Rapid and efficient synthesis of a new series of 2-aryl-5-fluoro-6-(4-phenylpiperazin-1-yl)-1*H*-benzimidazoles using microwave heating

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A new series of 2-aryl-5-fluoro-6-(4-phenylpiperazin-1-yl)-1*H*-benzimidazoles was synthesised from the reaction of 4-fluoro-5-(4-phenylpiperazin-1-yl)benzene-1,2-diamine and iminoester hydrochlorides. 4-Fluoro-5-(4-phenylpiperazin-1-yl)benzene-1,2-diamine was prepared from the reduction of 5-fluoro-2-nitro-4-(4-phenylpiperazin-1-yl)aniline by using Pd/C (10%) catalyst and hydrazine hydrate under microwave irradiation. The structures of newly synthesised compounds were identified by ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis data.

Keywords: benzimidazole, piperazine, microwave, Pd/C catalyst, fluorine atom

Benzimidazoles have generated a great deal of interest because of their important roles in organic synthesis and the pharmaceutical industry.[1-7] The benzimidazole system can be found in some medicinal compounds such as omeprazole, thiabendazole and albendazole.[8-12] Recently, it was reported that some benzimidazoles derivatives containing fluorine atom and 1-piperazinyl moiety have a valuable biological activity.[13,14] Several reports of substituted benzimidazoles containing fluorine and piperazine substituents describe important pharmacological effects.[15-18] In addition to these, two important papers describe benzimidazoles containing piperazine units which are effective at the opioid receptor.[19,20]

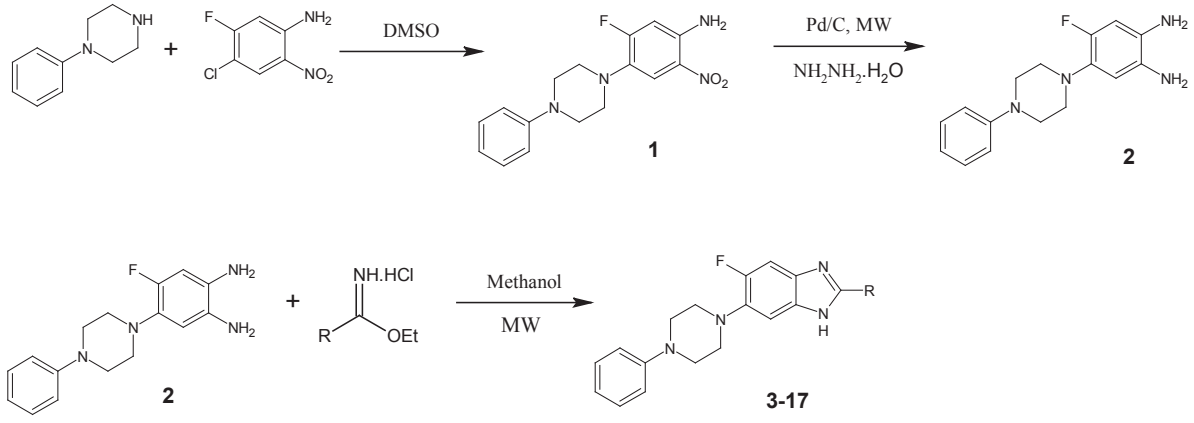
Heterocyclic compounds containing a fluorine atom and piperazinyl group are components of many drugs such as norfloxacin, ciprofloxacin, perfloxacin, eperezolid, ranbezolid.[21-23] Therefore, synthesis of these heterocyclic compounds continues to play an important role in medicinal chemistry. To this end, we now report a facile and efficient synthesis of some new 2-aryl-5-fluoro-(4-phenylpiperazin-1-yl)-1H-benzimidazoles using microwave heating.

Results and discussion

The synthetic pathway used for the target compounds is shown in Scheme 1. 5-Fluoro-2-nitro-4-(4-phenylpiperazin-1-yl)aniline (**1**) was prepared from the reaction of 4-chloro-5-fluoro-2-nitroaniline and N-phenylpiperazine in dimethyl sulfoxide. In order to prepare 4-fluoro-5-(4-phenylpiperazin-1-yl)benzene-1,2-diamine (**2**), compound **1** was treated with a Pd/C (10%) catalyst and hydrazine hydrate under microwave irradiation. This reaction reduced the nitro group to an amine. The iminoester hydrochlorides were synthesised according to the Pinner method.[24] Then, these compounds were reacted with compound **2** to synthesise the corresponding benzimidazole derivatives (**3**–**17**).

The synthesis of 4-fluoro-5-(4-phenylpiperazin-1-yl) benzene-1,2-diamine (**2**) was performed under microwave irradiation in ethanol by using Pd/C (10%) catalyst and hydrazine monohydrate. Using this method, the compound was easily synthesised in good yield without the need for further purification before the next step. However, this compound could not be synthesised by a conventional heating procedure in the presence of Pd/C catalyst even after 50 h reflux in ethanol. Another important point is that compound **2** darkens upon exposure to air or light.[14] Consequently we took special care in the synthesis of compound **2**.

The products were characterised using ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectra data. In the ^{1}H NMR spectra, the NH proton of compounds **3–17** was observed at about 12.20 ppm although in some of the spectra, this signal was not observed. Four CH_2 protons belonging to the piperazine were observed at about 3.10 and 3.30 ppm as multiplets. In the ^{13}C NMR spectra of compounds **3–17**, the piperazine CH_2 carbons appeared at about 49 and 51ppm. A correct number of aromatic carbon signals appeared between 102 and 163



Scheme 1 The synthetic routes for the target compounds.

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Table 1 The synthesis of compounds **3–17**

Compound	R	Yield/%	Melting point/°C
3	$-CH_3$	80	147–148
4	$-CH_2CH_3$	85	245–246
5	$-C_6H_5$	90	231–232
6	$-CH_2C_6H_5$	92	194–195
7	$-CH_2C_6H_4F_{(p)}$	89	201–202
8	$-CH_2C_6H_4Cl_{(p)}$	90	209–210
9	$-CH_2C_6H_4Br_{(p)}$	90	213–214
10	$-CH_2C_6H_4OCH_{3(p)}$	87	199–200
11	$-CH_2C_6H_4NO_{2(p)}$	85	153–154
12	$-CH_2C_6H_4CH_{3(p)}$	90	207–208
13	$-CH_2C_6H_3FClCl_{(3,4)}$	82	121–122
14	$-CH_2C_6H_4F_{(m)}$	83	154–155
15	$-CH_2C_6H_4Cl_{(m)}$	89	119–120
16	$-CH_2C_6H_4Br_{(m)}$	89	161–162
17	$-CH_2C_6H_4CH_{3(m)}$	87	190–191

ppm. In the ^{13}C NMR spectra of the benzimidazole, the number of aromatic C-atoms are less than proposed because of tautomerism of imidazole hydrogen between the two nitrogen atoms.[25-27] The number of ^{13}C-signals of compounds **3–17** indicates two (or four) aromatic C-atoms. The C=N carbon of benzimidazole was observed at about 151 ppm. The one-bond ^{13}C–^{9}F coupling constants are very large and consequently the carbon directly bound to the fluorine atom appeared as a doublet with a coupling constant of ~250 Hz.[28] All compounds gave the correct elemental analysis and mass spectral data.

Conclusion

In conclusion, we have synthesised a new series of potentially biologically active 2-aryl-5-fluoro-6-(4-phenylpiperazin-1-yl)-1*H*-benzimidazole derivatives by a microwave technique in good yields, and short reaction time.

Experimental

All the chemicals were supplied from Merck, Aldrich and Fluka. Melting points were determined in capillary tubes on a Buchi oil heated melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were performed on Varian-Mercury 400 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. The coupling constants (*J*) are given in Hz. Mass spectra were recorded on Thermo Scientific Quantum Access max LC-MS spectrometer. The elemental compositions were determined on a Carlo Erba 1106 CHN analyser; the experimental values were in agreement (±0.4%) with calculated ones. All the reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness). A monomode CEM-Discover microwave apparatus was used in the standard configuration. All experiments were carried out in microwave process vials (35 mL) with control of the temperature by IR detection temperature sensor. The temperature was computer-monitored and maintained constant by a discrete modulation of the microwave power. After completion of the reaction, the vial was cooled to 60 °C using air jet cooling.

Synthesis of 5-fluoro-2-nitro-4-(4-phenylpiperazin-1-yl)aniline **(1):** A mixture of 4-chloro-5-fluoro-2-nitroaniline (0.01 mol) and N-phenylpiperazine (0.03 mol) in dimethyl sulfoxide (10 mL) was heated in a oil bath for 4 h at 145-150 °C. The mixture was cooled to room temperature. Then, it was poured to ice-cold water. The precipitated product was filtered, dried and recrystallised from ethanol to give pure product. M.p. 179–180°C (lit.[14] 180–181°C).

Synthesis of 4-fluoro-5-(4-phenylpiperazin-1-yl)benzene-1,2-diamine **(2):** The Pd/C (10%) catalyst and hydrazine hydrate (0.06 mol) were added to the solution of 5-fluoro-2-nitro-4-(4-phenylpiperazin-1-yl)aniline (**1**) (0.01 mol) in ethanol (10 mL). Then, the mixture was stirred for 10 min. at room temperature and it was irradiated in the microwave at 145 °C for 40 min. (hold time) at 250 W. Then, the mixture was cooled to room temperature and the catalyst was separated by filtration. The combined filtrates were poured into water and the product precipitated. The product was filtered and dried. M.p. 116–117°C (lit.[14] 117–118°C). ^1H NMR (400 MHz, DMSO-d_6) δ 2.93 (m, 4H), 3.21 (m, 4H), 4.28 (s, 2H), 4.38 (s, 2H), 6.33–6.38 (m, 2H), 6.77 (t, *J*=7.6, 1H), 6.93 (d, *J*=8.0, 2H), 7.22 (t, *J*=8.0, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.07 ($2CH_2$), 51.65 ($2CH_2$), 103.17 (d, *J*=24.3), 106.88, 115.94 (2C), 119.38, 129.40 (2C), 129.76 (d, *J*=10.8), 131.31 (d, *J*=18.6), 131.42, 148.73 (d, *J*=230.5), 151.50. Anal. calcd for $C_{16}H_{19}FN_4$: C, 67.11; H, 6.69; N, 19.57; found: C, 67.05; H, 6.65; N, 19.51%. ESI-MS: 287.35 $[M+1]^+$.

Synthesis of compounds **3–17;** *general procedure*

A mixture of 4-fluoro-5-(4-phenylpiperazin-1-yl)benzene-1,2-diamine (**2**) (0.01 mol) and corresponding iminoester hydrochloride (0.012 mol) in methanol (10 mL) was irradiated in microwave in a closed vessel with pressure control at 60 °C for 10 min. Then, the mixture was poured onto water. The precipitate formed was filtered and recrystallised from ethanol:water (1:3)

5-Fluoro-2-methyl-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(3)**: ^1H NMR (400 MHz, DMSO-d_6) δ 2.48 (s, 3H), 3.09 (m, 4H), 3.27 (m, 4H), 6.78 (t, *J*=7.2, 1H), 6.98 (d, *J*=7.6, 2H), 7.10 (d, *J*=7.6, 1H), 7.20–7.26 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.06, 49.02 ($2CH_2$), 51.64 ($2CH_2$), 116.01 (2C), 119.49, 129.42 (2C), 135.96 (d, *J*=11.5), 151.46 (C=N), 151.53, 152.04, 152.95 (d, *J*=186.1). Anal. calcd for $C_{18}H_{19}FN_4$: C, 69.66; H, 6.17; N, 18.05; found: C, 69.61; H, 6.19; N, 18.02%. ESI-MS: 311.17 $[M+1]^+$.

5-Fluoro-2-ethyl-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(4)**: ^1H NMR (400 MHz, DMSO-d_6) δ 1.26 (t, *J*=8.0, 3H), 2.78 (q, *J*=8.0, 2H), 2.95 (m, 4H), 3.28 (m, 4H), 6.78 (t, *J*=7.6, 1H), 6.99 (d, *J*=7.8, 2H), 7.11 (d, *J*=7.6, 1H), 7.20–7.28 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.37, 21.81, 48.98 ($2CH_2$), 51.48, 51.50, 102.25 (d, *J*=25.8), 103.99, 116.04 (2C), 116.15, 119.55, 129.42 (2C), 132.86, 137.06 (d, *J*=11.5), 151.41 (C=N), 152.00, 155.52 (d, *J*=229.7). Anal. calcd for $C_{19}H_{21}FN_4$: C, 70.35; H, 6.52; N, 17.27; found: C, 70.30; H, 6.49; N, 17.23%. ESI-MS: 325.21 $[M+1]^+$.

*5-Fluoro-2-phenyl-6-(4-phenylpiperazin-1-yl)-1*H*-benzimidazole* **(5)**: ^1H NMR (400 MHz, DMSO-d_6) δ 3.15 (m, 4H), 3.41 (m, 4H),), 6.79 (t, *J*=7.2, 1H), 7.00 (d, *J*=8.4, 2H), 7.12 (d, *J*=7.6, 1H), 7.25 (t, *J*=7.6, 2H), 7.44–7.47 (m, 2H), 7.50–7.54 (m, 2H), 8.11 (d, *J*=6.8, 1H), 12.86 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.02 ($2xCH_2$), 51.50 ($2xCH_2$), 102.10 (d, *J*=25), 116.03 (2C), 119.53, 126.59 (2C), 129.40 (2C), 129.50 (2C), 130.09, 130.56, 151.45, 151.97 (C=N), 155.64 (d, *J*= 229). Anal. calcd for $C_{23}H_{21}FN_4$: C, 74.17; H, 5.68; N, 15.04; found: C, 74.13; H, 5.63; N, 15.09%. ESI-MS: 373.30 $[M+1]^+$.

*5-Fluoro-2-benzyl-6-(4-phenypiperazin-1-yl)-1*H*-benzimidazole* **(6)**: ^1H NMR (400 MHz, DMSO-d_6) δ 3.10 (m, 4H), 3.28 (m, 4H), 4.12 (s, 2H), 6.79 (d, *J*=7.2, 1H), 6.99 (t, *J*=8.0, 2H), 7.20–7.30 (m, 9H), 12.18 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.34, 49.01 ($2CH_2$), 51.64 ($2CH_2$), 101.98 (d, *J*=25), 116.02 (2C), 119.50, 126.95, 128.91 (2C), 129.15 (2C), 129.43 (2C), 138.14, 151.46 (C=N), 153.31 (d, *J*=230).. Anal. calcd for $C_{24}H_{23}FN_4$: C, 74.59; H, 6.00; N, 14.50; found: C, 74.55; H, 6.01; N, 14.46%. ESI-MS: 387.32 $[M+1]^+$.

*5-Fluoro-2-(4-fluorobenzyl)-6-(4-phenylpiperazin-1-yl)-1*H*-benzimidazole* **(7):** ^1H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.28 (m, 4H), 4.11 (s, 2H), 6.78 (t, *J*=6.8, 1H), 6.98 (d, *J*=7.6, 2H), 7.12–7.32 (m, 8H), 12.18 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.30, 49.98 ($2CH_2$), 51.62 ($2CH_2$), 115.49, 115.70, 116.00 (2C), 116.04, 119.49, 129.41, 130.97, 131.06, 134.20, 134.24, 151.44 (C=N), 154.19, 154.20, 161.46 (d, *J*= 240). Anal. calcd for $C_{24}H_{22}F_2N_4$: C, 71.27; H, 5.48; N, 13.85; found: C, 71.22; H, 5.45; N, 13.80%. ESI-MS: 405.28 $[M+1]^+$.

*5-Fluoro-2-(4-chlorobenzyl)-6-(4-phenylpiperazin-1-yl)-1*H*-benzimidazole* **(8):** ^1H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.31 (m, 4H), 4.12 (s, 2H), 6.78 (t, *J*=7.2, 1H), 6.98 (d, *J*=8.4, 2H), 7.20–7.36 (m, 8H), 12.19 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.54, 49.00 ($2CH_2$), 51.62 ($2CH_2$), 116.00, 116.03, 119.49, 128.76, 128.82 (2C), 129.41 (2C), 131.01, 131.05 (2C), 131.65, 137.07, 151.43 (C=N), 153.87 (d, *J*=

238). Anal. calcd for $C_{24}H_{22}ClFN_4$: C, 68.48; H, 5.27; N, 13.31; found: C, 68.44; H, 5.23; N, 13.24%. ESI-MS: 423.30, 421.27 $[M+1]^+$.

5-Fluoro-2-(4-bromobenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(9):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.29 (m, 4H), 4.18 (s, 2H), 6.79 (t, *J*=7.2, 1H), 6.99 (d, *J*=8.4, 2H), 7.14–7.36 (m, 6H), 7.51 (d, *J*=8.4, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.06, 48.98 ($2CH_2$), 51.51 ($2CH_2$), 103.60, 116.03 (2C), 119.53, 120.38, 129.41 (2C), 131.53 (2C), 131.86 (2C), 136.79, 136.87, 137.00, 151.39 (C=N), 153.56 (d, *J*= 238). Anal. calcd for $C_{24}H_{22}BrFN_4$: C, 61.94; H, 4.77; N, 12.04; found: C, 61.90; H, 4.72; N, 12.01%. ESI-MS: 467.29 $[M+2]^+$, 465.26 $[M]^+$.

5-Fluoro-2-(4-methoxybenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(10):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (m, 4H), 3.27 (m, 4H), 3.69 (s, 3H), 4.06 (s, 2H), 6.79 (t, *J*=7.2, 1H), 6.89 (d, *J*=8.4, 2H), 6.97 (d, *J*=8.0, 2H), 7.20-7.31 (m, 6H), 12.15 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.53, 49.02 ($2CH_2$), 51.64 ($2CH_2$), 55.47, 114.30, 114.33 (2C), 116.01 (2C), 119.50, 129.41 (2C), 130.00, 130.20 (2C), 136.26, 151.45 (C=N), 153.15 (d, *J*=240), 158.44. Anal. calcd for $C_{25}H_{25}FN_4O$: C, 72.09; H, 6.05; N, 13.45; found: C, 72.03; H, 6.01; N, 13.38%. ESI-MS: 417.32 $[M+1]^+$.

5-Fluoro-2-(4-nitrobenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(11):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.27 (m, 4H), 4.30 (s, 2H), 6.78 (t, *J*=6.8, 1H), 6.97 (d, *J*=7.6, 2H), 7.19–7.25 (m, 4H), 7.57 (d, *J*=8.4, 2H), 8.18 (d, *J*=8.8, 2H), 12.31 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.95, 48.99 ($2CH_2$), 51.57 ($2CH_2$), 100.05, 115.99, 116.02 (2C), 119.45, 124.02 (2C), 129.40 (2C), 130.53 (2C), 146.05, 146.74, 151.42 (C=N), 152.98 (d, *J*=238). Anal. calcd for $C_{24}H_{22}FN_5O_2$: C, 66.81; H, 5.14; N, 16.23; found: C, 66.75; H, 5.10; N, 16.17%. ESI-MS: 432.29 $[M+1]^+$.

5-Fluoro-2-(4-methylbenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(12):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H), 3.09 (m, 4H), 3.28 (m, 4H), 4.36 (s, 2H), 6.78 (t, *J*=6.8, 1H), 6.98 (d, *J*=8.0, 2H), 7.10 (d, *J*=7.6, 2H), 7.16–7.24 (m, 6H), 12.13 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.05, 34.95, 49.01 ($2CH_2$), 51.63 ($2CH_2$), 116.00, 116.03, 119.48, 129.00, 129.01, 129.40, 129.43, 129.48, 135.03, 135.15, 135.87, 135.95, 151.44 (C=N), 154.53 (d, *J*=236). Anal. calcd for $C_{25}H_{25}FN_4$: C, 74.97; H, 6.29; N, 13.99; found: C, 74.92; H, 6.25; N, 13.95%. ESI-MS: 401.29 $[M+1]^+$.

5-Fluoro-2-(3,4-dichlorobenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(13):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (m, 4H), 3.26 (m, 4H), 4.16 (s, 2H), 6.78 (t, *J*=7.2, 1H), 6.96 (d, *J*=8.0, 2H), 7.15 (d, *J*=8.0, 1H), 7.22 (t, *J*=8.0, 2H), 7.26–7.33 (m, 2H), 7.54 (d, *J*=8.0, 1H), 7.58 (s, 1H), 12.29 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.21, 49.01 ($2CH_2$), 51.59 ($2CH_2$), 114.08, 116.00, 116.03, 119.49, 129.39, 129.70, 129.76, 130.78, 130.98, 131.27, 131.40, 136.40, 136.52, 139.11, 139.28, 147.81, 151.43 (C=N), 153.17 (d, *J*=237), 153.36. Anal. calcd for $C_{24}H_{21}Cl_2FN_4$: C, 63.30; H, 4.65; N, 12.30; found: C, 63.22; H, 4.60; N, 12.23%. ESI-MS: 457.35, 455.25 $[M+1]^+$.

5-Fluoro-2-(3-fluorobenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(14):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.27 (m, 4H), 4.17 (s, 2H), 6.78 (t, *J*=6.8, 1H), 6.96 (d, *J*=5.6, 2H), 7.02–7.33 (m, 8H), 12.20 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.94, 49.01 ($2CH_2$), 51.61 ($2CH_2$), 113.68, 113.88, 115.89, 116.01 (2C), 116.11, 119.50, 125.32 (2C), 129.41 (2C), 130.78 (d, *J*=8.6), 136.41 (d, *J*=11.0), 140.82, 140.89, 151.45, 152.96 (d, *J*=236.2), 153.71 (C=N), 162.62 (d, *J*=242). Anal. calcd for $C_{24}H_{22}F_2N_4$: C, 71.27; H, 5.48; N, 13.85; found: C, 71.20; H, 5.42; N, 13.81%. ESI-MS: 405.24 $[M+1]^+$.

5-Fluoro-2-(3-chlorobenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(15):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.27 (m, 4H), 4.17 (s, 2H), 6.79 (t, *J*=7.2, 1H), 6.96 (d, *J*=7.6, 2H), 7.19–7.39 (m, 8H), 12.25 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.85, 49.02 ($2CH_2$), 51.60 ($2CH_2$), 116.01 (2C), 119.50, 126.92, 127.96, 129.07, 129.41 (2C), 129.68, 130.72, 133.50, 136.35, 140.53, 151.44 (C=N), 152.94 (d, *J*= 236), 153.66. Anal. calcd for $C_{24}H_{22}ClFN_4$: C, 68.48; H, 5.27; N, 13.31; found: C, 68.41; H, 5.19; N, 13.22%. ESI-MS: 423.34, 421.31 $[M+1]^+$.

5-Fluoro-2-(3-bromobenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(16):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 4H), 3.27 (m, 4H), 4.15 (s, 2H), 6.78 (t, *J*=6.8, 1H), 6.97 (d, *J*=7.8, 2H), 7.20–7.42 (m, 7H), 7.53 (s, 1H), 12.25 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.78, 49.01 ($2CH_2$), 51.60 ($2CH_2$), 116.01 (2C), 119.50, 122.12, 128.36, 129.42 (2C), 129.81, 129.88, 131.05, 131.92, 136.30, 140.83, 141.07, 151.44 (C=N), 153.66 (d, *J*=240). Anal. calcd for $C_{24}H_{22}BrFN_4$: C, 61.94; H, 4.77; N, 12.04; found: C, 61.88; H, 4.69; N, 11.97%. ESI-MS: 467.19 $[M+2]^+$, 465.30 $[M]^+$.

5-Fluoro-2-(3-methylbenzyl)-6-(4-phenylpiperazin-1-yl)-1H-benzimidazole **(17):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H), 3.09 (m, 4H), 3.27 (m, 4H), 4.07 (s, 2H), 6.79 (t, *J*=6.8, 1H), 6.96–7.29 (m, 10H), 12.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.43, 35.33, 49.02 ($2CH_2$), 51.63 ($2CH_2$), 116.01 (2C), 119.50, 126.24, 127.52, 127.59, 128.82 (2C), 129.42 (2C), 129.75 (2C), 136.32, 137.94, 138.22, 151.45 (C=N), 153.12 (d, *J*=240). Anal. calcd for $C_{25}H_{25}FN_4$: C, 74.97; H, 6.29; N, 13.99; found: C, 74.89; H, 6.21; N, 13.90%. ESI-MS: 401.29 $[M+1]^+$.

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