COMPUTER-AIDED PREDICTION OF PRODRUG ACTIVITY USING THE PASS SYSTEM

Yu. V. Borodina,[1] D. A. Filimonov,[1] and V. V. Poroikov[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 12, pp. 39 – 42, December, 1996.

Original article submitted May 13, 1996.

For the rational use of new drug preparations, ensuring the maximum therapeutic effect with simultaneous decrease or prevention of undesired side reactions, it is important that the biological activity of the substance be exhaustively characterized at early stages of the drug's development, including data on both positive and the possible negative effects.

We have developed a computer system for prediction of the activity spectrum of substances (PASS) [1], capable of simultaneously predicting more than 100 types of pharmacological activity, mechanisms of action, and specific toxicity effects for a candidate drug proceeding from its structural formula. It was shown that the average accuracy of prognosis of the main effect and side reactions is about 80%, the efficiency of application of the new approach to the screening of potential substances amounts to 500 – 800%, and the exactness of the computer-aided prognosis exceeds by 300% the predictions of experts [1 – 3].

An important circumstance is that many of the biologically active compounds appear in the organism in the form of inactive precursors. The lack of a priori data on the metabolism of these compounds hinders reliable assessment of their biological action.

Below we report on prognosis of the spectrum of biological activity for more than 300 prodrugs and the corresponding drugs with known biological action.

Verification of Predicting Ability of the PASS System for Prodrug Selection

We have prepared a learning set including more than 300 prodrugs and the corresponding drugs [4 – 44]. Table 1 lists the types of biological activity represented in the sample set.

The PASS system determined the probabilities of manifestation of each activity by a given substance and compared these estimates with the frequency of occurrence of this activity type in the learning set. From this comparison, an efficiency coefficient is calculated as the ratio of a posteriori to a priori probabilities.

Should this coefficient exceed a preset threshold, the compound tested is classified as possessing the given activity type. In this work, the threshold for the efficiency coefficient was established as equal to 3. We have predicted the spectra of biological activity for each drug – prodrug couple and analyzed the results of prediction of the main activity types.

Table 2 gives examples of the main activity predictions. On the average, the predictions were correct in 74% of cases.

Table 3 presents a summary of predictions for the activities of four major types, most frequently occurring in the in-

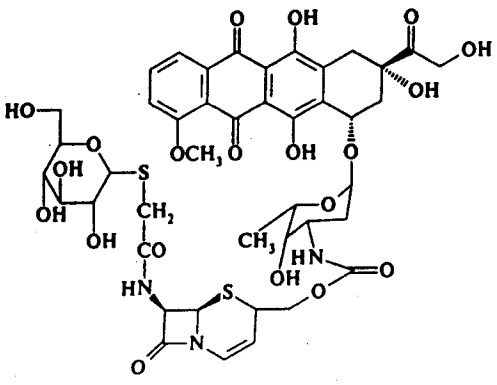
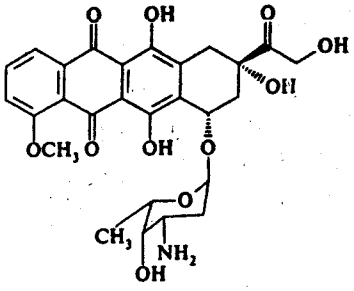
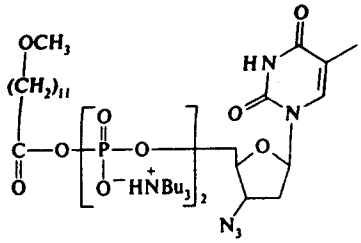
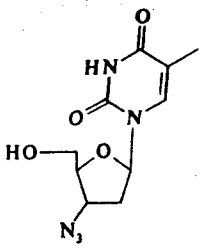
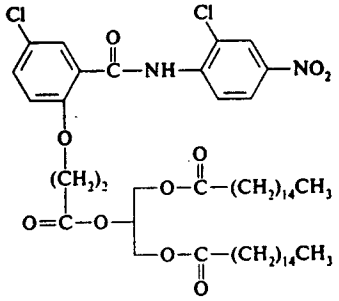
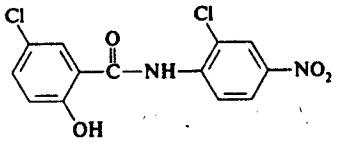
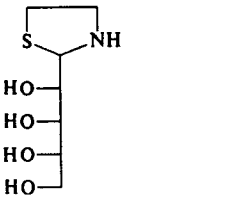
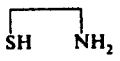
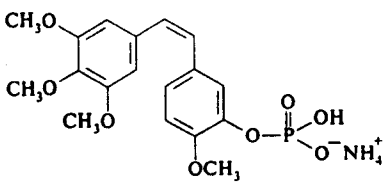
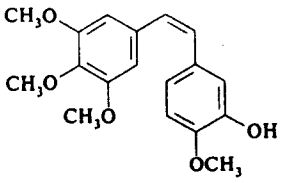
TABLE 1. Types of Biological Activity Rrpresented in the Learning Sample Set

Activity No.	Activity type	Frequency of occurrence, %
1	Antitumor	25
2	Antibacterial	17
3	Antiviral	11
4	Antiinflammatory	8
5	Nucleotide exchange regulator	6
6	Anticonvulsive	5
7	Dopaminergic	4
8	Antihypertensive	4
9	Antioxidnt	4
10	β-Adrenalinoblocking	3
11	Antihelminthic	2
12	Adrenomimetic	2
13	Radioprotector	2
14	Narcotic	2
15	Estrogen	1
16	Coronarovasodilator	1
17	Glucocorticoid	< 1
18	Analgesic (non-narcotic)	< 1
19	Bronchodilator	< 1
20	Androgen	< 1
21	Tranquilizer	< 1
22	Immunodepressant	< 1
23	Analgesic (narcotic)	< 1

[1] Institute of Biomedical Chemistry, Russian Academy of Medical Sciences, Moscow, Russia.

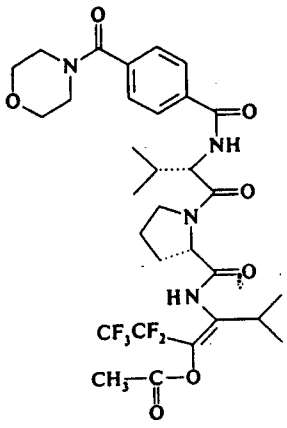
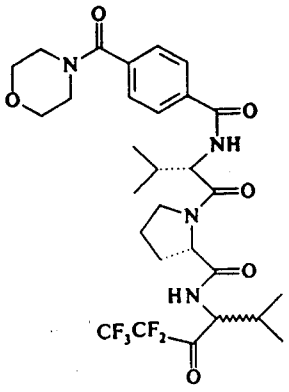
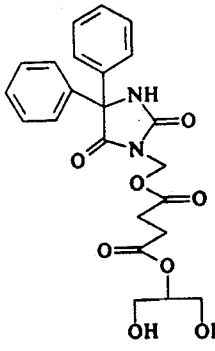
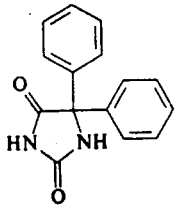
0091-150X/96/3012-0760$15.00

TABLE 2. Examples of Prognosis of the Main Activity Type for Prodrugs and the Corresponding Drugs

Prodrug	Drug	Activity No.	Ref.	P/Q*
	 Doxorubicin	1	[5]	+/+
	 Zidovudine (AZT)	3	[6]	+/+
	 Phenasal (Niclosamide)	11	[7]	+/+
	 Mercamin (Cysteamine)	13	[8]	+/+
	 Combretastatin A_4	1	[9]	–/–

itial set. These results can be compared with estimates for the accuracy of prognosis of the same activity types made by the PASS system using the sliding control method [2]. As is seen, a higher predicting accuracy is obtained for the antitumor and antibacterial activity, while a lower quality of prognosis is observed for the antiviral and antiinflammatory activity. On

TABLE 2. (Continued)

Prodrug	Drug	Activity No.	Ref.	P/Q*
	 MDL 101146	4	[10]	+/–
	 Diphenin (Phenytion)	6	[11]	–/+

* *P* and *Q* are estimates for the presence (+) or absence (–) of the biological activity of the prodrug and drug, respectively.

TABLE 3. Results of Prognosis of Four Activity Types for Prodrugs

Activity	Frequency of occurrence	Prognosis accuracy for prodrugs, %	Prognosis accuracy for sliding control method, %
Antitumor	25	92	76
Antibacterial	17	90	75
Antiviral	11	65	71
Antiinflammatory	8	44	73

the average, the accuracy of prodrug prognosis is close to the estimate obtained by the sliding control method (73 and 74%, respectively) for all compounds of the PASS learning set.

Thus, the results of prediction of the main type of biological activity for the prodrugs and the corresponding drugs are correct on the average in 74% of cases.

Therefore, the computer aided PASS system can be used to predict the pharmacological effects of drugs proceeding from the structural formulas of their inactive precursors.

This work was partly supported by the State Scientific-Technological Program "Creation of New Drugs by Methods of Chemical and Biological Synthesis," Direction 04 "Computer Design of New Drugs," Project 04.02.13.

REFERENCES

1. D. A. Filimonov, V. V. Poroikov, E. I. Karaicheva, et al., *Éksp. Klin. Farmakol.*, **58**(2), 56 – 62 (1995).
2. D. A. Filimonov and V. V. Poroikov, *Bioactive Compound Design: Possibilities for Industrial Use*, BIOS Scientific Publishers (1996), pp. 47 – 56.
3. V. V. Poroikov and D. A. Filimonov, *QSAR and Molecular Modeling: Concepts, Computational Tools and Biological Applications*, Prous Science Publishers, Barcelona (1996) p. 49 – 50.
4. *Prodrugs: Chemical Aspect*, in: *Itogi Nauki Tekhn., Ser. Org. Khim.*, Vol 19, VINITI, Moscow (1991).
5. V. M. Vrudhula, H. P. Svensson, and P. D. Senter, *J. Med. Chem.*, **38**(8), 1380 – 1385 (1995).
6. D. Bonnaffe, B. Dupraz, J. Ughetto-Monfrin, et al., *Nucleosides Nucleotides*, **14**(3 – 5), 783 – 787 (1995).
7. L. El Kihel, P. M. Loiseau, J. Bourass, et al., *Arzneim.-Forsch.*, **44**(11), 1259 – 1264 (1994).
8. J. C. Roberts, K. E. Koch, S. R. Detrick, et al., *Radiat. Res.*, **143**(2), 203 – 213 (1995).
9. G. R. Pettit, C. Temple, V. L. Narayanan, et al., *Anti-Cancer Drug Design*, **10**(4), 299 – 309 (1995).

0. J. P. Burkhart, J. R. Koehl, S. Mehdi, et al., *J. Med. Chem.*, 38(2), 223 – 233 (1995).
1. G. K. E. Scriba, D. M. Lambert, and J. H. Poupaert, *J. Pharm. Sci.*, 84(3), 300 – 302 (1995).
2. T. Kawaguchi, H. Sakairi, S. Kimura, et al., *Chem. Pharm. Bull.*, 43(3), 501 – 504 (1995).
3. F. M. Menger, Y. Guo, and A. S. Lee, *Bioconjugate Chem.*, 5(2), 162 – 166 (1994).
4. K.-Y. Moon, F. N. Shirota, N. Baturay, et al., *J. Med. Chem.*, 38(5), 848 – 851 (1995).
5. X. Guo, M. Lernertung, H. X. Chen, et al., *Biochem. Pharmacol.*, 49(8), 1111 – 1116 (1995).
6. A.-S. Charvet, M. Camplo, and P. Faury, *J. Med. Chem.*, 37(14), 2216 – 2223 (1994).
7. K. Shanmuganathan, T. Koudiakova, S. Nampalli, et al., *J. Med. Chem.*, 37(6), 821 – 827 (1994).
8. T. C. Burnette, J. A. Harrington, J. E. Reardon, et al., *J. Biol. Chem.*, 270(26), 15827 – 15831 (1995).
9. J. H. Bateson, G. Burton, S. C. M. Fell, et al., *J. Antibiot.*, 47(2), 253 – 256 (1994).
0. S. K. Davidsen, J. B. Summers, D. H. Albert, et al., *J. Med. Chem.*, 37(26), 4423 – 4429 (1994).
1. T. J. Carty, A. Marfat, and P. F. Moore, *Agents Actions*, 39(3 – 4), 157 – 165 (1993).
2. J. Takata, Y. Karube, Y. Nagata, et al., *J. Pharm. Sci.*, 84(1), 96 – 100 (1995).
3. J. Patel, M. J. Katovich, K. B. Sloan, et al., *J. Pharm. Sci.*, 84(2), 174 – 178 (1995).
4. R. Kumar, L. Wang, L. I. Wiebe, et al., *J. Med. Chem.*, 37(25), 4297 – 4306 (1994).
5. H. Ford, Jr., M. A. Siddiqui, et al., *J. Med. Chem.*, 38(7), 1189 – 1195 (1995).
6. C. Desseaux, C. Gouyette, Y. Henin, et al., *Tetrahedron*, 51(24), 6739 – 6756 (1995).
27. R. B. Greenwald, A. Pendri, and D. Bolikal, *J. Org. Chem.*, 60(2), 331 – 336 (1995).
28. R. G. G. Leenders, K. A. A. Gerrits, R. Ruijtenbeek, et al., *Tetrahedron Lett.*, 36(10), 1701 – 1704 (1995).
29. D. E. Ken, *Cancer Res.*, 55(16), 3558 – 3563 (1995).
30. V. M. Vrudhula, H. P. Svensson, K. A. Kennedy, et al., *Bioconjugate Chem.*, 4(5), 334 – 340 (1993).
31. H. Okada, T. Koyanagi, and N. Yamada, *Chem. Pharm. Bull.*, 42(1), 57 – 61 (1994).
32. C. J. Springer, I. Niculescu-Duvaz, and R. B. Pedley, *J. Med. Chem.*, 37(15), 2361 – 2370 (1994).
33. K. A. Lamb, S. P. Denyer, F. D. Sanderson, et al., *J. Pharm. Pharmacol.*, 46, 965 – 973 (1994).
34. C. Clerici, G. Gentili, E. Boschetti, et al., *Digestive Diseases Sci.*, 39(12), 2601 – 2606 (1994).
35. S. De Lombaert, M. D. Erion, J. Tan, et al., *J. Med. Chem.*, 37(4), 498 – 511 (1994).
36. K. Watanabe, H. Hayashi, and Y. Mori, *Pharmacol. Res.*, 28(1), 59 – 70 (1993).
37. S. De Lombaert, L. Blanchard, C. Berry, et al., *Bioorg. Med. Chem. Lett.*, 5(2), 151 – 154 (1995).
38. G. K. E. Scriba, D. M. Lambert, and J. H. Poupaert, *J. Pharm. Pharmacol.*, 47, 197 – 203 (1995).
39. G. K. E. Scriba, *Arch. Pharm.*, 326(8), 477 – 481 (1993).
40. H. T. Nagasawa, S. P. Kawle, J. A. Elberling, et al., *J. Med. Chem.*, 38(11), 1865 – 1871 (1995).
41. A. Nudelman and R. Kelner, *Arch. Pharm.* 326(11), 907 – 909 (1993).
42. S. Ahmed, T. Imai, and M. Otagiri, *J. Pharm. Sci.*, 84(7), 877 – 883 (1995).
43. C. Meier, L. Habel, W. Laux, et al., *Nucleosides Nucleotides*, 14(3 – 5), 759 – 762 (1995).
44. G. R. Pettit, S. Freeman, M. J. Simpson, et al., *Anti-Cancer Drug Design*, 10(3), 243 – 250 (1995).