

Comparative QSAR Study of Tyrosine Kinase Inhibitors

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I. Introduction

It is an accepted fact today that “there is a critical need for new targets, in addition to DNA, for anti-cancer drug development”.¹ Traditionally anticancer drugs have been targeted to inhibit DNA synthesis and function or the intracellular organelles required for successful segregation of the chromosomes during mitosis. Regardless of which mechanism such compounds employ, it appears that the drugs can ultimately work by stimulating self-destructive (apoptotic) pathways within the tumor. Unfortunately, such *cytotoxic* approaches appear to be limited both in the degree of efficacy of cell killing that they can induce and in the amount of selectivity they can show between transformed, i.e., tumor cells and normal cells, especially in organs which require rapid cellular proliferation for full potency. Drug treatment does offer some success against some cancers; however, the majority of human cancers remain resistant, and there is urgent need for more effective anticancer drugs. A new approach is to use the signaling pathways that mediate the effects of growth factors and oncogenes on cell proliferation as molecular targets for anticancer drug development (an oncogene is any gene that encodes a protein able to transform cells in culture or to induce cancer in animals. Oncogenes are usually derived from normal cellular

genes, either by mutation or by misregulated expression). Such approaches might simply attenuate the effect of these aberrant signaling pathways and prevent the tumors from growing further, in which case they would be said to be cytostatic approaches, or they might induce tumor cell death and then they would be cytotoxic. The belief that kinases frequently act like oncogenes explains much of the commercial interest in the phosphorylation and dephosphorylation involved in signal transduction, the subject of this thematic issue of *Chemical Reviews*.

Five types of proteins participate in growth control of mammalian cells: growth factors, growth factor receptors, intracellular transducers, nuclear transcription factors, and cell cycle control proteins. Genes for each type of growth-controlling protein have given rise to one or more oncogenes.

When a growth factor binds to its cognate receptor, usually, but not always, on the cell surface, the later sends a growth signal to the cell nucleus through one or more signal transduction pathways.^{2a} Some cell surface receptors have an extracellular ligand binding domain attached to an integral protein tyrosine kinase (PTK) in their cytoplasmic domain. These receptors transmit the growth signal by phosphorylating tyrosine residues on themselves as well as one or more target proteins, thus initiating a cascade of events. The genes for such receptors become oncogenes when they are mutated in such a way that the receptor remains active even in the absence of its bound ligand or when the receptors are overexpressed on the cell surface, over-amplifying the intrinsic, weak, growth signal in the tissue concerned. A third possibility is that the cell type will start to express itself as the ligand for the growth factor, causing an autocrine loop, which leads to uncontrolled proliferation. All three of these cases can lead to abrogation of the normal, exclusive, control of intracellular proliferative activity by secretion of growth factors from distant cells (paracrine) or neighboring cells (metacrine). Once the inappropriate signaling from the PTK reaches the nucleus, it stimulates cellular proliferation, independent of external control, and a cell containing a constitutively activated or overexpressed oncogene grows independently of the factors that are supposed to regulate its growth.

The receptors having integral PTK are known as receptor tyrosine kinases (RTKs). RTKs form a large and important class of cell-surface receptors whose

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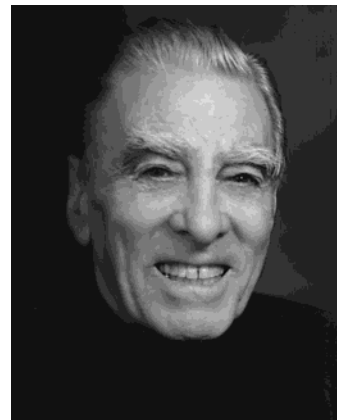


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Rajni Garg received her M.Sc. degree in Chemistry (1984) from Meerut University and M.Phil. (1988) degree from Delhi University, India. Her M.Phil. dissertation work was on peptide synthesis. She was a faculty member in the Chemistry Department of Birla Institute of Technology and Science, Pilani, India, from 1991 to 1996, where she taught organic and physical chemistry. She received her Ph.D. degree in 1996 under the supervision of Professor S. P. Gupta. Her doctoral work was on QSAR studies on anti-HIV agents. In February 1997, she joined Professor Corwin Hansch as a postdoctoral researcher, and she is currently involved in building a C-QSAR databank. Her research interests include QSAR and computer-assisted drug design.

ligands are soluble or membrane-bound peptide/protein,^{2b} including insulin and epidermal growth factor. Binding of a ligand to this type of receptor stimulates the receptor's protein tyrosine kinase activity, which subsequently stimulates a signal-transduction cascade leading to changes in cellular physiology and/or patterns of gene expression. RTK signaling pathways have a wide spectrum of functions including regulation of cell proliferation and differentiation, promotion of cell survival, and adjustments in cellular metabolism. These pleiotropic effects allow activating mutations in growth factor systems to play a major role in carcinogenesis.



Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in Organic Chemistry from New York University in 1944. After working with the DuPont Company, first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. Dr. Hansch is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.

All the RTKs compromise an extracellular domain controlling a ligand-binding site, a single hydrophobic transmembrane α -helix, and a cytosolic domain that includes a region with protein tyrosine kinase activity. Although most RTKs are monomeric proteins, some such as the insulin receptor are covalent dimers (strictly speaking $\alpha\alpha\beta\beta$ heterotetramers in the case of insulin receptor), and it appears likely that many of the "monomers" exist as inactive dimers or higher oligomers even in the absence of ligand. Binding of ligand causes most RTKs to unequivocally dimerize; the PTK of each receptor monomer then phosphorylates a distinct set of tyrosine residues in the cytosolic domain of its dimer partner, a process termed autophosphorylation. The phosphotyrosine residues of activated RTKs play a crucial role in transducing hormone signals to intracellular signaling molecules.

Two different classes of proteins associate with the cytosolic domain of activated RTKs: Adapter proteins (e.g., GRB2) that couple the activated receptors to other signaling molecules but have no intrinsic signaling properties and enzymes involved in signaling pathways. These proteins bind to different phosphotyrosine residues on RTKs via a conserved polypeptide domain called the Src homology 2 (SH2) domain. PTKs are enzymes that transfer the γ -phosphate of ATP to specific tyrosine residues in a wide variety of functional proteins. Nearly 100 different PTKs have been sequenced so far,³ and estimates of over 1000 or more human PTKs have been proposed.⁴ A potential role of PTKs in tumorigenesis is evident by their ability to transform normal cells to a neoplastic phenotype when expressed in a mutated, unregulated form or to an abnormally high level. Indeed, one-half of the proto-oncogenes identified to date encode for proteins having PTK activity.^{5,6} This potential to transform normal cells is compatible with existing data implicating tyrosine phosphorylation and des-

phosphorylation as events ultimately associated with growth, regression, and mitogenesis.^{7–13}

Further, it is well accepted that tumor cells have an absolute requirement of a persistent supply of blood vessels to nourish their growth and to facilitate metastasis.^{14a,b} The angiogenic cascade leading to tumor vascularization can be subdivided into two general phases: the prevascular phase referred to as the “angiogenic switch” and the vascular phase.¹⁵ The transformation of tumor cells to an angiogenic phenotype is a key event in the progression to malignant disease.^{14c,16–21} In the absence of supporting vasculature, the rate of diffusion of nutrients and wastes from surroundings limits tissue growth to that of approximately 1–2 mm in diameter.²² However, once the switch to an angiogenic phenotype has occurred, avascular tumors then can acquire their own blood supply to support a rapid growth once tumor cells undergo transformation to an angiogenic phenotype. These malignant cells in turn induce phenotypical changes in endothelial cells as well as other cell types^{23–25} to initiate the process of neovascularization.²⁶ This angiogenic switch is largely mediated through the angiogenic growth factors, which can induce the required migration, proliferation, and morphological changes in the endothelial cells destined to produce the tumor neovasculature. All of the known major angiogenic growth factors are ligands for RTKs. Thus, the pursuit of antiangiogenic agents capable of blocking tumor vascularization represents an attractive strategy for controlling malignant tumor growth. Thus, the fundamental role that PTKs appear to play in cancer has made them attractive therapeutic targets and has provided the impetus for an extensive effort to develop specific inhibitors of these enzymes as chemotherapeutic agents.^{27–31}

One of the more intensely studied RTKs is the epidemic growth factor receptor (EGFR or erbB) PTK. It belongs to the larger family of type I of RTKs which contains four members: EGFR kinase (c-erbB-1 gene product), the p185^{erbB2} (c-erbB-2 gene product), and the recently identified c-erbB-3 and c-erbB-4 gene products.^{32–36} The EGFR family normally has to dimerize to become active TKs. This can be achieved by dimerizing with themselves (homodimerization) or with the other family members (heterodimerization).³⁷ EGF and transforming growth factor- α (TGF- α) are natural ligands of EGFR.³⁸ Others are amphiregulin (AR),³⁹ epiregulin,⁴⁰ cripto,⁴¹ betacellulin,⁴² and heregulin/neuregulin.⁴³ These ligands under the right cellular circumstances can lead to EGFR-EGFR and c-erbB-4-c-erbB-4 homodimers and all six of the possible heterodimers. Although c-erbB-3 does not appear to have a functional kinase domain, its heterodimers with the other three c-erbBs are active kinases, but understandably no ligand for c-erbB-3 homodimers has yet been found. Nor for that matter is there a ligand for c-erbB-2 homodimers, although with several ligands c-erbB-2 heterodimers seem to be the preferred species induced.

EGFR is overexpressed in numerous tumors,⁴⁴ including those derived from brain, lung, bladder,

colon, breast, head, and neck. Such overexpression has been correlated with poor prognosis in some of these diseases. The gene product is frequently mutated in the extracytoplasmic domain of the receptor in gliomas,⁴⁵ prostate cancer,⁴⁶ breast cancer,⁴⁷ and non-small-cell lung cancer.⁴⁸ This mutation makes the receptor constitutively active.⁴⁹ In addition, the receptor need not be overexpressed or mutated since the ligands for the receptor (EGF or TGF- α) can be produced within the same cancerous tissues or cell that expresses EGFR. This suggests that paracrine or autocrine loops stimulate hyperproliferation as in prostate cancer,⁵⁰ head and neck cancer,⁵¹ ovarian cancer,⁵² small-cell lung cancer,⁵³ and bladder cancer.⁵⁴ Furthermore, both oncogenic Ras mutations^{55a} and ionizing radiation^{55b} have been shown to stimulate EGFR autocrine loops by upregulation of TGF- α . Several mitogenic hormones, such as bradykinin,^{56a} thrombin,^{56b} and thromboxane,^{56c} which bind to GPCRs, have also been shown to lead to activation of EGFR via a variety of different mechanisms,^{56d} and blockade of EGFR can abrogate their mitogenic activity.^{56e} EGFR hyperactivation has also been implicated in other diseases including polycystic kidney disease,^{57a} psoriasis,^{57b,c} and asthma.^{57d}

Since in many types of proliferative diseases the phosphorylation event mediated by EGFR kinases is a necessary signal for cell division to occur and since the hyperactivation of these kinases has been associated with these diseases, an inhibitor that inhibits EGFR TK has potential therapeutic value. Such agents have been extensively studied, especially in the pharmaceutical industry, as potential anticancer agents.

Inhibitors for several other receptor and nonreceptor TKs have been published in the past few years, and more are claimed in patent applications. The most frequently published upon TK targets of inhibitors (after EGFR) are platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and insulin-like growth factor-I receptor (IGR-IR). Among the purley intracellular TKs are Abl and the Src family TKs. Experimental evidence has shown that VEGF and its cognate receptor tyrosine kinases, VEGF-R1 (Flt-1) and VEGF-R2 (Flk-1), play direct roles in tumor angiogenesis by promoting endothelial cell proliferation and vascular permeability.⁵⁸ Importantly, VEGF-R2 has been shown to be expressed selectively in endothelial cells.⁵⁹

In addition, studies have indicated that FGF, PDGF, and their cognate RTKs may play a direct or indirect role in the tumor angiogenic process. For instance, FGF was found to be a mitogen of different cell types including vascular endothelial cells and fibroblasts and, in some cases, may induce the expression of VEGF.⁶⁰ In vitro angiogenesis assays have indicated that both VEGF and FGF cooperate during new blood vessel development.⁶¹ PDGF has been shown to stimulate the growth of pericytes and fibroblast like cells which have been shown to be required for the formation of the capillaries during

angiogenesis. Additionally, PDGF has been shown to play a role in angiogenesis leading to up regulation of VEGF expression.⁶⁰ Further, both FGF and PDGF may be involved in the hypothesized "angiogenic switch" following VEGF signaling during early stages of tumor growth.⁶²

The cytoplasmic protein p60^{c-Src} (c-Src) is a ubiquitous nonreceptor TK which is overexpressed and/or activated in many types of tumors,⁶³ including colon^{64,65} and small and non-small-cell lung cancer,⁶⁶ neuroblastoma,⁶⁷ and breast cancer.⁶⁸ In the latter case, 70% of the elevation in TK activity has been attributed to c-Src. The protein is also involved in oncogenic signal transduction by the RTKs EGFR and PDGF- β receptor.⁶⁹ Hence, c-Src has been suggested as an important anticancer target. A recent crystal structure determination of a fragment of human c-Src containing regulatory and kinase domains has been published.^{70a} c-Src is the founder member of a large family of NRTKs, the Src family, of which at least 10 are known.^{70b} Most family members are mainly expressed in cells of the immune system, where they appear to be very important in many aspects of immune cell signaling, and as a result there have been extensive studies of inhibitors of several Src family members, especially Lck and Fyn, as immunomodulatory agents.

A number of compounds have been studied to find their inhibitory activities against these PTKs. In this work, we have tried to rationalize their biological activities using QSAR.

II. Methods and Materials

The inhibitory activity of the various series studied for the different tyrosine kinases have been taken from the literature. Reference is mentioned with the respective data sets. The activity is expressed in molar concentration, log1/*C*. I₅₀ or IC₅₀ is the 50% inhibition concentration. The QSAR have been divided into five groups according to the type of tyrosine kinase.

All the physicochemical parameters were auto-loaded from C-QSAR database, and the regression analysis was executed with the C-QSAR program.⁷¹ To understand in detail the utility of C-QSAR program in correlation analysis, see refs 72–74. The program includes our commonly used substituent parameters.⁷³

The parameters used in this report have been discussed in detail along with their applications.⁷⁴ Here we provide a brief definition. Clog *P* is the calculated⁷⁵ log of octanol/water partition coefficient. It is for the neutral form of the molecules.

Molar refractivity is defined as follows

$$MR = \left(\frac{n^2 - 1}{n^2 + 2} \right) \left(\frac{MW}{d} \right)$$

where *n* is the refractive index, MW is the molecular weight, and *d* is the density of the substance. Since there can be little variation in *n*, MR is a measure of volume with a correction for polarizability. We have scaled our values by 0.1. MR can be used for a

Table 1. I₅₀ of 2-(*X*-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (**I**)⁷⁶

no.	substituent X	log 1/ <i>C</i>			Clog <i>P</i>
		obsd	calcd (eq 1)	Δ	
1	H	6.59	6.58	0.00	5.01
2	3-Br	6.17	6.23	-0.05	5.88
3	4-Me	6.32	6.38	-0.06	5.51
4	2-OMe ^a	6.18	6.61	-0.43	4.94
5	3-OMe ^a	7.52	6.61	0.91	4.94
6	4-OMe	6.66	6.61	0.05	4.94
7	3-OH	6.82	6.85	-0.03	4.35
8	3-CH ₂ OH	7.05	7.01	0.04	3.98
9	3-Me,4-OMe	6.60	6.41	0.19	5.44
10	3,5-di-OMe	6.48	6.62	-0.14	4.91
11	4-(CH ₂) ₃ CO ₂ C ₂ H ₅	6.16	6.15	0.00	6.06

^a Data points not included in deriving equation.

substituent or for the whole molecule. MgVol is the molar volume calculated by the method of McGowan. B1, B5, and *L* are Verloop's sterimol parameters. B1 is largely a measure of the width of the first atom of a substituent. B5 is an attempt to define the overall volume, and *L* is the length of the substituent moiety.

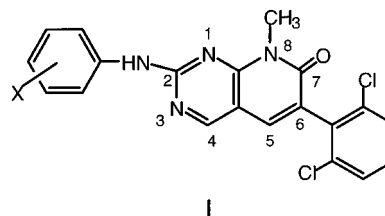
The electronic parameters σ , σ^+ , and σ^- apply to the substituent effects on aromatic systems, and σ^* and σ_I are the measures of the field/inductive effect and are normally used with the unconjugated systems. They are highly collinear, but sometimes one gives a bit better result than the others. The indicator variable, *I*, is assigned the value of 1 or 0 for special features with special effects that cannot be parameterized and has been explained wherever used.

In the QSAR equations, *n* is the number of data points, *r*² is the square of the correlation coefficient, *q*² is the measure of quality of fit, and *s* is the standard deviation. The number in the parenthesis are for 95% confidence intervals. Also listed is the Clog *P* range for each set of congeners.

III. Results and Discussion

A. Inhibitors of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase

I₅₀ of 2-(*X*-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (**I**) (Table 1)⁷⁶



$$\log 1/C = -0.41(\pm 0.12)\text{Clog } P + 8.63(\pm 0.63) \quad (1)$$

$$n = 9, r^2 = 0.901, q^2 = 0.860, s = 0.099, \text{Clog } P = 3.98-6.06$$

Outliers: 2-OMe; 3-OMe

Klutchko et al.⁷⁶ reported the inhibitory activity of analogues of 2-(*X*-phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones. The various

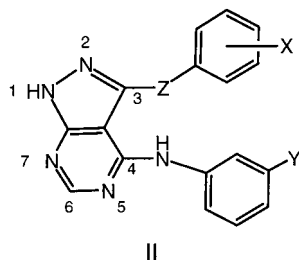
Table 2. I_{50} of 3-[Z-(X-Phenyl)]-4-(3-Y-phenylamino)pyrazolo[3,4-d]pyrimidines (II)³²

no.	substituents			log 1/C			Clog P	π'_Y
	X	Y	Z	obsd	calcd (eq 2)	Δ		
1	H	H	NH	7.24	7.42	-0.19	5.46	0.00
2	3-Cl	H	NH	7.08	7.11	-0.03	6.19	0.00
3	3-Cl	Cl	NH	7.48	7.47	0.02	6.92	-1.63
4	3-Cl	3-Br	NH ^a	6.89	7.40	-0.52	7.07	-1.63
5	3-Cl	3-Me	NH	6.89	6.72	0.17	6.69	0.43
6	4-OMe	3-Cl	NH	7.52	7.81	-0.29	6.12	-1.63
7	4-OH	3-Cl	NH	8.10	8.07	0.03	5.52	-1.63
8	3-OMe	3-Cl	NH	8.10	7.81	0.29	6.12	-1.63
9	3-OH	3-Cl	NH ^a	9.00	8.07	0.93	5.52	-1.63
10	4-NH ₂	3-Cl	NH	8.30	8.31	-0.01	4.96	-1.63
11	4-NMe ₂	3-Cl	NH	7.54	7.71	-0.17	6.36	-1.63
12	H	3-Cl	NHCH ₂	8.16	8.01	0.15	5.66	-1.63
13	3-Cl	3-Cl	NHCH ₂	7.59	7.70	-0.12	6.37	-1.63
14	3-OMe	3-Cl	NHCH ₂	8.10	8.05	0.05	5.58	-1.63
15	4-OMe	3-Cl	NHCH ₂	8.16	8.05	0.11	5.58	-1.63

^a Data points not included in deriving equation.

derivatives were obtained by different X-substituents (Table 1). They were tested for their ability to inhibit phosphorylation of a synthetic glutamate-tyrosine polymer by recombinant (human) EGFR-TK. We obtained eq 1 from their data. The negative coefficient of Clog P suggests that an increase in the hydrophobicity would reduce the activity of the molecules.

I_{50} of 3-[Z-(X-Phenyl)]-4-(3-Y-phenylamino)pyrazolo[3,4-d]pyrimidines (II) (Table 2)³²



$$\log 1/C = -0.43(\pm 0.21)\text{Clog } P - 0.41(\pm 0.15)\pi'_Y + 9.78(\pm 1.30) \quad (2)$$

$$n = 13, r^2 = 0.883, q^2 = 0.794, s = 0.176, \text{Clog } P = 4.96-7.07$$

Outliers: X = 3-Cl, Y = 3-Br, Z = NH;
X = 3-OH, Y = 3-Cl, Z = NH

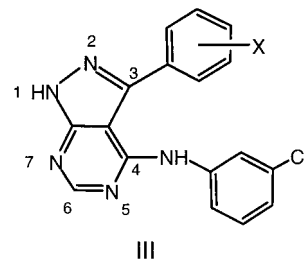
Traxler et al.³² tested 4-(phenylamino)pyrazolo[3,4-d]pyrimidines (III) for inhibition of the TK activity of the recombinant intracellular domain of EGFR (ICD) using angiotensin II as the phosphate-acceptor substrate in A431 cells. Equation 2 was obtained by us. It is evident from the negative Clog P and π'_Y that hydrophobicity is not important for the activity. π'_Y is the calculated π value for the hydrophobicity of Y-substituents. It appears that Y-substituents also interact with a site which is hydrophilic. It should be noted here that the mutual correlation of L_Y and π'_Y is high ($r^2 = 0.787$).

I_{50} of 3-(X-Phenyl)-4-(3-Cl-phenylamino)pyrazolo[3,4-d]pyrimidines (III) (Table 3)³²

Table 3. I_{50} of 3-(X-Phenyl)-4-(3-Cl-phenylamino)pyrazolo[3,4-d]pyrimidines (III)³²

no.	substituent X	log 1/C			Clog P
		obsd	calcd (eq 3)	Δ	
1	H ^a	7.72	6.99	0.73	5.63
2	3-OH	7.59	7.84	-0.25	4.96
3	4-OMe	7.02	7.08	-0.07	5.55
4	4-OH	8.22	7.84	0.39	4.96
5	3-NO ₂	7.43	7.30	0.13	5.38
6	3-NH ₂	8.30	8.56	-0.26	4.40
7	4-NHCOCMe ₃	6.57	6.65	-0.08	5.89
8	4-NH ₂	8.70	8.56	0.14	4.40

^a Data point not included in deriving equation.



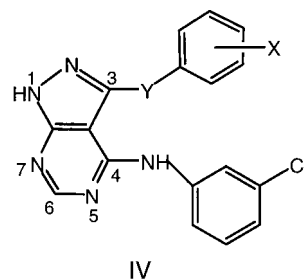
$$\log 1/C = -1.28(\pm 0.48)\text{Clog } P + 14.21(\pm 2.43) \quad (3)$$

$$n = 7, r^2 = 0.906, q^2 = 0.833, s = 0.255, \text{Clog } P = 4.40-5.89$$

Outlier: X = H

This series was also tested by Traxler et al.³² for the same system as for eq 2. Once again, a negative Clog P indicates that hydrophobicity is not conducive to activity.

I_{50} of 3-[Y-(X-Phenyl)]-4-(3-Cl-phenylamino)pyrazolo[3,4-d]pyrimidines (IV) (Table 4)⁷⁷



$$\log 1/C = -0.44(\pm 0.28)\text{Clog } P - 0.45(\pm 0.31)\text{CMR} - 0.50(\pm 0.42)I_Y + 15.07(\pm 2.64) \quad (4)$$

$$n = 12, r^2 = 0.868, q^2 = 0.669, s = 0.271, \text{Clog } P = 4.28-6.76$$

Outlier: X = 3-OH, Y = - (i.e., no Y-substituent)

Analogues of IV constitute yet another series of 4-phenylaminopyrazolo[3,4-d]pyrimidines studied by Traxler and Furet⁷⁷ for the inhibition of EGFR protein tyrosine kinase. They used a pharmacophore model of EGFR-PTK constructed by homology to the X-ray crystal structure of the cyclic AMP-dependent protein kinase. Equation 4 gave the best correlation. Here the indicator variable $I_Y = 1$ is for compounds not having Y-substituents, i.e., no linker chain for

Table 4. I_{50} of 3-[Y-(X-Phenyl)]-4-(3-Cl-phenylamino)pyrazolo[3,4-*d*]pyrimidines (IV)⁷⁷

no.	substituents		log 1/C			Clog <i>P</i>	CMR	<i>I_Y</i>
	X	Y	obsd	calcd (eq 4)	Δ			
1	3-Cl	NH	7.48	7.68	-0.20	6.76	9.92	0
2	3-OH	NH	9.00	8.44	0.56	5.37	9.58	0
3	3-OMe	NH	8.10	7.97	0.12	5.97	10.04	0
4	4-NH ₂	NH	8.30	8.59	-0.29	4.81	9.79	0
5	H	NHCH ₂	8.16	8.24	-0.09	5.51	9.89	0
6	3-Cl	NHCH ₂	7.59	7.71	-0.12	6.22	10.38	0
7	3-OMe	NHCH ₂	8.10	8.00	0.10	5.43	10.51	0
8	3-NH ₂	NHCH ₂	8.52	8.61	-0.09	4.28	10.26	0
9	4-OH	-	8.22	8.33	-0.11	4.86	9.21	1
10	4-NH ₂	-	8.70	8.48	0.22	4.30	9.42	1
11	4-NHCOOCMe ₃	-	6.57	6.51	0.06	6.23	11.93	1
12	3-OH ^a	-	7.59	8.33	-0.74	4.86	9.21	1
13	3-NH ₂	-	8.30	8.48	-0.18	4.30	9.42	1

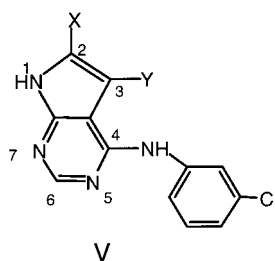
^a Data point not included in deriving equation.**Table 5.** I_{50} of 4-(3-Cl-Phenylamino)-2-X,3-Y-pyrrolo[3,4-*d*]pyrimidines (V)⁷⁷

no.	substituents		log 1/C				
	X	Y	obsd	calcd (eq 5)	Δ	Clog <i>P</i>	MR _X
1	Me	Me	7.57	7.44	0.13	4.81	0.57
2	C ₆ H ₅	Me	7.82	7.69	0.14	6.16	2.54
3	Me	C ₆ H ₅	6.64	6.91	-0.27	5.95	0.57
4	C ₆ H ₅	C ₆ H ₅	7.02	6.90	0.12	7.85	2.54
5	CONHMe	H	8.52	8.42	0.11	3.57	1.46
6	pyridin-2-yl	H	8.16	8.27	-0.12	4.69	2.30
7	4-OMe-C ₆ H ₄	H	7.82	8.10	-0.28	5.88	3.17
8	4-OH-C ₆ H ₄	H	8.52	8.17	0.35	5.29	2.72
9	4-NH ₂ -C ₆ H ₄	H	8.52	8.55	-0.03	4.73	2.98
10	3-NH ₂ -C ₆ H ₄	H	8.40	8.55	-0.15	4.73	2.98
11	4-COOH-C ₆ H ₄	H ^a	9.00	8.16	0.84	5.71	3.13

^a Data point not included in deriving equation.

4-(X-phenyl) groups. Its negative coefficient indicates that the absence of the linker chain is detrimental to the activity. Probably the flexibility imparted by it to the phenyl group is required for proper binding to the receptor. In addition to negative Clog *P*, the negative CMR (for the whole molecule) indicates that activity also decreases with an increase in the size of the molecule as well as its hydrophobicity.

I_{50} of 4-(3-Cl-Phenylamino)-2-X, 3-Y-pyrrolo[3,4-*d*]pyrimidines (V) (Table 5)⁷⁷



$$\log 1/C = -0.47(\pm 0.16)\text{Clog } P + 0.45(\pm 0.19)\text{MR}_X + 9.43(\pm 0.89) \quad (5)$$

$$n = 10, r^2 = 0.907, q^2 = 0.796, s = 0.230, \text{Clog } P = 3.57-7.85$$

Outlier: X = 4-COOH-C₆H₄, Y = H

This series was also studied for inhibitory activity by Traxler and Furet.⁷⁷ In eq 5, the coefficient of Clog

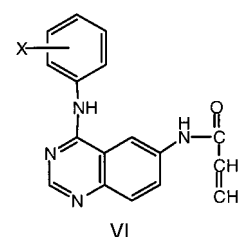
Table 6. I_{50} of *N*-[4-(X-Phenylamino)quinazolin-6-yl]acrylamide (VI)⁷⁸

no.	substituent X	log 1/C			Clog <i>P</i>
		obsd	calcd (eq 6)	Δ	
1	3-Br	9.16	9.13	0.02	5.09
2	3-Cl ^a	8.80	9.24	-0.45	4.94
3	3-Me	9.38	9.43	-0.05	4.69
4	3-CF ₃	9.04	9.10	-0.06	5.13
5	3-Br,4-F	9.16	9.02	0.15	5.24
6	3-Cl,4-F	9.13	9.13	-0.01	5.09
7	4-OC ₆ H ₅	8.24	8.22	0.02	6.29
8	4-OCH ₂ C ₆ H ₅	8.44	8.52	-0.07	5.90

^a Data point not included in deriving equation.

P once again confirms that an increase in the hydrophobicity of the molecules would decrease the activity. MR for X-substituents seems to have a positive effect on the activity.

I_{50} of *N*-[4-(X-Phenylamino)quinazolin-6-yl]acrylamide (VI) (Table 6)⁷⁸



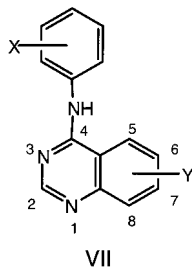
$$\log 1/C = -0.76(\pm 0.16)\text{Clog } P + 12.97(\pm 0.83) \quad (6)$$

$$n = 7, r^2 = 0.969, q^2 = 0.949, s = 0.081, \text{Clog } P = 4.69-6.29$$

Outlier: 3-Cl

Small et al.⁷⁸ reported the IC_{50} data of these compounds. The compounds were evaluated for their potency for inhibition of phosphorylation of poly-(glutamic acid)/tyrosine random copolymer substrate by EGFR. This was prepared from human A431 cell vesicles by immunoaffinity. The best correlation is given by eq 6. Once again, it is evident that an increase in the hydrophobicity of the compounds is detrimental to the activity.

I_{50} of 4-(X-Phenylamino)-Y-quinazoline (VII) (Table 7)⁷⁹



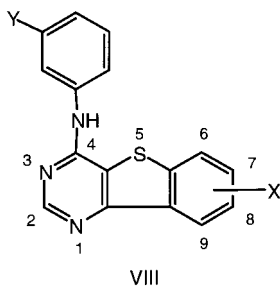
$$\log 1/C = -1.78(\pm 0.32)\sigma_Y^- + 1.01(\pm 0.77)B_{1Y,7} + 2.14(\pm 0.52)B_{1X,3} + 1.42(\pm 0.46)I - 0.45(\pm 0.25)\text{Clog } P + 4.69(\pm 1.34) \quad (7)$$

$$n = 51, r^2 = 0.852, q^2 = 0.811, s = 0.551, \text{Clog } P = 3.55-8.35$$

Outliers: see Table 7

IC_{50} data of this series was reported by Bridges et al.⁷⁹ EGFR was prepared from human A431 carcinoma cells by immunopurification.^{80a} Equation 7 gave the best correlation. In this equation the indicator variable $I = 1$ is for 6,7-di-OMe derivatives. Its positive coefficient indicates that the presence of 6,7-di-OMe groups is conducive to the activity. Y-substituents at 7-position enhance the activity by a positive steric effect shown by $B_{1Y,7}$. The same is true for the X-substituents at the 3-position of the 4-phenylamino moiety. Electron-donating groups as Y-substituents enhance the activity as evident by negative σ_Y^- . The σ values are parametrized with respect to the 1,3-N- in the quinazoline ring. This indicates that the increased electron density on these nitrogens improves the binding of the molecules to the receptor. A negative influence of hydrophobicity is observed again.

I_{50} of X-Substituted 4-(3-Y-phenylamino)benzothieno[3,2-d]pyrimidines (VIII) (Table 8)⁸¹



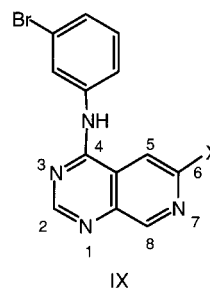
$$\log 1/C = -1.85(\pm 0.53)\text{Clog } P + 3.81(\pm 1.11)MR_Y + 0.87(\pm 0.37)L_{X,8} - 0.61(\pm 0.42)\sigma_X + 13.22(\pm 2.21) \quad (8)$$

$$n = 16, r^2 = 0.919, q^2 = 0.834, s = 0.316, \text{Clog } P = 4.39-6.54$$

Outliers: X = H, Y = 3-Br; X = 7-NHC₂H₅, 8-F, Y = 3-Br; X = 6-OMe, Y = 3-Br; X = 7,8-di-OMe, Y = 3-Br

Showalter et al.⁸¹ investigated this series of compounds for inhibitory action against EGFR prepared from human A431 carcinoma by immunopurification.^{80a} The enzyme assay was carried out using a substrate based on a portion of phospholipase C- γ 1 having the sequence Lys-His-Lys-Lys-Leu-Ala-Gly-Ser-Ala-Tyr⁴⁷²-Glu-Glu-Val.^{80b} Equation 8 was obtained from their data. Again, we find a detrimental role of hydrophobicity. MR for the Y-groups attached to the 3-position of 4-phenylamino moiety has a positive effect on the activity. The length of the X-substituents on the 8-position seems to promote the activity as indicated by positive $L_{X,8}$. Also, electron-releasing X-substituents enhance the activity. σ_X is parametrized with respect to the pyrimidine nitrogens. Most likely, an increased electron density on these nitrogens helps binding of the molecules to the receptor. An increase in the hydrophobicity of the compounds is detrimental to the activity.

I_{50} of 6-X-4-(3-Br-Phenylamino)pyrido[3,4-d]pyrimidines (IX) (Table 9)⁸²

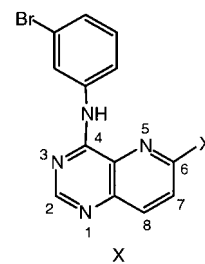


$$\log 1/C = -4.17(\pm 1.34)\sigma_X + 7.62(\pm 0.67) \quad (9)$$

$$n = 7, r^2 = 0.927, q^2 = 0.836, s = 0.540, \text{Clog } P = 3.75-5.93$$

Rewcastle et al.⁸² studied this series of compounds, where the variation in the molecules is brought out by different X-groups at 6-position. The EGFR was prepared from human A431 carcinoma cell-shed membrane vesicles by immunoaffinity chromatography as described by Gill et al.^{80a} and Fry et al.^{80b} Equation 9 indicates that electron-donating X-groups enhance the activity.

I_{50} of 6-X-4-(3-Br-Phenylamino)pyrido[3,2-d]pyrimidines (X) (Table 10)⁸²



$$\log 1/C = 1.20(\pm 0.59)MR + 7.29(\pm 0.37) \quad (10)$$

$$n = 6, r^2 = 0.888, q^2 = 0.823, s = 0.178, \text{Clog } P = 3.95-4.89$$

Outlier: X = NMe₂

Table 7. I₅₀ of 4-(X-Phenylamino)-Y-quinazoline (VII)⁷⁹

no.	substituents		log 1/C			σ^-_Y	B1 _{Y,7}	B1 _{X,3}	I	Clog P
	X	Y	obsd	calcd (eq 7)	Δ					
1	H	H	6.46	6.19	0.27	0.00	1.00	1.00	0	3.86
2	3-F	H	7.25	6.81	0.44	0.00	1.00	1.35	0	4.04
3	3-Cl	H	7.64	7.47	0.17	0.00	1.00	1.80	0	4.61
4	3-Br	H	7.57	7.70	-0.13	0.00	1.00	1.95	0	4.76
5	3-I	H	7.10	7.99	-0.90	0.00	1.00	2.15	0	5.02
6	3-CF ₃	H ^a	6.24	7.76	-1.52	0.00	1.00	1.99	0	4.81
7	H	6-OMe ^a	7.26	5.82	1.44	0.12	1.00	1.00	0	4.26
8	3-Br	6-OMe	7.52	7.34	0.19	0.12	1.00	1.95	0	5.15
9	H	6-NH ₂	6.11	6.60	-0.49	-0.16	1.00	1.00	0	3.55
10	3-CF ₃	6-NH ₂ ^a	6.24	8.17	-1.93	-0.16	1.00	1.99	0	4.49
11	3-Br	6-NH ₂	9.11	8.11	1.00	-0.16	1.00	1.95	0	4.45
12	H	6-NO ₂	5.30	5.00	0.30	0.71	1.00	1.00	0	3.68
13	3-Br	6-NO ₂	6.05	6.52	-0.47	0.71	1.00	1.95	0	4.56
14	H	7-OMe	6.92	6.86	0.06	-0.26	1.35	1.00	0	4.26
15	3-Br	7-OMe	8.00	8.37	-0.37	-0.26	1.35	1.95	0	5.15
16	H	7-NH ₂	7.00	7.80	-0.80	-0.63	1.35	1.00	0	3.55
17	3-F	7-NH ₂	8.70	8.41	0.29	-0.63	1.35	1.35	0	3.73
18	3-Cl	7-NH ₂	9.60	9.07	0.53	-0.63	1.35	1.80	0	4.30
19	3-Br	7-NH ₂	10.00	9.31	0.69	-0.63	1.35	1.95	0	4.45
20	3-I	7-NH ₂	9.46	9.60	-0.14	-0.63	1.35	2.15	0	4.71
21	3-CF ₃	7-NH ₂	8.48	9.37	-0.89	-0.63	1.35	1.99	0	4.49
22	H	7-NO ₂	4.92	4.73	0.20	1.27	1.70	1.00	0	3.68
23	3-F	7-NO ₂	5.22	5.35	-0.14	1.27	1.70	1.35	0	3.84
24	3-Cl	7-NO ₂	6.09	6.01	0.08	1.27	1.70	1.80	0	4.41
25	3-Br	7-NO ₂	6.00	6.25	-0.25	1.27	1.70	1.95	0	4.56
26	3-I	7-NO ₂	6.27	6.54	-0.27	1.27	1.70	2.15	0	4.82
27	H	6,7-di-OMe	7.54	8.16	-0.62	-0.14	1.35	1.00	1	4.29
28	3-F	6,7-di-OMe	8.42	8.78	-0.36	-0.14	1.35	1.35	1	4.46
29	3-Cl	6,7-di-OMe	9.51	9.44	0.07	-0.14	1.35	1.80	1	5.03
30	3-Br	6,7-di-OMe	10.60	9.68	0.93	-0.14	1.35	1.95	1	5.18
31	3-I	6,7-di-OMe	9.05	9.97	-0.92	-0.14	1.35	2.15	1	5.44
32	3-CF ₃	6,7-di-OMe	9.62	9.74	-0.12	-0.14	1.35	1.99	1	5.23
33	3-Br	6-NHMe	8.40	7.89	0.51	-0.21	1.00	1.95	0	5.25
34	3-Br	6-NMe ₂	7.08	7.70	-0.63	-0.16	1.00	1.95	0	5.48
35	3-Br	6-NHCOOMe	7.92	7.68	0.24	-0.02	1.00	1.95	0	4.92
36	3-Br	7-OH	8.33	8.60	-0.28	-0.37	1.35	1.95	0	5.06
37	3-Br	7-NHCOMe	7.40	8.12	-0.72	0.00	1.35	1.95	0	4.62
38	3-Br	7-NHMe	8.16	8.09	0.07	-0.12	1.35	1.95	0	5.25
39	3-Br	7-NHC ₂ H ₅	7.92	7.88	0.04	-0.12	1.35	1.95	0	5.77
40	3-Br	7-NMe ₂	7.96	7.99	-0.03	-0.12	1.35	1.95	0	5.48
41	3-Br	6,7-di-NH ₂	9.92	9.72	0.20	-0.79	1.35	1.95	0	4.13
42	3-Br	6-NH ₂ ,7-NHMe	9.16	8.50	0.67	-0.28	1.35	1.95	0	4.93
43	3-Br	6-NH ₂ ,7-NMe ₂ ^a	6.80	8.40	-1.60	-0.28	1.35	1.95	0	5.17
44	3-Br	6-NH ₂ ,7-OMe	8.42	8.71	-0.29	-0.42	1.35	1.95	0	5.03
45	3-Br	6-NH ₂ ,7-Cl	8.19	8.30	-0.11	0.03	1.80	1.95	0	5.20
46	3-Br	6-NO ₂ ,7-NH ₂	7.28	7.91	-0.63	0.08	1.35	1.95	0	4.80
47	3-Br	6-NO ₂ ,7-NHMe	7.17	6.83	0.33	0.59	1.35	1.95	0	5.22
48	3-Br	6-NO ₂ ,7-NMe ₂	5.70	6.81	-1.11	0.59	1.35	1.95	0	5.28
49	3-Br	6-NO ₂ ,7-NHCOMe	7.55	7.11	0.44	0.71	1.35	1.95	0	3.97
50	3-Br	6-NO ₂ ,7-OMe	7.82	7.31	0.52	0.45	1.35	1.95	0	4.66
51	3-Br	6-NO ₂ ,7-Cl	7.60	6.80	0.80	0.90	1.80	1.95	0	5.08
52	3-Br	6,7-di-OH ^a	9.77	8.24	1.53	-0.25	1.35	1.95	0	5.43
53	3-Br	6,7-di-OC ₂ H ₅ ^a	11.22	7.80	3.42	-0.18	1.35	1.95	0	6.24
54	3-Br	6,7-di-OC ₃ H ₇ ^a	9.77	7.39	2.38	-0.18	1.35	1.95	0	7.29
55	3-Br	6,7-di-OC ₄ H ₉	6.98	6.97	0.01	-0.18	1.35	1.95	0	8.35
56	3-Br	5,6-di-OMe ^a	5.86	7.79	-1.92	-0.14	1.00	1.95	0	5.18
57	3-Br	5,6,7-tri-OMe	9.17	8.60	0.57	-0.40	1.35	1.95	0	5.20
58	2-Br	6,7-di-OMe	6.89	7.81	-0.92	-0.14	1.35	1.00	1	5.18
59	4-Br	6,7-di-OMe	9.02	7.81	1.21	-0.14	1.35	1.00	1	5.18
60	3,4-di-Br	6,7-di-OMe	10.14	9.41	0.73	-0.14	1.35	1.95	1	5.85
61	3,5-di-Br	6,7-di-OMe ^a	6.95	9.33	-2.39	-0.14	1.35	1.95	1	6.05

^a Data points not included in deriving equation.

Table 8. I_{50} of X-Substituted-4-(3-Y-phenylamino)benzothieno[3,2-d]pyrimidines (VIII)⁸¹

no.	substituents		log 1/C			Clog P	MR _Y	L _{X,8}	σ _X
	X	Y	obsd	calcd (eq 8)	Δ				
1	H	3-Br ^a	8.75	6.98	1.76	6.18	0.89	2.06	0.00
2	8-NO ₂	H	7.24	6.86	0.38	5.04	0.10	3.44	0.71
3	8-NO ₂	3-Me	7.96	7.70	0.26	5.54	0.57	3.44	0.71
4	8-NO ₂	3-CF ₃	6.34	6.66	-0.32	5.97	0.50	3.44	0.71
5	8-NO ₂	3-Br	7.91	8.22	-0.31	5.93	0.89	3.44	0.71
6	8-NH ₂	H	8.03	8.03	-0.00	4.39	0.10	2.78	-0.16
7	8-NH ₂	3-Me	8.68	8.87	-0.19	4.88	0.57	2.78	-0.16
8	8-NH ₂	3-CF ₃	7.33	7.82	-0.49	5.32	0.50	2.78	-0.16
9	8-NH ₂	3-Br	9.57	9.38	0.19	5.27	0.89	2.78	-0.16
10	7-NO ₂	3-Br	7.32	6.97	0.35	5.93	0.89	2.06	0.78
11	7-NH ₂	3-Br	9.33	9.06	0.27	5.27	0.89	2.06	-0.66
12	7-NH ₂ , 8-F	3-Br	9.00	9.12	-0.12	5.41	0.89	2.65	-0.32
13	7-NHC ₂ H ₅ , 8-F	3-Br ^a	8.10	6.56	1.54	6.77	0.89	2.65	-0.27
14	7-OMe	3-Br	7.10	7.00	0.10	6.26	0.89	2.06	-0.27
15	8-NHMe	3-Br	8.96	8.68	0.28	6.02	0.89	3.53	-0.21
16	8-NMe ₂	3-Br	7.70	7.70	0.01	6.54	0.89	3.53	-0.16
17	6-OMe	3-Br ^a	7.90	6.76	1.14	6.26	0.89	2.06	0.12
18	6-NO ₂	3-Br	6.80	7.01	-0.21	5.93	0.89	2.06	0.71
19	6-NH ₂	3-Br	8.57	8.75	-0.18	5.27	0.89	2.06	-0.16
20	7,8-di-OMe	3-Br ^a	6.35	9.08	-2.73	6.00	0.89	0.98	-0.15

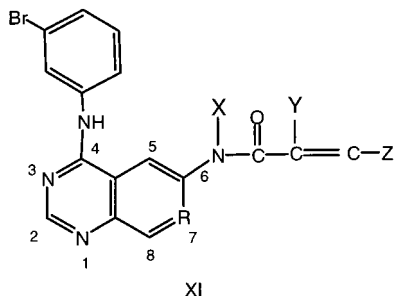
^a Data points not included in deriving equation.

Table 9. I_{50} of 6-X-4-(3-Br-Phenylamino)pyrido[3,4-d]pyrimidines (IX)⁸²

no.	substituent X	log 1/C			
		obsd	calcd (eq 9)	Δ	σ _X
1	H	7.29	7.62	-0.33	0.00
2	NH ₂	9.89	10.37	-0.49	-0.66
3	Cl	7.40	6.66	0.74	0.23
4	F	6.91	7.37	-0.46	0.06
5	NHMe	11.10	10.54	0.56	-0.70
6	NMe ₂	11.22	11.08	0.14	-0.83
7	OMe	8.59	8.75	-0.16	-0.27

Rewcastle et al.⁸² tested this series also. The only variation in the analogues is that of 6-X-substituents. MR for X-substituents seems to be having a positive steric interaction with the receptor.

I_{50} of 4-(3-Br-Phenylamino)quinazolin-6-yl-acrylamides and 4-(X-Phenylamino)pyrido[3,4-d]pyrimidin-6-yl-acrylamides (XI) (Table 11)⁸³



$$\log 1/C = -0.24(\pm 0.14)\text{Clog } P - 3.91(\pm 1.59)\text{CMR} + 0.16(\pm 0.07)(\text{CMR})^2 + 33.17(\pm 8.89) \quad (11)$$

$$n = 20, r^2 = 0.826, q^2 = 0.724, s = 0.184, \text{Clog } P = 3.54 - 6.39$$

$$\text{inversion point} = 11.99 (11.80 - 12.33)$$

Outliers: see Table 11

Table 10. I_{50} of 6-X-4-(3-Br-phenylamino)pyrido[3,2-d]pyrimidines (X)⁸²

no.	substituent X	log 1/C			
		obsd	calcd (eq 10)	Δ	MR
1	H	7.47	7.42	0.05	0.10
2	NH ₂	8.12	7.95	0.17	0.54
3	Cl	7.75	8.02	-0.27	0.60
4	F	7.36	7.41	-0.05	0.09
5	NHMe	8.51	8.54	-0.03	1.03
6	NMe ₂ ^a	8.02	9.16	-1.15	1.56
7	OMe	8.37	8.24	0.13	0.79

^a Data point not included in deriving equation.

IC_{50} data for analogues of XI were reported by Smaill et al.⁸³ The compounds were evaluated for their ability to inhibit tyrosine phosphorylation of a 14-residue polypeptide, a portion of phospholipase C-γ1 (as explained for data set 8) by EGF-stimulated full-length EGFR enzyme isolated from human A431 cells.^{80b} Equation 11 obtained from their data indicates a negative effect for hydrophobicity. The steric interaction depicted by CMR seems to have a dual effect. First, with the increase in size, the activity decreases to a minimum, up to CMR = 11.99, and then with further increase in size it increases. We believe that this indicates an allosteric interaction.⁹⁸

I_{50} of 4-(X-Phenylamino)-7-Y-quinazolin-6-yl-acrylamide (XII) (Table 12)⁸⁴

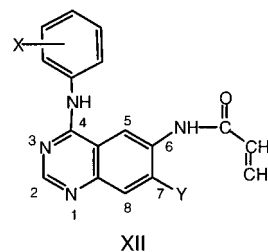


Table 11. I_{50} of 4-(3-Br-Phenylamino)quinazolin-6-yl-acrylamides and 4-(X-Phenylamino)pyrido[3,4-*d*]pyrimidin-6-yl-acrylamides (XI)⁸³

no.	substituents				log 1/C			Clog <i>P</i>	CMR
	R	X	Y	Z	obsd	calcd (eq 11)	Δ		
1	N	H	H	H ^a	9.04	9.93	-0.89	4.14	9.25
2	C	H	H	H ^a	9.16	9.57	-0.41	4.88	9.46
3	N	Me	H	H	9.77	9.47	0.31	4.49	9.71
4	N	H	Me	H ^a	8.80	9.47	-0.68	4.45	9.71
5	C	H	Me	H	8.92	9.15	-0.22	5.18	9.92
6	N	H	H	Me	9.30	9.42	-0.12	4.67	9.71
7	C	H	H	Me	9.26	9.09	0.17	5.40	9.92
8	N	H	H	<i>cis</i> -Cl	9.16	9.47	-0.31	4.39	9.74
9	C	H	H	CF ₃ ^a	8.76	9.20	-0.45	4.81	9.97
10	N	H	H	CH=CH ₂	8.96	8.93	0.03	4.78	10.45
11	C	H	H	=CH ₂ ^a	8.80	9.13	-0.34	5.18	9.94
12	N	H	H	C ₆ H ₅	8.04	8.15	-0.11	6.39	11.99
13	C	H	H	COMe	8.92	9.01	-0.09	4.37	10.50
14	C	H	H	COOH	9.43	9.16	0.28	4.44	10.19
15	C	H	H	COOC ₂ H ₅	8.57	8.50	0.07	5.50	11.11
16	N	H	H	COOC ₂ H ₅	8.82	8.74	0.08	4.77	10.90
17	N	(CH ₂) ₂ NMe ₂	H	H	8.38	8.60	-0.22	4.74	11.47
18	N	(CH ₂) ₃ -N-morpholinyl	H	H	8.57	8.61	-0.04	5.00	12.84
19	C	(CH ₂) ₃ -N-morpholinyl	H	H	8.48	8.46	0.02	5.86	13.05
20	C	H	H	COO(CH ₂) ₃ NMe ₂	8.62	8.50	0.12	5.47	12.87
21	C	H	H	CONH(CH ₂) ₃ NMe ₂ ^a	9.36	8.75	0.60	4.73	13.09
22	N	H	H	CONH(CH ₂) ₃ NMe ₂	8.96	8.86	0.10	4.00	12.88
23	N	H	H	CONH(CH ₂) ₃ N(C ₂ H ₅) ₂	9.14	9.01	0.12	5.05	13.81
24	N	H	H	CONH(CH ₂) ₃ - <i>N</i> -morpholinyl	9.09	9.28	-0.19	3.89	13.78
25	N	H	H	CONH(CH ₂) ₃ - <i>N</i> -imidazolyl	9.25	9.13	0.12	3.54	13.31
26	N	Me	H	CONH(CH ₂) ₃ NMe ₂	8.84	8.95	-0.12	4.31	13.34

^a Data points not included in deriving equation.**Table 12.** I_{50} of 4-(X-Phenylamino)-7-Y-quinazolin-6-yl-acrylamide (XII)⁸⁴

no.	substituents		log 1/C			MgVol	<i>I</i>	σ _X
	X	Y	obsd	calcd (eq 12)	Δ			
1	3-Br	O(CH ₂) ₃ -4-Me-piperidine ^a	8.77	8.33	0.44	3.70	0.00	0.39
2	3-Br	O(CH ₂) ₃ -morpholine	8.44	8.42	0.02	3.48	0.00	0.39
3	3-Br	O(CH ₂) ₄ -NMe ₂	8.41	8.46	-0.05	3.39	0.00	0.39
4	3-Br	O(CH ₂) ₃ -imidazolyl	8.52	8.50	0.03	3.29	0.00	0.39
5	3-Br	S(CH ₂) ₃ -N(C ₂ H ₅) ₂ ^a	9.11	8.36	0.75	3.63	0.00	0.39
6	3-Me	H	9.38	9.30	0.08	2.35	0.00	-0.07
7	3-Me	O(CH ₂) ₃ -4-Me-piperidine	8.70	8.75	-0.06	3.67	0.00	-0.07
8	3-Me	O(CH ₂) ₃ -morpholine	8.82	8.85	-0.02	3.44	0.00	-0.07
9	3-Br,4-F	H	9.16	9.17	-0.01	2.40	1.00	0.45
10	3-Br,4-F	O(CH ₂) ₃ -morpholine	8.75	8.71	0.03	3.49	1.00	0.45
11	3-Cl,4-F	H	9.13	9.21	-0.08	2.35	1.00	0.43
12	3-Cl,4-F	O(CH ₂) ₃ -morpholine	8.82	8.75	0.07	3.44	1.00	0.43
13	3-Cl,4-F	[O(CH ₂) ₂] ₂ (CH ₂) ₂ OH	8.77	8.78	-0.01	3.37	1.00	0.43

^a Data points not included in deriving equation.

$$\log 1/C = -0.41(\pm 0.09)\text{MgVol} + 0.35(\pm 0.12)I - 0.89(\pm 0.26)\sigma_X + 10.21(\pm 0.31) \quad (12)$$

$$n = 11, r^2 = 0.972, q^2 = 0.907, s = 0.061, \text{Clog } P = 4.04 - 6.80$$

Outliers: X = 3-Br, Y = O(CH₂)₃-4-Me-piperidine; X = 3-Br, Y = S(CH₂)₃N(C₂H₅)₂

These compounds were tested by Smaill et al.⁸⁴ This series is for irreversible inhibitors of the enzyme. The IC₅₀ data obtained was for the inhibition of phosphorylation of a random glutamic acid/tyrosine copolymer substrate by isolated EGFR enzyme.

In eq 12, the indicator variable *I* = 1 for X = 4-F derivatives. 4-F groups attached to phenylamino moiety are present along with 3-Br/3-Cl in the compounds. The positive coefficient suggests that presence of 4-F is conducive to the activity. Also, electron donating X-substituents enhance the activity as shown by a negative σ_X. It seems the overall volume of the compounds should not increase as it is detrimental to the activity, evident by a negative MgVol (McGowan volume).

The analogues of XII were also investigated for inhibition of EGF-stimulated autophosphorylation of EGFR in human A431 cells. Equation 13 was derived by us for the reported IC₅₀ data (Table 13).

Table 13. I_{50} of 4-(X-Phenylamino)-7-Y-quinazolin-6-yl-acrylamide (XII)⁸⁴

no.	substituents		log 1/C			Clog P	CMR
	X	Y	obsd	calcd (eq 13)	Δ		
1	3-Br	O(CH ₂) ₃ -4-Me-piperidine ^a	8.52	6.93	1.59	6.69	13.98
2	3-Br	O(CH ₂) ₃ -morpholine	8.28	8.15	0.13	5.11	13.20
3	3-Br	O(CH ₂) ₄ -NMe ₂	8.10	8.17	-0.06	5.06	12.76
4	3-Br	O(CH ₂) ₃ -imidazolyl	7.68	7.70	-0.03	4.76	12.73
5	3-Br	S(CH ₂) ₃ -N(C ₂ H ₅) ₂	6.71	6.69	0.02	6.80	13.88
6	3-Me	H ^a	8.33	7.62	0.71	4.47	9.14
7	3-Me	O(CH ₂) ₃ -4-Me-piperidine	7.75	7.79	-0.04	6.30	13.66
8	3-Me	O(CH ₂) ₃ -morpholine	7.57	7.58	-0.01	4.71	12.89
9	3-Br,4-F	H	8.57	8.62	-0.05	5.03	9.47
10	3-Br,4-F	O(CH ₂) ₃ -morpholine	8.33	8.29	0.04	5.26	13.22
11	3-Cl,4-F	H	8.51	8.45	0.06	4.88	9.19
12	3-Cl,4-F	O(CH ₂) ₃ -morpholine	8.13	8.19	-0.06	5.11	12.93

^a Data points not included in deriving equation.**Table 14.** I_{50} of 7-Amino-4-(X-phenylamino)pyrido[4,3-d]pyrimidines (XIII)⁸⁵

no.	substituent X	log 1/C			B_{12}	σ^-_X	B_{53}	Clog P	CMR
		obsd	calcd (eq 14)	Δ					
1	H	6.60	6.38	0.22	1.00	0.00	1.00	2.86	6.99
2	2-NO ₂ ^a	5.90	3.49	2.41	1.70	1.27	1.00	2.78	7.60
3	3-NO ₂ ^a	7.40	5.84	1.56	1.00	0.71	2.44	2.63	7.60
4	4-NO ₂	4.19	4.00	0.19	1.00	1.27	1.00	2.63	7.60
5	2-Br ^a	6.62	5.44	1.19	1.95	0.25	1.00	3.74	7.77
6	3-Br	8.00	6.94	1.06	1.00	0.39	1.95	3.74	7.77
7	4-Br	7.05	6.35	0.69	1.00	0.25	1.00	3.74	7.77
8	2-CF ₃	5.00	5.18	-0.18	1.99	0.65	1.00	3.77	7.50
9	3-CF ₃	7.82	7.70	0.13	1.00	0.43	2.61	3.77	7.50
10	4-CF ₃	5.33	6.14	-0.81	1.00	0.65	1.00	3.77	7.50
11	2-OMe	5.43	5.72	-0.28	1.35	-0.26	1.00	2.79	7.61
12	3-OMe	6.89	7.25	-0.36	1.00	0.12	3.07	2.79	7.61
13	4-OMe	6.17	6.05	0.12	1.00	-0.26	1.00	2.79	7.61
14	2-NH ₂	5.28	5.09	0.19	1.35	-0.63	1.00	1.64	7.36
15	3-NH ₂	5.81	5.63	0.18	1.00	-0.16	1.97	1.64	7.36
16	4-NH ₂	5.23	5.43	-0.20	1.00	-0.63	1.00	1.64	7.36
17	2-NMe ₂	4.16	4.03	0.14	2.56	-0.12	1.00	3.03	8.29
18	3-NMe ₂	5.75	5.86	-0.11	1.00	-0.16	1.35	3.03	8.29
19	4-NMe ₂	5.31	5.53	-0.22	1.00	-0.12	1.00	3.03	8.29
20	3-F	6.08	6.40	-0.33	1.00	0.34	1.35	3.02	7.01
21	3-Cl	6.92	6.94	-0.02	1.00	0.37	1.80	3.59	7.48
22	3-I	6.59	6.96	-0.38	1.00	0.35	2.15	4.00	8.30
23	3-OH ^a	7.16	6.08	1.07	1.00	0.12	1.93	2.20	7.15
24	3-Me	7.40	7.44	-0.04	1.00	-0.07	2.04	3.36	7.46

^a Data points not included in deriving equation.

$$\log 1/C = 12.53(\pm 2.22)\text{Clog } P - 1.12(\pm 0.19)(\text{Clog } P)^2 - 0.15(\pm 0.04)\text{CMR} - 24.64(\pm 2.26) \quad (13)$$

$$n = 10, r^2 = 0.987, q^2 = 0.966, s = 0.077, \text{Clog } P = 4.47 - 6.80$$

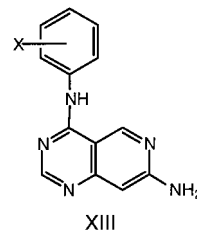
$$\text{Opt. Clog } P = 5.59 \quad (5.53 - 5.64)$$

Outliers: X = 3-Br, Y = O(CH₂)₃-4-Me-piperidine; X = 3-Me, Y = H

In eq 13, we obtained a parabolic correlation with Clog P. By this equation it appears that the hydrophobicity plays an important positive role up to a Clog P of 5.6. With a further increase in the hydrophobicity of the compounds, the activity decreases. Looking at the coefficients we can say that the activity increases rapidly and then falls off rapidly with Clog P. In addition, CMR also shows a border-

line detrimental effect by steric interaction as evident by its relatively small negative coefficient.

I_{50} of 7-Amino-4-(X-phenylamino)-pyrido[4,3-d]pyrimidines (XIII) (Table 14)⁸⁵



$$\log 1/C = -0.97(\pm 0.62)B_{12} - 1.23(\pm 0.65)\sigma^-_X + 0.80(\pm 0.39)B_{53} + 1.13(\pm 0.44)\text{Clog } P - 0.91(\pm 0.66)\text{CMR} + 9.67(\pm 4.61) \quad (14)$$

$$n = 20, r^2 = 0.866, q^2 = 0.728, s = 0.467, \text{Clog } P = 1.64 - 4.00$$

Outliers: 2-NO₂; 3-NO₂; 2-Br; 3-OH

Table 15. I_{50} Data of 1-Phenyl-X-benzimidazoles (XIV)⁸⁶

no.	substituent X	log 1/C			Clog <i>P</i>	σ_1	B5 ₄	B5 ₅
		obsd	calcd (eq 15)	Δ				
1	H ^a	5.03	6.17	-1.14	3.47	0.00	1.00	1.00
2	4-OH	4.85	5.10	-0.25	3.53	0.29	1.93	1.00
3	5-OH	6.36	5.96	0.40	3.53	0.29	1.00	1.93
4	5-OMe	6.37	6.29	0.08	3.71	0.27	1.00	3.07
5	5-OC ₂ H ₅	6.62	6.17	0.45	4.24	0.28	1.00	3.36
6	5-OC ₃ H ₇	6.60	6.31	0.29	4.77	0.28	1.00	4.42
7	5-OCHMe ₂ ^a	5.51	6.33	-0.82	4.55	0.26	1.00	4.10
8	5-OC ₄ H ₉	5.89	6.24	-0.35	5.30	0.28	1.00	4.79
9	5-OCH ₂ (oxiranyl) ^a	6.50	4.37	2.12	3.71	0.27	3.07	1.00
10	5-SH	5.48	5.90	-0.42	4.17	0.26	1.00	2.33
11	5-SMe	6.13	6.21	-0.08	4.17	0.25	1.00	3.26
12	4,5-di-OH	4.60	4.87	-0.27	3.65	0.58	1.93	1.93
13	4-OH,5-OMe	5.15	5.30	-0.15	3.55	0.56	1.93	3.07
14	4-OMe,5-OH	4.30	4.25	0.06	3.55	0.56	3.07	1.93
15	4,5-di-OMe	4.30	4.61	-0.31	3.62	0.54	3.07	3.07
16	4-Br,5-OH	4.30	4.43	-0.13	4.15	0.73	1.95	1.93
17	4-CH ₂ CH=CH ₂ ,5-OH	4.30	3.85	0.45	4.60	0.31	3.78	1.93
18	5,6-di-OMe	5.92	5.87	0.05	3.62	0.54	1.00	3.07
19	5,6-di-OH	5.64	5.43	0.21	3.65	0.58	1.00	1.93
20	5-OMe,6-Me	6.00	6.17	-0.17	4.21	0.23	1.00	3.07
21	5-OH,6-Me	5.60	5.85	-0.24	4.03	0.25	1.00	1.93
22	5-OMe,6-COOH ^a	4.68	5.94	-1.27	3.28	0.57	1.00	3.07
23	5-OH,6-COOH	5.37	5.22	0.15	4.19	0.59	1.00	1.93
24	5-OMe,6-COOMe	6.06	5.83	0.23	3.49	0.59	1.00	3.07
25	5-OMe,6-CH ₂ OH	6.43	6.48	-0.05	2.67	0.38	1.00	3.07
26	5-OMe,6-CHO	6.00	5.94	0.06	3.44	0.54	1.00	3.07
27	5-OCH ₂ CH=CH ₂	6.22	—	—	4.48	—	1.00	4.42
28	5-O(CH ₂) ₄ OH	6.35	—	—	3.31	—	1.00	—
29	5-OCH ₂ CH(OH)CH ₂ OH	6.51	—	—	2.01	—	1.00	—
30	5-O(CH ₂) ₂ NH ₂	6.19	—	—	2.91	—	1.00	—
31	5-O(CH ₂) ₂ NMe ₂	5.82	—	—	3.81	—	1.00	5.37
32	5-O(CH ₂) ₃ NMe ₂	6.82	—	—	4.16	—	1.00	—
33	5-O(CH ₂) ₄ NMe ₂	6.80	—	—	4.09	—	1.00	—
34	5-O(CH ₂) ₂ N-morpholinyl	6.14	—	—	3.75	—	1.00	—
35	5-O(CH ₂) ₃ N-morpholinyl	6.77	—	—	4.15	—	1.00	—
36	5-O(CH ₂) ₄ N-morpholinyl	6.57	—	—	4.26	—	1.00	—
37	5-S(CH ₂) ₃ N-morpholinyl	4.30	—	—	4.51	—	1.00	—
38	5-OCSNMe ₂	5.34	—	—	3.09	—	1.00	—
39	4-Br, 5-OCH ₂ CH=CH ₂	4.30	—	—	5.12	—	1.95	4.42
40	4,5-CH ₂ CH(Me)O-	4.54	—	—	4.36	—	—	—
41	5,6-OCH ₂ O-	5.66	—	—	3.52	—	1.00	—

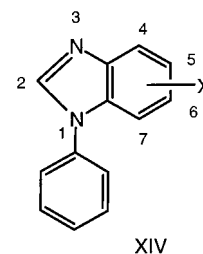
^aData points not included in deriving equation.

Analogues of **XIII** were evaluated for their ability to inhibit tyrosine phosphorylation of a polypeptide (a portion of phospholipase C- γ 1) by full-length EGFR enzyme isolated from human A431 carcinoma cells^{80a,b} by Thompson et al.⁸⁵ These compounds have different X-groups attached to the different C-atoms of the phenyl of the 4-phenylamino moiety. Thus, the equation obtained reflects the influence of the substituents on the IC₅₀ attached to this portion of the molecule.

As observed in eq 12, electron-releasing X-groups enhance the activity. The negative coefficient of CMR implies that an increase in the size of the molecule decreases the activity. Here since size change is by X-groups, the bigger groups at any position of the phenyl, except at the 3-position, seem to create steric hindrance. However, the substituents at the 3-position appear to be conducive to the activity. The positive B5₃ indicates a positive steric interaction of these substituents.

B. Inhibitors of Platelet-Derived Growth Factor Receptor (PDGFR) Tyrosine Kinase

I_{50} data of 1-Phenyl-X-benzimidazoles (XIV) (Table 15)⁸⁶



$$\log 1/C = -0.36(\pm 0.28)\text{Clog } P - 1.66(\pm 0.94)\sigma_1 - 0.61(\pm 0.18)\text{B5}_4 + 0.32(\pm 0.18)\text{B5}_5 + 7.71(\pm 1.22) \quad (15)$$

$$n = 22, r^2 = 0.892, q^2 = 0.768, s = 0.292, \text{Clog } P = 2.67-5.30$$

Outliers: H; 5-OCHMe₂; 5-OCH₂ (oxiranyl); 5-OMe, 6-COOH

Quite a few compounds could not be included in the regression because of the lack of σ_1 values.

Analogues of **XIV** were evaluated for their ability to inhibit the phosphorylation of a model glutamate tyrosine copolymer substrate by isolated mouse

Table 16. I_{50} of 2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (**I**)⁷⁶

no.	substituent X	log 1/C				σ^-_X	MR ₄
		obsd	calcd (eq 16)	Δ	Clog P		
1	H	6.40	6.20	0.20	5.01	0.00	0.10
2	4-Cl	5.59	5.53	0.05	5.73	0.19	0.60
3	3-Br	5.51	5.57	-0.06	5.88	0.39	0.10
4	4-Me	5.92	5.90	0.02	5.51	-0.17	0.57
5	2-OMe ^a	5.75	6.42	-0.68	4.94	-0.26	0.10
6	3-OMe	6.28	6.15	0.13	4.94	0.12	0.10
7	4-OMe	6.17	6.09	0.08	4.94	-0.26	0.79
8	3-OH	6.39	6.39	0.00	4.35	0.12	0.10
9	4-OH	6.55	6.65	-0.10	4.35	-0.37	0.29
10	3-CH ₂ OH	6.68	6.62	0.05	3.98	0.00	0.10
11	3-Me, 4-OMe	5.82	5.94	-0.12	5.44	-0.33	0.79
12	3,5-di-OMe	5.77	6.07	-0.30	4.91	0.24	0.10
13	3-CO ₂ C ₂ H ₅	5.77	5.73	0.05	5.54	0.37	0.10
14	4-CO ₂ C ₂ H ₅	4.67	4.67	0.01	5.54	0.75	1.75

^a Data point not included in deriving equation.

PDGF- β receptor tyrosine kinase enzyme by Palmer et al.⁸⁶ They used cDNA for human PDGF- β RTK to obtain a fragment of DNA that codes for the intracellular TK domain. This was used to obtain recombinant protein using baculovirus vector followed by SF9 insect cell infection. IC₅₀ values are the concentration of inhibitor required to reduce by 50% the level of ³²P (from added [³²P]ATP) incorporated into the glutamate-tyrosine copolymer substrate. In this equation, σ_I is a summation of the σ_I values of all the substituents at different positions of each molecule (15 compounds could not be included in the regression because of the lack of σ_I values). Its negative coefficient implies that electron-releasing groups enhance the activity by the field/inductive effect. Groups attached to the 4-position show a steric interaction which is detrimental to activity, but groups attached to the 5-position seem to be having a positive steric effect on the activity. For both the positions, the B5-sterimol parameter, which has a negative or positive interaction, indicates that bulky groups decrease the activity when attached to the 4-position but improve the activity when attached to the 5-position. It seems that hydrophobicity has a small negative effect on the activity.

I_{50} of 2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (**I**) (Table 16)⁷⁶

$$\log 1/C = -0.41(\pm 0.18)\text{Clog } P - 0.72(\pm 0.32)\sigma^-_X - 0.48(\pm 0.21)\text{MR}_4 + 8.29(\pm 0.91) \quad (16)$$

$$n = 13, r^2 = 0.946, q^2 = 0.914, s = 0.144, \text{Clog } P = 3.98-6.06$$

Outlier: 2-OMe

Klutchko et al.⁷⁶ reported the IC₅₀ data of the compounds of this series. The compounds were evaluated for their ability to prevent phosphorylation of a synthetic glutamate-tyrosine polymer by isolated mouse PDGF- β receptor TK. In the equation, negative σ^- shows that electron-releasing X-groups

Table 17. I_{50} of 2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (**I**)⁸⁷

no.	substituent X	log 1/C			
		obsd	calcd (eq 17)	Δ	Clog P
1	3-CH ₂ OH	6.86	6.84	0.02	4.05
2	4-N-morpholinyl	6.20	6.26	-0.06	4.91
3	3-SMe	5.78	5.75	0.03	5.65
4	4-F	5.90	6.03	-0.12	5.25
5	4-OCH ₂ CH ₃	5.63	5.82	-0.19	5.55
6	4-O(CH ₂) ₂ N(COMe)CH ₂ CH ₃	6.33	6.17	0.17	5.04
7	3-Me, 4-F	5.85	5.69	0.16	5.75

enhance the activity by through resonance. Bigger X-groups at the 4-position have a negative steric interaction which is detrimental to the activity, as evident by negative MR₄. Once again, we see that the hydrophobicity inhibits the activity.

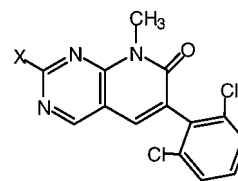
I_{50} of 2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (**I**) (Table 17)⁸⁷

$$\log 1/C = -0.68(\pm 0.27)\text{Clog } P + 9.61(\pm 1.38) \quad (17)$$

$$n = 7, r^2 = 0.897, q^2 = 0.829, s = 0.148, \text{Clog } P = 4.05-5.75$$

Equation 16 was derived for the IC₅₀ data reported by Kraker et al.⁸⁷ Compounds were evaluated for their ability to prevent phosphorylation the same way as for the compounds of data sets 15 and 16. Like eqs 15 and 16, here also we find that an increase in the hydrophobicity is not good for activity.

I_{50} of 2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (**XV**) (Table 18)⁷⁶



XV

$$\log 1/C = -0.22(\pm 0.09)\text{L}_X + 0.38(\pm 0.13)\text{B5}_X + 5.02(\pm 0.58) \quad (18)$$

$$n = 8, r^2 = 0.937, q^2 = 0.729, s = 0.147, \text{Clog } P = 2.21-5.07$$

Outliers: X = NHC₄H₉; X = NH-cy-C₆H₁₁

Twelve compounds could not be included in the regression for lack of parameter values (Table 18). These compounds were also tested by Klutchko et al.⁷⁶ Unlike the other series studied by them (analogues of **I**), here the variation in the molecules is brought about by different X-groups at the 2-position of the pyridopyrimidine itself. Equation 18 derived for the IC₅₀ data indicates that the length of the X-groups has a negative steric interaction with the binding site, but the positive B5 for the same groups shows that bigger and bulkier groups enhance the activity.

Table 18. I_{50} of 2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (XV)⁷⁶

no.	substituent X	log 1/C			L_X	$B5_X$
		obsd	calcd (eq 18)	Δ		
1	NH ₂	5.31	5.17	0.14	2.78	1.97
2	NHCOMe	5.28	5.29	-0.01	5.09	3.61
3	NHMe	5.21	5.43	-0.22	3.53	3.08
4	NHC ₂ H ₅	5.40	5.28	0.12	4.83	3.42
5	NHCHMe ₂	5.50	5.55	-0.05	4.83	4.13
6	NHC ₄ H ₉ ^a	4.99	5.39	-0.40	6.88	4.87
7	NH-cy-C ₆ H ₁₁ ^a	4.90	5.91	-1.00	6.07	5.77
8	NH(CH ₂) ₂ OH	5.19	5.29	-0.10	5.93	4.08
9	NHCH ₂ C ₆ H ₅	4.62	4.58	0.04	8.24	3.53
10	NHC ₆ H ₅	6.40	6.31	0.09	4.53	5.95
11	NH(CH ₂) ₃ N(C ₂ H ₅) ₂ ^b	5.05	4.63	-	-	-
12	NH(CH ₂) ₃ -N-morpholine ^b	5.17	3.53	-	-	-
13	NH(CH ₂) ₃ -N-Me-piperazin-1-yl ^b	5.55	2.64	-	-	-
14	NH(CH ₂) ₄ -N-Me-piperazin-1-yl ^b	6.05	2.66	-	-	-
15	NH(CH ₂) ₅ -N-Me-piperazin-1-yl ^b	6.15	3.19	-	-	-
16	NHCH ₂ -2-pyridyl ^b	5.32	2.99	-	-	-
17	NHCH ₂ -3-pyridyl ^b	5.18	2.99	-	-	-
18	NH(CH ₂) ₂ -2-pyridyl ^b	5.03	3.63	-	-	-
19	NH(CH ₂) ₅ CO ₂ H ^b	6.14	3.73	-	-	-
20	NH-3-pyridyl ^b	6.92	3.58	-	-	-
21	NH-3-(6-OMe-pyridyl) ^b	6.40	3.96	-	-	-
22	NH-4-pyridyl ^b	7.00	3.58	-	-	-

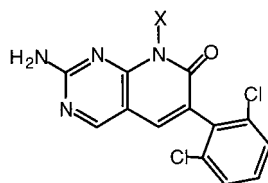
^a Data points not included in deriving equation. ^b Data points not included in deriving equation because of the lack of parameter values.

Table 19. I_{50} of 2-Amino-6-(2,6-di-Cl-phenyl)-8-X-8H-pyrido[2,3-d]pyrimidin-7-ones (XVI)⁸⁸

no.	substituent X	log 1/C			σ^*	π'_X
		obsd	calcd (eq 19)	Δ		
1	Me ^a	5.42	6.00	-0.46	0.00	0.15
2	C ₂ H ₅	6.01	6.04	-0.03	-0.10	0.68
3	C ₃ H ₇	5.92	5.94	-0.02	-0.12	1.20
4	C ₄ H ₉	5.92	5.83	0.10	-0.13	1.73
5	CH ₂ CHMe ₂	5.80	5.86	-0.06	-0.13	1.60
6	CH ₂ CO ₂ Me ^a	5.30	4.23	1.07	1.06	0.33
7	CH ₂ CO ₂ H	4.30	4.33	-0.03	1.05	0.01
8	CH ₂ C ₆ H ₅	5.38	5.21	0.17	0.22	1.91
9	(CH ₂) ₃ NMe ₂	5.75	5.73	0.01	0.08	0.71
10	(CH ₂) ₃ OCH ₂ C ₆ H ₅	5.17	5.31	-0.14	0.08	2.45
11	(CH ₂) ₃ OH	5.96	5.95	0.01	0.08	-0.18

^a Data points not included in deriving equation.

I_{50} of 2-Amino-6-(2,6-di-Cl-phenyl)-8-X-8H-pyrido[2,3-d]pyrimidin-7-ones (XVI) (Table 19)⁸⁸



XVI

$$\log 1/C = -1.63(\pm 0.26)\sigma^* - 0.25(\pm 0.11)\pi'_X + 6.04(\pm 0.16) \quad (19)$$

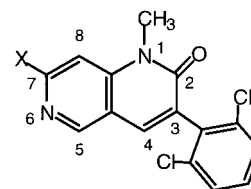
$$n = 9, r^2 = 0.975, q^2 = 0.915, s = 0.102, \text{Clog } P = 1.89-4.52$$

Outliers: Me; CH₂COOMe

Equation 19 was derived from the results of Boschelli et al.⁸⁸ for the inhibitory activity toward

PDGFR-TK. Here, the different X-groups, responsible for variation in the congeners, are attached to the 8-N of the pyrido[2,3-d]pyrimidine moiety. σ^* is for the aliphatic groups, and it appears that electron-releasing groups enhance the activity. Negative π'_X indicates that the X-substituents should not be hydrophobic. It should be noted here that Clog P and π'_X are highly collinear ($r^2 = 0.990$).

I_{50} of 7-X-3-(2,6-Di-Cl-phenyl)-1-Me-1,6-naphthyridin-2(1H)-ones (XVII) (Table 20)⁸⁹



XVII

$$\log 1/C = -2.73(\pm 0.89)\text{CMR} + 0.13(\pm 0.04)(\text{CMR})^2 + 19.19(\pm 4.94) \quad (20)$$

$$n = 11, r^2 = 0.938, q^2 = 0.895, s = 0.173, \text{Clog } P = 2.94-6.83$$

$$\text{inversion point} = 10.44 (9.96-10.75)$$

Outliers: 7-NH-(CH₂)₅-4-Me-piperazin-1-yl;
7-NHC₆H₅; 7-NH-[4-CON(C₂H₅)₂-C₆H₄]

These compounds were tested for their ability to inhibit the phosphorylation of a random glutamate-tyrosine (4:1) copolymer substrate of isolated mouse PDGF- β receptor TK enzyme by Thompson et al.⁸⁹ Equation 20 gave the best correlation for the reported IC₅₀ data. This is again an interesting QSAR which shows that the activity first decreases with the

Table 20. I_{50} of 7-X-3-(2,6-Di-Cl-phenyl)-1-Me-1,6-naphthyridin-2(1H)-ones (XVII)⁸⁹

no.	substituent X	log 1/C			CMR
		obsd	calcd (eq 20)	Δ	
1	7-NH ₂	5.44	5.42	0.02	8.49
2	7-NHMe	5.10	5.21	-0.12	8.96
3	7-NH(CH ₂) ₃ N(C ₂ H ₅) ₂	5.34	5.29	0.05	12.11
4	7-NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	5.55	5.63	-0.08	12.76
5	7-NH(CH ₂) ₄ (4-Me-piperazin-1-yl)	5.96	5.94	0.02	13.23
6	7-NH(CH ₂) ₅ (4-Me-piperazin-1-yl) ^a	5.00	6.31	-1.30	13.69
7	7-NH(CH ₂) ₃ (N-morpholinyl)	5.24	5.28	-0.04	12.09
8	7-NHC ₆ H ₅ ^a	5.85	4.97	0.89	11.01
9	7-NH(4-pyridinyl)	5.16	4.94	0.22	10.79
10	7-NH(4-OMe-C ₆ H ₄)	5.17	5.11	0.06	11.62
11	7-NH(4-O(CH ₂) ₂ N(C ₂ H ₅) ₂ -C ₆ H ₄)	7.00	6.88	0.12	14.31
12	7-NH(4-Me-piperazin-1-yl-C ₆ H ₄)	6.59	6.47	0.11	13.88
13	7-NH(N-morpholinyl-C ₆ H ₄)	5.55	5.92	-0.37	13.21
14	7-NH(4-CON(C ₂ H ₅) ₂ -C ₆ H ₄) ^a	4.80	6.34	-1.54	13.73

^a Data points not included in deriving equation.**Table 21.** I_{50} of 2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (XV)⁸⁹

no.	substituent X	log 1/C			CMR
		obsd	calcd (eq 21)	Δ	
1	NH ₂	5.31	5.38	-0.07	8.28
2	NHMe	5.21	5.11	0.10	8.75
3	NH(CH ₂) ₃ N(C ₂ H ₅) ₂	5.05	5.17	-0.12	11.90
4	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	5.55	5.61	-0.06	12.55
5	NH(CH ₂) ₄ (4-Me-piperazin-1-yl)	6.05	6.00	0.05	13.02
6	NH(CH ₂) ₅ (4-Me-piperazin-1-yl)	6.15	6.47	-0.32	13.48
7	NH(CH ₂) ₃ (N-morpholinyl)	5.17	5.16	0.01	11.87
8	NHC ₆ H ₅ ^a	6.40	4.77	1.63	10.79
9	NH(4-pyridinyl) ^a	7.00	4.74	2.26	10.58
10	NH(4-OMe-C ₆ H ₄) ^a	6.17	4.95	1.22	11.41
11	NH(4-O(CH ₂) ₂ N(C ₂ H ₅) ₂ -C ₆ H ₄)	7.10	7.20	-0.10	14.10
12	NH(4-Me-piperazin-1-yl-C ₆ H ₄)	6.96	6.68	0.28	13.67
13	NH(N-morpholinyl-C ₆ H ₄)	6.19	5.98	0.21	12.99
14	NH(4-CON(C ₂ H ₅) ₂ -C ₆ H ₄)	6.54	6.51	0.03	13.52

^a Data points not included in deriving equation.

increase in CMR up to a CMR value of 10.44, and with a further increase in the size, the activity increases. This is another example of an allosteric effect.

I_{50} of 2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (XV) (Table 21)⁸⁹

$$\log 1/C = -3.46(\pm 1.07)\text{CMR} + 0.17(\pm 0.05)(\text{CMR})^2 + 22.45(\pm 5.73) \quad (21)$$

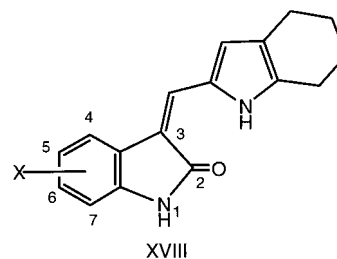
$$n = 11, r^2 = 0.949, q^2 = 0.915, s = 0.184, \text{Clog } P = 2.29 - 6.1$$

$$\text{inversion point} = 10.26 (9.86 - 10.52)$$

Outliers: NH-C₆H₅; NH-(4-pyridinyl);
NH-(4-OMe-C₆H₄)

These compounds were also evaluated for their inhibitory activity against PDGF- β receptor TK by Thompson et al.⁸⁹ Like eq 20, eq 21 also depicts an inverted parabolic correlation with CMR.

I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XVIII) (Table 22)⁹⁰



$$\log 1/C = -0.77(\pm 0.41)\text{CMR} + 12.41(\pm 3.89) \quad (22)$$

$$n = 6, r^2 = 0.873, q^2 = 0.721, s = 0.351, \text{Clog } P = 1.89 - 5.30$$

Outliers: H; 6-(2-OMe-C₆H₄)

Analogues of XVIII were evaluated for their inhibitory activity toward tyrosine phosphorylation for the PDGF- β receptor TK by Sun et al.⁹⁰

The specific study was carried out for inhibition of ligand-dependent tyrosine phosphorylation by the indolin-2-ones in a panel of NIH3T3 mouse fibroblast lines engineered to overexpress human PDGF- β receptor (for details see Sun et al.⁹¹). From eq 22, it appears that the overall size of the molecule creates a steric hindrance in binding to the receptor. Since

Table 22. I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-methylene]-1,3-dihydroindol-2-ones (XVIII)⁹⁰

no.	substituent X	log 1/ <i>C</i>			CMR
		obsd	calcd (eq 22)	Δ	
1	H ^a	5.26	6.24	-0.98	8.05
2	5-Br	6.04	5.65	0.39	8.83
3	5-SO ₂ NH ₂	4.94	5.29	-0.35	9.29
4	5-COOH	5.99	5.74	0.25	8.71
5	6-OMe	5.46	5.77	-0.31	8.67
6	6-C ₆ H ₅	4.15	4.32	-0.17	10.56
7	6-(2-OMe-C ₆ H ₄) ^a	4.86	3.84	1.01	11.18
8	6-(4-OMe-C ₆ H ₄)	4.03	3.84	0.18	11.18

^a Data points not included in deriving equation.

Table 23. I_{50} of 2-(*X*-Phenylamino)-6-(2,6-di-*Cl*-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (I)⁷⁶

no.	substituent X	log 1/ <i>C</i>			Clog <i>P</i>	σ^-	MR ₄
		obsd	calcd (eq 23)	Δ			
1	H	6.34	6.46	-0.12	5.01	0.00	0.10
2	4-Cl	5.52	5.60	-0.08	5.73	0.19	0.60
3	3-Br	5.62	5.62	-0.00	5.88	0.39	0.10
4	4-Me	6.04	6.08	-0.04	5.51	-0.17	0.57
5	2-OMe ^a	5.50	6.74	-1.25	4.94	-0.26	0.10
6	3-OMe	6.43	6.38	0.05	4.94	0.12	0.10
7	4-OMe	6.39	6.35	0.04	4.94	-0.26	0.79
8	3-OH	6.75	6.70	0.05	4.35	0.12	0.10
9	4-OH	6.82	7.06	-0.23	4.35	-0.37	0.29
10	3-CH ₂ OH	7.10	7.01	0.09	3.98	0.00	0.10
11	3-Me,4-OMe	6.35	6.15	0.20	5.44	-0.33	0.79
12	3,5-di-OMe	6.37	6.28	0.08	4.91	0.24	0.10
13	3-CO ₂ C ₂ H ₅	5.82	5.83	-0.00	5.54	0.37	0.10
14	4-CO ₂ C ₂ H ₅	4.47	4.51	-0.04	5.54	0.75	1.75

^a Data point not included in deriving equation.

the variation in size is due to X-substituents at the 5,6-positions, bigger groups at these positions would reduce the activity.

C. Inhibitors of Fibroblast Growth Factor Receptor (FGFR) Tyrosine Kinase

I_{50} of 2-(*X*-Phenylamino)-6-(2,6-di-*Cl*-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (I) (Table 23)⁷⁶

$$\log 1/C = -0.53(\pm 0.16)\text{Clog } P - 0.95(\pm 0.28)\sigma^-_X - 0.58(\pm 0.18)\text{MR}_4 + 9.19(\pm 0.78) \quad (23)$$

$$n = 13, r^2 = 0.975, q^2 = 0.858, s = 0.124, \text{Clog } P = 3.98-6.06$$

Outlier: 2-OMe

The inhibitory activity of these compounds against human FGF-1 receptor tyrosine kinase was also tested by Klutchko et al.⁷⁶ They used recombinant human FGFR-1 tyrosine kinase to study the inhibitory activity. The IC₅₀ values are the concentration of inhibitor required to reduce to 50% the level of ³²P (from added [³²P]ATP) incorporated into a synthetic glutamate-tyrosine copolymer substrate using recombinant. These analogues were also tested for their

Table 24. I_{50} of 2-(*X*-Phenylamino)-6-(2,6-di-*Cl*-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (I)⁸⁷

no.	substituent X	log 1/ <i>C</i>			Clog <i>P</i>
		obsd	calcd (eq 24)	Δ	
1	3-CH ₂ OH	7.21	7.25	-0.04	4.05
2	4- <i>N</i> -morpholinyl ^a	7.01	6.63	0.37	4.91
3	3-SMe	5.90	6.10	-0.20	5.65
4	4-F ^a	6.03	6.39	-0.36	5.25
5	4-OCH ₂ CH ₃	6.35	6.18	0.17	5.55
6	4-O(CH ₂) ₂ N(COMe)CH ₂ CH ₃	6.61	6.54	0.07	5.04
7	3-Me,4-F	6.03	6.03	-0.00	5.75

^a Data points not included in deriving equation.

inhibitory activity against EGFR (eq 1) and PDGFR (eq 16) tyrosine kinases as well. Like eqs 1 and 16, here also Clog *P* has a negative coefficient, indicating a decrease in the activity with an increase in the hydrophobicity. Also like eq 16, the electron-releasing groups enhance the activity and the size of the para substituents has a detrimental effect on the activity. Interestingly, the outlier, 2-OMe, is also the same in these two cases.

I_{50} of 2-(*X*-Phenylamino)-6-(2,6-di-*Cl*-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (I) (Table 24)⁸⁷

$$\log 1/C = -0.72(\pm 0.36)\text{Clog } P + 10.16(\pm 1.88) \quad (24)$$

$$n = 5, r^2 = 0.931, q^2 = 0.777, s = 0.158, \text{Clog } P = 4.05-5.75$$

Outliers: 4-*N*-morpholinyl; 4-F

Analogues of I were tested by Kraker et al.⁸⁷ for their inhibitory activity against human FGF-1 receptor tyrosine kinase. IC₅₀ values were obtained in a similar way as for the data set of the QSAR 23. As with eqs 1, 16, and 17, eq 24 again conveys the negative influence of the hydrophobicity on the activity of the compounds.

I_{50} of 2-*X*-6-(2,6-Di-*Cl*-phenyl)-8-Me-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones (XV) (Table 25)⁸⁹

$$\log 1/C = 0.57(\pm 0.20)\text{Clog } P + 1.08(\pm 0.47)I_{\text{PIP}} + 3.83(\pm 0.94) \quad (25)$$

$$n = 11, r^2 = 0.857, q^2 = 0.791, s = 0.246, \text{Clog } P = 2.29-6.18$$

Outliers: NH₂; NH(CH₂)₃N(C₂H₅)₂; NH(4-pyridinyl)

IC₅₀ for this series was also obtained the same way as for the compounds of Table 23 (eq 23) by Thompson et al.⁸⁹ In this equation, *I*_{PIP} is an indicator variable given a value of 1 for the X-substituents having the piperazine group. It appears that the presence of this group is conducive to activity. Contrary to eqs 23 and 24, this analysis shows a positive effect of the hydrophobicity.

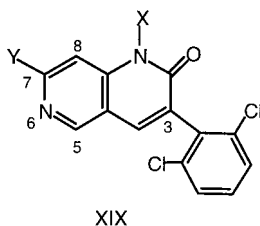
I_{50} of 1-*X*,7-*Y*-3-(2,6-Di-*Cl*-phenyl)-6-naphthyridin-2(1*H*)-ones (XIX) (Table 26)⁸⁹

Table 25. I_{50} of 2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (XV)⁸⁹

no.	substituent X	log 1/C			Clog P	I _{PIP}
		obsd	calcd (eq 25)	Δ		
1	NH ₂ ^a	5.89	5.13	0.76	2.29	0
2	NHMe	5.60	5.60	0.01	3.11	0
3	NH(CH ₂) ₃ N(C ₂ H ₅) ₂ ^a	4.85	6.50	-1.65	4.70	0
4	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	6.42	6.44	-0.02	2.70	1
5	NH(CH ₂) ₄ (4-Me-piperazin-1-yl)	6.50	6.45	0.05	2.71	1
6	NH(CH ₂) ₅ (4-Me-piperazin-1-yl)	6.62	6.75	-0.13	3.24	1
7	NH(CH ₂) ₃ (N-morpholinyl)	5.85	5.87	-0.02	3.60	0
8	NHC ₆ H ₅	6.34	6.72	-0.38	5.09	0
9	NH(4-pyridinyl) ^a	6.72	5.92	0.80	3.68	0
10	NH(4-OMe-C ₆ H ₄)	6.39	6.68	-0.29	5.02	0
11	NH(4-O(CH ₂) ₂ N(C ₂ H ₅) ₂ -C ₆ H ₄)	7.37	7.34	0.03	6.18	0
12	NH(4-Me-piperazin-1-yl-C ₆ H ₄)	7.55	7.45	0.10	4.48	1
13	NH(N-morpholinyl-C ₆ H ₄)	7.00	6.62	0.38	4.91	0
14	NH(4-CON(C ₂ H ₅) ₂ -C ₆ H ₄)	6.75	6.47	0.28	4.65	0

^a Data points not included in deriving equation.**Table 26.** I_{50} of 1-X,7-Y-3-(2,6-Di-Cl-phenyl)-6-naphthyridin-2(1H)-ones (XIX)⁸⁹

no.	substituents		log 1/C			CMR	I _Y
	X	Y	obsd	calcd (eq 26)	Δ		
1	Me	NH ₂	6.42	6.60	-0.18	8.49	0
2	Me	NHMe	6.68	6.56	0.12	8.96	0
3	Me	NH(CH ₂) ₂ N(C ₂ H ₅) ₂ ^a	4.48	6.68	-2.19	11.65	0
4	Me	NH(CH ₂) ₃ N(C ₂ H ₅) ₂	6.82	6.75	0.07	12.11	0
5	Me	NH(CH ₂) ₄ N(C ₂ H ₅) ₂	7.10	6.85	0.25	12.57	0
6	Me	NH(CH ₂) ₅ N(C ₂ H ₅) ₂	7.10	6.96	0.14	13.04	0
7	Me	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	6.77	6.89	-0.12	12.76	0
8	Me	NH(CH ₂) ₄ (4-Me-piperazin-1-yl)	6.77	7.01	-0.24	13.23	0
9	Me	NH(CH ₂) ₅ (4-Me-piperazin-1-yl)	6.96	7.15	-0.19	13.69	0
10	Me	NH(CH ₂) ₃ (N-morpholinyl) ^a	6.24	6.75	-0.51	12.09	0
11	Me	NH(CH ₂) ₄ (N-morpholinyl)	6.64	6.84	-0.21	12.55	0
12	Me	NH(CH ₂) ₃ (imidazol-1-yl)	6.68	6.67	0.01	11.62	0
13	Me	NHC ₆ H ₅	5.66	5.57	0.09	11.01	1
14	Me	NH(4-pyridinyl) ^a	5.46	6.58	-1.12	10.79	0
15	Me	NH(4-OMe-C ₆ H ₄)	5.66	5.65	0.01	11.62	1
16	Me	NH(4-O(CH ₂) ₂ N(C ₂ H ₅) ₂ -C ₆ H ₄) ^a	6.89	6.34	0.55	14.31	1
17	Me	NH(4-O(CH ₂) ₃ N(C ₂ H ₅) ₂ -C ₆ H ₄)	6.60	6.51	0.09	14.77	1
18	Me	NH[4-O(CH ₂) ₂ -(4-Me-piperazin-1-yl)-C ₆ H ₄]	6.68	6.59	0.09	14.97	1
19	Me	NH[4-O(CH ₂) ₃ -(4-Me-piperazin-1-yl)-C ₆ H ₄]	6.92	6.79	0.13	15.43	1
20	Me	NH[(4-Me-piperazin-1-yl)-C ₆ H ₄] ^a	7.38	6.19	1.19	13.88	1
21	Me	NH(N-morpholinyl-C ₆ H ₄) ^a	5.06	5.98	-0.92	13.21	1
22	Me	NH(4-CON(C ₂ H ₅) ₂ -C ₆ H ₄)	5.72	6.14	-0.42	13.73	1
23	H	NH(CH ₂) ₄ N(C ₂ H ₅) ₂	6.77	6.75	0.02	12.11	0
24	H	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	7.14	6.79	0.35	12.30	0
25	H	NH(4-O(CH ₂) ₃ N(C ₂ H ₅) ₂ -C ₆ H ₄)	6.36	6.34	0.02	14.31	1

^a Data points not included in deriving equation.

$$\log 1/C = -0.78(\pm 0.61)\text{CMR} + 0.04(\pm 0.03)(\text{CMR})^2 - 1.02(\pm 0.25)I_Y + 10.34(\pm 3.60) \quad (26)$$

$$n = 19, r^2 = 0.837, q^2 = 0.732, s = 0.204, \text{Clog } P = 2.95 - 7.18$$

$$\text{inversion point} = 9.76 \text{ (5.85-10.79)}$$

Outliers: see Table 26

Equation 26 was obtained from the IC_{50} data for the recombinant FGF-1 receptor, which consisted of a protein truncate encoding the intracellular TK domain. The study was conducted by Thompson et al.⁸⁹ The indicator parameter I_Y was given a value of 1 for the Y-substituents having an NH-C₆H₄ group. The negative coefficient shows that the presence of this group is detrimental to the activity. Again, we obtained an inverted parabolic correlation with CMR. The coefficient with the square term of CMR is small because of the large (CMR)² values, i.e., the size of the molecules. It does indicate a change in the steric interaction with the binding site bringing in a change in the activity of the derivatives.

I_{50} of 2-Amino-6-(2,6-di-Cl-phenyl)-8-X-8H-pyrido[2,3-d]pyrimidin-7-ones (XVI) (Table 27)⁸⁸

Table 27. I_{50} of 2-Amino-6-(2,6-di-Cl-phenyl)-8-X-8H-pyrido[2,3-d]pyrimidin-7-ones (XVI)⁸⁸

no.	substituent X	log 1/C			σ^*	π'_X
		obsd	calcd (eq 27)	Δ		
1	Me	5.89	5.88	0.00	0.00	0.15
2	C ₂ H ₅	6.27	6.24	0.03	-0.10	0.68
3	C ₃ H ₇	6.29	6.33	-0.04	-0.12	1.20
4	C ₄ H ₉	6.24	6.19	0.04	-0.13	1.73
5	CH ₂ CHMe ₂	6.30	6.25	0.05	-0.13	1.60
6	CH ₂ CO ₂ Me ^a	5.77	5.31	0.46	1.06	0.33
7	CH ₂ CO ₂ H	5.10	5.08	0.02	1.05	0.01
8	CH ₂ C ₆ H ₅	5.85	5.87	-0.01	0.22	1.91
9	(CH ₂) ₃ NMe ₂	6.06	6.13	-0.08	0.08	0.71
10	(CH ₂) ₃ OCH ₂ C ₆ H ₅	5.50	5.52	-0.02	0.08	2.45
11	(CH ₂) ₃ OH ^a	6.43	5.55	0.89	0.08	-0.18

^a Data points not included in deriving equation.

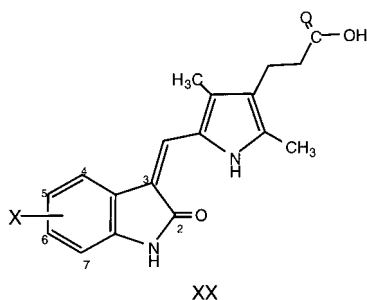
$$\log 1/C = -0.66(\pm 0.18)\sigma^* + 0.87(\pm 0.28)\pi'_X - 0.39(\pm 0.11)(\pi'_X)^2 + 5.76(\pm 0.15) \quad (27)$$

$$n = 9, r^2 = 0.990, q^2 = 0.913, s = 0.053, \text{opt. } \pi'_X = 1.12(1.02-1.21), \text{Clog } P = 1.89-3.80$$

Outliers: CH₂COOMe; (CH₂)₃OH

Boschelli et al.⁸⁸ tested analogues of XVI for the inhibition of recombinant FGFR TK. In eq 27, π'_X is the calculated π value for the variant groups. The QSAR is a parabolic correlation indicating that the activity increases up to an optimum value of $\pi'_X = 1.24$ and then decreases. Like eq 19, σ^* shows that electron-releasing groups have a positive influence on the activity.

I_{50} of X-Substituted 3-[(3,5-Di-Me-4-carboxyethyl-pyrrol-2-yl)methylidene]indolin-2-ones (XX) (Table 28)⁹¹



$$\log 1/C = 0.61(\pm 0.23)B5_5 + 4.73(\pm 0.41) \quad (28)$$

$$n = 8, r^2 = 0.876, q^2 = 0.797, s = 0.214, \text{Clog } P = 0.83-4.23$$

Outlier: 6-(3-OMe-C₆H₄)

These compounds were evaluated for their inhibitory activity against recombinant FGF-R1 by Sun et al.⁹¹ Equation 28 derived from their data reveals that X-groups attached to the 5-positions favor the receptor binding by positive steric interaction in terms of B5.

Table 28. I_{50} of X-Substituted 3-[(3,5-di-Me-4-carboxyethyl-pyrrol-2-yl)methylidene]indolin-2-ones (XX)⁹¹

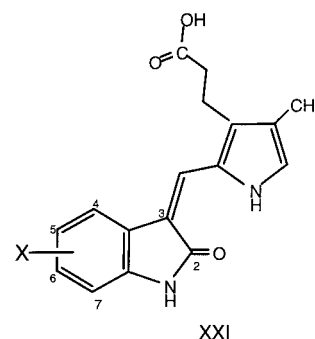
no.	substituent X	log 1/C			B5 ₅
		obsd	calcd (eq 28)	Δ	
1	H	5.52	5.34	0.18	1.00
2	5-Br	5.69	5.93	-0.24	1.95
3	5-COOH	6.55	6.36	0.19	2.66
4	5-SO ₂ NH ₂	6.55	6.60	-0.05	3.05
5	6-OMe	5.27	5.34	-0.07	1.00
6	6-C ₆ H ₅	5.64	5.34	0.30	1.00
7	6-(3-OMe-C ₆ H ₄) ^a	5.85	5.34	0.51	1.00
8	6-(2-OMe-C ₆ H ₄)	5.14	5.34	-0.21	1.00
9	6-(4-OMe-C ₆ H ₄)	5.24	5.34	-0.10	1.00

^a Data point not included in deriving equation.

Table 29. I_{50} of 3-[(3-Carboxyethyl-4-Me-pyrrol-2-yl)methylidene]indolin-2-ones (XXI)⁹¹

no.	substituent X	log 1/C			CMR
		obsd	calcd (eq 29)	Δ	
1	H	7.52	7.63	-0.11	8.42
2	4-Me	7.52	7.36	0.17	8.88
3	5-Br	7.10	7.17	-0.07	9.20
4	6-(3-OMe-C ₆ H ₄)	5.92	5.77	0.16	11.55
5	6-(3-OC ₂ H ₅ -C ₆ H ₄)	5.35	5.49	-0.14	12.01

I_{50} of 3-[(3-Carboxyethyl-4-Me-pyrrol-2-yl)methylidene]indolin-2-ones (XXI) (Table 29)⁹¹



$$\log 1/C = -0.60(\pm 0.17)CMR + 12.66(\pm 1.69) \quad (29)$$

$$n = 5, r^2 = 0.977, q^2 = 0.927, s = 0.173, \text{Clog } P = 1.90-4.26$$

Sun et al.⁹¹ investigated these compounds also for their inhibitory activity against recombinant FGF-R1. Equation 29 derived from their data points to the negative influence of the size of the molecule. However, it should be noted here that there is high mutual correlation between Clog P and CMR ($r^2 = 0.922$). We have kept the equation with CMR because it is statistically better than that with Clog P ($r^2 = 0.924$, $q^2 = 0.758$, $s = 0.315$, the coefficient of Clog $P = -0.993$). Thus, it is hard to predict here if it is a negative steric effect or negative hydrophobic effect.

I_{50} of 5,6-Substituted 3-[(4,5,6,7-tetrahydro-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XVIII) (Table 30)⁹⁰

Table 30. I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XVIII)⁹⁰

no.	substituent X	log 1/C			L_5
		obsd	calcd (eq 30)	Δ	
1	H	4.98	4.83	0.15	2.06
2	5-Br ^a	4.88	6.45	-1.57	3.82
3	5-SO ₂ NH ₂	6.66	6.63	0.02	4.02
4	5-COOH	6.51	6.53	-0.02	3.91
5	6-(3-OMe-C ₆ H ₄)	4.76	4.83	-0.07	2.06
6	6-(2-OMe-C ₆ H ₄)	4.75	4.83	-0.08	2.06

^a Data point not included in deriving equation.**Table 31.** I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-3-carboxyethyl-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XXII)⁹⁰

no.	substituent X	log 1/C			L_5
		obsd	calcd (eq 31)	Δ	
1	H ^a	6.57	5.95	0.62	2.06
2	5-Br	6.57	6.61	-0.04	3.82
3	5-SO ₂ NH ₂	6.70	6.68	0.02	4.02
4	5-COOH	6.66	6.64	0.02	3.91
5	6-OMe	5.97	5.95	0.02	2.06
6	6-C ₆ H ₅	5.90	5.95	-0.05	2.06
7	6-(3-OMe-C ₆ H ₄)	5.87	5.95	-0.08	2.06
8	6-(2-OMe-C ₆ H ₄) ^a	7.10	5.95	1.15	2.06
9	6-(4-OMe-C ₆ H ₄)	6.06	5.95	0.11	2.06

^a Data points not included in deriving equation.

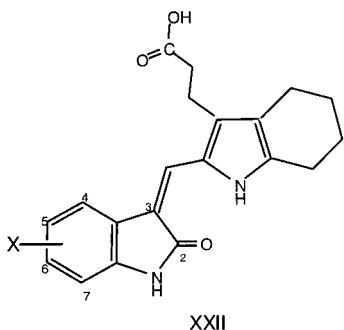
$$\log 1/C = 0.92(\pm 0.16)L_5 + 2.93(\pm 0.49) \quad (30)$$

$$n = 5, r^2 = 0.991, q^2 = 0.979, s = 0.108, \\ \text{Clog } P = 1.89 - 5.25$$

Outlier: 5-Br

As tested for the inhibitory activity against PDGF- β R TK (eq 22), these compounds were also evaluated for their inhibitory activity toward tyrosine phosphorylation for FGF-R1 TK. Equation 30 derived from the reported data indicates that substituents at the 5-position enhance the activity by virtue of their length.

I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-3-carboxyethyl-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XXII) (Table 31)⁹⁰



$$\log 1/C = 0.38(\pm 0.07)L_5 + 5.17(\pm 0.21) \quad (31)$$

$$n = 7, r^2 = 0.973, q^2 = 0.952, s = 0.067, \\ \text{Clog } P = 1.50 - 4.91$$

Outliers: H; 6-(2-OMe-C₆H₄)**Table 32.** I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XVIII)⁹⁰

no.	substituent X	log 1/C			L_5
		obsd	calcd (eq 32)	Δ	
1	H ^a	6.32	4.81	1.51	2.06
2	5-Br	7.16	7.32	-0.17	3.82
3	5-SO ₂ NH ₂	7.52	7.61	-0.09	4.02
4	5-COOH	7.70	7.45	0.25	3.91
5	6-OMe	4.92	4.81	0.11	2.06
6	6-(2-OMe-C ₆ H ₄)	4.70	4.81	-0.11	2.06

^a Data point not included in deriving equation.**Table 33.** I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-3-carboxyethyl-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XXII)⁹⁰

no.	substituent X	log 1/C			Clog <i>P</i>	B ₅	I ₆
		obsd	calcd (eq 33)	Δ			
1	H	7.05	7.00	0.05	3.02	1.00	0
2	5-Br	7.52	7.55	-0.03	4.14	1.00	0
3	5-SO ₂ NH ₂	6.22	6.24	-0.02	1.50	1.00	0
4	5-COOH ^a	8.40	7.01	1.38	3.06	1.00	0
5	6-OMe	6.42	6.47	-0.05	3.09	3.07	1
6	6-C ₆ H ₅	7.30	7.38	-0.07	4.91	3.11	1
7	6-(3-OMe-C ₆ H ₄)	7.16	7.35	-0.20	4.86	-	1
8	6-(2-OMe-C ₆ H ₄)	7.22	7.07	0.15	4.30	-	1
9	6-(4-OMe-C ₆ H ₄)	7.52	7.35	0.17	4.86	3.11	1

^a Data point not included in deriving equation.

This is yet another series tested by Sun et al.⁹⁰ Equation 31 also points to a positive steric interaction of 5-position substituents. Again, like eq 22, the length of the X-groups appears to be conducive to the activity. However, it may be noted here that there exists a high mutual correlation between L_5 with B_{15} and B_{55} (r^2 for L_5 vs B_{15} = 0.927 and for L_5 vs B_{55} = 0.905)

D. Inhibitors of Vascular Endothelial Growth Factor Receptor (VEGF-R2) Tyrosine Kinase

I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XVIII) (Table 32)⁹⁰

$$\log 1/C = 1.43(\pm 0.31)L_5 + 1.86(\pm 1.03) \quad (32)$$

$$n = 5, r^2 = 0.986, q^2 = 0.964, s = 0.201, \\ \text{Clog } P = 1.89 - 4.69$$

Outlier: H

Analogues of XVIII were also investigated for inhibitory activity toward tyrosine kinase phosphorylation for the VEGF-R2 TK. Equation 32 indicates a positive contribution by the length of the substituents at the 5-position.

I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-3-carboxyethyl-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XXII) (Table 33)⁹⁰

Table 34. I_{50} of **X-3-[(3,5-Di-Me-4-carboxyethyl-pyrrol-2-yl)methylidenyl]indolin-2-ones (XX)**⁹¹

no.	substituent X	log 1/C			Clog P	L ₅
		obsd	calcd (eq 34)	Δ		
1	H	5.61	5.27	0.34	2.35	2.06
2	5-Br ^a	5.76	7.71	-1.94	3.47	3.82
3	5-COOH	7.16	7.02	0.13	2.38	3.91
4	5-SO ₂ NH ₂	5.90	6.03	-0.13	0.83	4.02
5	6-OMe	5.08	5.33	-0.25	2.42	2.06
6	6-C ₆ H ₅	6.85	6.61	0.24	4.23	2.06
7	6-(3-OMe-C ₆ H ₄)	6.52	6.58	-0.05	4.18	2.06
8	6-(2-OMe-C ₆ H ₄) ^a	5.36	6.18	-0.82	3.62	2.06
9	6-(4-OMe-C ₆ H ₄)	6.28	6.58	-0.29	4.18	2.06

^a Data points not included in deriving equation.

$$\log 1/C = 0.50(\pm 0.15)\text{Clog } P - 0.56(\pm 0.35)I_6 + 5.49(\pm 0.49) \quad (33)$$

$$n = 8, r^2 = 0.937, q^2 = 0.886, s = 0.143, \text{Clog } P = 1.50-4.91$$

Outlier: 5-COOH

Equation 33 was obtained from the IC₅₀ data obtained by Sun et al.⁹⁰ This equation shows that the hydrophobicity has a positive contribution to the activity. Although most of the equations obtained for inhibition of phosphorylation by TK associated with different growth factor receptors reveal a detrimental effect of the hydrophobicity, this is one of the few equations where we observe a positive effect. It is important to test compounds with a wider and higher range of Clog P. The indicator parameter $I_6 = 1$ for 6-X-substituents. The presence of substituents at the 6-position appears to have a negative effect on the activity, possibly because of steric hindrance in binding to the active site. We could not obtain a statistically strong equation to depict this because of the lack of the parameter values; however the assumption that there is steric interaction in binding is made on the basis of the following equation derived for the same data.

$$\log 1/C = 0.52(\pm 0.16)\text{Clog } P - 0.27(\pm 0.18)B_5 + 5.70(\pm 0.48) \quad (33a)$$

$$n = 6, r^2 = 0.975, q^2 = 0.918, s = 0.115$$

Outlier: 5-COOH

I_{50} of **X-3-[(3,5-Di-Me-4-carboxyethyl-pyrrol-2-yl)-methylidenyl]indolin-2-ones (XX)** (Table 34)⁹¹

$$\log 1/C = 0.71(\pm 0.37)\text{Clog } P + 0.93(\pm 0.52)L_5 + 1.70(\pm 2.28) \quad (34)$$

$$n = 7, r^2 = 0.886, q^2 = 0.651, s = 0.299, \text{Clog } P = 0.83-4.23$$

Outliers: 5-Br; 6-(2-OMe-C₆H₄)

The inhibitory activity of this series was also reported by Sun et al.⁹¹ Equation 34 is consistent with eq 33, where we find a positive role of the hydrophobicity. Also, the length of the 5-position substituents promotes the activity.

Table 35. I_{50} of **2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido-[2,3-d]pyrimidin-7-ones (I)**⁷⁶

no.	substituent X	log 1/C			Clog P	MR ₃
		obsd	calcd (eq 35)	Δ		
1	H	7.70	7.36	0.34	5.01	0.10
2	4-Cl	6.85	6.97	-0.12	5.73	0.10
3	3-Br	7.22	7.24	-0.02	5.88	0.89
4	4-Me	7.30	7.09	0.21	5.51	0.10
5	2-OMe ^a	5.92	7.41	-1.48	4.94	0.10
6	3-OMe ^a	7.30	7.71	-0.41	4.94	0.79
7	4-OMe	7.70	7.41	0.29	4.94	0.10
8	3-OH	7.70	7.81	-0.11	4.35	0.29
9	4-OH	7.40	7.73	-0.33	4.35	0.10
10	3-CH ₂ OH	8.22	8.21	0.01	3.98	0.72
11	3-Me,4-OMe	7.30	7.34	-0.04	5.44	0.57
12	3,5-di-OMe	7.70	7.73	-0.03	4.91	0.79
13	3-CO ₂ C ₂ H ₅	7.85	7.82	0.04	5.54	1.75
14	4-CO ₂ C ₂ H ₅	7.10	7.08	0.02	5.54	0.10
15	4-(CH ₂) ₃ CO ₂ C ₂ H ₅	6.52	6.79	-0.27	6.06	0.10

^a Data points not included in deriving equation.

E. Inhibitors of Nonreceptor Tyrosine Kinase

The nonreceptor tyrosine kinases (NRTKs) contain no extracellular or transmembrane portion but possess modular domains that are responsible for subcellular targeting and regulation of catalytic activity. Since c-Src is likely involved in cellular signaling and amplification of mitogenic signals initiated by other branches of signal transduction pathways, the inhibition of this and other Src kinase family members may provide opportunities for therapeutic intervention in cancer as well as a variety of other proliferative and immunological diseases.

I_{50} of **2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (I)** (Table 35)⁷⁶

$$\log 1/C = -0.55(\pm 0.21)\text{Clog } P + 0.45(\pm 0.28)\text{MR}_3 + 10.06(\pm 1.11) \quad (35)$$

$$n = 13, r^2 = 0.814, q^2 = 0.710, s = 0.213, \text{Clog } P = 3.98-6.06$$

Outliers: 2-OMe; 3-OMe

Equation 35 gave the best correlation for the IC₅₀ data reported by Klutchko et al.⁷⁶ It shows that there is no positive contribution by the hydrophobicity but the meta substituents on the phenylamino moiety have a positive steric interaction.

Kraker et al.⁸⁷ also tested analogues of **I** using recombinant enzyme expressed in a bucalovirus-infected insect cell system. We derived eq 36 from their IC₅₀ data (Table 36).

$$\log 1/C = -0.35(\pm 0.19)\text{Clog } P + 9.71(\pm 0.98) \quad (36)$$

$$n = 6, r^2 = 0.865, q^2 = 0.548, s = 0.097, \text{Clog } P = 4.05-5.75$$

Outlier: 4-F

This is one more equation to support the earlier equations which indicate that the hydrophobicity does not enhance the activity.

I_{50} of **2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (XV)** (Table 37)⁸⁹

Table 36. I_{50} of 2-(X-Phenylamino)-6-(2,6-di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (I)⁸⁷

no.	substituent X	log 1/C			Clog P
		obsd	calcd (eq 36)	Δ	
1	3-CH ₂ OH	8.25	8.31	-0.06	4.05
2	4-N-morpholinyl	8.08	8.01	0.07	4.91
3	3-SMe	7.61	7.75	-0.14	5.65
4	4-F ^a	7.18	7.89	-0.71	5.25
5	4-OCH ₂ CH ₃	7.79	7.79	-0.00	5.55
6	4-O(CH ₂) ₂ N(COMe)CH ₂ CH ₃	8.04	7.97	0.08	5.04
7	3-Me,4-F	7.78	7.72	0.05	5.75

^a Data point not included in deriving equation.

$$\log 1/C = 0.33(\pm 0.19)\text{Clog } P + 0.14(\pm 0.12)\text{CMR} + 4.33(\pm 1.29) \quad (37)$$

$$n = 11, r^2 = 0.846, q^2 = 0.632, s = 0.289, \text{Clog } P = 2.29 - 6.18$$

Outliers: NH(CH₂)₃N(C₂H₅)₂;NH(CH₂)₃-N-morpholinyl; NH-(4-pyridinyl)

These compounds were tested by Thompson et al.⁸⁹ for their ability to prevent phosphorylation of a model glutamate-tyrosine copolymer substrate by isolated avian c-Src tyrosine kinase enzyme. This equation indicates a positive contribution of both Clog P and CMR, which is different from most of the other equations that we have derived so far.

 I_{50} of 1-X,7-Y-3-(2,6-Di-Cl-phenyl)-6-naphthyridin-2(1H)-ones (XIX) (Table 38)⁸⁹

$$\log 1/C = -5.40(\pm 3.11)\text{MgVol} + 1.08(\pm 0.51)(\text{MgVol})^2 - 0.75(\pm 0.38)I_Y - 0.51(\pm 0.36)I_X - 13.53(\pm 4.75) \quad (38)$$

$$n = 23, r^2 = 0.844, q^2 = 0.741, s = 0.269, \text{Clog } P = 2.94 - 7.18$$

inversion point = 2.51(2.01-2.71)

Outliers: X = Me, Y = NH(CH₂)₂N(C₂H₅)₂;X = Me, Y = NH[4-CON(C₂H₅)₂C₆H₄]

These compounds were also evaluated by Thompson et al.⁸⁹ Equation 38 gave the best correlation for

Table 37. I_{50} of 2-X-6-(2,6-Di-Cl-phenyl)-8-Me-8H-pyrido[2,3-d]pyrimidin-7-ones (XV)⁸⁹

no.	substituent X	log 1/C			Clog P	CMR
		obsd	calcd (eq 37)	Δ		
1	NH ₂	6.59	6.27	0.32	2.29	8.28
2	NHMe	6.13	6.61	-0.49	3.11	8.75
3	NH(CH ₂) ₃ N(C ₂ H ₅) ₂ ^a	6.02	7.59	-1.57	4.70	11.90
4	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	6.82	7.02	-0.19	2.70	12.55
5	NH(CH ₂) ₄ (4-Me-piperazin-1-yl)	7.16	7.09	0.06	2.71	13.02
6	NH(CH ₂) ₅ (4-Me-piperazin-1-yl)	7.22	7.33	-0.11	3.24	13.48
7	NH(CH ₂) ₃ (N-morpholinyl) ^a	6.28	7.22	-0.95	3.60	11.87
8	NHC ₆ H ₅	7.70	7.56	0.14	5.09	10.79
9	NH(4-pyridinyl) ^a	8.00	7.06	0.94	3.68	10.58
10	NH-(4-OMe-C ₆ H ₄)	7.70	7.63	0.07	5.02	11.41
11	NH-(4-O(CH ₂) ₂ N(C ₂ H ₅) ₂ -C ₆ H ₄)	8.05	8.40	-0.35	6.18	14.10
12	NH-[(4-Me-piperazin-1-yl)-C ₆ H ₄]	8.00	7.77	0.23	4.48	13.67
13	NH-(N-morpholinyl-C ₆ H ₄)	8.10	7.82	0.28	4.91	12.99
14	NH-(4-CON(C ₂ H ₅) ₂ -C ₆ H ₄)	7.85	7.81	0.05	4.65	13.52

^a Data points not included in deriving equation.

the reported IC₅₀ data. Once again, we get a parabolic correlation with an optimum value which is a minimum and not the maximum. MgVol is the measure of volume of the molecule per McGowan's calculations. It may be noted here that MgVol and CMR may be correlated (r^2 for MgVol vs CMR = 0.986). Hence, eq 38 reveals that volume/size of the molecule has dual steric interaction with the active site. At first the activity decreases with an increase in the size up to MgVol = 2.51, and then with a further increase, the activity increases. In the equation the indicator variables $I_X = 1$ for X = Me and $I_Y = 1$ for Y = NHC₆H₄-(4-O-derivatives). It appears that the presence of Me as X and NHC₆H₄-(4-O-derivatives) as Y is not conducive to the activity.

 I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-3-carboxyethyl-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XXII) (Table 39)⁹⁰

$$\log 1/C = 0.49(\pm 0.10)\text{CMR} + 0.91(\pm 1.08) \quad (39)$$

$$n = 7, r^2 = 0.972, q^2 = 0.937, s = 0.116, \text{Clog } P = 1.50 - 4.86$$

Outliers: 5-COOH; 6-(2-OMe-C₆H₄)

Sun et al.⁹⁰ tested these compounds also to study their inhibitory activity toward tyrosine phosphorylation for the p60^{c-Src} tyrosine kinase. Here we find that the size of the molecule has a positive contribution to the activity.

F. Inhibitors of Src-Homology 2 (SH2)

In addition to a TK domain, NRTKs often contain within the same polypeptide chain several protein-protein or protein-lipid interaction modules such as SH2, SH3, and pleckstrin homology domains.⁹⁷ Src homology (SH2) domains play a critical role in mitogenic intracellular signal transduction by mediating a variety of protein-protein interactions as well as in hormone and immune cell signaling. SH2 domains bind to phosphorylated tyrosine residues in very specific sequences but do not bind to the unphosphorylated proteins. Through SH2-phosphotyrosine interactions, tyrosine kinases and phosphatases can control specific, reversible, protein-

Table 38. I_{50} of 1-X,7-Y-3-(2,6-Di-Cl-phenyl)-6-naphthyridin-2(1H)-ones (XIX)⁸⁹

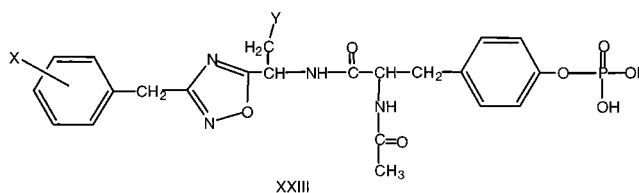
no.	substituents		log 1/C			Mg Vol	I_Y	I_X
	X	Y	obsd	calcd (eq 38)	Δ			
1	Me	NH ₂	6.46	6.37	0.08	2.16	0	1
2	Me	NHMe	6.38	6.29	0.09	2.30	0	1
3	Me	NH(CH ₂) ₂ N(C ₂ H ₅) ₂ ^a	4.89	6.61	-1.72	3.10	0	1
4	Me	NH(CH ₂) ₃ N(C ₂ H ₅) ₂	6.52	6.81	-0.28	3.24	0	1
5	Me	NH(CH ₂) ₄ N(C ₂ H ₅) ₂	7.36	7.05	0.31	3.38	0	1
6	Me	NH(CH ₂) ₅ N(C ₂ H ₅) ₂	7.62	7.33	0.29	3.52	0	1
7	Me	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	7.23	7.03	0.20	3.37	0	1
8	Me	NH(CH ₂) ₄ (4-Me-piperazin-1-yl)	7.39	7.31	0.07	3.51	0	1
9	Me	NH(CH ₂) ₅ (4-Me-piperazin-1-yl)	7.46	7.64	-0.18	3.66	0	1
10	Me	NH(CH ₂) ₃ (N-morpholinyl)	6.70	6.73	-0.03	3.19	0	1
11	Me	NH(CH ₂) ₄ (N-morpholinyl)	7.35	6.96	0.39	3.33	0	1
12	Me	NH(CH ₂) ₃ (imidazol-1-yl)	6.27	6.50	-0.23	3.01	0	1
13	Me	NHC ₆ H ₅	6.10	6.30	-0.20	2.76	0	1
14	Me	NH(4-pyridinyl)	6.26	6.28	-0.02	2.72	0	1
15	Me	NH(4-OMe-C ₆ H ₄)	5.75	5.70	0.05	2.96	1	1
16	Me	NH(4-O(CH ₂) ₂ N(C ₂ H ₅) ₂ -C ₆ H ₄)	7.11	7.17	-0.06	3.77	1	1
17	Me	NH(4-O(CH ₂) ₃ N(C ₂ H ₅) ₂ -C ₆ H ₄)	7.50	7.57	-0.08	3.91	1	1
18	Me	NH[4-O(CH ₂) ₂ -(4-Me-piperazin-1-yl)-C ₆ H ₄]	7.80	7.55	0.25	3.90	1	1
19	Me	NH[4-O(CH ₂) ₃ -(4-Me-piperazin-1-yl)-C ₆ H ₄]	7.55	7.99	-0.43	4.04	1	1
20	Me	NH[(4-Me-piperazin-1-yl)C ₆ H ₄]	7.64	7.41	0.23	3.56	0	1
21	Me	NH(N-morpholinyl-C ₆ H ₄)	6.60	7.04	-0.44	3.38	0	1
22	Me	NH(4-CON(C ₂ H ₅) ₂ -C ₆ H ₄) ^a	6.00	7.47	-1.47	3.58	0	1
23	H	NH(CH ₂) ₄ N(C ₂ H ₅) ₂	7.38	7.31	0.06	3.24	0	0
24	H	NH(CH ₂) ₃ (4-Me-piperazin-1-yl)	6.96	7.30	-0.34	3.23	0	0
25	H	NH(4-O(CH ₂) ₃ N(C ₂ H ₅) ₂ -C ₆ H ₄)	7.96	7.68	0.28	3.77	1	0

^a Data points not included in deriving equation.**Table 39.** I_{50} of 5,6-Substituted-3-[(4,5,6,7-tetrahydro-3-carboxyethyl-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones (XXII)⁹⁰

no.	substituent X	log 1/C			CMR
		obsd	calcd (eq 39)	Δ	
1	H	5.72	5.61	0.12	9.63
2	5-Br	5.90	5.99	-0.09	10.41
3	5-SO ₂ NH ₂	6.17	6.21	-0.05	10.87
4	5-COOH ^a	7.22	5.93	1.30	10.29
5	6-OMe	5.86	5.91	-0.05	10.25
6	6-C ₆ H ₅	6.96	6.83	0.13	12.14
7	6-(3-OMe-C ₆ H ₄)	7.00	7.14	-0.14	12.76
8	6-(2-OMe-C ₆ H ₄) ^a	6.08	7.14	-1.06	12.76
9	6-(4-OMe-C ₆ H ₄)	7.22	7.14	0.09	12.76

^a Data points not included in deriving equation.

protein interactions and thereby the intracellular localization of many signaling molecules. In recent years, three particular SH2-containing targets have been subjected to intense study. The Src SH2 is the most widely studied target, in part because the domain can be used to bind to other proteins but also to control the activity of Src kinase itself by interacting with a phosphotyrosine at the C-terminus of Src. Loss of this tyrosine leads to constitutively active, oncogenic mutant Srcs. The growth receptor-bound protein 2 (Grb2) is another SH2-containing target which has gained some attention recently. It is a very important adapter molecule connecting many RTKs into the Ras-Raf-Mak kinase pathway. The third is Zap-70, a TK that is solely expressed in T-cells and natural killer cells. The importance of ZAP-70 in regulating T-cell functions has made it one of the primary targets for immune suppression.⁹²

 I_{50} of 3-[(CH₂-(X-C₆H₄))-5-[CH(CH₂-Y)NHC(=O)CH(NHC(=O)CH₃)CH₂(4-H₂PO₄-phenyl)]-1,2,4-oxadiazole (XXIII) (Table 40)⁹³

$$\log 1/C = -0.41(\pm 0.22)I_Y - 2.11(\pm 1.46)L_{X,4} + 0.39(\pm 0.24)(L_{X,4})^2 + 6.73(\pm 2.11) \quad (40)$$

$$n = 14, r^2 = 0.846, q^2 = 0.736, s = 0.172, \text{Clog } P = -1.50 - 0.762$$

$$\text{inversion point} = 2.71 (2.14 - 2.91)$$

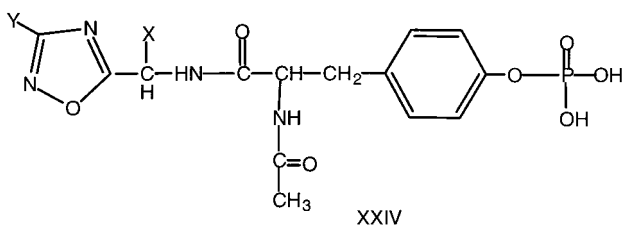
$$\text{Outlier: } X = \text{H}, Y = \text{CH}_2\text{CONH}_2$$

Vu et al.⁹³ studied the Zap-70 SH2 binding for 1,2,4-oxadiazole analogues deriving from glutamine (XXIII). Equation 40 obtained from their data reveals that X-groups have a dual steric interaction for their length at the 4-position. The activity first decreases with an increase in length up to $L_{X,4} = 2.71$, and with further increases in L , it increases leading to a positive steric interaction. The indicator I_Y used here was assigned a value of unity for $Y = \text{CH}_2\text{CONH}_2$. It looks like the presence of a Y-substituent such as CH_2CONH_2 is not good for the binding and hence the inhibitory activity.

 I_{50} of 3-Y-5-[CH(X)NHC(=O)CH(NHC(=O)CH₃)CH₂(4-H₂PO₄-phenyl)]-1,2,4-oxadiazole (XXIV) (Table 41)⁹³

Table 40. I_{50} of Analogs of 1,2,4-Oxadiazol-5-yl (XXIII)⁹³

no.	substituents		log 1/C		Δ	I_Y	$L_{X,4}$
	X	Y	obsd	calcd (eq 40)			
1	H	CH ₂ CONH ₂ ^a	4.14	3.62	0.52	1	2.06
2	4-Me	CH ₂ CONH ₂	3.54	3.47	0.06	1	2.87
3	4-Cl	CH ₂ CONH ₂	3.69	3.72	-0.03	1	3.52
4	3-Cl	CH ₂ CONH ₂	3.59	3.62	-0.04	1	2.06
5	3,4-di-Cl	CH ₂ CONH ₂	3.69	3.72	-0.03	1	3.52
6	2,4,6-tri-Me	CH ₂ CONH ₂	3.51	3.47	0.04	1	2.87
7	4-Me	H	4.19	3.89	0.30	0	2.87
8	4-Cl	H	4.18	4.13	0.05	0	3.52
9	3-Cl	H	4.17	4.04	0.13	0	2.06
10	3,4-di-Cl	H	4.14	4.13	0.01	0	3.52
11	4-CF ₃	H	3.68	4.01	-0.33	0	3.30
12	3-CF ₃	H	3.94	4.04	-0.10	0	2.06
13	4-F	H	3.70	3.88	-0.18	0	2.65
14	4-Br	H	4.51	4.36	0.15	0	3.82
15	4-I	H	4.75	4.78	-0.03	0	4.23

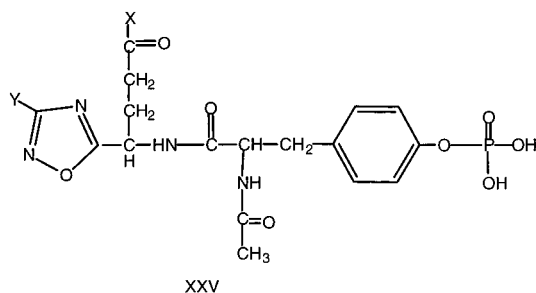
^a Data point not included in deriving equation.

$$\log 1/C = 0.65(\pm 0.13)B5_X + 0.60(\pm 0.20)\pi'_Y + 0.66(\pm 0.73) \quad (41)$$

$$n = 8, r^2 = 0.972, q^2 = 0.931, s = 0.105, \text{Clog } P = -0.88 - 1.63$$

Buchanan et al.⁹⁴ investigated these compounds for their inhibitory activity toward the SH2 domain of the tyrosine kinase p60^{c-Src}. Equation 41 was obtained by us. It indicates a positive contribution of the hydrophobicity by Y-substituents. It also looks as though the bigger X-groups are conducive to the activity.

I_{50} of 3-Y-5-[CH(CH₂CH₂CO-X)NHCOCH(NHCO-CH₃)CH₂(4-H₂PO₄-phenyl)]-1,2,4-oxadiazole (XXV) (Table 42)⁹⁴



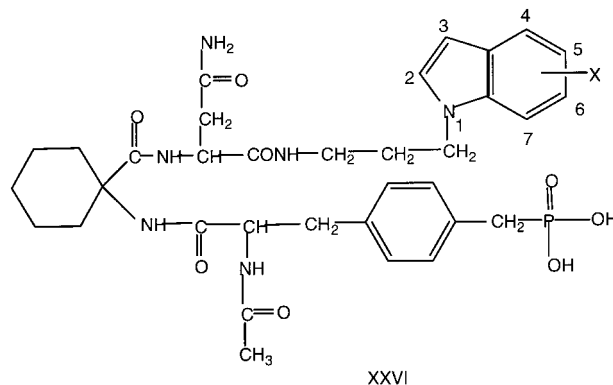
$$\log 1/C = 0.79(\pm 0.23)\text{Clog } P + 4.61(\pm 0.18) \quad (42)$$

$$n = 11, r^2 = 0.874, q^2 = 0.819, s = 0.226, \text{Clog } P = -1.50 - 0.84$$

Outliers: X = NH₂, Y = CH₂C₆H₅; X = NH₂, Y = CH₂-(1-naphthyl); X = NH₂, Y = CH₂C₆H₁₁

This is another series of SH2 ligands studied by Buchanan et al.⁹⁴ Once again, it indicates a positive effect of the hydrophobicity.

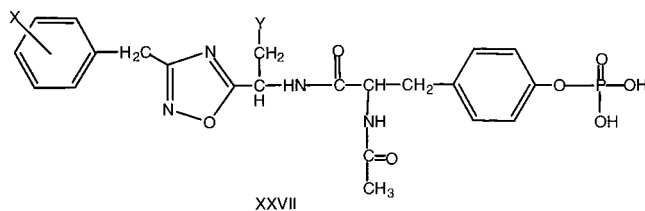
Vu et al.⁹³ also investigated analogues of XXV for Grb2 SH2 domain and that of XXVI for ZAP-70 SH2 domain. We obtained eqs 43 and 44 from their data for the two series (Tables 43 and 44), respectively.



$$\log 1/C = -2.14(\pm 1.24)\text{Clog } P + 11.53(\pm 2.05) \quad (43)$$

$$n = 5, r^2 = 0.910, q^2 = 0.806, s = 0.370, \text{Clog } P = 0.90 - 2.08$$

Outlier: X = 5-Me



$$\log 1/C = 0.32(\pm 0.15)\text{Clog } P + 0.96(\pm 0.21)B1_{X,4} + 3.12(\pm 0.34) \quad (44)$$

$$n = 13, r^2 = 0.950, q^2 = 0.900, s = 0.119, \text{Clog } P = -1.50 - 0.76$$

Outlier: X = 2,4-di-Cl, Y = CH₂CONH₂

In eq 44, B1 of *para*-X-groups appears to have a steric interaction. Hydrophobicity also seems to be conducive to the activity.

IV. Conclusions

One must bear in mind that the chemical structures considered in this review are quite varied and not simple. Often less than 10 compounds comprised a test set; hence, generalizations are hard to make. In general, there are three factors to consider in the development of a QSAR: hydrophobic, electronic, and steric. One needs variation in these properties of substituents at each position of the parent structure to be sure that these properties are considered. Of course with the present varied structures, this would be a tall order. Hence, we regard this review as a first start that we believe will help others to design new structures that will more clearly establish the nature of the receptor sites.

An overview of the occurrences of three major properties is helpful. Considering the hydrophobicity, 16 of the QSAR lack hydrophobic terms. Eighteen have negative hydrophobic terms (eqs 1, 2, 3, 4, 5, 6,

Table 41. I_{50} of Analogs of 1,2,4-Oxadiazol-5-yl (XXIV)⁹⁴

no.	substituents		log 1/C			B5 _X	π'_{γ}
	X	Y	obsd	calcd (eq 41)	Δ		
1	H	CH ₂ -C ₆ H ₁₁	3.05	3.05	0.00	1.00	2.92
2	CH ₂ CH ₂ COOH	CH ₂ CHMe ₂	3.78	3.83	-0.05	3.31	1.73
3	CH ₂ CH ₂ COOH	(CH ₂) ₂ CHMe ₂	4.22	4.15	0.07	3.31	2.26
4	CH ₂ CH ₂ COOH	CH ₂ -C ₆ H ₁₁	4.54	4.55	-0.01	3.31	2.92
5	C ₂ H ₅	(CH ₂) ₅ CH ₃	4.60	4.45	0.15	3.17	2.91
6	C ₂ H ₅	(CH ₂) ₆ CH ₃	4.66	4.76	-0.11	3.17	3.44
7	C ₂ H ₅	(CH ₂) ₄ CH ₃	4.19	4.14	0.05	3.17	2.39
8	C ₂ H ₅	CH ₂ CH ₂ CHMe ₂	3.96	4.06	-0.10	3.17	2.26

Table 42. I_{50} of Analogs of 1,2,4-Oxadiazol-5-yl (XXV)⁹⁴

no.	substituents		log 1/C			Clog <i>P</i>
	X	Y	obsd	calcd (eq 42)	Δ	
1	NH ₂	(CH ₂) ₅ CH ₃	4.62	4.27	0.35	-0.43
2	NH ₂	CH ₂ C ₆ H ₅ ^a	4.14	3.42	0.73	-1.50
3	NH ₂	CH ₂ -(1-naphthyl) ^a	3.87	4.35	-0.48	-0.33
4	NH ₂	CH ₂ CH ₂ C ₆ H ₅	3.81	3.72	0.09	-1.13
5	NH ₂	CH ₂ -C ₆ H ₁₁ ^a	3.56	4.28	-0.72	-0.42
6	NH ₂	(CH ₂) ₂ CHMe ₂	3.50	3.75	-0.25	-1.09
7	NH ₂	(CH ₂) ₃ CH ₃	3.42	3.43	-0.02	-1.49
8	OH	(CH ₂) ₆ CH ₃	5.16	5.27	-0.12	0.84
9	OH	(CH ₂) ₅ CH ₃	5.10	4.86	0.24	0.31
10	OH	(CH ₂) ₄ CH ₃	4.68	4.44	0.24	-0.22
11	OH	CH ₂ C ₆ H ₁₁	4.54	4.86	-0.32	0.31
12	OH	(CH ₂) ₂ CHMe ₂	4.22	4.33	-0.12	-0.35
13	OH	CH ₂ C ₆ H ₅	4.04	4.00	0.04	-0.77
14	OH	CH ₂ CHMe ₂	3.78	3.91	-0.13	-0.88

^a Data points not included in deriving equation.**Table 43.** I_{50} of Analogs of (XXVI)⁹³

no.	substituent X	log 1/C			Clog <i>P</i>
		obsd	calcd (eq 43)	Δ	
1	H	8.92	8.69	0.23	1.33
2	2-Me	7.83	7.62	0.22	1.83
3	3-Me	7.09	7.62	-0.53	1.83
4	5-Me ^a	9.40	7.62	1.78	1.83
5	5-OH	9.52	9.61	-0.08	0.90
6	5-Cl	7.23	7.07	0.16	2.08

^a Data point not included in deriving equation.

7, 8, 11, 15, 16, 17, 19, 23, 24, 35, 36, and 43). Ten have positive terms (eqs 13, 14, 25, 27, 33, 34, 37, 41, 42, and 44). Only QSAR 13, where we get a parabolic correlation with Clog *P*, defines an upper limit for Clog *P* (optimum) of 5.6.

However, from our results if we analyze the role of hydrophobicity with respect to individual receptor tyrosine kinases, we see that among the 14 equations for EGFR TK (QSAR 1–14), nine (eqs 1–8 and 11) have negative coefficients with the hydrophobic term and QSAR 14 has a positive coefficient. Looking at the range of Clog *P* of the molecules in these data sets, we see that data set 14 has a Clog *P* range = 1.64–4.00 and all others have between 3.55 and 7.85, whereas QSAR 13 shows a parabolic correlation giving an optimum value of Clog *P* of 5.6. It appears that binding site of EGFR TK requires molecules to have an optimum hydrophobicity. A variation beyond this value will effect the binding in a negative fashion. However, this can be confirmed only if a data set is prepared in such a way that the analogues

Table 44. I_{50} of Analogs of (XXVII)⁹³

no.	substituents		log 1/C			Clog <i>P</i>	B1 _{X,4}
	X	Y	obsd	calcd (eq 44)	Δ		
1	4-Me	CH ₂ CONH ₂	4.19	4.25	-0.06	-1.01	1.52
2	4-Cl	CH ₂ CONH ₂	4.59	4.59	0.00	-0.79	1.80
3	3-Cl	CH ₂ CONH ₂	4.03	4.82	0.21	-0.79	1.00
4	3,4-di-Cl	CH ₂ CONH ₂	4.85	4.78	0.07	-0.20	1.80
5	2,4-di-Cl	CH ₂ CONH ₂ ^a	3.74	4.82	-1.08	-0.08	1.80
6	4-Me	H	4.48	4.56	-0.08	-0.05	1.52
7	4-Cl	H	4.85	4.90	-0.05	0.17	1.80
8	3-Cl	H	4.22	4.13	0.09	0.17	1.00
9	3,4-di-Cl	H	5.22	5.09	0.13	0.76	1.80
10	4-CF ₃	H	5.16	5.14	0.02	0.34	1.99
11	3-CF ₃	H	4.02	4.19	-0.17	0.34	1.00
12	4-F	H	4.14	4.29	-0.15	-0.40	1.35
13	4-Br	H	5.16	5.09	0.07	0.32	1.95
14	4-I	H	5.30	5.37	-0.07	0.58	2.15

^a Data point not included in deriving equation.

therein have a Clog *P* value between 1.5 and 8.0. Another important point to be noted here is that QSAR 6 and 11–13 are for compounds which form irreversible series.

In the case of PDGFR TK inhibitors, we have eight QSAR (15–22). Out of these, QSAR 16–19 and 21 are derived for pyrido[2,3-*d*]pyrimidines. QSAR 16 and 17 are for compounds having variation due to the different substituents in the phenylamino moiety attached to the 2-position (analogues of **I**). Both of them have negative Clog *P*. Most likely, the phenylamino group interacts with a hydrophobic binding site which is relatively small. QSAR 18 and 21 are for compounds having variation in the 2-position (analogues of **XV**). Both indicate steric interactions with 18 having a negative *L* term and positive B5 for the X-groups at this position. QSAR 21 indicates an inversion in the activity. This is discussed later. QSAR 19 is for compounds having variation due to different groups attached to 8-N- (**XVI**). Here the hydrophobic term, π'_{γ} for the X-substituents, has a negative coefficient.

For FGFR TK inhibitors, QSAR 23 and 24 are also derived for analogues of **I**. Once again, we see a negative coefficient for Clog *P*. QSAR 25, developed for analogues of **XV**, looks different in terms of Clog *P* but indicates that the presence of a piperazinyl at the 2-position is good for activity. QSAR 27 is for compounds having different X-groups attached to 8-N-. It looks like substituents at this position do interact with a hydrophobic site, but the parabolic correlation with π' indicates a limitation to the hydrophobicity of the substituents (optimum for

$\pi' = 1.12$). Other QSAR (28–31), which are developed for indolin-2-ones, do not have any Clog P terms.

QSAR 32–34 are for VEGF–R2 TK inhibitors. All the series are for different derivatives of indolin-2-ones and have very small numbers of compounds. It may not be proper to comment much on the basis of these QSAR, but further work may be worthwhile to search for analogues as two show positive Clog P terms, eqs 33 and 34. Both of them have a range of Clog P on the lower side (1.50–4.91 and 0.83–4.23). It looks like the groups attached at the 5-position have a positive influence in terms of the length and bulkier groups at the 6-position decrease the activity as indicated by negative B_5 (eqs 33 and 33a).

We do not observe any one parameter to be important for nonreceptor TK inhibitors (QSAR 35 and 36). These equations were derived for compounds having variation because of different groups attached to phenylamino group at the 2-position. Both of them show negative Clog P . Nothing much can be said about the other equations at this time.

QSAR 40–44 were derived for inhibitors of Src homology-2 (SH2). Equations 40 and 44 are for Zap-70-SH2 domain; eqs 41 and 42 are for SH2 domain of c-Src; eq 43 is for Grb2 SH2 domain. The molecules, except **XXXI**, are derivatives of 1,2,4-oxadiazole, and all have a strikingly low range of Clog P (–1.50 to 2.08). Not much can be said at this time with such a small number of equations with different parameters significant. It appears from eqs 40 and 44 for inhibitors of ZAP-70 SH2 domain that X-groups attached to the benzyl moiety at the 3-position of oxadiazole have steric interactions with the receptor. Positive $B_{1X,4}$ indicates small atoms at the 4-position enhance activity, while an inverted parabola with $L_{X,4}$ indicates a possible allosteric interaction.

We could not study the electronic effect of the substituents in all the sets. This was because either the substituents are such that σ value is not available or there is not much variation in the σ values. Of course, the biggest limitation was the smaller number of data points in each set where we could not explore more parameters to derive statistically satisfactory QSAR. However, it is interesting to note that wherever we could include electronic terms in the regression analysis, the coefficient is negative (QSAR 7, 8, 9, 12, 14, 15, 16, 19, 23, and 27). This indicates that increasing the electron density on the parent structure increases activity. This holds true for three examples that have field/inductive parameters σ_I or σ^* . Hence, one should capitalize by using electron-releasing substituents in modifying a parent structure. According to the pharmacophore model reported by Furet et al.,⁷⁷ nitrogen of the pyridopyrimidines forms a hydrogen bond with the NH group in the binding site.

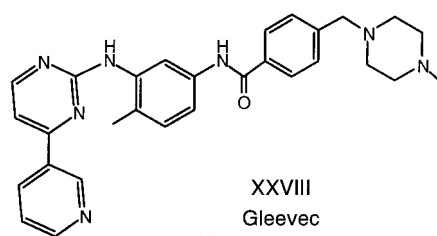
Sterimol parameters (B_1 , B_5 , and L) occur in many of the QSAR, sometimes as positive and sometimes as negative terms. It is difficult to generalize on these factors; still wherever we have a negative coefficient one should consider reducing the size of the substituents. For example, it appears that in the case of benzopyrimidines and pyridopyrimidines with sub-

stituted phenylamino groups, the *meta*-substituents have positive steric interactions, evident by positive $B_{1X,3}$ in QSAR 7 and $B_{5,3}$ in QSAR 14. Positive MR is seen in QSAR 8 and 35.

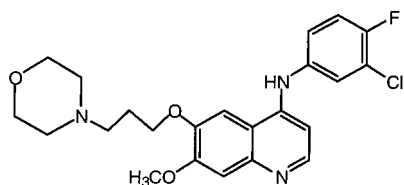
Of great interest to us are QSAR 11, 20, 21, and 26. In these examples CMR has a negative coefficient and CMR^2 has a positive coefficient. This describes an inverted parabola. That is, activity first decreases as CMR increases but then at a certain point turns around and increases. The inversion points for four examples are 11.99, 10.44, 10.26, and 9.76, respectively. Two other QSAR where we get inverted parabolic correlations are 38 (MgVol, inversion point 2.51) and 40 ($L_{X,4}$ inversion point 2.71). Clearly a change in mechanism occurs that we have ascribed to an allosteric effect. The term “allostery” from Greek origin means “another shape”. How well this fits the Monod, Wyman, Changeux^{95,96} model for allosteric effects is not yet known. To detect this phenomenon we would need congeners with CMR values of at least 12. There are three QSAR with negative CMR terms (eqs 4, 22, and 29). QSAR 4 has one congener having CMR = 12. QSAR 22 has been tested with one molecule with a CMR value of 11.2, and QSAR 29 has too few data points to make any estimates. The instances when we have inverted CMR correlations are two examples (eqs 20 and 21) with PDGFR, one with EGFR (eq 11), and one with FGFR (eq 26). The structures of these molecules are so varied that it is difficult to associate an allosteric reaction with any one of the parent structures. However, the same congeners are used in eqs 20 and 26, which suggests something of significance for this parent structure. The allosteric potential of these inhibitors needs further exploration.⁹⁷

There is a great interest in tyrosine kinase and its ability to show an allosteric effect.^{95–97,100} As mentioned in the Introduction, the tyrosine kinase receptor that can exist as dimer or a tetramer is exactly where one would expect to see allosteric effects. At the moment our database of QSAR contains 1333 examples based on CMR or Clog P . About 30 of these indicate an allosteric effect. We have recently described 11 such examples⁹⁸ where the QSAR with CMR is an inverted parabolic relationship. We have also found a number of instances where Clog P yields an inverted parabolic equation.⁹⁹

In the end we would like to consider the compounds which are in the advanced stage of clinical trials (**XXVIII–XXXIV**). Out of these **XXVIII** has been approved recently by the FDA for treating chronic Myelogenous leukemia. Their Clog P and CMR values are also shown.



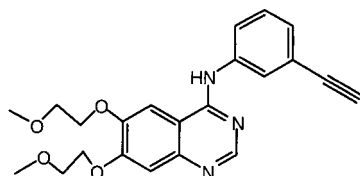
ClogP = 4.53; CMR = 14.63



XXIX

Iressa
ZD 1839

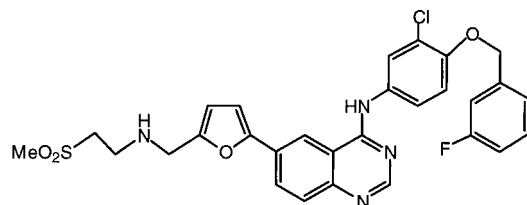
ClogP = 5.60; CMR = 11.70



XXX

OSI-774
(CP358774)

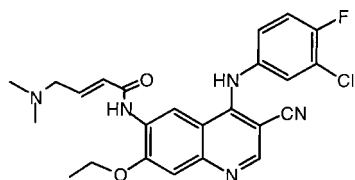
ClogP = 4.06; CMR = 11.03



XXXI

GW 2016

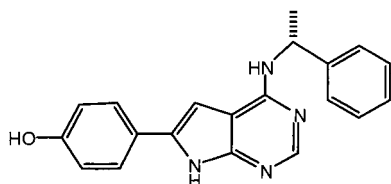
ClogP = 5.61; CMR = 14.84



XXXII

EKB-569

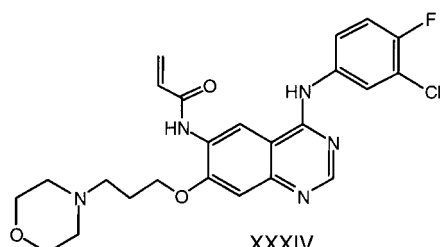
ClogP = 4.76; CMR = 12.25



XXXIII

PKI-166

ClogP = 4.41; CMR = 9.86



XXXIV

PD 183805
(CI-1033)

ClogP = 5.11; CMR = 12.93

The interesting fact about compounds **XXVIII–XXXIV** is that all of these compounds have rather high Clog *P* and CMR values. The CMR values are near or beyond the inversion points that we have found in QSAR 11, 20, 21, and 26. Interestingly, the Clog *P* also ranges from 4.06 to 5.61, near the optimum Clog *P* observed in QSAR 13. The question arises of whether the relatively high Clog *P* is necessary or is this accidental because of the necessity for high CMR. Clog *P* and CMR can be collinear unless care is taken in substituent selection. Of course Clog *P* is important in bioavailability; however, usually values in the range of 1.5–3 suffice for this purpose. A point that also needs to be considered is that just because a receptor can show an allosteric interaction does not mean that it will do so with every series of ligands.

In summary, it must be reiterated that our present review is only the beginning for defining how the tyrosine kinases interact with a variety of ligands. It does, however, provide a variety of suggestions to assist further studies.

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