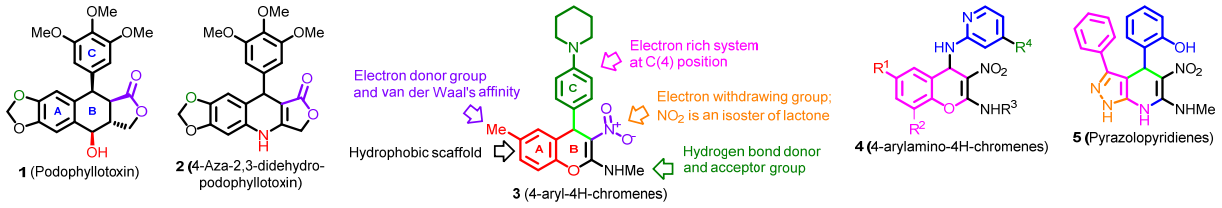
PODOPHLLOTOXIN MIMICS: SYNTHESIS AND BIOLOGICAL ACTIVITY

H. Surya Prakash Rao
Department of Chemistry, Pondicherry University, Pondicherry – 605 014. India

ABSTRACT

In recent years synthesis and biological evaluation of diversity oriented scaffolds have been in practice in drug discovery regimen. Among the naturally occurring anticancer agents, podophyllotoxin (POD) **1** (Figure 1),[1] a lignan isolated from the rhizomes of *Podophyllum peltatum*, *Podophyllum hexandrum* and *Sinopodophyllum hexandrum* gained importance owing to its promising activity against human papilloma virus (HPV) and some types of cancer.[2] POD and its sibling lignans destabilize the polymerization of tubulins and also suppress cellular nucleoside transport both of which lead to cellular necrosis.[3] However, POD exhibits acute toxic side effects which prevent its generic use. Presently it is used for treatments of genital warts (*Condylomata acuminate*) as an ingredient in topical application.[4] It is difficult to isolate POD in pure form or synthesize in industrial scale. Therefore, necessity exists for the development of an easy, reliable industrial-scale synthesis of its mimics which have equal to or better pharmacological properties. In recent years mimics of POD like **2** which possess its pharmacophore features have appeared.[5] Unlike POD its surrogate proved to be a better anti-cancer drug candidate.[6] It has almost equal potency, lower toxicity and extremely easy to synthesize in large quantities. Moreover, it is possible to synthesize a combinatorial library of analogs of **2** to enable discovery of better drugs.[7] We have been interested to synthesize mimics of POD **1** for over a decade.[8] We have introduced 4-aryl-4H-chromenes like **3-5** as lead compounds for anti-cancer drugs. The chromenes **3-5** have several pharmacophore features of **1** as shown in Figure. In the seminar we will give details of this study.



---

1 Bhanot, A.; Sharma, R.; Noolvi, M. *Int. J. Phytomedicine*. **2011**, *3*, 9-26.
2 (a) Kelly, M. G.; Hartwell, J. L. *J. Natl. Cancer Inst*. **1954**, *14*, 967-1010. (b) Imbert, T. F. Discovery of Podophyllotoxins. *Biochimie*. **1998**, *80*, 207-222. (c) Liu, Y. Q.; Tian, J.; Qian, K.; Zhao, X. B.; Morris-Natschke, S. L.; Yang, L.; Nan, X.; Tian, X.; Lee, K. H.. *Med Res Rev.* **2015**, *35*, 1-62.
3 Loike, J. D.; Horwitz, S. B. *Biochemistry*, **1976**, *15*, 5435-5437.
4 Sundharam, J. A. *Indian J Dermatol Venereol Leprol.* **1990**, *56*, 10-14.
5 You, Y. *Curr Pharm Des.* **2005**, *11*, 1695-717.
6 Magedov, I. V.; Manpadi, M.; Slambrouck, S. V.; Steelant, W. F.; Rozhkova, E.; Przheval'skii, N. M.; Rogelj, S.; Kornienko, A. *J. Med. Chem.* **2007**, *50*, 5183-5192.
7 Magedov, I. V.; Frolova, L.; Manpadi, M.; Bhoga, U. D.; Tang, H.; Evdokimov, N. M.; George, O.; Georgiou, K. H.; Renner, K. H.; Getlic, M.; Kinnibrugh, T. L.; Fernandes, M. A.; van Slambrouck, S.; Steelant, W. F. A.; Shuster, C. B.; Rogelj, S.; van Otterlo, V. L. A.; Kornienko, A. *J. Med. Chem.* **2011**, *12*, 4234-4246.
8 (a) Rao, H. S. P.; Tangeti, V. S.; Adigopula, L. N. *Res. Chem. Intermed.* **2016**, *42*, 7285–7303 (b) Parthiban, A.; Kumaravel, M.; Muthukumaran, J.; Rukkumani, R.; Krishna, R.; Rao. H. S. P. *Med. Chem. Res.* **2016**, *25*, 1308-1315 (c) Parthiban, A.; Kumaravel, M.; Muthukumaran, J.; Rukkumani, R.; Krishna, R.; Rao, H. S. P. *Med. Chem. Res.* **2015**, *24*, 1226-1240. (d) Rao, H. S. P.; Geetha, K.; Kamalraj, M. *RSC Adv.* **2011**, *1*, 1050-1059. (e) Rao, H. S. P.; Geetha, K.; Kamalraj, M. Synthesis of 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes, *Tetrahedron*, **2011**, *67*, 8146-8154. (f) Rao, H. S. P.; Geetha, K. *Tetrahedron Lett.* **2009**, *50*, 3836-3839. (g) Rao, H.S.P.; Adigopula, L.N.; Ramadas, K.. *ACS. Comb. Sci.* **2017**, *19*, 279-285.