An Approach towards the Quantitative Structure–Activity Relationships of Caffeic Acid and its Derivatives

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Caffeic acid and its derivatives are already known to possess a wide range of biological activities. We have developed quantitative structure–activity relationships (QSARs) for different series of caffeic acid derivatives (including caffeic acid) in order to understand the chemical–biological interactions governing antitumor activity against six different tumor cell lines, nitric oxide production, anti-HIV and enzymatic activities, and binding affinity to the lck *domain. QSAR results have shown that the different activities of caffeic acid and its derivatives are largely dependent on their hydrophobicity or molar refractivity, with a bilinear correlation being the most important.*

Introduction

Caffeic acid and its derivatives are ubiquitously distributed in the plant kingdom and have been reported to be present in propolis, olives, coffee beans, fruits, and vegetables. They are found in both simple forms, including esters, sugar esters, amides, and glycosides, and in rather more complex forms, such as dimers, trimers, and flavonoid-based derivatives.[1] These naturally occurring or synthetic phenolic compounds elicit several interesting and varied biological responses, such as antibacterial,[2–6] antifungal,[6,7] antiinflammatory,[4,8] antiplatelet,[9,10] antiviral,[3,11–17] anticancer,[18–24] antiatherosclerotic,[25] antioxidant,[7,26–28] immunomodulatory,[29] neutrophile elastase,[30–32] lipoxygenase,[33,34] vasorelaxant,[35] apoptosis,[36] radical-scavenging,[37] and antimutagenicity[37] activities; they also activate TREK-1 potassium channels.[38] Caffeic acid derivatives have also been reported to block completely the production of reactive oxygen species in human neutrophils and in the cell-free xanthine/xanthine oxidase system.[39]

The radical-scavenging and antioxidative activities of caffeic acid and its derivatives are mainly due to the presence of two phenolic alcohol groups at *ortho* positions. These electron-donating groups at *ortho* positions are also responsible for lowering the O–H bond dissociation enthalpy and increasing the rate of hydrogen-atom transfer to peroxyl radicals.[40] The olefinic linkage in the side chain also maximizes the stabilization of the phenoxyl radical.[41]

In a recent study on the cytotoxicity of a series of caffeic acid esters versus L1210 leukemia and MCF-7 breast cancer cells, the quantitative structure–activity relationships (QSARs) described by Equations (1) and (2) were obtained, respectively.[23]

Inhibition of growth of L1210 cells by caffeic acid esters :

$$\log 1/C = 0.46(\pm 0.12)\log P_{\text{calcd}} + 3.84(\pm 0.37) \quad (1)$$

$n = 9$, $r^2 = 0.915$, $q^2 = 0.881$, $s = 0.165$

Inhibition of growth of MCF-7 cells by caffeic acid esters :

$$\log 1/C = 0.37(\pm 0.07)\log P_{\text{calcd}} + 2.64(\pm 0.20) \quad (2)$$

$n = 9$, $r^2 = 0.956$, $q^2 = 0.931$, $s = 0.075$

In these equations, C is the molar concentration of caffeic acid ester that induces 50% inhibition of growth after 48 h. $\log P_{\text{calcd}}$ is the calculated partition coefficient of each compound. The number of data points in the study is represented by n, the correlation coefficient by r, the standard deviation by s, and the cross-validated r^2 by q^2. QSARs 1 and 2 showed that the cytotoxicity of caffeic acid esters against L1210 leukemia and MCF-7 breast cancer cells, respectively, are well correlated by hydrophobicity alone. In these equations, the absence of an electronic term, such as sigma-plus (σ^+) or homolytic bond dissociation energy (BDE), is to be expected since the catecholic moiety is present and constant in all of the analogues.

In this paper, we would like to report QSAR studies on different series of caffeic acid derivatives (including caffeic acid) with respect to the different biological activities. In the past 42 years, since the advent of this methodology,[42] the use of QSARs has become increasingly helpful in understanding chemical–biological interactions in drug and pesticide research, as well as in areas of toxicology.[43] This method is useful in elucidating the mechanisms of chemical–biological interaction in various biomolecules, particularly enzymes, membranes, organelles, and cells.[43,44] It has also been utilized for the evaluation of absorption, distribution, metabolism, and excretion (ADME) phenomena in many organisms and in whole animal studies. The QSAR approach employs extrathermodynamically derived and computational-based descriptors to correlate biological

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activity in isolated receptors, cellular systems, and in vivo. The three standard classifications routinely used in QSAR analysis, electronic, hydrophobic, and steric, including topological indices, have been invaluable in helping to delineate a large number of receptor–ligand interactions that are critical in biological processes.[43] QSAR models can stand alone, augment other graphical approaches, or be examined in tandem with equations of a similar mechanistic genre to establish authenticity and reliability.[45]

Results and Discussion

QSAR for antiproliferative activity

Nagaoka et al.[20] studied the antiproliferative activity of caffeic acid phenethyl ester (CAPE) together with its twenty-two analogues **1** (Table 1) towards six different tumor cell lines, that is, the murine Lewis lung carcinoma (LLC), murine B16-BL6 malonoma (B16-BL6), murine colon 26-L5 carcinoma (colon 26-L5), human HT-1080 fibrosarcoma (HT-1080), human cervix HeLa adenocarcinoma (HeLa), and human lung A549 adenocarcinoma (A549) cell lines. We derived six equations [Eqs. (3)–(8)], where β is a disposable parameter, from their results. The hydrophobicity of the molecules correlates with the activity in a bilinear fashion in five equations [Eqs. (3)–(7)]. This suggests that the activity of caffeic acid esters **1** first increases with an increase in hydrophobicity to an optimum $\log P_{calcd}$ value (6.69, 5.74, 5.38, 5.26, and 6.79, respectively) and then decreases linearly. In Equation (8), we obtained a bilinear correlation with the calculated molar refractivity (CMR), which is in contrast to the implications of Equations (3)–(7). This correlation shows that the activity against human lung A549 adenocarcinoma (A549) cell lines increases with an increase in the overall size and polarizability of compounds **1** up to an optimum CMR value (11.31) and then decreases linearly.

Inhibition of growth of murine LLC cells by caffeic acid esters **1** (Table 1) : [20]

$$\log 1/C = 0.16(\pm0.04)\log P_{calcd} - 1.0(\pm0.17)\log(\beta \times 10^{\log P_{calcd}}+1)+5.06(\pm0.16) \quad (3)$$

$n = 22$, $r^2 = 0.892$, $q^2 = 0.846$, $s = 0.116$

optimum $\log P_{calcd} = 6.69$

$\log \beta = -7.41$

range in $\log 1/C = 4.88 - 6.13$

outlier : $(CH_2)_2{-}cy{-}C_6H_{11}$

Inhibition of growth of murine B16-BL6 cells by caffeic acid esters **1** (Table 1) : [20]

$$\log 1/C = 0.11(\pm0.05)\log P_{calcd} - 0.56(\pm0.12)\log(\beta \times 10^{\log P_{calcd}}+1)+5.21(\pm0.21) \quad (4)$$

$n = 21$, $r^2 = 0.901$, $q^2 = 0.846$, $s = 0.116$

optimum $\log P_{calcd} = 5.74$

$\log \beta = -6.36$

range in $\log 1/C = 4.76 - 5.83$

outliers : CH_2Ph, CH_3

Inhibition of growth of murine colon 26-L5 cells by caffeic acid esters **1** (Table 1) : [20]

$$\log 1/C = 0.59(\pm0.14)\log P_{calcd} - 1.41(\pm0.28)\log(\beta \times 10^{\log P_{calcd}}+1)+4.73(\pm0.54) \quad (5)$$

$n = 20$, $r^2 = 0.878$, $q^2 = 0.843$, $s = 0.313$

optimum $\log P_{calcd} = 5.38$

$\log \beta = -5.52$

range in $\log 1/C = 4.79 - 7.70$

outliers : $(CH_2)_7CH_3$, $(CH_2)_9CH_3$, $(CH_2)_{13}CH_3$

Inhibition of growth of human HT-1080 cells by caffeic acid esters **1** (Table 1) : [20]

$$\log 1/C = 0.15(\pm0.04)\log P_{calcd} - 0.45(\pm0.09)\log(\beta \times 10^{\log P_{calcd}}+1)+4.29(\pm0.15) \quad (6)$$

$n = 19$, $r^2 = 0.891$, $q^2 = 0.849$, $s = 0.089$

optimum $\log P_{calcd} = 5.26$

$\log \beta = -5.54$

range in $\log 1/C = 4.20 - 5.13$

outliers : $(CH_2)_8Ph$, $(CH_2)_7CH_3$, $(CH_2)_{13}CH_3$, $(CH_2)_{15}CH_3$

Inhibition of growth of human cervix HeLa cells by caffeic acid esters **1** (Table 1) : [20]

$$\log 1/C = 0.26(\pm0.06)\log P_{calcd} - 1.52(\pm0.38)\log(\beta \times 10^{\log P_{calcd}}+1)+4.09(\pm0.26) \quad (7)$$

$n = 18$, $r^2 = 0.877$, $q^2 = 0.838$, $s = 0.167$

optimum $\log P_{calcd} = 6.79$

$\log \beta = -7.48$

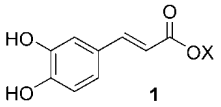
range in $\log 1/C = 4.57 - 5.73$

outliers : $(CH_2)_3Ph$, $(CH_2)_4Ph$, $(CH_2)_6Ph$, $(CH_2)_3CH_3$, $(CH_2)_{15}CH_3$

Inhibition of growth of human lung A549 cells by caffeic acid esters **1** (Table 1) : [20]

$$\log 1/C = 0.08(\pm0.02)CMR - 0.42(\pm0.12)\log(\beta \times 10^{CMR}+1)+3.87(\pm0.15) \quad (8)$$

Table 1. *Biological and physicochemical constants used to derive QSAR Equations (3)–(8) for the inhibition of growth of LLC, B16-BL6, colon 26 L5, HT-1080, HeLa, and A549 cells, respectively, as well as to derive QSAR Equation (9) for the production of nitric oxide in lipopolysaccharide-activated murine macrophase-like J774.1 cells by caffeic acid esters* ***1****.*



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No.	X	log 1/*C* [Eq. (3)]			log 1/*C* [Eq. (4)]			log 1/*C* [Eq. (5)]			log 1/*C* [Eq. (6)]			log 1/*C* [Eq. (7)]			log 1/*C* [Eq. (8)]			log 1/*C* [Eq. (9)]			log P_{calcd}	CMR
		obsd	calcd	Δ	obsd	calcd	Δ	obsd	calcd	Δ	obsd	calcd	Δ	obsd	calcd	Δ	obsd	calcd	Δ	obsd	calcd	Δ		
1a	CH_2Ph	5.24	5.54	−0.30	5.10[a]	3.85	1.25	5.87	6.47	−0.60	4.92	4.75	0.17	4.60	4.85	−0.25	4.71[a]	1.20	3.51	4.86	4.98	−0.12	2.97	7.83
1b	$(CH_2)_2Ph$	5.59	5.59	0.00	5.66	5.56	0.10	6.82	6.67	0.16	4.84	4.80	0.04	4.97	4.93	0.04	4.49	4.51	−0.02	5.12	5.02	0.09	3.30	8.29
1c	$(CH_2)_3Ph$	5.63	5.65	−0.02	5.67	5.60	0.06	7.00	6.88	0.12	4.74	4.86	−0.11	4.66[a]	−0.55	5.21	4.63	4.54	0.08	5.13	5.08	0.06	3.68	8.76
1d	$(CH_2)_4Ph$	5.64	5.74	−0.10	5.70	5.66	0.04	7.70	7.17	0.53	4.88	4.93	−0.06	4.70[a]	−1.22	5.92	4.50	4.58	−0.08	5.17	5.15	0.02	4.21	9.22
1e	$(CH_2)_5Ph$	5.90	5.82	0.07	5.67	5.71	−0.04	7.10	7.42	−0.32	5.13	4.99	0.14	4.97	5.30	−0.33	4.66	4.62	0.04	5.20	5.22	−0.02	4.74	9.68
1f	$(CH_2)_6Ph$	5.85	5.91	−0.05	5.73	5.76	−0.02	7.10	7.55	−0.46	4.98	5.02	−0.04	5.04[a]	−2.55	7.59	4.67	4.65	0.02	5.32	5.29	0.03	5.26	10.15
1g	$(CH_2)_8Ph$	6.08	6.04	0.03	5.74	5.73	0.01	7.05	7.23	−0.18	4.69[a]	2.42	2.27	5.58	5.67	−0.08	4.65	4.70	−0.05	5.27	5.34	−0.07	6.32	11.08
1h	$(CH_2)_{12}Ph$	5.09	5.35	−0.26	4.76	4.95	−0.18	5.76	5.58	0.18	4.20	4.29	−0.08	4.74	4.73	0.00	4.67[a]	−0.54	5.21	4.94	4.99	−0.04	8.44	12.93
1i	$CH_2CH{=}CHPh$	5.67	5.64	0.03	5.55	5.59	−0.04	6.66	6.82	−0.17	4.77	4.84	−0.07	4.94	5.00	−0.06	4.30[a]	0.87	3.43	5.02	5.06	−0.04	3.57	8.81
1j	(*Z*)-$(CH_2)_6CH{=}CHPh$	6.06	6.01	0.04	5.75	5.77	−0.02	7.70	7.40	0.30	4.98	4.95	0.03	5.71	5.61	0.10	4.65	4.70	−0.05	5.27	5.34	−0.07	6.02	11.13
1k	(*E*)-$(CH_2)_6CH{=}CHPh$	6.00	6.01	−0.02	5.83	5.77	0.06	7.70	7.40	0.30	4.99	4.95	0.04	5.72	5.61	0.11	4.47[a]	0.08	4.40	5.48	5.34	0.14	6.02	11.13
1l	(*Z*)-$(CH_2)_{10}CH{=}CHPh$	5.71	5.57	0.14	5.14	5.08	0.06	5.93	5.83	0.10	4.43	4.38	0.05	5.14	5.05	0.08	4.42	4.42	−0.01	5.29[a]	2.82	2.47	8.13	12.98
1m	(*E*)-$(CH_2)_{10}CH{=}CHPh$	5.62	5.57	0.04	5.14	5.08	0.06	5.60	5.83	−0.22	4.42	4.38	0.04	5.07	5.05	0.01	4.43	4.42	0.00	5.17	5.05	0.12	8.13	12.98
1n	$(CH_2)_2$-cy-C_6H_{11}[b]	6.13[a]	1.40	4.73	5.70	5.68	0.02	7.52	7.26	0.26	4.93	4.95	−0.03	5.02	5.21	−0.19	4.55	4.52	0.04	5.10	5.17	−0.07	4.38	8.39
1o	CH_3	5.34	5.26	0.08	4.78[a]	4.66	0.12	5.49	5.44	0.05	4.45	4.48	−0.03	4.57	4.39	0.18	4.36	4.28	0.08	4.69	4.72	−0.04	1.20	5.32
1p	CH_2CH_3	5.36	5.34	0.02	5.33	5.39	−0.06	5.94	5.75	0.19	4.48	4.56	−0.08	4.61	4.53	0.08	4.21	4.32	−0.11	4.79	4.80	−0.01	1.73	5.78
1q	$(CH_2)_2CH_3$	5.48	5.43	0.06	5.41	5.45	−0.04	5.82	6.06	−0.24	4.75	4.64	0.11	4.66	4.67	−0.01	4.37	4.35	0.02	4.89	4.88	0.01	2.26	6.25
1r	$(CH_2)_3CH_3$	5.61	5.51	0.09	5.56	5.51	0.05	6.57	6.37	0.20	4.69	4.72	−0.03	5.40[a]	0.57	4.83	4.37	4.39	−0.02	5.05	4.95	0.10	2.79	6.71
1s	$(CH_2)_7CH_3$	5.92	5.85	0.07	5.65	5.73	−0.08	6.66[a]	0.71	5.95	4.70[a]	2.84	1.86	5.62	5.34	0.28	4.46	4.53	−0.07	5.22	5.24	−0.03	4.90	8.56
1t	$(CH_2)_9CH_3$	5.94	6.01	−0.07	5.69	5.77	−0.08	6.60[a]	−0.16	6.76	4.85	4.96	−0.11	5.73	5.60	0.14	4.67	4.60	0.07	5.33	5.34	−0.01	5.96	9.49
1u	$(CH_2)_{11}CH_3$	6.11	6.04	0.07	5.74	5.55	0.20	6.54	6.72	−0.19	4.72	4.70	0.02	5.70	5.69	0.00	4.67	4.67	0.00	5.22	5.26	−0.04	7.02	10.42
1v	$(CH_2)_{13}CH_3$	5.59	5.61	−0.02	4.83	5.11	−0.27	4.79[a]	−1.9	6.69	4.70[a]	1.90	2.80	5.00	5.11	−0.11	4.73	4.70	0.03	5.07	5.06	0.01	8.08	11.35
1w	$(CH_2)_{15}CH_3$	4.88	4.80	0.08	4.81	4.63	0.18	4.99	5.01	−0.01	4.43[a]	1.59	2.84	4.86[a]	−7.44	12.3	4.63	4.61	0.01	4.80	4.84	−0.04	9.14	12.27

[a] Not included in the derivation of the respective QSAR equations. [b] cy = cyclohexyl.

$n = 19$, $r^2 = 0.864$, $q^2 = 0.810$, $s = 0.059$

optimum CMR = 11.31

$\log\beta = -11.96$

range in $\log 1/C = 4.21 - 4.73$

outliers : CH_2Ph, $(CH_2)_{12}Ph$, $CH_2CH{=}CHPh$; (E)-$(CH_2)_6CH{=}CHPh$

QSAR for nitric oxide inhibitors

Nagaoka et al.[21] also studied the inhibitory activity of caffeic acid phenethyl ester (CAPE) together with its twenty-two analogues **1** toward nitric oxide production in lipopolysaccharide-activated murine macrophage-like J774.1 cells. Equation (9), which was obtained from their data, indicates a bilinear correlation with $\log P_{calcd}$.

Inhibitory effects of caffeic acid esters **1** on nitric oxide production in lipopolysaccaride-activated murine macrophage-like J774.1 cells (Table 1):[21]

$$\log 1/C = 0.14(\pm0.03)\log P_{calcd} - 0.36(\pm0.07)\log(\beta \times 10^{\log P_{calcd}}+1)+4.55(\pm0.11) \quad (9)$$

$n = 22$, $r^2 = 0.886$, $q^2 = 0.849$, $s = 0.073$

optimum $\log P_{calcd} = 6.11$

$\log\beta = -6.28$

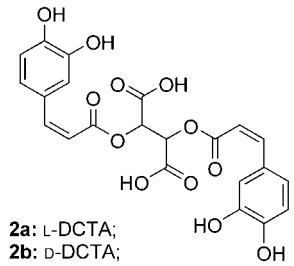
range in $\log 1/C = 4.69 - 5.48$

outlier : (Z)-$(CH_2)_{10}CH{=}CHPh$

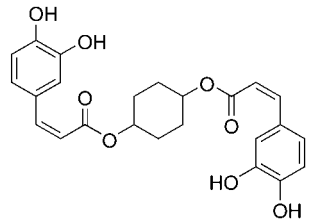
From this equation, it appears that hydrophobicity plays an important role in the production of nitric oxide in lipopolysaccharide-activated murine macrophage-like J774.1 cells up to a $\log P_{calcd}$ value of 6.11 and the production of nitric oxide then decreases linearly with further increases in the hydrophobicity of the compounds.

QSAR for anti-HIV activity

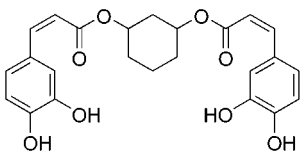
Dicaffeoyltartaric acids (DCTAs) and dicaffeoylquinic acids (DCQAs) are well-known potent and selective inhibitors of human immunodeficiency virus type 1 (HIV-1) integrase. They also inhibit HIV-1 replication at nontoxic concentrations. Since integrase is an excellent target for anti-HIV therapy, King et al.[15] studied the inhibitory activity of DCTA and DCQA analogues **2a**–**m** (Scheme 1) against HIV-1 integrase (wild-type HIV_{NL4-3} IN; Table 2). We derived Equation (10) from their data and found that it indicates a negative effect of the hydrophobicity and CMR (overall size and polarizability) of the molecules. This suggests that the activity of **2a**–**m** will increase with increasing hydrophilicity and/or decreasing CMR.



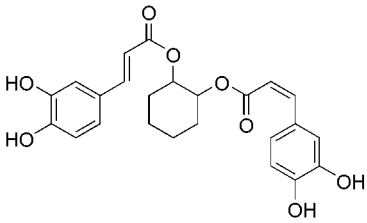
2a: L-DCTA;
2b: D-DCTA;
2c: *meso*-DCTA
(DCTA = dicaffeoyltartaric acid)



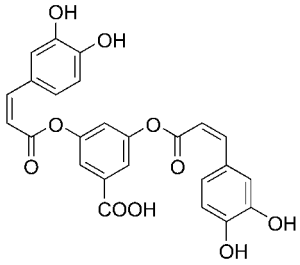
2d: 1,4-*trans*-dicaffeoylcyclohexane
2e: 1,4-*cis*-dicaffeoylcyclohexane



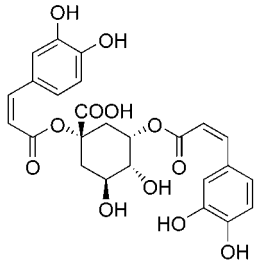
2f: 1,3-*trans*-dicaffeoylcyclohexane
2g: 1,3-*cis*-dicaffeoylcyclohexane



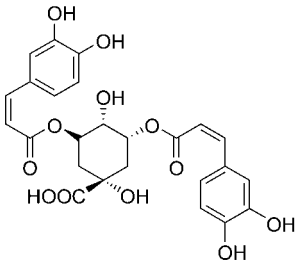
2h: 1,2-*cis*-dicaffeoylcyclohexane



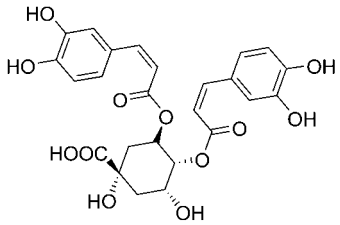
2i: 3,5-dicaffeoylbenzoic acid



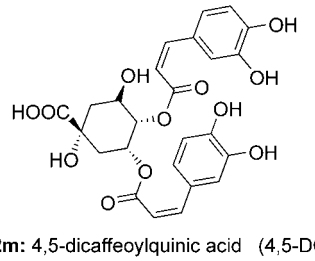
2j: 1,5-dicaffeoylquinic acid (1,5-DCQA)



2k: 3,5-dicaffeoylquinic acid (3,5-DCQA)



2l: 3,4-dicaffeoylquinic acid (3,4-DCQA)



2m: 4,5-dicaffeoylquinic acid (4,5-DCQA)

Scheme 1. *Structure of dicaffeoyltartaric acid (DCTA) and dicaffeoylquinic acid (DCQA) analogues* ***2a–m.***

Inhibition of **2a** − **m** against wild-type HIV_{NL4-3} IN (Table 2) : [15]

$$\log 1/C = -0.27(\pm0.07)\log P_{calcd} - 0.89(\pm0.21)CMR+17.53(\pm2.58) \quad (10)$$

*Table 2. Biological and physicochemical constants used to derive QSAR Equation (10) for the inhibition of DCTA and DCQA analogues **2a–m** against wild-type HIV_{NL4-3} IN.*

No.	Compound	log 1/C [Eq. (10)] obsd	calcd	Δ	log P_{calcd}	CMR
2a	L-DCTA	6.74	7.02	−0.28	0.14	11.76
2b	D-DCTA	7.15	7.02	0.13	0.14	11.76
2c	*meso*-DCTA	7.10	7.02	0.07	0.14	11.76
2d	cyclohexane-1,4-*trans*-$(OCAF)_2$[a]	5.99	5.89	0.09	3.11	12.14
2e	cyclohexane-1,4-*cis*-$(OCAF)_2$[a]	6.00	5.89	0.10	3.11	12.14
2f	cyclohexane-1,3-*trans*-$(OCAF)_2$[a]	5.74	5.79	−0.05	3.49	12.14
2g	cyclohexane-1,3-*cis*-$(OCAF)_2$[a]	5.79	5.79	0.00	3.49	12.14
2h	cyclohexane-1,2-*cis*-$(OCAF)_2$[a]	5.08[b]	5.76	−0.68	3.61	12.14
2i	1-COOH-3,5-$(OCAF)_2$-C_6H_3[a]	5.16	5.27	−0.11	3.57	12.69
2j	1,5-DCQA	5.80	5.93	−0.13	−0.20	13.09
2k	3,5-DCQA	5.89	5.90	−0.01	−0.09	13.09
2l	3,4-DCQA	5.85	5.95	−0.09	−0.27	13.09
2m	4,5-DCQA	6.22	5.95	0.28	−0.27	13.09

[a] CAF = caffeoyl = COCH=CH[3,4-$(OH)_2$-C_6H_3]. [b] Not included in the derivation of QSAR Equation (10).

$n = 12$, $r^2 = 0.939$, $q^2 = 0.884$, $s = 0.162$

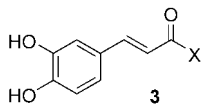
range in $\log 1/C = 5.08 - 7.15$

outlier : cyclohexane-1,2-*cis*-$(OCAF)_2$

QSAR for enzymatic activity

Sugiura et al.[33] studied the synthesis and inhibitory activity of various caffeic acid derivatives **3** (including caffeic acid) on 5-lipoxygenase (5-LO) and 12-lipoxygenase (12-LO; Table 3). We derived Equations (11) and (12), respectively, from their results.

*Table 3. Biological and physicochemical constants used to derive QSAR Equations (11) and (12) for the inhibitory activity of caffeic acid derivatives **3** toward 5-lipoxygenase and 12-lipoxygenase, respectively.*



3

No.	X	log 1/C [Eq. (11)] obsd	calcd	Δ	log 1/C [Eq. (12)] obsd	calcd	Δ	log P_{calcd}	CMR
3a	OC_2H_5	6.78	6.59	0.19	5.19	5.33	−0.14	1.73	5.78
3b	OC_4H_9	7.17	7.24	−0.07	5.73	5.71	0.02	2.79	6.71
3c	OC_9H_{19}	6.73[a]	4.26	2.46	5.74	5.77	−0.03	5.43	9.03
3d	OH	6.00	6.03	−0.03	5.00	4.92	0.08	0.97	4.85
3e	NHC_8H_{17}	7.38	7.38	0.00	–	–	–	4.24	8.78
3f	$NHC_{10}H_{21}$	7.35	7.21	0.14	5.49	5.59	−0.10	5.30	9.71
3g	$NHC_{11}H_{23}$	7.19	7.11	0.08	5.43	5.46	−0.03	5.83	10.17
3h	$NHC_{13}H_{27}$	6.81	6.91	−0.10	5.28	5.21	0.07	6.89	11.10
3i	C_3H_7	6.56	6.74	−0.18	5.08[a]	1.11	3.97	1.94	6.09
3j	C_5H_{11}	7.46	7.32	0.13	5.46[a]	0.85	4.60	3.00	7.02
3k	C_7H_{15}	7.24	7.40	−0.16	6.06	5.95	0.11	4.06	7.95

[a] Not included in the derivation of QSAR Equations (11) and (12), respectively.

The hydrophobicity of the molecules correlates with the activity in a bilinear fashion in Equation (11). This suggests that the inhibitory activity of compounds **3** toward 5-LO first increases with an increase in hydrophobicity to an optimum log P_{calcd} value of 3.67 and then decreases linearly. In contrast to Equation (11), we obtained a bilinear correlation with CMR in Equation (12). This correlation suggests that the overall size and polarizability of the compounds **3** initially increases the inhibitory activity toward 12-LO up to an optimum value of CMR at 7.87 and then decreases linearly.

Inhibitory activity of caffeic acid derivatives **3** toward 5-LO (Table 3) : [33]

$$\log 1/C = 0.77(\pm 0.24)\log P_{calcd} - 0.96(\pm 0.34)\log(\beta \times 10^{\log P_{calcd}} + 1) + 5.28(\pm 0.53) \quad (11)$$

$n = 10$, $r^2 = 0.917$, $q^2 = 0.837$, $s = 0.161$

optimum log $P_{calcd} = 3.67$

$\log \beta = -3.06$

range in $\log 1/C = 6.00 - 7.46$

outlier : OC_9H_{19}

Inhibitory activity of caffeic acid derivatives **3** toward 12-LO (Table 3) : [33]

$$\log 1/C = 0.44(\pm 0.16)\mathrm{CMR} - 0.72(\pm 0.28)\log(\beta \times 10^{\mathrm{CMR}} + 1) + 2.79(\pm 1.03) \quad (12)$$

$n = 8$, $r^2 = 0.934$, $q^2 = 0.758$, $s = 0.117$

optimum CMR = 7.87

$\log \beta = -7.66$

range in $\log 1/C = 5.00 - 6.06$

outliers : C_3H_7, C_5H_{11}

With respect to Equation (11), it is important to note that there is a high mutual correlation between log P_{calcd} and CMR ($r^2 = 0.992$, $q^2 = 0.988$). By considering CMR in place of log P_{calcd}, we can derive Equation (11 A).

$$\log 1/C = 0.67(\pm 0.25)\mathrm{CMR} - 0.85(\pm 0.36)\log(\beta \times 10^{\mathrm{CMR}} + 1) + 2.76(\pm 1.53) \quad (11\mathrm{A})$$

$n = 10$, $r^2 = 0.889$, $q^2 = 0.788$, $s = 0.185$

optimum CMR = 7.86

$\log \beta = -7.29$

Thus, it is very hard to predict for this data set if there is a positive hydrophobic or positive steric

effect. We prefer Equation (11) because it is statistically better than Equation (11 A).

With respect to Equation (12), there is also a high mutual correlation between CMR and $\log P_{calcd}$ ($r^2 = 0.987$, $q^2 = 0.981$). By considering $\log P_{calcd}$ in place of CMR, we can derive Equation (12 A).

$$\log 1/C = 0.46(\pm 0.22)\log P_{calcd} - 0.76(\pm 0.37)\log(\beta \times 10^{\log P_{calcd}} + 1) + 4.49(\pm 0.51) \quad (12A)$$

$n = 8$, $r^2 = 0.898$, $q^2 = 0.732$, $s = 0.145$

optimum $\log P_{calcd} = 3.84$

$\log \beta = -3.65$

On comparing Equation (12) to Equation (12 A), it is very hard to predict for this data set if there is a positive steric or positive hydrophobic effect. We prefer Equation (12) because it is statistically better than Equation (12 A).

Melzig et al.[32] studied the inhibition of neutrophil elastase activity by caffeic acid derivatives **4a–i** (Scheme 2; Table 4). We derived Equation (13) from their data and observed a good correlation with $\log P_{calcd}$. In this equation we observed a positive $\log P_{calcd}$ term, a result showing that more hydrophobic molecules would have better activity for this data set.

Table 4. *Biological and physicochemical constants used to derive QSAR Equation (13) for the inhibition of neutrophil elastase by caffeic acid derivatives **4a–i**.*

No.	Compound	log 1/C [Eq. (13)] obsd	calcd	Δ	$\log P_{calcd}$
4a	caffeic acid	4.03	4.44	−0.41	0.97
4b	rosmarinic acid	5.15	4.49	0.66	1.10
4c	caffeic acid phenethyl ester	4.43[a]	5.31	−0.88	3.30
4d	*trans*-drimenylcaffeic acid ester	6.70	6.68	0.01	6.98
4e	caffeic acid bornyl ester	5.80	5.97	−0.18	5.06
4f	1,5-dicaffeoylquinic acid	3.82	4.01	−0.18	−0.20
4g	4-O-caffeoylquinic acid	3.32	3.56	−0.24	−1.40
4h	3-O-caffeoylquinic acid	3.35	3.38	−0.03	−1.88
4i	2-O-caffeoylmalic acid	4.47	4.11	0.37	0.07

[a] Not included in the derivation of QSAR Equation (13).

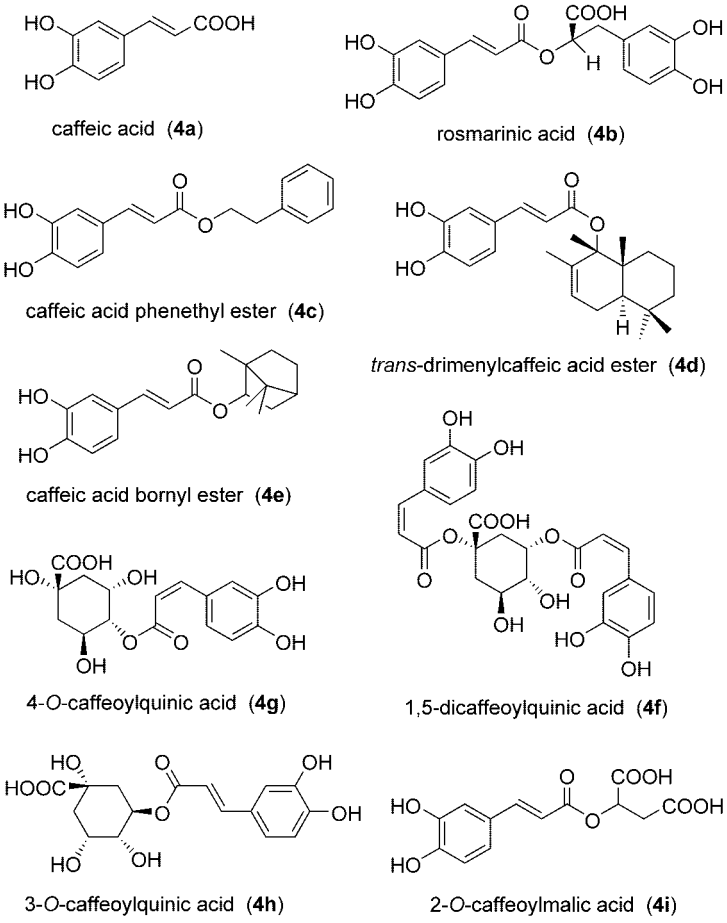
Inhibition of neutrophil elastase by caffeic acid derivatives **4a–i** (Table 4)[32]

$$\log 1/C = 0.37(\pm 0.11)\log P_{calcd} + 4.08(\pm 0.36) \quad (13)$$

$n = 8$, $r^2 = 0.916$, $q^2 = 0.883$, $s = 0.380$

range in $\log 1/C = 3.32 - 6.70$

outlier : caffeic acid phenethyl ester



Scheme 2. *Structure of caffeic acid derivatives **4a–i**.*

QSAR for binding affinity to the *lck* SH2 domain

The inhibition activity of rosmarinic acid and its derivatives **5a–e** (Scheme 3) on the interaction between the *lck* SH2 domain and *N*-acetyl-*O*-phosphono-L-tyrosyl-L-α-glutamyl-L-α-glutamyl-L-isoleucyl-L-glutamic acid (Ac-pYEEIE) was investigated by Park et al. (Table 5).[46] Equation (14) was derived from their results and shows a good correlation with the molar volume (MgVol). A negative coefficient of MgVol indicates that the smaller molecule will be best for this data set.

The binding affinity of rosmarinic acid and its derivatives **5a–e** for the *lck* SH2 domain (Table 5):[46]

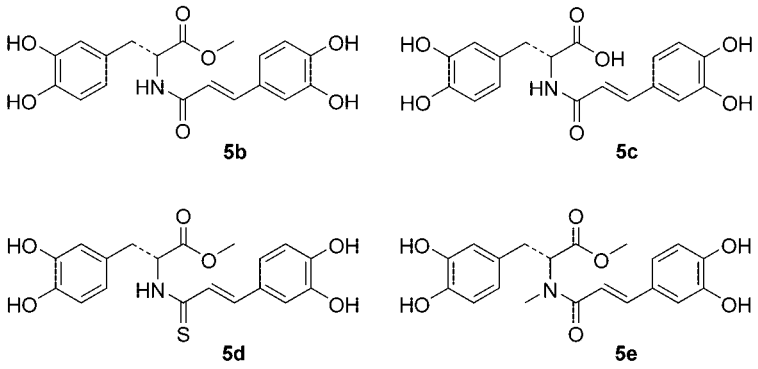
$$\log 1/C = -2.96(\pm 1.86)\mathrm{MgVol} + 12.09(\pm 4.98) \quad (14)$$

$n = 5$, $r^2 = 0.895$, $q^2 = 0.752$, $s = 0.168$

range in $\log 1/C = 3.79 - 4.70$

Conclusion

An analysis of our QSAR results on caffeic acid and its derivatives brings up a number of points of interest. On considering the most important factor, that is, hydrophobicity for this paper containing 12 biological QSARs, only 3 of the QSARs [Eqs. (8), (12), and (14)] lack hydrophobic terms. Eight QSARs [Eqs. (3)–(7), (9), (11), and (13)] have positive hydrophobic terms. The role of hydrophobicity is brought out by seven of the QSARs



Scheme 3. *Structure of rosmarinic acid derivatives* ***5b–e****. The structure of rosmarinic acid is shown in series 4 of the caffeic acid derivatives as* ***4b****.*

Table 5. *Biological and physicochemical constants used to derive QSAR Equation (14) for the binding affinity of rosmarinic acid* ***5a*** *and its derivatives* ***5b–e*** *for the* lck *SH2 domain.*

No.	log 1/*C* [Eq. (14)]			MgVol
	obsd	calcd	Δ	
5a	4.62	4.66	−0.04	2.51
5b	3.92	4.12	−0.21	2.69
5c	4.70	4.54	0.16	2.55
5d	3.79	3.81	−0.02	2.80
5e	3.83	3.71	0.12	2.83

Table 6. *Optimum log P_{calcd} values for QSARs defined by Equations (3)–(7), (9), and (11).*

QSAR	optimum log P_{calcd}	log β
3	6.69	−7.41
4	5.74	−6.36
5	5.38	−5.52
6	5.26	−5.54
7	6.79	−7.48
9	6.11	−6.28
11	3.67	−3.06

[Eqs. (3)–(7), (9), and (11)], where we get bilinear log P_{calcd} terms. Optimum log P_{calcd} values are as shown in Table 6.

Steric factors are obviously important. MgVol and CMR are two physicochemical parameters that are indicative of the overall volume/size of the molecules. Although MgVol is purely a prediction of the size of a molecule, CMR also represents more or less the same thing, with correction for polarizability, as discussed in the Experimental Section.

Only one QSAR [Eq. (14)] among the 12 biological QSARs has a MgVol term and, interestingly, it is with a negative coefficient. Negative CMR along with negative log P_{calcd} also appears in one QSAR [Eq. (10)]. There are two QSARs [Eqs. (8) and (12)] where we get a bilinear CMR term. Optimum CMR values are as shown in Table 7.

Finally, we can predict that the different activities of caffeic acid and its derivatives are mainly dependent on either their hydrophobicity or their overall size and polarizability, with a bilinear correlation of hydrophobicity or CMR being the most important.

Table 7. *Optimum CMR values for QSARs defined by Equations (8) and (12).*

QSAR	optimum CMR	log β
8	11.31	−11.96
12	7.87	−7.66

Experimental Section

All the data for caffeic acid and its derivatives have been collected from the literature (see individual QSARs for respective references). *C* is the molar concentration of a compound and log 1/*C* is the dependent variable that defines the biological parameter for QSAR equations. Physicochemical descriptors are autoloaded and multiregression analyses to derive the QSAR are executed with the C-QSAR program.[47] For in-depth knowledge about the utility of QSAR program in comparative correlation analysis, see refs. [48–50]. When comparing different QSARs, however, it must be borne in mind that variations in quality in testing in different laboratories will have an effect that cannot be estimated.

The parameters used in this paper have been already discussed in detail, along with their applications.[43] log P_{calcd} is a calculated partition coefficient in an octanol/water system and is a measure of the hydrophobicity of the whole molecule.[48] CMR is the calculated molar refractivity for the whole molecule. Molar refractivity is calculated from the Lorentz–Lorenz equation and is described as follows: $(i^2-1/i^2+2)(M_W/d)$, where i is the refractive index, M_W is the molecular weight, and d is the density of a substance. Since there is a very little variation in i, the molar refractivity is largely a measure of volume with a small correction for polarizability. Molar refractivity can be used for a substituent or for the whole molecule. MgVol is the molar volume calculated by using the method of McGowan.

In the QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the square of the correlation coefficient, q is a measure of the quality of fit, q^2 is a measure of the goodness of fit of the data and approaches the value of r^2 as the quality of the fit improves, and s is the standard deviation. All the QSARs reported here are derived by us and were not given with the original data sets taken from the literature as referenced.

Keywords: caffeic acid · hydrophobicity · molar refractivity · molar volume · structure–activity relationships

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