questered into two subsets containing electron-releasing and electron-attracting substituents, respectively (227).

5.2.4 Inhibition of Growth of T. pyriformis by Phenols (using σ) (227)

$$\begin{aligned}\text{Log } 1/C &= 0.64(\pm 0.04)\text{Clog } P \\ &+ 0.61(\pm 0.12)\sigma + 1.84(\pm 0.13)\end{aligned} \tag{1.102}$$

$$n = 119, \quad r^2 = 0.896, \quad s = 0.265$$

5.2.5 Inhibition of Growth of T. *pyriformis* by Electron-Releasing Phenols (227)

$$\begin{aligned}\text{Log } 1/C &= 0.66(\pm 0.05)\text{Clog P} \\ &+ 1.63(\pm 0.15)\end{aligned} \tag{1.103}$$

$$n = 44, \quad r^2 = 0.946, \quad s = 0.182$$

5.2.6 Inhibition of Growth of T. *pyriformis* by Electron-Attracting Phenols (227)

$$\begin{aligned}\text{Log } 1/C &= 0.63(\pm 0.07)\text{Clog P} \\ &+ 0.54(\pm 0.16)\sum\sigma \\ &+ 1.92(\pm 0.18)\end{aligned} \tag{1.104}$$

$$n = 100, \quad r^2 = 0.836, \quad s = 0.327$$

There is excellent agreement between QSAR 1.101 and QSAR 1.104, in terms of the importance of hydrophobicity and electron demand of the substituents: the coefficients with Clog P are similar and there is a good correspondence between E_{LUMO} and σ. Nevertheless, separation of the phenols into subsets, based on their electronic attributes, indicates that different mechanisms of toxicity might be operative in this organism, a phenomenon that has been duplicated in mammalian cells (228). In a recent extension of toxicity studies on aromatics, Cronin and Schultz used a two-parameter or response-surface approach to define toxicity (229). In addition, indicator variables and group counts were included to broaden the applicability of the approach. An excellent comparison of the different modeling approaches (MLR, PLS, and Bayesian-regularized neural networks) in QSAR is also made (229).

5.2.7 Inhibition of Growth of T. pyriformis by Aromatic Compounds (229)

$$\begin{aligned}\text{Log } 1/\text{IgC}_{50} &= 0.633\log P - 0.526E_{\text{LUMO}} \\ &+ 0.721I_{2,4\text{ AP}} - 1.61I_{\text{strong acid}} \\ &+ 0.314\sum\text{H-donor} - 1.39\end{aligned} \tag{1.105}$$

$$n = 268, \quad r^2 = 0.780, \quad s = 0.393$$

The indicator variables $I_{2,4}$ ▬ and $I_{\text{strong acid}}$ suggest that 2- and 4-amino-substituted phenols enhance toxicity, whereas strong acids decrease toxicity, respectively. The H-bond donor parameter may be correcting for the added potency of amino phenols. The low r^2 may be attributed to inherent variability in biological data and to the commingling of data from four different studies. The wide variety of compounds with different toxicity mechanisms, present in this combined study, would also be a contributing factor to the low r^2. Overall, this regression-based approach shows adequate predictability and is transparent, thus aiding in mechanistic interpretation.

5.3 Interactions *In Vivo*

The paucity of QSAR studies in whole animals is understandable in terms of the costs, the heterogeneity of the biological data, and the complexity of the results. Nevertheless, in the few studies that have been done, excellent QSAR have been obtained, despite the small number of subjects in the data set (164). One particular example is insightful. The renal and nonrenal clearance rates of a series of 11 β-blockers, including bufuralol, tolamolol, propranolol, alprenolol, oxprenolol, acebutol, timolol, metoprolol, prindolol, atenolol, and nadolol were measured (230). The following QSAR were formulated using those data (164).

5.3.1 Renal Clearance of β-Adrenoreceptor Antagonists

$$\begin{aligned}\text{Log k} &= -0.42(\pm 0.12)\text{Clog P} \\ &+ 2.35(\pm 0.24)\end{aligned} \tag{1.106}$$

$$n = 10, \quad r^2 = 0.888, \quad s = 0.185$$