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Design, synthesis and preliminary evaluation of new cinnamoyl pyrrolidine derivatives as potent gelatinase inhibitors

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Abstract—A series of new cinnamoyl pyrrolidine derivatives have been synthesized based on the L-hydroxyproline scaffold and inhibiting activities on gelatinase (MMP-2 and -9) and APN were tested. Structure–activity relationship studies showed that the side chain with aromatic ring at **C4** in pyrrolidine ring showed better inhibitory activities on gelatinase than aliphatic side chain. Most compounds exhibited poor activities on APN compared with MMP-2. Within this series, three compounds, **A8**, **B9** and **C10**, have the good potency (IC_{50} = 5.2–9.7 nM) and could be used as lead compounds in the future.

1. Introduction

As a family of zinc-dependent proteinases, matrix metalloproteinases (MMPs) were involved in the degradation of the extracellular matrix and the processes of tumor growth, invasion, and metastasis. The studies showed that MMPs overexpressed by malignant tumors have been associated with an aggressive malignant phenotype and poor prognosis in patients with cancer.[1–3] Currently, the mammal MMP gene family consists of at least 25 structurally related members,[4] among which, gelatinase (MMP-2) proved to be in high correlation with cancer.[5]

The interaction of MMP inhibitors with MMPs is illustrated in Figure 1 according to the complex of CGS27023A with MMP-3.[6] The figure shows that the *p*-(methoxyphenyl)-sulfonyl fragment inserts into S1 pocket of the enzyme, while the pyridine and isopropyl group are located in S2 pocket and S1 domain, respectively. Two hydrogen bonds existed between the inhibitor and the enzyme, which includes the oxygen atom of sulfonylamide with NH of Leu164 and NH of hydroxamic acid with carbonyl O of Ala165. Considering the S1 pocket of gelatinase is much deeper than that of MMP-3, we introduced a bigger fragment, the cinnamoyl group, to L-hydroxyproline scaffold which is known as the substrate of MMPs. The cinnamoyl group was chosen because cinnamic acid is proved to inhibit A5491 human cancer of lung gland and the caffic acid is proved to inhibit MMP-2 and -9.[7] In this study, we linked cinnamic acid, caffic acid and its analogs with hydroxyproline derivatives in order to find compounds with potent inhibitory activity (Tables 1–3).

2. Chemistry

The target compounds were synthesized via the route outlined in Scheme 1. Methyl 4-hydroxy-L-pyrrolidine-

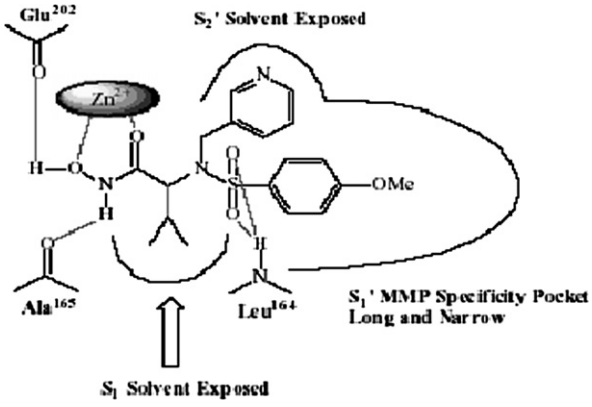

Figure 1. Mode of binding of CGS 27023A with MMP-3 (Ref. 6).

Keywords: Cinnamoyl pyrrolidine derivatives; MMPs inhibitors; IC_{50}.
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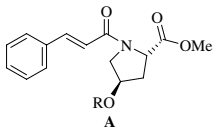
Table 1. The inhibitory activities of series **A** compounds



A

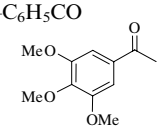
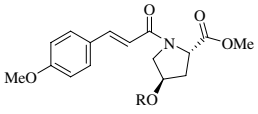
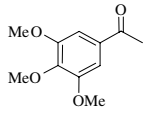
Compound	R	IC_{50} (nmol)	
		MMP2, 9	APN
A0	H	11.2	147.4
A1	CH_3CO	128.4	264.6
A2	CH_3CH_2CO	98.1	216.3
A3	$CH_3CH_2CH_2CO$	85.6	211
A4	C_6H_5CO	52.4	163.2
A5	*p*-Cl–C_6H_5CO	31.8	149.7
A6		259.5	80.1
A7	$C_6H_5CH_2CH_2CO$	43.6	359.4
A8	$C_6H_5CH{=}CHCO$	5.2	75.2
A9	*p*-CH_3O–$C_6H_4CH{=}CHCO$	12.3	132.5
A10	3,4-$(OMe)_2$ $C_6H_3CH{=}CHCO$	13.1	296.2

Table 2. The inhibitory activities of series **B** compounds



B

Compound	R	IC_{50} (nmol)	
		MMP-2, 9	APN
B0	H	439.8	296.9
B1	CH_3CO	316.4	563.1
B2	CH_3CH_2CO	280.2	328.5
B3	$CH_3CH_2CH_2CO$	195	261.3
B4	C_6H_5CO	109.9	211.4
B5	*p*-Cl–C6H5CO	42.8	165.3
B6		562.6	856.6
B7	$C_6H_5CH_2CH_2CO$	73.4	213
B8	$C_6H_5CH{=}CHCO$	39.1	—
B9	*p*-CH_3O–$C_6H_4CH{=}CHCO$	7.8	128.6
B10	3,4- (OMe)2 C6H3CH=CHCO	121.3	88.7

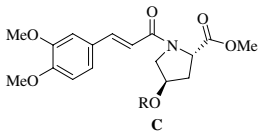
carboxylate hydrochloride was prepared according to the literature[10] and then converted to amide compounds with cinnamoyl chloride, *p*-methyl cinnamoyl chloride, and caffeoyl chloride to form the amide. The final target compounds were synthesized by esterification with different acyl chloride eventually.

3. Results and discussion

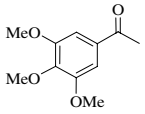
3.1. Structure–activity relationship in vitro

Preliminary activity assay was carried out in vitro on gelatinase and APN so as to identify the compound

Table 3. The inhibitory activities of series B compounds



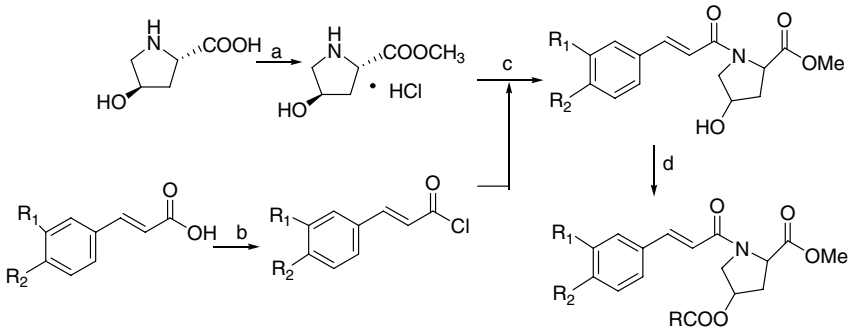
C

Compound	R	IC_{50} (nmol)	
		MMP	APN
C1	CH_3CO	320.2	808.3
C2	CH_3CH_2CO	293.4	543.6
C3	$CH_3CH_2CH_2CO$	221.1	356.8
C4	C_6H_5CO	201.2	289.6
C5	*p*-Cl–C_6H_5CO	111.8	195.1
C6		—	—
C7	$C_6H_5CH_2CH_2CO$	168.3	226
C8	$C_6H_5CH{=}CHCO$	86.5	189.2
C9	*p*-CH_3O–$C_6H_4CH{=}CHCO$	28.7	103.4
C10	3,4-$(OMe)_2C_6H_3CH{=}CHCO$	9.7	88.3

selectivity. Similarly as MMPs, APN is also a family of zinc-dependent metalloproteinases associated with malignant tumor with two zinc ions in the catalytic domain. In MMP inhibition assay, gelatinase (MMP-2) and (trinitrobenzenesulfonic acid) TNBS were purchased from Sigma, and the substrate was synthesized as described by Vijaykumar et al.[8] The gelatinase, substrate, and inhibitor were dissolved in sodium borate solution (pH 8.5, 50 mmol/L) and incubated for 30 min at 37 °C, and then 0.03% TNBS was added and incubated for another 20 min, the resulting solution detected under 450 nm wavelength to gain absorption. The inhibitory activities of compounds against APN were also carried out with L-leucine *p*-nitroanilide as substrate. The results of their inhibitory activities (IC_{50}) are reported in Figures 2–4.

3.1.1. Structure–activity relationship in vitro for series A compounds. When the side chain (R) was aliphatic, longer, and more flexible side chain linked to the pyrrolidine ring at **C4** showed better activity at gelatinase.

As a strong inhibitor against MMP-2, compound **A0** might be a different case because hydroxy group could possibly form hydrogen bond with the residue of the enzyme which stabilized the binding between the enzyme and the compound. Compounds with aromatic side chain showed higher activity compared to aliphatic derivatives. The possible reason may be due to the π system of the aromatic ring enhancing the interaction with the hydrophobic region of the enzyme. Substitution on aromatic ring also has impact on bioactivity. For example, compound **A5** which is substituted with chlorine in para position shows a slightly better inhibitory activity compared with **A4**. While compound **A6** substituted with trimethoxy group showed lower activity. It is worthy to note that increasing conjugate system between ester and aromatic ring will keep up or improve activities



Scheme 1. Reagents: (a) MeOH, HCl; (b) $SOCl_2$, C_6H_6; (c) Py, Et_3N; (d) RCOCl, Et_3N, CH_2Cl_2 **A0–A10**: $R_1 = H$, $R_2 = H$; **B0–B10**: $R_1 = H$, $R_2 = OMe$; **C1–C10**: $R_1 = OMe$, $R_2 = OMe$.

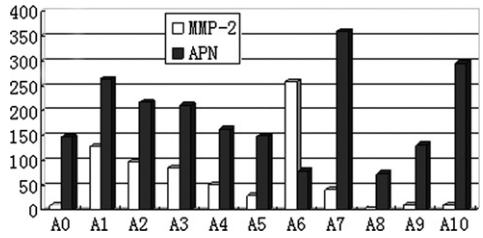


Figure 2. The comparison chart of activity for **A0–10** series compounds designed.

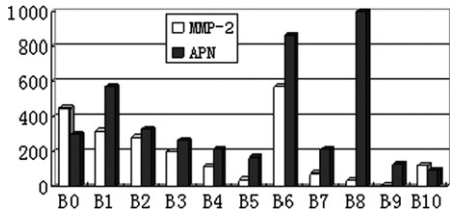


Figure 3. Comparison with activities for B series compounds.

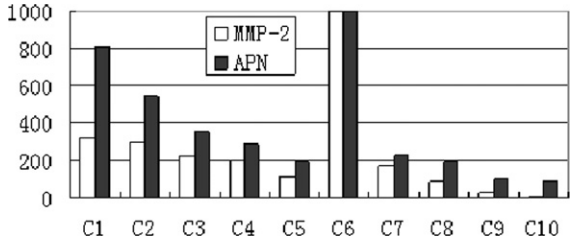


Figure 4. Comparison chart of activities for **C** series compounds designed.

compared with strong inhibitor compound **A0**, such as compounds **A8**–**A10**.

For series **A** compounds, the inhibitory activity against APN is lower than against MMP-2, but the varying tendency is similar to that of MMP-2. For example, the compounds with aliphatic side chain (R) exhibited low inhibitory activity, but the compound with aromatic ring showed better. Although compound **A8** had good activity on both enzymes, the other compounds showed different result. For example, compound **A6** had low activity against MMP-2, but showed good activity against APN. Compounds **A7** and **A10** both showed high activity against MMP-2, but low affinity to APN. It was difficult to explain the reasons for these differences. One possible reason might be that MMP was a kind of endopeptidase and could cut the peptide to parts form the specific amino acid residue of MMP; but APN was a different kind of exopeptidase and focused on hydrolyzing the amino acid only from the side of N of the peptide. The differences in the function between the two kinds of enzymes were due to the differences of their structure. As the two kinds of metal enzymes had differences in structure, there were different requirements in structure to their respective antagonists.

3.1.2. Structure–activity relationship in vitro of B series compounds. The inhibitory activity of **B** series compounds was similar to that of **A** series compounds. It was the same that the compound with longer aliphatic side chain (R) showed better inhibitory activity. In addition, the compounds with aromatic side chain have higher affinity than the compounds with aliphatic side chain. Compound **B5** displayed good activity against MMP-2, and it might be due to the chloride atom. Compound **B6** containing galloyl substituent which was protected by methoxy group also exhibited low activity. The difference was that compound **B10** showed poor inhibitory activity against MMP-2. Compound **B9** showed high inhibitory activity against APN. However, it had special examples in **B** series compounds. The inhibition ratio of compound **B8** against APN was not changed with the concentration strongly, and the IC_{50} value was very high, while compound **B10** showed better inhibitory activity against APN than MMP-2.

3.1.3. Structure–activity relationship in vitro of C series compounds. The inhibitory activity of **C** series compounds was familiar to those of A and B series on the whole. From **C1** to **C10**, when R side chain was aliphatic, the inhibitory activity of the compounds against MMP-2 was stronger as the length increased. The inhibitory activity of the aromatic substitute was obviously stronger than aliphatic. Compound **C10** showed good inhibitory activity against MMP-2. Compound **C6** containing trimethoxy substitute side chain had low affinity. **C** series compounds showed better inhibitory activity against MMP-2 than to APN on the whole.

4. Conclusion

Comparing the inhibitory activity of **A**, **B**, and **C** series compounds in vitro, it was demonstrated that compound with small N1 side chain would exhibit high activity, and most compounds had better inhibitory activity to MMP-2 than to APN. According to the 3D structure of the target enzyme, FlexX Docking was used for modeling the target compounds with the enzyme. We selected target compounds **B9** and **C10** to the FlexX docking utilizing SYBYL 7.0 of TRIPOS Company of USA (Fig. 5).

Figure 5 shows compounds **B9** and **C10** binding with MMP-2. The carboxylic ester group chelates with the catalytic zinc 166, and the hydrophobic side chain of **C4** extends into S1′ pocket of the enzyme, while the side chain of N1 inserts into S1 pocket of the enzyme. Furthermore, the compounds bind with the enzyme backbone by hydrogen bond. Unlike others, the side chain N1 of compound **A0** extends into S1′ pocket.

We also carried out the FlexX Docking of compound **A8** with the enzyme MMP-2 (Fig. 6) and human leukotriene **A4** hydrolase (LTA4H) which is the homology enzyme of APN[9] (Fig. 7). The side chains of **C4** and N1 insert into S1′ pocket and S1 pocket, respectively. The carboxylic ester group chelates with the catalytic zinc 166 with a distance of 1.21 Å. However, the molecule could not extend into the hydrophobic pocket of the active region when compound **A8** docked with LTA4H. Meanwhile, two oxygen atoms in **C4** ester were far from the catalytic zinc with the distance of 6.14 and 5.43 Å, respectively, which leads to the compound failing to chelate with the catalytic zinc perfectly. It illustrated indirectly that if the three dimensional structure of the active site of the enzymes was different, the structural requirements to their inhibitors were also different. In the same way, if a compound had special selectivity to a certain specified enzyme, it might become a promising lead compound which could avoid the multi-side effects of drugs with broad-spectrum effects.

5. Experimental

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. All reactions were monitored by thin-layer chromatography on 0.25-mm silica gel plates (60GF-254) and visualized with UV light, or iodine vapor. 1H NMR spectra were determined on a Brucker AM600 spectrometer using TMS as an internal standard. ESI MS were determined on an API 4000 spectrometer.

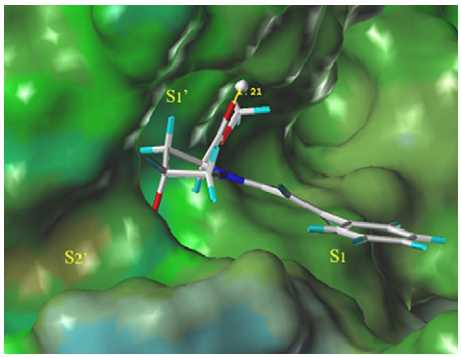


Figure 6. the FlexX docking of compound **A8** with MMP-2.

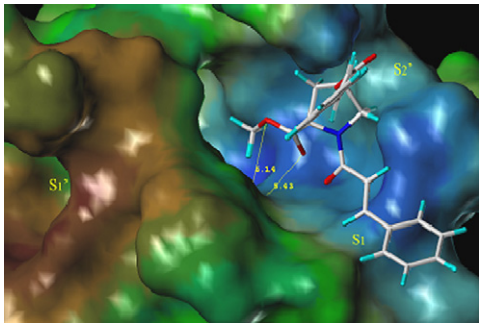


Figure 7. the FlexX docking of compound **A8** with LTA4H.

5.1. (2*S*,4*R*)-Methyl-4-hydroxy-2-pyrrolidine-carboxylatehydroxychloride (1)

The title compound was prepared as described by Jordis in (1*S*, 4*S*)-2-thia-5-azabicyclo [2.2.1] heptane.[7]

5.1.1. (2*S*,4*R*,*E*)-Methyl-1-cinnamoyl-4-hydroxypyrrolidine-2-carboxylate (A0). Compound **1** (1.85 g, 11 mmol)-was suspended in 20 ml Py and 3 ml Et_3N. After stirred for 20 min at room temperature, the resulting mixture was filtrated. The filtrate was cooled to −5 °C, and at this temperature, 20 ml CH_2Cl_2 with 1.67 g (10 mmol) compound **1** was added. After stirred for 3 h, the resulting mixture was filtered to remove white precipitation, and

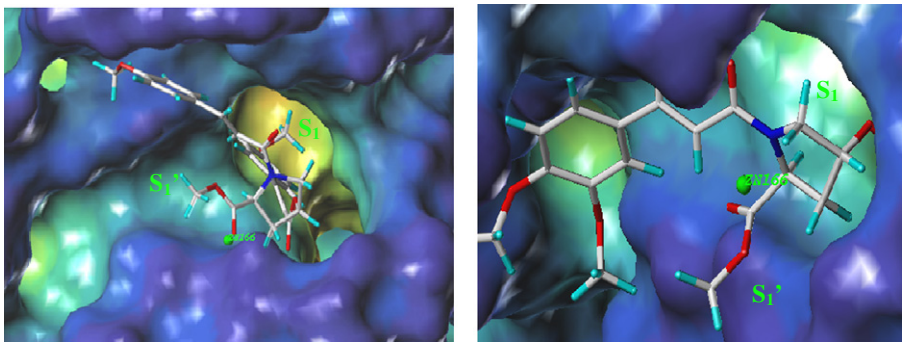


Figure 5. The FlexX docking of compound **B9** (left) and compound **C10** (right) with MMP-2.

the filtrate was rotary evaporated. Small amount toluene was added to remove Py. The resulting crude oil was dissolved with 200 ml CH_2Cl_2, washed with 3 N HCl, H_2O, saturated salt solution, and dried over Na_2SO_4, anhydrous. The yellow crude product was recrystallized with CH_2Cl_2 to provide 2.23 g of white crystal, yield 81.0%, mp 138.8–140.2 °C. IR (KBr, cm^{-1}): 3431.76 (OH), 2949.61 (CH), 1743.99 1646.36 (C=O), 1592.39, 1432.23 (C=C), 1199.09 (C–O). ESI-MS [M+1]:276.4; ^1H NMR (DMSO-d_6, ppm): 7.61 (m, 2H), 7.43 (d, 1H, J = 15.6 Hz), 7.40 (m, 3H), 7.01 (d, 1H), 5.20 (m, 1H), 4.44 (t, 1H, J = 7.8 Hz), 4.29 (s, 1H), 3.80, 3.68 (m, 2,H), 3.63 (s, 3H), 2.14, 1.92 (m, 2H).

5.1.2. (2*S*,4*R*,*E*)-Methyl 4-acetoxy-1-cinnamoylpyrrolidine-2-carboxylate (A1). Compound **A0** (2.75 g, 10 mmol) was resolved in 40 ml CH_2Cl_2 and 4.5 ml Et_3N. After 5 ml CH_2Cl_2 with 0.8 ml acetyl chloride was added dropwise at 0 °C and stirred for 4 h, CH_2Cl_2 was added to dilute the reaction mixture. Then the organic phase was washed with 1 N HCl, H_2O, saturated salt solution, dried over Na_2SO_4 anhydrous, and rotary evaporated. The resulting crude oil was chromatographed over flash silica with petro ether/EtOAc (2:1–1:2) to provide 2.2 g of white crystal, yield 69.4%, mp 76.5–78.5 °C. IR (KBr, cm^{-1}): 2950.86 (CH), 1742.83, 1651.77 (C=O), 1604.22, 1429.61 (C=C), 1248.79 (C–O). ESI-MS [M+1]:318.5; ^1H NMR (DMSO-d_6, ppm): 7.74 (m, 2H, Ar–H), 7.49 (d, 1H=CH, J = 15.6 Hz), 7.40 (m, 3H), 7.03 (d, 1H, J = 15.6 Hz), 5.34 (m, 1H), 4.46 (t, 1H, J = 8.4 Hz), 3.97 (m, 2H), 3.65 (s, 3H), 2.36, 2.17 (m, 2H), 2.02 (s, 3H).

5.1.3. Compounds A2, A3, A4, A5, and A7 were prepared as described for compound A1

5.1.4. (2*S*,4*R*,*E*)-Methyl 1-cinnamoyl-4-(propionyloxy)pyrrolidine-2-carboxylate (A2). White solid, yield 70.1%, mp 77.2–78.6 °C. IR (KBr, cm^{-1}):2950.37 (CH), 1746.63 and 1650.68 (C=O), 1606.35, 1428.49 (C=C), 1183.77 (C–O). ESI-MS [M+1]: 332.6; ^1H NMR (DMSO-*d*textsubscript6, ppm): 7.74 (m, 2H), 7.50 (d, 1H, J = 15.6 Hz), 7.41 (m, 3H), 7.03 (d, 1H, J = 15.6 Hz), 5.35 (m, 1H), 4.45 (t, 1H, J = 7.8 Hz), 3.97, 3.96 (m, 2H), 3.64 (s, 3H), 2.34 (q, 2H, J = 4.8 Hz, 1.8 Hz), 2.31, 2.17 (m, 2H), 1.01 (t, 3H, J = 3 Hz, 1.8 Hz).

5.1.5. (2*S*,4*R*,*E*)-Methyl 4-(butyloxy)-1-cinnamoylpyrrolidine-2-carboxylate (A3). Pale yellow solid, yield 62.3%, mp 66.3–68.5 °C. IR (KBr, cm^{-1}): 2963.15 (CH), 1739.01,1654.47 (C=O), 1612.41, 1416.49 (C=C), 1177.24 (C–O). ESI-MS [M+1]: 346.2; ^1H NMR (DMSO-d_6, ppm): 7.74 (m, 2H), 7.51 (d, 1H, J = 15.6 Hz), 7.41 (m, 3H), 7.04 (d, 1H, J = 15.6 Hz), 5.36 (m, 1H), 4.47 (t, 1H, J = 7.8 Hz), 3.98, 3.97 (m, 2H), 3.65 (s, 3H), 2.35, 2.19 (m, 2H), 2.28 (t, 2H, J = 7.2 Hz), 1.52 (m, 2H), 0.86 (t, 3H, J = 3.2 Hz).

5.1.6. (2*S*,4*R*,*E*)-Methyl 4-(benzoyloxy)-1-cinnamoylpyrrolidine-2-carboxylate (A4). White crystal, yield 73.2%, mp 106–107 °C. IR (KBr, cm^{-1}): 2953.13 (CH), 1707.35, 1651.46 (C=O), 1606.50, 1418.66 (C=C), 1267.03 (C–O). ESI-MS [M+1]: 380.4; ^1H NMR (DMSO-d_6, ppm): 7.79 (m, 2H), 7.73 (m, 2H), 7.65 (d, 1H, J = 15.6 Hz), 7.51 (m, 3H), 7.40 (m, 3H), 7.08 (d, 1H, J = 15.6 Hz), 5.62 (m, 1H), 4.61 (t, 1H, J = 8.4 Hz), 4.17, 4.08 (m, 2H), 3.67 (s, 3H), 2.56, 2.28 (m, 2H).

5.1.7. (2*S*,4*R*,*E*)-Methyl 4-(4-chloro benzoyloxy)-1-cinnamoylpyrrolidine-2-carboxylate (A5). White crystal, yield 69.1%, mp 64.1–66.2 °C. IR (KBr, cm^{-1}): 2951.13 (CH), 1745.97, 1709.36 (C=O), 1611.52, 1418.58 (C=C), 1267.74 (C–O). ESI-MS [M+1]: 414.5; ^1H NMR (DMSO-d_6, ppm): 7.98 (m, 2H), 7.73 (m, 2H), 7.71 (m, 2H), 7.60 (d, 1H, J = 15.6 Hz), 7.51 (m, 3H), 7.06 (d, 1H, J = 15.6 Hz), 5.61 (m, 1H), 4.61 (t, 1H, J = 8.4 Hz), 4.17, 4.06 (m, 2H), 3.67 (s, 3H), 2.29, 1.98 (m, 2H).

5.1.8. (2*S*,4*R*,*E*)-Methyl1-cinnamoyl-4-(3-phenylpropanoyloxy)pyrrolidine-2-carboxylate (A7). White crystal, yield 72.4%, mp 119.1–120.8 °C. IR (KBr, cm^{-1}): 2953.14 (CH), 1733.05, 1707.32 (C=O), 1606.48, 1418.78 (C=O), 1267.04 (C–O). ESI-MS [M+1]: 408.4; ^1H NMR (DMSO -d_6, ppm): 7.74 (m, 2H), 7.49 (d, 1H, J = 15.6 Hz), 7.41 (m, 3H), 7.21 (m, 4H), 7.12 (m, 1H), 7.0 (d, 1H, J = 15.6 Hz), 5.33 (m, 1H), 4.38 (t, 1H, J = 8.4 Hz), 3.93, 3.86 (m, 2H), 3.64 (s, 3H), 2.82 (t, 2H, J = 7.2 Hz), 2.63 (t, 2H, J = 7.8 Hz), 2.14, 2.11 (m, 2H).

5.1.9. (2*S*,4*R*,*E*)-Methyl1-cinnamoyl-4-(3,4,5-trimethoxybenzoyloxy)pyrrolidine-2-carboxylate (A6).

5.1.10. Compound 3,4,5-trimethoxybenzoic acyl chloride (3). 2.38 g 3, 4,5-3,4,5-trimethoxybenzoic acid was dissolved in 15 ml $SOCl_2$, and refluxed for 5 h, the resulting solution was rotary evaporated to get pale yellow crystal.

5.1.11. (2*S*,4*R*,*E*)-methyl1-cinnamoyl-4-(3,4,5-trimethoxybenzoyloxy)pyrrolidine-2-carboxylate (A6). Compound **A0** (1.38 g, 5 mmol)was dissolved in 20 ml CH_2Cl_2 and 3 ml Et_3N. After 5 ml CH_2Cl_2 with 3.86 g compound **3** was added dropwise at 0 °C and stirred for 4 h, CH_2Cl_2 was added to dilute the reaction mixture. Then the organic phase was washed with 1 N HCl, H_2O, saturated salt solution, dried over Na_2SO_4, anhydrous and rotary evaporated. The resulting yellow crude oil was chromatographed over flash silica with petro ether/EtOAc (2:1–1:2) to provide 1.4 g of white powder, yield 54.2%, mp 63–65 °C. IR (KBr, cm^{-1}): 2944.28 (CH), 1715.53 and 1654.63 (C=O), 1416.02 (C=O), 1223.03 and 1127.88 (C–O). ESI-MS [M+1]: 470.7. ^1H NMR (DMSO-d_6, ppm): 7.73 (m, 2H), 7.49 (d, 1H, J = 15.6 Hz), 7.40 (m, 3H), 7.24 (s, 1H), 7.23 (s, 1H), 7.05 (d, 1H, J = 15.6 Hz), 5.57 (m, 1H), 4.66 (t, 1H, J = 8.4 Hz), 4.11 (m, 2H), 3.81 (s, 6H), 3.72 (s, 3H), 3.67 (s, 3H), 2.56, 2.29 (m, 2H).

5.1.12. Compounds A8, A9, and A10 were prepared as described for compound A6

5.1.13. (2*S*,4*R*,*E*)-Methyl 1-cinnamoyl-4-(cinnamoyloxy)pyrrolidine-2-carboxylate (A8). White powder, yield 60.1%, mp 53.6–54.7 °C. IR (KBr, cm^{-1}): 2951 (CH), 1746.4 and 1653.65 (C=C), 1167.74 (C–O). ESI-MS

[M+1]: 394.4. ^{1}H NMR (DMSO-d_6, ppm): 7.74 (m, 4H), 7.71 (d, 1H, J = 15.6 Hz), 7.51 (d, 1H, J = 15.6 Hz), 7.42 (m, 6H), 7.06 (d, 1H, J = 15.6 Hz), 6.67 (d, 1H, J = 15.6 Hz), 5.51 (m, 1H), 4.55 (t, 1H, J = 8.4 Hz), 4.06, 4.02 (m, 2H), 3.67 (s, 3H), 2.26, 1.98 (m, 2H).

5.1.14. (2*S*,4*R*,*E*)-Methyl 1-cinnamoyl-4-((*E*)-3-(4-methoxyphenyl)acryloyloxy)-pyrrolidine-2-carboxylate. Pale yellow powder, yield 59.8%, mp 121.1–122.8 °C. IR (KBr, cm^{-1}): 2952.6 (CH), 1710.46 and 1653.34 (C=O), 1603.64 (C=C), 1161.94 (C–O). ESI-MS [M+1]436.6; ^{1}H NMR (DMSO-d_6, ppm): 7.74 (m, 2H), 7.68 (m, 2H), 7.66 (d, 1H, J = 16.2 Hz), 7.51 (d, 1H, J = 15 Hz), 7.41 (m, 3H), 7.05 (d, 1H, J = 15.6 Hz), 6.95 (m, 2H), 6.50 (d, 1H, J = 15.6 Hz), 5.49 (m, 1H), 4.53 (t, 1H, J = 7.8 Hz), 3.78 (m, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 2.49, 2.23 (m, 2H).

5.1.15. (2*S*,4*R*,*E*)-Methyl 1-cinnamoyl-4-((E)-3-(3,4-dimethoxyphenyl)acryloyloxy)-pyrrolidine-2-carboxylate (A10).. White crystal, yield 56.3%, mp 136.6–137.5 °C. IR (KBr, cm^{-1}): 2976.86 (CH), 1740.86 1711.44 (C=O), 1599.21, 1514.10 (C=C), 1248.84 (C–O). ESI-MS [M+1]:466.6; ^{1}H NMR (DMSO-d_6, ppm): 7.75 (m, 2H), 7.63 (d, 1H, J = 15.6 Hz), 7.51 (d, 1H, J = 15.6 Hz), 7.38 (m, 4H), 7.25 (m, 1H), 7.07 (d, 1H, J = 15.6 Hz), 6.97 (d, 1H, J = 8.4 Hz), 6.58 (d, 1H, J = 16.2 Hz), 5.50 (m, 1H), 4.53 (t, 1H, J = 7.8 Hz), 4.08, 4.03 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 2.23, 1.98 (m, 2H).

5.2. Compounds obtained from Scheme 1

5.2.1. (*E*) 4-Methoxyl cinnamoyl chloride (4). 4-methoxyl cinnamic acid (17.8 g, 100 mmol) was dissolved in 40 ml $SOCl_2$ and120 ml benzene, and refluxed for 3 h. The resulting solution rotary evaporated to get pale yellow crystal.

5.2.2. (2*S*,4*R*,*E*)-Methyl 4-hydroxy-1-(3-(4-methoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (B0). Compound 1 (3.63 g, 20 mmol) was suspended in 50 ml Py and 5 ml Et_3N. After stirred for 20 min at room temperature, the resulting mixture was filtered. The filtrate was cooled to −5 °C, and at this temperature 40 ml CH_2Cl_2 with 4.27 g 4 (24 mmol) was added. After stirred for 5 h, the resulting mixture was filtrated to remove white precipitation, and the filtrate was rotary evaporated. Small amount toluene was added to remove Py. The resulting crude oil was dissolved with 200 ml CH_2Cl_2, washed with 3 N HCl, H_2O, saturated salt solution, and dried over Na_2SO_4, anhydrous. The organic phase was rotary evaporated to provide pale yellow crude product. The crude solid was recrystallized with EtOAc-CHX (2:1) to get 3.83 g of pale yellow lamellar crystal, yield 62.3%, mp139.4–140.6 °C. IR (KBr, cm^{-1}): 3197.98 (OH), 2952.18 (CH), 1731.41 and 1646.46 (C=O), 1573.98 and 1513.61 (C=C), 1255.35 (C–O). ESI-MS [M+1]:306.5. ^{1}H NMR (DMSO-d_6, ppm): 7.68 (m, 2H), 7.43 (d, 1H, J = 15.6 Hz), 6.96 (m, 2H), 6.86 (d, 1H, J = 15.6 Hz), 5.22 (m, 1H), 4.42 (t, 1H, J = 8.4 Hz), 4.40, 3.82 (m, 2H), 3.78 (s, 3H), 3.68 (s, 1H), 3.62 (s, 3H), 2.13, 1.92 (m, 2H).

5.2.3. (2*S*,4*R*,*E*)-Methyl4-acetoxy-1-(3-(4-methoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (B1). Compound **B0** (1.50 g, 5 mmol) was taken in CH_2Cl_2 (20 ml) and Et_3N (3 ml) was added at 0 °C. Five milliliters of CH_2Cl_2 with 0.5 ml acetyl chloride was added dropwise and the resulting mixture was stirred for 2 h at room temperature. The following mixture was washed with 1 N HCl, H_2O, saturated salt solution, and dried over Na_2SO_4, anhydrous, filtered, and evaporated to give pale yellow oil, which was chromatographed over flash silica with petro ether-Ac (3:1 to 1:1) to provide 0.9 g white crystal, yield 53.4%, mp 123–124 °C. IR (KBr, cm^{-1}): 2952.03 (CH), 1736.90 and 649.05 (C=O), 1598.43, 1512.26 (C=C), 1261.28 (C–O). ESI-MS [M+1]:348.5; ^{1}H NMR (DMSO-d_6, ppm): 7.68 (m, 2H), 7.44 (d, 1H, J = 15.6 Hz), 6.96 (m, 2H), 6.87 (d, 1H, J = 15.6 Hz), 5.33 (m, 1H), 4.44 (t, 1H, J = 8.4 Hz), 3.95, 3.79 (m, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 2.34, 2.16 (m, 2H), 2.02 (s, 3H).

5.2.4. Compounds B2, B3, B4, B5, and B7 were prepared as described for compound B1

5.2.5. (2*S*,4*R*,*E*)-Methyl1-(3-(4-methoxyphenyl)acryloyl)-4-(propionyloxy)pyrrolidine-2-carboxylate (B2). White solid, yield 59.2%, mp 86–88 °C. IR (KBr, cm^{-1}): 2962.46 (CH), 1732.24 and 1652.0 (C=O), 1601.38 and 1513.86 (C=C), 1259.28 and 1175.32 (C–O). ESI-MS [M+1]: 362.5. ^{1}H NMR (DMSO-d_6, ppm): 7.68 (m, 2H), 7.45 (d, 1H, J = 15.6 Hz), 6.97 (m, 2H), 6.87 (d, 1H, J = 15.6 Hz), 5.34 (m, 1H), 4.44 (t, 1H, J = 8.4 Hz), 3.95, 3.94 (m, 2H), 3.79 (s, 3H), 3.64 (s, 3H), 2.50 (m, 1H), 2.34 (q, 2H, J = 2.4 Hz, 4.2 Hz), 2.16 (m, 1H), 1.00 (t, 3H, J = 7.2 Hz).

5.2.6. (2*S*,4*R*,*E*)-methyl4-(butyryloxy)-1-(3-(4-methoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (B3). White solid, yield 63.8%, mp 54–56 °C. IR (KBr, cm^{-1}): 2962.38 (CH), 1731.99, 1652.09 (C=O), 1601.13, 1513.94 (C=C), 1259.49, 1175.19 (C–O). ESI-MS [M+1]: 376.5. ^{1}H NMR (DMSO-d_6, ppm): 7.69 (m, 2H, Ar–H), 7.44 (d, 1H=CH, J = 15.6 Hz), 6.97 (m, 2H), 6.86 (d, 1H, J = 15.6 Hz), 5.35 (m, 1H), 4.44 (t, 1H, J = 7.8 Hz), 3.96 (m, 2H), 3.79 (s, 3H), 3.64 (s, 3H), 2.34, 2.15 (m, 2H), 2.28 (t, 2H, J = 7.2 Hz), 1.53 (m, 2H), 0.86 (t, 3H, J = 1.8 Hz).

5.2.7. (2*S*,4*R*,*E*)-Methyl4-(benzoyloxy)-1-(3-(4-methoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (B4). White crystal, yield 71.1%, mp 119.6–120.8 °C. IR (KBr, cm^{-1}): 2958.74 (CH), 1731.86, 1649.15 (C=O), 1599.83, 1513.58 (C=C), 1262.25 (C–O). ESI-MS [M+1]: 410.6. ^{1}H NMR (DMSO-d_6, ppm): 7.96 (m, 2H), 7.66 (m, 3H), 7.52 (m, 2H), 7.44 (d, 1H, J = 15.6 Hz), 6.98 (m, 2H), 6.89 (d, 1H, J = 15.6 Hz), 5.61 (m, 1H), 4.58 (t, 1H, J = 8.4 Hz), 4.06, 4.04 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2.29, 2.27 (m, 2H).

5.2.8. (2*S*,4*R*,*E*)-Methyl-4-(4-chlorobenzoyloxy)-1-(3-(4-methoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (B5). White crystal, yield 69.5%, mp 108–110 °C. IR (KBr, cm^{-1}): 2956.81 (CH), 1730.09 (C=O), 1600.74 and 1513.55 (C=C), 1264.97 (C–O). ESI-MS[M+1]:444.7; ^{1}H NMR(DMSO-d_6, ppm): 7.97 (m, 2H), 7.67 (m,

2H), 7.58 (m, 2H), 7.43 (d, 1H, J = 15.6 Hz), 6.95 (m, 2H), 6.88 (d, 1H, J = 15.6 Hz), 5.60 (m, 1H), 4.57 (t, 1H, J = 7.8 Hz), 4.14, 4.06 (m, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 2.32, 2.26 (m, 2H).

5.2.9. (2*S*,4*R*,*E*)-Methyl1-(3-(4-methoxyphenyl)acryloyl)-4-(3- phenylpropanoyloxy)pyrrolidine-2-carboxylate (B7). Yellow solid, yield 54.4%, mp 61–64 °C. IR(KBr, cm^{-1}): 2952.5 (CH), 1739.5, 1651.3 (C═O), 1602.06, 1513.03 (C═C), 1250.3, 1174.55 (C–O). ESI-MS[M+1]: 438.6; ^{1}H NMR(DMSO-d_6, ppm): 7.48 (d, 1H, J = 15.6 Hz), 7.23 (m, 6H), 7.12 (m, 1H), 6.97 (m, 2H), 6.84 (d, 1H, J = 15.6 Hz), 5.33 (m, 1H), 4.40 (t, 1H, J = 8.4 Hz), 3.94, 3.86 (m, 2H), 3.79 (s, 3H), 3.64 (s, 3H,), 2.83 (t, 2H, J = 7.2 Hz), 2.53 (t, 2H, J = 7.8 Hz), 2.14, 2.11 (m, 2H).

5.2.10. (2*S*,4*R*,*E*)-Methyl-1-(3-(4-methoxyphenyl)acryloyl)-4-(3,4,5trimethoxy-benzoyloxy)pyrrolidine-2-carboxylate (B6). Compound **B0** (1.53 g, 5 mmol) was taken in CH_2Cl_2 (20 ml) and Et_3N (1.5 ml) was added at 0 °C. Five milliliters of CH_2Cl_2 with 3.6 g compound **3** was added dropwise and the resulting mixture was stirred for 4 h at room temperature. CH_2Cl_2 was added to dilute the reaction mixture. The organic layer was washed with 1 N HCl, H_2O, saturated salt solution, and dried over Na_2SO_4, anhydrous, filtered, and evaporated to give pale yellow oil, which was chromatographed over flash silica with chloroform-methanol (50:1–30:1) to provide 1.6 g white powder, yield 64.2%, mp 66–68 °C. IR(KBr, cm^{-1}): 2943.53 (CH), 1715.57 and 1651.85 (C═O), 1601.85 and 1513.13 (C═C), 1222.81, 1174.46 and 1127.7 (C–O). ESI-MS[M+1]: 500.6. ^{1}H NMR(DMSO-d_6, ppm): 7.68 (m, 2H), 7.44 (d, 1H, J = 15.6 Hz), 7.24 (m, 2H), 6.96 (s, 1H), 6.94 (s, 1H), 6.89 (d, 1H, J = 15.6 Hz), 5.56 (m, 1H), 4.64 (t, 1H, J = 7.8 Hz), 4.09 (m, 2H), 3.81 (s, 3H), 3.78 (s, 6H), 3.72 (s, 3H), 3.67 (s, 3H), 2.51, 2.28 (m, 2H).

5.2.11. Compounds B8, B9, and B10 were prepared as described for compound B6.

5.2.12. (2*S*,4*R*)-Methyl4-(cinnamoyloxy)-1-((*E*)-3-(4-methoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (B8). White needle crystal, yield 62.1%, mp 64.5–65.7 °C. IR(KBr, cm^{-1}): 2952.15 (CH), 1712.15, 1650.98 (C═O), 1601.52, 1512.88 (C═C), 1250.25, 1173.37 (C–O). ESI-MS[M+1]: 436.7. ^{1}H NMR (DMSO-d_6, ppm): 7.74 (m, 2H), 7.70 (m, 2H), 7.68 (d, 1H, J = 15.6 Hz), 7.45 (d, 1H, J = 15.6 Hz), 7.41 (m, 3H), 6.98 (m, 2H), 6.92 (d, 1H, J = 15.6 Hz), 6.68 (d, 1H, J = 15.6 Hz), 5.50 (m, 1H), 4.52 (t, 1H, J = 8.4 Hz), 4.06, 4.01 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2. 42, 2.24 (m, 2H).

5.2.13. (2*S*,4*R*)-Methyl 1-((*E*)-3-(4- methoxyphenyl)acryloyl)-4-((*E*)-3-(4-methoxyphenyl)acryloyloxy)pyrrolidine-2-carboxylate(B9). Pale yellow powder, yield 55.6%, mp 61.2–63.4 °C. IR (KBr, cm^{-1}): 2953.09 (CH), 1709.24, 1651.24 (C═O), 1603.15, 1513.17 (C═C), 1251.38, 1173.21 (C–O). ESI-MS[M+1]: 446.6; ^{1}H NMR(DMSO-d_6, ppm): 7.68 (m, 4H), 7.63 (d, 1H, J = 15.6 Hz), 7.45 (d, 1H, J = 15.6 Hz), 6.97 (m, 4H), 6.91 (d, 1H, J = 15.6 Hz), 6.52 (d, 1H, J = 15.6 Hz), 5.48 (m, 1H), 4.51 (t, 1H, J = 8.4 Hz), 4.01, 3.99 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 2.43, 2.23 (m, 2H).

5.2.14. (2*S*,4*R*,*E*)-Methyl 4-((*E*)-3-(3,4-dimethoxyphenyl)acryloyloxy)-1-((*E*)-3-(4-methoxyphenyl)acryloyl) pyrrolidine-2-carboxylate(B10). White solid, yield 49.3%, mp 141–143 °C. IR (KBr, cm^{-1}): 2938.5 (CH), 1744.4, 1645.77 (C═O), 1514.3 (C═O), 1140 (C–O). ESI-MS[M+1]:496.7; ^{1}H NMR (DMSO-d_6, ppm): 7.70 (m, 2H), 7.60 (d, 1H, J = 15.6 Hz), 7.46 (m, 1H), 7.37 (s, 1H), 7.25 (d, 1H, J = 7.8 Hz), 6.96 (m, 3H), 6.91 (d, 1H, J = 15.6 Hz), 6.58 (d, 1H, J = 16.6 Hz), 5.49 (m, 1H), 4.51 (t, 1H, J = 8.4 Hz), 4.05, 3.98 (m, 2H), 3.91 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.24, 2.21 (m, 2H).

5.3. Compounds getting from Scheme 1

5.3.1. (*E*)-3-(3,4-dimethoxyphenyl)-2-propenoic acid (5)[108]. Caffeic acid (18 g, 0.1 mol) was dissolved in cool 90 ml NaOH solution (4 mol/L), in which process the inner temperature was required under 20 °C. After Me_2SO_4 20 ml was added dropwise and stirred for 20 min, 50 ml NaOH solution (4 mol/L) and 20 ml Me_2SO_4 were dropped into the reaction system constantaneously. The inner temperature was required under 35 °C. The resulting mixture was slowly heated to 90 °C in 1 h and maintained at this temperature for 1 h, and then the solution was refluxed for 1.5 h, after 50 ml NaOH solution (4 mol/L) was added, another 2 h of refluxing was applied. The pH of the resulting solution was regulated to 2 by concentrated HCl. Two to three hours later, mass brown solid was attained by filtering, and wash to neutrality with water. The gross was recrystallized in EtOH and H_2O to get 16.4 g (yield 78.8%)light yellow crystal, mp179.4-181.1 °C, which did not appear blue in Fe $(SCN)_3$/$FeCl_3$.

5.3.2. (E)-3-(3, 4-Dimethoxyphenyl)-2-acrolyl chloride (6). Compound 5 (10.4 g, 50 mmol)was dissolved in 20 ml $SOCl_2$ and 150 ml benzene, and refluxed for 3 h. The resulting solution was rotary evaporated to get light yellow crystal.

5.3.3. (2*S*,4*R*,*E*)-Methyl 4-hydroxyl-1-(3-(3,4-dimethoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (C0). Compound 1 (1.82 g,10 mmol) was suspended in 20 ml Py and 3 ml Et_3N. After stirred for 20 min at room temperature, the resulting mixture was filtered. The filtrate was cooled to −5 °C, and at this temperature10 ml CH_2Cl_2 with 2.82 g 6 (12 mmol) was added. After stirred for 4 h, the resulting mixture was filtered to remove white precipitation, and the filtrate was rotary evaporated. The resulting crude oil was chromatographed over flash silica with petro ether/EtOAc (3:1–1:4) to provide 2.4 g of pale yellow solid, yield 71.9%, mp 62.5–64.5 °C.

5.3.4. (2*S*,4*R*,*E*)-Methyl 4-acetoxy-1-(3-(3,4-dimethoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (C1). In nitrogen atmosphere, compound C0 (3.35 g, 10 mmol) was taken in CH_2Cl_2 (20 ml) and Et_3N (4.5 ml) was added at 0 °C. Five milliliters of $CH_2Cl_2$with 0.8 ml acetyl

chloride was added dropwise and the resulting mixture was stirred for 3 h at room temperature .CH_2Cl_2 was added to dilute the reaction mixture. Then the organic phase was washed with 1 N HCl, H_2O, saturated salt solution, dried over Na_2SO_4 anhydrous, filtered, and evaporated to give pale yellow oil, which was chromatographed over flash silica with petro ether-acetone (4:1–1:2) to provide 2.8 g light yellow solid, yield 74.2%, mp 45.6–47.6 °C. IR (KBr, cm^{-1}): 2953.3 (CH), 1746.2, 1603.3 (C═O), 1513.2 (C═C), 1262.7 (C–O). ESI-MS[M+1]: 378.6. ^1H NMR (DMSO-d_6, ppm): 7.43 (d, 1H, J = 15 Hz), 7.37 (s, 1H), 7.21 (m, 1H), 6.96 (d, 1H, J = 8.4 Hz), 6.89 (d, 1H, J = 15.6 Hz), 5.34 (m, 1H), 4.44 (t, 1H, J = 8.4 Hz), 3.95 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H), 2.36, 2.15 (m, 2H), 2.02 (s, 3H).

5.3.5. Compounds C2, C3, C4, C5, and C7 were prepared as described for compound C1

5.3.6. (2*S*,4*R*,*E*)-Methyl1-(-3-(3,4-dimethoxyphenyl) acryloyl)-4-propionyloxypyrrolidine-2-carboxylate (C2). Light yellow solid, yield 64.3%, mp 62.6–63.8 °C. IR (KBr, cm^{-1}): 2951.0 (CH), 1739.6, 1651.0 (C═O), 513.7 (C═C), 1266.3 (C–O). ESI-MS [M+1]: 392.3; ^1H NMR (DMSO-d_6, ppm): 7.45 (d, 1H, J = 15.6 Hz), 7.36 (s, 1H), 7.22 (m, 1H), 6.98 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 15.6 Hz), 5.36 (m, 1H), 4.46 (t, 1H, J = 8.4 Hz), 3.97, 3.92 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.64 (s, 3H), 2.34 (q, 2H, J = 4.8 Hz, 3 Hz), 2.17, 1.98 (m, 2H), 1.01 (t, 3H, J = 7.8 Hz).

5.3.7. (2*S*,4*R*,*E*)-Methyl 4-butyryloxy-1-(-3-(3,4-dimethoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (C3). White solid, yield 57.6%, mp 46.5–47.7 °C. IR (KBr, cm^{-1}): 2961.9 (CH), 1738.9 and 1650.9 (C═O), 1513.7 (C═C), 1266.0 (C═O). ESI-MS[M+1]: 406.6; ^1H NMR (DMSO-d_6, ppm): 7.43 (d, 1H, J = 15.6 Hz), 7.37 (s, 1H), 7.23 (m, 1H), 6.97 (d, 1H, J = 7.8 Hz), 6.88 (d, 1H, J = 15 Hz), 5.36 (m, 1H), 4.44 (t, 1H, J = 7.8 Hz), 3.96 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H), 2.34 (m, 1H)2.29 (t, 2H, J = 4.8 Hz), 2.15 (m, 1H), 1.52 (m, 2H), 0.86 (t, 2H, J = 7.8 Hz).

5.3.8. (2*S*,4*R*,*E*)-Methyl 4-benzoyloxy-1-(-3-(3,4-dimethoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (C4). White crystal, yield 66.2%, mp 72.4–73.6 °C.IR (KBr, cm^{-1}): 2952.56 (CH), 1719.8 and 1650.6 (C═O), 1513.3 (C═C), 1268.8 (C–O). ESI-MS[M+1]: 440.6. ^1H NMR (DMSO-d_6, ppm): 7.97 (m, 2H), 7.65 (m, 1H), 7.51 (m, 2H), 7.43 (d, 1H, J = 15.6 Hz), 7.36 (s, 1H), 7.18 (m, 1H), 6.95 (m, 1H), 6.89 (d, 1H, J = 14.4 Hz), 5.63 (m, 1H), 4.60 (t, 1H, J = 7.8 Hz), 4.11, 4.07 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 2.50, 2.30 (m, 2H).

5.3.9. (2*S*,4*R*,*E*)-Methyl 4-(chlorobenzoyloxy)-1-(-3-(3,4-dimethoxyphenyol)acryloyl)pyrrolidine-2-carboxylate (C5). White needle crystal, yield 63.2%, mp 65.0–67.1 °C. IR (KBr, cm^{-1}): 2952.64 (CH), 1722.17, 1650.89 (C═O), 1513.26 (C═C), 1269.02 (C–O). ESI-MS[M+1]: 474.4. ^1H NMR (DMSO-d_6, ppm): 7.98 (m, 2H), 7.60 (m, 2H), 7.43 (d, 1H, J = 15.6 Hz), 7.35 (s, 1H), 7.22 (m, 1H), 6.97 (d, 1H, J = 8.4 Hz), 6.90 (d, 1H, J = 15.6 Hz), 5.63 (m, 1H), 4.60 (t,1H, J = 7.8 Hz), 4.13, 4.07 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 2.28, 1.98 (m, 2H).

5.3.10. (2*S*,4*R*,*E*)-Methyl-(-3-(3,4-dimethoxyphenyl)acryloyl)-4-(3- phenylpropanoyloxy)pyrrolidine-2-carboxylate (C7). White needle crystal, yield 58.3%, mp 134.5–135.5 °C. IR (KBr, cm^{-1}): 2948.6 (CH), 1739.95, 1650.0 (C═O), 1515.5, 1429.1 (C═C), 1265.2 (C–O). ESI-MS[M+1]:468.4; ^1H NMR (DMSO -d_6, ppm): 7.42 (d, 1H, J = 15.6 Hz), 7.37 (s, 1H), 7.22 (m, 5H), 7.13 (m, 1H), 6.97 (d, 1H, J = 7.8 Hz), 6.86 (d, 1H, J = 15.6 Hz), 5.63 (m, 1H), 4.39 (t, 1H, J = 7.8 Hz), 4.07 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 2.82 (t, 2H, J = 7.2 Hz), 2.6 (t, 2H, J = 7.2 Hz), 2.49, 1.98 (m, 2H).

5.3.11. Compounds C6, C8, C9, and C10 were prepared as described for compound B6

5.3.12. (2*S*,4*R*,*E*)-Methyl1-(-3-(3,4-dimethoxyphenyl) acryloyl-4-(3,4,5-trimethoxybenzonyloxy)pyrrolidine-2-carboxylate (C6). White solid, yield 56.8%, mp 72–74 °C. IR (KBr, cm^{-1}): 2942.65 (CH), 1715.33, 1651.25 (C═C), 1224.13 (C–O). ESI-MS[M+1]: 530.4; ^1H NMR (DMSO-d_6, ppm): 7.45 (d, 1H, J = 15.6 Hz), 7.36 (s, 1H), 7.24 (m, 2H), 7.16 (d, 1H, J = 4.8 Hz), 6.96 (d, 1H, J = 8.4 Hz), 6.90 (d, 1H, J = 15.6 Hz), 5.58 (m, 1H), 4.65 (t, 1H, J = 7.8 Hz), 4.10 (m, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.78 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 2.58, 2.29 (m, 2H).

5.3.13. (2*S*,4*R*)-Methyl4-cinnamoyloxy-1-((E)-3-(3,4-dimethoxyphenyl)acryloyl)pyrrolidine-2-carboxylate (C8). Pale yellow solid, yield 54.7%, mp 59.6–61.5 °C. IR (KBr, cm^{-1}): 2952.9 (CH), 1746.4, 1711.8, 1650 (C═O), 1514.0 (C═C), 1162.3 (C–O). ESI-MS [M+1]: 466.5; ^1H NMR (DMSO-d_6, ppm): 7.73 (m, 3H, Ar–H), 7.42 (m, 5H), 7.22 (m, 1H), 6.96 (d, 1H, J = 8.4 Hz), 6.91 (d, 1H, J = 15.6 Hz), 6.68 (d, 1H, J = 15.6 Hz), 5.51 (m, 1H), 4.53 (t, 1H, J = 7.8 Hz), 4.04 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 2.49, 2.25 (m, 2H).

5.3.14. (2*S*,4*R*)-Methyl1-((*E*)-3-(3,4-dimethoxyphenyl) acryloyl)-4-((E)-3-(4-methoxy-phenyl)acryloyloxy) pyrrolidine-2-carboxylate (C9). Light yellow solid, yield 55.6%, mp 52.6–53.8 °C. IR (KBr, cm^{-1}): 2953.7 (CH), 1741.1, 1650.5 (C═O), 1598.5, 1513.8 (C═C), 1266.1 (C–O). ESI-MS [M+1]:496.8; ^1H NMR (DMSO-d_6, ppm): 6.75 (m, 3H), 6.50 (d, 1H, J = 15.6 Hz), 6.40 (d, 1H, J = 15.6 Hz), 6.16 (m, 4H), 6.04 (d, 1H, J = 15.6 Hz), 5.61 (d, 1H, J = 15.6 Hz), 5.59 (m, 1H), 3.87 (t, 1H, J = 7.8 Hz), 3.31, 3.29 (m, 2H), 3.08 (s, 3H), 3.06 (s, 3H), 3.02 (s, 3H), 2.97 (s, 3H), 1.75, 1.51 (m, 2H).

5.3.15. (2*S*,4*R*,*E*)-Methyl1-((E)-3-(3,4-dimethoxyphenyl) acryloyl)-4-((*E*)-3-(3,4-dime-thoxyphenyl)acryloyloxy) pyrrolidine-2-carboxylate (C10). Pale yellow solid, yield 52.8%, mp 75.5–77.4 °C. IR (KBr, cm^{-1}): 2938.5 (CH), 1744.4 and 1645.77 (C═O), 1514.3 (C═O), 1140 (C–O). ESI-MS [M+1]: 526.6. ^1H NMR (DMSO-d_6, ppm): 7.63 (d, 1H, J = 15.6 Hz), 7.44 (d, 1H, J = 15 Hz), 7.37 (m, 2H), 7.24 (m, 2H), 6.97 (m, 2H), 6.92 (d, 1H, J = 15.6 Hz), 6.58 (d, 1H, J = 16.2 Hz), 5.51 (m, 1H),

4.51 (t, 1H, J = 8.4 Hz), 4.06, 4.01 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 2.23, 1.98 (m, 2H).

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