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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and CoMFA studies of OEA derivatives as FAAH inhibitors

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Abstract A total of 26 novel oleoylethanolamide derivatives were designed, synthesized, and characterized. All synthesized targets compounds were screened for their inhibitory activities against fatty acid amide hydrolase. Among of them, 13 compounds inhibit fatty acid amide hydrolase by 50% at the concentration of 100 μM. Of these compounds, the most active one is compound **9**, which inhibit fatty acid amide hydrolase activity 98.35% at the concentration of 100 μM. Comparative molecular field analysis analyzes were performed based on obtained biological activities data and resulted in a statistically reliable comparative molecular field analysis model with high predictive abilities ($r^2 = 0.978$, $q^2 = 0.613$).

Keywords OEA derivatives · Synthesis · FAAH inhibitors · CoMFA analyzes

Introduction

Oleoylethanolamide (OEA) (Fig. 1) is an endogenous lipid amide produced in many mammalian tissues (Thabuis et al. 2008; Jin et al. 2003; Pavón et al. 2010; Dipasquale et al. 2010) and participates in controlling appetite (Rodríguez et al. 2001; Nielsen et al. 2004) stimulating lipid lipolysis (Guzmán et al. 2004) and regulating energy balance (Serrano et al. 2006; Gonzálezyanes et al. 2005) through the activation of PPAR-α (Capasso and Izzo 2008), GRP119 (Overton et al. 2006), TRPV1 (Ahern 2003) and so on. Its endogenous level in corresponding tissues are primarily regulated by enzymes responded for synthesis and hydrolysis of OEA. It is biosynthesized through a phospholid precursor, N-oleyl-phosphatidyl-ethanolamine by the catalytic action of N-acyl-phosphatidyl-ethanolamine-selective phospholipase D (NAPE-PLD) (Ueda et al. 2010) and hydrolyzed to oleyl acid and ethanolamne mainly catalyzed by fatty acid amide hydrolase (FAAH) (Sun et al. 2005). Due to the rapid inactivation of OEA, the biological activities remain very weak. It is sure that increasing the concentration of OEA in tissues may lead to beneficial therapeutic effects on anorexia, lipolysis, and energy balance. The enzymes inhibition could be a convenient way to elevate OEA levels in tissues and enhance its biological activities. So FAAH has emerged as an interesting new therapeutic target for a range of clinical disorders (Hardouin et al. 2007).

FAAH is a membrane-bond enzyme to be identified for N-acylethanolamine hydrolysis (Ueda et al. 2002). It consists of 579 amino acid residues and belongs to the family of amidase enzymes (Cravatt et al. 1996). Site-directed mutagenesis and crystal structure analysis revealed the presence of a catalytic triad composed of Ser-241, Ser-217, and Lys-142 (Solorzano et al. 2010; Solorzano et al. 2009).

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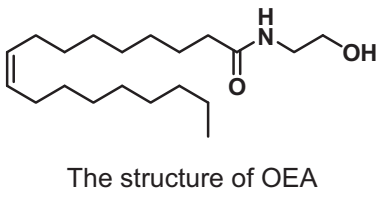


Fig. 1 The chemical structure of OEA

Because of the exciting therapeutic potential of inhibiting FAAH, there has been increasing interests in the development of potent inhibitors. Structurally, the majority of FAAH inhibitors can be classified into three types. The first type is substrate analogs, such as analogs of anandamide (AEA), OEA, and palmitoylethanolamide (PEA), which were designed on the base of structures of long-chain fatty acids (Vandevoorde et al. 2003; Patterson et al. 1996; Jonsson et al. 2001; Bisogno et al. 1998). The series of carbamates, including URB524 and URB 597, were the second class of FAAH inhibitors. These inhibitors share a common structural feature: carbamate group and irreversible inhibits FAAH (Myllymäki et al. 2007). The last type was the α-ketoheterocycle base inhibitors, which bind to FAAH via reversible hemiketal formation with an active site (Kimball et al. 2008).

In our present work, a series of OEA analogs were reported as FAAH inhibitors. The activities of these compounds against FAAH were tested in vitro. A comparative molecular field analysis (CoMFA) study was carried out based on the obtained data and helped in understanding the interaction between the ligands and receptor.

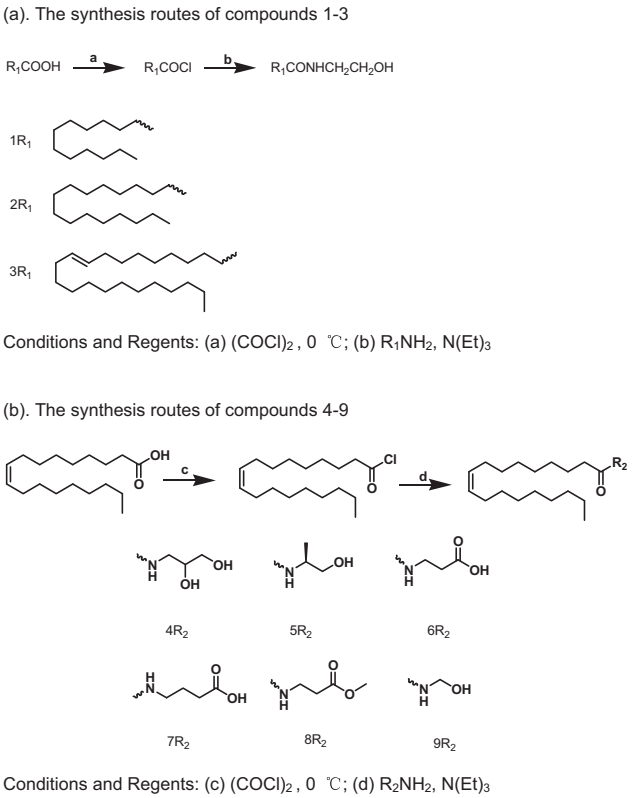
Experimental procedures

General

Solvents were distilled prior to use and dried by standard methods (Perrin and Armarego 1988). All reagents were purchased from Sigma-Aldrich (Shanghai, China) in the highest quality commercially available. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on Bruker 400 spectrometer. Unless otherwise indicate, NMR spectra were reported in $CDCl_3$ at 400 MHz for ^{1}H and 100 MHz for ^{13}C and chemical shifts were expressed in part per million relative to internal Me_4Si. Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected.

Synthesis of compounds

Compounds **1–22** were prepared by the amidation or esterification of oleic acid with corresponding amine or alcohol. Compounds **23–26** were synthesized by the amidation of oleylamine with corresponding sulfonyl chlorides.



Scheme 1 **a** The synthesis routes of compounds **1–3**. **b** The synthesis routes of compounds **4–9**

*General method for the synthesis of compounds **1–9***

The synthetic routes for the compounds **1–9** are summarized in Scheme 1. Excess oxayl chloride and a catalytic amount of N,N-dimethylformamide (DMF) were added to the stirred solution of suitable fatty acid in dry CH_2Cl_2, at 0 °C and under N_2 atmosphere. After stirring for 30 min at 0 °C, the mixture was stirred at room temperature for 3 h, crude fatty acyl chloride was obtained. The resulting crud fatty acyl chloride was concentrated and used in the next step. Coupling fatty acyl chloride with a variety of RH in the presence of Et_3N for 3 h gave the corresponding compounds which can be further purified by column chromatography.

N-(2-hydroxyethyl)dodecanamide (**1**) M.p. 79.8–81.8 °C; infrared (IR) (KBr) ν_{max}: 3294, 3094, 2918, 2849, 1642, 1561, 1469, 1052, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.85$ (3H, t, $J = 6.8$ Hz, CH_3), 1.23–1.27 (16H, m, H-4-11), 1.55–1.63 (2H, m, H-3), 2.15–2.19 (2H, t, $J = 7.6$ Hz, H-2), 3.35–3.39 (2H, dd, $J_1 = 5.4$ Hz, $J_2 = 10.0$ Hz, $NHCH_2$), 3.66 (2H, t, $J = 5.2$ Hz, CH_2OH), 6.42 (1H, brs,

NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.18$ (CH_3, C-17), 22.76 (CH_2, C-1), 25.87 (CH_2, C-9), 29.42 (CH_2, C-8), 29.47 (CH_2, C-7), 29.60 (CH_2, C-3), 29.60 (CH_2, C-4), 29.70 (CH_2, C-5), 29.71 (CH_2, C-6), 31.99 (CH_2, C-2), 36.78 (CH_2, $COCH_2$), 42.48 (CH_2, $NHCH_2$), 62.14 (CH_2, CH_2OH), 174.77 (C, C=O); electron impact mass spectrometry (EIMS) *m/z* 244.2 $[M + H]^+$, 266.3 $[M + Na]^+$.

N-(2-hydroxyethyl)palmitamide (**2**) M.p. 98.4–98.5 °C; IR (KBr) ν_{max}: 3296, 3086, 2918, 2850, 1640, 1553, 1472, 1058, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.88$ (3H, t, $J = 6.8$ Hz, CH_3), 1.25–1.2 (22H, m, H-4-15), 1.61–1.65 (2H, m, H-3), 2.18–2.22 (2H, t, $J = 7.6$ Hz, H-2), 3.40–3.44 (2H, dd, $J_1 = 5.6$ Hz, $J_2 = 10.0$ Hz, $NHCH_2$), 3.67 (t, 2H, $J = 4.8$ Hz, CH_2OH), 5.95 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.26$ (CH_3, C-16), 22.84 (CH_2, C-15), 25.87 (CH_2, C-7), 29.44 (CH_2, C-6), 29.50 (CH_2, C-5), 29.55 (CH_2, C-13), 29.63 (CH_2, C-1), 29.67 (CH_2, C-2), 29.72 (CH_2, C-3), 29.76 (CH_2, C-10), 29.80 (CH_2, C-4), 29.82 (CH_2, C-11), 29.84 (CH_2, C-12), 32.07 (CH_2, C-14), 36.85 (CH_2, $COCH_2$), 42.65 (CH_2, $NHCH_2$), 62.85 (CH_2, CH_2OH), 174.69 (C, C=O); EIMS *m/z* 300.3 $[M + H]^+$, 322.4 $[M + Na]^+$.

(Z)-N-(2-hydroxyethyl)docos-13-enamide (**3**) M.p. 74.7–75.6 °C; IR (KBr) ν_{max}: 3300, 3093, 3003, 2919, 2850, 1644, 1562, 1466, 1060, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (3H, t, $J = 6.8$ Hz, CH_3), 1.25 (28H, m, H-4-11, 16–21), 1.62 (2H, m, H-3), 1.98–2.02 (4H, m, H-12, 15), 2.19 (2H, t, $J = 7.6$ Hz, H-2), 3.38–3.42 (2H, dd, $J_1 = 5.4$ Hz, $J_2 = 10.4$ Hz, $NHCH_2$), 3.70 (2H, t, $J = 5.0$ Hz, CH_2OH), 5.30–5.37(2H, m, H-13, 14), 6.12 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.23$ (CH_3, C-22), 22.80 (CH_2, C-21), 25.87 (CH_2, C-12), 27.31 (CH_2, C-3), 27.34 (CH_2, C-15), 29.30 (CH_2, C-11), 29.44 (CH_2, C-10), 29.49 (CH_2, C-19), 29.57 (CH_2, C-9), 29.64 (CH_2, C-8), 29.69 (CH_2, C-7), 29.75 ($2CH_2$, C-6, 18), 29.78 ($2CH_2$, C-5, 17), 29.83 (CH_2, C-4), 29.90 (CH_2, C-16), 32.03 (CH_2, C-20), 36.82 (CH_2, $COCH_2$), 42.57 (CH_2, $NHCH_2$), 62.55 (CH_2, CH_2OH), 129.99 (CH, CH=CH), 130.03 (CH, CH=CH), 174.70 (C, C=O); EIMS *m/z* 382.6 $[M + H]^+$, 403.5 $[M + Na]^+$.

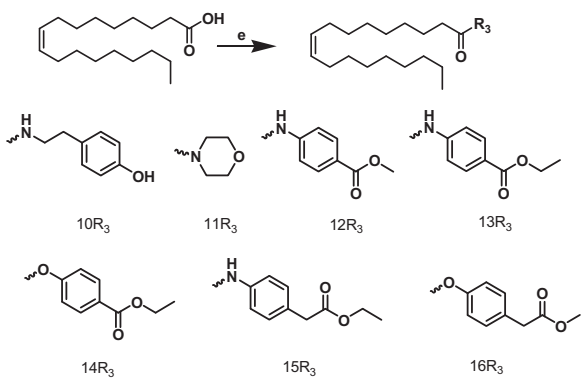
N-(2,3-dihydroxypropyl)oleamide (**4**) M.p. 63.6–65.8 °C; IR (KBr) ν_{max}: 3316, 3005, 2921, 2850, 1640, 1548, 1464, 1055, 954, 720 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 0.87 (3H, t, $J = 6.8$ Hz, CH_3), 1.25–1.29 (20H, m, H-4-7, 12-17), 1.59–1.63(2H, m, H-3), 1.97–2.01 (4H, m, H-8,11), 2.18–2.22 (2H, t, $J = 7.6$ Hz, H-2), 3.32–3.41(2H, m, $NHCH_2$), 3.42–3.44 (2H, m, CH_2OH), 3.50–3.78 (2H, m, CHOH), 5.32–5.35 (2H, m, H-9, 10), 6.33 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.22$ (CH_3, C-20), 22.80 (CH_2, C-18), 25.87 (CH_2, C-8), 27.31 (CH_2, C-3), 27.37 (CH_2, C-12), 29.28 (CH_2, C-7), 29.40 (CH_2, C-6), 29.44 (CH_2, C-16), 29.46 (CH_2, C-15), 29.65 (CH_2, C-5), 29.75 (CH_2, C-14), 29.86 (CH_2, C-4), 29.90 (CH_2, C-13), 32.03 (CH_2, C-17), 36.70 (CH_2, $COCH_2$), 42.32 (CH_2, $NHCH_2$), 63.81 (CH_2, CH_2OH), 71.28 (CH, CHOH), 129.83 (CH, CH=CH), 130.18 (CH, CH=CH), 175.45 (C, C=O); EIMS *m/z* 356.2 $[M + H]^+$, 378.5 $[M + Na]^+$.

(S)-N-(1-hydroxypropan-2-yl)oleamide (**5**) M.p. 34.9–37.4 °C; $[\alpha]^{20}_D = -11.2°$(*c* 1.37, $CHCl_3$); IR (KBr) ν_{max}: 3303, 3082, 3005, 2925, 2854, 1642, 1546, 1460, 1053, 803, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.85$ (3H, t, $J =$ 6.8 Hz, CH_3), 1.13–1.15 (3H, d, $J = 6.8$ Hz, $NHCHCH_3$), 1.24–1.27 (20H, m, H-4-7, 12–17), 1.57–1.60 (2H, m, H-3), 1.95–2.03 (4H, m, H-8, 11), 2.15 (2H, t, $J = 7.6$ Hz, H-2), 3.47–3.62 (2H, m, CH_2OH), 4.00 (1H, m, NHCH), 5.28–5.36 (2H, m, H-9, 10), 6.00 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.20$ (CH_3, C-20), 17.13 (CH_3, C-24), 22.76 (CH_2, C-18), 25.87 (CH_2, C-8), 27.26 (CH_2, C-3), 27.30 (CH_2, C-12), 29.24 (CH_2, C-7), 29.34 (CH_2, C-6), 29.37 (CH_2, C-16), 29.40 (CH_2, C-15), 29.60 ($2CH_2$, C-5, 14), 29.80 (CH_2, C-4), 29.84 (CH_2, C-13), 31.98 (CH_2, C-17), 36.89 (CH_2, $COCH_2$), 47.71 (CH, NHCH), 66.93 (CH_2, CH_2OH), 129.78 (CH, CH=CH), 130.08 (CH, CH=CH), 174.16 (C, C=O); EIMS *m/z* 340.3 $[M + H]^+$, 362.3 $[M + Na]^+$.

3-Oleamidopropanoic acid (**6**) M.p. 73–75 °C; IR (KBr) ν_{max}: 3424, 3302, 3000, 2955, 2918, 1692, 1636, 1551, 1426, 1194, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 0.87 (3H, t, $J = 6.6$ Hz, CH_3), 1.26–1.29 (20H, m, H-4-7, 12–17), 1.58–1.62 (2H, m, H-3), 1.98–2.01 (4H, m, H-8,11), 2.15–2.19 (2H, t, $J = 7.8$ Hz, H-2), 2.58–2.61 (2H, t, $J = 5.8$ Hz, CH_2CO), 3.52–3.53 (2H, m, $NHCH_2$), 5.32–5.35 (2H, m, H-9,10), 6.12–6.15 (1H, brs, NH); 13C NMR ($CDCl_3$, 100 MHz): $\delta = 14.24$ (CH_3, C-20), 22.82 (CH_2, C-18), 25.81 (CH_2, C-8), 27.33 (CH_2, C-3), 27.38 (CH_2, C-12), 29.28 (CH_2, C-7), 29.37 (CH_2, C-6), 29.47 (CH_2, C-16), 29.55 (CH_2, C-15), 29.67 (CH_2, C-5), 29.78 (CH_2, C-14), 29.85 (CH_2, C-4), 29.91 (CH_2, C-13), 32.05 (CH_2, C-17), 34.02 (CH_2, CH_2COOH), 34.93 (CH_2, $NHCH_2$), 36.86 (CH_2, $COCH_2$), 129.88 (CH, CH=CH), 130.18 (CH, CH=CH), 173.28 (C, CONH), 176.28 (C, COOH); EIMS *m/z* 354.3 $[M + H]^+$, 376.2 $[M + Na]^+$.

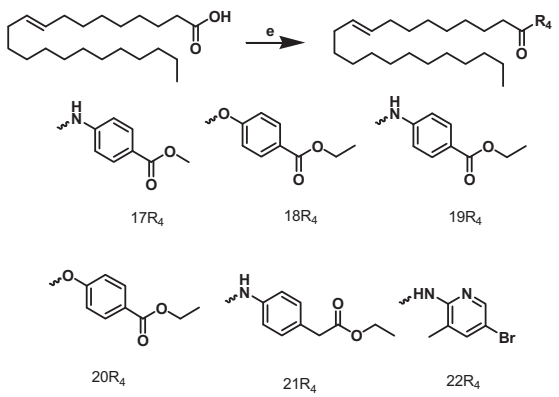
4-Oleamidobutanoic acid (**7**) M.p. 61.4–63.2 °C. IR (KBr) ν_{max}: 3308, 3068, 3006, 2922, 2851, 1690, 1631, 1560,1468, 1078, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (3H, t, $J = 6.8$ Hz, CH_3), 1.26–1.29 (20H, m, H-4-7, 12-17), 1.59–1.62(2H, m, H-3), 1.82–1.87 (2H, m, H-2'),1.99–2.05 (4H, m, H-8,11), 2.15–2.19 (2H, t, $J = 7.6$ Hz, H-2), 2.37–2.41 (3H, t, $J = 7.0$ Hz, H-3', CH_2CO), 3.29–3.34 (2H, m, $NHCH_2$), 5.33–5.35 (2H, m, H-9, 10),

(a). The synthesis routes of compounds 10-16



Conditions and Regents: (e) CH_2Cl_2, EDC, DMAP, $N(Et)_3$

(b). The synthesis routes of compounds 17-22



Conditions and Regents: (e) CH_2Cl_2, EDC, DMAP, $N(Et)_3$

Scheme 2 a The synthesis routes of compounds **10–16**. **b** The synthesis routes of compounds **17–22**

5.89 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 14.22 (CH_3, C-20), 22.81 (CH_2, C-18), 24.87 (CH_2, C-22), 25.87 (CH_2, C-8), 27.32 (CH_2, C-3), 27.37 (CH_2, C-12), 29.28 (CH_2, C-7), 29.39 (CH_2, C-6), 29.40 (CH_2, C-16), 29.44 (CH_2, C-15), 29.46 (CH_2, C-5), 29.66 (CH_2, C-14), 29.86 (CH_2, C-4), 29.90 (CH_2, C-13), 31.66 (CH_2, C-17), 32.04 (CH_2, CH_2COOH), 36.88 (CH_2, $COCH_2$), 39.00 (CH_2, $NHCH_2$), 129.86 (CH, CH=CH), 130.16 (CH, CH=CH), 174.27 (C, CONH), 177.64 (C, COOH); EIMS *m/z* 368.2 $[M + H]^+$, 390.6 $[M + Na]^+$.

Methyl 3-oleamidopropanoate (**8**) M.p. 45.7–47.1 °C. IR (KBr) ν_{max}: 3304, 3082, 3004, 2925, 2853,1740, 1641, 1554, 1466, 1073, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.86$ (3H, t,$J = 7.0$ Hz, CH_3), 1.23–1.27 (20H, m, H-4-7, 12-17), 1.56–1.60 (2H, m, H-3), 1.96–2.03 (4H, m, H-8,11), 2.11–2.15 (2H, t, $J = 7.6$ Hz, H-2), 2.51–2.54 (2H, t, $J = 5.8$ Hz, H-2'), 3.47–3.52 (2H, m, $NHCH_2$), 3.68 (3H, s, O–CH_3), 5.30–5.35 (2H, m, H-9, 10), 6.01 (1H, brs, NH); ^{13}CNMR ($CDCl_3$, 100 MHz): $\delta = 14.20$ (CH_3, C-20), 22.78 (CH_2, C-18), 25.79 (CH_2, C-8), 27.29 (CH_2, C-3), 27.32 (CH_2, C-12), 29.2 4 (CH_2, C-7), 29.36 (CH_2, C-6), 29.40 (CH_2, C-16), 29.42 (CH_2, C-15), 29.62 (CH_2, C-5), 29.70 (CH_2, C-14), 29.81 (CH_2, C-4), 29.87 (CH_2, C-13), 32.00 (CH_2, C-17), 33.97 (CH_2, CH_2COOCH_3), 34.86 (CH_2, $NHCH_2$), 36.86 (CH_2, $COCH_2$), 51.85 (CH_3, O–CH_3), 129.84 (CH, CH=CH), 130.09 (CH, CH=CH), 173.30 (C, CONH), 173.30 (C, $COOCH_3$); EIMS *m/z* 368.3 $[M + H]^+$, 390.2 $[M + Na]^+$.

N-hydroxyoleamide (**9**) M.p. 60.0–61.3 °C; IR (KBr) ν_{max}: 3273, 3000, 2918, 2849, 1663, 1618, 1464, 1430, 1023, 968, 848, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (3H, t, $J = 6.6$ Hz, CH_3), 1.26–1.28 (20H, m, H-4-7, 12-17), 1.61 (2H, m, H-3), 2.01 (4H, m, H-8, 11), 2.13 (2H, t, $J = 7.4$ Hz, H-2), 5.29–5.38 (2H, m, H-9, 10), 8.02 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.17$ (CH_3, C-20), 22.75 (CH_2, C-18), 25.49 (CH_2, C-8), 27.26 (CH_2, C-3), 27.31 (CH_2, C-10), 29.21 (CH_2, C-7), 29.28 (CH_2, C-6), 29.41 (CH_2, C-14), 29.61 (CH_2, C-13), 29.69 (CH_2, C-5), 29.79 (CH_2, C-12), 29.85 (CH_2, C-4), 31.98 (CH_2, C-11), 31.98 (CH_2, C-15), 33.12 (CH_2, $COCH_2$), 129.74 (CH, CH=CH), 130.11 (CH, CH=CH), 171.94 (C, C=O); EIMS *m/z* 299.5 $[M + H]^+$, 321.6 $[M + Na]^+$.

General method for the synthesis of compounds ***10–22***

As shown in Scheme 2, the synthesis of compounds 10–22 will be finished. To a mixture of acid (1 mmol), amine (1.5 mmol) or alcohol (1.5 mmol), Et_3N (0.27 mL, 2 mmol) and 4-dimethylaminopyridine (DMAP) (15 mg) in anhydrous CH_2Cl_2 (12 mL), was added dropwise 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (287 mg, 1.5 mmol) in CH_2Cl_2 (3.5 mL) under N_2 atmosphere. The resulting solution was stirred at room temperature for 4 h, quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford compounds **10–22**.

N-(4-hydroxyphenethyl)oleamide (**10**) M.p. 72.1 °C; IR (KBr) ν_{max}: 3419, 3303, 3078, 3005, 2919, 2850, 1640, 1615, 1560, 1466, 828, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.88$ (3H, t, $J = 6.8$ Hz, CH_3), 1.26 (20H, m, H-4-7, 12-17), 1.58 (2H, m, H-3), 2.00 (4H, m, H-8, 11), 2.13 (2H, t, $J = 7.6$ Hz, H-20), 2.72 (1H, t, $J = 7.0$ Hz, H-2'), 3.48 (3H, m, $NHCH_2$, H-1), 5.29–5.39(2H, m, H-9, 10),

5.64 (1H, brs, NH), 7.00 (2H, d, $J = 8.4$ Hz, H-4', 8'), 6.81 (2H, dd, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz, H-5', 6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.23$ (CH_3, C-20), 22.80 (CH_2, C-18), 25.87 (CH_2, C-8), 27.30 (CH_2, C-3), 27.35 (CH_2, C-12), 29.25 (CH_2, C-7), 29.34 (CH_2, C-6), 29.44 (CH_2, C-16), 29.64 (CH_2, C-15), 29.73 (CH_2, C-5), 29.77 (CH_2, C-14), 29.83 (CH_2, C-4), 29.89 (CH_2, C-13), 32.02 (CH_2, C-17), 34.87 (CH_2, C-22), 36.95 (CH_2, $COCH_2$), 40.60 (CH, $NHCH_2$), 115.79 (CH, C-25), 129.80 (CH, C-27), 129.87 (2CH, C-24, 28), 129.90 (CH=CH, C-1, 2), 130.13 (C, C-23), 155.37 (C, C–OH), 174.02 (C, C=O); EIMS *m/z* 402.3 $[M + H]^+$, 424.1 $[M + Na]^+$.

(Z)-1-morpholinooctadec-9-en-1-one (**11**) IR (KBr) ν_{max}:3003, 2924, 2853, 1652, 1557, 1456, 1427, 849, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (3H, t, $J = 6.8$ Hz, CH_3), 1.25–1.30 (20H, m, H-4-7, 12–17), 1.61 (2H, m, H-3), 2.00 (4H, m, H-8, 11), 2.29 (2H, t, $J = 8.0$ Hz, H-2), 3.44 (2H, t, J=4.4 Hz, N–CH_2), 3.60 (2H, d, $J = 4.4$ Hz, N–CH_2), 3.65 (4H, t, $J = 4.8$ Hz, CH_2O, CH_2O), 5.29–5.38 (2H, m, H-9, 10); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.08$ (CH_3, C-20), 22.60 (CH_2, C-16), 25.45 (CH_2, C-8), 27.18 (CH_2, C-3), 27.23 (CH_2, C-10), 29.15 (CH_2, C-7), 29.32 (CH_2, C-6), 29.44 (CH_2, C-14), 29.51 (CH_2, C-13), 29.61 (CH_2, C-5), 29.71 (CH_2, C-12), 29.77 (CH_2, C-4), 31.53 (CH_2, C-11), 31.90 (CH_2, C-15), 33.12 (CH_2, $COCH_2$), 41.90 (CH_2, NCH_2), 46.09 (CH_2, NCH_2), 66.70 (CH_2, O–CH_2), 66.98 (CH_2, O–CH_2), 129.74 (CH, CH=CH), 130.11 (CH, CH=CH), 171.86 (C, C=O); EIMS *m/z* 352.6 $[M + H]^+$, 374.4 $[M + Na]^+$.

Methyl 4-oleamidobenzoate (**12**) M.p. 74.4–74.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.88$ (3H, t, $J = 6.8$ Hz, CH_3), 1.26–1.31 (20H, m, H4–7, H12–17), 1.69–1.76 (2H, m, H-3), 1.98–2.02 (4H, m, H-8, 11), 2.38 (2H, t, $J = 7.6$ Hz, H-2), 3.90 (3H, s, O–CH_3), 5.30–5.39 (2H, m, H-9,-10), 7.61 (2H, d, $J = 8.4$ Hz, H-2',6'), 7.64 (1H, brs, NH), 7.98 (2H, d, $J = 8.4$ Hz, H-3",-5'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.11$ (CH_3, C-18), 22.68 (CH_2, C-15), 25.48 (CH_2, C-13), 27.16 (CH_2, C-6), 27.28 (CH_2, C-3), 29.11 (CH_2, C-14), 29.23 (CH_2, C-9), 29.27 (CH_2, C-11), 29.33 (CH_2, C-8), 29.53 (CH_2, C-10), 29.66 (CH_2, C-7), 29.70 (CH_2, C-5), 29.77 (CH_2, C-4), 31.90 (CH_2, C-12), 37.86 (CH_2, $COCH_2$), 52.01 (CH_3, OCH_3), 118.78 (CH, C-22), 125.40 (CH, C-26), 129.69 (C, C-24), 130.04 (2CH, C-23, 25), 130.82 (CH=CH, C-1, 2), 142.28 (C, NH–C), 166.68 (C, $COOCH_3$), 171.80 (C, CONH); EIMS *m/z* 406.5 $[M + Na]^+$.

Ethyl 4-oleamidobenzoate (**13**) M.p. 58.2–59.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.89$ (3H, t, $J = 6.8$ Hz, CH_3),1.26–1.41 (20H, m, H4–7, H12–17) 1.38 (3H, t, J = 7.2 Hz, O–CH_2CH_3), 1.68–1.75 (2H, m, H-3), 1.98–2.06 (4H, m, H-8,-11), 2.37 (2H, t, $J = 7.6$ Hz, H-2), 4.35 (2H, q, $J = 7.2$ Hz, O–CH_2CH_3), 5.30-5.36 (2H, m, H-9,-10), 7.61 (2H, d, $J = 8.4$ Hz, H-3',-5'), 7.71 (1H, brs, NH), 8.00 (2H, d, $J = 8.4$ Hz, H-2',-6'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.01 ($2CH_3$, C-18, 31), 14.33 (CH_2, C-15), 27.16 (CH_2, C-6), 27.22 (CH_2, C-3), 29.11 (CH_2, C-13), 29.23 (CH_2, C-14), 29.27 (CH_2, C-9), 29.32 (CH_2, C-11), 29.52 (CH_2, C-8), 29.70 ($2CH_2$, C-7, 10), 29.76 ($2CH_2$, C-4, 5), 31.90 (CH_2, C-12), 37.85 (CH_2, $COCH_2$), 60.87 (CH_2, O–CH_2), 118.75 (C, C-26), 125.74 (C, C-22), 129.69 (C, C-24), 130.34 (2CH, C-23, 25), 130.75 (CH=CH, C1, 2), 142.23 (C, NH–C), 166.23 (C, O–C = O), 171.81 (C, CONH); EIMS *m/z* 398.5 $[M + H]^+$.

Ethyl 4-(oleoyloxy)benzoate (**14**) ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (3H, t, $J = 6.8$ Hz, CH_3), 1.29–1.36 (20H, m, H4–7, H12–17), 1.39 (3H, t, $J = 7.2$ Hz, O–CH_2CH_3), 1.74–1.81 (2H, m, H-3), 2.01–2.06 (4H, m, H-8, −11), 2.59 (2H, t, $J = 7.2$ Hz, H-2), 4.39 (2H, q, $J = 7.2$ Hz, O–CH_2CH_3), 5.36–5.39 (2H, m, H-9, 10), 7.17 (2H, d, J = 8.8 Hz, H-3',-5'), 8.08 (2H, d, $J = 8.8$ Hz, H-2',-6'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.08 (CH_3, C-18), 14.30 (CH_3, C-31), 22.67 (CH_2, C-15), 24.83 (CH_2, C-13), 27.15 (CH_2, C-6), 27.23 (CH_2, C-3), 29.06 (CH_2, C-14), 29.23 (CH_2, C-11), 29.31 (CH_2, C-9), 29.43 (CH_2, C-8), 29.52 (CH_2, C-10), 29.58 (CH_2, C-7), 29.67 (CH_2, C-5), 29.76 (CH_2, C-4), 29.89 (CH_2, C-12), 34.38 (CH_2, $COCH_2$), 61.62 (CH_2, C-29), 121.51 (C, C-24), 127.96 (CH, C-26), 129.67 (CH, C-22), 130.06 (2CH, C-23, 25), 131.06 (CH=CH, C-3, 6), 154.37 (C, O–C), 165.81 (C, O–CO–ph), 171.68 (C, O–C=O); EIMS *m/z* 405.6 $[M + Na]^+$.

Ethyl 2-(4-oleamidophenyl)acetate (**15**) M.p. 61.7–63.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.89$ (3H, t, $J = 6.8$ Hz, CH_3), 1.23 (3H, t, $J = 7.2$ Hz, O–CH_2CH_3), 1.26–1.32 (20H, m, H4–7, H12–17), 1.67–1.72 (2H, m, H-3), 1.99–2.02 (4H, m, H-8,−11), 2.33 (2H, t, $J = 7.6$ Hz, H-2), 3.57 (2H, s, $COCH_2$), 4.14 (2H, q, $J = 7.2$ Hz, O–CH_2CH_3), 5.33–5.36 (2H, m, H-9,−10), 7.20 (2H, d, $J = 8.4$ Hz, H-3',-5'), 7.46 (2H, d, $J = 8.4$ Hz, H-2', 6'), 7.54 (1H, brs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.11$ (CH_3, C-18), 14.17 (CH_3, C-31), 22.68 (CH_2, C-15), 25.64 (CH_2, C-13), 27.18 (CH_2, C-6), 27.23 (CH_2, C-3), 29.15 (CH_2, C-14), 29.27 (CH_2, C-9), 29.32 (CH_2, C-11), 29.53 (CH_2, C-8), 29.66 (CH_2, C-10), 29.72 (CH_2, C-7), 29.77 ($2CH_2$, C-4, 5), 31.90 (CH_2, C-12), 37.71 (CH_2, CH_2CONH), 40.81 (CH_2, $COCH_2$), 60.89 (CH_2, O-CH_2), 119.98 (CH, C-22, 26), 129.73 (CH, C-23, 25), 130.00 (CH=CH, C-1, 2), 130.30 (C, C-24), 137.08 (C, NH–C), 170.58 (C, O–C = O), 171.75 (C, CONH); EIMS *m/z* 444.5 $[M + H]^+$.

4-(2-Methoxy-2-oxoethyl)phenyl oleate (**16**) IR (KBr) ν_{max}: 3005, 2925, 2854, 1743,1609, 1508, 1460, 1018, 916, 848, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.88$ (3H, t, $J = 6.8$ Hz, CH_3), 1.27–1.34 (20H, m, H-4–7, 12–17), 1.71–1.78 (2H, m, H-3), 2.03 (4H, m, H-8, 11), 2.54 (2H, t, $J = 7.4$ Hz, H-2), 3.61 (2H, s, ph–CH_2), 3.69 (3H, s, OCH_3), 5.34–5.37 (2H, m, H-9, 10), 7.02–7.05 (2H, m, H-2', 6'), 7.27–7.31 (2H, m, H-3', 5'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.22$ (CH_3, C-20), 22.79 (CH_2, C-18), 25.04 (CH_2, C-8), 27.34 (CH_2, C-3), 27.36 (CH_2, C-12), 29.20 (CH_2, C-7), 29.27 (CH_2, C-16), 29.43 (CH_2, C-6), 29.64 (CH_2, C-15), 29.70 (CH_2, C-5), 29.79 (CH_2, C-14), 29.88 (CH_2, C-4), 29.90 (CH_2, C-13), 32.02 (CH_2, C-17), 34.49 (CH_2, $COCH_2$), 40.65 (CH_2, ph–CH_2), 52.17 (CH_3, O–CH_3), 121.78 (CH, C-22), 128.01 (CH, C-26), 128.19 (CH, C-25), 129.82 (CH, C-23), 130.14 (CH, CH=CH), 130.36 (CH, CH=CH), 131.48 (C, C-24), 149.97 (C, O–C), 171.85 (C, ph–O–C=O), 172.34 (C, CH_3O–C=O); EIMS *m/z* 430.3 $[M + H]^+$, 453.3 $[M + Na]^+$.

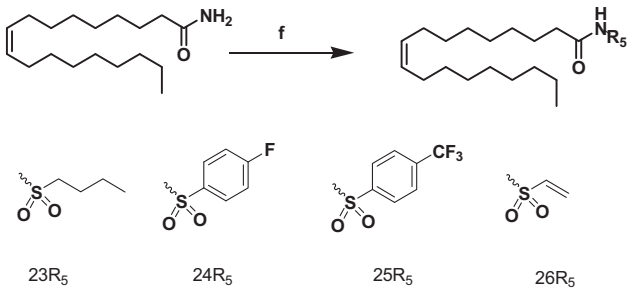
Methyl (Z)-4-(docos-13-enamido)benzoate (**17**) M.p. 81.3–81.5 °C; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (3H, t, $J = 6.8$ Hz, CH_3), 1.28–1.33 (28H, m, H4–11, H16–22), 1.70–1.77 (2H, m, H-3), 2.00–2.05 (4H, m, H-12, -15), 2.39 (2H, t, $J = 7.6$ Hz, H-2), 3.91 (3H, s, O–CH_3), 5.35–5.40 (2H, m, H-13,-14), 7.63 (2H, d, $J = 8.4$ Hz, H-3',-5'), 7.62 (1H, brs, NH), 7.98 (2H, d, $J = 8.4$ Hz, H-2', -6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.31$ (CH_3, C-22), 22.80 (CH_2, C-15), 25.57 (CH_2, C-18), 27.31 (CH_2, C-6), 27.45 (CH_2, C-3), 29.26 (CH_2, C-19), 29.32 (CH_2, C-16), 29.37 (CH_2, C-11), 29.47 ($3CH_2$, C-13, 14, 17), 29.52 ($2CH_2$, C-8, 9), 29.55 ($2CH_2$, C-7,10), 29.61 ($2CH_2$, C-4, 5), 29.77 (CH_2, C-12), 31.90 (CH_2, $COCH_2$), 52.00 (CH_3, O–CH_3), 118.75 (C, C-30), 125.42 (C, C-26), 129.87 (C, CO–C), 129.92 (2CH, C-27, 29), 130.82 (CH=CH, C-1, 2), 142.27 (C, NH–C), 166.66 (C, ph–C = O), 171.79 (C, CONH); EIMS *m/z* 472.5 $[M + H]^+$.

Methyl (Z)-4-(docos-13-enoyloxy)benzoate (**18**) M.p. 37.0–37.8 °C; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (3H, t, $J = 6.8$ Hz, CH_3), 1.28–1.30 (m, 28H, H4–11, H16–21), 1.74–1.81 (m, 2H, H-3), 2.02–2.06 (m, 4H, H-12, -15), 2.59 (t, $J = 7.6$ Hz, 2H, H-2), 3.93 (s, 3H, OCH_3), 5.33–5.41 (m, 2H, H-13, -14), 7.18 (d, $J = 8.8$ Hz, 2H, H-3', -5'), 8.08 (d, $J = 8.8$ Hz, 2H, H-2', -6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.16$ (CH_3, C-22), 22.68 (CH_2, C-15), 24.85 (CH_2, C-18), 27.21 ($2CH_2$, C-3, 6), 29.09 (CH_2, C-19), 29.24 (CH_2, C-16), 29.32 (CH_2, C-11), 29.45 (CH_2, C-17), 29.53 ($2CH_2$, C-13, 14), 29.59 ($2CH_2$, C-8, 9), 29.59 ($2CH_2$, C-7, 10), 29.78 ($2CH_2$, C-4, 5), 31.91 (CH_2, C-12), 34.40 (CH_2, $COCH_2$), 52.14 (CH_3, O–CH_3), 121.59 (2CH, C-26, 30), 127.60 (C, C-28), 129.87 (2CH, C-27, 29), 131.12 (CH=CH, C-1, 2), 154.45 (C, O–C), 166.31 (C, ph–C = O), 171.69 (C, O–C = O); EIMS *m/z* 472.4 $[M + H]^+$, 495.5 $[M + Na]^+$.

Ethyl (Z)-4-(docos-13-enamido)benzoate (**19**) M.p. 77.2–77.4 °C; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.89$ (3H, t, $J = 6.8$ Hz, CH_3), 1.27–1.42 (28H, m, H4–11, H16–21), 1.40 (3H, t, $J = 7.2$ Hz, O–CH_2CH_3), 1.71–1.77 (2H, m, H-3), 2.00–2.05 (4H, m, H-12, -15), 2.39 (2H, t, $J = 7.2$ Hz, H-2), 4.37 (2H, q, $J = 7.2$ Hz, O–CH_2CH_3), 5.32–5.40(2H, m, H-13,-14), 7.63 (2H, d, $J = 8.4$ Hz, H-3', -5'), 7.62 (1H, brs, NH), 8.00 (2H, d, $J = 8.4$ Hz, H-2', 6'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.31 ($2CH_3$, C-11, 35), 22.80 (CH_2, C-26), 25.57 (CH_2, C-15), 27.31 (CH_2, C-21), 27.45 (CH_2, C-16), 29.26 (CH_2, C-14), 29.32 (CH_2, C-24), 29.37 (CH_2, C-30), 29.47 ($3CH_2$, C-25, 27, 28), 29.52 ($2CH_2$, C-23, 32), 29.55 ($2CH_2$, C-22, 31), 29.61 ($2CH_2$, C-19, 20), 29.77 (CH_2, C-29), 31.90 (CH_2, $COCH_2$), 52.00 (CH_2, O–CH_2), 118.75 (2CH, C-3, 7), 125.42 (CH, C-5), 129.87 (CH, C-6), 129.92 (CH, C-4), 130.82 (CH=CH, C-17, 18), 142.27 (C, NH–C), 166.66 (C, ph–C = O), 171.79 (C, CONH); EIMS *m/z* 486.6 $[M + H]^+$.

Ethyl (Z)-4-(docos-13-enoyloxy)benzoate (**20**) ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (3H, t, $J = 6.8$ Hz, CH_3), 1.28–1.31 (28H, m, H4–11, H16–21), 1.40 (3H, t, $J = 7.2$ Hz, O–CH_2CH_3), 1.74–1.81 (2H, m, H-3), 1.99–2.06 (4H, m, H-12, -15), 2.59 (2H, t, $J = 7.2$ Hz, H-3), 4.93 (2H, t, $J = 7.2$ Hz, O–CH_2CH_3), 5.36–5.38 (2H, m, H-13, -14), 7.17 (2H, d, $J = 8.8$ Hz, H-3', -5'), 8.09 (2H, d, $J = 8.8$ Hz, H-2', -6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.11$ (CH_3, C-22), 14.32 (CH_3, C-35), 22.69 (CH_2, C-8), 24.85 (CH_2, C-18), 27.22 ($2CH_2$, C-11, 14), 29.09 (CH_2, C-19), 29.25 (CH_2, C-9), 29.32 (CH_2, C-4), 29.45 ($3CH_2$, C-6, 7, 17), 29.53 ($2CH_2$, C-1, 2), 29.59 ($2CH_2$, C-3, 10), 29.78 ($2CH_2$, C-12, 13), 31.92 (CH_2, C-5), 34.40 (CH_2, $COCH_2$), 61.03 (CH_2, O–CH_2), 121.53 (2CH, C-26, 30), 127.95 (C, C-28), 129,87 (CH, C-29), 129.91 (CH, C-27), 131.07 (CH=CH, C-15, 16), 154.36 (C, O–C), 165.83 (C, ph–C=O), 171.76 (C, O–C=O); EIMS *m/z* 509.6 $[M + Na]^+$.

Ethyl (Z)-2-(4-(docos-13-enamido)phenyl)acetate (**21**) M. p. 91.3–92.0 °C; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.88$ (3H, t, $J = 6.8$ Hz, CH_3), 1.23 (2H, t, $J = 7.6$ Hz, O–CH_2CH_3) 1.24–1.31 (28H, m, H4–11, H16–21), 1.68–1.75 (2H, m, H-3), 1.98–2.03 (4H, m, H-12, -15), 2.32 (2H, t, $J = 7.2$ Hz, H-32), 3.56 (2H, s, CH_2CO), 4.13 (2H, q, $J = 7.6$ Hz, O–CH_2CH_3), 5.30–5.38 (2H, m, H-13, -14), 7.20 (2H, d, $J = 8.4$ Hz, H-3', -5'), 7.44 (1H, brs, NH), 7.45 (2H, d, $J = 8.4$ Hz, H-2', -6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.09$ (CH_3, C-33), 14.16 (CH_3, C-36), 22.67 (CH_2, C-26), 25.56 (CH_2, C-29), 27.22 ($2CH_2$, C-14, 17), 29.32 (CH_2, C-30), 29.40 (CH_2, C-27), 29.52 (CH_2, C-22), 29.56 ($3CH_2$, C-24, 25, 28), 29.62 ($4CH_2$, C-18–21), 29.77



Scheme 3 The synthesis routes of compounds **23–26**

(2CH_2, C-15, 16), 31.90 (CH_2, C-23), 37.15 (CH_2, $COCH_2$), 40.82 (CH_2, ph–CH_2), 60.87 (CH_2, O–CH_2), 119.96 (2CH, C-2, 6), 127.96 (2CH, C-3, 5), 129.75 (C, C-4), 129.90 (CH=CH, C-12, 13), 137.06 (C, NH–C), 171.49 (C, O–C = O), 171.69 (C, CONH); EIMS *m/z* 522.5 $[M + Na]^+$.

N-(5-bromo-3-methylpyridin-2-yl)oleamide (**22**) M.p. 66.8–67.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (3H, t, $J = 6.8$ Hz, CH_3), 1.28–1.34 (20H, m, H-4–7, H12–17), 1.70–1.74 (2H, m, H-3), 1.99–2.09 (4H, m, H-8, 11), 2.21 (3H, s, ph–CH_3), 2.37 (2H, t, $J = 8.0$ Hz, H-2), 5.35–5.39 (2H, m, H-9, 10), 7.10 (1H, brs, NH), 7.40 (S, H, H-4'), 7.8 (1H, s, H-6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.13$ (CH_3, C-18), 17.62 (CH_3, C-27), 22.70 (CH_2, C-1), 25.75 (CH_2, C-15), 27.18 (CH_2, C-8), 27.24 (CH_2, C-5), 29.15 (CH_2, C-16), 29.29 (CH_2, C-11), 29.34 (CH_2, C-13), 29.38 (CH_2, C-10), 29.54 (CH_2, C-12), 29.67 (CH_2, C-9), 29.72 (CH_2, C-7), 29.78 (CH_2, C-6), 31.29 (CH_2, C-14), 37.53 (CH_2, $COCH_2$), 124.88 (C, C–Br), 129.64 (C, C–CH_3), 135.05 (CH, CH=CH), 138.38 (CH, CH=CH), 140.08 (CH, C-23), 140.83 (C, NH–C–N), 141.53 (CH, *N* = CH), 174.05 (C, CONH); EIMS *m/z* 451.5 $[M + H]^+$, 453.3 $[M + H]^+$.

*General method for the synthesis of compounds **23–26***

The method of the synthesis of compounds **23–26** were shown in Scheme 3. Oleylamine (1 mmol), Et_3N (0.27 mL, 2 mmol) and DMAP (15 mg) in anhydrous CH_2Cl_2 (12 mL) were poured into a two flask. The solution was cooled in an ice bath and magnetically stirred. Sulfonyl chloride was added dropwisely. The reaction mixture was stirred for 12 h at room temperature and then washed with 5%sodium bicarbonate solution, 1 M HCl and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford compounds **23–26**.

(Z)-N-(octadec-9-en-1-yl)butane-1-sulfonamide (**23**) M.p. 53.2–54.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (3H, t, $J = 6.8$ Hz, H-18), 0.96 (3H, t, $J = 7.6$ Hz, H-4'),1.26–1.28 (22H, m, H3–7, H11–17), 1.44–1.51 (2H, m, H-2), 1.56–1.59 (2H, m, H-3'), 1.75–1.83 (2H, m, H-2'), 1.95–2.04 (4H, m, H-8, -11), 2.99–3.03 (2H, m, H-1'), 3.07– 3.12 (2H, m, H-1), 4.53 (1H, brt, $J = 6.0$ Hz, NH), 5.34–5.39 (2H, m, H-9, -10); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 13.59$ (CH_3, C-26), 14.10 (CH_3, C-19), 22.67 (2CH_2, C-24, 25), 25.66 (CH_2, C-15), 26.59 (CH_2, C-13), 27.17 (CH_2, C-6), 27.20 (CH_2, C-3), 29.15 (CH_2, C-17), 29.31 (CH_2, C-14), 29.35 (CH_2, C-11), 29.51 (CH_2, C-9), 29.56 (CH_2, C-8), 29.65 (CH_2, C-10), 29.69 (CH_2, C-7), 29.72 (CH_2, C-5), 29.75 (CH_2, C-4), 31.90 (CH_2, C-12), 43.29 (CH_2, NH–CH_2), 52.29 (CH_2, S–CH_2), 129.74 (CH, CH=CH), 129.98 (CH, CH=CH); EIMS *m/z* 424.7 $[M + Na]^+$.

(Z)-4-fluoro-N-(octadec-9-en-1-yl)benzenesulfonamide (**24**) M.p. 61.3–61.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.87$ (3H, t, $J = 6.8$ Hz, H-18), 1.21–1.26 (22H, m, H3–7, 12–17), 1.41–1.47 (2H, m, H-2), 1.95–2.01 (4H, m, H-8, -11), 2.90–2.96 (2H, m, H-1), 4.78 (1H, t, $J = 5.8$ Hz, NH), 5.32–5.38 (2H, m, H-9, -10), 7.19 (2H, m, H-3', -5'), 7.89 (2H, m, H-2', 6'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.06$ (CH_3, C-18), 22.70 (CH_2, C-15), 26.45 (CH_2, C-13), 27.12 (CH_2, C-6), 27.17 (CH_2, C-3), 28.97 (CH_2, C-17), 29.11 (CH_2, C-14), 29.27 (CH_2, C-11), 29.39 (CH_2, C-9), 29.48 (CH_2, C-8), 29.57 (CH_2, C-10), 29.61 (CH_2, C-7), 29.65 (CH_2, C-5), 29.72 (CH_2, C-4), 31.86 (CH_2, C-12), 43.19 (CH_2, NH–CH_2), 116.12 (CH, C-27), 116.35 (CH, C-25), 129.69 (CH, CH=CH), 129.78 (CH, CH=CH), 136.10 (CH, C-28), 136.12 (CH, C-24), 163.71 (C, S–C), 166.24 (C, F–C); EIMS *m/z* 426.2 $[M + H]^+$.

(Z)-N-(octadec-9-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (**25**) M.p. 47.6–48.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.89$ (3H, t, $J = 6.8$ Hz, H-18), 1.24–1.28 (22H, m, H3–7, H12–17), 1.43–1.50 (2H, m, H-2), 1.98–2.03 (4H, m, H-8, -11), 2.97–3.02 (2H, m, H-1), 4.83 (1H, t, $J =$ 6.0 Hz, NH), 5.32–5.40 (2H, m, H-9, -10), 7.80 (2H, d, $J =$ 8.4 Hz, H-24, -28), 8.02 (2H, d, $J = 8.4$ Hz, H-25, −27); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.10$ (CH_3, C-18), 22.68 (CH_2, C-15), 26.47 (CH_2, C-13), 27.15 (CH_2, C-6), 27.21 (CH_2, C-3), 29.15 (CH_2, C-17), 29.27 (CH_2, C-14), 29.32 (CH_2, C-11), 29.42 (CH_2, C-9), 29.51 (CH_2, C-8), 29.56 (CH_2, C-10), 29.51 (CH_2, C-7), 29.68 (CH_2, C-5), 29.76 (CH_2, C-4), 31.90 (CH_2, C-12), 43.13 (CH_2, NH–CH_2), 126.25 (C, CF_3), 126.29 (CH, C-27), 127.56 (CH, C-25), 129.71 (2CH, C-24, 28), 130.03 (CH=CH,

Table 1 Inhibition of compounds (100 μM) **1-26** on FAAH

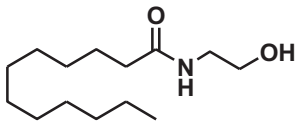
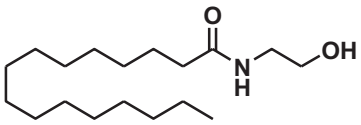
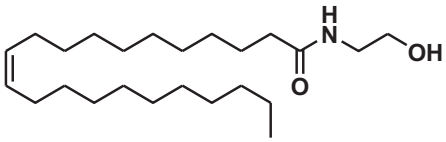
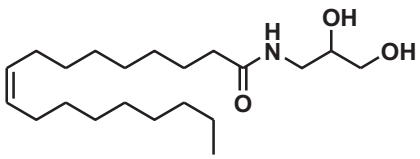
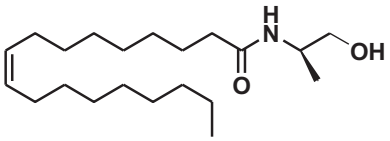
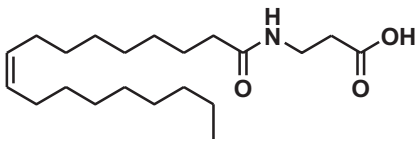
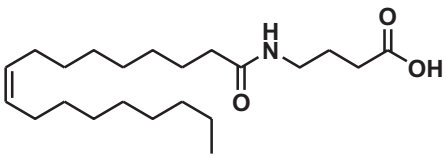
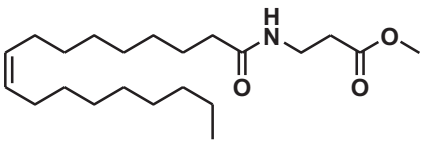
Compound number	Structure	Inhibitory (%)
1		50.45
2		31.54
3[a]		32.83
4		86.96
5		21.59
6		84.27
7		97.77
8[a]		86.34

Table 1 continued

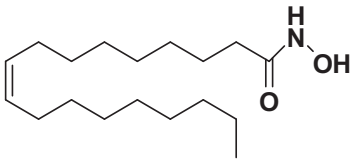
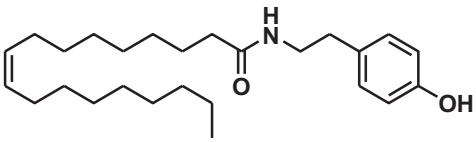
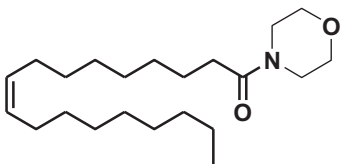
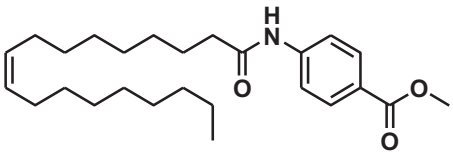
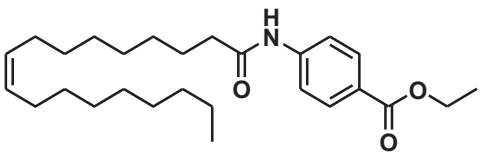
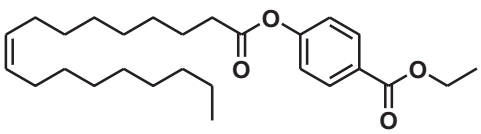
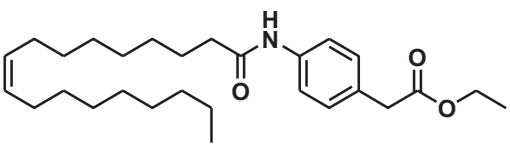
Compound number	Structure	Inhibitory (%)
9		98.35
10		73.86
11		64.95
12		19.18
13[a]		31.83
14		34.70
15		64.28

Table 1 continued

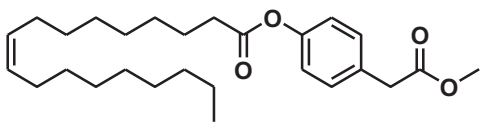
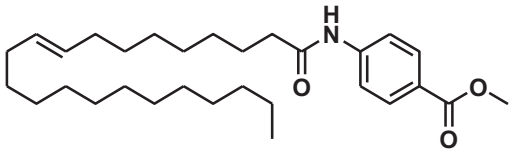
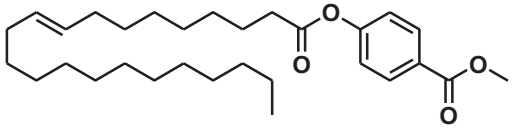
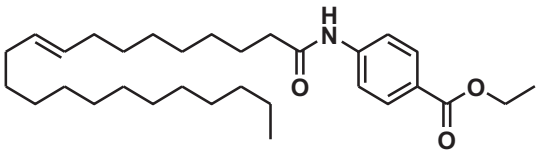
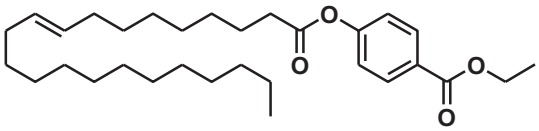
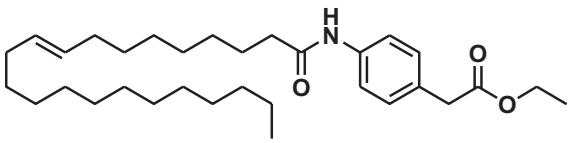
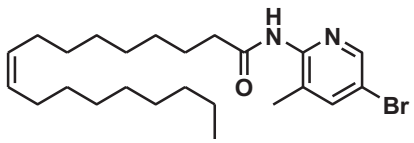
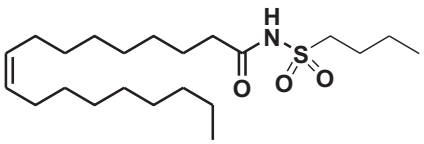
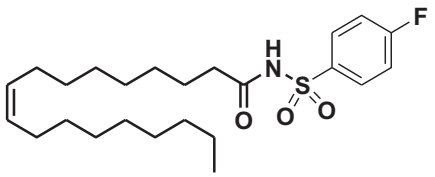
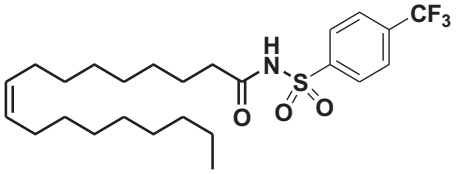
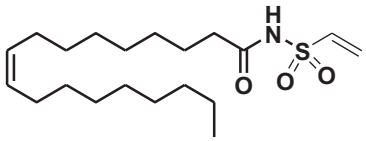
Compound number	Structure	Inhibitory (%)
16		84.90
17[a]		15.58
18		23.84
19[a]		7.20
20		19.21
21		10.42
22		33.54
23		25.94

Table 1 continued

Compound number	Structure	Inhibitory (%)
24		42.03
25		61.46
26[a]		59.11

[a] Compounds of testing set

C-1, 2), 134.17 (C, C-26), 143.71 (C, S–C); EIMS *m/z* 498.6 $[M + Na]^+$.

(Z)-N-(octadec-9-en-1-yl)ethenesulfonamide (**26**) ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.90$ (3H, t, $J = 6.8$ Hz, CH_3), 1.25–1.28 (22H, m, H3–7, H12–17), 150–1.57 (2H, m, H-2), 1.95–2.04 (4H, m, H-8, -11), 2.97–3.02 (2H, m, H-1), 4.50–4.54 (1H, m, NH), 5.32–5.38 (2H, m, H-9, -10), 5.93 (1H, d, $J = 9.96$ Hz, H-1'), 6.23 (1H, d, $J = 16.37$ Hz, H-1'), 6.51 (1H, dd, $J = 9.96$ Hz, 16.37 Hz, H-2'); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.11$ (CH_3, C-19), 22.69 (CH_2, C-15), 24.85 (CH_2, C-13), 27.22 ($2CH_2$, C-3, 6), 29.09 (CH_2, C-17), 29.25 (CH_2, C-14), 29.32 (CH_2, C-11), 29.45 (CH_2, C-9), 29.53 (CH_2, C-8), 29.59 ($2CH_2$, C-7, 10), 29.78 ($2CH_2$, C-4, 5), 31.92 (CH_2, C-12), 61.03 (CH_2, NH–CH_2), 121.53 (CH_2, CH=CH_2), 129.87 (CH, CH=CH), 129.91 (CH, CH=CH), 131.07 (CH, S–CH=CH_2); EIMS *m/z* 358.4 $[M + H]^+$.

Biological activity

FAAH protein expression and purification

The inhibitory activities on FAAH were tested by recombinant rat FAAH protein. The protein was obtained through HEK-293 cells over expressing rFAAH. The extraction procedure of FAAH protein was following. First, HEK293-rFAAH were harvested, washed with phosphate buffer (PBS), sonicated in 20 mM Tris-HCL (pH 7.5) containing 0.32 M sucrose, and centrifuged at $800 \times g$ for 15 min at 4 °C. Then, the supernatants were collected and protein concentrations were measured by BCA protein assay kit (Pierce, Shanghai, China).

Inhibition of FAAH in vitro

FAAH activity was measured by incubating 30 μg of protein derived from HEK293-rFAAH cell extract at 37 °C after adding 25 μM anandamide as substrate in Tris-HCl buffer (50 mM, pH 8.0) containing fatty acid-free BSA (0.05%). The reactions were terminated by adding 0.2 mL methanol containing 1 nmol of heptadecanoic acid as internal standard and analyzed by liquid chromatography/mass spectroscopy (LC/MS). FAAH can hydrolyze the substrate AEA and produce arachidonic acid under normal circumstance. If its activity was inhibited, the product of enzyme reaction, arachidonic acid, will decrease. The inhibition ratio can be calculated according to the content of arachidonic acid before and after the addition of inhibitor.

We use an Agilent 1200-LC system coupled to a 3200Q TRAP-MS detector equipped with an electrospray ionization (ESI) interface (Agilent Technologies, Shanghai, China).

Fatty acids were eluted on an XDB Eclipse C18 column (4.6 × 50 mm i.d., 1.8 μm Agilent Technologies) isocratically at 0.6 mL/min for 4 min with a solvent mixture of 95% methanol and 5% water, both containing 0.25% acetic acid and 5 mM ammonium acetate. The column temperature was 40 °C. Electrospray ionization was in the negative mode, capillary voltage was −4.5 kV, Heptadecanoic acid was used as internal standard ($m/z = 303$ for arachidonic acid).

CoMFA analysis

Molecular buliding

Molecular building was done with a molecular sketch program, HyperChem6.0, on a Windows system. All CoMFA analysis were performed using Sybyl7.0 on the Unix system. All parameters used in CoMFA were default except for explained specially. Partial atomic charges were calculated using the Gasteiger–Marisili method. The molecular geometry of each compound was minimized using a Powell method with a convergence criterion of 0.01 kcal/mol per Å in a standard Tripos force field.

Data set and alignment

In our present work, 26 compounds with available values of inhibition rates were employed for the 3D-QSAR analysis. Based on the inhibition rates, 26 compounds was sorted from high inhibition to low inhibition. Then the six compounds (**3**, **8**, **13**, **17**, **19**, and **26**) were selected as the test set, which represent high (**8**and **26**, 86.34 and 59.11% inhibition), medium (**3**and **13**, 32.83 and 31.83%) and low inhibitory activities (**17**and **19**, 15.58 and 7.20%). And the remaining 20 compounds (**1**, **2**, **4**, **5**, **6**, **7**, **9**, **10**, **11**, **12**, **14**, **15**, **16**, **18**, **20**, **21**, **22**, **23**, **24**, and **25**) were selected as the training set for model construction.

Partial least squares (PLS) analysis and models validation of 3D-QSAR model

PLS analysis was used to construct a linear correlation between the 3D-field (steric and electrostatic field) and the FAAH inhbitory activities. To select the best model, the cross-validation analysis was performed using the leave-one-out method in which one compound was removed from the data set and its activity was predicted using the model built from rest of the data set. It resulted in the cross-validation correlation coefficient (q^2) and the optimum number of components N.

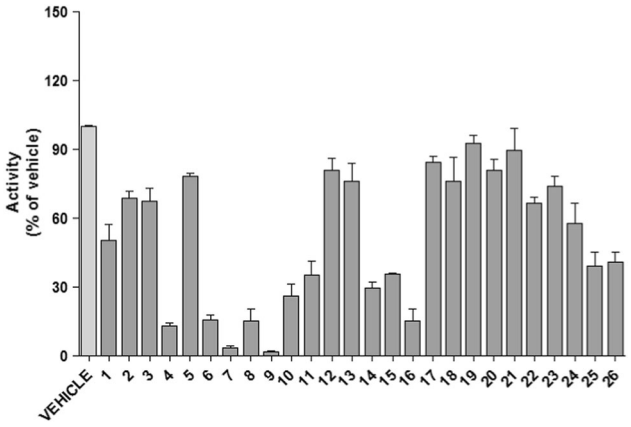


Fig. 2 Effects of compounds on FAAH at 100 μM. Data are means of three separate determinations every group

Results

Synthesis

Three sets of OEA analogs have been prepared (Table 1). The first set contains nine amides **1–9**, differing by the nature of flexible hydrophilic head group. These compounds have been prepared from oleic chlorid and corresponding amines at room temperature. The second set includes ten amides or eaters compounds **10–22**, varying at the nature of rigid acromatic head group. The third set is four sulfamide analogs, which were synthesized from oleylamine and corresponding sulfonyl chloride.

Inhibition of FAAH

Compounds **1–26** have been evaluated their activities against FAAH using the previously reported assay procedure (Table 1, Fig. 2). As results shown in Table 1, most of these compounds, except compounds **2**, **11**, **12**, **13**, and **14**, reduce the production from the FAAH substrate in vitro. It is worthwhile noted that, among the designed three set of OEA analogs, every set includes some compounds with high potential inhibitory activities on FAAH, for example, compound **4** in the first set, compounds **16** and **20** in the second set, and compound **24** in the third set. Of these compounds, the most active one is compound **9**, which inhibit FAAH activity 98.35% at the concentration of 100 μM.

3D- QSAR analysis

The contour maps of CoMFA model were presented in Fig. 3. For the CoMFA model, partial least squares (PLS) regression produced an excellent cross-validated correlation coefficient (q^2) of 0.613 with an optimized component of 4,

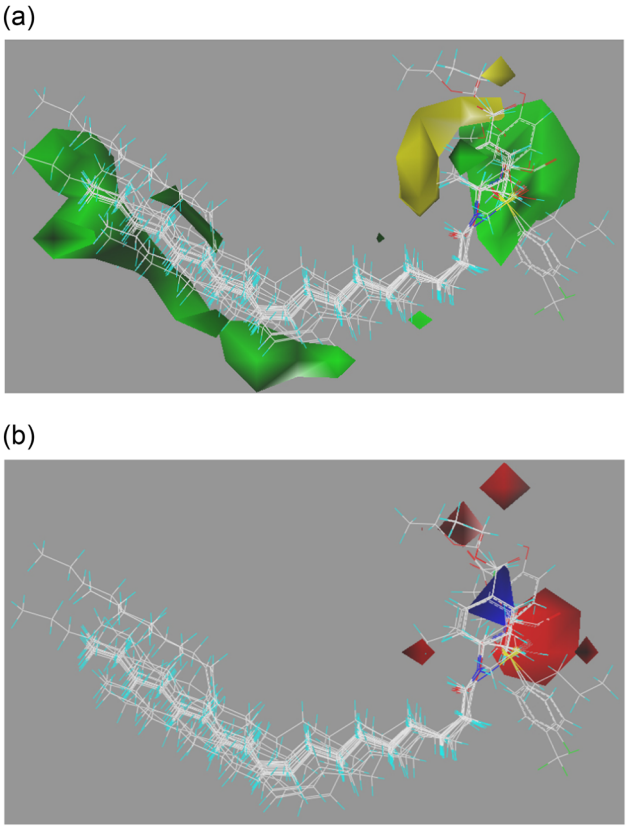


Fig. 3 CoMFA contour maps for **a** steric field: *green/yellow* contours indicate regions where steric bulky groups increase/decrease activity. Favored and disfavored levels of these displayed fields are fixed at 80% and at 20%, respectively; **b** electrostatic field: *red/blue* contours indicate regions where negative charge increase/decrease activity. Favored and disfavored levels of these displayed fields are fixed at 80% and at 20% (color figure online)

Table 2 Statistical results from the CoMFA model

Model	r^2	q^2	SEE	F	N
CoMFA	0.613	0.978	4.813%	168.797	4

r^2 non-validated correlational coefficient

q^2 cross-validated correlational coefficient

SEE standard error of estimate

F *F*-test valid

N the number of components

which suggested that the model was reliable and it should be a useful tool for predicting the biological activity. The noncross-validated PLS analysis gave a high correlation coefficient (r^2) of 0.978, and a low standard error estimate (SEE) of 4.813%. The contributions of steric and electrostatic fields to this model were 0.8 and 0.2, respectively. All these statistical parameters for the CoMFA models were given in Table 2. In addition, Fig. 4 shows the correlation between the experimental and CoMFA predicted activities

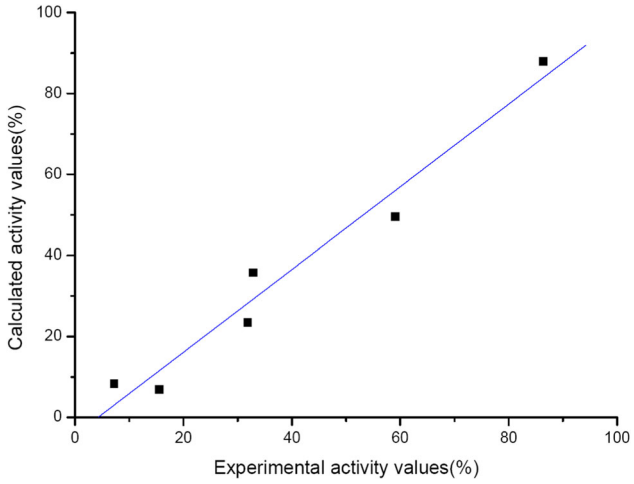


Fig. 4 The correlation between the experimental and CoMFA predicted activities of the testing set. ($N = 6$, $r^2 = 0.981$, SEE = 6.60%, $F = 102.92$, $P < 0.01$)

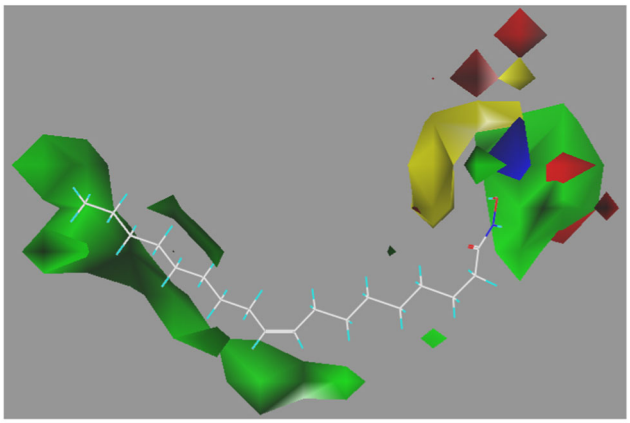


Fig. 5 CoMFA contour maps with the most active compound **9**

of the testing set of compounds, with a correlation coefficient of 0.981. These analyzes have demonstrated that the CoMFA models are quite convincing and sufficient in guiding further plausible modification in the molecules for obtaining better activity.

Discussion

OEA was used as the backbone of SAR to optimize study for developing potent FAAH inhibitors. Based on the structure of OEA, three series of OEA derivatives were designed, synthesized and performed the enzymatic assay to evaluated the inhibitory effect on FAAH. First, three compounds **1–3** were synthesized by altering the length of carbon chain, while leaving the general template of this natural ligand unaltered. Second, seven compounds were

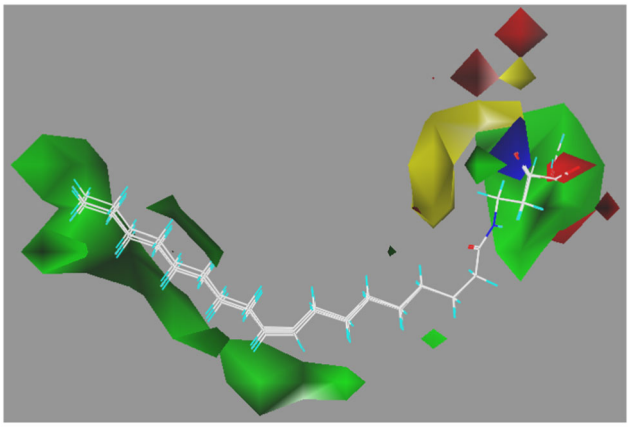
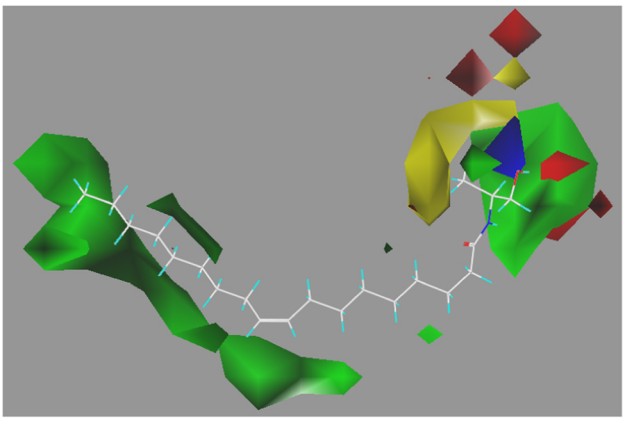


Fig. 6 CoMFA contour maps with compounds **6**, **7**, and **8**

(a)



(b)

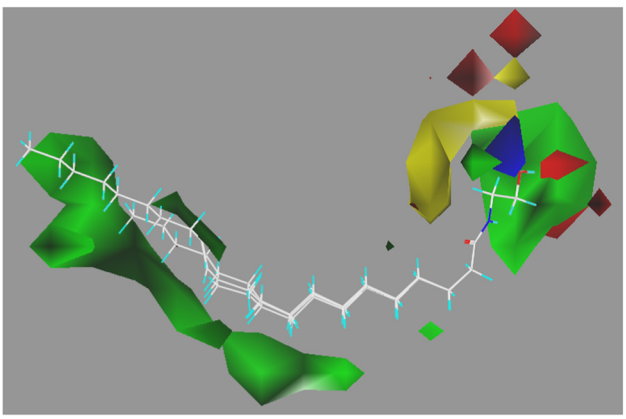
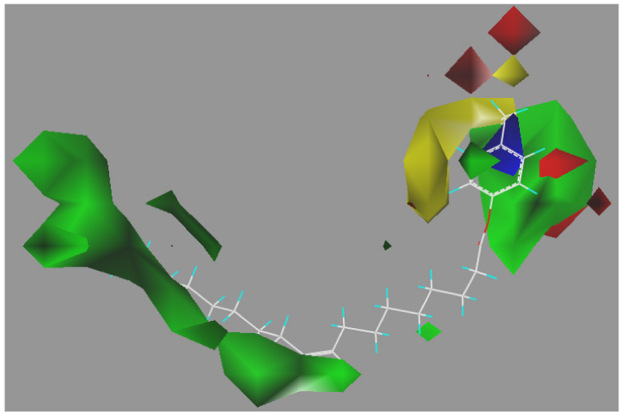


Fig. 7 CoMFA contour maps with compound 5**a** and compound **1**, **2**, and **3b**

obtained by modifying the hydrophilic head group of OEA in two different ways. On the one hand, compounds **4–10** were synthesized by replacing ethanolamine moiety with some other flexible hydrophilic groups. On the other hand, we designed eleven compounds **12–22** by converting the flexible head group into rigid group which are mainly *p*-substituted aryl groups. The third series of OEA derivatives are 4 sulfamide analogs **23–26**, which have a common functional group, sulfamide.

(a)



(b)

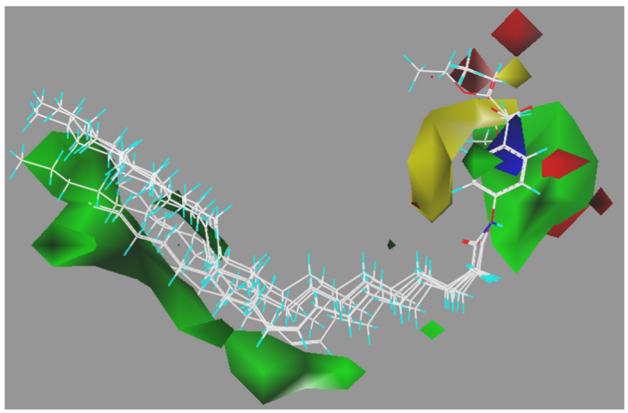


Fig. 8 CoMFA contour maps with compound **16a** and compound **12–21b**

In order to have a better understanding of the structure–activity relationship, a CoMFA model was build on the basis of the structures of compounds and their activities on FAAH inhibitory. The analysis of PLS indicated that the model was statistically reliable to explain which differences in structures lead to dramatically increasement or descreasment on biologically activities, as well as to bring new insights into design of this series of FAAH inhibitors. CoMFA model with the most potent compound **9** were displayed in Fig. 5. In steric contour, green color indicated that sterically favored regions where addition of bulky group increase the activity, while yellow color indicated sterically disfavored regions where addition of bulky group decrease the activity. In electronicstatic contour, the

blue color defines a region where an increase in the positive charge will result in an increase in the activity, whereas the red color defines a region of space where increasing electron density is favorable. Compound **9** fits all these criteria. As shown in steric contours, a long carbon chain near the green regions and an electronegative oxygen of carbonyl group near the red region were observed. Other disfavorable groups exist near the yellow and blue regions. This explained why compound **9** always displayed higher activity than any other compounds. In addition, another three compounds **6**, **7**, **8** show relative higher activities not only because that head groups of $-CH_2CH_2COOH$ (**6**), $-CH_2CH_2CH_2COOH$ (**7**), and $-CH_2CH_2COOCH_3$ (**8**) occupy the green regions, but also the two oxygens in carbonyl group and hydroxyl locate in the red region (Fig. 6). In case of compound **5**, a methyl group was found overlapping the yellow region where large steric bulky would not be preferred, and this explain why compound **5** are less active than compounds **1**, **2** and **3** which have similar structures, except for a methyl group (Fig. 7). As for structurally similar compounds **12–21**, molecule **16** shows obviously higher activity than others mainly due to the location of the head groups of these compounds. In steric contour, the head groups of compound **16** locate at the green region, while the others extend to the yellow region where large steric disfavorable (Fig. 8) is. In summary, the contour maps give some common features possessed by those compounds with higher activities. These features can be considered during the design of new inhibitors of OEA analogs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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