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FULL PAPER

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Synthesis and elastase inhibition activities of novel aryl, substituted aryl, and heteroaryl oxime ester derivatives

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Abstract

Fifteen novel aryl, substituted aryl and heteroaryl γ-hydroxy- (**2a–e**), γ-methoxyimino- (**3a–e**), and γ-benzyloxyimino- (**4a–e**) butyric acid methyl esters were investigated for their enzyme inhibition, and the synthesis of 10 compounds (**3a–e**, **4a–e**) is given in this study. The other five compounds (**2a–e**) were synthesized before in another study. Compounds **3a–e** and **4a–e** were synthesized in this work as original compounds and characterized by ^{1}H and ^{13}C NMR, IR, mass, and elemental analyses. Their (*E*/*Z*)-isomerisation ratios were analyzed by ^{1}H and ^{13}C NMR. All of them are of pure (*E*)-configuration. Due to the literature survey, the elastase inhibition activity was not studied for these compounds. Elastase inhibition ability was investigated in this work for five γ-hydroxy- (**2a–e**), five γ-methoxy- (**3a–e**), and five γ-benzyloxyimino- (**4a–e**) butyric acid methyl esters. All these 15 compounds showed elastase inhibition activity. Compound **2b** was the best one and exhibited a better activity than the standard ursolic acid whereas compound **2a** worked like the standard. All these compounds can be novel elastase inhibitor agents in the pharmaceutical and cosmetic industries.

KEYWORDS
elastase inhibition, oxime ester derivatives, ursolic acid

1 | INTRODUCTION

Oxime and oxime ether derivatives are valuable starting compounds for synthesis of many natural, pharmaceutical, and cosmetic products. They show biological activities like antiprotozoan, antibacterial, antifungal, antioxidant, and DNA cleavage abilities.[1]

Elastase (EC.3.4.21.37) is a serine protease of the chymotrypsin family. This enzyme can hydrolyze all extracellular matrix components such as elastin, fibronectin, proteoglycans, and collagens. Elastases are particularly abundant in the skin, lung, arteries, and ligaments. Elastase is known to cause rheumatoid arthritis, pulmonary emphysema, cystic fibrosis, ischemia reperfusion injury, acute respiratory distress, Wegener's granulomatosis, and delayed wound healing.[2,3] Also, elastases are stimulated neutrophils which migrate to injured neutrophils tissue. Human neutrophil elastase (HNE) plays a pivotal role both in intracellular and extracellular innate immune responses against bacteria.[4] HNE has also been implicated in the progression of various types of cancer and other important neutrophil driven inflammatory diseases[5,6] such as inflammatory bowel disease and rheumatoid arthritis.

Elastase activity increases significantly with age and results in reduced skin elastic properties. With age, especially for people over 40 years of age, the elasticity of skin is significantly decreased by elastase and also results in sagging. Inhibiting the activity of elastase may be a useful approach to prevent UV induced skin alterations and premature skin aging.[7]

Due to all, looking for new elastase inhibitors is one of the important searching subjects in our century, therefore, we aimed in this

study firstly the synthesis of 10 novel aryl, substituted aryl, and heteroaryl γ-hydroxy-, γ-methoxy-, and γ-benzyloxyimino butyric acid methyl ester derivatives (γ-KOMED) going out from their corresponding keto methyl esters (**1a–e**). **1a–e** were converted to their original series of aryl, substituted aryl and heteroaryl γ-methoxy- (**3a–e**) and γ-benzyloxyimino- (**4a–e**) butyric acid methyl esters. **2a–e** were synthesized before by our group.[8] **2b**, **2c**, **2d** were original compounds. All the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, mass, and elemental analyses. (*E*/*Z*)-Isomerisation was analyzed by ^{1}H and ^{13}NMR. All the synthesized fifteen compounds **2a–e**, **3a–e**, and **4a–e** are of pure (*E*)-configuration.

The second aim of this study was to investigate the elastase inhibition effect of these 15 compounds. Elastase inhibition ability is a very valuable criterium for antiaging purposes in cosmetic and pharmaceutical industries for healing health problems. In the literature survey there is no data on the elastase inhibiton of these mentioned fifteen compounds. Thirdly, the relationship between the structure and elastase inhibition activity was discussed in this present study.

2 | RESULTS

2.1 | Chemistry

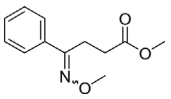
γ-Hydrox**y-** (**2a–e**), *O*-methyl- (**3a–e**), and *O*-benzyl imino methyl esters (**4a–e**) were synthesized in high yields from their corresponding γ-keto esters (Scheme 1).

The five hydroxyimino compounds (**2a–e**) were synthesized and characterized in a previous study by our group.[8] The other ten substances (**3a–e**; **4a–e**) were synthesized in this work for the first time. All these 15 compounds (**2a–e**; **3a–e**; **4a–e**) are original except **2a** and **2e** and all of them were isolated as their pure (*E*)-isomers. Their (*E*/*Z*)-isomerization was analyzed by ^{1}H-NMR and ^{13}C-NMR spectra according to the splitting ratio of methoxy and benzyloxy signals.

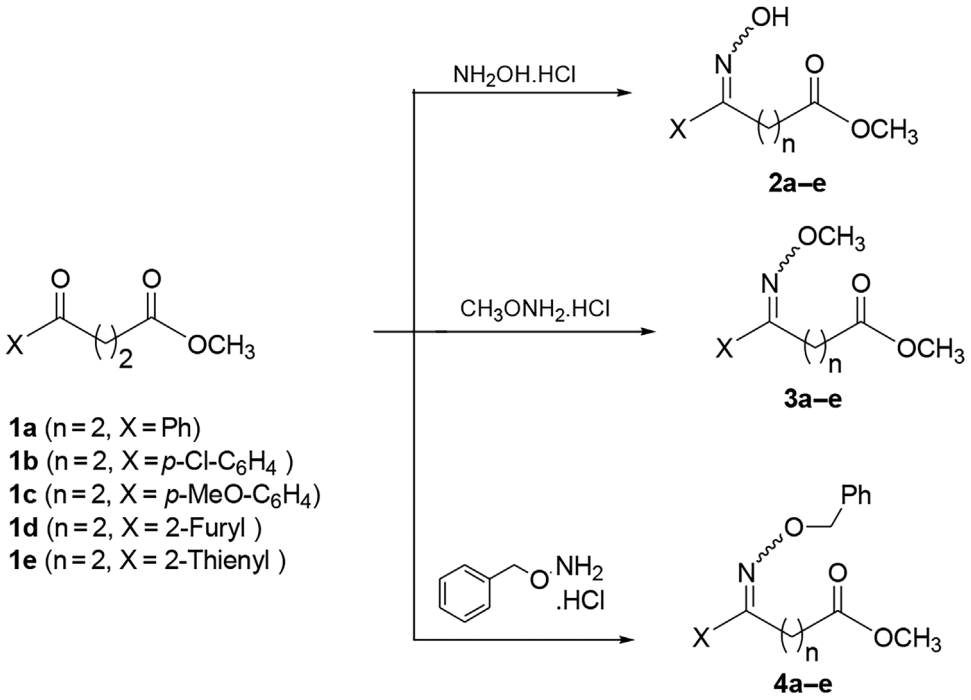
In the previous study of our group, oxime and oxime ether derivatives of the keto methyl ester isomers with C_{14} carbon chain were synthesized as their (*E*/*Z*)-mixtures.[1] ^{1}H-NMR and ^{13}C-NMR of these isomers had given two signals especially for methoxy and benzyloxy peaks due to their existance percent. ^{1}H-NMR and ^{13}C-NMR spectra of the synthesized (**2a–e**; **3a–e**; **4a–e**) showed only one signal for methoxy and benzyloxy groups. According to the literature, (*E*)-signal resonated at lower field than (*Z*)-signal.[1,9] NMR spectra of the obtained (**2a–e**; **3a–e**; **4a–e**) were similar to the ppm values of (*E*)-signals as seen in the previous study.[1] Therefore, the configuration of the compounds synthesized in this paper were attributed to (*E*)-structure. The groups aryl, substituted aryl, and heteroaryl let these substances exist in (*E*)-configuration because of the interaction between phenyl, oxime groups, and steric hindrance of the methylene protons.

2.2 | Characterization of the synthesized compounds

Methyl γ-methoxyimino-γ-phenylbutanoate 3a



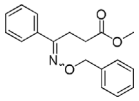
Yield: 96%; colorless oil. Anal. calcd. for $C_{12}H_{15}NO_3C$, 65.14; H, 6.83; N, 6.33. Found: C, 65.19; H, 6.85; N, 6.30. IR (neat, cm^{-1}) *v* 3043, 2944,



SCHEME 1 Synthesis of **2a–e**, **3a–e**, and **4a–e** from **1a–e**

2816, 1734, 1603, 1492, 1436, 1324, 1203, 1150, 1046, 740, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.29–7.27 (m, 3H), 3.90 (s, 3H, $NOCH_3$), 3.57 (s, 3H, $COOCH_3$), 2.97 (t, *J* = 7.5 Hz, 2H), 2.48 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9 (C═O), 155.7 (C═N), 134.1, 128.2, 127.5, 125.2, 61.0 (═N—O$\underline{C}H_3$), 50.7 (COO$\underline{C}H_3$), 29.6 ($\underline{C}H_2$), 21.3 ($\underline{C}H_2$). MS (*m/z*) = 51, 65, 77, 104, 119, 130, 162, 190, 207, 221 (M^+).

γ-Benzyloxyimino-γ-phenyl-butyric acid methyl ester 4a



Yield: 75%; colorless oil. Anal. calcd. for $C_{19}H_{21}NO_3C$, 73.29; H, 6.80; N, 4.50. Found: C, 73.27; H, 6.83; N, 4.52. IR (neat, cm^{-1}) *v* 3020, 2944, 2870, 1731, 1603, 1485, 1436, 1360, 1206, 1010, 735, 690. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2H), 7.31–7.24 (m, 8H), 5.14 (s, OCH_2), 3.51 (s, 3H, $COOCH_3$), 2.99 (t, *J* = 10.0 Hz, 2H), 2.47 (t, *J* = 10.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2 (C═O), 157.2 (C═N), 138.2, 135.4, 129.5, 128.7, 128.6, 128.4, 128.0, 126.5, 76.6 (O$\underline{C}H_2$), 51.9 (COO$\underline{C}H_3$), 30.9 ($\underline{C}H_2$), 22.7 ($\underline{C}H_2$). MS (*m/z*) = 51, 65, 77, 91, 105, 130, 161, 174, 193, 220, 238, 265, 280, 297 (M^+).

2.3 | Elastase inhibition activity

Elastase inhibition activities of the 15 as γ-KOMED named substances are given in Tables 1–3. This elastase inhibition ability was not studied before according to the literature survey. The elastase inhibitor activities of the γ-KOMEDs were found to increase in a dose depending manner. A higher elastase inhibitory activity is associated with a lower IC_{50} value.

Elastase inhibition activities of aryl, substituted aryl and heteroaryl-γ-hydroxyimino butyric acid methyl esters (**2a–e**) are given in Table 1. Elastase inhibitor activities of the **2a–e** were found to increase in a dose depending manner. A higher elastase inhibitory activity is associated with a lower IC_{50} value. All of the components **2a–e** showed good elastase antielastase activity (Table 1). The highest elastase inhibition activity was seen for **2b** compound. Elastase inhibitory activity of compounds **2a–e** and standard decreased in order of **2b** > ursolic acid > **2a** > **2c** > **2d** > **2e** (Table 1).

Differently substituted γ-methoxyimino methyl esters (**3a–e**) showed the highest antielastase activity for **3b** (Table 2). Elastase inhibitory activity of *O*-methyl substituted keto oxime esters and standard decreased in order of ursolic acid > **3b** > **3a** > **3c** > **3e** > **3d** (Table 2).

The antielastase activity of *O*-benzyl substituted keto oxime esters and standard decreased in order of ursolic acid > **4a** ≥ **4b**> **4c** > **4e** > **4d**. The highest elastase inhibiton activity was obtained for **4a** compound among the *O*-benzyl substituted keto oxime esters (Table 3).

3 | DISCUSSION

Elastase has a serine residue with a free hydroxyl group on its active center. This hydroxyl group may form an ester bond or go to a transesterification. The inhibition effect may be explained firstly by the formation of an transesterification between the hydroxyl group of serine[10] and methoxy of the ester group of **2a–e**, **3a–e**, and **4a–e**. The second effect indicates to an interaction between the oxime, oxime ether groups, and hydroxyl of serine due to a hydrogen bridge formation. Besides, the substituents phenyl, substituted phenyl and heteroaryl groups are playing the third role in this elastase inhibition.

TABLE 1 Elastase inhibition values of aryl, substituted aryl and heteroaryl γ-hydroxyiminobutyric acid methyl esters (**2a–e**)

Compounds and standard	Concentration (μM)	Inhibition (%)[a]	IC_{50} (μM)[a]
2a	1 100 500	24.19 ± 0.66 41.03 ± 2.65 51.12 ± 4.31	491.49 ± 43.54
2b	1 10 100	12.86 ± 4.29 16.76 ± 1.44 32.38 ± 1.65	193.61 ± 8.61
2c	10 250 1000	7.55 ± 0.33 14.88 ± 2.06 29.17 ± 4.29	2015.81 ± 366.62
2d	100 500 1000	6.25 ± 1.12 15.51 ± 1.00 24.78 ± 3.80	2251.87 ± 360.77
2e	1 25 1000	4.00 ± 1.07 10.97 ± 0.64 20.21 ± 0.95	3287.80 ± 112.10
Ursolic acid	1 10 250	22.29 ± 2.66 27.67 ± 2.02 37.61 ± 2.16	486.19 ± 44.22

[a]Mean ± SD.

TABLE 2 Elastase inhibition values of aryl, substituted aryl and heteroaryl γ-methoxyiminobutyric acid methyl esters (**3a–e**)

Compounds and standard	Concentration (μM)	Inhibition (%)[a]	IC_{50} (μM)[a]
3a	10 100 500	8.80 ± 0.32 23.17 ± 0.61 27.19 ± 1.37	1249.03 ± 111.70
3b	10 100 500	10.48 ± 1.19 23.67 ± 0.32 33.43 ± 2.00	891.78 ± 71.25
3c	1 10 500	3.04 ± 0.69 15.78 ± 0.30 25.00 ± 5.29	1550.54 ± 160.14
3d	250 500 2000	7.81 ± 0.00 24.78 ± 0.45 28.57 ± 2.23	4697.58 ± 476.42
3e	500 1000 2000	9.03 ± 0.94 15.23 ± 1.08 27.28 ± 1.17	3865.74 ± 143.40
Ursolic acid	1 10 250	22.29 ± 2.66 27.67 ± 2.02 37.61 ± 2.16	486.19 ± 44.22

[a]Mean ± SD.

Five different substituents were used for γ-KOMEDs. Furyl, thiophenyl as heteroaryl and phenyl, chlorophenyl as electron withdrawing and methoxy as electron giving groups. The substituent phenyl group showed a better inhibition than the heteroaryl groups furyl and thiophenyl. Electron withdrawing groups on phenyl like chloro (+M, −I) increased the inhibition and electron serving groups like methoxy (+M, +I) decreased the inhibition effect more than the inhibition of phenyl group. All of the components showed good antielastase activities (Table 1). The highest elastase inhibition activity was seen for **2b** compound of hydroxyimino derivatives. IC_{50} value of **2b** was 193.61 μM. **2b** was the best inhibition agent than the standard ursolic acid. IC_{50} value of ursolic acid was 486.19 μM. Chloro is the most electronegative group and accelerated the transesterification between serine and **2b** by making the elimination of methoxy group easier. **2b** is a novel and a new elastase inhibitor gained in this present study. Ursolic acid has an ester and free hydroxyl group like **2b** but no chloro substituent, therefore, ursolic acid is less effective than **2b**. The other hydroxyimino compounds are also effective as antielastase inhibitors.

TABLE 3 Elastase inhibition values of aryl, substituted aryl and heteroaryl γ-benzyloxyiminobutyric acid methyl esters (**4a–e**)

Compounds and standard	Concentration (μM)	Inhibition (%)[a]	IC_{50} (μM)[a]
4a	10 100 1000	7.93 ± 1.82 29.47 ± 0.30 42.66 ± 1.91	1229.88 ± 88.94
4b	1 10 100	15.43 ± 1.14 19.43 ± 3.57 41.14 ± 0.57	1233.06 ± 11.40
4c	1 250 500	7.74 ± 2.98 15.79 ± 4.03 25.50 ± 2.68	1292.35 ± 86.51
4d	12 250 2000	16.67 ± 1.66 25.00 ± 3.74 34.34 ± 0.15	4059.70 ± 307.48
4e	100 1000 2000	26.22 ± 1.53 48.42 ± 1.89 55.81 ± 0.73	1456.56 ± 75.61
Ursolic acid	1 10 250	22.29 ± 2.66 27.67 ± 2.02 37.61 ± 2.16	486.19 ± 44.22

[a]Mean ± SD.

The lowest elastase inhibition activity was found for **2e** with IC_{50} value 3287.80 μM. **2e** with a large and less electronegative sulfur atom is placed at the bottom of the free oxime ester range. Heteroaryl groups can be aromatic with the help of heteroatoms O and S. O is more electronegative than S, therefore, thiophenyl group could not be so effective as furyl group. (Table 1).

Looking at Table 2 differently substituted γ-methoxyimino methyl esters (**3a–e**) showed the highest antielastase activity for **3b** with IC_{50} value 891.78 μM. Elastase inhibitory activity of *O*-methyl substituted keto oxime esters and standard decreased in order of ursolic acid > **3b** > **3a** > **3c** > **3e** > **3d** (Table 2). Compound **3d** proved to be of the lowest potent showing an enzyme inhibitory activity with an IC_{50} = 4679.58 μM (Table 2).

In the range of *O*-benzyl substituted keto oxime esters (**4a–e**), compounds **4b** and **4a** showed similar antielastase activities. IC_{50} values of these compounds are 1233.06 and 1229.88 μM, respectively. The antielastase activity of *O*-benzyl substituted keto oxime esters and standard decreased in order of ursolic acid > **4a** ≥ **4b** > **4c** > **4e** > **4d** (Table 3). The lowest elastase inhibiton activity was obtained for **4d** compound among the *O*-benzyl substituted keto oxime esters. IC_{50} value was 4059.70 μM.

These synthesized compounds showed good elastase inhibitory activities between 193.61–4697.58 μM among the γ-KOMED compounds. The best inhibition was found for **2b** compound followed by **2a**, **3b**, **4a**, **4b**, and **3a**. Compound **2b** showed the highest potent activity (IC_{50} = 193.61 μM) than that of the standard ursolic acid (IC_{50} = 486.19 μM). Compound **2a** showed similar antielastase activity such as ursolic acid.

The elastase inhibition ability studied in this work has been effected by the structure of the mentioned 15 novel oximes and oxime ethers according to the obtained results (Tables 1–3). For a good elastase inhibition should the carbonium cation of the ester group too much positively charged. More positive charge on the estercarbonium cation increased the elastase inhibition and transesterification occurs easier. This situation was affected by free oxime, oxime-ether and phenyl, substituted phenyl, and heteroaryl groups. The phenyl group with its aromatic behavior showed a better inhibition than the heteroaryl groups furyl and thiophenyl for γ-hydroxy-, γ-methoxy-, and γ-benzyl-oxyiminobutyric acid methyl esters. Ursolic acid was the standard in these investigations. Inhibition of phenyl is increased by −I groups like chloro and decreased by +I groups like methoxy. Chlorophenyl substituted γ-hydroxy- was better than γ-methoxy- and this was better than γ-benzyloxyiminomethylester (Tables 1–3). The free oxime, γ-hydroxyimino had no +I effect. +I effect of benzyloxyimino is more than γ-methoxyimino. The inhibition range with chlorophenyl substituent was γ-hydroxy- > γ-methoxy- > γ-benzyloxyiminoester. Electronegative group chloro made the phenyl ring for inhibition more active than electron sending methoxy group. Phenyl ring is less effective with activating methoxy group. Phenyl substituted inhibition range was γ-hydroxy- > γ-benzyloxy- ≥ γ-methoxyester. +I effect substitution on phenyl ring like methoxy gave an inhibition ratio of γ-benzyloxy- > γ-methoxy- > γ-hydroxyiminoester. Due to the (*E*)-configuration of the substances the electron sending effect of methoxy was countereffected by γ-benzyloxy more than γ-methoxy- and γ-hydroxyimino, because +I effect of benzyloxy > methoxy > hydroxy. Two opposite forces on γ-carbon atom directed the inhibition ability. One belonged to methoxyphenyl and the other to benzyloxy and methoxy of imino group. Both groups exhibited + effect. +I effect decreased the elastase inhibition of the substances. With chlorophenyl and hydroxy imino groups was the γ-carbon atom mostly positive charged by their −I effects and the best inhibition was obtained in this way with **2b**. −I effected groups together with hydroxyimino increased the elastase inhibition of the substances.

Heteroaryl groups like furyl and thiophenyl decreased the inhibition ability. Furyl with its electronegative behavior made the γ-hydroxyimino ester more active than thiophenyl substituted one. Sulfur atom is better nucleophilic than oxygen and has an electron serving effect. Thiophenyl decreased the inhibition more than furyl for γ-hydroxyimino esters but furyl decreased more than thiophenyl for γ-methoxyimino and benzyloxyimino esters. Furyl's electron withdrawing effect on γ-carbon atom is supported by hydroxyimino effect. This effect of furyl was decomposed by benzyloxy more than methoxy. The inhibition range with furyl substituent was γ-hydroxyimino > γ-benzyloxyimino > γ-methoxy iminoesters. Thiophenyl's electron sending effect is counter effected mostly by γ-benzyloxy- than γ-hydroxy- and than γ-methoxyiminoester. The inhibition range with thiophenyl substituent was γ-benzyloxy- > γ-hydroxy- > γ-methoxyiminoester. The best inhibition range obtained was **2b** > ursolic acid > **3b** > **4a** ≥ **4b**. **3b** (methoxyether) and **4a**, **4b** (benzyloxy ethers) decreased the inhibition of the standard twofold and threefold, respectively. The worst inhibition range decreased as **3d** > **4d** > **3e** > **2e**. **3d** decreased the inhibition ∼10-fold than the standard.

4 | CONCLUSION

Oximes and oximeethers are valuable compounds in organic, pharmacautical, and cosmetic areas. They have many biological activities but their elastase inhibitions were not investigated until today. Many of them have shown good elastase inhibition in this study. The elastase inhibition makes these substances protectors against several skin deseases and skin aging. They can be used in agriculture, pharmacy, and cosmetic industries due to their antielastase activities. **2a** and **2b** are new inhibitors and skin protectors. **2a** is like and **2b** is better than ursolic acid.

5 | EXPERIMENTAL

5.1 | Chemicals

All reagents used in this study were commercially available from commercial suppliers. Hydroxylamine hydrochloride, *O*-methylhydroxylamine hydrochloride, and *O*-benzylhydroxylamine hydrochloride were purchased from Sigma–Aldrich. γ-Keto-methyl esters as starting materials were synthesized by Friedel–Crafts acylation.[11] The reaction products were purified by column chromatography on silica gel (mesh 0.063–0.200 mm) with hexane-ethylacetate. NMR spectra were recorded at 500 MHz for ^{1}H and 150 MHz ^{13}C using Me_4Si as the internal standard in $CDCl_3$. GC-MS spectra were recorded on Shimadzu

QP2010 Plus. IR spectra were recorded on Bruker Vertex 70. A Buchi melting point B-540 apparatus was used for melting point determinations. The chemical yields are expressed with the pure isolated substances.

The full experimental details and spectroscopic data and the ^{1}H and ^{13}C NMR spectra can be found in the Supporting Information. The InChI codes of the investigated compounds together with some biological activity data are also provided as Supporting Information.

5.2 | General procedure for the synthesis of aryl, substituted aryl-, and heteroaryl-γ-hydroxyimino butyric acid methyl esters (2a–2e)[8]

As a general procedure, the keto ester (1.0 eq) **1a–j** was dissolved in ethanol. Hydroxylamine hydrochloride (2.0 eq) was introduced into the reaction medium and the mixture was stirred overnight. Saturated ammonium chloride was used to dilute the mixture and it was extracted with ethyl acetate. Combined organic layers were washed with water and brine and dried over sodium sulfate. The solvent was evaporated and the crude product was subjected to column chromatography on silica gel and as eluent (*n*-hexane/ethyl acetate 7:3) to yield the oximes **2a–e**. The products **2a–e** were synthesized and characterized according to literature.[8]

5.3 | General procedure for the synthesis of *O*-methyl- and *O*-benzyliminobutyric acid methyl esters (3a–e) and esters (4a–e)[12]

To a solution of keto ester (1.0 eq.) **1a–e** in pyridine was added a solution of alkoxyamine hydrochloride (1.1 eq.) in pyridine at room temperature. The resulting solution was stirred for 6–12 h. After the consumption of the starting material, the reaction mixture was diluted with water, and then extracted with ethyl acetate. The organic phase was combined, dried over anhydydrous Na_2SO_4 and concentrated under reduced pressure The residue was purifed by column chromatography on silica gel (*n*-hexane/ethyl acetate = 7:3) to give the desired products **3a–e** and **4a–e**.

5.4 | Elastase inhibitory activities

Elastase inhibitory activity of the synthesized (γ-KOMED) compounds was estimated according to the method of James et al.[13] *N*-Succinyl-Ala-Ala-Ala-paranitroanalide (STANA) was used as a substrate in this method. The absorbance change was measured at 410 nm using a spectrophotometer. The percent inhibiton of elastase was calculated as follows:

$$\text{Inhibition } (\%) = (A - B/A) \times 100$$

where *A* is the enzyme activity without inhibitor and *B* is the activity in the presence of inhibitor. Ursolic acid was used as a standard compound.

The results are given as half maximal inhibitory concentrations (IC_{50}) values, calculated from the regression equations preparad from the concentrations of samples.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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