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# Utilization of reversed-phase TLC and topological indices to the lipophilicity investigations of naproxen

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ABSTRACT

*Aim:* The lipophilicity of naproxen by reversed-phase thin-layer chromatography (RP-TLC) and new methods of calculation of partition coefficients were developed.
*Methods:* Naproxen was investigated with the use RP-TLC on RP2 (Kieselgel 60 $F_{254}$ silanisiert), $RP8F_{254s}$, $RP18F_{254s}$, $DiolF_{254s}$, and $CNF_{254s}$ plates, and methanol–water ($pH_{water}$ = 2.56; 5.73; 8.50) and 1,4-dioxane–water ($pH_{water}$ = 5.73) in different volume compositions as the mobile phases. The chromatographic parameters of lipophilicity ($R_{MW}$) of the studied naproxen were determined and compared both, with measured ($logP_{exp}$), and calculated partition coefficients (AlogPs, AClogP, AB/logP, miLogP, AlogP, mlogP, $logP_{Kowwin}$, xlogP2, and xlogP3). New methods were proposed for calculation of logP for naproxen using the $R_F$ value and the numerical value of topological index ($^1\chi$, $^2\chi$, $^1\chi^v$, $^oB$).
*Results:* It was apparent that the lipophilicities $R_{MW(RP18,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 5.73)}$, $R_{MW(RP8,\ pH\ =\ 8.50)}$, $R_{MW(CN,\ pH\ =\ 2.56)}$, and $R_{MW(RP8,\ pH\ =\ 5.73,\ d)}$ values were most similar to the experimental partition coefficient. Therefore, the $RP8F_{254s}$ plate is the best for lipophilicity analysis of naproxen.
*Conclusion:* The logP values calculated for naproxen by the use of $R_F$ values and topological index $^oB$, using the new approach, correlate the best with experimental partition coefficient.


## 1. Introduction

Lipophilicity is one of the parameters of drugs which influence their biological activities. Lipophilicity is defined by the partitioning of a compound between a nonaqueous and an aqueous phase and is expressed as logP. The different partition chromatographic techniques, and theoretical methods have been widely used as a reliable alternative to classical determination of logP.[1–8] Topological indices and the $R_F$ values were also used to prediction of lipophilicity of substances investigated.[9–18]

Naproxen has pharmacological and pharmaceutical significance. It is a non-steroidal anti-inflammatory drug. It is used for reduction of pain, fever, inflammation and stiffness caused by conditions (for example: osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, menstrual cramps, tendinitis, bursitis, and others).[19]

Therefore, the aims of this work were:

- to determine the lipophilicity of naproxen by RP-TLC method on $RP2F_{254}$, $RP8F_{254s}$, $RP18F_{254s}$, Diol $F_{254s}$, and $CNF_{254s}$ plates using a methanol–water and 1,4-dioxane-water as mobile phases;
- to determine the influence of pH water on the lipophilicity of naproxen;
- to propose new methods of calculation of partition coefficients on the basis of numerical value of topological index as well as on the basis of $R_F$ value received by RP-TLC technique for studied naproxen.

The experimental n-octanol-water partition coefficient and chromatographic parameters of lipophilicity values were compared with lipophilicity values estimated by computational methods for naproxen.

## 2. Material and methods

### 2.1. Chemicals and standard solutions

The following components of the mobile phase: methanol (E. Merck, Germany; for liquid chromatography), 1,4-dioxane (POCh, Gliwice, Poland, analytical grade) and distilled water (pH = 5.73) were used for RP-TLC analysis. Distilled water was acidified with hydrochloric acid (35–38%, pure for analysis, POCh, Gliwice, Poland) to pH = 2.56, and alkalized with ammonia (25%, pure for

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**Table 1**
Parameters of the linear regression (±SE) relating the $R_M$ values of naproxen to the methanol content ($\varphi$) of methanol–water (pH = 2.56) mobile phase (according to eq. (1): $R_M = R_{MW} - S \cdot \varphi$) for analysis performed on particular plates.[a]

| Chromatographic support (symbol of lipophilic parameter) | $R_{MW}$ (±SE) | S (±SE) | $n$ | $r$ | SEE | F | Range of the volume fraction of methanol ($\varphi$) | Eq. no. |
|---|---|---|---|---|---|---|---|---|
| RP18 ($R_{MW(RP18,\ pH\ =\ 2.56)}$) | 2.934 (±0.266) | 3.96 (±0.35) | 6 | 0.985 | 0.146 | 131 | 1.00÷0.50 | (6) |
| RP8 ($R_{MW(RP8,\ pH\ =\ 2.56)}$) | 2.983 (±0.167) | 4.01 (±0.22) | 6 | 0.994 | 0.091 | 340 | 1.00÷0.50 | (7) |
| RP2 ($R_{MW(RP2,\ pH\ =\ 2.56)}$) | 0.970 (±0.162) | 2.60 (±0.24) | 8 | 0.976 | 0.152 | 122 | 1.00÷0.30 | (8) |
| Diol ($R_{MW(Diol,\ pH\ =\ 2.56)}$) | 1.055 (±0.211) | 2.63 (±0.31) | 8 | 0.962 | 0.198 | 74 | 1.00÷0.30 | (9) |
| CN ($R_{MW(CN,\ pH\ =\ 2.56)}$) | 2.404 (±0.062) | 3.57 (±0.08) | 7 | 0.998 | 0.045 | 1759 | 1.00÷0.40 | (10) |

[a] Where: SE – standard error; $n$ – number of points to drive the particular regression equation; $r$ – correlation coefficient; SEE – standard error of the estimation; F – the values of the Fisher test; for all regression equation the significance level ($p$) is < 0.0005.

analysis, POCh, Gliwice, Poland) to pH = 8.50. The pH of water was measured by use of pehameter (Elmetron, Poland). The commercial sample of naproxen (Sigma Aldrich, lot: 097K1452, meets USP testing specifications) was used as test solute. Standard solution of naproxen (20 mg/10 mL) was prepared in ethanol (99.8%, pure for analysis, POCh, Gliwice, Poland).

### 2.2. Application of reversed-phase thin-layer chromatography for determination of chromatographic parameters of lipophilicity

Reversed partition thin-layer chromatography (RP-TLC) was done on $RP2F_{254}$ (E. Merck, #1.05474), $RP8F_{254s}$ (E. Merck, #1.15424), $RP18F_{254s}$ (E. Merck, #1.05559), Diol $F_{254s}$ (E. Merck, #1.05636) and $CNF_{254s}$ (E. Merck, #1.12571) plates. Solution of examined naproxen was spotted on chromatographic plates in quantity of 10 μg of naproxen in 5 μL of solution. The chromatograms were developed by using the mixtures of methanol + water ($pH_{water}$ = 2.56; 5.73; 8.50), 1,4-dioxane + water ($pH_{water}$ = 5.73), and the content of organic modifier in mobile phase was gradually varied by 10% (%, v/v) from 30 to 100 (%, v/v).

Fifty mL of mobile phase was placed into a classical chromatographic chamber (Camag, Switzerland). The chamber was saturated with solvent for 20 min. The chromatograms were developed at the room temperature, e.g., 22 °C. The development distance was 7.5 cm. The plates were dried at the room temperature, e.g., 22 °C. A Camag densitometer was used to obtainment of $R_F$ values. Densitometric scanning was then performed at 254 nm. The radiation source was a deuterium lamp emitting a continuous spectrum between 190 and 450 nm. The slit dimensions were 10.00 × 0.40 mm, Macro; the optimized optical system was light; the scanning speed was 20 mm $s^{-1}$; the data resolution was 100 μm $step^{-1}$; the measurement type was remission; and the measurement mode was absorption; the optical filter was second order. The chromatograms were done in triplicate and mean $R_F$ values were used to calculate $R_M$.

The $R_M$ values obtained for studied naproxen on $RP2F_{254}$, $RP8F_{254s}$, $RP18F_{254s}$, Diol $F_{254s}$, and CN $F_{254s}$ plates, using the methanol–water and 1,4-dioxane–water mobile phases were extrapolated to zero concentration of organic modifier in eluent ($R_{MW}$), in accordance with Soczewiński–Wachtmeister[4] equation:

$$R_M = R_{MW} - S \cdot \varphi \quad (1)$$

where: $R_M$ is the $R_M$ value of examined substance by content $\varphi$ of volume fraction of organic modifier in mobile phase; $R_{MW}$ is the theoretical value of $R_M$ of naproxen extrapolated to zero concentration of methanol in mobile phase; $S$ is the slope of the regression curve; $\varphi$ is the volume fraction of organic modifier in the mobile phase.

### 2.3. Calculation of theoretical partition coefficients

The values of theoretical partition coefficients such as: AlogPs, AClogP, AB/logP, miLogP, AlogP, mlogP, $logP_{Kowwin}$, xlogP2, and xlogP3 [5–8] were calculated with the use of the Internet databases.

### 2.4. Topological indices

Selected topological indices based on adjacency matrix: Randić ($^1\chi$, $^2\chi$, and $^1\chi^v$),[20] and also based on distance matrix: Pyka ($^oB$)[21] were calculated. Pyka index was calculated by building a distance matrix and determining its elements by means of values given by Barysz et al.[22]

### 2.5. New methods of calculation logP for naproxen

New methods of calculation logP were proposed for naproxen, namely according to the equations (2)–(5):

$$\log P = {}^oB + R_F \quad (2)$$

$$\log P = {}^2\chi \cdot R_F \quad (3)$$

$$\log P = {}^1\chi \cdot R_F \quad (4)$$

$$\log P = {}^1\chi \cdot R_F \quad (5)$$

where $^oB$, $^1\chi$, $^1\chi^v$, and $^2\chi$ are topological indices, and $R_F$ is retardation factor of naproxen.

**Table 2**
Parameters of the linear regression (±SE) relating the $R_M$ values of naproxen to the methanol content ($\varphi$) of methanol–water (pH = 5.73) mobile phase (according to eq. (1): $R_M = R_{MW} - S \cdot \varphi$) for analysis performed on particular plates.[a]

| Chromatographic support (symbol of lipophilic parameter) | $R_{MW}$ (±SE) | S (±SE) | $n$ | $r$ | SEE | F | Range of the volume fraction of methanol ($\varphi$) | Eq. no. |
|---|---|---|---|---|---|---|---|---|
| RP18 ($R_{MW(RP18,\ pH\ =\ 5.73)}$) | 1.351 (±0.066) | 1.73 (±0.09) | 7 | 0.993 | 0.048 | 361 | 0.90÷0.30 | (11) |
| RP8 ($R_{MW(RP8,\ pH\ =\ 5.73)}$) | 2.785 (±0.130) | 3.81 (±0.18) | 7 | 0.994 | 0.095 | 454 | 1.00÷0.40 | (12) |
| RP2 ($R_{MW(RP2,\ pH\ =\ 5.73)}$) | 0.385 (±0.106) | 2.18 (±0.15) | 8 | 0.985 | 0.100 | 199 | 1.00÷0.30 | (13) |
| Diol ($R_{MW(Diol),\ pH\ =\ 5.73}$) | 1.172 (±0.116) | 2.37 (±0.16) | 7 | 0.989 | 0.084 | 221 | 0.90÷0.30 | (14) |
| CN ($R_{MW(CN,\ pH\ =\ 5.73)}$) | 1.752 (±0.112) | 2.89 (±0.16) | 8 | 0.991 | 0.106 | 315 | 1.00÷0.30 | (15) |

[a] Where: SE – standard error; $n$ – number of points to drive the particular regression equation; $r$ – correlation coefficient; SEE – standard error of the estimation; F – the values of the Fisher test; for all regression equation the significance level ($p$) is <0.0005.

**Table 3**
Parameters of the linear regression (±SE) relating the $R_M$ values of naproxen to the methanol content ($\varphi$) of methanol–water (pH = 8.50) mobile phase (according to eq. (1): $R_M = R_{MW} - S\cdot\varphi$) for analysis performed on particular plates.[a]

| Chromatographic support (symbol of lipophilic parameter) | $R_{MW}$ (±SE) | S (±SE) | $n$ | $r$ | SEE | F | Range of the volume fraction of methanol ($\varphi$) | Eq. no. |
|---|---|---|---|---|---|---|---|---|
| RP18 ($R_{MW(RP18,\ pH\ =\ 8.50)}$) | 1.415 (±0.102) | 1.87 (±0.14) | 7 | 0.986 | 0.074 | 177 | 0.90÷0.30 | (16) |
| RP8 ($R_{MW(RP8,\ pH\ =\ 8.50)}$) | 2.861 (±0.124) | 3.40 (±0.16) | 6 | 0.996 | 0.067 | 444 | 0.90÷0.30 | (17) |
| RP2 ($R_{MW(RP2,\ pH\ =\ 8.50)}$) | 0.452 (±0.175) | 2.07 (±0.25) | 7 | 0.965 | 0.162 | 68 | 1.00÷0.30 (except 0.60) | (18) |
| Diol ($R_{MW(Diol,\ pH\ =\ 8.50)}$) | 1.210 (±0.146) | 2.92 (±0.22) | 7 | 0.986 | 0.131 | 172 | 1.00÷0.30 (except 0.90) | (19) |
| CN ($R_{MW(CN,\ pH\ =\ 8.50)}$) | 1.911 (±0.102) | 3.09 (±0.15) | 8 | 0.993 | 0.096 | 432 | 1.00÷0.30 | (20) |

[a] Where: SE – standard error; $n$ – number of points to drive the particular regression equation; $r$ – correlation coefficient; SEE – standard error of the estimation; F – the values of the Fisher test; for all regression equation the significance level ($p$) is <0.0005.

## 3. Results and discussion

The lipophilicity of naproxen was investigated with the use reversed-phase thin-layer chromatography on $RP2F_{254}$, $RP8F_{254s}$, $RP18F_{254s}$, Diol $F_{254s}$, and $CNF_{254s}$ plates, using methanol–water ($pH_{water}$ = 2.56; 5.73; 8.50) and 1,4-dioxane–water ($pH_{water}$ = 5.73) in different volume compositions as the mobile phases. The $R_M$ values obtained for studied naproxen were extrapolated to zero concentration of organic modifier in mobile phase in accordance with Soczewiński–Wachtmeister equation (1). The terms of the regression equations (eqs. (6)–(25)) describing the dependence of the $R_M$ values of the naproxen on organic modifier content ($\varphi$) of the mobile phase are listed in Tables 1–4 for analysis performed on particular plates using methanol–water ($pH_{water}$ = 2.56; 5.73; 8.50) and 1,4-dioxane–water ($pH_{water}$ = 5.73) in different volume compositions as the mobile phases, respectively. The high correlation coefficients ($r$), the values of the Fisher test (F), the significance levels ($p$), and small values of the standard errors of the estimates (S) were indicated that all the equations obtained were highly significant. The equation (23) is an exception ($r$ = 0.375, $F$ = 0.82, $p$ = 0.4070).

The $R_{MW}$ value of naproxen dependence on chromatographic support, and the composition of mobile phase. The obtained $R_{MW}$ values were from −0.572 to 2.983. Generally, the highest lipophilicity of naproxen was obtained on particular chromatographic plates and using methanol–water ($pH_{water}$ = 2.56). The smaller influence of pH water on the lipophilicity of naproxen was observed on $RP8F_{254s}$ plates.

All determined chromatographic parameters of lipophilicity for naproxen are lower in relation to its value of the experimental partition coefficient. Experimental $n$-octanol-water partition coefficient ($logP_{exp}$)[8] for naproxen is equal 3.18.

Similarity analysis was also used for comparison of experimental partition coefficient ($logP_{exp}$) with chromatographic lipophilicity of naproxen. The results (Euclidean distance, single linkage) are presented in Fig. 1. It was apparent that the

**Table 4**
Parameters of the linear regression (±SE) relating the $R_M$ values of naproxen to the dioxane content ($\varphi$) of 1,4-dioxane–water (pH = 5.73) Mobile phase (according to eq. (1): $R_M = R_{MW} - S\cdot\varphi$) for analysis performed on particular plates.[a]

| Chromatographic support (symbol of lipophilic parameter) | $R_{MW}$ (±SE) | S (±SE) | $n$ | $r$ | SEE | F | Range of the volume fraction of dioxane ($\varphi$) | Eq. no. |
|---|---|---|---|---|---|---|---|---|
| RP18 ($R_{MW(RP18,\ pH\ =\ 5.73,\ d)}$) | 1.728 (±0.186) | 2.79 (±0.29) | 7 | 0.973 | 0.156 | 90 | 0.90÷0.30 | (21) |
| RP8 ($R_{MW(RP8,\ pH\ =\ 5.73),\ d}$) | 2.356 (±0.141) | 3.65 (±0.21) | 6 | 0.993 | 0.088 | 303 | 0.90÷0.40 | (22) |
| RP2 ($R_{MW(RP2,\ pH\ =\ 5.73,\ d)}$) | −0.572 (±0.249) | 0.35 (±0.39) | 7 | 0.375 | 0.206 | 0.82 | 0.90÷0.30 | (23) |
| Diol ($R_{MW(Diol),\ pH\ =\ 5.73,\ d}$) | 0.420 (±0.142) | 2.01 (±0.22) | 7 | 0.970 | 0.119 | 79 | 0.90÷0.30 | (24) |
| CN ($R_{MW(CN,\ pH\ =\ 5.73,\ d)}$) | 1.565 (±0.081) | 2.89 (±0.12) | 8 | 0.995 | 0.076 | 607 | 1.00÷0.30 | (25) |

[a] Where: SE – standard error; $n$ – number of points to drive the particular regression equation; $r$ – correlation coefficient; SEE – standard error of the estimation; F – the values of the Fisher test; for all regression equation the significance level ($p$) is <0.0005 [except is equation (23): $p$ = 0.4070].

**Table 5**
Lipophilicity parameter (logP) calculated on the basis of topological indices and selected $R_F$ values from $RP18F_{254}$, $RP8F_{254}$, and $CNF_{254}$ plates for naproxen.

| LogP for naproxen calculated using equation | logP calculated on the basis of topological index and $R_F$ value obtained by the use | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Methanol + water (pH = 2.56) | | Methanol + water (pH = 5.73) | | Methanol + water (pH = 8.50) | | 1,4-Dioxane + water (pH = 5.73) | | |
| | 8:2 (v/v) | 7:3 (v/v) | 8:2 (v/v) | 7:3 (v/v) | 8:2 (v/v) | 7:3 (v/v) | 8:2 (v/v) | 7:3 (v/v) | 6:4 (v/v) |
| $RP18F_{254}$ plates | | | | | | | | | |
| $logP = {}^{o}B + R_F$ | ***3.239*** | ***2.918*** | ***3.150*** | ***3.065*** | ***3.145*** | ***3.113*** | ***3.259*** | ***3.092*** | ***3.082*** |
| $logP = {}^{2}\chi\cdot R_F$ | ***3.374*** | 1.814 | ***2.942*** | 2.528 | ***2.918*** | 2.762 | 3.472 | 2.660 | 2.611 |
| $logP = {}^{1}\chi\cdot R_F$ | 4.369 | 2.348 | 3.808 | ***3.273*** | 3.777 | 3.576 | 4.495 | 3.443 | ***3.380*** |
| $logP = {}^{1}\chi^{v}\cdot R_F$ | 3.762 | 2.021 | ***3.280*** | 2.819 | ***3.252*** | ***3.079*** | 3.871 | ***2.965*** | ***2.911*** |
| $RP8F_{254}$ plates | | | | | | | | | |
| $logP = {}^{o}B + R_F$ | ***3.158*** | ***3.012*** | ***3.158*** | ***3.025*** | **3.158** | **2.985** | **3.305** | **3.099** | ***3.007*** |
| $logP = {}^{2}\chi\cdot R_F$ | ***2.981*** | 2.271 | ***2.981*** | 2.334 | **2.981** | 2.140 | 3.696 | 2.694 | 2.246 |
| $logP = {}^{1}\chi\cdot R_F$ | 3.859 | ***2.940*** | 3.859 | ***3.022*** | 3.859 | 2.770 | 4.784 | 3.487 | ***2.908*** |
| $logP = {}^{1}\chi^{v}\cdot R_F$ | ***3.323*** | 2.532 | ***3.323*** | 2.602 | **3.323** | 2.385 | 4.120 | **3.003** | 2.504 |
| $CNF_{254}$ plates | | | | | | | | | |
| $logP = {}^{o}B + R_F$ | ***3.278*** | ***3.092*** | ***3.318*** | ***3.177*** | ***3.282*** | ***3.150*** | ***3.423*** | ***3.282*** | ***3.145*** |
| $logP = {}^{2}\chi\cdot R_F$ | 3.564 | 2.660 | 3.759 | ***3.073*** | 3.584 | ***2.942*** | 4.269 | 3.584 | ***2.918*** |
| $logP = {}^{1}\chi\cdot R_F$ | 4.614 | ***3.443*** | 4.866 | 3.978 | 4.639 | 3.808 | 5.527 | 4.639 | 3.777 |
| $logP = {}^{1}\chi^{v}\cdot R_F$ | 3.974 | ***2.965*** | 4.190 | 3.426 | 3.995 | ***3.280*** | 4.760 | 3.995 | ***3.252*** |

The best results of logP for naproxen are by bold and italics

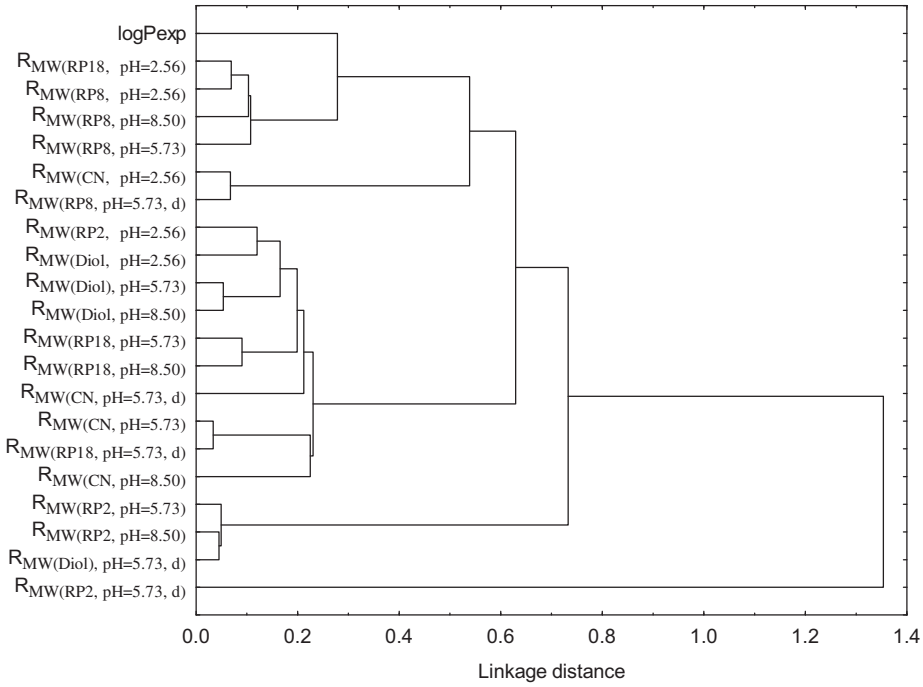


**Fig. 1.** Similarity analysis of the chromatographic parameters of lipophilicity $R_{Mw}$ and the experimental n-octanol-water partition coefficients ($logP_{exp}$) for naproxen (Euclidean distance, single linkage).

lipophilicities $R_{MW(RP18,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 5.73)}$, $R_{MW(RP8,\ pH\ =\ 8.50)}$, $R_{MW(CN,\ pH\ =\ 2.56)}$, and $R_{MW(RP8,\ pH\ =\ 5.73,\ d)}$ values were most similar to the experimental partition coefficient. Therefore, the $RP8F_{254s}$ plates are the best for lipophilicity analysis of naproxen.

The theoretical partition coefficients calculated using different software products for naproxen are equal: AlogPs = 3.29, AClogP = 2.80, AB/logP = 3.01, miLogP = 3.38, AlogP = 2.82, mlogP = 2.76, $logP_{Kowwin}$ = 3.10, xlogP2 = 2.84, xlogP3 = 3.34, and = 3.04. Comparing all calculation procedures, generally AlogPs, $logP_{Kowwin}$, xlogP3, AB/logP, and are more appropriate for chromatographic parameter of lipophilicity $R_{MW(RP18,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 5.73)}$, $R_{MW(RP8,\ pH\ =\ 8.50)}$, $R_{MW(CN,\ pH\ =\ 2.56)}$, $R_{MW(RP8,\ pH\ =\ 5.73)}$ and experimental *n*-octanol-water partition coefficient of studied naproxen.

New methods of logP calculation for naproxen using the $R_F$ value and the numerical value of topological index ($^1\chi$, $^2\chi$, $^1\chi^v$, $^oB$) were proposed. Calculated topological indices for naproxen are equal to $^1\chi = 6.2950$, $^2\chi = 5.4209$, $^1\chi^v = 4.8625$, $^oB = 2.5453$. These topological indices and $R_F$ values obtained on $RP8F_{254s}$, $RP18F_{254s}$, and $CNF_{254s}$ plates were used for the logP calculation for naproxen. Lipophilicity parameters (logP) calculated by use of the equations (2)–(5) and selected $R_F$ values from $RP18F_{254}$, $RP8F_{254}$, and $CNF_{254}$ plates for naproxen are presented in Table 5. The logP values calculated for naproxen by use of $R_F$ values and topological index $^oB$, using the new approach, correlate the best with experimental partition coefficient. From the data presented in this work it is apparent that the topological index $^oB$ describes additional important elements of chemical structure of investigated compounds not given by the other topological indices. Topological index $^oB$ proposed earlier by Pyka was used to determination of lipophilicity and other physicochemical parameters for many compounds.[9–11,14,16–18]

## 4. Conclusions

It was stated that the $RP8F_{254s}$ plate and methanol–water mobile phase are suitable for the estimation of lipophilicity of examined naproxen. The chromatographic parameter of lipophilicity $R_{MW}$, AlogPs, $logP_{Kowwin}$, xlogP3, AB/logP, and the logP values calculated by the use of $R_F$ values and topological index $^oB$ may be the alternative methods of lipophilicity determination of examined naproxen.

## Conflicts of interest

All authors have none to declare.

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