# COMPUTER-AIDED SEARCH FOR POTENTIAL DRUGS EXHIBITING A COMBINED ANTIHYPERTENSIVE EFFECT

**A. A. Lagunin,[1] D. A. Filimonov,[1] and V. V. Poroikov[1]**

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 35, No. 7, pp. 28 – 34, July, 2001.

*Original article submitted April 10, 2001.*

Despite considerable progress in the study and therapy of arterial hypertension, the search for new effective antihypertensive drugs is still an important task. Insufficient knowledge of the factors determining the onset of primary arterial hypertension and the interplay of mechanisms involved in arterial pressure regulation in the normal and pathological states accounts for the predominantly symptomatic therapy requiring long-term drug administration. In order to increase the efficacy of such therapy and reduce the side effects, it is necessary to develop new antihypertensive drugs that possess increased selectivity and are effective in lower concentrations. This can be achieved by using drugs employing combined mechanisms of antihypertensive action. The search for such compounds is motivated by substances that simultaneously inhibit angiotensin-converting enzymes and neutral endopeptidases (see review [1]).

Angiotensin-converting enzyme (ACE, EC [3.4.15.1]) catalyzes the reaction of angiotensin I transformation into angiotensin II. The latter hormone binds to angiotensin receptors to produce contraction of the blood vessel. ACE inhibition leads to a decrease in the blood angiotensin II level and, hence, in the vasopressor action. In addition, ACE is involved in the degradation of bradykinin, a peptide producing a vasodilator effect. Therefore, ACE inhibition leads to an increase in the bradykinin content in the blood and, hence, produces a vasodilator action. One of the neutral endopeptidase (NEP, EC [3.4.24.11]) functions is to produce cleavage of the atrial natriuretic factor (ANF) [2]. In the organism, ANF is secreted in response to an increase in the central venous pressure accompanying cardiac insufficiency. The main effects produced by this peptide consist in increasing the renal excretion of water and sodium, facilitating the relaxation of smooth muscles in venous vessels, and inhibiting the secretion or action of hormones such as aldosterone, angiotensin II, endothelin, and antidiuretic hormone [3, 4]. NEP, as well as ACE, is involved in the process of bradykinin degradation. Thus, any substance inhibiting both NEP and ACE would produce a more pronounced therapeutic action in the treatment of hypertension as compared to the effect of agents suppressing only ACE or NEP activity.

Investigations initiated in the late 1980s resulted in the discovery of substances producing combined effects: calcium channel blockers and beta 1 adrenoblockers [5] and calcium channel blockers and alpha 1 adrenoblockers [6]. Somewhat later, compounds were found simultaneously belonging to calcium channels blockers and 5HT 2A receptor antagonists [7]. In the middle 1990s, a number of papers were published devoted to combined antagonists of endothelin and angiotensin receptors [8], antagonists of alpha 1 adrenoreceptors and 5HT 2A receptors, and inhibitors of endothelin-converting enzyme (ECE) and ACE [9, 10], NEP and ECE [11, 12], and ACE and NEP [13, 14]. Examples of compounds producing combined antihypertensive effects are given in Table 1. According to the Pharmaprojects data base [15], more than 70 molecular targets are currently under investigation, the action upon which may reduce the arterial pressure. It is impossible to perform experimental screening for millions of substances allowing for all possible antihypertensive mechanisms. In this situation, one solution is to use computer-aided approaches in the evaluation of the biological activity of potential chemical agents.

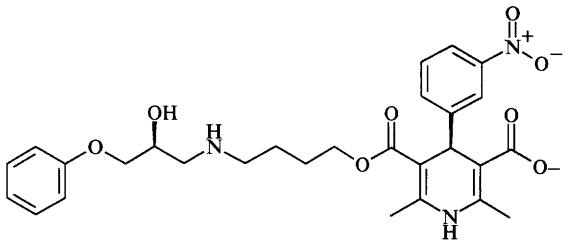
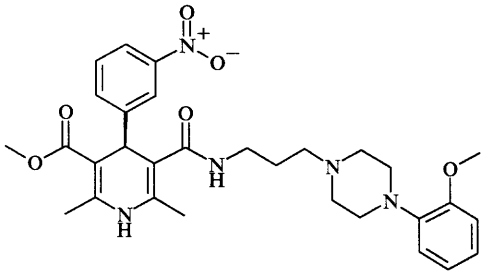
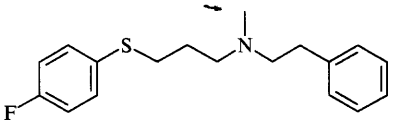
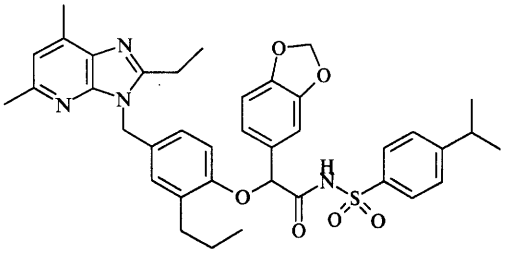
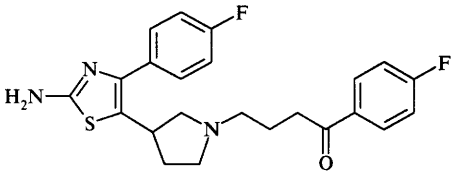
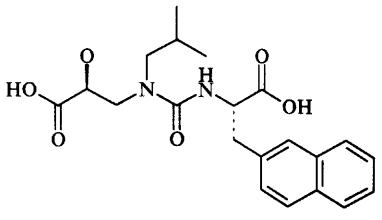
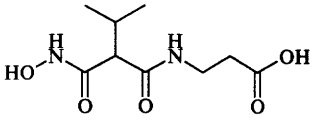
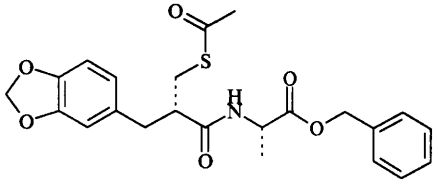
Manifestations of a certain type of biological activity, including the corresponding molecular mechanisms of action, depend on the structure of chemical compounds. Entering the organism, most compounds are capable of exhibiting several types of activity. The list of all pharmacological effects, biochemical mechanisms, and specific toxicity types (mutagen, carcinogen, teratogen, embryotoxicant) which a given compound can exhibit in biological systems is called the biological activity spectrum of this compound. In order to forecast the biological activity spectra of substances proceeding from their structural formulas, we developed a special PASS (Prediction of Activity Spectrum of Substances) program [16]. The PASS Version 1.41 is capable of predicting 565 biologi-

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



0091-150X/01/3507-0375$25.00 © 2001 Plenum Publishing Corporation

**TABLE 1.** Examples of Compounds with Experimentally Confirmed Combined Antihypertensive Action

| Molecular mechanisms | Chemical structure | CAS number |
|---|---|---|
| Blocker of calcium channels and beta 1 adrenoreceptors |  | 99047-26-4 |
| Blocker of calcium channels and alpha 1 adrenoreceptors |  | 100305-61-1 |
| Blocker of calcium channels and 5HT 2A receptors |  | 152859-37-5 |
| Blocker of endothelin 1 receptors and angiotensin II receptors |  | 158692-23-0 |
| Blocker of alpha 1 adrenoreceptors and 5HT 2A receptors |  | 183949-64-6 |
| Inhibitor of endothelin-converting enzyme and angiotensin-converting enzyme |  | 179463-81-1 |
| Inhibitor of neutral endopeptidase and endothelin-converting enzyme |  | 151927-77-4 |
| Inhibitor of angiotensin-converting enzyme and neutral endopeptidase |  | 135038-57-2 |

cal activity types, of which 50 are significant for arterial pressure regulation.

The purpose of this study was to assess the potential of the PASS program in the search for new antihypertensive compounds capable of producing a combined effect.

## MATERIALS AND METHODS

The PASS program predicts the spectrum of biological activity of low-molecular-weight organic substances proceeding from their structural formulas [16]. The total list of activity types that can be predicted by PASS can be found on the Web-site: http://www.ibmh.msk.su/PASS. The structures of chemical compounds are described in terms of the MNA (Multilevel Neighborhoods of Atoms) descriptors [17]. The biological activity prognosis is based on an analysis of the quantitative structure – activity relationships (QSAR). Data on these relationships are stored in the SAR Base data file of the PASS program. Each compound included in the learning set is represented by a set of MNA descriptors and a list of biological activity types exhibited by this substance. The compound to be tested, provided with a set of descriptors, is characterized by the calculated probabilities of belonging to the class of compounds possessing or not possessing a certain type of biological activity. The learning set of PASS Version 1.41 includes 35,154 chemical compounds characterized by 35,712 various MNA descriptors.

The results of prognosis are presented in the form of a list of biological activity types with the corresponding probabilities of being active (Pa) or inactive (Pi) in this respect. The results of such assessment should be interpreted as follows:

(i) If a certain type of biological activity was predicted with $Pa > 0.7$, a given compound would most probably exhibit this activity in experiment; however, it is also highly probable that this substance is an analog of a well-known drug.

(ii) If $0.5 < Pa \leq 0.7$, there is also a large probability that the compound would show the given activity in experiment. This probability is smaller than that in the preceding case, but the substance is less similar to the existing drugs of this type.

(iii) If $Pa \leq 0.5$, the probability that the given compound would exhibit this activity in experiment is still smaller; however, should the experiment be indicative of this activity, the given substance may reveal an essentially new base structure.

For evaluating the probability of manifestation of the combined (twofold or double) mechanisms of action, we employed the arithmetic mean of the probability of manifestation of a given pair of the biological activity types:

$$Pm = (Pa_1 + Pa_2)/2.$$

It was assumed that a given compound would exhibit the combined effect in experiment, provided that $Pm > 50\%$ and

**TABLE 2.** Molecular Mechanisms of Antihypertensive Action Named after the Biological Activity Type Lists of the PASS Program and MDDR 99.2 Database

| Number of compounds | MPA*, % | Biological activity type (PASS) | Biological activity type (MDDR 99.2) |
|---|---|---|---|
| 9 | 86.08 | 5 Hydroxytryptamine 1B agonist | 5 HT1B Agonist |
| 12 | 81.885 | 5 Hydroxytryptamine 2A antagonist | 5 HT2A Antagonist |
| 35 | 89.317 | Adenosine A1 receptor antagonist | Adenosine (A1) Antagonist |
| 21 | 97.507 | Adenosine A2 receptor agonist | Adenosine (A2) Agonist |
| 14 | 84.492 | Aldosterone antagonist | Aldosterone antagonist |
| 102 | 89.015 | Alpha 1 adrenoreceptor antagonist | Adrenergic (alpha1) Blocker |
| 55 | 78.03 | Alpha 2 adrenoreceptor antagonist | Adrenergic (alpha2) Blocker |
| 290 | 85.563 | Alpha adrenoreceptor antagonist | Adrenergic (alpha) Blocker |
| 18 | 91.545 | Angiotensin AT2 receptor antagonist | Angiotensin II AT2 Antagonist |
| 31 | 95.027 | Angiotensin AT1 receptor antagonist | Angiotensin II AT1 Antagonist |
| 470 | 97.212 | Angiotensin II receptor antagonist | Angiotensin II Blocker |
| 132 | 94.685 | Angiotensin converting enzyme inhibitor | ACE inhibitor |
| 42 | 93.079 | Antidiuretic hormone antagonist | Vasopressin Antagonist |
| 5 | 90.009 | Atrial natriuretic polypeptide agonist | Atrial Natriuretic Polypeptide |
| 22 | 92.788 | Beta 1 adrenoreceptor antagonist | Adrenergic (beta1) Blocker |
| 335 | 87.854 | Calcium channel antagonist | Calcium Channel Blocker |
| 24 | 94.343 | Dopamine D1 agonist | Dopamine (D1) Agonist |
| 51 | 86.649 | Endothelin A receptor antagonist | Endothelin ETA Antagonist |
| 27 | 84.955 | Endothelin B receptor antagonist | Endothelin ETB Antagonist |
| 26 | 84.148 | Endothelin-converting enzyme inhibitor | Endothelin Formation Inhibitor |
| 157 | 90.719 | Endothelin receptor antagonist | Endothelin Antagonist |
| 11 | 71.701 | Neuropeptide Y antagonist | Neuropeptide Y Antagonist |
| 63 | 96.121 | Neutral endopeptidase inhibitor | Neutral Endopeptidase Inhibitor |
| 19 | 92.256 | Nitric oxide donor | Nitric Oxide Donor |
| 4 | 78.04 | Phosphodiesterase I inhibitor | Phosphodiesterase I Inhibitor |
| 130 | 91.752 | Phosphodiesterase IV inhibitor | Phosphodiesterase IV Inhibitor |
| 160 | 94.765 | Potassium channel activator | Potassium Channel Activator |
| 223 | 97.766 | Renin inhibitor | Renin inhibitor |
| 17 | 88.606 | Vasopressin 1 antagonist | Vasopressin V1 Antagonist |
| 14 | 91.673 | Vasopressin 2 antagonist | Vasopressin V2 Antagonist |

* MPA is the mean predicting accuracy for each biological activity type determined by the leave-one-out procedure.

**TABLE 3.** A Comparison of Experimental Data and Predictions Concerning the Combined Antihypertensive Action Mechanisms for Compounds of the MDDR 99.2 Datbase for Pa > 30%, Pa > 40%, and Pa > 50%

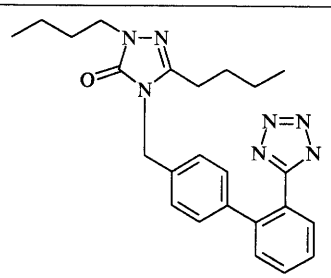
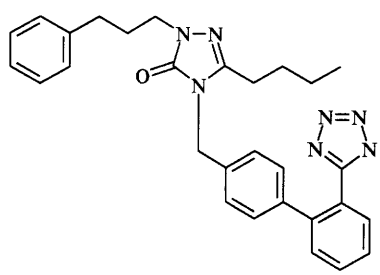
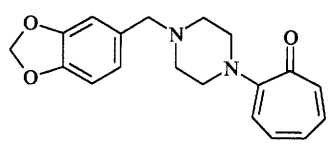
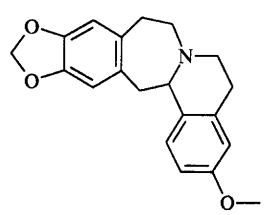
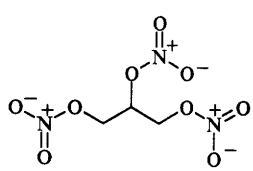
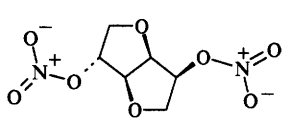
| Combined Antihypertensive Action | N* | Pa > 30% | Pa > 40% | Pa > 50% |
|---|---|---|---|---|
| Angiotensin AT1 receptor antagonist/Angiotensin AT2 receptor antagonist | 23 | 23 (760) | 22 (337) | 21 (128) |
| Endothelin B receptor antagonist/Endothelin A receptor antagonist | 89 | 74 (1637) | 65 (905) | 43 (558) |
| Neutral endopeptidase inhibitor/Angiotensin converting enzyme inhibitor | 216 | 151 (389) | 115 (215) | 70 (117) |
| Neutral endopeptidase inhibitor/Endothelin-converting enzyme inhibitor | 31 | 28 (538) | 15 (180) | 7 (72) |
| Vasopressin 2 antagonist/Vasopressin 1 antagonist | 74 | 68 (119) | 54 (72) | 39 (44) |
| Angiotensin II receptor antagonist/5 Hydroxytryptamine 2A antagonist | – | – (177) | – (44) | – (23) |
| Endothelin-converting enzyme inhibitor/Angiotensin converting enzyme inhibitor | 11 | 3 (501) | 1 (122) | 0 (19) |
| Calcium channel antagonist/Beta 1 adrenoreceptor antagonist | 16 | 16 (662) | 10 (339) | 10 (106) |
| Neuropeptide Y antagonist/Antidiuretic hormone antagonist | – | – (1137) | – (232) | – (27) |
| Alpha 1 adrenoreceptor antagonist/5 Hydroxytryptamine 2A antagonist | 16 | 16 (1914) | 16 (886) | 14 (229) |
| Alpha adrenoreceptor antagonist/5 Hydroxytryptamine 2A antagonist | – | – (3136) | – (1704) | – (794) |
| Angiotensin AT1 receptor antagonist/5 Hydroxytryptamine 2A antagonist | – | – (191) | – (42) | – (16) |
| Endothelin receptor antagonist/Alpha adrenoreceptor antagonist | – | – (438) | – (103) | – (26) |
| Endothelin receptor antagonist/Angiotensin AT1 receptor antagonist | – | – (339) | – (118) | – (30) |
| Neuropeptide Y antagonist/Atrial natriuretic polypeptide agonist | – | – (2683) | – (1225) | – (457) |
| Nitric oxide donor/Beta 1 adrenoreceptor antagonist | – | – (92) | – (32) | – (12) |
| Nitric oxide donor/Calcium channel antagonist | – | – (171) | – (60) | – (16) |
| Calcium channel antagonist/Alpha 1 adrenoreceptor antagonist | 6 | 4 (1109) | 3 (554) | 3 (156) |
| Calcium channel antagonist/Alpha adrenoreceptor antagonist | 9 | 9 (1515) | 9 (606) | 1 (160) |
| Endothelin receptor antagonist/Alpha 2 adrenoreceptor antagonist | – | – (427) | – (153) | – (39) |
| Neuropeptide Y antagonist/Calcium channel antagonist | – | – (491) | – (515) | – (245) |
| Renin inhibitor/Endothelin-converting enzyme inhibitor | – | – (591) | – (127) | – (18) |
| Renin inhibitor/Neuropeptide Y antagonist | – | – (896) | – (123) | – (6) |
| Endothelin B receptor antagonist/Alpha adrenoreceptor antagonist | – | – (777) | – (288) | – (80) |
| Endothelin receptor antagonist/Calcium channel antagonist | – | – (258) | – (65) | – (10) |
| Endothelin-converting enzyme inhibitor/Endothelin B receptor antagonist | – | – (799) | – (186) | – (28) |
| Neuropeptide Y antagonist/Angiotensin converting enzyme inhibitor | – | – (1432) | – (240) | – (35) |
| Neuropeptide Y antagonist/Endothelin-converting enzyme inhibitor | – | – (3245) | – (1041) | – (126) |
| Phosphodiesterase I inhibitor/Adenosine A1 receptor antagonist | – | – (311) | – (91) | – (16) |
| Phosphodiesterase I inhibitor/Angiotensin AT1 receptor antagonist | – | – (470) | – (130) | – (13) |
| Potassium channel activator/Nitric oxide donor | – | – (72) | – (19) | – (2) |
| 5 Hydroxytryptamine 2A antagonist/5 Hydroxytryptamine 1B agonist | – | – (791) | – (248) | – (40) |
| Dopamine D1 agonist/Alpha adrenoreceptor antagonist | – | – (399) | – (118) | – (14) |
| Endothelin B receptor antagonist/Alpha 2 adrenoreceptor antagonist | – | – (674) | – (305) | – (101) |
| Endothelin A receptor antagonist/Alpha 2 adrenoreceptor antagonist | – | – (596) | – (283) | – (77) |
| Endothelin receptor antagonist/Angiotensin AT2 receptor antagonist | – | – (310) | – (122) | – (42) |
| Neuropeptide Y antagonist/Alpha adrenoreceptor antagonist | – | – (686) | – (187) | – (53) |
| Neutral endopeptidase inhibitor/Neuropeptide Y antagonist | – | – (738) | – (111) | – (14) |
| Nitric oxide donor/Neuropeptide Y antagonist | – | – (82) | – (26) | – (6) |
| Phosphodiesterase I inhibitor/Angiotensin II receptor antagonist | – | – (799) | – (487) | – (195) |
| Phosphodiesterase I inhibitor/Endothelin receptor antagonist | – | – (172) | – (80) | – (29) |
| Potassium channel activator/Neuropeptide Y antagonist | – | – (101) | – (27) | – (2) |
| 5 Hydroxytryptamine 2A antagonist/Alpha 2 adrenoreceptor antagonist | | – (1178) | – (408) | – (84) |
| Renin inhibitor/5 Hydroxytryptamine 2A antagonist | – | – (123) | – (11) | – (1) |
| Endothelin A receptor antagonist/Alpha adrenoreceptor antagonist | – | – (814) | – (302) | – (69) |
| Endothelin B receptor antagonist/Angiotensin AT1 receptor antagonist | – | – (258) | – (52) | – (2) |
| Endothelin receptor antagonist/Angiotensin II receptor antagonist | 8 | 1 (427) | 1 (101) | 0 (2) |
| Neuropeptide Y antagonist/Alpha 1 adrenoreceptor antagonist | – | – (329) | – (107) | – (25) |
| Neuropeptide Y antagonist/Alpha 2 adrenoreceptor antagonist | – | – (223) | – (59) | – (5) |
| Neuropeptide Y antagonist/Endothelin B receptor antagonist | – | – (2238) | – (542) | – (48) |
| Neuropeptide Y antagonist/Endothelin receptor antagonist | – | – (1384) | – (354) | – (46) |
| Neutral endopeptidase inhibitor/Atrial natriuretic polypeptide agonist | – | – (273) | – (63) | – (2) |
| Nitric oxide donor/Alpha 1 adrenoreceptor antagonist | – | – (91) | – (38) | – (13) |
| Nitric oxide donor Alpha adrenoreceptor antagonist | – | – (107) | – (66) | – (24) |
| Phosphodiesterase I inhibitor/Alpha adrenoreceptor antagonist | – | – (446) | – (146) | – (32) |

**TABLE 3.** (Continued)

| Combined Antihypertensive Action | N* | Pa > 30% | Pa > 40% | Pa > 50% |
|---|---|---|---|---|
| Phosphodiesterase IV inhibitor/Calcium channel antagonist | – | – (328) | – (94) | – (27) |
| Calcium channel antagonist 5/Hydroxytryptamine 2A antagonist | 14 | 2 (825) | 0 (208) | 0 (17) |
| Total: | 516 | 395 | 313 | 208 |
| Prediction accuracy: | | (76.55 %) | (60.66 %) | (40.31 %) |

**Note**: N* is the number of compounds in the MDDR 99.2 database exhibiting the given combined antihypertensive action mechanism.

**TABLE 4.** Examples of Compounds in the MDDR 99.2 Database with Previously Unknown Combined Antihypertensive Action Mechanisms in the Predicted Biological Activity Spectra

| Predicted combination | | | Chemical structure | Reg. No. |
|---|---|---|---|---|
| 0.877 | 0.002 | Angiotensin II receptor antagonist |  | 199339 |
| 0.706 | 0.004 | Angiotensin AT1 receptor antagonist | | |
| 0.570 | 0.008 | 5 Hydroxytryptamine 2A antagonist | | |
| 0.830 | 0.002 | Angiotensin II receptor antagonist |  | 185554 |
| 0.652 | 0.004 | Angiotensin AT1 receptor antagonist | | |
| 0.514 | 0.011 | 5 Hydroxytryptamine 2A antagonist | | |
| 0.666 | 0.008 | Alpha adrenoreceptor antagonist |  | 263909 |
| 0.493 | 0.006 | Endothelin B receptor antagonist | | |
| 0.465 | 0.005 | Endothelin A receptor antagonist | | |
| 0.454 | 0.005 | Endothelin receptor antagonist | | |
| 0.393 | 0.012 | Alpha 2 adrenoreceptor antagonist | | |
| 0.794 | 0.004 | Alpha 2 adrenoreceptor antagonist |  | 159011 |
| 0.714 | 0.007 | Alpha adrenoreceptor antagonist | | |
| 0.396 | 0.006 | Endothelin A receptor antagonist | | |
| 0.333 | 0.006 | Endothelin receptor antagonist | | |
| 0.943 | 0.001 | Beta 1 adrenoreceptor antagonist |  | 091426 |
| 0.913 | 0.003 | Beta adrenoreceptor antagonist | | |
| 0.734 | 0.001 | Nitric oxide donor | | |
| 0.855 | 0.003 | Beta 1 adrenoreceptor antagonist |  | 113598 |
| 0.539 | 0.002 | Nitric oxide donor | | |

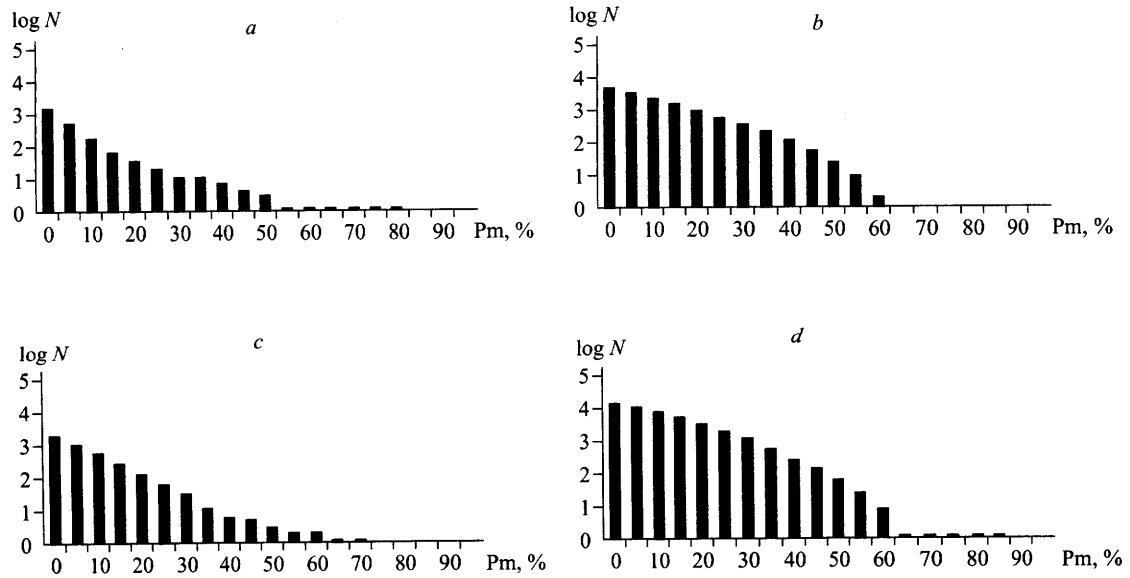



**Fig. 1.** Logarithm of the number of compounds $N$ in AsInEx and ChemBridge versus the probability Pm of manifestation of the combined antihypertensive action: (*a*) ACE and NEP inhibitor; (*b*) endothelin and alpha adrenoreceptor antagonist; (*c*) ACE and ECE inhibitor; (*d*) calcium channel blocker and alpha 1 adrenoreceptor antagonist.

the probability of manifestations of each particular type of activity (Pa) exceeds 30%.

As a test set, we used MDDR 99.2 – a database of biologically active compounds of the MDL Information System Inc. [18]. The MDDR (MDL Drug Data Report) database contains information on the structure and biological activity of substances developed as potential drugs. The MDDR includes data from patents, conference reports, scientific journals, and commercial communications of various chemical and pharmaceutical companies on about 105,372 compounds involving 98,184 unique structures. In addition, we employed databases for the available chemicals (Chembridge) [19] and AsInEx (99.7) [20] containing information about a total of 183,462 compounds.

Among the biological activity types predictable by PASS, we selected 30 molecular mechanisms producing an antihypertensive effect, which are also encountered in the descriptions of compounds provided by the MDDR 99.2 database. Table 2 lists the selected activity types, their names according to MDDR 99.2 and PASS, and indicates the number of compounds in the learning set possessing these activity types, as well as the mean predicting accuracy (MPA, %) for each activity type determined using the sliding control (leave-one-out) procedure. Descriptions of the chemical compounds contained in the MDDR 99.2 database include 15 pairs of the combined action mechanisms producing antihypertensive effect.

## RESULTS AND DISCUSSION

Using 30 molecular mechanisms producing an antihypertensive action considered in this study, we can theoretically make $(30^2 - 30)/2 = 435$ various pair combinations. All compounds in the MDDR 99.2 database were characterized by predicted biological activity spectra. Each spectrum was checked for the presence of any of these 435 combinations of the antihypertensive action. Table 3 shows all the possible combinations for which the MDDR 99.2 database contains at least one compound satisfying the selection conditions indicated above. On the whole, there were 57 such combinations of which 12 were encountered in the MDDR 99.2 database. In Table 3, the "MDDR 99.2" column indicates the number of compounds exhibiting the corresponding combined mechanisms of antihypertensive action. The columns Pa > 30%, Pa > 40%, and Pa > 50% give the numbers of compounds in the MDDR 99.2 database for which the combined antihypertensive action was correctly predicted with a probability above 30, 40, and 50%, respectively. Values in parentheses indicate the numbers of compounds in the database for which the probability of exhibiting a given mechanism of the antihypertensive action exceeds 30, 40, and 50%.

The prediction was considered as correct when it contained the names of both particular mechanisms described in the MDDR 99.2 database for a given substance. If only one of the two mechanisms was predicted, the prognosis was rejected as incorrect. The mean predicting accuracy for compounds producing a combined antihypertensive action amounts to 76.6% (for Pa > 30%), 60.7 (Pa > 40%), and 40.3 (Pa > 50%). The fraction of compounds with known combined action among all substances for which this combined effect was predicted increased from 3.8% (for Pa > 30%) to 6.9% (Pa > 40%) and 12.9% (Pa > 50%). The selection criterion was satisfied by 12 pairs of 15% (80%). Such high mean accuracy in predicting the combined mechanisms of antihy-

pertensive action shows the expediency of using the PASS program in the search for a required combination of the mechanisms of drug action. The results of such investigations allow the main directions of search for compounds exhibiting new combined mechanisms of antihypertensive action to be outlined. An analysis of the data presented in Table 3 indicates that there are compounds capable of exhibiting (with Pm above 50%) previously unknown mechanisms of antihypertensive action, such as, for example, antagonists of both angiotensin II and 5HT 2A receptors, antagonists of endothelin and alpha 1 adrenoreceptors, nitric oxide donors, and beta 1 adrenoreceptor blockers. Examples of such compounds are given in Table 4.

The approach outlined above was applied to databases of samples of available chemicals [ChemBridge (Express-pick, May 1999) and AsInEx (99.7)]. The results of this analysis (see Fig. 1) allowed compounds to be established that possess a high probability of exhibiting a combined antihypertensive action. The most promising of these substances were selected for biological testing.

Thus, our investigation showed that, using the predicted spectrum of biological activity, it is possible to reveal new chemical compounds exhibiting combined mechanisms of antihypertensive action. Taking into account the broad spectrum of biological activities predictable by the PASS program, this approach can also be used in the search for compounds exhibiting combined mechanisms of action in some other pharmacological groups. This can be important, for example, in fighting the resistance of microorganisms and tumor cells with respect to existing drugs.

## ACKNOWLEDGMENTS

The authors are grateful to Prof. O. A. Gomazkov for fruitful discussions and to the MDL Information Systems Inc. for permission to use the ISIS/Base and the MDDR database.

## REFERENCES

1. J. R. Asher and A. J. Naftilan, *Curr. Hypertens. Rep.*, **2**(4), 384 – 391 (2000).
2. B. P. Roques, F. Noble, V. Daugee, et al., *Pharmacol. Rev.*, **45**, 87 – 146 (1993).
3. H. Rusoaho, *Pharmacol. Rev.*, **44**, 479 – 602 (1992).
4. A. Turner and K. Tanzawa, *FASEB J.*, **11**, 355 – 367 (1997).
5. B. W. Main, *FASEB J.*, **2**(4), Abst. 1797 (1988).
6. M. J. Panzenbeck, *FASEB J.*, **3**(4), Abst. 4607 (1989).
7. D. P. Taylor, *Soc. Neurosci. Abst.*, **20** (Part 1), Abst. 81.12 (1994).
8. T. F. Walsh, *Bioorg. Med. Chem. Lett.*, **5**(11), 1155 (1995).
9. B. A. McKittrick, *Bioorg. Med. Chem. Lett.*, **6**(14), 1629 (1996).
10. G. M. Ksander, *J. Cardiovasc. Pharmacol.*, **31**(Suppl. 1), S71 (1998).
11. A. J. Trapani, S. De Lombaert, S. Kuzmich, et al., *J. Cardiovasc. Pharmacol.*, **26**(Suppl. 3), S69 – 71 (1995).
12. A. J. Trapani, S. De Lombaert, M. E. Beil, et al., *Life Sci.*, **67**(9), 1025 – 1033 (2000).
13. M. C. Fournie-Zaluski, P. Coric, V. Thery, et al., *J. Med. Chem.*, **39**(13), 594 – 608 (1996).
14. N. C. Trippodo, J. A. Robl, M. M. Asaad, et al., *J. Pharmacol. Exp. Ther.*, **275**(2), 745 – 752 (1995).
15. http://www.pjbpubs.com/pharma.
16. V. V. Poroikov, D. A. Filimonov, Yu. Borodina, et al., *J. Chem. Inform. Comput. Sci.*, **40**(6), 1349 – 1355 (2000).
17. D. Filimonov, V. Poroikov, Yu. Borodina, et al., *J. Chem. Inf. Comput. Sci*, **39**, 666 – 670 (1999).
18. http://www.mdli.com.
19. http://www.chembridge.com.
20. http://www.asinex.com.