Star- and comb-shaped betulin-based polyanhydrides with anticancer activity—synthesis and characterization

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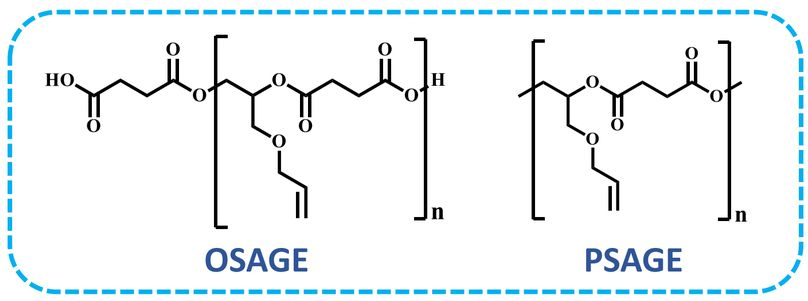
Introduction & Aim

Polyanhydrides based on betulin are promising materials for use in controlled drug delivery systems. Due to the broad biological activity of betulin derivatives and lack of toxicity in vitro and in vivo, these polymers can be used both as polymeric prodrug and as carriers of other biologically active compounds. Branched polymers offer significantly different physical properties from linear polymers and can provide several advantages for drug delivery application. **The aim of this work was to obtain betulin based highly branched polyanhydrides with star or comb-shaped architecture.**

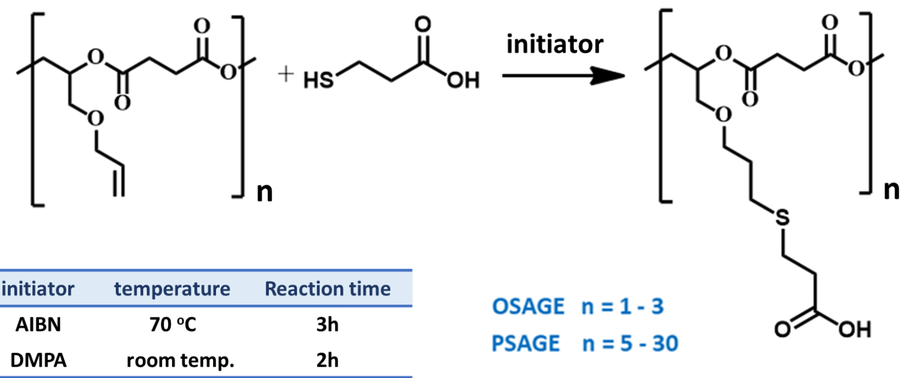
Branching agent synthesis

Branched polyanhydrides were obtained using modified succinic acid derivatives (OSAGE and PSAGE) as branching agents.



Chemical structure of OSAGE and PSAGE

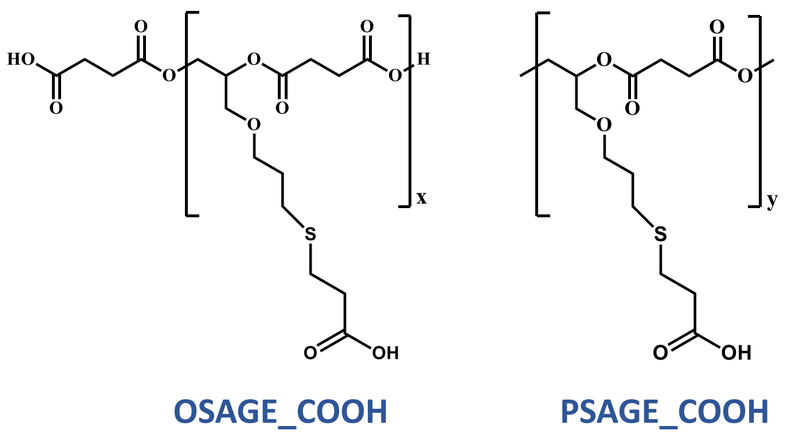
Allyl groups in OSAGE and PSAGE were converted to carboxyl ones using 3-mercaptopropionic acid in thiol-ene reaction.



initiator	temperature	Reaction time
AIBN	70 °C	3h
DMPA	room temp.	2h

Scheme of succinic acid derivatives modification

The modifications were intended to introduce additional carboxyl groups to the OSAGE and PSAGE molecules



Chemical structure of modified succinic acid derivatives

Conclusions

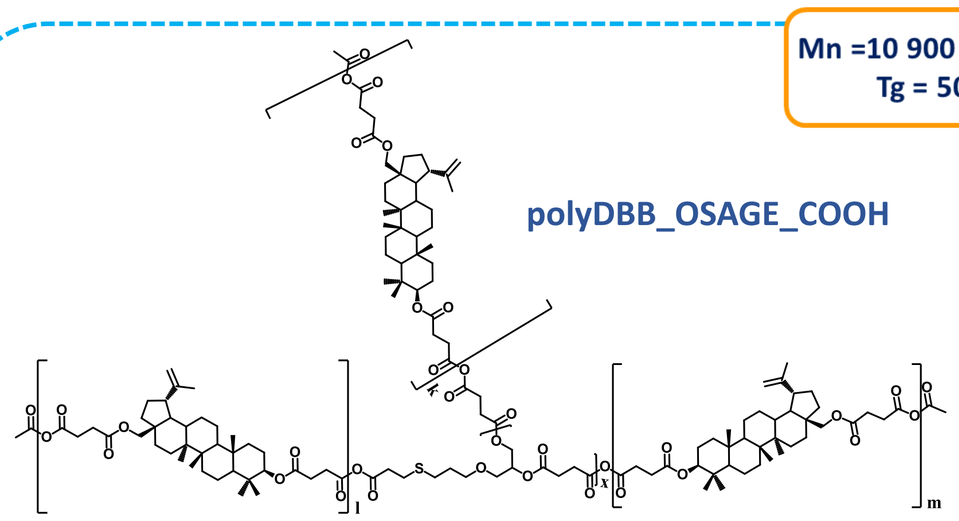
- New branched polyanhydrides based on DBB were synthesized.
- Succinic acid derivatives modified with 3-mercaptopropionic acid was used as the branching agent.
- The described polymers have been shown to be effective in inhibiting the growth of tumor cells, with no cytotoxicity to normal cells.
- Betulin-based branched polyanhydrides can be used in the pharmaceutical industry, as matrices for controlled drug delivery systems

Branched polyanhydrides synthesis

Highly branched polyanhydrides with different DBB contents and different architectures were obtained through the two-step melt polycondensation of DBB and polycarboxylic derivatives of succinic acid oligomers (OSAGE-COOH and PSAGE-COOH). The content of DBB in the polymers ranged from 70 to 95 wt %.

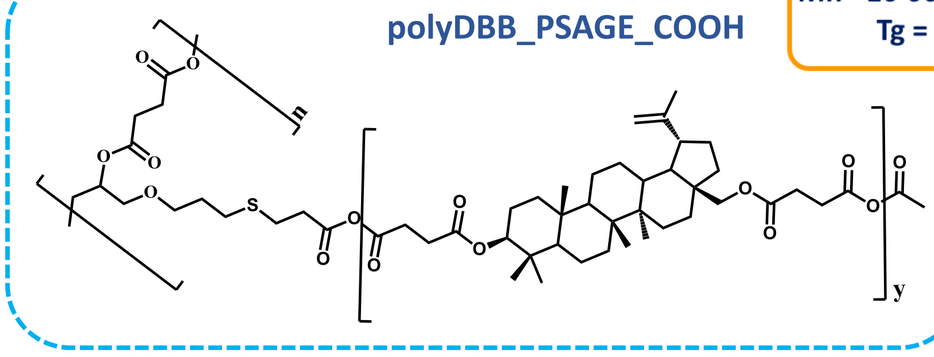
Mn =10 900 – 15 600 g/mol
Tg = 50 – 168 °C

polyDBB_OSAGE_COOH

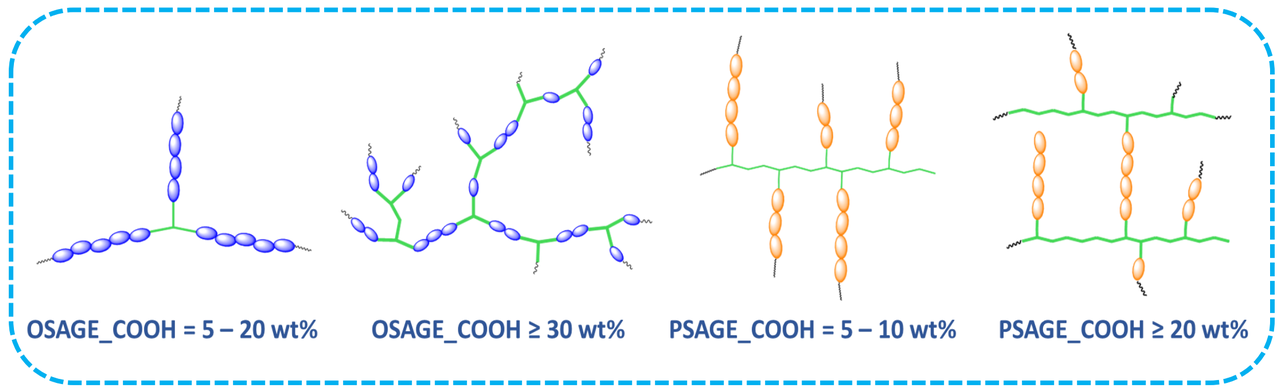


Mn =10 000 – 17 800 g/mol
Tg = 58 – 143 °C

polyDBB_PSAGE_COOH



Structures of branched polyanhydrides



Hypothetical structures of branched polyanhydrides based on DBB : comonomer ratio calculated from ^{1}H NMR spectra.

Characteristic of branched polyanhydrides.

Polyanhydride	Comonomer content [wt%]	Number of DBB molecules per 1 comonomer molecule in copolymers (^{1}H NMR)
polyDBB_OSAGE_COOH	5	16
	10	13
	20	3
	30	1.6
polyDBB_PSAGE_COOH	5	25
	10	21
	20	17

Cytostatic activity of polyanhydrides

Polyanhydride	HeLa	U-87	KB	MCF	A549	HDF
polyDBB_PSAGE_10	2.51	2.36	2.07	2.84	2.26	5.13
polyDBB_PSAGE_5	5.22	5.93	5.19	5.83	5.62	14.88
polyDBB_OSAGE_10	7.03	7.84	7.81	7.11	7.37	16.04
polyDBB_OSAGE_5	6.91	6.03	6.72	6.18	6.04	12.36

The cytotoxic activity of test compounds against different types of tumor cells, expressed as IC_{50}

The results of cytotoxicity studies of polymers indicate their efficacy in inhibiting the growth of tumor cells, with no cytotoxicity to normal cells.