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A FACILE SYNTHESIS OF 2-ACYL AND 2-ALKYLAMINO BENZIMIDAZOLES FOR 5-LIPOXYGENASE INHIBITORS

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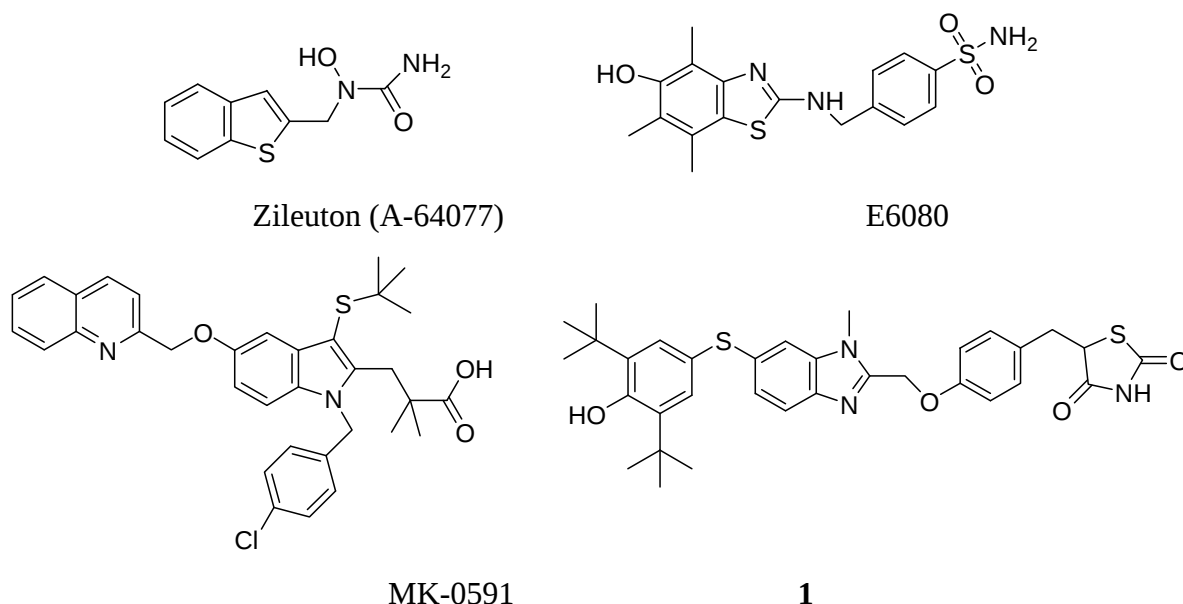
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Abstract – 2-Acylaminobenzimidazoles (**2a-r**) have been synthesized from *o*-phenylenediamines (**4**) with benzoylcarbonimidodithioic acid dimethyl ester (**5a**) or isobutyrylcarbonimidodithioic acid dimethyl ester (**5b**) in good yield. 2-Alkylaminobenzimidazoles could be prepared by the reaction of *o*-Phenylenediamines (**4a, b**) with benzyl isothiocyanate in moderate yields **8a, b** or the reaction of 2-chlorobenzimidazole (**9**) with benzylamines (**10a, b**) in moderate yield **11a, b**. Finally, the carbamate derivative of 2-aminobenzimidazole (**13**) was prepared by the reaction with pseudourea (**12**) in low yield. Most of the prepared analogues were evaluated in leukotriene inhibition assay and it found that benzamide derivatives (**2a-i**) are quite active among others.

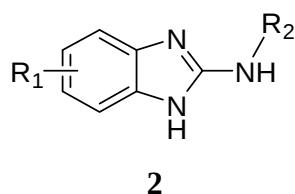
INTRODUCTION

The lipoxygenase enzyme pathway involves the conversion of arachidonic acid to the leukotrienes which are one of key modulators in inflammatory pathological processes¹ (*i.e.* asthma and chronic obstructive pulmonary disease) as well as in cancer proliferation, especially prostate and pancreatic cancer.² The research efforts toward discovery of lipoxygenase inhibitors has been made because of the potential therapeutic interest of inhibiting the lipoxygenase pathway.³ Zileuton, which has been marketed, and E6080 inhibited leukotriene production for antihistaminic and antiallergic agent.⁴ Furthermore, the drug MK-0591 inhibited the leukotriene production by inhibiting 5-lipoxygenase activating protein.⁵ Finally,

the substituted benzimidazole derivative (**1**) was claimed as 5-lipoxygenase inhibitor as well as peroxisome proliferators-activated receptor (PPAR) antagonist.⁶

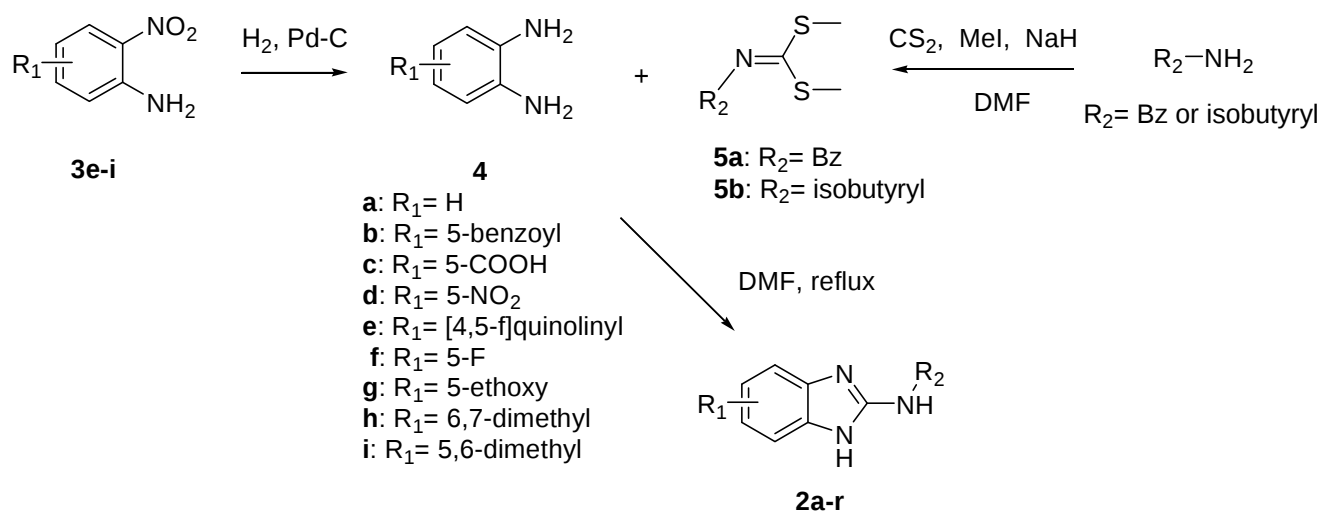


Most of these classes of inhibitors have the common fused heterocycles as their core structures for 5-lipoxygenase inhibitory activities. And we were interested in 2-substituted aminobenzimidazole (**2**) for the further investigation.



RESULTS AND DISCUSSION

2-Aminobenzimidazoles could be synthesized by reacting of *o*-phenylenediamines (**4**) with the carbonimidodithioic acid dimethyl esters (**5a**, **b**) in good yield.⁷ *o*-Phenylenediamines are commercially available **4a-d** or were readily prepared from *o*-nitroanilines (**3e-i**) by catalytic hydrogenation. The corresponding carbonimidodithioic acid dimethyl esters⁷ (**5a**, **b**) were prepared by reacting of benzamide or isobutyrylamide with carbondisulfide and iodomethane in DMF in the presence of sodium hydride. The 1:1 mixture of *o*-diamines (**4**) and carbonimidodithioic acid dimethyl esters (**5a**, **b**) was heated to reflux and the subsequent cyclization occurred spontaneously to give 2-acylaminobenzimidazoles by removal of MeSH. After removal of DMF, the residue could be purified by recrystallization from MeOH in good yields (Table 1). The obtained products (**2**) were examined in leukotriene inhibition assay in mice mast cell lines.

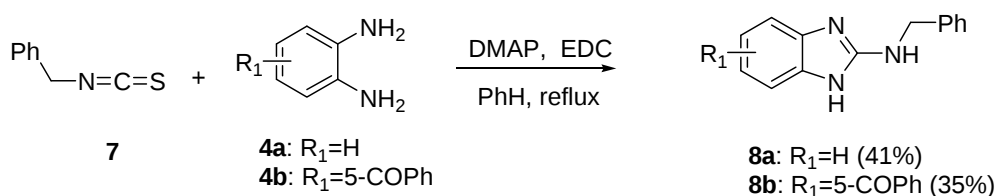


Scheme 1. Synthesis of 2-acylaminobenzimidazoles from *o*-phenylenediamine and carbonimidodithioic esters.

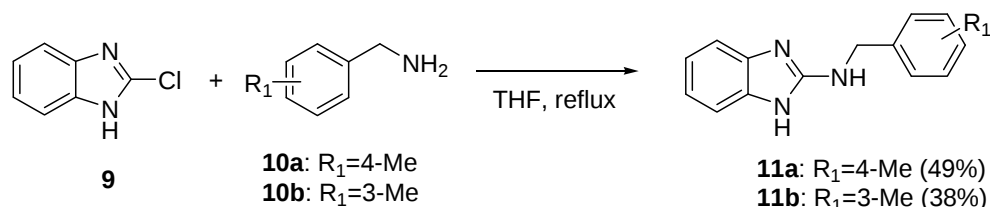
Table 1. The structure and yield of 2-acylaminobenzoimidazoles (2).

Compound	R ₁	R ₂	Yield(%)	Compound	R ₁	R ₂	Yield(%)
2a	H	Benzoyl	79	2j	H	Isobutyryl	40
2b	5-Benzoyl	Benzoyl	96	2k	5-Benzoyl	Isobutyryl	68
2c	5-COOH	Benzoyl	54	2l	5-COOH	Isobutyryl	90
2d	5-NO ₂	Benzoyl	67	2m	5-NO ₂	Isobutyryl	39
2e	[4,5-f]Quinolinyl	Benzoyl	46	2n	[4,5-f]Quinolinyl	Isobutyryl	57
2f	5-F	Benzoyl	49	2o	5-F	Isobutyryl	44
2g	5-Ethoxy	Benzoyl	63	2p	5-Ethoxy	Isobutyryl	48
2h	5,7-Dimethyl	Benzoyl	56	2q	5,7-Dimethyl	Isobutyryl	40
2i	4,5-Dimethyl	Benzoyl	57	2r	4,5-Dimethyl	Isobutyryl	39

Next, we have interested in preparing 2-alkylaminobenzimidazoles by the same methodology using benzylcarbonimidodithioic acid dimethyl ester instead. However, the reaction was failed to give the corresponding 2-alkylamino analogues because of the poor electrophilicity of methylene carbon in benzylcarbonimidodithioic acid dimethyl ester. Thus, two synthetic routes were examined to prepare the corresponding analogues. *o*-Phenylenediamines (**4a, b**) were reacted with benzyl isothiocyanate (**7**) in the presence of DMAP and EDC and gave 2-alkylaminobenzimidazoles (**8a, b**) in moderate yields (Scheme 2). Because of the promising activity on leukotriene inhibition of **8a**, we tried to prepare other analogues by this methodology but it was failed to give those analogues. Thus, two more benzylaminobenzimidazoles (**11a, b**) were readily prepared by reacting of the commercially available 2-chlorobenzimidazole (**9**) with benzylamines (**10a,b**), shown in Scheme 3.⁸

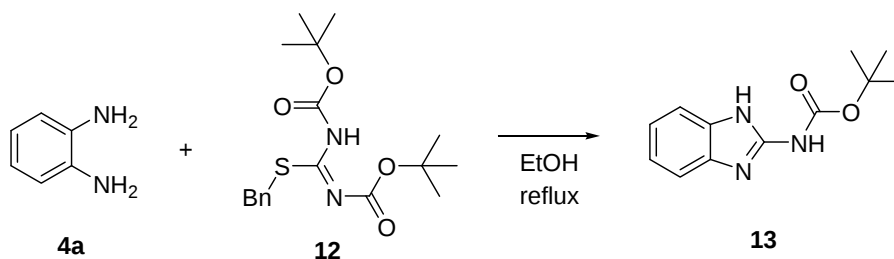


Scheme 2. Synthesis of 2-alkylaminobenzimidazoles from *o*-phenylenediamine and benzyl isothiocyanate.



Scheme 3. Synthesis of 2-alkylaminobenzimidazoles from 2-chlorobenzimidazole and benzylamines.

Finally, upon preparing amides and amines on 2-position of benzoimidazoles were we interested in preparing carbamate moiety for the next analogue design. The reactions of *o*-phenylenediamine (**4a**) with pseudourea (**12**) gave the desired 2-benzimidazolylcarbamate (**13**) in low yield (Scheme 4).

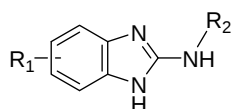


Scheme 4. Synthesis 2-benzimidazolylcarbamate from *o*-phenylenediamine and pseudourea.

Once, 2-acylamino (**2a-r**), 2-alkylamino (**8a, b**) and 2-carbamate derivatives (**13**) were in our hands, we had evaluated leukotriene inhibition of these analogues at 1 μ M in mouse mast cell lines (Table 2). Most of benzamide derivatives of benzoimidazoles (**2a-i**) are active to inhibit leukotriene and 5-nitro and benzoyl substituted analogues are most active. 2-isobutylamide derivatives (**2j-r**) are also active but less active compared to 2-benzamide counterparts. Activities of 2-benzyl derivatives (**8a, b**) are quite mixed-up and difficult to explain relationship between the structures and activities. In overall, 2-amide derivatives (**2a-r**) are more active than 2-alkylamino analogues (**8a, b**) and bigger substituents on 2 position are better in their activities among 2-amide derivatives.

In summary, 2-acyl and 2-alkylaminobenzimidazoles were prepared from *o*-phenylnenediamines with various cyclization reagents and most of the prepared analogues were evaluated in cellular leukotriene inhibition assay.

Table 2. *In vitro* leukotriene inhibition of 2-substituted aminobenzimidazoles in mice mast cell lines.



Compd.	R ₁	R ₂	(%) Inhibition at 1uM	Compd.	R ₁	R ₂	(%) Inhibition at 1uM
2a	H	Benzoyl	50	2l	5-COOH	Isobutyryl	42
2b	5-Benzoyl	Benzoyl	93	2m	5-NO ₂	Isobutyryl	61
2c	5-COOH	Benzoyl	36	2n	[4,5-f]Quinoliny	Isobutyryl	45
2d	5-NO ₂	Benzoyl	88	2o	5-F	Isobutyryl	21
2e	[4,5-f]Quinoliny	Benzoyl	80	2p	5-Ethoxy	Isobutyryl	28
2f	5-F	Benzoyl	76	2q	5,7-Dimethyl	Isobutyryl	5
2g	5-Ethoxy	Benzoyl	76	2r	4,5-Dimethyl	Isobutyryl	32
2h	5,7-Dimethyl	Benzoyl	84	8a	H	Benzyl	67
2i	4,5-Dimethyl	Benzoyl	77	8b	5-Benzoyl	Benzyl	-29
2j	H	Isobutyryl	71	13	H	tert-butoxy-carbonyl	-15
2k	5-Benzoyl	Isobutyryl	71				

EXPERIMENTAL

General procedures for carbonimidodithioic acid dimethyl esters (**5a**, **b**).

To a solution of benzamide (2.00 g, 16.51 mmol) or isobutyrylamide (1.00 g, 11.47 mmol) in DMF (0.25 M) was added carbon disulfide (4 equiv), iodomethane (3 equiv) and sodium hydride (60%, 2 equiv) at 0 °C. After 5 h at room temperature, the reaction was quenched by water. The mixture was extracted with ethyl acetate and the combined organic phase was dried over MgSO₄. After concentrated in reduced pressure, the residue was purified by flash column chromatography (EtOAc : n-Hexane = 1 : 7) to give the products.

Carbonimidodithioic acid, benzoyl-, dimethyl ester (**5a**)

Yield: 41%; ¹H NMR (300 MHz, CDCl₃) δ 8.13 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 6.6 Hz, 1H), 7.55 (t, *J* = 6.6 Hz, 2H), 2.47 (s, 6H), 1.19 (s, 3H), 1.17 (s, 3H).

Isobutyrylcarbonimidodithioic acid dimethyl ester (**5b**)

Yield: 64%; ¹H NMR (300 MHz, CDCl₃) δ 2.71-2.62 (m, 1H), 2.47 (s, 6H), 1.19 (s, 3H), 1.17 (s, 3H).

General procedure for 2-acylaminobenzimidazoles (**2a-r**).

To a solution of carbonimidodithioic acid dimethyl esters (**5a** or **5b**) in DMF (0.5 M) was added 1,2-phenylenediamine (1 equiv) and mixture was heated to 150 °C for 9 h. After cooled to room temperature, the solvent was removed by vacuum distillation. The residue was recrystallized from MeOH to give the products.

N-(1*H*-Benzimidazol-2-yl)benzamide (**2a**)

Yield: 79 %; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.24 (br s, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.45 (m, 5H), 7.16-7.12 (m, 2H); ¹³C NMR (DMSO-*d*₆) δ 168.39, 148.93, 134.41, 132.03, 128.37, 128.28, 121.54, 113.35.

N-(5-Benzoyl-1*H*-benzimidazol-2-yl)benzamide (**2b**)

Yield: 96 %; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.42 (br s, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.88 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.59-7.51 (m, 8H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 195.61, 138.34, 132.58, 131.95, 129.39, 128.56, 128.41, 128.33, 124.03.

2-Benzoylamino-1*H*-benzimidazole-5-carboxylic acid (**2c**)

Yield: 54 %; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.47 (br s, 1H), 8.11 (t, *J* = 7.5 Hz, 2H), 7.94 (s, 1H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.64 (dd, *J* = 5.6 Hz, 1H), 7.53 (dd, *J* = 5.8 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 167.93, 167.33, 149.67, 133.30, 132.52, 128.55, 128.31, 123.83, 123.16, 115.38, 113.69.

N-(5-Nitro-1*H*-benzimidazol-2-yl)benzamide (**2d**)

Yield: 67 %; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.58 (br s, 1H), 8.32 (s, 1H), 8.09-8.01 (m, 3H), 7.64-7.49 (m, 4H); ¹³C NMR (DMSO-*d*₆) δ 166.81, 150.89, 145.81, 142.08, 132.61, 128.42, 128.19, 117.31.

N-(3*H*-Imidazo[4,5-*f*]quinolin-2-yl)benzamide (**2e**)

Yield: 46 %; ^1H NMR (300 MHz, DMSO- d_6) δ 12.7 (br s, 1H), 8.79 (s, 1H), 8.72 (d, J = 6.6 Hz, 1H), 8.12 (d, J = 7.2 Hz, 2H), 7.93 (t, J = 9.2 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.62-7.49 (m, 4H); ^{13}C NMR (DMSO- d_6) δ 166.18, 147.62, 146.40, 145.17, 132.92, 132.28, 129.22, 128.39, 128.05, 122.60, 120.65, 116.71; HRMS (m/z) (MH^+) calc. for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{ONa}$ 289.1089; found 289.1094.

N-(5-Fluoro-1*H*-benzimidazol-2-yl)benzamide (**2f**)

Yield: 49 %; ^1H NMR (300 MHz, DMSO- d_6) δ 12.21 (br s, 1H), 8.07 (d, J = 7.6 Hz, 2H), 7.58-7.39 (m, 4H), 7.21 (d, J = 9.4 Hz, 1H), 6.94 (t, J = 4.8 Hz, 1H); ^{13}C NMR (DMSO- d_6) δ 167.09, 159.38, 157.05, 148.81, 133.34, 132.39, 128.49, 128.23, 113.99, 108.94, 108.69, 100.65; HRMS (m/z) (MNa^+) calc. for $\text{C}_{14}\text{H}_{10}\text{N}_3\text{OFNa}$ 278.0706; found 278.0704.

N-(5-Ethoxy-1*H*-benzimidazol-2-yl)benzamide (**2g**)

Yield: 63 %; ^1H NMR (300 MHz, DMSO- d_6) δ 12.08 (br s, 1H), 8.08 (d, J = 7.0 Hz, 2H), 7.57-7.44 (m, 3H), 7.28 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 6.70 (d, J = 9.0 Hz, 1H), 3.96 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 168.21, 154.51, 148.76, 134.48, 131.93, 128.34, 128.23, 113.77, 110.43, 98.17, 63.46, 14.81; HRMS (m/z) (MNa^+) calc. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2\text{Na}$ 304.1062; found 304.1069.

N-(5,7-Dimethyl-1*H*-benzimidazol-2-yl)benzamide (**2h**)

Yield: 56 %; ^1H NMR (300 MHz, DMSO- d_6) δ 12.09 (br s, 1H), 8.11 (d, J = 7.4 Hz, 2H), 7.56-7.44 (m, 3H), 7.17 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 168.72, 148.98, 134.81, 131.84, 130.10, 128.91, 128.30, 128.26, 123.37, 121.88, 109.03, 19.08, 13.24; HRMS (m/z) (MNa^+) calc. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{ONa}$ 288.1113; found 288.1117.

N-(4,5-Dimethyl-1*H*-benzimidazol-2-yl)benzamide (**2i**)

Yield: 57 %; ^1H NMR (300 MHz, DMSO- d_6) δ 12.08 (br s, 1H), 8.10 (d, J = 8.0 Hz, 3H), 7.56-7.44 (m, 3H), 7.08 (s, 1H), 6.73 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 168.33, 148.45, 134.57, 132.17, 131.91, 130.47, 128.34, 128.23, 123.74, 123.55, 109.67, 21.27, 16.54; HRMS (m/z) (MNa^+) calc. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{ONa}$ 288.1113; found 288.1100.

N-(1*H*-Benzimidazol-2-yl)isobutyramide (**2j**)

Yield: 40 %; ^1H NMR (300 MHz, DMSO- d_6) δ 11.83 (br s, 1H), 7.42 (s, 2H), 7.09-7.03 (m, 2H), 2.78-2.71 (m, 1H), 1.14 (d, J = 6.9 Hz, 6H); ESI (m/z) 202.3 ($\text{M}^+ - 1$).

N-(5-Benzoyl-1*H*-benzimidazol-2-yl) isobutyrylamide (**2k**)

Yield: 68 %; ^1H NMR (300 MHz, DMSO- d_6) δ 12.41 (br, NH), 11.69 (br, NH), 8.7.4 (m, 8H), 3.26 (m, 1H), 1.15 (d, J = 6.9 Hz, 6H); ESI (m/z) 330.5 (MNa^+).

2-Isobutyrylamino-1*H*-benzimidazole-5-carboxylic acid (**2l**)

Yield: 90 %; ^1H NMR (300 MHz, DMSO- d_6) δ 11.83 (br s, 1H), 8.38 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 2.80-2.60 (m, 1H), 1.15 (d, J = 6.9 Hz, 6H); ESI (m/z) 246.3 ($\text{M}^+ - 1$).

N-(5-Nitro-1*H*-benzimidazol-2-yl)isobutyrylamide (**2m**)

Yield: 39 %; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.67 (br s, 1H), 11.85 (s, NH), 8.31 (s, 1H), 8.04 (d, J = 6.6 Hz, 1H), 7.56 (d, J = 9.3 Hz, 1H), 3.26 (m, 1H), 1.16 (d, J = 6 Hz, 6H); ESI (m/z) 247.3 ($\text{M}^+ - 1$).

N-(3*H*-Imidazo[4,5-*f*]quinolin-2-yl)isobutyrylamide (**2n**)

Yield: 57 %; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.83 (s, 1H), 8.56 (s, 1H), 7.93 (t, J = 9.2 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.23 (s, 1H), 2.80-2.60 (m, 1H), 1.16 (d, J = 6 Hz, 6H).

N-(5-Fluoro-1*H*-benzimidazol-2-yl)isobutyrylamide (**2o**)

Yield: 44 %; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.13 (br s, 1H), 7.40 (s, 1H), 7.20 (s, 1H), 6.90 (t, J = 9.1 Hz, 1H), 3.26 (m, 1H), 1.13 (d, J = 6.9 Hz, 6H); ESI (m/z) 220.3 ($\text{M}^+ - 1$).

N-(5-Ethoxy-1*H*-benzimidazol-2-yl)isobutyrylamide (**2p**)

Yield: 48 %; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.87 (br s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.68 (d, J = 8.85 Hz, 1H), 3.99 (q, J = 6.9 Hz, 2H), 2.86 (m, 1H), 1.32 (t, J = 6.9 Hz, 3H), 1.13 (d, J = 6.6 Hz, 6H); ESI (m/z) 246.3 ($\text{M}^+ - 1$).

N-(5,7-Dimethyl-1*H*-benzimidazol-2-yl)isobutyrylamide (**2q**)

Yield: 40 %; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.83 (br s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 2.86 (m, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 1.13 (d, J = 7.5 Hz, 6H); ESI (m/z) 230.3 ($\text{M}^+ - 1$); HRMS (m/z) (M^+) calc. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}$ 254.1395; found 254.1369.

N-(4,5-Dimethyl-1*H*-benzimidazol-2-yl)isobutyrylamide (**2r**)

Yield: 9 %; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.82 (br s, 1H), 7.06 (s, 1H), 6.72 (s, 1H), 2.86 (m, 1H), 1.13 (d, J = 6.9 Hz, 6H); ESI (m/z) 230.3 ($\text{M}^+ - 1$); HRMS (m/z) (M^+) calc. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}$ 254.1395; found 254.1357.

Synthesis for 2-alkylaminobenzimidazoles.

2-Benzylamino-1*H*-benzimidazole (**8a**)

To a solution of benzyl isothiocyanate (0.18 mL, 1.34 mmol) in benzene (45 mL) was added 1,2-phenylenediamine (145 mg, 1.34 mmol) and the mixture was heated to reflux for 15 min. And then, EDC (98 mg, 0.51 mmol) and DMAP (16 mg, 0.13 mmol) were added and the reaction mixture was heated to reflux for 5 h. After cooled to room temperature, 10 % HCl solution added to pH 1-2 and the aqueous layer was separated. The aqueous layer was neutralized with saturated NaHCO_3 solution and extracted with ethyl acetate. The combined organic layer was dried over MgSO_4 and the solvent was removed in reduced pressure. The residue was purified by column chromatography (10% MeOH in CHCl_3) to give the product (**8a**) (145 mg, 41%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.94 (br s, 1H), 7.72 (br s, 1H), 7.31 (d, J = 4.8 Hz, 4H), 7.31-7.21 (m, 1H), 6.98 (t, J = 7.4 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.84 (s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 181.45, 144.35, 139.34, 128.26, 128.15, 127.48, 127.21, 126.68, 116.49, 115.82, 93.38, 30.69; ESI (m/z) 224.2 (MH^+).

5-Benzoyl-2-benzylamino-1*H*-benzimidazole (**8b**)

Benzyl isothiocyanate (**7**) (0.2 mL, 1.51 mmol), 3,4-Diaminobenzophenone (**4b**) (0.32 g, 1.51 mmol), EDC(0.43 g, 2.26 mmol) and DMAP(0.02 g, 0.15 mmol) were used for the same procedures as **6a** to give the product **6b** (171 mg, 35 %). ^1H NMR (300 MHz, DMSO- d_6) δ 8.91 (s, 1H), 8.02 (br s, 1H), 7.67-7.22 (m, 13H), 5.92 (s, 2H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 193.12, 182.00, 149.49, 141.34, 139.09, 138.61, 132.05, 131.20, 130.05, 128.82, 128.15, 128.09, 127.19, 126.65, 124.22, 114.56, 59.67, 45.27; ESI (m/z) 328.2 (MH^+).

2-(4-Methylbenzyl)amino-1H-benzimidazole (**11a**)

2-Chlorobenzimidazole (200 mg, 1.31 mmol) was dissolved in 4-methylbenzylamine(1 mL, 7.86 mmol) and the mixture was heated to 120°C in sealed tube for 2h. After cooled to room temperature and 4-methylbenzylamine was removed *in vacuo*. The residue was recrystallized from MeOH to give the product (**11a**) (152 mg, 49 %). ^1H NMR (300 MHz, DMSO- d_6) δ 8.43 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.27-7.12 (m, 6H), 4.69 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 161.21, 140.43, 136.60, 135.69, 133.49, 129.19, 128.83, 127.86, 127.79, 63.67, 20.97, 20.62; ; ESI (m/z) 205.1(MH^+).

2-(3-Methylbenzyl)amino-1H-benzimidazole (**11b**)

2-Chlorobenzimidazole (200 mg, 1.31 mmol), 3-methylbenzylamine (0.83 mL, 6.55 mmol) in THF (1 mL) were used for the product (**11b**) (102 mg, 38 %). ^1H NMR (300 MHz, DMSO- d_6) δ 8.27 (s, 1H), 7.56 (s, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.24-6.97 (m, 6H), 4.69 (s, 2H), 2.27 (d, J = 9.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.08, 139.19, 138.29, 138.08, 136.17, 131.52, 128.75, 128.43, 128.37, 127.69, 125.83, 125.06, 65.11, 21.38, 21.21; ESI (m/z) 205.1(MH^+).

Synthesis of 1H-benzimidazol-2-yl-carbamic acid *tert*-butyl ester (**13**)

To a solution of 2-benzyl-1,3-bis(*tert*-butoxycarbonyl)-2-thiopseudourea (200 mg, 1.85 mmol) in MeOH (25 mL) was added 1,2-phenylenediamine (680 mg, 1.85 mmol) and the reaction mixture was heated to reflux for 10 h. After cooled to room temperature and the solvent was removed *in vacuo*. The residue was recrystallized from MeOH to give the product (**14**) (15 mg, 4 %). ^1H NMR (300 MHz, DMSO- d_6) δ 11.76 (br s, 1H), 7.45 (d, J = 3.0 Hz, 2H), 7.06 (d, J = 3.0 Hz, 2H), 1.53 (s, 9H); ESI (m/z) 233.9 (M^+).

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