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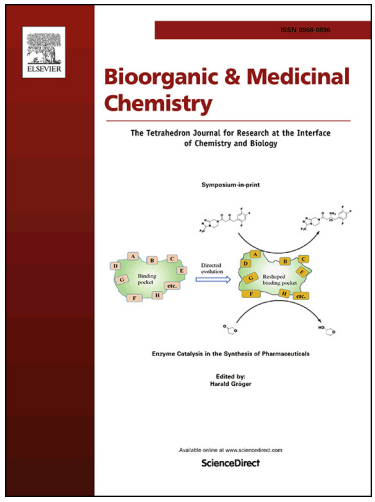

Identification of New Dual FABP4/5 Inhibitors Based on a Naphthalene-1-sulfonamide FABP4 Inhibitor

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Identification of New Dual FABP4/5 Inhibitors Based on a Naphthalene-1-sulfonamide FABP4 Inhibitor

Yulong He [a,1], Huixia Dou [b,c,1], Dingding Gao [a, d, 1], Ting Wang [b], Mingming Zhang [a, *], Heyao Wang [b,*], Yingxia Li [a,*]

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Abstract

Fatty acid binding protein 4 (FABP4) and fatty acid binding 5 (FABP5) are mainly expressed in adipocytes and/or macrophages and play essential roles in energy metabolism and inflammation. When FABP4 function is diminished, FABP5 expression is highly increased possibly as a functional compensation. Dual FABP4/5 inhibitors are expected to provide beneficial synergistic effect on treating diabetes, atherosclerosis, and inflammation-related diseases. Starting from our previously reported selective FABP4 inhibitor **8**, structural biology information was used to modulate the selectivity profile and to design potent dual FABP4/5 inhibitors with good selectivity against FABP3. Two compounds **A16** and **B8** were identified to show inhibitory activities against both FABP4/5 and good selectivity over FABP3, which could also reduce the level of forskolin-stimulated lipolysis in mature 3T3-L1 adipocytes. Compared with compound **8**, these two compounds exhibited better anti-inflammatory effects in lipopolysaccharide-stimulated RAW264.7 murine macrophages, with decreased levels of pro-inflammatory cytokines TNFα and MCP-1 and apparently inhibited IKK/NF-κB pathway.

Keywords

Dual FABP4/5 inhibitor; Structure-based design; Lipolysis inhibition; Anti-inflammatory effects

1 Introduction

FABPs are small (14-15kDa) cytosolic proteins that modulate lipid trafficking and inflammatory responses in cells.[1] They could reversibly bind to long-chain fatty acids and other hydrophobic ligands with high affinity and extensive selectivity.[2-3] Since the first report of FABPs in 1972, at least ten members have been confirmed.[4-5] Different isoforms of the FABPs exhibit unique patterns of tissue expression and are involved in active lipid metabolism.[6] FABP4, also known as aP2 or adipocyte FABP (A-FABP), was first identified in mature adipocytes and also expressed in macrophages and dendritic cells.[7-10] It has been proved to transport hydrophobic fatty acids within cells to various destinations for fatty acid oxidation, membrane homeostasis or nuclear signaling.[11] Previous studies have demonstrated that FABP4 knockout animals are partially protected from insulin resistance associated with genetic or dietary obesity.[12-13]Ablation of FABP4 protected apolipoprotein E (ApoE)-deficient mice against atherosclerosis with or

without high-cholesterol western-style diets.[9] These results demonstrated a crucial role of FABP4 in the development of the metabolic syndrome.

Interestingly, under standard laboratory conditions, mice deficient in *Fabp4* did not differ from their wide-type in breeding, behavior or development.[12] Researchers have discovered that the loss of FABP4 in adipocytes is compensated by FABP5 (also known as E-FABP or mal 1), which is highly expressed in epidermal cells and present in the normal adipocytes and macrophage cells only in small amounts.[14] Studies have shown that FABP5 deficiency mildly increased systemic insulin sensitivity in dietary and genetically obese mice.[15] FABP5-deficient mice have also demonstrated favorable protection against atherosclerosis on a western-style hyper-cholesterol diet.[16] As described above, FABP4 or FABP5 single-knockout mice exhibited only modest phenotypes, but the FABP4 and FABP5 double-knockout mice displayed significant protection from insulin resistance, type 2 diabetes, and atherosclerosis, indicating a synergistic effect because of the dual deletion of FABP4 and FABP5.[17-18] Therefore, it is of high significance to develop dual FABP4 and FABP5 inhibitors to treat inflammatory and metabolic diseases. In addition, FABP4 and FABP5 also played an important role in tumourigenesis in different cancer types, including bladder, breast, prostate, colorectal, oral, ovarian cancer and acute myeloid leukemia.[19-25] Pharmacological inhibition of FABP anandamide transporters (FABP5 and FBAP7) resulted in beneficial effects on stress, inflammation and pain.[26-29]

In the past few years, a number of small molecule inhibitors towards FABP4/FBAP5 have been identified and classified based on structures (**Figure 1**),[30] for example, imidazole derivatives (**1**), indole derivatives (**2**), thiophene derivatives (**3**), bicyclic pyridine derivatives (**4**), urea derivatives (**5**), non-carboxylic acids (**6**), quinoline derivatives (**7**).[31-37] Among these, compound **6** is a novel FABP4/5 inhibitor whose efficacy was evaluated in *vitro* and in *vivo*.[36] Dual FABP4/5 inhibitor **7** possessed good potency and favorable physicochemical properties.[37] Therefore, both compounds could be used as suitable tool compounds.

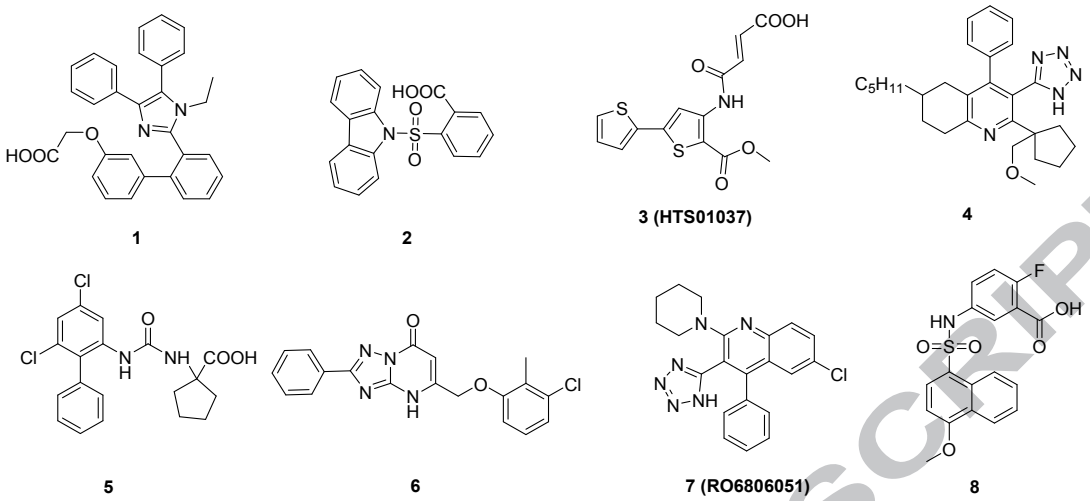


Figure 1. Structures of the representative FABP4/5 inhibitors.

Our research group previously reported the discovery of a potent and selective naphthalene-1-sulfonamide FABP4 inhibitor **8**.[38] It's worth noting that a corrigendum to this work[38] has been published recently (The Ki values in Tables 3 do not match with the corresponding compound structures and compound codes in the published article. This was caused due to the rearrangement of structures in the tables during the publishing process).[39]In this work, the lead compound **8** was further optimized to improve its FABP5 potency while maintaining the FABP4 activity based on the differences between these two pockets. Most of the analogs showed comparable inhibitory activities against FABP4 and FABP5. Particularly, compound **A16** and **B8** exhibited stronger inhibitory activity towards FABP4/5 than positive control compound **6**. In addition, **A16** and **B8** showed favorable inhibitory activity against forskolin-stimulated lipolysis in 3T3-L1 adipocytes and anti-inflammatory effects in lipopolysaccharide-stimulated RAW264.7 macrophages.

2 Results and Discussion

2.1 Structure-Based Design

To provide a better structural understanding for the design of potent dual FABP4/5 inhibitors, the co-crystal structures of several published FABP4 or/and FABP5 ligands were reviewed to get detailed insights into binding features.[40-42] As presented in Figure **2A** (X-ray crystal of FABP4 in complex with compound **8**),[38-39] the carboxyl group of forms hydrogen bonds with Arg 106, Arg 126 and Tyr 128, and the naphthalene ring forms a π-π interaction with Phe 16. In addition, the oxygen atom of the sulfonamide forms hydrogen bonds through water molecules with Tyr 19, Gln

95, Glu 72, Arg 78 and Ala 75, which is a unique binding mode of compound **8** with FABP4. As shown in Figure **2B** (X-ray crystal of FABP5 in complex with compound **7**),[37] the tetrazole group is engaged in multiple hydrogen bonds with Arg 129, Tyr 131 and Thr 56 directly or indirectly. The quinoline core forms a π-π interaction with Phe 19, and the phenyl group points into a pocket lined with residues Ala 39, Lys 40, Ser 58, and Lys 61. Subsequently, an overlay of these two crystal structures (Figure **2C**) indicates a similar binding mode of compound **8** in FABP4 and compound **7** in FABP5. From this analysis, it could be identified that the hydrophobic cavity of FABP5 where the phenyl group of compound **7** located was not optimally filled with the original methoxy substituent of compound **8**, and bulkier group may be ideally suited to target this region for dual FABP4/5 activity. We first focused our attention on increasing the size of 4-naphthalene substituent of compound 8 from methoxy to bulkier *O*-alkyl, *O*-phenyl, and benzyl substituents (Series A, **Figure 3**). Nest in Series B, phenyl or heteroaromatic ring with various substituents were introduced into the C3 position of naphthalene core to investigate the effect on potency.

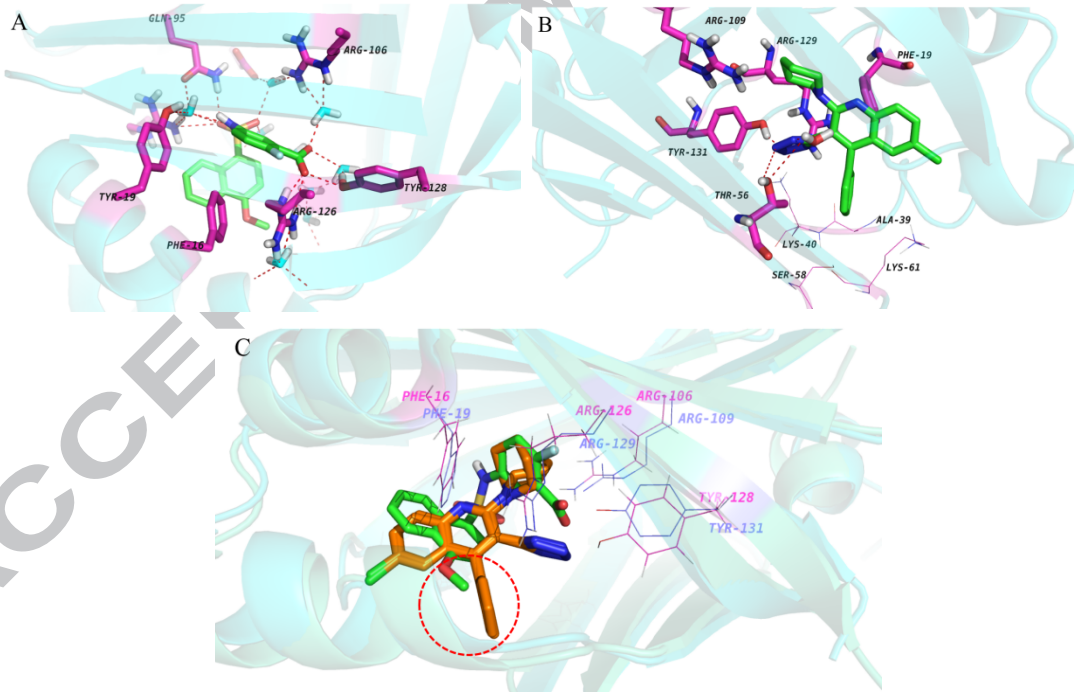


Figure 2. (A) Crystal structure of compound **8** with human FABP4 (PDB: 5Y0F); (B) Crystal structure of compound **7** with human FABP5 (PDB: 5HZ5); (C) An overlay of the complex crystal structure of **8** (protein: cyan, ligand: green, residues: magenta, PDB: 5Y0F) in FABP4 with **7** in FABP5 (protein: cyan, ligand: orange, residues: blue, PDB: 5HZ5). The pictures were generated using Pymol.

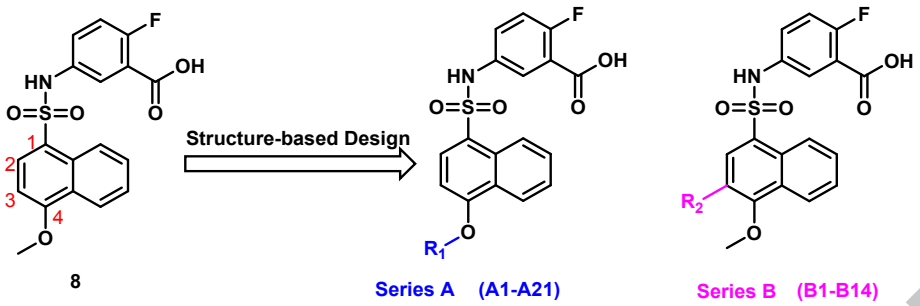
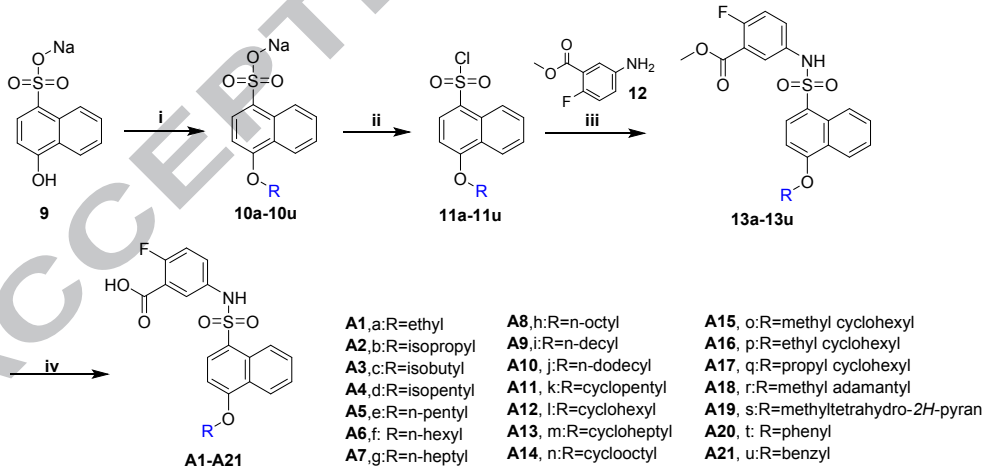


Figure 3. Structure-based design of target compounds

2.2 Chemistry

*2.2.1 Synthesis of Compounds **A1-A21***

The synthesis of target compounds **A1-A21** is outlined in Scheme **1**. Commercially available material **9** was converted to intermediates **10a-10u** by reacting with different alkyl bromides or substituted benzyl bromides in a mixed solvent of ethanol and water in the presence of sodium hydroxide. Then, the reaction of **10a-10u** with thionyl chloride in DMF led to the formation of compounds **11a-11u**, which were further coupled with the commercially available material **12** in the presence of pyridine to give intermediates **13a-13u**. Finally, methyl esters of **13a-13u** was hydrolyzed to give the target compounds **A1-A21**.

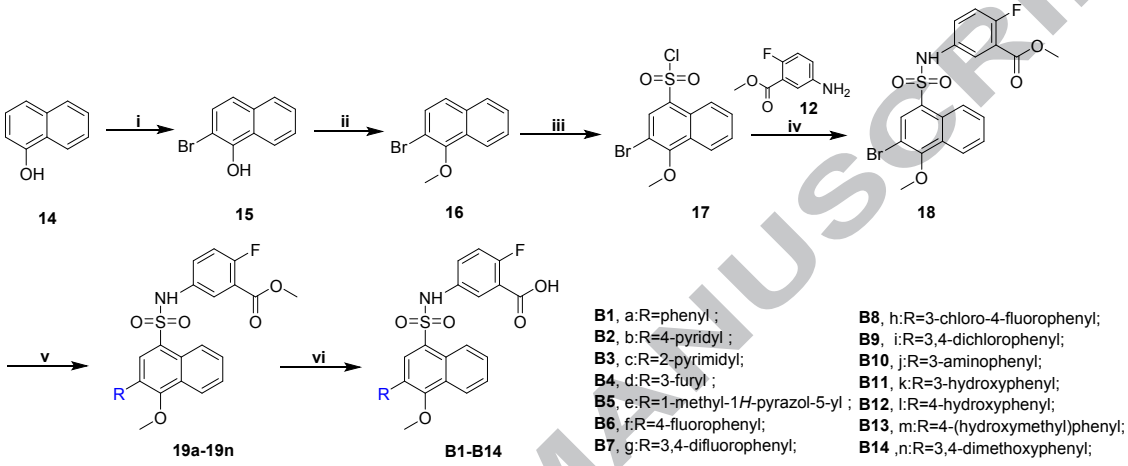


Scheme 1. Synthesis of compounds **A1-A21**. Reagents and conditions: (i) RX, NaOH, EtOH: H_2O = 1/1, 80 °C, overnight; (ii) $SOCl_2$, DMF, 1 h, rt ; (iii) Pyridine, acetone, 55 °C, 1 h ; (iv) NaOH, H_2O, MeOH, 1 h, rt.

*2.2.2 Synthesis of Compounds **B1-B14***

The series B compounds were synthesized as described in Scheme **2**. The reaction of **14** with NBS in the presence of catalytic amount of diethylamine provided intermediate **15**, which was

mixed with methyl iodide in acetonitrile leading to the formation of compound **16**. Treatment of **16** with chlorosulfonic acid in chloroform afforded chlorosulfonylation product **17**, which followed by reaction with **12** in acetone to give key intermediate **18**. Coupling of **18** with different substituted aryl boronic acids *via* Suzuki reaction provided **19a-19n**, which subsequently were hydrolyzed with sodium hydroxide to afford desired compounds **B1-B14**.



Scheme 2. Synthesis of compounds **B1-B14.** Reagents and conditions: (i) NBS, diethylamine, CH_2Cl_2, 40 °C, overnight; (ii) CH_3I, KOH, CH_3CN, 40 °C, 12 h ; (iii) HSO_3Cl, CH_3Cl, 0 °C to rt.; (iv) Pyridine, acetone, 55 °C, 1 h; (v) R-$B(OH)_2$, K_2CO_3, $PdCl_2(dppf).CH_2Cl_2$, DMF, H_2O ; (vi) NaOH, H_2O, MeOH, 1 h, rt.

2.3 Biochemical Evaluations and Structure-Activity Relationships.

All of the target compounds were evaluated for the inhibitory activity against FABP4 and FABP5 at a concentration of 25 μM, and compounds with inhibition rate of FABP4 and FABP5 above 50% were further selected to test IC_{50} values. Ligand binding was measured via displacement of 1-anilinonaphthalene-8-sulfonic acid (1,8-ANS), as described previously. [38-39] The binding of 1,8-ANS fluorescent probe molecule to FABP4/5 increases the fluorescence intensity. The excitation and emission wavelength of the binding of ANS to protein is 370/470 nm, and the compound can compete with ANS to bind FABP4/5. The inhibitory activity of the compounds against FABP4/5 can be detected by measuring the fluorescence value at 370/470 nm. Since compound **7** had spontaneous emission at 370/470 nm and interfered with the readout, it was not selected as positive control. Compound **6** and **8** were chosen as positive compounds.

The results of the tested compounds are summarized in Tables **1** and Table **2**. For Series A,

the gradually lengthened alkyl carbon chain (**A2-A7**) maintained the inhibitory activity against FABP4 but very considerably increased the inhibitory activity against FABP5. The result suggests that the sub-pocket in FABP5 is able to accommodate bulkier group, while further increasing the length of the alkyl chain (**A8-A10**) might cause a steric clash with the sub-pocket resulting in a decrease in activity. Among these compounds, **A7** showed strong and balanced activity towards both FABP4 (IC_{50} = 2.30 μM) and FABP5 (IC_{50} = 2.76 μM), indicating *n*-heptyl to be the optimal linear alkyl group. Next, aiming to reduce entropy loss and lock the ligand in its active conformation, we replaced the flexible alkyl group with a rigid cycloalkane substituent. The cyclopentyl **A11** showed an increased inhibition rate against FABP5. Expanding the cyclopentyl (**A11**) to cyclohexyl (**A12**) and cycloheptyl (**A13**) further increased the inhibitory activity against FABP5 with the IC_{50} ranging from 3.30 to 7.66 μM. These results encouraged us to go on with a more bulky group such as cyclooctyl (**A14**). However, it exhibited weak activities towards both FABP4 and FABP5. Then, the length of alkyl chain between the naphthalene core and the cycloalkane was explored. Compound **A15** with methylcyclohexyl group (FABP4: IC_{50} = 2.41 μM, FABP5: IC_{50} = 8.12 μM) showed comparable inhibitory activity with **A12** (FABP4: IC_{50} = 2.20 μM, FABP5: IC_{50} = 7.66 μM). Elongation to the ethyl (**A16**) and propyl (**A17**) resulted in retained potency on FABP4 and slightly improved activity against FABP5. Replacing the methylcyclohexane with 1-methyladamantane (**A18**) showed a decreased activity on FABP4 (IC_{50} = 14.78 μM). When a hydrophilic tetrahydropyran ring was introduced (**A19**), both of FABP4/5 inhibitory activities significantly declined. This may be due to the conformational difference between cyclohexyl and tetrahydropyran or changes in physicochemical properties.The phenyl analog **A20** and the benzyl analog **A21** showed increased inhibitory activities against FABP5 compared with compound **8**, but less potent compared with saturated cycloalkyl analogs **A12** and **A15**, indicating phenyl moiety can decrease the binding affinity..

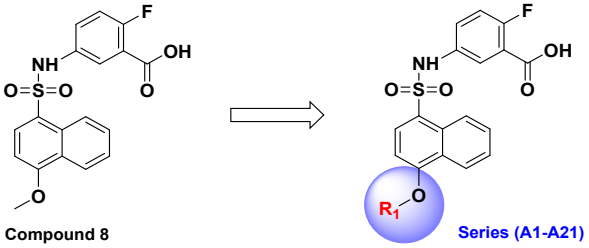
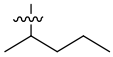
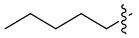
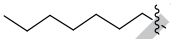
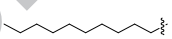
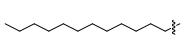
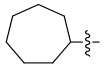
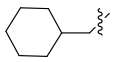
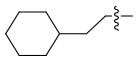
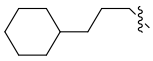
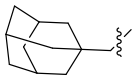
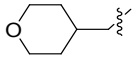
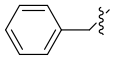


Table 1. Inhibitory activities of Series A compounds.

Compd.	R_1	FABP4		FABP5	
		@25μM Inhibition%	IC_{50} (μM)	@25μM Inhibition%	IC_{50} (μM)
A1		95%	2.64±0.19	13%	/
A2		85%	/	30%	/
A3		84%	/	48%	/
A4		90%	/	59%	/
A5		88%	2.99±0.00	53%	8.32±0.61
A6		94%	2.43±0.17	66%	4.17±0.37
A7		96%	2.30±0.05	71%	2.76±0.88
A8		91%	4.04±0.16	72%	4.19±0.83
A9		84%	4.73±0.25	61%	4.48±0.26
A10		71%	24.83±4.21	50%	23.42±0.32
A11		82%	/	54%	/
A12		84%	2.20±0.15	63%	7.66±0.60
A13		86%	2.37±0.08	71%	3.30±2.11

A14		23%	/	24%	/
A15		90%	2.41±0.11	65%	8.12±1.33
A16		92%	1.97±0.15	66%	4.85±1.03
A17		86%	3.59±0.26	65%	3.63±0.68
A18		47%	14.78±0.74	59%	4.61±3.52
A19		35%	/	20%	/
A20		84%	/	52%	/
A21		81%	3.15±0.11	42%	/
6		97%	6.34±0.01	52%	23.42±0.32
8		92%	1.69±0.12	5%	/

Based on the docking results (**Figure 2**), the alternative way to occupy the sub-pocket of FABP4 and FABP5 is to incorporate substituent at the C-3 of the naphthalene core. A series of aromatic groups were introduced and the results were shown in Table 2. Phenyl substituted **B1** exhibited comparable FABP4 inhibitory activity (IC_{50} = 1.19 μM) to compound **8** and improved potency on FABP5 (IC_{50} = 15.96 μM). Replacement of phenyl with pyridyl group caused a decrease in activity against FABP4 (IC_{50} = 3.54 μM) and FABP5 (IC_{50} = 17.18 μM) compared with **B1**. While the substituents of pyrimidine (**B3)**, furan **(B4)**, and N-methyl pyrazole (**B5)** demonstrated only moderate inhibitory rate against FABP4 and weak activity on FABP5. Further introducing halogens on the phenyl substituent led to compound **B6-B9**, which keep their activities and on FABP4 and 5 compared with B1. Incorporation of amino (**B10**) or hydroxyl (**B11**)

to the meta-position was well tolerated in FABP4 and FABP5 activity. Switching the hydroxyl from the *meta*-position to the *para*-position (**B12**) had no significant effect. While changing the hydroxyl to hydroxymethyl (**B13**) caused a dramatic loss in FABP4 and FABP5 potency. In addition, incorporation of two methoxy groups on the *meta*- and *para*-position of the phenyl (**B14**) was also not tolerated, which resulted in a significant loss of potency toward both FABP4 and FABP5. Therefore, we postulated that small groups introduced in the *meta*- or *para*-position of the phenyl was well tolerated in FABP4/5 potency, whereas bulky substituents were not preferred, such as methoxy and hydroxymethyl group.

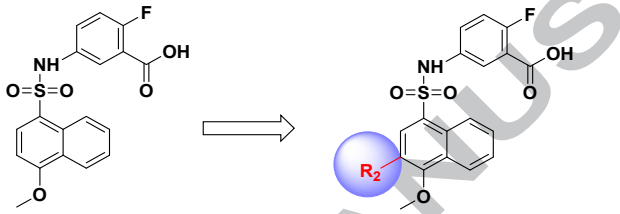
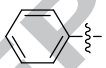
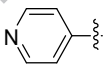
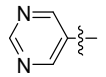
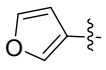
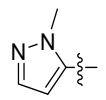
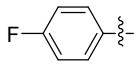
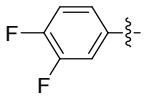
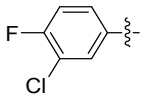
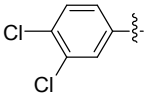
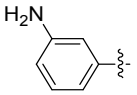
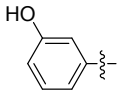
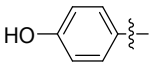
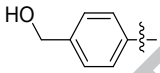
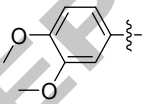


Table 2. Inhibitory activities of Series B compounds

Compd.	R_2	FABP4		FABP5	
		@25μM Inhibition %	IC_{50}(μM)	@25μM Inhibition%	IC_{50}(μM)
B1		97%	1.19±0.03	68%	15.96±2.31
B2		83%	3.54±0.27	42%	17.18±1.15
B3		57%	/	27% (100μM)	/
B4		90%	3.53±0.13	36%	30.94±3.07
B5		88%	/	48% (100μM)	/

B6		96%	1.74±0.04	65%	10.00±1.44
B7		88%	2.98±0.28	54%	17.13±5.12
B8		97%	1.58±0.66	71%	10.08±1.99
B9		85%	4.38±0.14	60%	14.63±1.92
B10		91%	1.70±0.05	53%	20.86±3.58
B11		90%	1.89±0.08	67%	17.74±6.92
B12		95%	1.19±0.07	59%	15.77±1.82
B13		19%	/	29%	/
B14		26%	/	26%	/
6		97%	6.34±0.01	52%	23.42±0.32
8		92%	1.69±0.12	5%	/

2.4 FABP3 Selectivity Evaluation

Fatty acid binding protein 3 (FABP3), also known as H-FABP, is mainly expressed in cardiac muscle tissue and plays an important role in cell proliferation, apoptosis and gene transcription.[43] Studies in a zebrafish model demonstrated that silencing of FABP3 leads to apoptosis-induced

mitochondrial dysfunction [44] and knocking down of FABP3 impairs cardiac development.[45] Therefore, selectivity versus FABP3 is thought to be critical for FABP4 inhibitors as therapeutic agents. The phenyl ring of compound **8** would clash with large side chain of Leu 115 and Leu 117 in FABP3 and exhibited good selectivity over FABP3 (Figure **S1**). Based on the results above, two representative compound **A16** and **B8** were selected to test their inhibitory activity against FABP3 (Table 3, compound **6** as a positive control). **A16** and **B8** both showed weak inhibitory activity against FABP3 and much better selectivity profile over FABP3 than positive control **6**. In detail, compound **A16** showed a 28.3-fold selectivity of FABP4 and 11.4-fold preference of FABP5 over FABP3. **B8** exhibited comparative selectivity of FABP4 (29.6-fold) but a lower preference of FABP5 (4.6-fold) over FABP3. Therefore, compound **A16** and **B8** may have lower cardiac toxicity, which is an important benefit for further study.

Table 3. Selectivity of representative compounds against FABP3

Compd	FABP4 IC_{50} (μM)	FABP5 IC_{50} (μM)	FABP3 IC_{50} (μM)	FABP3/FABP 4	FABP3/FABP 5
6	6.34±0.01	23.42±0.32	1.95±0.01	0.31	0.08
A16	1.97±0.15	4.85±1.03	55.62±1.32	28.23	11.46
B8	1.58±0.66	10.08±1.99	46.84±1.14	29.64	4.64

2.5 Molecular Docking Studies of A16 with FABP4 and FABP5 Protein

In order to gain further insight into the binding interactions with FABP4 and FABP5, compound **A16** was selected to perform docking studies. Before docking, the important water molecules which formed key hydrogen bonds with FABP4 or FABP5 was retained. The predicted binding mode of **A16** with FABP4 was presented in Figure **S2**. The carboxy group forms important hydrogen bonds with residues Arg 126 and Tyr 128. The naphthalene ring formed an edge-to-face π-π stacking interaction with Phe 16. One oxygen of the sulfonamide group formed two hydrogen bonds with Arg 78 and Gln 95. Besides, the ethyl cyclohexyl moiety occupied the hydrophobic pocket formed by Ala 36, Ser 55, Phe 57, Ser 53 and Pro 38. We can infer that the compound with ethyl cyclohexyl group (**A16**) maintains a similar binding mode with FABP4 as

the lead compound **8**.

On the other hand, the interactions between **A16** and FABP5 were demonstrated in Figure **4A**. The carboxy group formed one hydrogen bond with Arg 129 and an indirect hydrogen bond with Arg 109 via a water molecular. The naphthalene moiety formed an edge-to-face π-π stacking interaction with Phe 19. Moreover, another Pi-cation interaction was observed between the phenyl ring and Arg 109. One oxygen of the sulfonamide group formed a hydrogen bond with Thr 63. An overlay of **A16** with compound **7** in FABP5 was exhibited in Figure **4B**. Interestingly, the key binding interactions of **A16** and compound **7** were almost the same. Most importantly, the ethylcyclohexyl moiety of **A16** occupied the pocket where the phenyl ring of compound **7** located, which was consistent with our initial design strategy. This might be the reason that compound **A16** along with some designed compounds showed potent dual FABP4/FABP5 inhibitory activities.

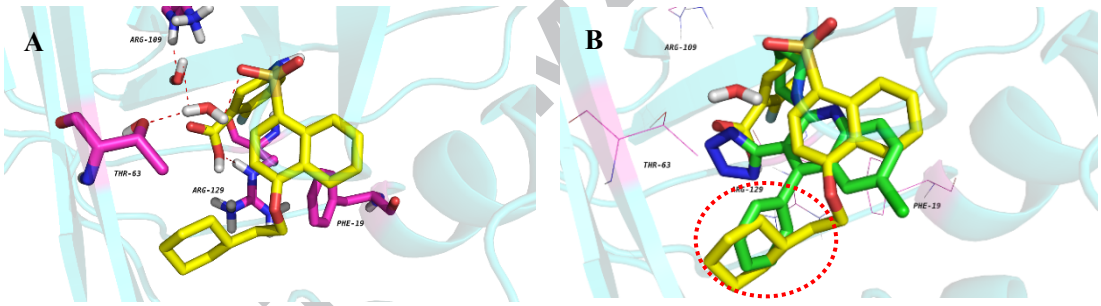


Figure 4. (A) Predicted binding mode of **A16** with FABP5 (protein: cyan, ligand: yellow, residues: magenta, PDB: 5HZ5); (B) A comparison of the binding mode of **A16** (yellow) and compound **7** (green) with FABP5 (cyan). The pictures were generated using Pymol.

2.6 Lipolysis Inhibition in 3T3-L1 Adipocytes

There have been reported cases that targeted ablation or chemical inhibition of FABP4 could decrease the lipolysis effects in adipocytes.[33, 46] In our previous study,[38-39] the selective FABP4 inhibitor **8** exhibited inhibitory ability of forskolin-stimulated lipolysis in mature adipocytes. Here, the effects of our dual FABP4/5 inhibitors **A16** and **B8** on the lipolysis of 3T3-L1 adipocytes was investigated, with the reported FABP4/5 inhibitor **6** as positive control. Firstly, an MTT assay was carried out to evaluate the cytotoxicity effects of the above-mentioned compounds on 3T3-L1 pre-adipocytes. As illustrated in Figure **5A**, compound **6** slightly inhibited cell survival at 30 μM and 60 μM. In comparison, our compounds have no effect on cell viability even at 60 μM. As shown

in Figure **5B**, all compounds at 30 μM attenuated forskolin-stimulated lipolysis in 3T3-L1 cells, and the FABP 4/5 dual inhibitor **A16** and **B8** showed slightly better lipolytic inhibition compared with positive control (compound **6**) and FABP4 selective inhibitor **8**. It is worth noting that compound **A16** with higher selectivity fold (FABP4/5 = 2.46x) showed slightly better activity than **B8** (FABP4/5 = 6.38x), which indicates that dual inhibition of FABP4 and FABP5 may provide beneficial effects on a number of metabolic parameters.

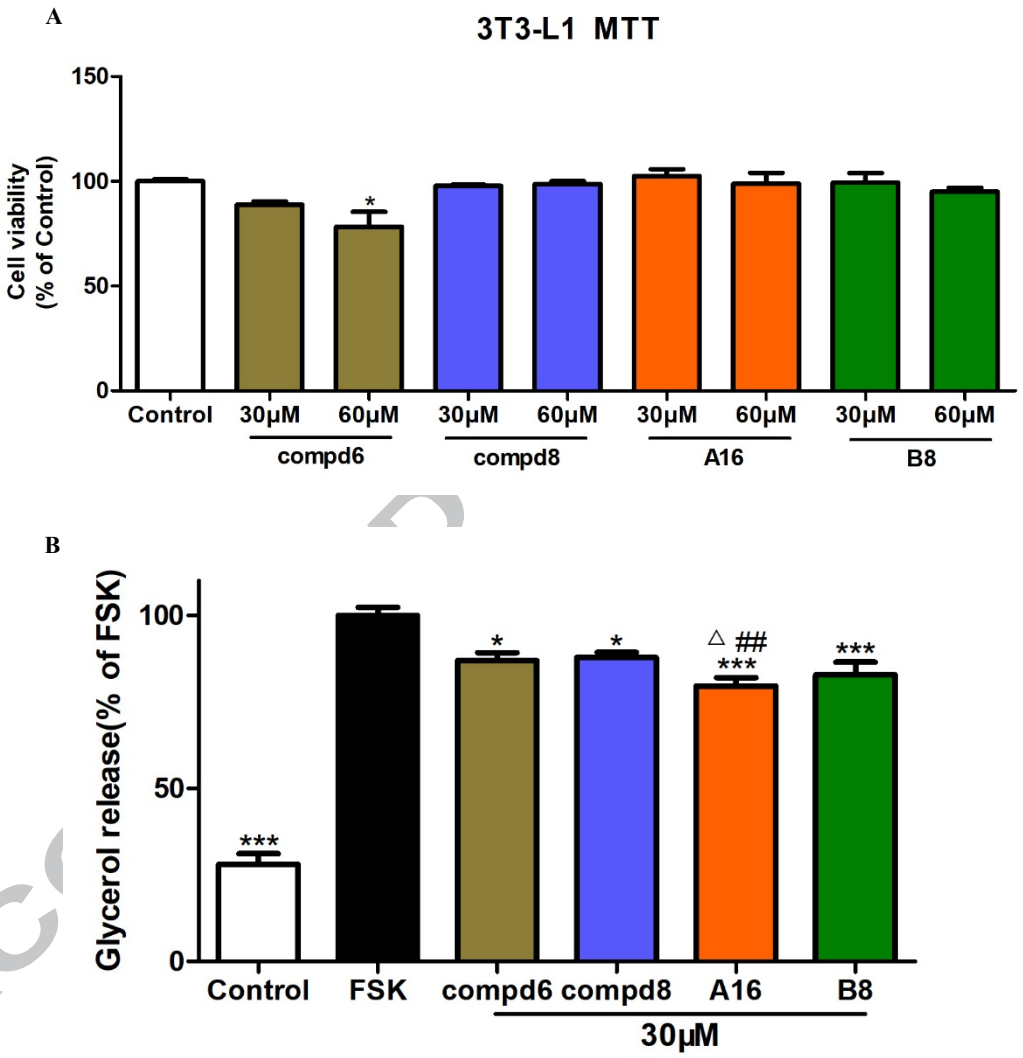
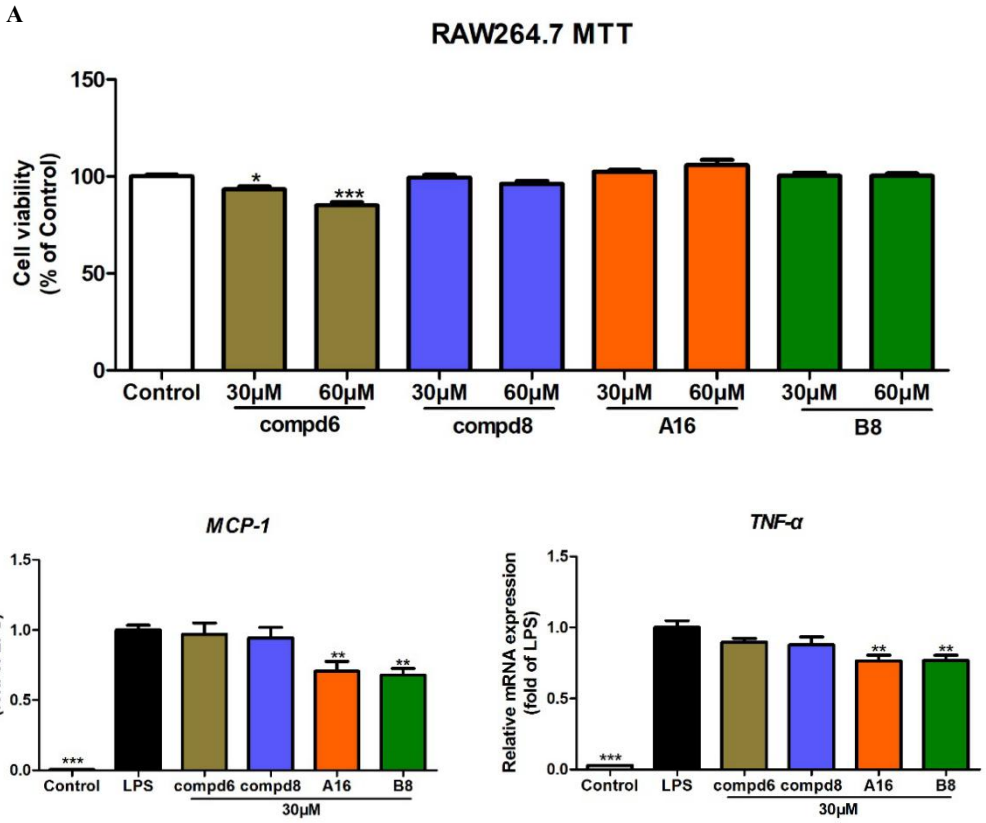


Figure 5. (A) Effects of compounds **A16**, **B8**, **6**, and **8** on the viability of 3T3-L1 preadipocytes. Cell viability was determined by MTT assay. **P*<0.05, ****P*<0.001 *vs*. control group. (B) Effect of FABP4/5 inhibitors **A16** and **B8** on the release of glycerol from forskolin-stimulated mature 3T3-L1 adipocytes. Compound **6** and **8** were used as the positive controls. **P* < 0.05, ****P* < 0.001 *vs*. FSK group. $^{\triangle}P < 0.05$ *vs* compd 6 group. $^{\#\#}P < 0.01$ *vs* compd 8 group.

*2.7 Anti-inflammatory Effects of **A16** and **B8** on RAW264.7 Macrophages*

It has been demonstrated that genetic ablation or knockdown of FABP4 can decrease inflammatory responses in macrophages.[47-48] The inflammatory response was extensively studied in RAW 264.7 murine macrophage for compound **8**, **A16**, and **B8** (**6** as a positive control). Firstly, a RAW264.7-MTT evaluation was conducted to test the effects of these compounds on cell viability and the results were shown in Figure **6A**. Compound **6** dose-dependently affects cell viability at at 30 and 60 μM, while compound **8**, **A16**, and **B8** have no effects. As quantitative PCR results shown in Figure **6B**, the expression level of pro-inflammatory cytokines MCP-1/CCL2, TNFα, IL-6 and pro-inflammatory enzyme COX-2 were robustly increased with the cell stimulated by lipopolysaccharide (LPS). Compared with FABP4 selective inhibitor **8**, the expression of inflammatory cytokines were down-regulated by both of the dual FABP4/5 inhibitors **A16** and **B8** at 30 μM with statistical significance (compared to the LPS group), especially reflected in the decreased expression of MCP-1 (29% and 32% decrease for **A16** and **B8**, respectively) and TNFα (24% and 23% decrease for **A16** and **B8**, respectively). These results also demonstrated that dual inhibition of FABP4 and FABP5 may provide a beneficial anti-inflammatory effect.



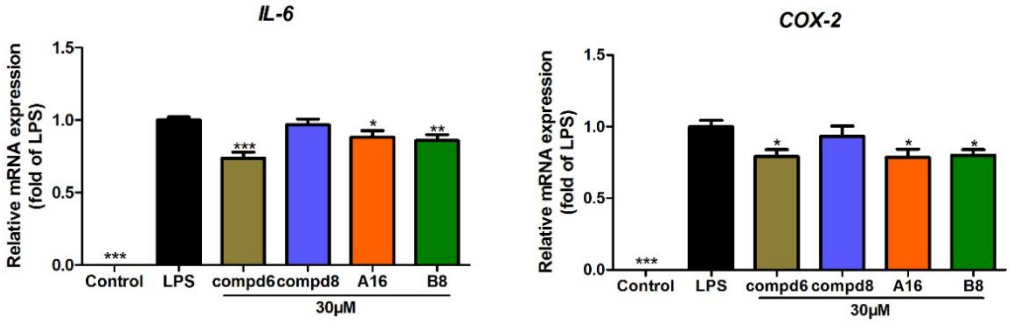


Figure 6. (A) Effects of compounds **6**, **8**, **A16**, and **B8** on the viability of RAW264.7 macrophages. Cell viability was determined by MTT assay. **P*<0.05, ****P*<0.001 *vs*. control group. (B) Effects of compounds **6**, **8**, **A16**, and **B8** on the expression of pro-inflammatory cytokines of MCP-1, TNF-α, IL-6 and COX-2 in LPS-induced RAW264.7 macrophages. Expression levels of cytokines were measured by quantitative PCR. **P*<0.05, ***P* < 0.01, ****P* < 0.001 *vs*. LPS group.

2.8 The Anti-inflammatory Mechanism of A16 and B8

As compounds **A16** and **B8** exhibited anti-inflammatory effects in LPS-stimulated RAW 264.7 cells. We preliminarily explored the mechanism of their anti-inflammatory effects. Studies have shown that FABP4 can induce inflammatory responses through the activation of the IKK-NF-κB and JNK-AP-1 pathways.[48-49] In order to confirm whether our compounds work through this mechanism, the level of NF-κB and IKK was examined using a western-blot analysis. As shown in Figure **7**, compared with the positive control (compound **6**), there was an obvious decrease of p-NF-κB and p-IKK levels when treated with compound **8**, **A16** and **B8**, especially for the IKK activity at 60 μM, whose phosphorylation was apparently inhibited. The dual FABP4/5 inhibitor **B8** were more potent than compound **8** on inhibiting the IKK phosphorylation. So, we could infer that our compounds exerted anti-inflammatory activity at least partly by regulating the IKK-NF-κB pathway.

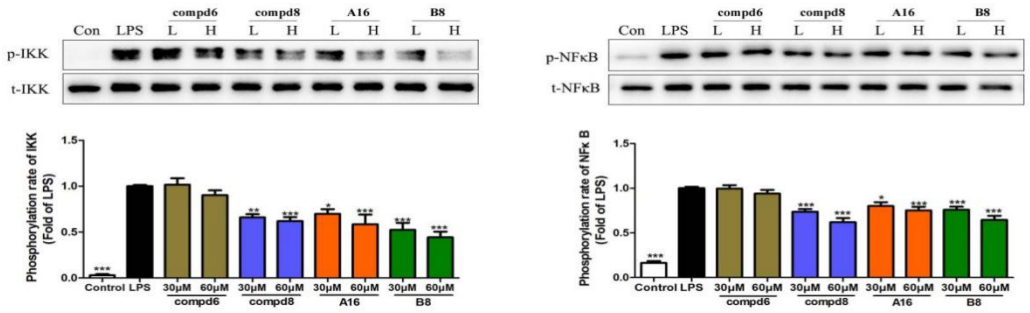


Figure 7. Effects of compounds **6**, **8**, **A16**, and **B8** on the expression of p-NF-κB/NF-κB, p-IKK/IKK in LPS-induced RAW264.7 macrophage, which were analyzed by western blot.

*P<0.05, ***P < 0.001 *vs*. LPS group.

3. Conclusion

In the current study, we reported the identification of dual FABP4/5 inhibitors starting from a potent and selective FABP4 inhibitor **8**. By comparing the crystal structures of dual FABP4/5 inhibitor **7** with FABP5 and FABP4 selective inhibitor **8** with FABP4, bulkier substituents were introduced into compound **8** to occupy the key binding pocket of FABP5, which led to the discovery of two series of new dual FABP4/5 inhibitors with naphthalene-1-sulfonamide core. Two potent dual FABP4/5 inhibitors **A16** and **B8** were identified. Compared with positive control **6**, **A16** and **B8** exhibited better potency against FABP4/5 and higher selectivity profile over FABP3. Molecular docking study of **A16** with FABP4 and FABP5 validated our initial hypothesis. **A16** and **B8** were more potent than compound **6** and selective FABP4 inhibitor **8** in cellular level assay, not only reflected in the inhibition of forskolin-stimulated lipolysis in mature 3T3-L1 adipocytes, but also the anti-inflammatory effects in lipopolysaccharide-stimulated RAW264.7 macrophage. All these results demonstrated that dual suppression of FABP4 and FABP5 may provide beneficial effects on metaflammation-related diseases. **A16** and **B8** would be promising molecules for further investigation.

4. Experimental Section

4.1 Chemistry Methods

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All starting materials were commercially available. Nuclear magnetic resonance (NMR) spectroscopy were recorded with a 400MHz Varian or Bruker 600MHz NMR spectrometer at ambient temperature. Chemical shifts (δ) were expressed in parts per million (ppm) downfield from tetramethylsilane, and coupling constants (J) values were described as hertz. MS was measured on Agilent 6120 quadrupole LC/MS. High resolution mass spectrometry (HRMS) determinations for all new compounds were carried out on AB SCIWX TRIPLETOF 5600+.

4.2. Synthesis of Series A compounds

*4.2.1. 5-((4-Ethoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A1**)*

*(i) Sodium 4-ethoxynaphthalene-1-sulfonate (**10a**)*

To a solution of sodium 4-hydroxynaphthalene-1-sulfonate (2.0 g, 8.12 mmol) in ethanol (6 mL) was added water (6 mL), sodium hydroxide (813 mg, 20.31 mmol) and bromoethane (1.33 g, 12.18 mmol). The mixture was stirred at 80 °C overnight in a seal tube. The mixture was cooled and white solid precipitated. The resulting precipitated solid was filtered and the filtercake was washed with dichloromethane to give **10a** as a white solid. (1.92 g, yield 86.2 %). ESI-MS: $[M-H]^-$ m/z: 251.1.

*(ii) 4-Ethoxynaphthalene-1-sulfonyl chloride (**11a**)*

To a solution of **10a** (0.8 g, 2.92 mmol) in dimethyl formamide (10 mL) was added thionyl chloride (520 mg, 4.38 mmol) dropwise at 0 °C. Then, the mixture was moved to room temperature and stirred for another 1 h. The mixture was poured into ice water and extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to give the desired product (0.5 g, yield 63.3 %) as a yellow oil. $\boldsymbol{R_f}$ = 0.8 (1:4, ethyl acetate : petroleum ether). The product was used for the next step without further purification.

*(iii) Methyl 5-((4-ethoxynaphthalene)-1-sulfonamido)-2-fluorobenzoate (**13a**)*

To a solution of **11a** (500 mg, 1.85 mmol) in acetone (10 mL) was added **12** (380 mg, 1.85 mmol) and pyridine (0.45 mL, 5.54 mmol). The mixture was stirred at 55 °C for 1 h. The mixture was concentrated, diluted with ethyl acetate and washed with 1M HCl and brine twice. Then, the ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was purified by silica column eluting with petroleum ether/ethyl acetate (5/1–2/1) to give the desired product (0.33 g, yield 44.3 %) as grey solid. $\boldsymbol{R_f}$ = 0.3 (1:3, ethyl acetate: petroleum ether) .^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.63 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 8.4, 3.1 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.65 – 7.61 (m, 1H), 7.53 – 7.50 (m, 1H), 7.26 – 7.23 (m, 1H), 7.18 – 7.13 (m, 1H), 7.04 – 7.00 (m, 1H), 4.27 – 4.23 (m, 2H), 3.77 (s, 3H), 1.47 – 1.42 (m, 3H). ESI-MS: $[M-H]^-$ m/z : 402.1.

*(iv) 5-((4-Ethoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A1**)*

To a mixture of **13a** (330 mg, 0.82 mmol) in methanol (5 mL) was added sodium hydroxide (1 M, 10 mL), and the mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum, and the residue was acidified to pH = 2 with HCl (1 M) solution. The solution was extracted with ethyl acetate twice and the combined organic layer was dried over anhydrous

sodium sulfate and concentrated in vacuum. The resulting residue was purified via silica gel chromatography to give the desired compound as a white solid (233 mg, yield 73.2 %). mp 196–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 10.69 (s, 1H), 8.63 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.48 (dd, J = 6.4, 2.9 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.11 (t, J = 9.6 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 4.27 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.27, 158.29, 158.03, 156.34, 133.68, 132.07, 128.46, 126.20, 125.02, 124.92, 124.76, 123.97, 122.42, 122.01, 119.49, 117.64, 103.16, 64.21, 14.18. ESI-HRMS [M-H]$^-$ calcd for $C_{19}H_{16}FNO_5S$: 388.0660, found: 388.0651.

*4.2.2. 2-Fluoro-5-((4-isopropoxynaphthalene)-1-sulfonamido)benzoic acid (**A2**)*

Compound **A2** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 75.3 %. mp 208–209 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 10.69 (s, 1H), 8.62 (d, J = 8.5 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.49 (dd, J = 6.5, 3.1 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 (d, J = 9.8 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 4.93 – 4.91 (m, 1H), 1.40 (d, J = 6.5 Hz 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.02, 157.28, 156.33, 133.73, 132.05, 128.70, 126.08, 125.60, 124.95, 124.38, 123.93, 122.63, 121.93, 119.39, 117.67, 103.95, 70.61, 21.35. ESI-HRMS [M-H]$^-$ calcd for $C_{20}H_{18}FNO_5S$: 402.0817, found: 402.0809.

*4.2.3. 5-((4-(Sec-butoxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A3**)*

Compound **A3** was prepared as a white solid in a similar manner as described for compound **A1**. Yield: 78.5 %. mp 198–200 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 10.71 (s, 1H), 8.63 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.50 – 7.49 (m, 1H), 7.24 (d, J = 9.2 Hz, 1H), 7.15 (d, J = 9.9 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 4.73 – 4.70 (m, 1H), 1.80 – 1.71 (m, 2H), 1.35 (d, J = 5.9 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.00, 157.53, 156.32, 133.74, 132.03, 128.72, 126.12, 125.63, 124.87, 124.37, 123.96, 122.55, 121.88, 119.34, 117.67, 103.90, 75.25, 28.26, 18.48, 9.25. ESI-HRMS [M-H]$^-$ calcd for $C_{21}H_{20}FNO_5S$: 416.0973, found: 416.0971.

*4.2.4. 2-Fluoro-5-((4-(pentan-2-yloxy)naphthalene)-1-sulfonamido)benzoic acid (**A4**)*

Compound **A4** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 44.8 %. mp 183–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 10.70 (s, 1H),

8.61 (d, *J* = 8.6 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 6.4, 2.9 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 (d, *J* = 9.8 Hz, 1H), 7.10 – 7.04 (m, 1H), 4.78 (q, *J* = 6.1 Hz, 1H), 1.80 – 1.76 (m, 1H), 1.69 – 1.65 (m, 1H), 1.48 – 1.37 (m, 2H), 1.34 (d, *J* = 6.0 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.26, 158.00, 157.54, 156.31, 133.73, 132.05, 128.72, 126.13, 125.62, 124.86, 124.36, 123.96, 122.56, 121.89, 119.46, 117.66, 103.84, 73.99, 37.61, 18.97, 17.92, 13.71. ESI-HRMS $[M–H]^-$ calcd for $C_{22}H_{22}FNO_5S$: 430.1130, found: 430.1132.

*4.2.5. 2-Fluoro-5-((4-(pentyloxy)naphthalene)-1-sulfonamido)benzoic acid (**A5**)*

Compound **A5** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 75.4 %. mp 187–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 10.68 (s, 1H), 8.63 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.22 – 7.20 (m, 1H), 7.11 (t, *J* = 9.6 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.21 (t, *J* = 6.4 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.52 – 1.44 (m, 2H), 1.43 – 1.33 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.23, 158.40, 158.02, 156.34, 133.70, 132.08, 128.46, 126.24, 125.07, 124.91, 124.73, 123.99, 122.34, 121.94, 119.38, 117.66, 103.14, 68.37, 27.94, 27.61, 21.68, 13.71. ESI-HRMS $[M-H]^-$ calcd for $C_{22}H_{22}FNO_5S$: 430.1130, found: 430.1129.

*4.2.6. 2-Fluoro-5-((4-(hexyloxy)naphthalene)-1-sulfonamido)benzoic acid (**A6**)*

Compound **A6** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 66.1 %. mp 190–192 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 10.69 (s, 1H), 8.63 (d, *J* = 8.6 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.10 (t, *J* = 9.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.50 – 1.46 (m, 2H), 1.35 – 1.28 (m, 4H), 0.88 – 0.85 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.27, 158.40, 158.02, 156.34, 133.70, 132.08, 128.47, 126.23, 125.08, 124.84, 124.75, 124.00, 122.33, 121.93, 119.47, 117.63, 103.14, 68.38, 30.76, 28.18, 25.08, 21.86, 13.68. ESI-HRMS $[M-H]^-$ calcd for $C_{23}H_{24}FNO_5S$: 444.1286, found: 444.1290.

*4.2.7 2-Fluoro-5-((4-(heptyloxy)naphthalene)-1-sulfonamido)benzoic acid (**A7**)*

Compound **A7** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 87.4 %. mp 175–177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 10.73 (s, 1H),

8.64 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.24 – 7.20 (m, 1H), 7.12 (t, *J* = 9.6 Hz, 1H), 7.03 (d, *J* = 6.9, 1H), 4.20 (s, 2H), 1.86 – 1.82 (m, 2H), 1.50 – 1.45 (m, 2H), 1.35 – 1.27 (m, 6H), 0.87 – 0.83 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.40, 158.03, 156.35, 133.71, 132.08, 128.47, 126.22, 125.08, 124.85, 124.74, 124.00, 122.33, 121.92, 119.36, 117.65, 103.13, 68.38, 31.03, 28.23, 25.39, 21.86, 13.73. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{26}FNO_5S$: 458.1443, found: 458.1447.

*4.4.8 2-Fluoro-5-((4-(octyloxy)naphthalene)-1-sulfonamido)benzoic acid (**A8**)*

Compound **A8** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 61.9 %. mp 152–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 10.69 (s, 1H), 8.63 (d, *J* = 8.6 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 6.5, 2.8 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.11 (t, *J* = 9.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 1.86 – 1.82 (m, 2H), 1.51 – 1.47 (m, 2H), 1.35 – 1.23 (m, 8H), 0.86 – 0.82 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.40, 158.02, 156.34, 133.70, 132.08, 128.47, 126.22, 125.08, 124.88, 124.74, 124.00, 122.33, 121.92, 119.37, 117.65, 103.15, 68.39, 31.04, 28.51, 28.45, 28.21, 25.41, 21.89, 13.76. ESI-HRMS [M-H]$^-$ calcd for $C_{25}H_{28}FNO_5S$: 472.1599, found: 472.1601.

*4.2.9 5-((4-(Decyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A9**)*

Compound **A9** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 63.7 %. mp 143–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.63 (d, *J* = 8.7 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 6.5, 2.8 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.08 (t, *J* = 9.6 Hz, 1H) ,7.03 (d, *J* = 8.4 Hz, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 1.85 – 1.82 (m, 2H), 1.50 – 1.46 (m, 2H), 1.34 – 1.21 (m, 12H), 0.84 – 0.81 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.38, 158.38, 157.94, 156.26, 133.64, 132.05, 128.48, 126.18, 125.08, 124.80, 124.53, 124.03, 122.31, 121.92, 120.11, 117.51, 103.13, 68.36, 31.11, 28.78, 28.74, 28.52, 28.49, 28.21, 25.40, 21.90, 13.75. ESI-HRMS [M-H]$^-$ calcd for $C_{27}H_{32}FNO_5S$: 500.1912, found: 500.1916.

*4.2.10 5-((4-(Dodecyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A10**)*

Compound **A10** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 83.1 %. mp 150–152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 10.68 (s, 1H),

8.63 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.10 (t, *J* = 9.6 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.51 – 1.44 (m, 2H), 1.36 – 1.21 (m, 16H), 0.83 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.28, 158.39,158.00,156.32, 133.70, 132.06, 128.48, 126.16, 125.08, 124.78, 124.02, 122.31, 121.91, 119.56, 117.59, 103.10, 68.36, 31.11, 28.84, 28.78, 28.53, 28.21, 25.40, 21.91, 13.74. ESI-HRMS $[M-H]^-$ calcd for $C_{29}H_{36}FNO_5S$: 528.2225, found:528.2231.

*4.2.11 5-((4-(Cyclopentyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A11**)*

Compound **A11** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 46.0 %. mp 217–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 10.72 (s, 1H), 8.64 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 5.7 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.66 – 7.62 (m, 1H), 7.51 – 7.49 (m, 1H), 7.26 – 7.23 (m, 1H), 7.14 (t, *J* = 10.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 5.10 (s, 1H), 2.01 (s, 2H), 1.86 – 1.77 (m, 4H), 1.65 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.02, 157.41, 156.34, 133.73, 131.98, 128.62, 126.15, 125.52, 124.96, 124.46, 123.95, 122.55, 121.95, 119.35, 117.67, 104.18, 79.99, 32.08, 23.52. ESI-HRMS $[M-H]^-$ calcd for $C_{22}H_{20}FNO_5S$: 428.0973, found: 428.0975.

*4.2.12 5-((4-(Cyclohexyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A12**)*

Compound **A12** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 65.3 %. mp 213–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 8.62 (d, *J* = 8.7 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.24 – 7.10 (m, 1H), 7.15 – 7.10 (m, 2H), 4.72 (s, 1H), 1.99 – 1.96 (m, 2H), 1.74 (s, 2H), 1.65 – 1.61 (m, 2H), 1.55 – 1.37 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.00, 157.10, 156.31, 133.76, 132.00, 128.75, 126.13, 125.70, 124.88, 124.35, 123.95, 122.59, 121.84, 119.35, 117.67, 104.08, 74.94, 30.53, 24.85, 22.69. ESI-HRMS $[M-H]^-$ calcd for $C_{23}H_{22}FNO_5S$: 442.1130, found: 442.1131.

*4.2.13 5-((4-(Cycloheptyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A13**)*

Compound **A13** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 58.2 %. mp 200–202°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 10.71 (s, 1H), 8.62 (d, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 6.6, 2.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.13 (t, *J* = 9.6 Hz,

1H), 7.03 (d, *J* = 8.5 Hz, 1H), 4.87 – 4.85 (m, 1H), 2.04 – 1.99 (m, 2H), 1.89 – 1.83 (m, 2H), 1.71 – 1.66 (m, 2H), 1.62 – 1.52 (m, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.01, 157.12, 156.33, 133.76, 132.03, 128.74, 126.12, 125.70, 124.90, 124.30, 123.96, 122.60, 121.90, 119.36, 117.67, 104.09, 77.59, 32.63, 27.69, 22.16. ESI-HRMS $[M-H]^-$ calcd for $C_{24}H_{24}FNO_5S$: 456.1286, found: 456.1286.

*4.2.14 5-((4-(Cyclooctyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A14**)*

Compound **A14** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 42.7%. mp 185–187°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 10.73 (s, 1H), 8.62 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.10 (m, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 4.85 – 4.81 (m, 1H), 1.94 – 1.90 (m, 4H), 1.79 –1.71 (m, 2H), 1.59 – 1.53 (m, 8H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.25, 158.02, 157.04, 156.33, 133.75, 132.05, 128.76, 126.10, 125.76, 124.92, 124.30, 123.96, 122.62, 121.93, 119.39, 117.66, 104.11, 77.75, 30.51, 26.42, 24.76, 22.12. ESI-HRMS $[M-H]^-$ calcd for $C_{25}H_{26}FNO_5S$: 470.1443, found: 470.1440.

*4.2.15 5-((4-(Cyclohexylmethoxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A15**)*

Compound **A15** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 63.0%. mp 213–214°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 10.73 (s, 1H), 8.64 (d, *J* = 8.6 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.51 (dd, *J* = 6.4, 2.9 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.12 (t, *J* = 9.7 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 4.01 (d, *J* = 5.7 Hz, 2H), 1.87 (d, *J* = 11.6 Hz, 3H), 1.73 (d, *J* = 12.4 Hz, 2H), 1.67 (d, *J* = 11.8 Hz, 1H), 1.33 – 1.08 (m, 5H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.25, 158.44, 158.01, 156.32, 133.70, 132.09, 128.45, 126.29, 125.12, 124.85, 124.71, 124.00, 122.34, 121.90, 119.45, 117.65, 103.13, 73.33, 36.86, 29.03, 25.80, 25.11. ESI-HRMS $[M-H]^-$ calcd for $C_{24}H_{24}FNO_5S$: 456.1286, found: 456.1284.

*4.2.16 5-((4-(2-Cyclohexylethoxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A16**)*

Compound **A16** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 53.5 %. m.p 200–201°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 10.73 (s, 1H), 8.62 (d, *J* = 8.6 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.50 – 7.48 (m, 1H), 7.23 – 7.19 (m, 1H), 7.11 (t, *J* = 9.6 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 4.22 (t, *J* = 6.3 Hz, 2H), 1.77 – 1.72 (m, 4H), 1.67 – 1.50 (m, 4H), 1.25 – 1.14 (m,

3H), 1.02 – 0.96 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.26, 158.41, 158.02, 156.34 133.72, 132.07, 128.46, 126.25, 125.08, 124.85, 124.75, 124.00, 122.35, 121.89, 119.39, 117.66, 103.16, 66.55, 35.57, 34.07, 32.47, 25.83, 25.53. ESI-HRMS [M-H]$^-$ calcd for $C_{25}H_{26}FNO_5S$:470.1443, found: 470.1443.

*4.2.17 5-((4-(3-Cyclohexylpropoxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A17**)*

Compound **A17** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 78.1%. mp 176–177°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H), 10.73 (s, 1H), 8.64 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 6.3, 2.9 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.12 (t, J = 9.6 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 4.18 (t, J = 6.3 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.73 – 1.59 (m, 5H), 1.36 (dd, J = 9.6, 5.8 Hz, 2H), 1.30 – 1.07 (m, 4H), 0.88 (q, J = 11.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.23, 158.40, 158.03, 156.34, 133.70, 132.08, 128.46, 126.23, 125.07, 124.88, 124.73, 124.00, 122.32, 121.92, 119.35, 117.66, 103.14, 68.73, 36.55, 33.16, 32.62, 25.98, 25.62. ESI-HRMS [M-H]$^-$ calcd for $C_{26}H_{28}FNO_5S$: 484.1559, found: 484.1602.

*4.2.18 5-((4-(Adamantan-1-ylmethoxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A18**)*

Compound **A18** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 48.1%. mp 144–146°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 10.71 (s, 1H), 8.63 (d, J = 8.6 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.50 (dd, J = 6.4, 2.8 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.11 (t, J = 9.6 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 3.78 (s, 2H), 2.02 (s, 3H), 1.74 – 1.71 (m, 12H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.58, 158.00, 156.32, 133.71, 132.13, 128.45, 126.36, 125.21, 124.81, 124.67, 124.02, 122.29, 121.82, 119.30, 117.68, 103.10, 77.93, 38.94, 33.29, 27.35. ESI-HRMS [M-H]$^-$ calcd for $C_{28}H_{28}FNO_5S$: 508.1599, found: 508.1600.

*4.2.19 2-Fluoro-5-((4-((tetrahydro-2H-pyran-4-yl)methoxy)naphthalene)-1-sulfonamido)benzoic acid (**A19**)*

Compound **A19** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 65.1 %. mp 156–158°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.52 (d, J = 5.6 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 7.11 (t, J = 9.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.99 (s, 2H), 3.87 (d, J = 11.2 Hz, 2H), 3.32 (t, J = 11.7 Hz, 2H), 2.08 (s, 1H),

1.69 (d, *J* = 13.1 Hz, 2H), 1.38 (q, *J* = 13.1 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.30, 158.03, 156.35, 133.69, 132.07, 128.45, 126.32, 125.09, 124.94, 124.83, 124.01, 122.33, 121.93, 119.37, 117.68, 103.20, 72.59, 66.47, 34.24, 28.97. ESI-HRMS [M-H]$^-$ calcd for $C_{23}H_{22}FNO_5S$: 458.1079, found:458.1077.

*4.2.20 2-Fluoro-5-((4-phenoxynaphthalene)-1-sulfonamido)benzoic acid (**A20**)*

Compound **A20** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 45.9 %. mp 221–223°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.19 (m, 3H), 7.13 (t, *J* = 9.5 Hz, 1H), 6.74 (dd, *J* = 8.3, 2.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.21, 158.16, 157.83, 156.48, 154.62, 133.49, 131.49, 130.34, 128.91, 127.43, 127.00, 125.52, 125.26, 125.15, 124.24, 122.38, 120.25, 119.54, 117.73, 108.06. ESI-HRMS [M-H]$^-$ calcd for $C_{23}H_{16}FNO_5S$: 436.0660, found: 436.0662.

*4.2.21 5-((4-(Benzyloxy)naphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**A21**)*

Compound **A21** was prepared as a white solid in a similar manner as described for compound **A1**. Yield 56.7%. mp 162–164°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.66 (d, *J* = 8.6 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.55 – 7.51 (m, 3H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.38 – 7.35 (m, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.10 (m, 2H), 5.34 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.24, 158.07, 158.02, 156.38, 135.99, 133.68, 131.91, 128.50, 128.42, 128.01, 127.66, 126.41, 125.21, 125.01, 124.03, 122.46, 122.01, 119.38, 117.70, 103.80, 70.01. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{18}FNO_5S$: 450.0817, found: 450.0813.

4.3. Synthesis of Series B compounds

*4.3.1. 2-Fluoro-5-((4-methoxy-3-phenylnaphthalene)-1-sulfonamido)benzoic acid (**B1**)*

*(i) 2-Bromonaphthalen-1-ol (**15**)*

1-Naphthol (10 g, 69.36 mmol) and diisopropylamine (0.972 mL, 6.94 mmol) was dissolved in dichloromethane (100 mL). N-Bromosuccinimide (13.58 g, 76.3 mmol) was carefully added and the reaction mixture was stirred at 40 °C overnight. The resulting mixture was allowed to cool to room temperature, quenched with 2M H_2SO_4, and extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The

crude product was purified by silica gel column eluting with petroleum ether: ethyl acetate (20/1) to give the desired product (11.2 g, yield 72.4 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.21 (m, 1H), 7.76 – 7.73 (m, 1H), 7.50 – 7.48 (m, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.97 (s, 1H). ESI-MS: $[M-H]^-$ m/z :221.0.

*(ii) 2-Bromo-1-methoxynaphthalene (**16**)*

A solution of **15** (10 g, 44.83 mmol), potassium hydroxide (5.03 g, 89.66 mmol), and methyl iodide (16.74 mL, 268.98 mmol) in acetonitrile (80 mL) was stirred at 40 °C for 12 h. The mixture was washed with water, extracted with dichloromethane, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by silica gel column eluting with petroleum ether: ethyl acetate (20/1) to give the desired product (9.1 g, yield 85.6%) as a white solid. $\boldsymbol{R_f}$ = 0.5 (1:6, ethyl acetate:petroleum ether).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 7.2 Hz,1H), 7.59 – 7.49 (m, 4H), 4.01 (s, 3H).

*(iii) 3-Bromo-4-methoxynaphthalene-1-sulfonyl chloride (**17**)*

To a solution of **16** (8.0 g, 33.74 mmol) in chloroform (50 mL) was added chlorosulfonic acid (3.74 mL, 50.61 mmol) dropwise at 0 °C, then the mixture was warmed to room temperature and stirred for another 1 h. The mixture was poured into ice water and extracted with ethyl acetate (150 mL× 2). The ethyl acetate layer was washed with water, dried over anhydrous sodium sulfate and concentrated to give the desired product (9.3 g, yield 82.1%) as a colorless oil. $\boldsymbol{R_f}$ = 0.8 (1:4, ethyl acetate:petroleum ether). ESI-MS: $[M-H]^-$ m/z: 314.7.

*(iv) Methyl 5-((3-bromo-4-methoxynaphthalene)-1-sulfonamido)-2-fluorobenzoate (**18**)*

To a solution of **17** (8.0 g, 23.84 mmol) in acetone (40 mL) was added pyridine (4.8 mL, 59.6 mmol) and **12** (4.03 g, 23.84 mmol), then the mixture was stirred at 55 °C for 1 h. The mixture was concentrated and the residue was diluted with ethyl acetate (200 mL). The ethyl acetate layer was washed with 1M HCl solution and brine, dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was washed with ethyl acetate to give the desired product (7.5 g, yield 67.2%) as a grey solid. $\boldsymbol{R_f}$ = 0.4 (1:2, ethyl acetate:petroleum ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.26 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.32 – 7.27 (m, 1H), 7.21 (t, J = 19.3 Hz, 1H), 3.97 (s, 3H), 3.79 (s, 3H). ESI-MS: $[M-H]^-$ m/z: 466.0.

*(v) Methyl 2-fluoro-5-((4-methoxy-3-phenylnaphthalene)-1-sulfonamido)benzonate (**19a**)*

To a mixture of **18** (250 mg, 0.534 mmol) in dimethyl formamide (6 mL) was added water (0.1 mL), potassium carbonate (147 mg, 1.07 mmol), phenylboronic acid (98 mg, 0.8 mmol) and [1,1'-bis (diphenylphosphino) ferrocene] dichloropalladium (II)] (40 mg, 0.053 mmol). The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The mixture was poured into water and extracted with ethyl acetate (50 mL × 2), the ethyl acetate layer then was washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was purified by silica gel column eluting with petroleum ether: ethyl acetate (5/1–2/1) to give the desired product (210 mg, yield 84.5%). as a white solid. $\boldsymbol{R_f}$ = 0.3 (1:3, ethyl acetate:petroleum ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.70 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.17 (s, 1H), 7.82 – 7.78 (m, 1H), 7.76 – 7.73 (m, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.57 – 7.53 (m, 3H), 7.49 – 7.44 (m, 1H), 7.33 – 7.29 (m, 1H), 7.23 – 7.18 (m, 1H), 3.73 (s, 3H), 3.53 (s, 3H). ESI-MS: $[M-H]^-$ m/z: 464.1.

*(vi) 2-Fluoro-5-((4-methoxy-3-phenylnaphthalene)-1-sulfonamido) benzoic acid (**B1**)*

To a solution of methyl 2-fluoro-5-((4-methoxy-3-phenylnaphthalene)-1-sulfonamido) benzoate (210 mg, 0.45 mmol) in methanol (5 mL) was added 1 M sodium hydroxide (9 mL), the mixture was stirred at room temperature for 1 h. The mixture was concentrated and diluted with water, the water solution was washed with ethyl acetate (50 mL × 2). The water solution was then acidified to pH = 2 by 1M HCl and white solid precipitated out. The white mixture then was extracted with ethyl acetate (50 mL × 3). The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to give the desired product (160 mg, yield 78.5%) as a white solid. $\boldsymbol{R_f}$ = 0.3 (1:3:0.5, ethyl acetate:petroleum ether:acetic acid). mp 232–234°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.71 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.16 (s, 1H), 7.81 – 7.78 (m, 1H), 7.76 – 7.72 (m, 1H), 7.61 – 7.59 (m, 2H), 7.56 – 7.52 (m, 3H), 7.48 – 7.44 (m, 1H), 7.30 – 7.26 (m, 1H), 7.19 – 7.14 (m, 1H), 3.53 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.25, 158.16, 157.05, 156.48, 136.37, 133.53, 132.98, 129.30, 128.76, 128.66, 128.53, 128.13, 127.90, 127.40, 127.12, 125.27, 124.26, 123.27, 121.65, 119.41, 117.91, 61.31. ESI-HRMS $[M-H]^-$ calcd for $C_{24}H_{18}FNO_5S$: 450.0817, found: 450.0826.

*4.3.2 2-Fluoro-5-((4-methoxy-3-(pyridin-4-yl)naphthalene)-1-sulfonamido)benzoic acid (**B2**)*

Compound **B2** was prepared as a brown solid in a similar manner as described for compound **B1**. Yield 65.3 %. mp 231–233°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 – 8.72 (m, 3H), 8.31 (d,

J = 8.3 Hz, 1H), 8.19 (s, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 5.0 Hz, 2H), 7.58 – 7.51 (m, 1H), 7.29 – 7.25 (m, 1H), 7.12 (t, *J* = 9.6 Hz, 1H), 3.59 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ 164.52, 157.99, 157.68, 156.31，149.97, 143.98, 133.50, 131.88, 130.10, 129.10, 128.78, 128.47, 127.65, 124.76, 124.66, 124.54, 123.54, 123.41, 121.64, 117.66, 62.06. ESI-HRMS [M-H]$^-$ calcd for $C_{23}H_{17}FN_2O_5S$:451.0769, found: 451.0770.

*4.3.3 2-Fluoro-5-((4-methoxy-3-(pyrimidin-4-yl)naphthalene)-1-sulfonamido)benzoic acid (**B3**)*

Compound **B3** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 55.9 %. mp 230–232^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 11.00 (s, 1H), 9.28 (s, 1H), 9.07 (s, 2H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.32 – 8.28 (m, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.53 (s, 1H), 7.32 – 7.28 (m, 1H), 7.14 (t, *J* = 9.7 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.28, 158.08, 158.01, 157.48, 156.48, 156.40, 133.40, 132.03, 130.25, 129.19, 128.91, 128.26, 127.74, 125.15, 124.46, 123.40, 121.59, 121.44, 119.34, 117.92, 62.27. ESI-HRMS [M-H]$^-$ calcd for $C_{22}H_{16}FN_3O_5S$:452.0722, found: 452.0727.

*4.3.4 2-Fluoro-5-((3-(furan-3-yl)-4-methoxynaphthalene)-1-sulfonamido)benzoic acid (**B4**)*

Compound **B4** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 56.2 %. mp 218–220^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 10.92 (s, 1H), 8.69 (d, *J* = 6.2Hz, 1H), 8.33 (d, *J* = 13.1 Hz, 2H), 8.21 (d, *J* = 6.2 Hz, 1H), 7.87 (s, 1H), 7.76 – 7.70 (m, 2H), 7.59 – 7.56 (m, 1H), 7.32 – 7.28 (m, 1H), 7.17 – 7.12 (m, 1H), 7.02 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.26, 158.17, 156.49, 156.24, 143.97, 141.98, 133.48, 130.54, 130.06, 128.68, 128.10, 127.76, 127.48, 125.23, 124.47, 123.01, 121.90, 120.25, 119.39, 119.28, 117.89, 60.85. ESI-HRMS [M-H]$^-$ calcd for $C_{22}H_{16}FNO_6S$: 440.0610, found: 440.0615.

*4.3.5 2-Fluoro-5-((4-methoxy-3-(1-methyl-1H-pyrazol-5-yl)naphthalene)-1-sulfonamido)benzoic acid (**B5**)*

Compound **B5** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 58.8%. mp 230–232 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 10.96 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.01 (s, 1H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.60 (s, 1H), 7.48 – 7.46 (m, 1H), 7.26 – 7.24 (m, 1H), 7.16 (t, *J* = 9.6 Hz, 1H), 6.49 (s, 1H), 3.63 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.31, 158.15, 158.09, 156.46, 138.26, 137.69, 133.42, 133.10, 129.27, 128.76, 128.14, 127.60, 125.33, 124.32, 123.47,

121.69, 119.53, 117.86, 115.74, 107.15, 61.15, 36.73. ESI-HRMS [M-H]$^-$ calcd for $C_{22}H_{18}FN_3O_5S$: 454.0878, found: 454.0885.

*4.3.6 2-Fluoro-5-((3-(4-fluorophenyl)-4-methoxynaphthalene)-1-sulfonamido)benzoic acid (**B6**)*

Compound **B6** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 52.2 %. mp 268–270^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.71 (d, J = 7.0 Hz, 1H), 8.29 (d, J = 6.5 Hz, 1H), 8.16 (s, 1H), 7.82 – 7.78 (m, 1H), 7.76 – 7.72 (m, 1H), 7.68 – 7.64 (m, 2H), 7.56 – 7.53 (m, 1H), 7.38 – 7.34 (m, 2H), 7.30 – 7.26 (m, 1H), 7.19 – 7.14 (m, 1H), 3.54 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.25, 162.51, 160.88, 158.16, 157.07, 156.48, 133.50, 132.84, 130.93, 129.41, 128.58, 128.18, 127.44, 126.22, 125.25, 124.28, 123.26, 121.59, 119.37, 117.90, 115.64, 61.31. ESI-HRMS [M–H]$^-$ calcd for $C_{24}H_{17}F_2NO_5S$: 468.0723, found: 468.0730.

*4.3.7 5-((3-(3,4-Difluorophenyl)-4-methoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**B7**)*

Compound **B7** was prepared as a brown solid in a similar manner as described for compound **B1**. Yield 65.6%. mp 248–249^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 10.94 (s, 1H), 8.71 (d, J = 7.7 Hz, 1H), 8.29 (d, J = 8.4Hz, 1H), 8.16 (s, 1H), 7.84 – 7.79 (m, 1H), 7.77 – 7.67 (m, 2H), 7.63 – 7.58 (m, 1H), 7.56 – 7.52 (m, 1H), 7.48 – 7.44 (m, 1H), 7.30 – 7.26 (m, 1H), 7.15 (t, J = 10.3 Hz, 1H), 3.57 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.27, 158.14, 157.26, 156.46, 150.03, 148.39, 133.64, 133.45, 132.58, 129.52, 128.81, 128.50, 127.53, 125.97, 125.26, 125.19, 124.30, 123.33, 121.59, 119.35, 118.06, 117.94, 117.75, 61.57. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{16}F3NO_5S$: 486.0629, found: 486.0637.

*4.3.8 5-((3-(3-Chloro-4-fluorophenyl)-4-methoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**B8**)*

Compound **B8** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 59.3%. mp 231–233^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J = 8.5 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 8.14 (s, 1H), 7.83 – 7.79 (m, 2H), 7.77 – 7.73 (m, 1H), 7.64 – 7.62 (m, 1H), 7.57 (t, J = 8.9 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.29 – 7.25 (m, 1H), 7.14 (t, J = 9.6 Hz, 1H), 3.57 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.33, 158.13, 157.62, 157.24, 156.44, 155.97, 133.94, 133.44, 132.44, 130.81, 129.65, 128.81, 128.48, 127.56, 125.13, 124.33, 123.33, 121.78, 119.76, 117.84, 117.22, 61.64. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{16}ClF_2NO_5S$: 502.0333, found: 502.0343.

*4.3.9 5-((3-(3, 4-Dichlorophenyl)-4-methoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**B9**)*

Compound **B9** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 72.1 %. mp 235–237°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 10.96 (s, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.16 (s, 1H), 7.89 – 7.75 (m, 4H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.31 – 7.27 (m, 1H), 7.16 (t, *J* = 9.6 Hz, 1H), 3.59 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.22, 158.17, 157.37, 156.49, 136.82, 133.43, 132.23, 131.31, 130.81, 130.75, 130.59, 129.71, 129.17, 128.94, 128.51, 127.62, 125.33, 124.89, 124.34, 123.38, 121.79, 119.45, 117.91, 61.79. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{16}Cl_2FNO_5S$: 518.0038, found: 518.0051.

*4.3.10 5-((3-(3-Aminophenyl)-4-methoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**B10**)*

Compound **B10** was prepared as a white solid in a similar manner as describe for compound **B1**. Yield 58.1 %. mp 192–194°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.12 (s, 1H), 7.79 – 7.70 (m, 2H), 7.52 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.20 – 7.14 (m, 2H), 6.80 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.64 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.57 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.28, 158.12, 157.21, 156.58, 156.44, 133.56, 133.05, 129.95, 129.18, 128.74, 128.09, 127.71, 127.25, 126.71, 125.14, 124.22, 123.10, 121.67, 119.60, 117.84, 115.55, 60.81. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{19}FN_2O_5S$: 465.0926, found:465.0934.

*4.3.11 2-Fluoro-5-((3-(3-hydroxyphenyl)-4-methoxynaphthalene)-1-sulfonamido) benzoic acid (**B11**)*

Compound **B11** was prepared as a white solid in a similar manner as described for compound **B1**. Yield: 52.8 %. mp 244–245 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.68 (d, *J* = 8.5 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.11 (s, 1H), 7.80 – 7.71 (m, 2H), 7.50 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.15 (t, *J* = 9.6 Hz, 1H), 7.01 (s, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.85 (d, *J* = 7.0 Hz 1H), 3.56 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.27, 158.15, 156.83, 156.46, 148.77, 137.06, 133.52, 133.23, 129.14, 128.87, 128.27, 127.89, 127.66, 127.24, 125.15, 124.18, 123.22, 121.82, 119.55, 117.84, 116.21, 113.99, 113.47, 61.06. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{18}FNO_6S$: 466.0766, found: 466.0772.

*4.3.12 2-Fluoro-5-((3-(4-hydroxyphenyl)-4-methoxynaphthalene)-1-sulfonamido) benzoic acid (**B12**)*

Compound **B12** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 50.3 %. mp 230–231°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 10.92 (s, 1H), 9.78 (s, 1H), 8.68 (d, *J* = 8.3 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.14 (s, 1H), 7.79 – 7.71 (m, 2H), 7.56 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.18 (t, *J* = 9.6 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 3.54 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.26,158.17, 157.37, 156.93, 156.48, 137.59, 133.45, 132.88, 129.73, 129.21, 128.63, 128.43, 128.05, 127.33, 127.08, 125.18, 124.23, 123.26, 122.03, 119.37, 117.81, 115.58, 114.95, 61.23. ESI-HRMS [M-H]$^-$ calcd for $C_{24}H_{18}FNO_6S$: 466.0766, found: 466.0775.

*4.3.13 2-Fluoro-5-((3-(4-(hydroxymethyl)phenyl)-4-methoxynaphthalene)-1-sulfonamido) benzoic acid (**B13**)*

Compound **B13** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 51.5 %. mp 240–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.29 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.15 (s, 1H), 7.81 – 7.71 (m, 2H), 7.58 – 7.54 (m, 3H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.19 – 7.14 (m, 1H), 5.30 (s, 1H), 4.60 (s, 2H), 3.54 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.26, 158.15, 157.00, 156.47, 142.31, 134.65, 133.54, 132.97, 129.32, 128.65, 128.48, 128.06, 127.38, 127.07, 126.65, 125.26,124.27, 123.23, 121.69, 119.50, 117.88, 62.46, 61.25. ESI-HRMS [M-H]$^-$ calcd for $C_{25}H_{20}FNO_6S$: 480.0923, found: 480.0936.

*4.3.14 5-((3-(3,4-Dimethoxyphenyl)-4-methoxynaphthalene)-1-sulfonamido)-2-fluorobenzoic acid (**B14**)*

Compound **B14** was prepared as a white solid in a similar manner as described for compound **B1**. Yield 45.5 %. mp 191–193°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 10.89 (s, 1H), 8.69 (d, *J* = 8.4 Hz 1H), 8.28 (dd, *J* = 8.4 Hz, 1H), 8.13 (s, 1H), 7.79 – 7.70 (m, 2H), 7.54 (dd, *J* = 6.4, 3.0 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.19 – 7.08 (m, 4H), 3.83 (s, 3H), 3.80 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.21, 158.20, 156.72, 156.51, 148.57, 133.58, 132.86, 129.24, 128.72, 128.26, 127.86, 127.32, 126.91, 125.47, 124.25, 123.16, 121.86, 121.22, 119.37, 117.88, 112.16, 111.84, 61.03, 55.41, 54.72. ESI-HRMS [M-H]$^-$ calcd for $C_{26}H_{22}FNO_7S$: 510.1028, found: 510.1037.

4.4 In vitro FABPs Inhibition Assay

The inhibitory activities of the compounds against FABPs were measured in a fluorescence-based assay using the probe 8-anilino-1-naphthalene-sulfonic acid (1,8-ANS). Briefly, 10 μM of 1,8-ANS in 0.01M phosphate buffered solution (PBS, pH 7.4) was mixed with FABPs protein to a final concentration of 10 μM, then various concentrations of compounds were added and incubated for 3 min at room temperature. The fluorescence signal at 370 nm (excitation) / 470 nm (emission) of the reaction mixture was then determined with a Flexstation III instrument (Molecular Devices, CA, USA). Compound **6** was synthesized in-house according to reference 50. Each compound was tested in triplicate and the data are presented as mean ± SD.

4.5 Lipolysis Assay

For forskolin-stimulated lipolysis, fully differentiated 3T3-L1 cells were cultured with DMEM for 4 h followed by incubation with compounds at 30 μM for 24 h. Then the cells were washed twice with Krebs-Ringer Hepes buffer (KRBH buffer,135 mM NaCl, 3.6 mM KCl, 0.5 mM KH_2PO_4, 0.5 mM $MgSO_4$, 2 mM $NaHCO_3$, 1.5 mM $CaCl_2$, and 10 mM HEPES, pH7.4) containing 0.1% BSA and stimulated with 20 μM forskolin diluted in KRBH buffer for 2 h. Thereafter culture supernatants were assayed for glycerol levels using a free glycerol reagent kit (Applygen Technologies Inc, China).

4.6 RNA Isolation and Quantitative RT-PCR

RAW264.7 cells were plated in a 24-well plate and cultured overnight. Compounds at the concentration of 30 μM were added and incubated for 12 h prior to stimulation with LPS (100 ng/mL) or DMSO for 6 h. Total RNA was extracted from RAW264.7 cells using the TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. Reverse-transcription reactions were performed using All-in-One cDNA Synthesis SuperMix (Biomake, China) to obtain complementary DNA (cDNA). mRNA levels were quantified by real-time PCR using SYBR Green qPCR Master Mix (Biomake, China) and an ABI VIIA7 Real-Time PCR machine (Applied Biosystems, USA) according to the manufacturer's instructions. The amplification program was as follows: initial denaturation at 95°C for 5 min (Hold Stage), followed by 40 cycles of 95°C for 15 s, 60°C for 45 s (PCR Stage),and 95°C for 15 s, 60°C for 1 min , 95°C for 15 s (Melt Curve Stage). The primers used for PCR amplification are shown in Table 1.The

relative expression levels of target genes were normalized to the amount of β-actin mRNA.

Table 4. Primer sequences

Gene name	Primer sequence
β-Actin	Forward: CACGATGGAGGGGCCGGACTCATC
	Reverse: TAAAGACCTCTATGCCAACACAGT
TNF-α	Forward: ATGGGAAGGGAATGAATCCACC
	Reverse: GTCCACATCCTGTAGGGCGTCT
MCP-1	Forward: CCACTCACCTGCTGCTACTCAT
	Reverse: TGGTGATCCTCTTGTAGCTCTCC
IL-6	Forward: TCTGAAGGACTCTGGCTTTG
	Reverse: GATGGATGCTACCAAACTGGA
COX-2	Forward: TGCCTGGTCTGATGATGTATG
	Reverse: AGTAGTCGCACACTCTGTTGT

4.7 Western Blot Analysis

RAW264.7 cells (2×10^5 cells/mL) were plated in growth medium in 12-well plates. After overnight incubation, the cells were pretreated with 30 μM and 60 μM compounds for 12 h following 100 ng/mL LPS induction for 10 min, the cells were lysed in RIPA Lysis Buffer (Beyotime, China) and clarified by centrifugation (Eppendorf, Germany).The levels of protein expression were determined using Western blot analysis as previously described.[38-39]

4.8 Statistical Analysis

The IC_{50} values for compounds against FABPs were expressed as mean ± standard deviation (SD) of three independent experiments, and calculated by nonlinear regression using GraphPad Prism software (San Diego, CA, USA). Statistical analysis of different groups was assessed by t test or one-way analysis of variance (ANOVA) followed by Dunnett's test analysis, and a value of $p < 0.05$ was considered significant.

4.9 Molecular Modeling

The crystal structure of FABP5 in complex with compound **7** (PDB code 5HZ5) and FABP4 in complex with compound **8** (PDB code 5Y0F) was obtained from PDB Protein Data Bank for docking simulation. The protein was prepared with Protein Preparation Wizard panel in Maestro 10.0. After adding the missing hydrogen atom, the important water molecules which formed key hydrogen bonds with FABP4 or FABP5 were retained. Then the protein was submitted to several restrained minimization to relieve static clashes using OPLS2005 force field. At last, the protein was adjusted and minimized up to 0.30 Å RMSD. The size of the grid box was defined as 15 Å ×

15 Å × 15 Å centered in the co-crystal ligand using Receptor Grid Generation. Compounds for docking were built using 2D Sketcher and were prepared with LigPrep module. Molecular docking was conducted using glide module with standard precision scoring (SP) mode. The figures were generated using Pymol.

Note

The authors declare no competing financial interest.

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Highlights:

1. Dual FABP4/5 inhibitors **A16** and **B8** were identified by applying a structure-based design strategy.
2. **A16** and **B8** reduced the level of forskolin-stimulated lipolysis in mature 3T3-L1 adipocytes, suggesting the potential advantages of dual FABP4/5 inhibition.
3. Compared with previous lead compound **8**, **A16** and **B8** exhibited better anti-inflammatory effects in lipopolysaccharide-stimulated RAW264.7 murine macrophages, which was reflected in the decreased expression of pro-inflammatory cytokines TNFα and MCP-1.
4. **A16** and **B8** exerted anti-inflammatory action at least partly by regulating the IKK-NF-κB pathways.

Identification of New Dual FABP4/5 Inhibitors Based on a Naphthalene-1-sulfonamide FABP4 Inhibitor

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