Synthesis and biological activity of analogs of 1,25-dihydroxyvitamin D_2

Narasimha Bolla Rao[1], Aoife Corcoran[2], Kaori Yasuda[3], Michał Chodyński[1], Krzysztof Krajewski[1], Piotr Cmoch[1], Ewa Marcinkowska[2], Geoffrey Brown[4], Toshiyuki Sakaki[3], Andrzej Kutner[1]

[1]Pharmaceutical Research Institute, 01-793 Warsaw, Poland; [2]Faculty of Biotechnology, University of Wroclaw, 50-383 Wroclaw, Poland; [3]Department of Biotechnology, Faculty of Engineering, Toyama Prefectural University, 5180 Kurokawa, Imizu, Toyama 939-0398, Japan; [4]School of Immunity and Infection, University of Birmningham, B15 2TT, UK

DECIDE Project No. 315902

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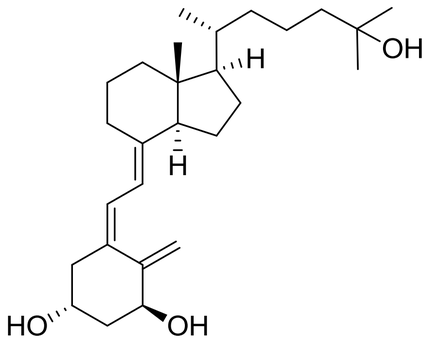
MARIE CURIE ACTIONS

Introduction

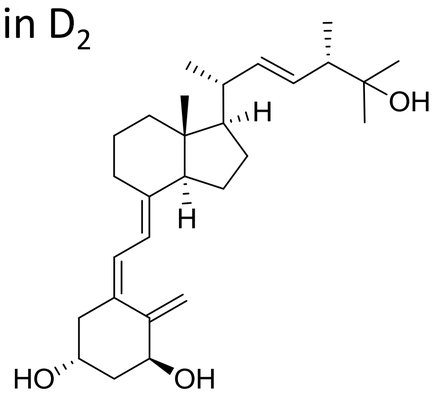
- To understand the complexity of mechanism of functions of vitamin D numerous laboratories have endeavoured studies over several decades.
- This has been driven by interests to find analogues with selective activity as therapeutics against cancer, cardiovascular and immune diseases. In this regard we pursued the design and synthesis and biological evaluation of 1,25D2 analogues.
- An improved synthetic strategy was developed for previously obtained PRI-1906 and PRI-1907. 24(*Z*) isomers PRI-1916 and PRI-1917 were also obtained and identified.

Design

Structures of 1α,25-dihydroxyvitamin D_3 and 1 α,25-dihydroxyvitamin D_2

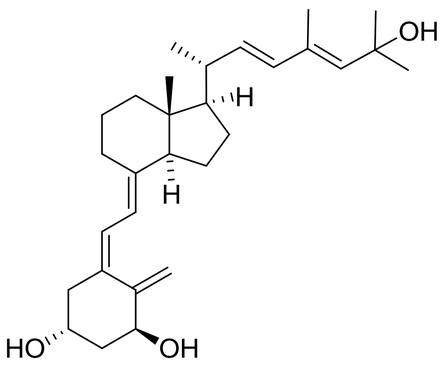


1,25D3

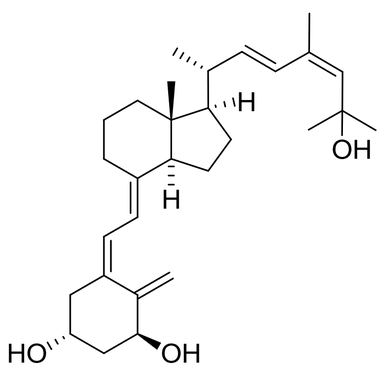


1,25D2

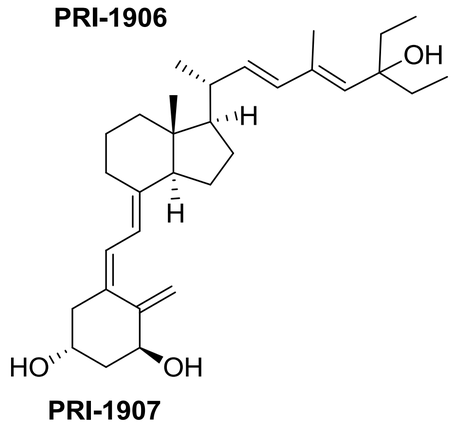
Structures of side-chain homologated and unsaturated analogues of 1,25-D2.



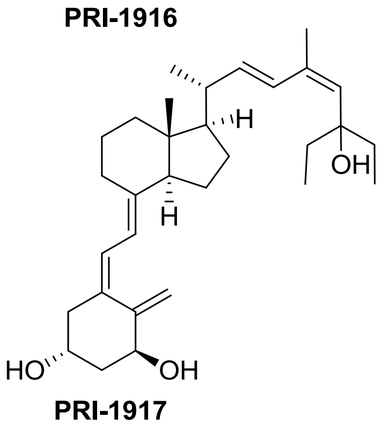
PRI-1906



PRI-1916

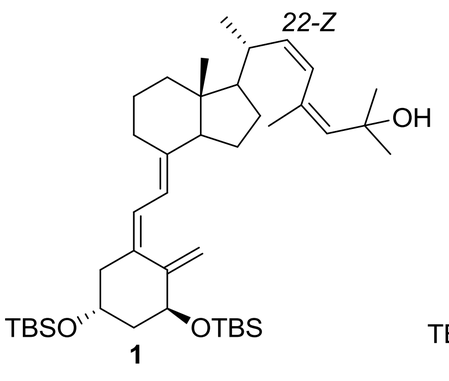


PRI-1907

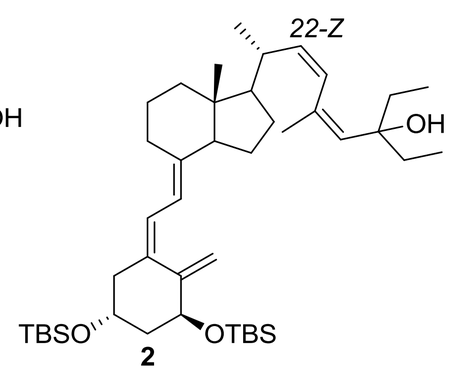


PRI-1917

Hypothetical structures of 22*Z*-analogs

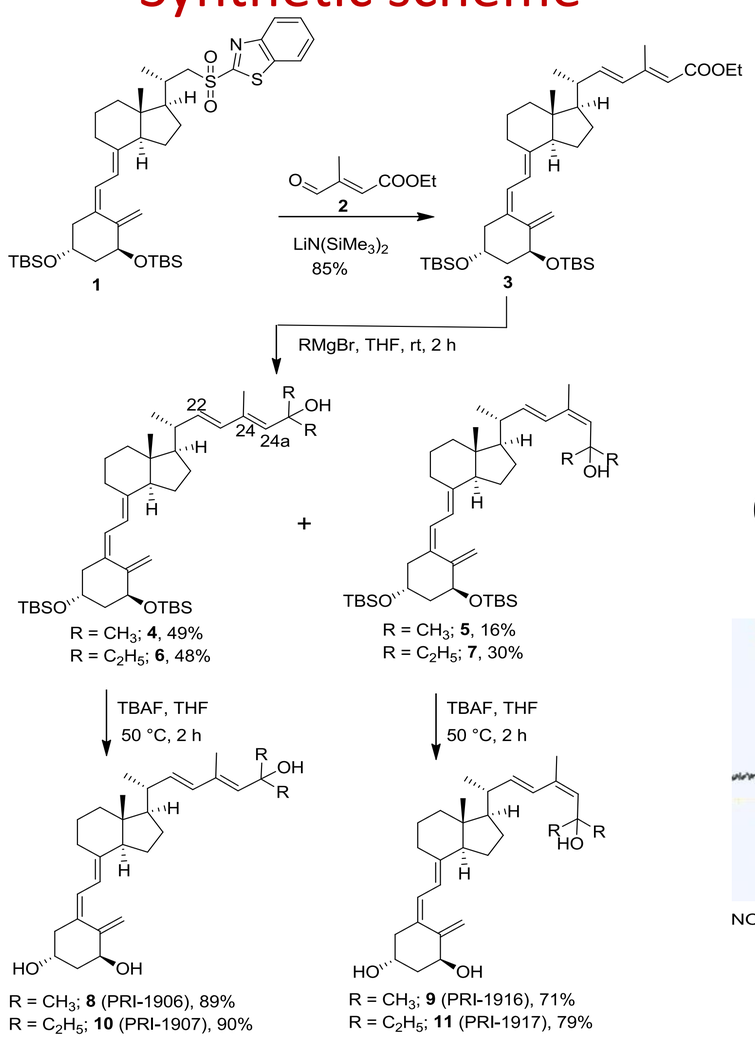


1



2

Synthetic scheme



R = CH_3; **4**, 49%
R = C_2H_5; **6**, 48%

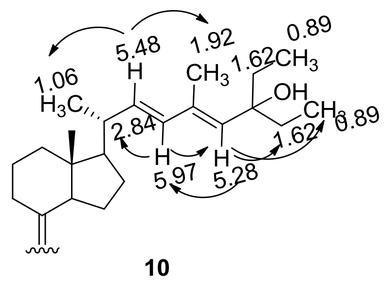
R = CH_3; **5**, 16%
R = C_2H_5; **7**, 30%

R = CH_3; **8** (PRI-1906), 89%
R = C_2H_5; **10** (PRI-1907), 90%

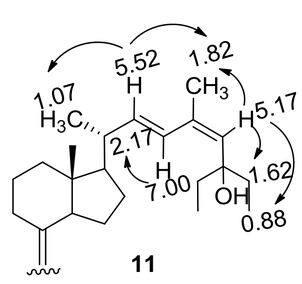
R = CH_3; **9** (PRI-1916), 71%
R = C_2H_5; **11** (PRI-1917), 79%

Characterisation

NOE NMR experimental proof for the new structures

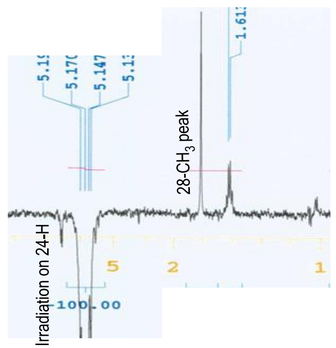


10

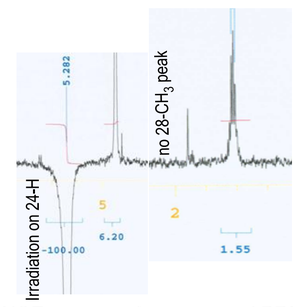


11

600 MHz-^{1}H NMR Spectra showing NOE effects

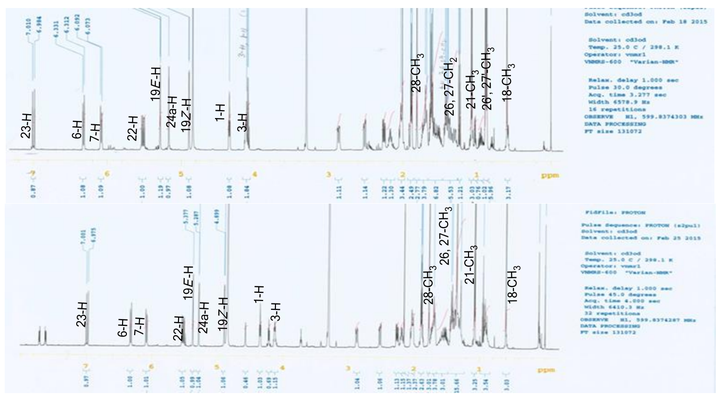


NOE spectrum for compound **PRI-1907**

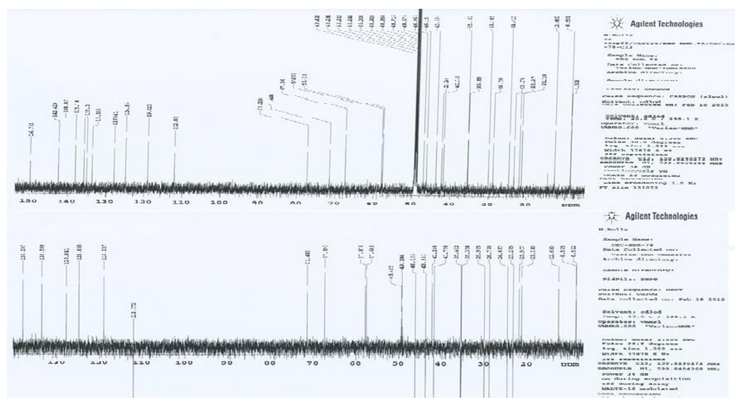


NOE spectrum for compound **PRI-1917**

600 MHz-NMR spectra of PRI-1916 and PRI-1917



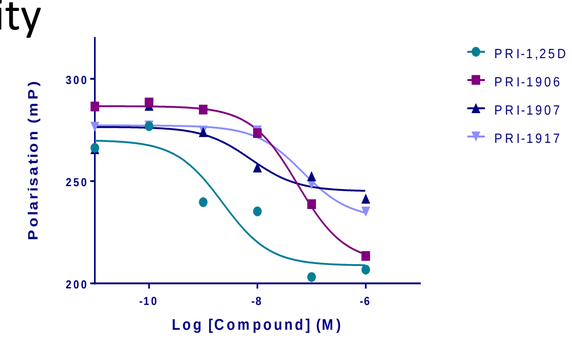
600 MHz ^{13}C and DEPT NMR spectra of PRI-1917



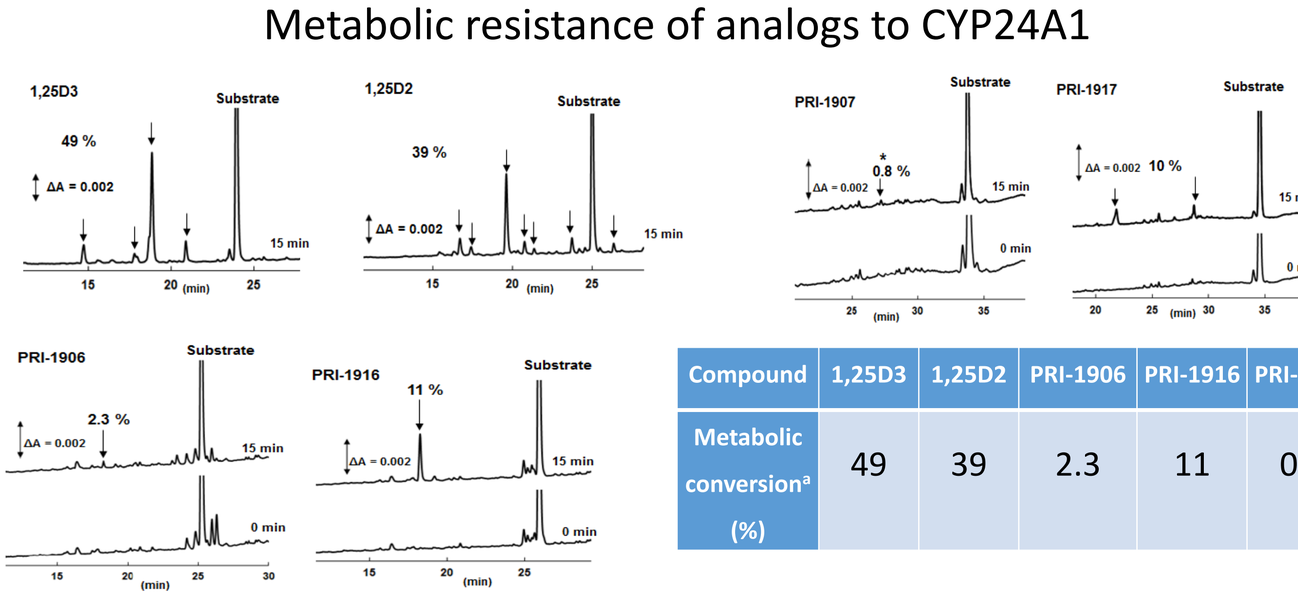
Biological evaluation

Human VDR binding affinity

Compound	1,25D3	PRI-1906	PRI-1916	PRI-1907	PRI-1917
IC_{50}	2.232e^{-09}	5.561e^{-008}	6.048e^{-09}	6.172e^{-09}	6.848 e^{-008}
Relative binding affinity[a]	100	4	37	38	3



Metabolic resistance of analogs to CYP24A1



Compound	1,25D3	1,25D2	PRI-1906	PRI-1916	PRI-1907	PRI-1917
Metabolic conversion[a] (%)	49	39	2.3	11	0.8	10

Reference: Bolla, N. R.; Corcoran, A.; Yasuda, K.; Chodyński, M.; Krajewski, K.; Cmoch, P.; Marcinkowska, E.; Brown, G.; Sakaki, T.; Kutner, A., *J. Steroid Biochem. Mol. Biol.* online 28 August 2015. doi:10.1016/j.jsbmb.2015.08.025

Acknowledgements:

The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013 under REA grant agreement number 315902. One author (NRB) gratefully acknowledges receipt of a Marie Curie Research Associate post.