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Synthesis and biological evaluation of benzimidazole derivatives as potent AMP-activated protein kinase activators

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Abstract—Design, synthesis and structure–activity relationships of beU:/AP/DTD501/BMC/4818nzimidazole derivatives as activators of the AMP-activated protein kinase (AMPK) are presented in this paper. AMPK is the central component of a protein kinase cascade that plays a key role in the regulation of energy balance. Once activated, AMPK initiates a series of responses that are aimed at restoring the energy balance of the cell and recent studies have indicated that AMPK plays an important role in regulation of the whole-body energy metabolism. The following study based on the lead compound **S27847** involved modification of three regions of this compound. Preliminary structure–activity relationships are being described.

1. Introduction

The AMP-activated protein kinase (AMPK) is the central component of a protein kinase cascade that plays a major role in energy sensing. AMPK itself plays a key role in the regulation of metabolism within the muscle cell and has been already identified as a potential target for type 2 diabetes mellitus and obesity.[1–4] AMPK is activated following depletion of cellular ATP together with a concomitant rise in AMP.[5,6] AMP increases AMPK activity by direct allosteric activation and by promoting the phosphorylation of AMPK by an upstream kinase, AMPK kinase (AMPKK). Recently, several studies have demonstrated that AMPK is activated by a second mechanism that does not appear to involve changes in adenine nucleotides. However, the molecular basis for this activation is not yet understood.[7,8] Once activated, AMPK phosphorylates several downstream substrates, with an overall effect of switching-off the ATP-consuming pathways (e.g., fatty acid synthesis and cholesterol synthesis) and switching-on the ATP-generating pathways (e.g., fatty acid oxidation and glycolysis).[5,9–11]

A major development in AMPK research came with the finding that 5-amino-4-imidazolecarboxamide (AICA) riboside (Fig. 1) could be used to activate AMPK phar-

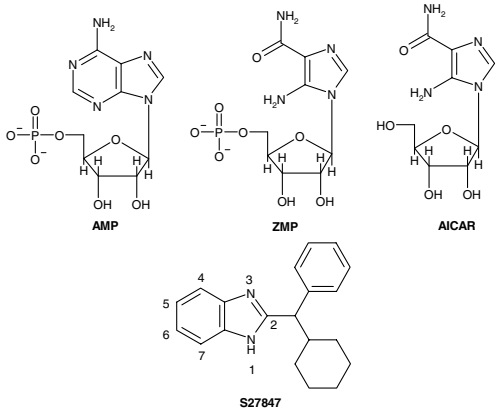

Figure 1. Structures of AMP, ZMP, AICAR and compound **S27847**.

Keywords: AMP-activated protein kinase; Benzimidazole derivatives.
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macologically in cells.[12,13] AICA riboside (AICAR) is converted in cells to the monophosphate derivative, ZMP, which can accumulate to high levels, and mimics the effects of AMP on the AMPK cascade. Until recently, AICAR was the only pharmacological activator of AMPK to be described and many studies investigating the physiological consequences of AMPK activation relied solely on its use. In this paper, we describe the synthesis and biological evaluation of benzimidazole derivatives as potent AMPK activators. A screening of a general library afforded **S27847** as a better mediator of AMPK activation in primary cultured hepatocytes and in muscle cells H-2K than the reference AMPK activator AICAR. The benzimidazole scaffold of **S27847** made it attractive in terms of possible diversifications.

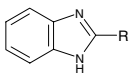
Here we report our efforts to improve AMPK activation starting from the lead compound **S27847** (racemate compound): first, by modification of the cyclohexylphenyl moiety and second, by introducing diversity on the aromatic moiety of the benzimidazole ring. These results will provide a useful aid for further work on the potential benefit of therapeutic agents aimed at targeting AMPK in disease such as type 2 diabetes or other obesity-related diseases.

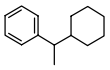
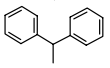
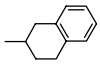
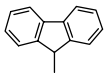
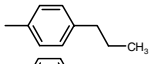
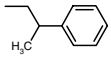
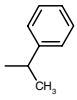
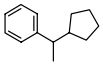
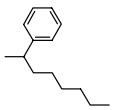
2. Chemistry

Synthesis of **S27847** analogs (compounds **2**–**74**, Tables 1–6) is depicted in Schemes 1–13. In the A series, compounds **2**–**32** have been modified at the C-2 position with the aim of evaluating the optimal substituent (Table 1, Fig. 2). Several aromatic and/or alicyclic groups replaced the cyclohexylphenylmethyl moiety. In the B series (compounds **33**–**38**, Table 2, Fig. 2), the replacement of the cyclohexyl group by an amine was carried out in order to enhance activity and optimize solubility simultaneously. In addition, two compounds in which the C2 atom was replaced with a nitrogen atom were synthesized (compounds **39**–**40**, C series, Table 3, Fig. 2). In addition, replacement of the imidazole moiety with other heterocycles was attempted to evaluate the importance of this pattern on activity (compounds **41**–**43**, D series, Table 4, Fig. 2). In the E series (compounds **44**–**67**, Table 5, Fig. 2), diversity was introduced on the phenyl moiety of the benzimidazole core while maintaining the cyclohexylphenylmethyl substituent at C-2 position. It consisted in various substitutions of phenyl moiety (compounds **44**–**48** and **51**–**67**) or in the replacement of the latter by a purine (compound **49**) or a pyridine (compound **50**). In the F series (compounds **68**–**74**, Table 6, Fig. 2), the combination of the methoxy group at the C-5 position and several other substituents at the C-2 position (compounds **68**–**72**) was realized. Two analogs with an amino substituent in N-1 position (compounds **73** and **74**) were also synthesized while preserving cyclohexylphenylmethyl group at the C-2 position.

The presence of bulky substituents led us logically to consider a two-step procedure. Substituted or unsubstituted 1,2-phenylenediamine was first treated with the

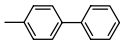
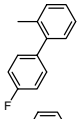
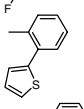
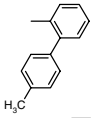
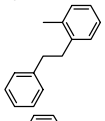
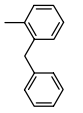
Table 1. AMP-Kinase activity for compounds **1**–**32** (A series)



Compound	R	REA[a] at 100 μM
1 or **S27847**		**4.5**
2		1.1
3		1.1
4		1.1
5		1.1
6		2.8
7		1.4
8		1.2
9		1.3
10		1.2
11		1.2
12		1.0
13		1.0
14		1.2
15		1.0
16		1.4
17		1.1
18		0.8
19		**7.1**
20		**5.4**
21		0.9
22		1.1

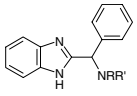
(*continued on next page*)

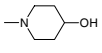
Table 1 (*continued*)

Compound	R	REA[a] at 100 μM
23		**5.1**
24		1.1
25		**7.2**
26		0.9
27		1.1
28		**4.7**
29		0.6
30		1.1
31		1.2
32		0.8
AICAR		2.3[b]

[a] Relative enzyme activity (enzyme activity relative to buffer blank).
[b] Relative enzyme activity at 500 μM.

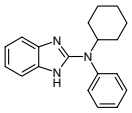
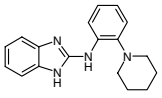
Table 2. AMP-Kinase activity for compounds **33**–**38** (B series)



Compound	-NRR′	REA[a] at 100 μM
33		**6.1**
34		1.0
35		1.0
36		0.9
37		1.2
38		**5.8**
1 or **S27847**		**4.5**
AICAR		2.3[b]

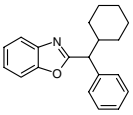
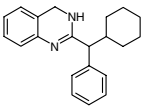
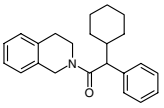
[a] Relative enzyme activity (enzyme activity relative to buffer blank).
[b] Relative enzyme activity at 500 μM.

Table 3. AMP-Kinase activity for compounds **39** and **40** (C series)

Compound	Structure	REA[a] at 100 μM
39		**4.3**
40		3.1
1 or **S27847**		**4.5**
AICAR		2.3[b]

[a] Relative enzyme activity (enzyme activity relative to buffer blank).
[b] Relative enzyme activity at 500 μM.

Table 4. AMP-Kinase activity for compounds **41**–**43** (D series)

Compound	Structure	REA[a] at 100 μM
41		0.6
42		1.8
43		0.8
1 or **S27847**		**4.5**
AICAR		2.3[b]

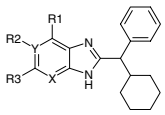
[a] Relative enzyme activity (enzyme activity relative to buffer blank).
[b] Relative enzyme activity at 500 μM.

appropriate activated carboxylic acid. Cyclodehydration of the resulting monoacylated derivative led to the benzimidazole derivative (Scheme 1). Under optimal conditions, the DCC coupling in THF or DMF between an appropriate carboxylic acid and substituted or unsubstituted *o*-phenylenediamine, followed by reflux of the monoacylated derivative in neat acetic acid, led to the isolation of desired compounds with good yields.[14]

In the case of expensive or commercially unavailable acids, the use of more than two equivalents of acid with regard to *o*-phenylenediamine was a major inconvenience. A coupling using PyBrop activation[15] and an excess of amine, to avoid formation of diacylated derivatives, has been preferred for compounds **3i**, **6i**, **8i**, **9i**, **19i**, **22i**, **25**–**29i**, **33**–**36i** and **38i** (Scheme 1). In this case, diisopropylethylamine (DIEA) was used as a base with that coupling reagent.

Synthesis of monoacylated precursor **37i** necessitated a coupling using EDC/HOBt activation and DIEA as a base to avoid reaction with the hydroxy group (Scheme 1).

Table 5. AMP-Kinase activity for compounds **44–67** (E series)



Compound	R_1	R_2	R_3	X	Y	REA[a] at 100 μM
44	NO_2	H	H	CH	C	1.0
45	NH_2	H	H	CH	C	**4.3**
46	NHEt	H	H	CH	C	3.2
47	NHCOMe	H	H	CH	C	0.7
48	Me	H	H	CH	C	2.1
49	H	—	H	N	N	0.9
50	H	H	H	N	C	1.1
51	H	Me	H	CH	C	2.0
52	H	OMe	H	CH	C	**6.9**
53	H	F	H	CH	C	1.8
54	H	Cl	H	CH	C	**4.0**
55	H	CF_3	H	CH	C	1.7
56	H	COOMe	H	CH	C	0.8
57	H	COOH	H	CH	C	0.6
58	H	OCOMe	H	CH	C	1.2
59	Me	Me	H	CH	C	2.1
60	H	Me	Me	CH	C	**5.0**
61	H	OMe	OMe	CH	C	**4.6**
62	H	Cl	Cl	CH	C	1.9
63	H	Phenyl		CH	C	0.8
64	H	Piperidine	H	CH	C	3.7
65	H	Methylpiperazine	H	CH	C	2.7
66	H	Morpholine	H	CH	C	**4.4**
67	H	Thiomorpholine	H	CH	C	2.2
1	H	H	H	H	H	**4.5**
AICAR						2.3[b]

[a] Relative enzyme activity (enzyme activity relative to buffer blank).
[b] Relative enzyme activity at 500 μM.

Compounds **49i** and **50i** were synthesized starting, respectively, from 4,5-diaminopyrimidine and 2,3-diaminopyridine by reaction, in the presence of DIEA, with acyl chloride of cyclohexylphenylacetic acid, prepared beforehand using thionyl chloride (Scheme 1).

Two different acidic conditions of cyclization were applied: refluxing in neat AcOH or in the presence of HCl. Compound **50** was obtained by treating the corresponding monoacylated precursor **50i** with *p*-toluenesulfonic acid in toluene at reflux (Scheme 1).

For several compounds, the starting material was 2-nitroaniline, both substituted or not, which was reacted with commercially available or previously synthesized acyl chlorides. In most cases, reduction of the nitro group followed by the cyclodehydration step of the resulting monoacylated derivative was realized 'one pot' using iron in refluxing neat acetic acid,[16] tin chloride in the presence of 12 N HCl in refluxing ethanol or iron in the presence of 12 N HCl in refluxing ethanol (Scheme 1).

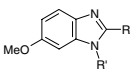
In the case of dicyclohexylmethyl benzimidazole **3**, no cyclization was observed in refluxing neat acetic acid from monoacylated precursor **3i**. Under these conditions the acetylated derivative **3j** was obtained. The benzimidazole **3** was finally synthesized by cyclization of compound **3j** using *p*-toluenesulfonic acid in refluxing toluene (Scheme 2), conditions previously reported for the preparation of 2-substituted benzoxazoles and benzimidazoles, when starting from the corresponding symmetrical diacylated precursors.[14,17]

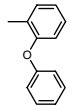
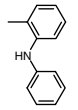
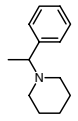
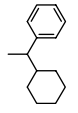
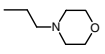
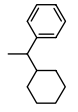
Nitrothiourea **39i** and **40i** were obtained starting from 2-nitrophenylisothiocyanate by reaction with the appropriate amine, *N*-cyclohexylaniline and 2-(1-piperidino)aniline, respectively, in THF.[18] Then treatment with tin chloride in ethanol at reflux led to reduction of nitro group and consecutive cylization affording benzimidazoles **39** and **40** (Scheme 3).

The compounds **41–43** (D series) were synthesized under conditions described previously. In the case of compound **41**, coupling between 2-aminophenol and cyclohexylphenylacetic acid, using DCC activation in THF, and treatment with *p*-toluenesulfonic acid in refluxing toluene were applied to afford the expected benzoxazole (Scheme 4).[17,19]

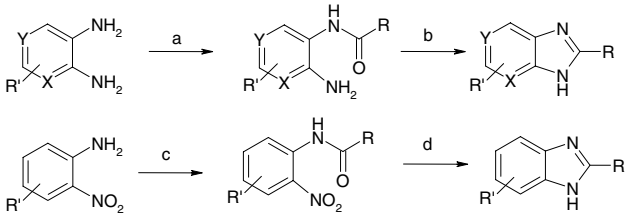
For compound **42**, coupling between 2-aminobenzylamine and cyclohexylphenylacetic acid, using DCC activation and DIEA as a base in DMF, and consecutive reflux in neat acetic acid led to the obtention of the expected dihydroquinazoline (Scheme 5).

Table 6. AMP-kinase activity for compounds **68–74** (F series)

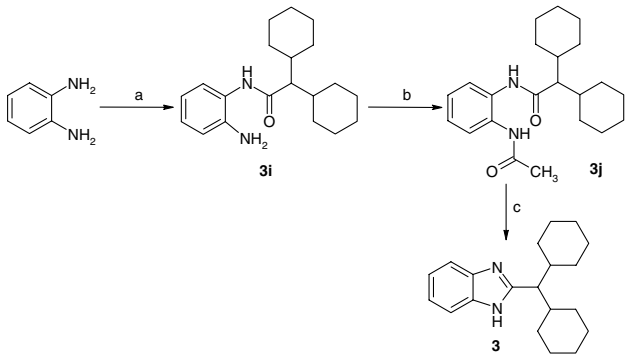


Compound	R	R′	REA[a] at 100 μM
68		H	3.1
69		H	1.8
70		H	1.0
71		H	**4.7**
72		H	**6.9**
73			0.9
74			1.0
1 or **S27847**			**4.5**
AICAR			2.3[b]

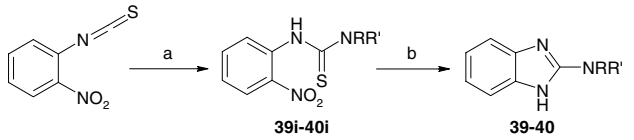
[a] Relative enzyme activity (enzyme activity relative to buffer blank).
[b] Relative enzyme activity at 500 μM.



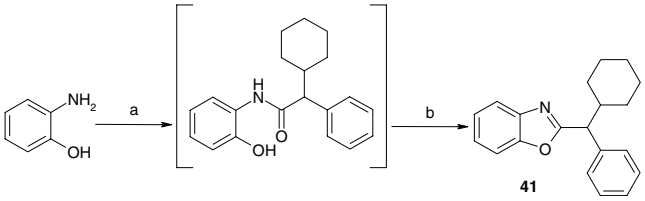
Scheme 1. Reagents and conditions: (a) RCOOH, DCC, DIEA, DMF or THF, rt, 12 h or RCOOH, PyBrop, DIEA, CH_2Cl_2, rt, 12 h or EDC, HOBt, DIEA, DCM, rt, 12 h; (b) neat AcOH, reflux, 5 h or 4 N HCl, MeOH/dioxane 1:1, reflux, 8 h or *p*-TsOH, toluene, reflux, 72 h; (c) RCOCl, pyridine, THF, rt, 4 h or RCOCl, DIEA, CH_2Cl_2, 12 h; (d) Fe, neat AcOH, reflux, 5 h or $SnCl_2$, 12 N HCl, EtOH, reflux, 24 h or Fe, 12 N HCl, EtOH, reflux, 8 h.



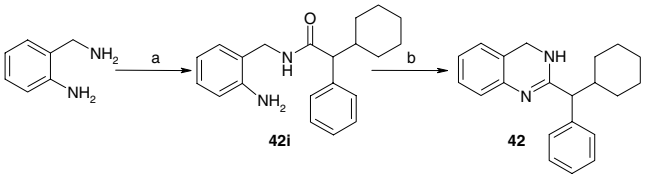
Scheme 2. Reagents and conditions: (a) dicyclohexylacetic acid, PyBrop, DIEA, CH_2Cl_2, rt, 12 h; (b) neat AcOH, reflux, 5 h; (c) *p*-TsOH, toluene, reflux, 24 h.



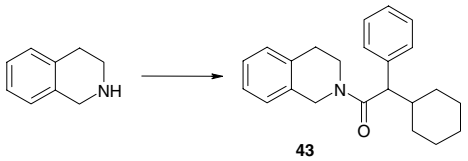
Scheme 3. Reagents and conditions: (a) RR′NH, THF, rt, 12 h; (b) $SnCl_2$, EtOH, reflux, 5 h.



Scheme 4. Reagents and conditions: (a) cyclohexylphenylacetic acid, DCC, THF, rt, 12 h; (b) *p*-TsOH, toluene, reflux, 8 h.



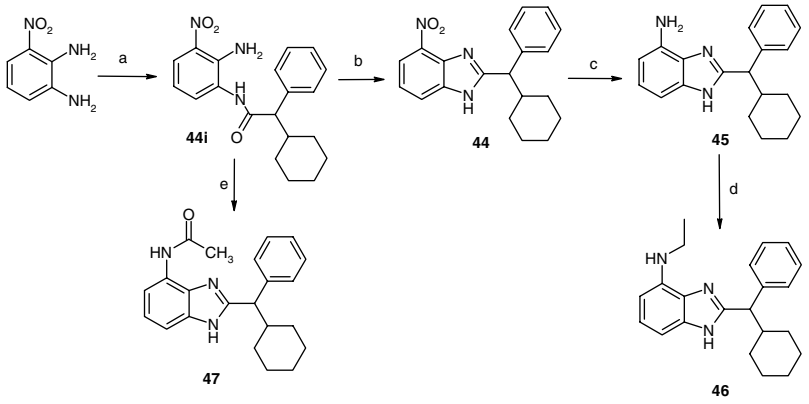
Scheme 5. Reagents and conditions: (a) cyclohexylphenylacetic acid, DCC, DIEA, DMF, rt, 12 h; (b) neat AcOH, reflux, 24 h.



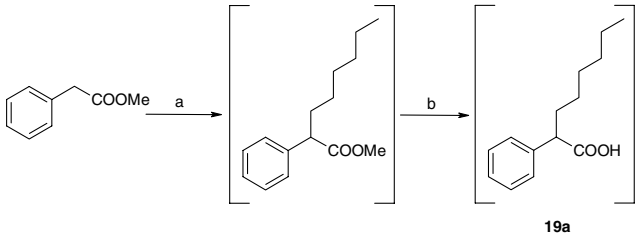
Scheme 6. Reagents and conditions: cyclohexylphenylacetic acid, PyBrop, DIEA, CH_2Cl_2, rt, 12 h.

Tetrahydroquinoline **43** was prepared by a coupling between cyclohexylphenylacetic acid and 1,2,3,4-tetrahydroquinoline using PyBrop activation and DIEA as a base in dichloromethane (Scheme 6).

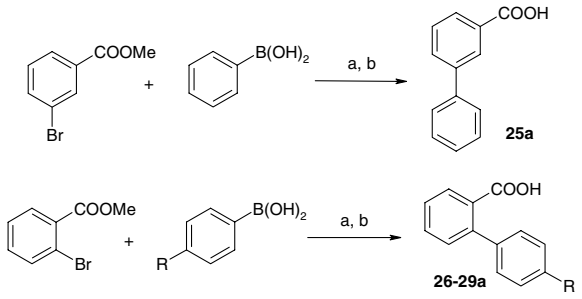
The reaction between 3-nitro-*o*-phenylenediamine and the acyl chloride of cyclohexylphenylacetic acid led to expected compound **44i**, which was cyclized in benzimidazole **44** in neat acetic acid at reflux (Scheme 7).



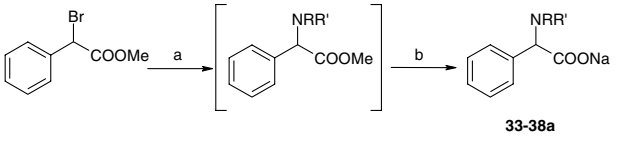
Scheme 7. Reagents and conditions: (a) cyclohexylphenylacetyl chloride, DIEA, CH_2Cl_2, rt, 12 h; (b) neat AcOH, reflux, 5 h; (c) Fe, 12 N HCl, EtOH, reflux, 6 h; (d) CH_3CHO, $NaBH_3CN$, MeOH, rt, 24 h; (e) Fe, neat AcOH, reflux, 5 h.



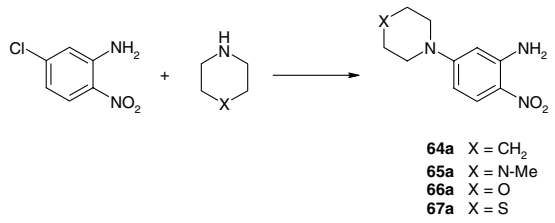
Scheme 8. Reagents and conditions: (a) 1-bromohexane, NaH, THF, rt, 12 h; (b) NaOH 1 M/MeOH 1:1, reflux, 4 h.



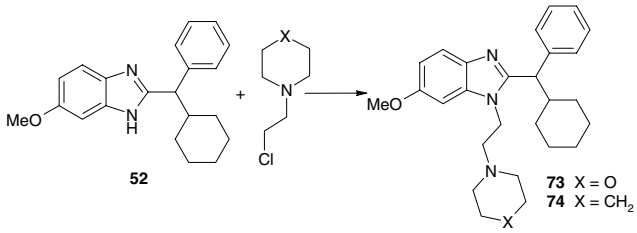
Scheme 9. Reagents and conditions: (a) KF, $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, THF, N_2, rt, 24 h; (b) NaOH, MeOH, reflux, 6 h.



Scheme 10. Reagents and conditions: (a) RR′NH, DIEA, CH_3CN, rt, 4 h; (b) NaOH, MeOH, reflux, 8 h.

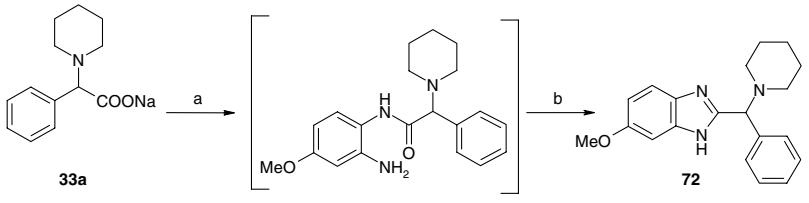


Scheme 12. Reagents and conditions: K_2CO_3, DMF, reflux, 24 h.



Scheme 13. Reagents and conditions: NaH, KI, THF, reflux, 12 h (compound **73**) or 6 h (compound **74**).

When the cyclization conditions adoped for monoacylated precursors from 2-nitroaniline: neat acetic acid at reflux in the presence of iron, were used, only compound **47**, in which the newly formed amino group is acylated, was obtained. The amino derivative **45** was eventually synthesized by action of iron and 12 N HCl in refluxing ethanol. Functionalization of the amino group in compound **45** by an ethyl group was performed using acetaldehyde and sodium cyanoborohydride in MeOH and led to analog **46** (Scheme 7).



Scheme 11. Reagents and conditions: (a) 3-methoxy-*o*-phenylenediamine, PyBroP, DIEA, CH_2Cl_2, rt, 12 h; (b) 4 N HCl, MeOH/dioxane 1:1, reflux, 72 h.

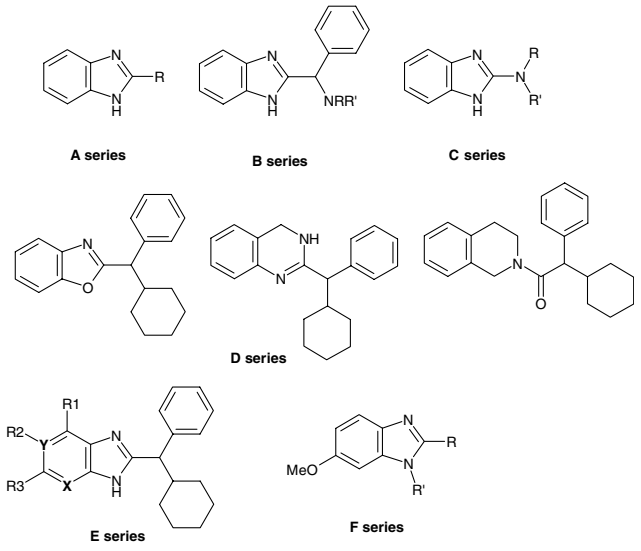


Figure 2. Structures of **S27847** analogs.

The saponification of the methyl ester in compound **56**, by treatment with aqueous NaOH 1 M in refluxing methanol, led to benzimidazole **57**.

Some starting materials, which were not commercially available, were synthesized for the purpose of this study. In the case of compound **19**, the acid **19a** was obtained by reaction between methylphenylacetate and 1-bromohexane (Scheme 8). The acidic hydrogen in the α-position of the ester group was removed in the presence of sodium hydride as a base to form the corresponding carbanion, which was reacted with 1-bromohexane.[20] A treatment with a mixture of NaOH 1 M/MeOH allowed the formation of the carboxylate.

Acids **25**–**29a**, commercially unavailable, were obtained using a Suzuki coupling starting from the corresponding boronic acid derivatives and methyl 3-bromobenzoate for compound **25a** or methyl 2-bromobenzoate for compounds **26**–**29a** (Scheme 9). The conditions described by Buchwald and co-workers were applied using potassium fluoride as a base, palladium acetate as a catalyser and 2-(di-*tert*-butylphosphino)biphenyl as a ligand in THF.[21] A final basic treatment using aqueous NaOH in refluxing methanol led to saponification of the ester function.

The substitution of the bromine atom of methyl-α-bromophenyl acetate by the appropriate amine, protected if necessary, in the presence of DIEA in acetonitrile, and subsequent basic treatment in methanol afforded the corresponding sodium salts **33**–**38a** commercially unavailable (Scheme 10).

The coupling reaction between the sodium salt **33a** and 3-methoxy-*o*-phenylenediamine using PyBroP activation and DIEA as base in dichloromethane afforded the expected monocylated precursor, which was cyclized directly into compound **72** at reflux in the presence of HCl (Scheme 11).

Another substitution reaction of the chlorine atom of 5-chloro-2-nitroaniline by the appropriate cyclic secondary amine in the presence of potassium carbonate in refluxing DMF led to corresponding amines **64**–**67a** (Scheme 12).[22]

Both analogs **73** and **74**, with a substituent in N-1 position, were synthesized by substitution of the chlorine atom of *N*-(2-chloroethyl)morpholine or 1-(2-chloroethyl)piperidine, respectively, by the amino group of compound **52** in the presence of sodium hydride and potassium iodide in refluxing THF (Scheme 13).

3. Results and discussion

3.1. Activation of the AMP-kinase

Compounds were assayed for activation of the AMP-kinase on fresh rat hepatocytes. Compounds were incubated with hepatocytes during 1 h. The level of AMPK activation was determined on cell lysates by measurement of phosphorylation of a peptide substrate (SAMS peptide, a synthetic peptide substrate with the amino acid sequence HMRSAMSGLHLVKRR).[23] The biochemical results are presented as relative enzyme activity (enzyme activity relative to buffer blank) (Tables 1–6).

Compounds **2**–**32** of series A (Table 1) were designed with the aim of evaluating the optimal substituent at the C-2 position. Three compounds showed activities higher than that of the lead compound **S27847** (or **1**): compounds **19** (R: 1-phenylheptyl), **20** (R: *trans*-2-phenylcyclopropyl) and **23** (R: biphenyl-2-yl). In some cases, minor structural modifications led to a complete loss of activity, for example in the case of compound **18** that differs from **1** only by the cyclopentyl/cyclohexyl replacement. Activation of AMPK is slightly increased for the linear analog **19** of benzimidazole **S27847** (or **1**). As compound **23** possessed the advantage of being more favourable for modifications, several other analogs were synthesized (compounds **24**–**32**) and revealed different behaviours. The *para* biphenyl derivative **24** was totally inactive whereas the *meta* analog **25** revealed an activity slightly greater than that of the *ortho* variant **23**. Among compounds **26**–**32**, where the second phenyl moiety was modified, only the replacement by a thiophenyl group (compound **28**) resulted in an unaffected activity in comparison with those of the lead compound **S27847** (or **1**) and with compound **23**. An interesting structure–activity relationship could be deduced from this series of compounds: a phenyl group associated with another group whether cyclohexyl (compound **1**), cyclopropyl (compound **20**), hexyl (compound **19**) or aromatic (compounds **23**, **25** and **28**), in C-2 position appears to impact an AMPK activity.

With the aim of introducing minor structural modifications on **S27847** (or **1**), a series of compounds, in which the phenyl group was conserved and the cyclohexyl group replaced by an amine, was designed (B series, compounds **33**–**38**, Table 2). Compounds **33** and **38**, piperidine and cyclohexylamine analogs, respectively, possessed an interesting activity with respect to the lead

compound, including an improvement of solubility. However, like in the preceding series, minor structural modifications resulted in a complete loss of activity, for example, the replacement of piperidine by homopiperidine (compound **35**) or by morpholine (compound **34**) clearly illustrates that effect. In the two series A and B the structural modifications around **S27847** (or **1**) led to the introduction of preliminary SAR and to the identification of novel activators of AMPK (compounds **33** and **38**) presenting more 'lead-like' properties (better solubility, lower lipophilicity ($c\log P$)) than those of compound **S27847**.

In the series C, the carbon atom in position 2 of benzimidazole was replaced by a nitrogen atom (compounds **39** and **40**, Table 3). Two aromatic amines were selected: one primary with 2-(1-piperidino)aniline (compound **40**) and one secondary with *N*-cyclohexylaniline (compound **39**), while the phenyl group was preserved in position 2 of benzimidazole, as with active compounds of series A. Benzimidazole **39**, analog of compound **S27847** (or **1**) with a nitrogen atom in position 2, possessed an activity similar to that of the latter. Compound **40** showed a slightly lower activity. Consequently, the replacement of the carbon atom in position 2 of benzimidazole by a secondary or tertiary amine seemed to be a favourable outcome though activity was unaffected.

With the aim of studying the influence of benzimidazolyl pattern on activity, isosteric replacements were tested. Three compounds were synthesized: a benzoxazolyl analog in which one of the nitrogen atoms was replaced by an oxygen atom, a 3,4-dihydroquinazolinyl analog with a six-membered ring and a 1,2,3,4-tetrahydroisoquinolinyl analog with a larger cycle and only one cyclic nitrogen atom (compounds **41**–**43**, respectively, D series, Table 4). These attempts to replace benzimidazole led to a total loss of activity. These results showed that there was an activity-contribution of the nitrogen atom donor of the hydrogen bound in position 1 (replaced by an oxygen atom, acceptor of hydrogen bound in compound **41**) and of the aromaticity of the structure (which was absent in compound **42**) as well.

In a second step, our research consisted in the study of the influence of structural modifications of the phenyl moiety of benzimidazole while maintaining the cyclohexylphenylmethyl group at C-2 position (compounds **44**–**67**, E series, Table 5). In this series, a methoxy group in position 5 only (equivalent to position 6 when N-1 is not substituted, compound **52**) or in both positions 5 and 6 (compound **61**) proved favourable for activity. For the methyl group, only the substitution in positions 5 and 6 simultaneously was favourable (compound **60**). A methyl group in position 4 (compound **48**), in position 5 (compound **51**) or in positions 4 and 5 (compound **59**) led to a loss of activity. The introduction of electron-withdrawing groups appeared to be detrimental to activity (compounds **44**: NO_2, **55**: CF_3, **56**: COOMe and **57**: COOH). Except for the case of compound **54** (Cl in position 5), the introduction of electrodonating mesomer groups proved unfavourable for activity (compounds **53**: F, **58**: OCOMe and **62**: Cl in positions 5 and 6). Purine and pyridine derivatives **49** and **50** were also inactive. An additional phenyl group on the benzimidazole pattern (compound **63**) affected strongly the activity. Compound **45**, which possessed a primary amino group in position 7, presented a good activity as compared to that of the lead compound **S27847** (or **1**). The ethyl analog **46**, synthesized with the aim of avoiding the potential toxicity of benzimidazole **45** due to aromatic amine function, demonstrated a slightly lower activity, whereas its acetyl derivative **47** was totally inactive. With compounds **64**–**67**, which possessed an alicyclic amine in position 5, the activation of AMPK was equivalent to the lead compound **S27847** (or **1**), only in the case of the morpholine derivative **66**.

In the last series of compounds (E series, compounds **44**–**67**), the benzimidazole **52**, possessing a methoxy group in position 5, was the more potent activator of AMPK. With the aim of increasing activity, a combination of methoxy group in position 5 and optimal groups in C-2 position from A series was evaluated: with an *ortho*-biphenyl group for compound **68** and with phenylpiperidinylmethyl group for compound **72** (F series, Table 6). In parallel, several analogs of compound **68** were synthesized (compounds **69**–**71**, F series, Table 6). Compared with the lead compound **S27847** (or **1**), only compounds **71** and **72** presented a better activation of AMPK. In the case of analog **72**, a combination of compounds **33** and **52**, the replacement of the cyclohexyl group by a piperidine did not improve activity when compared with compound **52**. The effect of the alkylation of nitrogen atom in position 1 was studied by substitution of compound **52** with amino chains: 1-ethylmorpholine group for compound **73** and 1-ethylpiperidinyl group for compound **74**. In both cases, the modification led to a complete loss of activity. This result confirmed the requirement for the presence of a hydrogen bond donating atom at position 1 to preserve activity.

In conclusion, the overall function of AMPK in regulating energy balance makes it an attractive target for therapeutic agents aimed at reducing body weight. However studies investigating the physiological consequences of AMPK activation relied until now solely on few very weak pharmacological AMPK activators like AICAR. Here, we described new activators of higher potency of this kinase and structure–activity relationships. Their exact molecular mode of action still remains to be elucidated. However, being either direct or indirect[25] activators of AMPK, this novel class of AMPK activators might facilitate the elucidation of a role of AMPK in the regulation of cellular processes and might represent a promising therapeutic potential in the treatment of obesity and type 2 diabetes mellitus.

4. Experimental

4.1. Chemistry

All reactions were monitored using thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent.

^{1}H- and ^{13}C NMR spectra were measured in DMSO-d_6 using a Brücker 300 MHz spectrometer. Mass spectra were recorded on a Maldi mass spectrometer (MALDI-TOF-MS). Chromatography was carried out using silica gel 60 (230–400 mesh ASTM) from Macherey-Nagel. Thick-layer chromatography (TLC) was performed using silica gel from Merck and the compounds were extracted from silica gel using the following solvent system: CH_2Cl_2/MeOH 80:20. The melting point (mp) of benzimidazoles was determined on a Büchi 535 capillary mp apparatus and is uncorrected. The purity of final compounds was checked by high pressure liquid chromatography (P_{HPLC}) with a C18 Xterra or TSK GEL column. Analytical HPLC was performed on a Shimadzu system equipped with a UV detector set at 254 nm. Compounds were dissolved in MeOH and injected through a 50 μL loop. The following eluent systems were used: A (H_2O/TFA, 100:0.05) and B (CH_3CN/H_2O/TFA, 80:20:0.05). HPLC retention times (t_R) were obtained at flow rates of 1 mL/min using different methods: a gradient run from 100% eluent A to 100% eluent B in 7 min 30 s for method A and in 10 min for method B.

4.1.1. General procedure A for synthesis of monoacylated precursors 1i, 4–5i, 7i, 10–11i, 14–15i, 17–18i, 20i, 23i and 30–32i. To a solution of appropriate acid (5.77 mmol, 1 equiv) in 23 mL of DMF were added a solution of DCC 1 M in CH_2Cl_2 (2.89 mL, 2.89 mmol, 0.5 equiv), DIEA (1.1 mL, 6.35 mmol, 1.1 equiv) and *o*-phenylenediamine (250 mg, 2.31 mmol, 0.4 equiv). After stirring for 12 h at room temperature, the mixture was filtered and the solvent evaporated. The residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC or by trituration in Et_2O to afford expected monoacylated compound.

4.1.2. General procedure B for synthesis of monoacylated precursors 2i, 12–13i and 24i. To a solution of acid (0.94 mmol, 1 equiv) in 5 mL of dry CH_2Cl_2 was added thionyl chloride (172 μL, 2.35 mmol, 2.5 equiv). Following reflux of the mixture for 1 h 30 min, the solvent and the excess of thionyl chloride were evaporated. To a solution of this residue in 3 mL of dry THF was added a solution of 2-nitroaniline (195 mg, 1.41 mmol, 1.5 equiv) and pyridine (380 μL, 4.7 mmol, 5 equiv) in 3 mL of dry THF. After stirring the mixture for 4 h at room temperature, the solvent was evaporated, the residue diluted with CH_2Cl_2 and washed with aqueous $KHSO_4$ 5%, aqueous $NaHCO_3$ 5% and aqueous saturated NaCl. The organic layer was dried over $MgSO_4$, concentrated and the residue purified by trituration in a Et_2O/pentane mixture or by TLC to afford expected compound. In the case of commercially available acyl chloride, the first step was not necessary.

4.1.3. General procedure C for synthesis of non-commercially available acids 25–29a. To a solution of methyl 2-bromobenzoate or methyl 3-bromobenzoate (1.5 mmol, 1 equiv) in 10 mL of THF were added KF (261 mg, 4.5 mmol, 3 equiv), palladium acetate (1.5 mol %), 2-(di-*tert*-butylphosphino)biphenyl (3 mol %) and appropriate boronic acid (3 mmol, 2 equiv). After stirring the mixture for 24 h under N_2 and at room temperature, the solvent was evaporated, the residue diluted with CH_2Cl_2, the organic layer washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The residue was diluted with 10 mL of methanol in the presence of aqueous NaOH 2.5 M (900 μL, 2.25 mmol, 1.5 equiv). Following reflux of the mixture for 6 h, the methanol was evaporated, the residue acidified with aqueous HCl 1 M and the expected acid extracted with CH_2Cl_2. The solvent was evaporated to give expected compound, directly used for synthesis of corresponding monoacylated precursor.

4.1.4. General procedure D for synthesis of non-commercially available sodium salts 33–38a. To a solution of methyl-α-bromophenyl acetate (500 mg, 2.18 mmol, 1 equiv) in 5 mL of acetonitrile were added DIEA (970 μL, 2.18 mmol, 1 equiv) and appropriate amine (2.62 mmol, 1.2 equiv). After stirring the mixture for 4 h at room temperature, the solvent was evaporated. To a solution of this residue in 5 mL of methanol was added aqueous NaOH 2.5 M (1.75 mL, 4.36 mmol, 2 equiv). Following reflux of the mixture for 8 h, the solvent was evaporated to afford expected acid which was not isolated.

4.1.5. General procedure E for synthesis of monoacylated precursors 3i, 6i, 22i, 25–29i, 33–36i and 38i. To a solution of appropriate acid (3.0 mmol, 1 equiv) in 12 mL of dry CH_2Cl_2 were added DIEA (1.25 mL, 7.5 mmol, 2.5 equiv), PyBrop (2.1 g, 4.5 mmol, 1.5 equiv), and then *o*-phenylenediamine (650 mg, 6.0 mmol, 2 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC or by trituration in a Et_2O/pentane mixture to afford expected monoacylated compound.

4.1.6. General procedure F for synthesis of monoacylated precursors 48i, 51–52i, 54–56i, 59–63i and 68–71i. To a solution of appropriate acid (2.47 mmol, 2.4 equiv) in 10 mL of THF were added a solution of DCC 1 M in CH_2Cl_2 (1.24 mL, 1.24 mmol, 1.2 equiv), DIEA (430 μL, 2.47 mmol, 2.4 equiv) and appropriate substituted *o*-phenylenediamine (1.03 mmol, 1 equiv). After stirring for 12 h at room temperature, the mixture was filtered and the solvent evaporated. The residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC to afford expected monoacylated compound.

4.1.7. General procedure G for synthesis of commercially unavailable substituted 2-nitroanilines 64–67a. To a solution of 5-chloro-2-nitroaniline (500 mg, 2.9 mmol, 1 equiv) in 10 mL of DMF were added appropriate amine (11.6 mmol, 4 equiv) and K_2CO_3 (812 mg, 5.8 mmol, 2 equiv). Following reflux of the mixture for 24 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by

TLC or by trituration in a Et_2O/pentane mixture to afford expected substituted 2-nitroaniline.

4.1.8. General procedure H for synthesis of monoacylated precursors 53i, 58i and 64–67i. To a solution of cyclohexylphenylacetic acid (785 mg, 3.6 mmol, 1.2 equiv) in 5 mL of dry CH_2Cl_2 was added thionyl chloride (1.3 mL, 18 mmol, 6 equiv). After stirring the mixture for 1 h at room temperature, the solvent and the excess of thionyl chloride were evaporated. To a solution of this residue in 20 mL of dry CH_2Cl_2 were added DIEA (1.04 mL, 6 mmol, 2 equiv) and appropriate substituted 2-nitroaniline (3 mmol, 1 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%. The organic layer was dried over $MgSO_4$, concentrated and the residue purified by TLC to afford expected compound.

4.1.9. *N*-(2-Aminophenyl)-2-cyclohexyl-2-phenylacetamide (1i). Compound **1i** was prepared according to the general procedure A starting from cyclohexylphenylacetic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 42%; white solid; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.50; t_R (TSK gel, method B): 6.82 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.30 (s, 1H, NH), 7.33–7.30 (m, 2H, ArH), 7.26–7.21 (m, 2H, ArH), 7.18–7.12 (m, 1H, ArH), 7.02 (m, 1H, ArH), 6.80 (m, 1H, ArH), 6.60 (m, 1H, ArH), 6.43 (m, 1H, ArH), 4.60 (s, 2H, NH_2), 3.31 (d, J = 10.7 Hz, 1H, CH), 1.95–1.00 (m, 11H, H cyclohexyl); ^{13}C NMR δ: 172.3, 142.5, 140.4, 129.1, 127.5, 126.7, 125.9, 124.1, 117.1, 116.9, 59.2, 40.6, 32.1, 31.1, 26.8, 26.3; MALDI-TOF-MS m/z: 309 $[M+H]^+$.

4.1.10. *N*-(2-Nitrophenyl)-2,2-diphenylacetamide (2i). Compound **2i** was prepared according to the general procedure B starting from diphenylacetic acid and was obtained after purification by trituration in Et_2O. Yield: 70%; yellow solid; R_f (cyclohexane/AcOEt 8:2): 0.50; t_R (C18 Xterra, method B): 8.54 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.40 (s, 1H, NH), 8.86 (dd, J = 1.3, 8.5 Hz, 1H, ArH), 8.16 (dd, J = 1.5, 8.5 Hz, 1H, ArH), 7.63 (m, 1H, ArH), 7.36 (m, 10H, ArH), 7.16 (m, 1H, ArH), 5.16 (s, 1H, CH); ^{13}C NMR δ: 186.8, 136.3, 129.5, 129.4, 128.6, 128.2, 126.2, 123.9, 122.5, 61.5; MALDI-TOF-MS m/z: 333 $[M+H]^+$.

4.1.11. *N*-(2-Aminophenyl)-2,2-dicyclohexylacetamide (3i). Compound **3i** was prepared according to the general procedure E starting from dicyclohexylacetic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 30%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0,65; t_R (C18 Xterra, method B): 7.31 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.11 (s, 1H, NH), 7.07 (m, 1H, ArH), 6.88 (m, 1H, ArH), 6.70 (m, 1H, ArH), 6.53 (m, 1H, ArH), 4.71 (s, 2H, NH_2), 2.09 (t, J = 7.2 Hz, 1H, CH), 1.68 (m, 12H, CH + CH_2), 1.10 (m, 10H, CH_2); ^{13}C NMR δ: 173.,2, 142.8, 126.6, 126.2, 124.6, 117.2, 116.9, 57.3, 36.9, 31.8, 29.9, 27.1, 27.0, 26.9; MALDI-TOF-MS m/z: 315 $[M+H]^+$.

4.1.12. *N*-(2-Aminophenyl)-2-phenylacetamide (4i). Compound **4i** was prepared according to the general procedure A starting from phenylacetic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 51%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (C18 Xterra, method B): 4.02 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.35 (s, 1H, NH), 7.32–7.21 (m, 5H, H phenyl), 7.12 (m, 1H, ArH), 6.87 (m, 1H, ArH), 6.69 (m, 1H, ArH), 6.50 (m, 1H, ArH), 4.80 (s, 2H, NH_2), 3.62 (s, 2H, CH_2); ^{13}C NMR δ: 169.9, 142.8, 137.2, 129.9, 129.1, 127.3, 126.8, 126.1, 124.1, 117.0, 116.7, 43.5; MALDI-TOF-MS m/z: 227 $[M+H]^+$.

4.1.13. *N*-(2-Aminophenyl)-2-cyclohexylacetamide (5i). Compound **5i** was prepared according to the general procedure A starting from cyclohexylacetic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 76%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.80; t_R (C18 Xterra, method B): 4.83 min, P_{HPLC}: 95%; ^{1}H NMR δ: 9.10 (s, 1H, NH), 7.14 (m, 1H, ArH), 6.88 (m, 1H, ArH), 6.69 (m, 1H, ArH), 6.53 (m, 1H, ArH), 4.78 (s, 2H, NH_2), 2.18 (d, J = 6.8 Hz, 2H, CH_2), 1.73–0.95 (m, 11H, H cyclohexyl); ^{13}C NMR δ: 171.2, 157.5, 142.7, 126.5, 126.1, 117.1, 116.8, 44.5, 35.7, 34.2, 33.4, 26.7, 26.5, 25.3; MALDI-TOF-MS m/z: 233 $[M+H]^+$.

4.1.14. *N*-(2-Aminophenyl)-2-naphthalen-2-ylacetamide (6i). Compound **6i** was prepared according to the general procedure E starting from 2-naphthylacetic acid, but was not purified and directly cyclized.

4.1.15. *N*-(2-Aminophenyl)-2-naphthalen-1-ylacetamide (7i). Compound **7i** was prepared according to the general procedure A starting from 1-naphthylacetic acid and was obtained after purification by TLC (AcOEt/cyclohexane 7:3). Yield: 58%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.30; t_R (TSK gel, method B): 5.32 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.48 (s, 1H, NH), 8.16 (d, J = 8.9 Hz, 1H, ArH naphthyl), 7.92 (d, J = 7.4 Hz, 1H, ArH naphthyl), 7.83 (d, J = 6.3 Hz, 1H, ArH naphthyl), 7.58–7.44 (m, 4H, ArH naphthyl), 7.14 (d, J = 7.8 Hz, 1H, ArH), 6.88 (t, J = 7.8 Hz, 1H, ArH), 6.70 (d, J = 7.9 Hz, 1H, ArH), 6.49 (t, J = 7.7 Hz, 1H, ArH), 4.84 (s, 2H, NH_2), 4.14 (s, 2H, CH_2); ^{13}C NMR δ: 169.9, 142.8, 134.2, 133.6, 132.9, 129.3, 128.0, 126.9, 126.8, 126.5, 126.4, 126.2, 125.1, 124.2, 117.0, 116.7, 41.2; MALDI-TOF-MS m/z: 277 $[M+H]^+$.

4.1.16. *N*-(2-Aminophenyl)-2-(1*H*-indol-3-yl)acetamide (8i). To a solution of 3-indoleacetic acid (737 mg, 4.21 mmol, 1.3 equiv) in 16 mL of dry CH_2Cl_2 were added DIEA (1.12 mL, 6.48 mmol, 2 equiv), PyBroP (1.96 g, 4.21 mmol, 1.3 equiv) and then *o*-phenylenediamine (350 mg, 3.24 mmol, 1 equiv). After stirring the mixture for 12 h at room temperature, the expected product was precipitated in DCM, filtered and washed with Et_2O to afford compound **8i**. Yield: 42%; white solid; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.55; t_R (TSK gel, method B): 4.42 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.85 (s, 1H, NH indolyl), 9.22 (s, 1H, NH), 7.58 (d, J = 7.7 Hz, 1H, ArH indolyl), 7.31 (d, J = 8.0 Hz, 1H, ArH indolyl), 7.21 (d, J = 2.3 Hz, 1H, ArH indolyl), 7.10 (dd, J = 1.3, 7.8 Hz, 1H, ArH), 7.02 (td, J = 1.2, 7.8 Hz, 1H, ArH indolyl), 6.93 (td, J = 0.9, 7.9 Hz, 1H, ArH

indolyl), 6.83 (td, $J = 1.5$, 7.9 Hz, 1H, ArH), 6.65 (dd, $J = 1.3$, 7.9 Hz, 1H, ArH), 6.47 (td, $J = 1.3$, 7.6 Hz, 1H, ArH), 4.75 (s, 2H, NH_2), 3.69 (s, 2H, CH_2); ^{13}C NMR δ: 170.5, 142.7, 136.9, 126.6, 126.0, 124.7, 121.8, 119.5, 119.2, 117.1, 116.7, 112.2, 33.9; MALDI-TOF-MS *m*/*z*: 266 $[M+H]^+$.

4.1.17. *N*-(2-Aminophenyl)-2-benzo[*b*]thiophen-3-ylacetamide (9i). To a solution of benzothiophene-3-acetic acid (533 mg, 2.77 mmol, 1.2 equiv) in 16 mL of dry CH_2Cl_2 were added DIEA (0.80 mL, 4.62 mmol, 2 equiv), PyBroP (1.29 g, 2.77 mmol, 1.2 equiv) and then *o*-phenylenediamine (250 mg, 2.31 mmol, 1 equiv). After stirring the mixture for 12 h at room temperature, the expected product was precipitated in DCM, filtered, washed with Et_2O and purified by TLC (CH_2Cl_2/MeOH 9.6:0.4) to afford compound **9i**. Yield: 37%; white solid; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.30; t_R (TSK gel, method B): 5.34 min, P_{HPLC}: 99%; ^1H NMR δ: 9.37 (s, 1H, NH), 7.88 (m, 2H, ArH benzothiophenyl), 7.51 (s, 1H, ArH benzothiophenyl), 7.33 (m, 2H, ArH benzothiophenyl), 7.07 (m, 1H, ArH), 6.79 (m, 1H, ArH), 6.61 (m, 1H, ArH), 6.44 (m, 1H ArH), 4.77 (s, 2H, NH_2), 3.85 (s, 2H, CH_2); ^{13}C NMR δ: 169.1, 162.7, 142.8, 131.4, 126.8, 126.2, 125.4, 125.1, 124.9, 124.1, 123.7, 122.9, 117.0, 116.7, 36.7; MALDI-TOF-MS *m*/*z*: 283 $[M+H]^+$.

4.1.18. 1,2,3,4-Tetrahydronaphthalene-2-carboxylic acid (2-aminophenyl)amide (10i). Compound **10i** was prepared according to the general procedure A starting from 1,2,3,4 tetrahydro-2-naphthoic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 70%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.65; t_R (C18 Xterra, method B): 5.19 min, P_{HPLC}: 99%; ^1H NMR δ: 9.22 (s, 1H, NH), 7.22 (m, 1H, ArH), 7.19–7.08 (m, 4H, ArH naphthyl), 6.88 (m, 1H, ArH), 6.75 (m, 1H, ArH), 6.56 (m, 1H, ArH), 4.84 (s, 2H, NH_2), 2.95-2.77 (m, 5H, CH + $2CH_2$), 2.10 (m, 2H, CH_2); ^{13}C NMR δ: 174.5, 142.8, 136.5, 136.3, 129.7, 129.4, 126.7, 126.5, 126.2, 124.3, 117.1, 116.8, 41.6, 32.8, 29.1, 27.3; MALDI-TOF-MS *m*/*z*: 267 $[M+H]^+$.

4.1.19. 9*H*-Fluorene-9-carboxylic acid (2-aminophenyl) amide (11i). Compound **11i** was prepared according to the general procedure A starting from 9-fluorenecarboxylic acid and was obtained after purification by trituration in Et_2O. Yield: 63%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.65; t_R (C18 Xterra, method B): 5.85 min, P_{HPLC}: 99%; ^1H NMR δ: 9.86 (s, 1H, NH), 7.88 (m, 2H, ArH), 7.65 (m, 2H, ArH), 7.44–7.34 (m, 4H, ArH), 7.17 (m, 1H, ArH), 6.94–6.89 (m, 1H, ArH), 6.76 (m, 1H, ArH), 6.57–6.51 (m, 1H, ArH), 5.07 (s, 1H, CH), 4.90 (s, 2H, NH_2), 2.95-2.77 (m, 5H, CH + 2 CH_2), 2.10 (m, 2H, CH_2); ^{13}C NMR δ: 169.5, 143.8, 142.9, 142.3, 128.6, 128.1, 127.1, 126.4, 125.8, 124.1, 121.0, 117.1, 116.8, 55.7; MALDI-TOF-MS *m*/*z*: 301 $[M+H]^+$.

4.1.20. *N*-(2-Nitrophenyl)-4-propylbenzamide (12i). Compound **12i** was prepared according to the general procedure B starting from commercial 4-propylbenzoyl chloride and was obtained after purification by TLC (cyclohexane/AcOEt 7:3). Yield: 33%; yellow solid; R_f (cyclohexane/AcOEt 8:2): 0.50; t_R (TSK gel, method A): 7.58 min, P_{HPLC}: 99%; ^1H NMR δ: 10.70 (s, 1H, NH), 8.02 (m, 1H, ArH), 7.88 (m, 2H, ArH), 7.83–7.72 (m, 2H, ArH), 7.44–7.37 (m, 3H, ArH), 2.64 (t, $J = 7.4$ Hz, 2H, CH_2), 1.64 (m, 2H, CH_2), 0.90 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR δ: 165.8, 147.6, 143.3, 134.6, 132.3, 131.6, 129.2, 128.4, 126.4, 126.0, 125.6, 37.6, 24.5, 14.2; MALDI-TOF-MS *m*/*z*: 285 $[M+H]^+$.

4.1.21. *N*-(2-Nitrophenyl)-2-phenylbutyramide (13i). Compound **13i** was prepared according to the general procedure B starting from commercial 2-phenylbutyryl chloride, but was not purified and directly cyclized.

4.1.22. *N*-(2-Aminophenyl)-3-phenylbutyramide (14i). Compound **14i** was prepared according to the general procedure A starting from 3-phenylbutyric acid and was obtained after purification by trituration in Et_2O. Yield: 88%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (C18 Xterra, method B): 4.95 min, P_{HPLC}: 99%; ^1H NMR δ: 9.10 (s, 1H, NH), 7.33–7.16 (m, 5H, ArH), 7.03 (dd, $J = 1.4$, 7.8 Hz, 1H, ArH), 6.87 (td, $J = 1.5$, 7.9 Hz, 1H, ArH), 6.67 (dd, $J = 1.4$, 8.0 Hz, 1H, ArH), 6.50 (td, $J = 1.4$, 7.7 Hz, 1H, ArH), 4.66 (s, 2H, NH_2), 3.26 (m, 1H, CH), 2.58 (m, 2H, CH_2), 1.26 (d, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR δ: 170.4, 146.9, 142.7, 128.9, 127.4, 126.7, 126.5, 126.1, 123.9, 116.7, 116.4, 44.8, 37.0, 22.4; MALDI-TOF-MS *m*/*z*: 255 $[M+H]^+$.

4.1.23. *N*-(2-Aminophenyl)-2-phenylpropionamide (15i). Compound **15i** was prepared according to the general procedure A starting from 2-phenylpropionic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 72%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (C18 Xterra, method B): 4.42 min, P_{HPLC}: 99%; ^1H NMR δ: 9.21 (s, 1H, NH), 7.35–7.31 (m, 2H, ArH), 7.28–7.22 (m, 2H, ArH), 7.19–7.13 (m, 1H, ArH), 7.06–7.02 (m, 1H, ArH), 6.83–6.78 (m, 1H, ArH), 6.64–6.60 (m, 1H, ArH), 6.47–6.42 (m, 1H, ArH), 4.68 (s, 2H, NH_2), 3.80 (q, $J = 7.0$ Hz, 1H, CH), 1.34 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR δ: 173.1, 143.1, 142.7, 129.2, 128.3, 128.1, 127.5, 126.7, 126.1, 124.1, 117.1, 116.7, 46.2, 19.5; MALDI-TOF-MS *m*/*z*: 241 $[M+H]^+$.

4.1.24. *N*-(2-Aminophenyl)-2-iodobenzamide (16i). To a solution of 2-iodobenzoic acid (6.2 g, 25 mmol, 1 equiv) in 100 mL THF were added a solution of DCC 1 M in CH_2Cl_2 (12.5 mL, 12.5 mmol, 0.5 equiv), DIEA (4.3 mL, 25 mmol, 1 equiv) and *o*-phenylenediamine (1.08 g, 10 mmol, 0.4 equiv). After stirring for 12 h at room temperature, the mixture was filtered and the solvent evaporated. The residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. Compound **16i** was not purified and directly cyclized.

4.1.25. 1-Phenylcyclopentanecarboxylic acid (2-aminophenyl) amide (17i). Compound **17i** was prepared according to the general procedure A starting from 1-

phenyl-1-cyclopentanecarboxylic acid, but was not purified and directly cyclized.

4.1.26. *N*-(2-Aminophenyl)-2-cyclopentyl-2-phenylacetamide (18i). Compound **18i** was prepared according to the general procedure A starting from α-phenylcyclopentylacetic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 56%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.55; t_R (TSK gel, method B): 6.19 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.38 (s, 1H, NH), 7.44 (m, 2H, ArH), 7.32 (m, 3H, ArH), 7.24 (m, 1H, ArH), 7.09 (m, 1H, ArH), 7.88 (m, 1H, ArH), 6.69 (m, 1H, ArH), 6.52 (m, 1H, ArH), 4.70 (s, 2H, NH_2), 3.44 (d, J = 11.0 Hz, 1H, CH), 2.57 (m, 1H, CH cyclopentyl), 1.64–1.33 (m, 8H, CH_2 cyclopentyl); ^{13}C NMR δ: 172.5, 142.6, 141.4, 129.1, 128.9, 127.5, 126.7, 125.9, 124.1, 117.1, 116.8, 58.4, 43.5, 31.8, 31.1, 25.5, 25.2; MALDI-TOF-MS m/z: 295 $[M+H]^+$.

4.1.27. 2-Phenyloctanoic acid (2-aminophenyl)amide (19i). To a solution of methylphenylacetate (500 mg, 3.33 mmol, 1 equiv) in 10 mL THF were added NaH (60% suspension, 200 mg, 4.99 mmol, 1.5 equiv), washed previously with hexane, and 1-bromohexane (560 μL, 3.99 mmol, 1.2 equiv). After stirring the mixture for 12 h at room temperature, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous HCl 1 M and with water, dried over $MgSO_4$ and concentrated. The ester was diluted with 10 mL of a NaOH 1 M/MeOH 1:1 mixture. Following reflux for 4 h, the mixture was concentrated, acidified with aqueous HCl 1 M, extracted with CH_2Cl_2, the organic layer dried over $MgSO_4$ and concentrated to afford compound **19a**. To a solution of the crude acid **19a** (3.3 mmol, 1 equiv) in 15 mL of CH_2Cl_2 were added DIEA (1.4 mL, 8.25 mmol, 2.5 equiv), PyBrop (2 g, 4.3 mmol, 1.3 equiv) and *o*-phenylenediamine (464 mg, 4.3 mmol, 1.3 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated to afford compound **19i**, which was not purified and directly cyclized.

4.1.28. 2-Phenylcyclopropanecarboxylic acid (2-aminophenyl)amide (20i). Compound **20i** was prepared according to the general procedure A using *trans*-2-phenylcyclopropane-1-carboxylic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 54%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.55; t_R (TSK gel, method A): 4.31 min, P_{HPLC}: 95%; ^{1}H NMR δ: 9.48 (s, 1H, NH), 7.32–7.16 (m, 6H, 5H phenyl + 1H ArH), 6.88 (td, J = 1.4, 7.9 Hz, 1H, ArH), 6.71 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 6.53 (td, J = 1.3, 7.7 Hz, 1H, ArH), 4.84 (s, 2H, NH_2), 2.35 (m, 1H, CH), 2.15 (m, 1H, CH), 1.44 (m, 1H, CH_2), 1.31 (m, 1H, CH_2); ^{13}C NMR δ: 170.7, 162.7, 142.3, 141.9, 129.2, 126.9, 126.8, 126.4, 125.5, 124.5, 117.1, 116.8, 27.0, 25.4, 16.7; MALDI-TOF-MS m/z: 253 $[M+H]^+$.

4.1.29. 2-(2-Aminophenylcarbamoyl)piperidine-1-carboxylic acid *tert*-butyl ester (22i). Compound **22i** was prepared according to the general procedure E starting from *N*-Boc-pipecolinic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 60%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.70; t_R (TSK gel, method A): 4.75 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.24 (s, 1H, NH), 7.10 (d, J = 7.9 Hz, 1H, ArH), 6.92 (td, J = 1.4, 7.9 Hz, 1H, ArH), 6.74 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 6.56 (td, J = 1.3, 7.7 Hz, 1H, ArH), 4.70 (s, 2H, NH_2), 3.80 (d, J = 12.5 Hz, 1H, CH), 2.13 (d, J = 13.7 Hz, 1H, CH_2), 1.74–1.58 (m, 3H, CH_2), 1.38 (m, 13H, CH_2 + CH_3); ^{13}C NMR δ: 126.9, 126.4, 117.4, 117.0, 41.6, 28.9, 28.4, 25.1, 20.5; MALDI-TOF-MS m/z: 320 $[M+H]^+$ and 220 $[M-Boc]$.

4.1.30. Biphenyl-2-carboxylic acid (2-aminophenyl)amide (23i). Compound **23i** was prepared according to the general procedure A starting from 2-biphenylcarboxylic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 47%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.50; t_R (C18 Xterra, method B): 5.35 min, P_{HPLC}: 95%; ^{1}H NMR δ: 7.63–7.31 (m, 9H, ArH), 7.99 (m, 1H, ArH), 6.88 (m, 1H, ArH), 6.67 (m, 1H, ArH), 6.50 (m, 1H, ArH), 4.66 (s, 2H, NH_2); ^{13}C NMR δ: 168.9, 143.3, 141.1, 140.1, 138.1, 130.7, 130.4, 129.3, 129.2, 128.8, 128.2, 128.0, 127.1, 126.5, 123.8, 116.8, 116.6; MALDI-TOF-MS m/z: 289 $[M+H]^+$.

4.1.31. Biphenyl-4-carboxylic acid (2-nitrophenyl)amide (24i). Compound **24i** was prepared according to the general procedure B starting from commercial 4-biphenylcarbonyl chloride, but was not purified and directly cyclized.

4.1.32. Biphenyl-3-carboxylic acid (2-aminophenyl)amide (25i). Compound **25i** was prepared according to the general procedure E starting from biphenyl-3-carboxylic acid **25a**, synthesized according to the general procedure C and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 73%; white solid; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.60; t_R (TSK gel, method A): 5.16 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.88 (s, 1H, NH), 8.29 (s, 1H, ArH biphenyl), 7.97 (d, J = 7.7 Hz, 1H, ArH biphenyl), 7.88 (d, J = 7.7 Hz, 1H, ArH biphenyl), 7.79 (m, 2H, ArH biphenyl), 7.61 (t, J = 7.7 Hz, 1H, ArH biphenyl), 7.51 (m, 2H, ArH biphenyl), 7.41 (m, 1H, ArH biphenyl), 7.20 (dd, J = 1.1, 7.8 Hz, 1H, ArH), 7.03 (td, J = 1.5, 7.4 Hz, 1H, ArH), 6.87 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 6.70 (td, J = 1.0, 7.6 Hz, 1H, ArH), 4.80 (s, 2H, NH_2); ^{13}C NMR δ: 140.8, 140.2, 135.8, 130.2, 129.6, 128.4, 127.6, 127.5, 127.3, 126.6, 118.1, 117.5; MALDI-TOF-MS m/z: 289 $[M+H]^+$.

4.1.33. *N*-(2-Aminophenyl)-2-furan-2-ylbenzamide (26i). Compound **26i** was prepared according to the general procedure E starting from 2-furan-2-ylbenzoic acid **26a**, synthesized according to the general procedure C. Compound **26i** was not isolated and directly cyclized.

4.1.34. 4′-Fluorobiphenyl-2-carboxylic acid (2-aminophenyl)amide (27i). Compound **27i** was prepared according to the general procedure E starting from 4′-fluorobiphenyl-2-carboxylic acid **27a**, synthesized according to the general procedure C. Compound **27i** was not isolated and directly cyclized.

4.1.35. *N*-(2-Aminophenyl)-2-thiophen-2-ylbenzamide (28i). Compound **28i** was prepared according to the general procedure E starting from 2-thiophen-2-ylbenzoic acid **28a**, synthesized according to the general procedure C, and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 86%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.60; t_R (TSK gel, method A): 4.48 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.71 (s, 1H, NH), 7.62–7.44 (m, 5H, 4H ArH phenyl + 1H ArH thiophenyl), 7.28 (dd, J = 1.3, 3.6 Hz, 1H, ArH thiophenyl), 7.20 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 7.10 (dd, J = 3.6, 5.2 Hz, 1H, ArH thiophenyl), 6.97 (td, J = 1.4, 8.1 Hz, 1H, ArH), 6.80 (d, J = 7.9 Hz, 1H, ArH), 6.65 (t, J = 7.6 Hz, 1H, ArH), 5.35 (s, 2H, NH_2); ^{13}C NMR δ: 173.1, 168.6, 168.5, 146.3, 141.8, 137.5, 132.0, 130.3, 128.7, 128.4, 128.2, 127.4, 127.0, 126.9, 126.2, 125.8, 118.5, 117.7; MALDI-TOF-MS m/z: 295 $[M+H]^+$.

4.1.36. 4′-Methylbiphenyl-2-carboxylic acid (2-aminophenyl)amide (29i). Compound **29i** was prepared according to the general procedure E starting from 4′-methylbiphenyl-2-carboxylic acid **29a**, synthesized according to the general procedure C, and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 63%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.50; t_R (TSK gel, method A): 5.03 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.43 (s, 1H, NH), 7.61 (dd, J = 1.0, 7.1 Hz, 1H, ArH biphenyl), 7.52 (dd, J = 1.5, 7.4 Hz, 1H, ArH biphenyl), 7.47–7.41 (m, 2H, ArH biphenyl), 7.39 (d, J = 8.0 Hz, 2H, ArH biphenyl), 7.22 (d, J = 7.9 Hz, 2H, ArH biphenyl), 7.05 (dd, J = 1.4, 7.8 Hz, 1 H, ArH), 6.90 (td, J = 1.5, 8.0 Hz, 1H, ArH), 6.69 (dd, J = 1.4, 8.0 Hz, 1H, ArH), 6.52 (td, J = 1.4, 7.6 Hz, 1H, ArH), 4.68 (s, 2H, NH_2), 2.33 (s, 3H, CH_3); ^{13}C NMR δ: 168.7, 142.9, 139.8, 137.9, 137.7, 137.2, 130.4, 130.2, 129.5, 128.9, 128.6, 127.5, 126.8, 126.3, 123.6, 116.6, 116.4, 21,3; MALDI-TOF-MS m/z: 303 $[M+H]^+$.

4.1.37. *N*-(2-Aminophenyl)-2-phenethylbenzamide (30i). Compound **30i** was prepared according to the general procedure A starting from 2-bibenzylcarboxylic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 98%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.75; t_R (TSK gel, method B): 6.67 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.55 (s, 1H, NH), 7.44 (m, 1H, ArH bibenzyl), 7.31–7.03 (m, 9H, 1 ArH + 8 ArH bibenzyl), 6.85 (t, J = 8.5 Hz, 1H, ArH), 6.67 (dd, J = 1.3, 8.0 Hz, 1H, ArH), 6.49 (td, J = 1.3, 7.8 Hz, 1H, ArH), 4.81 (s, 2H, NH_2), 2.92 (m, 2H, 1H CH_2 + 1H CH_2), 2.77 (m, 2H, 1H CH_2 + 1H CH_2); ^{13}C NMR δ: 168.9, 143.3, 142.5, 140.3, 137.8, 130.7, 130.4, 129.1, 128.5, 127.1, 126.7, 126.3, 124.2, 117.2, 117.1, 38.2, 36.0; MALDI-TOF-MS m/z: 317 $[M+H]^+$.

4.1.38. *N*-(2-Aminophenyl)-2-benzylbenzamide (31i). Compound **31i** was prepared according to the general procedure A starting from α-phenyl-*o*-toluic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 62%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.60; t_R (TSK gel, method B): 6.08 min, P_{HPLC}: 95%; ^{1}H NMR δ: 9.57 (s, 1H, NH), 7.50 (m, 1H, ArH phenyl-*o*-toluic), 7.38–7.07 (m, 9H, 1H ArH + 8H ArH phenyl-*o*-toluic), 6.89 (t, J = 8.0 Hz, 1H, ArH), 6.69 (dd, J = 1.2, 8.0 Hz, 1H, ArH), 6.51 (td, J = 1.3, 7.7 Hz, 1H, ArH), 4.85 (s, 2H, NH_2), 4.10 (s, 2H, CH_2); ^{13}C NMR δ: 168.9, 143.4, 141.8, 139.8, 132.5, 132.2, 131.2, 130.5, 129.7, 129.5, 129.2, 128.6, 127.2, 126.9, 126.8, 126.6, 124.0, 117.1, 116.9, 38.7; MALDI-TOF-MS m/z: 303 $[M+H]^+$.

4.1.39. *N*-(2-Aminophenyl)-3-bromobenzamide (32i). Compound **32i** was prepared according to the general procedure A starting from 3-bromobenzoic acid and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 46%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.70; t_R (TSK gel, method A): 4.57 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.74 (s, 1H, NH), 8.17 (s, 1H, ArH phenyl), 7.97 (d, J = 7.8 Hz, 1H, ArH phenyl), 7.77 (d, J = 7.9 Hz, 1H, ArH phenyl), 7.48 (t, J = 7.8 Hz, 1H, ArH phenyl), 7.13 (dd, J = 1.0, 7.7 Hz, 1H, ArH), 6.97 (td, J = 1.5, 7.9 Hz, 1H, ArH), 6.77 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 6.58 (td, J = 1.3, 7.6 Hz, 1H, ArH), 4.94 (s, 2H, NH_2); ^{13}C NMR δ: 144.2, 137.7, 134.9, 131.3, 127.7, 127.6, 123.6, 116.9, 116.8; MALDI-TOF-MS m/z: 292 $[M+H]^+$.

4.1.40. *N*-(2-Aminophenyl)-2-phenyl-2-piperidin-1-ylacetamide (33i). Compound **33i** was prepared according to the general procedure E starting from phenylpiperidin-1-ylacetic acid **33a**, synthesized according to the general procedure D, and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1). Yield: 90%; white solid; R_f (CH_2Cl_2/MeOH/NH_4OH 9.7:0.3:0.1): 0.65; t_R (TSK gel, method A): 3.59 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.49 (s, 1H, NH), 7.48 (m, 2H, ArH phenyl), 7.37–7.26 (m, 3H, ArH phenyl), 7.17 (m, 1H, ArH), 6.93–6.87 (m, 1H, ArH), 6.73 (m, 1H, ArH), 6.58–6.53 (m, 1H, ArH), 4.65 (s, 2H, NH_2), 4.03 (s, 1H, CH), 2.37 (m, 4H, 2 CH_2), 1.54 (m, 4H, 2 CH_2), 1.23 (m, 2H, CH_2); ^{13}C NMR δ: 170.3, 142.5, 138.1, 129.6, 129.0, 128.5, 126.7, 125.7, 124.5, 117.5, 117.2, 76.0, 52.8, 26.4, 24.9; MALDI-TOF-MS m/z: 310 $[M+H]^+$.

4.1.41. *N*-(2-Aminophenyl)-2-morpholin-4-yl-2-phenylacetamide (34i). Compound **34i** was prepared according to the general procedure E starting from morpholin-4-ylphenylacetic acid **34a**, synthesized according to the general procedure D, but was not isolated.

4.1.42. *N*-(2-Aminophenyl)-2-azepan-1-yl-2-phenylacetamide (35i). Compound **35i** was prepared according to the general procedure E starting from azepan-1-ylphenylacetic acid **35a**, synthesized according to the general procedure D, and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.9:0.1:0.1). Yield: 44%; white solid; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.50; t_R (TSK gel, method A): 3.78 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.44 (s, 1H, NH), 7.50 (m, 2H, ArH phenyl), 7.41–7.31 (m, 3H, ArH phenyl), 7.18 (d, J = 7.8 Hz, 1H, ArH), 6.90 (t, J = 7.3 Hz, 1H, ArH), 6.72 (d, J = 8.0 Hz, 1H, ArH), 6.55 (t, J = 7.4 Hz, 1H, ArH), 4.66 (s, 2H, NH_2), 4.38 (s, 1H, CH), 2.65 (m, 4H, 2 CH_2), 1.58 (m, 8H, 4 CH_2); ^{13}C NMR δ: 170.7, 142.3, 139.1, 129.2, 128.9, 128.7, 128.1, 126.5, 126.1, 125.5, 124.2, 117.2, 116.9, 74.4, 53.3, 29.1, 26.9; MALDI-TOF-MS m/z: 324 $[M+H]^+$.

4.1.43. {1-[(2-Aminophenylcarbamoyl)phenylmethyl]pyrrolidin-3-yl}carbamic acid *tert*-butyl ester (36i). Compound **36i** was prepared according to the general procedure E starting from (3-*tert*-butoxycarbonylaminopyrrolidin-1-yl)phenylacetic acid **36a**, synthesized according to the general procedure D, and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 54%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.35; t_R (TSK gel, method A): 4.50 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.56 (s, 1H, NH), 7.57 (m, 2H, ArH), 7.43–7.34 (m, 3H, ArH), 7.14-7.06 (m, 2H, ArH + NH), 6.98–6.93 (m, 1H, ArH), 6.76 (m, 1H, ArH), 6.62–6.56 (m, 1H, ArH), 4.63 (s, 2H, NH_2), 4.03 (m, 2H, 2 CH), 2.83–2.53 (m, 2H, CH_2), 2.49–2.32 (m, 2H, CH_2), 2.11 (m, 1H, CH_2), 1.61 (m, 1H, CH_2), 1.14 (m, 9H, 3 CH_3); ^{13}C NMR δ: 143.3, 139.2, 129.1, 128.7, 127.2, 126.7, 125.7, 123.9, 117.4, 117.1, 74.8, 58.7, 51.5, 51.1, 31.8, 29.1; MALDI-TOF-MS *m*/*z*: 411 $[M+H]^+$.

4.1.44. *N*-(2-Aminophenyl)-2-(4-hydroxypiperidin-1-yl)-2-phenylacetamide (37i). To a solution of (4-hydroxypiperidin-1-yl)phenylacetic acid **37a** (430 mg, 2.18 mmol, 1 equiv), synthesized according to the general procedure D, in 10 mL CH_2Cl_2 were added EDC (627 mg, 3.27 mmol, 1.5 equiv), HOBt (441 mg, 3.27 mmol, 1.5 equiv), DIEA (570 μL, 3.27 mmol, 1.5 equiv), and then *o*-phenylenediamine (588 mg, 5.45 mmol, 2.5 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2/MeOH 9.6:0.4) to afford compound **37i**. Yield: 31%; white solid; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.35; t_R (TSK gel, method A): 3.26 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.49 (s, 1H, NH), 7.48–7.45 (m, 2H, ArH phenyl), 7.37–7.25 (m, 3H, ArH phenyl), 7.17 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 6.89 (td, J = 1.5, 7.9 Hz, 1H, ArH), 6.72 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 6.55 (td, J = 1.4, 7.7 Hz, 1H, ArH), 4.64 (s, 2H, NH_2), 4.53 (d, J = 3.4 Hz, 1H, OH), 4.01 (s, 1H, CH), 3.45 (m, 1H, CH), 2.77 (m, 1H, CH_2), 2.59 (m, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.01 (m, 1H, CH_2), 1.70 (m, 2H, CH_2), 1.44 (m, 2H, CH_2); ^{13}C NMR δ: 170.1, 142.3, 138.1, 129.3, 129.0, 128.8, 128.3, 126.5, 125.5, 124.2, 117.3, 117.0, 75.1, 66.7, 49.7, 49.1, 34.9; MALDI-TOF-MS *m*/*z*: 326 $[M+H]^+$.

4.1.45. *N*-(2-Aminophenyl)-2-cyclohexylamino-2-phenylacetamide (38i). Compound **38i** was prepared according to the general procedure E starting from cyclohexylaminophenylacetic acid **38a**, synthesized according to the general procedure D, and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1). Yield: 82%; white solid; R_f (CH_2Cl_2/MeOH/NH_4OH 9.7:0.3:0.1): 0.70; t_R (TSK gel, method A): 3.92 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.53 (s, 1H, NH), 7.49 (m, 2H, ArH phenyl), 7.37–7.24 (m, 3H, ArH phenyl), 7.19 (dd, J = 1.4, 7.8 Hz, 1H, ArH), 6.90 (td, J = 1.4, 8.0 Hz, 1H, ArH), 6.72 (dd, J = 1.3, 7.9 Hz, 1H, ArH), 6.55 (td, J = 1.2, 7.2 Hz, 1H, ArH), 4.72 (s, 2H, NH_2), 4.54 (s, 1H, CH), 2.38 (m, 1H, CH), 1.89–1.13 (m, 10H, CH_2 cyclohexyl); ^{13}C NMR δ: 171.9, 142.0, 128.9, 128.7, 126.4, 125.0, 117.2, 116.8, 63.6, 54.7, 33.5, 33.4, 26.4, 24.9; MALDI-TOF-MS *m*/*z*: 324 $[M+H]^+$.

4.1.46. 1-Cyclohexyl-3-(2-nitrophenyl)-1-phenylthiourea (39i). To a solution of 2-nitrophenylisothiocyanate (500 mg, 2.77 mmol, 1 equiv) in 10 mL THF was added *N*-cyclohexylaniline (969 mg, 5.54 mmol, 2 equiv). After stirring the mixture for 12 h at room temperature, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (cyclohexane/AcOEt 9:1) to afford compound **39i**. Yield: 89%; white solid; R_f (CH_2Cl_2): 0.50; t_R (TSK gel, method A): 7.71 min, P_{HPLC}: 99%; ^{1}H NMR δ: 8.65 (s, 1H, NH thiourea), 7.95 (dd, J = 1.5, 8.0 Hz, 1H, ArH nitrophenyl), 7.91 (dd, J = 1.2, 8.2 Hz, 1H, ArH nitrophenyl), 7.75 (td, J = 1.5, 7.5 Hz, 1H, ArH nitrophenyl), 7.56–7.49 (m, 3H, ArH), 7.30 (td, J = 1.4, 8.5 Hz, 1H, ArH nitrophenyl), 7.27 (m, 2H, ArH), 5.23 (m, 1H, CH), 1.95 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.52 (m, 1H, CH_2), 1.33-1.28 (m, 2H, CH_2), 0.95-0.87 (m, 3H, CH_2); ^{13}C NMR δ: 180.9, 143.9, 138.2, 135.5, 133.9, 130.5, 130.4, 129.9, 129.7, 129.5, 126.3, 125.1, 60.1, 31.7, 25.9, 25.5; MALDI-TOF-MS *m*/*z*: 356 $[M+H]^+$.

4.1.47. 1-(2-Nitrophenyl)-3-(2-piperidin-1-ylphenyl)thiourea (40i). To a solution of 2-nitrophenylisothiocyanate (500 mg, 2.77 mmol, 1 equiv) in 10 mL THF was added 2-(1-piperidino)aniline (586 mg, 3.33 mmol, 1.2 equiv). After stirring the mixture for 12 h at room temperature, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (cyclohexane/AcOEt 9:1) to afford compound **40i**. Yield: 81%; yellow solid; R_f (CH_2Cl_2): 0.80; t_R (TSK gel, method A): 4.97 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.24 (s, 1H, NH thiourea), 9.50 (s, 1H, NH thiourea), 8.01 (d, J = 8.2 Hz, 1H, ArH nitrophenyl), 7.90 (d, J = 8.1 Hz, 1H, ArH nitrophenyl), 7.75 (m, 1H, ArH), 7.73 (t, J = 7.3 Hz, 1H, ArH nitrophenyl), 7.43 (t, J = 7.3 Hz, 1H, ArH nitrophenyl), 7.16–7.04 (m, 3H, ArH), 2.81 (t, J = 4.7 Hz, 4H, 2 CH_2), 1.65 (m, 4H, 2 CH_2), 1.51 (m, 2H, CH_2); ^{13}C NMR δ: 180.5, 147.5, 144.6, 134.2, 133.8, 132.7, 129.9, 126.9, 126.7, 126.6, 125.4, 123.1, 120.1, 53.0, 26.5, 24.4; MALDI-TOF-MS *m*/*z*: 357 $[M+H]^+$.

4.1.48. *N*-(2-Aminobenzyl)-2-cyclohexyl-2-phenylacetamide (42i). To a solution of cyclohexylphenylacetic acid (1.78 g, 8.17 mmol, 1 equiv) in 32 mL DMF were added a solution of DCC 1 M in CH_2Cl_2 (4.09 mL, 4.09 mmol, 0.5 equiv), DIEA (1.56 mL, 8.99 mmol, 1.1 equiv) and 2-aminobenzylamine (400 mg, 3.27 mmol, 0.4 equiv). After stirring for 12 h at room temperature, the mixture was filtered and the solvent evaporated. The residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2/MeOH 9.8:0.2) to afford compound **42i**. Yield: 79%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.50; t_R (TSK gel, method B): 6.72 min, P_{HPLC}: 99%; ^{1}H NMR δ: 8.42 (t, J = 5.9 Hz, 1H, NH), 7.34–7.20 (m, 5H, ArH phenyl), 6.91 (td, J = 1.5, 7.0 Hz, 1H, ArH), 6.42 (td, J = 0.9, 7.4 Hz, 1H, ArH), 5.01 (s, 2H, NH_2), 4.17 (dd, J = 6.6, 15.0 Hz, 1H, CH_2), 3.95

(dd, J = 5.5, 15.0 Hz, 1H, CH_2), 3.14 (d, J = 10.7 Hz, 1H, CH), 1.96 (m, 1H, CH), 1.79–1.56 (m, 4H, H cyclohexyl), 1.23–0.92 (m, 5H, H cyclohexyl), 0.70 (m, 1H, H cyclohexyl); ^{13}C NMR δ: 173.7, 146.9, 140.6, 129.6, 129.1, 128.9, 128.6, 127.4, 116.4, 115.3, 59.2, 40.9, 39.9, 32.1, 30.1, 28.5, 26.8, 26.4, 26.3; MALDI-TOF-MS m/z: 323 $[M+H]^+$.

4.1.49. *N*-(2-Amino-6-nitrophenyl)-2-cyclohexyl-2-phenylacetamide (44i). To a solution of cyclohexylphenylacetic acid (713 mg, 3.27 mmol, 1 equiv) in 15 mL of dry CH_2Cl_2 was added thionyl chloride (600 μL, 8.17 mmol, 2.5 equiv). After stirring the mixture for 1 h at room temperature, the solvent and the excess of thionyl chloride were evaporated. To a solution of this residue in 10 mL of dry CH_2Cl_2 were added DIEA (835 μL, 4.9 mmol, 1.5 equiv) and 3-nitro-*o*-phenylenediamine (200 mg, 1.30 mmol, 0.4 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2) to afford compound **44i**. Yield: 96%; yellow solid; R_f (CH_2Cl_2): 0.35; t_R (TSK gel, method B): 8.39 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.46 (s, 1H, NH), 7.78 (d, J = 8.7 Hz, 1H, ArH), 7.41 (d, J = 7.6 Hz, 1H, ArH), 7.34-7.16 (m, 5H, ArH), 6.71 (s, 2H, NH_2), 6.56 (t, J = 7.6 Hz, 1H, ArH), 3.37 (d, J = 10.6 Hz, 1H, CH), 1.92 (m, 1H, CH), 1.78–1.50 (m, 4H, H cyclohexyl), 1.22–1.00 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 173.2, 140.9, 139.9, 132.8, 129.1, 127.7, 126.7, 123.6, 115.5, 59.2, 32.1, 31.0, 26.8, 26.3, 26.2; MALDI-TOF-MS m/z: not observed.

4.1.50. *N*-(2-Amino-3-methylphenyl)-2-cyclohexyl-2-phenylacetamide (48i). Compound **48i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 2,3-diaminotoluene and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 45%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.65; t_R (TSK gel, method B): 7.76 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.33 (s, 1H, NH), 7.39 (m, 2H, ArH phenyl), 7.30 (m, 2H, ArH phenyl), 7.22 (m, 1H, ArH phenyl), 6.90 (d, J = 6.8 Hz, 1H, ArH), 6.79 (d, J = 6.8 Hz, 1H, ArH), 6.43 (t, J = 7.6 Hz, 1H, ArH), 4.37 (s, 2H, NH_2), 3.46 (d, J = 16.8 Hz, 1H, CH), 2.04 (s, 3H, CH_3), 2.02 (m, 1H, CH), 1.86 (m, 1H, H cyclohexyl), 1.82 (m, 1H, H cyclohexyl), 1.57 (m, 2H, H cyclohexyl), 1.25–1.04 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 172.5, 162.7, 140.7, 140.4, 129.1, 128.0, 127.5, 124.3, 123.6, 123.5, 116.6, 59.2, 34.2, 32.1, 26.8, 26.3, 25.3, 18.6; MALDI-TOF-MS m/z: 323 $[M+H]^+$.

4.1.51. *N*-(5-Aminopyrimidin-4-yl)-2-cyclohexyl-2-phenylacetamide (49i). To a solution of cyclohexylphenylacetic acid (450 mg, 2.04 mmol, 1 equiv) in 10 mL of dry CH_2Cl_2 was added thionyl chloride (370 μL, 5.1 mmol, 2.5 equiv). After stirring the mixture for 1 h at room temperature, the solvent and the excess of thionyl chloride were evaporated. To a solution of this residue in 10 mL of dry CH_2Cl_2 were added DIEA (530 μL, 3.06 mmol, 1.5 equiv) and 4,5-diaminopyrimidine (150 mg, 1.36 mmol, 0.67 equiv). After stirring the mixture for 12 h at room temperature, the product was precipitated, filtered and washed with Et_2O to afford compound **49i**. Yield: 88%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (TSK gel, method B): 6.72 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.70 (s, 1H, NH), 8.27 (s, 1H, ArH), 8.22 (s, 1H, ArH), 7.40–7.22 (m, 5H, ArH), 5.03 (s, 2H, NH_2), 3.60 (d, J = 10.7 Hz, 1H, CH), 2.02 (m, 1H, CH), 1.84 (m, 1H, H cyclohexyl), 1.70 (m, 1H, H cyclohexyl), 1.26 (m, 2H, H cyclohexyl), 1.27–1.05 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 173.3, 147.4, 145.9, 144.4, 139.3, 135.4, 129.0, 128.9, 127.6, 58.4, 40.5, 31.9, 30.6, 26.5, 26.0, 25.9; MALDI-TOF-MS m/z: 311 $[M+H]^+$.

4.1.52. *N*-(3-Amino-pyridin-2-yl)-2-cyclohexyl-2-phenylacetamide (50i). To a solution of cyclohexylphenylacetic acid (1.25 g, 5.75 mmol, 1 equiv) in 30 mL of dry CH_2Cl_2 was added thionyl chloride (2.1 mL, 28.75 mmol, 5 equiv). After stirring the mixture for 30 min at room temperature, the solvent and the excess thionyl chloride were evaporated. To a solution of this residue in 10 mL of dry CH_2Cl_2 were added DIEA (1.5 mL, 8.62 mmol, 1.5 equiv) and 2,3-diaminopyridine (250 mg, 2.3 mmol, 0.4 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. Compound **50i** was not purified and directly cyclized.

4.1.53. *N*-(2-Amino-4-methylphenyl)-2-cyclohexyl-2-phenylacetamide and *N*-(2-amino-5-methylphenyl)-2-cyclohexyl-2-phenylacetamide (51i). Compound **51i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 3,4-diaminotoluene and was obtained in melange after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 63%; brown solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.65; t_R (TSK gel, method B): 6.96 min (33%)–7.16 min (67%), P_{HPLC}: 99%; ^{1}H NMR δ: 9.38 (s, 0.33H, NH), 9.34 (s, 0.67H, NH), 7.42 (m, 2H, ArH phenyl), 7.35–7.30 (m, 2H, ArH phenyl), 7.27–7.20 (m, 1H, ArH phenyl), 6.98 (s, 0.33H, ArH), 6.95 (s, 0.67H, ArH), 6.70 (m, 0.33H, ArH), 6.62 (m, 0.33H, ArH), 6.52 (m, 0.67H, ArH), 6.36 (m, 0.67H, ArH), 4.62 (s, 2H, NH_2), 3.40 (m, 1H, CH), 2.15 (s, 0.67× 3H, CH_3), 2.12 (s, 0.33× 3H, CH_3), 2.02 (m, 1H, CH), 1.84 (m, 1H, H cyclohexyl), 1.73 (m, 1H, H cyclohexyl), 1.60 (m, 2H, H cyclohexyl), 1.27–1.09 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 172.2, 142.3, 140.5, 139.7, 135.7, 129.1, 127.5, 127.2, 126.1, 125.9, 124.3, 121.8, 117.9, 117.3, 117.1, 59.2, 40.9, 32.1, 31.0, 26.9, 26.4, 26.3, 21.6, 20.9; MALDI-TOF-MS m/z: 323 $[M+H]^+$.

4.1.54. *N*-(2-Amino-4-methoxyphenyl)-2-cyclohexyl-2-phenylacetamide (52i). Compound **52i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 4-methoxy-*o*-phenylenediamine.2HCl and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 50%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (TSK gel, method B): 7.27 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.26 (s, 1H, NH), 7.40–7.37 (m, 2H, ArH phenyl), 7.33–7.30 (m, 2H, ArH phenyl), 7.24–7.20 (m, 1H, ArH phenyl), 6.90 (d, J = 8.6 Hz, 1H, ArH), 6.25 (d, J = 2.7 Hz, 1H,

ArH), 6.10 (dd, J = 2.8, 8.6 Hz, 1H, ArH), 4.66 (s, 2H, NH_2), 3.62 (s, 3H, CH_3), 3.34 (m, 1H, CH), 1.99 (m, 1H, CH), 1.84 (m, 1H, H cyclohexyl), 1.72 (m, 1H, H cyclohexyl), 1.58 (m, 2H, H cyclohexyl), 1.23–1.05 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 172.1, 158.3, 143.9, 140.2, 128.9, 128.8, 127.2, 127.0, 125.3, 117.3, 102.5, 101.4, 58.9, 55.4, 40.5, 30.8, 26.6, 26.0; MALDI-TOF-MS m/z: 339 $[M+H]^+$.

4.1.55. 2-Cyclohexyl-*N*-(4-fluoro-2-nitrophenyl)-2-phenylacetamide (53i). Compound **53i** was prepared according to the general procedure H starting from 3-fluoro-2-nitroaniline and was obtained after purification by TLC (cyclohexane/AcOEt 9:1). Yield: 70%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.40; t_R (TSK gel, method B): 9.95 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.42 (s, 1H, NH), 7.88-7.84 (m, 1H, ArH), 7.57–7.51 (m, 2H, ArH), 7.36–7.21 (m, 5H, ArH), 3.37 (d, J = 10.6 Hz, 1H, CH), 2.03 (m, 1H, CH), 1.82 (m, 1H, H cyclohexyl), 1.64 (m, 1H, H cyclohexyl), 1.56 (m, 5H, H cyclohexyl), 1.37–0.70 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 172.1, 160.0, 156.8, 138.9, 128.9, 128.8, 128.2, 128.1, 127.5, 121.7, 121.4, 112.8, 58.9, 40.9, 31.7, 30.7, 26.5, 26.0, 25.9; MALDI-TOF-MS m/z: 357 $[M+H]^+$.

4.1.56. *N*-(2-Amino-4-chlorophenyl)-2-cyclohexyl-2-phenylacetamide and *N*-(2-amino-5-chlorophenyl)-2-cyclohexyl-2-phenylacetamide (54i). Compound **54i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 4-chloro-*o*-phenylenediamine and was obtained in melange after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 48%; white solid; R_f (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1): 0.55; t_R (TSK gel, method A): 6.79 min (25%)–6.92 min (75%), P_{HPLC}: 99%; ^{1}H NMR δ: 9.36 (s, 1H, NH), 7.40–7.20 (m, 5H, ArH phenyl + 0.25H, ArH), 7.17 (d, J = 8.5 Hz, 0.75H, ArH), 6.89 (dd, J = 2.4, 8.5 Hz, 0.25H, ArH), 6.73 (d, J = 2.4 Hz, 0.75H, ArH), 6.68 (d, J = 8.5 Hz, 0.25H, ArH), 6.51 (dd, J = 2.4, 8.5 Hz, 0.75H, ArH), 5.01 (s, 0.75× 2H, NH_2), 4.94 (s, 0.25× 2H, NH_2), 3.39 (d, J = 10.6 Hz, 0.25H, CH), 3.37 (d, J = 10.7 Hz, 0.75H, CH), 2.02 (m, 1H, CH), 1.80-1.07 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 172.3, 143.6, 139.9, 130.1, 128.9, 127.4, 126.8, 124.2, 117.4, 116.1, 115.4, 59.0, 40.4, 31.9, 30.8, 26.6, 26.0; MALDI-TOF-MS m/z: 343 $[M+H]^+$.

4.1.57. *N*-(2-Amino-5-trifluoromethylphenyl)-2-cyclohexyl-2-phenylacetamide (55i). Compound **55i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 4-trifluoromethyl-*o*-phenylenediamine and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 63%; orange solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.75; t_R (TSK gel, method B): 8.82 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.39 (s, 1H, NH), 7.64 (m, 1H, ArH), 7.42 (m, 2H, ArH phenyl), 7.32 (m, 2H, ArH phenyl), 7.25 (m, 1H, ArH phenyl), 7.18 (m, 1H, ArH), 6.80 (m, 1H, ArH), 5.48 (s, 2H, NH_2), 3.42 (d, J = 10.7 Hz, 1H, CH), 2.02 (m, 1H, CH), 1.79–1.58 (m, 5H, H cyclohexyl), 1.27–1.09 (m, 5H, H cyclohexyl); ^{13}C NMR δ: 172.8, 162.7, 145.1, 140.0, 129.5, 129.1, 128.8, 127.7, 123.3, 121.8, 115.9, 59.3, 41.2, 32.1, 31.0, 26.8, 26.3, 26.2; MALDI-TOF-MS m/z: 377 $[M+H]^+$.

4.1.58. 4-Amino-3-(2-cyclohexyl-2-phenylacetylamino)benzoic acid methyl ester (56i). Compound **56i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and methyl-3,4-diaminobenzoate and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 67%; white solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.45; t_R (TSK gel, method B): 8.17 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.36 (s, 1H, NH), 7.86 (d, J = 2.0 Hz, 1H, ArH), 7.50 (dd, J = 2.0, 8.4 Hz, 1H, ArH), 7.39 (m, 2H, ArH phenyl), 7.33 (m, 2H, ArH phenyl), 7.24 (m, 1H, ArH phenyl), 6.71 (d, J = 8.4 Hz, 1H, ArH), 5.57 (s, 2H, NH_2), 3.73 (s, 3H, OCH_3), 3.40 (d, J = 10.7 Hz, 1H, CH), 2.02 (m, 1H, CH), 1.85-1.71 (m, 2H, H cyclohexyl), 1.59 (m, 2H, H cyclohexyl), 1.31–1.06 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 172.7, 166.9, 162.7, 146.9, 140.1, 129.1, 128.4, 127.6, 127.1, 122.8, 117.2, 115.5, 59.3, 52.2, 40.9, 32.1, 31.0, 26.8, 26.3; MALDI-TOF-MS m/z: 367 $[M+H]^+$.

4.1.59. 2-Cyclohexyl-*N*-(4-hydroxy-2-nitrophenyl)-2-phenylacetamide (58i). Compound **58i** was prepared according to the general procedure H starting from 4-amino-3-nitrophenol and was obtained after purification by TLC (CH_2Cl_2). Yield: 62%; yellow solid; R_f (CH_2Cl_2): 0.55; t_R (TSK gel, method B): 6.98 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.52–7.48 (m, 2H, NH + ArH), 7.39–7.28 (m, 6H, OH + ArH), 7.10 (m, 1H, ArH), 7.02 (m, 1H, ArH), 3.58 (d, J = 10.3 Hz, 1H, CH), 2.02 (m, 1H, CH), 1.97–1.04 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 173.1, 145.3, 139.5, 137.7, 131.3, 129.7, 129.5, 129.3, 128.3, 121.1, 117.5, 58.9, 41.3, 32.1, 30.5, 26.6, 26.3, 26.1; MALDI-TOF-MS m/z: not observed.

4.1.60. *N*-(2-Amino-3,4-dimethylphenyl)-2-cyclohexyl-2-phenylacetamide (59i). Compound **59i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 3,4-dimethyl-*o*-phenylenediamine and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 61%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.45; t_R (TSK gel, method B): 7.46 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.29 (s, 1H, NH), 7.39 (m, 2H, ArH phenyl), 7.31 (m, 2H, ArH phenyl), 7.23 (m, 1H, ArH phenyl), 6.77 (d, J = 7.9 Hz, 1H, ArH), 6.37 (d, J = 8.0 Hz, 1H, ArH), 4.32 (s, 2H, NH_2), 3.38 (d, J = 10.7 Hz, 1H, CH), 2.13 (s, 3H, CH_3), 1.98 (m, 1H, CH), 1.96 (s, 3H, CH_3), 1.85 (m, 1H, H cyclohexyl), 1.74 (m, 1H, H cyclohexyl), 1.59 (m, 2H, H cyclohexyl), 1.25–0.73 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 172.5, 140.8, 140.5, 129.1, 127.5, 123.7, 121.9, 121.6, 118.6, 59.2, 39.8, 32.1, 31.0, 26.9, 26.3, 21.0; MALDI-TOF-MS m/z: 337 $[M+H]^+$.

4.1.61. *N*-(2-Amino-4,5-dimethylphenyl)-2-cyclohexyl-2-phenylacetamide (60i). Compound **60i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 4,5-dimethyl-*o*-phenylenediamine and was obtained after purification by

TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 74%; white solid; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.40; t_R (TSK gel, method B): 6.98 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.31 (s, 1H, NH), 7.40–7.37 (m, 2H, ArH), 7.33–7.24 (m, 3H, ArH), 6.83 (s, 1H, ArH), 6.48 (s, 1H, ArH), 4.50 (s, 2H, NH_2), 3.37 (m, 1H, CH), 2.05 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.57–1.13 (m, 11H, H cyclohexyl); ^{13}C NMR δ: 172.1, 162.7, 140.5, 140.2, 134.2, 129.2, 129.0, 128.2, 127.7, 124.5, 121.9, 118.3, 59.2, 32.1, 26.9, 26.3, 19.9, 19.2; MALDI-TOF-MS *m/z*: 337 $[M+H]^+$.

4.1.62. *N*-(2-Amino-4,5-dimethoxyphenyl)-2-cyclohexyl-2-phenylacetamide (61i). Compound **61i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 4,5-dimethoxy-*o*-phenylenediamine.2HCl and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.5:0.5). Yield: 94%; white solid; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.50; t_R (TSK gel, method B): 6.50 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.31 (s, 1H, NH), 7.39–7.19 (m, 5H, ArH), 6.69 (s, 1H, ArH), 6.36 (s, 1H, ArH), 4.35 (s, 2H, NH_2), 3.63 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.32 (d, J = 10.7 Hz, 1H, CH), 1.99 (m, 1H, CH cyclohexyl), 1.85–1.01 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 172.0, 162.7, 140.4, 136.8, 129.1, 129.0, 127.5, 125.5, 111.9, 102.1, 59.2, 57.4, 56.2, 40.9, 34.2, 32.2, 26.8, 26.3; MALDI-TOF-MS *m/z*: 369 $[M+H]^+$.

4.1.63. *N*-(2-Amino-4,5-dichlorophenyl)-2-cyclohexyl-2-phenylacetamide (62i). Compound **62i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 4,5-dichloro-*o*-phenylenediamine and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield: 45%; white solid; R_f (CH_2Cl_2): 0.40; t_R (TSK gel, method B): 9.25 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.34 (s, 1H, NH), 7.50 (s, 1H, ArH), 7.34–7.15 (m, 5H, ArH), 6.84 (s, 1H, ArH), 5.19 (s, 2H, NH_2), 3.34 (d, J = 10.6 Hz, 1H, CH), 1.95 (m, 1H, CH), 1.70-1.11 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 172.7, 142.0, 132.9, 129.1, 127.7, 125.6, 124.1, 116.7, 59.3, 32.1, 31.0, 26.8, 26.3, 26.2; MALDI-TOF-MS *m/z*: 377 $[M+H]^+$.

4.1.64. *N*-(3-Aminonaphthalen-2-yl)-2-cyclohexyl-2-phenylacetamide (63i). Compound **63i** was prepared according to the general procedure F starting from cyclohexylphenylacetic acid and 2,3-diaminonaphthalene and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 34%; ligth yellow solid; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.65; t_R (TSK gel, method B): 8.14 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.43 (s, 1H, NH), 7.82 (s, 1H, ArH), 7.55 (d, J = 8.0 Hz, 1H, ArH), 7.44 (d, J = 8.0 Hz, 1H, ArH), 7.39 (m, 2H, ArH), 7.28 (m, 2H, ArH), 7.19 (m, 2H, ArH), 7.07 (m, 2H, ArH), 6.94 (s, 1H, ArH), 5.03 (s, 2H, NH_2), 3.43 (d, J = 10.7 Hz, 1H, CH), 2.01 (m, 1H, CH), 1.93–1.10 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 172.9, 140.2, 129.1, 127.9, 127.6, 126.8, 126.1, 125.6, 122.6, 109.4, 59.4, 40.9, 34.2, 32.2, 31.1, 26.8; MALDI-TOF-MS *m/z*: not observed.

4.1.65. 2-Nitro-5-piperidin-1-ylphenylamine (64a). Compound **64a** was prepared according to the general procedure G starting from piperidine (1.15 mL, 11.6 mmol, 4 equiv) and was obtained after purification by TLC (CH_2Cl_2). Yield: 87%; yellow solid; R_f (CH_2Cl_2): 0.45; t_R (TSK gel, method B): 6.59 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.78 (d, J = 9.8 Hz, 1H, ArH), 7.22 (s, 2H, NH_2), 6.36 (dd, J = 2.7, 9.8 Hz, 1H, ArH), 6.18 (d, J = 2.7 Hz, 1H, ArH), 3.35 (t, J = 5.8 Hz, 4H, 2 CH_2), 1.57 (m, 6H, 3 CH_2); MALDI-TOF-MS *m/z*: 222 $[M+H]^+$.

4.1.66. 2-Cyclohexyl-*N*-(2-nitro-5-piperidin-1-ylphenyl)-2-phenylacetamide (64i). Compound **64i** was prepared according to the general procedure H starting from compound **64a** and was obtained after purification by TLC (cyclohexane/AcOEt 8:2). Yield: 75%; orange solid; R_f (cyclohexane/AcOEt 8:2): 0.50; t_R (TSK gel, method B): 11.30 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.80 (s, 1H, NH), 7.95 (d, J = 9.6 Hz, 1H, ArH), 7.84 (d, J = 2.7 Hz, 1H, ArH), 7.40–7.22 (m, 5H, ArH phenyl), 6.73 (dd, J = 2.6, 9.7 Hz, 1H, ArH), 3.47–3.44 (m, 5H, CH + CH_2 piperidinyl), 2.04 (m, 1H, CH cyclohexyl), 1.84–1.58 (m, 10H, CH_2 cyclohexyl + CH_2 piperidinyl), 1.30–0.84 (m, 6H, CH_2 cyclohexyl); ^{13}C NMR δ: 137.4, 129.3, 129.2, 127.9, 109.4, 103.6, 61.2, 48.6, 40.9, 32.1, 30.7, 26.7, 26.3, 25.8, 24.6; MALDI-TOF-MS *m/z*: 422 $[M+H]^+$.

4.1.67. 5-(4-Methylpiperazin-1-yl)-2-nitrophenylamine (65a). Compound **65a** was prepared according to the general procedure G starting from 1-methylpiperazine (1.29 mL, 11.6 mmol, 4 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 75%; yellow solid; R_f (cyclohexane/AcOEt 7:3): 0.55; t_R (TSK gel, method B): 3.47 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.70 (d, J = 9.7 Hz, 1H, ArH), 7.17 (s, 2H, NH_2), 6.29 (dd, J = 2.7, 9.8 Hz, 1H, ArH), 6.12 (d, J = 2.7 Hz, 1H, ArH), 3.21 (t, J = 5.0 Hz, 4H, 2 CH_2), 2.30 (t, J = 5.0 Hz, 4H, 2 CH_2), 2.10 (s, 3H, CH_3); MALDI-TOF-MS *m/z*: 237 $[M+H]^+$.

4.1.68. 2-Cyclohexyl-*N*-[5-(4-methylpiperazin-1-yl)-2-nitrophenyl]-2-phenylacetamide (65i). Compound **65i** was prepared according to the general procedure H starting from compound **65a** and was obtained after purification by TLC (cyclohexane/AcOEt 8:2). Yield: 28%; orange solid; R_f (CH_2Cl_2/MeOH 9:1): 0.40; t_R (TSK gel, method A): 6.25 min, P_{HPLC}: 99%; ^{1}H NMR δ: 11.06 (s, 1H, NH), 8.24 (d, J = 2.8 Hz, 1H, ArH), 8.00 (d, J = 9.7 Hz, 1H, ArH), 7.33–7.15 (m, 5H, ArH phenyl), 6.42 (dd, J = 2.8, 9.7 Hz, 1H, ArH), 3.37 (t, J = 5.0 Hz, 4H, CH_2 piperazinyl), 3.12 (d, J = 10.5 Hz, 1H, CH cyclohexyl), 2.40 (t, J = 5.0 Hz, 4H, CH_2 piperazinyl), 2.20 (s, 3H, CH_3), 2.11–2.06 (m, 1H, CH cyclohexyl), 1.89–1.04 (m, 10H, CH_2 cyclohexyl); ^{13}C NMR δ: 127.8, 127.7, 127.5, 126.5, 106.8, 101.5, 62.3, 52.7, 45.8, 44.9, 39.6, 31.3, 25.4, 25.3; MALDI-TOF-MS *m/z*: 437 $[M+H]^+$.

4.1.69. 5-Morpholin-4-yl-2-nitrophenylamine (66a). Compound **66a** was prepared according to the general procedure G starting from morpholine (1.01 mL, 11.6 mmol, 4 equiv) and was obtained after purification by trituration

in a Et_2O/pentane mixture. Yield: 56%; yellow solid; R_f (cyclohexane/AcOEt 7:3): 0.60; t_R (TSK gel, method B): 5.15 min, P_{HPLC}: 99%; ^1H NMR δ: 7.73 (d, $J = 9.7$ Hz, 1H, ArH), 7.20 (s, 2H, NH_2), 6.30 (dd, $J = 2.7$, 9.7 Hz, 1H, ArH), 6.12 (d, $J = 2.7$ Hz, 1H, ArH), 3.61 (t, $J = 4.8$ Hz, 4H, 2 CH_2), 3.18 (t, $J = 5.0$ Hz, 4H, 2 CH_2); MALDI-TOF-MS m/z: 224 $[M+H]^+$.

4.1.70. 2-Cyclohexyl-*N*-(5-morpholin-4-yl-2-nitrophenyl)-2-phenylacetamide (66i). Compound **66i** was prepared according to the general procedure H starting from compound **66a**, but was not purified and directly reduced and cyclized.

4.1.71. 2-Nitro-5-thiomorpholin-4-ylphenylamine (67a). Compound **67a** was prepared according to the general procedure G starting from thiomorpholine (1.10 mL, 11.6 mmol, 4 equiv) and was obtained after purification by TLC (CH_2Cl_2). Yield: 74%; yellow solid; R_f (CH_2Cl_2): 0.60; t_R (TSK gel, method B): 5.97 min, P_{HPLC}: 99%; ^1H NMR δ: 7.80 (d, $J = 9.7$ Hz, 1H, ArH), 7.23 (s, 2H, NH_2), 6.35 (dd, $J = 2.7$, 9.8 Hz, 1H, ArH), 6.20 (d, $J = 2.7$ Hz, 1H, ArH), 3.74 (t, $J = 5.0$ Hz, 4H, 2 CH_2), 2.60 (t, $J = 5.0$ Hz, 4H, 2 CH_2); MALDI-TOF-MS m/z: 240 $[M+H]^+$.

4.1.72. 2-Cyclohexyl-*N*-(2-nitro-5-thiomorpholin-4-ylphenyl)-2-phenylacetamide (67i). Compound **67i** was prepared according to the general procedure H starting from compound **67a** and was obtained after purification by TLC (CH_2Cl_2). Yield: 83%; yellow solid; R_f (CH_2Cl_2): 0.80; t_R (TSK gel, method A): 8.53 min, P_{HPLC}: 99%; ^1H NMR δ: 10.73 (s, 1H, NH), 7.96 (d, $J = 9.6$ Hz, 1H, ArH), 7.78 (d, $J = 2.8$ Hz, 1H, ArH), 7.40–7.21 (m, 5H, ArH phenyl), 6.75 (dd, $J = 2.8$, 9.6 Hz, 1H, ArH), 3.80 (m, 4H, 2 CH_2 thiomorpholinyl), 3.47 (d, $J = 10.4$ Hz, 1H, CH), 2.64 (m, 4H, 2 CH_2 thiomorpholinyl), 2.04 (m, 1H, CH cyclohexyl), 1.83 (m, 1H, CH_2 cyclohexyl), 1.69 (m, 1H, CH_2 cyclohexyl), 1.58 (m, 2H, CH_2 cyclohexyl), 1.26–0.76 (m, 6H, CH_2 cyclohexyl); ^{13}C NMR δ: 173.1, 154.4, 139.2, 137.2, 129.3, 129.2, 129.0, 127.9, 109.8, 104.5, 50.4, 40.9, 32.1, 30.7, 26.7, 26.3, 26.1; MALDI-TOF-MS m/z: 440 $[M+H]^+$.

4.1.73. Biphenyl-2-carboxylic acid (2-amino-4-methoxyphenyl)amide (68i). Compound **68i** was prepared according to the general procedure F starting from 2-biphenylcarboxylic acid and 4-methoxy-*o*-phenylenediamine·2HCl and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 45%; light yellow solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.35; t_R (TSK gel, method B): 5.92 min, P_{HPLC}: 91%; ^1H NMR δ: 9.20 (s, 1H, NH), 7.57 (m, 1H, ArH), 7.46–7.32 (m, 9H, ArH biphenyl), 6.75 (d, $J = 8.6$ Hz, 1H, ArH), 6.20 (d, $J = 2.8$ Hz, 1H, ArH), 6.04 (dd, $J = 2.8$, 8.6 Hz, 1H, ArH), 4.61 (s, 2H, NH_2), 3.58 (s, 3H, CH_3); ^{13}C NMR δ: 169.0, 158.8, 144.8, 141.2, 140.0, 138.2, 130.6, 130.3, 129.5, 129.3, 129.1, 128.8, 128.1, 127.9, 127.8, 117.1, 102.5, 101.4, 55.7; MALDI-TOF-MS m/z: 319 $[M+H]^+$.

4.1.74. *N*-(2-Amino-4-methoxyphenyl)-2-phenoxybenzamide (69i). Compound **69i** was prepared according to the general procedure F starting from 2-phenoxybenzoic acid and 4-methoxy-*o*-phenylenediamine.2HCl and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 38%; red-orange oil; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (TSK gel, method B): 6.54 min, P_{HPLC}: 99%; ^1H NMR δ: 9.37 (s, 1H, NH), 7.73 (m, 1H, ArH), 7.49–7.36 (m, 3H, ArH), 7.24 (m, 1H, ArH), 7.14 (m, 1H, ArH), 7.07 (m, 2H, ArH), 6.97 (m, 1H, ArH), 6.92 (m, 1H, ArH), 6.27 (m, 1H, ArH), 6.10 (m, 1H, ArH), 4.82 (s, 2H, NH_2), 3.63 (s, 3H, CH_3); ^{13}C NMR δ: 163.5, 145.3, 134.8, 133.2, 131.6, 128.4, 125.3, 125.2, 120.5, 120.3, 103.4, 102.2, 98.7, 56.4; MALDI-TOF-MS m/z: 335 $[M+H]^+$.

4.1.75. *N*-(2-Amino-4-methoxyphenyl)-2-phenylaminobenzamide (70i). Compound **70i** was prepared according to the general procedure F starting from *N*-phenylanthranilic acid and 4-methoxy-*o*-phenylenediamine.2HCl and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 33%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.75; t_R (TSK gel, method B): 6.85 min, P_{HPLC}: 99%; ^1H NMR δ: 9.55 (s, 1H, NH), 9.48 (s, 1H, NH), 7.85 (m, 1H, ArH), 7.38–7.25 (m, 4H, ArH), 7.13 (m, 2H, ArH), 6.99–6.84 (m, 3H, ArH), 6.33 (m, 1H, ArH), 6.14 (m, 1H, ArH), 4.92 (s, 2H, NH_2), 3.66 (s, 3H, CH_3); ^{13}C NMR δ: 132.8, 130.5, 130.2, 128.9, 122.5, 120.1, 119.1, 116.9, 116.0, 102.7, 101.4, 55.7; MALDI-TOF-MS m/z: 334 $[M+H]^+$.

4.1.76. *N*-(2-Amino-4-methoxyphenyl)-2-cyclohexylbenzamide (71i). Compound **71i** was prepared according to the general procedure F starting from 2-cyclohexylbenzoic acid and 4-methoxy-*o*-phenylenediamine.2HCl and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 77%; white solid; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.45; t_R (TSK gel, method B): 7.06 min, P_{HPLC}: 93%; ^1H NMR δ: 9.43 (s, 1H, NH), 7.38 (m, 3H, ArH), 7.20 (m, 1H, ArH), 7.00 (d, $J = 8.6$ Hz, 1H, ArH), 6.30 (d, $J = 2.8$ Hz, 1H, ArH), 6.15 (dd, $J = 2.8$, 8.6 Hz, 1H, ArH), 4.85 (s, 2H, NH_2), 3.63 (s, 3H, CH_3), 2.86 (m, 1H, CH), 1.81–1.26 (m, 10H, CH_2); ^{13}C NMR δ: 169.3, 158.9, 145.4, 144.8, 138.2, 130.1, 127.9, 127.7, 126.9, 126.2, 125.8, 117.5, 102.9, 101.8, 55.7, 41.2, 34.6, 27.4, 26.5; MALDI-TOF-MS m/z: 325 $[M+H]^+$.

4.1.77. General procedure I for synthesis of benzimidazoles 1, 3i′, 4–11, 14–15, 17–18, 20, 23, 32–35, 44, 48–49, 51–52, 54–56 and 59–63. The monoacylated precursor was diluted with neat acetic acid (0.2 M). Following reflux of the mixture for 5 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole was obtained after purification by trituration in a Et_2O/pentane or hexane/AcOEt mixture or by TLC.

4.1.78. General Procedure J for synthesis of benzimidazoles 2, 12–13, 24, 47, 53 and 58. To a solution of monoacylated precursor in neat acetic acid (0.2 M) was added iron (2 equiv). Following reflux of the mixture for 5 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole

was obtained after purification by trituration in a Et_2O/pentane mixture or by TLC.

4.1.79. General procedure K for synthesis of benzimidazoles 16, 19, 25–31, 36–38 and 68–71. To a solution of monoacylated precursor in a MeOH/dioxane 1:1 mixture (0.1 M) was added aqueous HCl 4 N (10 equiv). Following reflux of the mixture for 8 h, the solvents were evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole was obtained after purification by trituration in a Et_2O/pentane mixture or by TLC.

4.1.80. General procedure L for synthesis of benzimidazoles 64–65 and 67. To a solution of nitro monoacylated precursor (2 mmol, 1 equiv) in 10 mL of absolute EtOH were added $SnCl_2$ (4 mmol, 2 equiv) and HCl 12 N (20 mmol, 10 equiv). Following reflux of the mixture for 24 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole was obtained after purification by TLC.

4.1.81. 2-(Cyclohexylphenylmethyl)-1*H*-benzoimidazole (1). Compound **1** was prepared according to the general procedure I starting from compound **1o** (250 mg, 0.81 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 51%; white solid; mp 195–197 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.45; t_R (TSK gel, method B): 5.06 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.18 (s, 1H, NH), 7.53 (m, 1H, ArH), 7.45 (m, 1H, ArH), 7.37 (m, 1H, ArH), 7.25 (m, 2H, ArH), 7.17 (m, 1H, ArH), 7.07 (m, 2H, ArH), 3.80 (d, J = 10.7 Hz, 1H, CH), 2.29 (m, 1H, CH), 1.58–0.91 (m, 10H, CH_2 cyclohexyl); ^{13}C NMR δ: 157.2, 144.2, 141.7, 134.7, 129.2, 129.1, 127.4, 122.3, 121.7, 119.2, 53.3, 41.9, 32.3, 31.6, 29.8, 26.8, 26.4; MALDI-TOF-MS m/z: 291 $[M+H]^+$.

4.1.82. 2-Benzhydryl-1*H*-benzoimidazole (2). Compound **2** was prepared according to the general procedure J starting from compound **2i** (200 mg, 0.6 mmol, 1 equiv) and was obtained after purification by TLC (cyclohexane/AcOEt 7:3). Yield: 58%; white solid; mp 210–212 °C; R_f (cyclohexane/AcOEt 7:3): 0.45; t_R (C18 Xterra, method B): 5.35 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.31 (s, 1H, NH), 7.40–7.11 (m, 14H, ArH), 5.74 (s, 1H, CH); ^{13}C NMR δ: 156.1, 142.3, 129.5, 129.3, 122.7, 121.9, 119.4, 112.0, 51.6; MALDI-TOF-MS m/z: 285 $[M+H]^+$.

4.1.83. *N*-(2-Acetylaminophenyl)-2,2-dicyclohexylacetamide (3i′). Compound **3i′** was prepared according to the general procedure I starting from compound **3i** (150 mg, 0.48 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.6:0.4). Yield: 47%; white solid; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.55; t_R (TSK gel, method B): 8.87 min, P_{HPLC}: 99%; ^{1}H NMR δ: 9.22 (s, 1H, NH), 9.21 (s, 1H, NH), 7.34–7.25 (m, 2H, ArH), 7.08–7.04 (m, 2H, ArH), 3.19 (s, 3H, CH_3), 1.95 (m, 1H, CH), 1.58–1.54 (m, 12H, H cyclohexyl), 1.62–0.83 (m, 10H, H cyclohexyl); MALDI-TOF-MS m/z: 357 $[M+H]^+$.

4.1.84. 2-Dicyclohexylmethyl-1*H*-benzoimidazole (3). To a solution of compound **3i′** (130 mg, 0.36 mmol, 1 equiv) in 3.5 mL of toluene was added *p*-toluenesulfonic acid (135 mg, 0.72 mmol, 2 equiv). Following reflux of the mixture for 24 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The residue was purified by TLC (CH_2Cl_2/MeOH 9.6:0.4) to afford compound **3**. Yield: 65%; white solid; mp 205–207 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.50; t_R (TSK gel, method B): 6.44 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.16 (s, 1H, NH), 7.68 (m, 1 H, ArH), 7.55 (m, 1H, ArH), 7.25 (m, 2H, ArH), 2.69 (t, J = 7.5 Hz, 1H, CH), 2.09 (m, 2H, CH), 1.93–0.85 (m, 20H, H cyclohexyl); ^{13}C NMR δ: 176.3, 156.9, 121.9, 121.4, 118.9, 111.5, 57.4, 51.8, 32.2, 31.6, 30.1, 30.0, 26.9; MALDI-TOF-MS m/z: 297 $[M+H]^+$.

4.1.85. 2-Benzyl-1*H*-benzoimidazole (4). Compound **4** was prepared according to the general procedure I starting from compound **4i** (150 mg, 0.66 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 75%; white solid; mp 179–180 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.45; t_R (C18 Xterra, method B): 4.30 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.27 (s, 1H, NH), 7.52–7.10 (m, 9H, ArH), 4.17 (s, 2H, CH_2); ^{13}C NMR δ: 154.4, 138.5, 129.6, 129.3, 127.4, 122.5, 121.8, 119.2, 111.8, 35.8; MALDI-TOF-MS m/z: 209 $[M+H]^+$.

4.1.86. 2-Cyclohexylmethyl-1*H*-benzoimidazole (5). Compound **5** was prepared according to the general procedure I starting from compound **5i** (150 mg, 0.64 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 84%; white solid; mp 195–197 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.45; t_R (C18 Xterra, method B): 4.89 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.49–7.44 (m, 2H, ArH), 7.14–7.10 (m, 2H, ArH), 2.69 (d, J = 7.1 Hz, 2H, CH_2), 1.69–1.16 (m, 11H, CH + CH_2 cyclohexyl); ^{13}C NMR δ: 154.9, 121.7, 118.8, 111.5, 48.3, 37.1, 34.2, 33.5, 26.5; MALDI-TOF-MS m/z: 215 $[M+H]^+$.

4.1.87. 2-Naphthalen-2-ylmethyl-1*H*-benzoimidazole (6). Compound **6** was prepared according to the general procedure I starting from crude compound **6i** (1.07 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 34% global; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.65; t_R (TSK gel, method A): 4.72 min, P_{HPLC}: 92%; ^{1}H NMR δ: 12.20 (s, 1H, NH), 7.88–7.83 (m, 4H, ArH), 7.53–7.42 (m, 5H, ArH), 7.14–7.09 (m, 2H, ArH), 4.35 (s, 2H, CH_2); ^{13}C NMR δ: 154.3, 134.4, 132.5, 129.3, 128.3, 127.1, 126.6, 126.5, 124.9, 122.5, 121.8, 119.1, 111.8, 33.6; MALDI-TOF-MS m/z: 259 $[M+H]^+$.

4.1.88. 2-Naphthalen-1-ylmethyl-1*H*-benzoimidazole (7). Compound **7** was prepared according to the general procedure I starting from compound **7i** (370 mg, 1.34 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 78%; light yellow solid; mp > 225 °C; R_f (CH_2Cl_2/

MeOH 9.6:0.4): 0.40; t_R (TSK gel, method B): 5.21 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.17 (s, 1H, NH), 8.15 (m, 1H, ArH), 7.88 (m, 1H, ArH), 7.80 (m, 1H, ArH), 7.46 (m, 5H, ArH), 7.33 (m, 1H, ArH), 7.05 (m, 2H, ArH), 4.59 (s, 2H, CH_2); ^{13}C NMR δ: 154.3, 134.4, 132.5, 129.3, 128.3, 127.1, 126.6, 126.5, 124.9, 122.5, 121.8, 119.1, 111.8, 33.6; MALDI-TOF-MS *m*/*z*: 259 $[M+H]^+$.

4.1.89. 2-(1*H*-Indol-3-ylmethyl)-1*H*-benzoimidazole (8). Compound **8** was prepared according to the general procedure I starting from compound **8i** (300 mg, 1.13 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 78%; white solid; mp 173–175 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.25; t_R (TSK gel, method B): 4.65 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.03 (s, 1H, NH), 10.91 (s, 1H, NH), 7.45 (m, 2H, ArH), 7.30 (m, 2H, ArH), 7.23 (m, 1H, ArH), 7.02 (m, 3H, ArH), 6.87 (m, 1H, ArH), 4.22 (s, 2H, CH_2); ^{13}C NMR δ: 162.7, 155.2, 144.2, 137.1, 135.3, 127.8, 124.6, 122.2, 121.9, 121.6, 119.3, 118.9, 112.3, 110.7, 26.3; MALDI-TOF-MS *m*/*z*: 248 $[M+H]^+$.

4.1.90. 2-Benzo[*b*]thiophen-3-ylmethyl-1*H*-benzoimidazole (9). Compound **9** was prepared according to the general procedure I starting from compound **9i** (220 mg, 0.78 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 97%; white solid; mp 217–219 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.45; t_R (TSK gel, method B): 5.14 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.28 (s, 1H, NH), 7.96 (m, 1H, ArH benzothiophenyl), 7.84 (m, 1H, ArH benzothiophenyl), 7.57 (s, 1H, ArH benzothiophenyl), 7.52 (m, 1H, ArH), 7.40-7.32 (m, 3H, ArH benzothiophenyl + ArH), 7.10 (m, 2H, ArH), 4.42 (s, 2H, CH_2); ^{13}C NMR δ: 140.6, 139.3, 125.5, 125.2, 124.9, 123.8, 122.9, 122.5, 121.8, 119.1, 118.7, 111.8, 29.3; MALDI-TOF-MS *m*/*z*: 265 $[M+H]^+$.

4.1.91. 2-(1,2,3,4-Tetrahydronaphthalen-2-yl)-1*H*-benzoimidazole (10). Compound **10** was prepared according to the general procedure I starting from compound **10i** (200 mg, 0.75 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 75%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.45; t_R (C18 Xterra, method B): 5.06 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.55 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.24–7.10 (m, 6H, ArH), 3.32 (m, 3H, CH + CH_2), 3.17 (m, 2H, CH_2), 2.90 (m, 2H, CH_2); ^{13}C NMR δ: 158.8, 143.9, 136.5, 136.2, 135.2, 129.8, 129.6, 126.6, 126.5, 122.4, 121.7, 119.2, 111.7, 48.4, 35.2, 34.5, 29.2; MALDI-TOF-MS *m*/*z*: 249 $[M+H]^+$.

4.1.92. 2-(9*H*-Fluoren-9-yl)-1*H*-benzoimidazole (11). Compound **11** was prepared according to the general procedure I starting from compound **11i** (110 mg, 0.36 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.5:0.5). Yield: 95%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.50; t_R (C18 Xterra, method B): 5.36 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.16 (s, 1H, NH), 7.96 (m, 2H, ArH), 7.52–7.42 (m, 5H, ArH), 7.35–7.28 (m, 3H, ArH), 7.11–7.08 (m, 2H, ArH), 5.53 (s, 1H, CH), 3.17 (m, 2H, CH_2), 2.90 (m, 2H, CH_2); ^{13}C NMR δ: 158.8, 143.9, 136.5, 136.2, 135.2, 129.8, 129.6, 126.6, 126.5, 122.4, 121.7, 119.2, 111.7, 48.4, 35.2, 34.5, 29.2; MALDI-TOF-MS *m*/*z*: 283 $[M+H]^+$.

4.1.93. 2-(4-Propylphenyl)-1*H*-benzoimidazole (12). Compound **12** was prepared according to the general procedure J starting from compound **12i** (500 mg, 1.76 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.6:0.4). Yield: 75%; white solid; mp 197–198 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.50; t_R (C18 Xterra, method B): 5.65 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.74 (s, 1H, NH), 8.01 (m, 2H, ArH), 7.54 (m, 2H, ArH), 7.27 (m, 2H, ArH), 7.11 (m, 2H, ArH), 2.53 (t, J = 7.3 Hz, 2H, CH_2), 1.56 (m, 2H, CH_2), 0.83 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR δ: 152.3, 145.0, 129.7, 128.6, 127.2, 123.1, 122.4, 119.5, 112.0, 37.9, 26.4, 14.5; MALDI-TOF-MS *m*/*z*: 237 $[M+H]^+$.

4.1.94. 2-(1-Phenylpropyl)-1*H*-benzoimidazole (13). Compound **13** was prepared according to the general procedure J starting from crude compound **13i** (1.85 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.9:0.1:0.1). Yield: 40% global; white solid; mp 178–180 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.9:0.1:0.1): 0.45; t_R (C18 Xterra, method B): 5.22 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.31–7.02 (m, 9H, ArH), 4.00 (t, J = 7.7 Hz, 1H, CH), 2.25-2.18 (m, 1H, CH_2), 2.01–1.91 (m, 1H, CH_2), 0.79 (t, J = 7.3 Hz, 1H, CH_3); ^{13}C NMR δ: 157.5, 143.1, 129.8, 128.6, 127.4, 122.0, 119.3, 111.8, 48.1, 28.4, 13.3; MALDI-TOF-MS *m*/*z*: 237 $[M+H]^+$.

4.1.95. 2-(2-Phenylpropyl)-1*H*-benzoimidazole (14). Compound **14** was prepared according to the general procedure I starting from compound **14i** (250 mg, 0.98 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 78%; white solid; mp 152–154 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.55; t_R (C18 Xterra, method B): 4.67 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.18 (s, 1H, NH), 7.47–7.07 (m, 9H, ArH), 3.42 (m, 1H, CH), 3.13–2.98 (m, 2H, CH_2), 1.23 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR δ: 176.4, 154.6, 147.1, 129.2, 127.6, 126.9, 122.2, 121.7, 118.9, 111.6, 39.2, 37.9, 22.6; MALDI-TOF-MS *m*/*z*: 237 $[M+H]^+$.

4.1.96. 2-(1-Phenylethyl)-1*H*-benzoimidazole (15). Compound **15** was prepared according to the general procedure I starting from compound **15i** (250 mg, 1.04 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 87%; white solid; mp 197–199 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.40; t_R (C18 Xterra, method B): 4.28 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.18 (s, 1H, NH), 7.57–7.07 (m, 9H, ArH), 4.37 (q, J = 7.2 Hz, 1H, CH), 1.69 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR δ: 158.2, 144.5, 129.3, 128.2, 127.4, 122.5, 121.7, 119.2, 111.8, 40.2, 21.3; MALDI-TOF-MS *m*/*z*: 223 $[M+H]^+$.

4.1.97. 2-(2-Iodophenyl)-1*H*-benzoimidazole (16). Compound **16** was prepared according to the general procedure K starting from crude compound **16i** (5 mmol,

1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 78% global; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.65; t_R (TSK gel, method B): 4.65 min, P_{HPLC}: 99%; ^1H NMR δ: 12.73 (s, 1H, NH), 8.09 (m, 1H, ArH), 7.66–7.54 (m, 4H, ArH), 7.32–7.22 (m, 3H, ArH); ^{13}C NMR δ: 153.4, 140.5, 137.4, 132.2, 132.0, 129.0, 122.9, 98.2; MALDI-TOF-MS *m/z*: 321 $[M+H]^+$.

4.1.98. 2-(1-Phenylcyclopentyl)-1*H*-benzoimidazole (17). Compound **17** was prepared according to the general procedure I starting from crude compound **17i** (1.85 mmol, 1 equiv) and was obtained after purification by trituration in a hexane/AcOEt mixture. Yield: 30% global; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.65; t_R (C18 Xterra, method B): 5.37 min, P_{HPLC}: 99%; ^1H NMR δ: 7.57–7.54 (m, 1H, ArH), 7.36–7.25 (m, 5H, ArH), 7.19–7.06 (m, 3H, ArH), 2.88 (m, 2H, CH_2), 2.15-2.07 (m, 2H, CH_2), 1.75–1.48 (m, 5H, CH + CH_2); ^{13}C NMR δ: 129.1, 127.4, 127.0, 122.5, 121.6, 119.3, 111.7, 38.1, 34.2, 23.9; MALDI-TOF-MS *m/z*: 263 $[M+H]^+$.

4.1.99. 2-(Cyclopentylphenylmethyl)-1*H*-benzoimidazole (18). Compound **18** was prepared according to the general procedure I starting from compound **18i** (250 mg, 0.88 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1). Yield: 63%; white solid; mp 208–210 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1): 0.55; t_R (TSK gel, method B): 5.60 min, P_{HPLC}: 99%; ^1H NMR δ: 12.26 (s, 1H, NH), 7.50–7.31 (m, 4H, ArH), 7.26 (m, 2H, ArH), 7.16 (m, 1H, ArH), 7.07 (m, 1H, ArH), 3.85 (d, J = 11.2 Hz, 1H, CH), 2.85 (m, 1H, CH), 1.64-1.42 (m, 6H, CH_2 cyclopentyl), 1.10 (m, 2H, CH_2 cyclopentyl); ^{13}C NMR δ: 157.8, 142.9, 129.2, 128.9, 127.4, 122.3, 121.7, 119.2, 111.7, 52.5, 44.6, 32.2, 25.6, 25.5; MALDI-TOF-MS *m/z*: 277 $[M+H]^+$.

4.1.100. 2-(1-Phenylheptyl)-1*H*-benzoimidazole (19). Compound **19** was prepared according to the general procedure K starting from crude compound **19i** (3.33 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 20% global; white solid; mp 107–115 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.80; t_R (TSK gel, method A): 5.74 min, P_{HPLC}: 99%; ^1H NMR δ: 12.21 (s, 1H, NH), 7.55 (m, 1H, ArH), 7.39–7.35 (m, 3H, ArH), 7.32–7.27 (m, 2H, ArH), 7.21 (m, 1H, ArH), 7.13–7.06 (m, 2H, ArH), 4.15 (t, J = 7.7 Hz, 1H, CH), 2.28 (m, 1H, CH_2), 2.01 (m, 1H, CH_2), 1.29–1.18 (m, 8H, 4 CH_2), 0.81 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR δ: 157.4, 143.8, 143.0, 129.0, 128.3, 127.2, 122.2, 121.5, 118.9, 111.5, 46.0, 35.1, 31.7, 29.1, 27.9, 22.6, 14.5; MALDI-TOF-MS *m/z*: 293 $[M+H]^+$.

4.1.101. 2-(*trans*-2-Phenylcyclopropyl)-1*H*-benzoimidazole (20). Compound **20** was prepared according to the general procedure I starting from compound **20i** (350 mg, 1.38 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.6:0.4). Yield: 74%; white solid; mp 150–154 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.70; t_R (TSK gel, method B): 4.99 min, P_{HPLC}: 99%; ^1H NMR δ: 12.28 (s, 1H, NH), 7.44 (m, 2H, ArH), 7.30 (m, 2H, ArH phenyl), 7.22–7.16 (m, 3H, ArH phenyl), 7.13–7.07 (m, 2H, ArH), 2.53 (m, 1H, CH), 2.34 (m, 1H, CH), 1.78 (m, 1H, CH_2), 1.59 (m, 1H, CH_2); ^{13}C NMR δ: 141.7, 129.0, 126.6, 126.3, 121.7, 27.5, 22.1, 17.9; MALDI-TOF-MS *m/z*: 235 $[M+H]^+$.

4.1.102. 2-Phenyl-1*H*-benzoimidazole (21). White solid (commercially available). Mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.40; t_R (TSK gel, method B): 3.48 min, P_{HPLC}: 100%; ^1H NMR δ: 8.21-8.16 (m, 2H, ArH), 7.64–7.46 (m, 5H, ArH), 7.24–7.20 (m, 2H, ArH); ^{13}C NMR δ: 154.0, 151.8, 145.9, 130.8, 130.5, 129.6, 127.1, 122.7; MALDI-TOF-MS *m/z*: 195 $[M+H]^+$.

4.1.103. 2-Piperidin-2-yl-1*H*-benzoimidazole (22). To a solution of compound **22i** (550 mg, 1.70 mmol, 1 equiv) in 10 mL of a MeOH/dioxane 1:1 mixture was added 5 mL of aqueous HCl 4 N. Following reflux of the mixture for 20 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The benzimidazole **22** was obtained after purification by TLC (CH_2Cl_2/MeOH 9:1). Yield: 44%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9:1): 0.40; t_R (TSK gel, method A): 2.82 min, P_{HPLC}: 99%; ^1H NMR δ: 7.48–7.45 (m, 2H, ArH), 7.13–7.01 (m, 2H, ArH), 3.88 (dd, J = 2.8, 10.0 Hz, 1H, CH), 3.03 (m, 1H, CH_2), 2.70 (m, 1H, CH_2), 1.94 (m, 1H, CH_2), 1.81 (m, 1H, CH_2), 1.64–1.43 (m, 4H, CH_2); ^{13}C NMR δ: 160.2, 157.8, 145.3, 121.7, 55.7, 46.6, 32.1, 26.2, 24.6; MALDI-TOF-MS *m/z*: 202 $[M+H]^+$.

4.1.104. 2-Biphenyl-2-yl-1*H*-benzoimidazole (23). Compound **23** was prepared according to the general procedure I starting from compound **23i** (200 mg, 0.70 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 74%; white solid; mp 212–213 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.40; t_R (C18 Xterra, method B): 5.06 min, P_{HPLC}: 99%; ^1H NMR δ: 12.07 (s, 1H, NH), 7.72–7.69 (m, 1H, ArH), 7.63–7.48 (m, 4H, ArH), 7.33–7.25 (m, 1H, ArH), 7.24–7.10 (m, 7H, ArH); ^{13}C NMR δ: 152.9, 144.3, 141.8, 140.9, 135.4, 131.9, 131.3, 131.0, 130.7, 129.6, 128.9, 128.2, 127.9, 122.9, 122.1, 119.7, 112.1; MALDI-TOF-MS *m/z*: 271 $[M+H]^+$.

4.1.105. 2-Biphenyl-4-yl-1*H*-benzoimidazole (24). Compound **24** was prepared according to the general procedure J starting from crude compound **24o** (1.85 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.1:0.1). Yield: 60% global; white solid; mp 178–180 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.9:0.1:0.1): 0.40; t_R (C18 Xterra, method B): 6.16 min, P_{HPLC}: 99%; ^1H NMR δ: 8.27 (d, J = 8.4 Hz, 2H, ArH), 7.87 (d, J = 8.4 Hz, 2H, ArH), 7.78 (d, J = 7.2 Hz, 2H, ArH biphenyl), 7.62 (m, 2H, ArH biphenyl), 7.51 (t, J = 7.1 Hz, 2H, ArH biphenyl), 7.41 (m, 1H, ArH biphenyl), 7.24–7.18 (m, 2H, ArH biphenyl); ^{13}C NMR δ: 151.8, 142.1, 140.1, 129.9, 128.7, 128.0, 127.9, 127.5, 122.9, 115.3; MALDI-TOF-MS *m/z*: 271 $[M+H]^+$.

4.1.106. 2-Biphenyl-3-yl-1*H*-benzoimidazole (25). Compound **25** was prepared according to the general procedure K starting from compound **25i** (300 mg, 1.04 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 78%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.50; t_R (TSK gel, method A): 4.94 min, P_{HPLC}: 99%; ^{1}H NMR δ: 13.00 (s, 1H, NH), 8.48 (t, J = 1.6 Hz, 1H, ArH), 8.19 (dt, J = 1.2, 7.8 Hz, 1H, ArH), 7.81–7.77 (m, 3H, ArH), 7.69–7.61 (m, 2H, ArH), 7.56–7.50 (m, 3H, ArH), 7.46–7.40 (m, 1H, ArH), 7.22 (m, 2H, ArH); ^{13}C NMR δ: 130.3, 129.7, 128.6, 128.5, 127.4, 126.1, 125.2, 123.3, 111.9; MALDI-TOF-MS m/z: 271 $[M+H]^+$.

4.1.107. 2-(2-Furan-2-ylphenyl)-1*H*-benzoimidazole (26). Compound **26** was prepared according to the general procedure K starting from compound **26i** (400 mg, 1.43 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 54%; light yellow solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.45; t_R (TSK gel, method A): 3.92 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.53 (s, 1H, NH), 7.85 (dd, J = 1.6, 8.0 Hz, 1H, ArH), 7.64–7.48 (m, 4H, ArH), 7.47 (m, 2H, ArH), 7.24–7.18 (m, 2H, ArH), 6.40 (m, 1H, ArH), 5.84 (m, 1H, ArH); ^{13}C NMR δ: 143.8, 132.2, 130.8, 128.3, 127.4, 123.1, 112.7, 109.4; MALDI-TOF-MS m/z: 261 $[M+H]^+$.

4.1.108. 2-(4′-Fluorobiphenyl-2-yl)-1*H*-benzoimidazole (27). Compound **27** was prepared according to the general procedure K starting from crude compound **27i** (1.1 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 30% global; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.50; t_R (TSK gel, method A): 4.45 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.10 (s, 1H, NH), 7.74 (d, J = 7.4 Hz, 1H, ArH), 7.61–7.49 (m, 5H, ArH), 7.38–7.33 (m, 1H, ArH), 7.23–7.06 (m, 5H, ArH); ^{13}C NMR δ: 140.7, 137.4, 131.9, 131.7, 131.5, 131.4, 131.0, 130.7, 128.4, 123.0, 122.1, 119.7, 115.9, 115.7, 112.1; MALDI-TOF-MS m/z: 289 $[M+H]^+$.

4.1.109. 2-(2-Thiophen-2-ylphenyl)-1*H*-benzoimidazole (28). Compound **28** was prepared according to the general procedure K starting from compound **28i** (700 mg, 2.38 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 56%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.60; t_R (TSK gel, method A): 4.19 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.42 (s, 1H, NH), 7.69 (d, J = 7.8 Hz, 1H, ArH), 7.63–7.55 (m, 3H, ArH), 7.52–7.43 (m, 3H, ArH), 7.19 (m, 2H, ArH), 6.96–6.90 (m, 2H, ArH); ^{13}C NMR δ: 152.1, 142.0, 134.4, 131.9, 130.7, 130.4, 128.1, 128.0, 127.6, 127.0, 121.9; MALDI-TOF-MS m/z: 277 $[M+H]^+$.

4.1.110. 2-(4′-Methylbiphenyl-2-yl)-1*H*-benzoimidazole (29). Compound **29** was prepared according to the general procedure K starting from compound **29i** (600 mg, 1.98 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 42%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.55; t_R (TSK gel, method A): 4.68 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.07 (s, 1H, NH), 7.70-7.67 (m, 1H, ArH), 7.62–7.56 (m, 4H, ArH), 7.34 (m, 1H, ArH), 7.13 (m, 2H, ArH), 7.11–7.03 (m, 4H, ArH), 2.24 (s, 3H, CH_3); ^{13}C NMR δ: 152.8, 144.1, 141.5, 137.8, 136.9, 135.1, 131.7, 131.0, 130.7, 130.4, 129.4, 129.2, 127.7, 122.6, 121.8, 119.4, 111.9, 21.2; MALDI-TOF-MS m/z: 277 $[M+H]^+$.

4.1.111. 2-(2-Phenethylphenyl)-1*H*-benzoimidazole (30). Compound **30** was prepared according to the general procedure K starting from compound **30i** (800 mg, 2.53 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 44%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.55; t_R (TSK gel, method B): 5.88 min, P_{HPLC}: 97%; ^{1}H NMR δ: 12.59 (s, 1H, NH), 7.64–7.60 (m, 2H, ArH), 7.43 (m, 1H, ArH), 7.31–7.26 (m, 3H, ArH), 7.15–7.08 (m, 6H, ArH), 7.05–7.02 (m, 1H, ArH), 3.20 (m, 2H, CH_2), 2.69 (m, 2H, CH_2); ^{13}C NMR δ: 152.6, 144.7, 142.8, 142.1, 135.2, 131.6, 130.6, 130.5, 130.3, 129.2, 129.0, 127.1, 126.6, 123.2, 122.3, 119.7, 112.1, 37.9, 26.9; MALDI-TOF-MS m/z: 299 $[M+H]^+$.

4.1.112. 2-(2-Benzylphenyl)-1*H*-benzoimidazole (31). Compound **31** was prepared according to the general procedure K starting from compound **31i** (450 mg, 1.49 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 61%; white solid; mp 196–198 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.80; t_R (TSK gel, method B): 5.49 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.68 (s, 1H, NH), 7.72–7.67 (m, 2H, ArH), 7.53 (m, 1H, ArH), 7.45–7.31 (m, 3H, ArH), 7.22–7.05 (m, 7H, ArH), 4.54 (m, 2H, CH_2); ^{13}C NMR δ: 141.9, 141.3, 131.6, 130.4, 130.1, 129.3, 128.8, 126.9, 126.4, 38.6; MALDI-TOF-MS m/z: 285 $[M+H]^+$.

4.1.113. 2-(3-Bromophenyl)-1*H*-benzoimidazole (32). Compound **32** was prepared according to the general procedure I starting from compound **32i** (480 mg, 1.65 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 86%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.60; t_R (TSK gel, method A): 4.17 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.80 (s, 1H, NH), 8.37 (s, 1H, ArH), 8.18 (d, J = 7.8 Hz, 1H, ArH), 7.68 (d, J = 8.0 Hz, 1H, ArH), 7.61 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.22 (m, 2H, ArH); ^{13}C NMR δ: 150.2, 133.0, 131.8, 129.5, 125.9, 123.0, 97.7; MALDI-TOF-MS m/z: 274 $[M+H]^+$.

4.1.114. 2-(Phenylpiperidin-1-ylmethyl)-1*H*-benzoimidazole (33). Compound **33** was prepared according to the general procedure I starting from compound **33i** (450 mg, 1.45 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 64%; white solid; mp 197–201 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1): 0.45; t_R (TSK gel, method A): 4.25 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.21 (s, 1H, NH), 7.44 (m, 3H, ArH), 7.33 (m, 1H, ArH), 7.25 (m, 2H, ArH), 7.17 (m, 1H, ArH), 7.02 (m, 2H, ArH), 4.54 (s, 1H, CH), 2.27 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 1.44 (m, 4H, CH_2), 1.30 (m, 2H, CH_2); ^{13}C NMR δ: 155.6, 143.6, 140.1, 135.2, 129.2, 128.3, 122.7,

121.8, 119.3, 112.1, 71.1, 53.2, 26.4, 24.9; MALDI-TOF-MS *m/z*: 292 $[M+H]^+$.

4.1.115. 2-(Morpholin-4-ylphenylmethyl)-1*H*-benzoimidazole (34). Compound **34** was prepared according to the general procedure I starting from crude compound **34i** (2 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 25% global; white solid; mp > 225 °C; R_f (cyclohexane/AcOEt 8:2): 0.65; t_R (TSK gel, method A): 4.29 min, P_{HPLC}: 99%; ^1H NMR δ: 12.38 (s, 1H, NH), 7.58–7.44 (m, 3H, ArH), 7.37–7.32 (m, 2H, ArH), 7.29–7.23 (m, 2H, ArH), 7.11 (m, 2H, ArH), 4.64 (s, 1H, CH), 3.60 (m, 4H, 2 CH_2), 2.40 (m, 2H, CH_2), 2.29 (m, 2H, CH_2); ^{13}C NMR δ: 129.1, 128.3, 70.7, 66.8, 52.5; MALDI-TOF-MS *m/z*: 294 $[M+H]^+$.

4.1.116. 2-(Azepan-1-ylphenylmethyl)-1*H*-benzoimidazole (35). Compound **35** was prepared according to the general procedure I starting from compound **35i** (300 mg, 0.92 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 68%; white solid; mp 191–194 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.45; t_R (TSK gel, method A): 4.61 min, P_{HPLC}: 99%; ^1H NMR δ: 12.23 (s, 1H, NH), 7.52 (m, 3H, ArH), 7.43 (m, 1H, ArH), 7.33 (m, 2H, ArH), 7.23 (m, 1H, ArH), 7.11 (m, 2H, ArH), 4.99 (s, 1H, CH), 2.64 (m, 4H, 2 CH_2), 1.58 (m, 8H, 4 CH_2); ^{13}C NMR δ: 162.7, 156.0, 143.6, 141.2, 135.2, 129.1, 129.0, 128.2, 122.7, 121.8, 119.4, 112.1, 69.6, 53.7, 29.0, 27.2; MALDI-TOF-MS *m/z*: 306 $[M+H]^+$.

4.1.117. 1-[(1*H*-Benzoimidazol-2-yl)phenylmethyl]pyrrolidin-3-ylamine (36). Compound **36** was prepared according to the general procedure K starting from compound **36i** (450 mg, 1.09 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1). Yield: 20%; white solid; mp 74–80 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.6:0.4:0.1): 0.30; t_R (TSK gel, method A): 3.38–3.45 min, P_{HPLC}: 99%; ^1H NMR δ: 12.23 (s, 1H, NH), 7.48 (d, J = 7.7 Hz, 2H, ArH phenyl), 7.33 (m, 2H, ArH), 7.24 (t, J = 7.2 Hz, 2H, ArH phenyl), 7.16 (d, J = 7.2 Hz, 1H, ArH phenyl), 7.02 (m, 2H, ArH), 4.60 (m, 3H, CH + NH_2), 3.35 (m, 1H, CH), 2.52 (m, 2H, CH_2), 2.30 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 1.96 (m, 1H, CH_2), 1.40 (m, 1H, CH_2); ^{13}C NMR δ: 156.2, 156.1, 141.0, 129.0, 128.6, 128.1, 121.9, 115.6, 69.7, 69.6, 61.9, 61.7, 51.9, 50.8, 34.1; MALDI-TOF-MS *m/z*: 293 $[M+H]^+$.

4.1.118. 1-[(1*H*-Benzoimidazol-2-yl)phenylmethyl] piperidin-4-ol (37). Compound **37** was prepared according to the general procedure K starting from compound **37i** (220 mg, 0.67 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.6:0.4:0.1). Yield: 40%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.6:0.4:0.1): 0.40; t_R (TSK gel, method A): 3.94 min, P_{HPLC}: 99%; ^1H NMR δ: 12.29 (s, 1H, NH), 7.53 (m, 3H, ArH), 7.43 (m, 1H, ArH), 7.34 (m, 2H, ArH), 7.25 (m, 1H, ArH), 7.12 (m, 2H, ArH), 4.64 (s, 1H, CH), 4.57 (d, J = 4.0 Hz, 1H, OH), 3.45 (m, 1H, CH), 2.67 (m, 1H, CH_2), 2.51 (m, 1H, CH_2), 2.12 (m, 1H, CH_2), 1.99 (m, 1H, CH_2), 1.72 (m, 2H, CH_2), 1.45 (m, 2H, CH_2); ^{13}C NMR δ: 155.7, 140.3, 129.3, 129.1, 128.3, 122.7, 121.8, 119.3, 112.2, 70.5, 67.0, 50.2, 50.0, 35.1; MALDI-TOF-MS *m/z*: 308 $[M+H]^+$.

4.1.119. [(1*H*-Benzoimidazol-2-yl)phenylmethyl]cyclohexylamine (38). Compound **38** was prepared according to the general procedure K starting from compound **38i** (450 mg, 1.4 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 30%; white solid; mp 174–175 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.6:0.4:0.1): 0.45; t_R (TSK gel, method A): 4.51 min, P_{HPLC}: 99%; ^1H NMR δ: 12.26 (s, 1H, NH benzimidazolyl), 7.47 (m, 4H, ArH), 7.34 (m, 2H, ArH), 7.22 (m, 1H, ArH), 7.11 (m, 2H, ArH), 5.24 (s, 1H, CH), 2.33 (m, 1H, CH), 1.86 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.49 (m, 1H, CH_2), 1.10 (m, 5H, CH_2); ^{13}C NMR δ: 128.9, 128.0, 127.9, 58.7, 54.5, 33.2, 26.3, 25.0; MALDI-TOF-MS *m/z*: 307 $[M+H]^+$.

4.1.120. (1*H*-Benzoimidazol-2-yl)cyclohexylphenylamine (39). To a solution of compound **39i** (300 mg, 0.84 mmol, 1 equiv) in 7 mL of absolute EtOH was added tin chloride (316 mg, 1.68 mmol, 2 equiv). Following reflux of the mixture for 5 h, the solvent was evaporated and the residue purified by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1) to afford compound **39**. Yield: 41%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1): 0.40; t_R (TSK gel, method A): 5.18 min, P_{HPLC}: 99%; ^1H NMR δ: 10.37 (s, 1H, NH benzimidazolyl), 7.50–7.37 (m, 3H, ArH), 7.28–7.20 (m, 5H, ArH), 4.41 (m, 1H, CH cyclohexyl), 1.94 (m, 2H, CH_2 cyclohexyl), 1.71 (m, 2H, CH_2 cyclohexyl), 1.54 (m, 1H, CH_2 cyclohexyl), 1.42–1.32 (m, 2H, CH_2 cyclohexyl), 1.13–1.06 (m, 2H, CH_2 cyclohexyl), 0.91 (m, 1H, CH_2 cyclohexyl); ^{13}C NMR δ: 155.8, 140.4, 131.4, 130.5, 128.5, 57.7, 32.2, 26.3, 26.0; MALDI-TOF-MS *m/z*: 292 $[M+H]^+$.

4.1.121. (1*H*-Benzoimidazol-2-yl)-(2-piperidin-1-ylphenyl)amine (40). To a solution of compound **40i** (750 mg, 2.1 mmol, 1 equiv) in 10 mL of absolute EtOH was added tin chloride (792 mg, 4.2 mmol, 2 equiv). Following reflux of the mixture for 5 h, the solvent was evaporated and the residue purified by two successive TLC (CH_2Cl_2/MeOH 9.8:0.2, then cyclohexane/AcOEt/NH_4OH 7:3:0.05) to afford compound **40**. Yield: 25%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.25; t_R (TSK gel, method A): 4.25 min, P_{HPLC}: 99%; ^1H NMR δ: 11.59 (s, 1H, NH benzimidazolyl), 8.59 (dd, J = 1.4, 8.1 Hz, 1H, ArH), 8.28 (s, 1H, NH), 7.35–7.29 (m, 2H, ArH benzimidazolyl), 7.18 (dd, J = 1.4, 7.8 Hz, 1H, ArH), 7.12 (td, J = 1.2, 7.9 Hz, 1H, ArH), 7.02–6.98 (m, 2H, ArH benzimidazolyl), 6.92 (td, J = 1.5, 7.6 Hz, 1H, ArH), 2.78 (t, J = 5.0 Hz, 4H, 2 CH_2), 1.78 (m, 4H, 2 CH_2), 1.59 (m, 2H, CH_2); ^{13}C NMR δ: 151.2, 141.9, 135.5, 125.1, 121.5, 120.9, 120.4, 117.3, 116.6, 53.8, 26.6, 24.3; MALDI-TOF-MS *m/z*: 293 $[M+H]^+$.

4.1.122. 2-(Cyclohexylphenylmethyl)benzooxazole (41). To a solution of 2-aminophenol (300 mg, 2.75 mmol, 1 equiv) in 10 mL of THF were added cyclohexylphenyl-

acetic acid (660 mg, 3.02 mmol, 1.1 equiv) and a solution of DCC 1 M in CH_2Cl_2 (3.02 mL, 3.02 mmol, 1.1 equiv). After stirring for 12 h at room temperature, the mixture was flitrated and the solvents were evaporated. The residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. To a solution of the residue in 10 mL of toluene was added *para*-toluenesulfonic acid (2.61 g, 13.75 mmol, 5 equiv). Following reflux of the mixture for 8 h, the solvent was evaporated, the residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, and concentrated, and the residue purified by TLC (cyclohexane/AcOEt 8:2) to afford compound **41**. Yield: 40%; white solid; mp 87–89 °C; R_f (cyclohexane/AcOEt 8:2): 0.70; t_R (TSK gel, method B): 10.48 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.62 (m, 1H, ArH), 7.55 (m, 1H, ArH), 7.34 (m, 2H, ArH), 7.22 (m, 4H, ArH), 7.13 (m, 1H, ArH), 3.95 (d, J = 10.3 Hz, 1H, CH), 2.14 (m, 1H, CH), 1.55-0.80 (m, 10H, CH_2 cyclohexyl); ^{13}C NMR δ: 168.2, 150.8, 141.5, 139.3, 129.5, 129.3, 128.0, 125.7, 125.2, 120.3, 111.5, 52.4, 41.9, 32.0, 31.1, 26.6, 26.3; MALDI-TOF-MS *m*/*z*: 292 $[M+H]^+$.

4.1.123. 2-(Cyclohexylphenylmethyl)-3,4-dihydroquinazoline (42). Compound **42i** (400 mg, 1.24 mmol, 1 equiv) was diltued in 10 mL of neat acetic acid. Following reflux of the mixture for 24 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2/MeOH 9.5:0.5) to afford compound **42**. Yield: 40%; light yellow solid; mp 117–119 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.35; t_R (TSK gel, method B): 6.26 min, P_{HPLC}: 99%; ^{1}H NMR δ: 10.83 (s, 1H, NH), 7.68 (m, 1H, ArH phenyl), 7.37 (m, 2H, ArH), 7.31 (m, 2H, ArH), 7.22 (m, 2H, ArH phenyl), 7.15 (m, 1H, ArH phenyl), 7.01 (m, 1H, ArH phenyl), 3.67 (d, J = 5.6 Hz, 2H, CH_2), 3.18 (d, J = 10.7 Hz, 1H, CH), 2.11 (m, 1H, CH), 1.89 (m, 1H, H cyclohexyl), 1.72 (m, 1H, H cyclohexyl), 1.58 (m, 2H, H cyclohexyl), 1.26-1.05 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 171.9, 140.1, 138.1, 129.3, 129.2, 129.0, 127.9, 127.7, 124.7, 123.2, 60.9, 44.5, 40.9, 32.2, 30.9, 26.8, 26.3; MALDI-TOF-MS *m*/*z*: 305 $[M+H]^+$.

4.1.124. 2-Cyclohexyl-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-phenyl-ethanone (43). To a solution of cyclohexylphenylacetic acid (394 mg, 1.8 mmol, 1.2 equiv) in 10 mL of dry CH_2Cl_2 were added PybroP (838 mg, 1.8 mmol, 1.2 equiv), DIEA (520 μL, 3 mmol, 2 equiv) and 1,2,3,4-tetrahydroquinoline (200 mg, 1.5 mmol, 1 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2) to afford compound **43**. Yield: 75%; white solid; mp 106–108 °C; R_f (CH_2Cl_2): 0.65; t_R (TSK gel, method B): 9.45 min, P_{HPLC}: 100%; ^{1}H NMR δ: 7.27–7.11 (m, 9H, ArH) 7.29–7.07 (m, 7H, ArH), 7.07 (m, 1H, ArH), 6.88 (m, 1H, ArH), 6.70 (m, 1H, ArH), 6.53 (m, 1H, ArH), 4.71 (s, 2H, NH_2), 2.09 (t, J = 7.2 Hz, 1H, CH), 1.68 (m, 12H, CH + CH_2), 1.10 (m, 10H, CH_2); ^{13}C NMR δ: 173.2, 142.8, 126.6, 126.2, 124.6, 117.2, 116.9, 57.3, 36.9, 31.8, 29.9, 27.1, 27.0, 26.9; MALDI-TOF-MS *m*/*z*: 334 $[M+H]^+$.

4.1.125. 2-(Cyclohexylphenylmethyl)-4-nitro-1*H*-benzoimidazole (44). Compound **44** was prepared according to the general procedure I starting from compound **44i** (200 mg, 0.56 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 95%; yellow solid; mp 167-169 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.80; t_R (TSK gel, method B): 7.72 min, P_{HPLC}: 99%; ^{1}H NMR δ: 13.02 (s, 1H, NH), 7.99 (m, 2H, ArH), 7.43 (m, 2H, ArH), 7.31–7.19 (m, 3H, ArH), 7.10 (m, 1H, ArH), 4.10 (d, J = 10.7 Hz, 1H, CH), 2.24 (m, 1H, CH), 1.50-0.97 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 161.2, 147.5, 141.2, 133.5, 129.5, 129.1, 128.5, 127.5, 127.2, 121.8, 118.9, 51.6, 42.4, 32.2, 31.5, 26.7, 26.2; MALDI-TOF-MS *m*/*z*: not observed.

4.1.126. 2-(Cyclohexylphenylmethyl)-1*H*-benzoimidazol-4-ylamine (45). To a solution of compound **44** (300 mg, 0.89 mmol, 1 equiv) in 5 mL of EtOH were added iron (299 mg, 5.34 mmol, 6 equiv) and HCl 12 N (200 μL, 2.3 mmol, 2.5 equiv). Following reflux of the mixture for 6 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2/MeOH 9.6:0.4) to afford compound **45**. Yield: 44%; grey-green solid; mp 96–99 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.50; t_R (TSK gel, method B): 6.02 min, P_{HPLC}: 99%; ^{1}H NMR δ (isomere mixture 75:25): 11.70 (s, 0.75H, NH), 11.44 (s, 0.25H, NH), 7.21 (m, 2H, ArH), 7.04 (m, 2H, ArH), 6.93 (m, 1H, ArH), 6.56-6.32 (m, 2H, ArH), 6.03 (m, 1H, ArH), 5.05 (s, 1.5H, NH_2), 5.00 (s, 0.5H, NH_2), 3.52 (d, J = 10.9 Hz, 0.75H, CH), 3.50 (d, J = 10.6 Hz, 0.25H, CH), 2.02 (m, 1H, CH), 1.35–0.81 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 154.1, 142.0, 140.2, 129.2, 127.3, 123.4, 122.6, 107.8, 106.4, 104.9, 99.7, 53.6, 41.8, 32.4, 31.7, 26.8, 26.4; MALDI-TOF-MS *m*/*z*: 306 $[M+H]^+$.

4.1.127. [2-(Cyclohexylphenylmethyl)-1*H*-benzoimidazol-4-yl]ethylamine (46). To a solution of compound **45** (250 mg, 0.82 mmol, 1 equiv) in 2.5 mL of methanol were added, at 0 °C, acetaldehyde (46 μL, 0.82 mmol, 1 equiv) and sodium cyanoborohydride (51.5 mg, 0.82 mmol, 1 equiv). After stirring the mixture for 24 h at room temperature, the solvent was evaporated and the residue purified by TLC (cyclohexane/AcOEt 6:4) to afford compound **46**. Yield: 30%; white solid; mp 90–98 °C; R_f (cyclohexane/AcOEt 6:4): 0.65; t_R (TSK gel, method A): 5.77 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.00 (s, 1H, NH), 7.44 (d, J = 7.4 Hz, 2H, ArH phenyl), 7.27 (t, J = 7.2 Hz, 2H, ArH phenyl), 7.15 (t, J = 7.3 Hz, 1 H, ArH phenyl), 6.85 (t, J = 7.9 Hz, 1H, ArH), 6.58 (d, J = 7.2 Hz, 1H, ArH), 6.15 (d, J = 7.5 Hz, 1H, ArH), 5.21 (t, J = 5.8 Hz, 1H, NH), 3.22 (m, 2H, CH_2 ethyl), 2.28 (m, 1H, CH cyclohexyl), 1.61–1.50 (m, 4H, H cyclohexyl), 1.30 (m, 1H, H cyclohexyl), 1.22 (t, J = 7.1 Hz, 3H, CH_3 ethyl), 1.21–1.07 (m, 5H, H cyclohexyl); ^{13}C NMR δ: 141.8, 128.9, 127.1, 53.3, 41.6, 32.1, 31.5, 26.6, 26.2, 15.3; MALDI-TOF-MS *m*/*z*: 334 $[M+H]^+$.

4.1.128. *N*-[2-(Cyclohexylphenylmethyl)-1*H*-benzoimidazol-4-yl]acetamide (47). Compound **47** was prepared according to the general procedure J starting from compound **44i** (198 mg, 0.56 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 75%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.40; t_R (TSK gel, method B): 5.74 min, P_{HPLC}: 99%; ^{1}H NMR δ (isomere mixture 70:30): 12.37 (s, 0.7H, NH), 11.64 (s, 0.3H, NH), 9.76 (s, 0.3H, $NHCOCH_3$), 9.63 (s, 0.7H, $NHCOCH_3$), 7.45 (m, 2H, ArH), 7.20-7.08 (m, 2H, ArH), 7.01 (m, 1H, ArH), 3.88 (d, J = 10.6 Hz, 0.3H, CH), 3.83 (d, J = 11.1 Hz, 0.7H, CH), 2.27 (m, 1H, CH), 2.14 (s, 2.1H, CH_3), 2.08 (s, 0.9H, CH_3), 1.57–0.8 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 156.1, 141.6, 135.3, 129.9, 129.3, 129.2, 127.4, 124.0, 122.6, 121.7, 115.6, 115.2, 106.9, 53.8, 52.6, 42.3, 32.4, 32.3, 31.7, 26.7, 26.4, 24.9, 24.4; MALDI-TOF-MS m/z: 348 $[M+H]^+$.

4.1.129. 2-(Cyclohexylphenylmethyl)-4-methyl-1*H*-benzoimidazole (48). Compound **48** was prepared according to the general procedure I starting from compound **48i** (180 mg, 0.56 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 90%; light brown solid; mp 95–97 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.55; t_R (TSK gel, method B): 6.52 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.10 (s, 1H, NH), 7.42 (m, 2H, ArH), 7.33–7.21 (m, 3H, ArH), 7.12 (m, 1H, ArH), 6.93 (m, 1H, ArH), 6.83 (m, 1H, ArH), 3.76 (m, 1H, CH), 2.38 (s, 3H, CH_3), 2.21 (m, 1H, CH), 1.54-0.84 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 141.9, 130.5, 129.3, 129.1, 127.3, 122.8, 122.2, 116.6, 109.1, 53.2, 42.1, 32.4, 31.7, 26.8, 26.4, 18.0; MALDI-TOF-MS m/z: 305 $[M+H]^+$.

4.1.130. 8-(Cyclohexylphenylmethyl)-9*H*-purine (49). Compound **49** was prepared according to the general procedure I starting from compound **49i** (300 mg, 0.96 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 98%; white solid; mp 208–210 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.45; t_R (TSK gel, method B): 6.16 min, P_{HPLC}: 99%; ^{1}H NMR δ: 13.00 (s, 1H, NH), 8.97 (s, 1H, ArH), 8.80 (s, 1H, ArH), 7.22 (m, 2H, ArH phenyl), 7.06 (m, 2H, ArH phenyl), 6.96 (m, 1H, ArH phenyl), 3.89 (d, J = 10.8 Hz, 1H, CH), 2.33 (m, 1H, CH), 1.59–0.98 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 152.4, 140.5, 129.3, 127.8, 53.5, 41.7, 32.2, 31.4, 26.7, 26.3; MALDI-TOF-MS m/z: 293 $[M+H]^+$.

4.1.131. 2-(Cyclohexylphenylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (50). To a solution of crude compond **50i** (5.75 mmol, 1 equiv) in 10 mL of toluene was added *p*-toluenesulfonic acid (2.19 g, 11.5 mmol, 2 equiv). Following reflux of the mixture for 72 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, the organic layer washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2/MeOH 9.7:0.3) to afford compound **50**. Yield: 40%; white solid; mp 221–223 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.40; t_R (TSK gel, method B): 5.66 min, P_{HPLC}: 88%; ^{1}H NMR δ (isomeres mixture 70:30): 12.93 (s, 1H, NH), 8.29 (dd, J = 1.5, 4.8 Hz, 0.3H, ArH), 8.19 (dd, J = 1.5, 4.8 Hz, 0.7H, ArH), 7.93 (dd, J = 1.4, 7.9 Hz, 0.7H, ArH), 7.79 (dd, J = 1.5, 7.9 Hz, 0.3H, ArH), 7.47 (m, 2H, ArH phenyl), 7.32–7.22 (m, 2H, ArH phenyl), 7.21–7.12 (m, 2H, ArH + ArH phenyl), 3.85 (d, J = 10.6 Hz, 0.3H, CH), 3.83 (d, J = 10.8 Hz, 0.7H, CH), 2.34 (m, 1H, CH cyclohexyl), 1.59–1.36 (m, 5H, H cyclohexyl), 1.22–1.08 (m, 5H, H cyclohexyl); ^{13}C NMR δ: 159.6, 143.3, 142.9, 141.0, 135.6, 128.9, 128.8, 126.8, 126.1, 119.1, 117.5, 53.3, 41.4, 32.1, 31.3, 26.5, 26.1; MALDI-TOF-MS m/z: 292 $[M+H]^+$.

4.1.132. 2-(Cyclohexylphenylmethyl)-6-methyl-1*H*-benzoimidazole (51). Compound **51** was prepared according to the general procedure I starting from compound **51i** (400 mg, 1.24 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.7:0.3:0.1). Yield: 56%; orange solid; mp 202–204 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1): 0.75; t_R (TSK gel, method B): 6.53 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.03 (s, 1H, NH), 7.37 (m, 2H, ArH), 7.23 (m, 4H, ArH), 7.09 (m, 1H, ArH), 6.83 (m, 1H, ArH), 3.69 (d, J = 10.7 Hz, 1H, CH), 2.28 (s, 3H, CH_3), 2.18 (m, 1H, CH), 1.51–0.71 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 156.9, 141.8, 129.3, 129.1, 127.3, 123.3, 111.7, 53.3, 42.8, 32.3, 31.7, 31.4, 26.8, 26.4, 22.1; MALDI-TOF-MS m/z: 305 $[M+H]^+$.

4.1.133. 2-(Cyclohexylphenylmethyl)-6-methoxy-1*H*-benzoimidazole (52). Compound **52** was prepared according to the general procedure I starting from compound **52i** (450 mg, 1.33 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1). Yield: 45%; white solid; mp 75–77 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.7:0.3:0.1): 0.50; t_R (TSK gel, method B): 6.26 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.02 (s, 1H, NH), 7.42 (m, 2H, ArH), 7.35–7.23 (m, 3H, ArH), 7.17–7.12 (m, 1H, ArH), 6.96 (m, 1H, ArH), 6.69 (m, 1H, ArH), 3.74 (d, J = 13.0 Hz, 1H, CH), 3.71 (s, 3H, CH_3), 2.24 (m, 1H, CH), 1.57–1.06 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 156.8, 156.0, 141.8, 129.2, 129.1, 127.3, 111.3, 56.3, 53.3, 42.0, 32.3, 31.7, 26.8, 26.4; MALDI-TOF-MS m/z: 321 $[M+H]^+$.

4.1.134. 2-(Cyclohexylphenylmethyl)-6-fluoro-1*H*-benzoimidazole (53). Compound **53** was prepared according to the general procedure J starting from compound **53i** (300 mg, 0.84 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 73%; light brown solid; mp 207–209 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.55; t_R (TSK gel, method B): 6.39 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.62–7.18 (m, 8H, ArH), 4.36 (d, J = 10.3 Hz, 1H, CH), 2.50 (m, 1H, CH), 1.69–0.90 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 128.8, 128.6, 127.8, 113.6, 100.5, 51.2, 40.2, 31.6, 30.5, 25.8, 25.6; MALDI-TOF-MS m/z: 309 $[M+H]^+$.

4.1.135. 6-Chloro-2-(cyclohexylphenylmethyl)-1*H*-benzoimidazole (54). Compound **54** was prepared according to the general procedure I starting from compound **54i** (175 mg, 0.51 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.9:0.1). Yield:

60%; white solid; mp 198–200 °C; R_f (CH_2Cl_2): 0.50; t_R (TSK gel, method B): 6.47 min, P_{HPLC}: 99%; ^1H NMR δ: 12.47 (s, 1H, NH), 7.58-7.40 (m, 4H, ArH), 7.24 (m, 2H, ArH), 7.19–7.08 (m, 2H, ArH), 3.79 (d, J = 10.7 Hz, 1H, CH), 2.24 (m, 1H, CH), 1.56-0.88 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 141.4, 129.2, 127.5, 122.2, 118.6, 111.6, 53.2, 41.9, 32.3, 31.5, 26.7, 26.3; MALDI-TOF-MS m/z: 325 $[M+H]^+$.

4.1.136. 2-(Cyclohexylphenylmethyl)-6-trifluoromethyl-1*H*-benzoimidazole (55). Compound **55** was prepared according to the general procedure I starting from compound **55i** (440 mg, 1.17 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 78%; white solid; mp 200–203 °C; R_f (CH_2Cl_2/MeOH 9.9:0.1): 0.45; t_R (TSK gel, method B): 7.25 min, P_{HPLC}: 99%; ^1H NMR δ: 12.73 (s, 1H, NH), 7.92 (m, 1H, ArH), 7.73 (m, 1H, ArH), 7.58 (m, 1H, ArH), 7.43 (m, 2H, ArH), 7.28 (m, 2H, ArH), 7.17 (m, 1H, ArH), 3.86 (d, J = 10.7 Hz, 1H, CH), 2.30 (m, 1H, CH), 2.19 (m, 1H, CH), 1.60–0.83 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 160.5, 159.9, 141.2, 129.3, 128.8, 127.6, 119.9, 119.1, 118.6, 116.5, 112.6, 109.4, 53.2, 41.9, 32.3, 31.5, 26.7, 26.3; MALDI-TOF-MS m/z: 321 $[M+H]^+$.

4.1.137. 2-(Cyclohexylphenylmethyl)-3*H*-benzoimi-dazole-5-carboxylic acid methyl ester (56). Compound **56** was prepared according to the general procedure I starting from compound **56i** (500 mg, 1.36 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.6:0.4:0.1). Yield: 80%; white solid; mp 117–119 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.60; t_R (TSK gel, method B): 6.45 min, P_{HPLC}: 99%; ^1H NMR δ: 12.51 (s, 1H, NH), 7.94 (s, 1H, ArH), 7.60 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.30 (m, 2H, ArH phenyl), 7.13 (m, 2H, ArH phenyl), 7.02 (m, 1H, ArH phenyl), 3.70 (d, J = 10.7 Hz, 1H, CH), 3.67 (s, 3H, CH_3), 2.13 (m, 1H, CH), 1.42–0.83 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 167.7, 141.2, 129.3, 127.5, 123.5, 123.4, 53.3, 52.7, 41.9, 32.3, 31.5, 26.7, 26.3; MALDI-TOF-MS m/z: 349 $[M+H]^+$.

4.1.138. 2-(Cyclohexylphenylmethyl)-3*H*-benzoimidazole-5-carboxylic acid (57). Compound **56** (150 mg, 0.43 mmol, 1 equiv) was diluted with 10 mL of a aqueous NaOH 2.5 N/MeOH 1:1 mixture. Following reflux of the mixture for 2 h, the methanol was evaporated, the aqueous layer acidified with aqueous HCl 1 M and extracted with CH_2Cl_2, the organic layer dried over $MgSO_4$ and concentrated to afford compound **57**. Yield: 97%; white solid; mp 210–213 °C; R_f (CH_2Cl_2/MeOH 9.2:0.8): 0.40; t_R (TSK gel, method B): 5.98 min, P_{HPLC}: 99%; ^1H NMR δ: 8.17 (s, 1H, ArH), 7.89 (dd, J = 1.3, 8.5 Hz, 1H, ArH), 7.67 (d, J = 8.5 Hz, 1H, ArH), 7.50 (d, J = 7.2 Hz, 2H, ArH phenyl), 7.34 (t, J = 7.2 Hz, 2H, ArH phenyl), 7.24 (m, 1H, ArH phenyl), 4.07 (d, J = 10.9 Hz, 1H, CH), 2.43 (m, 1H, CH), 1.61–1.49 (m, 4H, H cyclohexyl), 1.42–1.37 (m, 1H, H cyclohexyl), 1.27–0.90 (m, 5H, H cyclohexyl); ^{13}C NMR δ: 167.9, 158.6, 139.5, 129.3, 129.0, 127.9, 126.3, 125.0, 116.8, 114.9, 52.1, 48.4, 31.9, 31.1, 26.4, 25.9; MALDI-TOF-MS m/z: 335 $[M+H]^+$.

4.1.139. Acetic acid 2-(cyclohexylphenylmethyl)-3*H*-benzoimidazol-5-yl ester (58). Compound **58** was prepared according to the general procedure J starting from compound **58i** (430 mg, 1.28 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.3:0.7). Yield: 46%; white solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.45; t_R (TSK gel, method B): 7.44 min, P_{HPLC}: 99%; ^1H NMR δ: 12.10 (s, 1H, NH), 7.37–7.23 (m, 6H, ArH), 6.90 (m, 1H, ArH), 6.58 (m, 2H, ArH), 3.52 (d, J = 10.3 Hz, 1H, CH), 2.37 (s, 3H, CH_3), 1.89 (m, 1H, H cyclohexyl), 1.72 (m, 1H, H cyclohexyl), 1.53 (m, 2H, H cyclohexyl), 1.17–1.05 (m, 6H, H cyclohexyl); ^{13}C NMR δ: 137.9, 129.2, 129.1, 128.0, 104.1, 58.0, 41.1, 38.3, 31.9, 30.3, 26.4, 25.9; MALDI-TOF-MS m/z: 349 $[M+H]^+$.

4.1.140. 2-(Cyclohexylphenylmethyl)-4,5-dimethyl-1*H*-benzoimidazole (59). Compound **59** was prepared according to the general procedure I starting from compound **59i** (430 mg, 1.28 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 81%; white solid; mp 209–212 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.50; t_R (TSK gel, method B): 7.05 min, P_{HPLC}: 99%; ^1H NMR δ: 12.05 (s, 1H, NH), 7.47 (m, 2H, ArH), 7.30-7.21 (m, 2H, ArH), 7.19–7.13 (m, 2H, ArH), 6.90 (m, 1H, ArH), 3.80 (d, J = 10.7 Hz, 1H, CH), 2.37–2.25 (m, 7H, 1 CH + 2 CH_3), 2.19 (m, 1H, CH), 1.58–0.81 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 141.9, 129.3, 129.1, 128.6, 127.3, 124.1, 53.4, 41.9, 32.3, 31.7, 26.8, 26.4, 19.8; MALDI-TOF-MS m/z: 319 $[M+H]^+$.

4.1.141. 2-(Cyclohexylphenylmethyl)-5,6-dimethyl-1*H*-benzoimidazole (60). Compound **60** was prepared according to the general procedure I starting from compound **60i** (400 mg, 1.19 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.7:0.3:0.1). Yield: 55%; white solid; mp 210–213 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.50; t_R (TSK gel, method B): 6.79 min, P_{HPLC}: 99%; ^1H NMR δ: 12.09 (s, 1H, NH), 7.43 (m, 2H, ArH), 7.27 (m, 3H, ArH), 7.16 (m, 2H, ArH), 3.74 (d, J = 10.7 Hz, 1H, CH), 2.24 (m, 7H, 1 CH + 2 CH_3), 1.57-1.05 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 156.3, 142.8, 141.9, 133.2, 130.6, 129.7, 129.3, 129.1, 127.3, 119.4, 111.8, 53.3, 42.1, 32.3, 31.7, 26.8, 26.4, 20.7; MALDI-TOF-MS m/z: 319 $[M+H]^+$.

4.1.142. 2-(Cyclohexylphenylmethyl)-5,6-dimethoxy-1*H*-benzoimidazole (61). Compound **61** was prepared according to the general procedure I starting from compound **61i** (330 mg, 0.89 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9.5:0.5:0.1). Yield: 38%; white solid; mp 76–80 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.5:0.5:0.1): 0.50; t_R (TSK gel, method B): 6.33 min, P_{HPLC}: 99%; ^1H NMR δ: 11.97 (s, 1H, NH), 7.45 (m, 2H, ArH), 7.30 (m, 2H, ArH), 7.21–6.96 (m, 3H, ArH), 3.77 (m, 4H, CH + CH_3), 3.35 (s, 3H, CH_3), 2.27 (m, 1H, CH), 1.71–1.07 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 155.5, 146.6, 142.1, 129.2, 129.1, 127.2, 56.8, 53.1, 48.4, 42.2, 34.2, 32.3, 31.7, 26.8, 26.4, 26.2, 25.3; MALDI-TOF-MS m/z: 351 $[M+H]^+$.

4.1.143. 5,6-Dichloro-2-(cyclohexylphenylmethyl)-1*H*-benzoimidazole (62). Compound **62** was prepared according to the general procedure I starting from compound **62i** (220 mg, 0.58 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 72%; white solid; mp 211–214 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.40; t_R (TSK gel, method B): 7.31 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.52 (s, 1H, NH), 7.79–7.65 (m, 2H, ArH), 7.42–7.39 (m, 2H, ArH), 7.29–7.22 (m, 2H, ArH), 7.19–7.14 (m, 1H, ArH), 3.81 (d, J = 10.7 Hz, 1H, CH), 2.24 (m, 1H, CH), 1.56–1.08 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 160.2, 141.1, 129.9, 129.3, 127.6, 124.5, 120.4, 113.4, 53.1, 41.9, 32.2, 31.5, 26.7, 26.3; MALDI-TOF-MS *m*/*z*: 359 $[M+H]^+$.

4.1.144. 2-(Cyclohexylphenylmethyl)-1*H*-naphtho[2,3-*d*]imidazole (63). Compound **63** was prepared according to the general procedure I starting from compound **63i** (250 mg, 0.69 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 63%; brown solid; mp > 225 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.45; t_R (TSK gel, method B): 7.26 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.37 (s, 1H, NH), 8.09 (s, 1H, ArH), 7.93 (m, 2H, ArH), 7.86 (s, 1H, ArH), 7.51 (m, 2H, ArH), 7.37–7.29 (m, 4H, ArH), 7.20 (m, 1H, ArH), 3.90 (d, J = 10.7 Hz, 1H, CH), 2.37 (m, 1H, CH), 1.77-0.91 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 144.9, 141.3, 135.7, 130.5, 130.2, 129.3, 129.2, 128.8, 128.1, 127.6, 124.3, 123.6, 115.5, 106.9, 53.6, 41.9, 32.3, 31.6, 26.8, 26.4; MALDI-TOF-MS *m*/*z*: 341 $[M+H]^+$.

4.1.145. 2-(Cyclohexylphenylmethyl)-6-piperidin-1-yl-1*H*-benzoimidazole (64). Compound **64** was prepared according to the general procedure L starting from compound **64i** (750 mg, 1.78 mmol, 1 equiv) and was obtained after purification by TLC (cyclohexane/AcOEt/NH_4OH 6:4:0.1). Yield: 33%; white solid; mp 115–120 °C; R_f (CH_2Cl_2/MeOH 9.6:0.4): 0.55; t_R (TSK gel, method A): 5.56 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.00 (s, 1H, NH), 7.44 (m, 2H, ArH phenyl), 7.31–7.25 (m, 3H, 1 ArH + 2 ArH phenyl), 7.20–7.14 (m, 1H, ArH phenyl), 6.90 (s, 1H, ArH), 6.82 (m, 1H, ArH), 3.74 (d, J = 10.7 Hz, 1H, CH), 3.00 (t, J = 5.1 Hz, 4H, CH_2 piperidinyl), 2.24 (m, 1H, CH), 1.67–1.47 (m, 10H, CH_2 cyclohexyl + CH_2 piperidinyl), 1.39–0.95 (m, 6H, CH_2 cyclohexyl); ^{13}C NMR δ: 156.3, 149.1, 141.2, 129.2, 129.1, 127.3, 114.9, 53.3, 52.8, 41.9, 32.3, 31.7, 26.8, 26.5, 26.4, 24.8; MALDI-TOF-MS *m*/*z*: 374 $[M+H]^+$.

4.1.146. 2-(Cyclohexylphenylmethyl)-6-(4-methylpiperazin-1-yl)- 1*H*-benzoimidazole (65). Compound **65** was prepared according to the general procedure L starting from compound **65i** (500 mg, 2.1 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1). Yield: 15%; white solid; mp 98–103 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1): 0.30; t_R (TSK gel, method A): 5.48 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.00 (s, 1H, NH), 7.42 (m, 2H, ArH), 7.27 (m, 3H, ArH), 7.17 (m, 1H, ArH), 6.82 (m, 2H, ArH), 3.75 (d, J = 10.7 Hz, 1H, CH), 3.04 (m, 4H, 2 CH_2), 2.50 (m, 4H, 2 CH_2), 2.23 (m, 4H, CH + CH_3), 1.59-1.07 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 129.2, 129.1, 127.3, 113.6, 67.1, 55.6, 53.3, 50.9, 46.5, 43.2, 32.3, 31.7, 26.8, 26.4; MALDI-TOF-MS *m*/*z*: 389 $[M+H]^+$.

4.1.147. 2-(Cyclohexylphenylmethyl)-6-morpholin-4-yl-1*H*-benzoimidazole (66). To a solution of crude compound **66i** (1.57 mmol, 1 equiv) in 10 mL of EtOH were added iron (132 mg, 2.35 mmol, 1.5 equiv) and HCl 12 N (1.3 mL, 15.7 mmol, 10 equiv). Following reflux of the mixture for 8 h, the solvent was evaporated, the residue diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole **66** was obtained after purification by TLC (CH_2Cl_2/MeOH 9:1). Yield: 25%; light green solid; mp 114–116 °C; R_f (CH_2Cl_2/MeOH 9.2:0.8): 0.60; t_R (TSK gel, method B): 6.40 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.00 (s, 1H, NH), 7.43 (m, 2H, ArH), 7.28 (m, 3H, ArH), 7.16 (m, 1H, ArH), 6.83 (m, 2H, ArH), 3.76–3.71 (m, 5H, CH + 2 CH_2), 3.01 (t, J = 4.7 Hz, 4H, 2 CH_2), 2.23 (m, 1H, CH), 1.58–1.01 (m, 10H, H cyclohexyl); ^{13}C NMR δ: 141.9, 129.2, 129.1, 127.3, 67.1, 53.3, 51.4, 42.0, 32.3, 31.7, 26.8, 26.4; MALDI-TOF-MS *m*/*z*: 376 $[M+H]^+$.

4.1.148. 2-(Cyclohexylphenylmethyl)-6-thiomorpholin-4-yl-1*H*-benzoimidazole (67). Compound **67** was prepared according to the general procedure L starting from compound **67i** (700 mg, 1.6 mmol, 1 equiv) and was obtained after purification by TLC (cyclohexane/AcOEt/NH_4OH 6:4:0.1). Yield: 32%; white solid; mp 109–117 °C; R_f (cyclohexane/AcOEt/NH_4OH 7:3:0.1): 0.35; t_R (TSK gel, method A): 5.61 min, P_{HPLC}: 99%; ^{1}H NMR δ: 7.44 (m, 2H, ArH), 7.35–7.26 (m, 3H, ArH), 7.20–7.14 (m, 1H, ArH), 6.96 (m, 1H, ArH), 6.82 (m, 1H, ArH), 3.76 (d, J = 10.7 Hz, 1H, CH), 3.35 (t, J = 4.9 Hz, 4H, 2 CH_2), 2.71 (t, J = 5.0 Hz, 4H, 2 CH_2), 2.25 (m, 1H, CH), 1.59-1.50 (m, 4H, H cyclohexyl), 1.36 (m, 1H, H cyclohexyl), 1.23–0.96 (m, 5H, H cyclohexyl); ^{13}C NMR δ: 156.3, 148.3, 141.6, 129.0, 128.9, 127.1, 115.6, 115.3, 54.1, 52.9, 41.7, 31.4, 27.3, 26.6, 26.1; MALDI-TOF-MS *m*/*z*: 392 $[M+H]^+$.

4.1.149. 2-Biphenyl-2-yl-6-methoxy-1*H*-benzoimidazole (68). Compound **68** was prepared according to the general procedure K starting from compound **68i** (300 mg, 0.94 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 38%; white solid; mp 92–94 °C; R_f (CH_2Cl_2/MeOH/NH_4OH 9.6:0.4:0.1): 0.55; t_R (TSK gel, method B): 5.48 min, P_{HPLC}: 99%; ^{1}H NMR δ: 11.75 (s, 1H, NH), 7.63 (m, 1H, ArH), 7.54 (m, 1H, ArH), 7.46 (m, 2H, ArH), 7.29 (m, 1H, ArH), 7.22–7.11 (m, 5H, ArH), 6.87 (m, 1H, ArH), 6.70 (m, 1H, ArH), 3.69 (s, 3H, OCH_3); ^{13}C NMR δ: 175.2, 141.1, 131.9, 131.3, 131.1, 130.5, 129.6, 128.9, 128.2, 127.9, 112.0, 98.1, 56.2; MALDI-TOF-MS *m*/*z*: 301 $[M+H]^+$.

4.1.150. 6-Methoxy-2-(2-phenoxyphenyl)-1*H*-benzoimidazole (69). Compound **69** was prepared according to the general procedure K starting from compound **69i** (240 mg, 0.72 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.7:0.3). Yield: 80%; white solid; mp 62–72 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.65; t_R (TSK gel, method B): 6.25 min, P_{HPLC}:

99%; ^{1}H NMR δ: 12.10 (s, 1H, NH), 8.34 (m, 1H, ArH), 7.54–7.40 (m, 4H, ArH), 7.30–7.18 (m, 5H, ArH), 6.90 (m, 1H, ArH), 6.85 (m, 1H, ArH), 3.79 (s, 3H, OCH_3); ^{13}C NMR δ: 156.5, 155.6, 131.7, 131.1, 130.9, 125.3, 124.3, 121.6, 121.1, 120.2, 118.7, 113.0, 112.5, 56.2; MALDI-TOF-MS *m*/*z*: 317 $[M+H]^+$.

4.1.151. [2-(6-Methoxy-1*H*-benzoimidazol-2-yl)phenyl]phenylamine (70). Compound **70** was prepared according to the general procedure K starting from compound **70i** (230 mg, 0.69 mmol, 1 equiv) and was obtained after purification by TLC (CH_2Cl_2/MeOH 9.8:0.2). Yield: 83%; white solid; mp 64–75 °C; R_f (CH_2Cl_2/MeOH 9.8:0.2): 0.60; t_R (TSK gel, method B): 6.05 min, P_{HPLC}: 99%; ^{1}H NMR δ (isomere mixture 60:40): 12.79 (s, 1H, NH), 11.21 (s, 0.4H, NH), 11.15 (s, 0.6H, NH), 7.99 (m, 1H, ArH), 7.80 (m, 0.6H, ArH), 7.60 (m, 0.4H, ArH), 7.39–7.27 (m, 6.4H, ArH), 7.05-7.00 (m, 1.6H, ArH), 6.95–6.89 (m, 2H, ArH), 6.85 (m, 1H, ArH), 3.81 (s, 3H, OCH_3); ^{13}C NMR δ: 157.0, 151.5, 143.9, 142.1, 134.8, 130.9, 130.8, 130.1, 128.3, 122.9, 121.1, 119.5, 118.6, 114.9, 113.9, 113.4, 112.0, 111.8, 101.4, 94.9, 56.1; MALDI-TOF-MS *m*/*z*: 316 $[M+H]^+$.

4.1.152. 2-(2-Cyclohexylphenyl)-6-methoxy-1*H*-benzoimidazole (71). Compound **71** was prepared according to the general procedure K starting from compound **71i** (400 mg, 1.23 mmol, 1 equiv) and was obtained after purification by trituration in a Et_2O/pentane mixture. Yield: 80%; white solid; mp 76–84 °C; R_f (CH_2Cl_2/MeOH 9.7:0.3): 0.40; t_R (TSK gel, method B): 6.39 min, P_{HPLC}: 97%; ^{1}H NMR δ: 12.37 (s, 1H, NH), 7.51–7.23 (m, 5H, ArH), 7.15 (m, 1H, ArH), 6.78 (m, 1H, ArH), 3.77 (s, 3H, OCH_3), 3.29 (m, 1H, CH), 1.70–1.16 (m, 10H, CH_2); ^{13}C NMR δ: 147.7, 130.7, 130.2, 127.4, 126.4, 125.5, 120.3, 112.9, 112.3, 111.7, 102.2, 95.1, 56.3, 48.3, 39.8, 34.6, 34.2, 27.3, 26.5, 25.3; MALDI-TOF-MS *m*/*z*: 307 $[M+H]^+$.

4.1.153. 6-Methoxy-2-(phenylpiperidin-1-ylmethyl)-1*H*-benzoimidazole (72). To a solution of phenylpiperidin-1-ylacetic acid **33a** (2.18 mmol, 1 equiv), synthesized according to the general procedure D, in 10 mL of dry CH_2Cl_2 were added DIEA (760 μL, 4.36 mmol, 2 equiv), PyBrop (1.32 g, 2.83 mmol, 1.3 equiv) and 3-methoxy-*o*-phenylenediamine·2HCl (690 mg, 3.27 mmol, 1.5 equiv). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue diluted with 9 mL of an aqueous HCl 4 N/MeOH/dioxane 1:1:1 mixture. Following reflux of the mixture for 72 h, the solvents were evaporated, the residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and the residue purified by TLC (CH_2Cl_2/MeOH 9.5:0.5) to afford compound **72**. Yield: 20% global; white solid; mp 174–175 °C; R_f (CH_2Cl_2/MeOH 9.5:0.5): 0.75; t_R (TSK gel, method A): 4.31 min, P_{HPLC}: 99%; ^{1}H NMR δ: 12.10 (s, 1H, NH), 7.52 (m, 2H, ArH), 7.38–7.21 (m, 4H, ArH), 6.90 (m, 1H, ArH), 6.77–6.69 (m, 1H, ArH), 4.58 (s, 1H, CH), 3.74 (s, 3H, CH_3), 2.36–2.21 (m, 4H, 2 CH_2), 1.52 (m, 4H, 2 CH_2), 1.38 (m, 2H, CH_2); ^{13}C NMR δ: 154.3, 140.0, 128.9, 128.0, 119.5, 112.1, 110.9, 95.2, 70.9, 56.0, 52.9, 26.1, 24.7; MALDI-TOF-MS *m*/*z*: 322 $[M+H]^+$.

4.1.154. 2-(Cyclohexylphenylmethyl)-6-methoxy-1-(2-morpholin-4-ylethyl)-1*H*-benzoimidazole (73). To a solution of compound **52** (250 mg, 0.78 mmol, 1 equiv) in 5 mL of THF were added sodium hydride (60% suspension in oil, 187 mg, 4.68 mmol, 6 equiv), previously washed with hexane, potassium iodide (39 mg, 0.23 mmol, 0.3 equiv) and *N*-(2-chloroethyl)morpholine·HCl (174 mg, 0.93 mmol, 1.2 equiv). Following reflux of the mixture for 12 h, compound **73** was directly purified by TLC (CH_2Cl_2/MeOH/NH_4OH 9.9:0.1:0.1). Yield: 53%; yellow oil; R_f (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1): 0.65; t_R (TSK gel, method B): 5.47 min, P_{HPLC}: 99%; ^{1}H NMR δ (isomere mixture 60:40): 7.46 (m, 0.6H, ArH), 7.38–7.32 (m, 2H, ArH phenyl), 7.27–7.20 (m, 2.4H, 0.4H ArH + 2H ArH phenyl), 7.17–7.10 (m, 1.4H, 0.4H ArH + 1H ArH phenyl), 6.91 (m, 0.6H, ArH), 6.75–6.70 (m, 1H, ArH), 4.21–4.07 (m, 2H, CH_2), 3.92 (d, J = 10.0 Hz, 1H, CH), 3.72 (s, 3H, CH_3), 3.52–3.44 (m, 4H, CH_2), 2.38–2.22 (m, 7H, 1H CH + 6H CH_2), 2.09 (m, 1H, CH_2), 1.67–0.99 (m, 9H, CH_2 cyclohexyl); ^{13}C NMR δ: 156.3, 129.5, 129.2, 127.4, 119.9, 111.9, 111.3, 102.3, 94.8, 66.9, 58.2, 58.1, 54.4, 53.9, 49.8, 42.8, 40.9, 32.5, 31.5, 26.9, 26.6; MALDI-TOF-MS *m*/*z*: 434 $[M+H]^+$.

4.1.155. 2-(Cyclohexylphenylmethyl)-6-methoxy-1-(2-piperidin-1- ylethyl)-1*H*-benzoimidazole (74). To a solution of compound **52** (250 mg, 0.78 mmol, 1 equiv) in 5 mL of THF were added sodium hydride (60% suspension in oil, 187 mg, 4.68 mmol, 6 equiv), previously washed with hexane, potassium iodide (39 mg, 0.23 mmol, 0.3 equiv) and 1-(2-chloroethyl)piperidine.HCl (286 mg, 1.56 mmol, 2 equiv). Following reflux of the mixture for 6 h, compound **74** was directly purified by TLC (CH_2Cl_2/MeOH/NH_4OH 9.8:0.2:0.1). Yield: 95%; yellow oil; R_f (CH_2Cl_2/MeOH/NH_4OH 9.9:0.1:0.1): 0.60; t_R (TSK gel, method B): 5.57 min (50%)–5.66 min (50%), P_{HPLC}: 99%; ^{1}H NMR δ (isomere mixture 50:50): 7.47 (m, 0.5H, ArH), 7.36–7.31 (m, 2H, ArH phenyl), 7.25–7.19 (m, 2.5H, 0.5H ArH + 2H ArH phenyl), 7.17–7.10 (m, 1.5H, 0.5H ArH + 1H ArH phenyl), 6.90 (m, 0.5H, ArH), 6.74–6.69 (m, 1H, ArH), 4.15-4.02 (m, 2H, CH_2), 3.94 (d, J = 10.0 Hz, 1H, CH), 3.72 (s, 3H, CH_3), 2.32–2.03 (m, 8H, 1H CH + 7H CH_2), 1.70–0.99 (m, 15H, CH_2); ^{13}C NMR δ: 164.4, 143.9, 141.3, 137.6, 129.4, 129.2, 127.4, 119.9, 111.9, 111.2, 102.3, 94.8, 58.6, 56.4, 56.2, 55.2, 54.7, 49.8, 42.6, 41.2, 32.5, 31.4, 26.9, 26.6, 26.3, 24.6; MALDI-TOF-MS *m*/*z*: 432 $[M+H]^+$.

4.2. Biological testing

4.2.1. Animals. Animal studies were conducted according to the French Guidelines for the Care and Use of Experimental Animals. Female Wistar rats (200–300 g body weight) from Iffa-Credo (L'Arbresle, France) were used. They were housed in plastic cages at a constant temperature (22 °C) with light from 07.00 to 19.00 h for at least 1 week before the experiments.

4.2.2. Isolation and primary culture of hepatocytes. Hepatocytes were isolated by the collagenase method.[24]

Cell viability was assessed by the Trypan Blue exclusion test and was always higher than 85%. Hepatocytes were seeded at a density of 8×10^6 cells/dish in 100-mm Petri dishes in medium M199 with Earle's salts (Life Technologies, Inc., Paisley, UK) supplemented with 100 U/mL penicillin, 100 mg/mL streptomycin, 0.1% (w/v) bovine serum albumin, 2% (v/v) Ultroser G (IBF, Villeneuve la Garenne, France), 100 nM dexamethasone (Sigma), 1 nM insulin (Actrapid, Novo-Nordisk, Copenhagen, Denmark), and 100 nM triiodothyronine (T3) (Sigma). After cell attachment (4 h), the hepatocytes were cultured for 16–18 h in the presence of 5 mM glucose in a medium similar to the seeding medium but free of Ultroser and albumin and containing 100 nM insulin.

4.2.3. Measurement of AMPK activity. After 1 h incubation with the different products, hepatocytes were directly lysed in the culture medium by adding 1.5 mL of buffer A (final concentrations of 50 mM Tris–HCl, pH 7.5, 50 mM NaF, 5 mM sodium pyrophosphate, 1 mM EDTA, 10% glycerol, 1 mM dithiothreitol, and 1% Triton X-100). The cellular debris were pelleted by centrifugation at 4000*g* for 15 min, and the resulting supernatant was removed, adjusted to 10% with PEG 6000 (Appligene, Illkirch, France) and kept on ice for 20 min. Following further centrifugation (10,000*g*, 15 min), the pellet of proteins was resuspended in 400 μL of buffer A. Aliquots (5 μL) were used to assay the AMPK activity by the SAMS peptide phosphorylation assay in the presence of saturating concentrations of 5′-AMP (200 μM) as described previously.[23]

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