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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, in vitro cytotoxicity and anti-platelet activity of new 1,3-bentzenedisulfonamides

Liu Xiu-jie[1,2] · Zhang Zhi-hao[1,2] · Deng Qing-song[1] · Chen Xin[1] · Wang Chao-qing[1]

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Abstract

To obtain more active and selective anti-platelet candidate drugs, we tried to introduce a methyl group at the 5-position and 6-position of the parent benzene ring first time, respectively or simultaneously. The idea could inspect compound with tetra-substituted or penta-substituted characteristics rather than retained classical 1,3,4-position triple substitutions characteristic whether it continues to have anti-platelet activity in vitro. The biological evaluation revealed that most of compounds with this novel structure were more potent than the positive control drug Picotamide. At the concentration of 1.3 μmol/L, using Arachidonic acid as an inducer, it was found that the anti-platelet activity in vitro of five compounds **1a**, **1b**, **1c**, **2f**, and **3d** was higher than that of Picotamide and the series **1** compounds were generally higher than that of the series **2** and **3**. And with ADP as an inducer, the activity in vitro of nine compounds **2a**, **2b**, **2d**, **2f**, **2g**, **2h**, **3a**, **3b**, and **3c** was more elevated than that of Picotamide and the compounds of series **2** and **3** were all evidently even more active than that of series **1**. The proportion of newly designed target compounds with active is higher than that of previously developed series of compounds. Based on the in vitro activity results, a preliminary analysis of the structure–activity relationship was deduced. Meanwhile, cytotoxic effects in vitro of 11 target compounds **1b**, **1c**, **2f**, **2a**, **2b**, **3a**, **3b**, **3c**, **2d**, **2g**, and **2h** on L-929 cells were analyzed, but the data analysis shows that at two concentrations, target compounds have higher effect on L-929 cells than that of control drug Picotamide. The reason or mechanism for obtaining higher in vitro activity and higher cytotoxicity of the target compound under tetra- or penta- substitutions requires further relevant research work before conclusion can be drawn.

Keywords Synthesis · Anti-platelet activity · Picotamide · 5(6)-Methyl-l,3-benzenedisulfonamides · Cytotoxicity

Abbreviations

AA	arachidonic acid
ADP	adenosine triphosphate
CCK-8	cell counting kit-8
DMSO	dimethyl sulfoxide
PGI_2	prostaglandin I_2
SARs	structure–activity relationships
TLC	thin layer chromatography
TXA_2	thromboxane A_2

Introduction

Cardiovascular diseases and various diseases induced by them have high morbidity and high mortality worldwide (Vijaya Bhaskar Reddy et al. 2011; Liu et al. 2018). The pathogenesis of many cardiovascular diseases is associated with platelet aggregation and thrombosis (Youssef et al. 2011; Lu et al. 2018; Fontenele et al. 2009). Clinical evidence has clearly demonstrated that anti-platelet aggregation drugs can be used to prevent and treat thrombotic diseases (Mirfazli et al. 2014). Despite the documented utility of all these drugs, their efficacy and selectivity are not sufficiently high and there are substantial rooms to improve for the anti-platelet drugs. (Moura et al. 2016). Picotamide (Fig. 1), is a known anti-platelet aggregation drug, which is a derivative of 4-methoxyisophthalic acid and inhibits the synthesis of thromboxane A_2 (TXA_2) receptor and TXA_2 without interfering with prostacyclin (PGI_2) (Giridhar et al. 2012; Liu et al. 2018), which has the advantages of broad spectrum of anti-platelet activity, unique structure, good safety, and low synthesis cost,

✉ Liu Xiu-jie
liuxiujie@hotmail.com

[1] School of Chemistry and Chemical Engineering, Tianjin University of Technology, 300384 Tianjin, China

[2] Tianjin Key Laboratory of Organic Solar Cells and Photochemical Conversion, 300384 Tianjin, China

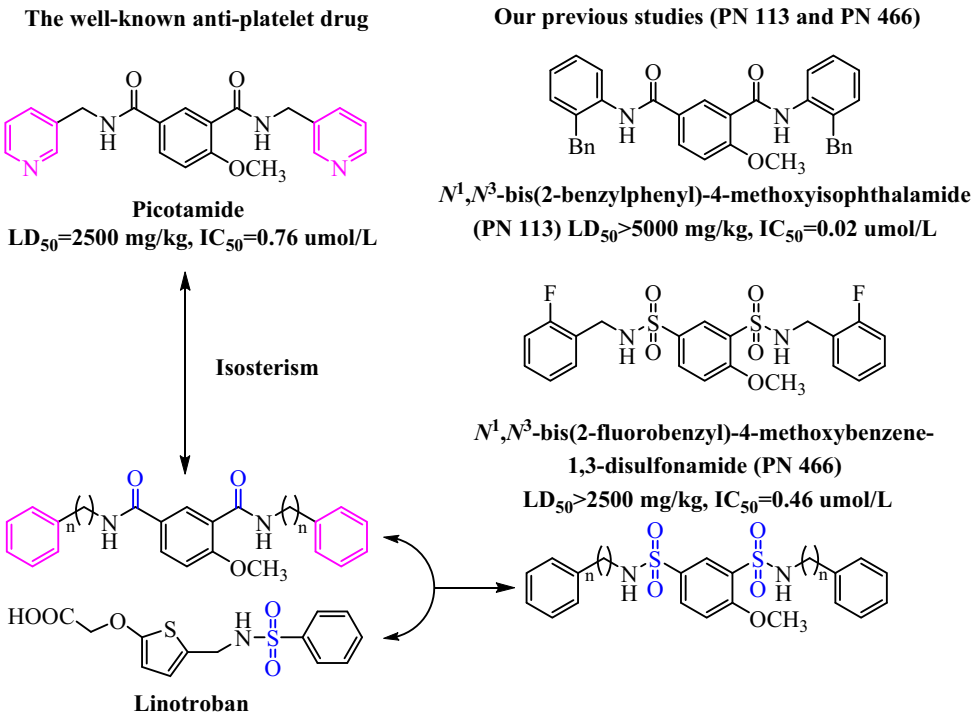


Fig. 1 Structures of Picotamide and previous developed compounds

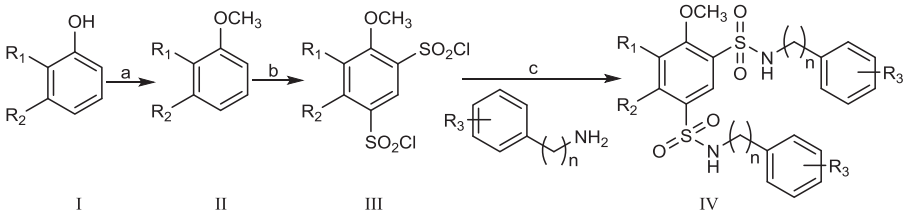
constitutes our attempt to change the structure of Picotamide (Liu et al. 2006, 2012, 2015).

In our previous studies, on the basis of the principles described in the literature, we retained the 1,3,4-position trisubstituted features of the parent benzene ring structure. Side chains' modification was supported by the principle of electronic isosteric, a series of new 4-methoxy-1,3-phthalamide compounds (Fig. 1) were designed and prepared by replacing two pyridyl groups in the side chain of Picotamide structure with different phenyl groups. And according to the principle of biological isosteric, a series of new 4-methoxy-1,3-benzenedisulfonamides (Fig. 1) were designed and prepared by replacing the formyl groups with sulfonyl groups. Some designed compounds, such as PN 113 and PN 466, have more than 20 times in vitro anti-platelet activity and lower acute toxicity than Picotamide (Li et al. 2015; Deng et al. 2017), which indicates that our structural transformation work is promising.

Structural design and synthetic routes

Based on the previous synthetic experience and reference pharmacological experimental results, it is attempted to introduce a methyl group at the 5-position or 6-position of the parent benzene ring, respectively or simultaneously, to investigate newly designed compounds have the tetra-substituted or penta-substituted character rather than 1,3,4-trisubstituted feature whether it continues to have anti-platelet activity. A total of 15 target compounds were prepared and divided into three new series, including series **1** (**1a–c**), series **2** (**2a–h**) and series **3** (**3a–d**). In the structural design of the series **1** compound, a methyl group is introduced to the 5-position of the parent benzene ring, and three substituent, 2-isopropyl, 3-methyl and 2-fluoro are respectively introduced into two side chain benzene rings. In series **2**, a methyl group is introduced into the 6-position of the parent phenyl ring, and eight substituent, 2-isopropyl, 3-isopropyl, 4-isopropyl,benzyl, 2-fluoro, 2-chloro, 3-ethyl and 4-ethyl are respectively introduced into two side chain benzene rings for comparison of the effects of the 2-position fluorine and chlorine on the activity, and the effects of the 3-position and 4-position ethyl and isopropyl groups on the activity are compared. In series **3**, two methyl groups are introduced simultaneously at the 5 and 6-position of the parent benzene ring, and four groups, 3-methyl, 3-isopropyl, 4-isopropyl and 2-fluoro, are respectively introduced into the side chain benzene of each compound, so that four compounds **3a**, **3b**, **3c**, and **3d** are used to comparing the in vitro activity differences between the 3-position methyl group and isopropyl group moreover the isopropyl group at 3-position and 4-position. Synthetic routes to target compounds **1a–c**, **2a–h**, and **3a–d**, are shown in Fig. 2.

Because the synthesis method is very similar to the previous one, the only difference is that the raw material anisole is replaced by its methyl substitution, which leads to a very smooth synthesis and a high yield. This provides



Compd	R_1	R_2	R_3	n	Compd	R_1	R_2	R_3	n
1a	CH_3	H	*o*-$CH(CH_3)_2$	0	**2f**	H	CH_3	*o*-Cl	1
1b	CH_3	H	*m*-CH_3	0	**2g**	H	CH_3	*m*-CH_2CH_3	0
1c	CH_3	H	*o*-F	1	**2h**	H	CH_3	*p*-CH_2CH_3	0
2a	H	CH_3	*o*-$CH(CH_3)_2$	0	**3a**	CH_3	CH_3	*m*-CH_3	0
2b	H	CH_3	*m*-$CH(CH_3)_2$	0	**3b**	CH_3	CH_3	*m*-$CH(CH_3)_2$	0
2c	H	CH_3	*p*-$CH(CH_3)_2$	0	**3c**	CH_3	CH_3	*p*-$CH(CH_3)_2$	0
2d	H	CH_3	H	1	**3d**	CH_3	CH_3	*o*-F	1
2e	H	CH_3	*o*-F	1					

Reagents and conditions: a)$(CH_3)_2SO_4$; b)$ClSO_4OH$,$SOCl_2$,CH_2Cl_2,40℃,NaCl,DMF,50℃,9h; c)TEA,THF,r.t,24h

Fig. 2 Synthetic routes to the target compounds **1a–c** (series **1**), **2a–h** (series **2**), and **3a–d** (series **3**)

convenience for future related research and theoretical basis for further research.

Biological assays

Evaluation of in vitro anti-platelet aggregation activity

The in vitro anti-platelet aggregation activities of 15 target compounds were measured by Born turbidimetry (Born 1962; Violi et al. 1988). Blood samples from anesthetized rats were injected intravenously into test tubes containing 3.8% sodium citrate (1:9, v/v) by syringe. Platelet aggregation was assessed in platelet-rich plasma (PRP). Citrated whole blood was obtained by centrifugation at room temperature for 10 min (500–800 rpm). The platelet aggregation rate was measured by platelet aggregation analyzer after AA and ADP stimulation. The platelet-poor plasma (PPP) was set to zero at first. PPP was obtained by centrifuging PRP at room temperature for 15 min (3000 rpm). Compounds (1.3 μmol/L) were added to PRP (200 μL) in the solution of dimethyl sulfoxide (DMSO) (5 μL), and DMSO without test compound was added to the reference sample (according to the preliminary experiment, 5 μL DMSO seems to have no significant effect on platelet aggregation). After incubation for 2 min, platelet aggregation was assessed, platelet aggregation inhibition rate was calculated, and platelet aggregation was monitored for 5 min. The negative control group was DMSO (0.5% v/v), and the positive drugs were Picotamide and Aspirin. The results were expressed as mean of three independent experiments. The platelet aggregation inhibition rate (%) was calculated according to the following formula:

$$\text{Inhibition}\% = (1 - D/S) \times 100\%;$$

Table 1 Anti-platelet activities of new 4-methoxy-1,3-benzenedisulfonamides

Compd.	Dose (1×10^{-6} mol/L)	Inhibition rate (%)	
		AA	ADP
DMSO	1.3	–	–
1a	1.3	22.3	16.0
1b	1.3	29.5	18.6
1c	1.3	36.7	12.9
2a	1.3	13.2	54.1
2b	1.3	12.5	53.2
2c	1.3	0.9	40.4
2d	1.3	17.4	48.4
2e	1.3	2.0	36.9
2f	1.3	28.8	44.9
2g	1.3	7.7	49.6
2h	1.3	19.9	52.0
3a	1.3	9.9	53.2
3b	1.3	13.1	54.1
3c	1.3	19.7	57.6
3d	1.3	21.4	36.5
Aspirin	1.3	33.6	56.1
Picotamide	1.3	21.1	41.7

where *D* is the platelet aggregation in the presence of test compounds, and *S* is the platelet aggregation in the presence of solvent. The primary screening data for all compounds (1.3 μmol/L) in vitro activity on anti-platelet aggregation of the synthesized compounds are given in Table 1. The statistical analysis was performed with ANOVA followed by Tukey's test.

In vitro anti-platelet activity screening results showed that most of the compounds were more active than the positive control drug Picotamide when AA or ADP as an inducer.

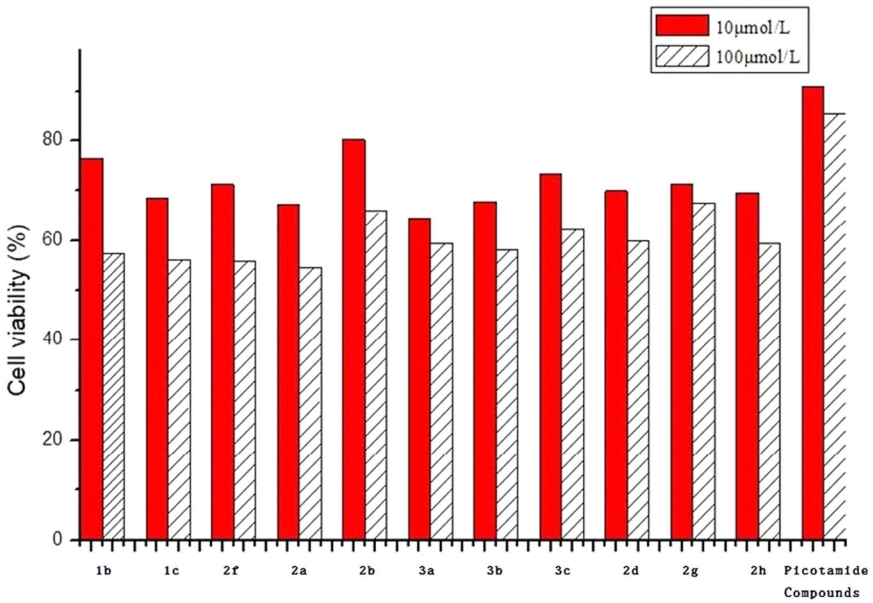


Fig. 3 Cell viability(%) of cytotoxicity of target compounds and Picotamide

Cytotoxicity test

Eleven compounds **1b**, **1c**, **2f**, **2a**, **2b**, **3a**, **3b**, **3c**, **2d**, **2g** and **2h** with anti-platelet activity were selected to continue the in vitro cytotoxicity test. Mouse fibroblast cells (L-929) were chosen to evaluate the in vitro cytotoxicity of the materials and the drugs via cell counting kit-8 (CCK-8) assays. L-929 was cultivated in a humidified 5% carbon dioxide atmosphere at 37 °C on 96-well microplates, with 1×10^4 cells per well immersed in complete growth medium. The cells with 100 ml of RPMI-1640 per well were allowed to attach for 24 h. Subsequently, the cells were then exposed to target compounds at a range of concentrations at 37 °C for 48 h. Target compounds concentration of 10 and 100 μmol l^{-1} were added to L-929 cells. After incubation for 48 h, the medium was removed and replaced with 100 μL of fresh complete medium of RPMI-1640. Then, CCK-8 solution was added to the 96-well plates at 10 μL per well and incubated for a further 30 min, and the absorbance at 450 nm was measured on a microplate reader (Bio-TekFLx800 fluorescence microplate reader). This process was repeated eight times in parallel. Figure 3 shows relative cell viability (%) relative to control wells at two concentrations tested. Its results were calculated as:

$$\text{Cell viability}(\%) = \text{Abs}(\text{test cell})/\text{Abs}(\text{controlled cell}) \times 100\%$$

The data analysis shown at two concentrations, target compounds have higher effect on L-929 cells than that of control drug Picotamide.

Results and discussion

1. As showed in Table 1, the five compounds **1a**, **1b**, **1c**, **2f**, and **3d** showed significant in vitro inhibitory activity against the platelet aggregation agonist AA and their order of inhibition rate is: **1c** (36.7%) > Aspirin (33.6%) > **1b** (29.5%) > **2f** (28.8%) > **1a** (22.3%) > **3d** (21.4%) > Picotamide (21.1%). The results showed at the concentration of 1.3 μmol/L, among them, the inhibition rate of compound **1c** (2-F) was the most highest and higher than both Aspirin and Picotamide. And the activity in vitro of the series 1 obtained by introducing a methyl group to the 5-position of the parent benzene ring was generally higher than that of the series **2** and series **3**.

2. Also as illustrated in Table 1, nine compounds **2a**, **2b**, **2d**, **2f-h** and **3a-c** have obvious anti-platelet aggregation activities when using ADP as an inducer. The inhibition rate order of series 2 is: Aspirin (56.1%) > **2a** (54.1%) > **2b** (53.2%) > **2h** (52.0%) > **2g** (49.6%) > **2d** (48.4%) > **2f** (44.9%) > Picotamide (41.7%). It was found that two compounds **2a** (2-$CH(CH3)_2$) and **2b** (3-$CH(CH_3)_2$) obtained in the *ortho*-linked and *meta*-linked isopropyl groups had higher inhibition rates. It seems increase in the two side chain phenyl 2-position and 3-position steric hindrance effects are beneficial to the in vitro activity. The inhibition rate order of series 3 is: **3c** (57.6%) > Aspirin (56.1%) > **3b** (54.1%) > **3a** (53.2%) > Picotamide (41.7%) and at the concentration of 1.3 μmol/L, **3c** (4-$CH(CH_3)_2$) possessed the highest inhibition rate. In general, the compounds of series **2** obtained by introducing a methyl group to the 6-position of the parent benzene ring and series **3** obtained by introducing two methyl groups to the 5-position and 6-position of the parent benzene ring simultaneously

were evidently having even more higher in vitro inhibitory activity than those of series **1**.

3. The results of cytotoxicity effect on L-929 cells of 11 target compounds **1b**, **1c**, **2f**, **2a**, **2b**, **3a**, **3b**, **3c**, **2d**, **2g** and **2h** & control drug Picotamide are given in Fig. 3. The data analysis has shown that even if at lower concentration of 10 μmol/L, each of target compounds have higher effect on L-929 cells than that on control drug Picotamide, only the effect of **2b** is close to Picotamide. At the concentration of 100 μmol/L, the effect change of Picotamide on cells is not evident, but the toxicity of every target compound is further increased and obviously more than that of Picotamide.

Conclusion

This study reported for the first time that 15 compounds of the new structure were divided into three series depending on the number of newly introduced methyl groups and the position of the substituted parent benzene ring. The parent structure of these target compounds have tetra-substituted or penta-substituted character, which is significantly different from the structure of the 1,3-benzenedisulfonamide, which we have previously prepared with 1,3,4-trisubstituted features, subverting the theory we have followed in our previous work. The principle is that the prepared compound has high in vitro anti-platelet activity only when the trisubstitution of the 1,3,4-position on the parent phenyl ring is maintained (Tong et al. 1992).

The results of in vitro anti-platelet activity pharmacological experiments indicated that most of newly designed compounds were more active than the positive control drug Picotamide. With AA as an inducer, it was found that the anti-platelet activity in vitro of the five compounds **1a**, **1b**, **1c**, **2f**, and **3d** was higher than Picotamide, and nearly 33% of the compounds have a higher inhibition rate. With ADP as an inducer, nine compounds **2a**, **2b**, **2d**, **2f**, **2g**, **2h**, **3a**, **3b**, and **3d** were more active than that of Picotamide, and nearly 60% of the compounds have a higher inhibition rate. Compared with the activity percentage of nearly 15% that previous developed series compounds, the percentage of newly designed compounds with higher active was more than doubled with AA as an inducer, while was four times when using ADP as an inducer.

A preliminary study of the structure–activity relationship showed that the target compounds of series **1** were generally more active than the other two series of compounds when AA is used as an inducer. The compounds of series **2** and series **3** were all evidently even more active than those of series **1** when ADP is used as an inducer. The chemical structure at this time is characterized, in that a methyl group is introduced simultaneously or separately at the 5-position or 6-position of the side chain benzene ring. The two compounds **2a** and **2b** in series **2** exhibited higher in vitro anti-platelet activity, and their chemical structural features were the introduction of an isopropyl group at the *ortho* or *meta* position of the side chain benzene ring. Comparison of the in vitro activities of the compounds of series **3** revealed that, under the induction of ADP, when the volume of the *para*-group of the side chain benzene ring was appropriately increased, the increase in inhibitory activity in vitro was facilitated.

Meanwhile, cytotoxic effects in vitro of 11 target compounds **1b**, **1c**, **2f**, **2a**, **2b**, **3a**, **3b**, **3c**, **2d**, **2g**, and **2h** on L-929 cells were analyzed, but the data analysis shown that at two concentrations, target compounds have higher effect on L-929 cells than that of control drug Picotamide.

In this study, more active compounds were found, but in vitro cytotoxicity was evidently higher than that of Picotamide. The reason for the higher number of compounds with higher anti-platelet activity in vitro and higher cytotoxicity under tetra- or penta-substitutions needs to be clarified after more relevant research work is carried out in the future.

Experiments

All chemical reagents were purchased from Aladdin Industrial Corporation (P.R. China), Energy Chemical (P.R. China), and Tianjin Heng shan (P.R. China) and used without further purification. The reagents of cell viability were purchased from Beyotime Biotechnology (P.R. China), other biological reagents arachidonic acid (AA) was purchased from Sigma and adenosine diphosphate (ADP) was purchased from Solarbio life sciences. The melting points were determined with a Kofler micro-melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker 400 MHz spectrometers (Bruker, Rheinstetten, Germany), pick positions are illustrated in parts per million (d) in DMSO-d_6 solution and TMS (0.05% v/v) as internal standard, and coupling constant values (*J*) are given in Hertz. Signal multiplicities are reported by: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and brs (broad signal). Analytical thin-layer chromatography (TLC) was performed with Merck silica gel plates and visualized with UV irradiation (254 nm). High-resolution mass spectra (HRMS) were recorded on an Agilent 6520B UPLC-Q-TOF mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Melting points were obtained by an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were taken by a PerkinElmer 843 spectrometer with KBr as diluent.

Synthesis (II) (take 2-methylanisole as an example)

In a 250 ml three-necked flask equipped with a thermometer, a magnetic stirring and a relux condenser, was placed

NaOH (4.0 g, 100 mmol) and water (40 ml), the reaction flask was then was heated to 30 °C and the *o*-cresol (5.4 g, 0.05 mol) was added gradually. The mixture was heated to 50 °C, the dimethylsulfate (7.56 g, 0.06 mol) was added gradually and was magnetic stirred for 8 h. The liquid were divided and retained the upper liquid, used NaOH and sodium chloride solution washed upper liquid six times. This yellow oily liquid was poured into a conical flask and could be directly put into the next reaction without drying next step.

3-methylanisole and 2, 3-dimethyl anisole were prepared in a similar manner.

Synthesis of intermediate 5-methyl-4-methoxy-1,3-benzenedisulfonylchloride (IIIa)

0.4 g (10.0 mmol) of NaCl was added to a dry (250 ml) four-necked flask equipped with a tail gas absorption device, a thermometer, and a mechanical stirrer, and 10.00 ml of dichloromethane was added. In an ice salt bath, when the temperature of the system decreased to 0 °C, 9.2 ml (70.0 mmol) of chlorosulfonic acid is added to the four-necked flask, and 1.2 ml (10.0 mmol) of *o*-methylanisole is added to the constant drop, followed by stirring for 30 min. The ice salt bath removed, stirred for 15 min at room temperature, and heated up to 40 °C for 3 h. 2–3 drops of DMF was added, raised the temperature to 50 °C, and continued the reaction for 4 h. 2.9 ml (20.0 mmol) of thionyl chloride was dropped into the reaction flask and allowed to react for 2 h. The reaction solution was slowly poured into a 500-ml beaker containing crushed ice, rapidly stirred, and the crude product was filtered off with suction, dried, and recrystallized from cyclohexane to obtain white needle crystals intermediate (**IIIa**), yield, 49%; m.p. 90–94 °C.

Synthesis ofintermediate 6-methyl-4-methoxy-1,3-benzenedisulfonyl chloride (IIIb)

White acicular crystal. Yield, 50.3%; m.p.: 115.8–117.1 °C.

Synthesis of intermediate 5,6-dimethyl-4-methoxy-1,3-benzenedisulfonyl chloride (IIIc)

White acicular crystal. Yield, 51.0%; m.p.: 116.9–118.1 °C.

General procedure for synthesis of compound (IV) (Take N^1, N^3-bis(2-isopropylphenyl)-4-methoxy- 5-methyl-1,3-benzenedisulfonamide (1a) as an example)

0.65 g (4.80 mmol) *ortho* isopropyl aniline, placed in 100 ml single mouthed bottle, amount of 10 ml dissolved in tetrahydrofuran, stirred with the magnetic stirrer; another 0.60 g (2.00 mmol) intermediate (**IIIa**) dissolved in 20 ml tetrahydrofuran, the solution is added drop by drop into the single mouthed bottle, immediately formed white turbidity (monitored by TLC, ethyl acetate–petroleum ether, volume ratio = 1:1). The solution was concentrated in vacuo, and the pH value was adjusted to 3.0–4.0 by hydrochloric acid, the solid was collected and dried, residues were recrystallized from ethanol to give compound **1a** (solid red light). Yield: 42.7%; m.p.: 149.3–150 °C.

Other 14 compounds **1b**, **1c**, **2a**-**h**, **3a**-**d** were prepared in the same manner.

Synthesis and spectral characterization of the synthesized compounds

N^1,N^3-bis(2-isopropylphenyl)-4-methoxy-5-methyl-1,3-benzenedisulfonamide (1a)

Following the general procedure, compound **1a** was synthesized from 0.65 g (4.80 mmol) *o*-isopropyl aniline, 0.60 g (2.00 mmol) intermediate (**IIIa**). It was generated as red light solid (0.42 g). Yield = 42.7%; m.p.: 149.3–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (s, 1H, SO_2NH), 7.69 (s, 1H, SO_2NH), 7.23–7.17 (m, 3H, Ar–H), 7.16–7.11 (m, 1H, Ar–H), 7.02–6.93 (m, 5H, Ar–H), 6.71 (s, 1H, Ar–H), 4.01 (s, 3H, OCH_3), 3.24 (dt, J = 13.6, 6.8 Hz, 1H, CH), 3.04 (dt, J = 13.6, 6.8 Hz, 1H, CH), 2.33 (s, 3H, CH_3), 1.08 (d, J = 6.8 Hz, 6H, 2 × CH_3), 0.98 (d, J = 6.8 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 158.98, 143.67, 143.46, 135.30, 134.75, 134.35, 132.37, 131.97,127.56, 127.12, 126.60, 126.25, 125.81, 124.65, 62.37, 27.46, 27.16, 23.46, 23.25, 16.24; IR (cm^{-1}): 3134.72, 1490.74, 1401.05, 1260.31, 987.46, 843.51; ESI-MS: $[M + H]^+$ *m/z* (%) 517.6185.

N^1,N^3-bis(3-methylphenyl)-4-methoxy-5-methyl-1,3-benzenedisulfonamide (1b)

Following the general procedure, compound **1b** was synthesized from 0.52 g (4.80 mmol) *m*-methylaniline, 0.60 g (2.00 mmol) intermediate (**IIIa**). It was generated as white solid (0.4 g). Yield = 43.4%; m.p.: 171.3–172.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (d, J = 4.0 Hz, 2H, 2 × SO_2NH), 8.14 (d, J = 1.9 Hz, 1H, Ar–H), 7.81 (d, J = 1.7 Hz, 1H, Ar–H), 7.05 (dt, J = 23.5, 7.8 Hz, 2H, Ar–H), 6.91-6.76 (m, 6H, Ar–H), 3.87 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3), 2.16 (d, J = 8.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 159.47, 138.95, 137.63, 135.01, 134.05, 129.38, 127.12, 125.60, 124.84, 121.37, 120.03, 117.74, 116.34, 62.16, 21.42, 16.59; IR (cm^{-1}): 3415.26, 3247.50, 1612.93, 1399.49, 1272.44, 988.82, 833.39, 706.75; ESI-MS: $[M + H]^+$ *m/z* (%) 461.5653.

N^1,N^3-bis(2-fluorobenzyl)-4-methoxy-5-methyl-1,3-benzenedisulfonamide (1c)

Following the general procedure, the desired compound **1c** was synthesized from 0.60 g (4.80 mmol) of *o*-fluorobenzylamine aniline, 0.60 g (2.00 mmol) intermediate (**III a**). It was generated as white solid (0.41 g). Yield = 40.3%; m.p.: 146–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.38 (s,1H, SO_2NH), 8.17 (s, 1H, SO_2NH), 7.96 (d, J = 2.1 Hz, 1H, Ar–H), 7.72 (d, J = 2.0 Hz, 1H, Ar–H), 7.33 (dd, J = 20.2, 11.9 Hz, 2H, Ar–H), 7.28-7.20 (m, 2H, Ar–H), 7.05 (dt, J = 18.6, 8.5 Hz, 4H), 4.12 (dd, J = 24.0, 6.2 Hz, 4H, 2 × CH_2), 3.85 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm):161.44, 159.19, 158.65, 136.15, 135.28, 134.58, 134.19, 130.65, 129.83, 125.90, 124.87, 124.70, 124.24, 115.33, 61.91, 16.32; IR (cm^{-1}): 3348.18, 3284.59, 1617.60, 1402.04, 864.64, 757.68, 569.00; ESI-MS: [M + H] + *m*/*z* (%) 497.5409.

N^1,N^3-bis(2-isopropylphenyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2a)

Following the general procedure, compound **2a** was synthesized from 0.65 g (2.00 mmol) of *o*-isopropylaniline, 0.60 g (2.00 mmol) intermediate (**IIIb**). It was generated as white crystal (0.39 g). Yield = 37.5%; m.p.: 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 2H, 2 × SO_2NH), 7.23 (d, J = 9.4 Hz, 1 H, Ar–H),7.16 (t, J = 11.6 Hz, 2H, Ar–H), 7.05 (dd, J = 20.8, 7.0 Hz, 2H, Ar–H), 6.97 (dd, J = 15.0, 6.9 Hz, 2H, Ar–H), 6.86 (d, J = 9.5 Hz, 2H, Ar–H), 6.64 (s, 1H, Ar–H), 4.02 (s, 3H, OCH_3), 3.21 (dt, J = 13.7, 6.8 Hz, 1H, $CH(CH_3)_2$), 3.07 (dt, J = 13.6, 6.8 Hz, 1H, $CH(CH_3)_2$), 1.15 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$), 1.08 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$); IR (cm^{-1}): 3415.44, 3259.85, 1593.58, 1403.53, 1259.55, 920.09, 758.07; ESI-MS: $[M + H]^+$ *m*/*z* (%) 517.6609.

N^1,N^3-bis(3-isopropylphenyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2b)

Following the general procedure, the desired compound **2b** was synthesized from 0.37 g (2.74 mmol) of *m*-isopropylaniline, 0.30 g (1.00 mmol) intermediate (**IIIb**). It was generated as grayish white crystal (0.28 g). Yield = 44.6%; m.p.: 205–207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.33 (s, 1H, SO_2NH), 10.04 (s, 1H, SO_2NH), 8.26 (s, 1H, H-2), 7.13 (s, 1H, Ar–H), 7.06 (dd, J = 18.2, 7.8 Hz, 2H, Ar–H), 6.92 (s, 2H, Ar–H), 6.90–6.80 (m, 3H, Ar–H), 6.76 (d, J = 8.0 Hz, 1H, Ar–H), 3.88 (s, 3H, OCH_3), 2.71–2.68 (m, 2H, 2 × $CH(CH_3)_2$), 2.50 (s, 3H, CH_3), 1.07 (t, J = 6.2 Hz, 12H, 2 × $CH(CH_3)_2$); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.66, 149.49, 149.22, 145.12, 137.41, 137.17, 132.25, 129.05, 128.81, 123.96, 122.03, 117.62, 117.31, 116.68, 116.57, 56.77, 33.21, 23.63, 20.06; IR (cm^{-1}): 3416.22, 3263.25, 2963.46, 1592.59, 1553.61, 1499.90, 1481.38, 1407.05, 1313.30, 970.05,788.31; ESI-MS: $[M + H]^+$*m*/*z* (%) 517.1831.

N^1,N^3-bis(4-isopropylphenyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2c)

Following the general procedure, compound **2c** was synthesized from 0.36 g (2.72 mmol) of p-isopropylaniline, 0.30 g (1.00 mmol) intermediate (**IIIb**). It was generated as grayish brown crystal (0.28 g). Yield = 44.6%; m.p.: 204–206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.36 (s,1H, SO_2NH), 10.08 (s, 1H, SO_2NH), 8.29 (s, 1H, H-2), 7.18 (s, 1H, Ar–H), 7.10-7.04 (m, 4H, Ar–H), 6.97 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 7.9 Hz, 1H, Ar–H), 3.91 (s, 3 H, OCH_3), 2.76 (td, J = 14.2, 7.0 Hz, 2H, 2 × $CH(CH_3)_2$), 2.54 (s, 3H, CH_3), 1.11 (t, J = 6.7 Hz, 12H, 2 × $CH(CH_3)_2$); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.72, 145.07, 143.90, 135.15, 134.94, 131.68, 129.60, 126.86, 126.52, 124.42, 119.60, 116.80, 114.24, 56.78, 32.66, 23.79, 20.11; IR (cm^{-1}): 3109.23, 2869.18, 1612.54, 1555.22, 1363.96,1093.69, 1018.25, 722.71, 632.16, 593.25; ESI-MS: $[M + H]^+$ *m*/*z* (%) 517.1831.

N^1,N^3-dibenzy-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2d)

Following the general procedure, compound **2d** was synthesized from 0.30 g (2.90 mmol) of benzylamine, 0.30 g (1.00 mmol) intermediate (**IIIb**). It was generated as brown crystal (0.24 g). Yield = 41.0%; m.p.: 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.29 (s, 1H, SO_2NH), 8.14 (s, 1H, H-2), 8.00 (t, J = 6.4 Hz, 1H, SO_2NH), 7.29-7.16 (m, 10H, Ar–H), 7.04 (s, 1H, Ar–H), 4.01 (dd, J = 24.7, 6.3 Hz, 4H, 2 × CH_2–Ar), 3.86 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.29, 144.13, 137.66, 130.30, 128.20, 127.96, 127.55, 127.15, 126.94, 125.79,116.27, 56.58, 46.24, 45.85, 20.13; IR (cm^{-1}): 3359.33, 3307.81, 1823.24, 1597.06, 1556.96, 1480.32, 1454.31, 1402.76, 1268.03, 1095.82, 854.16; ESI-MS: $[M + H]^+$ *m*/*z* (%) 461.1205.

N^1,N^3-bis(2-fluorobenzyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2e)

Following the general procedure, compound **2e** was synthesized from 0.50 g (4.00 mmol) of *o*-fluorobenzylamine, 0.30 g (1.00 mmol) intermediate (**IIIb**). It was generated as white crystal (0.25 g). Yield = 41%; m.p.: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.31 (s, 1H, SO_2NH), 8.13 (s, 1H, H-2), 7.99 (s, 1H, SO_2NH),7.34 (dd, J = 13.2, 6.1 Hz, 2H), 7.30-7.15 (m, 2H), 7.12 (d, J = 7.4 Hz, 1H), 7.10-7.00

(m, 2H), 7.00-6.90 (m, 2H), 4.08 (dd, $J = 25.9$, 6.1 Hz, 4H, $2 \times NHCH_2$–Ar), 3.84 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.08, 160.84, 158.65, 158.34, 144.34, 130.54, 130.38, 130.12, 129.92, 129.33, 125.34, 124.26, 116.06, 115.11, 114.87, 114.62, 56.52, 39.63, 38.98, 20.06; IR (cm^{-1}): 3415.09, 3280.53, 1619.37, 1595.12, 1493.82, 1381.61, 1255.09, 1146.29, 974.20, 762.75, 636.62; ESI-MS: $[M + H]^+$ *m/z* (%) 497.1017.

N^1,N^3-bis(2-chlorobenzyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2f)

Following the general procedure, compound **2f** was synthesized from 0.68 g (2.00 mmol) of *o*-chlorobenzylamine, 0.60 g (2.00 mmol) intermediate (**IIIb**). It was generated as white crystal (0.42 g). Yield = 39.6%; m.p.: 192–194 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.31 (s, 1H, SO_2NH), 8.13 (s, 1H, H-2), 7.99 (s, 1H, SO_2NH), 7.34 (dd, $J = 13.2$, 6.1 Hz, 2H), 7.30–7.15 (m, 2H), 7.12 (d, $J = 7.4$ Hz, 1H), 7.10–7.00 (m, 2H), 7.00-6.90 (m, 2H), 4.08 (dd, $J = 25.9$, 6.1 Hz, 4H, $2 \times NHCH_2$-Ar), 3.84 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.08, 160.84, 158.65, 158.34, 144.34, 130.54, 130.38, 130.12, 129.92, 129.33, 125.34, 124.26, 116.06, 115.11, 114.87, 114.62, 56.52, 39.63, 38.98, 20.06; IR (cm^{-1}): 3415.09, 3280.53, 1619.37, 1595.12, 1493.82, 1381.61, 1255.09, 1146.29, 974.20, 762.75, 636.62; ESI-MS: $[M + H]^+$ *m/z* (%) 497.1017.

N^1,N^3-bis(3-ethylphenyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2g)

Following the general procedure, compound **2g** was synthesized from 0.37 g (2.97 mmol) of m-ethylaniline, 0.30 g (1.00 mmol) intermediate (**IIIb**). It was generated as brown crystal (0.40 g). Yield = 65.6%; m.p: 237–239 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.38 (s,1H, SO_2NH), 10.09 (s, 1H, SO_2NH), 8.31 (dd, $J = 6.3$, 3.3 Hz, 1H, H-2), 7.14 (s, 1H, H-5), 7.10-7.01 (m, 2H), 6.85 (dd, $J = 27.3$, 17.0 Hz, 6H, Ar–H), 3.90 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3), 2.45 (q, $J = 7.5$ Hz, 4H, $2 \times CH_2CH_3$), 1.07–1.05 (m, 6H, $2 \times CH_2CH_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.69, 145.09, 139.23, 135.03, 134.82, 131.92, 129.33, 128.34, 124.09, 119.68, 119.46, 116.76, 56.81, 27.42, 20.11, 15.40; IR (cm^{-1}): 3415.29, 3267.30, 2969.71, 1594.77, 1554.52, 1482.07, 1459.68, 1399.01, 1148.43, 966.31, 847.45; ESI-MS: $[M + H]^+$ *m/z* (%) 489.1524.

N^1,N^3-bis(4-ethylphenyl)-4-methoxy-6-methyl-1,3-benzenedisulfonamide (2h)

Following the general procedure, compound **2h** was synthesized from 0.37 g (2.97 mmol) of *p*-ethylaniline, 0.30 g (1.00 mmol) intermediate (**III b**). It was generated as brown crystal (0.42 g). Yield = 68.9%; m.p.: 193–195 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H, SO_2NH), 10.06 (s, 1H, SO_2NH), 8.25 (s, 1H, H-2), 7.17 (s, 1H, H-5), 7.05–6.98 (m, 4H, Ar–H), 6.92 (dd, $J = 19.6$, 8.4 Hz, 4H, Ar–H), 3.92 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3), 2.46 (s, 4H, $2 \times CH_2CH_3$), 1.09 (q, $J = 7.4$ Hz, 6H, $2 \times CH_2CH_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.69, 145.09, 139.23, 135.03, 134.82, 131.92, 129.33, 128.34, 124.09, 119.68, 119.46, 116.76, 56.81, 27.42, 20.11, 15.40; IR (cm^{-1}): 3414.90, 3321.86, 2969.28, 1594.76, 1555.39, 1513.35, 1481.46, 1459.22, 1398.47, 1020.00, 970.74; ESI-MS: $[M + H]^+$ *m/z* (%) 489.1518.

N^1,N^3-bis(3-methylphenyl)-4-methoxy-5,6-dimethyl-1,3-benzenedisulfonamide (3a)

Following the general procedure, compound **3a** was synthesized from 0.52 g (4.80 mmol) of m-methylaniline, 0.60 g (2.00 mmol) intermediate (**IIIc**). It was generated as brown crystal (0.39 g). Yield = 41.0%; m.p.: 174.5–175.1 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.59 (s, 1H, SO_2NH), 10.33 (s, 1H, SO_2NH), 8.29 (s, 1H, Ar–H), 7.04 (dt, $J = 18.3$, 7.8 Hz, 2H, Ar–H), 6.88 (s, 2H, Ar–H), 6.80 (dd, $J = 14.3$, 6.2Hz, 4 H,Ar–H), 3.82 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3), 2.16 (d, $J = 6.4$ Hz, 6H, $2 \times CH_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.94, 144.47, 138.98, 137.73, 135.93, 134.39, 130.73, 129.42, 128.95, 124.88, 120.11, 116.21, 62.62, 21.48, 17.31, 13.45; IR (cm^{-1}): 3273.66, 3134.03, 1611.22, 1400.22, 1247.25, 726.05, 610.10; ESI-MS: $[M + H]^+$ *m/z* (%) 475.4827.

N^1,N^3-bis(3-isopropylphenyl)-4-methoxy-5,6-dimethyl-1,3-benzenedisulfonamide (3b)

Following the general procedure, compound **3b** was synthesized from 0.65 g (4.80 mmol) of *m*-isopropylaniline, 0.60 g (2.00 mmol) intermediate (**IIIc**). It was generated as brown crystal (0.39 g). Yield = 41.0%; m.p.: 202.6–204.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (s, 1H, SO_2NH), 7.24 (s, 1H, Ar–H), 7.22 (s, 1H, SO_2NH), 7.19–7.13 (m, 2H, Ar–H), 7.02-6.98 (m, 2H, Ar–H), 6.98–6.92 (m, 2H, Ar–H), 6.88 (d, $J = 8.9$ Hz, 1H, Ar–H), 6.66 (s, 1H, Ar–H), 4.01 (s, 3H, OCH_3), 3.27 (dt, $J = 13.6$, 6.8 Hz, 1H, $CH(CH_3)_2$), 3.01 (dt, $J = 13.6$, 6.8 Hz, 1H, $CH(CH_3)_2$), 2.50 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.11 (dd, $J = 8.8$, 6.9 Hz, 12H, $2 \times CH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 158.41, 144.40, 143.08, 142.52, 135.17, 134.95, 132.58, 132.29, 131.35, 129.05, 126.98, 126.41, 124.57, 124.16, 62.86, 58.49, 27.55, 27.14, 23.45, 23.24, 18.42, 17.44, 13.32; IR (cm^{-1}): 3290.71, 2967.95, 1491.90, 1249.95, 945.18, 624.01; ESI-MS: $[M + H]^+$ *m/z* (%)531.5875.

N^1,N^3-bis(4-isopropylphenyl)-4-methoxy-5,6-dimethyl-1,3-benzenedisulfonamide (3c)

Following the general procedure, the desired compound **3c** was synthesized from 0.65 g (4.80 mmol) of *p*-isopropylaniline, 0.60 g (2.00 mmol) intermediate (**IIIc**). It was generated as brown crystal (0.47 g). Yield = 44.3%; m.p.: 178.1–179.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.58 (s, 1H, SO_2NH), 10.33 (s, 1H, SO_2NH), 8.31 (s, 1H, Ar–H), 7.08 (dd, J = 14.3, 8.5 Hz, 4H, Ar–H), 6.95 (dd, J = 8.6, 2.9 Hz, 4H, Ar–H), 3.82 (s, 3H, OCH_3), 3.16 (dt, J = 13.6, 7.3 Hz, 2H, 2 × $CH(CH_3)_2$), 2.52 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.11 (t, J = 7.3 Hz, 12H, 2 × $CH(CH_3)_2$); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 158.95, 144.45, 144.23, 143.94, 135.99, 135.55, 134.68, 131.02, 128.72, 127.40, 119.42, 62.62, 24.25, 17.30, 13.49; IR (cm^{-1}): 3290.71, 2967.95, 1491.90, 1249.95, 945.18, 732.32; ESI-MS:$[M + H]^+$ m/z (%) 531.6980.

N^1,N^3-bis(2-fluorobenzyl)-4-methoxy-5,6-dimethyl-1,3-benzenedisulfonamide (3d)

Following the general procedure, compound **3d** was synthesized from 0.60 g (4.80 mmol) of o-fluorobenzylamine, 0.60 g (2.00 mmol) intermediate (**IIIc**). It was generated as brown crystal (0.51 g). Yield = 50.0%; m.p.: 172.1–173.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.49 (s, 1H, SO_2NH), 8.08 (s, 1H, SO_2NH), 8.05 (s, 1H, Ar–H), 7.35 (t, J = 7.6 Hz,1H, Ar–H), 7.23 (dt, J = 20.0, 8.5 Hz, 3H, Ar–H), 7.05 (dd, J = 17.4, 7.6 Hz, 2H, Ar–H), 7.01–6.92 (m, 2H, Ar–H), 4.10 (t, J = 6.2 Hz, 4H, 2 × CH_2), 3.77 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3), 2.06 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.28, 158.85, 158.13, 143.31, 134.96, 131.67, 130.62, 129.92, 129.59, 127.74, 124.99, 124.47, 115.27, 62.32, 17.20, 13.07; IR (cm^{-1}): 3304.17, 1617.37, 1587.80, 1457.09, 1235.70, 997.31, 762.75; ESI-MS: $[M + H]^+$ m/z (%) 511.5706.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

Born GVR (1962) Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 194(4832):927–929

Deng QS, Zhang QX, Wang CQ, Liu XJ (2017) Synthesis and in vitro activity on anti-platelet aggregation of N^1, N^3-benzhydryl-4-methoxy-1,3-benzenedisulfonam-idederivatives. Chin J Med Chem 22(5):355–359+366

Fontenele JB, Leal LK, Silveira ER, Felix FH, Bezerra Felipe CF, Viana GS (2009) Anti-platelet effects of piplartine, analkamide isolated from *Piper tuberculatum*: possible involvement of cyclooxygenase blockade and antioxidant activity. J Pharm Pharmacol 61(4):511–515

Giridhar R, Tamboli RS, Ramajayam R, Prajapati DG, Yadav MR (2012) Assessment of anti-platelet activity of 2-aminopyrimidines. Cheminform 50(33):428–432

Li GA, Wang X, Meng X, Lin YB, Li X, Liu XJ (2015) Design, synthesis of novel N, N'- bis-(halogenophenyl)-4-methoxybenzene-1,3-disulfonamides and evaluation of their anti- platelet aggregation activity. Acta Pharm Sin 50(2):185–190

Liu XJ, Wang CQ, Meng J, Shi XX, Yan YN, Liu XG (2018) Design, synthesis and biological evaluation of 4-methoxy diarylisophthalates as anti-platelet agents. Med Chem Res 27(2):488–496

Liu XJ, Wang SQ, Zhang J, Zhang FX, Li GZ, Wang BJ, Shao YL, Zhang LG, Fang L, Cheng MS (2006) Design, synthesis, and activities of novel derivatives of isophthalamide and benzene-1,3-disulfonamide. Chem Res Chin Univ 22(3):356–359

Liu XJ, Wang Y, Liu LL, Chen GL (2018) Synthesis and in vitro activities on anti-platelet aggregation of 4-methoxyisophthalamides. Med Chem Res 27(8):1971–1983

Liu XJ, Shi TE, Wang X, Wei TT, Meng X (2015) Synthesis and the evaluations in vitro anti-platelet aggregation activities of 4-ethoxyisophthalamides. Cardiovasc Hematol Agents Med Chem 13(2):124–128

Liu XJ, Shi XX, Zhong YL, Liu N, Liu K (2012) Design, synthesis and in vitro activities on anti-platelet aggregation of 4-methoxybenzene-1,3-isophthalamides. Bioorg Med Chem Lett 22(21):6591–6595

Lu N, Li L, Zheng X, Zhang S, Li Y, Yuan J, Wei Q, Xu Y, Meng F (2018) Synthesis of a novel series of amino acid prodrugs based on thienopyridine scaffolds and evaluation of their anti-platelet activity. Molecules 23(5):1041

Moura LA, de Almeida AC, da Silva AV, de Souza VR, Ferreira VF, Menezes MV, Kaiser CR, Ferreira SB, Fuly AL (2016) Synthesis, anticlotting and anti-platelet effects of 1,2,3-triazoles derivatives. Med Chem 12(8):733–741

Tong ZE, Chen WH, Peng SX (1992) Synthesis of a platelet anti-aggregant—pieotamide and its analogues. J China Pharm Univ 23 (1):1–4

Vijaya Bhaskar Reddy M, Tsai WJ, Qian K, Lee KH, Wu TS (2011) Structure–activity relationships of chalcone analogs as potential inhibitors of ADP- and collagen-induced platelet aggregation. Bioorg Med Chem 19(24):7711–7719

Violi F, Ghiselli A, Iuliano L, Praticò D, Alessandri C, Balsano F (1988) Inhibition bypicotamide of thromboxane production in vitro and ex vivo. Eur J Clin Pharmacol 33(6):599–602

Mirfazli SS, Kobarfard F, Firoozpour L, Asadipour A, Esfahanizadeh M, Tabib K, Shafiee A, Foroumadi A (2014) N-substituted indolecarbohydrazide derivatives: synthesis and evaluation of their anti-platelet aggregation activity. Daru 22(1):65

Youssef KM, Al-Omar MA, El-Subbagh HI, Abou-Zeid LA, Abdel-Gader AGM, Haress NG, Al-Tuwaijri AS (2011) Synthesis, anti-platelet aggregation activity, and molecular modeling study of novel substituted-piperazine analogues. Med Chem Res 20(7):898–911