Monatshefte für Chemie 120, 913–921 (1989)

Monatshefte für Chemie
Chemical Monthly

Quantum Pharmacological Studies on Antimalarial Drugs

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Summary. Linear models for the relation between electronic structure and antimalarial activity of chloroquine drugs have been investigated, based on CNDO/2 molecular orbital calculations. The results indicate that changes in electron density on the atoms N1, N2, C4, C9, and C10 have the strongest influence on the pharmacological activity, so that these atoms can be assumed to form the main active center of these drugs. Correlations improve, if substitution on the nucleus of chloroquine and side chain variations are treated separately. The models found seem to be a useful tool for designing new drugs within the chloroquine series.

Keywords. Pharmacological activity; QSAR antimalarial; Electronic structure.

Quantenchemisch-pharmakologische Untersuchungen von Antimalaria-Wirkstoffen

Zusammenfassung. Auf der Basis von CNDO/2-Rechnungen wurden lineare Modelle für die Relation zwischen Elektronenverteilung und der Antimalaria-Aktivität von Chlorochinen untersucht. Es zeigte sich, daß Veränderungen in den Elektronendichten der Atome N1, N2, C4, C9 und C10 den stärksten Einfluß auf die pharmakologische Wirkung haben. Es kann somit angenommen werden, daß diese Atome die hauptsächlich aktiven Zentren der Verbindung sind. Die Korrelation wird verbessert, wenn die Substitution am Chlorochin-Kern und Variationen der Seitenketten separat behandelt werden. Die aufgefundenen Modellvorstellungen sollten ein nützliches Werkzeug zur gezielten Synthese neuer Wirkstoffe innerhalb der Chlorochin-Reihe darstellen.

Introduction

Numerous studies on quantitative structure-activity relations (QSAR) of drugs have been performed in the past two decades. Most of them are based on topological parameters, however, comparatively few make use of quantitative molecular orbital theory. Such studies have been reported so far on diuretics [1], barbiturates [2, 3], and antibiotics [4–9], but no such investigation has been performed for antimalarial drugs. In a first study of correlations between quantum chemically calculated molecular properties and the antimalarial activity of primaquines in laboratory animals we could show that linear models correlating the atomic net charges resulting from CNDO/2 MO calculations and the logarithm of the pharmacological activity seem to be a useful approach to a QSAR of such drugs, helpful also for obtaining information about the active center of the drug [10].

In this work we have investigated whether similar correlations could be established between electronic structure and antimalarial activity of chloroquine derivatives in human beings.

Method

The molecular backbone of chloroquine-type drugs is illustrated in Fig. 1. 21 pharmacologically well-characterized compounds have been considered for our investigation, whose activity data have been reported in literature [11]. Their geometries were taken from experimental data [12] supported by standard assumptions where necessary. The CNDO/2 MO SCF method was used in its standard parametrization [13]. As in our previous study [10], atomic populations according to Mulliken [14] were chosen as variables for a multilinear regression analysis, relating the electronic structure of the compounds to their pharmacological activity. All atoms of the quinoline ring and nitrogen of the amino group were taken into this consideration. Several models, containing the charges q of a few of these atoms as variables were tested by parameter fitting according to the equation

$$\ln A = P(i) * q(i) + D, \tag{1}$$

where A is the activity of the drug relative to the standard chloroquine = 100, $P(i)$ the fitted parameter and q (i) the atomic net charge of the i-th atom.

Results and Discussion

Pharmacological data and calculated CNDO/2 atomic net charges of the compounds are reported in Tables 1 a–c. In addition to the atomic charges, the overall charge of the quinoline ring q(ring) and the calculated dipole moment μ are reported. This additional data had been included also in our previous approach on primaquine drugs and, although not improving significantly those results, were considered here for reasons of completeness and because dipole moments had been used for QSARs in early approaches [15, 16] on other drugs.

Evaluation of correlations using varying sets of atoms showed that only models containing charges of nitrogen atoms and ring atoms of the heterocyclic quinoline part seemed to be useful for QSAR establishment. Results are reported therefore for such models, namely:

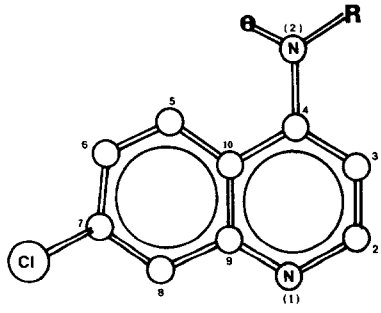

Fig. 1. Molecular backbone of chloroquine drugs

Model no.	Atoms included (numbers cf. Fig. 1)
1	N1, C2, C3, C4
2	N1, C2, C3, C4, N2
3	N1, C4, C9, C10, N2
4	N1, C2, C9, C10, N2
5	N1, C2, C3, C4, C9, C10, N2
6	As model 5, in addition q(ring) and μ

The reliability of the possible QSARs has been characterized by 3 data, the correlation coefficient R, the average deviation of calculated from observed ln A (c av.), and the maximal deviation observed throughout the series (c max.).

The results of the investigation performed with the whole set of data are listed in Table 2, and they show that correlations seem to exist, but that they are far

Table 1 a. Results of CNDO/2 MO SCF calculations on quinoline drugs (activities relative to chloroquine, electron densities in atomic units, dipole moments in Debye)

No.	Substituents in position	Activity	Electron density at various atoms				
			N1	C2	C3	C4	C5
1	7-Cl	100	5.1953	3.8725	4.1075	3.8402	3.9805
2	7-F	50	5.2014	3.8687	4.1141	3.8352	3.9624
3	7-CF_3	50	5.1943	3.8716	4.1066	3.8406	3.9807
4	7-OCH_3	14	5.2044	3.8690	4.1166	3.8349	3.9641
5	7-CH_3	7	5.2015	3.8733	4.1128	3.8397	3.9795
6	7-H	7	5.1983	3.8757	4.1097	3.8423	3.9842
7	6-Cl	100	5.1978	3.8710	4.1100	3.8372	3.9712
8	8-Cl	3	5.1863	3.8713	4.1092	3.8386	3.9741
9	5-Cl	3	5.1970	3.8725	4.4403	3.8352	3.9048
	Additional to 7-Cl						
10	6-CH_3	25	5.1896	3.8777	4.1042	3.8463	4.0043
11	2-CH_3	15	5.1794	3.8899	4.0363	3.8653	3.9776
12	8-NH_2	10	5.2196	3.8405	4.1216	3.8365	3.9779
13	8-NH_2	2	5.0841	3.8816	4.1009	3.8478	4.0096
	Different amino side chains						
14	$-NH-C_6H_{10}-N(C_2H_5)_2$	100	5.1885	3.8749	4.0810	3.8551	3.9398
15	$-NH-C_6H_{10}-NH-C_2H_5$	100	5.1885	3.8751	4.0810	3.8553	3.9398
16	$-NH-C_6H_{10}-NH-CH(CH_3)_2$	50	5.1882	3.8751	4.0809	3.8554	3.9390
17	$-NH-CH(CH_3)-(CH_2)_3-NHCH_3$	100	5.1947	3.8728	4.1076	3.8407	3.9809
18	$-NH-CH(CH_3)-(CH_2)_3-NHC_2H_5$	50	5.2026	3.8702	4.1078	3.8347	3.9766
19	$-NH-(CH_2)_3-N(C_2H_5)_2$	80	5.1970	3.8690	4.0909	3.8392	3.9796
20	$-NH(CH_2)_3-NH(CH_2-CH_2-OH)_2$	8	5.1962	3.8690	4.0905	3.8393	3.9795
21	$-NH-(CH_2)_3-N(C_6H_{13})_2$	6	5.1965	3.8686	4.0906	3.8392	3.9795

Table 1 b. Results of CNDO/2 MO SCF calculations on quinoline drugs (activities relative to chloroquine, electron densities in atomic units, dipole moments in Debye)

No.	Substituents in position	Activity	Electron density at various atoms				
			N1	C2	C3	C4	C5
1	7-Cl	100	4.0160	3.8820	4.0340	3.8812	4.0121
2	7-F	50	4.0784	3.7439	4.1011	3.8655	4.0283
3	7-CF_3	50	4.0066	4.0171	4.0232	3.8817	4.0093
4	7-OCH_3	14	4.0868	3.7941	4.0978	3.8667	4.0314
5	7-CH_3	7	4.0346	3.9330	4.0590	3.8805	4.0208
6	7-H	7	4.0195	3.9643	4.0413	3.8836	4.0149
7	6-Cl	100	3.9416	3.9577	4.0421	3.8766	4.0170
8	8-Cl	3	4.0226	3.9562	3.9626	3.8728	4.0160
9	5-Cl	3	4.0073	3.9673	4.0325	3.8825	4.0087
	Additional to 7-Cl						
10	6-CH_3	25	3.9725	3.8990	4.0248	3.8900	4.0074
11	2-CH_3	15	4.0235	3.8810	4.0364	3.8873	4.0127
12	2-CH_3	10	4.0206	3.8794	4.0387	3.8783	4.0180
13	8-NH_2	2	3.9968	3.9289	3.9079	3.9173	3.9984
	Different amino side chains						
14	$-NH-C_6H_{10}-N(C_2H_5)_2$	100	4.0618	3.8633	4.0669	3.8724	4.0412
15	$-NH-C_6H_{10}-NH-C_2H_5$	100	4.0618	3.8632	4.0672	3.8724	4.0414
16	$-NH-C_6H_{10}-NH-CH(CH_3)_2$	50	4.0620	3.8630	4.0671	3.8727	4.0411
17	$-NH-CH(CH_3)-(CH_2)_3-NHCH_3$	100	4.0161	3.8822	4.0338	3.8811	4.0125
18	$-NH-CH(CH_3)-(CH_2)_3-NHC_2H_5$	50	4.0167	3.8832	4.0376	3.8830	4.0084
19	$-NH-(CH_2)_3-N(C_2H_5)_2$	80	4.0173	3.8812	4.0350	3.8794	4.0138
20	$-NH(CH_2)_3-NH(CH_2-CH_2-OH)_2$	8	4.0169	3.8812	4.0347	3.8794	4.0138
21	$-NH-(CH_2)_3-N(C_6H_{13})_2$	6	4.0166	3.8809	4.0345	3.8792	4.0135

below the significance observed in the case of primaquines and laboratory animal data. At least two reasons can be assumed to be responsible for this. First, the less well defined sampling conditions in the cases of human patients compared to animal experiments and second the larger structural and chemical variation of the drugs in the case of chloroquine compounds. Whereas the first factor could not be investigated further by us, the second factor was to a certain extent accessible by separate evaluation of the models for compounds with nuclear substitution changes and side chain substitution changes, respectively. The results of this separate evaluations are shown in Tables 3 and 4 for the 13 compounds differing by substituents in the quinoline ring only, and the 8 compounds differing in their side chain with constant nuclear substituent.

Correlation coeficients improve considerably by this separation of compounds. The relatively small number of compounds did not allow, however, to test all models satisfactorily. However, from the data for all compounds and those differing in nuclear substitution, a few conclusions can be drawn:

Table 1c. Results of CNDO/2 MO SCF calculations on quinoline drugs (activities relative to chloroquine, electron densities in atomic units, dipole moments in Debye)

No.	Substituents in position	Activity	Electron density at		
			N2	Quinoline-ring	
			Dipole	moment	
1	7-Cl	100	5.2286	40.8212	6.2273
2	7-F	50	5.2291	40.7990	5.9566
3	7-CF_3	50	5.2285	40.9317	6.3465
4	7-OCH_3	14	5.2295	40.8658	5.2730
5	7-CH_3	7	5.2295	40.9347	4.6027
6	7-H	7	5.2295	40.9338	4.6960
7	6-Cl	100	5.2287	40.8213	4.1971
8	8-Cl	3	5.2284	40.8097	7.1293
9	5-Cl	3	5.2352	40.8181	2.6042
	Additional to 7-Cl				
10	6-CH_3	25	5.2291	40.8160	6.1213
11	3-CH_3	15	5.2430	40.7894	6.5283
12	2-CH_3	10	5.2289	40.7411	6.2948
13	8-NH_2	2	5.2288	40.7733	5.9918
	Different amino side chains				
14	$-NH-C_6H_{10}-N(C_2H_5)_2$	100	5.2159	40.8449	5.0315
15	$-NH-C_6H_{10}-NH-C_2H_5$	100	5.2160	40.8457	5.0462
16	$-NH-C_6H_{10}-NH-CH(CH_3)_2$	50	5.2157	40.8445	6.5381
17	$-NH-CH(CH_3)-(CH_2)_3-NHCH_3$	100	5.2288	40.8224	6.1072
18	$-NH-CH(CH_3)-(CH_2)_3-NHC_2H_5$	50	5.2269	40.8226	6.3085
19	$-NH-(CH_2)_3-N(C_2H_5)_2$	80	5.2223	40.8024	6.9968
20	$-NH(CH_2)_3-NH(CH_2-CH_2-OH)_2$	8	5.2221	40.8005	8.1678
21	$-NH-(CH_2)_3-N(C_6H_{13})_2$	6	5.2219	40.7991	8.0944

1. Addition of q(ring) and μ does not seem to improve the models sufficiently to justify their inclusion.

2. Size of parameters and correlation coefficients seem to indicate that C9 and C10 are slightly more important for the drugs' activity than C2 and C3. This leads to the assumption that N1...C9...C10...C4...N2 can be considered as main region of the active center of chloroquine but that the link via C2...C3 is also influential. For obtaining an acceptable correlation coefficient, inclusion of all of these atoms is required.

3. Inclusion of compounds with differing side chains leads to worse correlation data. Their separate treatment shows within the limits of the small number of compounds available that the same models (but with different parameters) can be applied. The less satisfactory results for side-chain substituted compounds indicates that steric factors may play a more important part within this series, whereas such contributions seem to be more constant within the drugs differing only in ring substituents.

Table 2. Parameters $P(i)$ (Eq. (1)) for linear QSAR models; complete data set of all 21 drug molecules; definition of models and c av./c max. see text; R is the correlation coefficient

Model	Parameters										c av.	c max.	R
	P(N1)	P(N2)	P(C2)	P(C3)	P(C4)	P(C9)	P(C10)	P(ring)	$P\mu$	D			
1	52.1	–	13.4	−1.5	54.0	–	–	–	–	3.2	1.179	2.196	0.243
2	93.2	−95.6	65.1	8.7	29.4	–	–	–	–	20.4	1.003	1.932	0.476
3	29.4	−91.4	–	–	92.2	93.6	−63.8	–	–	22.5	0.890	2.016	0.575
4	37.3	−82.7	66.3	–	–	−55.6	−10.7	–	–	16.6	0.980	1.908	0.546
5	140.0	−157.0	113.0	42.0	234.0	−163.0	−142.0	–	–	41.5	0.800	1.798	0.677
6	183.0	−252.0	154.0	61.0	347.0	−240.0	−245.0	−8.42	−0.30	68.7	0.758	1.481	0.733

Table 3. As Table 2, but using data set of drugs differing only in nuclear substituents (13 drug molecules)

Model	Parameters										*c* av.	*c* max.	*R*
	P(N1)	*P*(N2)	*P*(C2)	*P*(C3)	*P*(C4)	*P*(C9)	*P*(C10)	*P*(ring)	*P*μ	*D*			
1	53.1	–	27.9	−39.5	88.5	–	–	–	–	−14.1	1.084	1.971	0.298
2	147.2	−619.7	70.0	−241.6	−309.9	–	–	–	–	101.8	0.696	1.651	0.763
3	30.7	−208.2	–	–	147.4	−120.6	−83.1	–	–	55.0	0.722	2.266	0.619
4	61.1	−68.7	72.3	–	–	89.4	−81.7	–	–	6.4	0.953	1.807	0.511
5	279.0	−755.2	153.4	−274.2	−303.2	−103.7	−191.4	–	–	108.8	0.432	1.189	0.896
6	369.8	−877.3	236.3	−271.0	−232.1	−176.8	−300.3	−8.71	−0.084	136.8	0.274	0.820	0.955

Table 4. As Table 2, but using data set of drugs differing only in side chain (8 drug molecules)

Model	Parameters										*c* av.	*c* max.	*R*
	P(N1)	*P*(N2)	*P*(C2)	*P*(C3)	*P*(C4)	*P*(C9)	*P*(C10)	*P*(ring)	*P*μ	*D*			
1	775.1	–	−1403.0	404.5	1284.0	–	–	–	–	−163.9	0.479	1.470	0.767
2	1280.0	−3219.0	−7009.0	2755.0	3801.0	–	–	–	–	−90.8	0.494	1.101	0.818
3	2517.0	−271.4	–	–	4733.0	−318.6	−2216.0	–	–	261.4	0.486	1.051	0.820
4	361.8	−1541.0	5920.0	–	–	−8760.0	−3700.0	–	–	44.3	0.451	1.456	0.803
5													
6													

(models 5 and 6 not included due to too small data set)

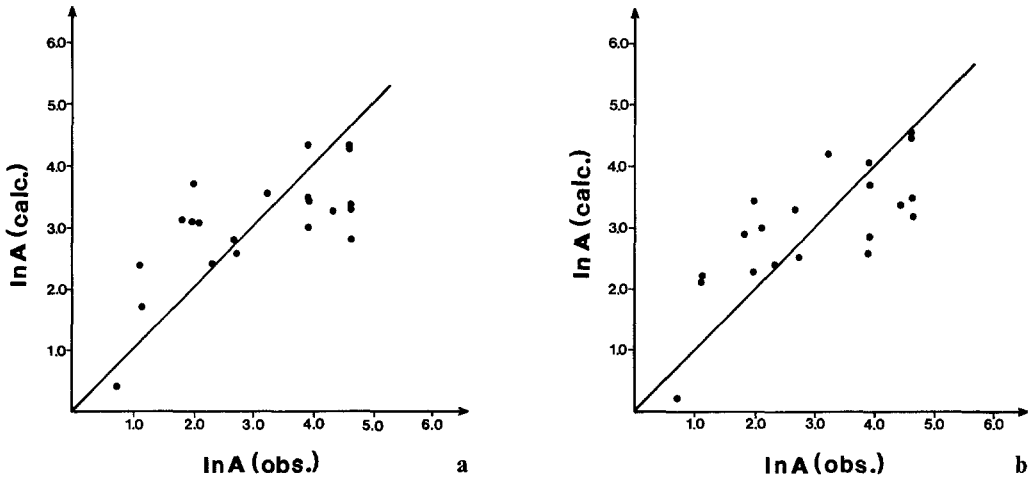

Fig. 2. Calculated versus observed antimalarial activity (ln A) for (**a**) models 5 and (**b**) model 6, for the full set of data, corresponding to fitted equations of Table 2

Taking into consideration all data (correlation coefficients, c av. and c max.), model 5 seems to be the most appropriate form of QSAR between electronic structure and antimalarial activity of chloroquine drugs. Correlations for the combined data sets are not very good (cf. Fig. 2), but if separate sets are considered, our model 5 appears to be a useful tool for the prediction of pharmaceutical activity of new chloroquine drugs, especially concerning other nuclear substituents. This model could therefore rationalize the search for new antimalarial drugs, necessary due to the rapid resistance development of plasmodium falcipare in tropical countries.

For the chemically similar type of primaquine drugs, the search of relations between atomic net charges and pharmacological activity had shown that the most important atoms are ring nitrogen, amino nitrogen, and C8/C9, which connect the two N atoms [10]. The similarity of this center with that found for chloroquine is quite obvious, and the structure of these hypothetical "active molecular regions" indicates that binding to nucleic bases of the plasmodium's RNA could occur, and that the bulky rest of the drug molecule could block further replication.

Within quantitative molecular orbital calculations, CNDO/2 is a strongly simplified approach, with numerous possible error sources. The inadequate charges for H atoms usually obtained by this method was the reason, not to include any of these atoms in our investigations, although especially the amino hydrogen might have some important influence. This and other methodical shortcomings could be avoided by using more reliable *ab initio* methods. Geometry optimization of the drug molecules could have been another possible way of improvement. However, the enormous effort in computer time even within the semiempirical framework, together with the fact that the active ring structure should remain rather rigid, made the restriction to experimental geometries necessary and tolerable. Some recent orientational calculations on a series of chloroquine molecules using the *ab initio* MO SCF method with minimal GLO basis sets have shown that at that level of accuracy no improvement compared to the CNDO/2 results can be achieved

[17], although computing time increases drastically. As the use of larger basis sets would lead to prohibitively expensive CP times, CNDO or similar semiempirical methods still seem to be a necessary and acceptable compromise for quantum pharmacological calculations on series of drug molecules of this size.

Acknowledgement

Financial support by the Austrian Federal Ministry for Science and Research (GZ. 18889/7–10/87) and generous supply of computing time by the computer center of Chulalongkorn University is gratefully acknowledged.

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Received June 13, 1988. Revised January 16, 1989. Accepted June 26, 1989