

Studies on quantitative structure activity relationship in 1-Aryl-2-[3'-methylprazolin-5'-oxo-1'-yl]-4- (phenyl/p-chlorophenyl)-imidazoles

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Abstract : The quantitative structure activity relationship {QCSR} of 1-aryl-2-[3'-methylprazolin-5'-oxo-1'-yl]-4-(phenyl/p-chlorophenyl)-imidazoles (IIIa-j) was carried out in terms of hydrophobic physicochemical parameter. A fair degree of correlation between observed and calculated activity was established.

(Keywords : QCSR, QSAR, MR, hydro-phobic physicochemical parameter)

Introduction

Quantitative Structure Activity Relationship

The fact that biological activity of a compound is a function of its chemical structure was proposed way back in 1869. Now-a-days this concept has been expanded to consider biological activity as a function of Physicochemical properties viz., structural, physical and chemical. QSAR study is an important emerging aspect of modern medicinal chemistry. This has engaged attention of many worker and most of published work, has been in direction of parameterization of QSAR methodology. It is hoped that in coming years, more instances of the application of QSAR approach may be seen for fractional design of an significant QSARs are being recognized as useful uses to predictable activities of compound which have not been even synthesized.

The fundamentals of any structure activity relationship imagine with the process that can cause biological effects. It involves the transport of chemical or its metabolites to the site of action. Then interaction with the site of action induces a stimulus.

Structurally diverse and structurally similar drugs can give the same biological effect. Structurally similar compound are involved with specific interaction with common receptor, e.g., in sulphonamides, physicochemical parameters and antibacterial activity have been corrected with inhibition of folate synthesis¹.

In general, compound receptor interaction can involve electrostatic effects (such as charge-charge interaction), hydrophobic interactions (such as formation of hydrophobic or hydrophilic pockets), secondary force interaction (such as induced dipole interactions or hydrogen bonding) and charge transfer interactions.

In second situation, structurally diverse compounds may undergo metabolism to some common intermediate e.g., metabolic activation of structurally diverse carcinogens to electrophiles has been postulated as the common intermediates in chemical carcinogenesis². In final category, structurally diverse compounds with common biological activity can possess a similar mechanism of action because the compounds have similar topography, which allows interaction with the common receptor.

The idea of correlating biological activity with chemical structure and physical properties involves different models which are shown by free and wilson³, Hansch and Fujita⁴⁻¹⁸.

QSAR Studies in a series Anti-histaminic 1-Aryl-2-[3'-methylprazolin-5'-oxo-1'-yl]-4- (phenyl/p-chlorophenyl)-Imidazoles (IIIa-i).

In view of the marked H_1 receptor antagonistic activity shown by 1-aryl-2-[3'-methylpyrazolin-5'-oxo-1'-yl]-4- (phenyl/p-chlorophenyl)-imidazoles in isolated guinea pig ileum test, the QSAR of this activity has been carried out in terms of hydrophobic physicochemical parameter, using multiparameter regression analysis. The antihistaminic activity has been described as $\log \frac{1}{c}$ where c is IC_{50} value.

In hydrophobic parameter, π is responsible for the transport of drug to active site and its hydrophobic association therein, while molar refractivity (MR) has been proposed¹⁹⁻²⁹ to be a measure of steric bulk and polar space at the receptor.

Experimental

Partition Coefficient k Partition coefficient for I and II were determined experimentally. The accurately weighed amount of the compound was partitioned between measured volume of purified CO_2 -free n-octanol saturated with water (V_1 ml) and measured volume of water (V_2 ml) on a mechanical shaker at 37°C, till the equilibrium was attained (120 hrs.). The octanol layer was separated, centrifuged at 2000 rpm and kept standing overnight. The concentration of compound in octanol layer before and after partition was determined from the standard curve drawn between concentration and absorbance at 210 nm on a Beckman UV spectrophotometer. The concentration in water layer was calculated by difference. The partition coefficient was calculated as $P = \frac{C_{octanol}}{C_{water}}$. The $\log P$ for I and II were, 0.36 and 1.52, respectively. The experimental value of $\log P$ 1.48 and 1.20 for I and II, respectively, were in clear agreement with corresponding calculated values (1.44 and 1.16). The $\log P$ values for each of the compound were calculated as listed in table.

Determination of R_m

There are the following steps for determination of R_m .

(a) Impregnation of Plates

Silica gel plates (60F₂₅₄, 20x20 cm, thickness 0.2 mm) were impregnated by placing them in a chromatographic chamber containing stationary phase [liquid paraffin (6.0 ml) + hexane (94.0 ml)] for 12-15 h till the solution had reached the top of the plates. The volatile component of the stationary phase was allowed to evaporate at room temperature for 48 h.

(b) Preparation of mobile phase

It was prepared by mixing (v/v) 0.01 M phosphate buffer (pH 7.4) and appropriate percentage of acetone.

Determination of R_f

The solution of compound in chloroform (0.3%) containing a few drops of the methanol were prepared and 1 μ l of each solution was spotted thrice on the impregnated plate at 1 cm apart and from the lower edge of plate. A migration of 15 cm on 20 cm away plates was obtained by cutting the layer at 17 cm from all of the. Each plate was run in mobile phase containing 40% lower edge. room temperature, 2) acetone phosphate buffer (pH 7.4) (V_1/V_2) at then plates were taken out from the chamber and dried at room temperature. The spots were located in UV light and temperature then plates were taken out from the chamber and dried at room temperature for 5-6 h. The spots were located in UV light and R_f values were calculated. Thus, the R_f values at 50%, 60%, 70% and 80% acetone concentration in buffer were calculated. The R_m for each compound was determined at different acetone concentration using the following formula:

$$R_m = \log \left(\frac{1}{R_f} - 1 \right)$$

After determining the R_m values for each concentration, a graph of R_m versus percentage of acetone concentration was plotted. From the computerized graph, the R_m values were extrapolated of 0% concentration of acetone which are required R_m values or partition values at physiological pH (=7.4).

The calculation of Rm values as well as multiparameter regression analysis was performed on 700 wang computer using standard regression programmers.

Substituent parameters used in regression analysis of 1-aryl-2-[3'-methyl prazolin-5-oxo-1'-yl]-4-[phenyl/-4-chlorophenyl]-imidazoles

Compound No.	Molecular Formula	Br	For	$\log \frac{1}{c}$	
				Forcd	Calculated
IIIa	$C_{19}H_{16}N_4O_2$	1.16	1.8074	0.721	0.678
IIIb	$C_{19}H_{16}N_4O_2$	1.16	1.8354	0.357	0.678
IIIc	$C_{20}H_{18}N_4O$	0.21	1.7032	0.620	0.471
IIId	$C_{19}H_{15}N_5O_3$	2.00	1.6898	0.624	0.861
IIIe	$C_{20}H_{16}N_4O_2$	1.38	1.0439	0.764	0.726
IIIf	$C_{19}H_{15}N_4O_2Cl$	2.15	2.0540	0.854	0.894
IIIg	$C_{20}H_{17}N_4OCL$	2.86	2.2300	1.022	1.048
IIIh	$C_{20}H_{17}N_4O_2Cl$	0.87	1.2016	0.752	0.615
IIIi	$C_{20}H_{17}N_4O_2Cl$	1.44	1.2100	0.699	0.739
IIIj	$C_{19}H_{14}N_4OCl_2$	1.42	1.2552	0.252	0.769

Reference

1. J. S. Shukla and K. Agarwal, *Indian Drugs* **19**, 312 (1982).
2. C. W. Parker, Am, *J. Med. Chem.*, **7**, 395 (1964)
3. S. H. Free and J.W. Wilson *J. Med Chem.*, **7**, 395 (1964).
4. A. Hansch and T. Fugita, *J. Am. Chem. Soc.*, **06**, 1616 (1964)
5. A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, **525**, 71 (1971).
6. R. P. Rekker, "The Hydrophobic Fragmental Constants, its Deviation and Application - A Mean of Characterising Membrane System," *Elsevier*, Amsterdam, (1977).
7. G. L. Baigi, A. M. Guerva, A. M. Barbara and M. F. Camba, *J. Med. Chem.*, **13**, 511 (1970).
8. R. A. Scherrer and S. M. Howard, *J. Med. Chem.*, **20**, 53 (1977).
9. R. W. Taff, "Steric Effects in Organic Chemistry," (Ed. M. S. Newmann), Wiley, New York, p. 556 (1956)
10. C. K. Hanock, E. A. Meyer and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211, (1961).
11. O. Exner, Coll. Czech. *Chem. Commun.*, **32**, 1 (1967).
12. A. Cammarata and J. Yaus, *J. Med. Chem.*, **13**, 93 (1970).
13. E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).
14. M. Yamazaki, W. Kakeye, T. Morishita, A. Kameda and M. Aoki, *Chem. Pharm. Bull.*, **18**, 708 (1970).
15. A. Leo, C. Hansch and C. Church, *J. Med. Chem.*, **12**, 766 (1969).
16. C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. W. Kaitani and E. J. Lein, *J. Med. Chem.*, **16**, 1207 (1973).
17. C. Hansel, S. D. Rackwell, P. Y. C. Jow, A. Leo and E. F. Steller, *J. Med. Chem.*, **20**, 204 (1977).
18. W. J. Dunn, *Eur. P. Med. Chem.*, **12**, 109 (1977)
19. C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, (1976)
20. C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).
21. C. Hansch, "Drug Design, Vol. I, (Ed. E. J. Ariens) Academic Press, New York, P. 271 (1971)
22. T. Fujita and T. Ban, *J. Med. Chem.*, **14**, 148 (1971).
23. P. N. Craig, *J. Med. Chem.*, **15**, 144 (1972).

24. P. N. Craig and C. Hansch, *J. med. Chem.*, **16**, 161 (1973).
25. A. Canumarate and T.M. Bustard, *J. Med. Chem.*, **17**, 981 (1974).
26. M. Yoshimoto and C. Hansch, *J. Med. Chem.* **19**, 81 (1976).
27. V. A. Rao, P. C. Jain and N. Anand, *Ind. J. Chem.*, **7**, 533 (1969).
28. W. J. Dunn, *Eur. J. Med. Chem.*, **12**, 109: (1977)
29. C. Sillipo and C. Hansch, *J. Am. Chem. Soc.*, **97** 6549 (1975).