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Potent and selective cathepsin K inhibitors

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Abstract—A novel series of cathepsin K inhibitors derived from Novartis compound **I** is described. Optimization of the P1, P3, and P1′ units led to the identification of 4-aminophenoxyacetic acid **24b** with an IC_{50} value of 4.8 nM, which possessed an excellent selectivity over other human cathepsins and good pharmacokinetic (PK) properties. Oral administration of compound **24b** to ovariectomized (OVX) rats showed a trend toward an improvement of bone mineral density (BMD) in the femur bone.

1. Introduction

Bone mass is regulated by the continuous equilibrium between the bone-resorbing process and the bone-forming process. It is known that an imbalance of this remodeling system causes osteoporosis. In the bone-resorbing process, osteoclasts adhere to the bone surface, and secrete acid and proteolytic enzymes to resorbe bone. One of the proteolytic enzymes is a lysosomal cysteine protease, cathepsin K,[1] which exhibits potent collagenolytic activity against type I collagen, one of the main constituents of bone matrix. Thus, selective inhibition of cathepsin K has been expected to provide an efficacious therapeutic treatment for bone diseases. In a previous paper, we reported biphenylamino acid amides as novel and potent cathepsin K inhibitors found by modification of Novartis compound **I**.[2] Herein, we wish to report on the detailed syntheses and structure–activity relationships of S-, O-, and NH-linked cathepsin K inhibitors. In addition, we wish to describe the selectivity over other human cathepsins, pharmacokinetics, and in vivo evaluation of several potent compounds.

We selected aryl amine based derivative **I** as a lead compound from among many kinds of compounds that inhibit cathepsin K,[3] because this compound had been shown to be a non-covalent and reversible inhibitor.[4] Scrutiny of the X-ray crystallographic data of cathepsin K complexed with inhibitors bearing a benzyloxycarbonyl (Cbz) group[5,6] revealed that the carbonyl oxygen of the Cbz group did not interact with the enzyme. Therefore, we envisaged to convert the Cbz group of Novartis compound **I** to a biphenyl group by tethering the carbonyl oxygen to the benzylic carbon, as shown in Figure 1. Such P3 sub-structures had not been reported when we started this project.[3c]

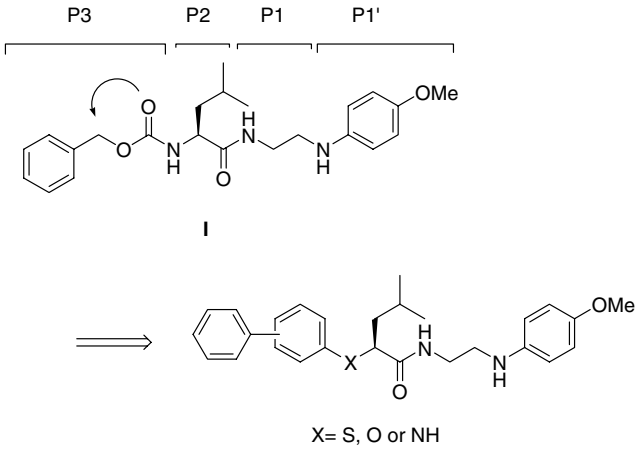

Figure 1. Modification of compound **I** to S-, O-, and NH-linked compounds.

Keywords: Cathepsin K; Inhibitor; SAR study; OVX rat assay.
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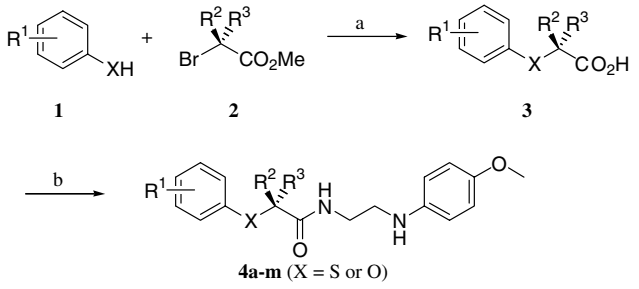
2. Chemistry

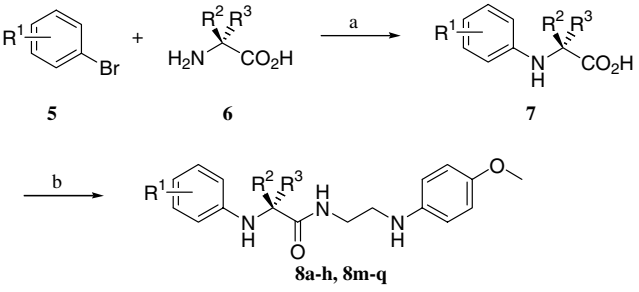
The preparation of S- and O-linked compounds is shown in Scheme 1. Phenoxycarboxylic acids **3** (X=O) were prepared by etheration of phenols **1** (X=O) with α-bromoesters **2**. Phenylsulfanylcarboxylic acids **3** (X=S) were prepared in the same manner. Carboxylic acids **3** were coupled with *N*-(4-methoxyphenyl)ethane-1,2-diamine[7] under usual reaction conditions (WSC·HCl and HOBt in DMF) to provide S- or O-linked compounds **4a**–**m**. As racemic methyl 2-bromo-4-methylpentanoate (**2**; R^2 = *i*-Bu, R^3 = H) was employed in these reactions, **4a** and **4c**–**f** were prepared as racemic compounds.

The synthesis of *N*-aryl amino acids **7** and the subsequent coupling to NH-linked compounds **8** are shown in Scheme 2. The preparation of *N*-aryl amino acids **7** was accomplished by coupling aryl bromides **5** with amino acids **6** using a copper catalyst.[8] Subsequent amidation of **7** afforded NH-linked compounds **8a**–**h** and **8m**–**q**.

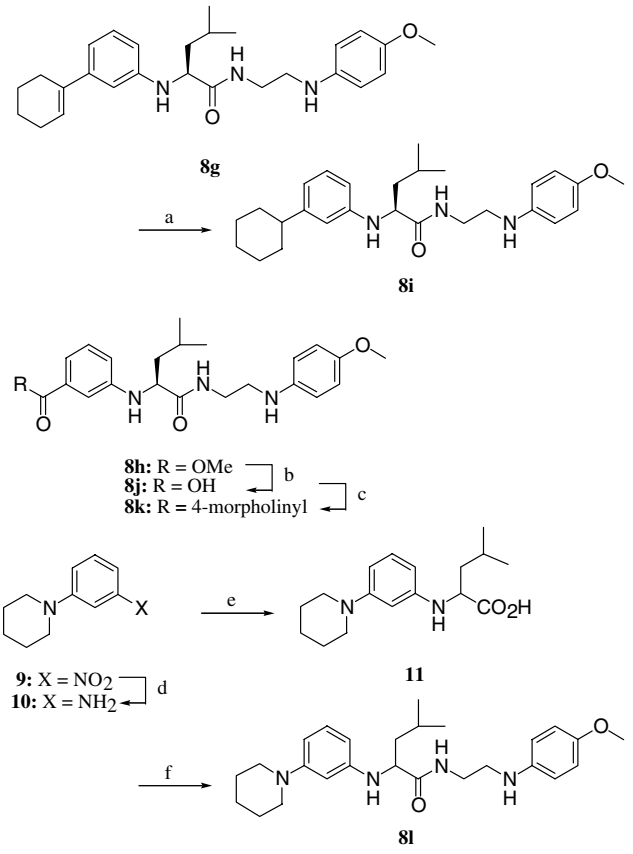
Scheme 3 shows the preparation of NH-linked compounds **8i**–**l**. Cyclohexane **8i** was prepared by hydrogenation of cyclohexene **8g**. Saponification of methyl ester **8h** provided carboxylic acid **8j**. Subsequent condensation with morpholine afforded amide **8k**. The preparation of piperidine **8l** was achieved by N-alkylation. Reduction of nitrobenzene **9** ($SnCl_2·2H_2O$ in EtOH) and N-alkylation (KOH in *t*-BuOH) provided carboxylic acid **11**. Subsequent amidation of **11** provided **8l**. As racemic 2-bromo-4-methylpentanoic acid[9] was employed in N-alkylation, **8l** was prepared as racemic compound.



Scheme 1. Synthesis of S- and O-linked compounds **4a**–**m**. Reagents and condition: (a) KOH, *t*-BuOH, reflux; (b) *N*-(4-methoxyphenyl)ethane-1,2-diamine, WSC·HCl, HOBt, DMF.



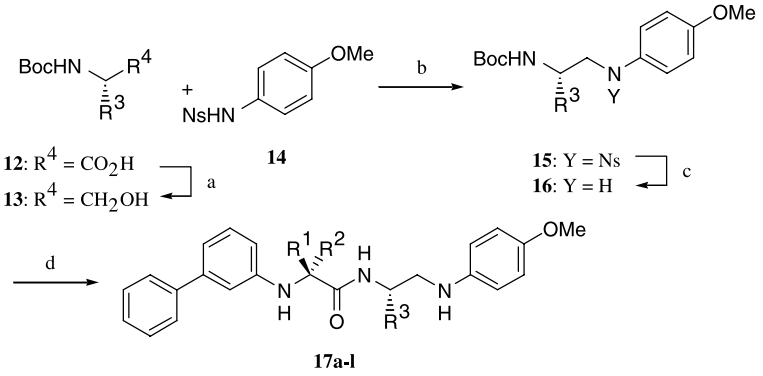
Scheme 2. Synthesis of NH-linked compounds **8a**–**h** and **8m**–**q**. Reagents and condition: (a) $CuBr·SMe_2$, K_2CO_3, DMA, 120 °C; (b) *N*-(4-methoxyphenyl)ethane-1,2-diamine, WSC·HCl, HOBt, DMF.



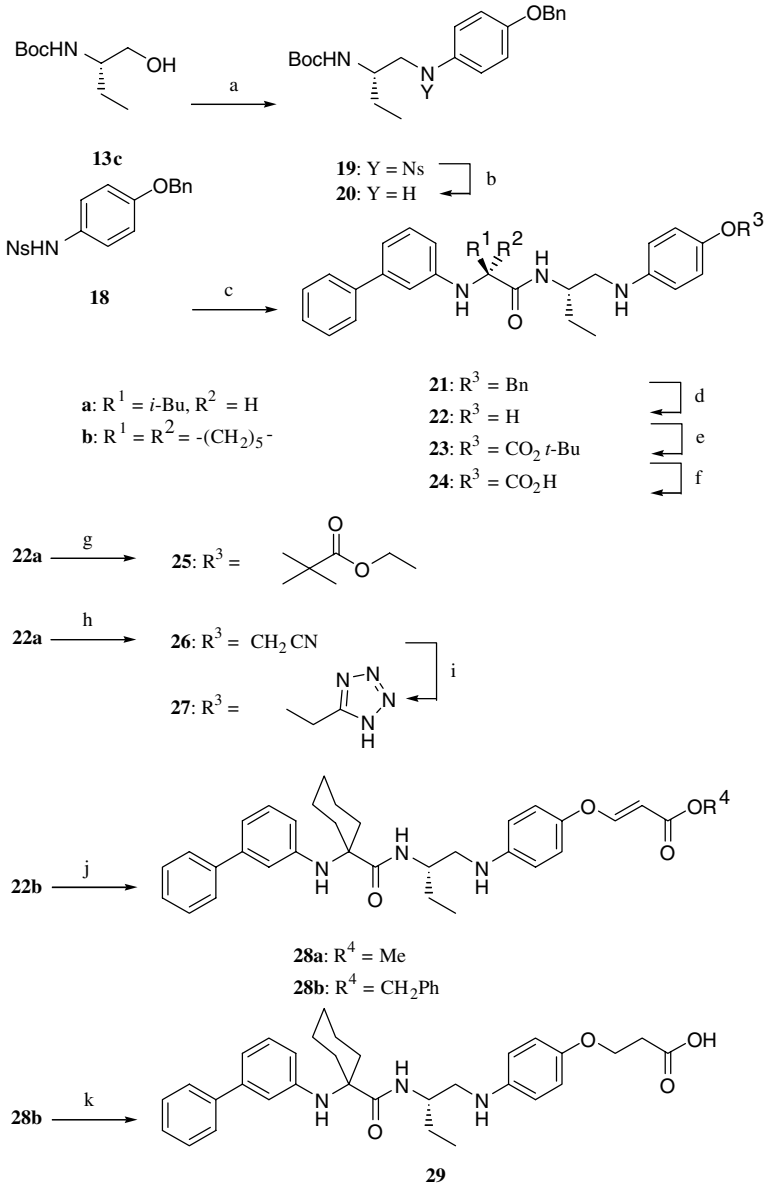
Scheme 3. Synthesis of NH-linked compounds **8i**–**l**. Reagents: (a) H_2, $Pd(OH)_2$/C, EtOH, 45%; (b) NaOH, MeOH/H_2O, 52%; (c) morpholine, WSC·HCl, HOBt, CH_2Cl_2, 70%; (d) $SnCl_2·2H_2O$, EtOH, reflux, 96%; (e) 2-bromo-4-methylpentanoic acid, KOH, *t*-BuOH, reflux, 42%; (f) *N*-(4-methoxyphenyl)ethane-1,2-diamine, WSC·HCl, HOBt, DMF, 61%.

As shown in Scheme 4, the preparation of branched compounds **17a**–**l** was accomplished using 2-nitrobenzenesulfonamides as intermediates.[10] Commercially available aminoalcohols were converted to corresponding *N*-Boc aminoalcohols **13**,[11] and other *N*-Boc aminoalcohols were prepared from the corresponding *N*-Boc amino acids **12**.[12] Mitsunobu reaction[13] of *N*-Boc aminoalcohols **13** with 2-nitrobenzenesulfonamide **14**[14] afforded branched *N*-Boc ethylenediamines **15**, which were deprotected with PhSH to provide branched ethylenediamines **16**. Deprotection of the Boc group and amidation with carboxylic acids **7** furnished branched compounds **17a**–**l**.

The preparation of compounds **23**–**29** is shown in Scheme 5. Mitsunobu reaction[13] of *N*-Boc aminoalcohol **13c** with 2-nitrobenzenesulfonamide **18** and subsequent deprotection provided **20**.[10] Coupling of **20** with carboxylic acids **7**, followed by cleavage of benzyl ether (H_2, Pd/C, and EtOH), provided phenols **22**. Alkylation of **22** with *tert*-butyl bromoacetate afforded esters **23**. Saponification of **23** furnished acids **24**. In a similar manner, ester **25** and nitrile **26** were prepared. Tetrazole **27** was prepared from **26** under usual reaction conditions. The preparation of propanoic acid **29** was achieved by complete reduction of acrylate **28b**, which was synthesized from phenol **22b**.[15]



Scheme 4. Synthesis of branched compounds **17a–l**. Reagents: (a) *N*-methylmorpholine, ethyl chloroformate, THF, then $NaBH_4$, MeOH; (b) DEAD, PPh_3, THF; (c) PhSH, K_2CO_3, MeCN; (d) HCl, 1,4-dioxane, then **7**, WSC·HCl, HOBt, CH_2Cl_2. Ns, 2-nitrobenzenesulfonyl.



Scheme 5. Synthesis of compounds **23–29**. Reagents and conditions: (a) DEAD, PPh_3, THF; (b) PhSH, K_2CO_3, MeCN, 82% (two steps); (c) TFA, CH_2Cl_2, then **7**, WSC·HCl, HOBt, DMF, 99% (**21a**), 84% (**21b**); (d) H_2, Pd/C, EtOH, 87% (**22a**), 99% (**22b**); (e) *tert*-butyl bromoacetate, NaH, DMF/THF, 81% (**23a**), 79% (**23b**); (f) TFA, CH_2Cl_2, then HCl, 1,4-dioxane, 74% (**24a**), 95% (**24b**); (g) ethyl 2-bromo-2-methylpropanoate, NaH, DMF/THF, 61%; (h) bromoacetonitrile, NaH, DMF/THF, 59%; (i) NaN_3, NH_4Cl, DMF, 100 °C, 69%; (j) *N*-methylmorpholine, methylpropiolate or benzylpropiolate, THF, 64% (**28a**), 66% (**28b**); (k) H_2, Pd/C, EtOH, 37%.

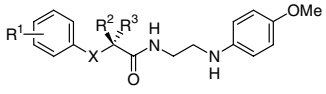
3. Results and discussion

The inhibitory activities of S- and O-linked compounds against recombinant human cathepsin K are summarized in Table 1. The assays were carried out at pH 3.8 since purified procathepsin K was efficiently activated at lower pH, such as pH 4.0.[16] In addition, the activity of mature cathepsin K at pH 3.8 was around 40% when compared to that at pH 6.0 using Cbz-Phe-Arg-AMC as a substrate (data not shown). Isobutyl and cyclohexyl groups were employed as the P2 unit, and isobutyl derivatives (**4a** and **4c–j**) were prepared as racemic mixtures. Compound **I** indicated an IC_{50} of 0.09 μM. This IC_{50} value obtained in our assay was similar to the reported value (0.07 μM).[4] Among the S-linked compounds, isobutyl derivative **4a** showed 10 times greater potency than cyclohexyl analogue **4b**. Phenyl ethers such as **4c** and **4g** exhibited an IC_{50} value of 3 μM. Although S-linked compound **4a** showed better potency than O-linked compounds **4c** and **4g**, further modifications of the O-linked compounds were performed, because thio ethers are metabolically unstable in general. Among isobutyl derivatives, the addition of a phenyl group to the phenoxy group in compound **4c** at the 3- or 4-position increased the inhibitory activity by 30 times (**4c**, **4e**, and **4f**), while substitution at the 2-position brought little improvement in activity (**4d**). Similar tendency was observed among cyclohexyl derivatives (**4h–j**). Interestingly, alkyl derivatives **4k–m** retained good inhibitory activities, and cyclohexyl derivative **4m** was 2-fold more potent than 4-biphenyl ether **4j**.

Then, the inhibitory activities of NH-linked compounds were examined as indicated in Table 2. Anilines **8a** and **8e** showed reduced potencies compared to phenyl ethers **4g** and **4c**, respectively. 2-Biphenylamine **8b** did not indicate any inhibitory activities, whereas biphenylamines **8c** and **8d** possessed increased activities compared to the corresponding biphenyl ethers **4i** and **4j**. The improvement in activity could be ascribed to a hydrogen bond between the amino group and the enzyme as mentioned in the literature.[3c] In the aryl amine series, 3-biphenylamine derivative **8c** displayed better activity than 4-biphenylamine derivative **8d**, and the *N*-(3-biphenyl)-L-leucyl group was found to be a better P2–P3 substituent than the 3-biphenylaminocyclohexylcarbonyl group (**8c** and **8f**). As *N*-(3-biphenyl)-L-leucine **8f** possessed 2-fold better inhibitory activity than compound **I**, the replacement of the terminal phenyl group of **8f** with other groups was examined. Cyclohexenyl and cyclohexyl groups did not enhance the activity (**8g** and **8i**). This was unlike the same displacement in aryl ether **4j**, which resulted in more potent **4m**. Replacement by more polar substituents such as a carboxy group reduced the activity by 15 times (**8j**). Morpholine amide **8k** and piperidine **8l** had activities in the micromolar range. Finally, the incorporation of alkoxy groups was examined. A methoxy group was introduced into the 3- or 4-position of the benzene ring of **8a**, and both compounds **8m** and **8n** displayed almost no activity. Bulkier alkoxy substituents increased the activity; however, the most effective derivative among the alkoxy compounds, **8p**, was 10-fold less potent than **8f**.

In the structure–activity relationship study described above, we found the 3-biphenylamino group was preferable as a P3 substituent. It was expected that the introduction of an alkyl group extending into the S1 pocket would enhance the inhibitory activity, and we synthesized derivatives with an alkyl side chain in the ethylenediamine moiety of compounds **8c** and **8f**. The effect of

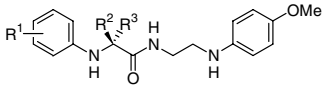
Table 1. Inhibitory activities of O- and S-linked compounds



Compound	X	R^1	R^2	R^3	IC_{50}[a] (μM)
I					0.09
4a[b]	S	H	*i*-Bu	H	1.6
4b	S	H	$-(CH_2)_5-$		20
4c[b]	O	H	*i*-Bu	H	3
4d[b]	O	2-Ph	*i*-Bu	H	1.2
4e[b]	O	3-Ph	*i*-Bu	H	0.09
4f[b]	O	4-Ph	*i*-Bu	H	0.1
4g	O	H	$-(CH_2)_5-$		3
4h	O	2-Ph	$-(CH_2)_5-$		>15
4i	O	3-Ph	$-(CH_2)_5-$		0.32
4j	O	4-Ph	$-(CH_2)_5-$		0.19
4k	O	4-Et	$-(CH_2)_5-$		0.13
4l	O	4-*i*-Pr	$-(CH_2)_5-$		0.2
4m	O	4-*c*-Hex	$-(CH_2)_5-$		0.099

[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] Racemic compound.

Table 2. Inhibitory activities of NH-linked compounds



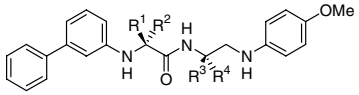
Compound	R^1	R^2	R^3	IC_{50}[a] (μM)
8a	H	$-(CH_2)_5-$		11
8b	2-Ph	$-(CH_2)_5-$		>20
8c	3-Ph	$-(CH_2)_5-$		0.083
8d	4-Ph	$-(CH_2)_5-$		0.1
8e	H	*i*-Bu	H	10
8f	3-Ph	*i*-Bu	H	0.04
8g	3-*c*-Hexenyl	*i*-Bu	H	0.059
8i	3-*c*-Hexyl	*i*-Bu	H	0.06
8j	3-CO_2H	*i*-Bu	H	0.95
8k	3-(4-Morpholinecarbonyl)	*i*-Bu	H	3.7
8l[c]	3-(1-Piperidyl)	*i*-Bu	H	4.5
8m	3-MeO	$-(CH_2)_5-$		NI[b]
8n	4-MeO	$-(CH_2)_5-$		>20
8o	3-*i*-PrO	$-(CH_2)_5-$		2
8p	3-*i*-BuO	$-(CH_2)_5-$		0.4
8q	3-$PhCH_2O$	$-(CH_2)_5-$		3

[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] Not inhibited at 20 μM.
[c] Racemic compound.

this side chain is summarized in Table 3. First, both stereoisomers of methyl derivatives **17a** and **17b** were prepared, and (*S*)-isomer **17a** was found to be more potent. Therefore, derivatives of various alkyl side chains with the (*S*)-configuration were examined. The incorporation of linear alkyl side chains increased inhibitory activity more than 10 times, and the best activity in this series was observed when an ethyl group was incorporated (**17c**). The substitution of a branched alkyl side chain such as isopropyl and isobutyl groups retained the potency (**17f** and **17g**), whereas the side chains containing a phenyl group were less suitable (**17h–j**). Among the L-leucine derivatives, ethyl derivative **17l** showed excellent inhibitory activity (IC_{50} = 3.8 nM).

Next the substituent on the benzene ring in the P1′ unit of **17c** and **17l** was examined. The result is summarized in Table 4. As previously reported,[4b] benzyl derivative **21b** retained good inhibitory activity. Unexpectedly, we found that the replacement of the phenyl group in compound **21b** with a tetrazole group led to moderate compound **27**, which was only 4-fold less potent than **21b**. We then synthesized carbonyl derivatives such as esters and carboxylic acids, although it had been shown that lipophilic groups are favorable for the S1′ pocket.[4b] *tert*-Butyl ester **23a** showed a 2-fold increase in the inhibitory activity compared to tetrazole **27**. Dimethyl derivative **25** and nitrile **26** exhibited moderate activities. Interestingly, the IC_{50} value of carboxylic acid derivative **24a** was 4.5 nM, which was more potent than ester **23a** and similar to that of methoxy derivative **17l**. 3-Biphenylaminocyclohexyl analogues of the above derivatives were also prepared and evaluated for inhibitory activity. Compound **24b** possessed good inhibitory activity with an IC_{50} of 4.8 nM. Acrylates **28a** and **28b** did not indicate potent activity. Propanoic acid **29** possessed excellent inhibitory activity (IC_{50} = 2.9 nM), but structural instability prevented further evaluation.

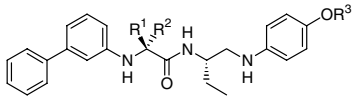
Table 3. Variation of P1 substituent: inhibitory activities of NH-linked compounds

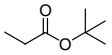
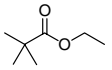
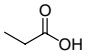
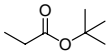
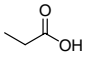
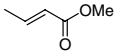
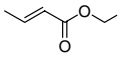
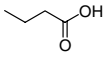


Compound	R^1	R^2	R^3	R^4	IC_{50}[a] (nM)
8c	$-(CH_2)_5-$		H	H	83
17a	$-(CH_2)_5-$		H	Me	10
17b	$-(CH_2)_5-$		Me	H	82
17c	$-(CH_2)_5-$		H	Et	2.7
17d	$-(CH_2)_5-$		H	*n*-Pr	3.9
17e	$-(CH_2)_5-$		H	*n*-Bu	5.6
17f	$-(CH_2)_5-$		H	*i*-Pr	7.7
17g	$-(CH_2)_5-$		H	*i*-Bu	7.0
17h	$-(CH_2)_5-$		H	Ph	19
17i	$-(CH_2)_5-$		H	CH_2Ph	26
17j	$-(CH_2)_5-$		H	$(CH_2)_2Ph$	30
8f	*i*-Bu	H	H	H	40
17k	*i*-Bu	H	H	Me	10
17l	*i*-Bu	H	H	Et	3.8

[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.

Table 4. Variation of P1′ substituent: inhibitory activities of NH-linked compounds



Compound	R^1	R^2	R^3	IC_{50}[a] (nM)
17c	$-(CH_2)_5-$		Me	2.7
17l	*i*-Bu	H	Me	3.8
21b	$-(CH_2)_5-$			2.8
27	*i*-Bu	H		11
23a	*i*-Bu	H		6.4
25	*i*-Bu	H		13
26	*i*-Bu	H		15
24a[b]	*i*-Bu	H		4.5
23b	$-(CH_2)_5-$			4.8
24b[b]	$-(CH_2)_5-$			4.8
28a	$-(CH_2)_5-$			32
28b	$-(CH_2)_5-$			32
29	$-(CH_2)_5-$			29

[a] Inhibition of recombinant human cathepsin K activity in a fluorescence assay using 8 μM Cbz-Phe-Arg-AMC as 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] 2HCl salt.

Several potent compounds were selected for further pharmacological evaluation. Table 5 summarizes in vitro metabolic stability in rat and human hepatic microsomes and pharmacokinetics in rats. Pharmacokinetic (PK) parameters were measured by orally administering rats a dose of 50 mg/kg in cremophor/EtOH (2:1). The metabolic stability of the compounds strongly depended on the structure of the P1′ substituent. Tetrazole **27** showed great metabolic stability, whereas benzyl ether **21b** was moderately stable. Although *tert*-butyl esters **23a** and **23b** proved to be metabolically unstable, acetic acids **24a** and **24b** were stable. These differences in met-

Table 5. Metabolic stability[a] and PK parameters[b] of cathepsin K inhibitors

Compound	Metabolic stability (%) (rat, human)	T_{max} (h)	C_{max} (μg/mL)	AUC (μg h/mL)
17c[c]	31, 75	3	2.8	35.6
17l	2, 8	4	0.57	7.4
21b	43, 41	6	7.3	93.8
27	98, 100	6	1.6	20.3
23a[c]	1, 29	3	0.4[d]	3.0[d]
26[c]	28, 35	3	0.8	6.7
24a[c]	98, 100	4	5.0	42.9
23b	0, 13	—	0	0
24b[c]	94, 100	4	9.2	103.9

[a] Percent remaining after 30 min of incubation in hepatic microsomes.
[b] Average of three rats dosed at 50 mg/kg po.
[c] 2HCl salt.
[d] Value of **24a**.

abolic stability could be ascribed to the polarity of the P1′ substituent. Comparison of methyl ethers **17c** and **17l** indicated the cyclohexyl group tended to be metabolically more stable than the *i*-butyl group. Considering the metabolic stability, tetrazole **27** and acetic acids **24a** and **24b** were expected to have good PK parameters. In fact, acetic acids **24a** and **24b** possessed good PK parameters, whereas tetrazole **27** did not. Esters **23a** and **23b** were not detected in the blood serum at all, but a small amount of **24a** was observed after treatment with **23a**. Interestingly, the derivatives from 3-biphenylaminocyclohexane carboxylic acid tended to have good PK parameters, whereas the derivatives from *N*-(3-biphenyl)-L-leucine had poor PK parameters. When acetic acid **24a** was administered, the C_{max} for **24a** was 5.0 μg/mL. On the other hand, C_{max} for **24b** (9.2 μg/mL) was 2-fold better than that for **24a**. Benzyl ether **21b** showed good PK parameters in spite of its moderate metabolic stability. These results suggest that the 3-biphenylaminocyclohexanecarbonyl group is more suitable than the 3-biphenyl-L-leucyl group with regard to pharmacokinetics.

Compounds **17c**, **17l**, **27**, **24a**, and **24b** were selected for evaluation of selectivity over other human cathepsins S, B, and L (Table 6). *N*-(3-Biphenyl)-L-leucine **17l** possessed potent inhibitory activity toward cathepsin S (IC_{50} = 4.6 nM), and had poor selectivity toward cathepsins B and L (10-fold compared to cathepsin K). The other *N*-(3-biphenyl)-L-leucine derivatives such as **27** and **24a** were also less selective. To the contrary, cyclohexyl derivative **24b** showed greater than 3000-fold selectivity over cathepsins S, B, and L. In particular, **17c** displayed less than 50% inhibition against cathepsins B and L at 20 μM. These results suggest that the 3-biphenylaminocyclohexanecarbonyl group is also more suitable than the *N*-(3-biphenyl)-L-leucyl group with regard to enzyme selectivity. The IC_{50} value of human cathepsin K at pH 5.5 was measured with compounds **17l**, **24a**, and **24b**, and all compounds possessed decreased activities compared to the IC_{50} values at pH 3.8. In compounds **17c**, **17l**, and **24b**, the IC_{50} values of rat cathepsin K were also measured, and these compounds showed the IC_{50} values of 29, 16, and 58 nM, respectively.

On the basis of the PK profile, we selected compound **24b** to evaluate for the effect on bone mineral density (BMD). Compound **24b** was orally administered to ovariectomized (OVX) rats at dose of 10 or 50 mg/kg (bid) in cremophor/EtOH (2:1) for 42 days. As shown in Figure 2, **24b** induced an improvement in the BMD of the femur bone; however, the improvement was not statistically significant.

4. Conclusion

Structural modifications of compound **I** led to the discovery of a new class of cathepsin K inhibitors. A structure–activity relationship study revealed that the 3-biphenylamino group and the 4-aminophenoxyacetic acid group were good substituents for the S3 and S1′ pockets, respectively. The most potent compounds, **24a** and **24b,** showed IC_{50} values of 4.5 and 4.8 nM, respectively. Further evaluation indicated compound

Table 6. IC_{50} values of inhibition of human cathepsins S, B, L, and K (nM)

Compound	**17c**	**17l**	**27**	**24a**	**24b**
Human cathepsin S[a,f]	—[h]	4.6	34	6.9	10,000
Human cathepsin B[b,f]	NI[i]	48	—[h]	120	>20,000
Human cathepsin L[c,f]	NI[i]	55	—[h]	120	>20,000
Human cathepsin K[d,f]	2.7	3.8 (19[g])	11	4.5 (31[g])	4.8 (27[g])
Rat cathepsin K[e,f]	29	16	—[h]	—[h]	58

[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] Inhibition of recombinant rat cathepsin K activity in a fluorescence assay using 8 μM Cbz-Leu-Arg-AMC as a substrate in 200 mM NaOAc and buffer (pH 3.8).
[f] The IC_{50} values represent the average of at least $n = 2$.
[g] IC_{50} values measured at pH 5.5.
[h] Not measured.
[i] Not inhibited at 20 μM.

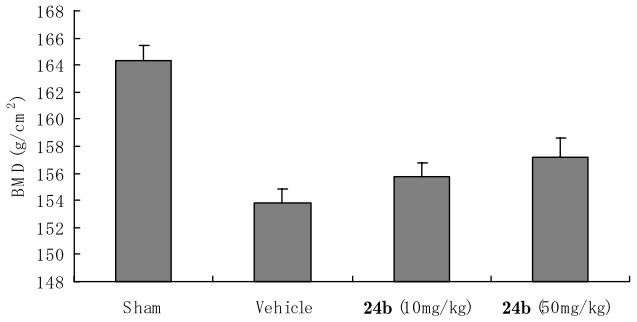


Figure 2. BMD when compound **24b** was administered to an OVX rat at doses of 10 and 50 mg/kg (bid, $n = 7$).

24b possessed good metabolic stability and PK parameters, and excellent selectivity to other human cathepsins. In an OVX rat assay, **24b** showed a trend toward an improvement of BMD in the femur bone.

5. Experimental

5.1. Materials and methods

Melting points were determined in a Yanaco micromelting 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 HR-MS 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).

5.2. General procedure for the preparation of amides (4)

A mixture of phenol or thiophenol **1** (0.50 mmol), α-bromoester **2** (0.50 mmol) and KOH (280 mg, 5.0 mmol) in *t*-BuOH (5 mL) was stirred at reflux for 24 h. HCl (1 M, 10 mL) was added to the cooled reaction mixture. The mixture was extracted with CH_2Cl_2 (5× 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide crude **3**. To residual **3** in DMF (3 mL) were added *N*-(4-methoxyphenyl)ethane-1,2-diamine[7] (83 mg, 0.50 mmol), HOBT (76 mg, 0.50 mmol), and WSC·HCl (96 mg, 0.50 mmol). After stirring 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 to provide amide **4**.

5.2.1. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-4-methyl-2-(phenylthio)pentanamide (4a). Yield: 45%; brown amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (6H, t, $J = 6.6$ Hz), 1.58–1.90 (3H, m), 3.09 (2H, t, $J = 5.9$ Hz), 3.30–3.50 (2H, m), 3.74 (3H, s), 3.78 (1H, dd, $J = 6.6$, 8.8 Hz), 6.46 (2H, d, $J = 8.8$ Hz), 6.76 (2H, d, $J = 8.8$ Hz), 7.21–7.33 (5H, m); IR (KBr): 3387, 3332, 2958, 1641, 1515, 1233, 1134, 1035, 814, 750 cm^{-1}; HR-MS found $[M+Na]^+$: 395.1775, calcd for $C_{21}H_{28}N_2O_2SNa$: 395.1769.

5.2.2. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-(phenylthio)cyclohexanecarboxamide (4b). Yield: 20%; light yellow solid; mp 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48–1.68 (4H, m), 1.71–1.80 (4H, m), 2.00–2.07 (2H, m), 3.21 (2H, t, $J = 6.6$ Hz), 3.49 (2H, q, $J = 5.9$ Hz), 3.75 (3H, s), 6.55 (2H, d, $J = 9.5$ Hz), 6.78 (2H, d, $J = 8.8$ Hz), 6.85 (1H, br s), 7.20 (2H, t, $J = 7.3$ Hz), 7.24–7.29 (1H, m), 7.39 (2H, d, $J = 6.6$ Hz); IR (KBr): 3375, 2934, 1643, 1513, 1255, 1235, 1035, 815, 749 cm^{-1}; HR-MS found $[M+H]^+$: 385.1949, calcd for $C_{22}H_{29}N_2O_2S$: 385.1950.

5.2.3. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-4-methyl-2-phenoxypentanamide (4c). Yield: 8%; brown amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, $J = 6.6$ Hz), 0.98 (3H, t, $J = 6.6$ Hz), 1.75–1.91 (3H, m), 3.13–3.17 (2H, m), 3.34–3.53 (2H, m), 3.73 (3H, s), 4.56 (1H, dd, $J = 4.4$, 8.8 Hz), 6.42 (2H, d, $J = 8.8$ Hz), 6.52–6.57 (1H, m), 6.74 (2H, d, $J = 8.8$ Hz), 6.90 (2H, d, $J = 8.1$ Hz), 7.02 (1H, t, $J = 7.3$ Hz), 7.26–7.31 (2H, m); IR (film): 3358, 2957, 1662, 1514, 1236, 1039, 821, 755, 693 cm^{-1}; HR-MS found $[M+H]^+$: 357.2184, calcd for $C_{21}H_{29}N_2O_3$: 357.2178.

5.2.4. 2-(Biphenyl-2-yloxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}-4-methylpentanamide (4d). Yield: 5%; brown amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, dd, $J = 2.2$, 6.6 Hz), 1.55–1.75 (3H, m), 3.02 (2H, t, $J = 5.9$ Hz), 3.27 (2H, t, $J = 5.9$ Hz), 3.74 (3H, s), 4.63 (1H, dd, $J = 4.4$, 8.1 Hz), 6.42 (2H, d, $J = 9.5$ Hz), 6.74 (2H, d, $J = 8.8$ Hz), 6.94 (1H, d, $J = 8.1$ Hz), 7.10 (1H, t, $J = 7.3$ Hz), 7.29–7.32 (1H, m), 7.35 (2H, d, $J = 6.6$ Hz), 7.40 (2H, t, $J = 7.3$ Hz), 7.47 (2H, d, $J = 8.1$ Hz); IR (KBr): 3395, 3231, 3088, 2956, 1649, 1580, 1516, 1482, 1433, 1236, 1134, 1034, 817, 755, 702 cm^{-1}; HR-MS found $[M+Na]^+$: 455.2314, calcd for $C_{27}H_{32}N_2O_3Na$: 455.2311.

5.2.5. 2-(Biphenyl-3-yloxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}-4-methylpentanamide (4e). Yield: 8%; brown amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, $J = 6.6$ Hz), 0.99 (3H, d, $J = 6.6$ Hz), 1.78–1.96 (3H, m), 3.14–3.19 (2H, m), 3.40–3.52 (2H, m), 3.71 (3H, s), 4.65 (1H, dd, $J = 4.4$, 8.8 Hz), 6.39 (2H, d, $J = 8.8$ Hz), 6.70 (2H, d, $J = 8.8$ Hz), 6.87 (1H, dd, $J = 2.9$, 8.8 Hz), 7.14 (1H, s), 7.25–7.26 (1H, m), 7.35 (2H, t, $J = 8.1$ Hz), 7.42 (2H, t, $J = 8.1$ Hz), 7.55 (2H, d, $J = 8.8$ Hz); IR (film): 3358, 2956, 1663, 1513, 1477, 1294, 1237, 1199, 1038, 819, 758, 698 cm^{-1}; HR-MS found $[M+Na]^+$: 455.2324, calcd for $C_{27}H_{32}N_2O_3$-Na: 455.2311.

5.2.6. 2-(Biphenyl-4-yloxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}-4-methylpentanamide (4f). Yield: 2%; light brown solid; mp 148–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, $J = 6.6$ Hz), 1.00 (3H, d, $J = 6.6$ Hz), 1.76–1.94 (3H, m), 3.17 (2H, t, $J = 5.9$ Hz), 3.33–3.60 (2H, m), 3.71 (3H, s), 4.60 (1H, dd, $J = 3.7$, 8.1 Hz), 6.42 (2H, d, $J = 8.8$ Hz), 6.70 (2H,

d, J = 8.8 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.40–7.53 (7H, m); IR (KBr): 3382, 2955, 1649, 1515, 1236, 819, 762, 694 cm^{-1}; HR-MS found $[M+Na]^+$: 455.2325, calcd for $C_{27}H_{32}N_2O_3Na$: 455.2311.

5.2.7. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-1-phenoxycyclohexanecarboxamide (4g). Yield: 36%; white solid; mp 87–90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23–1.66 (6H, m), 1.92–2.06 (4H, m), 3.17–3.21 (2H, m), 3.41–3.52 (2H, m), 3.73 (3H, s), 6.43 (2H, d, J = 7.3 Hz), 6.60–6.67 (1H, m), 6.74 (2H, d, J = 7.3 Hz), 6.89 (2H, d, J = 7.3 Hz), 6.94–7.01 (1H, m), 7.16–7.26 (2H, m); IR (KBr): 3372, 2942, 1648, 1514, 1235, 1147, 1040, 969, 815, 756, 694 cm^{-1}; HR-MS found $[M+H]^+$: 369.2177, calcd for $C_{22}H_{29}N_2O_3$: 369.2178.

5.2.8. 1-(Biphenyl-2-yloxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (4h). Yield: 44%; white solid; mp 120–122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99–1.38 (6H, m), 1.83 (2H, dt, J = 2.9, 13.9 Hz), 2.00 (2H, d, J = 13.9 Hz), 3.22 (2H, t, J = 5.9 Hz), 3.51 (2H, q, J = 5.9 Hz), 3.73 (3H, s), 6.47 (2H, d, J = 8.8 Hz), 6.64 (1H, t, J = 5.9 Hz), 6.75 (2H, d, J = 9.5 Hz), 6.82 (1H, d, J = 8.1 Hz), 7.03–7.10 (2H, m), 7.31–7.36 (2H, m), 7.40 (2H, t, J = 7.3 Hz), 7.49 (2H, d, J = 6.6 Hz); IR (KBr): 3318, 2936, 1647, 1515, 1477, 1432, 1235, 1147, 1038, 970, 817, 700 cm^{-1}; HR-MS found $[M+Na]^+$: 467.2305, calcd for $C_{28}H_{32}N_2O_3Na$: 467.2310.

5.2.9. 1-(Biphenyl-3-yloxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (4i). Yield: 26%; brown oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.70 (6H, m), 1.92–2.00 (2H, m), 2.11–2.14 (2H, m), 3.03–3.16 (2H, m), 3.19 (2H, t, J = 5.2 Hz), 3.61 (2H, q, J = 5.9 Hz), 3.72 (3H, s), 6.41 (2H, d, J = 8.8 Hz), 6.71 (2H, d, J = 8.8 Hz), 6.83–6.86 (1H, m), 7.15–7.16 (1H, m), 7.23–7.25 (2H, m), 7.32–7.35 (1H, m), 7.40 (2H, t, J = 8.1 Hz), 7.54 (2H, d, J = 8.1 Hz); IR (film): 3030, 2937, 1660, 1513, 1237, 1038, 972, 820, 759, 700 cm^{-1}; HR-MS found $[M+H]^+$: 445.2487, calcd for $C_{28}H_{33}N_2O_3$: 445.2491.

5.2.10. 1-(Biphenyl-4-yloxy)-*N*-{2-[(4-methoxyphenyl)-amino]ethyl}cyclohexanecarboxamide (4j). Yield: 24%; white solid; mp 157–159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.69 (6H, m), 1.91–1.99 (2H, m), 2.11–2.14 (2H, m), 2.12 (2H, d, J = 13.9 Hz), 3.20 (2H, t, J = 5.1 Hz), 3.52 (2H, q, J = 5.1 Hz), 3.71 (3H, s), 6.44 (2H, d, J = 8.1 Hz), 6.67 (1H, t, J = 5.9 Hz), 6.72 (2H, d, J = 8.8 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.30 (1H, t, J = 7.3 Hz), 7.38–7.42 (4H, m), 7.49–7.55 (2H, m); IR (KBr): 3376, 2941, 1648, 1512, 1487, 1233, 1147, 1039, 972, 816, 764, 695 cm^{-1}; HR-MS found $[M+Na]^+$: 467.2312, calcd for $C_{28}H_{32}N_2O_3Na$: 467.2311.

5.2.11. 1-(4-Ethylphenoxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (4k). Yield: 22%; White solid; mp 139–142 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, t, J = 7.3 Hz), 1.30–1.63 (6H, m), 1.89–1.95 (2H, m), 2.06 (2H, d, J = 13.9 Hz), 2.57 (2H, q, J = 7.3 Hz), 3.19 (2H, t, J = 5.9 Hz), 3.49 (2H, q, J = 5.9 Hz), 3.73 (3H, s), 6.43 (2H, d, J = 8.8 Hz), 6.66 (1H, t, J = 5.9 Hz), 6.74 (2H, d, J = 8.8 Hz), 6.80 (2H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.8 Hz); IR (KBr): 3369, 3331, 2942, 1647, 1510, 1231, 1149, 1040, 970, 815, 711 cm^{-1}; HR-MS found $[M+H]^+$: 397.2488, calcd for $C_{24}H_{33}N_2O_3$: 397.2491.

5.2.12. 1-(4-Isopropylphenoxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (4l). Yield: 14%; brown amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (6H, d, J = 6.6 Hz), 1.27–1.66 (6H, m), 1.87–1.95 (2H, m), 2.06 (2H, d, J = 13.2 Hz), 2.83 (1H, quint., J = 7.3 Hz), 3.19 (2H, t, J = 5.9 Hz), 3.49 (2H, q, J = 5.1 Hz), 3.73 (3H, s), 6.42 (2H, d, J = 8.8 Hz), 6.66 (1H, t, J = 5.9 Hz), 6.74 (2H, d, J = 8.8 Hz), 6.80 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz); IR (KBr): 3366, 2942, 1644, 1511, 1231, 1148, 967, 816, 706 cm^{-1}; HR-MS found $[M+H]^+$: 411.2666, calcd for $C_{25}H_{35}N_2O_3$: 411.2648.

5.2.13. 1-(4-Cyclohexylphenoxy)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (4m). Yield: 15%; white solid; mp 124–126 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.94 (20H, m), 2.06 (2H, d, J = 13.2 Hz), 2.39–2.41 (1H, m), 3.19 (2H, t, J = 5.1 Hz), 3.48 (2H, q, J = 5.1 Hz), 3.73 (3H, s), 6.41 (2H, d, J = 8.8 Hz), 6.64 (1H, t, J = 5.9 Hz), 6.73 (2H, d, J = 8.8 Hz), 6.79 (2H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.1 Hz); IR (KBr): 3373, 3322, 2926, 2852, 1647, 1512, 1232, 1147, 1039, 969, 818 cm^{-1}; HR-MS found $[M^+]$: 450.2881, calcd for $C_{28}H_{38}N_2O_3$: 450.2883.

5.3. 1-Bromo-3-cyclohex-1-en-1-ylbenzene (5g)

To a stirred solution of 1,3-dibromobenzene (1.8 mL, 15 mmol) in THF (50 mL) was added *n*-BuLi (1.59 M in hexane, 9.4 mL, 15 mmol) followed by cyclohexanone (1 mL, 10 mmol) at −78 °C under N_2 atmosphere. After stirring at −78 °C for 2 h, saturated aqueous solution of NH_4Cl (50 mL) was added. The mixture was extracted with EtOAc (2× 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (hexane/EtOAc, 3:1) to provide 1-(3-bromophenyl)cyclohexanol (1.85 g, 73%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–1.81 (10H, m), 7.21 (1H, t, J = 8.1 Hz), 7.37 (1H, dd, J = 2.2, 8.8 Hz), 7.42 (1H, dd, J = 2.9, 9.5 Hz), 7.67 (1H, t, J = 2.2 Hz); IR (film): 3405, 2935, 2856, 1593, 1565, 1448, 1259, 1207, 974, 782, 694 cm^{-1}; HR-MS found $[M^+]$: 254.0309, calcd for $C_{12}H_{15}OBr$: 254.0306. A mixture of 1-(3-bromophenyl)cyclohexanol (1.85 g, 7.3 mol) and $TsOH{\cdot}H_2O$ (126 mg, 0.7 mmol) in toluene (30 mL) was stirred at reflux for 30 min. The mixture was concentrated and purified by column chromatography (hexane) to provide cyclohexene **5g** (1.49 g, 87%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.62–1.68 (2H, m), 1.73–1.80 (2H, m), 2.18–2.23 (2H, m), 2.34–2.38 (2H, m), 6.11–6.13 (1H, m), 7.16 (1H, t, J = 8.1 Hz), 7.29 (1H, d, J = 8.1 Hz), 7.33 (1H, d, J = 7.3 Hz), 7.51 (1H, s); IR (film): 2929, 1591, 1559, 1476, 1074, 994, 777, 645 cm^{-1}; HR-MS found: $[M^+]$: 236.0199, calcd for $C_{12}H_{13}Br$: 236.0200.

5.4. General procedure for the preparation of carboxylic acids (7)

A mixture of aryl bromide **5** (64.99 mmol), amino acid **6** (64.99 mmol), K_2CO_3 (13.47 g, 97.49 mmol), and Cu-Br·SMe_2 (2.67 g, 13.00 mmol) in DMA (200 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 to provide carboxylic acid **7**.

5.4.1. 1-Anilinocyclohexanecarboxylic acid (7a). Yield: 17%; mp 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.38 (3H, m), 1.64–1.66 (3H, m), 1.98–1.99 (4H, m), 6.69 (2H, d, J = 8.8 Hz), 6.89 (1H, t, J = 8.1 Hz), 7.22 (2H, t, J = 8.1 Hz).

5.4.2. 1-(Biphenyl-2-ylamino)cyclohexanecarboxylic acid (7b). Yield: 2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82–1.93 (10H, m), 6.63 (1H, d, J = 7.8 Hz), 6.95 (1H, t, J = 7.8 Hz), 7.18 (1H, d, J = 7.8 Hz), 7.23 (1H, t, J = 7.8 Hz), 7.41–7.44 (3H, m); 7.50 (2H, t, J = 7.8 Hz); IR (KBr): 2928, 1700, 1510, 1437, 1319, 1283, 755, 703, cm^{-1}; HR-MS found [M$^+$]: 295.1557, calcd for $C_{19}H_{21}O_2N$: 295.1573.

5.4.3. 1-(Biphenyl-3-ylamino)cyclohexanecarboxylic acid (7c). 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 $C_{19}H_{21}NO_2$·0.1H_2O: C, 76.79; H, 7.19; N, 4.71. Found: C, 76.85; H, 7.12; N, 4.67.

5.4.4. 1-(Biphenyl-4-ylamino)cyclohexanecarboxylic acid (7d). Yield: 11%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39–1.49 (2H, m), 1.63–1.70 (2H, m), 1.99–2.04 (6H, m), 6.75 (2H, d, J = 8.1 Hz), 7.29 (1H, t, J = 7.3 Hz), 7.40 (2H, t, J = 8.1 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.53 (2H, d, J = 6.6 Hz); IR (KBr): 3404, 2934, 1613, 1525, 1489, 828, 761, 695, 612 cm^{-1}; HR-MS found [M$^+$]: 295.1567, calcd for $C_{19}H_{21}O_2N$: 295.1572.

5.4.5. *N*-Phenyl-L-leucine (7e). Yield: 17%; mp 171–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 5.9 Hz), 1.63–1.87 (3H, m), 4.03 (1H, dd, J = 5.1, 8.8 Hz), 6.65 (2H, d, J = 8.1 Hz), 6.80 (1H, t, J = 7.3 Hz), 7.20 (2H, t, J = 7.3 Hz).

5.4.6. *N*-Biphenyl-3-yl-L-leucine (7f). 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}; HR-MS found [M$^+$]: 283.1578, calcd for $C_{18}H_{21}O_2N$: 283.1572.

5.4.7. *N*-(3-Cyclohex-1-en-1-ylphenyl)-L-leucine (7g). Yield: 14%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.61–1.87 (7H, m), 2.16–2.20 (2H, m), 2.34–2.38 (2H, m), 4.04 (1H, dd, J = 5.9, 8.8 Hz), 6.06–6.08 (1H, m), 6.51 (1H, dd, J = 2.2, 8.8 Hz), 6.66 (1H, s), 6.83 (1H, d, J = 7.3 Hz), 7.13 (1H, t, J = 8.1 Hz); IR (KBr): 3295, 2926, 1713, 1605, 1483, 1333, 1197, 790, 692 cm^{-1}; HR-MS found [M$^+$]: 287.1867, calcd for $C_{18}H_{25}O_2N$: 287.1886.

5.4.8. *N*-[3-(Methoxycarbonyl)phenyl]-L-leucine (7h). Yield: 21%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, d, J = 6.6 Hz), 1.02 (3 H, d, J = 6.6 Hz), 1.66–1.89 (3H, m), 3.89 (3H, s), 4.12–4.16 (1H, m), 6.83 (1H, dd, J = 1.5, 8.1 Hz), 7.32–7.38 (2H, m), 7.44 (1H, d, J = 8.1 Hz).

5.4.9. 1-[(3-Methoxyphenyl)amino]cyclohexanecarboxylic acid (7m). Yield: 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.47 (3H, m), 1.62–1.70 (3H, m), 2.01 (4H, br s), 3.76 (3H, s), 6.27–6.32 (2H, m), 6.45 (1H, dd, J = 2.2, 8.1 Hz), 7.12 (1H, t, J = 8.1 Hz).

5.4.10. 1-[(3-Isopropoxyphenyl)amino]cyclohexanecarboxylic acid (7o). Yield: 18%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (6H, d, J = 6.6 Hz), 1.37 (3H, br s), 1.64–1.66 (3H, m), 1.99 (4H, br s), 4.44–4.53 (1H, m), 6.22 (1H, s), 6.25 (1H, d, J = 7.3 Hz), 6.43 (1H, d, J = 8.1 Hz), 7.10 (1H, t, J = 8.1 Hz).

5.4.11. 1-[(3-Isobutoxyphenyl)amino]cyclohexanecarboxylic acid (7p). Yield: 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (6H, d, J = 6.6 Hz), 1.38 (3H, br s), 1.64–1.66 (3H, m), 2.00–2.08 (5H, m), 3.67 (2H, t, J = 6.6 Hz), 6.24–6.27 (2H, m), 6.43–6.45 (1H, m), 7.10 (1H, t, J = 8.1 Hz).

5.4.12. 1-{[3-(Benzyloxy)phenyl]amino}cyclohexanecarboxylic acid HCl (7q). Yield: 42%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32–1.55 (6H, m), 1.81–1.89 (4H, m), 4.95 (2H, s), 6.34–6.47 (2H, m), 7.02 (1H, t, J = 8.1 Hz), 7.25–7.37 (4H, m); IR (KBr): 2953, 1748, 1615, 1598, 1573, 1456, 1393, 1265, 1159, 1134, 1014, 741, 690, 535, 471 cm^{-1}; MS (FAB) m/z: 326 [M+H]$^+$, 280, 200.

5.5. General procedure for the preparation of amides (8)

A mixture of *N*-(4-methoxyphenyl)ethane-1,2-diamine[7] (0.088 mmol), carboxylic acid **7** (0.088 mmol), HOBt (18 mg, 0.13 mmol), Et_3N (18 μL, 0.13 mmol), and WSC·HCl (25 mg, 0.13 mmol) in DMF (3 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 to provide amide **8**.

5.5.1. 1-Anilino-*N*-{2-[(4-methoxyphenyl)amino]ethyl}-cyclohexanecarboxamide (8a). Yield: 90%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–2.02 (10H, m), 3.19 (2H, t, J = 6.0 Hz), 3.47 (2H, dt, J = 6.0, 6.0 Hz), 3.73

(3H, s), 3.99 (1H, br s), 6.42 (2H, d, J = 8.9 Hz), 6.60 (2H, dd, J = 1.0, 8.5 Hz), 6.73 (2H, d, J = 8.9 Hz), 6.79 (1H, t, J = 7.4 Hz), 7.13 (2H, dd, J = 7.4, 8.5 Hz), 7.26 (1H, br s); IR (film): 3373, 1653, 1602, 1513, 1237, 753 cm^{-1}; MS (FAB) m/z: 367 [M^+]; Anal. Calcd for $C_{22}H_{29}N_3O_2 \cdot 0.2EtOAc$: C, 71.11; H, 8.01; N, 10.91. Found: C, 71.19; H, 8.33; N, 10.86.

5.5.2. 1-(Biphenyl-2-ylamino)-*N*-{2-[(4-methoxyphenyl)-amino]ethyl}cyclohexanecarboxamide (8b). Yield: 71%; white solid; mp 113–114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83–1.18 (2H, m), 1.44–1.56 (4H, m), 1.86–1.89 (4H, m), 3.21 (2H, t, J = 5.9 Hz), 3.47 (2H, q, J = 5.9 Hz), 3.74 (3H, s), 4.34 (1H, br s), 6.45 (2H, d, J = 8.8 Hz), 6.54 (1H, d, J = 8.1 Hz), 6.75 (2H, d, J = 8.8 Hz), 6.85 (1H, t, J = 8.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.16 (1H, d, J = 7.3 Hz), 7.19–7.22 (1H, m), 7.39–7.42 (2H, m), 7.47–7.51 (2H, m); IR (KBr): 3382, 2929, 1644, 1514, 1235, 1039, 818, 758, 706 cm^{-1}; HR-MS found: $[M+H]^+$: 444.2659, calcd for $C_{28}H_{34}N_3O_2$: 444.2651.

5.5.3. 1-(Biphenyl-3-ylamino)-*N*-{2-[(4-methoxyphenyl)-amino]ethyl}cyclohexanecarboxamide (8c). Yield: 74%; white amorphous substance; ^1H 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}. MS (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.

5.5.4. 1-(Biphenyl-4-ylamino)-*N*-{2-[(4-methoxyphenyl)-amino]ethyl}cyclohexanecarboxamide (8d). Yield: 98%; white solid; mp 131–134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (2H, br s), 1.64–1.67 (2H, m), 1.98–2.04 (6H, m), 3.20 (2H, t, J = 5.9 Hz), 3.50 (2H, q, J = 5.9 Hz), 3.71 (3H, s), 4.07 (1H, br s), 6.43 (2H, d, J = 8.8 Hz), 6.66 (2H, d, J = 8.8 Hz), 6.71 (2H, d, J = 8.8 Hz), 7.23–7.29 (1H, m), 7.35 (2H, d, J = 8.8 Hz), 7.39 (2H, t, J = 7.3 Hz), 7.49 (2H, d, J = 8.1 Hz); IR (KBr): 3375, 2935, 1653, 1611, 1513, 1235, 1038, 821, 764, 698 cm^{-1}; HR-MS found $[M+H]^+$: 444.2652, calcd for $C_{28}H_{34}N_3O_2$: 444.2651.

5.5.5. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-N^2-phenyl-L-leucinamide (8e). Yield: 49%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 6.3 Hz), 0.99 3H, (d, J = 6.3 Hz), 1 51–1.57 (1H, m), 1.74–1.86 (2H, m), 3.17 (2H, t, J = 5.9 Hz), 3.34–3.51 (2H, m), 3.73 (3H, s), 3.74–3.85 (1H, m), 6.40 (2H, d, J = 8.9 Hz), 6.60 (2H, d, J = 7.5 Hz), 6.72 (2H, d, J = 8.9 Hz), 6.82 (1H, t, J = 7.5 Hz), 7.04 (1H, br s), 7.19 (2H, t, J = 7.5 Hz); IR (film): 3361, 1654, 1604, 1513, 1237, 754 cm^{-1}; MS (FAB) m/z: 355 [M^+]; Anal. Calcd for $C_{21}H_{29}N_3O_2 \cdot 1H_2O$: C, 67.53; H, 8.37; N, 11.25. Found: C, 67.21; H, 7.93; N, 11.20.

5.5.6. N^2-Biphenyl-3-yl-N^1-{[(4-methoxyphenyl)amino]-methyl}-L-leucinamide (8f). Yield: 88%; white amorphous substance; ^1H 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}; HR-MS found $[M+H]^+$: 432.2653, calcd for $C_{27}H_{34}N_3O_2$: 432.2651.

5.5.7. N^2-(3-Cyclohex-1-en-1-ylphenyl)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}-L-leucinamide (8g). Yield: 74%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 5.9 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.51–1.87 (7H, m), 2.15–2.18 (2H, m), 2.33–2.35 (2H, m), 3.14–3.18 (2H, m), 3.32–3.52 (2H, m), 3.73 (3H, s), 3.74–3.81 (1H, m), 6.07–6.09 (1H, m), 6.38 (2H, d, J = 8.8 Hz), 6.47 (1H, dd, J = 2.2, 8.1 Hz), 6.62 (1H, s), 6.71 (2H, d, J = 8.8 Hz), 6.86 (1H, d, J = 8.1 Hz), 7.04 (1H, t, J = 5.9 Hz), 7.13 (1H, t, J = 8.1 Hz); IR (KBr): 3354, 2931, 1652, 1603, 1513, 1237, 1038, 821, 755 cm^{-1}; HR-MS found $[M^+]$: 435.2866, calcd for $C_{27}H_{37}N_3O_2$: 435.2886.

5.5.8. Methyl 3-({(1*S*)-1-[({2-[(4-methoxyphenyl)amino]ethyl}amino)carbonyl]-3-methylbutyl}amino)benzoate (8h). Yield: 52%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.53–1.86 (3H, m), 3.18 (2H, t, J = 5.9 Hz), 3.70 (2H, q, J = 5.9 Hz), 3.73 (3H, s), 3.87 (3H, s), 6.43 (2H, d, J = 8.8 Hz), 6.73 (2H, d, J = 8.8 Hz), 6.78–6.81 (1H, m), 7.21–7.31 (2H, m), 7.47 (1H, d, J = 7.3 Hz).

5.5.9. 1-[(3-Methoxyphenyl)amino]-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (8m). Yield: 74%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.35 (3H, m), 1.60–1.63 (3H, m), 1.95–1.97 (4H, m), 3.18 (2 H, t, J = 5.9 Hz), 3.44 (2H, q, J = 5.9 Hz), 3.71 (3H, s), 3.71 (3H, s), 4.03 (1H, br s), 6.17 (1H, d, J = 2.2 Hz), 6.20 (1H, dd, J = 2.2, 8.1 Hz), 6.35 (1H, dd, J = 2.2, 8.1 Hz), 6.42 (2H, d, J = 8.8 Hz), 6.72 (2H, t, J = 8.8 Hz), 7.02 (1H, t, J = 8.1 Hz), 7.22–7.26 (1H, m); IR (film): 3374, 2937, 1652, 1602, 1513, 1237, 1164, 1040, 822, 764, 696 cm^{-1}; MS (FAB) m/z: 397 $[M+H]^+$, 273, 242, 220, 204.

5.5.10. 1-[(4-Methoxyphenyl)amino]-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (8n). Yield: 23%; light yellow solid; mp 119–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.31 (3H, m), 1.60–1.63 (3H, m), 1.86–2.00 (4H, m), 3.20 (2H, t, J = 5.9 Hz), 3.49 (2H, q, J = 5.9 Hz), 3.70 (3H, s), 3.73 (3H, s), 6.47 (2H, d, J = 8.8 Hz), 6.54 (2H, d, J = 8.8 Hz), 6.66 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 8.8 Hz), 7.42 (1H, t, J = 5.9 Hz); IR (KBr): 3355, 2948, 1646, 1514, 1237, 1039, 823 cm^{-1}; HR-MS found $[M+H]^+$: 398.2438, calcd for $C_{23}H_{32}N_3O_3$: 398.2443.

5.5.11. 1-[(3-Isopropoxyphenyl)amino]-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (8o). Yield: 64%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, d, J = 6.6 Hz), 1.28–1.34 (3H, m), 1.61–1.63 (3H, m), 1.95–2.01 (4H, m), 3.20 (2H, t, J = 5.9 Hz), 3.46 (2H, q, J = 5.9 Hz), 3.72 (3H, s), 3.97 (1H, br s), 4.43–4.49 (1H, m), 6.16 (1H, s), 6.17 (1H, d, J = 7.3 Hz), 6.34 (1H, d, J = 7.3 Hz), 6.43 (2H, d, J = 8.8 Hz), 6.73 (2H, d, J = 8.8 Hz), 7.01 (1H, t, J = 7.3 Hz), 7.24–7.26 (1H, m); IR (film): 3373, 2936, 1653, 1601, 1513, 1237, 822, 757 cm^{-1}; HR-MS found $[M+H]^+$: 426.2736, calcd for $C_{25}H_{36}N_3O_3$: 426.2756.

5.5.12. 1-[(3-Isobutoxyphenyl)amino]-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (8p). Yield: 64%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (6H, d, J = 6.6 Hz), 1.32 (3H, br s), 1.62–1.64 (3H, m), 1.95–2.06 (5H, m), 3.19 (2H, t, J = 5.1 Hz), 3.45 (2H, q, J = 5.9 Hz), 3.64 (2H, d, J = 6.6 Hz), 3.72 (3H, s), 3.98 (1H, br s), 6.17–6.18 (2H, m), 6.35 (1H, d, J = 7.3 Hz), 6.41 (2H, d, J = 8.8 Hz), 6.72 (2H, d, J = 8.8 Hz), 7.01 (1H, t, J = 8.1 Hz), 7.21–7.23 (1H, m); IR (film): 3371, 2935, 1652, 1601, 1513, 1237, 1165, 1039, 821 cm^{-1}; HR-MS found $[M+H]^+$: 440.2920, calcd for $C_{26}H_{38}N_3O_3$: 440.2913.

5.5.13. 1-{[3-(Benzyloxy)phenyl]amino}-*N*-{2-[(4-methoxyphenyl)amino]ethyl}cyclohexanecarboxamide (8q). Yield: 99%; solid; mp 92–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.64 (6H, m), 1.90–1.99 (4H, m), 3.19 (2H, t, J = 5.9 Hz), 3.45 (2H, q, J = 5.1 Hz), 3.72 (3H, s), 3.98 (1H, br s), 4.98 (2H, s), 6.21–6.24 (2H, m), 6.41–6.44 (3H, m), 6.71 (2H, d, J = 8.8 Hz), 7.03 (1H, t, J = 8.1 Hz), 7.21 (1H, t, J = 5.9 Hz), 7.32–7.38 (4H, m); IR (film): 3374, 2936, 2858, 1652, 1600, 1513, 1237, 1165, 1038, 821, 734, 697 cm^{-1}; MS (FAB) m/z: 474 $[M+H]^+$, 473.

5.6. N^2-(3-Cyclohexylphenyl)-*N*-{2-[(4-methoxyphenyl)amino]ethyl}-L-leucinamide (8i)

A mixture of cyclohexene **8g** (17 mg, 39 μmol) and $Pd(OH)_2$/C (55 mg, 39 μmol) in EtOH (1 mL) was stirred under H_2 for 4 h. After removal of $Pd(OH)_2$/C by filtration, the filtrate was concentrated. The residue was purified by PTLC (hexane/EtOAc, 1:1) to provide cyclohexane **8i** (8 mg, 45%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.19–1.85 (13H, m), 2.38–2.43 (1H, m), 3.13–3.21 (2H, m), 3.35–3.53 (2H, m), 3.72 (3H, s), 3.79 (1H, br s), 6.37 (2H, d, J = 8.8 Hz), 6.41–6.46 (1H, m), 6.69–6.72 (3H, m), 7.05 (1H, t, J = 5.9 Hz), 7.12 (1H, t, J = 7.3 Hz); IR (film): 3359, 2927, 1655, 1607, 1513, 1137, 1039, 757 cm^{-1}; HR-MS found $[M+Na]^+$: 460.2927, calcd for $C_{27}H_{39}N_3O_2Na$: 460.2940.

5.7. 3-({(1*S*)-1-[({2-[(4-Methoxyphenyl)amino]ethyl}amino)carbonyl]-3-methylbutyl}amino)benzoic acid (8j)

A mixture of ester **8h** (1.94 g, 4.7 mmol) and 1 M NaOH (10 mL) in MeOH (30 mL) was stirred for 24 h. 1 M HCl (20 mL) was added to the reaction mixture and the mixture was extracted with EtOAc (3× 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (CH_2Cl_2/MeOH, 20:1) to provide benzoic acid **8j** (0.84 g, 52%) as a dark brown amorphous substance. ^{1}H NMR (400 MHz, CD_3OD) δ 0.82 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.52–1.71 (3H, m), 3.28–3.33 (2H, m), 3.60–3.67 (2H, m), 3.72 (1H, dd, J = 6.6, 8.8 Hz), 6.74–6.75 (5H, m), 7.10 (1H, t, J = 7.3 Hz), 7.16 (1H, s), 7.23 (1H, d, J = 6.6 Hz); IR (KBr): 3312, 2956, 1606, 1513, 1257, 1031, 758 cm^{-1}; HR-MS found: $[M+H]^+$: 400.2237, calcd for $C_{22}H_{30}N_3O_4$: 400.2237.

5.8. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-N^2-[3-(morpholin-4-ylcarbonyl)phenyl]-L-leucinamide (8k)

A mixture of benzoic acid **8j** (180 mg, 0.45 mmol), morpholine (118 μL, 1.35 mmol), HOBt (91 mg, 0.68 mmol), and WSC·HCl (129 mg, 0.68 mmol) in CH_2Cl_2 (5 mL) was stirred for 6 h. The reaction mixture was concentrated and purified by column chromatography (EtOAc) to provide amide **8k** (147 mg, 70%) as a brown amorphous substance. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 5.9 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.57–1.85 (3H, m), 3.17–3.21 (2H, m), 3.38–3.78 (10H, m), 3.73 (3H, s), 3.96 (1H, d, J = 3.7 Hz), 6.44 (2H, d, J = 8.8 Hz), 6.61 (1H, dd, J = 2.2, 7.3 Hz), 6.66 (1H, s), 6.72 (2H, d, J = 8.8 Hz), 6.77 (1H, d, J = 7.3 Hz), 6.92 (1H, t, J = 6.6 Hz), 7.18 (1H, t, J = 8.8 Hz); IR (KBr): 3340, 2956, 1606, 1514, 1463, 1237, 1115, 1030, 822, 750 cm^{-1}; HR-MS found $[M+H]^+$: 469.2812, calcd for $C_{26}H_{37}N_4O_4$: 469.2815.

5.9. 3-Piperidin-1-ylaniline (10)

A mixture of 1-fluoro-3-nitrobenzene (1.41 g, 10 mmol) and piperidine (5.4 mL, 55 mmol) in DMSO (10 mL) was stirred at 100 °C for 24 h. The reaction mixture was cooled, diluted with EtOAc (50 mL), and washed with water (2× 50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (hexane/EtOAc, 10:1) to provide nitrobenzene **9** (2.06 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.75 (6H, m), 3.27 (4H, t, J = 5.9 Hz), 7.18 (1H, dd, J = 2.2, 8.1 Hz), 7.34 (1H, t, J = 8.1 Hz), 7.59 (1H, dd, J = 1.5, 8.1 Hz), 7.71 (1H, t, J = 2.2 Hz). A mixture of nitrobenzene **9** (1.62 g, 7.85 mmol) and $SnCl_2{\cdot}2H_2O$ (7.08 g, 15.7 mmol) in EtOH (200 mL) was stirred at reflux for 30 min. The reaction mixture was cooled, poured into 1 M NaOH (50 mL), and filtered on a Celite pad. The filtrate was extracted with EtOAc (2× 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (hexane/EtOAc, 1:1) to provide aniline **10** (1.32 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53–1.71 (6H, m), 3.12 (4H, t, J = 5.9 Hz), 3.57 (2H, br s), 6.18 (1H, dd, J = 2.2, 8.8 Hz), 6.27 (1H, d, J = 2.2 Hz), 6.38 (1H, dd, J = 2.2, 8.8 Hz), 7.02 (1H, t, J = 8.8 Hz); IR (film): 3348, 2933, 1604, 1500, 1384, 1277, 1208, 1129, 967, 765, 691 cm^{-1}; HR-MS found $[M^+]$: 176.1315, calcd for $C_{11}H_{16}N_2$: 176.1313.

5.10. *N*-(3-Piperidin-1-ylphenyl)leucine (11)

A mixture of 2-bromo-4-methylpentanoic acid (390 mg, 2.0 mmol), aniline **10** (176 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× 50mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (EtOAc/MeOH, 10:1) to provide carboxylic acid **11** (123 mg, 42%). ^{1}H NMR (400 MHz, CD_3OD) δ 0.95 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.59–1.85 (9H, m), 3.22 (4H, t, J = 5.9 Hz), 3.95 (1H, t, J = 6.6 Hz), 6.38 (1H, d, J = 8.8 Hz), 6.48–6.50 (2H, m), 7.05–7.09 (1H, m); IR (KBr): 3343, 2954, 1716, 1599, 1468, 1210 cm^{-1}; HR-MS found $[M+H]^+$: 291.2074, calcd for $C_{17}H_{27}O_2N_2$: 291.2073.

5.11. *N*-{2-[(4-Methoxyphenyl)amino]ethyl}-N^2-(3-piperidin-1-ylphenyl)leucinamide (8l)

Compound **8l** was prepared according to the procedure for **8**, using appropriate starting materials. Yield: 61%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 5.9 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.49–1.85 (9H, m), 3.09–3.18 (6H, m), 3.32–3.52 (2H, m), 3.73–3.77 (1H, m), 3.73 (3H, s), 6.08 (1H, d, J = 8.1 Hz), 6.15 (1H, s), 6.40 (2H, d, J = 8.8 Hz), 6.72 (2H, d, J = 8.8 Hz), 7.04–7.08 (2H, m); IR (KBr): 3358, 2933, 1654, 1602, 1514, 1235, 1127, 1038, 821 cm^{-1}; HR-MS found $[M+Na]^+$: 461.2896, calcd for $C_{26}H_{38}N_4O_2Na$: 461.2892.

5.12. General procedure for the preparation of substituted *N*-Boc aminoalcohols (13) from *N*-Boc amino acids (12)

To a stirred solution of *N*-Boc amino acid **12** (1.7 mmol) in THF (10 mL) was added *N*-methylmorpholine (0.19 mL, 1.7 mmol) followed by ethyl chloroformate (0.16 mL, 1.7 mmol) at −10 °C. After stirring for 20 min, $NaBH_4$ (193 mg, 5.1 mmol) was added. MeOH (20 mL) was then added to the mixture dropwise over a period of 20 min at 0 °C. After stirring for 20 min, the reaction mixture was neutralized with 1 M $KHSO_4$. The mixture was extracted with EtOAc (3× 50 mL). The combined organic layers were washed with 1 M $KHSO_4$ (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography to provide *N*-Boc aminoalcohol **13**.

5.12.1. *tert*-Butyl [(1*S*)-1-(hydroxymethyl)butyl]carbamate (13d). Yield: 91%; mp 43–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.1 Hz), 1.33–1.51 (4H, m), 1.45 (9H, s), 2.38 (1H, br s), 3.51–3.70 (3H, m), 4.59 (1H, br s); IR (KBr): 3355, 1687, 1531, 1176 cm^{-1}; MS (FAB) *m*/*z*: 204 $[M+H]^+$, 148, 57.

5.12.2. *tert*-Butyl [(1*S*)-1-(hydroxymethyl)pentyl]carbamate (13e). Yield: 85%; mp 42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.0 Hz), 1.24–1.54 (6H, m), 1.45 (9H, s), 2.41 (1H, br s), 3.51–3.70 (3H, m), 4.60 (1H, br s); IR (KBr): 3359, 1684, 1531, 1174 cm^{-1}; MS (FAB) *m*/*z*: 218 $[M+H]^+$, 162, 118, 57; Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.45. Found: C, 60.58; H, 10.36; N, 6.41.

5.12.3. *tert*-Butyl [(1*S*)-1-(hydroxymethyl)-3-phenylpropyl]carbamate (13j). Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.74–1.86 (2H, m), 2.22 (1H, br s), 2.65–2.73 (2H, m), 3.56–3.71 (3H, m), 4.64 (1H, br s), 7.18–7.30 (5H, m); IR (KBr): 3375, 1686, 1517, 1245, 1175, 744, 700 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.79; H, 8.33; N, 5.29.

5.13. General procedure for the preparation of substituted *N*-Boc diamines (16)

To a stirred solution of *N*-Boc aminoalcohol **13** (100 mmol), 2-nitrobenzenesulfonamide **14**[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 the 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 **16**.

5.13.1. *tert*-Butyl {(1*S*)-2-[(4-methoxyphenyl)amino]-1-methylethyl}carbamate (16a). Yield: 73%; white solid; mp 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, J = 6.7 Hz), 1.45 (9H, s), 3.04 (1H, dd, J = 7.3, 12.3 Hz), 3.12 (1H, dd, J = 4.9, 12.3 Hz), 3.73 (1H, br s), 3.74 (3H, s), 3.92 (1H, br s), 4.50 (1H, br s), 6.58 (2H, d, J = 8.9 Hz), 6.77 (2H, d, J = 8.9 Hz); IR (KBr): 3390, 1679, 1515, 1239, 1169, 816 cm^{-1}; MS (EI) *m*/*z*: 280 $[M^+]$, 136, 57; Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.20; H, 8.86; N, 9.96.

5.13.2. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]-methyl}propyl)carbamate (16c). Yield: 83%; mp 97–99 °C; ^{1}H 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; HR-MS 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.

5.13.3. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}butyl)carbamate (16d). Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.0 Hz), 1.45 (9H, s), 1.19–1.48 (4H, m), 2.98–3.03 (1H, m), 3.17 (1H, dd, J = 4.4, 12.5 Hz), 3.74 (3H, s), 3.76–3.84 (1H,

m), 4.13–4.23 (1H, m), 4.42–4.48 (1H, m), 6.58 (2H, d, $J = 8.8$ Hz), 6.77 (2H, d, $J = 8.8$ Hz); IR (KBr): 3392, 3381, 2980, 2953, 2872, 1676, 1516 cm^{-1}; MS (FAB) *m/z*: 309 $[M+H]^+$, 308, 262, 253, 136, 57; HR-MS found $[M+H]^+$: 309.2188, calcd for $C_{17}H_{29}N_2O_3$: 309.2187.

5.13.4. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]-methyl}pentyl)carbamate (16e). Yield: 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, $J = 7.0$ Hz), 1.30–1.48 (6H, m), 1.45 (9H, s), 2.97–3.03 (1H, m), 3.18 (1H, dd, $J = 4.4$, 12.5 Hz), 3.74 (3H, s), 3.75–3.81 (2H, m), 4.41–4.48 (1H, m), 6.58 (2H, d, $J = 8.8$ Hz), 6.77 (2H, d, $J = 8.8$ Hz); IR (KBr): 3389, 2982, 2956, 2934, 2872, 1676, 1516 cm^{-1}; MS (FAB) *m/z*: 323 $[M+H]^+$, 322, 267, 136, 57; Anal. Calcd for $C_{18}H_{30}N_2O_3 \cdot 0.22H_2O$: C, 66.23; H, 9.40; N, 8.58. Found: C, 66.26; H, 9.24; N, 8.73.

5.13.5. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}-2-methylpropyl)carbamate (16f). Yield: 64%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, $J = 7.3$ Hz), 0.98 (3H, d, $J = 6.6$ Hz), 1.45 (9H, s), 1.83–1.88 (1H, m), 2.96–3.01 (1H, m), 3.19–3.23 (1H, m), 3.64–3.73 (2H, m), 3.74 (3H, s), 4.48–4.50 (1H, m), 6.57 (2H, d, $J = 8.8$ Hz), 6.78 (2H, d, $J = 8.8$ Hz); IR (KBr): 3376, 2973, 2957, 2935, 1680, 1518 cm^{-1}; MS (FAB) *m/z*: 309 $[M+H]^+$, 308, 253, 136, 57; Anal. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15; N, 9.08. Found: C, 65.91; H, 9.08; N, 9.09.

5.13.6. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}-3-methylbutyl)carbamate (16g). Yield: 76%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92–0.95 (6H, m), 1.32–1.38 (2H, m), 1.44 (9H, s), 1.68–1.74 (1H, m), 2.96–3.01 (1H, m), 3.17 (1H, dd, $J = 4.0$, 12.1 Hz), 3.74 (3H, s), 3.76 (1H, br s), 3.86–3.89 (1H, m), 4.40 (1H, br s), 6.57 (2H, d, $J = 8.8$ Hz), 6.77 (2H, d, $J = 8.8$ Hz); IR (KBr): 3405, 2978, 2953, 2911, 1678, 1516 cm^{-1}; MS (FAB) *m/z*: 323 $[M+H]^+$, 322, 267, 136, 57; Anal. Calcd for $C_{18}H_{30}N_2O_3 \cdot 0.2H_2O$: C, 66.31; H, 9.40; N, 8.59. Found: C, 66.30; H, 9.36; N, 8.60.

5.13.7. *tert*-Butyl {(1*S*)-2-[(4-methoxyphenyl)amino]-1-phenylethyl}carbamate (16h). Yield: 55%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 3.40–3.50 (3H, m), 3.74 (3H, s), 4.88–4.96 (1H, m), 5.08–5.16 (1H, m), 6.58 (2H, d, $J = 8.8$ Hz), 6.77 (2H, d, $J = 8.8$ Hz), 7.28–7.31 (3H, m), 7.35–7.39 (2H, m); IR (KBr): 3387, 3362, 2976, 2936, 1685, 1517 cm^{-1}; MS (FAB) *m/z*: 343 $[M+H]^+$, 342, 287, 226, 136, 57.

5.13.8. *tert*-Butyl {(1*S*)-1-benzyl-2-[(4-methoxyphenyl)amino]ethyl}carbamate (16i). Yield: 53%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 2.82–2.90 (2H, m), 3.00–3.04 (1H, m), 3.19 (1H, dd, $J = 4.4$, 12.5 Hz), 3.63 (1H, br s), 3.74 (3H, s), 4.01–4.10 (1H, m), 4.50–4.59 (1H, m), 6.54 (2H, d, $J = 8.8$ Hz), 6.76 (2H, d, $J = 8.8$ Hz), 7.19–7.25 (3H, m), 7.31 (2H, t, $J = 7.3$ Hz); IR (KBr): 3400, 3378, 2983, 2934, 2905, 1676, 1517 cm^{-1}; MS (FAB) *m/z*: 357 $[M+H]^+$, 356, 301, 136, 57; Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.60; H, 7.78; N, 7.83.

5.13.9. *tert*-Butyl ((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}-3-phenylpropyl)carbamate (16j). Yield: 53%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.72–1.81 (1H, m), 1.86–1.95 (1H, m), 3.04–3.09 (2H, m), 3.17–3.21 (2H, m), 3.69 (1H, br s), 3.74 (3H, s), 3.81–3.88 (1H, m), 4.48–4.54 (1H, m), 6.56 (2H, d, $J = 8.8$ Hz), 6.77 (2H, d, $J = 8.8$ Hz), 7.17–7.21 (3H, m), 7.27–7.30 (2H, m); IR (KBr): 3395, 3378, 2980, 2950, 2927, 2861, 1679, 1513 cm^{-1}; MS (FAB) *m/z*: 371 $[M+H]^+$, 370, 315, 136, 57; Anal. Calcd for $C_{22}H_{30}N_2O_3 \cdot 0.32H_2O$: C, 70.23; H, 8.21; N, 7.45. Found: C, 70.26; H, 7.99; N, 7.53.

5.14. General procedure for the preparation of amides (17)

A mixture of *N*-Boc diamine **16** (2.0 mmol) and 2 M HCl in 1,4-dioxane (6 mL, 12 mmol) was stirred for 30 min. The mixture was concentrated to provide a diamine HCl salt. To the residual solid in CH_2Cl_2 (20 mL) were added carboxylic acid (2.0 mmol), HOBt (405 mg, 3.0 mmol), and WSC·HCl (575 mg, 30 mmol), and the mixture was stirred 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 give **17**.

5.14.1. 1-(Biphenyl-3-ylamino)-*N*-{(1*S*)-2-[(4-methoxyphenyl)amino]-1-methylethyl}cyclohexanecarboxamide (17a). Yield: 74%; light brown amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, $J = 6.6$ Hz), 1.32–1.34 (3H, m), 1.60–1.66 (3H, m), 1.92–2.03 (4H, m), 3.03 (1H, dd, $J = 7.3$, 12.5 Hz), 3.09 (1H, dd, $J = 5.1$, 12.5 Hz), 3.64 (1H, br s), 3.72 (3H, s), 4.04 (1H, s), 4.20–4.27 (1H, m), 6.44 (2H, d, $J = 8.8$ Hz), 6.58 (1H, dd, $J = 2.2$, 8.1 Hz), 6.71 (2H, d, $J = 8.8$ Hz), 6.83–6.84 (1H, m), 7.03 (1H, d, $J = 8.1$ Hz), 7.08 (1H, d, $J = 8.8$ Hz), 7.15 (1H, t, $J = 8.1$ Hz), 7.31 (1H, t, $J = 7.3$ Hz), 7.38 (2H, t, $J = 7.3$ Hz), 7.53 (2H, d, $J = 7.3$ Hz); IR (KBr): 3368, 2933, 2856, 1652, 1601, 1513 cm^{-1}; MS (FAB) *m/z*: 457 $[M+H]^+$, 250.

5.14.2. 1-(Biphenyl-3-ylamino)-*N*-{(1*R*)-2-[(4-methoxyphenyl)amino]-1-methylethyl}cyclohexanecarboxamide (17b). Yield: 86%; yellow amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, $J = 6.6$ Hz), 1.32–1.34 (3H, m), 1.60–1.66 (3H, m), 1.92–2.03 (4H, m), 3.03 (1H, dd, $J = 7.3$, 12.5 Hz), 3.09 (1H, dd, $J = 5.1$, 12.5 Hz), 3.64 (1H, br s), 3.72 (3H, s), 4.04 (1H, s), 4.20–4.27 (1H, m), 6.44 (2H, d, $J = 8.8$ Hz), 6.58 (1H, dd, $J = 2.2$, 8.1 Hz), 6.71 (2H, d, $J = 8.8$ Hz), 6.83–6.84 (1H, m), 7.03 (1H, d, $J = 8.1$ Hz), 7.08 (1H, d, $J = 8.8$ Hz), 7.15 (1H, t, $J = 8.1$ Hz), 7.31 (1H, t, $J = 7.3$ Hz), 7.38 (2H, t, $J = 7.3$ Hz), 7.53 (2H, d, $J = 7.3$ Hz); IR (KBr): 3368, 2933, 2856, 1652, 1601, 1513 cm^{-1}; MS (FAB) *m/z*: 458 $[M+H]^+$, 457, 250; Anal. Calcd for $C_{29}H_{35}N_3O_2 \cdot 0.44H_2O$: C, 74.89; H, 7.77; N, 9.03. Found: C, 74.89; H, 7.48; N, 8.86.

5.14.3. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}propyl)cyclohexanecarboxamide (17c). Yield: 85%; brown amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.7 Hz), 1.24–1.48 (5H, m), 1.60–1.66 (3H, m), 1.94–2.08 (4H, m), 3.02 (1H, dd, J = 8.1, 12.5 Hz), 3.13 (1H, dd, J = 4.4, 12.5 Hz), 3.66 (1H, br s), 3.72 (3H, s), 4.03–4.09 (2H, m), 6.43 (2H, d, J = 8.8 Hz), 6.60 (1H, dd, J = 1.5, 8.1 Hz), 6.72 (2H, d, J = 8.8 Hz), 6.85 (1H, m), 7.01–7.05 (2H, m), 7.13 (1H, t, J = 8.1 Hz), 7.31 (1H, t, J = 7.3 Hz), 7.37 (2H, t, J = 7.3 Hz), 7.53 (2H, d, J = 7.3 Hz); IR (KBr): 3366, 2933, 2856, 1651, 1601, 1513 cm^{-1}; MS (FAB) *m*/*z*: 472 $[M+H]^+$, 471, 250, 136.

5.14.4. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}butyl)cyclohexanecarboxamide (17d). Yield: 72%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.3 Hz), 1.24–1.70 (10H, m), 1.92–2.07 (4H, m), 3.02 (1H, dd, J = 8.1, 12.5 Hz), 3.12 (1H, dd, J = 4.4, 12.5 Hz), 3.66 (1H, s), 3.72 (3H, s), 4.05 (1H, s), 4.09–4.18 (1H, m), 6.43 (2H, d, J = 8.8 Hz), 6.60 (1H, dd, J = 2.2, 8.1 Hz), 6.72 (2H, d, J = 8.8 Hz), 6.84 (1H, s), 7.01–7.04 (2H, m), 7.12 (1H, t, J = 8.1 Hz), 7.29–7.32 (1H, m), 7.36 (2H, t, J = 6.6 Hz), 7.53 (2H, d, J = 6.6 Hz); IR (KBr): 3366, 2932, 2857, 1651, 1601, 1513 cm^{-1}; MS (FAB) *m*/*z*: 486 $[M+H]^+$, 485, 250; Anal. Calcd for $C_{31}H_{39}N_3O_2{\cdot}0.32H_2O$: C, 75.77; H, 8.13; N, 8.55. Found: C, 75.76; H, 7.79; N, 8.61.

5.14.5. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}pentyl)cyclohexanecarboxamide (17e). Yield: 68%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, t, J = 6.6 Hz), 1.11–1.63 (12H, m), 1.88–2.00 (4H, m), 2.95 (1H, dd, J = 8.1, 12.5 Hz), 3.05 (1H, dd, J = 4.4, 12.5 Hz), 3.60 (1H, s), 3.65 (3H, s), 3.98 (1H, s), 4.02–4.09 (1H, m), 6.37 (2H, d, J = 8.8 Hz), 6.52 (1H, dd, J = 1.5, 8.1 Hz), 6.65 (2H, d, J = 8.8 Hz), 6.77 (1H, s), 6.96 (2H, t, J = 7.3 Hz), 7.05 (1H, t, J = 8.1 Hz), 7.21–7.25 (1H, m), 7.29 (2H, t, J = 7.3 Hz), 7.46 (2H, d, J = 7.3 Hz); IR (KBr): 3366, 3054, 3029, 2931, 1651, 1601, 1574, 1513 cm^{-1}; MS (FAB) *m*/*z*: 500 $[M+H]^+$, 499, 250, 136; Anal. Calcd for $C_{32}H_{41}N_3O_2{\cdot}0.30H_2O$: C, 76.09; H, 8.30; N, 8.32. Found: C, 76.10; H, 8.43; N, 8.30.

5.14.6. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}-2-methylpropyl)cyclohexanecarboxamide (17f). Yield: 64%; brown amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 7.3 Hz), 1.22–1.43 (3H, m), 1.58–1.69 (3H, m), 1.83–1.91 (1H, m), 1.94–2.05 (4H, m), 2.98 (1H, dd, J = 8.8, 11.7 Hz), 3.17 (1H, dd, J = 4.4, 11.7 Hz), 3.64 (1H, br s), 3.73 (3H, s), 3.97–4.04 (1H, m), 4.06 (1H, s), 6.41 (2H, dd, J = 8.8 Hz), 6.61 (1H, dd, J = 1.5, 8.1 Hz), 6.71 (2H, d, J = 8.8 Hz), 6.85–6.86 (1H, m), 7.01 (1H, d, J = 8.1 Hz), 7.10 (1H, t, J = 8.1 Hz), 7.14 (1H, d, J = 9.5 Hz), 7.30 (1H, t, J = 7.3 Hz), 7.36 (2H, t, J = 7.3 Hz), 7.52 (2H, d, J = 7.3 Hz); IR (KBr): 3368, 2932, 2857, 1654, 1601, 1513 cm^{-1}; MS (FAB) *m*/*z*: 486 $[M+H]^+$, 485, 250, 136; Anal. Calcd for $C_{31}H_{39}N_3O_2{\cdot}0.44H_2O$: C, 75.43; H, 8.14; N, 8.51. Found: C, 75.50; H, 7.79; N, 8.41.

5.14.7. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}-3-methylbutyl)cyclohexanecarboxamide (17g). Yield: 88%; light yellow amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 6.6 Hz), 0.83 (3H, d, J = 6.6 Hz), 1.26–1.39 (5H, m), 1.51–1.65 (4H, m), 1.94–2.02 (4H, m), 2.99 (1H, dd, J = 7.3, 11.7 Hz), 3.11 (1H, dd, J = 4.4, 11.7 Hz), 3.73 (1H, br s), 3.73 (3H, s), 4.04 (1H, s), 4.18–4.25 (1H, m), 6.45 (2H, d, J = 8.8 Hz), 6.59 (1H, dd, J = 1.5, 8.1 Hz), 6.73 (2H, d, J = 8.8 Hz), 6.83 (1H, s), 6.99–7.02 (2H, m), 7.11 (1H, t, J = 8.1 Hz), 7.30 (1H, t, J = 7.3 Hz), 7.36 (2H, t, J = 7.3 Hz), 7.52 (2H, d, J = 7.3 Hz); IR (film): 3368, 2934, 2858, 1650, 1601, 1513 cm^{-1}; MS (FAB) *m*/*z*: 500 $[M+H]^+$, 499, 250; Anal. Calcd for $C_{32}H_{41}N_3O_2{\cdot}0.38H_2O$: C, 75.88; H, 8.31; N, 7.52. Found: C, 75.90; H, 8.03; N, 8.30.

5.14.8. 1-(Biphenyl-3-ylamino)-*N*-{(1*S*)-2-[(4-methoxyphenyl)amino]-1-phenylethyl}cyclohexanecarboxamide (17h). Yield: 96%; white amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–2.05 (10H, m), 3.31–3.41 (3H, m), 3.70 (3H, s), 4.07 (1H, s), 5.19–5.24 (1H, m), 6.39 (2H, d, J = 8.8 Hz), 6.59 (1H, dd, J = 2.2, 8.1 Hz), 6.68 (2H, d, J = 8.8 Hz), 6.82 (1H, s), 7.04 (1H, d, J = 8.1 Hz), 7.17 (1H, t, J = 7.3 Hz), 7.21–7.26 (5H, m), 7.30–7.33 (1H, m), 7.37 (2H, t, J = 7.3 Hz), 7.48 (2H, d, J = 7.3 Hz), 7.64 (1H, d, J = 8.1 Hz); IR (KBr): 3369, 2934, 1658, 1601, 1513 cm^{-1}; MS (FAB) *m*/*z*: 520 $[M+H]^+$, 519, 250.

5.14.9. *N*-{(1*S*)-1-Benzyl-2-[(4-methoxyphenyl)amino]ethyl}-1-(biphenyl-3-ylamino)cyclohexanecarboxamide (17i). Yield: 86%; light yellow amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–2.04 (10H, m), 2.86 (2H, d, J = 6.6 Hz), 3.04 (1H, dd, J = 7.3, 12.5 Hz), 3.16 (1H, dd, J = 4.4, 12.5 Hz), 3.60 (1H, s), 3.71 (3H, s), 3.99 (1H, s), 4.37–4.47 (1H, m), 6.38 (2H, d, J = 8.8 Hz), 6.52 (1H, d, J = 8.1 Hz), 6.69 (2H, d, J = 8.8 Hz), 6.82 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.08–7.25 (7H, m), 7.29–7.32 (1H, m), 7.37 (2H, t, J = 6.6 Hz), 7.53 (2H, d, J = 7.3 Hz); IR (KBr): 3369, 2934, 2956, 1654, 1601, 1513 cm^{-1}; MS (FAB) *m*/*z*: 534 $[M+H]^+$, 533, 250; Anal. Calcd for $C_{35}H_{39}N_3O_2{\cdot}0.54H_2O$: C, 77.36; H, 7.43; N, 7.73. Found: C, 77.35; H, 7.51; N, 7.80.

5.14.10. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}-3-phenylpropyl)cyclohexanecarboxamide (17j). Yield: 97%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29–2.04 (12H, m), 2.53–2.66 (2H, m), 3.06 (1H, dd, J = 7.3, 12.5 Hz), 3.14 (1H, dd, J = 5.1, 12.5 Hz), 3.60 (1H, s), 3.71 (3H, s), 4.05 (1H, s), 4.14–4.22 (1H, m), 6.41 (2H, d, J = 8.8 Hz), 6.61 (1H, d, J = 1.5, 8.1 Hz), 6.70 (2H, d, J = 8.8 Hz), 6.86 (1H, s), 7.00–7.87 (11H, m), 7.52 (2H, d, J = 7.3 Hz); IR (KBr): 3367, 2935, 2856, 1653, 1602, 1513 cm^{-1}; MS (FAB) *m*/*z*: 548 $[M+H]^+$, 547, 250; Anal. Calcd for $C_{36}H_{41}N_3O_2{\cdot}0.84H_2O$: C, 76.82; H, 7.64; N, 7.47. Found: C, 76.68; H, 7.54; N, 7.61.

5.14.11. N^2-1,1′-Biphenyl-3-yl-N^1-{(1*S*)-2-[(4-methoxyphenyl)amino]-1-methylethyl}-L-leucinamide (17k). Yield: 98%; white amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 5.9 Hz), 1.19 (3H, d, J = 6.6 Hz), 1.56–1.91 (3H, m), 3.00 (1H, dd, J = 7.3, 12.5 Hz), 3.07 (1H, dd, J = 4.4, 12.5 Hz), 3.52 (1H, br s), 3.70 (3H, s), 3.74–3.79 (1H, m), 3.93 (1H, d, J = 2.9 Hz), 4.19–4.28 (1H, m), 6.36 (2H, d, J = 8.8 Hz), 6.58 (1H, d, J = 8.1 Hz), 6.67 (2H, d, J = 8.8 Hz), 6.82–6.84 (2H, m), 7.05 (1H, d, J = 7.3 Hz), 7.20 (1H, t, J = 7.3 Hz), 7.31–7.37 (3H, m), 7.52 (2H, d, J = 6.6 Hz); IR (KBr): 3353, 2956, 1650, 1605, 1513, 1323, 1235, 821, 758, 700 cm^{-1}; HR-MS found $[M+H]^+$: 446.2813, calcd for $C_{28}H_{36}N_3O_2$: 446.2807.

5.14.12. N^2-1,1′-Biphenyl-3-yl-N^1-((1*S*)-1-{[(4-methoxyphenyl)amino]methyl}propyl)-L-leucinamide (17l). Yield: 61%; white solid; mp 99–101 °C; ^{1}H 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}.

5.15. *N*-[4-(Benzyloxy)phenyl]-2-nitrobenzenesulfonamide (18)

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. The reaction mixture was stirred at room temperature 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 **18** (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.

5.16. *tert*-Butyl [(1*S*)-1-({[4-(benzyloxy)phenyl]amino}methyl)propyl]carbamate (20)

Compound **20** was prepared according to the procedure for **16**, 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.

5.17. General procedure for the preparation of amides (21)

Compound **21** was prepared according to the procedure for **17**, using appropriate starting materials.

5.17.1. *N*-[(1*S*)-1-({[4-(Benzyloxy)phenyl]amino}methyl)propyl]-N^2-biphenyl-3-yl-L-leucinamide (21a). 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.

5.17.2. *N*-[(1*S*)-1-({[4-(Benzyloxy)phenyl]amino}methyl)propyl]-1-(biphenyl-3-ylamino)cyclohexanecarboxamide (21b). Yield: 84%; light yellow amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.4 Hz), 1.24–1.70 (8H, m), 1.93–2.04 (4H, m), 3.02 (1H, dd, J = 7.7, 12.1 Hz), 3.12 (1H, dd, J = 4.6, 12.1 Hz), 3.67 (1H, br s), 4.00–4.10 (2H, m), 4.96 (2H, s), 6.42 (2H, d, J = 8.9 Hz), 6.59 (1H, dd, J = 2.0, 7.8 Hz), 6.78 (2H, d, J = 8.9 Hz), 6.85 (1H, br s), 7.01 (1H, d, J = 7.8 Hz), 7.03 (1H, br s), 7.12 (1H, t, J = 7.8 Hz), 7.27–7.55 (10H, m); IR (KBr): 3367, 1652, 1601, 1511, 1228, 758, 699 cm^{-1}; MS (FAB) m/z: 548 $[M+H]^+$, 250.

5.18. General procedure for the preparation of phenols (22)

A mixture of benzyl ether **21** (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 **22**.

5.18.1. N^2-Biphenyl-3-yl-*N*-((1*S*)-1-{[(4-hydroxyphenyl)amino]methyl}propyl)-L-leucinamide (22a). 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.

5.18.2. 1-(Biphenyl-3-ylamino)-*N*-((1*S*)-1-{[(4-hydroxyphenyl)amino]methyl}propyl)cyclohexanecarboxamide (22b). Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.4 Hz), 1.23–1.63 (8H, m), 1.95–2.08 (4H, m), 2.98 (1H, dd, J = 7.7, 12.2 Hz), 3.08 (1H, dd, J = 4.4, 12.2 Hz), 4.00–4.14 (2H, m), 6.34 (2H, d, J = 8.6 Hz), 6.59 (1H, dd, J = 2.0, 8.0 Hz), 6.67 (2H, d, J = 8.6 Hz), 6.86 (1H, t, J = 2.0 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.12 (1H, br s d, J = 8.9 Hz), 7.12 (1H, t, J = 8.0 Hz), 7.28–7.38 (3H, m), 7.51–7.53 (2H, m); IR (KBr): 3367, 1647, 1601, 1515, 1241, 1225, 758 cm^{-1}; MS (FAB) *m*/*z*: 458 $[M+H]^+$, 250.

5.19. General procedure for the preparation of *tert*-butyl acetates (23)

To a stirred solution of phenol **22** (10.4 mmol) in THF/DMF (100 mL, 4:1) was added NaH (55%, 452 mg, 10.4 mmol) followed by *tert*-butyl bromoacetate (1.84 mL, 12.5 mmol) at 0 °C. After stirring at room temperature for 1.5 h, water (100 mL) was added to the reaction mixture at 0 °C. The mixture was extracted with EtOAc (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography to provide *tert*-butyl acetate **23**.

5.19.1. *tert*-Butyl [4-({(2*S*)-2-[(*N*-biphenyl-3-yl-L-leucyl)amino]butyl}amino)phenoxy]acetate (23a). 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, 12.5Hz), 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.

5.19.2. *tert*-Butyl (4-{[(2*S*)-2-({[1-(biphenyl-3-ylamino)cyclohexyl]carbonyl}amino)butyl]amino}phenoxy)acetate (23b). Yield: 79%; amorphous substance; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.4 Hz), 1.24–1.67 (8H, m), 1.97–2.04 (4H, m), 3.01 (1H, dd, J = 7.8, 12.2 Hz), 3.13 (1H, dd, J = 4.5, 12.2 Hz), 3.72 (1H, br s), 4.00–4.11 (2H, m), 4.40 (2H, s), 6.41 (2H, d, J = 8.9 Hz), 6.59 (1H, dd, J = 2.0, 8.0 Hz), 6.72 (2H, d, J = 8.9 Hz), 6.85 (1H, t, J = 2.0 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.03 (1H, br d, J = 8.2 Hz), 7.11 (1H, t, J = 8.0 Hz), 7.29–7.38 (3H, m), 7.51–7.53 (2H, m); IR (KBr): 3370, 1750, 1653, 1601, 1512, 1217, 1154, 758 cm^{-1}; MS (FAB) *m*/*z*: 572 $[M+H]^+$, 325, 250; Anal. Calcd for $C_{35}H_{45}N_3O_4 \cdot 0.2H_2O$: C, 73.06; H, 7.95; N, 7.30. Found: C, 72.96; H, 7.87; N, 7.25.

5.20. General procedure for the preparation of acetic acids (24)

To a stirred solution of *tert*-butyl acetate **23** (6.59 mmol) in CH_2Cl_2 (25 mL) was added TFA (25 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was concentrated. HCl (4 M) in 1,4-dioxane (20 mL) was added to the residue. The mixture was concentrated, then triturated with Et_2O (20 mL) to provide acetic acid **24**.

5.20.1. [4-({(2*S*)-2-[(*N*-Biphenyl-3-yl-L-leucyl)amino]butyl}amino)phenoxy]acetic acid 2HCl (24a). Yield: 74%; colorless crystals; mp 89–91 °C; ^{1}H 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.

5.20.2. (4-{[(2*S*)-2-({[1-(Biphenyl-3-ylamino)cyclohexyl]carbonyl}amino)butyl]amino}phenoxy)acetic acid 2HCl (24b). Yield: 95%; amorphous substance; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.64 (3H, t, J = 7.4 Hz), 1.14–1.98 (12H, m), 3.07 (1H, dd, J = 5.0, 12.5 Hz), 3.28 (1H, dd, J = 6.5, 12.5 Hz), 3.96–4.01 (1H, br s), 4.68 (2H, s), 6.72–6.73 (1H, br d), 6.95 (2H, d, J = 9.0 Hz), 6.96–7.10 (2H, m), 7.19 (1H, t, J = 8.0 Hz), 7.25 (2H, br d, J = 9.0 Hz), 7.31–7.52 (5H, m), 8.07 (1H, br d, J = 8.7 Hz); IR (KBr): 3343, 1740, 1668, 1605, 1510, 1194, 1177, 1075, 759, 700 cm^{-1}; MS (FAB) *m*/*z*: 516 $[M+H]^+$, 250.

5.21. Ethyl 2-[4-({(2*S*)-2-[(*N*-biphenyl-3-yl-L-leucyl)amino]butyl}amino)phenoxy]-2-methylpropanoate (25)

Compound **25** was prepared according to the procedure for **23**, using appropriate starting materials. Yield: 61%; oil; ^{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), 1.27 (3H, t, J = 7.0 Hz), 1.40–1.70 (3H, m), 1.49 (6H, s), 1.77–1.92 (2H, m), 2.95 (1H, dd, J = 7.8, 12.1 Hz), 3.10 (1H, dd, J = 4.3, 12.1 Hz), 3.73–3.82 (1H, m), 3.88–4.10 (3H, m), 4.21 (2H, q, J = 7.0 Hz), 6.29 (2H, d, J = 8.6 Hz), 6.57 (1H, dd, J = 2.3, 7.8 Hz), 6.60 (2H, d, J = 8.6 Hz), 6.74–6.83 (2H, m), 6.97–7.03 (1H, m), 7.13 (1H, t, J = 7.8 Hz), 7.25–7.34 (3H, m), 7.46–7.54 (2H, m); IR (KBr): 2961, 1732, 1651, 1607, 1511, 1227, 1140 cm^{-1}; MS (FAB) *m*/*z*: 560 $[M+H]^+$, 444, 238; HR-MS found $[M+H]^+$: 560.3491, calcd for $C_{34}H_{46}N_3O_4$: 560.3488.

5.22. N^2-Biphenyl-3-yl-*N*-[(1*S*)-1-({[4-(cyanomethoxy)phenyl]amino}methyl)propyl]-L-leucinamide (26)

Compound **26** was prepared according to the procedure for **23**, using appropriate starting materials. Yield: 59%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.3 Hz), 0.95 (3H, d, J = 5.9 Hz), 1.02 (3H, d, J = 5.9 Hz), 1.40–1.68 (3H, m), 1.79–1.92 (2H, m), 2.97 (1H, dd, J = 8.5, 12.5 Hz), 3.13 (1H, dd, J = 3.7, 12.5 Hz), 3.72–3.81 (2H, m), 3.91–3.95 (1H, m), 4.02–

4.11 (1H, m), 4.60 (2H, s), 6.34 (2H, J = 8.8 Hz), 6.58 (1H, dd, J = 1.5, 8.1 Hz), 6.72–6.79 (1H, m), 6.74 (2H, d, J = 8.8 Hz), 6.82–6.85 (1H, m), 7.03–7.07 (1H, m), 7.18 (1H, t, J = 8.1 Hz), 7.30–7.38 (3H, m), 7.48–7.55 (2H, m); IR (KBr): 2962, 1652, 1606, 1512, 1215, 758 cm^{-1}; MS (FAB) m/z: 485 $[M+H]^+$, 446, 238; HR-MS found $[M+H]^+$: 485.2906, calcd for $C_{30}H_{37}N_4O_2$: 485.2917.

5.23. N^2-Biphenyl-3-yl-*N*-[(1*S*)-1-({[4-(1*H*-tetrazol-5-ylmethoxy)phenyl]amino}methyl)propyl]-L-leucinamide (27)

A mixture of nitrile **26** (1.13 g, 2.3 mmol), NaN_3 (454 mg), and NH_4Cl (374 mg) in DMF (25 mL) was stirred at 100 °C for 6 h. A saturated aqueous solution of NH_4Cl (50 mL) was added to the cooled reaction mixture. The mixture was extracted with EtOAc (5× 50 mL). The combined organic layers were washed with brine (2× 50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (EtOAc) to provide tetrazole **27** (0.75 g, 69%) as colorless crystals. Mp 154–158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 0.93 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 6.3 Hz), 1.36–1.45 (1H, m), 1.56–1.68 (2H, m), 1.77–1.92 (3H, m), 2.86 (1H, dd, J = 8.2, 12.9 Hz), 3.10 (1H, dd, J = 4.3, 12.9 Hz), 3.80–3.84 (1H, m), 4.04–4.11 (1H, m), 5.21–5.24 (2H, br s), 6.22 (2H, d, J = 8.8 Hz), 6.55–6.59 (1H, m), 6.58 (2H, d, J = 8.8 Hz), 6.79–6.86 (2H, m), 7.02 (1H, d, J = 7.8 Hz), 7.16 (1H, t, J = 7.8 Hz), 7.25–7.52 (6H, m); IR (KBr): 2960, 1637, 1605, 1512, 1231, 700 cm^{-1}; Anal. Calcd for $C_{30}H_{37}N_7O_2$: C, 68.29; H, 7.07; N, 18.58. Found: C, 68.43; H, 6.88; N, 18.35; MS (FAB) m/z: 528 $[M+H]^+$, 444, 238.

5.24. General procedure for the preparation of acrylates (28)

A mixture of phenol **22b** (81 mg, 0.18 mmol), *N*-methylmorpholine (40 μL, 0.36 mmol), and propiolate (0.36 mmol) in THF (3 mL) was stirred for 30 h under N_2 atmosphere. The reaction mixture was concentrated. The residue was purified by PTLC to provide acrylate **28**.

5.24.1. Methyl (2*E*)-3-(4-{[(2*S*)-2-({[1-(biphenyl-3-ylamino)cyclohexyl]carbonyl}amino)butyl]amino}phenoxy)acrylate (28a). Yield: 64%; amorphous substance; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 7.4 Hz), 1.30–1.67 (8H, m), 1.92–2.04 (4H, m), 3.01 (1H, dd, J = 8.2, 12.1 Hz), 3.14 (1H, dd, J = 4.3, 12.1 Hz), 3.70 (3H, s), 4.02–4.08 (1H, m), 5.40 (1H, d, J = 12.1 Hz), 6.40 (2H, d, J = 9.0 Hz), 6.56 (1H, d, J = 9.0 Hz), 6.80 (2H, d, J = 8.6 Hz), 6.82 (1H, d, J = 5.9 Hz), 7.01 (2H, t, J = 5.9 Hz), 7.08 (1H, t, J = 7.8 Hz), 7.28–7.35 (8H, m), 7.49 (2H, d, J = 8.6 Hz), 7.71 (1H, d, J = 12.1 Hz); IR (KBr): 3371, 2933, 1709, 1646, 1509, 1210, 1123, 828, 758, 701 cm^{-1}; HR-MS found $[M+H]^+$: 542.3016, calcd for $C_{33}H_{40}N_3O_4$: 542.3019.

5.24.2. Benzyl (2*E*)-3-(4-{[(2*S*)-2-({[1-(biphenyl-3-ylamino)cyclohexyl]carbonyl}amino)butyl]amino}phenoxy)acrylate (28b). Yield: 66%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 7.4 Hz), 1.24–1.66 (8H, m), 1.93–2.04 (4H, m), 2.99–3.04 (1H, m), 3.13–3.16 (1H, m), 4.03–4.09 (1H, m), 5.17 (2H, s), 5.44 (1H, d, J = 12.1 Hz), 6.41 (2H, d, J = 9.0 Hz), 6.58 (1H, d, J = 7.1 Hz), 6.81 (2H, d, J = 9.0 Hz), 6.85 (1H, s), 7.03 (2H, t, J = 7.8 Hz), 7.10 (1H, t, J = 7.1 Hz), 7.80–7.86 (8H, m), 7.51 (2H, d, J = 7.1 Hz), 7.76 (1H, d, J = 12.1 Hz); IR (KBr): 3374, 2935, 1705, 1645, 1509, 1320, 1287, 1208, 1116, 828, 757, 699 cm^{-1}; HR-MS found $[M+H]^+$: 618.3337, calcd for $C_{39}H_{44}N_3O_4$: 618.3329.

5.25. 3-(4-{[(2*S*)-2-({[1-(Biphenyl-3-ylamino)cyclohexyl]carbonyl}amino)butyl]amino}phenoxy)propanoic acid (29)

A mixture of acrylate **28b** (68 mg, 0.11 mmol) and Pd/C (10%, 12 mg, 0.011 mmol) in EtOH (5 mL) was stirred under H_2 for 20 h. After removal of Pd/C by filtration, the filtrate was concentrated. The residue was purified by PTLC (hexane/EtOAc, 1:1) to provide propanoic acid **29** (22 mg, 37%) as an amorphous substance. ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 7.4 Hz), 1.32–1.65 (8H, m), 1.95–2.04 (4H, m), 2.78 (2H, t, J = 6.3 Hz), 3.01 (1H, dd, J = 10.1, 12.5 Hz), 3.13 (1H, dd, J = 4.3, 12.5 Hz), 4.02–4.09 (1H, m), 4.16 (2H, t, J = 6.3 Hz), 6.42 (2H, d, J = 8.6 Hz), 6.59 (1H, d, J = 8.2 Hz), 6.72 (2H, d, J = 8.6 Hz), 6.85 (1H, s), 7.02 (1H, d, J = 7.8 Hz), 7.07 (1H, d, J = 7.8 Hz), 7.12 (1H, t, J = 7.8 Hz), 7.31 (1H, d, J = 7.0 Hz), 7.37 (2H, t, J = 7.0 Hz), 7.52 (2H, d, J = 7.0 Hz); IR (KBr): 3369, 2933, 1650, 1602, 1513, 1229, 758, 701 cm^{-1}; HR-MS found $[M+H]^+$: 530.3009, calcd for $C_{32}H_{40}N_3O_4$: 530.3027.

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