - 0.72(\pm0.27)\cdot \text{Mor24e} - 9.50(\pm1.91)\cdot \text{Mor12p} + 3.38(\pm0.55)\cdot \text{Mor18p} + 1.25(\pm0.52)$ $N = 64,\ R^2 = 0.726,\ S = 0.321,\ F = 15.946\ \ p < 10^{-5},\ \ \rho = 6.4,\ \ \text{AIC} = 0.141,\ \text{FIT} = 0.986,$ $q^2_{\text{CV-LOO}} = 0.619,\ \ S_{\text{CV-LOO}} = 0.379,\ q^2_{\text{CV-LGO}} = 0.594,\ S_{\text{CV-LGO}} = 0.391,$
QSAR Model 2	$-\log(IC_{50}) = -0.69(\pm0.12)\cdot \text{Mor07m} - 1.27(\pm0.26)\cdot \text{Mor11m} + 3.92(\pm0.54)\cdot \text{Mor16m} + 3.13(\pm0.57)\cdot \text{Mor18p} - 0.26(\pm0.06)\cdot \text{Mor03e} - 2.37(\pm0.65)\cdot \text{Mor26v} + 9.18(\pm2.08)\cdot \text{Mor12v} - 8.37(\pm1.97)\cdot \text{Mor12p} + 0.73(\pm0.51)$ $N = 64,\ R^2 = 0.691,\ S = 0.338,\ F = 15.350,\ p < 10^{-5},\ \rho = 7.11,\ \text{AIC} = 0.152,\ \text{FIT} = 0.\ 959,$ $q^2_{\text{CV-LOO}} = 0.591,\ \ S_{\text{CV-LOO}} = 0.389,\ q^2_{\text{CV-LGO}} = 0.579,\ S_{\text{CV-LGO}} = 0.423.$
QSAR Model 3	$-\log(IC_{50}) = -0.64(\pm0.12)\cdot \text{Mor07m} - 1.59(\pm0.28)\cdot \text{Mor11m} + 4.49(\pm0.55)\cdot \text{Mor16m} + 3.10(\pm0.56)\cdot \text{Mor18p} - 0.26(\pm0.06)\cdot \text{Mor03e} - 1.59(\pm0.67)\cdot \text{Mor26v} + 12.38(\pm2.23)\cdot \text{Mor12v} - 11.61(\pm2.13)\cdot \text{Mor12p} + 0.55(\pm0.19)\cdot \text{Mor06v} - 0.57(\pm0.28)\cdot \text{Mor14p} - 0.02(\pm0.71)$ $N = 64,\ R^2 = 0.701,\ S = 0.329,\ F = 18.8,\ p < 10^{-5},\ \rho = 8.0,\ \text{AIC} = 0.114,\ \text{FIT} = 1.162,$ $q^2_{\text{CV-LOO}} = 0.620,\ \ S_{\text{CV-LOO}} = 0.372,\ \ q^2_{\text{CV-LGO}} = 0.593,\ S_{\text{CV-LGO}} = 0.391$
QSAR Model 4	$-\log(IC_{50}) = -0.21(\pm0.04)\cdot \Omega^1\text{Mor07m} - 0.22(\pm0.04)\cdot \Omega^2\text{Mor11m} + 0.16(\pm0.04)\cdot \Omega^3\text{Mor16m} - 0.14(\pm0.04)\cdot \Omega^4\text{Mor26v} - 0.17(\pm0.04)\cdot \Omega^5\text{Mor03e} - 0.20(\pm0.04)\cdot \Omega^6\text{Mor12p} + 0.14(\pm0.04)\cdot \Omega^7\text{Mor18p} - 0.08(\pm0.04)\cdot \Omega^8\text{Mor24e} + 0.04(\pm0.04)\cdot \Omega^9\text{Mor12v} - 2.24(\pm0.04)$ $N = 64,\ R^2 = 0.727,\ S = 0.321,\ F = 15.946,\ p < 10^{-5},\ \rho = 6.4,\ \text{AIC} = 0.120,\ \text{FIT} = 0.991,$ $q^2_{\text{CV-LOO}} = 0.619,\ \ S_{\text{CV-LOO}} = 0.379.$
QSAR Model 5	$-\log(IC_{50}) = -0.21(\pm0.04)\cdot \Omega^1\text{Mor07m} - 0.22(\pm0.04)\cdot \Omega^2\text{Mor11m} + 0.16(\pm0.04)\cdot \Omega^3\text{Mor16m} - 0.14(\pm)\cdot \Omega^4\text{Mor26v} - 0.17(\pm0.04)\cdot \Omega^5\text{Mor03e} - 0.20(\pm0.04)\cdot \Omega^6\text{Mor12p} + 0.14(\pm0.04)\cdot \Omega^7\text{Mor18p} - 2.24(\pm0.04)$ $N = 64,\ R^2 = 0.701,\ S = 0.329,\ F = 18.8,\ p < 10^{-5},\ \rho = 8.0,\ \text{AIC} = 0.114,\ \text{FIT} = 1.162,$ $q^2_{\text{CV-LOO}} = 0.620,\ \ S_{\text{CV-LOO}} = 0.372,\ \ q^2_{\text{CV-LGO}} = 0.593,\ S_{\text{CV-LGO}} = 0.391$

QSAR Model 6	$$-\log(IC_{50}) = -0.21(\pm0.03)\cdot\Omega^{1}\text{Mor07m} - 0.26(\pm0.03)\cdot\Omega^{2}\text{Mor11m} + 0.14(\pm0.03)\cdot\Omega^{3}\text{Mor16m} - 0.11(\pm0.03)\cdot\Omega^{4}\text{Mor26v} - 0.16(\pm0.03)\cdot\Omega^{5}\text{Mor03e} - 0.18(\pm0.03)\cdot\Omega^{6}\text{Mor12p} + 0.17(\pm0.03)\cdot\Omega^{7}\text{Mor18p} - 2.21(\pm0.03)$$ $N = 58,\ R^2 = 0.822,\ S = 0.246,\ F = 33.001,\ p < 10^{-5},\ \rho = 8.0,\ \text{AIC} = 0.080,\ \text{FIT} = 2.158,$ $q^2_{\text{CV-LOO}} = 0.761,\ S_{\text{CV-LOO}} = 0.286,\ q^2_{\text{CV-LGO}} = 0.731,\ S_{\text{CV-LGO}} = 0.304.$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** N is the number of compounds included in the model, R^2 is the square of the correlation coefficient, S is the standard deviation of the regression, F is the Fisher ratio, p is the significance of the model, and ρ is the ratio between number of cases and adjustable parameter numbers. AIC is the Akaike's information criterion and FIT is the Kubinyi function. Furthermore, we calculated the validation parameters shown previously like cross-validated squared regression coefficient q^2 and the standard deviation Scv of the LOO and LGO procedures. Mor07m, Mor11m and Mor16m, signal 07, 11 and 16 respectively, weighted by atomic masses; Mor12v and Mor26v, signal12 and 26 respectively, weighted by atomic van der Waals volumes; Mor03e and Mor24e, signal 03 and 24 respectively, weighted by atomic Sanderson electronegativities, Mor12p and Mor18p, signal 12 and 18 respectively, weighted by atomic polarizabilities; N, number of compounds included in the model; R^2, square of correlation coefficient; S, standard deviation of the regression; F, Fisher ratio; p, significance of the model; ρ, ratio between number of cases and adjustable parameter numbers; AIC, Akaike's information criterion; FIT, Kubinyi function; q^2_{CV-LOO} and q^2_{CV-LGO}, cross-validated squared regression coefficient of the LOO and LGO procedures respectively; $S_{\text{CV-LOO}}$ and $S_{\text{CV-LGO}}$, cross-validated standard deviation of the LOO and LGO procedures respectively
Reference	QSAR studies about cytotoxicity of benzophenazines with dual inhibition toward both topoisomerases I and II: 3D-MoRSE descriptors and statistical considerations about variable selection. *Bioorganic & Medicinal Chemistry* 14 (2006) 7347–7358