# Carbonate Esters as Green Alternatives in Chromatographic Separations

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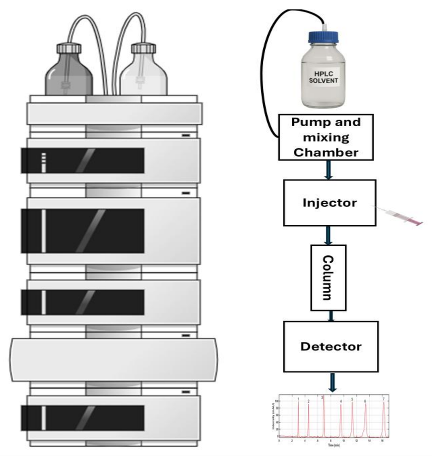
## Introduction

**High-performance liquid chromatography (HPLC)** is a powerful technique used to separate different drug molecules from a mixture, which is critical for drug discovery and impurity analysis. Reversed-phase liquid chromatography (RPLC) and mixed-mode chromatography (MMC) are widely used chromatographic methods in pharmaceutical industries and analytical chemistry research labs. Normal-phase liquid chromatography (NPLC) and polar organic liquid chromatography (POLC) are also employed for the separation of some polar drugs and chiral compounds. RPLC, POLC, and MMC typically require large volumes of acetonitrile (ACN), while NPLC largely depends on hexane. However, both solvents are toxic to humans and pose significant environmental risks. As a result, considerable efforts are being made to develop greener alternatives for chromatographic separations. The aim of our study is to identify environmentally friendly substitutes for the toxic solvents ACN and hexane. This research explores unconventional carbonate ester solvents—specifically dimethyl carbonate (DMC), diethyl carbonate (DEC), and propylene carbonate (PPC)—as potential green alternatives. Our findings suggest that in MMC, POLC, and RPLC, up to 50% of ACN can be replaced with PPC, and up to 60% with DMC, without compromising chromatographic performance. This substitution reduces toxicity and environmental impact, promoting greener and safer practices in both analytical and preparative separations.

**Basic HPLC Parts (Block Diagram)**

- **Solvent Bottle**: Holds the liquid that carries the sample.
- **Pump**: Pushes the liquid through the system.
- **Injector**: Where the sample is added.
- **Column**: Separates the sample into parts.
- **Detector**: Senses and shows the results.
- **Computer**: Displays a graph of what's in the sample.
- **Waste**: Collects used liquid.




## Demand and Toxicity of Solvents

**Acetonitrile**

- ACN can affect the **liver, kidneys, and central nervous system**
- Market size volume in 2022: 180 thousand tonnes
- Expected market size volume by 2032: 270 thousand tonnes (compound annual growth rate of 4.08%)

**Hexane**

- Hexane is **neurotoxic**
- Market size volume in 2022: 1300,000 tonnes
- Expected market size volume by 2032: 1800 thousand tonnes (compound annual growth rate of 3.24%)

https://www.chemanalyst.com/industry-report/acetonitrile-market-721

## Carbonate Esters as Green Alternatives

| Parameters | Acetonitrile | Hexane | PPC | DMC | DEC |
|---|---|---|---|---|---|
| Price (LC Grade, 4L) | \$327 | \$416.37 | \$260.92 | \$255.02 | \$176.36 |
| Viscosity (mPa.s) At 20 °C | 0.35m | 0.314m | 2.8 | 0.664 | 0.827 |
| Boiling point at 760 mm Hg (°C) | 81.6 | 68.70 | 241.6 | 90-91 | 126 |
| Solubility in Water (mg/L) | $8\times10^5$ | 9.5 | $1.75\times10^5$ | $1.39\times10^5$ | $1.88\times10^4$ |
| UV Cut Off (nm) | 190 | 195 | 219.5 | 217 | 215.7 |
| Polarity on $E_T$ (30) scale (Kcal/mol) | 45.6 | 42.7 | 46.2 | 38.5 | 42.8 |
| Dielectric Constant at 25°C | 38.5 | 2.0 | 64.9 | 3.2 | 3.1 |
| Flash Point (°C) | 6.0 | -22.0 | 116.0 | 18.0 | 25.0 |
| Relative Hazard/Toxicity on ChlorTox Scale | 0.45 | 1.1 | 0.13 | 0.13 | 0.09 |

https://pubchem.ncbi.nlm.nih.gov

## UV Cut-Off and Solvent Polarity

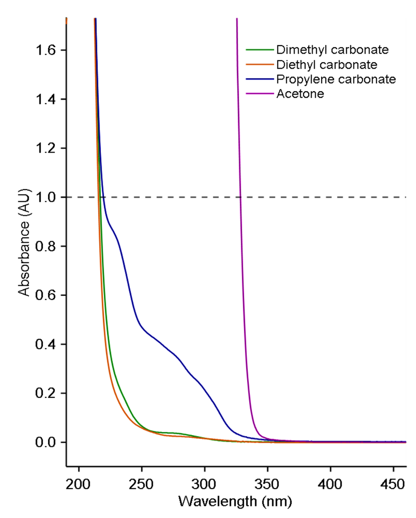
**Solvent cutoff & polarity study is essential to:**

- Ensure solvent doesn't interfere with UV detection (low UV cutoff).
- Select solvents with the right polarity to optimize separation and peak shape.

**Cut-off:** The wavelength at which the solvent absorbance in a 1 cm path length cell is equal to 1 using water in the reference cell.

UV cutoff of the carbonate ester solvents:

| DEC | DMC | PPC | ACN | Acetone |
|---|---|---|---|---|
| 215.7 nm | 217 nm | 219.5 nm | 190 nm | 328.5 nm |




## Solvatochromism

**What is solvatochromism?**

- The ability of a molecule to change its absorption or emission color based on solvent polarity.
- Used to study solvent-solute interactions and molecular environments.

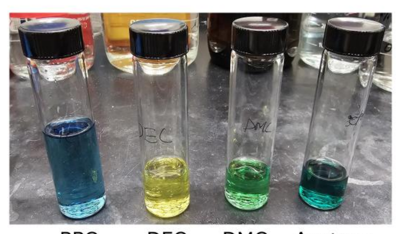
## Reichardt's Dye & $E_T$(30) calculation

**Reichardt's Dye (Betaine 30)**

- A solvatochromic betaine dye that shows "negative solvatochromism" (blue shift)
- Discovered by Christian Reichardt, a German chemist during his doctoral work under Karl Dimroth.
- Ideal for quantifying solvent polarity using "molecular electronic transition energy", $E_T$(30)
- **Advantages:** Wide solvatochromic range, strong absorption, stable in various solvents.

**List of Solvents in $E_T$(30) Scale:**


https://en.wikipedia.org/wiki/Reichardt%27s_dye



PPC DEC DMC Acetone

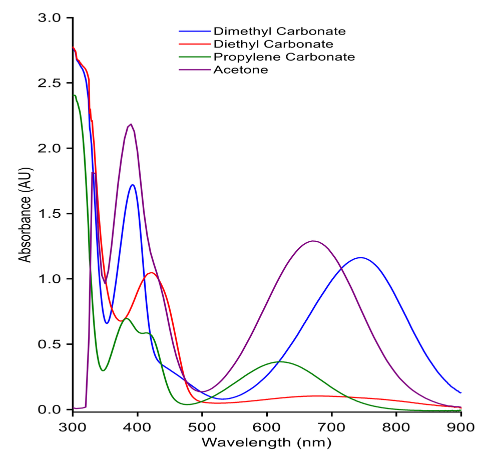
How to Calculate $E_T$(30):

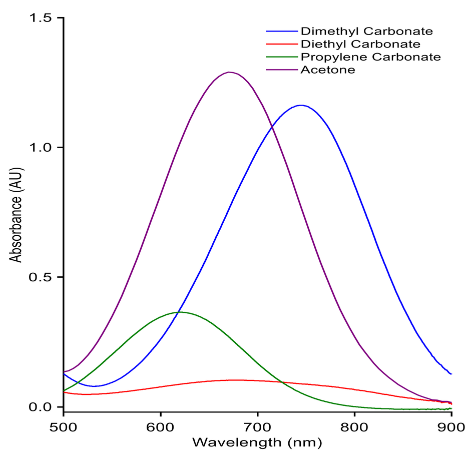
- $E_T(30) = h.c.N_A / \lambda max = 28591 / \lambda max$ (in kcal/mol)

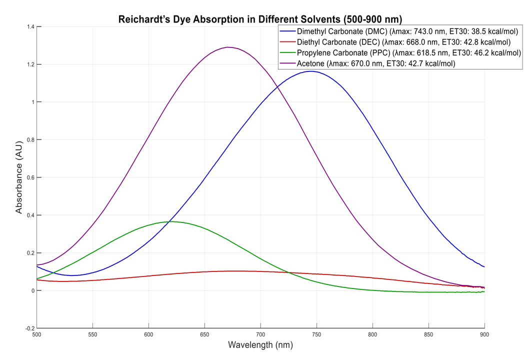
Where,
$\lambda max$ = Maximum absorption wavelength (nm) from UV-Vis spectrum
h= Planck's constant
c= speed of light
$N_A$ = Avogadro's constant

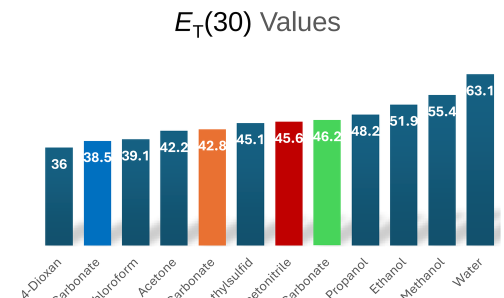
Reichardt, C. Solvatochromic Dyes as Solvent Polarity Indicators. *Chemical Reviews* **1994**, *94* (8), 2319–2358. https://doi.org/10.1021/cr00032a005.

## $E_T$(30) Values of Solvents

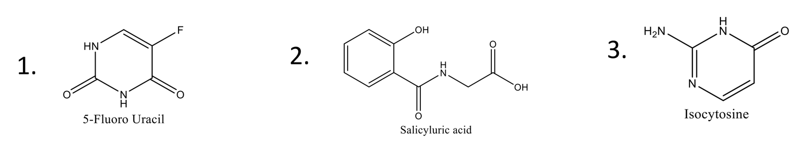



## Stability of Solvents in Mixed-Mode Chromatography




**Method Conditions**

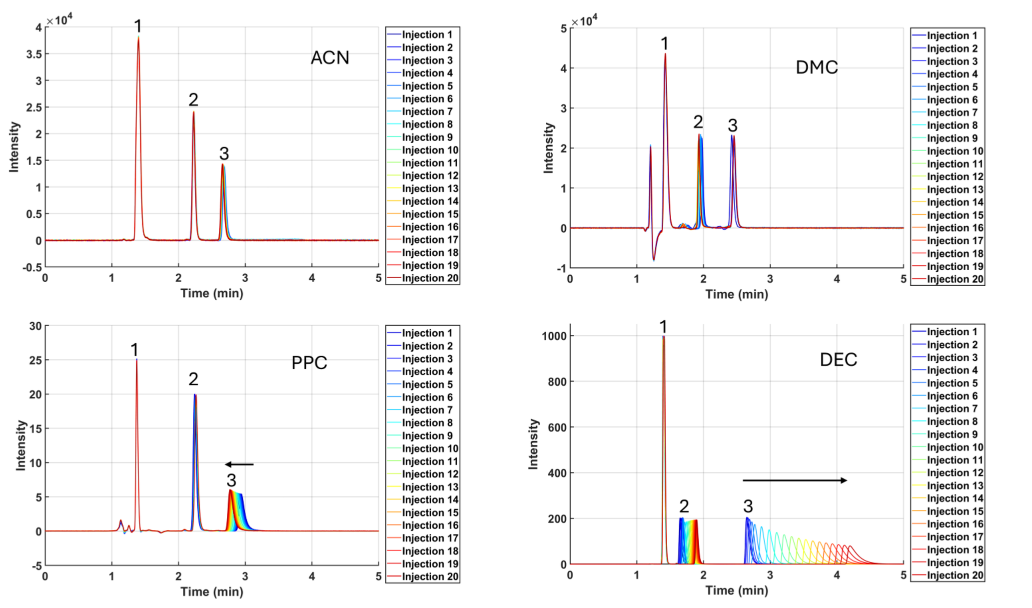
**Column:** Silica (100×4.6 mm, 2.7 µm)

**Mobile Phase:** 20 mM tetrabutylammonium perchlorate in X% DEC: (85-X)% ACN: 15% Water

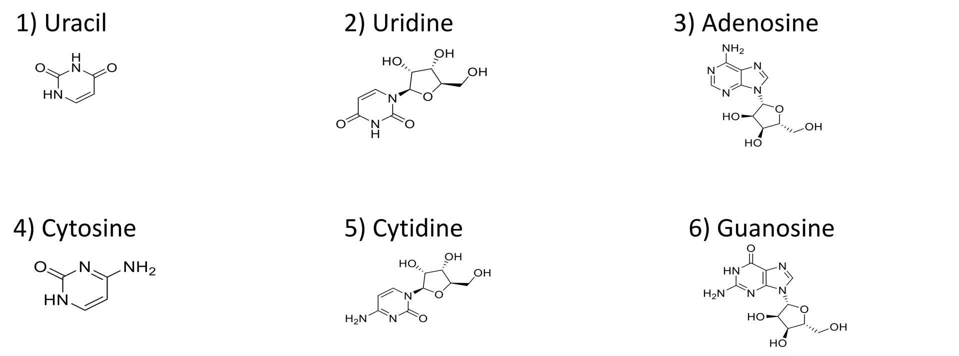
**Flow Rate:** 0.4 mL/min

**Temperature:** 25°C

**UV:** 256 nm




## Concentration Study-Nucleosides and Nitrogenous Bases Separation in Mixed-Mode Chromatography




**Method Conditions**

**Column:** FructoShell-N (150×4.6 mm, 2.7 µm)

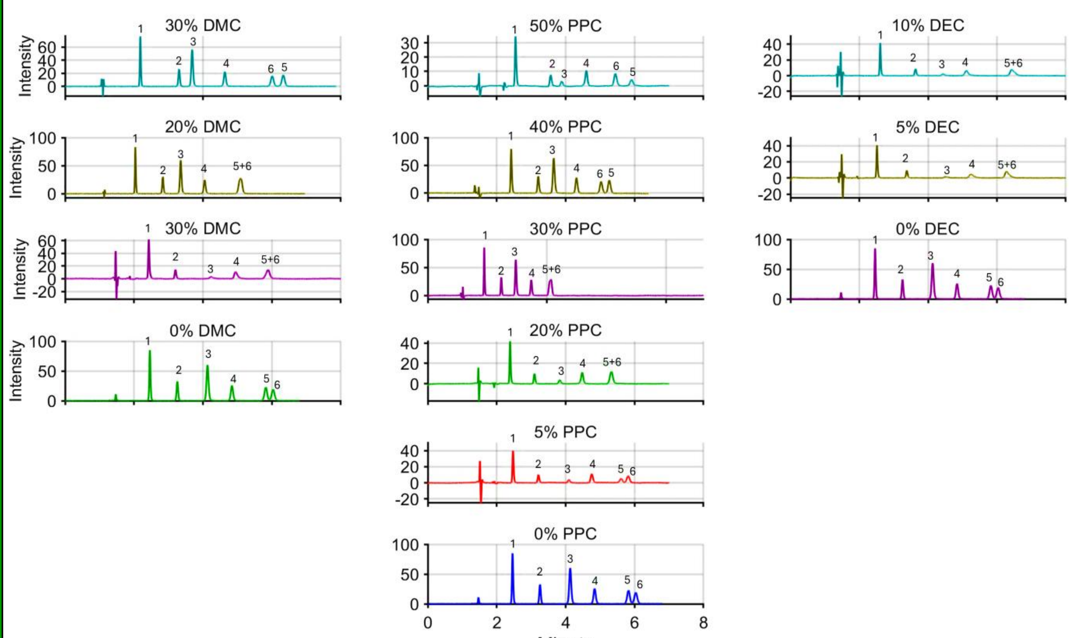
**Mobile Phase:** 20 mM tetrabutylammonium perchlorate in X% Green Solvent: (85-X)% ACN: 15% Water

**Flow Rate:** 1.0 mL/min

**Temperature:** Ambient

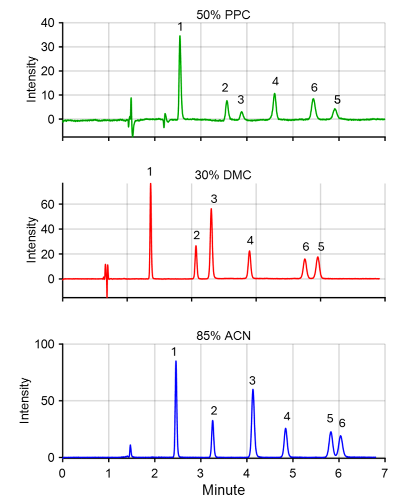
**UV:** 256 nm

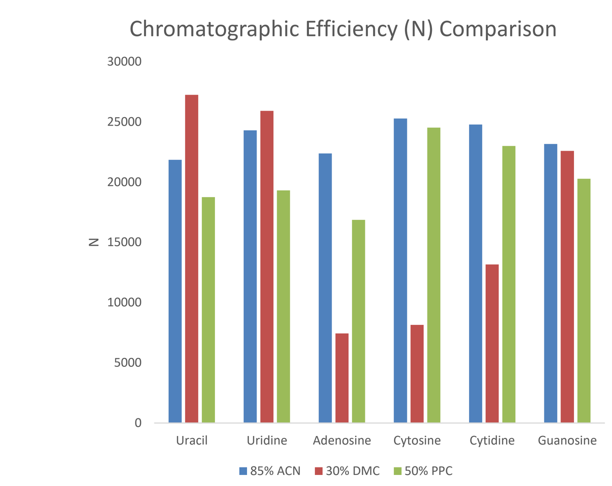
### Comparison of PPC, DMC, and DEC



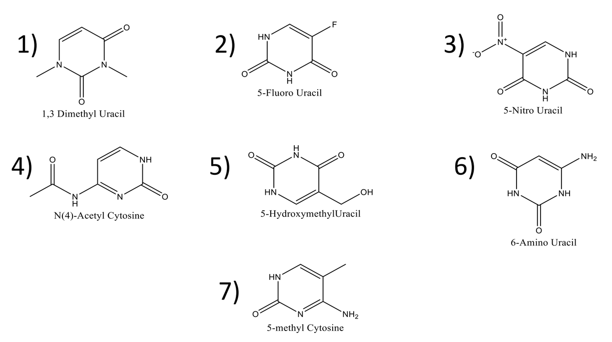

## Nucleosides and Bases Separation Comparison in 50% PPC, 30% DMC, and 85% ACN

**Efficiency:** Chromatographic efficiency is a measure of how well a column separates analytes, typically expressed as the number of theoretical plates (N).




## Functionalized Nucleosides and Bases Separation in Mixed-Mode Chromatography




**Method Conditions**

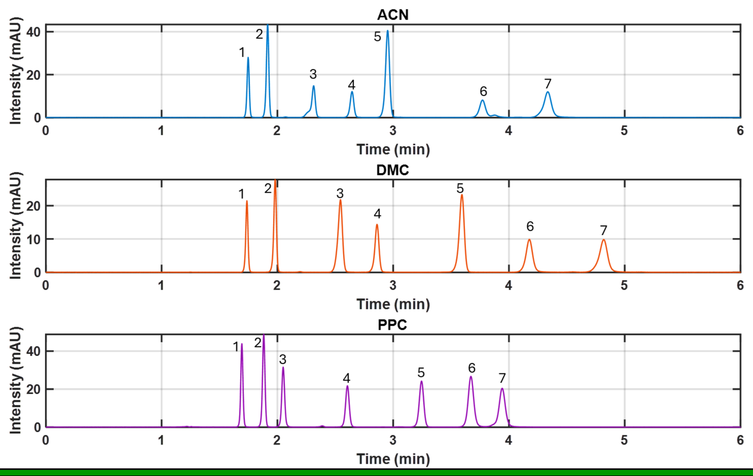
**Column:** FructoShell-N (150×4.6 mm, 2.7 µm)

**Mobile Phase:** 20 mM tetrabutylammonium perchlorate in X% Green Solvent: (85-X)% ACN: 15% Water

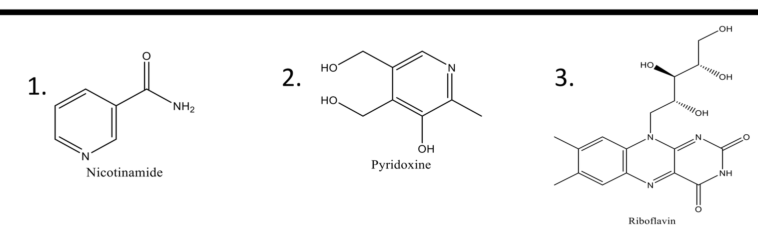
**Flow Rate:** 1.0 mL/min

**Temperature:** Ambient

**UV:** 256 nm




## Vitamins Separation in Mixed-Mode Chromatography




**Method Conditions**

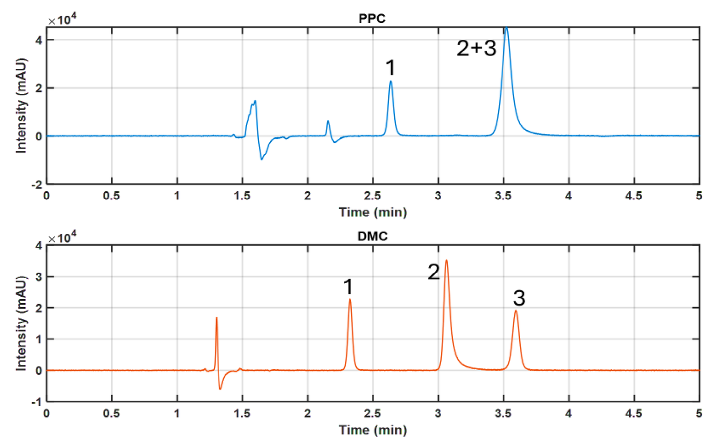
**Column:** FructoShell-N (150×4.6 mm, 2.7 µm)

**Mobile Phase:** 20 mM tetrabutylammonium perchlorate in X% Green Solvent: (85-X)% ACN: 15% Water

**Flow Rate:** 1.0 mL/min (for DMC) and 0.8 mL/min (for PPC)

**Temperature:** 25°C

**UV:** 256 nm




## Chiral Separation in Normal-Phase Liquid Chromatography

**Method Conditions**

**Column:** Whelko (150×4.6 mm, 2.7 µm)

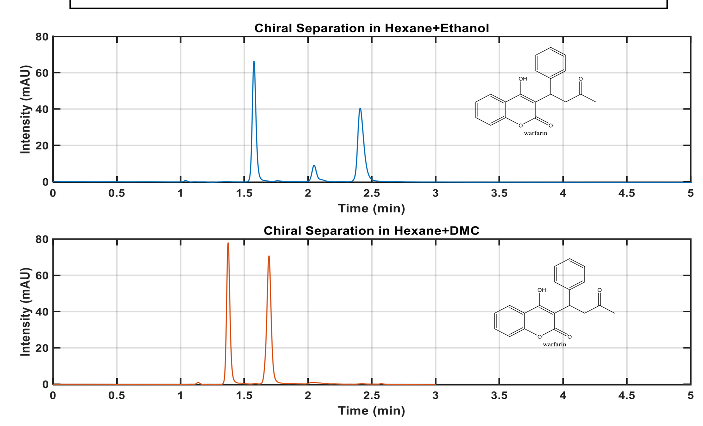
**Mobile Phase 1:** 80% Hexane:20 Ethanol

**Mobile Phase 2:** 80% Hexane:20 DMC

**Flow Rate:** 1.0 mL/min

**Temperature:** 25°C

**UV:** 256 nm




## Chiral Separation in Polar Organic Liquid Chromatography

**Method Conditions**

**Column:** Whelko (150×4.6 mm, 2.7 µm)

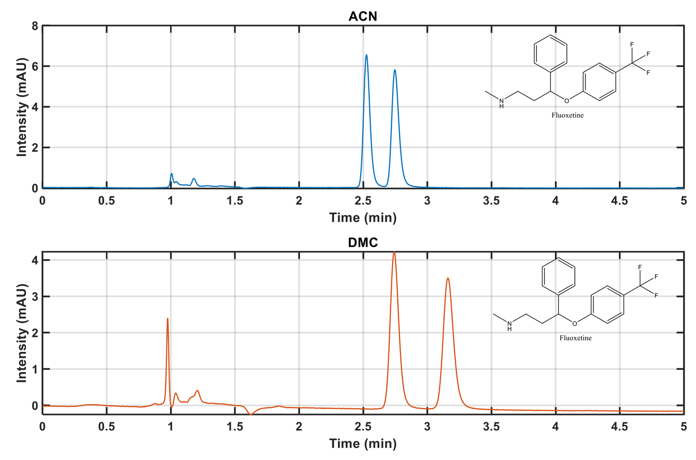
**Mobile Phase 1:** 60/40/0.3/0.2 ACN/Methanol/Acetic acid/Triethylamine

**Mobile Phase 2:** 60/40/0.3/0.2, DMC/ Methanol/Acetic acid/Triethylamine

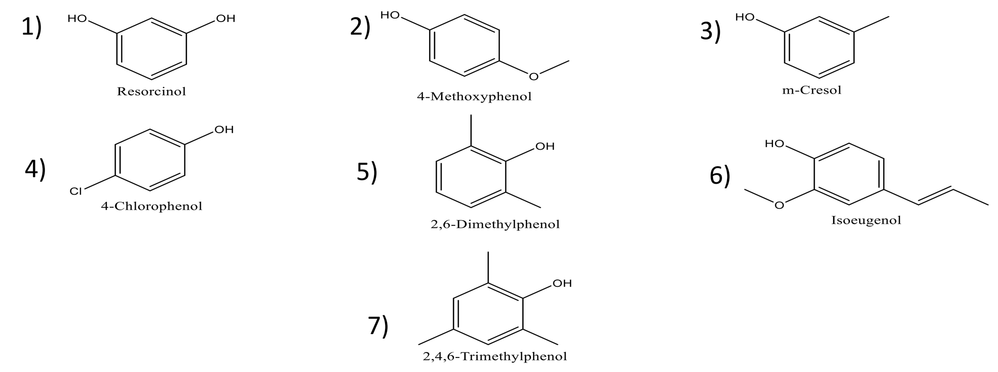
**Flow Rate:** 1.0 mL/min

**Temperature:** 25°C

**UV:** 256 nm




## Functionalized Phenols Separation in Reversed-Phase Liquid Chromatography




**Method Conditions**

**Column:** C18 (150×4.6 mm, 5 µm)

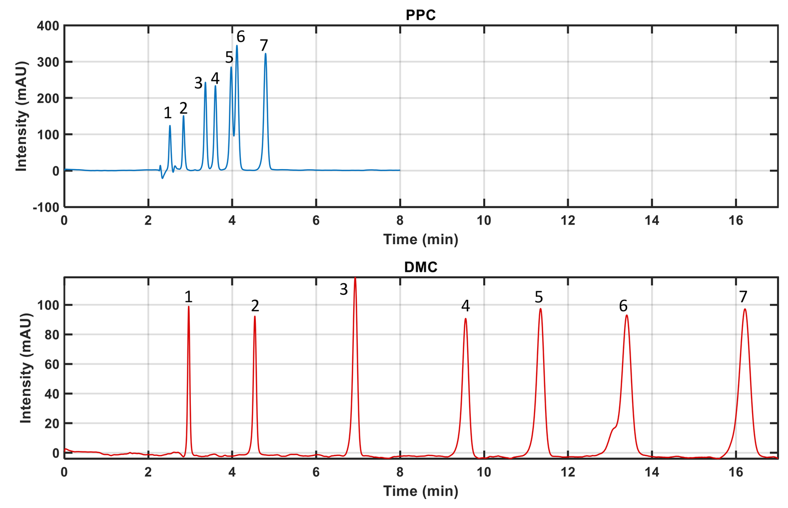
**Mobile Phase 1:** 30% PPC, 50% Methanol, and 20% Water

**Mobile Phase 2:** 20% PPC, 30% Methanol, and 50% Water

**Flow Rate:** 1.0 mL/min

**Temperature:** 25°C

**UV:** 256 nm




## Conclusions

- Pharmaceutical research and development, analytical chemistry research labs, and other research institutions use large volumes of acetonitrile, hexane, and other toxic solvents in separation processes.
- These solvents harm human health and disrupt the ecosystem, highlighting the need for green alternatives.
- DMC and PPC can replace these harmful solvents in large volumes, making liquid chromatography greener than traditional methods.
- Evaluations of solvent polarity, UV cut-off, stability, and chromatographic efficiency confirm their suitability for use in chromatography.
- In MMC, RPLC, and Polar Organic Mode, we successfully substituted up to 50%, 30%, and 60% of toxic ACN, respectively.
- Stability studies confirm that these solvents are stable for chromatographic applications.
- Overall, our approach makes chromatographic methods cheaper, less toxic for human health, and more environmentally friendly.

## References

1. Kalisz, O.; Tobiszewski, M.; Nowaczyk, A.; Bocian, S. Exploring the Potential of Green Chemistry in Reversed-Phase Liquid Chromatography: A Review of Sustainable Solvents. *TrAC Trends in Analytical Chemistry* **2024**, *181*, 118007. https://doi.org/10.1016/j.trac.2024.118007.
2. Felletti, S.; Matteo Spedicato; Bozza, D.; Chiara De Luca; Presini, F.; Pier Paolo Giovannini; Carraro, M.; Macis, M.; Cavazzini, A.; Catani, M.; Ricci, A.; Cabri, W. Dimethyl Carbonate as a Green Alternative to Acetonitrile in Reversed-Phase Liquid Chromatography. Part I: Separation of Small Molecules. *Journal of chromatography A/Journal of chromatography* **2023**, *1712*, 464477–464477. https://doi.org/10.1016/j.chroma.2023.464477.
3. Fayaz, T. K. S.; Chanduluru, H. K.; Obaydo, R. H.; Sanphui, P. Propylene Carbonate as an Ecofriendly Solvent: Stability Studies of Ripretinib in RPHPLC and Sustainable Evaluation Using Advanced Tools. *Sustainable Chemistry and Pharmacy* **2023**, *37*, 101355. https://doi.org/10.1016/j.scp.2023.101355.
4. Namboodiry Varsha; Bhoir Suvarna; Verma, P.; Mishra, S.; Ashok, B. REPLACEMENT of ACETONITRILE by MIXTURES of PROPYLENE CARBONATE and METHANOL as ORGANIC MODIFIER in MOBILE PHASES for RPLC SEPARATION MECHANISM: APPLICATION to the ASSAY of ALPRAZOLAM and SERTRALINE in COMBINED PHARMACEUTICAL FORMULATIONS. *Journal of Liquid Chromatography & Related Technologies* **2012**, *35* (18), 2643–2654. https://doi.org/10.1080/10826076.2011.637273.
5. Vaňkátová, P.; Kubíčková, A. Towards Greener Enantioselective Liquid Chromatography: An Exploratory Study on Chiral Liquid Crystals. *Analytica Chimica Acta* **2025**, *1342*, 343664. https://doi.org/10.1016/j.aca.2025.343664.

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