Optimal Lipophilicity of Sulfonium \( p \)-Toluenesulfonate as Anti-allergic Drug

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Abstract

In the development of the anti-allergic drug Suplatast Tosilate (IPD-1151T) we have reported the QSAR analysis using only the calculated \( \pi \) values, because the few log\( K \) values of sulfonium compounds had been measured till then. In this study, we measured the log\( K \) value of sulfonium compounds by using octylsilated silicagel plate (Merck HPTLC RP-8 F\(_{254S}\)). The log\( K \) values of the optimized compounds 52 and 67 (Suplatast Tosilate) of dimethylsulfonium \( p \)-toluenesulfonates derivatives were 0.07 and 0.06, respectively. Therefore, it was found that the desirable log\( K \) value of the sulfonium compound was approximately zero as the anti-allergic drug.

Key Words: Suplatast Tosilate, IPD-1151T, Anti-allergic Drug, log\( K \), Lipophilicity, Sulfonium Compound, Reversed-phase Thin-layer Chromatography

Area of Interest: Molecular Recognition

1. Introduction

Evaluation of lipophilicity is important not only for finding lead compounds but also because of optimization process in the search for drug candidate. The logarithm of the partition coefficient between n-octanol and water (log\( P \)) and the substituent lipophilic constant (\( \pi \)) are useful as lipophilic parameters in QSAR analysis. The \( \pi \) value is defined as the equation: \( \pi_X = \log P_X - \log P_H \), where log\( P_H \) is the log\( P \) value for the unsubstituted parent compound and log\( P_X \) is the value for a derivative [1][2]. And then in the case of onium compounds, such as ammonium and sulfonium...
compounds, the ion-pair formation-partition equilibrium constant (K) [4] has been measured as lipophilic parameter.

During the development of Suplatast Tosilate (IPD-1151T) (67) (Chart 1), which is a Th2 cytokine inhibitor and used as anti-allergic drug [3], we have reported some QSAR analysis by using only the calculated π values as lipophilic parameter [5][6][7][8][9][10], because the logK values of sulfonium compounds had been previously only rarely measured.

Chart 1. The compound design scheme for the development of Suplatast Tosilate (IPD-1151T)

We could comprehend the relative lipophilicity of sulfonium compounds in the developmental process (Chart 1), but we did not determine a suitable logK value for the anti-allergic activity and toxicity. In this study we measured the logK values of sulfonium p-toluenesulfonates by reversed-phase thin-layer chromatography (RP-TLC) [2][11].

2. Materials and Methods

2.1 Method for measuring logK of sulfonium p-toluenesulfonates by reversed-phase thin-layer chromatography (RP-TLC)

The logK_{TLC} of sulfonium compounds was measured by using octylsililated silicagel plates (Merck HPTLC RP-8 F254S) and 50% (V/V) aqueous ethanol as stationary and mobile phases. The R_{M} values of compounds were obtained from the TLC-relation factor (R_{f}) by the equation: R_{M} = log (1/R_{f} -1) [2][11]. R_{f} is mathematically described by the ratio: R_{f} = migration distance of substance / migration distance of solvent front. Aliquots (0.5μl, 5mM) of the compounds in ethanol were applied to the gel layer at 1.0 cm intervals in a line 2.0 cm from the bottom edge, and 0.5 cm from each side of the plates. The peripheries of the plate were left free to minimize edge effects. The distance migrated by the leading edge of each spot was detected by UV light (254 nm) when the migration distance of solvent front was 5.0 cm. As a control substance, caffeine with an R_{f} value of 0.782, was run with every chromatogram, and chromatography was carried out at the temperature...
of 25 ± 0.1 °C. The standard deviation of R_M measured under these conditions was from 0.01 to 0.04.

2.2 Calculation of the \( \pi \) values for substituents of sulfonium \( p \)-toluenesulfonate

The \( \pi \) values for substituents of sulfonium \( p \)-toluenesulfonates were calculated as a substituent of benzene by Bio-Loom [12]. For example, the log\( P \) values of toluene and benzene are reported as 2.73 and 2.13, respectively in Bio-Loom. Therefore, the \( \pi \) value of the methyl moiety was calculated as being 0.60 by the following calculation. When the measured log\( P \) values of the applicable benzene derivatives were not available the calculated log\( P \) values by Bio-Loom were used.

\[
\pi_{\text{CH}_3} = \log P_{\text{toluene}} - \log P_{\text{benzene}}
\]

\[
= 2.73 - 2.13
\]

\[= 0.60\]

2.3 Homologous Passive Cutaneous Anaphylaxis (PCA) in the Rat

Antiserum containing homocytotropic antibody was obtained from rats that had been immunized with 2,4-dinitrophenyl-coupled ascaris (DNP-As) mixed with killed Bordetella pertussis according to the method of Tada et al [13]. The antibody titer of the serum (rat anti-DNP-As serum) was about 1:256 as estimated by 48-hr homologous passive cutaneous anaphylaxis (PCA). The antiserum diluted 20-fold with 0.9% saline was injected intradermally in 0.1 mL doses into 3 sites on one side of the shaved backs of 7 or 8 normal rats. The same dose of physiological saline was similarly injected into the other side. After 48 hr, 1.0 mL of 0.25% Evans blue solution containing 2.0 mg of antigen was administered to each animal intravenously. Thirty minutes later, the animals were killed by exsanguination, and the skins were removed to measure the PCA bluing lesion. The amount of the dye was then estimated colorimetrically after extraction by the method of Harada et al [14].

3. Results and Discussion

3.1 Measurement of the log\( K_{\text{TLC}} \) values of sulfonium \( p \)-toluenesulfonates by RP-TLC

The R_M values of uracil, sulfanilamide, allopurinol, caffeine, sulfamethyzole, phthalimide, aspirin, indole, benzophenone and biphenyl were determined as the standard compounds. Their log\( P \) values ranged from -1 to 4 (Table 1). A linear correlation between R_M and log\( P \), shown in Figure 1, was obtained (eq 1). In this equation, \( n \) is number of compounds, \( r \) is the correlation coefficient, \( s \) is the standard deviation, and the figures in parentheses are the 95% confidence intervals of the regression coefficient and residual variances. Therefore, the experimental lipophilicity log\( K_{\text{TLC}} \) of the sulfonium \( p \)-toluenesulfonates was determined by eq (1). (Table 2).

\[
\log P = 2.491 \times R_M + 1.788 \\
(\pm 0.212) \quad (\pm 0.153) \\
( n = 10, \ r = 0.995, \ s = 0.187 )
\]
Table 1. $R_M$ and log$P$ values of standard compounds

| compd      | log$P$ | $R_M^a$ |
|------------|--------|---------|
| Uracil     | -1.07  | -1.159  |
| Sulfanilamide | -0.62  | -1.024  |
| Allopurinol | -0.55  | -0.902  |
| Caffeine   | 0.01   | -0.555  |
| Sulfamethyzol | 0.26  | -0.698  |
| Phthalimide | 1.15   | -0.211  |
| Aspirin    | 1.19   | -0.306  |
| Indole     | 2.14   | 0.161   |
| Benzophenone | 3.18  | 0.523   |
| Biphenyl   | 4.01   | 0.886   |

$aR_M = \log(1/R_f -1)$

Figure 1. Plot of log$P$ vs. $R_M$.

3.2 Prediction of log$K$ of sulfonium $p$-toluenesulfonates

The log$P_H$ values of compounds lacking the dimethylsulfonio moiety:$(\text{CH}_3)_2\text{S}^+$ from their parent compounds (1-16) were either the measured log$P$ or calculated values by Bio-Loom. And the $\Sigma \pi_i$ values represent the summation of the $\pi$ values of all substituents of sulfonium $p$-toluenesulfonates (1-17) (Table 2). There was some correlation between log$K_{TLC}$ and log$P_H$ or $\Sigma \pi_i$ (eq 2 and eq 3), but their correlation coefficients were not good. In contrast, there was good correlation between log$P_H$ and $\pi_{\text{SCH}_3}$ (eq 4) (Figure 2), where this $\pi_{\text{SCH}_3}$ is defined as the value of log$K_{TLC}$ minus log$P_H$ and $\pi_{\text{SCH}_3}$,calcd was calculated by eq (4). Then, the log$K_{\text{calcd}}$ values were estimated in the following equation: log$K_{\text{calcd}} = \log P_H + \pi_{\text{SCH}_3}$,calcd, but the correlation between log$K_{\text{calcd}}$ and log$K_{TLC}$ was not good as shown by eq 5 ($r = 0.740$). Therefore, we have concluded that it is difficult to predict the precise log$K$ of sulfonium compounds by using $\pi_{\text{SCH}_3}$ or $\Sigma \pi_i$. 
Table 2. $\log K_{\text{TLC}}$ and $\pi S(\text{CH}3)$.

| No | Sulfonium Cation | $\log K_{\text{TLC}}$ | $\Sigma \pi_i$ | $\pi S(\text{CH}3)$ | Compound without (CH3)2S+ | log$K_{\text{calcd}}$ |
|----|------------------|-----------------------|---------------|-------------------|--------------------------|----------------------|
| 1  | (CH3)2S+CH2CH2OH | -0.95                 | 0.43          | -0.64             | CH3CH2OH                 | -0.31                | -0.73                | -1.04                |
| 2  | (CH3)2S+CH2CH2NHCOCH3 | -0.99                | 0.26          | -0.44             | CH3CH2NHCOCH3           | -0.55$^a$            | -0.53                | -1.08                |
| 3  | (CH3)2S+CH2CH2OCH3 | -0.93                 | 1.12          | -1.41             | CH3CH2OCH3              | 0.48$^a$             | -1.36                | -0.88                |
| 4  | (CH3)2S+CH2CH2COOH | -0.9                   | 0.91         | -1.23             | CH3CH2COOH              | 0.33                 | -1.24                | -0.91                |
| 5  | (CH3)2S+CH2CH2OCOCH3 | -1.12                 | 1.37          | -1.85             | CH3CH2OCOCH3            | 0.73                 | -1.56                | -0.83                |
| 6  | (CH3)2S+CH2CH2OH   | -1.13                 | 1.68          | -2.17             | CH3CH2CH3               | 1.04$^a$             | -1.81                | -0.77                |
| 7  | (CH3)2S+           | -1.1                   | 1.8           | -2.19             | CH4                      | 1.09                 | -1.86                | -0.77                |
| 8  | (CH3)2S+CH2CH2SCH3 | -0.79                 | 2.01          | -2.33             | CH3CH2SCH3              | 1.54                 | -2.21                | -0.67                |
| 9  | (CH3)2S+CH2CH2OCH3 | -0.54                 | 2.06          | -2.11             | CH3CH2OCH3              | 1.57$^a$             | -2.24                | -0.67                |
| 10 | (CH3)2S+CH2CH2CH3  | -0.48                 | 2.79          | -2.84             | CH3CH2CH3               | 2.36                 | -2.88                | -0.52                |
| 11 | (CH3)2S+           | -0.28                 | 3.83          | -3.72             | CH3                     | 3.44                 | -3.75                | -0.31                |
| 12 | (CH3)2S+           | -0.43                 | 4.62          | -4.67             | OCH3                    | 4.24                 | -4.39                | -0.15                |
| 13 | (CH3)2S+           | -0.25                 | 3.08          | -2.38             | COCH3                   | 2.13                 | -2.69                | -0.56                |
| 14 | (CH3)2S+OCH3       | -0.26                 | 3.02          | -2.37             | OCH3                    | 2.11                 | -2.68                | -0.57                |
| 15 | (CH3)2S+COCH3      | -0.41                 | 2.54          | -1.99             | COCH3                   | 1.58                 | -2.25                | -0.67                |
| 16 | (CH3)2S+COOH       | -0.45                 | 2.82          | -2.32             | COOH                    | 1.87                 | -2.48                | -0.61                |
| 17 | (CH3)2S+CH2CH2OH   | -0.69                 | 1.71          | -                     | CH3CH2OCH3              |                  |                     |                     |

$^a$log$P_H$ value was calculated by Bio-Loom (ver. 5.0)

\[
\begin{align*}
\log K_{\text{TLC}} &= 0.194 \log P_H - 0.976 \\
&\quad (\pm 0.100) \quad (\pm 0.193) \\
&\quad (n = 16, r = 0.742, s = 0.229) \\
\log K_{\text{TLC}} &= 0.216 \Sigma \pi_i - 1.147 \\
&\quad (\pm 0.221) \quad (\pm 0.092) \\
&\quad (n = 17, r = 0.792, s = 0.202) \\
\pi S(\text{CH}3) &= -0.806 \log P_H - 0.976 \\
&\quad (\pm 0.100) \quad (\pm 0.193) \\
&\quad (n = 16, r = 0.977, s = 0.229) \\
\log K_{\text{TLC}} &= 0.999 \log P_{\text{calcd}} - 0.001 \\
&\quad (\pm 0.521) \quad (\pm 0.379) \\
&\quad (n = 16, r = 0.740, s = 0.230)
\end{align*}
\]
3.3 The primary lead compound: 2-phenoxyethyldimethylsulfoniun \( p \)-toluenesulfonate (20)

The PCA reaction is a model of the type I allergic reaction [13]. There was some correlation between \( \log K_{TLC} \) and \( \text{logit(PCA)}: \log \left( \frac{[\text{PCA inhibition %}]}{100 - \text{PCA inhibition %}} \right) \) in intraperitoneal (ip) administration of compounds (1, 3, 18-25, 27-31) as shown in eq (6) (Table 3). Compound 20, however, having the strongest PCA inhibitory activity was considered as an outlier (Figure 3). Then, a similar eq (7) was obtained without compound 20, and the optimal \( \log K_{TLC} \) value of PCA inhibition (ip) was calculated as 0.70 by using eq (7). The compound 20 was thus considered as a good outlier, and we selected this compound as the primary lead compound. The \( \log K_{TLC} \) of compound 20 was 0.64.

\[
\text{logit (PCA)} = -0.294 (\log K_{TLC})^2 + 0.338 \log K_{TLC} - 0.404 \\
\quad (\pm 0.426) \quad (\pm 0.276) \quad (\pm 0.296) \\
\quad (n = 15, r = 0.642, s = 0.271)
\]

\[
\text{logit (PCA)} = -0.222 (\log K_{TLC})^2 + 0.309 \log K_{TLC} - 0.496 \\
\quad (\pm 0.216) \quad (\pm 0.198) \quad (\pm 0.218) \\
\quad (n = 14, r = 0.732, s = 0.213)
\]
Table 3. log\(K_{TLC}\) and PCA inhibitory activities in ip administration

| No | Sulfonium Cation | log\(K_{TLC}\) | \(\Sigma \pi_i\) | PCA (ip) inhibition (%)\(^a\) |
|----|------------------|-----------------|----------------|-----------------------------|
| 1  | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)OH | -0.95 | 0.43 | 5.7 |
| 3  | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)OCH\(_3\) | -0.93 | 1.12 | 15.1 |
| 18 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 0.53 | 2.45 | 19.7 |
| 19 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 0.91 | 3.01 | 41.8 |
| 20 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 0.64 | 3.23 | 72.7 |
| 21 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 1.29 | 4.24 | 30.5 |
| 22 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 1.52 | 4.8 | 23.3 |
| 23 | CH\(_3\)\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 0.47 | 3.65 | 29.5 |
| 24 | CH\(_3\)\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 0.81 | 4.07 | 18.7 |
| 25 | (CH\(_3\))\(_2\)S\(^+\)(CH\(_2\))\(_2\)O | 0.72 | 3.61 | 30 |
| 26 | (CH\(_3\))\(_2\)S\(^+\)(CH\(_2\))\(_2\)O | 0.89 | 4.14 | -3.9 |
| 27 | (CH\(_3\))\(_2\)S\(^+\)(CH\(_2\))\(_2\)O | 1.02 | 4.67 | 14.8 |
| 28 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\)O | 0.68 | 3.63 | 31.5 |
| 29 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CHO | 0.64 | 3.63 | 36.2 |
| 30 | H\(_3\)C-S\(^+\)O | 0.56 | 4.45 | 42 |
| 31 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\) | 0.62 | 4.19 | 26.1 |
| 32 | (CH\(_3\))\(_2\)S\(^+\)CH\(_2\)CH\(_2\) | 0.5 | 3.15 | -29.2 |

\(^a\)Dose(ip) 20mg/kg in rat
3.4 Lead optimization of compound 20 and lipophilicity of the optimized compound 52

As the next step, several typical substituents were incorporated into the primary lead compound 20 (Table 4); however, the coefficient of correlation was low, Hammett \( \sigma \) was correlated with logit PCA in 13 compounds (33-44, 47) (eq 9). Equation 9 suggests that the electron-donating substituents (\( \sigma < 0 \)) are desirable for PCA inhibitory activity. There were 6 compounds with an inhibitory activity greater than 18% (36-39, 41, 43), and their log\( K_{TLC} \) values were 0.6 to 1.12 (mean = 0.96), except for compound 39 (log\( K_{TLC} \) = -0.42). Therefore, a compound that has a negative Hammett \( \sigma \) and log\( K_{TLC} \) of about 1.0 is considered to be a desirable compound for PCA inhibitory activity in ip administration (Figure 4).

\[
\text{Logit PCA} = -1.02 \sigma - 0.639 \\
(\pm 0.641) (\pm 0.160) \\
(n = 13, r = 0.725, s = 0.261)
\]

![Figure 4. Plot of Hammett \( \sigma \) vs. log\( K_{TLC} \)](image)

On the other hand, the primary lead compound 20 showed the strong PCA inhibitory activity in ip administration (dose: 20 mg/kg, PCA inhibition: 72.7%), but the activity was remarkably attenuated in the oral (po) administration (dose: 50 mg, inhibition: 7.5%) (Table 5). Then, the 2,3-dihydroxypropoxy moiety: \(-\text{OCH}_2\text{CH(OH)}\text{CH}_2\text{OH}\) was selected as an alkoxy group electron-donating moiety, and para (48), meta (49), and ortho (50) substituted derivatives were synthesized [7]. As a result, compared with the other positions, the para position produced better PCA inhibitory activity and toxicity (LD\(_{50}\)). Then several compounds (51-54) were synthesized considering their lipophilicity. The correlations between log\( K_{TLC} \) and PCA inhibitory activity in po administration and acute toxicity: log(1/LD\(_{50}\)) are shown in Figures 5 and 6. The PCA inhibitory activity of compounds 51-54 were improved by the introduction of lipophilic groups (Me, Et, Ph) to
the 2,3-dihydroxypropoxy moiety (48), which yielded compound 52 that was exceptionally stronger than the other compounds (48, 51, 53, 54) (eq 11: without 52). In addition, the optimal value of log\(K_{TLC}\) was not calculated, because the coefficient of \((\log K_{TLC})^2\) of eq (12) (including 52) exceeded the 95% confidence intervals. On the other hand, the acute toxicity (LD\(_{50}\)) of compounds 20, 48-51, 53, 54 became stronger than that of compound 48 (eq 13), except for compound 52. Therefore compound 52 having log\(K_{TLC}\) of 0.07 was considered a good outlier with respect to activity and toxicity.

Table 4. log\(K_{TLC}\) and PCA inhibitory activity in ip administration

| No | Sulfonium Cation | \(\text{log}K_{TLC}\) | \(\Sigma \pi i\) | \(\sigma\) | PCA (ip) inhibition (%) | With \(\sigma_p\) |
|----|----------------|-----------------|----------------|-----|----------------------|-------------|
| 20 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O- | 0.64 | 3.23 | 0 | 72.7 | 0.23 |
| 33 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-Cl | 1.22 | 4.08 | 0.23 | 14.9 | 3.72 |
| 34 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-Cl | 1.29 | 4.08 | 0.37 | 13.3 | 3.7 |
| 35 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-Cl | 0.91 | 4.08 | 0.23\(^a\) | 4.2 | 3.7 |
| 36 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-CH\(_3\) | 1.12 | 3.73 | -0.17 | 38.5 | 3.7 |
| 37 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-CH\(_3\) | 1.08 | 3.73 | -0.07 | 34.8 | 3.7 |
| 38 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-CH\(_3\) | 0.92 | 3.73 | -0.17\(^a\) | 18.6 | 3.7 |
| 39 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-OH | -0.42 | 2.74 | -0.37 | 41.9 | 2.7 |
| 40 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-OH | -0.4 | 2.74 | 0.12 | 13.7 | 2.7 |
| 41 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-OCH\(_3\) | 0.6 | 3.32 | -0.27 | 23.8 | 3.3 |
| 42 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-OCH\(_3\) | 0.71 | 3.32 | 0.12 | 6.9 | 3.3 |
| 43 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-OC\(_2\)H\(_5\) | 1.06 | 3.85 | -0.24 | 31.3 | 3.8 |
| 44 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-OC\(_2\)H\(_5\) | 1.06 | 3.85 | 0.1 | 11.8 | 3.8 |
| 45 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-C(CH\(_3\))\(_3\) | 2.21 | 4.55 | -0.2 | -50.9 | 4.5 |
| 46 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-C(CH\(_3\))\(_3\) | 2.17 | 4.55 | -0.1 | -31.2 | 4.5 |
| 47 | (CH\(_3\))\(_2\)S+CH\(_2\)CH\(_2\)O-COOH | -0.24 | 3.19 | -0.32 | 13.4 | 3.2 |

\(^a\sigma_p\) value was adopted, \(^b\)Dose(ip) 20mg/kg in rat.
Consequently, compound 52 was initially selected as a candidate for preclinical study [7]. Nevertheless, we considered that the cholinergic toxicity of this compound was not completely eliminated, and therefore we continued further to examine new lead compounds [8].

Table 5. $\log K_{TLC}$ and PCA inhibition (%)

| No | Sulfonium Cation | $\log K_{TLC}$ | PCA (po) inhibition (%) | LD$_{50}(ip)$a (mmol/kg) |
|----|------------------|----------------|-------------------------|-------------------------|
| 20 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{CHOH}\) | 0.64 | 7.5 | - | 0.79 |
| 48 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OH}\) | -1.12 | 19.8 | 25.3 | 0.79 |
| 49 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OH}\) | -0.7 | - | 20.4 | 0.52 |
| 50 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OH}\) | -0.57 | - | 13.4 | 0.64 |
| 51 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OCH}_3\) | -0.71 | - | 21.1 | 0.66 |
| 52 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OC}_2\mathrm{H}_5\) | 0.07 | 24.8 | - | 0.84 |
| 53 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OC}_2\mathrm{H}_5\) | 1.11 | 23.7 | - | 0.29 |
| 54 | \((\mathrm{CH}_3)_2S\mathrm{CH}_2\mathrm{OCH}_2\mathrm{CH}_2\mathrm{OC}_2\mathrm{H}_5\) | 1.12 | 23.1 | - | 0.26 |

aLD$_{50}$ in mice

$logit\text{PCA} = 0.038 \log K_{TLC} - 0.557$

$(\pm 0.025)$  $(\pm 0.026)$

$(n = 4, r = 0.977, s = 0.012)$

$logit\text{PCA} = -0.024 (\log K_{TLC})^2 + 0.042 \log K_{TLC} - 0.531$

$(\pm 0.167)$  $(\pm 0.015)$  $(\pm 0.234)$

$(n = 5, r = 0.977, s = 0.012)$
log(1/LD_{50}) = 0.402 \log K_{\text{TLC}} - 0.726 \\
\text{(± 0.215)} \hspace{1cm} \text{(± 0.189)} \\
(n = 7, r = 0.907, s = 0.195)

Figure 5. Plot of PCA inhibitory activity vs. log K_{\text{TLC}}

Figure 6. Plot of log(1/LD_{50}) vs. log K_{\text{TLC}}

3.5 The optimization of secondary lead compound (55) and the lipophilicity of Suplatast Tosilate (IPD-1151T)

The amide moiety is a bioisostere of the ether moiety of the primary lead compound (20). Compound 55 was selected as the secondary lead compound, because it had some PCA inhibitory activity (27.1% 100mg/kg, ip) [8]. Typical substituents were then introduced into the benzene ring (Table 6). The plot of Hammett \( \sigma \) vs. log\( K_{\text{TLC}} \) for compounds (55-64) is shown in Figure 7. The compounds having an electron-donating substituent (60-64) had some PCA inhibitory activity, while the compounds (56, 58, 59) having an electron-withdrawing substituent except for compound 57, had no activity.

On the other hand, there was no discernible correlation between PCA inhibitory activity and log\( K_{\text{TLC}} \) in these compounds. Nevertheless, the relatively low lipophilic substituents such as acetyl (57), carboxymethyl(60), methoxy(62), hydroxyl moieties (63) except methyl (61) and propoxy groups (64) were more desirable than trifluoro (56), chloro (58), and fluoro (59) moieties. Then, as a low lipophilic and electron-donating moiety, the 2,3-dihydroxypropoxy moiety: -OCH_{2}CH(OH)CH_{2}OH was introduced to compound 55 as in the case of the primary lead compound 20. Compound 65 had the strongest PCA inhibitory activity in ip administration among these phenylcarbamoyl derivatives (55-65); furthermore, it had some inhibitory activity (18.6%) in po administration (Table 6).
Table 6. log$K_{TLC}$ and PCA inhibition (%)

\[
(CH_3)_2S^+CH_2CH_2CONH - R - CH_3 - SO_3^-
\]

| No | R     | log$K_{TLC}$ | $\Sigma \pi_i$ | Hammett $\sigma$ | PCA inhibition(%)$^a$(50mg/kg) |
|----|-------|-------------|----------------|-----------------|--------------------------------|
| 55 | H     | 0.02        | 2.32           | 0               | -8.3                           |
| 56 | CF$_3$ | 2.15        | 3.2            | 0.54            | -10.3                          |
| 57 | COCH$_3$ | 0.24      | 2.24           | 0.5             | 25.1                           |
| 58 | Cl    | 1.2         | 3.3            | 0.23            | 0.3                            |
| 59 | F     | 1.25        | 2.73           | 0.06            | 1.2                            |
| 60 | CH$_2$COOH | -1.28    | 1.6            | -0.07           | 25.5                           |
| 61 | CH$_3$ | 2.1         | 2.83           | -0.17           | 22                             |
| 62 | OCH$_3$ | 0.33       | 2.4            | -0.27           | 17.4                           |
| 63 | OH    | -1.12       | 1.66           | -0.37           | 9.7                            |
| 64 | OCH$_2$CH$_2$CH$_3$ | 2.2     | 3.37           | -0.25           | 29.8                           |
| 65 | OCH$_2$CH(OH)CH$_2$OH | -1.81   | -1.85          | -               | 34.9                           |

$^a$ PCA inhibition (ip) in rat, $^b$ PCA inhibition (po) in rat.

Figure 7. Plot of Hammett $\sigma$ vs. log$K_{TLC}$ and PCA inhibition % (the figures in parentheses)
The lipophilicity of compound 65 was very low (log\(K_{TLC}\): -1.81); therefore, some substituents were introduced to the 2,3-dihydroxypropoxy moiety: \(-\text{OCH}_{2}\text{CH(OH)}\text{CH}_{2}\text{OH}\) (Table 7) to improve the inhibitory activity in po administration. When the values of log\(K_{TLC}\) exceeded zero, their inhibitory activity deteriorated slowly (Figure 8). The log\(K_{TLC}\) values of the originally optimized compound 52 and the final compound 67 (Suplatast Tosilate) were 0.07 and 0.06, respectively. Consequently, the optimal lipophilicity of sulfonoiunm \(p\)-touensulfonate derivatives was found to be about zero as an anti-allergic drug.

**Table 7.** Plot of Hammett s vs. log\(K_{TLC}\), the numerical % values are PCA inhibitory activity.

\[
\text{(CH}_3\text{)}_2\text{S}^+\text{CH}_2\text{CH}_2\text{CONH} -\text{OCH}_2\text{CHCH}_2 -\text{OR}_1\text{ CH}_3\text{SO}_3^-
\]

| No | \(R_1\) | \(R_2\) | \(\log K_{TLC}\) | PCA inhibition (%)<sup>a</sup> |
|----|--------|--------|-----------------|------------------|
| 65 | H      | H      | -1.81           | 1.4 18.6         |
| 66 | CH\(_3\) | H      | -0.38           | 17.7 24.8        |
| 67 | CH\(_2\)\(_2\)CH\(_3\) | H      | 0.06            | 28.9 35.5        |
| 68 | (CH\(_2\))\(_2\)CH\(_3\) | H      | 2               | 16.3 13.8        |
| 69 | (CH\(_2\))\(_2\)CH\(_3\) | H      | 2.94            | 7.9 4.4          |
| 70 | \(C_6\)\(_H_11\) | H      | 1.48            | 10.2 -7.4        |
| 71 | \(C_6\)\(_H_5\) | H      | 1.52            | 14.4 4.6         |
| 72 | CH\(_3\) | CH\(_3\) | 0.57          | 17.9 10.5        |
| 73 | CH\(_2\)\(_2\)CH\(_3\) | CH\(_2\)\(_2\)CH\(_3\) | 1.26 | 0.1 5.1       |

<sup>a</sup> PCA inhibition (po) in rat.

**Figure 8.** PCA inhibition(%) in 20mg and 50mg/kg (po) vs. \(\log K_{TLC}\)
4. Conclusions

In order to know the absolute log\(K\) value of sulfonium \(p\)-toluenesulfonate derivatives for drug design and development, we measured \(R_M: \log (1/R_f -1)\) and obtained \(\log K_{TLC}\) by using octylsililated silicagel plates (Merck HPTLC RP-8 F\(_{254}\)) and 50\% (V/V) aqueous ethanol as stationary and mobile phases. The resulting \(\log K_{TLC}\) values of the optimized compounds 52 and 67 (Suplatast tosilate; IPD-1151T) were 0.07 and 0.06, respectively, in phenoxyethyl and phenylcarbamoylthethyldimethylsulfonium derivatives. Therefore, it was found that the desirable \(\log K_{TLC}\) was approximately zero for the sulfonium \(p\)-toluenesulfonates as an anti-allergic drug.

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