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Investigation of Interactions of *Ortho*- and *Para*-*N*-Aryl-Substituted 2-Trifluoromethylcinnamanilides †

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Abstract: Unsubstituted (2*E*)-*N*-phenyl-3-[2-(trifluoromethyl)phenyl]prop-2-enamide and six other *ortho*- or *para*-halogen-substituted anilides of 2-(trifluoromethyl)cinnamic acid were prepared. As the benzene nucleus of cinnamic acid itself is substituted in $C_{(2)}$ position with a trifluoromethyl moiety that is spatially close to both the amide bond and the halogen (F, Cl, CF_3) *ortho*-substitution of the anilide ring, interesting intramolecular interactions can be expected. Other derivatives are substituted at the *para*-position of the anilide ring, so that intermolecular interactions can be expected. Thus, it can be assumed that the predicted properties, especially lipophilicity, will differ significantly from the experimentally determined values. All the discussed compounds were analyzed using the reversed-phase high performance liquid chromatography method. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using an end-capped non-polar C18 stationary reversed-phase column. In the present study, the structure-lipophilicity relationships of the studied compounds are discussed.

Keywords: *N*-arylcinnamamides; synthesis; lipophilicity determinations; structure-lipophilicity relationships

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1. Introduction

Permeability, solubility and clearance, i.e., lipophilicity-dependent parameters, affect the bioavailability of drugs. More lipophilic drugs pass better through membranes by passive processes, on the other hand, they are less soluble in water, bind more to components of plasma and are more extensively metabolized (i.e., faster eliminated) or, conversely, are increasingly accumulated in adipose tissues. Thus, lipophilicity is an extremely important physicochemical parameter that crucially affects the absorption, distribution, metabolism, excretion, and toxicity of any biologically active compound. It should be noted that pesticides tend to have higher lipophilicity due to the need to penetrate more lipophilic barriers on the surfaces of plants, fungi and insects, but in principle the same laws also apply to this category of bioactive agents. Studies show that the optimal range of lipophilicity (expressed as a logarithm of partition coefficient *n*-octanol-water) log *P* 0–3 is recommended for optimal gastrointestinal absorption by passive diffusion permeability after oral administration, as there is a good balance between permeability and solubility in this range. As above-mentioned, the high lipophilicity of the compounds leads to their limited solubility, toxicity, rapid metabolism, and overall inappropriate

pharmacokinetic profile, so there is a need to monitor and control the lipophilic properties of drugs [1–5].

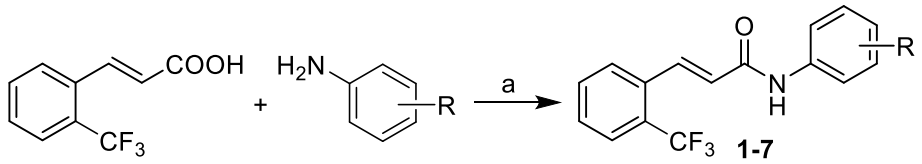
Lipophilicity reflects the primary backbone/scaffold of the molecule, but is strongly affected by the subsequent substitution of this scaffold with lipophilic/hydrophilic or even ionizable substituents. In addition, the substituents enhance the interactions of the molecule with the environment, i.e., the solvent, other small molecules and also affect interactions with biomolecules (lipid/glycolipid structures, enzymes, target proteins). Weak intra- and intermolecular interactions of molecules with the environment thus affect the final shape of the molecule and thus the ability/ease of binding to receptors/active sites of specific shapes [1–4,6].

Since lipophilicity can be understood as a physicochemical property of fundamental importance in medicinal chemistry, lipo-hydrophilic properties of newly prepared cinnamic acid derivatives was extensively studied both by prediction using chemical software and liquid chromatography, where it was found that compound retention in the reversed-phase column is affected by their lipophilicity and shows a significant correlation with the *n*-octanol/water partition coefficient [1,6–8].

The studied anilides of 2-(trifluoromethyl)cinnamic acid are substituted in position $C_{(2)}$ by the CF_3 group (which is spatially close to the amide bond –CONH–) and at the same time the compounds are substituted in the anilide part either in the *ortho* ($C_{(2)}$′) or *para* ($C_{(4)}$′) position by groups (F, Cl, CF_3) capable of forming weak interactions, so differences between in silico predicted and experimental results are expected.

2. Results and Discussion

Following the previously published ring-substituted arylcinnamanilides/arylcinnamates, which showed a wide range of biological properties [9–13], new derivatives were prepared by microwave synthesis. Briefly, 2-(trifluoromethyl)cinnamic acid dissolved in dry chlorobenzene in the presence of phosphorus trichloride and the appropriate aniline in a microwave reactor provided the desired *N*-arylcinnamamides **1–7**, see Scheme 1.

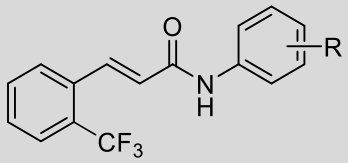


Scheme 1. Synthesis of ring-substituted (2*E*)-*N*-aryl-3-[2-(trifluoromethyl)phenyl]prop-2-enamides **1–7**.

Reagents and conditions: (a) PCl_3, chlorobenzene, MW, 130 °C, 50 min [9,12].

The lipophilicities (log *P*/Clog *P* data) of all seven compounds were calculated by means of commercially available programs ACD/Percepta ver. 2012 and ChemBioDraw Ultra 13.0. In addition, the lipophilicity of the prepared compounds was studied using the reversed-phase high performance liquid chromatography (RP-HPLC). The procedure is to measure the retention time under isocratic conditions with methanol as the organic modifier in the mobile phase using end-capped non-polar C18 stationary RP columns and then calculate the logarithm of the capacity factor *k* [7–9,12]. Furthermore, the distribution coefficients *D* at pH 7.4 and 6.5 were determined and their logarithms were calculated. The distribution coefficient, which takes into account possible ionization, is a more reliable expression of lipophilicity at physiological pH, and log $D_{7.4}$ values (at pH 7.4) are particularly important because they resemble actual physiological values. Likewise, from the point of view of absorption after oral administration, the partition coefficient at pH 6.5 (log $D_{6.5}$) is important because it is the pH in the small intestine [1,2,14,15]. All the results are shown in Table 1.

Table 1. Structure of ring-substituted (2*E*)-*N*-aryl-3-[2-(trifluoromethyl)phenyl]prop-2-enamides **1–7**, calculated lipophilicities (log *P*/Clog *P*), and experimentally determined log *k*, log $D_{7.4}$, and log $D_{6.5}$ values of investigated compounds.

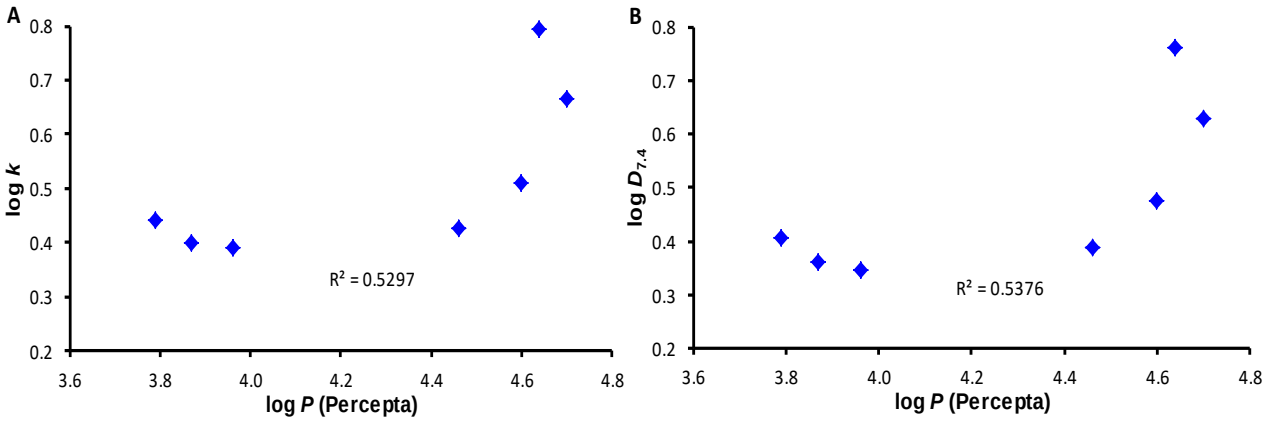


Comp.	R	log *P* [a]	log *P*/Clog *P* [b]	log *k*	log $D_{7.4}$	log $D_{6.5}$
1	H	3.96	4.10/4.5470	0.3897	0.3470	0.3457
2	2-F	3.87	4.26/4.3476	0.4001	0.3607	0.3570
3	4-F	3.79	4.26/4.9476	0.4425	0.4055	0.4009
4	2-Cl	4.60	4.66/4.6676	0.5100	0.4769	0.4708
5	4-Cl	4.70	4.66/5.5176	0.6651	0.6304	0.6250
6	2-CF3	4.46	5.02/4.4308	0.4247	0.3874	0.3814
7	4-CF3	4.64	5.02/5.8808	0.7948	0.7603	0.7532

[a] ACD/Percepta ver. 2012, [b] ChemBioDraw Ultra 13.0.

Log *P* values calculated by the ChemBioDraw software for individual anilide positional isomers are not distinguished; therefore, these values are listed only in Table 1 without other discussion. On the other hand, the predicted log *P* (ACD/Percepta) and Clog *P* (ChemBioDraw) values of compounds **1–7** are distinguished for the individual *ortho* and *para* positional isomers.

The graphs of Figure 1 show the agreement of the dependences of the experimentally determined values of lipophilicity (log *k*, log $D_{7.4}$, log $D_{6.5}$) on log *P* values. It is evident from the individual graphs that the correlation coefficients R^2 ($n = 7$) is low (range 0.5297–0.5376), indicating significant interactions of the compounds in the aqueous medium and/or with the aqueous medium, which this prediction program is not able to capture. These observations are completely different from previous experiments with the anilides of unsubstituted cinnamic acid [9,12], 3,4-dichlorocinnamic acid [16], 3-(trifluoromethyl)cinnamic acid and 4-(trifluoromethyl)cinnamic acid [17], where consensus expressed by the correlation coefficients was approximately $R^2 = 0.90$, and thus it was possible to state that the log *P* values predicted by ACD/Percepta recognized the hydro-lipophilic properties in good agreement with the experimentally determined values [9,12,16,17]. However, in the case of anilides of 2-(trifluoromethyl)cinnamic acid, this program failed.



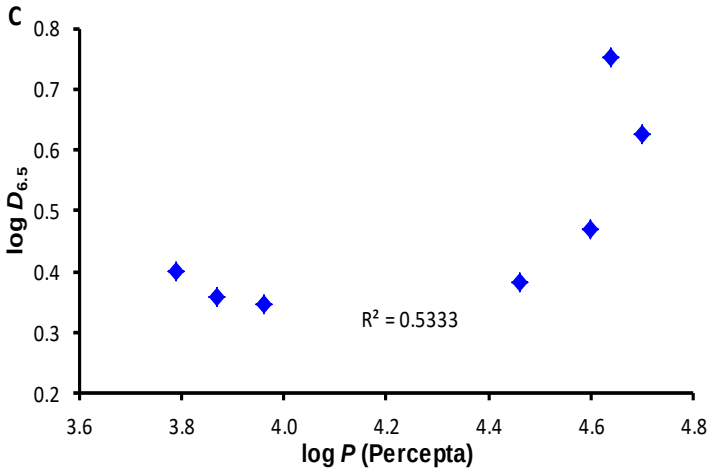


Figure 1. Comparison of predicted log *P* (ACD/Percepta) values with experimentally found log *k* (**A**), log $D_{7.4}$ (**B**), and log $D_{6.5}$ (**C**) values of ring-substituted (2*E*)-*N*-aryl-3-[2-(trifluoromethyl)phenyl]prop-2-enamides **1**–**7**.

The presence of intra and intermolecular interactions reflects Clog *P* values much better. Clog *P* is the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions. The dependences of the experimentally obtained data (log *k*, log $D_{7.4}$, log $D_{6.5}$) on the predicted Clog *P* data are shown in the graphs of Figure 2. The mutual consensus is considerably higher, as expressed by the correlation coefficients in the range 0.9004–0.9038. However, the most significant correlations are shown in the graphs of Figure 3, where the experimental values of log *k* are compared with log *D*. There it is possible to observe correlation coefficients of 0.99.

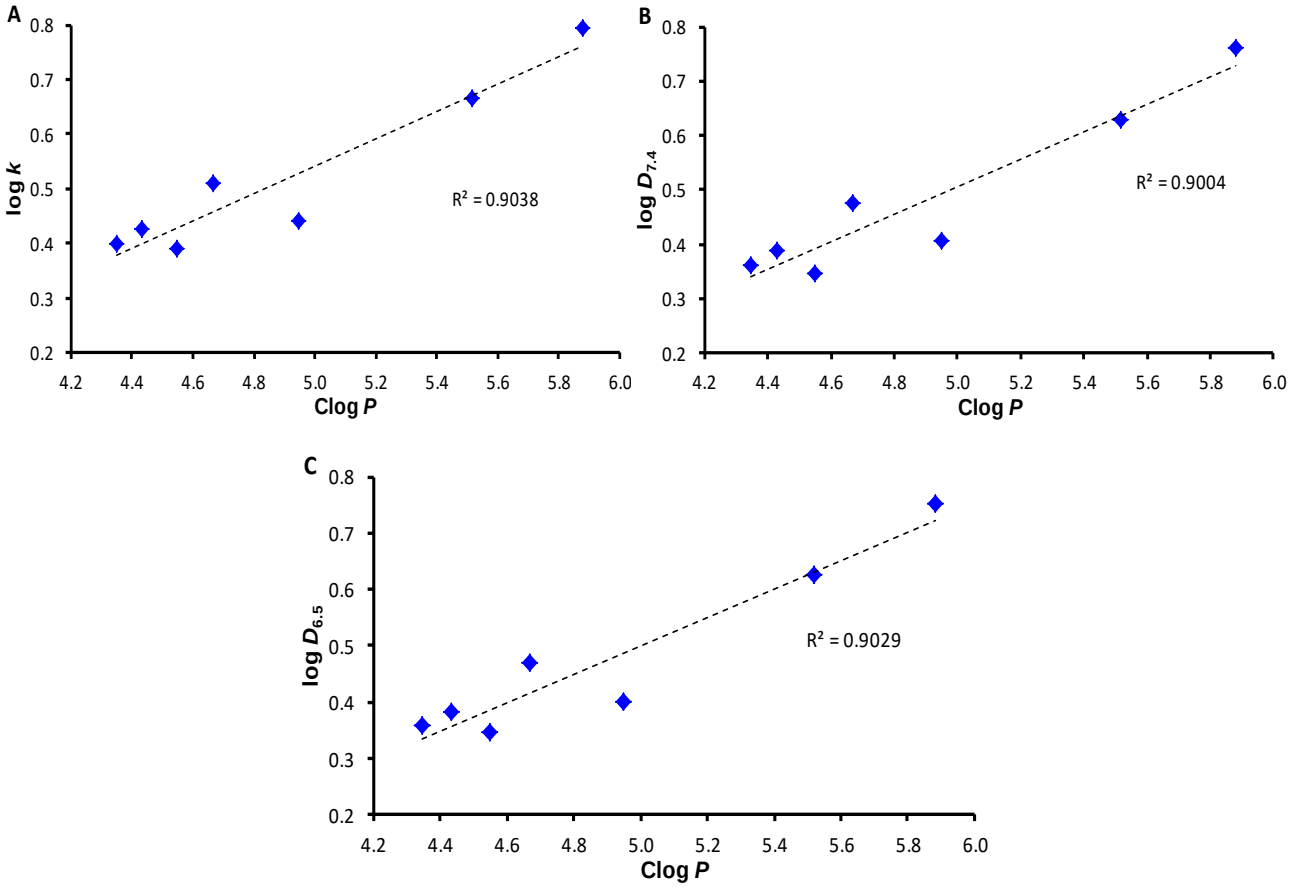


Figure 2. Comparison of predicted Clog *P* (ChemBioDraw) values with experimentally found log *k* (**A**), log $D_{7.4}$ (**B**), and log $D_{6.5}$ (**C**) values of ring-substituted (2*E*)-*N*-aryl-3-[2-(trifluoromethyl)phenyl]prop-2-enamides **1**–**7**.

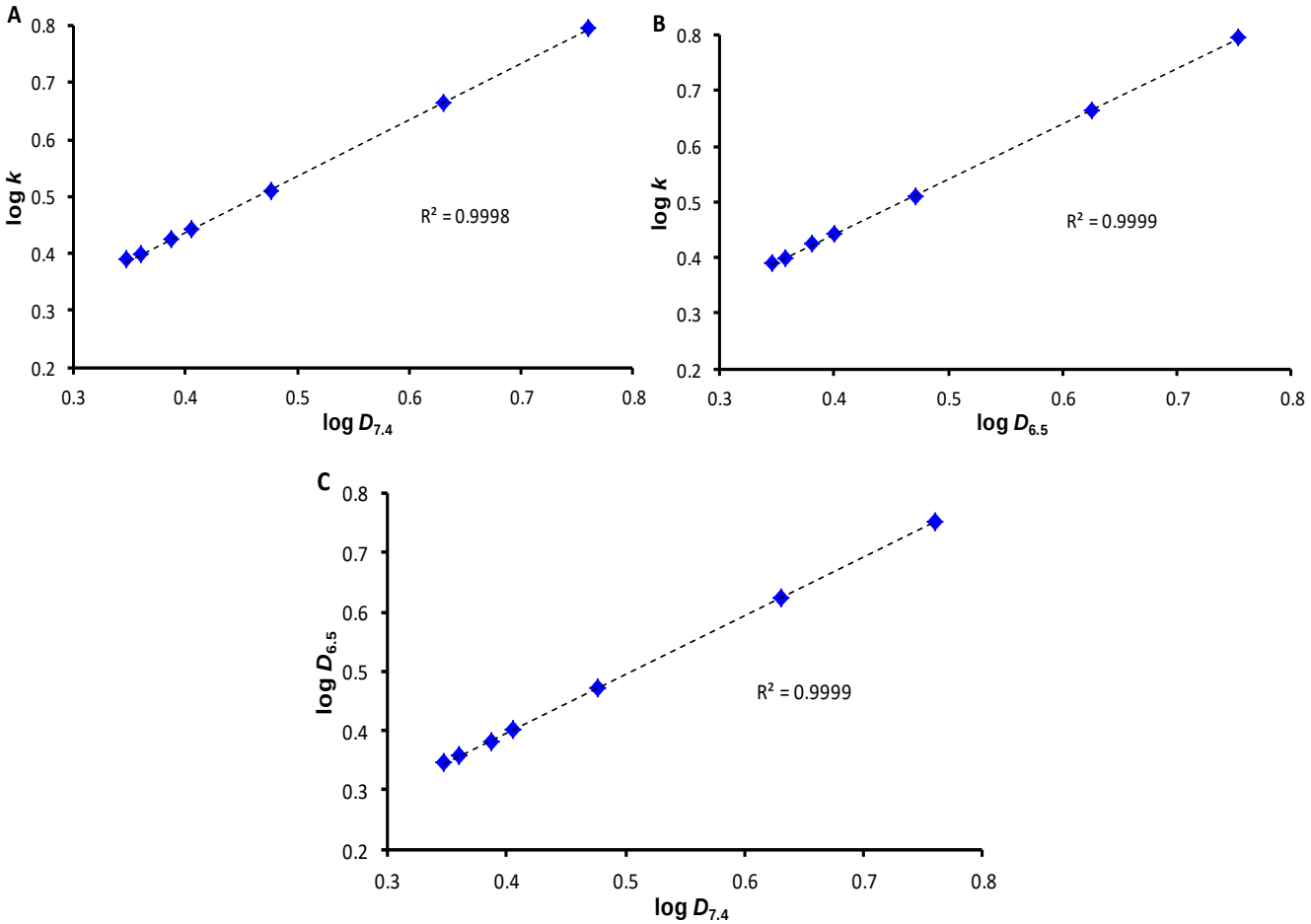


Figure 3. Comparison of experimentally found log *k* values with log $D_{7.4}$ (**A**) and log $D_{6.5}$ (**B**) values and log $D_{7.4}$ with log $D_{6.5}$ (**C**) of discussed compounds **1**–**7**.

The order of lipophilicity of the individual derivatives **1**–**7** is shown in Table 2. Thus, from the increasing order of lipophilicity values, it can be seen that unsubstituted compound **1** has the lowest lipophilicity and *ortho*-substituted derivatives **2**, **4**, **6** demonstrated lower lipophilicity than *para*-substituted compounds **3**, **5**, **7**. Very interesting is the unexpected fact that derivative **6** (R = 2-CF_3) is less lipophilic than compound **4** (R = 2-Cl), while for *para*-substituted derivatives **5**, **7** the order is exactly the opposite; this order is logical and expected.

Table 2. Discussed compounds ordered according to increasing values of lipophilicity of individual derivatives.

Log *P*	4-F	<	2-F	<	H	<	2-CF_3	<	2-Cl	<	4-CF_3	<	4-Cl
Clog *P*	2-F	<	2-CF_3	<	H	<	2-Cl	<	4-F	<	4-Cl	<	4-CF_3
Log *k*	H	<	2-F	<	2-CF_3	<	4-F	<	2-Cl	<	4-Cl	<	4-CF_3
Log $D_{7.4}$	H	<	2-F	<	2-CF_3	<	4-F	<	2-Cl	<	4-Cl	<	4-CF_3
Log $D_{6.5}$	H	<	2-F	<	2-CF_3	<	4-F	<	2-Cl	<	4-Cl	<	4-CF_3

Based on all these observed differences between the predicted and experimentally obtained values in comparison with other previously described cinnamic acid derivatives, it can be concluded that mainly fluorinated substituents cause significant interactions of the investigated compounds with the aqueous environment. These interactions are not taken into account in ACD/Percepta and so this software cannot be used to predict physicochemical properties. The interactions then affect the observed properties and it is possible to assume the projection of these interactions into the size of biological activities and

structure-lipophilicity relationships and structure-activity relationships, respectively, which will be investigated in detail.

3. Experimental

3.1. General

All reagents were purchased from Merck (Sigma-Aldrich, St. Louis, MO, USA) and Alfa (Alfa-Aesar, Ward Hill, MA, USA). Reactions were performed using an Anton-Paar Monowave 50 microwave reactor (Graz, Austria). All ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA 600II device (600 MHz for ^{1}H and 150 MHz for ^{13}C, JEOL, Tokyo, Japan) in dimethyl sulfoxide-d_6 (DMSO-d_6). ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm. High-resolution mass spectra were measured using a high-performance liquid chromatograph Dionex UltiMate® 3000 (Thermo Scientific, West Palm Beach, FL, USA) coupled with an LTQ Orbitrap XLTM Hybrid Ion Trap-Orbitrap Fourier Transform Mass Spectrometer (Thermo Scientific) equipped with a HESI II (heated electrospray ionization) source in the positive mode.

3.2. Synthesis

General procedure for synthesis of target compounds **1–7**: 2-(Trifluoromethyl)cinnamic acid (1 mM) was suspended in dry chlorobenzene (6 mL) at ambient temperature and phosphorus trichloride (0.5 mM, 0.5 eq.), and the corresponding substituted aniline (1 mM, 1 eq.) were added dropwise. The reaction mixture was transferred to the microwave reactor, where the synthesis was performed (50 min, 130 °C). Then the mixture was cooled to 40 °C, and then the solvent was removed to dryness under reduced pressure. The residue was washed with hydrochloride acid and water. The crude product was recrystallized from ethanol.

(2E)-N-Phenyl-3-[2-(trifluoromethyl)phenyl]prop-2-enamide (**1**). Yield 64%; ^{1}H-NMR (DMSO-d_6) δ: 10.35 (s, 1H), 7.91–7.81 (m, 3H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.72–7.69 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.37–7.32 (m, 2H), 7.11–7.07 (m, 1H), 6.91 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 162.66, 138.96, 134.76 (m), 133.24, 133.16, 129.82, 128.86, 127.87, 126.91, 126.91 (q, *J* = 29.9 Hz), 126.20 (q, *J* = 4.8 Hz), 124.18 (q, *J* = 273.6 Hz), 123.67, 119.31; HR-MS: for $C_{16}H_{13}ONF_3$ $[M + H]^+$ calculated 292.0944 *m*/*z*, found 292.0937 *m*/*z*.

(2E)-N-(2-Fluorophenyl)-3-[2-(trifluoromethyl)phenyl]prop-2-enamide (**2**). Yield 74%; ^{1}H-NMR (DMSO-d_6), δ: 10.11 (s, 1H) 8.14–8.11 (m, 1H), 7.91–7.77 (m, 4H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.32–7.27 (m, 1H), 7.23–7.14 (m, 3H). ^{13}C-NMR (DMSO-d_6), δ: 163.14, 153.32 (d, *J* = 245.7 Hz), 153.19 (m), 133.17 (m), 129.94, 127.89, 126.97 (q, *J* = 28.9 Hz), 126.45, 126.23 (q, *J* = 5.8 Hz), 126.12 (d, *J* = 10.6 Hz), 125.34 (m), 124.49 (d, *J* = 3.9 Hz), 124.18 (q, *J* = 274.6 Hz), 123.61, 115.60, 115.41. HR-MS: for $C_{16}H_{12}ONF_4$ $[M + H]^+$ calculated 310.0850 *m*/*z*, found 310.0842 *m*/*z*.

(2E)-N-(4-Fluorophenyl)-3-[2-(trifluoromethyl)phenyl]prop-2-enamide (**3**). Yield 69%; ^{1}H-NMR (DMSO-d_6) δ: 10.41 (s, 1H), 7.91–7.76 (m, 4H), 7.74–7.70 (m, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.21–7.17 (m, 2H), 6.87 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 162.57, 158.22 (d, *J* = 239.9 Hz), 135.38 (d, *J* = 2.9 Hz), 134.83, 133.17, 129.85, 127.89, 126.92 (q, *J* = 28.9 Hz), 126.71, 126.21 (q, *J* = 5.8 Hz), 124.17 (q, *J* = 274.6 Hz), 121.07 (d, *J* = 8.7 Hz), 115.55, 115.39; HR-MS: for $C_{16}H_{12}ONF_4$ $[M + H]^+$ calculated 310.0850 *m*/*z*, found 310.0842 *m*/*z*.

(2E)-N-(2-Chlorophenyl)-3-[2-(trifluoromethyl)phenyl]prop-2-enamide (**4**). Yield 70%; ^{1}H-NMR (DMSO-d_6), δ: 9.84 (s, 1H), 7.95–7.93 (m, 2H), 7.86 (dd, *J* = 15.1 Hz, *J* = 2.1 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.54–7.53 (m, 1H), 7.38–7.35 (m, 1H), 7.23–7.19 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 163.15, 153.31, 134.71, 133.15, 133.10, 129.96, 129.54, 127.95, 127.50, 126.97 (q, *J* = 28.9 Hz), 126.36 (m), 126.22 (q, *J* = 5.8 Hz), 125.77 (m), 125.55, 124.17 (q, *J* = 274.6 Hz); HR-MS: for $C_{16}H_{12}ONClF_3$ $[M + H]^+$ calculated 326.0554 *m*/*z*, found 326.0546 *m*/*z*.

(2E)-N-(4-Chlorophenyl)-3-[2-(trifluoromethyl)phenyl]prop-2-enamide (**5**). Yield 78%; NMR (DMSO-d_6) δ: 10.50 (s, 1H), 7.91–7.82 (m, 3H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.75–7.72 (m,

2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.43-7.39 (m, 2H), 6.88 (d, *J* = 15.1 Hz, 1H); ^{13}C-NMR (DMSO-*d*$_6$), δ: 162.79, 137.92, 135.06 (m), 133.20, 129.94, 128.80, 128.53, 127.91, 127.26, 126.95 (q, *J* = 28.9 Hz), 126.58, 126.24 (q, *J* = 5.8 Hz), 124.17 (q, *J* = 273.6 Hz), 120.87; HR-MS: for $C_{16}H_{12}ONClF_3$ $[M + H]^+$ calculated 326.0554 *m*/*z*, found 326.0545 *m*/*z*.

(2E)-N,3-bis [2-(Trifluoromethyl)phenyl]prop-2-enamide (**6**). Yield 75%; ^{1}H-NMR (DMSO-*d*$_6$), δ: 9.89 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.87–7.77 (m, 4H), 7.74–7.62 (m, 3H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (DMSO-*d*$_6$), δ: 163.84, 135.33 (q, *J* = 1.9 Hz), 135.00 (q, *J* = 1.9 Hz), 133.17, 133.05, 133.01 (q, *J* = 1.9 Hz), 129.98, 129.72, 127.94, 126.99 (q, *J* = 29.9 Hz), 126.81, 126.28 (m), 125.94, 124.29 (q, *J* = 29.9 Hz), 124.17 (q, *J* = 273.6 Hz), 123.60 (q, *J* = 273.6 Hz). HR-MS: for $C_{17}H_{12}ONF_6$ $[M + H]^+$ calculated 360.0818 *m*/*z*, found 360.0809 *m*/*z*.

(2E)-3-[2-(Trifluoromethyl)phenyl]-N-[4-(trifluoromethyl)phenyl]prop-2-enamide (**7**). Yield 66%; ^{1}H-NMR (DMSO-*d*$_6$) δ: 10.72 (s, 1H), 7.92–7.86 (m, 4H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.79 (*t*, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 15.1 Hz, 1H); ^{13}C-NMR (DMSO-*d*$_6$), δ: 163.21, 142.51, 135.61 (q, *J* = 1.9 Hz), 133.23, 132.97 (m), 130.06, 127.96, 127.02 (q, *J* = 29.9 Hz), 126.37, 126.21 (m), 124.35 (q, *J* = 270.7 Hz), 124.16 (q, *J* = 274.6 Hz), 123.63 (q, *J* = 31.8 Hz), 119.29. HR-MS: for $C_{17}H_{12}ONF_6$ $[M + H]^+$ calculated 360.0818 *m*/*z*, found 360.0809 *m*/*z*.

3.3. Lipophilicity Determination by HPLC

A HPLC separation module Waters Alliance 2695 XE equipped with a Waters Dual Absorbance Detector 2486 (Waters Corp., Milford, MA, USA) was used. A chromatographic column Symmetry® C18 5 μm, 4.6 × 250 mm, Part No. W21751W016 (Waters Corp., Milford, MA, USA) was used. The HPLC separation process was monitored by Empower® 3 Chromatography Manager Software (Waters Corp.). Isocratic elution by a mixture of MeOH p.a. (72%) and H_2O-HPLC Mili-Q grade (28%) as a mobile phase was used for the determination of capacity factor *k*. Isocratic elution by a mixture of MeOH p.a. (72%) and acetate buffered saline (pH 7.4 and pH 6.5) (28%) as a mobile phase was used for the determination of distribution coefficient expressed as $D_{7.4}$ and $D_{6.5}$. The total flow of the column was 1.0 mL/min, injection 20 μL, column temperature 40 °C, and sample temperature 10 °C. The detection wavelength of 210 nm was chosen. A KI methanolic solution was used for determination of the dead times (t_D). Retention times (t_R) were measured in minutes. The capacity factors *k* were calculated according to the formula $k = (t_R - t_D)/t_D$, where t_R is the retention time of the solute, and t_D is the dead time obtained using an unretained analyte. The distribution coefficients D_{pH} were calculated according to the formula $D_{pH} = (t_R - t_D)/t_D$. Each experiment was repeated three times. The log *k* values of individual compounds are shown in Table 1.

3.4. Lipophilicity Calculations

Log *P*, i.e., the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programs ACD/Percepta (Advanced Chemistry Development. Inc., Toronto, ON, Canada, 2012) and ChemBioDraw Ultra 13.0 (CambridgeSoft, PerkinElmer Inc., MA, USA). Clog *P* values were calculated using ChemBioDraw Ultra 13.0 (CambridgeSoft) software. The results are shown in Table 1.

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