10.1071/CH14312_AC



Australian Journal of Chemistry 2015, 68 (5), 783-792

**Supplementary Material**

# Investigation of the Rotational Isomerism of Quinapril and Quinaprilat by UPLC–DAD and Elucidation of the Conformational Equilibrium by NMR

*Maha Dendeni,*[A,D] *Nicolas Cimetiere,*[B,C] *Isabelle Soutrel,*[B] *Jean Paul Guegan,*[B] *Najib Ben Hamida,*[A] *and Abdeltif Amrane*[B,C]

[A]Laboratoire de Chimie Analytique et Electrochimie, Département de Chimie, Faculté des Sciences de Tunis, Campus Universitaire 2092 Tunis El Manar, Tunisie.

[B]Ecole Nationale Supérieure de Chimie de Rennes, CNRS, UMR 6226, Av. du Général Leclerc, CS 50837, 35708 Rennes Cedex 7, France.

[C]Université européenne de Bretagne, 35000 Rennes, France.

[D]Corresponding author. Email: maha.dendeni@gmail.com

## Part I : NMR Study

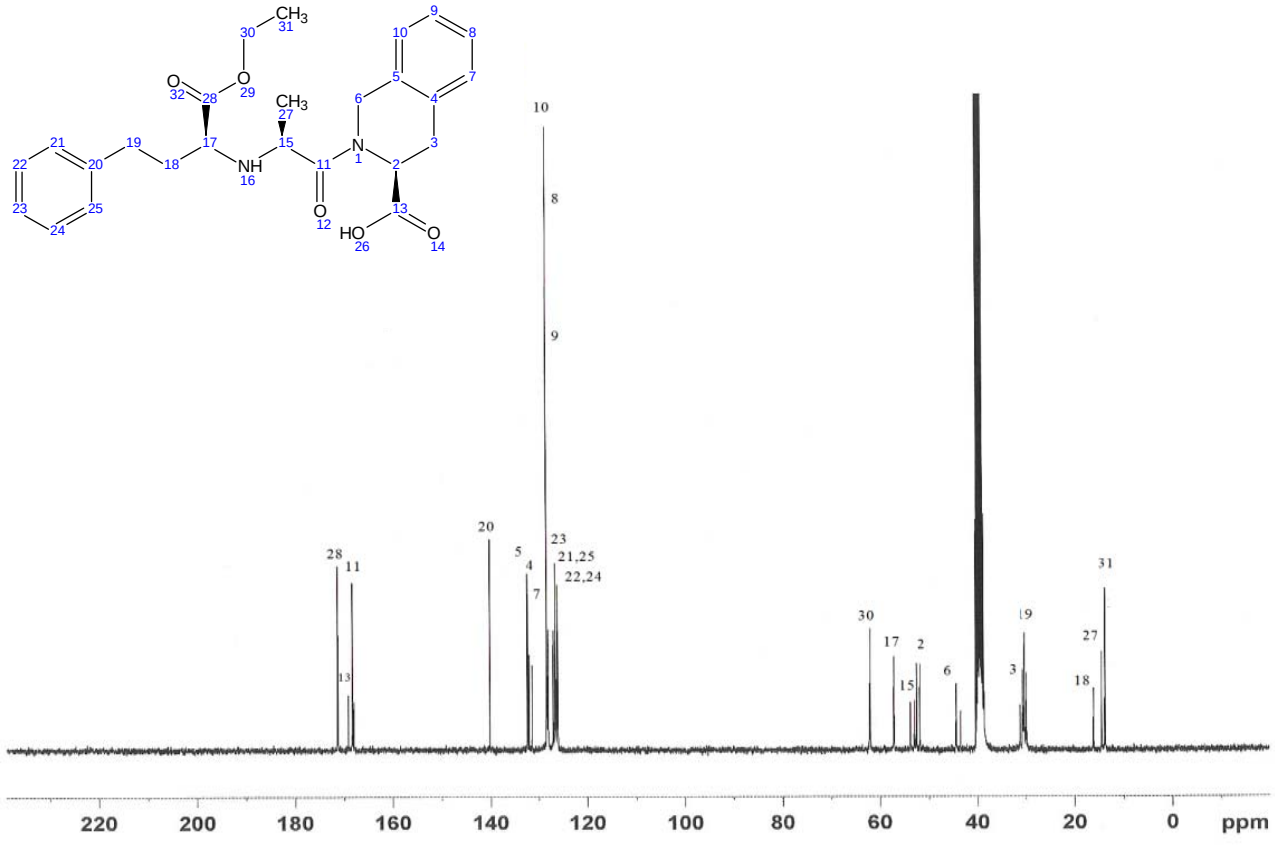


Fig. S.1. $^{13}C$ NMR spectrum of quinapril in DMSO-$d_6$ at T= 298, 6 K

**Table. 1** $^{1}H$ and $^{13}C$ chemical shifts δ, and multiplicity M for rotational isomers (cis and trans) of quinapril hydrochloride in$CD_2Cl_2$ solution at 298 K

| Carbon position | Isomere | Delta and M(H) | Delta C (hsqc) | Delta C correlated by HMBC | Delta C by Jmod | Mc |
|---|---|---|---|---|---|---|
| 31 | A | 1.24 t | 14.1 | 63.5(C30) | | CH3 |
| | B | 1.28 t | 14.2 | 63.6(C30) | | |
| 27 | A | 1.73 d | 16.3 | 55.1(C15); 169.4(C11) | | CH3 |
| | B | 1.64 d | 15.6 | 55.1(C15); 168.9(C11) | | |
| 18 | A | 2-2.5 m | 32.0 | | | CH2 |
| | B | 2-2.5 m | 32.2 | | | |
| 19 | A | 2.65-2.93 m | 31.4 | 140.0(C20) . 128 (arom) | | CH2 |
| | B | 2.65-2.93 m | * | 140.2(C20) . 128 (arom) | | |
| 3 | A | 3.22 m | 30.5 | 53.8(C2); 172.5(C13);132.9(C4) | | CH2 |
| | B B’ | 3.42 dd ; 3.18 m | 31.3 | | | |
| 17 | A | 3.89 t | 59.4 | 31.3(C19); 168.5(C28) | | CH |
| | B | 4.06 t | 59.3 | 31.4(C19); 168.9(C28) | | |
| 30 | A | 4.15-4.29 m | 63.5 | 14.1(C31); 168.5(C28) | | CH2 Et |
| | B | 4.15-4.29 m | 63.6 | | | |
| 6 | A | 4.63 dd | 45.9 | 53.8(C2) ; 131.8(C5) ; 168.9(C11); 126.7(C10) | | CH2 |
| | B B’ | 4.81 d ; 4.6 dd | 44.6 | 131.89(C5) | | |
| 15 | A | 4.71 m | 55.1 | 15.6(C27) | | CH |
| | B | 4.56 q | 55.0 | | | |
| 2 | A | 5.15 t | 53.8 | 30.5(C3); 132.9(C4) ;172.5(C13) | | CH |
| | B | 4.93 m | 55.1 | | | |
| 21.22. 23.24.25 | A . B | 7-7.25 m | * | | | CH arom |

| | | | | | |
|---|---|---|---|---|---|
| 7.8.9 | A.B | 7-7.25 m | * | | CH arom |
| 10 | A | 7-7.25 m | 126.45 | | CH arom |
| | B | 7-7.25 m | * | | CH arom |
| 4 | A | | | 132.9 | C q |
| | B | | | * | |
| 5 | A | | | 131.8 | Cq |
| | B | | | 131.9 | |
| 20 | A | | | 140.0 | C q |
| | B | | | 140.2 | |
| 11 | A | | | 168.5 | CO |
| | B | | | 169.4 | |
| 13 | A | | | 172.5 | COOH |
| | B | | | 171.9 | |
| 28 | A | | | 168.5 | COOEt |
| | B | | | * | |
| NH and OH | A | 8.8 ; 10.3 broad s | | | |
| | B | 9.23 ; 9.43 broad s | | | |

* : attribution in not possible.

## Part II: Deconvolution of overlapped peaks

### 1. Polynomial modified Gaussian function (first case) (PMG1)

This model, which is the most commonly used for the deconvolution of chromatographic peaks, has been recently introduced by Torres-Lapasio and co-workers [23].

The PMG1 model is based on an empirical modification of a standard Gaussian function [24-25]. It can be expressed by the following equation:

$$h(t) = h_m \, exp[-((t - t_m)/s)^2] \qquad h(t) \to 0 \; with \; t \to \infty \qquad (1)$$

Where;

*t*: The retention time,

*h(t)*: The peak intensity as a function of retention time,

$h_m$: Amplitude parameter,

$t_m$: The retention time at peak maximum

and *s* is a polynomial standard deviation defined as below

$$s = s_0 + s_1(t - t_m) + s_2(t - t_m)^2 + s_3(t - t_m)^3 + s_4(t - t_m)^4 \qquad (2)$$

Where $s_1$, $s_2$, $s_3$ and $s_4$ are fitting parameters. Five terms in the variable standard deviation are used in this study.

Thinks to the polynomial standard deviation s, the PMG1 function is more effective and characterized by a high flexibility allowing the deconvolution of overlapping peaks, however it exhibits the defect that $h$ ($t \to \infty$) $\pm 0$.

**2. Polynomial Modified Gaussian Function (Second case) (PMG2)**

PMG2 function can be expressed as:

$$f(t) = \frac{h_m s_0}{s} \, exp[-(\,(t - t_m)/s)^2] \qquad (3)$$

$$f(t \to \infty) = 0 \quad [23\text{-}24]$$

Where *s* is still given by eq (2) and $s_0$ corresponds to the standard constant deviation, then *f* (t→∞)=0 under all circumstances.

## Part III: Effects of chromatographic parameters

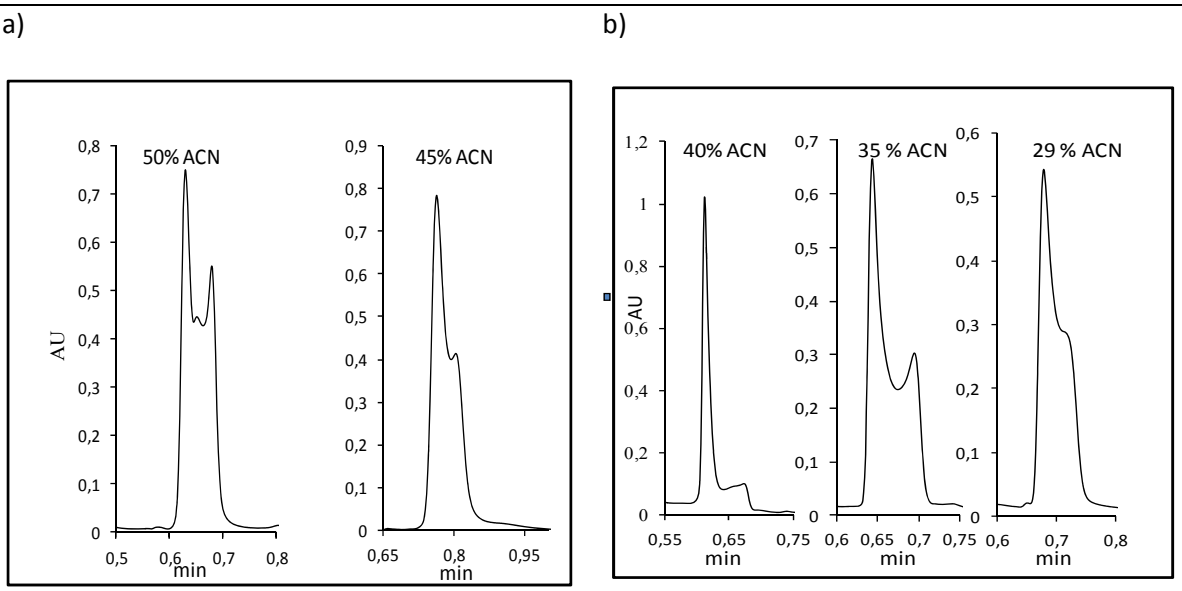


Fig.S.2. Effect of the mobile phase composition on the conformational equilibrium cis-trans of quinapril (a) and quinaprilat (b), flow rate 0.4 mL.min$^{-1}$, stationary phase BEH Acuity C18 2.1 mm I.D (100 mm x 1.7 µm), Column temperature 45°C, mobile phase: ammonium buffer (10 mM, pH 8)/ACN

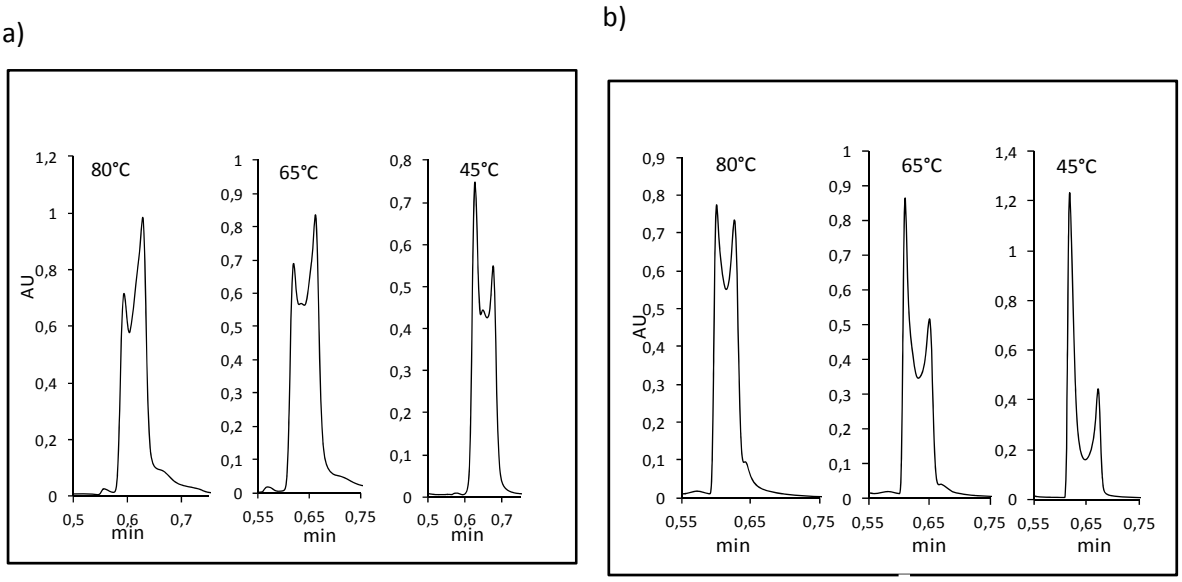


Fig. S.3. Effect of the column temperature on the separation of the two conformers of quinapril (a) and quinaprilat (b), Mobile phase Ammonium buffer 10 mM (pH 8)/ ACN ((a) (50/50) (v/v); (b) (65/35) (v/v)), flow rate 0.4 mL.min$^{-1}$, stationary phase BEH Acuity C18 2.1 mm I.D (100 mm x 1.7 µm).

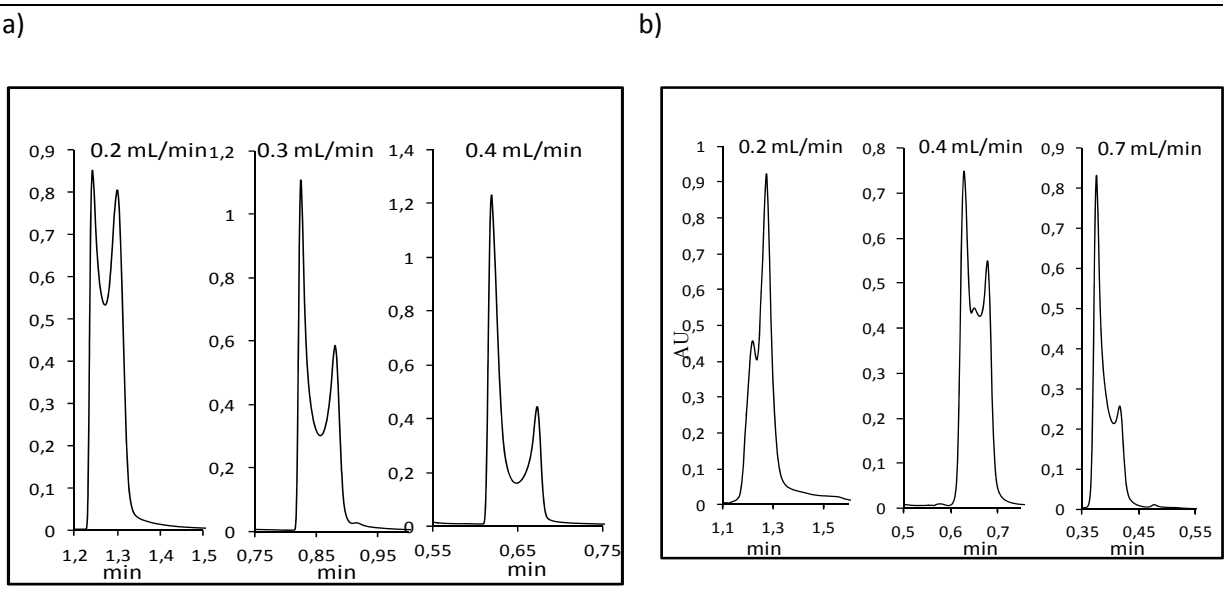


Fig. S.4. Effect of the flow rate on the separation of the two conformers of quinapril (a) and quinaprilat (b), Mobile phase Ammonium buffer 10mM (pH 8)/ ACN ((a) (50/50); (b) (65/35) (v/v)), flow rate 0.4 mL.min$^{-1}$, stationary phase BEH Acuity C18 2.1 mm I.D (100 mm x 1.7 µm).

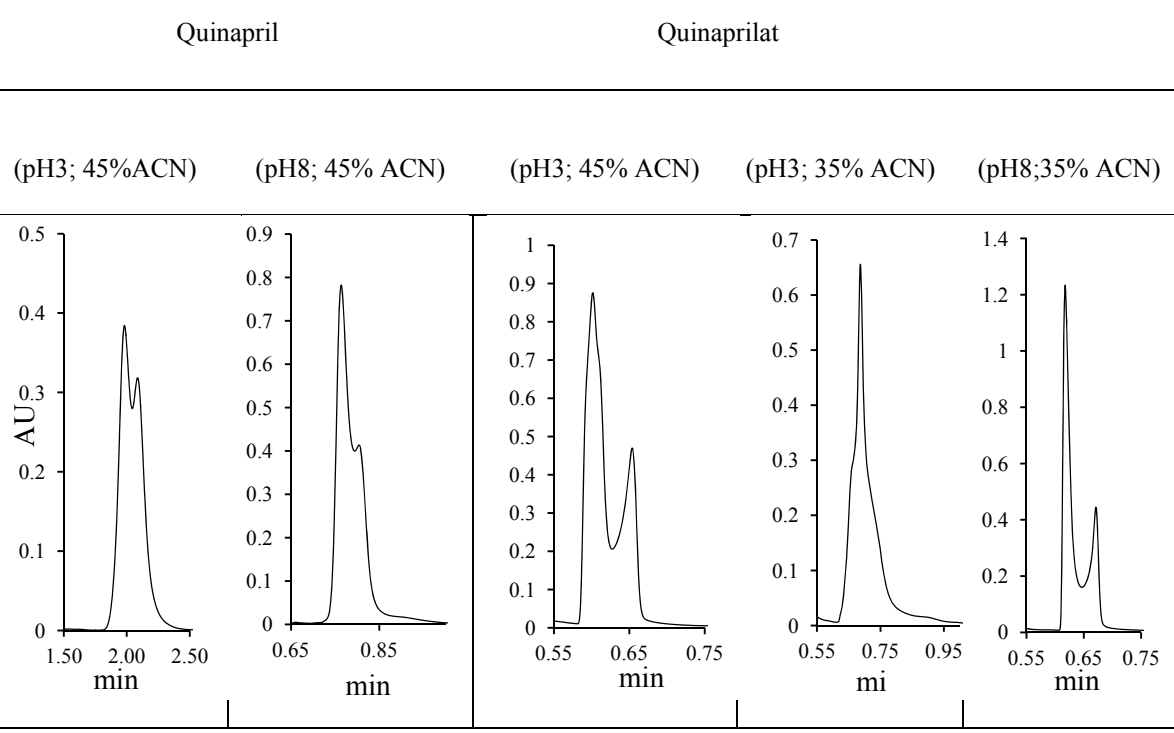


Fig. S.5. Effect of pH on the conformational equilibrium cis-trans of quinapril (a) and quinaprilat (b), flow rate 0.4 mL.min$^{-1}$, stationary phase BEH Acuity C18 2.1 mm I.D (100 mm x 1.7 µm), Column temperature 45°C, mobile phase: ammonium buffer (10 mM, pH 8) or phosphate buffer (10 mM, pH3)/ACN (55/45 (v/v))

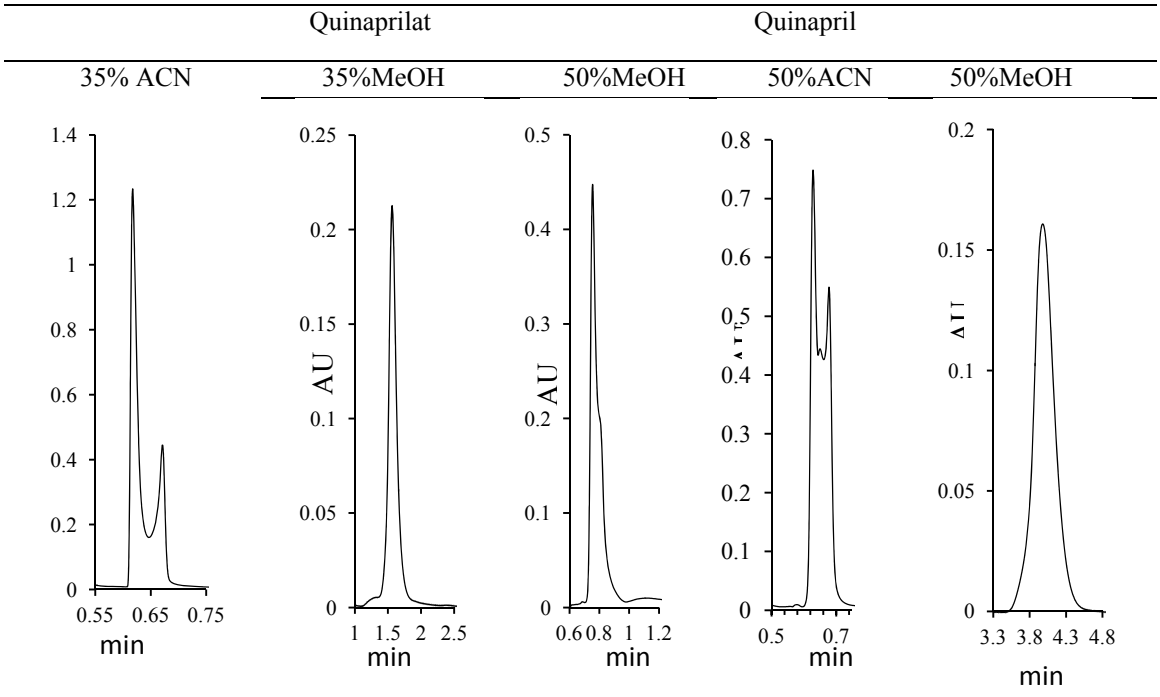


Fig. S.6.Effect of the organic modifier on the peak shape and retention time of quinapril and quinaprilat ; mobile phase: ammonium buffer (10 mM, pH 8)/organic modifier (concentrations are indicated); flow rate 0.4 mL.min$^{-1}$; column temperature 45 °C; stationary phase BEH Acuity C18 2.1 mm I.D (100 mm x 1.7 µm)

a) Quinaprilat b) Quinapril

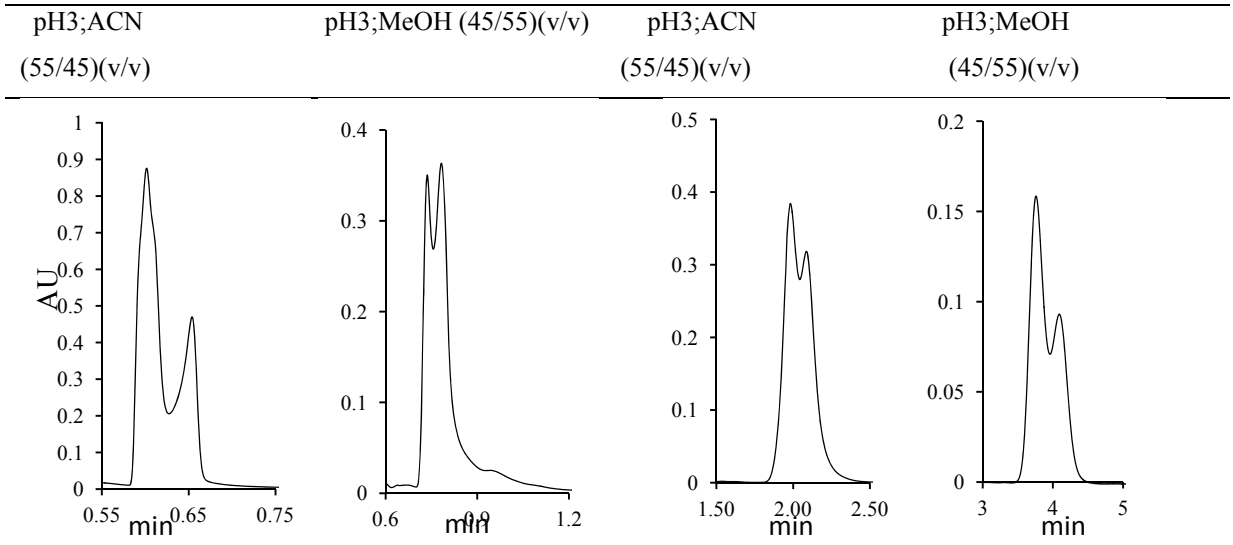


Fig. S.7. Effect of the organic modifier on the peak shape and retention time of quinapril and quinaprilat ; mobile phase: phosphate buffer (10mM, pH 3)/organic modifier (concentrations are indicated); flow rate 0.4 $mL.min^{-1}$; column temperature 45 °C; stationary phase BEH Acuity C18 2.1 mm I.D (100 mm x 1.7 µm).