Synthesis, HIV-1 integrase inhibitory activity and QSAR studies of coumarin analogues

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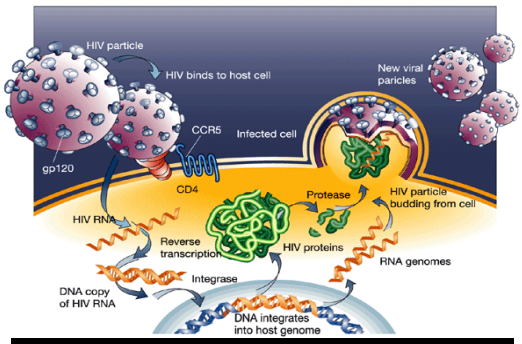
Introduction

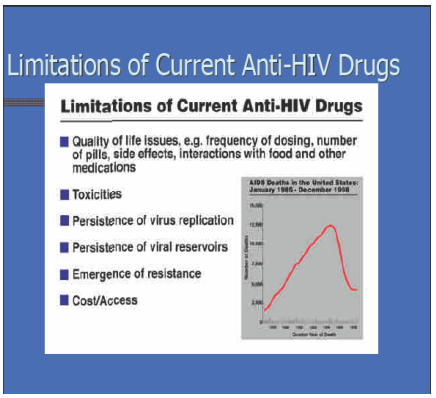
UNAIDS

Global summary of the AIDS epidemic, December 2007

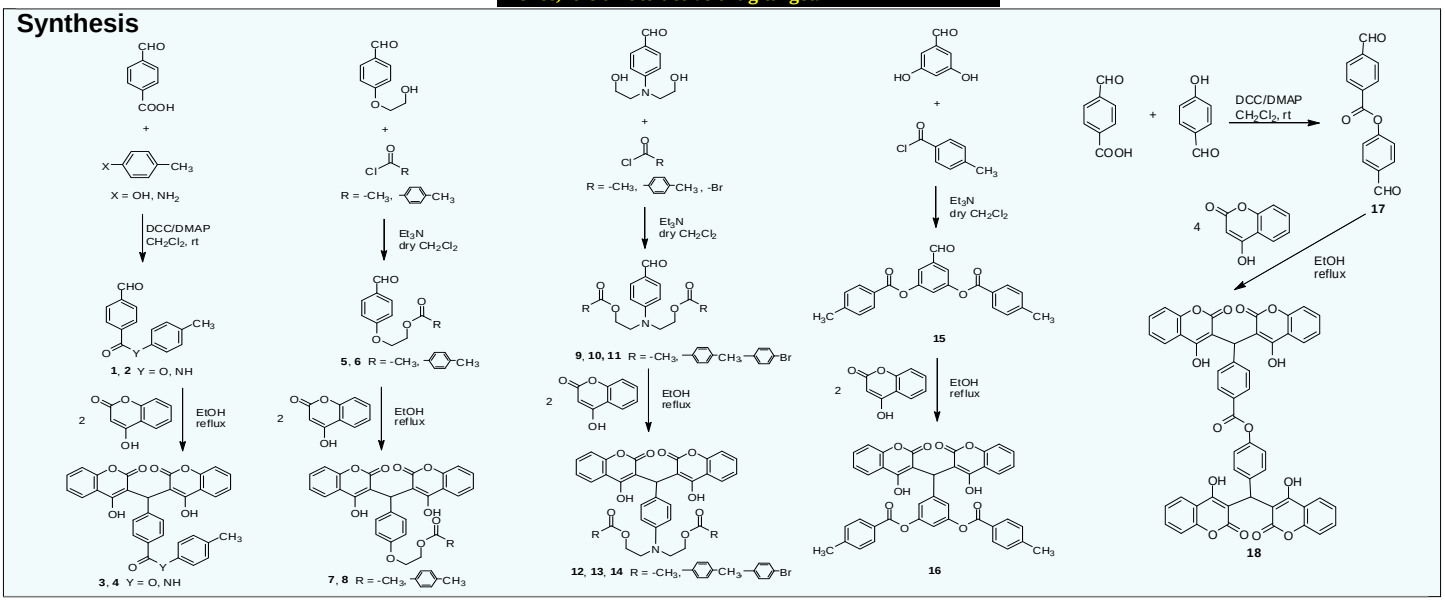
Number of people living with HIV in 2007	Total	33 million [30 – 36 million]
	Adults	30.8 million [28.2 – 34.0 million]
	Women	15.5 million [14.2 – 16.9 million]
	Children under 15 years	2.0 million [1.9 – 2.3 million]
People newly infected with HIV in 2007	Total	2.7 million [2.2 – 3.2 million]
	Adults	2.3 million [1.9 – 2.8 million]
	Children under 15 years	370 000 [330 000 – 410 000]
AIDS deaths in 2007	Total	2.0 million [1.8 – 2.3 million]
	Adults	1.8 million [1.6 – 2.1 million]
	Children under 15 years	270 000 [250 000 – 290 000]



The HIV integrase has a crucial role in viral replication. Moreover, it has no cellular homologue in humans. Hence, it is an attractive drug target.



Synthesis



Results

Tab 1 QSAR parameters and biological activities

Compd	$IC_{50}(\mu M)$*	pIC_{50}	logP	ε_{Lumo}	ε_{Homo}	NRB	MR
3	3.10	5.5086	4.99	-1.10	-8.91	7	151.162
4	23.1	4.6364	4.312	-1.10	-8.52	7	153.111
7	96.0	4.0177	3.219	-0.99	-9.09	8	135.300
8	23.1	4.6364	5.604	-0.99	-9.06	9	160.514
12	102	3.9914	3.343	-0.96	-8.73	12	158.709
13	1.80	5.7447	8.113	-0.92	-8.30	14	209.137
14	0.96	6.0177	8.796	-0.97	-8.38	14	214.300
16	0.58	6.2366	7.575	-0.94	-9.29	9	186.086
18	0.49	6.3098	6.716	-1.12	-9.25	9	232.034

**in vitro* IC_{50} (50% inhibitory concentration in μM) against HIV-1 IN

Fig 1. Molecular models of the minimum-energy conformation

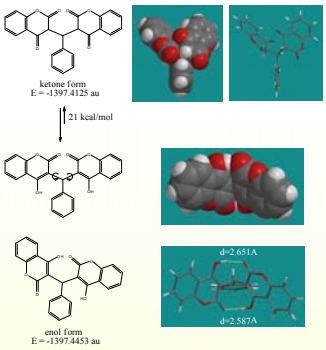
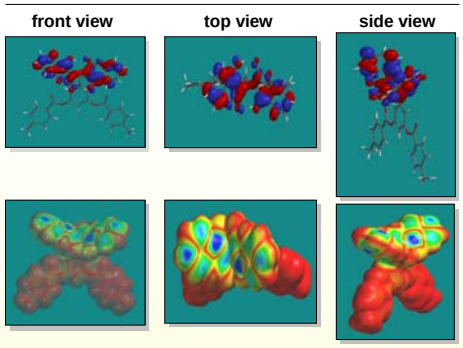


Fig 2. LUMO molecular orbital topology distribution for compound 16.



$$pIC_{50} = 2.942(\pm 0.515) + 0.391(\pm 0.084)\,LogP \cdots\cdots Eq(1)$$

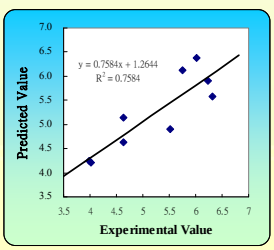
$$pIC_{50} = 2.139(\pm 1.060) + 0.279(\pm 0.155)\,LogP + 0.008(\pm 0.009)MR \cdots\cdots Eq(2)$$

$$pIC_{50} = 3.673(\pm 0.527) + 0.495(\pm 0.081)LogP - 0.135(\pm 0.061)NRB \cdots\cdots Eq(3)$$

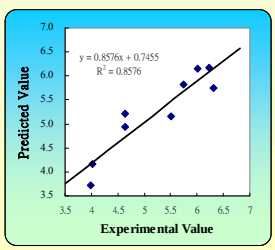
$$pIC_{50} = -1.903(\pm 1.962) + 0.442(\pm 0.066)LogP - 4.504(\pm 1.788)\varepsilon_{LUMO} \cdots Eq(4)$$

Conclusion

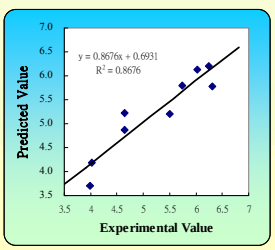
It was found that most of these synthesized compounds showed potent activity against HIV-1 integrase. A QSAR model revealed highly correlations between activity and LUMO and log P properties of tested compounds. These results would provide a tool for guiding the further design of more potent anti-HIV-1 agents.



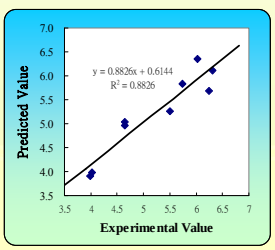
Correlation between the predicted pIC_{50} and the experimental pIC_{50} by Eq(1)



Correlation between the predicted pIC_{50} and the experimental pIC_{50} by Eq(2)



Correlation between the predicted pIC_{50} and the experimental pIC_{50} by Eq(3)



Correlation between the predicted pIC_{50} and the experimental pIC_{50} by Eq(4)

Acknowledgments

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