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Antiviral and Quantitative Structure Activity Relationship Study for Dihydropyridones Derived from Curcumin

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Abstract: Problem statement: Pyridones are known to have variety of biological activities like antitumor, antibacterial, anti-inflammatory and antimalarial activities. This study presents antiviral evaluation of dihydropyridones derived from curcumin, as well as curcumin for comparison. **Approach:** The compounds evaluated for their in vitro antiviral activities against the viruses: HIV-1, Bovin viral Diarrhea, Yellow Fever, Reovirus 1, Herpesvirus 1, Vaccinia, Vescular Stomatitis, Coxackie virus B2, Poliovirus 1 and Respiratory Syncytial viruses by using Microculture Tetrazolium assay (MTT) method. The method was based on the metabolic reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. **Results:** Antiviral biological activities represented as CC_{50} were within the range >100-26 for BHK-21, while they were within the range >90-≥13 against Respiratory Syncytial Virus when represented as EC_{50} for example. Both CC_{50} and EC_{50} values were found to increase with increasing chain length of the substituent on the nitrogen atom. **Conclusion:** The in vitro antiviral activities of the tested dihydropyridones can be enhanced by increasing chain length of the substituent on the nitrogen atom.

Key words: Dihydropyridones, curcumin, ant-HIV-1, QSAR, logP, AM1 Hamiltonian

INTRODUCTION

Dihydropyridones are important intermediates for the synthesis of natural products, particularly alkaloids (Dong *et al*., 2005; Comins and Ollinger, 2001; Elias *et al*., 2008) and they have been extensively investigated as valuable building block for the construction of piperidines, perhydroquinolens, indolizidines, quinolizidines and other alkaloid systems, with a wide range of a biological and pharmacological activities. These compounds are known for their antiproliferative and antitubolin activities (Magedov *et al*., 2008) and as potential selective inhibitors of receptor tyrosine kinase (Hu *et al*., 2008; Goodman *et al*., 2007). Their ability to induce leukaemic cell differentiation has been demonstrated (Pierce *et al*., 1981). In addition they have potent antimalarial activity (Yeats *et al*., 2008) and good anticonvulsant activity against acutely elicited Seizures (Revas *et al*., 2009). On the other hand curcumin is a principal curcuminoid of Indian curry and has known for its antitumor (Ran *et al*., 2009; Wohlmuth *et al*., 2010; Ljngman, 2009), antioxidant, anti-inflammatory (Takahashi *et al*., 2009; Kuhad *et al*., 2007; Michaelidou and H-Litina, 2005) and antiarthritic properties (Patil *et al*., 2009).

Very little was published about the antitumor activities of dihydropyridones and the aim of this study is to investigate the relationship between structure and antitumor activity of a series of dihydropyridones derived from curcumin.

MATERIALS AND METHODS

The screened dihydropyridones were synthesized via previously described method (Elias *et al*., 2008). These compounds as well as curcumin were evaluated for preliminary estimation of the in vitro tumor inhibiting activity against a variety of viruses included: HIV-1, Bovin Viral Diarrhea (BVDV), Yellow Fever (YFV), Reovirus 1 (Reo), Herpesvirus 1 (HSV-1), Vaccinia VV), Vescular Stomatitis (VSV), Coxackie virus B2 CVB-2), Poliovirus 1 (Sb-1) and Respiratory Syncytial (RSV) viruses, using microculture assay (MTT) method (Tang *et al*., 2010). This method is based on the metabolic reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT).

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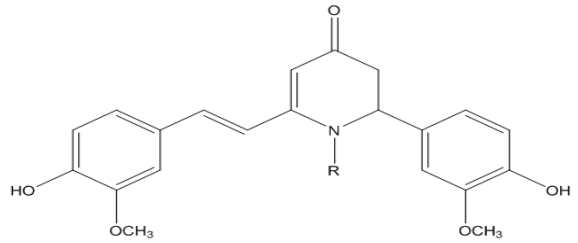

Fig. 1: The structural formula for the studied compounds

Molecular descriptors for the studied compounds, logP, hydration energy (ΔH), Refractivity (Ref) and Polaraizability (Pol) were calculated using HyperChem8.5 program, after geometry optimization with the semi empirical RM1 Hamiltonian. The general molecular structure of the studied molecules is shown in Fig. 1.

RESULTS

The results of the antiviral activities, represented as CC_{50} (μM) and EC_{50} (μM) are summarized in Table 1. The CC_{50} are within the range >100-26 for BHK-21 while EC_{50} values are within the range >90-≥13 against Respiratory Syncytial Virus. The calculated molecular descriptors are gathered in Table 2.

The values of logP, Refractivity, Polarizibility increase with increasing molecular weight while hydration energy decreases with increasing molecular weight except for molecule 6.

DISCUSSION

The tested compounds have variable antiviral activities (both CC_{50} and EC_{50}) with respect to curcumin. In some cases their activity is more than that of curcumin while in others it is less. It is obvious from Table 1 that while the CC_{50} values of curcumin is less than the majority of the studied compounds for MT-4, MDBK, BHK-21 and Vero-76, the situation is the opposite for compound 5 in the case of BHK-21 and the compounds 4 and 5 in the case of Vero-76. The values of CC_{50} in these cases are 26, 18 and 13 respectively indicating that the compounds 4 and 5 are more active than curumin. The biological activity expressed as EC_{50} is in the same direction as could be seen in Table 2. It is worth noting that the EC_{50} values of compounds 4 and 5 are much smaller than those of curcumin. In both cases the antiviral activity of the studied dihydropyridones increases with increasing chain length of the substituent on the nitrogen atom.

Table 1: Antiviral activities of the studied dihudropyridones represented as CC_{50} (μM)

Comp.	R	Cell line	CC_{50} (μM)[a]
1	$-CH_3$	MT-4[b]	>100
		MDBK[c]	>100
		BHK-21[d]	>100
		Vero-76[e]	90
2	$-C_2H_5$	MT4[b]	54
		MDBKc	>100
		BHK-21[d]	>100
		Vero-76[e]	84
3	$-C_3H_7$	MT4[b]	51
		MDBK[c]	>100
		BHK-21[d]	>100
		Vero-76[e]	>100
4	$-C_4H_9$	MT4[b]	36
		MDBK[c]	49
		BHK-21[d]	44
		Vero-76[e]	18
5	$-C_6H_{13}$	MT4[b]	20
		MDBK[c]	38
		BHK-21[d]	26
		Vero-76[e]	13
6	$-CH_2$-Ph	MT4[b]	53
		MDBK[c]	>100
		BHK-21[d]	67
		Vero-76[e]	92
Curcumin		MT4[b]	18
		MDBK[c]	11
		BHK-21[d]	32
		Vero-76[e]	60

[a]Compound concentration required to reduce cell proliferation by 50% as determined by the MTT method. [b]Compd. Concn. (μM) required to reduce the viability of mock-infected MT-4 ($CD4^+$ Human T-cells Containing an integrated HTLV-1 genome) cells by 50%, as determined by the colorimetric MTT method. [c]Compd. Concn. (μM) required to reduce the viability of mock-infected MDBK (Bovine normal kidney) Cells by 50%, as determined by the MTT method. [d]Compd. Concn. (μM) required to reduce the viability of mock-infected BHK (Hamster normal kidney fibroblast) monolayers by 50%, as determined by the MTT method. [e]Compd. Concn. (μM) required to reduce the viability of mock-infected VERO-76 (Monkey normal kidney) Monolayers by 50%, as determined by the MTT method

Comparison of the activity of compound 1 with 6 shows that the inclusion of a phenyl group in the substituent moiety shifted the threshold of potency from less to more activity in some cases like MT-4, HIV-1, BHK-21, YFV and Reo-1. For substituent longer than propyl group the compounds have activity comparable to that of curcumin and in the case where R is hexyl group the antiviral activity becomes higher to that of curcumin. Ignoring the data of compound 1 (CC_{50} >100) we tried to correlate the activity of the compounds 2-6 represented by $Log(1/CC_{50})$ against MT-4 with the molecular descriptors, logP, refractivity, polarizability, hydration energy and carbon number of the substituent (C_n). Very good models with R^2 values 0.938, 0.957, 0.968, 0.957 and 0.955 respectively, were obtained when the data of compound 6 are not involved. The models are shown in Eq. 1-5:

$$Log(1/CC_{50}) = 0.078logP - 0.512 \quad (1)$$
$$R^2 = 0.938, \quad S^2 = 0.017, \quad F = 30.3$$

Table 2: Antiviral activities of the studied dihudropyridones represented as EC_{50} (μM)[a]

Comp	R	HIV-1[b]	BDVD[c]	YFV[d]	Reo-1[e]	HSV-1[f]	VV[g]	VSV[h]	CVB-2[i]	Sb-1[j]	RSV[k]
1	$-CH_3$	>100	>100	>100	>100	>90	>90	>90	>90	>90	>90
2	$-C_2H_5$	>54	>100	>100	68	>84	>84	>84	>84	>84	>84
3	$-C_3H_7$	>51	>100	>100	50	>100	>100	>100	>100	>100	>100
4	$-C_4H_9$	>36	>49	>44	>44	>18	>18	>18	>18	>18	>18
5	$-C_6H_{13}$	>20	>38	>26	>26	>13	>13	>13	>13	>13	≥13
6	$-CH_2$-Ph	>53	>100	>67	>67	>92	>92	>92	>92	>92	>92
Curcumin		>18	>11	>32	>32	>60	>60	>60	>60	>60	>60

[a]Compound Concentration (μM) required to achieve 50% protection. [b]Compound Concentration (μM) required to achieve 50% protection of MT-4 cells from the HIV-1-induced cytopathogenicity, as determined by the MTT method. [c]Compd. Concn. (μM) required to achieve 50% protection of MDBK cells from the BVDV (Bovine Viral Diarrhea Virus)-induced cytopathogenicity, as determined by the MTT method. [d]Compound concentration (μM) required to achieve 50% protection of BHK (Kidney fibroblast) cells from the YFV (Yellow Fever Virus) and [e]Reo (Reovirus1)-induced cytopathogenicity, as determined by the MTT method. [f]Compd. Concn. (μM) required to reduce the plaque number of HSV-1 (Herpesvirus 1), [g]VV (Vaccinia Virus), [h]VSV (Vesicular Stomatitis Virus), [i]CVB-2 (Coxsackie virus B2), [j]Sb-1 (Poliovirus 1) and [k]RSV (Respiratory Syncytial Virus) by 50% in VERO-76 minelayers

Table 3: Calculated molecular descriptors, observed activity against MT-4 and the predicted activity for the stuied dihydropyridones

No	logP	Ref.	Pol.	ΔH	π	A_{obs}	A_{pred}	Resdual
2	3.29	114.03	43.11	-16.69	1.02	-0.238	-0.251	-0.013
3	3.67	118.56	44.64	-16.28	1.55	-0.232	-0.210	-0.013
4	4.16	123.16	46.78	-15.85	2.13	-0.192	-0.184	0.008
5	4.95	132.36	50.45	-15.01	3.10	-0.114	-0.121	-0.007
6	4.72	133.90	50.93	-17.76	2.01	-0.237	-0.237	0.000

Ref: Refractivity, Pol.: Polarizability, ΔH: Hydration energy, π: Hydrophobicity constant of the substituent, A_{obs}: Observed biological activity expressed by $Log(1/CC_{50})$, A_{pred}: Predicted biological activity.

$$Log(1/CC_{50}) = 0.007Ref-1.064 \quad (2)$$
$$R^2 = 0.957, \quad S^2 = 0.014, \quad F = 44.3$$

$$Log(1/CC_{50}) = 0.018Pol-1.011 \quad (3)$$
$$R^2 = 0.968, \quad S^2 = 0.012, \quad F = 36.3$$

$$Log(1/CC_{50}) = 0.077\Delta H + 1.047 \quad (4)$$
$$R^2 = 0.957, \quad S^2 = 0.014, \quad F = 28.4$$

$$Log(1/CC_{50}) = 0.033Cn-0.317 \quad (5)$$
$$R^2 = 0.955, \quad S^2 = 0.015, \quad F = 42.9$$

Equations 1-5 indicate a strong dependency of the activity on the alkyl chain length. However, when compound 6 involved in the regression equation poor models with low R^2 are predicted for all parameters except for ΔH. For example, in the case of the model including logP the correlation coefficient R^2 is 0.417, while for ΔH as a descriptor, a model with $R^2 = 0.713$ is obtained. This value became 0.957 when a double parameter regression equation including both ΔH and the hydrophobicity constant of the substituent (π) was used as shown in Eq. 6:

$$Log(1/CC_{50}) = 0.134\Delta H + 2.551\pi + 4.183 \quad (6)$$
$$R^2 = 0.957, \quad S^2 = 0.015, \quad F = 22.3$$

The predicted biological activities for the dihydropyridones from Eq. 6 represented as $Log(1/CC_{50})$ are shown in Table 3.

CONCLUSION

This study has shown that the antiviral activity of the studied compounds increases with increasing chain length of the substituent on the nitrogen atom as well the activity could be predicted to good estimate on the basis of a model involving both hydration energy and the hydrophoibicity constant of the substituent.

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