EVALUATION OF SOME SALICYALDEHYDE-DERIVED BAYLIS- HILLMAN ADDUCTS AND COUMARIN DERIVATIVES AS POTENTIAL ANTISICKLING COMPOUNDS

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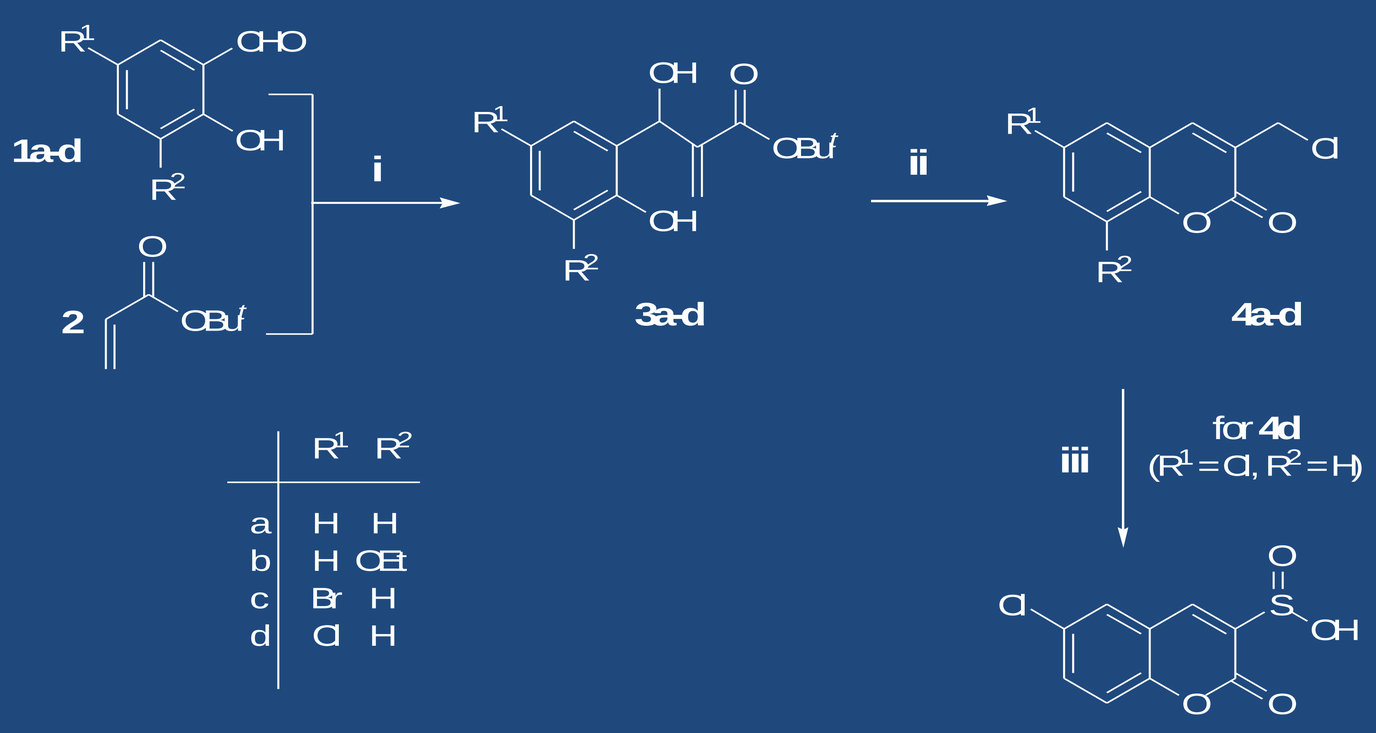
Sickle Cell Disease (SCD) is one of the most common genetic disorders caused by point mutation that changes glutamic acid (Glu6) to Valine (Val6) in the β-chain of haemoglobin. This structural modification leads to abnormal haemoglobin (HbS). Under low oxygen tension, HbSS polymerizes, distorting the biconcave-shaped red blood cells into sickled shape and less flexible thereby causing many clinical features that HbSS carriers suffer. In recent times, haematopoietic stem cell transplant (HSCT) appears to be the only curative treatment for sickle cell disease available today. However, lack of suitably matched donors, cost and the chronic use of immunosuppressive drugs with serious side effects have limited the use of HSCT for the treatment of SCD. Hence, there is need to continue the search for potent drugs that can be used to manage this disorder.

Simple Morita-Baylis Hillman adducts have become an important class of bioactive compounds with diverse biological activities such as anticancer, antimalarial, molluscidal activities[1, 2]. Coumarins form an important pharmacophore in Medicinal Chemistry and they have been reported to exhibit a variety of biological activities usually associated with low toxicity. Coumarins possess pharmacological activities such as anti-HIV anticoagulant, antibacterial, antioxidant, antimalarial, calcium channel blocking activities [3,4]. In continuation of our interest in exploring the biological applications of coumarins [5,6,7]. we herein report the antisickling potentials of some salicyaldehyde derived Baylis-Hillman adducts and 3-substituted coumarins.

In this study, various Baylis Hillman adducts were synthesized and then cyclized to 3-chloromethylcoumarins using acid catalysis (Scheme 1). Also, in an attempt to synthesize a hydroxyurea analogue, 6-chloro-3-(chloromethyl)coumarin (**4d**) was treated with thiourea in the hope of obtaining a nucleophilic substitution product but rather spectroscopic evidence suggests the formation of *chlor ocoumarin-3-sulfinic acid* **5d.** The synthesized compounds were screened for inhibitory and reversal antisickling activities on HbSS red blood cells using the modified Sofowora method [8]. The compounds showed progressive inhibition against sodium metabisulphite induced sickling from 0.5 mg/mL to 4 mg/mL and their activities were comparable with the standard drugs vanillic acid and *para*-hydroxybenzoic acid (Figures 1 and 2).



Scheme 1.
Reagents and conditions: i) DABCO, $CHCl_3$, r.t.; ii) HCl, AcOH, reflux; iii) Thiourea, EtOH/H_2O (1:1), r.t.

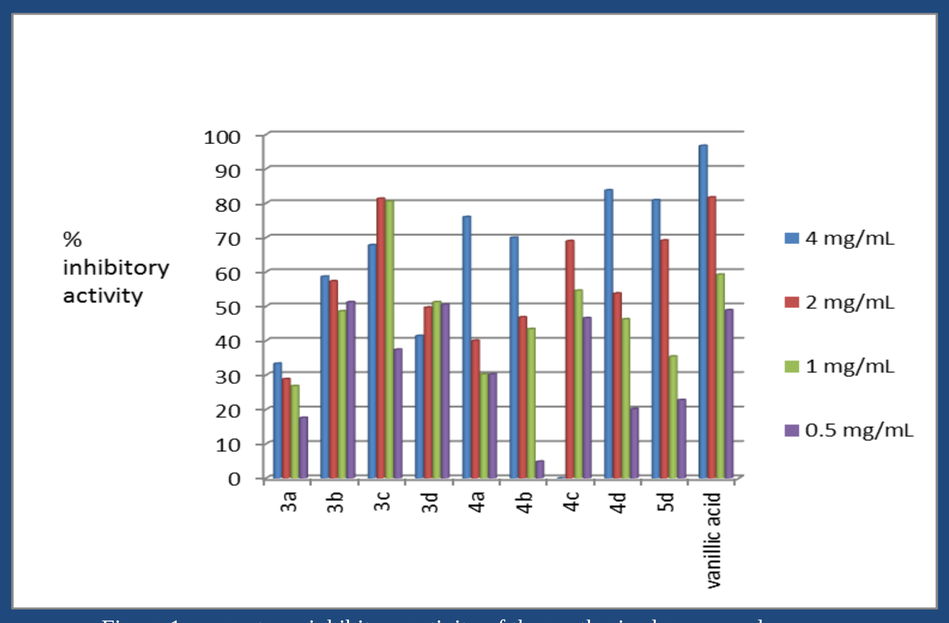


Figure 1: percentage inhibitory activity of the synthesized compounds and the standard drug Vanillic acid on HbSS red blood cells.

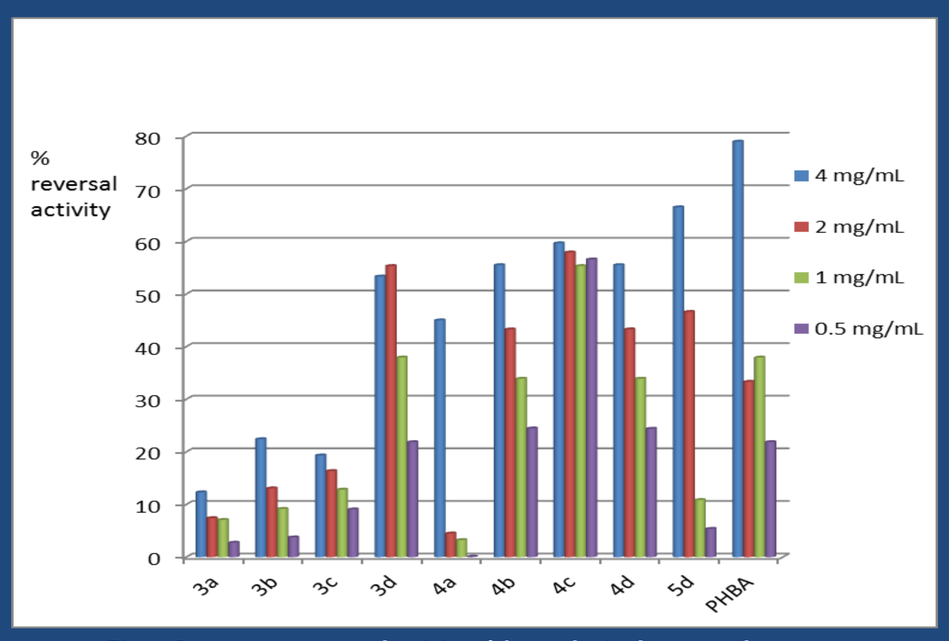


Figure 2: percentage reversal activity of the synthesized compounds and the standard drug p-hydroxybenzoic acid (PHBA) on HbSS red blood cells.

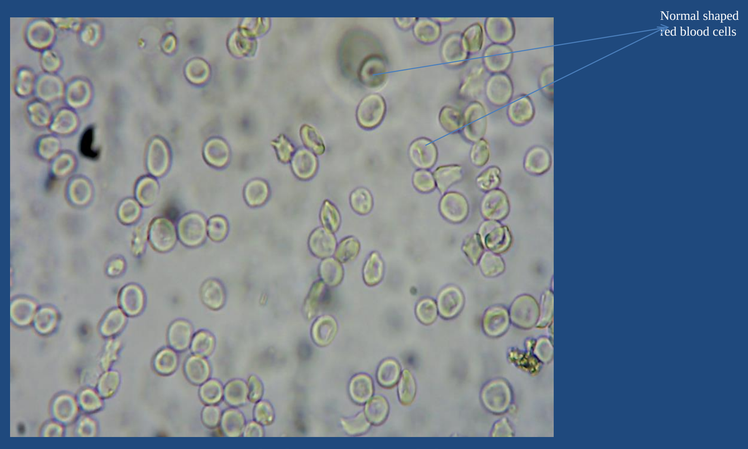


Figure 3: Micrograph showing the inhibitory activity of compound **4d** at 4 mg/mL (× 400 magnification)

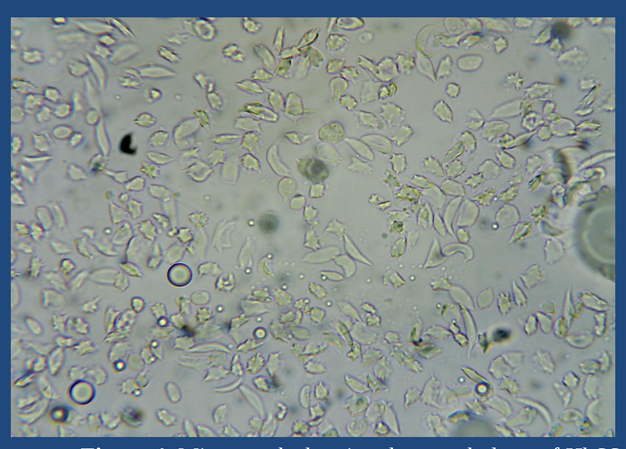


Figure 4: Micrograph showing the morphology of HbSS blood cells treated with phosphate buffered saline as negative control (× 400 magnification)

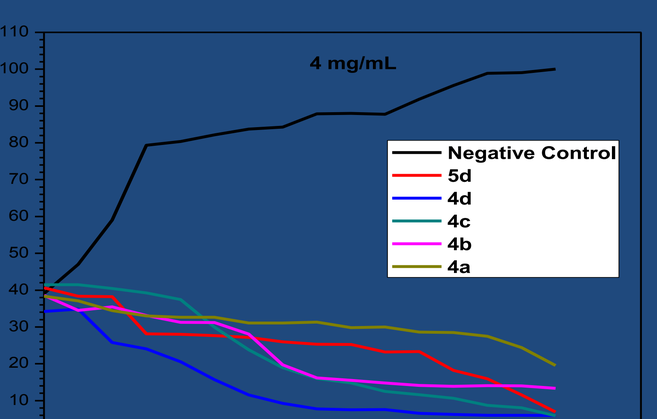


Figure 7: Rate of HbSS polymerization in the presence of 4 mg/mL of test compounds

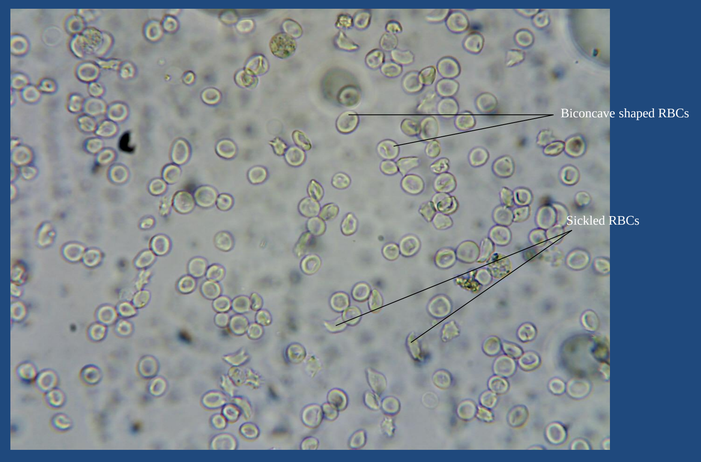


Figure 5: Micrograph showing the reversal activity of compound **5d** at 4 mg/mL, (x 400 magnification)

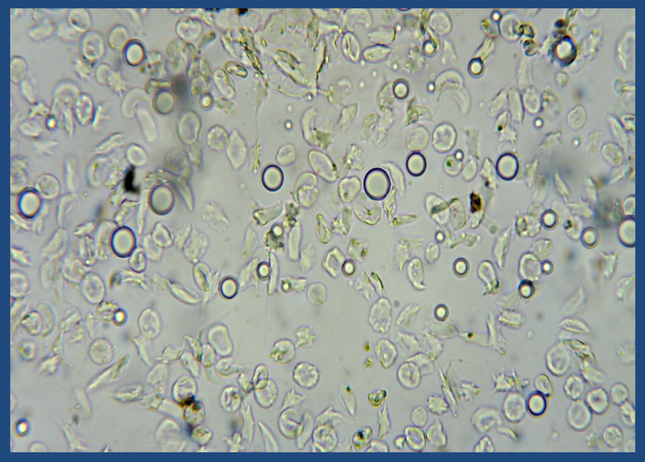


Figure 6: Untreated control (Negative control) (x 400 magnification)

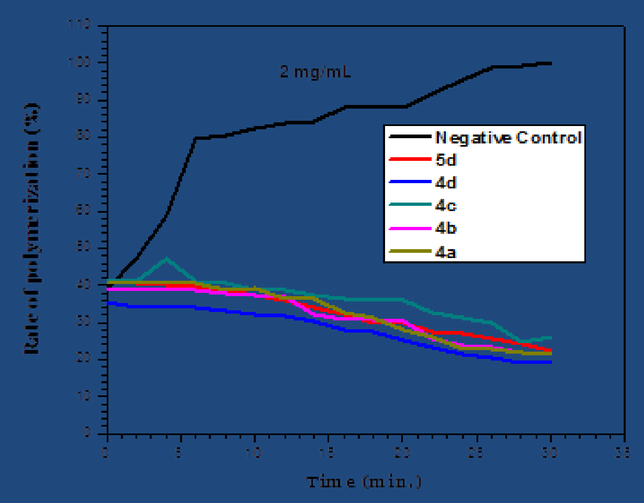


Figure 8: Rate of HbSS polymerization in the presence of 2 mg/mL of test compounds

Acknowledgements

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