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Development of chiral stationary phases based on small molecules and polymeric derivatives for enantioseparation of chiral drugs

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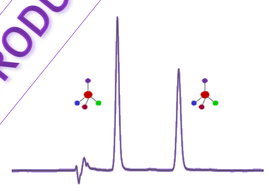
INTRODUCTION

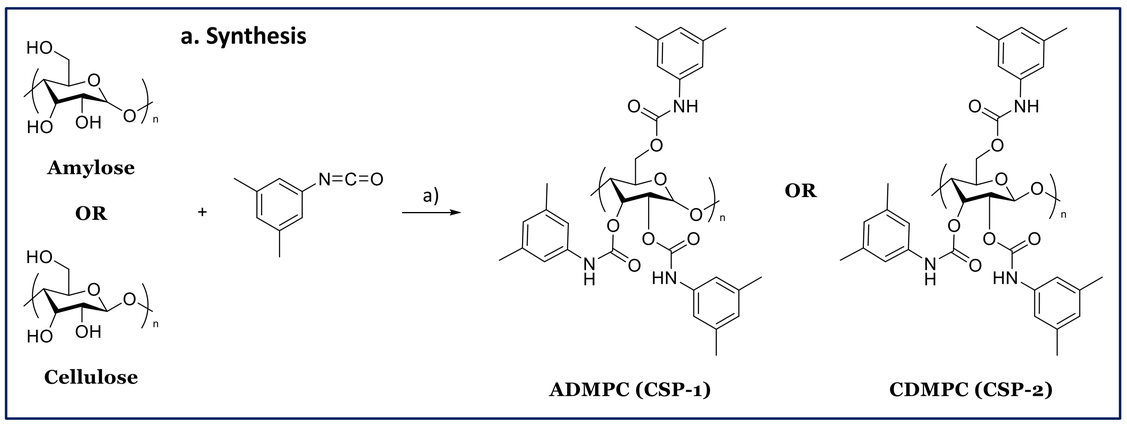


The improvement of effective methodologies to obtain both enantiomers with high enantiomeric purity is a very important task, especially in early stages of drug development. The development of chiral stationary phases (CSPs) for liquid chromatography (LC) brought a new breath to enantioseparation processes, proving to be the most helpful among the current methods to achieve chiral separations and to measure enantiomeric purity [1]. Polysaccharide-based [2,3] and small molecules-based [4,5] CSPs are widely used, both for analytical and preparative applications, being able to resolve several classes of racemates.
In this work, the preparation of three CSPs is reported and the best results of the LC evaluation are presented.

RESULTS AND DISCUSSION

1. Polysaccharide-based CSPs preparation (CSPs-1 and -2)

a. Synthesis

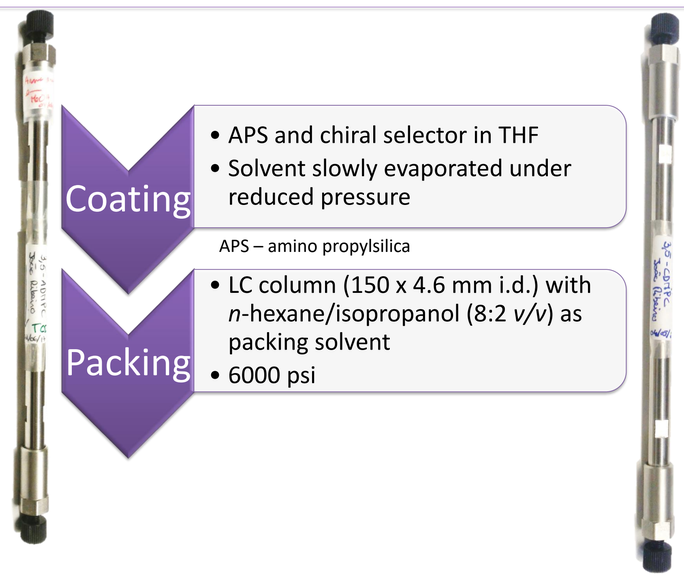


a) Dry pyridine, reflux, 76 h **η= 85% (ADMPC)** and **η= 93% (CDMPC)**

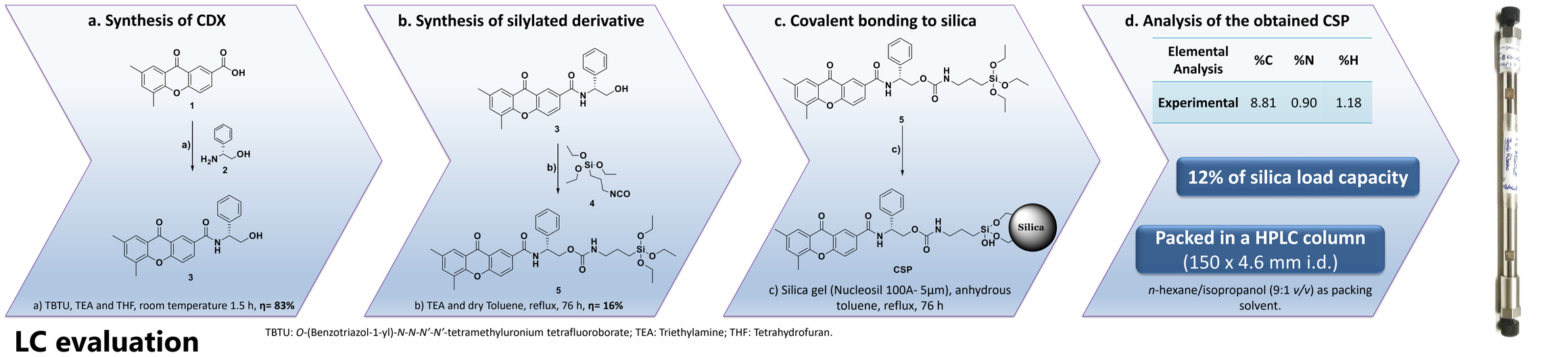
b. Analysis

IR Bond	υ (cm^{-1})	
	ADMPC	CDPMC
O-H	absent	absent
N-H (carbamate)	3292	3296
C=O (carbamate)	1713	1732
C=C (carbamate)	1614	1615

Elemental Analysis	%C	%N	%H
Theoretical	62.37	6.20	6.25
Experimental (ADMPC)	62.32	6.18	6.19
Experimental (CDMPC)	65.04	6.95	6.34



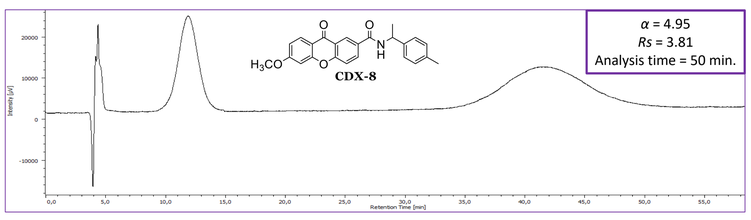
2. Small molecule CSP preparation (CSP-3)



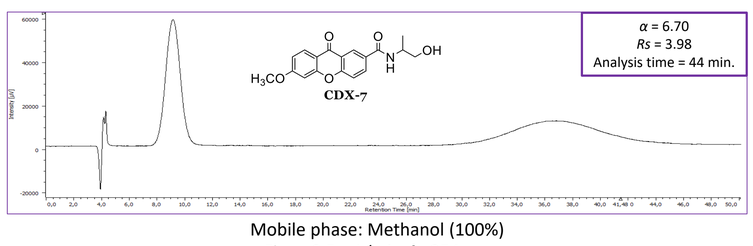
TBTU: *O*-(Benzotriazol-1-yl)-*N*-*N*-*N'*-*N'*-tetramethyluronium tetrafluoroborate; TEA: Triethylamine; THF: Tetrahydrofuran.

3. LC evaluation

a. Best chromatograms for CSP-1

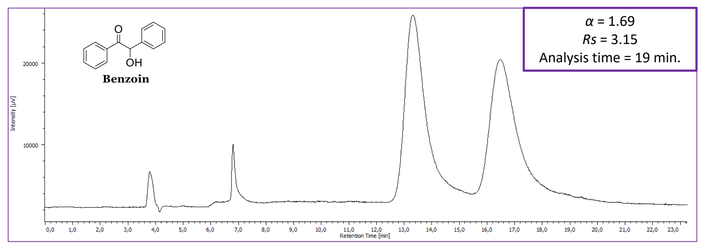


Mobile phase: Methanol (100%)
Flow rate: 0.5 mL/min; Detection: 254 nm

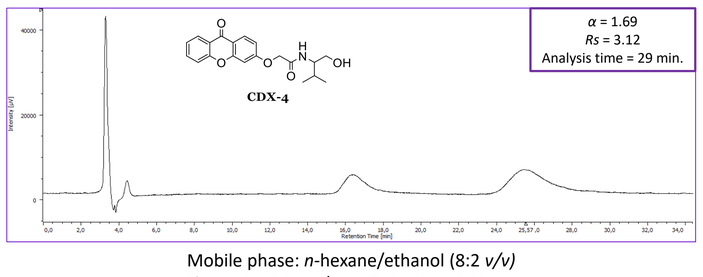


Mobile phase: Methanol (100%)
Flow: 0.5 mL/min; λ=254 nm

b. Best chromatograms for CSP-2

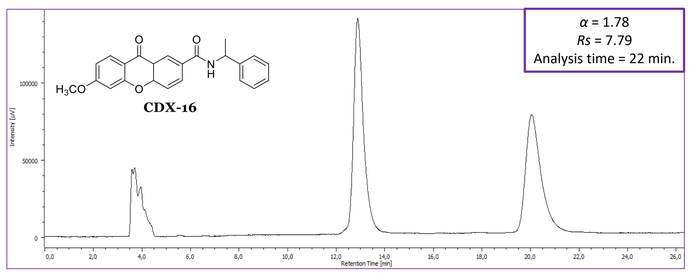


Mobile phase: *n*-hexane/2-propanol (9:1 *v/v*)
Flow rate: 0.5 mL/min; Detection: 254 nm

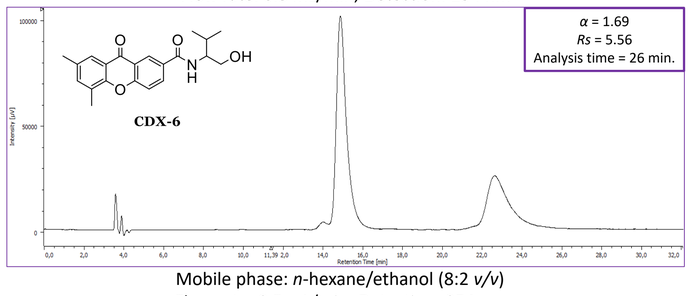


Mobile phase: *n*-hexane/ethanol (8:2 *v/v)*
Flow rate: 0.5 mL/min; Detection: 254 nm

c. Best chromatograms for CSP-3



Mobile phase: *n*-hexane/ethanol (8:2 *v/v*)
Flow rate: 0.5 mL/min; Detection: 254 nm



Mobile phase: *n*-hexane/ethanol (8:2 *v/v*)
Flow rate: 0.5 mL/min; Detection: 254 nm

CONCLUSIONS

The CSPs demonstrated good enantiorecognition abilities for different commercially available racemates as well as for several CDXs synthesized "in house". Moreover, the obtained results show that these CSPs were efficiently and well packed. The two polysaccharide-based CSPs prepared showed similar enantiorecognition abilities to those from literature.
In future work it is of interest the development of other CSPs based on small molecules and on polysaccharide derivatives with different substitution patterns.

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