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慢性呼吸系统疾病药物福多司坦衍生物的设计、合成及活性评价

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摘要 慢性阻塞性肺疾病由于其持续的症状影响患者的生活质量而受到越来越多的关注。福多司坦治疗 COPD 的显著优势体现在其高疗效和低副作用。本研究设计并合成了 Fudosteine 磺酰胺类衍生物系列Ⅰ，胺类衍生物系列Ⅱ,共两类福多司坦衍生物，并评价了其生物活性。结果显示，化合物 2.5f 表现出优异的抗炎活性，IC_{50} 为 1.08 mmol/L，与先导分子相比，具有更强的抗氧化能力；同时分子对接研究表明，化合物 2.5f 与 MUC5AC 蛋白形成氢键和疏水性相互作用。此外，在 PDE4A1 酶抑制活性的试验中，发现衍生物 1f 的抑制作用比福多司坦高 5 倍。DPPH 自由基清除实验进一步证实了所有受试化合物均表现出比福多司坦更强的抗氧化活性，本文为进一步研究 COPD 药物治疗奠定了坚实的基础。
关键词 福多司坦; 慢性阻塞性肺疾病; 胺类衍生物; 黏蛋白 5AC

Design, synthesis, and activity assessment of Fudosteine derivatives for chronic respiratory disorders.

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Abstract Chronic obstructive pulmonary disease has garnered increased attention as a result of its persistent symptoms, which undermine patients' quality of life. Fudosteine has substantial advantages in the treatment of COPD due to its high efficacy and low adverse effects. In this study, Fudosteine sulfonamide derivatives series I and amine derivatives series II were designed and synthesized, and their biological activities were evaluated.The results showed that compound 2.5f had outstanding anti-inflammatory action, with an IC_{50} of 1.08 mmol/L, and a higher antioxidant capacity than the lead molecule. At the same time, molecular docking investigations have revealed that compound 2.5f establishes hydrogen bonds and hydrophobic contacts with the MUC5AC protein. Furthermore, derivative 1f inhibited PDE4A1 enzyme activity five times more than fudosteine. DPPH free radical scavenging tests demonstrated that all examined substances had higher antioxidant activity than fudosteine. This study established a solid foundation for further research into COPD drug therapy.
Keywords Fudosteine; COPD; Amine derivatives; MUC5AC

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent condition marked by chronic inflammation of the respiratory system[1]. It results from inhaling harmful particles, particularly tobacco smoke and pollutants, along with genetic, developmental, and social factors[2]. COPD is characterized by chronic respiratory symptoms[3] and airflow limitations[4] that are not fully reversible and tend to progress over time. Exposure to harmful particles or gases leads to abnormalities in the airways or alveoli, resulting in respiratory discomfort and restricted airflow[5]. The primary clinical symptoms include dyspnea, persistent cough, and sputum production[6]. Globally, COPD is the leading cause of death and disability[7].

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Research indicates that the pathogenesis of COPD is closely linked to oxidative stress and nitrification stress[8]. This is evidenced by decreased plasma antioxidant capacity, diminished anti-nitrification ability, and a reduction in the number of sulfhydryl groups in proteins[9]. Fudosteine enhances intracellular thiol levels, effectively scavenging reactive oxygen species and neutralizing oxidants[10], which subsequently inhibits the expression of inflammatory genes. It has been shown to be effective in treating both stable COPD and acute exacerbations, with minimal side effects[11]. Since the early 1980s, new medications have emerged, with generic drugs initially used as phlegm regulators for cough and bronchitis associated with mucus obstruction[12]. Recent studies have suggested that steins may also be beneficial in treating chronic respiratory conditions such as emphysema, tuberculosis, and bronchiectasis[13]. Stein medications typically consist of one or two blocked sulfhydryl groups, except for Mecysteine Hydrochloride, which contains one unblocked group[14]. In the liver, these medications interact with disulfide bonds in mucin, processed by liver microsomal enzymes, leading to the formation of three active free sulfhydryl groups[15]. This process disrupts the molecular structure of mucus, facilitating its dissolution[16].

Fudosteine has a beneficial effect on the treatment of both stable and acute exacerbations of COPD, with minimal side effects[17]. It primarily reduces phlegm by enhancing the breakdown of disulfide bonds in mucin found in sputum and other secretions, while also lowering the expression of the epithelial mucin gene (MUC5AC) [18]. The expression of MUC5AC is considered a rate-limiting factor in the development of goblet cells[19]; thus, inhibiting its expression can effectively prevent excessive goblet cell proliferation in the respiratory tract[20]. In studies conducted by Komatsu et al. [21], an animal model of airway inflammation induced by endotoxin and antigen was used to evaluate the role of Fudosteine. The results indicated that Fudosteine significantly reduced the counts of neutrophils, goblet cells, and eosinophils in bronchoalveolar lavage fluid, which are all contributors to inflammation[22]. Given Fudosteine's favorable pharmacological profile—including strong efficacy, low side effects, and broad indications—this study aims to design and develop new COPD drugs with enhanced anti-inflammatory activity and improved free radical scavenging capabilities.

2 Results and discussion

2.1 Design strategy of compounds

The literature indicates that sulfonamide structures are widely utilized in pharmaceutical development and metal complex research[23]. Drug compounds containing sulfonamide fragments exhibit promising biological activities, including anti-tumor[24], anti-inflammatory[25], and anti-tuberculosis effects[26]. Cysteine (Cys), though not classified as an essential amino acid, benefits from the addition of amines to its N-terminus, which enhances its antioxidant and anti-inflammatory properties. Research by Rubio et al. [27] demonstrated that acetylcysteine effectively reduces elastase-induced emphysema in rat models. Additionally, Hu et al. synthesized several cysteine diamine analogues, some of which showed significant efficacy. Molecular docking studies of Fudosteine with MUC5AC (PDB code: 5ajo) revealed（Figure 1）that Fudosteine forms five hydrogen bonds with amino acids ASP-176, ARG-201, ASN-106, ARG-362, and HIS-226. Its terminal hydroxyl group further establishes two additional hydrogen bonds with ASP-176A and ARG-201A. These findings suggest that Fudosteine may be an effective treatment option for COPD.

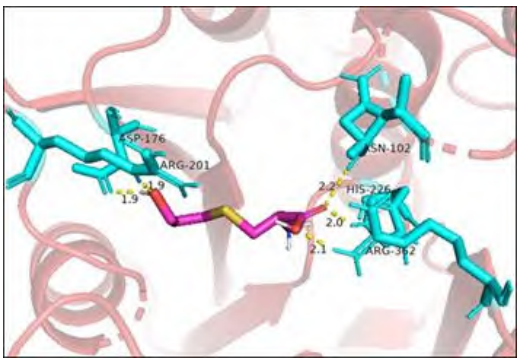
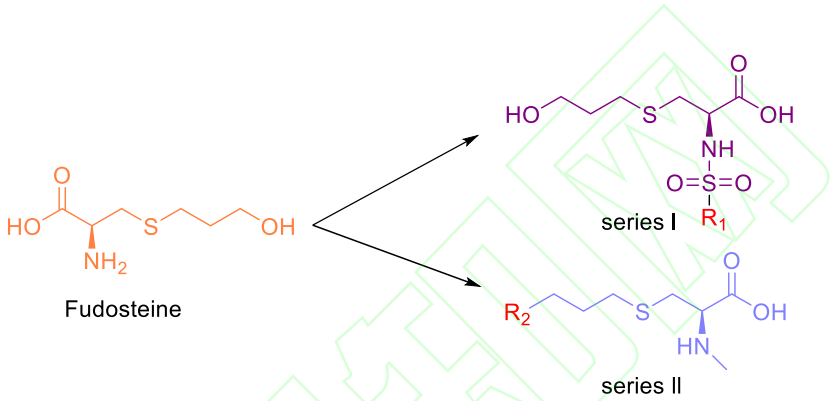


Figure 1 Docking image of Fudosteine and MUC5AC(A).

图 1 福多司坦和 MUC5AC 的对接图像（A）

In this study, Fudosteine served as the lead compound for structural modifications. The derivatives with substituents R1 and R2 were further explored to identify candidates with enhanced free radical scavenging and anti-inflammatory properties. As shown in Scheme 1, we synthesized two series: sulfonamide derivatives (Series I) and amine derivatives (Series II), by combining various sulfonamide and amine fragments with the lead compound. Prior to synthesis, all designed candidates underwent molecular docking studies similar to those conducted for Fudosteine, ensuring they also possessed the potential for COPD treatment.

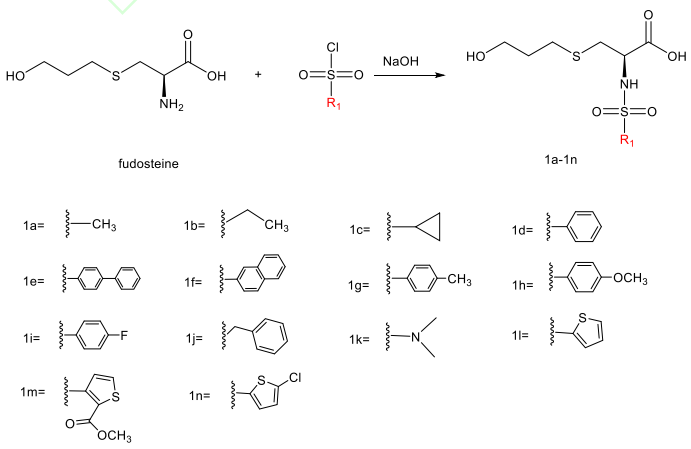


Scheme 1 General structural formula of Fudosteine derivatives.

方案 1 福多司坦衍生物的结构通式

2.2 Chemistry

The Scheme 2 outlines the general synthesis stages for Series I of Fudosteine derivatives. The sulfonamide derivatives (1a-1n) were synthesized through a substitution reaction between Fudosteine and various sulfonyl chlorides in the presence of an acid binding agent. Given that Fudosteine contains hydroxyl groups, the chemical process can easily produce sulfonic acid esters as byproducts. To minimize this issue, sodium hydroxide is used as the alkali, and water serves as the solvent, since sulfonates are prone to hydrolysis under strong alkaline conditions and Fudosteine is highly water-soluble.

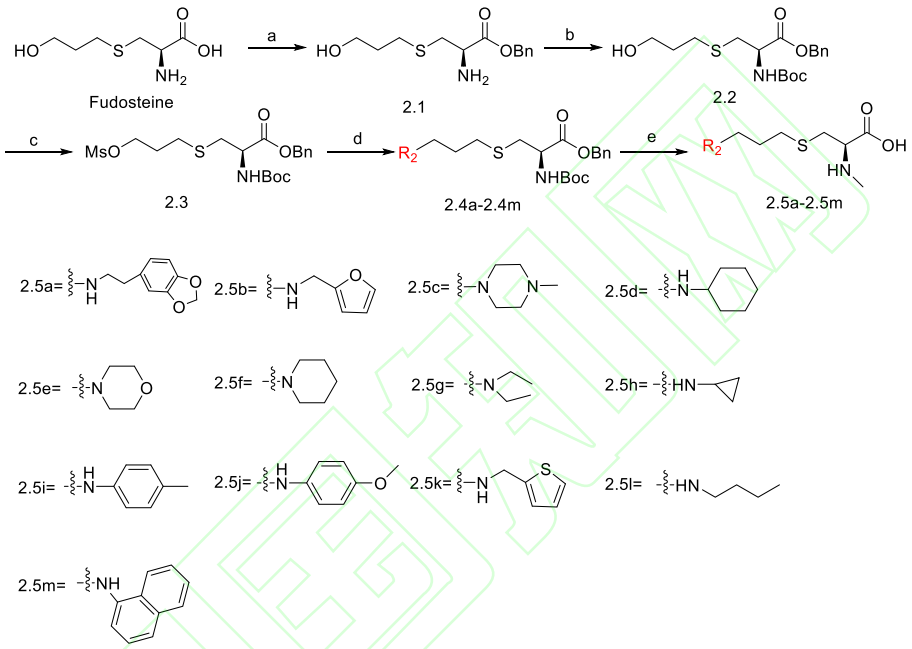


Scheme 2 Synthesis of series Ⅰ compounds.

方案 2 系列 I 化合物的合成

Regent and Codition:NaOH,H_2O,rt.

Fudosteine was utilized as the lead compound in the reaction with benzyl alcohol to produce compound 2.1. This product underwent protection using di-tert-butyl dicarbonate to yield compound 2.2. Subsequently, the terminal hydroxyl group was sulfonated with methyl sulfonyl chloride to obtain compound 2.3. Compound 2.3, generated through this three-step process, served as a common intermediate for the terminal hydroxyl derivative of Fudosteine. It was then subjected to aminolysis reactions with various amines, resulting in a series of corresponding Fudosteine amine derivatives, as illustrated in Scheme 3, through a two-step removal process.



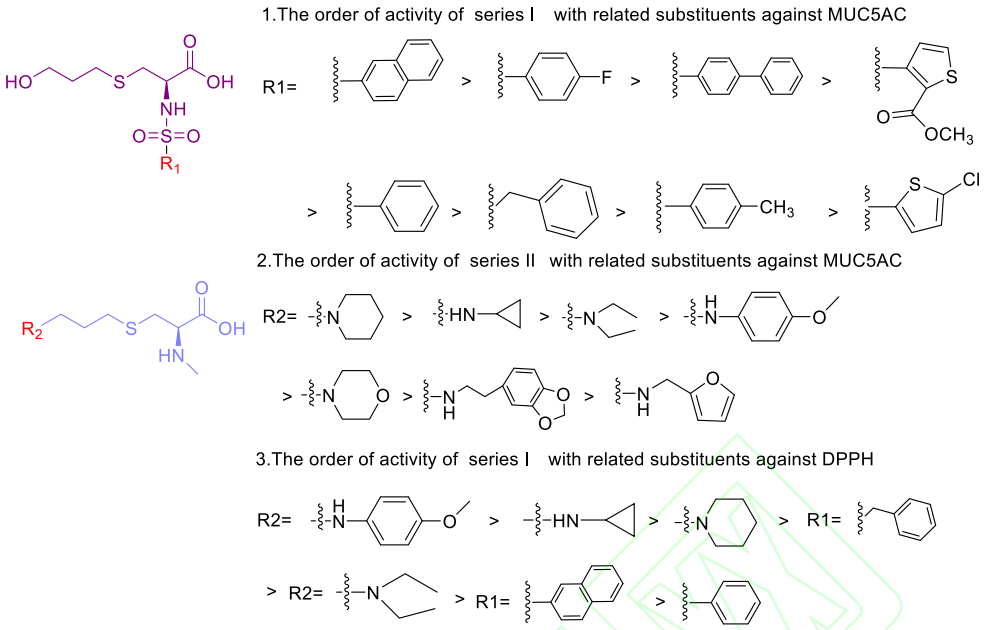
Scheme 3 Synthesis of series Ⅱ compounds.

方案 3 系列 II 化合物的合成

Regent and Conditiona:(a)$SOCl_2$,BuOH,Ar,-10°C-rt. (b)$(Boc)_2O$,TEA,DCM,rt.(c)MsCl,TEA,DCM,rt. (d)R_2,K_2CO_3,CH_3CN,80℃.(e)(1)TEA,DCM (2) 10%Pd/C,MeOH.

2.3 Structure-Activity Relationships (SAR) of the compound

The results indicated that the various substituents in Fudosteine derivatives significantly influenced their activity, with the activity order summarized in Scheme 4. The structure-activity relationships SAR against MUC5AC and 2,2-*d*iphenyl-1-picrylhydrazyl(DPPH) are as follows: (1) Generally, series II amine compounds exhibit stronger MUC5AC protein inhibition and greater DPPH free radical scavenging activity compared to series I sulfonamide derivatives. (2) Aliphatic amines showed superior activity compared to aromatic amines. (3) In contrast, sulfonamide derivatives displayed no activity. Notably, compound 1f demonstrated the highest overall activity. (4) Compound 2.5f exhibited exceptional anti-inflammatory and antioxidant properties, and all compounds displayed similar dual activity; however, compound 1f proved to be the most effective, with minimal impact on DPPH.



Scheme 4 The order of activities of compound with related substituents R_1 and R_2.

方案 4 具有相关取代基 R_1 和 R_2 的化合物的活性顺序

2.4 Biological

2.4.1 Inhibitory activity of Fudosteine derivatives against MUC5AC

The anti-secretory activity of MUC5AC protein in a tumour necrosis factor-α(TNF-α) induced human lung cancer cell line(NCI-H292) cell model was evaluated using synthetic derivatives 1a-1n and 2.5a-2.5m through enzyme linked immunosorbent assay(ELISA). The results are summarized in Table 1. Among the Fudosteine sulfonamide derivatives, compounds 1f and 1i demonstrated significantly higher inhibition of MUC5AC protein compared to Fudosteine itself. In contrast, derivatives 1d, 1e, 1g, 1j, and 1m exhibited minimal activity. The half maximal inhibitory concentration (IC_{50}) values for Fudosteine derivatives 2.5a-2.5m indicated that compounds 2.5e, 2.5f, 2.5g, 2.5h, and 2.5j had superior inhibitory effects on MUC5AC protein compared to the lead compound, Fudosteine (IC_{50} = 8.43 mmol/L), in the TNF-α-induced NCI-H292 cell model.

Table 1 Fudosteine derivatives inhibit MU5AC.

表 1 福多司坦衍生物抑制 MU5AC

Compound [a]	IC_{50}(mmol/L) [b]	Compound [a]	IC_{50}(mmol/L) [b]
1a	>70	2.5a	18.97
1b	>70	2.5b	39.51
1c	>70	2.5c	>70
1d	7.11	2.5d	>70
1e	5.34	2.5e	1.71
1f	1.05	2.5f	1.08
1g	11.34	2.5g	1.53
1h	>70	2.5h	1.38
1i	2.04	2.5i	>70
1j	8.07	2.5j	1.58
1k	>70	2.5k	>70
1l	>70	2.5l	>70
1m	7.02	2.5m	>70
1n	110.50	Fudosteine	8.43

[a] (synthesis of target compounds) [b] (half inhibitory concentration)

2.4.2 The Antioxidant Capacity of Fudosteine Derivatives

DPPH test of Fudosteine derivatives IC_{50} values indicate the free radical scavenging activity, with lower values reflecting greater antioxidant capability. Table 2 presents the DPPH free radical scavenging abilities of each derivative alongside Fudosteine. The results reveal that all derivatives exhibited higher antioxidant capacity than Fudosteine. Among the series I sulfonamides, compound 1g demonstrated the strongest DPPH scavenging activity, while compound 2.5j showed the highest antioxidant capacity in series II.

Table 2 The DPPH-scavenging action of Fudosteine and its analogues.

表 2 福多司坦及其类似物的 DPPH 清除作用

Compound [a]	IC_{50}(mg/ml) [b]	Compound [a]	IC_{50}(mg/ml) [b]
1a	8.157	2.5a	2.692
1b	5.16	2.5c	3.473
1c	2.176	2.5d	4.314
1d	1.689	2.5e	1.91
1e	2.96	2.5f	0.4976
1f	1.439	2.5g	1.009
1g	0.32	2.5h	0.01264
1h	15.85	2.5i	0.2314
1i	3.889	2.5j	0.003697
1j	0.9764	2.5k	1.138
1k	2.137	2.5l	0.9286
1l	37.2	2.5m	0.5969
1m	6.212	Fudosteine	52.32

[a] (synthesis of target compounds) [b] (half inhibitory concentration).

2.4.3 Fudosteine sulfonamide derivatives inhibit the phosphodiesterase 4A (PDE4A1) enzyme

The inhibitory and antioxidant activities of Fudosteine sulfonamide derivatives on MUC5AC protein were generally limited, possibly because the anti-inflammatory effects of series I derivatives may be mediated through alternative mechanisms. To further explore the anti-inflammatory potential of these derivatives, synthetic Fudosteine derivatives 1a-1n were tested for their inhibitory effects on the PDE4A enzyme. Phosphodiesterase (PDEs) is encoded by 21 genes and generates over 100 distinct isomers, with PDE4 specifically degrading cyclic 3',5'-adenosine monophosphate (cAMP) [28]. Research has indicated that PDE4 inhibitors can effectively reduce inflammation in COPD[29].

The compounds were evaluated at doses of 1 μM and 0.1 μM, using Fudosteine as a control. The experimental results are presented in Table 3 and Figure 2. At a concentration of 0.1 μM, Fudosteine inhibited the PDE4A1 enzyme more effectively than its derivatives. Among the derivatives, 1l exhibited no significant inhibitory effect, while 1d, 1g, 1h, 1m, and 1n demonstrated negative inhibitory effects. At a concentration of 1 μM, derivatives 2.1a, 2.1b, 1d, 2.1e, 1f, 1g, 1h, and 1l inhibited the PDE4A1 enzyme significantly better than the lead compound, Fudosteine. Derivatives 1c, 1j, and 1k showed comparable inhibition rates to Fudosteine. Notably, derivatives 1a, 1d, 1g, 1h, and 1l inhibited the enzyme at double the rate of Fudosteine, with derivative 1e achieving three times the inhibition. The most potent inhibitor was derivative 1f, which exhibited five times the potency of Fudosteine. Molecular docking studies indicated that the binding free energy of 1f with PDE4A1 ProteinData Bank(PDB) (PDB code: 2QYK) is lower (-6.16 kcal/mol) than that of Fudosteine with the same target. The interaction between 1f and PDE4A1 involves four hydrogen bonds: the carbonyl oxygen and amino hydrogen of 1f form hydrogen bonds with Gly315A and Glu606, respectively. Additionally, the naphthalene ring of 1f engages in hydrophobic interactions with Gln454A and Leu453A, while its alkyl side chain effectively binds to Arg469A and Phe461A.

Table 3 The inhibitory rate of Fudosteine series derivatives on PDE4A1 enzyme.

表 3 福多司坦系列衍生物对 PDE 4A1 酶的抑制率

Compound [a]	1 μM rates(%) [b]	0.1 μM rates(%) [b]	Compound [a]	1 μM rates(%) [b]	0.1 μM rates(%) [b]
1a	7.078507	1.930502	1h	9.438009	-1.287

1b	4.075504	4.075504	1i	2.788503	2.359502
1c	3.003003	2.145002	1j	3.646504	2.574003
1d	6.864007	-1.0725	1k	3.646504	0.858001
1e	10.93951	3.217503	1l	7.936508	0
1f	15.44402	2.145002	1m	2.574003	-1.5015
1g	7.293007	-1.287	Fudosteine	3.646504	8.580009

[a] (synthesis of target compounds) [b] (inhibitory rates)

A B

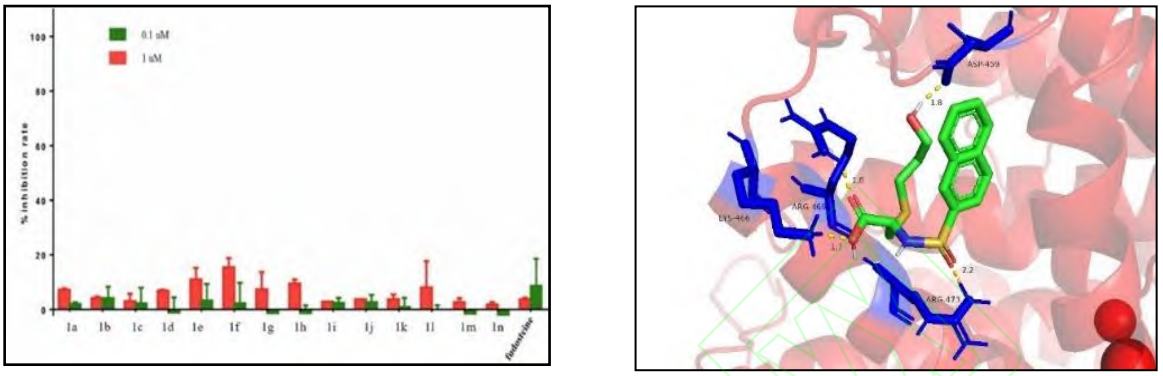


Figure 2 Inhibition rate of Fudosteine series Ⅰ derivatives on PDE4A1enzyme(A)Docking images of compound 1f with PED4A1(B).

图 2 福多司坦系列 Ⅰ 衍生物对 PDE4A1 酶的抑制率（A）化合物 1f 与 PED4A1 的对接图（B）

3 Conclusions

Currently, there are significant gaps in the management of COPD. To develop therapeutic agents with low toxicity and high efficacy, this study synthesized two series of sulfonamide derivatives and Fudosteine amines, enhancing their anti-inflammatory and antioxidant properties. Notably, compound 1f demonstrated superior PDE4 inhibitory and antioxidant activities compared to Fudosteine, while compound 2.5f exhibited a significantly greater inhibitory effect on MUC5AC protein than the lead compound. Additionally, 2.5f showed enhanced free radical scavenging ability. Molecular docking studies revealed that compounds 1f and 2.5f form bidentate hydrogen bonds and engage in hydrophobic interactions with various amino acid residues, which may contribute to their free radical scavenging capabilities. These findings offer new insights and highlight the potential of compound 2.5f for future COPD treatment development. However, its biological mechanisms remain to be fully elucidated. This article lays a theoretical foundation for ongoing research and development of medications for chronic obstructive pulmonary disease and serves as a valuable reference.

4 Experimental section

4.1 Biological activity detection

4.1.1 PDE4A1 enzyme inhibition rate

To prepare the Carboxyfluorescein(FAM)- Cyclic adenosine monophosphate(cAMP) Phosphodiesterase(PDE) IV (FAM-cAMP PDE IV) substrate working solution, add 20 μl of FAM-adenosine cyclophosphatase to 1980 μl of PDE buffer. Dispense 25 μl of this mixture into each well. The compound was dissolved in Dimethyl sulfoxide(DMSO-*d*) to create a 10 mM stock solution, which was then diluted with DMSO-*d* to obtain 100 μM and 10 μM solutions. For the working solutions, mix 5 μl of each diluent with 45 μl of PDE buffer to achieve final concentrations of 10 μM and 1 μM. Each experimental well received 5 μl of the compound solution, while the control wells received 5 μl of 10% DMSO-*d* in PDE buffer. The PDE4A1 recombinant enzyme stock solution was diluted to 12.5 pg/μl using PDE buffer, and 20 μl of this solution was added to all compound and vehicle control wells. For the blank control wells, 20 μl of PDE buffer was used. The reaction was conducted at room temperature for 1 hour. Subsequently, 80 μl of glue was mixed with 7920 μl of adhesive diluent. After thorough mixing, 100 μl of this solution was added to each well and allowed to react at room temperature for another

hour.Finally, FP is read from Envision. The original data computation formula is: inhibition rate (%) = (FPV - FPS) / (FPV - FPB) × 100%. (FPS = Sample FP, FPV = Vehicle Control FP, and FPB = Blank Control FP).

4.1.2 The inhibitory action of MUC5AC protein

Cells can be cultured. NCI-H292 cells were fed and planted into 96-well plates with a density of 2 × 104 cells per well. After the cells had adhered stably, the medications to be evaluated were introduced to each cell hole according to the experimental protocol and incubated for two hours. TNF-α was spotted into each cell well at a final concentration of 20 ng/mL. Place the cell culture plate in the cell incubator and incubate for 24 hours. MUC5AC content in cell supernatant was determined using the MUC5AC kit.

MUC5AC in cell supernatant was identified using ELISA. The compound's mother liquor solution was prepared using ultra-pure DMSO-*d*. The concentration of the first-stage mother liquor was 10 mg/mL, while that of the second-stage mother liquor was 1 mg/mL. The compound's concentration was determined to be 0.5,1.0,3.0,9.0, and 20.0 mg/mL, with the final concentration of DMSO-D being 0.5%, 1.0%, 3.0%, 0.9%, and 2.0%. In the ELISA plate, 100 μL of supernatant from each cell culture plate was spotted and 10 μL of a 10 x sample dilution was added to each well. The plate was then incubated at 4°C for 24 hours. Use the washing solution to clean the microplate five times. Each well received Horseradish Peroxidase（HRP）-conjugated secondary antibody, which was incubated for 30 minutes at room temperature. Use the washing solution to clean the microplate five times. Add the ELISA developer and allow 5-15 minutes to develop. Add the termination liquid. The microplate reader read the data.

Statistical analysis. Because of the considerable disparity in coating between ELISA plates, we created a blank control (3 replicates) for each. The statistical analysis began by comparing the statistical difference between the group with a drug concentration of 0 (BLANK group) and the lowest dose group (0.5mg/mL), followed by the statistical difference between the lowest dose group (0.5mg/mL) and the highest dose group (20mg/mL). If the lowest dose group (0.5mg/mL) was significantly lower than the BLANK group, it meant that the molecule must be active If there was no significant change in the lowest dose group (0.5mg/mL) compared to the BLANK group, but there was a significant difference between the highest dose group (20mg/mL) and the lowest dose group (0.5mg/mL), the substance was still declared active. If there is no significant difference between the highest dose group (20mg/mL) and the lowest dose group (0.5mg/mL), the substance is termed inert.

The statistical analysis was carried out using GraphPad Prism(PRISM 5.0) and Origin 8.5 software. Results were presented as mean ± standard deviation. The Student's t-test was used for statistical analysis of two sets of data, whereas the One-way Analysis of Variance(ANOVA) was employed for statistical analysis of multiple sets. * ($P < 0.05$) or * ($P < 0.01$) indicated a significant difference.

4.1.3 Assessment of DPPH free radical scavenging

The DPPH free radical solution was prepared in methanol to a final concentration of 3×10^{-3} M[30]. Fudosteine served as the positive control for DPPH scavenging. Samples of 200 μl at various concentrations were added to 200 μl of the DPPH solution (3×10^{-3} M) in methanol. The mixture was then incubated in the dark at 37°C for 30 minutes, after which the absorbance was measured at 517 nm. Each experiment was conducted in triplicate.

The formula for calculating DPPH scavenging rate is:

DPPH scavenging rate (%) = $[(A_{cont}-A_{test}) / A_{cont}] \times 100$, where Acont represents the absorbance of the control reaction and Atest is the absorbance of the test sample.

4.2. Chemistry

4.2.1 Materials and methods

Unless otherwise stated, all reagents and solvents are commercially available and can be used without additional treatment. The Varian Unity Inova 400 MHz instrument recorded the ^{1}H NMR and ^{13}C NMR spectra at 400 MHz and 100 MHz, respectively. The chemical shift was determined in ppm (δ), using tetramethylsilane as an internal standard. HRMS spectra were acquired using a Bruker Daltonics ESI-BioTOF Q instrument. Column chromatography was carried out using silica gel (200-300 mesh). Thin layer chromatography was used to observe the reaction on a glass slide that had been covered with GF-254 silica gel. The apparatus and reagents used for biological activity determination are listed below: Thermo Scientific

cell incubator; SpectraMax M5, Molecular Devices microplate reader; nCI-H292 cells from Shanghai Xinyu Biotechnology Co., Ltd.

4.2.2 The general process for preparing N-(ethylsulfonyl)-S-(3-hydroxypropyl)-L-cysteine was as follows:

Fudosteine (1.00 g, 0.006 mol) was dissolved in 30 mL of water, then sodium hydroxide (0.6 g, 0.015 mol) was added to dissolve. Methanesulfonyl chloride (0.64 g, 0.006 mol) was added in an ice bath. After the addition was done, the reaction was brought to room temperature. TCL monitoring indicated that the reaction was complete. The reaction solution was acidified with 2 mol/L hydrochloric acid to a pH of 2. After extraction with ethyl acetate, drying with anhydrous sodium sulfate, filtration, vacuum distillation and drying, white solid 1a was obtained with a yield of 38 %. Compounds 1a-1n were produced using a process identical to that used for 1a.

Synthesis of N- (ethylsulfonyl) -S- (3-hydroxypropyl) -L-cysteine (**1a**). White solid 1a, yield 38 %.^{1}H NMR (400 MHz, DMSO-d_6)δ: 4.01-3.96 (m, 1H), 3.44 (t, J = 6.2 Hz, 2H), 3.01 (s, 4.5 Hz, 3H), 2.87-2.82 (m, 1H), 2.75-2.7 (m, 1H), 2.59 (t, J = 7.4 Hz, 2H), 1.68 – 1.61 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 172.01, 59.32, 56.01, 41.21, 33.98, 32.36, 28.35. HRMS (ESI) calcd for $C_7H_{15}NO_5S_2Na$ [M+Na]+ 280.0289, found 280.0294.

Synthesis of compound S- (3-hydroxypropyl) -N- (propylsulfonyl) -L-cysteine (**1b**). The synthesis method is the same as 1a, white solid, yield 37 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 7.61 (d, J = 6.5 Hz, 1H), 3.91 (d, J = 5.5 Hz, 1H), 3.44 (t, J = 6.2 Hz, 2H), 3.05 – 2.91 (m, 2H), 2.83 (dd, J = 13.7, 5.7 Hz, 1H), 2.70 (dd, J = 13.6, 7.9 Hz, 1H), 2.58 (t, J = 7.3 Hz, 2H), 1.76 – 1.59 (m, 4H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 172.23, 59.41, 56.12, 54.39, 34.17, 32.44, 28.41, 16.97, 12.75. HRMS (ESI) calcd for $C_9H_{19}NO_5S_2Na$ [M+Na]+ 308.0602, found 308.0598.

Synthesis of N- (cyclopropylsulfonyl) -S- (3-hydroxypropyl) -L-cysteine (**1c**).The synthesis method is the same as 1a, white solid 1c, yield 42 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 12.98 (s, 1H), 7.70 (d, J = 9.0 Hz, 1H), 4.48 (s, 1H), 3.93 (dd, J = 15.3, 7.4 Hz, 1H), 3.45 (t, J = 6.2 Hz, 2H), 2.83 (dd, J = 13.7, 6.3 Hz, 1H), 2.74 (dd, J = 13.7, 7.5 Hz, 1H), 2.59 (t, J = 7.3 Hz, 2H), 2.56 – 2.50 (m, 1H), 1.70 – 1.61 (m, 2H), 0.91 (dd, J = 6.9, 4.3 Hz, 4H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 172.35, 59.49, 56.37, 34.13, 32.49, 30.80, 28.45, 5.29, 5.11. HRMS (ESI) calcd for $C_9H_{17}NO_5S_2Na$ [M+Na]+ 306.0446, found 306.0462.

Synthesis of compound S- (3-hydroxypropyl) -N- (phenylsulfonyl) -L-cysteine (**1d**). Fudosteine (1.01 g, 0.006 mol) was dissolved in 30 ml water, sodium hydroxide (0.60 g, 0.015 mol) was added to stir and dissolve, and benzenesulfonyl chloride (1.00 g, 0.006 mol) was added under ice bath conditions. After the addition was completed, the reaction was transferred to room temperature. After the reaction was completed, the reaction solution was acidified with 2 mol / L hydrochloric acid to pH = 2 to precipitate white solids. The white solids were collected by filtration and collected. The white solids were beaten with ethyl acetate, filtered and dried to obtain white solids for 1 d, with a yield of 36 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 12.82 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.3 Hz, 2H), 4.46 (s, 1H), 3.80 (d, J = 7.6 Hz, 1H), 3.38 (t, J = 6.2 Hz, 2H), 2.72 (dd, J = 13.7, 6.6 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.47 – 2.35 (m, 2H), 1.59 – 1.47 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.43, 141.17, 132.55, 129.12, 126.65, 59.40, 56.10, 33.68, 32.29, 28.25. HRMS (ESI) calcd for $C_{12}H_{17}NO_5S_2Na$ [M+Na]+ 342.0446, found 342.0438.

Synthesis of N- ([1,1 ' -biphenyl] -4-ylsulfonyl) -S- (3-hydroxypropyl) -L-cysteine (**1e**). The synthesis method is the same as 1d, white solid, yield 58 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 8.36 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 9.1 Hz, 4H), 7.74 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 3.85 (dd, J = 14.9, 7.1 Hz, 1H), 3.37 (t, J = 6.2 Hz, 2H), 2.75 (dd, J = 13.8, 6.5 Hz, 1H), 2.58 (dd, J = 13.7, 7.3 Hz, 1H), 2.48 – 2.38 (m, 2H), 1.59 – 1.45 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.45, 143.94, 139.93, 138.63, 129.25, 128.60, 127.38, 127.23, 127.15, 59.37, 56.08, 33.66, 32.26, 28.25. HRMS (ESI) calcd for $C_{18}H_{21}NO_5S_2Na$ [M+Na]+ 418.0759, found 418.0735.

Synthesis of compound S- (3-hydroxypropyl) -N- (naphthalen-2-ylsulfonyl) -L-cysteine (**1f**). The synthesis method is the same as 1d, rice white solid, yield 50 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 12.82 (s, 1H), 8.42 (d, J = 9.1 Hz, 2H), 8.12 (dd, J = 18.1, 8.3 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 8.7, 1.9 Hz, 1H), 7.75 – 7.60 (m, 2H), 4.42 (s, 1H), 3.87 (dd, J = 15.5, 7.1 Hz, 1H), 3.33 (s, 2H), 2.73 (dd, J = 13.7, 6.5 Hz, 1H), 2.55 (dd, J = 13.7, 7.4 Hz, 1H), 2.38 (dd, J = 20.4, 12.7, 7.7 Hz, 2H), 1.53 – 1.35 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.41, 138.16, 134.29, 131.72, 129.34, 129.22, 128.78, 127.90, 127.59, 127.32, 122.66, 59.30, 56.11, 33.68, 32.19, 28.21. HRMS (ESI) calcd for $C_{16}H_{19}NO_5S_2Na$

[M+Na]+ 392.0602, found 392.0577.

Synthesis of compound S- (3-hydroxypropyl) -N-tosyl-L-cysteine (**1g**). The synthesis method is the same as 1d, white solid, yield 46 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 12.81 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.46 (s, 1H), 3.77 (dd, J = 15.3, 7.0 Hz, 1H), 3.38 (t, J = 6.2 Hz, 2H), 2.71 (dd, J = 13.7, 6.7 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.48 – 2.38 (m, 2H), 2.38 (dd, J = 2.7 Hz, 3H), 1.56 – 1.47 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.45, 142.78, 138.30, 129.55, 126.74, 59.42, 56.03, 33.63, 32.29, 28.24, 21.13. HRMS (ESI) calcd for $C_{13}H_{19}NO_5S_2Na$ [M+Na]+ 356.0602, found 356.0601.

Synthesis of S- (3-hydroxypropyl) -N- ((4-methoxyphenyl) sulfonyl) -L-cysteine (**1h**). synthesis method is the same as 1d, white solid, yield 48 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 12.82 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 4.46 (s, 1H), 3.82 (s, 3H), 3.78 – 3.71 (m, 1H), 3.38 (t, J = 5.9 Hz, 2H), 2.70 (dd, J = 13.7, 6.8 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.47 – 2.35 (m, 2H), 1.57 – 1.48 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.50, 162.27, 132.78, 128.91, 114.23, 59.41, 56.01, 55.75, 33.62, 32.30, 28.25. HRMS (ESI) calcd for $C_{13}H_{19}NO_6S_2Na$ [M+Na]+ 372.0551, found 372.0571.

Synthesis of N- ((4-fluorophenyl) sulfonyl) -S- (3-hydroxypropyl) -L-cysteine (**1i**). The synthesis method is the same as 1a, white solid, yield 66 %.^{1}H NMR (400 MHz, DMSO- d_6)) δ: 12.86 (s, 1H), 8.37 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 8.9, 5.2 Hz, 2H), 7.40 (t, J = 8.9 Hz, 2H), 4.46 (s, 1H), 3.81 (dd, J = 15.1, 7.5 Hz, 1H), 3.39 (t, J = 6.2 Hz, 2H), 2.74 (dd, J = 13.8, 6.3 Hz, 1H), 2.58 (dd, J = 13.7, 7.5 Hz, 1H), 2.48 – 2.38 (m, 2H), 1.58 – 1.50 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.36, 162.97, 137.59, 129.77, 116.30, 59.37, 56.08, 33.71, 32.28, 28.25. HRMS (ESI) calcd for $C_{12}H_{16}FNO_5S_2Na$ [M+Na]+ 360.0352, found 360.0408.

Synthesis of N- (benzylsulfonyl) -S- (3-hydroxypropyl) -L-cysteine (**1j**).Synthesis method is the same as 1a, white solid, yield 52 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 13.02 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 1.9 Hz, 2H), 7.36 (d, J = 5.4 Hz, 2H), 7.35 (s, 1H), 4.49 (s, 1H), 4.41 – 4.31 (m, 2H), 3.95 (dd, J = 15.0, 6.8 Hz, 1H), 3.45 (t, J = 6.2 Hz, 2H), 2.80 (dd, J = 13.7, 6.3 Hz, 1H), 2.69 (dd, J = 13.7, 7.1 Hz, 1H), 2.57 (t, J = 7.3 Hz, 2H), 1.64 (dt, J = 13.1, 6.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 172.17, 131.03, 130.25, 128.37, 128.13, 59.44, 58.78, 56.22, 34.01, 32.45, 28.46. HRMS (ESI) calcd for $C_{13}H_{19}NO_5S_2Na$ [M+Na]+ 356.0602, found 356.0561.

Synthesis of N- (N, N-dimethylsulfamoyl) -S- (3-hydroxypropyl) -L-cysteine (**1k**). The synthesis method is the same as 1a, white solid, yield 36 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 7.77 (d, J = 9.1 Hz, 1H), 3.86 (dd, J = 14.9, 8.0 Hz, 1H), 3.50 (t, J = 6.2 Hz, 2H), 2.85 (dd, J = 13.6, 6.1 Hz, 1H), 2.76 (dd, J = 13.6, 7.9 Hz, 1H), 2.71 (s, 6H), 2.62 (dd, J = 13.7, 6.3 Hz, 2H), 1.74 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 172.39, 59.41, 56.76, 37.71, 33.81, 32.38, 28.40. HRMS (ESI) calcd for $C_8H_{18}N_2O_5S_2Na$ [M+Na]+ 309.0555, found 309.0583.

Synthesis of compound S- (3-hydroxypropyl) -N- (thiophen-2-ylsulfonyl) -L-cysteine (**1l**). The synthesis method is the same as 1d, white solid, yield 50 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 12.92 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 7.90 (dd, J = 5.0, 1.4 Hz, 1H), 7.58 (dd, J = 3.7, 1.4 Hz, 1H), 7.15 (dd, J = 5.0, 3.7 Hz, 1H), 4.47 (s, 1H), 3.85 (q, J = 7.3 Hz, 1H), 3.40 (t, J = 6.2 Hz, 2H), 2.75 (dd, J = 13.8, 6.5 Hz, 1H), 2.57 (dd, J = 13.7, 7.4 Hz, 1H), 2.45 (td, J = 7.1, 2.8 Hz, 2H), 1.60 – 1.52 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.32, 141.96, 132.70, 131.88, 127.60, 59.39, 56.23, 33.51, 32.29, 28.28. HRMS (ESI) calcd for $C_{10}H_{15}NO_5S_3Na$ [M+Na]+ 348.0010, found 348.0062.

Synthesis of compound S- (3-hydroxypropyl) -N- ((5- (methoxycarbonyl) thiophen-3-yl) sulfonyl) -L-cysteine (**1m**). ^{1}H NMR (400 MHz, DMSO- d_6)) δ: 13.05 (s, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 4.46 (s, 1H), 4.05 (dd, J = 13.6, 6.8 Hz, 1H), 3.87 (s, 3H), 3.40 (t, J = 6.2 Hz, 2H), 2.86 – 2.75 (m, 2H), 2.46 (d, J = 7.8 Hz, 2H), 1.61 – 1.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6)) δ: 171.26, 160.36, 144.20, 132.00, 131.63, 130.18, 59.40, 56.12, 53.28, 34.19, 32.36, 28.37. HRMS (ESI) calcd for $C_{12}H_{17}NO_7S_3Na$ [M+Na]+ 406.0065, found 406.0070.

Synthesis of N- ((5-chlorothiophen-2-yl) sulfonyl) -S- (3-hydroxypropyl) -L-cysteine (**1n**). ^{1}H NMR (400 MHz, DMSO- d_6) δ: 13.00 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 4.0 Hz, 1H), 7.22 (d, J = 4.0 Hz, 1H), 4.47 (s, 1H), 3.87 (dd, J = 14.0, 7.7 Hz, 1H), 3.41 (t, J = 5.9 Hz, 2H), 2.79 (dd, J = 13.8, 5.9 Hz, 1H), 2.62 (dd, J = 13.8, 7.9 Hz, 1H), 2.49 – 2.43 (m, 2H), 1.63 – 1.52 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 171.25, 140.49, 134.57, 131.74, 127.81, 59.41,

56.27, 33.64, 32.31, 28.36. HRMS (ESI) calcd for $C_{10}H_{14}ClNO_5S_3Na$ [M+Na]+ 381.9620, found 381.9627.

4.2.3 Synthesis of benzyl S- (3-hydroxypropyl) -L-cysteinate (2.1)

Under argon protection, benzyl alcohol (43.00 ml, 413 mmol, 15 eq.) was added to a three-necked round-bottom flask and cooled to-10 C.Subsequently, thionyl chloride (6.00 ml, 82.60 mmol, 3 eq.) was slowly added drop by drop to the reaction system at-10 C. The temperature of the reaction system was controlled not to exceed 0 C.After the addition of Fudosteine (5.00 g, 27.90 mmol, 1 eq.), the reaction was slowly heated to 60 °C and refluxed for 2 h. The excess thionyl chloride was removed by vacuum distillation to obtain a yellow oily liquid. The yellow oily liquid was separated and purified by column chromatography (dichloromethane : methanol = 100 : 1) to obtain yellow oily substance 2.1 with a yield of 51 %..^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.39 – 7.30 (m, 5H), 5.16 (d, J = 4.1 Hz, 2H), 3.70 (d, J = 7.1 Hz, 1H), 3.53 (t, J = 6.1 Hz, 2H), 2.87 (ddd, J = 20.6, 13.4, 5.8 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 1.86 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.4, 135.3, 128.7, 67.1, 54.7, 36.3, 32.6, 29.8.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3-hydroxypropyl) -L-cysteinate (**2.2**). Compound 2.1 (5.00 g, 18.6 mmol, 1eq.) was dissolved in dichloromethane and added to a three-necked round-bottom flask below 0 °C, and triethylamine (5.15 mL, 372 mmol, 2eq.) was slowly added. After dropping, Boc anhydride (6.49 g, 29.7 mmol) was added. Remove the ice bath and stir at room temperature until the TLC detection reaction is complete. The reaction solution was washed three times with saturated sodium carbonate solution and saturated sodium chloride respectively, dried with anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column (petroleum ether : ethyl acetate = 5 : 1) to obtain yellow oil 2.2 with a yield of 50 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 – 7.06 (m, 5H), 5.17 (q, J = 12.2 Hz, 2H), 4.56 (dd, J = 13.2, 5.5 Hz, 1H), 3.74 – 3.55 (m, 2H), 2.93 (ddd, J = 19.8, 13.9, 5.4 Hz, 2H), 2.68 – 2.50 (m, 2H), 1.74 (tq, J = 14.2, 7.2 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ: 171.28, 156.31, 135.67, 128.17, 127.92 , 79.46, 59.98, 53.89, 33.11, 27.26.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- ((methylsulfonyl) oxy) propyl) -L-cysteinate (**2.3**). Under the protection of argon, compound 2.2 (6.00 g, 16.30 mmol, 1eq.) was dissolved in dichloromethane and added to a three-necked round-bottom flask at 0 °C, and triethylamine (11.33 mL, 81 mmol, 5eq.) was slowly added. After dropping, methylsulfonyl chloride (5.00 mL, 65 mmol, 4eq.) was slowly added, the ice bath was removed, and the room temperature was stirred at 25 °C for 2.5 hours. The reaction was completely detected by TLC. The sulfonate was filtered out, dissolved in dichloromethane, washed with saturated sodium chloride, dried with anhydrous sodium sulfate, and finally separated and purified by silica gel column (petroleum ether : ethyl acetate = 5 : 1) to obtain yellow oil 2.3, with a yield of 99 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 – 7.27 (m, 5H), 5.26 – 5.11 (m, 2H), 4.54 (t, J = 16.7 Hz, 1H), 4.34 – 4.15 (m, 2H), 3.08 – 2.85 (m, 5H), 2.70 – 2.48 (m, 2H), 2.03 – 1.85 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.65, 155.09, 135.13, 128.60, 128.32, 80.09, 68.01, 67.39, 53.51, 37.22, 34.33, 28.65, 28.17.

Synthesis of benzyl S- (3- ((2- (benzo [d] [1,3] dioxol-5-yl) ethyl) amino) propyl) -N- (tert-butoxycarbonyl) -D-cysteinate (**2.4a ~ 2.4m**). 2.3 (0.50g, 1.10mmol, 1eq.), potassium carbonate (0.36g, 2.60mmol, 3eq.), KI (0.56g, 3.40mmol, 0.1eq.), piperonylamine (0.25mL, 2.2mmol, 1.2eq.) were dissolved in acetonitrile and added to a three-necked round-bottom flask, and refluxed at 80 °C until the TLC detection reaction was complete. The compound was isolated and purified by silica gel column chromatography (petroleum ether : ethyl acetate (v / v) = 3 : 1) to obtain a compound yellow oil 2.4a was 0.54 g, and the yield was 94 %. Similarly, compounds 2.4b ~ 2.4n were prepared. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 – 7.25 (m, 5H), 6.73 – 6.62 (m, 3H), 5.90 (d, J = 5.6 Hz, 3H), 5.22 – 5.06 (m, 2H), 3.73 – 3.58 (m, 1H), 2.97 – 2.38 (m, 12H), 1.70 (td, J = 14.5, 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.4, 147.9, 146.6, 135.3, 130.4, 128.7, 128.3, 121.7, 109.0, 108.5, 101.0, 67.1, 54.7, 49.6, 46.4, 36.3, 32.6, 29.8, 25.9.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- ((furan-2-ylmethyl) amino) propyl) -L-cysteinate (**2.4b**). The synthesis method is the same as 2.4 a, yellow oil, yield 67 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 – 7.18 (m, 6H), 6.33 – 6.25 (m, 1H), 6.14 (d, J = 3.0 Hz, 1H), 5.16 (d, J = 8.7 Hz, 2H), 4.65 – 4.47 (m, 1H), 3.73 (s, 2H), 2.94 (d, J = 4.8 Hz, 2H), 2.63 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 1.68 (dt, J = 14.4, 7.2 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.1, 155.3, 153.8, 141.8, 135.2, 128.7, 110.2, 106.9, 80.1, 67.4, 53.6, 47.4, 46.0, 34.5, 30.5, 29.5, 28.4.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (4-methylpiperazin-1-yl) propyl) -L-cysteinate (**2.4c**). The synthesis method is the same as 2.4 a, yellow oily substance, yield 71 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 – 7.17 (m, 5H), 5.14 (q, J = 12.3 Hz, 2H), 4.53 (d, J = 6.4 Hz, 1H), 2.90 (d, J = 17.7 Hz, 2H), 2.66 – 2.07 (m, 15H), 1.71 – 1.61 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.0, 155.2, 135.2, 128.8, 80.1, 67.4, 57.1, 55.1, 53.5, 53.2, 46.1, 34.6, 30.6, 28.4, 26.8.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (cyclohexylamino) propyl) -L-cysteinate (**2.4d**). The synthesis method is the same as 2.4 a, yellow oil, yield 75 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 – 7.12 (m, 5H), 5.17 (q, J = 12.3 Hz, 2H), 4.55 (s, 1H), 2.95 (s, 2H), 2.58 (dt, J = 48.9, 7.0 Hz, 4H), 2.37 (t, J = 10.3 Hz, 1H), 1.84 (d, J = 11.5 Hz, 2H), 1.78 – 1.62 (m, 4H), 1.57 – 1.31 (m, 9H), 1.29 – 0.92 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.1, 135.3, 128.8, 67.5, 56.9, 53.6, 45.7, 34.64, 33.1, 30.8, 30.3, 28.4, 26.3, 25.2.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3-morpholinopropyl) -L-cysteinate (**2.4e**). The synthesis method is the same as 2.4 a, yellow oily substance, yield 58 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 – 7.20 (m, 5H), 5.15 (q, J = 12.3 Hz, 2H), 4.52 (s, 1H), 3.75 (s, 4H), 2.94 (s, 2H), 2.65 – 2.32 (m, 8H), 1.84 – 1.71 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (151 MHz, CDCl3) δ: 170.99, 155.16, 135.11, 128.60, 128.49, 128.37, 80.17, 67.28, 66.84, 57.29, 53.65, 53.52, 34.59, 30.50, 28.32, 26.37.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (piperidin-1-yl) propyl) -L-cysteinate (**2.4f**). The synthesis method is the same as that of 2.4a, yellow oil, with a yield of 66 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 – 7.23 (m, 5H), 5.26 – 5.07 (m, 2H), 4.55 (d, J = 6.1 Hz, 1H), 2.97 (t, J = 15.9 Hz, 2H), 2.56 – 2.18 (m, 8H), 1.74 – 1.64 (m, 2H), 1.59 – 1.35 (m, 15H). ^{13}C NMR (151 MHz, CDCl3) δ: 171.02, 155.18, 135.24, 128.59, 128.46, 128.37, 80.06, 67.14, 57.79, 54.58, 53.50, 34.42, 30.83, 28.26, 26.82, 25.91, 24.30.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (dimethylamino) propyl) -L-cysteinate (**2.4g**). The synthesis method is the same as 2.4 a, yellow oil, yield 88 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J = 32.7 Hz, 5H), 5.17 (q, J = 12.4 Hz, 2H), 4.56 (s, 1H), 2.96 (s, 2H), 2.60 – 2.20 (m, 8H), 1.63 (t, J = 14.1 Hz, 2H), 1.52 – 1.28 (m, 9H), 1.11 – 0.68 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.82, 155.20, 135.19, 128.18, 79.94, 66.80, 53.65, 50.95, 46.21, 34.06, 30.99, 28.28, 26.62, 12.23.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (cyclopropylamino) propyl) -L-cysteinate (**2.4h**). The synthesis method is the same as 2.4 a, yellow oil, yield 53 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 – 7.21 (m, 5H), 5.16 (q, J = 12.3 Hz, 2H), 4.54 (s, 1H), 2.91 (t, J = 16.4 Hz, 2H), 2.70 (t, J = 6.9 Hz, 2H), 2.53 (dot, J = 14.3, 6.9 Hz, 2H), 2.06 (dd, J = 6.1, 2.5 Hz, 1H), 1.68 (dt, J = 14.0, 7.0 Hz, 2H), 1.46 (d, J = 30.4 Hz, 9H), 0.55 – 0.22 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.23, 135.17, 128.46, 128.34, 112.14, 79.83, 66.93, 54.21, 53.13, 36.13, 34.44, 30.76, 28.19, 26.67, 6.62.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (p-tolylamino) propyl) -L-cysteinate (**2.4i**). The synthesis method is the same as 2.4a.Yellow solid, yield 73 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J = 38.5 Hz, 5H), 6.99 (d, J = 8.0 Hz, 2H), 6.54 (d, J = 8.0 Hz, 2H), 5.19 (q, J = 12.2 Hz, 2H), 4.58 (s, 1H), 3.19 (dt, J = 13.3, 6.8 Hz, 2H), 3.04 – 2.88 (m, 2H), 2.67 – 2.48 (m, 2H), 2.24 (s, 3H), 1.90 – 1.74 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.06, 155.29, 155.04, 145.71, 135.09, 129.67, 128.57, 128.53, 128.43, 126.68, 112.97, 80.05, 67.22, 53.34, 42.76, 34.58, 29.96, 28.72, 28.06, 20.39.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- ((4-methoxyphenyl) amino) propyl) -L-cysteinate (**2.4j**). The synthesis method is the same as 2.4 a, yellow oil, yield 68 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J = 36.7 Hz, 5H), 6.84 – 6.48 (m, 4H), 5.18 (q, J = 12.3 Hz, 2H), 4.58 (s, 1H), 3.74 (s, 3H), 3.14 (dd, J = 16.9, 10.3 Hz, 2H), 3.04 – 2.89 (m, 2H), 2.68 – 2.50 (m, 2H), 1.89 – 1.74 (m, 2H), 1.36 (d, J = 63.6 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.85, 152.11, 142.08, 135.00, 128.61, 128.52, 128.37, 115.04, 114.21, 112.05, 79.83, 67.57, 55.67, 53.39, 43.41, 34.32, 29.90, 28.78, 28.14.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- ((thiophen-2-ylmethyl) amino) propyl) -L-cysteinate (**2.4k**). The synthesis method is the same as 2.4 a, light yellow oily substance, yield 77 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J = 35.3 Hz, 5H), 7.19 (d, J = 4.2 Hz, 1H), 6.91 (dd, J = 18.6, 11.4 Hz, 2H), 5.18 (q, J = 12.2 Hz, 2H), 4.63 – 4.48 (m, 1H),

3.95 (s, 2H), 2.96 (s, 2H), 2.76 – 2.47 (m, 4H), 1.77 – 1.64 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.94, 155.02, 143.87, 135.10, 128.46, 128.38, 128.34, 126.67, 124.66, 124.32, 79.73, 67.34, 53.27, 47.78, 47.07, 34.64, 30.26, 29.33, 28.03.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (butylamino) propyl) -L-cysteinate (**2.4l**). The synthesis method is the same as 2.4 a, light yellow oily substance, yield 74 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J = 34.2 Hz, 4H), 5.17 (q, J = 12.3 Hz, 2H), 4.56 (s, 1H), 2.95 (s, 2H), 2.70 – 2.44 (m, 6H), 1.70 (dd, J = 13.8, 6.8 Hz, 2H), 1.43 (s, 9H), 1.34 – 1.22 (m, 2H), 0.99 – 0.77 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.61, 156.07, 151.43, 134.71, 128.32, 67.14, 53.45, 49.29, 47.67, 34.36, 31.47, 30.52, 28.98, 28.11, 20.53, 13.70.

Synthesis of benzyl N- (tert-butoxycarbonyl) -S- (3- (naphthalen-1-ylamino) propyl) -L-cysteinate (**2.4m**). The synthesis method is the same as 2.4 a, light yellow oily substance, yield 66 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (dd, J = 18.3, 7.9 Hz, 3H), 7.52 – 7.21 (m, 8H), 6.60 (d, J = 7.4 Hz, 1H), 5.19 (dd, J = 24.6, 12.2 Hz, 2H), 4.64 (s, 1H), 3.38 (dd, J = 17.4, 11.2 Hz, 2H), 3.01 (dt, J = 13.3, 7.6 Hz, 2H), 2.76 – 2.58 (m, 2H), 1.98 (dd, J = 12.9, 6.4 Hz, 2H), 1.54 (d, J = 62.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.25, 142.14, 135.08, 134.40, 128.56, 126.36, 125.74, 124.89, 123.66, 120.90, 120.01, 119.00, 117.30, 117.16, 109.69, 104.22, 80.34, 67.41, 53.22, 42.63, 34.69, 30.35, 28.59, 28.34.

Synthesis of compound S- (3- ((2- (benzo [d] [1,3] dioxol-5-yl) ethyl) amino) propyl) -N-methyl-D-cysteine (**2.5a**). The compound 2.4a (0.61g, 1.20mmol, 1eq.) was dissolved in dichloromethane and added to a three-necked round bottom flask. Stir at 0 °C, add trifluoroacetic acid (5.00ml, 488mmol, 41eq.) to the reaction system, stir at room temperature, concentrate the reaction solution under reduced pressure, add ethyl acetate (30ml) to dissolve, wash with saturated sodium bicarbonate (3 × 15ml), dry the organic layer with anhydrous sodium sulfate, and concentrate under reduced pressure to obtain a yellow oily substance. 10 % palladium carbon (0.66g) was added to the three-necked round bottom flask, and the air in the reaction flask was replaced with a double-row tube. The system was placed in an argon atmosphere, and then replaced with hydrogen for three times. Methanol was added to the hydrogen balloon and stirred at 35 °C. The reaction system was reacted in a hydrogen environment for 72 hours, and the reaction was completely detected by TLC. The palladium carbon was removed by filtration, and the filtrate was vacuum distilled to obtain a yellow oil. Compound 2.5a was isolated and purified by silica gel column (dichloromethane : methanol (v / v) = 20 : 1) with a yield of 66 %. Similarly, compounds 2.5b ~ 2.5n were prepared. ^{1}H NMR (400 MHz, DMSO- d_6) δ: 6.78 (d, J = 4.8 Hz, 2H), 6.63 (d, J = 7.8 Hz, 1H), 5.93 (s, 2H), 3.55 (d, J = 42.6 Hz, 4H), 3.05 – 2.53 (m, 12H), 1.67 – 1.52 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 174.6, 147.2, 145.4, 133.9, 121.4, 109.0, 108.1, 100.6, 54.5, 51.6, 50.9, 47.7, 36.34, 35.15, 29.54, 29.12. HRMS (ESI) calcd for $C_{16}H_{24}N_2O_4S$ $[M+H]^+$ 341.1530, found 341.1589.

Synthesis of compound S- (3- ((furan-2-ylmethyl) amino) propyl) -N-methyl-D-cysteine (**2.5b**). The synthesis method is the same as that of 2.5a, yellow oil, and the yield is 49 %.^{1}H NMR (400 MHz, DMSO- d_6) δ: 7.52 (s, 1H), 6.28 (d, J = 55.4 Hz, 2H), 3.82 – 3.55 (m, 4H), 3.61 (s, 2H),2.72 (td, J = 13.2, 6.7 Hz, 6H), 1.60 (dt, J = 13.6, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 173.97, 153.84, 141.80, 110.13, 106.91, 66.98, 54.36, 47.73, 46.13, 37.27, 30.44, 29.77. HRMS (ESI) calcd for $C_{12}H_{21}N_2O_3S$ $[M+H]^+$ 273.1267, found 273.1251.

Synthesis of N-methyl-S- (3- (4-methylpiperazin-1-yl) propyl) -D-cysteine (**2.5c**). The synthesis method is the same as that of 2.5a, yellow oil, and the yield is 52 %.^{1}H NMR (400 MHz, CD_3OD) δ: 3.74 (s, 3H), 3.69 (t, J = 6.0 Hz, 1H), 2.97 – 2.43 (m, 12H), 2.37 (s, 3H), 1.83 – 1.75 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 175.29, 57.81, 55.31, 54.89, 53.25, 52.76, 45.60, 37.23, 30.99, 27.34. HRMS (ESI) calcd for $C_{12}H_{26}N_3O_2S$ $[M+H]^+$ 276.1740, found 276.1738.

Synthesis of compound S- (3- (cyclohexylamino) propyl) -N-methyl-D-cysteine (**2.5d**). The synthesis method is the same as that of 2.5a, yellow oil, and the yield is 55 %.^{1}H NMR (400 MHz, CD_3OD) δ: 3.73 (dd, J = 10.6, 3.0 Hz, 4H), 3.16 – 2.79 (m, 5H), 2.67 (t, J = 6.8 Hz, 2H), 2.12 (s, 2H), 1.93 (dd, J = 23.8, 16.4 Hz, 4H), 1.30 (ddd, J = 33.0, 20.5, 10.8 Hz, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ: 57.06, 54.31, 53.55, 43.09, 39.17, 35.44, 33.35, 29.00, 28.76, 28.62, 26.02, 25.78, 24.84, 24.69, 24.29, 24.06. HRMS (ESI) calcd for $C_{13}H_{27}N_2O_2S$ $[M+H]^+$ 275.1788, found 275.1786.

Synthesis of N-methyl-S- (3-morpholinopropyl) -D-cysteine (**2.5e**). The synthesis method is the same as 2.5a, yellow solid, yield 75 %. m.p.80-81℃.^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 3.65 (t, J = 6.0 Hz, 1H) 3.55 (s, 4H), 2.94

(s, 2H), 2.65 – 2.32 (m, 8H), 1.84 – 1.71 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.98, 70.19, 67.43, 66.15, 60.19, 34.58, 30.31, 28.36, 25.55. HRMS (ESI) calcd for $C_{11}H_{23}N_2O_3S$ $[M+H]^+$ 263.1424, found 263.1420.

Synthesis of N-methyl-S- (3- (piperidin-1-yl) propyl) -D-cysteine (**2.5f**). The synthesis method is the same as that of 2.5a, yellow oil, and the yield is 47 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (s, 3H), 3.60 (dd, J = 7.3, 4.7 Hz, 1H), 2.87 (dd, J = 13.5, 4.6 Hz, 1H), 2.71 (dd, J = 13.5, 7.5 Hz, 1H), 2.51 (t, J = 7.3 Hz, 2H), 2.31 (t, J = 7.2 Hz, 6H), 1.77 – 1.67 (m, 2H), 1.57 – 1.47 (m, 4H), 1.37 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.56, 58.03, 54.61, 54.19, 52.24, 37.36, 30.66, 26.95, 25.95, 24.43. HRMS (ESI) calcd for $C_{11}H_{23}N_2O_3S$ $[M+H]^+$ 261.1631, found 261.1634.

Synthesis of compound S- (3- (dimethylamino) propyl) -N-methyl-D-cysteine (**2.5g**). The synthesis method is the same as that of 2.5a, yellow oil, with a yield of 67 %.^{1}H NMR (400 MHz, CD_3OD) δ: 3.83 – 3.58 (m, 4H), 2.87 (ddd, J = 20.1, 13.6, 6.0 Hz, 2H), 2.64 (dq, J = 27.7, 7.0 Hz, 8H), 1.79 (dt, J = 14.7, 7.2 Hz, 2H), 1.11 (t, J = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ: 175.44, 54.98, 52.65, 52.29, 47.93, 37.47, 31.09, 26.73, 10.97. HRMS (ESI) calcd for $C_{11}H_{25}N_2O_2S$ $[M+H]^+$ 249.1631, found 249.1634.

Synthesis of compound S- (3- (cyclopropylamino) propyl) -N-methyl-D-cysteine (**2.5h**). The synthesis method is the same as that of 2.5a, yellow oil, and the yield is 54 %.^{1}H NMR (400 MHz, CD_3OD) δ: 3.74 (s, 3H), 3.65 (t, J = 6.0 Hz, 1H), 2.95 – 2.49 (m, 6H), 2.15 (ddd, J = 10.4, 6.9, 3.7 Hz, 1H), 1.83 – 1.73 (m, 2H), 0.58 – 0.27 (m, 4H). ^{13}C NMR (101 MHz, CD_3OD) δ: 175.4, 54.9, 52.6, 37.4, 31.1, 30.1, 5.9. HRMS (ESI) calcd for $C_{10}H_{21}N_2O_2S$ $[M+H]^+$ 233.1318, found 233.1316.

Synthesis of N-methyl-S- (3- (p-tolylamino) propyl) -D-cysteine (**2.5i**). The synthesis method is the same as 2.5a, yellow solid, yield 69 %. m.p.57-59℃.^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (d, J = 8.2 Hz, 2H), 6.54 (d, J = 8.2 Hz, 2H), 3.88 – 3.50 (m, 4H), 3.31 – 3.11 (m, 2H), 3.01 – 2.56 (m, 4H), 2.23 (s, 3H), 1.94 – 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 145.8, 129.7, 126.6, 113.0, 54.2, 52.3, 42.9, 37.3, 30.2, 29.1, 20.4. HRMS (ESI) calcd for $C_{14}H_{23}N_2O_2S$ $[M+H]^+$ 283.1475, found 283.1473.

Synthesis of compound S- (3- ((4-methoxyphenyl) amino) propyl) -N-methyl-D-cysteine (**2.5j**). The synthesis method is the same as 2.5a, yellow solid, yield 70 %. m.p.59-61℃.^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.67 (dd, J = 77.4, 8.7 Hz, 4H), 3.79 – 3.56 (m, 7H), 3.26 – 3.06 (m, 2H), 3.01 – 2.69 (m, 2H), 2.73 – 2.55 (m, 2H), 2.32 (s, 3H), 1.86 (p, J = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 152.1, 142.3, 114.9, 114.1, 55.8, 54.2, 52.3, 43.6, 37.2, 30.2, 29.2. HRMS (ESI) calcd for $C_{14}H_{23}N_2O_3S$ $[M+H]^+$ 299.1424, found 299.1425.

Synthesis of N-methyl-S- (3- ((thiophen-2-ylmethyl) amino) propyl) -D-cysteine (**2.5k**). The synthesis method is the same as that of 2.5a, yellow oil, yield 72 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (d, J = 4.8 Hz, 1H), 6.98 – 6.85 (m, 2H), 3.97 (s, 2H), 3.82 – 3.55 (m, 4H), 2.82 (ddd, J = 23.4, 13.4, 5.3 Hz, 4H), 2.60 (t, J = 7.1 Hz, 2H), 1.76 (dd, J = 13.8, 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 143.8, 126.6, 124.9, 124.3, 109.9, 54.1, 52.2, 48.2, 47.6, 37.2, 30.3, 29.7. HRMS (ESI) calcd for $C_{12}H_{21}N_2O_2S_2$ $[M+H]^+$ 289.1039, found 289.1039.

Synthesis of compound S- (3- (butylamino) propyl) -N-methyl-D-cysteine (**2.5l**). The synthesis method is the same as that of 2.5a, yellow oil, and the yield is 65 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (s, 4H), 3.19 – 2.43 (m, 8H), 2.09 – 1.88 (m, 2H), 1.64 (dd, J = 14.7, 7.3 Hz, 2H), 1.36 (dd, J = 14.6, 7.3 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.8, 172.3, 162.3, 145.8, 118.1, 115.5, 115.2, 113.1, 54.3, 52.4, 47.8, 46.3, 36.1, 29.6, 27.9, 25.4, 19.9, 13.5. HRMS (ESI) calcd for $C_{11}H_{25}N_2O_2S$ $[M+H]^+$ 249.1631, found 249.1629.

Synthesis of N-methyl-S- (3- (naphthalen-1-ylamino) propyl) -D-cysteine (**2.5m**). The synthesis method is the same as 2.5a, yellow oil, yield 59 %.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (t, J = 9.0 Hz, 2H), 7.54 – 7.14 (m, 4H), 6.61 (d, J = 7.4 Hz, 1H), 3.85 – 3.56 (m, 4H), 3.40 (t, J = 6.2 Hz, 2H), 3.05 – 2.62 (m, 4H), 2.04 (dd, J = 12.6, 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4 , 143.2 , 134.3 , 128.6 , 126.6, 125.7, 124.7, 123.4, 119.9, 117.3, 104.2 , 54.2, 52.3, 42.9, 37.2, 30.4, 29.7, 28.8. HRMS (ESI) calcd for $C_{17}H_{23}N_2O_2S$ $[M+H]^+$ 319.1475, found 319.1473.

Supporting Information:The spectra such as ^{1}H NMR, ^{13}C NMR and HMRS are all provided by relevant supporting information to ensure the accuracy and reliability of the data.

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References

[1] Sahu, S. K.;Rain, M. D. M.;Vyas, M. *Eur. J. Med. Chem. Rep.* **2024**, *11*, 100159.

[2] Fricke-Galindo, I.;Garcia-Carmona, S.;Alanis-Ponce, J.;Perez-Rubio, G.;Ramirez-Venegas, A.;Montiel-Lopez, F.;Robles-Hernandez, R.;Hernandez-Zenteno, R. J.;Valencia-Perez Rea, D.;Bautista-Becerril, B.;Ramirez-Diaz, M. E.;Cruz-Vicente, F.;Martinez-Gomez, M. L.;Sansores, R.;Falfan-Valencia, R. *Heliyon.* **2024**, *10*, e28675.

[3] Zeng, X.;Lan, Y.;Xiao, J.;Hu, L.;Tan, L.;Liang, M.;Wang, X.;Lu, S.;Peng, T.;Long, F. *Expert Rev. Proteomics.* **2023**, *19*, 311-324.

[4] Yadav, A. K.;Gu, W.;Zhang, T.;Xu, X.;Yu, L. *COPD: Journal of Chronic Obstructive Pulmonary Disease.* **2023**, *20*, 197-209.

[5] Doña, E.;Reinoso-Arija, R.;Carrasco-Hernandez, L.;Doménech, A.;Dorado, A.;Lopez-Campos, J. L. *Journal of Clinical Medicine.* **2023**, *12*, 5293.

[6] Durham, A. L.;Adcock, I. M. *Lung Cancer.* **2015**, *90*, 121-127.

[7] Prediletto, I.;Giancotti, G.;Nava, S. *Journal of Clinical Medicine.* **2023**, *12*, 3369.

[8] Osoata, G. O.;Hanazawa, T.;Brindicci, C.;Ito, M.;Barnes, P. J.;Kharitonov, S.;Ito, K. *Chest.* **2009**, *135*, 1513-1520.

[9] Antonela Antoniu, S. *Expert Opin. Invest. Drugs.* **2008**, *18*, 105-107.

[10] Ferraro, M.;Di Vincenzo, S.;Sangiorgi, C.;Leto Barone, S.;Gangemi, S.;Lanata, L.;Pace, E. *Pharmaceuticals.* **2022**, *15*, 218.

[11] Ueno-Iio, T.;Shibakura, M.;Iio, K.;Tanimoto, Y.;Kanehiro, A.;Tanimoto, M.;Kataoka, M. *Life Sci.* **2013**, *92*, 1015-1023.

[12] Adeloye, D.;Song, P.;Zhu, Y.;Campbell, H.;Sheikh, A.;Rudan, I. *The Lancet Respiratory Medicine.* **2022**, *10*, 447-458.

[13] Han, H.;Peng, G.;Meister, M.;Yao, H.;Yang, J. J.;Zou, M.-H.;Liu, Z.-R.;Ji, X. *Front. Pharmacol.* **2021**, *12*, 726586.

[14] Barnes, P. J. *Redox Biol.* **2020**, *33*, 101544.

[15] Barnes, P. J. *Clin. Sci.* **2017**, *131*, 1541-1558.

[16] Negro, R. W. D. *Lung.* **2008**, *186*, 70-73.

[17] Cazzola, M.;Page, C. P.;Wedzicha, J. A.;Celli, B. R.;Anzueto, A.;Matera, M. G. *Respiratory Research.* **2023**, *24*, 194.

[18] Barsh, G. S.;Van Buren, E.;Radicioni, G.;Lester, S.;O'Neal, W. K.;Dang, H.;Kasela, S.;Garudadri, S.;Curtis, J. L.;Han, M. K.;Krishnan, J. A.;Wan, E. S.;Silverman, E. K.;Hastie, A.;Ortega, V. E.;Lappalainen, T.;Nawijn, M. C.;Berge, M. v. d.;Christenson, S. A.;Li, Y.;Cho, M. H.;Kesimer, M.;Kelada, S. N. P. *PLos Genet.* **2023**, *19*, e1010445.

[19] Fu, H.-T.;Zhang, Y.;Zhang, P.;Wu, H.;Sun, X.-Q.;Shen, S.-Y.;Dou, D.-B. *Translational Cancer Research.* **2021**, *10*, 4047-4056.

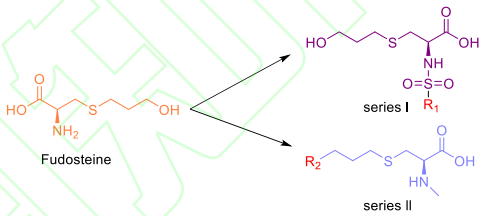
[20] Radicioni, G.;Ceppe, A.;Ford, A. A.;Alexis, N. E.;Barr, R. G.;Bleecker, E. R.;Christenson, S. A.;Cooper, C. B.;Han, M. K.;Hansel, N. N.;Hastie, A. T.;Hoffman, E. A.;Kanner, R. E.;Martinez, F. J.;Ozkan, E.;Paine, R.;Woodruff, P. G.;O'Neal, W. K.;Boucher, R. C.;Kesimer, M. *The Lancet Respiratory Medicine.* **2021**, *9*, 1241-1254.

[21] Komatsu, H.;Yamaguchi, S.;Komorita, N.;Goto, K.;Takagi, S.;Ochi, H.;Okumoto, T. *Pulm Pharmacol Ther.* **2005**, *18*, 121-127.

[22] Carpenter, J.;Wang, Y.;Gupta, R.;Li, Y.;Haridass, P.;Subramani, D. B.;Reidel, B.;Morton, L.;Ridley, C.;O'Neal, W. K.;Buisine, M.-P.;Ehre, C.;Thornton, D. J.;Kesimer, M. *Proceedings of the National Academy of Sciences.* **2021**, *118*, e2104490118.
[23] Nunes, J. H. B.;Nakahata, D. H.;Corbi, P. P.;Paiva, R. E. F. d. *Coord. Chem. Rev.* **2023**, *490*, 215228.
[24] Mahapatra, M.;Mekap, S. K.;Mal, S.;Sahoo, J.;Sahoo, S. K.;Paidesetty, S. K. *Arch. Pharm.* **2023**, *356*, 2200508.
[25] Ghomashi, R.;Ghomashi, S.;Aghaei, H.;Massah, A. R. *Curr. Med. Chem.* **2023**, *30*, 407-480.
[26] Whittaker, H.;Rothnie, K. J.;Quint, J. K. *Thorax.* **2024**, *79*, 202-208.
[27] Rubio ML M.-M. M., O. M., Peces-Barba G. *Oral Chest.* **2004**, *125*, 1500-1506.
[28] Wang, Y.;Wang, H.;Yang, G.;Hao, Q.;Yang, K.;Shen, H.;Wang, Y.;Wang, J. *Eur J Med Chem.* **2023**, *256*, 115374.
[29] Li, G.;He, D.;Cai, X.;Guan, W.;Zhang, Y.;Wu, J. Q.;Yao, H. *Eur J Med Chem.* **2023**, *250*, 115195.
[30] Wang, Y.;Wang, H.;Yang, G.;Hao, Q.;Yang, K.;Shen, H.;Wang, Y.;Wang, J. *Eur. J. Med. Chem.* **2023**, *256*, 115374.

图文摘要

Design, synthesis, and activity assessment of Fudosteine derivatives for chronic respiratory disorders



This article a total of 27 Fudosteine derivatives were produced, with separation yields ranging from 36% to 76%. Among these, the results revealed that compound 2.5f exhibited potent anti-inflammatory action, with an IC_{50} value of 1.08 mmol/L. Additionally, derivative 1f demonstrated the best PDE4A1 inhibitory activity, which was five times greater than that of Fudosteine.

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