RELATIONS BETWEEN STRUCTURE AND ANTITUBERCULOTIC ACTIVITY IN A GROUP OF 10-PIPERAZINO-10,11--DIHYDRODIBENZO[*b*,*f*]THIEPINS*

Karel WAISSER and Jana BOŘKOVÁ

Department of Inorganic and Organic Chemistry, Pharmaceutical Faculty, Charles University, 501 65 Hradec Králové

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

Relations between chemical structure and activity to *Mycobacterium tuberculosis* have been looked for within a group of the derivatives of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins prepared by Protiva et al. It has been found that the most reliable results are obtained with application of the model by Free and Wilson. The activity can be considered additive with regard to the contributions of the molecular segments varied.

At present our working team try to reach a general view of problems of relations between structure and antimycobacterial activity of compounds. These attempts have led to a series of review articles entitled "Compounds with Antituberculotic Activity"[1-6]. When dealing with the part on antituberculotic amines[6], we found that a large number of compounds of the said group were prepared under the guidance of Protiva in Research Institute of Pharmacy and Biochemistry Prague. Of course, the substances were synthetized for other purposes, predominantly as potential psychopharmacons. The antituberculotic activity only represented a side effect, and thus it often failed to be included in registers of Chemical Abstracts. Therefore, we decided to return to this topic and by publishing a study about relationships between structure and activity to *Mycobacterium tuberculosis* also to attract attention to the papers by Protiva et al. which are also included into the information data base about antimycobacterial compounds. This present study is restricted to derivatives of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins.

Our study is based on the method by Free and Wilson[7]. This method considers the resulting activity to be a sum of contributions of the molecular segments varied, which, however, usually represents a characteristic approach to antituberculotic

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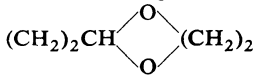
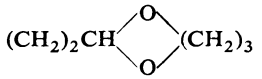
TABLE I

Survey of the 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins studied and values of logarithm of the minimum inhibition concentration towards *Mycobacterium tuberculosis*

Compound	R^1	R^2	R^3	R^4	R^5	R^6	log MIC[a]	Ref.
I	CH_3	H	H	H	F	H	1·90	10
II	CH_3	Cl	H	OCH_3	H	H	1·52	11
III	$(CH_2)_3OH$	SCH_3	H	F	H	H	1·47	12
IV	CH_3	SCH_3	H	F	H	H	1·15	12
V	$(CH_2)_3OH$	SCH_3	H	OCH_3	H	H	1·46	13
VI	$(CH_2)_2OH$	F	H	Cl	H	H	1·20	13
VII	CH_3	Cl	H	Cl	H	H	1·22	13
VIII	CH_3	F	H	Cl	H	H	1·24	13
IX	CH_3	H	H	F	H	H	1·58	14
X	CH_3	H	H	OCH_3	H	H	1·56	14
XI	H	Cl	OH	H	H	H	1·86	15
XII	CH_3	Cl	OH	H	H	H	2·14	15
XIII	H	Cl	OCH_3	H	H	H	1·54	15
XIV	CH_3	Cl	OCH_3	H	H	H	2·13	15
XV	$(CH_2)_2OH$	H	F	H	H	H	1·84	16
XVI	CH_3	H	F	H	H	H	1·28	16
XVII	CH_3	Cl	H	H	OCH_3	H	1·22	11
XVIII	CH_3	OCH_3	H	H	OCH_3	H	1·23	17
XIX	H	H	H	H	Cl	H	1·27	18
XX	CH_3	OCH_3	H	OCH_3	H	H	1·53	17
XXI	$(CH_2)_2OH$	H	F	H	Cl	H	1·50	16
XXII	CH_3	H	F	H	Cl	H	0·93	16
XXIII	CH_3	$SeCH_3$	H	H	H	H	1·79	19
XXIV	CH_3	$NHCOCH_3$	H	H	H	H	1·83	19
XXV	CH_3	I	H	H	H	H	2·06	20
XXVI		Cl	H	H	H	H	1·77	21
XXVII		Cl	H	H	H	H	1·75	21
XXVIII	$(CH_2)_3OH$	SCH_3	H	OH	H	H	1·78	13
XXIX	$(CH_2)_2C_6H_4F$	Cl	H	H	H	H	1·74	22
XXX	CH_3	Cl	Cl	H	H	H	1·65	23
XXXI	$(CH_2)_2OH$	Cl	F	H	H	H	1·24	16
XXXII	CH_3	Cl	H	H	H	OCH_3	1·87	24
XXXIII	CH_3	H	H	H	H	CF_3	1·85	25
XXXIV	CH_3	H	H	H	H	F	1·28	25
XXXV	$(CH_2)_2OCOCH_3$	H	H	H	Cl	H	1·50	18

[a] MIC in μmol/l.

amines containing simultaneously both aliphatic and aromatic structural fragments[8,9]. The relationships between structure and activity are regularly studied during development of any medicine even though not always they are expressed by means of mathematical equations. The analysis by Free and Wilson[7] introduces more exactness into the relationship by ascribing numerical values to effects of individual fragments varied (e.g. substituents). However, it cannot be successfully applied to every case, i.e. a number of cases are known where the presumed additivity does not exist.

CALCULATIONS

All the values of minimum inhibition concentrations were taken from papers by Protiva et al.[10–25] and were recalculated to molar concentrations (μmol l^{-1}), see Table I. In order to separate the activities into contributions of molecular fragments we used – for the first data set (compounds *I*–*XXII*) – the Multireg H program for the IQ 151 computer. The conditions controlling the introduction into the set were also fulfilled by compound *XXXI* which served for verification of prognostics of the calculation (log MIC found: 1·24; calculated: 1·34). The whole set of compounds (except compound *XV*) was also processed by an analogous procedure using an SM 4–20 computer (product of ZVT Žilina, Czechoslovakia) and the program by Purcell[26]. The compound *XV* served for verification of prognostics of the calculation (log MIC found: 1·72; calculated: 1·45). The linear regressions of the separated activity data with physical and physico-chemical parameters of substituents were

TABLE II

Contributions of substituents to resulting antituberculotic activity according to the analysis by Free and Wilson applied to compound set *I*–*XXII*

Substituent	Δ log MIC	Substituent	Δ log MIC
R^1: H	−0·422	R^3: F	−0·513
CH_3	−0·025	OCH_3	0·204
$(CH_2)_2OH$	0·339	OH	0·369
$(CH_2)_3OH$	0·298	R^4: H	0·205
R^2: H	0·095	Cl	−0·466
Cl	0·053	F	−0·151
F	−0·129	OCH_3	−0·166
OCH_3	0·063	R^5: H	0·103
SCH_3	−0·332	Cl	−0·204
R^3: H	0·065	OCH_3	−0·572

μ_0 = 1·490; statistical evaluation: r = 0·964, s = 0·159, F = 5·30, n = 22.

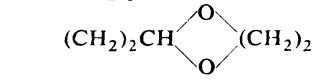
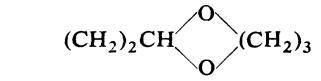
solved by means of the program W-6 (ref.[27]) using a Sharp PC 1211. The values of substituent constants and hydrophobic constants of fragments were taken from the monograph by Hansch and Leo[28]. The calculated contributions to the effect on the resulting activity due to molecular fragments (i.e. the substituents varied) are summarized in Tables II and III. The compounds for verification of prognostics of the calculation were chosen by the method of random numbers.

DISCUSSION

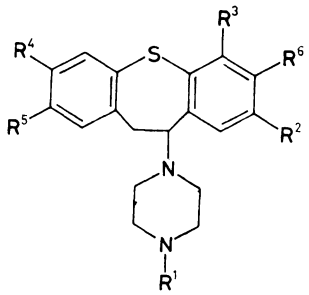
We tried to include into the treatment all the derivatives from the group of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins whose antituberculotic activity evaluated in vitro is given in the cited papers[10–25] by Protiva et al. Only excluded were the compounds of the minimum inhibition concentrations given within broad interval limits or compounds which were evaluated in the form of salts.

TABLE III

Contributions of substituents to resulting antituberculotic activity according to the analysis by Free and Wilson applied to the whole set of compounds except compound *XV*

Substituent	Δ log MIC	Substituent	Δ log MIC
R^1: H	−0·454	R^3: H	0·065
CH_3	0·001	F	−0·614
$(CH_2)_2OH$	0·211	OCH_3	0·353
$(CH_2)_3OH$	0·307	OH	0·518
	0·031	Cl	−0·059
		R^4: H	0·102
	0·011	Cl	−0·418
		F	−0·185
$(CH_2)_2C_6H_4F$	0·001	OCH_3	−0·167
$(CH_2)_2OCOCH_3$	−0·244	OH	0·139
R^2: H	0·125	R^5: H	0·047
Cl	−0·015	Cl	−0·088
F	−0·120	OCH_3	−0·489
OCH_3	0·027	R^6: H	0·015
SCH_3	−0·319	CF_3	−0·015
$SeCH_3$	0·035	F	−0·585
I	0·305	OCH_3	1·45
$NHCOCH_3$	0·075		

$\mu_0 = 1{\cdot}560$; statistical evaluation: $r = 0{\cdot}978$, $s = 0{\cdot}149$, $F = 4{\cdot}917$, $n = 34$.



The relationships between structure and activity are studied in every drug design, though they are not always expressed mathematically. The analysis by Free and Wilson[7] gives a more exact shape to the relationship by ascribing effects to the individual molecular fragments varied (e.g. substituents). However, it is not applicable to every case. Nevertheless, if in the method by Free and Wilson the effects of substituents are strictly additive like in the case investigated by us, it shows that it is no use to look for a regression equation of the Hansch type which contains – as one of the parameters – the square of overall lipophilicity of molecule[29].

When looking for relationship by the procedure by Free and Wilson we are advised to have each substituent type at a given position varied at least two times within the compound set. Therefore, in our first calculation we focused attention to that group of compounds (out of the whole set) which fulfils this requirement (compounds *I–XXII*). Thereafter, however, we analyzed the whole set of compounds in the same way. We found that the values ascribed to the same substituents in the two sets differ, but the differences are not large, and the correlation coefficients for mutual correlation between the contributions of substituents from the two calculations (see Tables II and III) lie within the interval of 0·974–0·998 for the individual positions varied.

Furthermore we tried to find relationships between data of effects of the individual substituents on the overall activity (Δ log MIC) and values of the substituent or fragment constants. In contrast to our earlier studies[8,9] dealing with antituberculotic arylalkylamines, however, we did not find any significant relationships. With the substituents R^3 and R^5 we found an only very little significant correlation with the σ_p values ($r \approx 0{\cdot}75$), and with the set of R^4 substituents we found a correlation between Δ log MIC and hydrophobic substituent constants ($r = 0{\cdot}876$). In most other positions the activity is probably affected by several parameters. In the sets investigated no equations of the Hansch type could be found. However, it is generally accepted that it is no use to look for an equation of the Hansch type if the substituent effects on activity are strictly additive[29]. In Calculations we have already stated that one compound was excluded from each set by the method of random numbers and this compound was then used for verification of the calculation. The structural pre-

requisites of the first 22 compounds are also fulfilled by compound *XXXI*. The activity value (log MIC) calculated from contribution effects of the individual fragments (see Table II) shows almost perfect accordance for the compound *XXXI*, the difference being as low as 0·1. For the calculation of the whole set we used 34 compounds, excluding compound *XV*. But even in this case the difference between the value calculated from data of Table III and the experimental value was only 0·27, which still lies within the interval explainable by experimental error.

From the combinations of contributions of effects of individual substituents on the overall activity it follows that in this set of compounds one can expect – when evaluating in vitro – the antituberculotic activity equal to or higher than that shown by commercial antituberculotics. On the basis of this study it is possible to suggest structures of new, probably highly efficient compounds. However, we were diverted from their synthesis by the large lipophilicity of the compounds. Our estimate of logarithm of separation coefficient of 10,11-dihydrodibenzo[*b*,*f*]thiepin is 4·75 (octanol–water system). The antituberculotics used, however, mostly belong to substances of low lipophilicity (log *P*: isoniazide −1·14, PAS 0·49, ethionamide 1). Nevertheless, we presume that the present study extends the general view of amines containing both aliphatic and aromatic parts, which amines belong among intensively studied antituberculotic compounds at present[30].

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