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QSAR Studies of Some Sulphonamidobenzophenone Oximes with Antiviral Activity

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Abstract

A study of quantitative structure-activity relationships (QSAR) has been performed for some sulphonamidobenzophenone oximes to investigate the mechanism of their antiviral activity against polio and rhino viruses.

It has been shown that viral macromolecule synthesis could be the target of their action and that the antiviral activity of the compounds is predominantly controlled by steric factors.

Ogata et al (1986) reported the synthesis of some *m*-sulphonamidobenzophenone oximes (Fig. 1a) with the partial structures of the *syn* and *anti* isomers of 6-[(hydroxyimino)-phenylmethyl]-1-[(1-methylethyl)sulphonyl]-1*H*-benzimidazole-2-amine (Wikel et al 1980; Fig. 1b), compounds which were virus-specific inhibitors of picornavirus multiplication. Biological evaluation of the compounds in the plaque inhibition test against poliovirus revealed that anti-oxime groups were more potent than the *syn* isomers (Ogata et al 1986). Selected compounds were studied to determine their mode of action. Because the compounds did not inactivate poliovirus on contact it was suggested that the inhibition occurred after the virus had entered the cell. The fact that the compounds showed pronounced activity between 2 and 4 h after absorption (the period of the virus growth cycle) suggested that viral macromolecule synthesis could be the target of their action.

Because viruses are largely packets of DNA, non-specific inhibition of DNA could be involved; for example, high concentrations of amides denature DNA (Hansch & Leo 1995). DNA is an important cellular receptor and many chemicals exert their effects through binding to DNA and their effectiveness depends upon the mode and intensity of the binding. There are three main types of binding: covalent, non-intercalative groove binding and intercalation. Weak forces, similar to those of Van der Waals or hydrogen bonding, are involved for the non-intercalative and intercalation binding.

Several equations modelling the inhibition of viral growth have been reported (Hansch & Leo 1995). For inhibition of

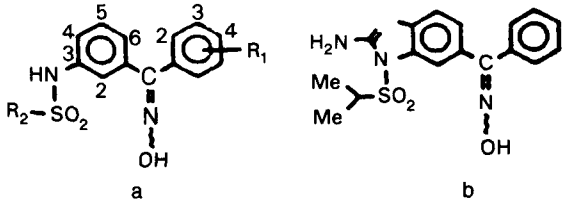

FIG. 1. General structure of *m*-sulphonamidobenzophenone oximes (a) and structures of 6-[(hydroxyimino)phenylmethyl]-1-[(1-methylethyl)sulphonyl]-1*H*-benzimidazole-2-amine (b).

influenza B virus by benzimidazoles:

$$\log\ 1/C = 0{\cdot}58\ \log\ P + 1{\cdot}58;\ r^2 = 0{\cdot}815,\ s = 0{\cdot}210 \quad (1)$$

and for inhibition of rhinovirus by oxazolines:

$$\log\ 1/C = 0{\cdot}39\ \log\ P + 1{\cdot}08\sigma_m + 4{\cdot}07;\ r^2 = 0{\cdot}815,\ s = 0{\cdot}187 \quad (2)$$

Log P is the overall lipophilicity of the examined molecules and σ_m is Hammett's electronic constant. Lipophilicity was found to be the most significant parameter in equations 1 and 2. For inhibition of HIV by purines:

$$\log\ 1/C = 0{\cdot}85\ \Sigma\pi + 12{\cdot}1\ \text{L-R}' - 1{\cdot}59\ \text{L-R}'^2 + 1{\cdot}17\ B_1\text{-3R} + 1{\cdot}53\ E_s\text{-2R} - 15{\cdot}3;\ r^2 = 0{\cdot}885,\ s = 0{\cdot}500,\ \text{L-R}' = 3{\cdot}8\ (3{\cdot}6\ \text{to}\ 3{\cdot}9) \quad (3)$$

where E_s-2R is the Taft steric constant for *ortho* substituents (Unger & Hansch 1976) and B_1-3R is the sterimol parameter for the width of R in the 3 (*meta*) position (Verloop et al 1976). The most important single variable in equation 3 is $\Sigma\pi$, the sum of π values for R and R′ groups. The two terms in $L_{R'}$ (L is the sterimol parameter for the length of the substituent R′) account for 75% of the variance, whereas $\Sigma\pi$ alone accounts for only 49%.

In previous expressions the antiviral activity was found to be predominantly controlled by the lipophilicity of the compounds. Because advances in QSAR studies have widened the scope of finding the mechanism of drug actions, a QSAR study has been performed on the inhibition of poliovirus growth in order to obtain a better understanding of the effects of sulphonamidobenzophenone oximes on DNA.

Materials and Methods

The data were taken from the literature (Ogata et al 1986). Some new sulphonamidobenzophenone oximes were synthesized and sixteen were tested for their antiviral activity against poliovirus type 1-Mahoney. CV-1 cells were used for the plaque inhibition assay. A confluent monolayer of these cells

in a flask was infected with 100-200 plaque-forming units (PFU) and then overlaid with agar (2% agar with 4% foetal bovine serum) containing different concentrations of the compound to be tested and incubated at 37°C. On the day plaque appeared the second overlay was added with the same medium plus neutral red (0·004%). The plaques were counted and the 50% plaque-inhibition concentration of each compound (ED50) was calculated from the dose-response curve (Ogata et al 1986) and were then used in our QSAR study.

The values for the substituent constants in Table 1 were taken from the literature (Verloop et al 1976; Hansch & Leo 1979; Hansch et al 1991; Silipo & Vittoria 1990; Hansch & Leo 1995).

The position of attachment of the substituent R_1 is indicated by 3′ or 4′ in the continuous variables given above. Regression analysis was undertaken by using the C-QSAR program (Biobyte).

Results and Discussion

The data in Table 1 were used to derive the quantitative structure-activity relationships (QSAR) given in equations 4-6.

$$\log\ 1/ED50 = -0{\cdot}62\ B_1\text{-}3' + 6{\cdot}73$$
$$n = 13,\ r = 0{\cdot}486,\ r^2 = 0{\cdot}23,\ s = 0{\cdot}213, \qquad (4)$$
$$F_{1,11} = 3{\cdot}403\ (\alpha\ 0{\cdot}1)$$

$$\log\ 1/ED50 = -0{\cdot}67\ B_1\text{-}4' - 1{\cdot}38\ B_1\text{-}3' + 8{\cdot}47$$
$$n = 13,\ r = 0{\cdot}74,\ r^2 = 0{\cdot}5,\ s = 0{\cdot}17, \qquad (5)$$
$$F_{1,10} = 6{\cdot}75\ (\alpha\ 0{\cdot}05)$$

$$\log\ 1/ED50 = 0{\cdot}793\Sigma\sigma - 0{\cdot}92B_1\text{-}4' - 1{\cdot}71B_1\text{-}3' + 9{\cdot}21$$
$$n = 13,\ r = 0{\cdot}862,\ r^2 = 0{\cdot}74,\ s = 0{\cdot}137, \qquad (6)$$
$$F_{1,9} = 6{\cdot}92\ (\alpha\ 0{\cdot}1),\ F_{3,9} = 8{\cdot}644\ (\alpha 0{\cdot}01)$$

Equations 4-6 show the development of the best correlation-equation 6 for sulphonamidobenzophenone oximes. In these expressions n represents the number of data points used, r is the correlation coefficient, s is the standard deviation. B_1-4′ and B_1-3′ are the Verloop's sterimol parameters for the minimum width of substituents R_1 in the 3′- and 4′- position of the phenyl ring and were devised to account for intermolecular effects between substituents 3′ or 4′, or both, and the macromolecular targets. (σ is the sum of the substituents' Hammett electronic constants and applies to substituents on all ring positions. The equations are highly significant in terms of the F statistic. Equation 6 accounts for 74% ($r^2 = 0{\cdot}743$) of the variance in the activity, which clearly indicates that electronic and steric factors both play a very important role in the anti-polio activity of this series of compounds. Steric effects are, unfortunately, those which are the most difficult to quantify.

The highly significant B_1-3′ term points to a negative steric effect of the first atom of groups in the 3′- position. The negative coefficient of B_1-4′ also means that the larger the atom attached to the ring the less effective the oxime will be. This suggests that the relatively high activity of compound 1 in Table 1 is a consequence of the low steric effect of H. In both positions, B_1 will be the decisive variable by which to judge the optimum interaction with the macromolecules. The $\Sigma\sigma$ term in equation 6, would seem to imply a role of slight significance for electron-donating groups in the 3′ and 4′- positions. The role of electronic factors in antiviral activity is not clear. In our example addition of terms in σ improves the correlation. Such a term would be expected to model hydrogen bonding if this played a role in bonding with the corresponding viral receptors. Substituents such as CH_3, Cl and OCH_3 do not, of course, form strong hydrogen-bonds. An attempt to parametrize the hydrogen-bonding effect as HB (an indicator variable), a value of 1 being given for hydrogen-bond acceptor groups such as $N(CH_3)_2$, did not result in an important correlation. It is, in general, difficult to accept that hydrogen-bonding capacity of groups can be represented by an indicator variable. An hydrogen-bonding parameter could be meaningful if simple, quantitative group donor and acceptor values were available. The quantitative study of the importance of hydrogen-bonding to drug performance has rarely been attempted directly; σ constants still remain the most general means of estimating the electronic effect of substituents on reaction centres. Their power derives from their taking into account (very often) the effects (e.g. hydrogen bonding, dipole interactions, etc) of dissolution on substituents; these effects are still difficult to calculate.

Table 1. The parameters used to derive equation 6.

No	R_1	R_2	log 1/C*	log 1/C†	$\Sigma\sigma$	B_1-4′	B_1-3′
1	4′-H	$N(CH_3)_2$	6·61	6·58	0·00	1·00	1·00
2	4′-Cl	$N(CH_3)_2$	5·88	6·02	0·23	1·80	1·00
3	4′-CH_3	$N(CH_3)_2$	5·87	5·96	−0·17	1·52	1·00
4	3′-OCH_3	$N(CH_3)_2$	6·01	6·07	0·12	1·00	1·35
5	4′-OCH_3	$N(CH_3)_2$	6·12	6·04	−0·27	1·35	1·00
6‡	4′-OCH_3	Pyrrolidino	5·53	6·04	−0·27	1·35	1·00
7	4′-OCH_3	$CH(CH_3)_2$	5·98	6·04	−0·27	1·35	1·00
8†	4′-OC_2H_5	$N(CH_3)_2$	4·82	6·06	−0·24	1·35	1·00
9	4′-SCH_3	$N(CH_3)_2$	6·06	5·93	0·00	1·70	1·00
10	3′-CH_2OH	$N(CH_3)_2$	5·84	5·68	0·00	1·00	1·52
11	4′-CH_2OH	$N(CH_3)_2$	5·94	6·10	0·00	1·52	1·00
12	4′-CH_2OH	$CH(CH_3)_2$	6·24	6·10	0·00	1·52	1·00
13	4′-CH_2OCH_3	$CH(CH_3)_2$	6·22	6·12	0·03	1·52	1·00
14	4′-CH_2OCH_3	$N(CH_3)_2$	6·16	6·12	0·03	1·52	1·00
15‡	3′,4′-$(OCH_3)_2$	$N(CH_3)_2$	5·84	5·54	−0·15	1·35	1·35
16§	3′,4′-OCH_2O	$N(CH_3)_2$	5·03	–	–	–	–
17	3′-NH_2	$N(CH_3)_2$	5·68	5·85	−0·16	1·00	1·35

*Observed by Ogata et al (1986). †Calculated using equation 6. ‡These points are not used in the derivation of equation 6. §This compound is not included in the derivation of equation 6 because its descriptors were not available.

Table 2. Correlation matrix showing the degrees of colinearity among $\Sigma\sigma$, B_1-4′, B_1-3′, and π.

	$\Sigma\sigma$	B_1-4′	B_1-3′	π
$\Sigma\sigma$	–	0·219	0·092	0·068
B_1-4'	–	–	−0·728	0·377
B_1-3'	–	–	–	−0·387
π	–	–	–	–

The degrees of colinearity among the parameters we have considered are shown in the correlation matrix given in Table 2.

The importance of lipophilicity in cell penetration is not clear from equation 6. This is important because Ogata et al (1986) suggested that inhibition occurred after the entrance of the virus into the cell. Equation 6 contains no π or log P term. Attempts to derive linear or parabolic equations representing the lipophilicity gave very poor equations ($r < 0{\cdot}16$). With whole cells it would be expected that there would be a lipophilic interaction with all parts of the compound because of its importance in membrane penetration. The calculated log P value for compound **1** (the most potent congener) was found to be 2·325.

An approach to include the dimensions of the substituents on positions 3′ or 4′, or both, in more directions in the regression analyses, using the molar refractivity (MR), scaled by 0·1, as a crude measure of general bulk, had no result ($r < 0{\cdot}1$, $r < 0{\cdot}2$).

Three data points, those for compounds **6**, **8** and **15**, are poorly predicted and omitted by use of the jack-knife procedure (C-QSAR, Biobyte). Compound **15** is disubstituted; in compound **16** the 3′-, 4′- OCH_2O group consists of a ring and as its descriptors were not available the compound was not included in the derivation of equation 6. Compound **8** is the most weakly active in the set whereas **6** is the only *syn* congener in the series.

Perusing the results in Table 1, in the light of equation 6 it is interesting to note that comparing compounds **13** and **14**, **5** and **7** (which differ in R_2 substituents), their ED50 values are in about the same range (**13** = 6·22, **14** = 6·16, **5** = 6·12, **7** = 5·98) and ED50 calculated are 6·12 for **13** and **14** and 6·04 for **5** and **7**. Compounds **1**, **5**, **9**, **10**, **12**, **13** and **14** in Table 1 were found to be more active than predicted. A general way in which QSAR are used to develop lead compounds is to study the modification of those derivatives which turn out to be more potent than predicted. It seems that an *anti* congener is substantially in the optimum steric range. No parametrization has been performed for R_2 substituents—the few structural modifications at this position did not, in fact, enable the use of parameters. If the problem is to be resolved there is a need for better variation of the R_2 substituents, with the purpose of defining a manageable data set characterized by adequate biological and structural variances. Unfortunately the compounds included in this set contain rather little variation (13 congeners with a dimethylamino group, 1 with a pyrrolidinyl and 3 with an isopropyl group). They are, however, fitted reasonably by equation 6 in terms of the significance of the *F*-test. The number of data points/variables is low for equation 6 and it might be insisted that little weight can be placed on this QSAR. It is, however, of practical value for the design of more and better new derivatives of this class of compound; the equation also provides a possible correlation with the directional steric parameters B_1-3′ and B_1-4′.

Analysis of the relationship between chemical structure and anti-viral activity revealed the possibility of hydrogen-bonding

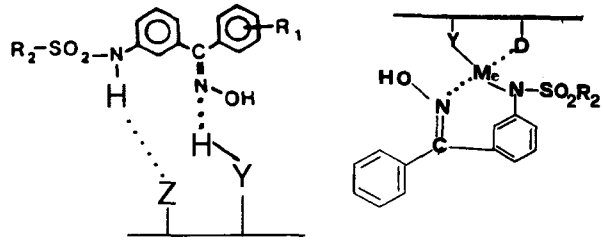

FIG. 2. Two hypothetical mechanisms for the interaction between the oximes and the viral target.

with the viral receptors. The similar molecular geometry of these compounds suggests that electronic effects of substituents should be related to their relative biological activities.

Two hypotheses are possible with regard to the mechanism of interaction between the oximes and the viral target: simultaneous participation of the nitrogen atom of the oxime group and the hydrogen atom in hydrogen-bond formation (Fig. 2) where Z is an electron-donor, Y could be O, S or NH and X is O or NH; and the participation of oximes in chelate complexes with metal ions bound to virus-specific proteins. The second hypothesis postulates the formation of a seven-membered chelate complex.

Both mechanisms require an *anti* conformation for the oximes and set limits on the possible distance between the groups taking part in the complex formation. All the terms except the $\Sigma\sigma$ term account for steric effects which emphasize the critical fit of the ligands to their macromolecular targets. Both substituents appear to contribute in the same way. The sterimol parameters B_1-3′ and B_1-4′, with their negative coefficients, emphasize the detrimental effect of 3′- and 4′- substitution.

The ease and success of finding better drugs depend upon how best we can rationalize their design. There is a need for most drugs to be selective about which biological site or sites they influence. The rational design of an antiviral agent, an agent with specific activity toward a selected target, requires that this target be so precisely defined that it can be hit selectively.

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