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Arylamine based cathepsin K inhibitors: Investigating P3 heterocyclic substituents

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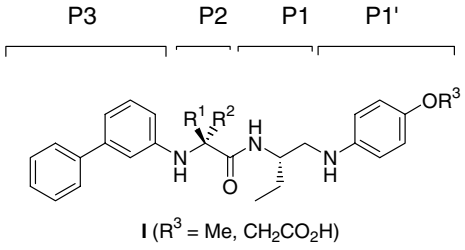
Abstract—A modification of novel cathepsin K inhibitors **I** was carried out. The structural design was aimed at reducing the lipophilic character of compounds **I** for obtaining better pharmacokinetic profiles. This modification afforded several less lipophilic compounds with good inhibitory activities and pharmacokinetic profiles, although the enzyme selectivity over cathepsin S was left at issue.

1. Introduction

Cathepsin K[1] is a member of the papain superfamily of cysteine proteases and highly expressed in osteoclasts. Cathepsin K is an attractive pharmaceutical target for the treatment of osteoporosis as its primary role is the degradation of type I collagen, one of the main constituents of bone matrix. We previously reported[2] the structure–activity relationships of novel *N*-(3-biphenyl)amino acid amides **I** as cathepsin K inhibitors derived from a Novartis compound[3] (Fig. 1). The SAR study revealed that the 3-biphenyl group was an effective P3 substituent, and the introduction of an ethyl group to the P1 unit significantly improved the inhibitory activity. However, the incorporation of these two lipophilic groups brought an increase in the log *P* value. Increase in lipophilicity sometimes causes lower solubility to water and higher affinity to cytochrome P450 enzymes, resulting in poor pharmacokinetics.[4] Therefore, we intended to lower the lipophilicity of compounds **I** by the replacement of the biphenyl group with heterocyclic groups in continued research. In this paper, we wish to report the effects of this modification on the inhibitory activities and pharmacokinetic profiles of cathepsin K inhibitors.



I (R^3 = Me, CH_2CO_2H)

Figure 1. Assumed binding mode of compound **I**.

2. Chemistry

As shown in Scheme 1, pyridine derivatives **5c**–**e** were prepared via Suzuki coupling.[5] A copper-catalyzed coupling of dibromobenzene (**1**) with amino acid **2** afforded carboxylic acid **3**.[6] Amidation of carboxylic acid **3** with *N*-(4-methoxyphenyl)ethane-1,2-diamine[7] followed by coupling with pyridineboronic acids provided pyridine derivatives **5c**–**e**.

The preparation of carboxylic acids is shown in Scheme 2. 3-Bromobiphenyl (**6**) and 1-bromonaphthalene (**8**) were coupled with amino acids under the conditions

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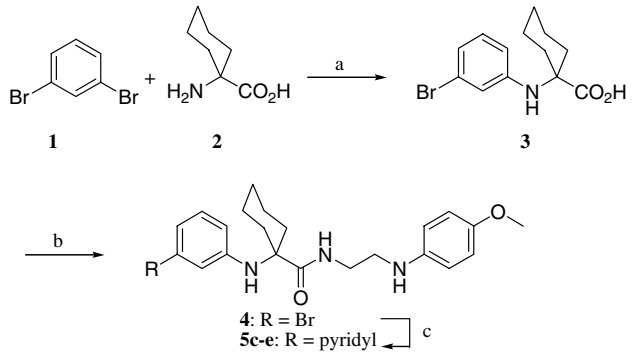
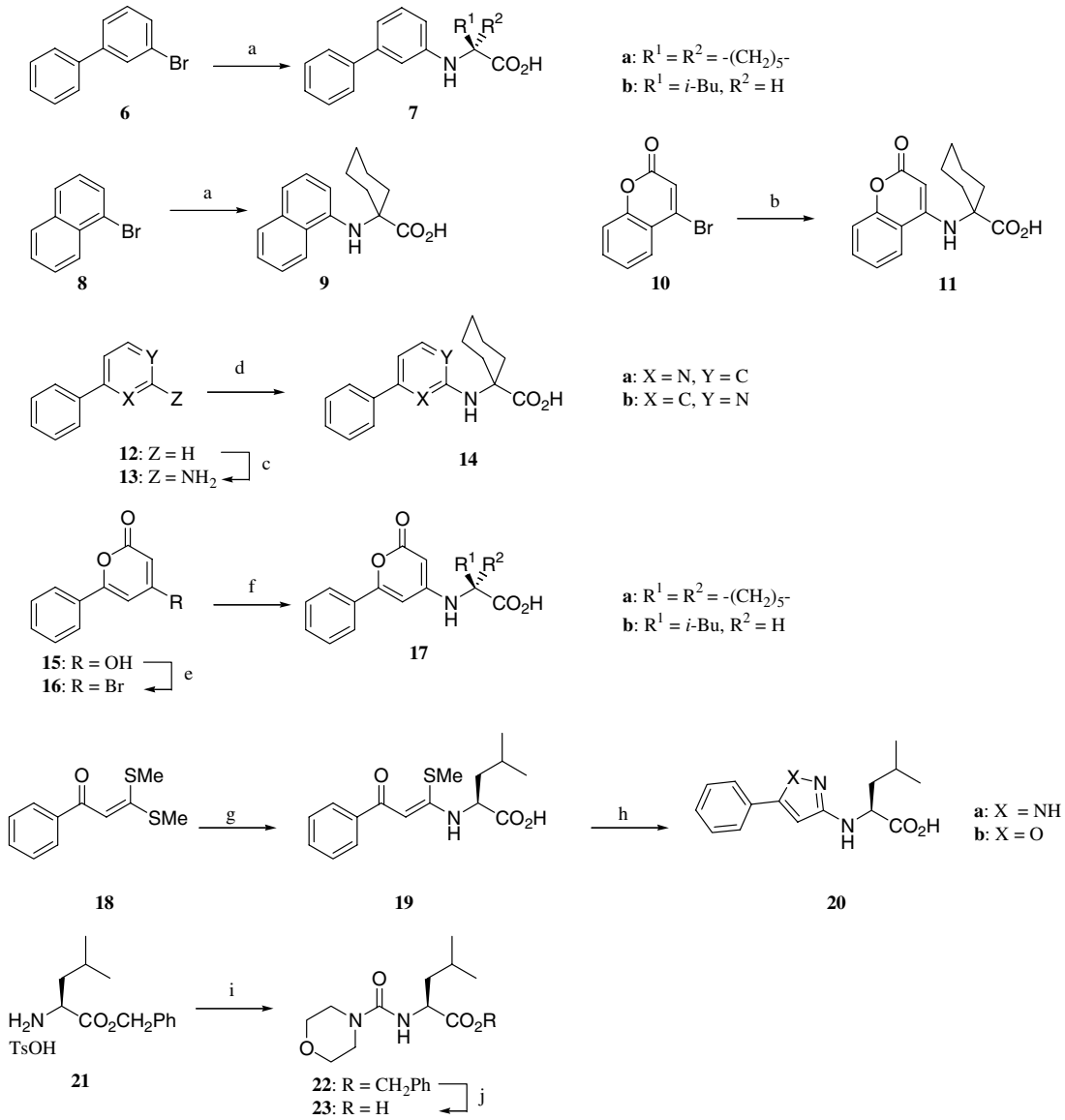


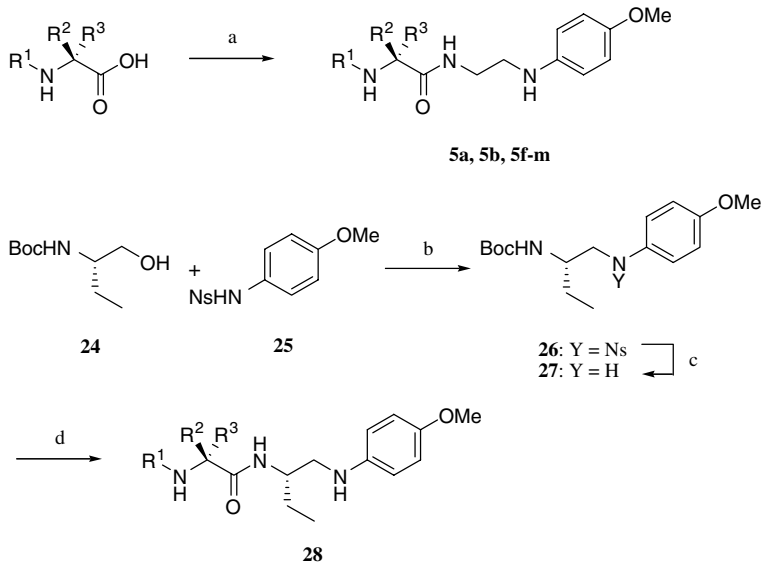
Scheme 1. Synthesis of pyridine derivatives **5c–e**. Reagents and conditions: (a) CuBr·SMe_2, K_2CO_3, DMA, 120 °C, 44%; (b) *N*-(4-methoxyphenyl)ethane-1,2-diamine, WSC·HCl, HOBt, DMF, 73%; (c) pyridineboronic acid, $Pd(Ph_3P)_4$, Na_2CO_3, toluene, H_2O, reflux.

described above to provide **7** and **9**, respectively. The preparation of coumarin **11** was achieved by N-alkylation of **2** with 4-bromocoumarin (**10**).[8] Amination of phenylpyridines **12**[9] followed by N-alkylation provided carboxylic acids **14**. Hydroxypyranone **15**[10] was converted to bromide **16** (PBr_3, DMF), followed by coupling with amino acids to afford pyranones **17**. Pyrazole **20a** and isoxazole **20b** were prepared from acetal **19**, which was synthesized from dithioacetal **18**.[11] Reaction of **19** with hydrazine or hydroxylamine afforded pyrazole **20a** or isoxazole **20b**, respectively. Urea **23** was prepared by hydrogenolysis of benzyl ether **22**, which was prepared from benzyl L-leucine (**21**).

As shown in Scheme 3, the acids prepared in Scheme 2 were coupled with *N*-(4-methoxyphenyl)ethane-1,2-di-

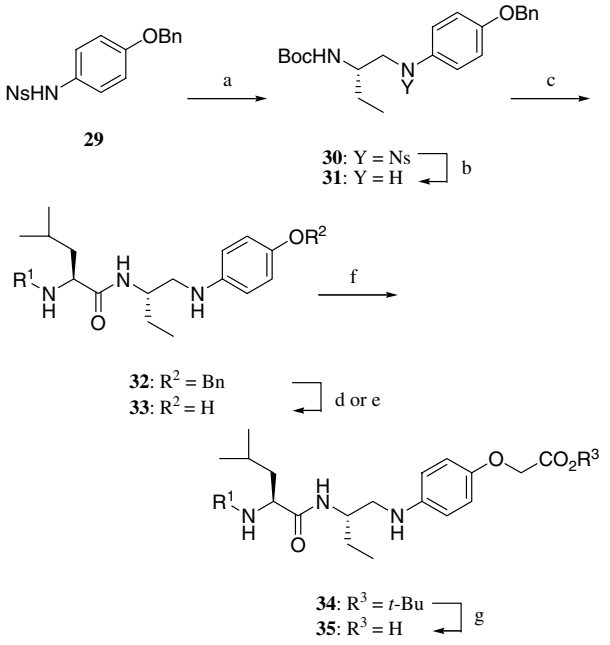


Scheme 2. Synthesis of carboxylic acids. Reagents and conditions: (a) **2** or L-leucine, CuBr·SMe_2, K_2CO_3, DMA, 120 °C, 43% (**7a**), 67% (**7b**); (b) **2**, K_2CO_3, Et_3N, *t*-BuOH, reflux; (c) $NaNH_2$, *N*,*N*-dimethylaniline, 160 °C, 47% (**13a**), 34% (**13b**); (d) methyl 1-bromocyclohexanecarboxylate, KOH, *t*-BuOH, reflux, 34% (**14a**), 5% (**14b**); (e) PBr_3, DMF, 60 °C, 56%; (f) **2** or L-leucine, K_2CO_3, *t*-BuOH, reflux, 80% (**17a**), 77% (**17b**); (g) L-leucine, NaOH, EtOH/H_2O, reflux, 70%; (h) H_2NNH_2·H_2O (for **20a**) or $HONH_2$·HCl, KOH (for **20b**), EtOH, reflux, 76% (**20b**); (i) 4-morpholinecarbonyl chloride, CH_2Cl_2, 99%; (j) H_2, Pd/C, EtOH, 99%.



Scheme 3. Synthesis of compounds **5a**, **5b**, **5f**–**m**, and **28**. Reagents and conditions: (a) *N*-(4-methoxyphenyl)ethane-1,2-diamine, WSC·HCl, HOBt, DMF; (b) DEAD, PPh_3, THF; (c) PhSH, K_2CO_3, MeCN, 83% (two steps); (d) HCl, 1,4-dioxane, then carboxylic acids, WSC·HCl, HOBt, CH_2Cl_2. Ns, 2-nitrobenzenesulfonyl.

amine[7] to provide methyl ethers **5a**, **5b**, and **5f**–**m**. The preparation of 1,2-diaminobutane **27** was achieved by Mitsunobu reaction[12] of *N*-Boc aminoalcohol **24**[13] with 2-nitrobenzenesulfonamide **25**[14] and subsequent deprotection with PhSH.[15] After deprotection of the Boc group of **27**, the reaction with the carboxylic acids provided methyl ethers **28**.



Scheme 4. Synthesis of compounds **32**, **34**, and **35**. Reagents and conditions: (a) **24**, DEAD, PPh_3, THF; (b) PhSH, K_2CO_3, MeCN, 82% (two steps); (c) HCl, 1,4-dioxane then N-substituted L-leucine, WSC·HCl, HOBt, DMF; (d) H_2, Pd/C, EtOH; (e) HCl, AcOH, reflux; (f) *tert*-butyl bromoacetate, NaH, DMF/THF; (g) TFA, CH_2Cl_2 then HCl, 1,4-dioxane. Ns, 2-nitrobenzenesulfonyl.

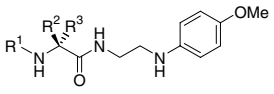
The preparations of benzyl ethers **32** and acetic acids **35** are shown in Scheme 4. Starting from 2-nitrobenzenesulfonamide **29**, the same synthetic route for the preparation of **28** shown in Scheme 3 provided benzyl ethers **32**. The cleavage of benzyl ether in **32** was accomplished under hydrogenolytic (H_2, Pd/C, EtOH) or acidic (concentrated HCl in refluxing AcOH) conditions to afford phenols **33**. Alkylation of phenols **33** with *tert*-butyl bromoacetate provided *tert*-butyl esters **34**, and subsequent acidic treatment furnished acids **35**.

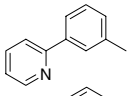
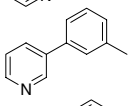
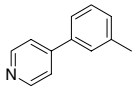
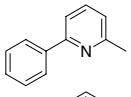
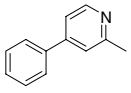
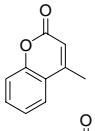
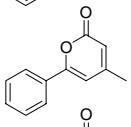
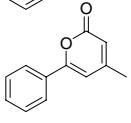
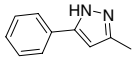
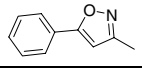
3. Results and discussion

The inhibitory activity against recombinant human cathepsin K at pH 3.8[16] is shown in Table 1. The compound from Novartis (R^1 = Cbz, R^2 = *i*-Bu, R^3 = H) possessed an IC_{50} of 0.09 μM with a c log *P* value of 3.6. This IC_{50} value obtained in our assay was similar to the reported value (0.07 μM).[3] At first, the terminal phenyl group of **5a** was replaced with 2-pyridyl (**5c**), 3-pyridyl (**5d**) or 4-pyridyl (**5e**) group, but the inhibitory activity decreased in all derivatives. Among them, 3-pyridyl derivative **5d** exhibited a moderate inhibitory activity of 0.65 μM. The replacement of the internal phenyl group of **5a** with a pyridine ring led to poor inhibitors **5f** and **5g**. The transformation of the biphenyl group to a naphthyl group[17] gave naphthalene **5h** with a moderate activity, whereas coumarin **5i** synthesized as a heterocyclic analogue to **5h** was 10-fold less potent than **5h**. The IC_{50} value of 6-phenylpyranone **5j** was 0.20 μM, which was two times less potent than 3-biphenylamine **5a**, and L-leucine derivative **5k** also possessed a moderate activity. Pyranones **5j** and **5k** also possessed an improved hydrophobicity compared to biphenyl derivatives **5a** and **5b**. The inhibitory activity of five-membered ring derivatives was next examined. Although pyrazole **5l** showed a poor inhibitory activity, isoxazole **5m** possessed a moderate activity.

As mentioned above, the replacement of the biphenyl group to heterocyclic groups was found to be unsuccessful. Therefore, we introduced an ethyl group into the P1 unit and changed the methoxy group in the P1′ unit to benzyl and acetic acid ethers for restoring the inhibitory activity. These structural modifications were applied to pyranone **5k** and isoxazole **5m** as the inhibitory activities and clog *P* values of both compounds were comparatively better among the compounds in Table 1. In addition, morpholinecarbonyl derivatives were prepared as shown in Table 2, since this substructure is commonly used in protease inhibitors as a hydrophobic N-terminal group.[18] In these modifications, the P2 subunit was fixed to an *i*-butyl group as L-leucine derivatives **5b** and **5k** had slight increases in potency relative to aminocyclohexylcarbonyl derivatives **5a** and **5j**. By incorporating an ethyl group in the ethylenediamine moiety, the activity was increased as we expected. Pyranone **28k**, and isoxazole **28m** displayed increased potencies of 30- and 100-fold compared to **5k** and **5m**, respectively. As previously reported,[2] the incorporation of an acetic acid group in the P1′ subunit of the biphenyl derivatives retained the potency (compounds **28b** and **35b**). Phenylpyranone and phenylisoxazole groups were found to be tolerable in all combinations including an acetic acid group. Benzyl ethers **32k**, **32m**, and **32n** exhibited excellent inhibitory activities (2.1, 4.4, and 6.8 nM, respectively) proving the existence of a large hydrophobic area in the S1′ pocket.[3] Interestingly, when a more polar morpholinecarbonyl group was employed in the P3 unit, benzyl ether **32n** retained the potency, but other morpholinecarbonyl derivatives **28n** and **35n** showed 10-fold decreased inhibitory activity to **32n**.

Table 1. IC_{50} values of cathepsin K inhibitors



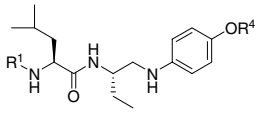
Compound	R^1	R^2	R^3	IC_{50}[a] (μM)	clog *P*[b]
	Cbz	*i*-Bu	H	0.09	3.6
5a	3-Biphenyl	–$(CH_2)_5$–		0.083	4.7
5b	3-Biphenyl	*i*-Bu	H	0.04	4.7
5c		–$(CH_2)_5$–		20	3.4
5d		–$(CH_2)_5$–		0.65	3.4
5e		–$(CH_2)_5$–		2.6	3.4
5f		–$(CH_2)_5$–		4.5	4.4
5g		–$(CH_2)_5$–		12	4.3
5h		–$(CH_2)_5$–		0.27	4.2
5i		–$(CH_2)_5$–		2.9	3.7
5j		–$(CH_2)_5$–		0.2	3.6
5k		*i*-Bu	H	0.16	3.8
5l		*i*-Bu	H	3.0	3.7
5m		*i*-Bu	H	0.6	3.2

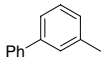
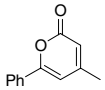
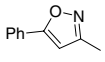
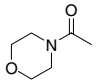
[a] Inhibition of recombinant human cathepsin K activity in a fluorescence assay using 8 μM Cbz-Phe-Arg-AMC as a substrate in 200 mM NaOAc, 10 mM DTT, 120 mM NaCl, and buffer (pH 3.8). The IC_{50} values represent the average of at least $n = 2$.

[b] The clog *P* values were calculated by ACD/Log P DB ver. 7.06 from Advanced Chemistry Development, Inc.

Several compounds were selected and orally administered to rats at a dose of 50 mg/kg in cremophor/EtOH (2:1) to investigate the pharmacokinetics (Table 3). Entries 1–4 show the PK parameters of methyl ethers **28**. Phenylpyranone **28k** and morpholinecarbonyl derivative **28n** possessed improved pharmacokinetics compared to biphenyl derivatives **28b**. Isoxazole **28m**, however, showed similar pharmacokinetics to **28b**. Compound **35b**, whose R^4 substituent was an acetic acid group, achieved improvement of the PK profile over methoxy derivative **28b** (entries 1 and 5), while this

Table 2. IC_{50} values (nM) of cathepsin K inhibitors[a]



R^1	R^4		
			Me
	—	4.5 (**35b**[b])	3.8 (**28b**)
	2.1 (**32k**)	6.9 (**35k**[b])	5.7 (**28k**)
	4.4 (**32m**)	7.3 (**35m**[b])	6.8 (**28m**)
	6.8 (**32n**)	74 (**35n**[b])	79 (**28n**)

[a] Inhibition of recombinant human cathepsin K activity in a fluorescence assay using 8 μM Cbz-Phe-Arg-AMC as a substrate in 200 mM NaOAc, 10 mM DTT, 120 mM NaCl, and buffer (pH 3.8). The IC_{50} values represent the average of at least $n = 2$.

[b] 2 HCl salt.

Table 3. PK parameters of heterocyclic substituted cathepsin K inhibitors[a]

Entry	Compound	T_{max} (h)	C_{max} (μg/mL)	AUC (μg h/mL)	c log P[b]
1	**28b**	4	0.57	7.4	5.6
2	**28k**	6	5.5	50.4	4.7
3	**28m**	4	0.37	4.7	4.1
4	**28n**	1	21	54.3	2.0
5	**35b**[c]	4	5.0	42.9	4.8
6	**35n**	1	0.067	0.55	1.2
7	**32n**	1	15.9	108	3.6

[a] Average of three rats dosed at 50 mg/kg po.
[b] The c log P values were calculated by ACD/Log P DB ver. 7.06 from Advanced Chemistry Development, Inc.
[c] 2 HCl salt.

replacement was not good for the PK properties of morpholinecarbonyl derivatives (entries 4 and 6). The unsatisfactory pharmacokinetics of urea **35n** might be ascribed to lower permeability of **35n** as the observed C_{max} and c log P values were considerably low. Morpholinecarbonyl derivatives possess a tendency of shorter T_{max} values compared to other biphenyl and heterocyclic derivatives. Nevertheless, the benzyl ether of morpholinylcarbonyl derivative **32n** showed a good C_{max} value of 15.9 μg/mL and the best AUC value of 108 μg h/mL. Thus, we obtained compounds with good inhibitory activities and improved PK profiles.

The selectivity over other human cathepsins S, B, and L of several potent compounds was also examined (Table 4). It was disappointing that all compounds possessed potent inhibitory activities against cathepsin S. Their IC_{50} values against cathepsin S were similar to those against cathepsin K measured at pH 3.8, but exceeded the values measured at pH 5.5. *N*-(3-Biphenyl)-L-leucine derivatives **28b**, phenylpyranone **28k**, and phenylisoxazole **28m**, possessing a methyl ether, showed unsatisfied selectivity over cathepsins B and L. Biphenylamine **35b**, possessing an acetic acid moiety, slightly increased the selectivity over cathepsins B and L. The benzyl group seemed to be the most effective among the three R^4 groups (Table 2) regarding the selectivity. A combination of the morpholinecarbonyl and benzyl groups gave the best compound, **32n**. Compound **32n** displayed more than 1000-fold selectivity over cathepsins B and L, although it still exhibited a high inhibition against cathepsin S.

Table 4. IC_{50} values of inhibition of human cathepsins S, B, L, and K (nM)

Compound	Cathepsin S[a,e]	Cathepsin B[b,e]	Cathepsin L[c,e]	Cathepsin K[d,e]
28b	4.6	48	55	3.8 (19[f])
28k	9.7	110	82	5.7 (36[f])
28m	6.5	180	230	6.8 (32[f])
32k	14	370	—[g]	2.1
32n	13	>20,000	>20,000	6.8
35b	6.9	120	120	4.5 (31[f])

[a] Inhibition of recombinant human cathepsin S activity in a fluorescence assay using 20 μM Cbz-Val-Val-Arg-MCA as a substrate in 60 mM KH_2PO_4–K_2HPO_4, 10 mM EDTA·2Na, 0.001% Triton X-100, 10 mM DTT, and buffer (pH 6.5).
[b] Inhibition of recombinant human cathepsin B activity in a fluorescence assay using 10 μM Cbz-Phe-Arg-MCA as a substrate in 340 mM NaOAc, 60 mM AcOH, 4 mM EDTA·2Na, 8 mM DTT, and buffer (pH 5.5).
[c] Inhibition of recombinant human cathepsin L activity in a fluorescence assay using 8 μM Cbz-Phe-Arg-MCA as a substrate in 340 mM NaOAc, 60 mM AcOH, 4 mM EDTA·2Na, 8 mM DTT, and buffer (pH 5.5).
[d] Inhibition of recombinant human cathepsin K activity in a fluorescence assay using 8 μM Cbz-Phe-Arg-AMC as a substrate in 200 mM NaOAc, 10 mM DTT, 120 mM NaCl, and buffer (pH 3.8).
[e] The IC_{50} values represent the average of at least $n = 2$.
[f] IC_{50} values measured at pH 5.5.
[g] Not measured.

4. Conclusion

In the novel series of *N*-(3-biphenyl)amino acid amides as cathepsin K inhibitors, the structural modification directed toward reducing the lipophilicity was carried out. The biphenyl group was replaced with heterocyclic groups; however, these modifications brought decreases in inhibitory activities. Further modification of the P1 and P1′ units led to the identification of pyranone derivative **28k**, which possessed a good inhibitory activity and improved pharmacokinetic profile. When a morpholinecarbonyl group was employed as the P3 substituent, benzyl ether **32n** indicated a good inhibitory activity with good PK property as well. Although the selectivity to cathepsin S should be improved, compound **32n** exhibited excellent selectivity over cathepsins B and L (more than 1000-fold). The information obtained in this study will be helpful to identify selective cathepsin K inhibitors with good PK profiles in future research.

5. Experimental

5.1. Materials and methods

Melting points were determined in a Yanaco micro melting point apparatus and are uncorrected. IR absorption spectra were recorded on a Jasco FT/IR-830 spectrophotometer. NMR spectra were recorded on a VARIAN Mercury 400 (400 MHz) instrument using tetramethylsilane as an internal standard. Low-resolution MS and HRMS were recorded on a JEOL JMS-AX505H. Elemental analyses were performed by Institute of Science and Technology, Inc. TLC analysis was performed on 60F254 plates (Merck 5715). Separation of the compounds by column chromatography was carried out with silica gel 60 (Merck, 230–400 mesh ASTM). The following abbreviations are used: DMA, *N*,*N*-dimethylacetamide; WSC·HCl, water-soluble carbodiimide hydrochloride (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride); HOBT, 3-hydroxybenztriazole hydrate; DMF, *N*,*N*-dimethylformamide.

5.2. 1-[(3-Bromophenyl)amino]cyclohexanecarboxylic acid (3)

A mixture of 1,3-dibromobenzene (**1**) (24.25 g, 103 mmol) 1-aminocyclohexanecarboxylic acid (**2**)

(14.72 g, 103 mmol), K_2CO_3 (21.31 g, 154 mmol), and $CuBr{\cdot}SMe_2$ (2.11 g, 10 mmol) in DMA (130 mL) was stirred at 120 °C for 3 h under N_2 atmosphere. The cooled reaction mixture was diluted with EtOAc (200 mL). The mixture was washed with 1 M HCl (3× 200 mL) and brine (200 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (EtOAc) to provide carboxylic acid **3** (13.55 g, 44%). Mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.70 (6H, m), 1.90–2.10 (4H, m), 6.57 (1H, ddd, J = 0.8, 2.3, 8.0 Hz), 6.83 (1H, dd, J = 1.7, 2.3 Hz), 6.97 (1H, ddd, J = 0.8, 1.7, 8.0 Hz), 7.05 (1H, t, J = 8.0 Hz); IR (KBr): 3250, 1705, 1592, 1479, 1227, 770 cm^{-1}; MS (EI) m/z: 297 [M$^+$], 252.

5.3. 1-(3-Bromophenylamino)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (4)

A mixture of *N*-(4-methoxyphenyl)ethane-1,2-diamine[7] (153 mg, 0.9 mmol), carboxylic acid **3** (250 mg, 0.8 mmol), HOBt (141 mg, 0.9 mmol), and WSC·HCl (177 mg, 0.9 mmol) in DMF (5 mL) was stirred for 10 h. The reaction mixture was diluted with EtOAc (10 mL). The mixture was washed with water (2× 10 mL) and saturated aqueous solution of $NaHCO_3$ (2× 10 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (hexane/EtOAc 1:1) to provide amide **4** (274 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–2.03 (10 H, m), 3.20 (2H, t, J = 5.8 Hz), 3.50 (1H, br s), 3.47 (2H, dt, J = 5.8, 5.9 Hz), 3.73 (3H, s), 4.03 (1H, s), 6.45 (2H, d, J = 8.9 Hz), 6.49 (1H, br d, J = 7.8 Hz), 6.74 (2H, d, J = 8.9 Hz), 6.77 (1H, t, J = 2.0 Hz), 6.90 (1H, br d, J = 7.8 Hz), 6.95 (1H, t, J = 7.8 Hz), 7.13 (1H, br t, J = 5.9 Hz).

5.4. General procedure for the preparation of amides 5

A mixture of amide **4** (270 mg, 0.60 mmol), pyridineboronic acid (82 mg, 0.67 mmol), $Pd(Ph_3P)_4$ (35 mg, 0.03 mmol), and 2 M aqueous solution of Na_2CO_3 (5 mL) in toluene (5 mL) was stirred at reflux for 20 h. The cooled reaction mixture was diluted with EtOAc (5 mL). The mixture was washed with water (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to provide amide **5**.

5.4.1. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(3-pyridin-2-ylphenyl)amino]cyclohexanecarboxamide (5c). Yield: 75%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–2.04 (10H, m), 3.27 (2H, t, J = 5.6 Hz), 3.45–3.49 (2H, m), 3.69 (3H, s), 4.12 (1H, s), 4.14 (1H, br s), 6.35 (2H, d, J = 8.9 Hz), 6.63–6.66 (1H, m), 6.67 (2H, d, J = 8.9 Hz), 7.18–7.26 (2H, m), 7.34 (1H, d, J = 7.5 Hz), 7.36 (1H, br s), 7.38 (1H, t, J = 2.0 Hz), 7.66–7.71 (2H, m), 8.63 (1H, br d, J = 4.7 Hz), IR (KBr): 1655, 1513, 1235, 771 cm^{-1}; Mass (FAB) m/z: 445 [M+H]$^+$; Anal. Calcd for $C_{27}H_{32}N_4O_2{\cdot}0.5H_2O$: C, 71.31; H, 7.33; N, 12.35. Found: C, 71.61; H, 7.07; N, 12.26.

5.4.2. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(3-pyridin-3-ylphenyl)amino]cyclohexanecarboxamide (5d). Yield: 53%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–2.04 (10H, m), 3.17 (2H, t, J = 5.8 Hz), 3.48 (2H, q, 5.8 Hz), 3.53 (1H, br s), 3.72 (3H, s), 4.17 (1H, s), 6.41 (2H, d, J = 8.9 Hz), 6.62 (1H, dd, J = 2.0, 8.0 Hz), 6.71 (2H, d, J = 8.9 Hz), 6.80 (1H, br s), 7.00 (1H, br d, J = 7.6 Hz), 7.21 (1H, dd, J = 7.6, 8.0 Hz), 7.26 (1H, dd, J = 4.8, 7.9 Hz), 7.25–7.30 (1H, br s), 7.79 (1H, ddd, J = 1.8, 2.1, 7.9 Hz), 8.56 (1H, d, J = 4.8 Hz), 8.79 (1H, d, J = 1.8 Hz); IR (KBr): 1654, 1605, 1513, 1236, 820, 780, 749 cm^{-1}; Mass (FAB) m/z: 445 [M+H]$^+$; Anal. Calcd for $C_{27}H_{32}N_4O_2{\cdot}0.22$EtOAc: C, 72.18; H, 7.33; N, 12.08. Found: C, 71.81; H, 6.94; N, 11.93.

5.4.3. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(3-pyridin-4-ylphenyl)amino]cyclohexanecarboxamide (5e). Yield: 89%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–2.06 (10H, m), 3.17 (2H, t, J = 5.7 Hz), 3.48 (2H, q, J = 5.7 Hz), 3.72 (2H, s), 4.17 (1H, s), 6.40 (2H, d, J = 8.9 Hz), 6.66 (1H, dd, J = 1.4, 8.1 Hz), 6.71 (2H, d, J = 8.9 Hz), 6.85 (1H, br s), 7.06 (1H, d, J = 7.7 Hz), 7.22 (1H, dd, J = 7.7, 8.1 Hz), 7.26 (1H, br s), 7.42 (2H, d, J = 5.4 Hz), 8.58 (2H, br s); IR (KBr): 1654, 1595, 1513, 1235, 823, 781 cm^{-1}; Mass (FAB) m/z: 445 [M+H]$^+$.

5.5. General procedure for the preparation of carboxylic acids 7

Compound **7** was prepared according to the procedure for **3**, using appropriate starting materials.

5.5.1. 1-(Biphenyl-3-ylamino)cyclohexanecarboxylic acid (7a). Yield: 43%; mp 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–2.03 (10H, m), 6.67 (1H, ddd, J = 1.0, 2.0, 8.0 Hz), 6.89 (1H, t, J = 2.0 Hz), 7.13 (1H, br d, J = 8.0 Hz), 7.29 (1H, t, J = 8.0 Hz), 7.36–7.33 (1H, m), 7.44–7.41 (2H, m), 7.55–7.52 (2H, m); IR (KBr): 3404, 1621, 757, 699 cm^{-1}; MS (EI) m/z: 295 [M$^+$]; Anal. Calcd for $C_{19}H_{21}NO_2{\cdot}0.1$ H_2O: C, 76.79; H, 7.19; N, 4.71. Found: C, 76.85; H, 7.12; N, 4.67.

5.5.2. *N*-Biphenyl-3-yl-L-leucine (7b). Yield: 67%; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 7.3 Hz), 0.97 (3H, d, J = 6.6 Hz), 1.62–1.89 (3H, m), 4.06–4.11 (1H, m), 6.58 (1H, d, J = 7.3 Hz), 6.82 (1H, s), 6.97 (1H, d, J = 7.3 Hz), 7.22 (1H, d, J = 7.3 Hz), 7.26–7.30 (1H, m), 7.37 (2H, t, J = 8.1 Hz), 7.51 (2H, d, J = 8.1 Hz); IR (KBr) 2957, 1714, 1605, 1481, 1333, 1201, 795, 745, 698 cm^{-1}; HRMS found [M$^+$] = 283.1578, calcd for $C_{18}H_{21}O_2N$: 283.1572.

5.6. [(2-Oxo-2*H*-chromen-4-yl)amino]cyclohexanecarboxylic acid (11)

A mixture of 4-bromocoumarin[8] (**10**) (225 mg, 1.0 mmol), amino acid **2** (286 mg, 2.0 mmol), K_2CO_3 (276 mg, 2.0 mmol), and Et_3N (280 μL, 2.0 mmol) in *t*-BuOH (10 mL) was stirred at reflux for 24 h. Water (30 mL) was added to the cooled reaction mixture. The mixture was extracted with Et_2O (2× 30 mL). The aqueous layer was acidified with 1 M HCl (30 mL) and

extracted with CH_2Cl_2 (2× 30 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to provide **11** as a brown syrup, which was used in the next reaction directly without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 1.55–2.22 (10H, m), 5.12 (1H, s), 7.21 (1H, dd, J = 1.1, 8.3 Hz), 7.26 (1H, dt, J = 1.1, 8.0 Hz), 7.51 (1H, dt, J = 1.4, 7.3 Hz), 7.96 (1H, dd, J = 1.3, 8.0 Hz).

5.7. General procedure for the preparation of pyridylamines 13

A mixture of phenylpyridine **12** (10.0 g, 64.4 mmol) and sodium amide (2.76 g, 70.8 mmol) in *N*,*N*-dimethylaniline (20 mL) was stirred at 160 °C for 24 h. The cooled reaction mixture was poured into water (200 mL) and extracted with ether (2× 100 mL). The combined ether layers were dried (Na_2SO_4), concentrated, and purified by column chromatography to provide pyridylamine **13**.

5.7.1. 6-Phenylpyridin-2-amine (13a). Yield: 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (2H, br s), 6.46 (1H, d, J = 8.1 Hz), 7.10 (1H, d, J = 7.3 Hz), 7.35–7.39 (1H, m), 7.43 (2H, t, J = 7.3 Hz), 7.50 (1H, t, J = 7.3 Hz), 7.93 (2H, d, J = 7.3 Hz).

5.7.2. 4-Phenylpyridin-2-amine (13b). Yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (2H, br s), 6.71 (1H, s), 6.90 (1H, dd, J = 1.5, 6.6 Hz), 7.41–7.47 (3H, m), 7.59 (2H, d, J = 7.3 Hz), 8.13 (1H, d, J = 5.1 Hz).

5.8. General procedure for the preparation of carboxylic acids 14

A mixture of methyl 1-bromocyclohexanecarboxylate (442 mg, 2.0 mmol), pyridylamine **13** (170 mg, 1.0 mmol), and KOH (1.12 g, 20 mmol) in *t*-BuOH (10 mL) was stirred at reflux for 24 h. HCl (1 M, 30 mL) was added to the cooled reaction mixture. The mixture was extracted with EtOAc (2× 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography to provide carboxylic acid **14**.

5.8.1. 1-[(6-Phenylpyridin-2-yl)amino]cyclohexanecarboxylic acid (14a). Yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39–1.47 (2H, m), 1.61–1.74 (2H, m), 2.02–2.12 (4H, m), 2.20–2.26 (2H, m), 4.44 (1H, br s), 6.60 (1H, d, J = 8.1 Hz), 7.16 (1H, d, J = 7.3 Hz), 7.41–7.50 (3H, m), 7.62 (1H, t, J = 8.1 Hz), 7.82 (2H, d, J = 8.8 Hz); IR (film): 2936, 1693, 1282, 1259, 1074, 924, 762, 694 cm^{-1}; HRMS found [M$^+$] = 296.1532, calcd for $C_{18}H_{20}O_2N_2$: 296.1524.

5.8.2. 1-[(4-Phenylpyridin-2-yl)amino]cyclohexanecarboxylic acid (14b). Yield: 5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.48 (2H, m), 1.57–1.68 (4H, m), 2.02–2.17 (4H, m), 4.89 (1H, br s), 6.85 (1H, s), 6.96 (1H, d, J = 6.6 Hz), 7.44–7.51 (3H, m), 7.60 (1H, d, J = 5.9 Hz), 8.03 (1H, d, J = 5.9 Hz); IR (KBr): 2930, 1659, 1253, 761, 696 cm^{-1}; HRMS found [M+H]$^+$ = 297.1614, calcd for $C_{18}H_{21}N_2O_2$: 297.1603.

5.9. 4-Bromo-6-phenyl-2*H*-pyran-2-one (16)

A mixture of 4-hydroxy-6-phenyl-2*H*-pyran-2-one[10] (**15**) (14.23 g, 75.6 mmol) and PBr_3 (28.7 mL, 302.4 mmol) in DMF (300 mL) was stirred at 60 °C for 10 h. The cooled reaction mixture was partitioned between EtOAc (300 mL) and water (300 mL). The organic layer was washed with water (3× 300 mL) and brine (300 mL). The organic layer was dried (Na_2SO_4) and concentrated. The byproduct was removed by trituration (CH_2Cl_2/hexane). The residue was concentrated to provide **16** (10.56 g, 56%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (1H, d, J = 1.5 Hz), 6.83 (1H, d, J = 1.5 Hz), 7.46–7.53 (3H, m), 7.80–7.84 (2H, m); IR (KBr): 1724, 1608, 1532, 1494, 1323, 1149, 855, 777 cm^{-1}; HRMS found [M$^+$] = 249.9628, calcd for $C_{11}H_7O_2Br$: 249.9629.

5.10. General procedure for the preparation of carboxylic acids 17

A mixture of **16** (10.35 g, 41.2 mmol), amino acid (82.4 mmol), and K_2CO_3 (11.39 g, 82.4 mmol) in *t*-BuOH (200 mL) was stirred at reflux for 3 h. HCl (1 M, 120 mL) was added to the cooled reaction mixture and the mixture was extracted with EtOAc (120 mL). The organic layer was washed with water (3× 100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated. The solid was washed with Et_2O to provide **17**.

5.10.1. 1-[(2-Oxo-6-phenyl-2*H*-pyran-4-yl)amino]cyclohexanecarboxylic acid (17a). Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–2.12 (10H, m), 5.70 (1H, s), 7.37–7.46 (4H, m), 7.84–7.86 (2H, m), 11.98 (1H, s).

5.10.2. *N*-(2-Oxo-6-phenyl-2*H*-pyran-4-yl)-L-leucine (17b). Yield: 77%; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 5.9 Hz), 1.60–1.76 (3H, m), 3.94–4.01 (1H, m), 4.84 (1H, s), 6.63 (1H, s), 7.46–7.53 (3H, m), 7.69–7.71 (2H, m); IR (KBr): 2964, 1746, 1652, 1610, 1542, 1194, 1068, 778, 692 cm^{-1}; HRMS found [M+H]$^+$ = 302.1393, calcd for $C_{17}H_{20}NO_4$: 302.1393.

5.11. *N*-[(1*Z*)-1-(Methylthio)-3-oxo-3-phenylprop-1-en-1-yl]-L-leucine (19)

A suspension of L-leucine (4.84 g, 36.8 mmol) and NaOH (1.50 g, 37.3 mmol) in 90% EtOH (150 mL) was stirred at reflux for 1 h. 3,3-Bis(methylthio)-1-phenylprop-2-en-1-one[11] (**18**) (4.18 g, 18.6 mmol) was added to the reaction mixture and the reaction mixture was stirred at reflux for 24 h. After removal of the solvent, the residue was partitioned with EtOAc (100 mL) and 0.2 M HCl (100 mL). The aqueous layer was extracted with EtOAc (3× 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide **19** (4.01 g, 70%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 6.2 Hz), 0.91 (3H, d, J = 6.2 Hz), 1.77 (2H, dd, J = 6.1, 12.6 Hz), 1.78–1.85 (1H, m), 2.39 (3H, s), 4.33 (1H, br s), 5.60 (1H, s), 7.28–7.41 (3H, m), 7.75–7.80 (2H, m); IR (KBr): 2959, 1721, 1561, 1472, 1280, 756 cm^{-1}; MS (FAB) *m*/*z*: 308.13 [M+H]$^+$.

5.12. *N*-(5-Phenyl-1*H*-pyrazol-3-yl)-L-leucine (20a)

A mixture of **19** (125 mg, 0.4 mmol) and hydrazine hydrate (0.12 mL, 2.0 mmol) in EtOH (2 mL) was stirred at reflux for 48 h. The mixture was concentrated to provide pyrazole **20a**, which was used in the next reaction directly without further purification.

5.13. *N*-(5-Phenylisoxazol-3-yl)-L-leucine (20b)

To a stirred solution of **19** (1.86 g, 6.1 mmol) and NaOH (1.50 g, 37.3 mmol) in EtOH (50 mL) was added a solution of $HONH_2{\cdot}HCl$ (1.69 g, 24.4 mmol) and KOH (1.37 g, 24.4 mmol) in water (25 mL). The reaction mixture was stirred at reflux for 5 h. The cooled mixture was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide isoxazole **20b** (1.27 g, 76%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (6H, t, J = 6.4 Hz), 1.63–1.94 (3H, m), 4.26 (1H, dd, J = 5.1, 8.8 Hz), 4.53 (1H, br s), 6.06 (1H, s), 7.39–7.44 (3H, m), 7.67–7.71 (2H, m); IR (KBr): 3362, 2958, 1723, 1625, 1579, 1561, 1450, 1209, 762, 688 cm^{-1}; MS (FAB) m/z: 275.13 $[M+H]^+$.

5.14. Benzyl *N*-(morpholin-4-ylcarbonyl)-L-leucine (22)

To a stirred solution of benzyl L-leucine *p*-toluenesulfonate (**21**) (3.94 g, 10 mmol) and Et_3N (4.2 mL, 30 mmol) in CH_2Cl_2 (100 mL) was added morpholinecarbonyl chloride (2.3 mL, 20 mmol). After stirring for 24 h, the reaction mixture was concentrated. The residue was purified by column chromatography (hexane/EtOAc 1:1) to provide urea **22** (3.34 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (6H, t, J = 4.9 Hz), 1.49–1.71 (3H, m), 3.33–3.41 (4H, m), 3.68 (4H, t, J = 4.9 Hz), 4.56–4.60 (1H, m), 4.83 (1H, d, J = 8.8 Hz), 5.13 (1H, d, J = 12.7 Hz), 5.20 (1H, d, J = 12.7 Hz), 7.32–7.38 (5H, m); IR (film): 3347, 2959, 1742, 1632, 1534, 1456, 1387, 1268, 1192, 1119, 999, 751, 698 cm^{-1}; HRMS found $[M+H]^+$ = 335.1977, calcd for $C_{18}H_{27}N_2O_4$: 335.1960.

5.15. *N*-(Morpholin-4-ylcarbonyl)-L-leucine (23)

A mixture of urea **22** (3.34 g, 10.0 mmol) and Pd/C (10%, 0.53 g, 0.50 mmol) in EtOH (100 mL) was stirred under H_2 for 3 h. After removal of Pd/C by filtration, the filtrate was concentrated. The residue was purified by column chromatography (EtOAc/MeOH 20:1) to provide **23** (2.44 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, t, J = 6.7 Hz), 1.53–1.78 (3H, m), 3.33–3.43 (4H, m), 3.69 (4H, t, J = 4.7 Hz), 4.35–4.40 (1H, m), 4.79 (1H, d, J = 6.3 Hz); IR (film): 3360, 2960, 1726, 1631, 1538, 1270, 1118, 1000, 860, 593 cm^{-1}; HRMS found $[M+H]^+$ = 245.1496, calcd for $C_{11}H_{21}N_2O_4$: 245.1518.

5.16. General procedure for the preparation of 5

Compound **5** was prepared according to the procedure for **4**, using appropriate starting materials.

5.16.1. 1-(Biphenyl-3-ylamino)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (5a). Yield: 74%; white amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04–1.35 (10H, m), 3.18 (2H, t, J = 5.8 Hz), 3.48 (2H, q, J = 5.8 Hz), 3.72 (3H, s), 4.08 (1H, br s), 6.39 (2H, d, J = 8.9 Hz), 6.57 (1H, ddd, J = 1.0, 2.0, 7.8 Hz), 6.70 (2H, d, J = 8.9 Hz), 6.83 (1H, t, J = 2.0 Hz), 7.03 (1H, br d, J = 7.8 Hz), 7.19 (1H, t, J = 7.8 Hz), 7.30 (1H, br s), 7.31–7.54 (5H, m); IR (KBr): 1655, 1600, 1513, 1235, 758 cm^{-1}. Mass (FAB) m/z: 444 $[M+H]^+$; Anal. Calcd for $C_{28}H_{33}N_3O_2{\cdot}0.3H_2O$: C, 74.62; H, 7.59; N, 8.94. Found: C, 74.50; H, 7.59; N, 9.04.

5.16.2. N^2-Biphenyl-3-yl-N^1-{[(4-methoxyphenyl)amino]methyl}-L-leucinamide (5b). Yield: 88%; white amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.54–1.90 (3H, m), 3.12–3.22 (2H, m), 3.36–3.54 (2H, m), 3.71 (3H, s), 3.81 (1H, d, J = 10.3 Hz), 3.93 (1H, br s), 6.39 (2H, d, J = 8.8 Hz), 6.59 (1H, d, J = 8.1 Hz), 6.70 (2H, d, J = 8.8 Hz), 6.83 (1H, s), 7.06 (2H, d, J = 7.3 Hz), 7.26 (1H, t, J = 7.3 Hz), 7.33 (1H, t, J = 6.6 Hz), 7.40 (2H, t, J = 6.6 Hz), 7.54 (2H, d, J = 6.6 Hz); IR (KBr): 3354, 2955, 1654, 1605, 1513, 1236, 1037, 821, 758, 700 cm^{-1}; HRMS found $[M+H]^+$ = 432.2653, calcd for $C_{27}H_{34}N_3O_2$: 432.2651.

5.16.3. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(6-phenylpyridin-2-yl)amino]cyclohexanecarboxamide (5f). Yield: 20%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.43 (2H, m), 1.65–1.68 (4H, m), 2.00–2.15 (4H, m), 3.06 (2H, t, J = 5.9 Hz), 3.40 (2H, q, J = 5.9 Hz), 3.70 (3H, s), 4.78 (1H, br s), 6.26 (2H, d, J = 8.8 Hz), 6.39 (1H, d, J = 8.1 Hz), 6.66 (2H, d, J = 8.8 Hz), 7.08–7.11 (1H, m), 7.19 (1H, d, J = 7.3 Hz), 7.36–7.48 (3H, m), 7.97 (2H, d, J = 8.8 Hz); IR (KBr): 3354, 2931, 1654, 1597, 1577, 1512, 1236, 1038, 820, 763, 694 cm^{-1}; HRMS found $[M+H]^+$ = 445.2589, calcd for $C_{27}H_{33}N_4O_2$: 445.2603.

5.16.4. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(4-phenylpyridin-2-yl)amino]cyclohexanecarboxamide (5g). Yield: 60%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.68 (6H, m), 1.99–2.10 (4H, m), 3.18 (2H, t, J = 5.9 Hz), 3.46 (2H, q, J = 5.9 Hz), 3.71 (3H, s), 4.84 (1H, br s), 6.37 (2H, d, J = 8.8 Hz), 6.61 (1H, s), 6.69 (2H, d, J = 6.6 Hz), 6.94 (1H, dd, J = 1.4, 6.6 Hz), 7.12–7.15 (1H, m), 7.40–7.41 (2H, m), 7.54–7.56 (2H, m), 8.17 (1H, d, J = 5.2 Hz); IR (KBr): 3352, 2930, 1611, 1514, 1236, 1039, 820, 764, 698 cm^{-1}; HRMS found $[M+Na]^+$ = 467.2418, calcd for $C_{27}H_{32}N_4O_2Na$: 467.2423.

5.16.5. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-(1-naphthylamino)cyclohexanecarboxamide (5h). Yield: 10% (two steps); amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–1.40 (3H, m), 1.65–1.67 (3H, m), 2.02–2.17 (4H, m), 3.15 (2H, t, J = 5.8 Hz), 3.42–3.46 (2H, m), 3.69 (3H, s), 4.87 (1H, s), 6.31 (2H, d, J = 8.9 Hz), 6.49 (1H, d, J = 8.0 Hz), 6.65 (2H, d, J = 8.9 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.18 (1H, br s), 7.28 (1H, d, J = 8.0 Hz), 7.46–7.52 (2H, m), 7.81–7.87

(2H, m); IR (KBr): 3386, 1654, 1513, 1236, 773 cm^{-1}; Mass (FAB) *m/z*: 417 $[M]^+$.

5.16.6. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(2-oxo-2*H*-chromen-4-yl)amino]cyclohexanecarboxamide (5i). Yield: 14% (two steps); white solid; mp 184–185 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–2.20 (10H, m); 3.24 (2H, t, J = 5.9 Hz), 3.49 (2H, q, J = 5.9 Hz), 3.71 (3H, s), 5.18 (1H, s), 5.28 (1H, s), 6.50 (2H, d, J = 8.8 Hz), 6.58 (1H, br s), 6.69 (2H, d, J = 8.8 Hz), 7.30 (1H, t, J = 8.1 Hz), 7.34 (1H, d, J = 8.8 Hz), 7.45 (1H, d, J = 8.1 Hz), 7.56 (1H, t, J = 6.6 Hz); IR (KBr): 3338, 2936, 1672, 1616, 1514, 1372, 1236, 1197, 1039, 950, 822 cm^{-1}; HRMS found $[M+H]^+$ = 436.2233, calcd for $C_{25}H_{30}N_3O_4$: 436.2237.

5.16.7. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-[(2-oxo-6-phenyl-2*H*-pyran-4-yl)amino]cyclohexanecarboxamide (5j). Yield: 14%; white solid; mp 212–214 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33–1.40 (2H, m), 1.51–1.74 (6H, m), 2.00 (2H, br s), 3.24 (2H, t, J = 5.9 Hz), 3.50 (2H, q, J = 5.9 Hz), 3.68 (3H, s), 4.65 (1H, br s), 5.13 (1H, s), 6.19 (1H, d, J = 2.2 Hz), 6.52 (2H, d, J = 8.8 Hz), 6.70 (2H, d, J = 8.8 Hz), 7.39–7.46 (3H, m), 7.75 (2H, d, J = 8.1 Hz); IR (KBr): 3332, 2936, 1671, 1514, 1237, 820, 767, 692 cm^{-1}; HRMS found $[M+H]^+$ = 462.2397, calcd for $C_{27}H_{32}N_3O_4$: 462.2393.

5.16.8. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-N^2-(2-oxo-6-phenyl-2*H*-pyran-4-yl)-L-leucinamide (5k). Yield: 89%; yellow amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 5.9 Hz), 0.95 (3H, d, J = 5.9 Hz), 1.62–1.75 (3H, m), 3.25 (2H, t, J = 5.9 Hz), 3.45–3.53 (2H, m), 3.67 (3H, s), 3.87 (1H, br s), 5.35 (1H, s), 6.06 (1H, br s), 6.27 (1H, s), 6.56 (2H, d, J = 8.8 Hz), 6.69 (2H, d, J = 8.8 Hz), 7.33–7.41 (3H, m), 7.66 (2H, d, J = 6.6 Hz), 7.87 (1H, br s); IR (KBr): 3278, 2955, 1657, 1549, 1514, 1237, 821, 768, 692 cm^{-1}; HRMS found $[M+H]^+$ = 450.2399, calcd for $C_{26}H_{32}N_3O_4$: 450.2393.

5.16.9. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-N^2-(5-phenyl-1*H*-pyrazol-3-yl)-L-leucinamide (5l). Yield: 3% (two steps); oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 6.6 Hz), 0.97 (3H, d, J = 6.6 Hz), 1.53–1.62 (1H, m), 1.76–1.82 (2H, m), 3.10–3.21 (2H, m), 3.37–3.57 (2H, m), 3.69 (3H, s), 3.88–3.92 (1H, m), 5.87 (1H, s), 6.43 (2H, d, J = 8.8 Hz), 6.66 (2H, d, J = 8.8 Hz), 7.24 (1H, br s), 7.32–7.39 (3H, m), 7.46 (2H, d, J = 6.6 Hz).

5.16.10. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-N^2-(5-phenylisoxazol-3-yl)-L-leucinamide (5m). Yield: 60%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3 H, d, J = 5.9 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.57–1.84 (3H, m), 3.24 (2H, t, J = 5.9 Hz), 3.50 (2H, q, J = 5.9 Hz), 3.71 (3H, s), 3.99–4.04 (1H, m), 4.35 (1H, br s), 6.03 (1H, s), 6.55 (2H, d, J = 8.8 Hz), 6.69–6.73 (1H, m), 6.71 (2H, d, J = 8.8 Hz), 7.41 (3H, t, J = 2.9 Hz), 7.64–7.66 (2H, m); IR (KBr): 3274, 2955, 1655, 1557, 1314, 1236, 1038, 821, 762, 689 cm^{-1}; HRMS found $[M+H]^+$ = 423.2397, calcd for $C_{24}H_{31}N_4O_3$: 423.2396.

5.17. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}propyl)carbamate (27)

To a stirred solution of *N*-Boc aminoalcohol **24**[13] (18.93 g, 100 mmol), 2-nitrobenzenesulfonamide **25**[14] (15.40 g, 100 mmol), and PPh_3 (26.20 g, 100 mmol) in THF (250 mL) was added a solution of DEAD (17.40 g, 100 mmol) in THF (100 mL) dropwise over 20 min at 0 °C under N_2 atmosphere. After stirring at room temperature for 3 h, the reaction mixture was concentrated. Et_2O (100 mL) was added to the residue and the precipitate was removed. The filtrate was concentrated. To a residual oil in MeCN (100 mL) were added PhSH (11.02 g, 100 mmol) and K_2CO_3 (20.74 g, 150 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with EtOAc (200 mL). The mixture was washed with water (200 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography to provide substituted *N*-Boc diamine **27** (12.16 g, 83%). Mp 97–99 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.45 (9H, s), 1.42–1.68 (2H, m), 2.99–3.04 (1H, m), 3.18 (1H, dd, J = 4.4, 11.7 Hz), 3.68–3.78 (2H, m), 3.74 (3H, s), 4.46 (1H, br s), 6.58 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz); IR (KBr): 3388, 1681, 1517, 1238, 1174, 1041, 816 cm^{-1}; MS (FAB) *m/z*: 295 $[M+H]^+$, 294, 239, 136, 57; HRMS found $[M+H]^+$ = 295.2023, calcd for $C_{16}H_{27}N_2O_3$: 295.2022; Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.16; H, 8.58; N, 9.57.

5.18. General procedure for the preparation of amides 28

A mixture of *N*-Boc diamine **27** (589 mg, 2.0 mmol) and 4 M HCl in 1,4-dioxane (3 mL, 12 mmol) in 1,4-dioxane (3 mL) was stirred for 30 min. The mixture was concentrated to provide a diamine HCl salt. To a residual solid in CH_2Cl_2 (20 mL) were added carboxylic acid (2.0 mmol), HOBt (405 mg, 3.0 mmol), Et_3N (418 μL, 3.0 mmol), and WSC·HCl (575 mg, 3.0 mmol). After stirring for 10 h, the reaction mixture was diluted with EtOAc (20 mL). The mixture was washed with water (2× 10 mL) and saturated aqueous solution of $NaHCO_3$ (2× 10 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography to provide amide **28**.

5.18.1. N^2-1,1′-Biphenyl-3-yl-N^1-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}propyl)-L-leucinamide (28b). Yield: 61%; white solid; mp 99–101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 7.3 Hz); 0.90 (3H, d, J = 5.9 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.37–1.88 (5H, m), 2.93 (1H, dd, J = 7.3, 12.5 Hz), 3.07 (1H, dd, J = 4.4, 12.5 Hz), 3.66 (3H, s), 3.72–3.75 (1H, m), 3.89 (1H, br s), 3.97–4.05 (1H, m), 6.31 (2H, d, J = 8.8 Hz), 6.55 (1H, d, J = 8.1 Hz), 6.62 (2H, d, J = 8.8 Hz), 6.73 (1H, d, J = 7.3 Hz), 6.80 (1H, s), 7.00 (1H, d, J = 7.3 Hz), 7.15 (1H, t, J = 7.3 Hz), 7.25–7.33 (3H, m), 7.47 (2H, d, J = 7.3 Hz); IR (KBr): 3336, 2961, 1645, 1606, 1514, 1479, 1235, 1038, 821, 759, 699 cm^{-1}.

5.18.2. N^1-((1*S*)-1-{[(4-Methoxyphenyl)amino]methyl}propyl)-N^2-(2-oxo-6-phenyl-2*H*-pyran-4-yl)-L-leucinamide (28k). Yield: 90%; white solid; mp 170–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 5.9 Hz); 0.95 (3H, d, J = 7.3 Hz), 0.96 (3H, d, J = 8.1 Hz), 1.62–1.74 (5H, m), 3.15 (1H, dd, J = 6.6, 12.5 Hz), 3.21 (1H, dd, J = 4.4, 12.5 Hz), 3.69 (3H, s), 3.98–4.11 (2H, m), 5.25 (1H, s), 6.34 (1H, d, J = 6.6 Hz), 6.20 (1H, s), 6.56 (2H, d, J = 8.8 Hz), 6.72 (2H, d, J = 8.8 Hz), 7.37–7.45 (3H, m), 7.71–7.74 (2H, m); IR (KBr): 3271, 3088, 2959, 1651, 1549, 1514, 1298, 1237, 820, 767, 693, 626 cm^{-1}; HRMS found $[M+H]^+$ = 478.2711, calcd for $C_{28}H_{36}N_4O_3$: 478.2706.

5.18.3. *N*-((1*S*)-1-{[(4-Methoxyphenyl)amino]methyl}propyl)-N^2-(5-phenylisoxazol-3-yl)-L-leucinamide (28m). Yield: 67%; white powder; mp 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 7.4 Hz), 0.97 (3H, d, J = 7.4 Hz), 1.43–1.55 (1H, m), 1.58–1.71 (2H, m), 1.74–1.86 (2H, m), 3.01 (1H, dd, J = 8.3, 12.3 Hz), 3.19 (1H, dd, J = 4.3, 12.3 Hz), 3.70 (3H, s), 3.95–4.01 (1H, m), 4.03–4.12 (1H, m), 4.51 (1H, d, J = 6.3 Hz), 6.06 (1H, s), 6.49–6.55 (3H, m), 6.66–6.72 (2H, m), 7.34–7.41 (3H, m), 7.55–7.60 (2H, m);IR (KBr): 3278, 3065, 1649, 1556, 1512, 1235, 1039, 820, 761, 690 cm^{-1}; MS (FAB) *m*/*z*: 451.27 $[M+H]^+$.

5.18.4. *N*-((1*S*)-1-{[(4-Methoxyphenyl)amino]methyl}propyl)-N^2-(morpholin-4-ylcarbonyl)-L-leucinamide (28n). Yield: 73%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91–0.96 (9H, m), 1.47–1.70 (5H, m), 3.09 (1H, dd, J = 7.3, 12.5 Hz), 3.19 (1H, dd, J = 5.1, 12.5 Hz), 3.33–3.36 (4H, m), 3.66 (4H, t, J = 4.4 Hz), 3.74 (3H, s), 3.99–4.02 (1H, m), 4.25–4.29 (1H, m), 4.84 (1H, d, J = 8.1 Hz), 6.17 (1H, d, J = 8.1 Hz), 6.58 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz); IR (KBr): 3284, 2957, 1623, 1515, 1239, 1119, 820 cm^{-1}; HRMS found $[M+H]^+$ = 421.2801, calcd for $C_{22}H_{37}N_4O_4$: 421.2815.

5.19. *N*-[4-(Benzyloxy)phenyl]-2-nitrobenzenesulfonamide (29)

To a stirred solution of 4-(benzyloxy)aniline hydrochloride (11.79 g, 50 mmol) and 2-nitrobenzenesulfonyl chloride (11.08 g, 50 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (14.6 mL, 105 mmol) dropwise at 0 °C. After stirring for 4 h, water (200 mL) was added to the reaction mixture. The organic layer was washed with 1 M HCl (100 mL) and saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and concentrated. Recrystallization from EtOH (350 mL) provided 2-nitrobenzenesulfonamide **29** (16.63 g, 87%). Mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (2H, s), 6.85 (1H, d, J = 8.9 Hz), 7.09 (1H, d, J = 8.9 Hz), 7.10 (1H, br s), 7.30–7.40 (5H, m), 7.55 (1H, dt, J = 1.2, 7.8 Hz), 7.68 (1H, dt, J = 1.4, 7.8 Hz), 7.75 (1H, dd, J = 1.4, 7.8 Hz), 7.85 (1H, dd, J = 1.2, 7.8 Hz); IR (KBr): 3312, 1540, 1507, 1166, 1005, 595 cm^{-1}; MS (FAB) *m*/*z*: 384 $[M^+]$; Anal. Calcd for $C_{19}H_{16}N_2O_5S$: C, 59.37; H, 4.20; N, 7.29; S, 8.34. Found: C, 59.21; H, 4.05; N, 7.27; S, 8.33.

5.20. *tert*-Butyl [(1*S*)-1-({[4-(benzyloxy)phenyl]amino}methyl)propyl]carbamate (31)

Compound **31** was prepared according to the procedure for **27**, using appropriate starting materials. Yield: 82%; mp 108–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 1.45 (9H, s), 1.40–1.66 (2H, m), 3.01 (1H, dd, J = 7.6, 12.2 Hz), 3.17 (1H, dd, J = 4.6, 12.2 Hz), 3.65–3.80 (2H, m), 4.46 (1H, br s), 4.99 (2H, s), 6.57 (2H, d, J = 8.9 Hz), 6.84 (2H, d, J = 8.9 Hz), 7.28–7.43 (5H, m); IR (KBr): 3375, 1683, 1514, 1245, 1175, 1018, 816 cm^{-1}; MS (FAB) *m*/*z*: 370 $[M^+]$, 223, 91, 57; Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.16; H, 7.93; N, 7.55.

5.21. General procedure for the preparation of amides 32

Compound **32** was prepared according to the procedure for **28**, using appropriate starting materials.

5.21.1. *N*-[(1*S*)-1-({[4-(Benzyloxy)phenyl]amino}methyl)propyl]-N^2-biphenyl-3-yl-L-leucinamide (32b). Yield: 99%; colorless crystals; mp 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 0.94 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.39–1.92 (5H, m), 2.96 (1H, dd, J = 7.3, 12.5 Hz), 3.11 (1H, dd, J = 4.4, 12.5 Hz), 3.40–3.55 (1H, br s), 3.74–3.82 (1H, m), 3.92–3.95 (1H, m), 4.00–4.12 (1H, m), 4.93 (2H, s), 6.33 (2H, d, J = 9.5 Hz), 6.58 (1H, dd, J = 2.2, 8.1 Hz), 6.72 (2H, d, J = 9.5 Hz), 6.74–6.85 (2H, m), 7.03 (1H, d, J = 8.1 Hz), 7.18 (1H, t, J = 8.1 Hz), 7.28–7.58 (10H, m); IR (KBr): 3324, 1624, 1511, 1231, 1214, 755 cm^{-1}; Anal. Calcd for $C_{35}H_{41}N_3O_2$: C, 78.47; H, 7.71; N, 7.84. Found: C, 78.47; H, 7.52; N, 7.78; MS (FAB) *m*/*z*: 536 $[M+H]^+$, 444, 238.

5.21.2. *N*-[(1*S*)-1-({[4-(Benzyloxy)phenyl]amino}methyl)propyl]-N^2-(2-oxo-6-phenyl-2*H*-pyran-4-yl)-L-leucinamide (32k). Yield: 74%; colorless crystals; mp 142–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 5.9 Hz), 0.93 (3H, d, J = 5.9 Hz), 0.95 (3H, t, J = 7.5 Hz), 1.52–1.72 (5H, m), 3.12–3.21 (2H, m), 4.03–4.09 (2H, m), 4.91 (2H, s), 5.33 (1H, d, J = 1.6 Hz), 5.72 (1H, br s), 6.22 (1H, d, J = 1.6 Hz), 6.53 (2H, d, J = 9.0 Hz), 6.77 (2H, d, J = 9.0 Hz), 7.14 (1H, br s), 7.27–7.39 (8H, m), 7.66–7.68 (2H, m); IR (KBr): 3269, 3088, 2959, 1650, 1549, 1512, 1298, 1232, 818, 767, 694 cm^{-1}; HRMS found $[M+H]^+$ = 554.3012, calcd for $C_{34}H_{40}N_3O_4$: 554.3024.

5.21.3. *N*-[(1*S*)-1-({[4-(Benzyloxy)phenyl]amino}methyl)propyl]-N^2-(5-phenylisoxazol-3-yl)-L-leucinamide (32m). Yield: 81%; mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 0.95 (3H, d, J = 6.1 Hz), 0.98 (3H, d, J = 6.1 Hz), 1.42–1.70 (3H, m), 1.74–1.83 (2H, m), 3.00 (1H, dd, J = 8.5, 12.2 Hz), 3.19 (1H, dd, J = 4.2, 12.2 Hz), 3.54 (1H, br s), 3.80 (1H, br s), 3.92–3.99 (1H, m), 4.01–4.12 (1H, m), 4.31 (1H, d, J = 5.8 Hz), 4.92 (2H, s), 6.04 (1H, s), 6.41 (1H, d, J = 9.1 Hz), 6.50 (2H, d, J = 8.9 Hz), 6.75 (2H, d, J = 8.9 Hz), 7.25–7.41 (8H, m), 7.53–7.58 (2H, m); IR (KBr): 3279, 2960, 1645, 1511, 1231, 1025, 816, 762, 692 cm^{-1}; MS (FAB) *m*/*z*: 527.30 $[M+H]^+$.

5.21.4. *N*-[(1*S*)-1-({[4-(Benzyloxy)phenyl]amino}methyl)propyl]-N^2-(morpholin-4-ylcarbonyl)-L-leucinamide (32n). Yield: 87%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.95 (9H, m), 1.49–1.69 (5H, m), 3.09 (1H, dd, J = 8.1, 12.5 Hz), 3.19 (1H, dd, J = 5.1, 12.5 Hz), 3.32–3.35 (4H, m), 3.64–3.66 (4H, m), 3.96–4.03 (1H, m), 4.24–4.30 (1H, m), 4.95 (1H, d, J = 8.1 Hz), 4.98 (2H, s), 6.32 (1H, d, J = 8.1 Hz), 6.56 (2H, d, J = 8.8 Hz), 6.83 (2H, d, J = 8.8 Hz), 7.28–7.42 (5H, m); IR (KBr): 3283, 2958, 1622, 1545, 1512, 1455, 1384, 1267, 1233, 1119, 1024, 1000, 819, 738, 696 cm^{-1}; HRMS found $[M+H]^+$ = 497.3124, calcd for $C_{28}H_{41}N_4O_4$: 497.3132.

5.22. General procedure for the preparation of phenols 33 via hydrogenolysis

A mixture of benzyl ether **32** (3.7 mmol) and Pd/C (10%, 0.40 g, 0.37 mmol) in EtOH (20 mL) was stirred under H_2 at 40 °C for 6 h. After removal of Pd/C by filtration, the filtrate was concentrated. The residue was purified by column chromatography to provide phenol **33**.

5.22.1. N^2-Biphenyl-3-yl-*N*-((1*S*)-1-{[(4-hydroxyphenyl)amino]methyl}propyl)-L-leucinamide (33b). Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 0.94 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 6.6 Hz), 1.53–1.93 (5H, m), 3.71 (1H, dd, J = 4.4, 9.5 Hz), 3.75–3.82 (1H, m), 3.85 (1H, dd, J = 3.7, 9.5 Hz), 4.91 (1H, br s), 6.47 (2H, d, J = 8.8 Hz), 6.54–6.62 (1H, m), 6.59 (2H, d, J = 8.8 Hz), 6.79–6.82 (1H, m), 6.96 (1H, d, J = 8.1 Hz), 7.03 (1H, br d, J = 9.5 Hz), 7.14 (1H, t, J = 8.1 Hz), 7.28–7.55 (6H, m); IR (KBr): 2961, 1649, 1605, 1509, 1228 cm^{-1}; MS (FAB) m/z: 447 $[M+H]^+$, 238.

5.22.2. *N*-((1*S*)-1-{[(4-Hydroxyphenyl)amino]methyl}propyl)-N^2-(2-oxo-6-phenyl-2*H*-pyran-4-yl)-L-leucinamide (33k). Yield: 95%; mp 171–175 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 0.84 (3H, d, J = 5.9 Hz), 0.87 (3H, t, J = 8.1 Hz), 0.90 (3H, d, J = 6.6 Hz), 1.37–1.69 (5H, m), 2.96–3.07 (2H, m), 3.86–3.92 (2H, m), 5.04 (1H, br s), 6.44 (2H, d, J = 8.8 Hz), 6.51 (2H, d, J = 8.8 Hz), 6.54 (1H, d, J = 2.2 Hz), 7.39–7.40 (3H, m), 7.71–7.73 (2H, m); IR (KBr): 3280, 2960, 1656, 1549, 1516, 1242, 822, 767, 627 cm^{-1}; HRMS found $[M+H]^+$ = 464.2546, calcd for $C_{27}H_{34}N_3O_4$: 464.2553.

5.22.3. *N*-((1*S*)-1-{[(4-Hydroxyphenyl)amino]methyl}propyl)-N^2-(morpholin-4-ylcarbonyl)-L-leucinamide (33n). Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 0.94 (3H, t, J = 7.3 Hz), 1.46–1.71 (5H, m), 3.10 (1H, dd, J = 7.3, 12.5 Hz), 3.17 (1H, dd, J = 4.4, 12.5 Hz), 3.33–3.35 (4H, m), 3.66 (4H, t, J = 4.4 Hz), 3.94–4.02 (1H, m), 4.23–4.29 (1H, m), 4.87 (1H, d, J = 8.1 Hz), 6.21 (1H, d, J = 8.1 Hz), 6.53 (2H, d, J = 8.8 Hz), 6.69 (2H, d, J = 8.8 Hz); IR (KBr): 3293, 2959, 1626, 1517, 1245, 1119, 1000, 822 cm^{-1}; HRMS found $[M+H]^+$ = 407.2665, calcd for $C_{21}H_{35}N_4O_4$: 407.2648.

5.23. *N*-((1*S*)-1-{[(4-Hydroxyphenyl)amino]methyl}propyl)-N^2-(5-phenylisoxazol-3-yl)-L-leucinamide (33m)

A mixture of benzyl ether **32m** (1.13 g, 2.2 mmol) and concentrated HCl (2.5 mL) in AcOH (5 mL) was stirred at reflux for 1 h. The cooled reaction mixture was poured into water (50 mL). The mixture was extracted with EtOAc (2× 50 mL). The organic layer was concentrated and purified by column chromatography (hexane/EtOAc 1:1) to provide phenol **33m** (0.52 g, 56%). Mp 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz), 0.91 (3H, d, J = 6.0 Hz), 0.95 (3H, d, J = 6.0 Hz), 1.40–1.51 (1H, m), 1.56–1.66 (2H, m), 1.70–1.82 (2H, m), 2.98 (1H, dd, J = 8.2, 12.5 Hz), 3.14 (1H, dd, J = 4.3, 12.5 Hz), 3.93–4.07 (2H, m), 4.56 (1H, d, J = 6.3 Hz), 6.02 (1H, s), 6.42 (2H, d, J = 8.6 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.60 (2H, d, J = 8.6 Hz), 7.32–7.37 (3H, m), 7.52–7.57 (2H, m); IR (KBr): 3297, 2961, 1649, 1626, 1515, 1240, 819, 761, 690 cm^{-1}; MS (FAB) m/z: 436.26 $[M^+]$.

5.24. General procedure for the preparation of *tert*-butyl acetates 34

To a stirred solution of phenol **33** (3.7 mmol) in THF (15 mL) was added NaH (55%, 0.18 g, 4.1 mmol), followed by a solution of *tert*-butyl bromoacetate (0.79 g, 4.1 mmol) in DMF (4 mL) at 0 °C. After stirring at room temperature for 1 h, water (100 mL) was added to the reaction mixture at 0 °C. The mixture was extracted with EtOAc (2× 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography to provide *tert*-butyl acetate **34**.

5.24.1. *tert*-Butyl [4-({(2*S*)-2-[(*N*-biphenyl-3-yl-L-leucyl)amino]butyl}amino)phenoxy]acetate (34b). Yield: 81%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 0.94 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 6.3 Hz), 1.40–1.50 (1H, m), 1.48 (9H, s), 1.55–1.66 (2H, m), 1.80–1.91 (2H, m), 2.95 (1H, dd, J = 7.4, 12.5 Hz), 3.10 (1H, dd, J = 4.7, 12.5 Hz), 3.74–3.78 (1H, m), 3.91–3.94 (1H, m), 4.00–4.08 (1H, m), 4.36 (2H, s), 6.30 (2H, d, J = 9.0 Hz), 6.56 (1H, dd, J = 2.2, 7.8 Hz), 6.65 (2H, d, J = 9.0 Hz), 6.74 (1H, d, J = 8.6 Hz), 6.82 (1H, t, J = 2.2 Hz), 7.01 (1H, d, J = 7.8 Hz), 7.15 (1H, t, J = 7.8 Hz), 7.27–7.37 (3H, m), 7.47–7.51 (2H, m); IR (KBr): 2961, 1751, 1652, 1605, 1513, 1217, 1155 cm^{-1}; Anal. Calcd for $C_{34}H_{45}N_3O_4$: C, 72.96; H, 8.10; N, 7.51. Found: C, 72.95; H, 8.00; N, 7.49; MS (FAB) m/z: 560 $[M+H]^+$, 446, 238.

5.24.2. *tert*-Butyl {4-[((2*S*)-2-{[*N*-(2-oxo-6-phenyl-2*H*-pyran-4-yl)-L-leucyl]amino}butyl)amino]phenoxy}acetate (34k). Yield: 76%; mp 122–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 5.9 Hz), 0.94 (3H, d, J = 5.9 Hz), 0.96 (3H, t, J = 7.3 Hz), 1.48 (9H, s), 1.53–1.73 (5H, m), 3.11–3.22 (2H, m), 4.02–4.10 (2H, m), 4.38 (2H, s), 5.33 (1H, d, J = 2.2 Hz), 5.71 (1H, br s), 6.24 (1H, d, J = 2.2 Hz), 6.53 (2H, d, J = 8.8 Hz), 6.73 (2H, d, J = 8.8 Hz), 7.14 (1H, br s), 7.38–7.43 (3H, m), 7.69–7.71 (2H, m); IR (KBr): 3272, 3088,

2961, 1653, 1549, 1513, 1368, 1299, 1215, 1155, 1066, 821, 767, 693 cm^{-1}; HRMS found $[M+Na]^+$ = 600.3064, calcd for $C_{33}H_{43}N_3O_6Na$: 600.3040.

5.24.3. *tert*-Butyl {4-[((2*S*)-2-{[*N*-(5-phenylisoxazol-3-yl)-L-leucyl]amino}butyl)amino]phenoxy}acetate (34m). Yield: 56%; mp 95–96 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz), 0.93 (3H, d, J = 6.3 Hz), 0.96 (3H, d, J = 6.3 Hz), 1.47 (9H, s), 1.56–1.70 (2H, m), 1.74–1.84 (2H, m), 2.99 (1H, dd, J = 8.2, 12.1 Hz), 3.16 (1H, dd, J = 4.3, 12.1 Hz), 3.86 (1H, br s), 3.97–4.07 (2H, m), 4.35 (2H, s), 4.91 (1H, br s), 6.06 (1H, s), 6.47 (2H, d, J = 8.6 Hz), 6.67 (2H, d, J = 8.6 Hz), 7.32–7.38 (3H, m), 7.53–7.58 (2H, m); IR (KBr): 3275, 2961, 1753, 1648, 1557, 1511, 1214, 1155, 820, 763, 690 cm^{-1}; MS (FAB) *m*/*z*: 551.32 $[M+H]^+$.

5.24.4. *tert*-Butyl {4-[((2*S*)-2-{[*N*-(morpholin-4-ylcarbonyl)-L-leucyl]amino}butyl)amino]phenoxy}acetate (34n). Yield: 76%; amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 5.9 Hz), 0.92 (3H, d, J = 5.9 Hz), 0.94 (3H, t, J = 7.4 Hz), 1.48 (9H, s), 1.49–1.68 (5H, m), 3.08 (1H, dd, J = 7.8, 12.5 Hz), 3.17 (1H, dd, J = 5.1, 12.5 Hz), 3.32–3.35 (4H, m), 3.65 (4H, t, J = 4.7 Hz), 3.94–4.02 (1H, m), 4.20–4.26 (1H, m), 4.40 (2H, s), 4.81 (1H, d, J = 7.8 Hz), 6.17 (1H, d, J = 8.7 Hz), 6.54 (2H, d, J = 9.0 Hz), 6.75 (2H, d, J = 9.0 Hz); IR (KBr): 3285, 2960, 1754, 1623, 1514, 1368, 1267, 1156, 1119, 1081, 1000, 820 cm^{-1}; HRMS found $[M+H]^+$ = 521.3344, calcd for $C_{27}H_{45}N_4O_6$: 521.3336.

5.25. General procedure for the preparation of acetic acids 35

To a stirred solution of *tert*-butyl acetate **34** (2.9 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was concentrated. 4 M HCl in 1,4-dioxane (3 mL) was added to the residue. The mixture was concentrated and triturated with Et_2O (20 mL) to provide acetic acid **35**.

5.25.1. [4-({(2*S*)-2-[(*N*-Biphenyl-3-yl-L-leucyl)amino]butyl}amino)phenoxy]acetic acid 2HCl (35b). Yield: 74%; colorless crystals; mp 89–91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74–0.90 (9H, m), 1.51–1.69 (4H, m), 2.11–2.22 (1H, m), 3.22–3.27 (1H, m), 3.65–3.72 (2H, m), 4.43–4.50 (2H, m), 4.47 (2H, s), 6.77 (2H, d, J = 7.4 Hz), 7.34–7.75 (9H, m), 8.03 (1H, br s), 9.52 (1H, m); IR (KBr): 2963, 1739, 1674, 1605, 1554, 1228, 1193 cm^{-1}; MS (FAB) *m*/*z*: 560 $[M+H]^+$, 444, 238.

5.25.2. {4-[((2*S*)-2-{[*N*-(2-Oxo-6-Phenyl-2*H*-pyran-4-yl)-L-leucyl]amino}butyl)amino]phenoxy}acetic acid 2HCl (35k). Yield: 46%; amorphous substance; ^1H NMR (400 MHz, CD_3OD) δ 0.97 (3H, d, J = 6.7 Hz), 1.00 (3H, t, J = 6.3 Hz), 1.02 (3H, d, J = 6.7 Hz), 1.59–1.84 (5H, m), 3.40 (2H, br s), 4.00–4.09 (2H, m), 4.65 (2H, s), 5.14 (1H, s), 6.66 (1H, s), 6.99 (2H, d, J = 8.6 Hz), 7.18 (2H, br s), 7.45–7.49 (3H, m), 7.78–7.80 (2H, m); IR (KBr): 3262, 3065, 2960, 1664, 1548, 1511, 1201, 1068, 830, 769, 692 cm^{-1}; HRMS found $[M+H]^+$ = 522.2594, calcd for $C_{29}H_{36}N_3O_6$: 522.2613.

5.25.3. {4-[((2*S*)-2-{[*N*-(5-Phenylisoxazol-3-yl)-L-leucyl]amino}butyl)amino]phenoxy}acetic acid 2HCl (35m). Yield: 86%; mp 118–121 °C; ^1H NMR (400 MHz, CD_3OD) δ 0.96 (3H, t, J = 6.7 Hz), 1.00 (3H, d, J = 6.3 Hz), 1.05 (3H, d, J = 6.3 Hz), 1.58–1.68 (2H, m), 1.69–1.76 (2H, m), 1.84–1.94 (1H, m), 3.31 (1H, d, J = 6.3 Hz), 3.48 (1H, d, J = 6.3 Hz), 4.00 (1H, br s), 4.65 (2H, s), 6.38 (1H, s), 7.00 (2H, d, J = 8.6 Hz), 7.33 (2H, d, J = 8.6 Hz), 7.41–7.49 (3H, m), 7.59–7.67 (2H, m); IR (KBr): 3265, 2961, 1740, 1625, 1546, 1511, 1198, 1075, 832, 763, 690 cm^{-1}; MS (FAB) *m*/*z*: 495.26 $[M+H]^+$.

5.25.4. {4-[((2*S*)-2-{[*N*-(Morpholin-4-ylcarbonyl)-L-leucyl]amino}butyl)amino]phenoxy}acetic acid 2HCl (35n). Yield: 93%; amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89–0.97 (9H, m), 1.55–1.74 (5H, m), 3.30–3.64 (10H, m), 3.84–3.92 (1H, m), 4.06–4.09 (1H, m), 4.70 (2H, s), 7.06 (2H, d, J = 8.8 Hz), 7.40 (2H, d, J = 8.8 Hz); IR (KBr): 3264, 2961, 1740, 1607, 1512, 1444, 1263, 1199, 1118, 1072, 833 cm^{-1}; HRMS found $[M+H]^+$ = 465.2700, calcd for $C_{23}H_{37}N_4O_6$: 465.2728.

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