# A Classical QSAR Study on Some Platelet Aggregation Inhibitors

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**Abstract**: Cardiovascular diseases are still the main cause of morbidity and mortality in the world. Anti-platelet drugs have found clinical application in the secondary prevention of vascular events including acute myocardial infarction, stroke and cardiovascular death. In the present review, we have developed sixteen quantitative structure-activity relationships (QSAR) for different sets of compounds that are X-phenols (**I**), X-catechols (**II**), caffeic acid amides (**III**), X-alcohols (**IV**), 1,4-naphthoquinones (**V**), tetrahydronaphthalenes (**VI**), phenoxyacetaldehyde guanylhydrazones (**VII**), pyrrolobenzylisoquinolines (**VIII**) and phosphonic acids (**IX**) with respect to their anti-platelet activities. QSAR results have shown that the anti-platelet activities of these compounds are largely dependent not only on their hydrophobicity, but also on the influence of their molar refractivity.

**Keywords**: Platelet aggregation inhibitors, Hydrophobicity, CMR, QSAR, Adenosine diphosphate (ADP), Arachidonic acid (AA), collagen (Col), Thrombin (Thr).

## INTRODUCTION

The activation and aggregation of platelets play a critical role in the pathophysiology of thrombotic diseases and would be expected to modify the natural history of cardiovascular diseases [1,2]. Cardiovascular diseases are one of the major causes of morbidity and mortality in the world. Anti-platelet drugs have found clinical application in the secondary prevention of vascular events, including acute myocardial infarction, stroke and cardiovascular death [3]. Aspirin and clopidogrel are two widely used anti-platelet drugs, which act by different mechanisms. The mechanism of action of aspirin involves irreversible inactivation of cyclooxygenase I for the lifespan of the platelet while clopidogrel is an irreversible ADP receptor antagonist. There is a recent trend towards combining these two mechanistically different anti-platelet agents in an effort to reduce coronary events [4,5]. It has been observed that the currently used anti-platelet drugs, including aspirin, clopidogrel, ticlopidine, and others, are effective against certain but not all of the many endogenous platelet activators. Because of the limited efficacy, a significant number of serious thromboembolic complications still occur, highlighting the need for a more effective drug. In the present review, quantitative structure activity relationships (QSAR) were developed for different sets of compounds that are X-phenols (**I**), X-catechols (**II**), caffeic acid amides (**III**), X-alcohols (**IV**), 1,4-naphthoquinones (**V**), tetrahydronaphthalenes (**VI**), phenoxyacetaldehyde guanylhydrazones (**VII**), pyrrolobenzylisoquinolines (**VIII**) and phosphonic acids (**IX**) with respect to their anti-platelet activities. QSAR results have shown that the anti-platelet activities of these compounds are largely dependent on their hydrophobicity, but the importance of their molar refractivity cannot be ignored.

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## EXPERIMENTAL

All the data have been collected from the literature (see individual QSAR for respective references). *C* is the molar concentration of a compound and log 1/*C* is the dependent variable that defines the biological parameter for QSAR equations. Physicochemical descriptors are auto-loaded, and multi-regression analyses (MRA) used to derive the QSAR executed with the C-QSAR program [6]. The parameters used in this report have already been discussed in detail along with their application [7]. Briefly, Clog *P* is the calculated partition coefficient in octanol/water and is a measure of hydrophobicity. Mlog *P* is the experimentally obtained partition coefficient in octanol/water and $\pi$ is the hydrophobic parameter for the substituents. CMR is the calculated molar refractivity for the whole molecule. MR is calculated as: $(n^2\text{-}1/n^2\text{+}2)(MW/\delta)$, where *n* is the refractive index, MW is the molecular weight, and $\delta$ is the density of a molecule. MR is dependent on volume and polarizability. MR can be used for a substituent or for the whole molecule. 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. Each regression equation includes 95% confidence limits for each term in parentheses. In QSAR equations, *n* is the number of data points, *r* is the correlation coefficient, $r^2$ is the goodness of fit, $q^2$ is the goodness of prediction and *s* is the standard deviation.

## RESULTS AND DISCUSSION

Kitagawa *et al*. [8] studied the anti-platelet activities of X-phenols (**I**) against bovine platelet aggregation induced by adenosine diphosphate (ADP), platelet activating factor (PAF), thrombin (Thr) and collagen (Col) respectively. We derived four QSAR equations (**1**-**4**) from their results in Table **1**, which showed excellent correlations between inhibition potencies and the hydrophobicity of X-phenols.

Inhibition of ADP induced bovine platelet aggregation by X-phenols (**I**) (Table **1**) [8].

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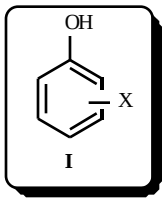
**Table 1. Biological and Physicochemical Constants Used to Derive QSAR Equations (1-4) for the Inhibition of ADP, PAF, Thr and Col Induced Bovine Platelet Aggregations Respectively by X-Phenols (I)**

| No. | X | log 1/C (Eq. 1) | | | log 1/C (Eq. 2) | | | log 1/C (Eq. 3) | | | log 1/C (Eq. 4) | | | Mlog *P* | CMR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | obsd | calcd | Δ | obsd | calcd | Δ | obsd | calcd | Δ | obsd | calcd | Δ | | |
| Ia | H | 2.93 | 2.87 | 0.06 | 2.89 | 3.00 | -0.10 | 2.94 | 2.91 | 0.03 | 2.93 | 3.12 | -0.19 | 1.47 | 2.84 |
| Ib | 3-CN | 3.02 | 3.05 | -0.03 | 3.22 | 3.19 | 0.03 | 2.95 | 3.08 | -0.13 | 3.31 | 3.31 | 0.00 | 1.70 | 3.32 |
| Ic | 4-NO2 | 3.25 | 3.21 | 0.04 | 3.55 | 3.37 | 0.17 | 3.20 | 3.23 | -0.03 | 3.67 | 3.48 | 0.19 | 1.91 | 3.45 |
| Id | 4-$CH_3$ | 3.00 | 3.24 | -0.24 | 3.14 | 3.40 | -0.26 | -- | -- | -- | -- | -- | -- | 1.94 | 3.31 |
| Ie | 4-$C_2H_5$ | 3.71 | 3.65 | 0.06 | 4.01 | 3.86 | 0.15 | 3.56 | 3.63 | -0.07 | -- | -- | -- | 2.47 | 3.77 |
| If | 4-Cl | 3.86 | 3.59 | 0.27 | 3.84 | 3.79 | 0.05 | 3.81 | 3.58 | 0.24 | 3.95 | 3.88 | 0.07 | 2.39 | 3.33 |
| Ig | 2,4-$Cl_2$ | 4.12 | 4.11 | 0.02 | 4.43 | 4.36 | 0.07 | 4.08 | 4.06 | 0.02 | 4.48 | 4.43 | 0.05 | 3.06 | 3.82 |
| Ih | 4-$C_6H_5$ | 4.15 | 4.22 | -0.06 | 4.51 | 4.48 | 0.03 | -- | -- | -- | 4.48 | 4.55 | -0.07 | 3.20 | 5.35 |
| Ii | 2-$CH(CH_3)_2$, 5- $CH_3$ | 3.98 | 4.30 | -0.31 | -- | -- | -- | -- | -- | -- | -- | -- | -- | 3.30 | 4.70 |
| Ij | 2,4,5-$Cl_3$ | 4.82 | 4.62 | 0.20 | 4.79 | 4.93 | -0.14 | 4.48 | 4.54 | -0.06 | 4.92 | 4.97 | -0.05 | 3.72 | 4.32 |




**I**

$$\log 1/C = 0.78(\pm 0.19)\text{Mlog } P + 1.73(\pm 0.49) \quad (1)$$

$n = 10$, $r^2 = 0.920$, $q^2 = 0.870$, $s = 0.187$

range in $\log 1/C = 2.93\text{-}4.82$

A comparison between observed and calculated log 1/*C* of X-phenols (**I**) used in equation (**1**) has been shown in Fig. (**1**).

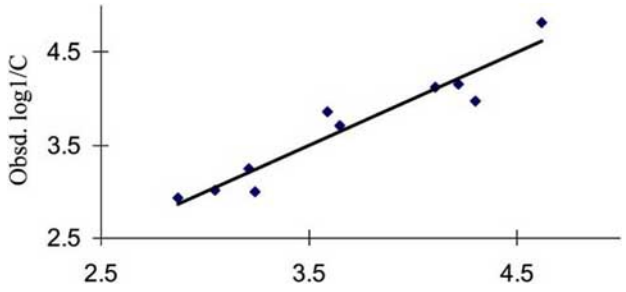



**Fig. (1).** Plot of observed *versus* calculated log1/C (Eq. **1**).

Inhibition of PAF induced bovine platelet aggregation by X-phenols (**I**) (Table **1**) [8].

$$\log 1/C = 0.86(\pm 0.17)\text{Mlog } P + 1.73(\pm 0.42) \quad (2)$$

$n = 9$, $r^2 = 0.956$, $q^2 = 0.923$, $s = 0.150$

range in $\log 1/C = 2.89\text{-}4.79$

Inhibition of Thr induced bovine platelet aggregation by X-phenols (**I**) (Table **1**) [8].

$$\log 1/C = 0.73(\pm 0.17)\text{Mlog } P + 1.84(\pm 0.42) \quad (3)$$

$n = 7$, $r^2 = 0.960$, $q^2 = 0.932$, $s = 0.128$

range in $\log 1/C = 2.94\text{-}4.48$

Inhibition of Col induced bovine platelet aggregation by X-phenols (**I**) (Table **1**) [8].

$$\log 1/C = 0.82(\pm 0.16)\text{Mlog } P + 1.91(\pm 0.42) \quad (4)$$

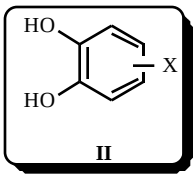
$n = 7$, $r^2 = 0.972$, $q^2 = 0.940$, $s = 0.131$

range in $\log 1/C = 2.93\text{-}4.92$

The correlations expressed by equations (**1-4**) express that highly hydrophobic X-phenols would be favored. Despite the fact that four different types of inducers are involved, QSAR (**1-4**) are very similar and explain 92%, 95.6%, 96%, and 97.2% of the variance in the platelet aggregation data respectively.

Kitagawa *et al*. [9] also studied the anti-platelet activities of X-catechols (**II**) against arachidonic acid (AA) induced rabbit platelet aggregation. We derived equation (**5**) from their results, which indicates that the hydrophobicity of X-catechols has good correlation with their activities.

Inhibition of AA induced rabbit platelet aggregation by X-catechols (**II**) (Table **2**) [9].




**II**

$$\log 1/C = 0.67(\pm 0.32)\text{Clog } P + 4.51(\pm 0.53) \quad (5)$$

$n = 6$, $r^2 = 0.893$, $q^2 = 0.773$, $s = 0.228$

range in $\log 1/C = 4.65\text{-}6.51$

This equation showed that 89.3% of the variance in anti-platelet activity has been correlated with hydrophobicity. A

**Table 2. Biological and Physicochemical Constants Used to Derive QSAR Equation (5) for the Inhibition of AA Induced Rabbit Platelet Aggregation by X-Catechols (II)**

| No. | X | log 1/C (Eq. 5) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|
| | | obsd. | calcd. | Δ | | |
| IIa | 3-OH | 4.65 | 4.65 | 0.00 | 0.21 | 3.15 |
| IIb | 4-$NO_2$ | 5.21 | 5.48 | -0.27 | 1.45 | 3.61 |
| IIc | 4-$CH_3$ | 5.30 | 5.43 | -0.13 | 1.38 | 3.46 |
| IId | H | 5.40 | 5.10 | 0.31 | 0.88 | 2.99 |
| IIe | 4-Cl | 5.79 | 5.83 | -0.05 | 1.98 | 3.49 |
| IIf | 4-$C_6H_5$ | 6.51 | 6.36 | 0.14 | 2.77 | 5.51 |

plot of the observed *versus* calculated log 1/*C* in Fig. (**2**) shows good correspondence between the two variables.

Hung *et al*. [10] studied the anti-platelet activities of caffeic acid amides (**III**) against rabbit platelet aggregation

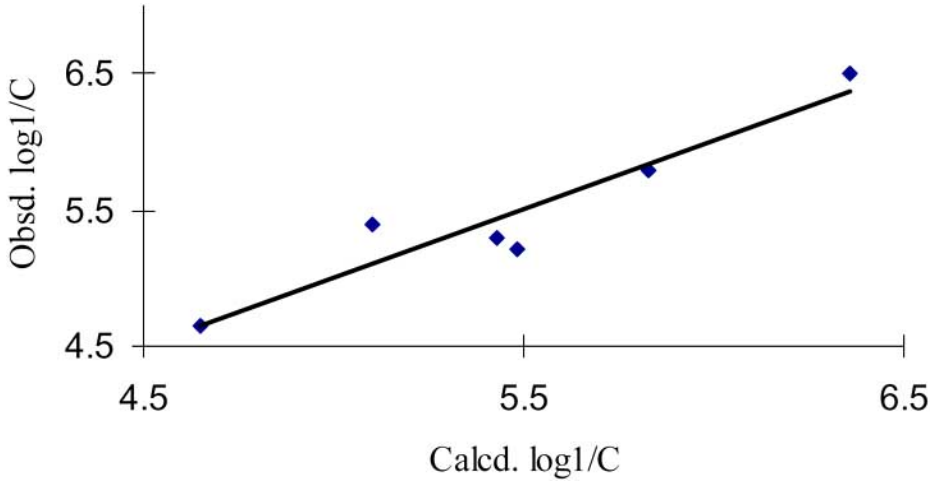



**Fig. (2).** Plot of observed *versus* calculated log1/C (Eq. **5**).

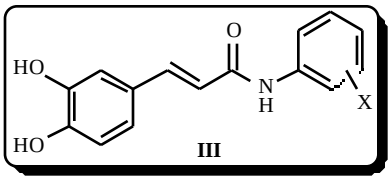
**Table 3. Biological and Physicochemical Constants Used to Derive QSAR Equations (6-8) for the Inhibition of AA, U46619 and MDA Induced rabbit Platelet Aggregations Respectively by Caffeic Acid Amides (III)**

| No | X | log 1/*C* (Eq. 6) | | | log 1/*C* (Eq. 7) | | | log 1/*C* (Eq. 8) | | | $\pi_X$ | Clog *P* | CMR | I |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | obsd | calcd | Δ | obsd | calcd | Δ | obsd | calcd. | Δ | | | | |
| IIIa[a] | H | 4.25 | 4.58 | -0.33 | --- | 3.91 | --- | 5.17 | 5.26 | -0.09 | 0.00 | 2.40 | 7.58 | 0 |
| IIIb | 2-OH | 4.23 | 4.16 | 0.07 | 3.98 | 3.96 | 0.02 | 5.24 | 4.89 | 0.35 | -0.67 | 1.96 | 7.73 | 0 |
| IIIc | 3-OH | 4.19 | 4.16 | 0.03 | --- | 3.96 | --- | 4.64 | 4.75 | -0.11 | -0.67 | 1.73 | 7.73 | 0 |
| IIId[a] | 4-OH | 4.60 | 4.16 | 0.44 | --- | 3.96 | --- | 4.71 | 4.75 | -0.04 | -0.67 | 1.73 | 7.73 | 0 |
| IIIe | 2-F | 4.67 | 4.67 | 0.00 | --- | 3.91 | --- | 5.06 | 5.13 | -0.07 | 0.14 | 2.20 | 7.60 | 0 |
| IIIf | 3-F | 4.59 | 4.67 | -0.08 | --- | 3.91 | --- | 5.57 | 5.51 | 0.06 | 0.14 | 2.80 | 7.60 | 0 |
| IIIg | 4-F | 4.66 | 4.67 | -0.01 | --- | 3.91 | --- | 5.64 | 5.51 | 0.13 | 0.14 | 2.80 | 7.60 | 0 |
| IIIh[b] | 2-Cl | 4.73 | 4.57 | 0.16 | --- | 4.06 | --- | 5.51 | 5.04 | 0.47 | 0.71 | 2.52 | 8.07 | 1 |
| IIIi[b] | 3-Cl | 4.38 | 4.57 | -0.19 | --- | 4.06 | --- | 4.66 | 5.58 | -0.92 | 0.71 | 3.37 | 8.07 | 1 |
| IIIj | 4-Cl | 4.59 | 4.57 | 0.02 | 4.02 | 4.06 | -0.04 | 5.46 | 5.58 | -0.12 | 0.71 | 3.37 | 8.07 | 1 |
| IIIk | 2-Br | 5.24 | 5.12 | 0.12 | --- | 4.15 | --- | 5.03 | 4.94 | 0.09 | 0.86 | 2.64 | 8.36 | 0 |
| IIIl[b] | 3-Br | 5.17 | 5.12 | 0.05 | --- | 4.15 | --- | 5.09 | 5.50 | -0.41 | 0.86 | 3.52 | 8.36 | 0 |
| IIIm[a, b] | 4-Br | 4.79 | 5.12 | -0.33 | 4.18 | 4.15 | 0.03 | 4.94 | 5.50 | -0.56 | 0.86 | 3.52 | 8.36 | 0 |
| IIIn | 3-CN | 4.19 | 4.22 | -0.03 | --- | 4.06 | --- | 4.76 | 4.99 | -0.23 | -0.57 | 2.43 | 8.06 | 0 |
| IIIo | 2-$COOC_2H_5$ | 4.75 | 4.90 | -0.15 | 4.42 | 4.40 | 0.03 | 4.97 | 4.91 | 0.06 | 0.51 | 3.37 | 9.16 | 0 |
| IIIp[a] | 3,4-$(OCH_3)_2$ | 4.22 | 4.55 | -0.33 | 4.25 | 4.29 | -0.04 | 4.32 | 4.35 | -0.03 | -0.04 | 2.15 | 8.81 | 0 |

[a]Not included in the derivation of QSAR (**6**); [b]Not included in the derivation of QSAR (**8**)

induced by arachidonic acid (AA), U46619 and MDA, respectively. The following QSAR equations (**6**, **7** and **8**) have been derived form their results.

Inhibition of AA induced rabbit platelet aggregation by caffeic acid amides (**III**) (Table **3**) [10].




**III**

$$\log 1/C = 0.63(\pm 0.15)\pi_X - 0.46(\pm 0.20)I + 4.58(\pm 0.09) \quad (6)$$

$n = 12$, $r^2 = 0.911$, $q^2 = 0.822$, $s = 0.113$

outliers: H; 4-OH; 4-Br; 3,4-$(OCH_3)_2$

range in log 1/*C* = 4.19-5.24

Clog *P* cannot be used to correlate the above data. Hydrophobic parameter of X-substituents ($\pi_X$) is the most significant parameter, which can explain more than sixty-three percent of the variance in the data. The indicator variable *I* takes the value of 1 for X = Cl. 91.1% of the variance in anti-platelet activity has been explained by this equation. When the equation (**6**) was derived without dropping any compound, the statistics were not acceptable ($r^2 = 0.654$, $q^2 = 0.465$). Four of the caffeic acid amides (**IIIa**, **IIId**, **IIIm** and **IIIp**) in Table (**3**) were deemed to be outliers on the basis of their deviations (2 x SD). A comparison between observed and calculated log 1/*C* has been shown in Fig. (**3**).

Inhibition of U46619 induced rabbit platelet aggregation by caffeic acid amides (**III**) (Table **3**) [10].

$$\log 1/C = 0.31(\pm 0.12)\text{CMR} + 1.58(\pm 1.02) \quad (7)$$

$n = 5$, $r^2 = 0.956$, $q^2 = 0.873$, $s = 0.043$

range in log 1/*C* = 3.98-4.42

Equation (**7**) showed that 95.6% of the variance in anti-platelet activity has been correlated with CMR. Clog *P* cannot be used to correlate the above data.

Inhibition of MDA induced rabbit platelet aggregation by caffeic acid amides (**III**) (Table **3**) [10].

$$\log 1/C = 0.64(\pm 0.22)\text{Clog } P - 0.61(\pm 0.24)\text{CMR} + 8.39(\pm 1.73) \quad (8)$$

$n = 12$, $r^2 = 0.859$, $q^2 = 0.782$, $s = 0.165$

outliers: 2-Cl; 3-Cl; 3-Br; 4-Br

range in log 1/*C* = 4.32-5.66

This equation is able to explain 85.9% of data variance. When the equation (**8**) was derived without dropping any compound, the statistics were not acceptable ($r^2 = 0.413$, $q^2 = 0.110$). Four compounds in Table (**3**) were deemed to be outliers on the basis of their deviations (2 x SD).

In another attempt, Kitagawa *et al*. [11] studied the anti-platelet activities of X-alcohols (**IV**) against adenosine

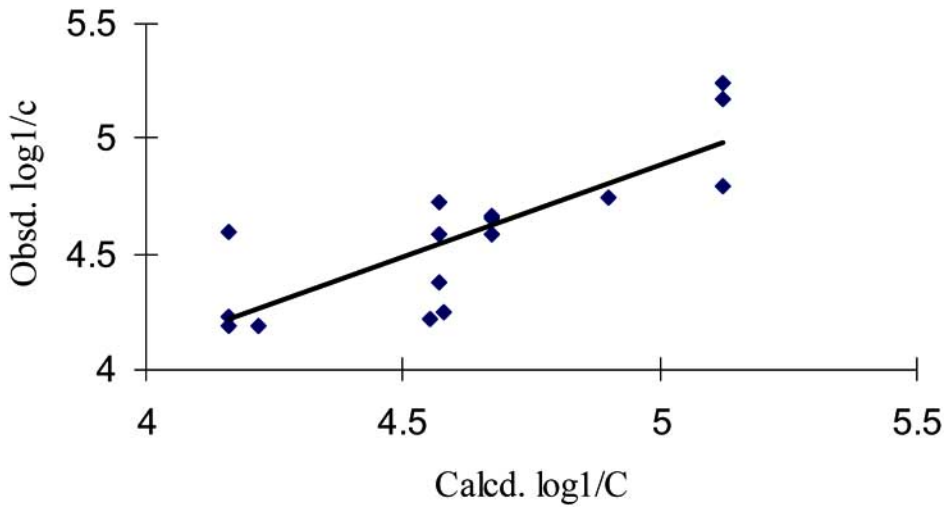


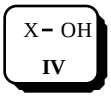

**Fig. (3).** Plot of observed *versus* calculated log1/C (Eq. **6**).

**Table 4. Biological and Physicochemical Constants Used to Derive QSAR Equation (9) and (9a) for the Inhibition of ADP Induced Bovine Platelet Aggregation by X-Alcohols (IV)**

| No. | X | log 1/*C* obsd | log 1/*C* (Eq. 9) | | log 1/*C* (Eq. 9a) | | Mlog *P* | CMR |
|---|---|---|---|---|---|---|---|---|
| | | | calcd | Δ | calcd | Δ | | |
| IVa | $C_3H_7$ | 0.56 | 0.51 | 0.05 | 0.50 | 0.06 | 0.34 | 1.72 |
| IVb | $C_4H_9$ | 1.01 | 1.05 | -0.04 | 1.05 | -0.04 | 0.88 | 2.19 |
| IVc | $C_5H_{11}$ | 1.52 | 1.57 | -0.05 | 1.61 | -0.09 | 1.40 | 2.65 |
| IVd | $C_6H_{13}$ | 2.24 | 2.20 | 0.04 | 2.17 | 0.07 | 2.03 | 3.11 |

diphosphate (ADP) induced bovine platelet aggregation. An excellent correlation between the activities of X-alcohols (**IV**) and their hydrophobic parameters has been derived as shown by equation (**9**).

Inhibition of ADP induced bovine platelet aggregation by X-alcohols (**IV**) (Table **4**) [11].




**IV**

$$\log 1/C = 1.00(\pm 0.22)\text{Mlog } P + 0.29(\pm 0.18) \quad (9)$$

$n = 4$, $r^2 = 0.995$, $q^2 = 0.964$, $s = 0.064$

range in $\log 1/C = 0.56\text{-}2.24$

Equation (**9**) explains 99.5% of the variance in anti-platelet activity data. A plot of the observed *versus* calculated log 1/*C* in Fig. (**4**) shows best correspondence between the two variables. It is interesting to note here that there is a high mutual correlation between Clog *P* & CMR ($r^2 = 0.998$, $q^2 = 0.990$). Thus, the equation (**9a**) was derived with CMR, which gave exactly the same statistics with that of Clog *P*. Now, it is very hard to predict which is the most important hydrophobic or polarizability. We prefer equation (**9**) because the variation at substituents in the compounds is only in the alkyl groups. The statistics of equation (**9**) is also better than that of equation (**9a**).

$$\log 1/C = 1.20(\pm 0.41)\text{CMR} - 1.56(\pm 1.01) \quad (9a)$$

$n = 4$, $r^2 = 0.988$, $q^2 = 0.921$, $s = 0.098$

Lien *et al*. [12] studied the anti-platelet activities of 1,4-naphthoquinones (**V**) against platelet aggregation induced by arachidonic acid (AA) and collagen (Col). From these data,

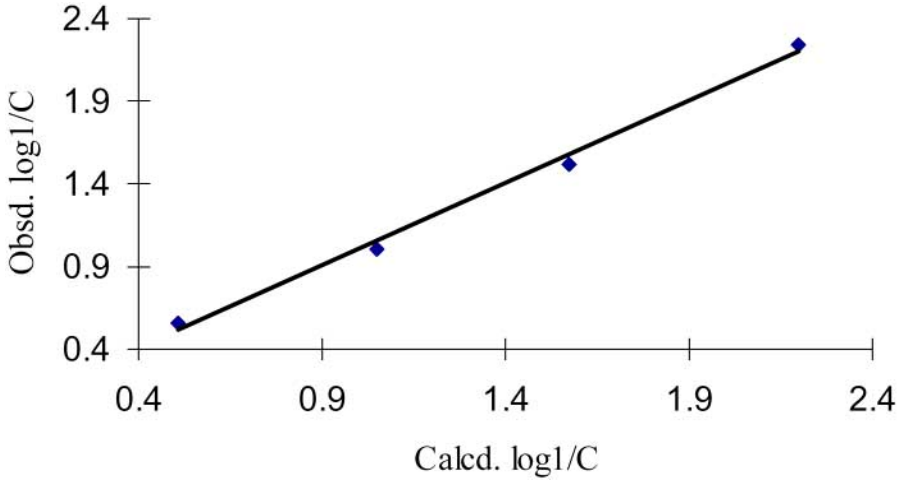



**Fig. (4).** Plot of observed *versus* calculated log1/C (Eq. **9**).

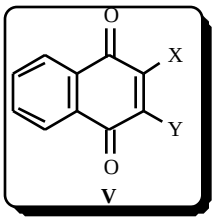
**Table 5. Biological and Physicochemical Constants Used to Derive QSAR Equations 10 and 11 for the Inhibition of AA Induced Platelet Aggregation and Col Induced Platelet Aggregation by 1,4-Naphthoquinones (V)**

| No. | X | Y | log 1/C (Eq. 10) | | | log 1/C (Eq. 11) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | obsd. | calcd | Δ | obsd. | calcd | Δ | | |
| Va[a] | $OCH_3$ | Cl | 4.72 | 4.48 | 0.24 | 4.47 | 4.44 | 0.02 | 2.55 | 5.37 |
| Vb | $OCH_3$ | H | 4.27 | 4.28 | -0.01 | 4.14 | 4.24 | -0.11 | 1.78 | 4.88 |
| Vc | $OC_2H_5$ | Cl | 4.47 | 4.58 | -0.11 | -- | -- | -- | 2.94 | 5.83 |
| Vd | $OC_2H_5$ | H | 4.42 | 4.38 | 0.04 | 4.36 | 4.34 | 0.02 | 2.17 | 5.34 |
| Ve | $O(CH_2)_2CH_3$ | Cl | 4.69 | 4.72 | -0.03 | 4.61 | 4.68 | -0.07 | 3.47 | 5.60 |
| Vf | $O(CH_2)_3CH_3$ | Cl | 4.70 | 4.86 | -0.16 | 4.66 | 4.82 | -0.16 | 4.00 | 6.76 |
| Vg | $O(CH_2)_4CH_3$ | Cl | 5.06 | 5.00 | 0.06 | 4.97 | 4.96 | 0.02 | 4.53 | 7.22 |
| Vh | $OCH_2C_6H_5$ | Cl | 4.97 | 4.88 | 0.09 | 4.92 | 4.84 | 0.09 | 4.08 | 7.88 |
| Vi | $O(CH_2)_2CH_3$ | H | 4.58 | 4.52 | 0.06 | 4.59 | 4.48 | 0.11 | 2.69 | 5.80 |
| Vj | $OCH(CH_3)_2$ | H | 4.44 | 4.46 | -0.02 | 4.46 | 4.42 | 0.04 | 2.47 | 5.80 |
| Vk | $O(CH_2)_3CH_3$ | H | 4.63 | 4.66 | -0.03 | 4.64 | 4.62 | 0.02 | 3.22 | 6.27 |
| Vl[b] | $O(CH_2)_4CH_3$ | H | 4.77 | 4.80 | -0.03 | 4.52 | 4.75 | -0.23 | 3.75 | 6.73 |
| Vm | $OCH_2C_6H_5$ | H | 4.82 | 4.68 | 0.14 | 4.66 | 4.64 | 0.03 | 3.30 | 7.39 |

[a]Not included in the derivation of QSAR (**10**); [b]Not included in the derivation of QSAR (**11**)

we derived equations (**10**) and (**11**), which gave excellent correlations between activities and hydrophobicity of the molecules (**V**).

Inhibition of AA induced platelet aggregation by 1,4-naphthoquinones (**V**) (Table **5**) [12].




**V**

$$\log 1/C = 0.26(\pm 0.07)\text{Clog } P + 3.81(\pm 0.23) \quad (10)$$

$n = 12$, $r^2 = 0.873$, $q^2 = 0.826$, $s = 0.086$

*outlier:* X = $OCH_3$, Y = Cl

range in log $1/C$ = 4.27-5.06

One compound was omitted on the basis of their deviation (2 x SD). A plot of the observed *versus* calculated log $1/C$ has been shown in Fig. (**5**).

Inhibition of Col induced platelet aggregation by 1,4-naphthoquinones (**V**) (Table **5**) [12].

$$\log 1/C = 0.26(\pm 0.07)\text{Clog } P + 3.78(\pm 0.22) \quad (11)$$

$n = 11$, $r^2 = 0.889$, $q^2 = 0.822$, $s = 0.084$

*outlier:* X = $O(CH_2)_4CH_3$, Y = H

range in log $1/C$ = 4.14-4.97

Despite the fact that two different types of inducers are involved, QSAR (**10**) and (**11**) are very similar and explain 87.3% and 88.9% of the variance in the platelet aggregation inhibitory data respectively.

Cimetiere *et al*. [13] studied the anti-platelet activities of tetrahydronaphthalenes (**VI**) against U46619 induced human platelet aggregation. Equation (**12**) was derived from their results, which indicates that the hydrophobicity of

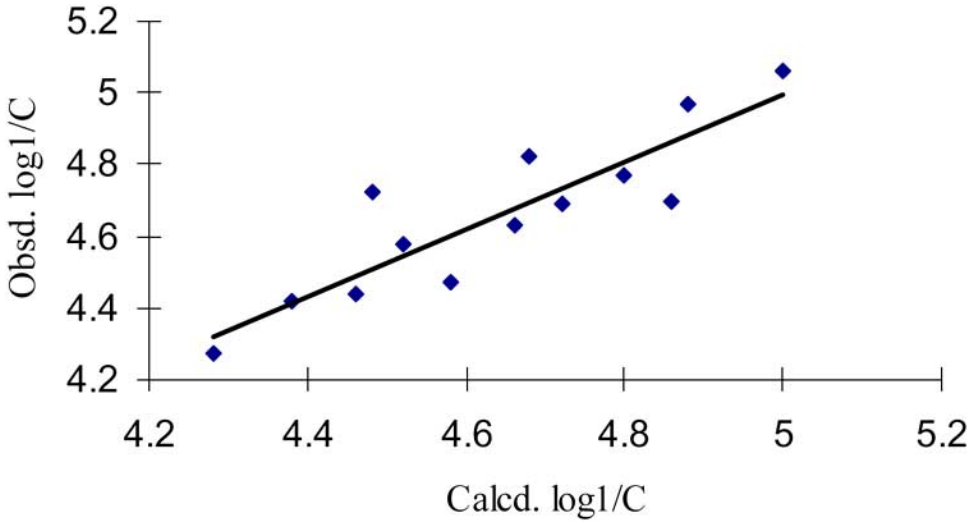



**Fig. (5).** Plot of observed *versus* calculated log1/C (Eq. **10**).

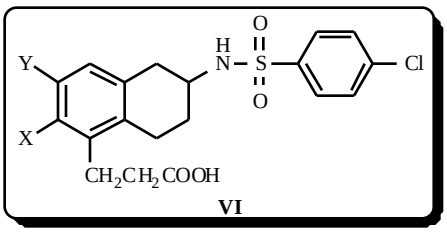
**Table 6. Biological and Physicochemical Constants Used to Derive QSAR Equation (12) for the Inhibition of U46619 Induced Platelet Aggregation by Tetrahydronaphthalenes (VI)**

| No. | X | Y | log1/C (Eq.12) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|---|
| | | | obsd | calcd | Δ | | |
| VIa | H | $CH_3$ | 6.55 | 6.73 | -0.18 | 4.59 | 10.65 |
| VIb | H | $CH_2C_6H_5$ | 8.22 | 7.83 | 0.39 | 6.16 | 13.17 |
| VIc | H | $CH_2C_6H_4$(4-F) | 7.96 | 7.93 | 0.02 | 6.30 | 13.18 |
| VId | H | $CH_2C_6H_4$(2-$CH_3$) | 8.10 | 8.15 | -0.05 | 6.60 | 13.63 |
| VIe[a] | H | $CH_2C_6H_4$(4-$C_6H_5$) | 7.31 | 9.16 | -1.85 | 8.04 | 15.68 |
| VIf | H | $CH_2C_6H_4$(3-$OCH_3$) | 7.46 | 7.78 | -0.32 | 6.07 | 13.78 |
| VIg | H | $CH_2C_6H_4$(3-CN) | 7.44 | 7.43 | 0.01 | 5.59 | 13.64 |
| VIh[a] | $CH_3$ | $CH_3$ | 5.77 | 7.01 | -1.24 | 4.99 | 11.12 |
| VIi | | Ramatroban | 6.42 | 6.29 | 0.13 | 3.97 | 10.83 |

[a]Not included in the derivation of QSAR (**12**)

tetrahydronaphthalenes (**VI**) has an excellent correlation with their activities.

Inhibition of U46619 induced platelet aggregation by tetrahydronaphthalenes (**VI**) (Table **6**) [13].




**VI**

$$\log 1/C = 0.71(\pm 0.27)\text{Clog } P + 3.49(\pm 1.51) \quad (12)$$

$n = 7$, $r^2 = 0.903$, $q^2 = 0.820$, $s = 0.246$

*outliers:* X = H, Y = $CH_2C_6H_4(4\text{-}C_6H_5)$; X = Y = $CH_3$

range in log 1/*C* = 5.77-8.22

Equation (**12**) showed that 90.3% of the variance in the anti-platelet activity has been correlated with hydrophobicity. When the linear correlation was derived without dropping any compound, the statistics were not acceptable ($r^2$ = 0.397, $q^2$ = -0.331). Two compounds in Table (**6**) were deemed to be outliers on the basis of their deviations (2 x SD). A comparison between observed and calculated log 1/*C* has been shown in Fig. (**6**).

Berge *et al*. [14] studied the anti-platelet activities of phenoxyacetaldehyde guanylhydrazones (**VII**) against adenosine diphosphate (ADP) induced human platelet aggregation. Equation (**13**) was derived from their results, which indicates that the hydrophobicity of X-substituents ($\pi_X$) of compounds (**VII**) has an excellent correlation with their activities.

Inhibition of ADP induced human platelet aggregation by phenoxyacetaldehyde guanylhydrazones (**VII**) (Table **7**) [14].

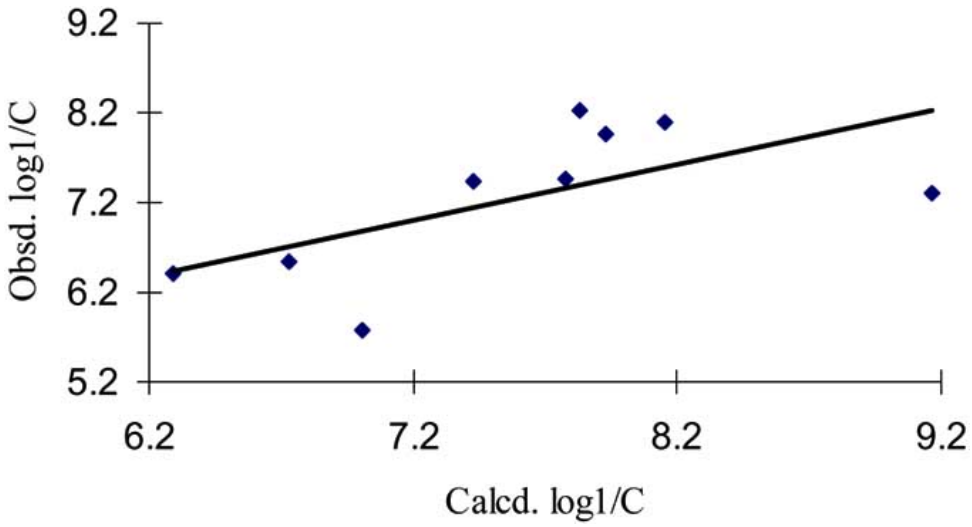
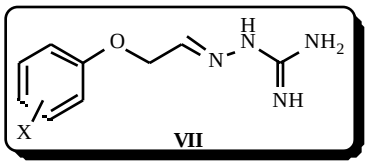



**Fig. (6).** Plot of observed *versus* calculated log1/C (Eq. **12**).

**Table 7. Biological and Physicochemical Constants Used to Derive QSAR Equation (13) for the Inhibition of ADP Induced Human Platelet Aggregation by Phenoxyacetaldehyde Guanylhydrazones (VII).**

| No. | X | log 1/C (Eq. 13) | | | $\pi_X$ | Clog *P* | CMR |
|---|---|---|---|---|---|---|---|
| | | obsd | calcd | Δ | | | |
| VIIa | H | 2.92 | 2.93 | -0.01 | 0.00 | 0.81 | 5.51 |
| VIIb | 2-Cl | 3.22 | 3.24 | -0.02 | 0.71 | 1.44 | 6.00 |
| VIIc | 3-Cl | 3.31 | 3.24 | 0.07 | 0.71 | 1.67 | 6.00 |
| VIId | 4-Cl | 3.25 | 3.24 | 0.01 | 0.71 | 1.67 | 6.00 |
| VIIe | 2-$OCH_3$ | 2.96 | 2.92 | 0.04 | -0.02 | 0.55 | 6.12 |
| VIIf | 4-$OCH_3$ | 2.86 | 2.92 | -0.06 | -0.02 | 0.90 | 6.12 |
| VIIg | 2-$CH_3$ | 3.29 | 3.18 | 0.11 | 0.56 | 1.31 | 5.97 |
| VIIh | 3-$CH_3$ | 3.17 | 3.18 | -0.01 | 0.56 | 1.31 | 5.97 |
| VIIi | 4-$CH_3$ | 3.09 | 3.18 | -0.09 | 0.56 | 1.31 | 5.97 |
| VIIj | 4-F | 3.01 | 2.99 | 0.02 | 0.14 | 1.10 | 5.52 |
| VIIk | 4-Br | 3.25 | 3.31 | -0.06 | 0.86 | 1.82 | 6.28 |




**VII**

$$\log 1/C = 0.44(\pm 0.13)\pi_X + 2.93(\pm 0.07) \quad (13)$$

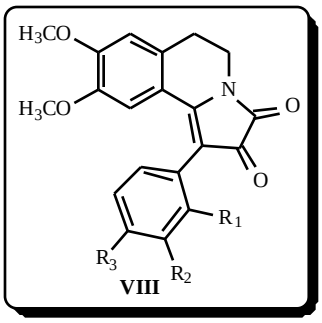
$n = 11$, $r^2 = 0.865$, $q^2 = 0.808$, $s = 0.062$

range in log $1/C$ = 2.86-3.31

Equation (**13**) explains 86.5% of the variance in anti-platelet activity data. A plot of the observed *versus* calculated log $1/C$ has been shown in Fig. (**7**).

Kuo *et al*. [15] studied the anti-platelet activities of pyrrolobenzylisoquinolines (**VIII**) against platelet aggregation induced by arachidonic acid (AA) and collagen (Col). From these data, we derived equations (**14**) and (**15**), which gave excellent correlations between activities and hydrophobicity of the molecules (**VIII**). It is surprising to obtain a negative coefficient with Clog *P*, which suggests that highly hydrophobic molecules (**VIII**) will be less active.

Inhibition of AA induced platelet aggregation by pyrrolobenzyl-isoquinolines (**VIII**) (Table **8**) [15].




**VIII**

$$\log 1/C = -0.59(\pm 0.28)\text{Clog } P + 5.77(\pm 0.68) \quad (14)$$

$n = 7$, $r^2 = 0.853$, $q^2 = 0.709$, $s = 0.114$

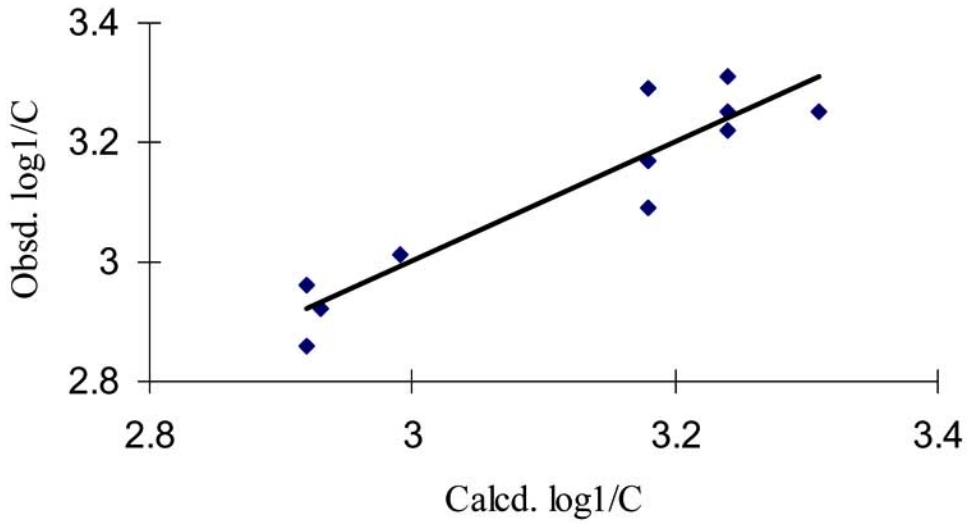



**Fig. (7).** Plot of observed *versus* calculated log1/C (Eq. **13**).

**Table 8. Biological and Physicochemical Constants Used to Derive QSAR Equations (14) and (15) for the Inhibition of AA Induced Platelet Aggregation and Col Induced Platelet Aggregation by Pyrrolobenzylisoquinolines (VIII).**

| No. | $R_1$ | $R_2$ | $R_3$ | log 1/C (Eq. 14) | | | log 1/C (Eq. 15) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | obsd | calcd | Δ | obsd | calcd | Δ | | |
| VIIIa | Cl | H | H | 4.11 | 4.27 | -0.16 | 4.35 | 4.54 | -0.19 | 2.55 | 9.62 |
| VIIIb | H | Cl | H | 4.27 | 4.27 | 0.00 | 4.43 | 4.54 | -0.11 | 2.55 | 9.62 |
| VIIIc | H | H | Cl | 4.28 | 4.27 | 0.01 | 4.52 | 4.54 | -0.01 | 2.55 | 9.62 |
| VIIId | Br | H | H | -- | 4.18 | -- | 4.40 | 4.43 | -0.03 | 2.70 | 9.90 |
| VIIIe | H | Br | H | 4.34 | 4.18 | 0.16 | 4.63 | 4.43 | 0.20 | 2.70 | 9.90 |
| VIIIf | H | H | Br | 4.14 | 4.18 | -0.04 | 4.53 | 4.43 | 0.09 | 2.70 | 9.90 |
| VIIIg[a] | $OCH_3$ | H | H | 4.18 | 4.74 | -0.55 | 4.45 | 5.10 | -0.66 | 1.75 | 9.74 |
| VIIIh | H | $OCH_3$ | H | 4.68 | 4.74 | -0.06 | 5.21 | 5.10 | 0.11 | 1.75 | 9.74 |
| VIIIi | H | H | $OCH_3$ | 4.82 | 4.74 | 0.08 | 5.04 | 5.10 | -0.06 | 1.75 | 9.74 |

[a]Not included in the derivation of QSAR (**14**) and (**15**)

*outlier:* $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$

range in log 1/*C* = 4.11-4.82

When linear correlation (**14**) was derived without dropping any compound, the statistics were not acceptable ($r^2 = 0.428$, $q^2 = -0.212$). One compound in Table (**8**) was deemed to be outlier on the basis of their deviation (2 x SD). A plot of the observed *versus* calculated log 1/*C* has been shown in Fig. (**8**).

Inhibition of Col induced platelet aggregation by pyrrolobenzylisoquinolines (**VIII**) (Table **8**) [15]

$$\log 1/C = -0.71(\pm 0.32)\text{Clog } P + 6.35(\pm 0.77) \quad (15)$$

$n = 8$, $r^2 = 0.835$, $q^2 = 0.703$, $s = 0.139$

*outlier:* $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$

range in log 1/*C* = 4.35-5.21

When linear equation (**15**) was derived without dropping any compound, the statistics ($r^2 = 0.452$, $q^2 = -0.134$) were not acceptable. One compound in Table (**8**) was deemed to be outlier on the basis of their deviation (2 x SD). Despite the fact that two different types of inducers are involved, QSAR (**14**) and (**15**) are very similar and explain 85.3% and 83.5% of the variance in the platelet aggregation inhibitory data respectively. Benzylisoquinoline derivatives are known for their interaction with various biological functions, such as analgesic, muscle relaxation, anticancer and cardiovascular activities.

Ingall *et al*. [16] studied the anti-platelet activities of phosphonic acids (**IX**) against platelet aggregation induced by adenosine diphosphate (ADP). From these data, we derived equation (**16**), which gave parabolic correlations with hydrophobicity. It suggests that the anti-platelet activities of phosphonic acids (**IX**) first increases with an increase in hydrophobicity to an optimum Clog *P* value of 3.36 and then decreases.

Inhibition of ADP induced platelet aggregation by phosphonic acids (**IX**) (Table **9**) [16].

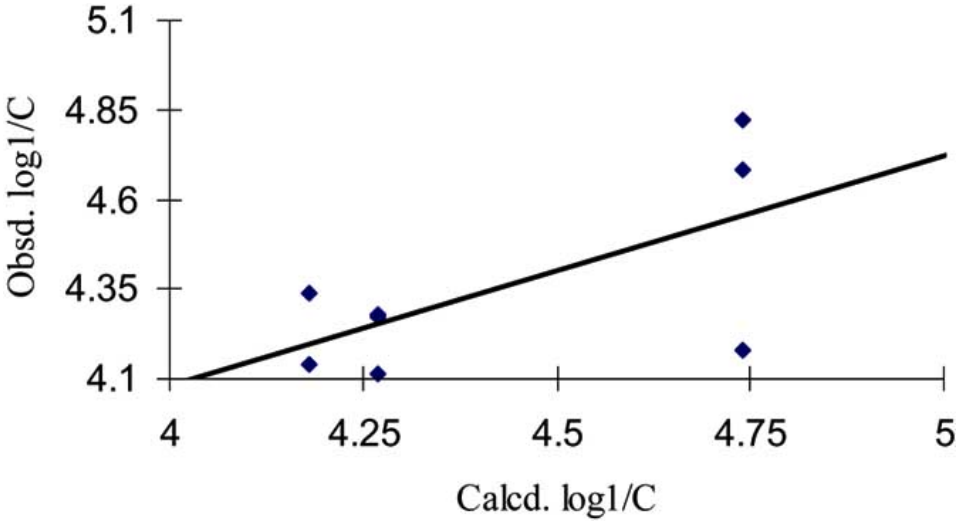
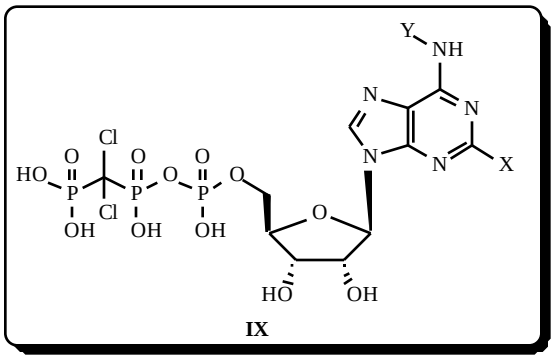



**Fig. (8).** Plot of observed *versus* calculated log1/C (Eq. **14**).

**Table 9. Biological and Physicochemical Constants Used to Derive QSAR Equation (16) for the Inhibition of ADP Induced Platelet Aggregation by Phosphonic Acids (IX).**

| No | X | Y | log1/C (Eq.16) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|---|
| | | | obsd. | calcd | Δ | | |
| IXa | H | H | 3.50 | 3.66 | -0.16 | -1.89 | 10.88 |
| IXb | $SC_2H_5$ | H | 6.53 | 6.82 | -0.29 | -0.14 | 12.61 |
| IXc | $SC_3H_7$ | H | 8.60 | 7.52 | 1.08 | 0.39 | 13.08 |
| IXd | $SC_3H_7$ | $CH_2CF_3$ | 9.48 | 9.33 | 0.15 | 3.48 | 14.05 |
| IXe | $SC_3H_7$ | $CH_2CH_2OCH_3$ | 7.81 | 8.39 | -0.58 | 1.22 | 14.62 |
| IXf | $SC_3H_7$ | $CH_2CH_2SCH_3$ | 9.42 | 8.86 | 0.56 | 1.84 | 15.28 |
| IXg | $SCH_2CH_2CF_3$ | H | 8.87 | 8.68 | 0.19 | 1.57 | 13.12 |
| IXh | $SCH_2CH_2CF_3$ | $CH_2CF_3$ | 9.14 | 8.99 | 0.15 | 4.66 | 14.10 |
| IXi | $SCH_2CH_2CF_3$ | $CH_2CH_2OCH_3$ | 8.02 | 9.15 | -1.13 | 2.40 | 14.67 |
| IXj | $SCH_2CH_2CF_3$ | $CH_2CH_2SCH_3$ | 9.35 | 9.31 | 0.04 | 3.02 | 15.32 |



**IX**

log1/*C* = 1.39(±0.47)Clog *P* – 0.21(±0.13)Clog $P^2$ + 7.01(±0.72) (16)

*n* = 10, $r^2$ = 0.894, $q^2$ = 0.796, *s* = 0.685

optimum Clog *P* = 3.36(2.42-6.89)

range in log 1/*C* = 3.50-9.48

Equation 16 has been able to explain more than 89% of the data variance. A plot of the observed *versus* calculated log 1/*C* has been shown in Fig. (**9**).

In the present review, four different series of compounds that is X-phenols (**I**), caffeic acid amides (**III**), 1,4-naphthoquinones (**V**), and pyrrolobenzylisoquinolines (**VIII**) were used as platelet aggregation under the influence of different kind of inducers. In the case of three series of compounds that are X-phenols (Eqs. **1-4**), 1,4-naphthoquinones (Eqs. **10** and **11**) and pyrrolobenzylisoquinolines (Eqs. **14** and **15**), we obtained very similar results. This indicates that the platelet aggregation does not depend on the nature of the inducers. But in one series of caffeic acid amides (Eqs. **6, 7** and **8**), we obtained different types of QSAR. The reason of this is not very clear.

To understand the effect of same inducers on the inhibition of platelet aggregation by different series of compounds, the following QSAR (Eqs. **17-21**) have been derived.

Inhibition of ADP induced platelet aggregation by X-phenols (**I**), X-alcohols (**IV**), phenoxyacetaldehyde guanylhydrazones (**VII**) and phosphonic acids (**IX**) (Table **10**) [8, 11, 14, 16].

log1/*C* = 0.64(±0.19)Clog *P* + 0.53(±0.05)CMR – 0.53(±0.41) (17)

*n* = 35, $r^2$ = 0.938, $q^2$ = 0.923, *s* = 0.668

range in log 1/*C* = 0.56-9.48

We derived equation (**17**) by considering all the data points, which were used in deriving equations (**1, 9, 13** and **16**) (Tables **1, 4, 7** and **9**). It is interesting to note here that the equation (**17**) of combined data set has an excellent correlation with Clog *P* and CMR, and surprisingly there is not any outlier, despite the fact that the work was done in different laboratories and with different series of compounds. Individual QSAR equations (**1, 9, 13** and **16**) have either linear or parabolic correlations with hydrophobic parameter but equation (**17**) has the correlation with hydrophobic parameter followed by molar refractivity, it may be due to the presence of compounds with different types of structure. A plot of the observed *versus* calculated log 1/*C* has been shown in Fig. (**10**).

Inhibition of Col induced platelet aggregation by X-phenols (**I**), 1,4-naphthoquinones (**V**) and pyrrolobenzylisoquinolines (**VIII**) (Table **11**) [8, 12, 15].

log1/*C* = 0.21(±0.13)Clog *P* + 0.69(±0.29)CMR – 0.04(±0.02)$CMR^2$ + 1.41(±0.70) (18)

*n* = 25, $r^2$ = 0.878, $q^2$ = 0.797, *s* = 0.174

optimum CMR = 7.81(7.38-8.76)

*outliers*: Ij, VIIIh, VIIIi

range in log 1/*C* = 2.93-5.21

We derived equation (**18**) by considering all the data points, which were used in deriving equations (**4, 11** and **15**) (Tables **1, 5** and **8**). A plot of the observed *versus* calculated log 1/*C* has been shown in Fig. (**11**).

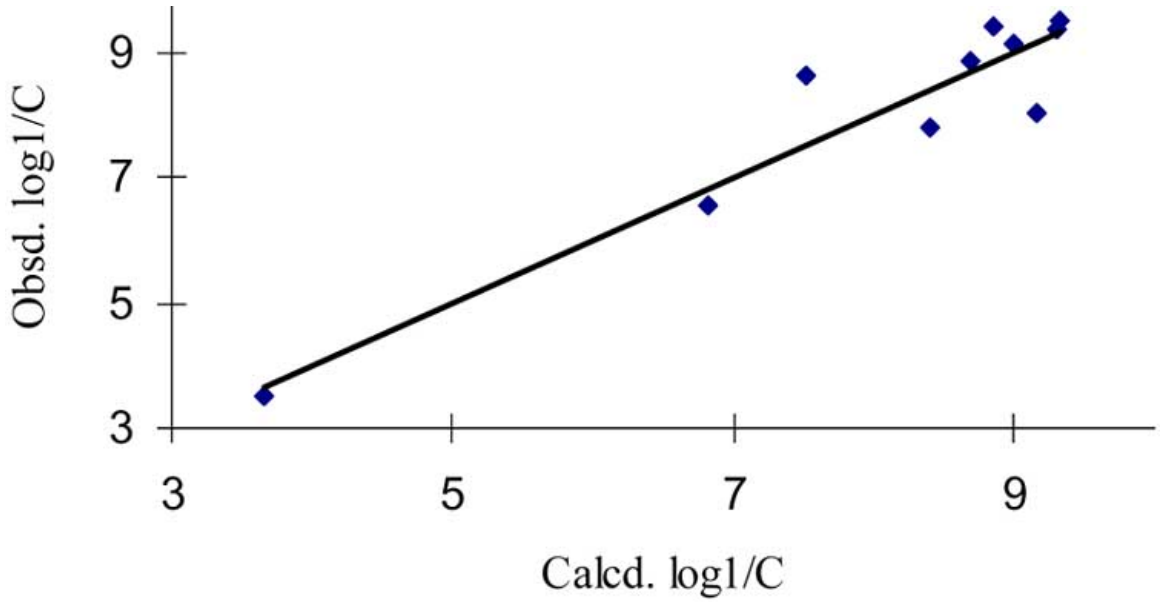



**Fig. (9).** Plot of observed *versus* calculated log1/C (Eq. **16**).

**Table 10. Biological and Physicochemical Constants Used to Derive QSAR Equation (17) for the Inhibition of ADP Induced Platelet Aggregation by X-Phenols (I), X-Alcohols (IV), Phenoxyacetaldehyde Guanylhydrazones (VII) and Phosphonic Acids (IX).**

| No. | compound | log 1/C (Eq. 17) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|
| | | obsd. | calcd | Δ | | |
| 1 | Ia | 2.93 | 2.04 | 0.89 | 1.47 | 2.84 |
| 2 | Ib | 3.02 | 2.44 | 0.58 | 1.70 | 3.32 |
| 3 | Ic | 3.25 | 2.64 | 0.61 | 1.91 | 3.45 |
| 4 | Id | 3.00 | 2.59 | 0.41 | 1.94 | 3.31 |
| 5 | Ie | 3.71 | 3.17 | 0.54 | 2.47 | 3.77 |
| 6 | If | 3.86 | 2.89 | 0.97 | 2.39 | 3.33 |
| 7 | Ig | 4.12 | 3.58 | 0.54 | 3.06 | 3.82 |
| 8 | Ih | 4.15 | 4.48 | -0.33 | 3.20 | 5.35 |
| 9 | Ii | 3.98 | 4.20 | -0.22 | 3.30 | 4.70 |
| 10 | Ij | 4.82 | 4.27 | 0.55 | 3.72 | 4.32 |
| 11 | IVa | 0.56 | 0.72 | -0.16 | 0.34 | 1.72 |
| 12 | IVb | 1.01 | 1.31 | -0.30 | 0.88 | 2.19 |
| 13 | IVc | 1.52 | 1.89 | -0.37 | 1.40 | 2.65 |
| 14 | IVd | 2.24 | 2.54 | -0.30 | 2.03 | 3.11 |
| 15 | VIIa | 2.92 | 3.03 | -0.11 | 0.81 | 5.51 |
| 16 | VIIb | 3.22 | 3.69 | -0.47 | 1.44 | 6.00 |
| 17 | VIIc | 3.31 | 3.84 | -0.53 | 1.67 | 6.00 |
| 18 | VIId | 3.25 | 3.84 | -0.59 | 1.67 | 6.00 |
| 19 | VIIe | 2.96 | 3.18 | -0.22 | 0.55 | 6.12 |
| 20 | VIIf | 2.86 | 3.41 | -0.55 | 0.90 | 6.12 |
| 21 | VIIg | 3.29 | 3.59 | -0.30 | 1.31 | 5.97 |
| 22 | VIIh | 3.17 | 3.59 | -0.42 | 1.31 | 5.97 |
| 23 | VIIi | 3.09 | 3.59 | -0.50 | 1.31 | 5.97 |
| 24 | VIIj | 3.01 | 3.22 | -0.21 | 1.10 | 5.52 |
| 25 | VIIk | 3.25 | 4.08 | -0.83 | 1.82 | 6.28 |
| 26 | IXa | 3.50 | 4.13 | -0.63 | -1.89 | 10.88 |
| 27 | IXb | 6.53 | 6.17 | 0.36 | -0.14 | 12.61 |
| 28 | IXc | 8.60 | 6.76 | 1.84 | 0.39 | 13.08 |
| 29 | IXd | 9.48 | 9.26 | 0.22 | 3.48 | 14.05 |
| 30 | IXe | 7.81 | 8.11 | -0.30 | 1.22 | 14.62 |
| 31 | IXf | 9.42 | 8.86 | 0.56 | 1.84 | 15.28 |
| 32 | IXg | 8.87 | 7.54 | 1.33 | 1.57 | 13.12 |
| 33 | IXh | 9.14 | 10.05 | -0.91 | 4.66 | 14.10 |
| 34 | IXi | 8.02 | 8.89 | -0.87 | 2.40 | 14.67 |
| 35 | IXj | 9.35 | 9.64 | -0.29 | 3.02 | 15.32 |

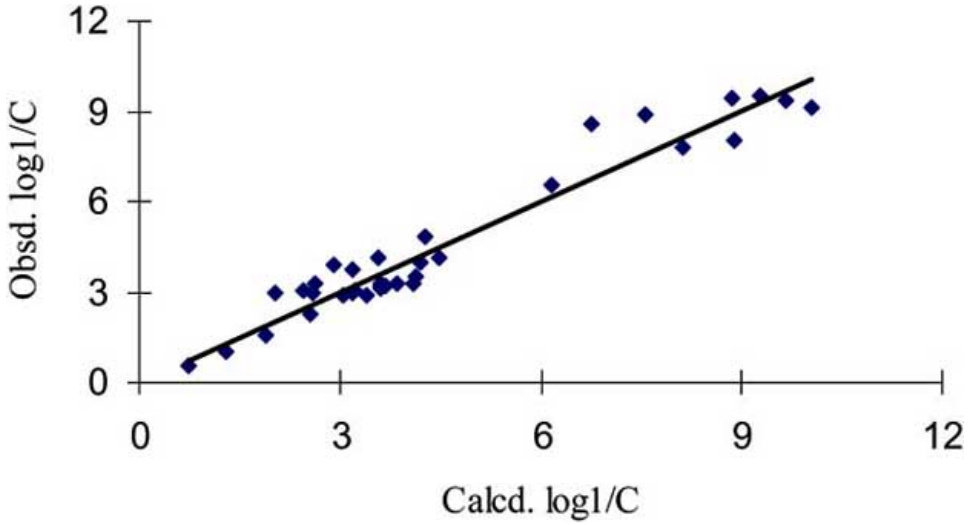



**Fig. (10).** Plot of observed *versus* calculated log1/C (Eq. **17**).

**Table 11. Biological and Physicochemical Constants Used to Derive QSAR Equation (18) for the Inhibition of Col Induced Platelet Aggregation by X-Phenols (I), 1,4-Naphthoquinones (V) and Pyrrolobenzylisoquinolines (VIII).**

| No. | compound | log 1/C (Eq. 18) | | | Clog *P* | CMR |
|---|---|---|---|---|---|---|
| | | obsd | calcd | Δ | | |
| 1 | Ia | 2.93 | 3.32 | -0.39 | 1.47 | 2.84 |
| 2 | Ib | 3.31 | 3.56 | -0.25 | 1.70 | 3.32 |
| 3 | Ic | 3.67 | 3.66 | 0.01 | 1.91 | 3.45 |
| 4 | If | 3.95 | 3.71 | 0.24 | 2.39 | 3.33 |
| 5 | Ig | 4.48 | 4.04 | 0.44 | 3.06 | 3.82 |
| 6 | Ih | 4.48 | 4.50 | -0.02 | 3.20 | 5.35 |
| 7[a] | Ij | 4.92 | 4.34 | 0.58 | 3.72 | 4.32 |
| 8 | Va | 4.44 | 4.37 | 0.07 | 2.55 | 5.37 |
| 9 | Vb | 4.24 | 4.09 | 0.15 | 1.78 | 4.88 |
| 10 | Vd | 4.34 | 4.28 | 0.06 | 2.17 | 5.34 |
| 11 | Ve | 4.68 | 4.61 | 0.07 | 3.47 | 5.60 |
| 12 | Vf | 4.82 | 4.89 | -0.07 | 4.00 | 6.76 |
| 13 | Vg | 4.96 | 5.03 | -0.07 | 4.53 | 7.22 |
| 14 | Vh | 4.84 | 4.95 | -0.11 | 4.08 | 7.88 |
| 15 | Vi | 4.48 | 4.48 | 0.00 | 2.69 | 5.80 |
| 16 | Vj | 4.42 | 4.44 | -0.02 | 2.47 | 5.80 |
| 17 | Vk | 4.62 | 4.67 | -0.05 | 3.22 | 6.27 |
| 18 | Vl | 4.75 | 4.83 | -0.08 | 3.75 | 6.73 |
| 19 | Vm | 4.64 | 4.78 | -0.14 | 3.30 | 7.39 |
| 20 | VIIIa | 4.35 | 4.49 | -0.14 | 2.55 | 9.62 |
| 21 | VIIIb | 4.43 | 4.49 | -0.06 | 2.55 | 9.62 |
| 22 | VIIIc | 4.52 | 4.49 | 0.03 | 2.55 | 9.62 |
| 23 | VIIId | 4.40 | 4.47 | -0.07 | 2.70 | 9.90 |
| 24 | VIIIe | 4.63 | 4.47 | 0.16 | 2.70 | 9.90 |
| 25 | VIIIf | 4.53 | 4.47 | 0.06 | 2.70 | 9.90 |
| 26 | VIIIg | 4.45 | 4.30 | 0.15 | 1.75 | 9.74 |
| 27[a] | VIIIh | 5.21 | 4.30 | 0.91 | 1.75 | 9.74 |
| 28[a] | VIIIi | 5.04 | 4.30 | 0.74 | 1.75 | 9.74 |

[a]Not included in the derivation of QSAR (**18**)

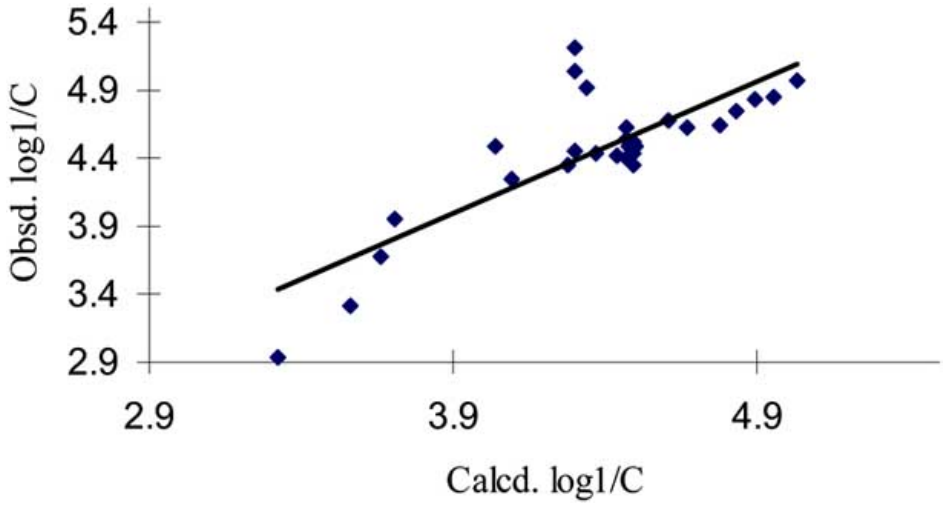



**Fig. (11).** Plot of observed *versus* calculated log1/C (Eq. **18**).

Inhibition of U46619 induced platelet aggregation by caffeic acid amides (**III**) and tetrahydronaphthalenes (**VI**) (Table **12**) [10, 13].

$\log 1/C = 0.70(\pm 0.12)\text{CMR} - 1.64(\pm 1.37)$ (19)

$n = 13$, $r^2 = 0.936$, $q^2 = 0.913$, $s = 0.451$

outlier: VIe

range in log $1/C$ = 3.98-8.22

We derived equation (**19**) by considering all the data points, which were used in deriving equations (**7** and **12**) (Tables **3** and **6**). A plot of the observed *versus* calculated log $1/C$ has been shown in Fig. (**12**). With respect to equation (**19**), it is important to note that there is a high mutual correlation between Clog P and CMR ($r^2$ = 0.887, $q^2$ = 0.838). By considering Clog *P* in place of CMR, we can derive equation (**19a**).

$\log 1/C = 1.01(\pm 0.25)\text{Clog } P + 1.52(\pm 1.20)$ (19a)

$n = 13$, $r^2 = 0.875$, $q^2 = 0.833$, $s = 0.628$

outlier: VIe

Thus, it is very hard to predict for this combined data set if there is a positive steric or positive hydrophobic effect.

**Table 12. Biological and Physicochemical Constants Used to Derive QSAR Equations (19) and (19a) for the Inhibition of U46619 Induced Platelet Aggregation by Caffeic Acid Amides (III) and Tetrahydronaphthalenes (VI)**

| No. | compound | log 1/C obsd | log 1/C (Eq. 19) | | log 1/C (Eq. 19a) | | CMR | Clog *P* |
|---|---|---|---|---|---|---|---|---|
| | | | calcd | Δ | calcd | Δ | | |
| 1 | IIIb | 3.98 | 3.80 | 0.18 | 3.49 | 0.49 | 7.73 | 1.96 |
| 2 | IIIj | 4.02 | 4.04 | -0.02 | 4.91 | -0.89 | 8.07 | 3.37 |
| 3 | IIIm | 4.18 | 4.25 | -0.07 | 5.06 | -0.88 | 8.36 | 3.52 |
| 4 | IIIo | 4.42 | 4.81 | -0.39 | 4.91 | -0.49 | 9.16 | 3.37 |
| 5 | IIIp | 4.25 | 4.56 | -0.31 | 3.69 | 0.56 | 8.81 | 2.15 |
| 6 | VIa | 6.55 | 5.86 | 0.69 | 6.14 | 0.41 | 10.65 | 4.59 |
| 7 | VIb | 8.22 | 7.63 | 0.59 | 7.72 | 0.50 | 13.17 | 6.16 |
| 8 | VIc | 7.96 | 7.64 | 0.32 | 7.86 | 0.10 | 13.18 | 6.30 |
| 9 | VId | 8.10 | 7.96 | 0.14 | 8.16 | -0.06 | 13.63 | 6.60 |
| 10[a] | VIe | 7.31 | 9.40 | -2.09 | 9.61 | -2.30 | 15.68 | 8.04 |
| 11 | VIf | 7.46 | 8.06 | -0.60 | 7.63 | -0.17 | 13.78 | 6.07 |
| 12 | VIg | 7.44 | 7.96 | -0.52 | 7.14 | 0.30 | 13.64 | 5.59 |
| 13 | VIh | 5.77 | 6.19 | -0.42 | 6.54 | -0.77 | 11.12 | 4.99 |
| 14 | VIi | 6.42 | 5.99 | 0.43 | 5.52 | 0.90 | 10.83 | 3.97 |

[a]Not included in the derivation of QSAR (**19**) and (**19a**)

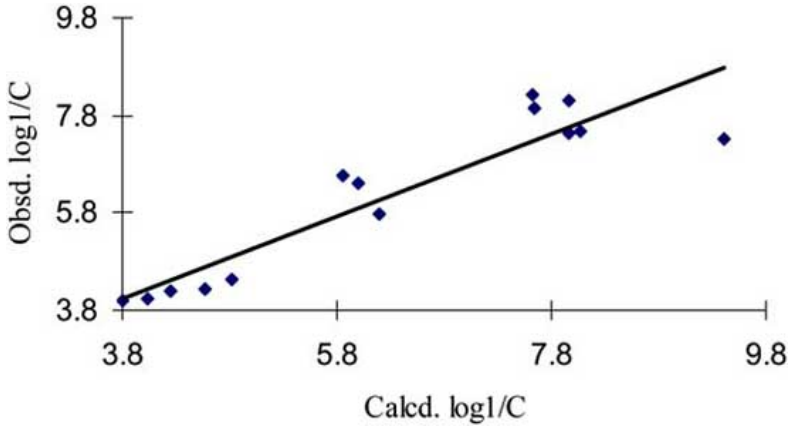



**Fig. (12).** Plot of observed *versus* calculated log1/C (Eq. **19**).

**Table 13. Biological and Physicochemical Constants Used to Derive QSAR Equations (20) and (21) for the Inhibition of AA Induced Platelet Aggregation by X-Catechols (II), Caffeic Acid Amides (III), 1,4-Naphthoquinones (V) and Pyrrolobenzylisoquinolines (VIII).**

| | | | log 1/C (Eq. 20) | | log 1/C (Eq. 21) | | | |
|---|---|---|---|---|---|---|---|---|
| **No.** | **compound** | **log 1/C obsd** | **calcd** | **Δ** | **calcd** | **Δ** | **CMR** | **Clog *P*** |
| 1[a] | IIa | 4.65 | -- | -- | 3.65 | 1.00 | 3.15 | 0.21 |
| 2 | IIb | 5.21 | 5.25 | -0.04 | -- | -- | 3.61 | 1.45 |
| 3 | IIc | 5.30 | 5.31 | -0.01 | -- | -- | 3.46 | 1.38 |
| 4 | IId | 5.40 | 5.41 | -0.01 | -- | -- | 2.99 | 0.88 |
| 5 | IIe | 5.79 | 5.48 | 0.31 | -- | -- | 3.49 | 1.98 |
| 6[a] | IIf | 6.51 | -- | -- | 4.54 | 1.97 | 5.51 | 2.77 |
| 7 | IIIa | 4.25 | 4.30 | -0.05 | -- | -- | 7.58 | 2.40 |
| 8 | IIIb | 4.23 | 4.15 | 0.08 | -- | -- | 7.73 | 1.96 |
| 9 | IIIc | 4.19 | 4.08 | 0.11 | -- | -- | 7.73 | 1.73 |
| 10 | IIId | 4.60 | -- | -- | 4.55 | 0.05 | 7.73 | 1.73 |
| 11 | IIIe | 4.67 | -- | -- | 4.64 | 0.03 | 7.60 | 2.20 |
| 12 | IIIf | 4.59 | 4.42 | 0.17 | -- | -- | 7.60 | 2.80 |
| 13 | IIIg | 4.66 | 4.42 | 0.24 | -- | -- | 7.60 | 2.80 |
| 14 | IIIh | 4.73 | -- | -- | 4.78 | -0.05 | 8.07 | 2.52 |
| 15 | IIIi | 4.38 | 4.55 | -0.17 | -- | -- | 8.07 | 3.37 |
| 16 | IIIj | 4.59 | 4.55 | 0.04 | -- | -- | 8.07 | 3.37 |
| 17[a] | IIIk | 5.24 | -- | -- | 4.84 | 0.40 | 8.36 | 2.64 |
| 18 | IIIl | 5.17 | -- | -- | 5.05 | 0.12 | 8.36 | 3.52 |
| 19 | IIIm | 4.79 | 4.59 | 0.20 | -- | -- | 8.36 | 3.52 |
| 20 | IIIn | 4.19 | 4.27 | -0.08 | -- | -- | 8.06 | 2.43 |
| 21 | IIIo | 4.75 | 4.54 | 0.21 | -- | -- | 9.16 | 3.37 |
| 22 | IIIp | 4.22 | 4.16 | 0.06 | -- | -- | 8.81 | 2.15 |
| 23 | Va | 4.72 | 4.85 | -0.13 | -- | -- | 5.37 | 2.55 |
| 24 | Vb | 4.27 | -- | -- | 4.23 | 0.04 | 4.88 | 1.78 |
| 25 | Vc | 4.47 | -- | -- | 4.61 | -0.14 | 5.83 | 2.94 |
| 26 | Vd | 4.42 | -- | -- | 4.37 | 0.05 | 5.34 | 2.17 |
| 27 | Ve | 4.69 | -- | -- | 4.71 | -0.02 | 5.60 | 3.47 |
| 28 | Vf | 4.70 | 4.92 | -0.22 | -- | -- | 6.76 | 4.0 |
| 29 | Vg | 5.06 | 5.01 | 0.05 | -- | -- | 7.22 | 4.53 |
| 30 | Vh | 4.97 | 4.79 | 0.18 | -- | -- | 7.88 | 4.08 |
| 31 | Vi | 4.58 | 4.76 | -0.18 | -- | -- | 5.80 | 2.69 |
| 32 | Vj | 4.44 | 4.69 | -0.25 | -- | -- | 5.80 | 2.47 |
| 33 | Vk | 4.63 | 4.79 | -0.16 | -- | -- | 6.27 | 3.22 |
| 34 | Vl | 4.77 | 4.85 | -0.08 | -- | -- | 6.73 | 3.75 |
| 35 | Vm | 4.82 | 4.60 | 0.22 | -- | -- | 7.39 | 3.30 |
| 36 | VIIIa | 4.11 | 4.31 | -0.20 | -- | -- | 9.62 | 2.55 |
| 37 | VIIIb | 4.27 | 4.31 | -0.04 | -- | -- | 9.62 | 2.55 |
| 38 | VIIIc | 4.28 | 4.31 | -0.03 | -- | -- | 9.62 | 2.55 |
| 39 | VIIIe | 4.34 | 4.39 | -0.05 | -- | -- | 9.90 | 2.70 |
| 40 | VIIIf | 4.14 | 4.39 | -0.25 | -- | -- | 9.90 | 2.70 |
| 41 | VIIIg | 4.18 | 4.08 | 0.10 | -- | -- | 9.74 | 1.75 |
| 42 | VIIIh | 4.68 | -- | -- | 4.79 | -0.11 | 9.74 | 1.75 |
| 43 | VIIIi | 4.82 | -- | -- | 4.79 | 0.03 | 9.74 | 1.75 |

[a]Not included in the derivation of QSAR (**21**)

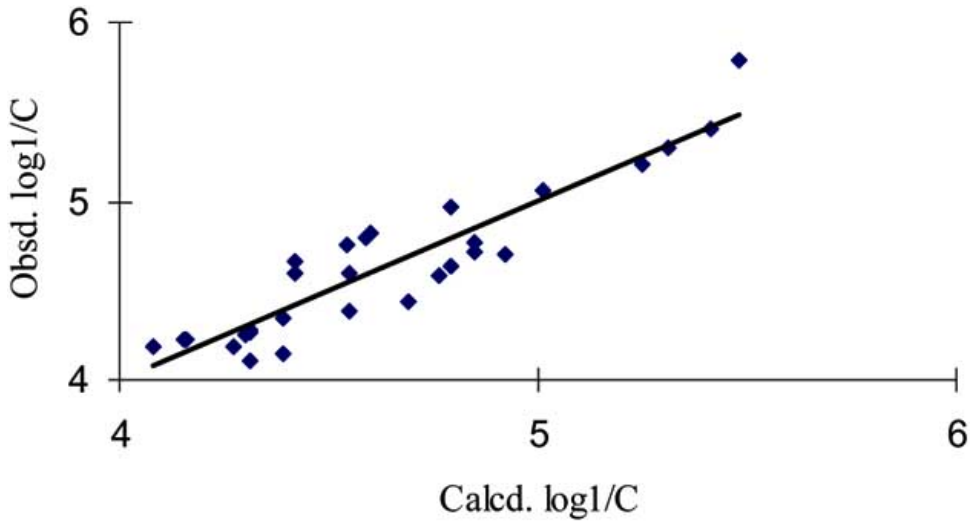



**Fig. (13).** Plot of observed *versus* calculated log1/C (Eq. **20**).

We prefer equation (**19**) because it is statistically better than that of equation (**19a**).

Inhibition of AA induced platelet aggregation by X-catechols (**II**), caffeic acid amides (**III**), 1,4-naphthoquinones (**V**) and pyrrolobenzylisoquinolines (**VIII**) (Table **13**) [9, 10, 12, 15].

$\log 1/C = 0.31(\pm 0.10)\text{Clog } P - 0.87(\pm 0.26)\text{CMR} + 0.05(\pm 0.02)\text{CMR}^2 + 7.29(\pm 0.69)$ (20)

$n = 30$, $r^2 = 0.858$, $q^2 = 0.814$, $s = 0.167$

inversion point for CMR = 8.77(8.17-10.03)

range in log $1/C$ = 4.11-5.79

$\log 1/C = 0.24(\pm 0.11)\text{Clog } P + 0.12(\pm 0.04)\text{CMR} + 3.23(\pm 0.45)$ (21)

$n = 10$, $r^2 = 0.892$, $q^2 = 0.731$, $s = 0.091$

*outliers*: IIa, IIf, IIIk

range in log $1/C$ = 4.27-6.51

From the forty-three data points of this combined data set, which were used in deriving equations (**5, 6, 10** and **14**) (Tables **2, 3, 5** and **8**), we were unable to derive a good QSAR due to the presence of thirteen outliers and so that is not acceptable. The presence of a large number of outliers may be due to their interaction with the receptor in a different mode. Thus, this combined data set was divided into two subsets on the basis of outliers and derived two equations (**20**) and (**21**) with good statistics [17-19]. It is interesting that equation (**20**) brings out an allosteric reaction in terms of CMR [20-27]. This means, at first the activity declines with an increase in CMR up to the inversion point (CMR = 8.77) and then the activity begins to increase. This implies a change in receptor structure.

On the other hand, equation (**21**) is a linear correlation with two parameters that are Clog *P* and CMR. A plot of the observed *versus* calculated log $1/C$ has been shown in Fig. (**13**).

## CONCLUSION

An analysis of our QSAR results on platelet aggregation inhibitors, which brings up a number of points of interest. The hydrophobic parameter is one of the most important determinants of the activity. Out of 16 QSAR, 15 contain a correlation between activity and hydrophobicity. A positive linear correlation is found in 12 equations (Eqs. **1-6** and **8-13**). The coefficient with hydrophobic parameter varies considerably, from a low value of 0.26 (Eqs. **10** and **11**) to a high value of 1.00 (Eq. **9**). These data suggest that although activity might be improved by increasing compound hydrophobicity, this will not enough to establish the upper limit of Clog *P* for maximum inhibition. QSAR (**16**) is an encouraging example, where we get a parabolic model in Clog *P* term. This means the maximum inhibition of the compounds (**IX**) will be at optimal Clog *P* = 3.36. We believe that this will be the predictive model to narrow the synthetic challenges in order to yield very specific platelet aggregation inhibitors. On the basis of this model, we predict three compounds that may be the next synthetic target selection (please see Table **14**).

QSAR (**17-21**) have been derived by combining the data of different series of compounds under the influence of same

**Table 14. Next Synthetic Target Selection from QSAR (16)**

| No | X | Y | Calcd. log 1/C from Eq.16 | Clog *P* |
|---|---|---|---|---|
| IXk | $SC_3H_7$ | $C_5H_{11}$ | 9.34 | 3.34 |
| IXl | $SCH_2CH_2CF_3$ | $OCH_2Ph$ | 9.34 | 3.43 |
| IXm | $SCH_2CH_2CF_3$ | COPh | 9.33 | 3.20 |

inducers. The results of these equations (**17-21**) have shown that two parameters, hydrophobic and molar refractivity, will be important. We can conclude that the anti-platelet activities of these compounds are largely dependent not only on their hydrophobicity, but also the effect of their molar refractivity.

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