Conversion of Sterically Hindered Diacylated 1,2-Phenylenediamines into 2-Substituted Benzimidazoles

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A series of bulky 2-substituted benzimidazoles was designed in order to find new leads for several biological targets. Formation by cyclodehydration from their monoacylated counterparts was shown to be strongly dependent upon the nature of the acyl group. In the case of a dicyclohexylmethyl group, cyclization was only observed in a *p*-toluenesulfonic acid/toluene mixture from the symmetrical diacylated precursor. Analysis of the mechanism was begun starting from mixed diacylated derivatives.

Key words benzimidazole; cyclization; mechanism

The use of 2-alkyl- and 2-aryl-substituted benzimidazoles has grown extensively in medicinal chemistry. Antihistamine Astemizole[1] and antiulcerative Omeprazole[2] both constitute notable clinical examples. In addition, benzimidazole-based compounds have shown important biological activities such as inhibition of phosphodiesterase IV,[3] antagonism of angiotensin I[4,5] and neuropeptide Y binding.[6] A number of routes have been developed for synthesis of 2-substituted benzimidazoles during last ten years. For example, lewis acids have been used in liquid-[7] or solid-phase[8] synthesis. In our programme, we targeted sterically hindered 2-substituted benzimidazoles.

Synthesis *via* Monoacylated Precursors The choice of bulky substituents for synthesis purposes led us logically to consider a two-step procedure whereby 1,2-phenylenediamine was first treated with the appropriate activated carboxylic acid, and which then allowed, in a second stage, the cyclodehydration of the resulting monoacylated derivative (Chart 1).

Amongst the different coupling reagents tested, the DCC-induced formation of symmetric anhydrides was retained for step 1, involved in the synthesis of compounds **1**—**12** (Table 2), and consequently enabled formation of a series of monoacylated precursors with good yield. Furthermore, for step 2, different acidic conditions relating to cyclodehydration (pure CH_3COOH, HCl (4 N), HCl (4 N) in dioxane/MeOH 1 : 1, CF_3COOH/DCM 1 : 1),[7,9—12] were compared (Table 1) for the case of the diphenylmethyl derivative (compound **1**, Table 2). After 4 h of reflux, total conversion into the 2-substituted benzimidazole was only observed with HCl 4 N in dioxane/MeOH 1 : 1 as solvent (entry 3, Table 1) or with pure acetic acid (entry 1, Table 1).

Under optimal conditions as determined previously: DCC coupling between an appropriate carboxylic acid and 1,2-phenylenediamine, followed by reflux of the monoacylated derivative in pure acetic acid and final purification by thick layer chromatography, led to the isolation of the desired compounds with good yields, except for the dicyclohexylmethyl compound **12** (Table 2). With respect to this compound, there was no cyclization observed after an 8 h reflux either with HCl 4 N in dioxane/MeOH 1 : 1 as solvent or with pure acetic acid.

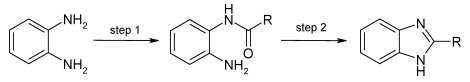


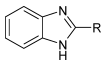
Chart 1. Synthesis of 2-Substituted Benzimidazoles *via* Monoacylated Intermediates

Synthesis *via* Diacylated Precursors and Discussion about the Mechanism of Cyclization Cyclization of compound **12** was observed however in the conditions previously reported for the preparation of 2-substituted benzoxazoles and benzimidazoles, when starting from the corresponding symmetrical diacylated precursor by action of *p*-toluenesul-

Table 1. Yields of Conversion into Compound **1** According to Cyclodehydration Conditions

Entry	Acid	Solvent	Reflux time (h)	Yield (%)
1	CH_3COOH	CH_3COOH	4	100
2	HCl (4 N)	HCl (4 N)	8	50
3	HCl (4 N)	Dioxane/MeOH 1 : 1	4	100
4	*p*TsOH	Toluene	8	95
5	CF_3COOH	DCM	8	0

Table 2. Cyclodehydration Yields of Compounds **1**—**12** *via* Monoacylated Intermediates



Compound	R	Yield (%)	Compound	R	Yield (%)
1		60	**7**		75
2		75	**8**		86
3		84	**9**		95
4		63	**10**		60
5		60	**11**		75
6		74	**12**		0

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Table 3. HPLC Conversion Ratio from Mixed Diacylated Precursors **16**—**30**

Reagent	R	R′	t (h)[a]	Conversion into **A** series derivative (%)	Conversion into **B** series derivative (%)
16			22	65	35
17			36	55	45
18			40	0	100
19			22	0	100
20			36	8	92
21			22	100	100
22			12	88	12
23			12	68	32
24			24	75	25
25			24	93	7
26			24	74	26
27			12	45	55
28			12	100	100
29			80	40	60
30			35	46	54

a) Time to reach 100% of conversion.

fonic acid in toluene at reflux.[13] In the case of benzoxazole formation it was demonstrated that cyclization proceeds through an initial ester hydrolysis with intermediate formation of phenol, requiring the adjacent amido group.[14] Though no such hypothesis for a mechanism has been reported for the case of benzimidazole formation.

Absence of cyclization when starting from the mono dicyclohexylmethyl derivative effectively eliminated the step involved in phenol formation as described for the benzoxazole series. Therefore, we analyzed the mechanism of cyclization by studying the transformation of a series of mixed diacylated materials, comprising either a dicyclohexylmethyl or a diphenylmethyl group and a variety of alkyl, alicyclic, aryl groups, as well as two compounds with a cyclohexylphenylmethyl group (Table 3). Mixed diacylated compounds were synthesized in two consecutive steps, according to the procedure described in Chart 2, and were then brought to reflux in a *p*-toluenesulfonic acid/toluene (0.2 M) mixture. After removal of acidic by-products by washing the reaction mixture with a sodium bicarbonate solution, a typical mixture of derivatives **16A**—**30A** and **16B**—**30B** corresponding to each substituent alternately introduced at the 2-position was obtained and analyzed by HPLC and mass spectrometry.

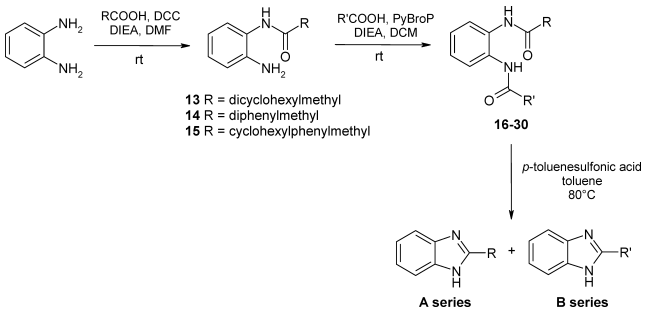

Chart 2. Synthesis of 2-Substituted Benzimidazoles *via* Mixed Diacylated Precursors

With the aim of confirming the nature of the two compounds obtained, each 2-benzimidazole was synthesized. The procedure described in Chart 1 was used for compound **18B** (Table 3). In the case of compound **17B** (or **23B**, Table 3), the monoacetylation was realized with propyl chloride on 2-nitroaniline. The 2-methyl and the 2-*tert*-butyl analogs (respectively **16B** or **22B** and **25B**, Table 3) are commercially available.

The rate of conversion of mixed diacylated 1,2-phenylenediamines **16**—**30** into the corresponding 2-substituted benzimidazoles of the **A** and/or **B** series was strongly dependent upon the nature of the acyl substituents and the transformation was generally complete after 12 to 80 h as shown by HPLC (Table 3).

Conversion of dicyclohexylmethyl acyl compound to the expected 2-benzimidazole **12** (dicyclohexylmethyl derivative) decreased gradually as the size of the opposing alkyl group increased (compounds **16**—**18**) and there was very little or no conversion in the case of an aromatic moiety (compounds **19**, **20**). The same trend was observed when a monocyclohexylmethyl group opposed a diphenylmethyl group (compound **26**) demonstrating thereby that the steric factor has no critical influence. The diphenylmethyl group was also preferentially converted into expected 2-benzimidazole **1** irrespective of the opposing alkyl or alicyclic group and a maximum of conversion was achieved in the case of the *tert*-butyl group (compounds **22**—**26**). Its association with a less bulky aromatic group, such as the benzyl compound **27**, led to a balanced conversion. This balance was also observed when a phenyl ring associated with a cyclohexyl group was opposed by an alicyclic group whether associated or not to a phenyl group (compounds **29**, **30**).

In the last two cases (compounds **29**, **30**), monoacylated derivatives corresponding to the hydrolysis of each amide bond and their cyclized counterparts appeared gradually in both HPLC and mass spectrometry. For compound **29**, they were identified by comparison with compounds **29A**, **29B**, **31** and **32** synthesized independently. HPLC signals for monoacylated intermediates were in good correlation with both conversion percentages related to their cyclized counterparts and with completion times (Chart 3, Figs. 1, 2).

For compounds **16**—**28**, no monoacylated intermediate was detected. So far as compounds **16**—**21** are concerned, these observations are consistent with the absence of cyclization accounted for the dicyclohexylmethyl monoacylated starting material. In this case, the formation of the corresponding 2-benzimidazoles can be explained by an alternate

amide-assisted hydrolysis with a conversion mixture dependent on the nature of the associated group R′. A mechanistic rationale for the conversion of mixed diacylated 1,2-phenylenediamines to benzimidazoles is proposed in Chart 4.

In the previous case as described for an acid-catalyzed amide-assisted phosphinic ester hydrolysis, it is the oxygen rather than the nitrogen atom of the amide which serves as the nucleophilic center.[15] In the present case, intramolecular attack of the amide oxygen on the carbon atom of the adjacent protonated amide of mixed diacylated 1,2-phenylenediamines **33** might afford two 1,2-dihydro-benzo[1,3,6]oxadiazepine intermediates **33′** and **33″**. These intermediates may then rearrange to the benzimidazoles **33A** and **33B** respec-

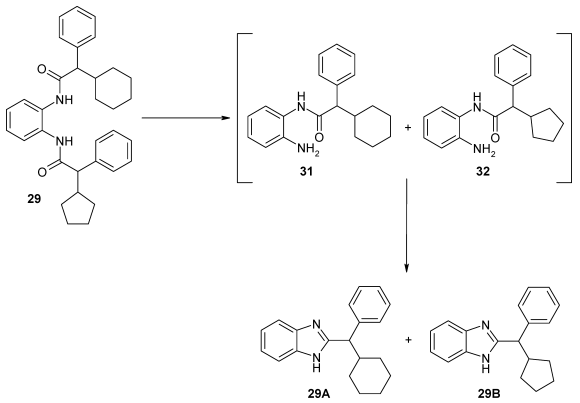

Chart 3. Proposed Mechanism for the Formation of Compounds **29A** and **29B**

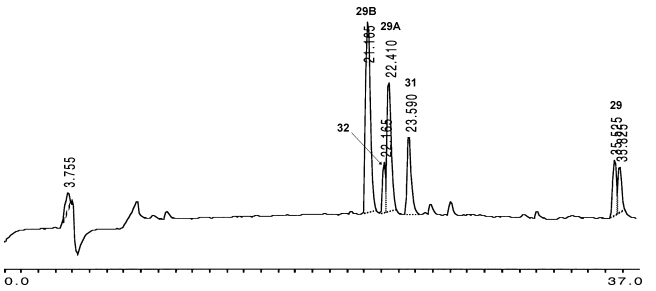

Fig. 1. HPLC Spectrum of the Reaction Mixture for the Formation of Compounds **29A** and **29B** from Compound **29** (Mixture of Diastereoiso-

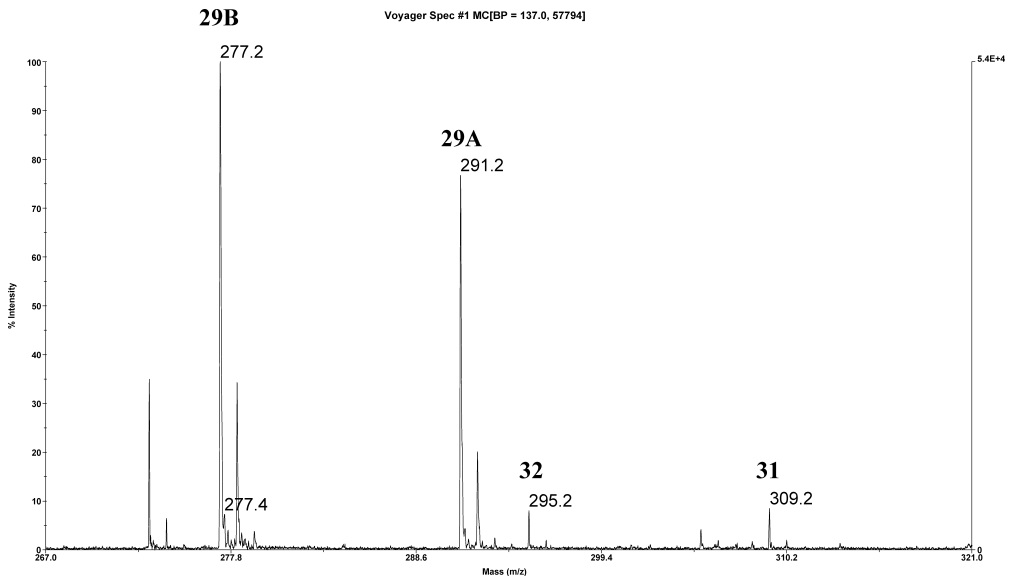

Fig. 2. MALDI-TOF Spectrum of the Reaction Mixture for the Formation of Compounds **29A** and **29B**
Reaction time: 48 h.

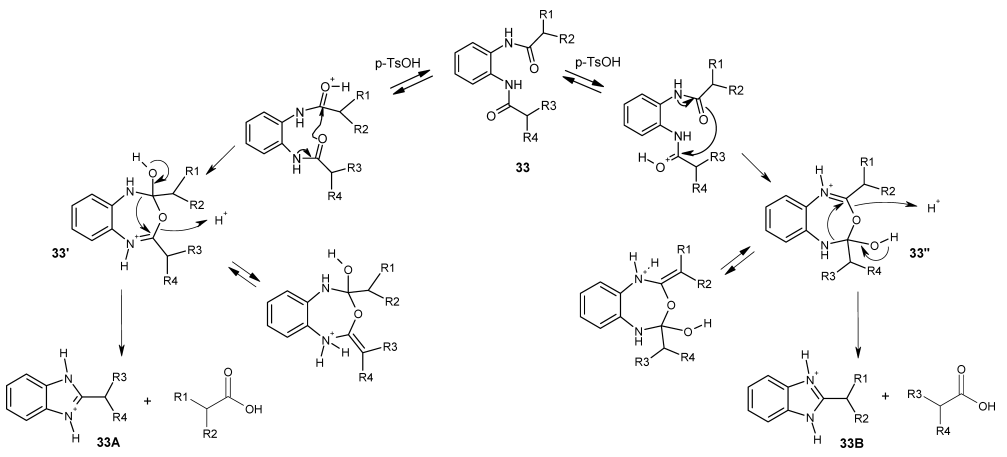

Chart 4. Proposed Mechanism for the Formation of 2-Substituted Benzimidazoles

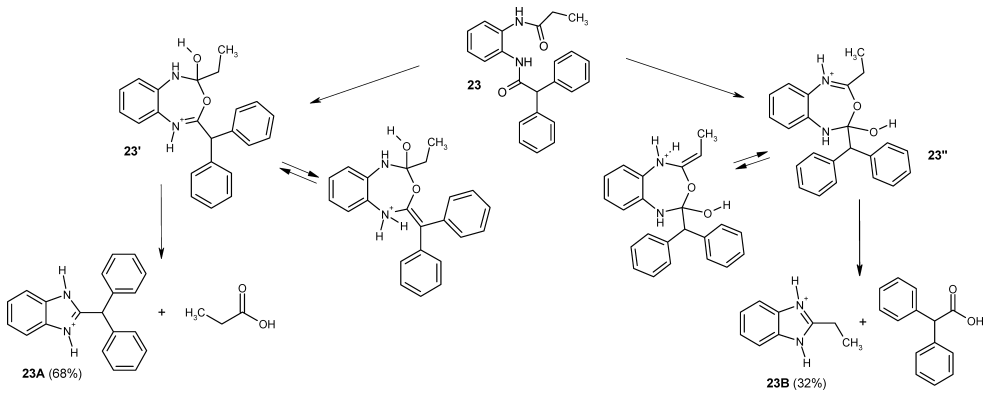

Chart 5. Proposed Mechanism for the Formation of Benzimidazoles **23A** and **B** from the Compound **23**

tively. A similar mechanism has been proposed for the conversion of *N*,*O*-diacylated-2-aminophenols to benzoxazoles.[14)]

Rate of conversion of mixed diacylated 1,2-phenylenediamines to 2-substituted benzimidazoles is strongly dependent upon the nature of the acyl substituents which improve or decrease the stabilization of one of the 1,2-dihydro-benzo-[1,3,6]oxadiazepine intermediates. For example, when a diphenylmethyl group is involved, the intermediates **23′**, leading to the 2-diphenylmethyl-benzimidazole, is better stabilized than the intermediate **23″** (Chart 5). This is consistent with the percentage observed for the formation of compounds **23A** and **B** (Table 3).

In conclusion, formation of bulky 2-substituted benzimidazoles from their monoacylated counterparts depends highly upon the nature of the acyl group. In the case of a diphenylmethyl group, cyclization can be observed with an appropriate choice of acidic media and completion times are in the same range as those reported for less bulky, symmetrical diacylated compounds.[13)] Conversely, in the case of a dicyclohexylmethyl group, cyclization can be only achieved in a *p*-toluenesulfonic acid/toluene (0.2 M) mixture, starting from a diacylated precursor. It was observed that the mechanism of cyclization starting from mixed diacylated precursors was not unique and was directly related to the nature of the acyl groups. In addition to the potential synthetic utility of the conversion described herein, the present study has also provided some mechanistic rationales for the conversion of mixed diacylated 1,2-phenylenediamines to benzimidazoles under acidic conditions.

Experimental

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-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 the benzimidazoles was determined on a Büchi 535 capillary mp apparatus and were uncorrected. The purity of the final compounds was verified by high performance 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 eluant 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% eluant A to 100% eluant B in 7 min 30 s for method A, in 10 min for method B and in 30 min for method C.

General Procedure for Synthesis of Benzimidazoles 2—4, 6, 8—11 and 18B To a solution of the appropriate acid (1 eq) in DMF (0.25 M) were added a solution of DCC in DCM (0.5 eq), DIEA (1.1 eq) and *o*-phenylenediamine (0.4 eq). After stirring for 12 h at room temperature, the mixture was filtered and the solvent evaporated. The residue was diluted with DCM, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and purified by TLC (CH_2Cl_2/MeOH 9.8 : 0.2, 9.5 : 0.5 or 9.9 : 0.1) to give the expected monoacylated compound. This latter was diluted in pure acetic acid (0.2 M). Following reflux of the mixture for 5 h, the solvent was evaporated, the residue diluted in DCM, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole was obtained after trituration in a Et_2O/pentane mixture or purification by TLC.

General Procedure for Synthesis of Benzimidazoles 1 and 7 To a solution of the appropriate acid (1 eq) in DCM (0.2 M) was added thionyl chloride (2.5 eq). Following reflux of the mixture for 1.5 h, the solvent and the excess of $SOCl_2$ were evaporated. The residue was diluted with THF (0.3 M) and this solution was added to a solution of 2-nitroaniline (1.5 eq) and pyridine (5 eq) in THF (0.3 M). After stirring for 5 h at room temperature, the solvent was evaporated. The residue was diluted in DCM, washed with aqueous $KHSO_4$ 5%, aqueous $NaHCO_3$ 5% and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, concentrated and the residue purified by trituration in Et_2O to give the expected monoacylated compound. This latter was diluted in pure acetic acid (0.2 M) in presence of iron (2 eq). Following reflux of the mixture for 8 h, the solvent was evaporated, the residue diluted with DCM, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$ and concentrated. The expected benzimidazole was obtained after purification by TLC.

General Procedure for Synthesis of Benzimidazoles 5 and 17B To a solution of 2-nitroaniline (255 mg, 1.85 mmol, 1 eq) and pyridine (0.74 ml, 9.25 mmol, 5 eq) in dry DCM (5 ml) was added respectively 4-biphenylcarbonyl chloride (216 mg, 2.22 mmol, 1.2 eq) or propyl chloride (194 μl, 2.22 mmol, 1.2 eq). After stirring for 12 h at room temperature, the mixture was washed with aqueous 5% $KHSO_4$, aqueous 5% $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated. The residue was diluted in pure acetic acid (10 ml) in presence of iron (305 mg, 5.55 mmol, 3 eq). Following reflux of the mixture for 2 h, the solvent was evaporated, the residue diluted with DCM, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and purified by TLC to give expected compound.

2-Benzhydryl-1*H*-benzoimidazole (1, 22—28A, 20B or 28B) (Tables 2, 3) A white solid (100 mg, 41%). mp 210—212 °C. Solvent for TLC: cyclohexane/AcOEt 7 : 3. *Rf* (cyclohexane/AcOEt 7 : 3): 0.45. t_R (C18 Xterra, method B): 5.35 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 12.31 (1H, s, NH), 7.40—7.11 (14H, m, ArH), 5.74 (1H, s, CH). ^{13}C-NMR δ: 156.1, 142.3, 129.5, 129.3, 122.7, 121.9, 119.4, 112.0, 51.6. Maldi-MS *m*/*z*: 285 $[M+H]^+$.

2-Benzyl-1*H*-benzoimidazole (2, 19B or 27B) (Tables 2, 3) A white solid (100 mg, 38%). mp 179—180 °C. Purified by trituration. *Rf* (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 (1H, s, NH), 7.52—7.10 (9H, m, ArH), 4.17 (2H, s, 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-MS *m*/*z*: 209 $[M+H]^+$.

2-Cyclohexylmethyl-1*H*-benzoimidazole (3, 26B or 30B) (Tables 2, 3) A white solid (115 mg, 64%). mp 202—205 °C. Purified by trituration. *Rf* (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 (2H, m, ArH), 7.14—7.10 (2H, m, ArH), 2.69 (2H, d, J=7.1 Hz, CH_2), 1.69—1.16 (11H, m, 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-MS *m/z*: 215 $[M+H]^+$.

2-(Cyclopentylphenylmethyl)-1*H*-benzoimidazole (4 or 29B) (Tables 2, 3) A white solid (150 mg, 35%). mp 208—210 °C. Solvent for TLC: CH_2Cl_2/MeOH/NH_4OH 9.8 : 0.8 : 0.1. *Rf* (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%. ^{1}H-NMR δ: 12.26 (1H, s, NH), 7.50—7.31 (4H, m, ArH), 7.26 (2H, m, ArH), 7.16 (1H, m, ArH), 7.07 (1H, m, ArH), 3.85 (1H, d, J=11.2 Hz, CH), 2.85 (1H, m, CH), 1.64—1.42 (6H, m, CH_2 cyclopentyl), 1.10 (2H, m, 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-MS *m/z*: 277 $[M+H]^+$.

2-Biphenyl-4-yl-1*H*-benzoimidazole (5) (Table 2) A white solid (299 mg, 60%). mp 178—180 °C. Solvent for TLC: CH_2Cl_2/MeOH/NH_4OH 9.8 : 0.1 : 0.1. *Rf* (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%. ^{1}H-NMR δ: 8.27 (2H, d, J=8.4 Hz, ArH benzimidazole), 7.87 (2H, d, J=8.4 Hz, ArH benzimidazole), 7.78 (2H, d, J=7.2 Hz, ArH biphenyl), 7.62 (2H, m, ArH biphenyl), 7.51 (2H, t, J=7.1 Hz, ArH biphenyl), 7.41 (1H, m, ArH biphenyl), 7.24—7.18 (2H, m, 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-MS *m/z*: 271 $[M+H]^+$.

2-Biphenyl-2-yl-1*H*-benzoimidazole (6) (Table 2) A white solid (140 mg, 33%). mp 212—213 °C. Solvent for TLC: CH_2Cl_2/MeOH 9.7 : 0.3. *Rf* (CH_2Cl_2/MeOH 9.7 : 0.3): 0.40. t_R (C18 Xterra, method B): 5.06 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 12.07 (1H, s, NH), 7.72—7.69 (1H, m, ArH), 7.63—7.48 (4H, m, ArH), 7.33—7.25 (1H, m, ArH), 7.24—7.10 (7H, m, 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-MS *m/z*: 271 $[M+H]^+$.

2-(4-Propylphenyl)-1*H*-benzoimidazole (7) (Table 2) A white solid (310 mg, 25%). mp 197—198 °C. Solvent for TLC: CH_2Cl_2/MeOH 9.6 : 0.4. *Rf* (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 (1H, s, NH), 8.01 (2H, m, ArH), 7.54 (2H, m, ArH), 7.27 (2H, m, ArH), 7.11 (2H, m, ArH), 2.53 (2H, t, J=7.3 Hz, CH_2), 1.56 (2H, m, CH_2), 0.83 (3H, t, J=7.3 Hz, 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-MS *m/z*: 237 $[M+H]^+$.

2-(1-Phenylethyl)-1*H*-benzoimidazole (8) (Table 2) A white solid (200 mg, 63%). mp 197—199 °C. Purified by trituration. *Rf* (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 (1H, s, NH), 7.57—7.07 (9H, m, ArH), 4.37 (1H, q, J=7.2 Hz, CH), 1.69 (3H, d, J=7.2 Hz, 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-MS *m/z*: 223 $[M+H]^+$.

2-(9*H*-Fluoren-9-yl)-1*H*-benzoimidazole (9) (Table 2) A white solid (100 mg, 60%). mp >225 °C. Solvent for TLC: CH_2Cl_2/MeOH 9.5 : 0.5. *Rf* (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 (1H, s, NH), 7.96 (2H, m, ArH), 7.52—7.42 (5H, m, ArH), 7.35—7.28 (3H, m, ArH), 7.11—7.08 (2H, m, ArH), 5.53 (1H, s, CH), 3.17 (2H, m, CH_2), 2.90 (2H, m, 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-MS *m/z*: 283 $[M+H]^+$.

2-(Cyclohexylphenylmethyl)-1*H*-benzoimidazole (10 or 29A, 30A) (Tables 2, 3) A white solid (120 mg, 21%). mp 195—197 °C. Solvent for TLC: CH_2Cl_2/MeOH 9.7 : 0.3. *Rf* (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 (1H, s, NH), 7.53 (1H, m, ArH), 7.45 (1H, m, ArH), 7.37 (1H, m, ArH), 7.25 (2H, m, ArH), 7.17 (1H, m, ArH), 7.07 (2H, m, ArH), 3.80 (1H, d, J=10.7 Hz, CH), 2.29 (1H, m, CH), 1.58—0.91 (10H, m, 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-MS *m/z*: 291 $[M+H]^+$.

2-(1,2,3,4-Tetrahydronaphthalen-2-yl)-1*H*-benzoimidazole (11) (Table 2) A white solid (140 mg, 53%). mp >225 °C. Purified by trituration. *Rf* (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 (1H, m, ArH), 7.43 (1H, m, ArH), 7.24—7.10 (6H, m, ArH), 3.32 (3H, m, CH+CH_2), 3.17 (2H, m, CH_2), 2.90 (2H, m, 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-MS *m/z*: 249 $[M+H]^+$.

2-Dicyclohexylmethyl-1*H*-benzoimidazole (12, 16—21A or 21B) (Tables 2, 3) A solution of diacylated compound **16** (130 mg, 0.36 mmol, 1 eq) and *para*-toluenesulfonic acid (135 mg, 0.72 mmol, 2 eq) in toluene (3.5 ml) was stirred for 24 h at reflux. Then the solvent was evaporated and the residue was diluted with DCM (20 ml), washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and purified by TLC (CH_2Cl_2/MeOH 9.6 : 0.4) to give compound **12**. A white solid (68 mg, 65%). mp 205—207 °C. *Rf* (CH_2Cl_2/MeOH 9.6 : 0.4): 0.5. t_R (TSK-GEL, method B): 6.44 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 12.16 (1H, s, NH), 7.68 (1H, m, ArH), 7.55 (1H, m, ArH), 7.25 (2H, m, ArH), 2.69 (1H, t, J=7.5 Hz, CH), 2.09 (2H, m, CH), 1.93—0.85 (20H, m, 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-MS *m/z*: 297 $[M+H]^+$.

Monoacylated Precursors (13—15) To a solution of dicyclohexylacetic, diphenylacetic or cyclohexylphenylacetic acid (10 mmol, 1 eq) in DMF (40 ml) were added a solution of DCC 1 M in DCM (5 ml, 5 mmol, 0.5 eq), DIEA (1.8 ml, 11 mmol, 1.1 eq) and *o*-phenylenediamine (433 mg, 4 mmol, 0.4 eq). After stirring for 12 h at room temperature, the mixture was filtered and the solvent evaporated. The residue was diluted with DCM, washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and purified by TLC (CH_2Cl_2/MeOH 9.8 : 0.2, 9.5 : 0.5 or 9.9 : 0.1 respectively) to give respectively compound **13**, **14** or **15**.

***N*-(2-Aminophenyl)-2,2-dicyclohexylacetamide (13) (Chart 2)** A white solid (378 mg, 30%). *Rf* (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 (1H, s, NH), 7.07 (1H, m, ArH), 6.88 (1H, m, ArH), 6.70 (1H, m, ArH), 6.53 (1H, m, ArH), 4.71 (2H, s, NH_2), 2.09 (1H, t, J=7.2 Hz, CH), 1.68 (12H, m, CH+CH_2), 1.10 (10H, m, CH_2). Maldi-MS *m/z*: 315 $[M+H]^+$.

***N*-(2-Aminophenyl)-2,2-diphenylacetamide (14) (Chart 2)** A white solid (751 mg, 62%). *Rf* (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: 9.60 (1H, s, NH), 7.40—7.23 (10H, m, ArH phenyl), 7.18 (1H, dd, J=1.4, 7.9 Hz, ArH), 7.18—7.12 (1H, td, J=1.5, 7.9 Hz, ArH), 6.71 (1H, dd, J=1.4, 8.0 Hz, ArH), 6.54 (1H, td, J=1.5, 7.4 Hz, ArH), 4.78 (2H, s, NH_2). Maldi-MS *m/z*: 303 $[M+H]^+$.

***N*-(2-Aminophenyl)-2-cyclohexyl-2-phenylacetamide (15) (Chart 2)** A white solid (519 mg, 42%). *Rf* (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 (1H, s, NH), 7.33—7.30 (2H, m, ArH), 7.26—7.21 (2H, m, ArH), 7.18—7.12 (1H, m, ArH), 7.02 (1H, m, ArH), 6.80 (1H, m, ArH), 6.60 (1H, m, ArH), 6.43 (1H, m, ArH), 4.60 (2H, s, NH_2), 3.31 (1H, d, J=10.7 Hz, CH), 1.95—1.00 (11H, m, H cyclohexyl). Maldi-MS *m/z*: 309 $[M+H]^+$.

Diacylated Derivatives (16—20, 22—30) To a solution of appropriate acid (1.1 eq) in dry DCM (0.25 M) were added DIEA (2 eq), PyBrop (1.3 eq) and compound **13**, **14** or **15** (1 eq). After stirring for 12 h at room temperature, the mixture was washed with aqueous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and purified by TLC (CH_2Cl_2/MeOH) to give expected compound.

***N*-(2-Acetylaminophenyl)-2,2-dicyclohexylacetamide (16) (Chart 2, Table 3)** A white solid (152 mg, 21%). Solvent for TLC: CH_2Cl_2/MeOH 9.9 : 0.1. *Rf* (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 (1H, s, NH), 9.21 (1H, s, NH), 7.34—7.25 (2H, m, ArH), 7.08—7.04 (2H, m, ArH), 3.19 (3H, s, CH_3), 1.95 (1H, m, CH), 1.58—1.54 (12H, m, H cyclohexyl), 1.62—0.83 (10H, m, H cyclohexyl). Maldi-MS *m/z*: 357 $[M+H]^+$.

***N*-[2-(2,2-Dicyclohexylacetylamino)phenyl]propionamide (17) (Chart 2, Table 3)** A white solid (115 mg, 20%). Solvent for TLC: CH_2Cl_2/MeOH 9.7 : 0.3. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.8): 0.20. t_R (Xterra, method B): 9.36 min, P_{HPLC}: 90%. ^{1}H-NMR δ: 9.36 (1H, s, NH), 9.21 (1H, s, NH), 7.46—7.43 (1H, m, ArH), 7.34—7.31 (1H, m, ArH), 7.15—7.08 (2H, m, ArH), 2.24 (2H, q, J=7.5 Hz, CH_2), 2.00 (1H, t, J=7.0 Hz, CH), 1.65—1.61 (12H, m, H cyclohexyl), 1.19—0.93 (12H, m, H cyclohexyl and 3H, t, J=7.5 Hz, CH_3). Maldi-MS *m/z*: 371 $[M+H]^+$.

***N*-[2-(2,2-Dicyclohexylacetylamino)phenyl]butyramide (18) (Chart 2, Table 3)** A white solid (120 mg, 18%). Solvent for TLC: CH_2Cl_2/MeOH 9.7 : 0.3. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.30. t_R (Xterra, method B): 9.87 min, P_{HPLC}: 90%. ^{1}H-NMR δ: 10.40 (1H, s, NH), 10.35 (1H, s, NH), 7.53—7.50 (1H, m, ArH), 7.43—7.39 (1H, m, ArH), 7.05—7.02 (2H, m, ArH), 2.26 (2H, q, J=7.4 Hz, CH_2), 2.18 (1H, t, J=7.3 Hz, CH), 1.74—1.49 (16H, m, H cyclohexyl+CH_2), 1.19—0.95 (8H, m, H cyclohexyl), 0.86 (3H, t, J=7.4 Hz, CH_3). Maldi-MS *m/z*: 385 $[M+H]^+$.

2,2-Dicyclohexyl-*N*-(2-phenylacetylaminophenyl)acetamide (19) (Chart 2, Table 3) A white solid (171 mg, 25%). Solvent for TLC: CH_2Cl_2/MeOH 9.8 : 0.2. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.60. t_R (Xterra, method B): 10.22 min, P_{HPLC}: 94%. ^{1}H-NMR δ: 9.60 (1H, s, NH), 9.17 (1H, s, NH), 7.46—7.39 (2H, m, ArH), 7.30—7.20 (5H, m, ArH), 7.13—7.11 (2H, m, ArH), 3.59 (2H, s, CH_2), 1.87 (1H, t, J=7.5 Hz, CH), 1.65—0.90

(22H, m, H cyclohexyl). Maldi-MS *m/z*: 433 $[M+H]^+$.

2,2-Dicyclohexyl-*N*-(2-diphenylacetylaminophenyl)acetamide (20) (Chart 2, Table 3) A white solid (160 mg, 44%). Solvent for TLC: CH_2Cl_2/MeOH 9.9 : 0.1. *Rf* (CH_2Cl_2): 0.55. t_R (TSK-GEL, method B): 11.38 min, P_{HPLC}: 95%. ^{1}H-NMR δ: 9.97 (1H, s, NH), 9.12 (1H, s, NH), 7.53—7.46 (2H, m, ArH), 7.39—7.23 (10H, m, ArH), 7.19—7.13 (2H, m, ArH), 5.06 (1H, s, CH), 1.83 (1H, t, J=7.0 Hz, CH), 1.59—0.90 (22H, m, H cyclohexyl). Maldi-MS *m/z*: 509 $[M+H]^+$.

2,2-Dicyclohexyl-*N*-[2-(2,2-dicyclohexylacetylamino)phenyl]acetamide (21) (Chart 2, Table 3) To a solution of *o*-phenylenediamine (130 mg, 1.21 mmol, 2.4 eq) in DCM (15 ml) were added dicyclohexylacetic acid (650 mg, 2.9 mmol, 1 eq), PyBrop (1.35 g, 2.9 mmol, 2.4 eq) and DIEA (0.63 ml, 3.63 mmol, 3 eq). After stirring for 12 h at room temperature, the mixture was washed with aqueuous $NaHCO_3$ 5%, dried over $MgSO_4$, concentrated and purified by TLC (CH_2Cl_2/MeOH 9.8 : 0.2) to give compound **21**. A white solid (600 mg, 95%). *Rf* (CH_2Cl_2/MeOH 9.8 : 0.4): 0.7. t_R (TSK-GEL, method C): 31.8 min, P_{HPLC}: 94%. ^{1}H-NMR δ: 9.41 (2H, s, NH), 7.60—7.54 (2H, m, ArH), 7.14—7.11 (2H, m, ArH), 1.98—1.93 (2H, m, CH), 1.75—0.93 (44H, m, H cyclohexyl). Maldi-MS *m/z*: 521 $[M+H]^+$.

***N*-(2-Acetylaminophenyl)-2,2-diphenylacetamide (22) (Chart 2, Table 3)** A white solid (120 mg, 49%). Solvent for TLC: CH_2Cl_2/MeOH 9.8 : 0.2. *Rf* (CH_2Cl_2/MeOH 9.5 : 0.5): 0.50. t_R (TSK-GEL, method A): 5.43 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 9.52 (1H, s, NH), 9.34 (1H, s, NH), 7.58—7.54 (1H, m, ArH), 7.39—7.32 (9H, m, ArH), 7.29—7.24 (2H, m, ArH), 7.17—7.13 (2H, m, ArH), 5.24 (1H, s, CH), 1.90 (3H, s, CH_3). Maldi-MS *m/z*: 335 $[M+H]^+$.

***N*-(2-Diphenylacetylaminophenyl)propionamide (23) (Chart 2, Table 3)** A white solid (83 mg, 25%). Solvent for TLC: CH_2Cl_2/MeOH 9.8 : 0.2. *Rf* (CH_2Cl_2/MeOH 9.5 : 0.5): 0.40, t_R (TSK-GEL, method A): 5.86 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 9.59 (1H, s, NH), 9.22 (1H, s, NH), 7.54—7.51 (1H, m, ArH), 7.42—7.28 (9H, m, ArH), 7.26—7.24 (2H, m, ArH), 7.17—7.14 (2H, m, ArH), 5.22 (1H, s, CH), 2.17 (2H, q, J=7.5 Hz, CH_2), 0.96 (3H, t, J=7.5 Hz, CH_3). Maldi-MS *m/z*: 359 $[M+H]^+$.

***N*-(2-Diphenylacetylaminophenyl)butyramide (24) (Chart 2, Table 3)** A white solid (154 mg, 61%). Solvent for TLC: CH_2Cl_2/MeOH 9.8 : 0.2. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.45. t_R (TSK-GEL, method B): 7.74 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 9.64 (1H, s, NH), 9.21 (1H, s, NH), 7.52—7.49 (1H, m, ArH), 7.43—7.30 (9H, m, ArH), 7.27—7.22 (2H, m, ArH), 7.17—7.13 (2H, m, ArH), 5.19 (1H, s, CH), 2.11 (2H, t, J=7.3 Hz, CH_2), 1.49—1.40 (2H, m, CH_2), 0.83 (2H, t, J=7.3 Hz, CH_3). Maldi-MS *m/z*: 373 $[M+H]^+$.

***N*-(2-Diphenylacetylaminophenyl)-2,2-dimethylpropionamide (25) (Chart 2, Table 3)** A white solid (160 mg, 61%). Solvent for TLC: CH_2Cl_2/MeOH 9.8 : 0.2. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.55. t_R (TSK-GEL, method B): 8.32 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 10.12 (1H, s, NH), 8.73 (1H, s, NH), 7.37—7.13 (14H, m, ArH), 5.20 (1H, s, CH), 0.93 (9H, s, CH_3). Maldi-MS *m/z*: 387 $[M+H]^+$.

***N*-[2-(2-Cyclohexylacetylamino)phenyl]-2,2-diphenylacetamide (26) (Chart 2, Table 3)** A white solid (135 mg, 45%). Solvent for TLC: CH_2Cl_2/MeOH 9.9 : 0.1. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.50. t_R (TSK-GEL, method B): 8.80 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 9.67 (1H, s, NH), 9.21 (1H, s, NH), 7.51—7.16 (14H, m, ArH), 5.16 (1H, s, CH), 3.33 (2H, d, J=9.2 Hz, CH_2), 1.95—0.95 (11H, m, H cyclohexyl). Maldi-MS *m/z*: 427 $[M+H]^+$.

2,2-Diphenyl-*N*-(2-phenylacetylaminophenyl)acetamide (27) (Chart 2, Table 3) A white solid (520 mg, 47%). Solvent for TLC: CH_2Cl_2/MeOH 9.9 : 0.1. *Rf* (CH_2Cl_2/MeOH 9.9 : 0.1): 0.45. t_R (TSK-GEL, method B): 8.44 min, P_{HPLC}: 95%. ^{1}H-NMR δ: 9.61 (1H, s, NH), 9.53 (1H, s, NH), 7.54—7.51 (1H, m, ArH), 7.45—7.41 (1H, m, ArH), 7.35—7.22 (15H, m, ArH), 7.16—7.13 (2H, m, ArH), 5.15 (1H, s, CH), 3.59 (2H, s, CH_2). Maldi-MS *m/z*: 421 $[M+H]^+$.

***N*-(2-Diphenylacetylaminophenyl)-2,2-diphenylacetamide (28) (Chart 2, Table 3)** A white solid (590 mg, 64%). Solvent for TLC: CH_2Cl_2/MeOH 9.8 : 0.2. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.70. t_R (TSK-GEL, method B): 9.21 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 9.74 (2H, s, NH), 7.52—7.49 (2H, m, ArH), 7.33—7.23 (20H, m, ArH), 7.18—7.15 (2H, m, ArH), 5.07 (2H, s, CH). Maldi-MS *m/z*: 497 $[M+H]^+$.

2-Cyclohexyl-*N*-[2-(2-cyclopentyl-2-phenylacetylamino)phenyl]-2-phenylacetamide (29) (Chart 2, Table 3) A white solid (100 mg, 22%). Solvent for TLC: CH_2Cl_2/MeOH 9.9 : 0.1. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.70. t_R (TSK-GEL, method B): 11.37 min, P_{HPLC}: 93%. ^{1}H-NMR δ: 9.59 (1H, s, NH), 9.47 (1H, s, NH), 7.44—7.24 (12H, m, ArH), 7.13—7.09 (2H, m, ArH), 3.17—3.12 (1H, m, CH), 3.10—3.04 (1H, m, CH), 1.98—0.93 (20H, m, H cyclohexyl+H cyclopentyl). Maldi-MS *m/z*: 495 $[M+H]^+$.

2-Cyclohexyl-*N*-[2-(2-cyclohexylacetylamino)phenyl]-2-phenylacetamide (30) (Chart 2, Table 3) A white solid (160 mg, 49%). Solvent for TLC: CH_2Cl_2/MeOH 9.9 : 0.1. *Rf* (CH_2Cl_2/MeOH 9.8 : 0.2): 0.65. t_R (TSK-GEL, method B): 10.39 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 9.66 (1H, s, NH), 9.09 (1H, s, NH), 7.45—7.29 (7H, m, ArH), 7.13—7.12 (2H, m, ArH), 3.31—3.24 (3H, m, CH+CH_2), 2.09—0.96 (22H, m, H cyclohexyl). Maldi-MS *m/z*: 433 $[M+H]^+$.

2-Methyl-1*H*-benzoimidazole (16B or 22B) (Table 3) A white solid (commercially available). mp 175—179 °C. *Rf* (CH_2Cl_2/MeOH 9 : 1): 0.45. t_R (TSK-GEL, method A): 2.60 min, P_{HPLC}: 100%. ^{1}H-NMR δ: 12.16 (1H, s, NH), 7.50—7.36 (2H, m, ArH), 7.12—7.06 (2H, m, ArH), 2.47 (3H, s, CH_3). ^{13}C-NMR δ: 158.3, 121.5, 118.6, 111.0, 15.2. Maldi-MS *m/z*: 133 $[M+H]^+$.

2-Ethyl-1*H*-benzoimidazole (17B or 23B) (Table 3) A white solid (68 mg, 25%). mp 145—147 °C. Solvent for TLC: cyclohexane/AcOEt 5 : 5. *Rf* (CH_2Cl_2/MeOH 9 : 1): 0.45. t_R (TSK-GEL, method A): 2.81 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 12.15 (1H, s, NH), 7.48—7.41 (2H, m, ArH), 7.13—7.07 (2H, m, ArH), 2.82 (2H, q, J=7.6 Hz, CH_2), 1.31 (3H, t, J=7.6 Hz, CH_3). ^{13}C-NMR δ: 156.7, 121.6, 115.0, 22.6, 12.8. Maldi-MS *m/z*: 147 $[M+H]^+$.

2-Propyl-1*H*-benzoimidazole (18B or 24B) (Table 3) A white solid (90 mg, 30%). mp 153—154 °C. Solvent for TLC: CH_2Cl_2/MeOH 9.3 : 0.7. *Rf* (CH_2Cl_2/MeOH 9.3 : 0.7): 0.50. t_R (C18 Xterra, method B): 3.77 min, P_{HPLC}: 99%. ^{1}H-NMR δ: 12.14 (1H, s, NH), 7.47—7.38 (2H, m, ArH), 7.10—7.06 (2H, m, ArH), 2.75 (2H, t, J=7.4 Hz, CH_2), 1.82—1.70 (2H, m, CH_2), 0.91 (3H, t, J=7.4 Hz, CH_3). ^{13}C-NMR δ: 155.8, 122.1, 121.6, 118.9, 111.5, 31.4, 21.8, 14.6. Maldi-MS *m/z*: 161 $[M+H]^+$.

2-*tert*-Butyl-1*H*-benzoimidazole (25B) (Table 3) A violet solid (commercially available). mp >250 °C. *Rf* (CH_2Cl_2/MeOH 9.3 : 0.7): 0.10. t_R (TSK-GEL, method A): 3.18 min, P_{HPLC}: 100%. ^{1}H-NMR δ: 12.08 (1H, s, NH), 7.54—7.39 (2H, m, ArH), 7.13—7.08 (2H, m, ArH), 1.37 (9H, s, CH_3). ^{13}C-NMR δ: 162.7, 122.0, 121.3, 118.9, 111.4, 29.9. Maldi-MS *m/z*: 175 $[M+H]^+$.

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