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hP, the Component of Log P Controlling Structure–activity Relationships Amongst Non-steroidal Anti-inflammatory Drugs

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Abstract

A range of 25 drugs and other compounds selected from published sources by strict criteria, has been used to confirm that their ability to inhibit the production of prostaglandin by mouse peritoneal macrophage does not correlate with log P but with hP, the parameter composed of only the hydrophobic contributions (atoms and groups composed of carbon, hydrogen and halogens). Other heteroatoms and physical properties can usually be ignored.

Anti-inflammatory activity does not depend upon pK_a or partition phenomena unless extreme, nor does it depend primarily upon the structural types within the range phenols, salicylic acids, mefenamic acids, areneacetic and profenic acids.

The partition coefficient P and its allies continue to provide a major means of studying drug activities (Leahy et al 1992). Typical applications to the non-steroidal anti-inflammatory drugs (NSAIDs) have been made by Gund & Jensen (1983), Nakashima et al (1985), Kuchar et al (1989) and Dearden et al (1989) amongst others. In order to achieve useful quantitative structure–activity relationships (QSAR) log P is commonly supplemented by other physical and chemical quantities including pK_a, $(\log P)^2$, Hammett sigma values, refractivities, and steric parameters, while yet further constants and coefficients emerge from the application of regression analysis as in studies undertaken by Habicht & Brune (1983) on salicylic acids, Dewhirst (1980) on phenols, Kuchar et al (1989) on 4-alkoxybenzeneacetic acids, Kaltenbronn et al (1983) on anthranilic acids, Nakashima et al (1985) on furo[3,2-b]indoles, and Moser et al (1990) on diclofenac congeners.

Thus in individual series a high degree of correlation can be achieved by a suitable selection of parameters, corrections, and coefficients, but as each series requires its own selection of modifications, no general correlation has yet been recognized and attempts to establish correlations independent of structural type have been uncommon. In a recent study, which also covered the related problem of peripheral analgesia, Dearden et al (1989) examined 19 of the more commonly used anti-inflammatory drugs by means of a programme incorporating some 40 parameters (including log P) without arriving at a clear correlation but noting that steric factors are more important than electronic factors in determining potency. A related study detecting a limited degree of clustering has been described by Gregg (1991). The applicability of log P in NSAID work is therefore far from unequivocal. The concept that drug activities vary in response to partitioning between solvent-like phases remains an assumption that may not always be valid, and the need to modify and supplement log P weakens that assumption as more and more additions and alterations have to be made. For these reasons I have re-examined the situation having in mind the idea that, far from needing supplementation, log P might already be too elaborate a parameter.

Individual studies often provide indications that anti-inflammatory activity improves as hydrophobic character increases, with limits presumably imposed by chain length, steric hindrance, and orientation as in reports by Gund & Jensen (1983), Nakashima et al (1985) and Habicht & Brune (1983). Because alkyl and aromatic groups constitute the extreme case of hydrophobic (water-repelling) character, and in log P systems provide the more regular of the various fragment values, their contributions can easily be assessed whereas functional group and heteroatom contributions vary over a wide range often depending upon location and upon adjacent groups within the molecule.

It is therefore reasonable to dissect log P into two parts, one representing the sum of all the strongly water-repelling features and a second representing the sum of all else.

Strongly hydrophobic groups include all hydrocarbon groups and the halogens. Other heteroatoms (mainly O, N, S, P) are ignored on the grounds that although they may have some ability to repel water, this will be submerged under attractive features including polarity. In most molecules there are relatively few heteroatoms so the approximation is seldom obtrusive. However, fluorine presents the difficulty that it repels water strongly yet tends to induce polarities that attract water. To extract the full water-repelling component, the listed fragmental constant for iodine has been taken as wholly due to water repulsion (the C-I bond being virtually non-polar) and used as the basis for normalization, the corresponding repulsions for the other halogens being taken as proportional to their van der Waals volumes. This procedure modifies only the fluorine value (Table 1).

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Table 1. hP values for halogens.

Halide	ArI	ArBr	ArCl	ArF	CF_3
van der Waals radius r (pm)	204	190	180	155	
$r^3(hal)/r^3(I)$	1·000	0·808	0·687	0·439	
log P	1·29	1·03	0·88	0·31	1·01
hP	1·29	1·04	0·89	0·57	1·90

Based on log P (octanol–water) fragmental values (Leahy et al 1992). For a halogen, hP hal = log $P_{iodine}[r^3(hal)/r^3(iodine)]$. The value for CF_3 includes the contribution from carbon.

Problems peculiar to heterocycles have received attention from Leahy et al (1989) and from Bradshaw & Taylor (1989). The heteroatoms in aromatic heterocycles contribute in variable measure to the aromaticity, thus contributing to the hydrophobic character while yet retaining some ability to interact with water. Thus the heteroatom cannot always be ignored as before. At one extreme the accepted log P value for the aromatic heterocycle might be used; at the other, we can calculate a value by taking log P for the analogous hydrocarbon and removing the appropriate number of CH fragment values. Thus benzofuran corresponds to naphthalene less two CH groups and takes the value 2·65, hardly different from the log P value (2·67), but for pyridine, regarded as benzene less one CH group, the calculation yields 1·77, widely different from the log P value 0·65; thiophene, regarded as benzene less two CH groups, yields 1·41 as opposed to log P 1·81. Since we seek the maximum hydrophobic character, the higher value is always selected. Values relevant here are collected in Table 2.

Hydrogen attached to carbon is always water-repelling, of course, but attached to some other elements, especially oxygen, is water-attracting and consequently not included in the hydrophobic count. Similarly, the NH hydrogen in pyrrole and similar systems is not counted. An exception has to be made for XH as part of an internally hydrogen-bonded arrangement (as for example in 2-hydroxybenzaldehyde) because such bonding greatly reduces the polarity of the whole system, as explained in standard texts such as that by Joesten & Schaad (1974). Of course the heteroatoms are similarly affected and some adjustment should be made to allow for the increase in their ability to repel water; I have followed assessments made by Franke (1984) and allowed 0·19 for the hydrogen and 1·00 for the heteroatoms. In salicylic acid, however, the hydrogen bonding that reduces the polarity of the phenolic OH group automatically increases that of the carboxy group, so no overall allowance has been made for the internal bonding in its derivatives.

Termed hP for present convenience, the total water-repelling capacity of a drug molecule is readily obtained by summing the contributions from hydrocarbon and heterocyclic groups along with halogens just as log P is obtained from fragment values. With the exceptions noted above, heteroatoms are ignored. The residue, mainly the water-attracting capacity, is then just as readily obtained in the form [(log P)–hP] whether log P is measured or calculated.

We have next to decide upon definitions and assays of anti-inflammatory activity. For assessing inflammation in-vivo, oedema in rat hind paw probably has the least subjective element in measurement and, because it has been found relatively reliable and reproducible, it marshals the most substantial array of results over the longest period as seen from accounts by several authors including van Arman (1979) and Grennan & Higham (1986). On the other hand, in-vitro (culture) assessments avoid many of the problems encountered with whole animal studies. Importantly for this study, in-vitro methods can also be extended to toxic compounds or very weakly active ones requiring concentrations too high to be coped with in-vivo. For these reasons we have followed current practice following Vane (1971) and identified anti-inflammatory effects with the inhibition of prostaglandin release in bovine or ovine seminal vesicle or in murine peritoneal macrophage preparations. Otterness & Bliven (1985) have demonstrated that oedema induced by carrageenan in the rat correlates significantly with the ability to inhibit prostaglandin synthesis. Because separate reports of individual activities can vary 10- or 100-fold, as in examples listed by Brune et al (1981), Williams (1990) and Swingle (1974) amongst others, I have sought to achieve consistency by confining this study to results validated by membership of a set of at least 10 compounds examined under identical conditions by a single author or laboratory. In the absence of contrary information, I have assumed that all the compounds under consideration act by essentially the same mechanism. I have also assumed that the results are not distorted by the fact that the induced isoform, cyclo-oxygenase COX-2, has activities somewhat different from those of the constituent isoform, COX-1 (Akarasereenont et al 1994).

Table 2. hP fragment values for groups and aromatic rings.

Group	CH_3	CH_2	CH	C	H
	0·70	0·53	0·36	0·19	0·17
Group	CF_3	F	Cl	Br	I
	1·90	0·57	0·89	1·04	1·29

Increment for internal H-bond as in enolic pentane-1,3-dione: 1·19

Benzene	C_6H_6	2·13	Phenyl	C_6H_5	1·96	Phenylene	C_6H_4	1·79
Naphthalene	$C_{10}H_8$	3·37	Furan	C_4H_4O	1·41	Thiophene	C_4H_4S	1·81
1-Pyrryl	C_4H_4N	1·41	Thiazole	C_3H_3NS	1·45	Benzofuran	C_8H_6O	2·65
Benzothiophene	C_8H_6S	2·65	1-Indolyl	C_8H_6N	2·65	Benzoxazole	C_7H_5NO	2·29
Indolizine	C_8H_7N	2·84	Pyridine	C_5H_5N	1·77	Quinoline	C_9H_7N	3·01

Based on log P (octanol–water) fragmental values given by Leahy et al (1989) (aromatic systems) and by Leahy et al (1992) (aliphatic groups). Halogen values are taken from Table 1. For aromatic heterocycles, the calculated hP value or the log P value is listed whichever is the larger (see text).

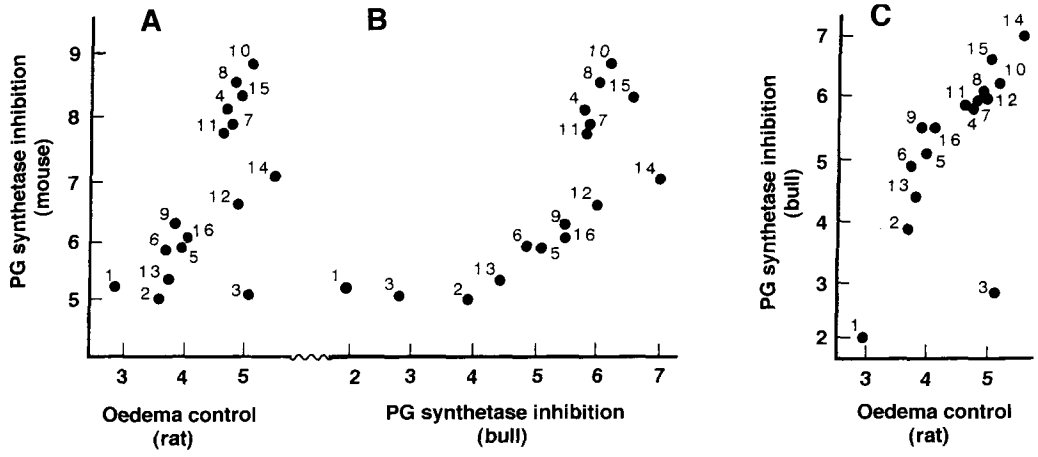

FIG. 1. Comparisons of biological assays. Data from Brune et al (1981), Dearden & Nicholson (1984), and Gregg (1991). A. Oedema control in rat hind paw [log 1/ED50 (mol kg^{-1})] vs inhibition of PGE_2 formation in mouse macrophage cultures [(log 1/IC50 (M)]. B. Oedema control in rat hind paw vs inhibition of PGE_2 formation in bovine seminal vesicle preparations [(log 1/IC50 (M)]. C. Inhibition of PGE_2 formation in bovine seminal preparations vs that in mouse macrophage cultures. Key: 1, aspirin; 2, azapropazone; 3, benoxaprofen; 4, diclofenac; 5, diflunisal; 6, fenclofenac; 7, flufenamate; 8, flurbiprofen; 9, ibuprofen; 10, indomethacin; 11, ketoprofen; 12, naproxen; 13, phenylbutazone; 14, piroxicam; 15a, sulindac (-S-); 15b, sulindac (-SO-); 16, tolmetin.

A preliminary list of drugs common to three major surveys was then constructed taking care to avoid pro-drugs like nabumetone where the extent of conversion would introduce an extra unknown. However, the sulphoxide sulindac was cautiously retained because drug and pro-drug can be examined independently in some assays. The list then contained 16 drugs which were used to compare assays by Dearden & Nicholson (1984) using rat paw oedema, Brune et al (1981) using mouse peritoneal macrophage inhibition in cultures, and Dearden et al (1989) and Gregg (1991) using bovine seminal vesicle methods. The three plots (Fig. 1A, B, C) show fair agreement, but to minimize any interference by species-dependent behaviour I concentrated upon mouse and rat assays. Benoxaprofen (point 3) behaves in a highly irregular manner and was therefore eliminated from all further studies; without this drug, the statistical correlation is satisfactory (Table 3). Aspirin (point 1) also behaved irregularly but was retained because of its central importance in the development and study of anti-inflammatory drugs. The mouse macrophage technique is regarded as the assay of choice for several reasons. It provides the best distribution of data points over the largest range (as much as six orders) of potency (rat paw oedema assays hardly cover three orders). It does not reduce sulphoxides, so that both sulindac and the true drug, the sulphide, can be examined separately. It requires almost neutral conditions giving greater confidence in results for drugs subject to hydrolysis, particularly in basic media, such as the ester, aspirin, and the 1-acylindole, indomethacin, long known to be somewhat labile not just in-vitro (Shen & Winter 1977) but also in-vivo (Harman et al 1964). Seminal vesicle assays commonly include an incubation at pH 8·5.

The list of selected drugs contains further members regarded as unacceptable for structural studies. Hughes et al (1988) adduced evidence that phenylbutazone cannot inhibit cyclo-oxygenase until it is first modified by the lipoxygenase component of prostaglandin synthetase, but unfortunately they were unable to identify the actual inhibitor so that neither this nor any congeneric drug can be used for structural correlations and analyses. Thus both phenylbutazone and azapropazone were rejected. Another, more general, defect arises from the poor range of data for analytical purposes. Clinically useful drugs populate only the higher reaches of potency making any scatter seem worse than it would in a broader view. Hence the surviving list of 13 recognized drugs has been fortified in Table 4 by data for five derivatives of phenol and six of salicylic acid, these being the simplest possible representatives of less active compounds that fulfil all the conditions; in effect, they allow the assay to cover six orders of potency as noted above.

Table 3. Statistical analyses for the mouse peritoneal macrophage assays. Regression equation: log 1/IC50 = ax + b.

Variable x	a	b	r	r^2	p(2 – t)	CI
Rat paw oedema	1·48	0·3	0·83	0·69	0·0001	0·55-0·94
clog P	0·63	3·96	0·52	0·27	0·0077	0·16-0·78
hP	0·91	2·0	0·90	0·81	< 0·0001	0·78-0·95
(log P)–hP	–0·75	4·9	–0·58	0·34	0·0022	–0·80-(–0·25)
tP	1·08	2·88	0·85	0·72	< 0·0001	0·69-0·93

Omitting the outlying entries with sulindac as sulphoxide. Log P refers to octanol/water system; hP refers to hydrophobic contributions only (see text). tP = hP – (log P)/2.

Table 4. Log P, hP and other parameters in assays of prostaglandin E_2 release by mouse peritoneal macrophage.

Compound		clog P	hP	pK_a	log P −hP	tP	Potency
1	Aspirin	1·25	2·87	3·49	−1·62	2·24	5·18
2	Diclofenac	4·77	5·89	4·07	−1·12	3·50	8·02
3	Diflunisal	4·42	4·53	3·00	−0·11	2·32	5·85
4	Fenclofenac	4·87	5·89	4·54	−1·02	3·45	5·79
5	Flufenamate	5·58	5·67	3·88	−0·09	2·88	7·80
6	Flurbiprofen	3·75	5·38	4·23	−1·63	3·50	8·48
7	Ibuprofen	3·83	5·33	4·27	−1·50	3·41	6·26
8	Indomethacin	3·38*	7·13	4·50	−3·75	5·44	8·77
9	Ketoprofen	2·79	5·91	4·58	−3·12	4·51	7·65
10	Naproxen	2·82	5·32	4·30	−2·50	3·91	6·56
11	Piroxicam	1·39*	5·85	6·30	−4·46	5·15	6·99
12a	Sulindac (S)	2·77	6·84		−4·07	5·45	8·24
12b	Sulindac (SO)	0·66	6·84	4·50	−6·18	6·51	5·43
13	Tolmetin	2·57	5·17	4·00	−2·60	3·88	6·02
14	Paracetamol	0·49	2·68	9·50	−2·19	2·45	4·10
15	Phenol	1·46	1·96	9·89	−0·50	1·23	3·54
16	2-Chlorophenol	2·16	2·68	8·48	−0·52	1·60	4·62
17	4-Chlorophenol	2·40	2·68	9·38	−0·28	1·48	4·86
18	2-Phenylphenol	3·09	3·75	10·01	−0·66	2·20	5·61
19	4-Phenylphenol	3·20	3·75	9·51	−0·55	2·15	6·04
20	Salicylic acid	2·27	1·98	2·97	0·29	0·84	3·33
21	5-Hydroxysalicylic acid	1·60	1·81	2·97	−0·21	1·01	4·61
22	5-Aminosalicylic acid	1·04	1·81	5·48	−0·77	1·29	2·94
23	5-Fluorosalicylic acid	2·41	2·38	2·63	−0·03	1·17	3·82
24	3-Cyclohexyl-salicylic acid	4·78	4·82	3·05	−0·04	2·43	4·90
25	5-Cyclohexyl-salicylic acid	4·78	4·82	3·05	−0·04	2·43	5·90

Potencies as given by Brune et al (1981) and by Habicht & Brune (1983) and quoted in the form log IC50 (M); clog P (or mlog P) and pK_a values are taken from the same authors when possible, otherwise from Gregg (1991). *Measured value.

When anti-inflammatory potencies (mouse macrophage) are plotted against log P values only the vaguest indication of a correlation emerges (Fig. 2A). No improvement attends the use of log values other than those based upon the octanol-water system or upon the use of distribution coefficients such as log $D_{7.2}$ (not illustrated). Whether compounds are carboxylic acids or phenols, the activity is independent of pK_a (Fig. 3).

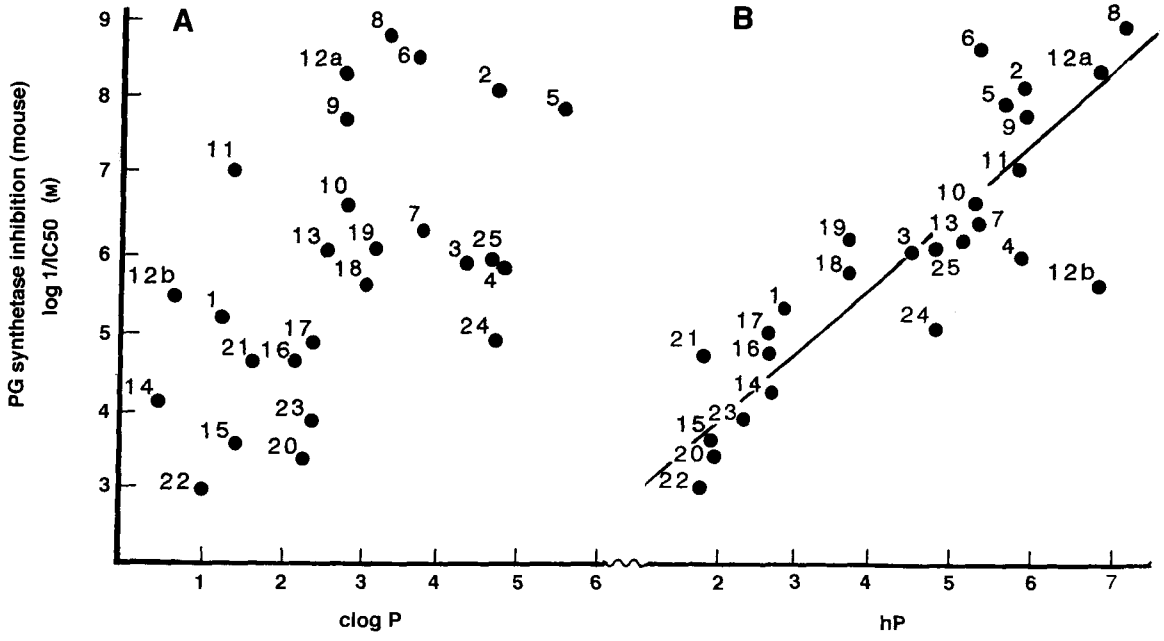

FIG. 2. Comparison of prostaglandin synthetase inhibition in mouse peritoneal macrophage (A) with clog P, and (B) with hP values. Sources, data, and key as in Table 4.

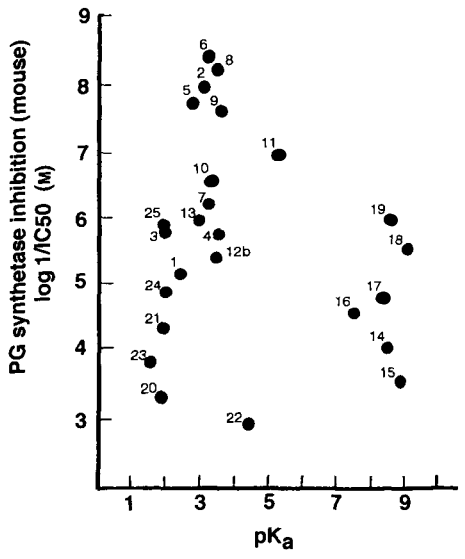

FIG. 3. Comparison of prostaglandin synthetase inhibition in mouse peritoneal macrophage with pK_a values. Data, sources and key as in Table 4.

When activities are plotted against hP values, however, an obvious linear correlation emerges (Fig. 2B) as confirmed statistically (Table 3). When hP is zero the intercept is 2·0 so that hP accounts for much but not all of the anti-inflammatory activity.

Only point 12b is seriously astray in Fig. 2B. This entry refers to sulindac in its pro-drug sulphoxide form, which retains its identity in this assay because the macrophage does not reduce it to the clinical drug, the corresponding sulphide (thioether). When this sulphide is separately examined it correlates well (point 12a), from which we conclude that it is only the highly polar sulphoxide group that causes the discrepancy, presumably because of its exceptional ability to bind water. Hence the sulphoxide was disregarded for statistical purposes. Examples are not numerous but suggested log P fragment values for sulphoxides are all strongly negative indicating a limit to our assumption that heteroatoms can be ignored. In extension, I note that neither Cullen (1984) nor Shen (1979) record any compound-containing group very strongly attractive to water ($^+NR3$, PO_3^-, SO_3^-, sugar or glucuronic acid residue, zwitterion) that has both appreciable anti-oedema activity and the ability to inhibit prostaglandin synthetase.

After sulindac, flurbiprofen exhibits the next largest deviation (point 6). According to Rome & Lands (1975), this drug differs from most anti-inflammatory drugs in being a non-reversible inhibitor of the enzyme, a property that could well explain an activity higher than expected. The anomalously high activity of 5-hydroxysalicylic acid (point 21) has long been known and attributed to a change of mechanism (Shen 1979); in all other series, extra OH groups induce not a small rise but rather a small fall in activity, being water-attractive.

It follows that, if hP correlates with activity, the quantity (log P)−hP should be responsible for the diffuse character of the log relationship. The plot (Fig. 4A) confirms this while indicating the existence of a second, weaker correlation with a negative slope roughly perpendicular to that of the hP plot. This suggests in turn that instead of ignoring heteroatom and other contributions these might be recombined with hP after change of algebraic sign. With division by 2 to bring the numbers back to about the original scale this procedure gives the quantity tP, i.e. hP−[(log P)/2)] (Table 4). The correlation (Fig. 4B) falls slightly short of that for hP but might be preferred because it leaves out none of the components of log P while remaining as good as that for the (purely biological) oedema control data (Table 3).

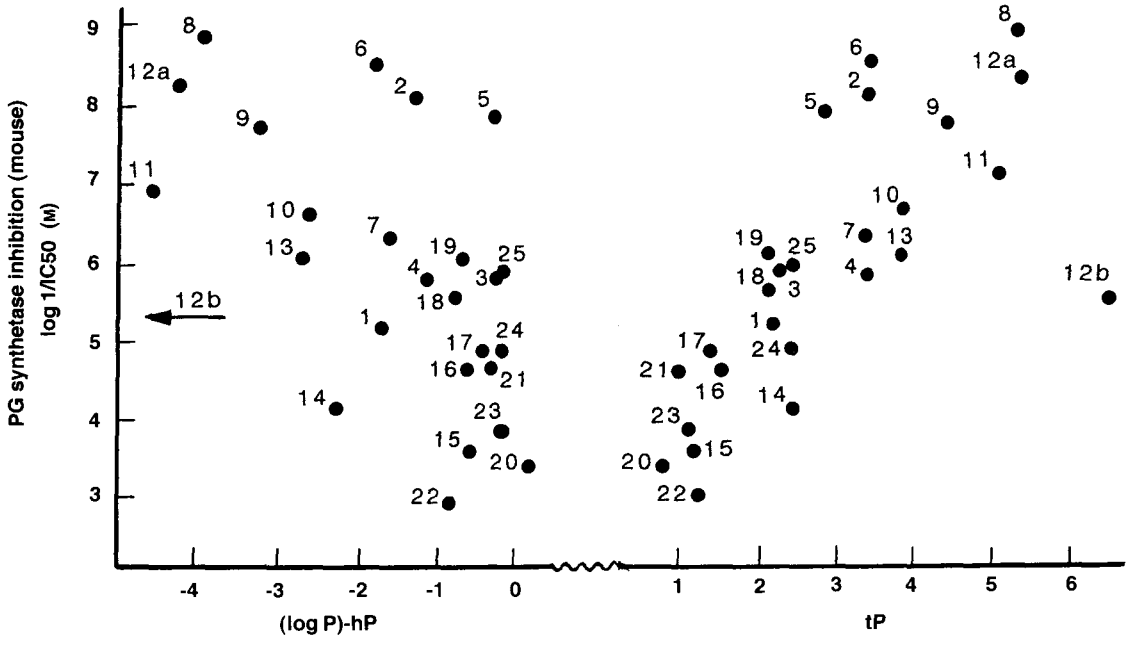

FIG. 4. Comparison of prostaglandin synthetase inhibition in mouse peritoneal macrophage (A) with (clog P)−hP values, and (B) with tP i.e. hP−[(log P)/2] values. Sources, data, and key as in Table 4.

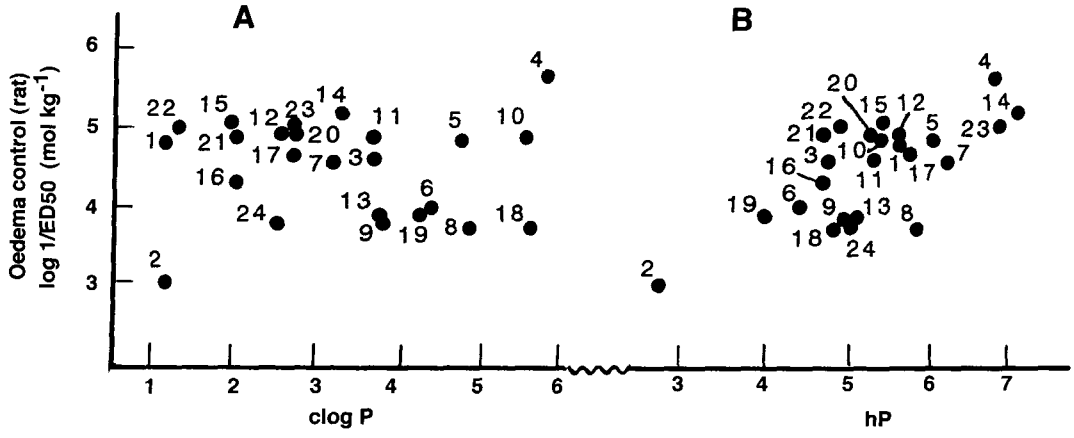

FIG. 5. Comparison of inhibition of carrageenan-induced rat hind paw oedema (A) with clog P, and (B) with hP values. Oedema results from Dearden & Nicholson (1984), and from Gregg (1991), supplemented by averages of values collated from the literature by McCormack Drug Research Ltd. Other data and sources as in Table 4. Key: 1, amfenac; 2, aspirin; 3, carprofen; 4, clidanac; 5, diclofenac; 6, diflunisal; 7, etodolac; 8, fenclofenac; 9, fenoprofen; 10, flufenamate; 11, flurbiprofen; 12, FPL4508; 13, ibuprofen; 14, indomethacin; 15, indoprofen; 16, isoxepac; 17, ketoprofen; 18, mefenamate; 19, monoflunisal; 20, naproxen; 21, oxepinac; 22, piroxicam; 23, sulindac; 24, tolmetin.

However, in other studies it has not produced better correlations, e.g. with seminal vesicle results, so we have continued the use of hP which also has the convenience of requiring neither the calculation nor the measurement of log P.

As noted already, the rat paw oedema assay covers a relatively restricted range of potencies even when supplemented by results for drugs not studied by synthetase inhibition methods. As far as possible I have chosen additional drugs in accordance with the criteria laid down previously but avoiding those for which only one unsupported report is available or, where the literature contains several values, using averages. The final list contains 23 drugs but the range of potencies remains short and the origins less than impeccably uniform. Nevertheless, the plot in Fig. 5A discloses little or no correlation between potency and clog P, whereas Fig. 5B indicates a considerable reorganization of data points strongly suggestive of gravitation towards a correlation line like that found in the macrophage assay.

If these conclusions are accepted, differences in anti-inflammatory activity are not primarily controlled by partition phenomena and log P except in extreme circumstances, notably ionic dissociation. On the other hand, hP is itself only a starting-point representing little more than a measure of carbon, hydrogen, and halogen atoms in existing drugs. It includes almost no structural information and owes its success in this study largely to the fact that the data points refer either to very simple compounds or to drugs from which redundant or deleterious structural aspects have already been removed by the grooming required for clinical success. By itself an hP value cannot determine whether a compound will be a drug or not.

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