A STATISTICAL STUDY OF THE INFORMATIONAL BASE OF BIOLOGICALLY ACTIVE PYRIDINE COMPOUNDS

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UDC 681.3:547.82:615.2

A computer analysis of the literature material clarified the types of activity most characteristic for pyridine derivatives.

This work was carried out with the aim of elucidating the role of the pyridine and a series of linear structural fragments (pyridine ring substituents) in the generation of specific activity and evaluating the probability of the manifestation of specific types of activity for pyridine compounds. The data bank used was founded in 1977 at the Research Institute for the Biological Testing of Chemical Compounds and the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR [1]. The bank is constantly updated and now contains information on 9000 compounds relative to 58 types of activity.

The bank data were treated using the ORAKUL program system which contains programs developed for the consecutive selection of compounds relative to activity, for the search of compounds relative to descriptive site codes and for the statistical analysis of the distribution of compounds relative to activity types [1].

Pyridine derivatives are commonly used in the synthesis of drugs. The features of the activity and mechanism for the action of some groups of pyridine compounds have already been examined [2-14].

The study of the bank of biologically active compounds showed that 46 types of activity are encountered among pyridine derivatives. We should note that the bank does not list several types of activity which have proved valuable for the use of pyridine compounds in medicine such as the reactivation of cholinesterease, radiation protection, laxative action, vitamin and antivitamin activity, and action on bradykinin metabolism [8, 9, 11, 13, 15]. Pyridine compounds comprise 4.8% of the total number of compounds in the bank. Thus, the frequency of encountering the pyridine structure in drugs is higher than for many other heteroaromatic systems. For example, the pyrimidine, furan and thiophene rings are found to be only about 2% of the bank compounds while the analogous percentages for the thiazole, pyrrole, and pyrazine rings are 1%, 0.7%, and 0.3%, respectively.

The distribution of pyridine compounds over five general activity groups given in Table 1 shows that this group accounts for a significant number of histamine agonists and antagonists and antiallergenics. Pyridine compounds less freqquently display activity on the central nervous system. In addiiton, analysis of Table 1 shows that the search for chemotherapeutic agents including pyridine derivatives is now receiving the most attention.

Pyridine compounds most frequently display eight types of pharmacological activity (Table 2). Antituberculosis, antihistaminic, and vasodilative actions are the most characteristic.

A statistical calculation carried out in accord with the principles of our previous work [16] indicates that the pyridine structure is a characteristic of the three types of activity mentioned above, i.e., the presence of this structure produces these activities with a probability reliably different from random. However, the probabilities for the existence of specific activities for pyridine compounds are low (0.06-0.11). This finding indicates that pyridine is only one of the pharmacophore elements. It is, however, a rather significant element. For example, according to Sycheva [5], if the pyridyl group in the hydrazide (I) and

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 109-113, January, 1985. Original article submitted July 23, 1984.

0009-3122/85/2101-0089$09.50

TABLE 1. Distribution of Pyridine Compounds according to Pharmacological Action

№	Pharmacological action	Number of compounds in the bank	
		active compounds	active pyridine compounds*
1	Histamine agonists and antagonists, antiallergic	342	43 (12,6)
2	Antiinflammatory	916	74 (8,1)
3	Cardiovascular	1050	65 (6,2)
4	Chemotherapeutic	2962	115 (3,9)
5	Action on the central nervous system	1933	58 (3,0)

*The percentage of the total number of compounds displaying the given type of activity is given in parentheses.

TABLE 2. Distribution of Pyridine Compounds Relative to Activity

№	Activity type	Number of compounds in the bank	
		active compounds	active pyridine compounds
1	Antituberculosis and antileprosy	215	38† (17,7)
2	Antihistamine	193	32† (16,6)
3	Vasodilative	206	25† (12,3)
4	Anticholinesterase	51	6 (11,8)
5	Analgesic	394	33 (8,4)
6	Antiinflammatory	522	41 (7,8)
7	Hypotensive	454	25 (5,5)
8	Antitumor	633	29 (4,6)

*The percentage of the total number of compounds displaying a given type of activity is given in parentheses.
†The pyridine fragment is a reliable characteristic for the given type of activity.

TABLE 3. Comparative Antituberculosis Activity of Pyridyl and Phenyl Compounds [5]

Compound	Maximum inhibiting concentration,* μmole/liter	Compound	Maximum inhibiting concentration,* μmole/liter
I	0,5—1	IV	256
II	512	V	128
III	64—128	VI	1024

*The $H_{37}Rv$ strain is sensitive.

thioamide of isonicotinic acid (V) is replaced by a phenyl group (IV and VI, respectively), the antituberculosis activity is significantly reduced (Table 3).

Catalytic methods and methods for the preparation of aldehyde and alcohol derivatives of pyridine [17-19] used as intermediates in the synthesis of drugs have been developed at the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR. Hence, it was worthwhile examining the information base of the data in the bank in order to find the most rational pathways for the assembly of pyridinaldehyde and hydroxymethypyridine drugs. Fragments of several pyridine derivatives which are readily synthesized from aldehydes and alcohols such as oximes, hydrazones, carbazones (CH=NR), amines (CH_2NR_2), ethylenes ($CH=CR_2$) and ethers (CH_2OR) were selected as linear descriptors. These fragments are rather widely represented in biologically active pyridine compounds. Two or three basic types of activity are characteristic for each type of derivative. A significant factor leading to activity is not only the nature of the substituent introduced into the ring but also its site relative to the heteroatom. Thus, pyridine derivatives with antituberculosis, antibacterial, and antitumor properties most frequently contain the CH=NR fragment (the most common of the fragments examined is encountered in 76 compounds in the bank) at C-2 or C-4 of the pyridine ring. Sycheva [5] has indicated that the hydrazides of nicotinic (II) and picolinic acids (III) have

TABLE 4. Antitumor Activity of Pyridinaldehyde Thiosemicarbazones [20]

Compound	Experimental model			
	Leukemia L 1210		Lewis carcinoma	
	dose, mg/kg	T/C*	dose, mg/kg	T/C†
VII	10	130	10	47
VIII	106	104	75	98
IX	284	99	200	104

*Ratio of the lifetime of mice receiving compound to lifetime of control mice.
†Ratio of the tumor mass in mice receiving compound to tumor mass in control mice.

TABLE 5. Comparison of the Distribution of Pharmacological Activity of Pyridyl and Phenyl Compounds

Activity	Statistical characteristics of the compounds											
	substituent											
	CH=NR			CH_2NR_2			CH=CR_2			CH_2OR		
	N_p	N_a	K_d	N_p	N_a	K_d	N_p	N_a	K_d	N_p	N_a	K_d
Antibacterial	14	19	3,05*									
Antituberculosis and antileprosy	26	35	3,08*									
Antitumor	23	11	8,67*							7	25	1,77
Histamine agonists and antagonists				11	34	2,94*	5	22	3,5*			
Antiallergenic							4	16	3,83*			
Hypotensive				7	25	2,54*				3	4	4,74*

*The reliability of the greater frequency for encountering pyridine compounds (evaluated according to Bol'shev and Smirnov [21]). The reliability level was 0.95.

significantly less antituberculosis activity than I (see Table 3). On the other hand, the thiosemicarbazone of 2-pyridinaldehyde (VII) has more pronounced antitumor activity than the thiosemicarbazones of 3- (VIII) and 4-pyridinaldehydes (IX) (Table 4) [20].

Aminomethylpyridines which are largely histamine agonists and antagonists and have a beneficial action on the cardiovascular system usually have the substituent at C-3. Derivatives of 2- and 3-vinylpyridines are largely histamine agonists and antagonists and antiallergenics. Of compounds with the general formula $PyCH_2OR$ (alcohols and ethers), 3-pyridylcarbinols have the greatest therapeutic value with antitumor, hypotensive and other types of activity.

In order to elucidate the significance of these linear fragments in combination with the pyridine structure for specific types of activity, we calculated the discrimination coefficient (K_d) in the frequency of encountering pyridyl and phenyl compounds with analogous structure among the pyridine and benzene derivatives in the bank using the equation:

$$K_d = \frac{n_p \cdot N_a}{N_p \cdot n_a} = \frac{n_p}{n_a} \cdot A,$$

where n_p and n_a are the number of pyridyl and phenyl compounds with a given activity, N_p and N_a are the total numbers of pyridyl and phenyl derivatives in the bank and $A = N_a/N_p$.

The significantly greater frequency for encountering pyridine compounds indicates the greater specificity of the heterocycle for all the types of activity given in Table 5. Indeed, for example, of the seven phenyl analogs containing the CH=NR fragment and found in the bank by the similarity coefficient [22] as a result of replacement of the pyridyl group by a phenyl group in the structural code, none display antitumor activity, in contrast to the corresponding pyridine derivatives such as the thiosemicarbazones of 3-hydroxy- and 3-methoxy-2-pyridinaldehydes [20].

Comparison of the data given in Tables 2 and 5 shows that in going from the total group of pyridine compounds to the group of pyridinaldehyde derivatives, for which the pyridine structure plays an extremely significant role, the range of activities expands.

This study of bank data containing chemical structures and their biological activities indicated the types of pharmacological activity most characteristic for compounds containing the pyridine ring and linear fragments of CH=NR, CH_2NR_2, $CH=CR_2$ and CH_2OR. The results of this statistical study will be useful for preliminary screening of newly synthesized chemical compounds.

LITERATURE CITED

1. L. A. Piruzyan, V. V. Avidon, A. B. Rozenblit, V. S. Arolovich, V. E. Golender, S. P. Kozlova, E. M. Mikhailovskii, and E. G. Gavrishchuk, Khim.-farm. Zh., No. 5, 35 (1977).
2. J. Supnewski, T. Bany, and I. Krupinska, Byull. Pol'sk. Akad. Nauk, 3, 57 (1955).
3. A. L. Mndzhoyan, V. G. Afrikyan, R. S. Oganesyan, L. S. Adzhibekyan, S. G. Karagezyan, and V. G. Sarafyan, Arm. Khim. Zh., 22, 922 (1969).
4. M. N. Shchukina, Khim.-farm. Zh., No. 4, 23 (1970).
5. T. P. Sycheva, Khim.-farm. Zh., No. 6, 3 (1971).
6. T. Bruzzese, A. Goi, and M. Riva, Arzneim.-Forsch., 22, 531 (1972).
7. M. A. Ignatenko and V. K. Promonenkov, Khim.-farm. Zh., No. 8, 20 (1978).
8. M. Majewski and B. Serafin, Wiadom. Chem., No. 5, 311 (1979).
9. M. Majewski and B. Serafin, Wiadom. Chem., No. 6, 405 (1979).
10. L. N. Yakhontov and Ya. S. Karpman, Khim. Geterotsikl. Soedin., No. 4, 435 (1981).
11. G. M. Bakhatova, A. A. Prokopov, G. Ya. Shvarts, R. D. Syubaev, and L. N. Yakhontov, Khim.-farm. Zh., No. 7, 50 (1981).
12. G. N. Dorofeenko, E. I. Sadekova, and G. A. Korol'chenko, Khim.-farm. Zh., No. 8, 920 (1982).
13. L. D. Smirnov and K. M. Dyumaev, Khim.-farm. Zh., No. 4, 412 (1982).
14. L. N. Yakhontov and R. G. Glushkov, Synthetic Drugs [in Russian], Izd. Mir, Moscow (1983).
15. R. Jauch, R. Hakwitz, K. Beschke, and H. Pelzer, Arzneim.-Forsch., 25, 1796 (1975).
16. A. B. Rozenblit and V. E. Golender, Logical Combinatory Methods in the Molecular Assembly of Drugs [in Russian], Izd. Zinatne, Riga (1983).
17. A. A. Avots, G. V. Glemite, I. Ya. Lazdyn'sh, L. Ya. Leitis, and M. V. Shimanskaya, Koks Khim., No. 8, 50 (1971).
18. M. V. Shimanskaya, Yu. Sh. Gol'dberg, and L. Ya. Leitis, USSR Inventor's Certificate No. 572,290; Byull. Izobr., No. 34, 16 (1977).
19. D. P. Yansone, L. Ya. Leitis, and M. V. Shimanskaya, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 4, 470 (1983).
20. F. A. French and E. J. Blanz, J. Med. Chem., 9, 585 (1966).
21. L. N. Bol'shev and N. V. Smirnov, Mathematical Statistical Tables [in Russian], Izd. Nauka, Moscow (1983).
22. V. V. Avidon and V. S. Arolovich, Zh. NTI, Ser. 2, No. 5, 26 (1975).