Synthesis of Six-membered Ring Analogues of RK-682 and Meldrum's acid derivatives. Evaluation on the Inhibition of Protein Tyrosine Phosphatases

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INTRODUCTION

Protein tyrosine phosphatases (PTPs) together with protein tyrosine kinases (PTKs) regulate protein tyrosine phosphorylation. Their abnormal functions are involved in the initiation and maintenance of the oncogenic state in human.[1] Several synthetic tetronic acid derivatives related to the natural product RK-682 (*R*)-**1** (Figure 1) have been evaluated as inhibitors of dual-specificity phosphatases VHR and CDC-25B and four derivatives were shown to be the most potent inhibitors of CDC-25B described so far.[2]

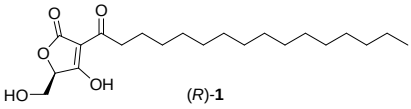


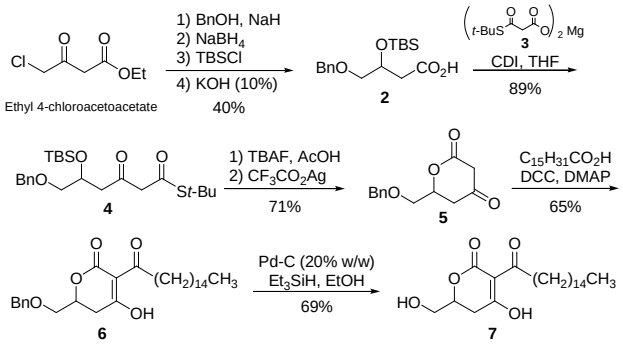
Figure 1. Natural product RK-682.

The scope of this work includes the synthesis of six-membered ring homologues of RK-682 and Meldrum's acid derivatives and evaluation of their inhibition against human protein tyrosine phosphatases (LMW-PTP, CDC-25B and PTP-1B).

RESULTS AND DISCUSSION

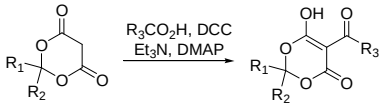
Ethyl 4-chloroacetoacetate was converted to intermediate **5** after 7 steps. Synthesis of six-membered ring homologues **6** and **7** was carried out via coupling between **5** and palmitic acid mediated by *N*,*N*'-dicyclohexylcarbodiimide (DCC) (Scheme 1).

Scheme 1. Synthesis of **6** and **7**.



Employing a similar DCC-mediated coupling,[3] compounds **8**-**16** were prepared from Meldrum's acid derivatives (Scheme 2).

Scheme 2. Synthesis of dioxinones.



8, $R_1 = R_2 = CH_3$, $R_3 = (CH_2)_{14}CH_3$, 79%
9, $R_1 = R_2 = CH_3$, $R_3 = (CH_2)_{16}CH_3$, 85%
10, $R_1 = R_2 = CH_3$, $R_3 = (CH_2)_8CH_3$, 65%
11, $R_1 = R_2 = CH_3$, $R_3 = CH(CH_3)_2$, 40%
12, $R_1 = R_2 = CH_3$, $R_3 = (CH_2)_2CH_3$, 55%
13, $R_1 = R_2 = CH_3$, $R_3 = CH_3$, 69%
14, $R_1 = CH_3$, $R_2 = CH_2CH_3$, $R_3 = (CH_2)_{14}CH_3$, 53%
15, $R_1 = R_2 = CH_2CH_3$, $R_3 = (CH_2)_{14}CH_3$, 60%
16, $R_1 = R_2 = CH_2CH_2$, $R_3 = (CH_2)_{14}CH_3$, 38%

The screening of their PTP inhibitory activity and comparison with racemic RK-682 (*rac*-**1**) has shown that the six-membered compounds **6** and **7** were inactive in the LMW-PTP inhibition assays, displayed reduced PTP-1B inhibitory activity but kept similar activity against CDC-25B. In contrast, dioxinanes **8** and **9** showed potent inhibitory activity for the three phosphatases analyzed (Table 1).

Table 1. Inhibition of LMW-PTP, CDC-25B and PTP-1B

	IC_{50} (μM)		
	LMW-PTP	**CDC-25B**	**PTP-1B**
rac-**1**	8.62 ± 2.98	12.43 ± 1.83	0.51 ± 0.01
6	> 100	3.45 ± 4.04	5.63 ± 0.76
7	> 100	13.63 ± 3.73	15.58 ± 0.23
8	20.02 ± 2.62	13.65 ± 2.34	1.08 ± 0.00
9	5.31 ± 0.35	6.50 ± 0.23	0.56 ± 0.11

CONCLUSION

Compounds **6** and **7** displayed greater selectivity to PTP-1B and CDC-25B than racemic RK-682. Dioxinones **8** and **9** have shown similar PTPase inhibitory activity as the natural compound RK-682.

ACKNOWLEDGEMENTS

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