QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON PROSTAGLANDIN SYNTHETASE (PGS) INHIBITORS

S. P. GUPTA, Y. S. PRABHAKAR and P. SINGH
Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, India.

ABSTRACT

The quantitative structure-activity relationship studies on some prostaglandin synthetase inhibitors are discussed. The inhibition activity is shown to be well-related with the hydrophobic constant and the electronic parameter of substituents in varying kinds of inhibitors like indoprofens, indandiones, triphenylacrylonitriles, etc. All the correlations suggest that hydrophobic and electronic interactions fully control the activity of prostaglandin synthetase inhibitors.

INTRODUCTION

THE prostaglandin synthetase (PGS) is an oxidoreductase and is involved in the biosynthesis of human prostaglandin E_2 starting from arachidonic acid[1]. Prostaglandin is one of the mediators which is liberated locally in tissues during inflammatory reactions. After the discovery that aspirin inhibits prostaglandin biosynthesis[2–4], it is believed that aspirin-like non-steroidal anti-inflammatory drugs block PGS[1], and in a recent review[5] it has been pointed out that in many cases the *in vivo* assays of anti-inflammatory activity of non-steroidal drugs were well correlated with their PGS inhibition activity. Hence the *in vitro* study of PGS inhibition is considered to be one of the most promising rational approaches for prediction of anti-inflammatory activity.

However, studies on structure-activity relationship are not available on PGS inhibitors. For a very limited series of indoprofen analogs (figure 1), Ceserani *et al*[6] related the PGS inhibition activity with partition coefficient K_p (equation (1)) and for a relatively bigger series of 2-aryl-1, 3-indandione derivatives (figure 2), Van de Berg *et al*[7] related the activity with the hydrophobic constant π and the electronic constant σ (equation (2)). Similarly for some phenols, Dewhirst[8] obtained (3) to (5). Equation (3) is for alkylphenols, (4) for 2-alkoxyphenols, and (5) for some other 2-substituted phenols.

$$pI_{50} = 0.49 \log K_p - 2.19 \quad n = 5,\ r = 0.97, \tag{1}$$

$$pI_{50} = 0.40\,\pi + 1.64\,\sigma + 3.47 \quad n = 24,\ r = 0.91,\ s = 0.24, \tag{2}$$

$$pI_{50} = 0.28\,\pi - 4.27\,\sigma + 3.00 \quad n = 20,\ r = 0.92, \tag{3}$$

$$pI_{50} = 0.77\,\pi - 0.25\,\sigma + 3.95 \quad n = 6,\ r = 0.99, \tag{4}$$

$$pI_{50} = 0.30\,\pi - 0.60\,\sigma + 3.58 \quad n = 8,\ r = 0.99. \tag{5}$$

In all these equations, n is the number of data points, r the correlation coefficient and s the standard deviation. The activity term pI_{50} is minus times the log of inhibitors' concentration leading to 50% inhibition of the enzyme.

All these studies show the importance of hydrophobic character of the molecules in PGS inhibition. Regarding the electronic character, while (2) shows the increase in the activity by electron-withdrawal by substituents in phenyl ring, (3)–(5) show the same effect to be produced by electron-donation (the positive value of σ measures the

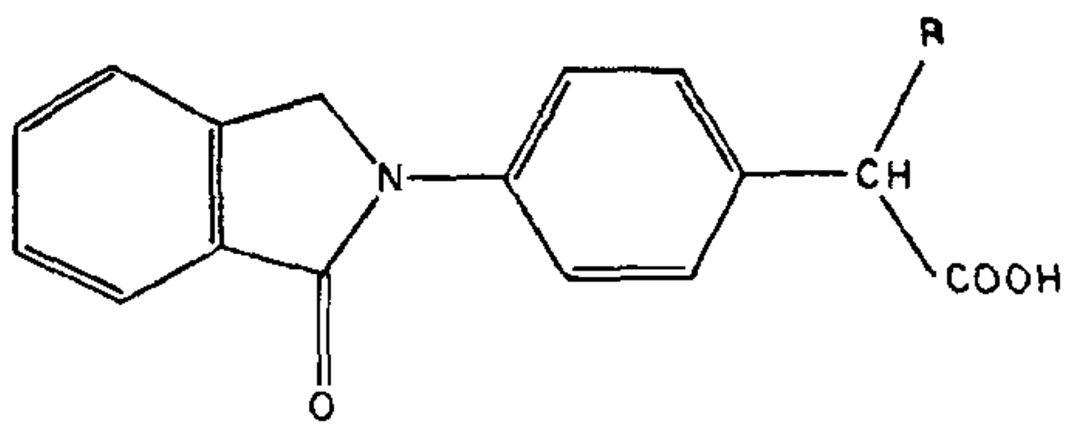

Figure 1. Indoprofen analogs.

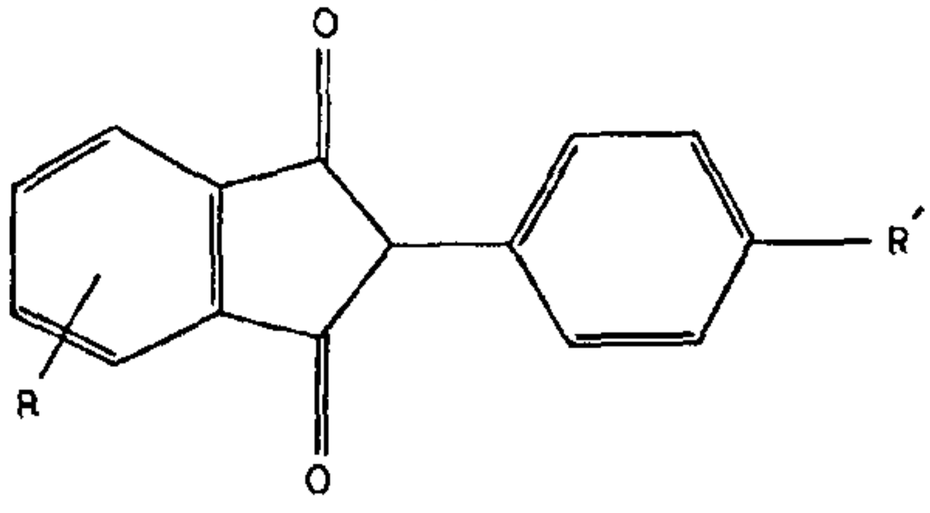

Figure 2. 2-Aryl-1, 3-indandione derivatives.

electron-withdrawal capability and the negative value measures the electron-donation capability of substituents).

In this communication we report a quantitative structure-activity relationship (QSAR) on some triphenylacrylonitriles and triphenylethylenes (figure 3) (table 1) studied by Gilbert *et al*[9]. With the use of π and σ values given in the table 2 for the substituents, the PGS inhibition data of table 1 could be correlated with these two parameters as follows: –

$$pI_{50} = 5.916 + 1.281\ (\pm 0.538)\ \pi.R_1$$
$$-0.005\,(\pm 0.437)\ \pi.R_2$$
$$+0.592\,(\pm 0.426)\ \pi.R_3$$
$$-1.415\,(\pm 0.60)I$$
$$-2.766\,(\pm 1.856)\ \sigma.R_1$$
$$n = 33,\ r = 0.864,\ s = 0.470,$$
$$F_{5,27} = 15.92, \qquad (6)$$

where I, the indicator parameter, has the value of unity for triphenylethylene derivatives and zero for triphenylacrylonitriles. Now (6) verifies the hydrophobic effect of the substituents and supports the positive role of electron-donation. However, the electron-donation was found to be effective from

Table 1 *PGS inhibition activity of some triphenylacrylonitriles and triphenylethylenes (figure 3)*

Compd. No.	R_1	R_2	R_3	X	pI_{50} Obs[9]	pI_{50} Calc equation (6)
1	H	H	H	CN	5.46	5.92
2	OH	H	H	CN	6.70	6.08
3	H	OH	H	CN	5.80	5.92
4	H	H	OH	CN	5.18	5.52
5	OH	OH	H	CN	5.70	6.08
6	OH	OH	F	CN	5.89	6.17
7	OH	CH_3	H	CN	6.10	6.08
8	CH_3	OH	H	CN	7.10	7.11
9	OH	H	Cl	CN	6.52	6.50
10	OH	Cl	CH_3	CN	5.70	6.41
11	OH	CH_3	F	CN	5.85	6.16
12	OH	CH_3	Cl	CN	6.40	6.50
13	OH	OH	OH	CN	5.25	5.69
14	H	H	OCH_3	CN	6.30	5.90
15	OCH_3	CH_3	H	CN	6.30	6.63
16	CH_3	OCH_3	H	CN	6.22	7.10
17	CH_3	OCH_3	OCH_3	CN	6.96	7.09
18	OCH_3	CH_3	OCH_3	CN	7.10	6.62
19	CH_3	OCH_3	F	CN	7.30	7.19
20	OCH_3	CH_3	F	CN	7.40	6.72
21	CH_3	OCH_3	Cl	CN	7.52	7.52
22	OCH_3	CH_3	Cl	CN	7.30	7.05
23	H	OCH_3	Cl	CN	6.89	6.34
24	OCH_3	H	Cl	CN	6.77	7.06
25	OCH_3	Cl	CH_3	CN	6.70	6.96
26	OCH_3	OCH_3	H	CN	6.82	6.64
27	OCH_3	OCH_3	F	CN	7.46	6.72
28	OCH_3	OCH_3	NH_2	CN	6.22	5.91
29	OCH_3	OCH_3	OCH_3	CN	7.30	6.63
30	OH	OH	H	H	4.80	4.67
31	OH	OH	H	CH_2NH_2	5.10	4.67
32	OH	OH	H	$CH_2NHCOCH_3$	4.85	4.67
33	OCH_3	OCH_3	H	$CONH_2$	4.48	5.22

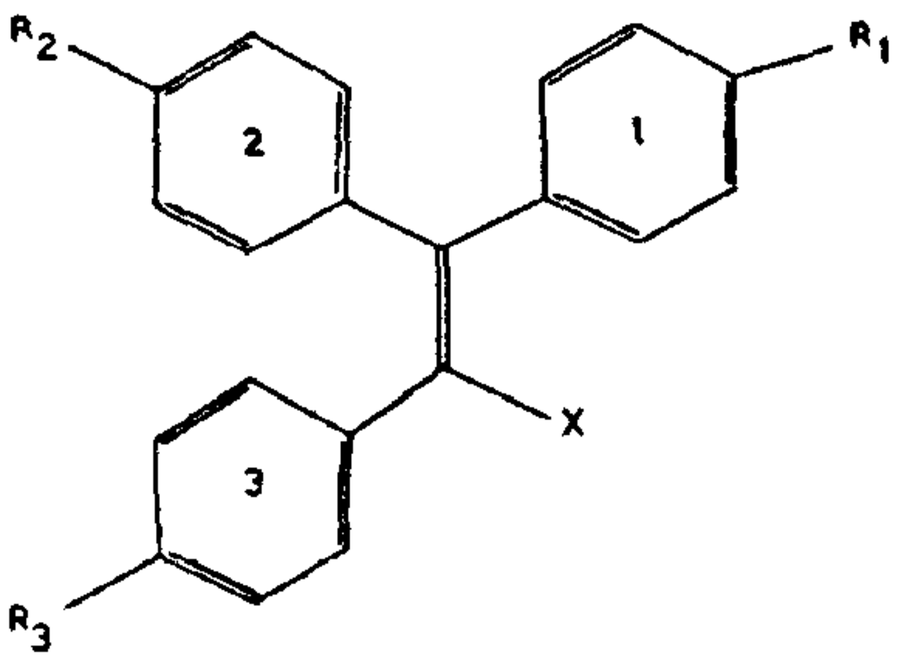

Figure 3. Triphenylacrylonitriles (X = CN) and triphenylethylenes (X = H or group other than CN).

Table 2 *π and σ values for some substituents*

Substituents	π^a	σ^a
H	0 0	0.0
OH	−0.67	−0.37
CH_3	0.56	−0.17
OCH_3	−0.02	−0.27
F	0.14	0.06
Cl	0.71	0.23
NH_2	−1.23	−0.66

[a] Ref. 10.

only one ring. The equation is significant at 99% level [$F_{5,27}(0.01) = 3.79$], but $\pi.R_2$ parameter is not very significant, as its coefficient is much lower than 95% confidence interval (±0.437). From this, one can suggest that only rings 1 and 2, with their substituents, are involved in hydrophobic interaction with the receptor.

The negative coefficient of *I* shows that *X* other than CN will reduce the activity. This means that probably CN group is involved in some electronic interaction with the receptor, and that the electronic character of this CN group is influenced through the electron-donation by the substituents in ring 1.

Thus all QSAR studies show that hydrophobic and electronic interactions are involved in PGS inhibition.

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ANNOUNCEMENT

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A Symposium on Mathematics (Theory of Numbers) dedicated to Dr S. Ramanujan will be held on Thursday 31st December, 1987 at 'Asutosh Bhavan', Calcutta.

Further particulars may be had from: Dr U. Basu, Secretary, Calcutta Mathematical Society, AE-374, Sector I, Salt Lake City, Calcutta 700 064.