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Topological model for the prediction of MRP1 inhibitory activity of pyrrolopyrimidines and templates derived from pyrrolopyrimidine

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Abstract—Relationship between Wiener's index—a distance-based topological descriptor and multidrug-resistance-associated protein (MRP1) inhibitory activity of pyrrolopyrimidines and their derivatives has been investigated. A dataset comprising of 82 analogues of pyrrolopyrimidine was selected for the present study. The values of Wiener's index were computed for each of the 82 analogues using an in-house computer program. Resultant data were analyzed and a suitable model was developed after identification of the active range. Subsequently, a biological activity was assigned to each analogue involved in the dataset using this model, which was then compared with the reported MRP1 inhibitory activity. Accuracy of prediction was found to be 88% using model based on Wiener's index.

The emergence of tumor cells resistant to a range of cytotoxic drugs is a serious problem in cancer chemotherapy. This phenomenon is called multidrug resistance (MDR). One form of MDR can be caused by members of the ATP-binding cassette (ABC) family of transport proteins.[1] These are large polytopic membrane proteins that actively transport drugs out of cells, resulting in a decreased intracellular concentration. In humans, two ABC transporters have been identified, which cause resistance in tumor cells: P-glycoprotein (Pgp)[2] and the multidrug-resistance-associated protein (MRP1).[3] Pgp transports drugs in an unmodified form, whereas MRP1 transports drugs conjugated to the anionic ligands glutathione (GSH), glucuronide, or sulfate, or transports them in an unmodified form, probably together with GSH.[4] The correlation between drug resistance and expression of the drug efflux pumps, Pgp and MRP1, has spurred intense research in the development of Pgp and MRP1 inhibitors.

Multidrug resistance mediated by P-glycoprotein or multidrug-resistance-associated protein remains a major obstacle in the successful treatment of cancer. Inhibition of Pgp and MRP transport is important for the high efficacy of anticancer drugs. While several Pgp inhibitors have entered clinical trials, development of specific MRP1 inhibitors is still in its infancy, although Eli Lilly has reported the raloxifene analogues[5] and isooxazoloquinoline analogues[6] as selective MRP1 inhibitors.

A contemporary trend in chemistry, pharmacology, toxicology, and pharmaceutical drug design is the correlation of physicochemical/biological/toxicological properties of biologically active molecules with certain structural aspects.[7] The basic assumption underlying this area of research, called structure–activity relationship, is that the structure of a molecule determines its behavior. This paradigm can be expressed as

$$P = f(S),$$

where P is any physical, pharmacological, toxicological activity of interest and S may represent either an empirical property of the total molecular structure, a relevant substructural fragment, or a theoretical structural descriptor.[8]

With the substantial increase in the available databases of chemical structures and properties, attempts have been made to develop structure–activity relationship models whereby existing molecules can be compared with other molecules (real or hypothetical) on the basis of various structural descriptors. The properties of the molecules of interest can then be predicted based on

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the molecular structure without the need for any experimental data.[9] The main problem in this area, however, was the development of easily calculable parameters, which encode sufficient structural information useful in the prediction of properties. Molecular topology has been demonstrated to be an excellent tool for a quick and accurate prediction of physicochemical and biological properties.[10] Through a relatively simple formalism such as molecular connectivity, a good molecular characterization with topological indices or descriptors (TIs) can be obtained. A topological index is a numerical descriptor of molecular structure and is sensitive to such key constitutional features as size, shape, symmetry, and heterogeneity of atomic environments in the molecule.[8]

In the present study, the relationship between Wiener's index—a distance-based topological descriptor and MRP1 inhibitory activity of pyrrolopyrimidines and derivatives derived from them has been investigated.

Wiener's index,[11,12] a well-known distance-based topological index, is defined as half-sum of all entries in the distance matrix of the hydrogen-suppressed molecular graph, that is

$$W = 1/2\left(\sum_{i=1}^{n} P_{ij}\right), \tag{1}$$

where P_{ij} is the path length that contains the least number of edges between vertex i and vertex j in graph G, and n is the maximum possible number of i and j.

A dataset[13,14] comprising of 82 analogues of pyrrolopyrimidines and their derivatives was selected for the present investigations. The basic structures for the various analogues are shown in Figure 1 and the various substituents listed in Table 1.

The values of Wiener's index were computed for each of the 82 analogues comprising the dataset using an in-house

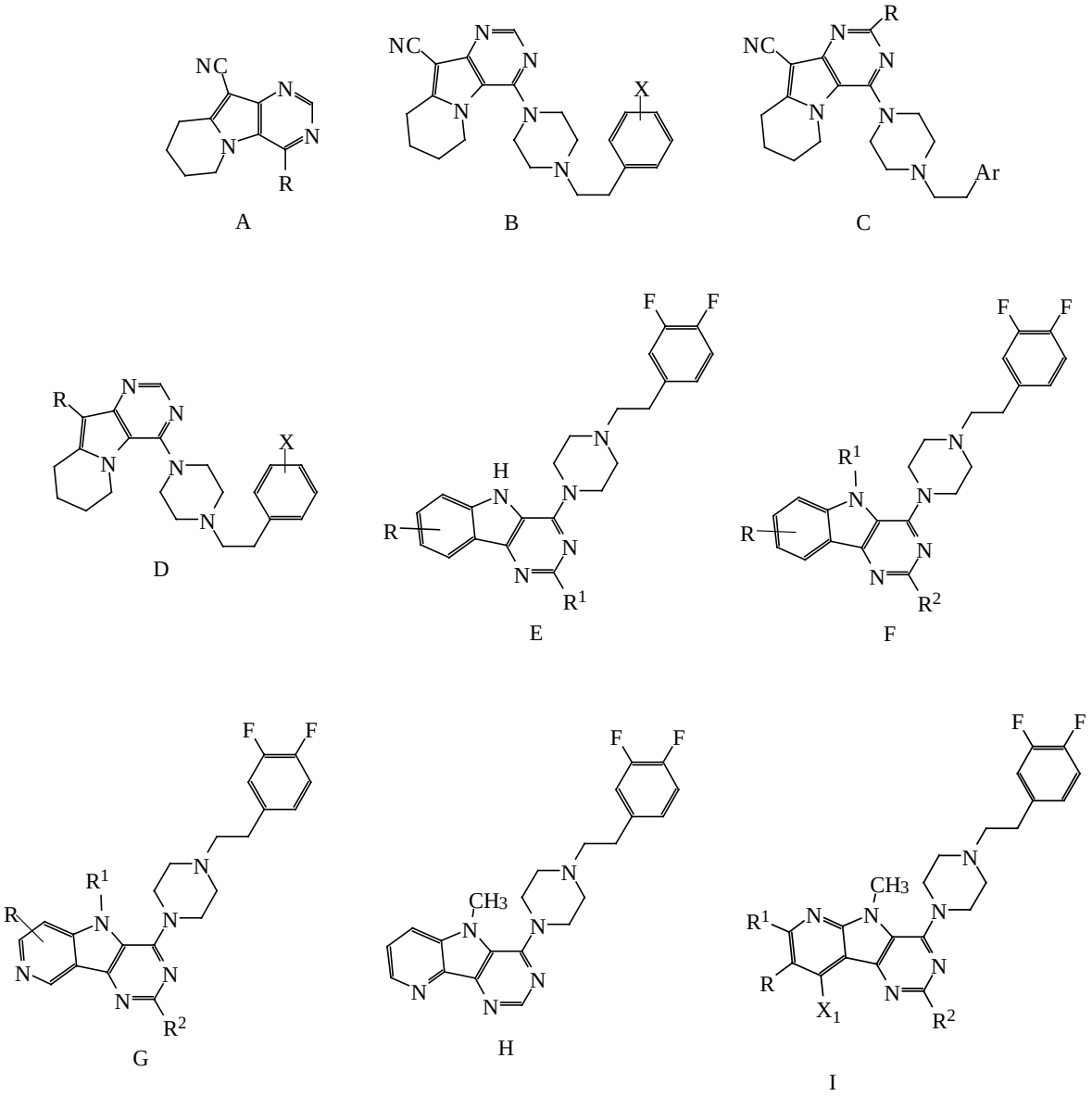
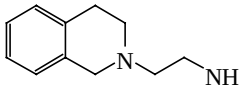
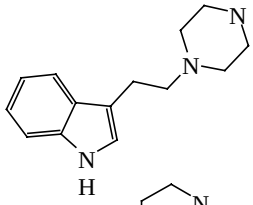
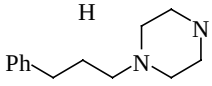
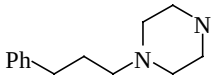
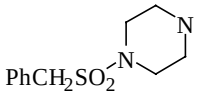
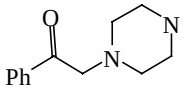
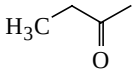
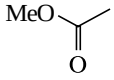
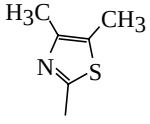
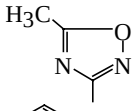
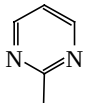


Figure 1. Basic structures of pyrrolopyrimidines and their derivatives.

Table 1. Relationship between Wiener's index and MRP1 inhibitory activity

Compound No.	R	X/R^1	Ar/R^2	X_1	W	MRP1 inhibitory activity	
						Predicted	Reported
A_1	$PhCH_2CH_2NH$	—	—	—	1376	–	–
A_2	$PhCH_2CH_2NCH_3$	—	—	—	1487	–	–
A_3	$PhCH_2SO_2NH$	—	—	—	1616	–	–
A_4		—	—	—	2178	–	–
A_5		—	—	—	3195	±	–
A_6		—	—	—	2405	–	–
A_7		—	—	—	2700	–	–
A_8		—	—	—	2773	–	–
A_9		—	—	—	2603	–	–
B_1	—	2-Cl	—	—	2643	–	–
B_2	—	3-Cl	—	—	2666	–	–
B_3	—	4-Cl	—	—	2689	–	–
B_4	—	$2\text{-}NO_2$	—	—	3181	–	–
B_5	—	$3\text{-}NO_2$	—	—	3250	±	–
B_6	—	$4\text{-}NO_2$	—	—	3319	±	–
B_7	—	3-MeO	—	—	2957	–	–
B_8	—	4-MeO	—	—	3003	–	–
B_9	—	3,4-F,F	—	—	2953	–	+
C_1	I	—	Ph	—	2590	–	–
C_2	Ph	—	Ph	—	3803	±	–
C_3	$4\text{-}CH_3CONHPh$	—	Ph	—	5251	±	–
C_4	3-Pyr	—	3,4-(F,F)-Ph	—	4531	+	+
C_5	4-Pyr	—	3,4-(F,F)-Ph	—	4552	+	+
C_6	$2\text{-}CH_3\text{-}Ph$	—	3,4-(F,F)-Ph	—	4820	+	–
D_1		—	H	—	2847	–	–
D_2		—	H	—	3929	±	–
D_3		—	H	—	2847	–	–
D_4		—	H	—	3352	±	–
D_5		—	H	—	3350	±	–
D_6		—	H	—	3351	±	–

(*continued on next page*)

Table 1 (*continued*)

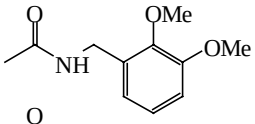
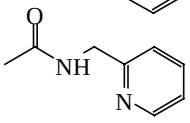
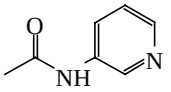
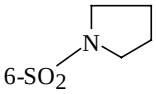
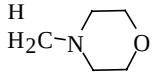
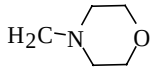
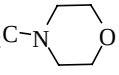
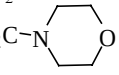
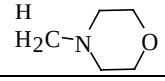
Compound No.	R	X/R[1]	Ar/R[2]	X_1	W	MRP1 inhibitory activity	
						Predicted	Reported
D_7	$CONH_2$	—	3,4-F,F	—	3190	±	+
D_8	CONHEt	—	3,4-F,F	—	3761	±	+
D_9		—	3,4-F,F	—	7289	±	+
D_{10}		—	3,4-F,F	—	5223	+	+
D_{11}		—	3,4-F,F	—	5119	+	+
E_1	5-CH_3	H	—	—	2769	–	–
E_2	6-NO_2	H	—	—	3348	±	+
E_3	6-MeO	H	—	—	3069	–	–
E_4	6-$NHCOCH_3$	H	—	—	3687	±	–
E_5	6-CO_2CH_3	H	—	—	3659	±	+
E_6	6-$CONH_2$	H	—	—	3348	±	–
E_7		H	—	—	4516	+	+
E_8	5-Cl	H	—	—	2769	–	–
E_9	5-CN	H	—	—	3023	–	–
E_{10}	5-$CONH_2$	H	—	—	3279	±	+
E_{11}	5-CONHPy-4	H	—	—	5322	±	–
E_{12}	5-NO_2	H	—	—	3279	±	+
E_{13}	5-NH_2	H	—	—	2769	–	–
E_{14}	7-MeO	H	—	—	3073	–	–
E_{15}	7-MeO, 8-NO_2	H	—	—	3838	±	–
E_{16}	5-NO_2, 6-MeO	H	—	—	3765	±	+
E_{17}	6-NO_2		—	—	5424	±	–
E_{18}	6,8-Di-NO_2		—	—	6418	±	+
F_1	5-NO_2	CH_3	H	—	3485	±	+
F_2	5-NO_2	$Ph(CH_2)_2$	H	—	5695	±	+
F_3	5-NO_2	CH_2Py-3	H	—	5243	±	–
F_4	5-NO_2	CH_2Py-4	H	—	5243	±	+
F_5	5-$CONH_2$	CH_3	H	—	3485	±	+
F_6	5-$CONH_2$	CH_2CO_2Et	H	—	4931	+	+
F_7	5-$CONH_2$	CH_2Py-4	H	—	5243	±	–
F_8	6-NO_2	CH_2CO_2Et	H	—	5018	+	+
F_9	5-$CONH_2$	CH_3		—	5597	±	+
G_1	H	CH_3	H	—	2734	–	+
G_2	H	CH_2Ph	H	—	4364	±	–
G_3	5-Cl	CH_3	H	—	2963	–	+
G_4	5-MeO	CH_3	H	—	3223	±	+
G_5	5-^{i}PrO	CH_3	H	—	3809	±	–
G_6	5-NMe_2	CH_3	H	—	3485	±	+
G_7	5-NHMe	CH_3	H	—	3264	±	+
G_8	5-$NHCH_2$Py-2	CH_3	H	—	5290	±	+
G_9	Morpholine	CH_3	H	—	4405	+	+
G_{10}	5-CH_3	CH_3	H	—	2963	–	+
G_{11}	7-Cl	CH_3	H	—	2988	–	–
G_{12}	5-Cl	CH_3	CH_2OMe	—	3693	±	+
G_{13}	5-Cl	CH_3		—	4947	+	+
H_1[a]					2545	–	–
I_1	H	H	H	CN	3023	–	–

Table 1 (*continued*)

Compound No.	R	X/R[1]	Ar/R[2]	X_1	W	MRP1 inhibitory activity	
						Predicted	Reported
I_2	CH_3	H	H	CN	3281	±	–
I_3	CH_3	H	H	$CONH_2$	3542	±	+
I_4	H	H	H	$CONH_2$	3279	±	+
I_5	CH_3	NO_2	H	$CONH_2$	4395	+	+
I_6	H	H		$CONH_2$	4470	+	+

+, Active compound. –, inactive compound; ±, compound in the transitional range where the activity could not be specifically assigned.
[a] Structure shown in Figure 1.

Table 2. Model for multidrug-resistance-associated protein inhibitory activity

Model index	Nature of range in the proposed model	Index value	Number of analogues falling in the range		Percent accuracy	Average IC_{50} (μM)		Accuracy of prediction
			Total	Correct		Total	Correct	
W	Inactive	<3190	30	26	86.7	4.32	4.97	88
	Lower transitional	3190–4364	29	NA	NA	0.52	NA	
	Active	4395–5223	12	11	91.7	0.16	0.12	
	Upper transitional	>5223	11	NA	NA	0.32	NA	

NA, not applicable.

computer program. For the selection and evaluation of range-specific features, exclusive activity ranges were discovered from a frequency distribution of the response level by maximization of the moving average with respect to the active compounds (<35% = inactive, 35–65% = transitional, and ⩾65% = active).[15] A suitable model was developed after identification of the active range. Subsequently, each analogue was assigned a biological activity using this model, which was then compared with the reported[13,14] MRP1 inhibitory activity. MRP1 inhibitory activity was reported[13,14] quantitatively as IC_{50} at different concentrations. The analogues possessing IC_{50} values of <0.25 μM were considered to be active and analogues possessing IC_{50} values of ⩾0.25 μM were considered to be inactive for the purpose of the present study.

Efficient discovery and creation of novel drug molecules depend on the ability to explore and quantify the relationships between molecular structure and function—particularly the biological activity. The inherent problem in the development of a suitable correlation between chemical structures and biological activity can be attributed to the non-quantitative nature of chemical structures. Graph theory was successfully employed through the translation of chemical structures into characteristic numerical descriptors by resorting to graph invariants.[16,17]

Though all the analogues in the dataset reportedly[13,14] possessed varying degrees of biological activity, only those analogues possessing IC_{50} values of <0.25 μM were considered to be active and analogues possessing IC_{50} values of ⩾0.25 μM were considered to be inactive for the purpose of the present study.

Retrofit analysis of the data in Tables 1 and 2 reveals the following information with regard to the model based upon Wiener's index:

- A total of 37 out of 42 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction of the proposed model was found to be 88% with respect to the MRP1 inhibitory activity.
- The active range had a Wiener's index value of 4395–5223. As many as 11 out of 12 analogues in the active range exhibited MRP1 inhibitory activity.
- The active range was ideally bracketed by two transitional ranges exhibiting a gradual change in biological activity from the inactive to active range.
- The average IC_{50} value was found to be 0.12 μM for the correctly predicted compounds indicating high potency of the active range.
- Biological activity of 26 out of 30 analogues in the inactive range was predicted correctly.

Investigations reveal significant correlation between Wiener's index—a distance-based topological descriptor and MRP1 inhibitory activity of pyrrolopyrimidines and their derivatives. The overall accuracy of prediction of the proposed model was found to be 88%. High predictability of the model based on Wiener's index offers a vast potential for providing lead structures for the development of potent MRP1 inhibitors.

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