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RESEARCH ARTICLE

Microwave-assisted synthesis of *sec/tert*-butyl 2-arylbenzimidazoles and their unexpected antiproliferative activity towards ER negative breast cancer cells

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Abstract

A new series of *N-sec/tert*-butyl 2-arylbenzimidazole derivatives was synthesised in 85–96% yields within 2–3.5 min by condensing ethyl 3-amino-4-butylamino benzoate with various substituted metabisulfite adducts of benzaldehyde under focused microwave irradiation. The benzimidazole analogues were characterised using ^{1}H NMR, ^{13}C NMR, high resolution MS and melting points. Evaluation of antiproliferative activity of the benzimidazole analogues against MCF-7 and MDA-MB-231 revealed several compounds with unexpected selective inhibitions of MDA-MB-231 in micromolar range. All analogues were found inactive towards MCF-7. The most potent inhibition against MDA-MB-231 human breast cancer cell line came from the unsubstituted 2-phenylbenzimidazole **10a**.

Keyword: 2-Arylbenzimidazole, Microwave synthesis, Breast cancer, MTS assay, Antiproliferative activity

Introduction

Breast cancer ranks as the top cancer in women, amounting to almost one-fifth of all female cancers. It is also the second leading cause of cancer mortality in women.[1–3] Apart from anti-oestrogen and radiation therapies and surgery, chemotherapy remains the mainstay treatment for breast cancer.

In oestrogen receptor positive (ER+) breast cancer, tamoxifen has made substantial reductions in the mortality rate in both early and advanced breast cancer patients for almost three decades.[4] Long term use of tamoxifen, however, is of limited success due to resistance in patients.[5] In contrast, patients with oestrogen-independent (ER-) breast cancer are often unresponsive to current treatments with poorer prognosis than hormone dependent breast cancer patients, thus they receive more aggressive chemotherapy. Despite considerable progress made in the discovery of novel chemotherapeutic agents for example imatinib, paclitaxel, ixabepilone; many current anti-cancer agents are still beseted with clinical problems such as toxicity, resistance and debilitating adverse effects.[6–8] Therefore, there is a clear need for new anti-cancer agents with enhanced selectivity towards breast cancer.

Small molecule inhibitors are the cornerstone of existing anti-cancer agents, and serve as lead compounds for many new chemotherapeutic agents.[1,2,8] Recently several structurally related bicyclic privileged scaffolds[9,10] were reported to exhibit strong inhibitory effects on breast cancer cell lines, for instance benzothiophene **1**[11], benzothiazole **2**[12], benzoxazole[13] and benzimidazoles **3, 4**[14,15] (Figure 1).

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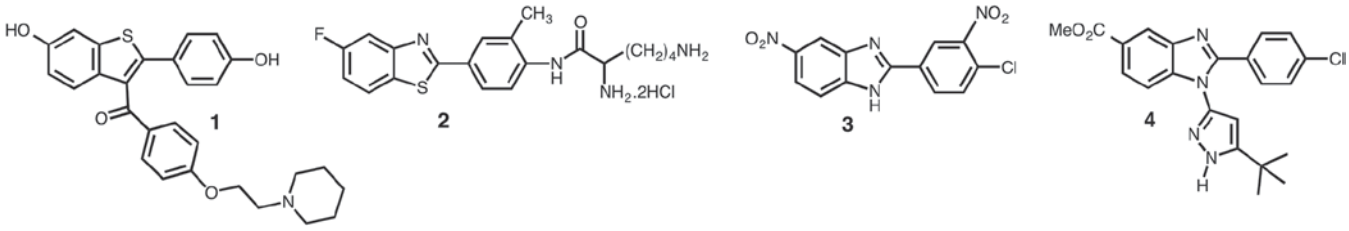


Figure 1. Some bicyclic privileged structures with cytotoxic activity against breast cell lines.

Of particular interest to us is the benzimidazole core, which exhibits a wide range of biological and pharmacological activities[16] including against several viruses such as HIV[17], human cytomegalovirus (HCMV)[18]; *Chlamydia* bacteria[19]; as topoisomerase inhibitors[20], angiotensin inhibitor[21], antitumour and anticancer agents.[11,22–25] The proton pump inhibitor Omeprazole, and the antihelmintic Albendazole are examples of benzimidazoles with established clinical use.[16] The remarkable biological significance of benzimidazole derivatives together with their close structural resemblance to benzimidazole analogues **3** and **4** (Figure 1) led us to surmise that this series of 2-arylbenzimidazole derivatives could exert anti-proliferative effects towards breast cancer cell lines. Thus in this paper, we report microwave assisted preparation of a new series of *N-sec/tert*-butyl-2-arylbenzimidazole derivatives and the evaluation of their antiproliferative activity against hormone dependent (MCF-7) and hormone independent (MDA-MB-231) breast cancer cell lines.

Materials and methods

Microwave-assisted syntheses were performed using CEM Discover™ microwave synthesizer. Melting points were measured on a Stuart SMP10 instrument and are uncorrected. Compounds **6–8** have been synthesised as previously described.[15,26,27] Preparative thin layer chromatography (PLC) was performed using Merck 60 GF254 silica gel coated (1 mm) on glass plates (20 × 20 cm). TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). Visualisation of TLC plates was performed under UV light and aided by $KMnO_4$ and iodine staining. Routine NMR (^1H and ^{13}C) spectra were recorded on a Bruker 300, 400 and 500 MHz instruments in $CDCl_3$. Acquisition of high resolution mass measurements of the compounds was performed on an Agilent 6520 Quadrupole Time of Flight Mass Spectrometer (Agilent Technologies, Santa Clara, CA, USA) operating in the MS mode. All commercially available starting materials and solvents are used without further purification.

General procedure for synthesis of benzimidazoles 10a-e, 11a-e

Ethyl-3-amino-4-(*sec*-/*tert*-butylamino) benzoates were prepared according to previous procedure.[27] Thus, a solution of ethyl-3-amino-4-(*sec*-/*tert*-butylamino) benzoate (200 mg, 0.84 mmol) and sodium bisulfite adduct of benzaldehyde (353 mg, 1.68 mmol) in DMF (1 ml) was irradiated under microwave conditions at 130°C for 2–3.5 min. The reaction mixture was then diluted in EtOAc (20 mL) and washed with H_2O (20 mL). The organic layer was collected and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product.

Ethyl 1-sec-butyl-2-phenyl-1H-benzimidazole-5-carboxylate (**10a**). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 0.65 (t, CH_3, 3H), 1.44 (t, CH_3, 3H), 1.70 (d, CH_3, 3H), 1.80–1.93 (m, CH_2, 1H), 2.10–2.22 (m, CH_2, 1H), 4.42 (q, CH_2, 2H), 4.50–4.54 (m, CH, 1H), 7.50–7.58 (m, 3H), 7.61–7.67 (m, 3H), 8.01 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 11.22, 14.45, 31.02, 39.04, 55.7, 61.34, 112.32, 123.20, 124.32, 124.85, 128.56, 129.32, 131.26, 137.64, 144.51, 156.24, 167.52; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{22}N_2O_2$ (M+H), 323.1754; found 323.1767.

Ethyl 1-sec-butyl-2-(4-fluorophenyl)-1H-benzimidazole-5-carboxylate (**10b**). ^1H NMR ($CDCl_3$, 500 MHz), δ(ppm): 0.64 (t, CH_3, 3H), 1.42 (t, CH_3, 3H), 1.70 (d, CH_3, 3H), 1.85–1.93 (m, CH_2, 1H), 2.13–2.22 (m, CH_2, 1H), 4.42 (q, CH_2, 2H), 4.45–4.49 (m, CH, 1H), 7.21–7.25 (m, 2H), 7.60–7.64 (m, 3H), 7.99–8.01 (dd, J = 8.5, 1.5 Hz), 8.54 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 10.94, 14.37, 19.89, 28.09, 55.18, 60.80, 111.70, 115.88, 116.05, 122.51, 123.83, 124.78, 126.80, 131.60, 136.68, 143.30, 155.17, 162.68, 164.68, 167.03; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{21}FN_2O_2$ (M+H), 341.1660; found 341.1666.

Ethyl 1-sec-butyl-2-(4-bromophenyl)-1H-benzimidazole-5-carboxylate (**10c**). ^1H NMR ($CDCl_3$, 500 MHz), δ(ppm): 0.64 (t, CH_3, 3H), 1.43 (t, CH_3, 3H), 1.70 (d, CH_3, 3H), 1.86–1.94 (m, CH_2, 1H), 2.13–2.22 (m, CH_2, 1H), 4.43 (q, CH_2, 2H), 4.45–4.47 (m, CH, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 8.00–8.02 (dd, J = 8.5, 1.0 Hz, 1H), 8.55 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 10.94, 14.38, 19.91, 28.12, 55.25, 60.83, 111.76, 122.60, 123.94, 124.52, 124.87, 129.61, 131.09, 132.04, 136.71, 143.36, 155.01, 167.00; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{21}BrN_2O_2$ (M+H), 401.0859; found 401.0872.

Ethyl 1-sec-butyl-2-(3-nitrophenyl)-1H-benzimidazole-5-carboxylate (**10d**). ^1H NMR ($CDCl_3$, 500 MHz), δ(ppm): 0.70 (t, CH_3, 3H), 1.45 (t, CH_3, 3H), 1.77 (d, CH_3, 3H), 1.92–2.01 (m, CH_2, 1H), 2.19–2.28 (m, CH_2, 1H), 4.45 (q, CH_2, 2H), 4.47–4.51 (m, CH, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.76–7.79 (m, 1H), 8.03–8.07 (m, 2H), 8.41–8.43 (m, 1H), 8.53–8.54 (m, 1H), 8.58 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 11.02, 14.38, 19.99, 28.25, 55.65, 60.94, 111.98, 122.89, 124.41, 124.52, 124.67,

125.28, 130.05, 132.41, 135.52, 136.72, 143.31, 148.31, 153.36, 166.87; Mass ESI *m/z* 368.3 (M+1). HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{21}N_3O_4$ (M+H), 368.1605; found 368.1620.

Ethyl 1-sec-butyl-2-(2-hydroxyphenyl)-1H-benzimidazole-5-carboxylate (**10e**). ^{1}H NMR ($CDCl_3$, 400 MHz), δ(ppm): 0.65 (t, CH_3, 3H), 1.45 (t, CH_3, 3H), 1.77 (d, CH_3, 3H), 1.91–2.02 (m, CH_2, 1H), 2.13–2.22 (m, CH_2, 1H), 4.413 (q, CH_2, 2H), 4.79–4.87 (m, CH, 1H), 6.97–7.02 (m, 1H), 7.13–7.15 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.35–7.39 (m, 1H), 7.40–7.44 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.69–7.99 (m, 1H), 8.44 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 11.21, 14.81, 20.01, 28.54, 56.30, 61.32, 112.59, 114.25, 118.73, 119.57, 121.90, 124.43, 125.56, 128.48, 132.19, 136.65, 142.10, 154.35, 158.40, 167.23; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{22}N_2O_3$ (M+H), 339.1703; found 339.1717.

Ethyl 1-tert-butyl-2-p-tolyl-1H-benzimidazole-5-carboxylate (**11a**). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 1.41 (t, CH_3, 3H), 1.62 (s, CH_3, 9H), 2.42 (s, CH_3, 3H), 4.41 (q, CH_2, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.97–8.00 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.47 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,), δ (ppm): 14.78, 21.81, 31.89, 59.80, 61.18, 114.57, 122.53, 122.83, 124.62, 128.89, 129.72, 132.71, 138.62, 139.65, 143.35, 155.95, 167.50; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{21}H_{24}N_2O_2$ (M+H), 337.1911; found 337.1922.

Ethyl 1-tert-butyl-2-(4-methoxyphenyl)-1H-benzimidazole-5-carboxylate (**11b**). ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 1.41 (t, CH_3, 3H), 1.62 (s, CH_3, 9H), 3.87 (s, OCH_3, 3H), 4.40 (q, CH_2, 2H), 6.96 (d, *J* = 9.0 Hz, 1H), 7.39–7.41(m, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.96–7.99 (m, 1H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 14.77, 31.87, 55.76, 60.07, 61.21, 114.11, 114.69, 122.39, 123.76, 124.88, 127.25, 131.32, 138.43, 142.67, 155.58, 160.86, 167.37; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{24}N_2O_3$ (M+H), 353.1860; found 353.1863.

Ethyl 1-tert-butyl-2-(2-chlorophenyl)-1H-benzimidazole-5-carboxylate (**11c**). ^{1}H NMR ($CDCl_3$, 500 MHz), δ(ppm): 1.43 (t, CH_3, 3H), 1.66 (s, CH_3, 9H), 4.43 (q, CH_2, 2H), 7.38–7.40 (m, 1H), 7.45–7.50 (m, 3H), 7.79 (d, *J* = 8.5 Hz), 8.03–8.05 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.52 (d, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 14.39, 30.39, 59.45, 60.80, 114.17, 122.64, 123.56, 124.49, 126.46, 129.32, 130.81, 131.44, 134.49, 135.08, 137.67, 143.17, 151.60, 167.00; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{21}ClN_2O_2$ (M+H), 357.1365; found 357.1378.

Ethyl 1-tert-butyl-2-(2,4-dichlorophenyl)-1H-benzimidazole-5-carboxylate (**11d**). ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.42 (t, CH_3, 3H), 1.65 (s, CH_3, 9H), 4.42 (q, CH_2, 2H), 7.37–7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 8.03–8.05 (dd, *J* = 9.0, 1.5 Hz, 1H), 8.50 (d, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 14.37, 30.45, 59.57, 60.85, 114.23, 122.63, 123.77, 124.70, 126.95, 129.28, 132.17, 133.60, 135.33, 136.32, 137.61, 143.03, 150.44, 166.87; EIMS *m/z* calcd for $C_{20}H_{20}Cl_2N_2O_2$ (M+H), 391.1; found 391.1 (100), 392.1 (19), 393.0 (59), 394.1 (14); HRMS (ESI/Q-TOF): calcd (M+H) 391.0974, found 391.2843; (M-Cl+H) calcd 357.1365, found 357.1362.

Ethyl 1-tert-butyl-2-(2-hydroxyphenyl)-1H-benzimidazole-5-carboxylate (**11e**). ^{1}H NMR ($CDCl_3$, 500 MHz), δ(ppm): 1.47 (t, CH_3, 3H), 1.70 (s, CH_3, 9H), 4.43 (q, CH_2, 2H), 6.53 (d, *J* = 8.5 Hz), 6.87–6.90 (m, 1H), 7.08–7.11 (m, 1H), 7.15–7.16 (dd, *J* = 7.5, 1.5 Hz 1H), 7.53 (d, *J* = 8.5 Hz), 7.61–7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 14.52, 30.21, 60.02, 60.63, 114.04, 119.52, 119.70, 120.27, 122.85, 123.58, 124.04, 130.09, 131.16, 136.90, 141.03, 152.91, 155.40, 166.46; HRMS (ESI/Q-TOF): *m/z* calcd for $C_{20}H_{22}N_2O_3$ (M+H), 339.1703; found 339.1710.

In vitro cytotoxicity assay

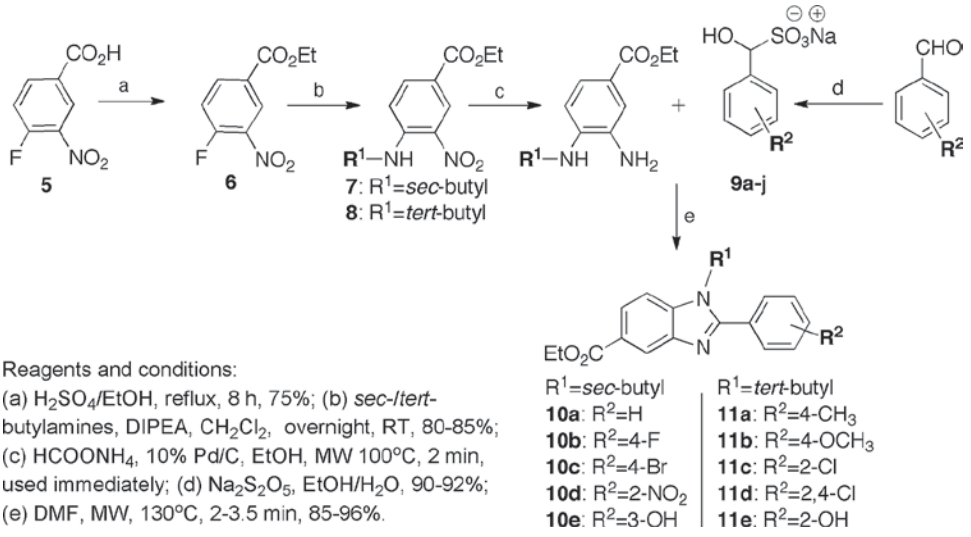
MCF-7 and MDA-MB-231 cell lines were purchased from ATCC and were grown, respectively, in DMEM and L-15 supplemented with 10% fetal bovine serum. Cytotoxicity of the compounds was evaluated using Cell Titer 96® Aqueous Non-Radioactive Cell Proliferation Assay (Promega), according to manufacturer's instructions. Briefly, 90 µL of MCF-7 and MDA-MB-231 at respective cell number (MCF-7: 2×10^4 cells/well; MDA-MB-231: 2.5×10^4 cells/well) were seeded in triplicates in 96-well plate and incubated for 24 h. Subsequently, 10 µL of test compounds at various concentrations were added into each well and incubated for 48 h. Following incubation, 20 µL of MTS-PMS solution was added into each well and the plate was incubated 2 h for MCF-7 and 5 h for MDA-MB-231. Cisplatin and DMSO were used as positive and negative controls in this assay. The optical density of each well was determined spectrophotometrically at 490 nm, with 655 nm as reference wavelength. The percentage growth inhibition was calculated according to the following formula:

Percentage of growth inhibition (%) = *Absorbance of negative control – Absorbance of test compound* Absorbance of negative control

Results and discussion

Microwave-assisted synthesis of 2-arylbenzimidazoles

Synthesis of our target benzimidazoles **10** and **11** began with esterification of benzoic acid **5** in the presence of catalytic sulfuric acid in ethanol by refluxing for 8 h to afford ethyl ester **6** in 75% yield (Scheme 1). The benzoate **6** was then treated with *sec*- or *tert*-butylamine and *N,N*-diisopropylethylamine (DIPEA) in dichloromethane overnight to afford compound **7** and **8**. Reduction of the aryl nitro **7** using 1.5 equivalent of ammonium formate in 10% Pd/C in ethanol gave a 30% yield; repeating it at 3.5 equivalent doubled the yield to 65%. When this reaction was performed under microwave conditions at 100°C for 2 min, the yields of the diamine intermediate improved significantly to 85%.[27] The pleasant smell compound was found to decompose by turning to dark red if kept any longer. Hence, the diamino compound was used immediately in the next step without further purification.



Scheme 1. Synthesis of N-sec/tert-butyl 2-arylbenzimidazoles **10a-e** and **11a-e**.

Table 1. Cyclocondensation reaction of aldehydes **9a-j** under microwave conditions and analytical data of the benzimidazole products **10a-e** and **11a-e**.

Aldehydes **9**	Aromatic substitution	Time (min)[a]	Products	Yield[b] (%)	Mp °C
a	H	2	**10a**	92	121
b	4-F	3	**10b**	94	160
c	4-Br	2	**10c**	96	122
d	3-NO_2	3	**10d**	89	109
e	2-OH	2.5	**10e**	95	178
f	4-CH_3	2	**11a**	91	165
g	4-OCH_3	2	**11b**	92	156
h	2-Cl	3.5	**11c**	85	155
i	2,4-Cl	3	**11d**	87	148
j	2-OH	2	**11e**	93	140

[a]Reaction time under optimised microwave conditions. [b]Isolated yield.

Benzimidazoles are typically prepared by condensing *o*-phenylenediamine with acid chloride, aldehydes and carboxylic acids.[28,29] To effect the condensation of phenylenediamines with carboxylic acids generally require harsh, dehydrating conditions; in contrast, access *via* aldehydes employs oxidative reagents for example, copper(II) acetate, 1,4-benzoquinone, I_2/KI, sodium metabisulfite and, interestingly, air.[30–32] Thus, we prefer using bisulfite adducts of aldehyde as this method has been reported to be more efficient and environmental friendly affording good to excellent yield of benzimidazoles when compared to other synthetic methods.[15,31] Initial condensation reactions of the unstable substituted *o*-phenylenediamines with sodium bisulfite adduct of some substituted benzaldehydes, by heating in DMF for 2–4 h, afforded moderate yields of benzimidazoles. The cyclocondensation reaction was further optimised under microwave conditions and then performed on commercially available aldehydes **9a-j** to assess the generality of the optimised reaction conditions. We found that this microwave-irradiated cyclocondensation reactions proceeded in 2–3.5 min and afforded excellent yields (85–96%) of 2-arylbenzimidazoles as shown in Table 1.

Table 2 Cytotoxicity of *sec-/tert*-butyl 2-arylbenzimidazoles against human breast cancer cell lines.

		IC_{50} (μM)	
Compound	R^2	MDA-MB-231[a,c]	MCF-7[b,d]
R^1 = *sec*-butyl			
10a	H	29.7	>200
10b	4-F	>200	>200
10c	4-Br	81.5	>200
10d	3-NO_2	36.8	>200
10e	2-OH	>200	>200
R^1 = *tert*-butyl			
11a	4-CH_3	>200	>200
11b	4-OCH_3	88.6	>200
11c	2-Cl	>200	>200
11d	2,4-Cl	47.6	>200
11e	2-OH	>200	>200

[a]The concentration required to inhibit the proliferation of the cells by 50% expressed as IC_{50} (μM). Values given represent the mean obtained from three consecutive experiments. [b]IC_{50} values could not be determined since the concentrations exceeded the range tested. [c]Hormone independent human breast cancer cell line. [d]Hormone dependent human breast cancer cell line.

Pharmacology

The newly synthesised compounds **10a-e** and **11a-e** were evaluated in *in vitro* antiproliferative (MTS assay) studies against two human breast cancer cell lines MDA-MB-231 and MCF-7. The inhibitory activities are summarised in Table 2. Several compounds were found to exhibit moderate antiproliferative activity towards MDA-MB-231 cell lines. The unsubstituted 2-phenylbenzimidazole **10a** emerged as the compound with most potent inhibition against MDA-MB-231 cell line (IC_{50} value of 29.7 μM) followed by 3-nitrophenyl **10d** and 2,4-dichlorophenyl **11d** with IC_{50} of 36.8 μM and 47.6 μM, respectively.

In the *sec*-butyl series, the replacement of the hydrogen on the *para*-position of **10a** with an isosteric fluoro in **10b**

seems detrimental to its activity. Unlike the fluoro **10b**, the 4-bromophenyl derivative **10c** (IC_{50} of 81.5 μM) showed a 2.7-fold reduced activity compared to the unsubstituted **10a**. In terms of substitution on the phenyl ring, the activity seen in 2,4-dichloro **11d** however, was abolished in its *ortho*-substituted analogue **11c**. Another *ortho*-substituted phenylbenzimidazoles **10e** and **11e** also showed no antiproliferative effects against both breast cancer cell lines. This suggests the unlikely role of the 2-substitution in the phenyl ring towards activity. All compounds showed no antiproliferative activity on MCF-7 cell lines (IC_{50} > 200 μM).

Various substituted benzimidazoles were previously reported to show potent antiproliferative activity on MCF-7 and other breast cancer cell lines; however with little or no selectivity.[11,23,33–38] In this study, even though these benzimidazole analogues showed moderate antiproliferative activity, their unexpected selectivity towards MDA-MB-231 is interesting and worth pursuing further. To date, such selectivity remains uncommon for benzimidazole derivatives.[22]

Conclusions

The synthesis of a new series of *N-sec/tert*-butyl substituted benzimidazole derivatives was accomplished in excellent yields (85–96%) and short reaction time (2–3.5 min) under optimised microwave conditions. The results of the antiproliferative studies showed that these *N-sec/tert*-butyl-2-arylbenzimidazoles unexpectedly exhibited antiproliferative activity selective towards MDA-MB-231 breast cancer cell lines, but completely inactive towards MCF-7. The unsubstituted *sec*-butyl-2-phenylbenzimidazole **10a** with IC_{50} of 29.7 μM is the most potent candidate of this series against MDA-MB-231 cancer cell line. Therefore it serves as the focus of our future studies in the quest for new chemotherapeutic agents with enhanced selectivity towards ER breast cancer.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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