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Synthesis and antitumour evaluation of novel 2-phenylbenzimidazoles

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Abstract

A new series of fluorinated and non-fluorinated 2-phenylbenzimidazoles bearing oxygenated substituents on the phenyl ring has been synthesized. Synthesis of the new series was based on our previous discovery of 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610) as a potent and selective antitumour agent *in vitro* (sub-nanomolar GI_{50} in sensitive human cancer cell lines), but with poor aqueous solubility and lack of a definitive cellular target limiting further development. In this study we test the hypothesis that 2-phenylbenzimidazoles with similar substitution patterns to PMX 610 would retain potent antitumour activity but with potentially superior pharmaceutical properties. In general the new compounds were less active than the former benzothiazole series *in vitro* when tested against the breast cancer cell lines MCF-7 and MDA 468; however the two most active compounds in the present series (**3j** and **3k**) exhibit low micromolar GI_{50} values in both cell lines and provide the opportunity for further chemical derivatization with a view to target identification.

Keywords: *Antitumour, benzimidazoles, synthesis, fluorination*

Introduction

The benzimidazole nucleus provides a versatile scaffold in medicinal chemistry for the design of new therapeutic agents, and a number of substituted benzimidazoles possessing a range of biological activities have been reported. Amongst the range of biological activities ascribed to benzimidazole derivatives have been antitumour, antiparasitic, antiviral and antimicrobial activity; this area of research has been recently reviewed [1]. Of particular interest to us have been reports of antitumour benzimidazoles with activity against cancer drug targets of current interest, as exemplified for example by a benzimidazole-based inhibitor of polo-like kinase 1 [2], 2-arylbenzimidazole-4-carboxamides as PARP-1 inhibitors [3], and our own work on thioredoxin-inhibitory antitumour quinols including benzimidazole derivatives [4].

In recent years we have employed the 2-phenyl benzothiazole scaffold as inspiration for several anticancer drug discovery projects to provide novel agents acting on unusual mechanistic targets. The development of the antitumour benzothiazole prodrug Phortress (Figure 1), currently in Phase 1 clinical development, illustrates a case in point [5]. Phortress evolved from the discovery (through cell-based screening) of a series of 2-(4-aminophenyl)benzothiazoles with potent and selective *in vitro* and *in vivo* antitumour activity [6]. Strategic installation of fluorine to circumvent deactivating metabolism led to the development of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F 203, Figure 1) as a lead compound from which the lysyl amide prodrug Phortress emerged as the clinical development candidate [7–10]. More recently a further series of substituted 2-phenylbenzothiazoles has been synthesized and tested for cellular

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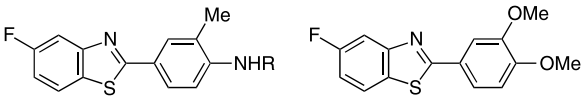


Antitumour 2-(4-A minophenyl) benzothiazoles
R=H (5F 203); R=lysyl amide (Phortress)

PMX 610(antitumour)

Figure 1. Antitumour benzothiazoles.

antitumour activity, leading to the identification of 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610, Figure 1) as a new potent and selective antitumour agent with a selectivity profile reminiscent of the (aminophenyl)benzothiazoles, but with a distinct intracellular mechanism of action [11–13]. Unfortunately the high lipophilicity associated with PMX 610 (estimated clogP 4.21; Crippen fragmentation [14]) compromised further *in vivo* development through poor solubility in standard aqueous formulations.

In this paper we report the synthesis and *in vitro* antitumour evaluation of a new series of 2-phenylbenzimidazole derivatives bearing oxygenated substituents on the phenyl ring, based on the structure of PMX 610. Substituted 2-phenylbenzimidazoles are commonly synthesized via two well-established types of condensation reaction [15]. The first method involves the thermal condensation of (substituted) o-phenylenediamine with carboxylic acids or their derivatives (e.g. nitriles, imidates or orthoesters). Alternatively aldehydes can be employed as reaction partners for o-phenylenediamines under oxidative conditions, since the initial product from the condensation reaction is formally a dihydrobenzimidazole.

The new analogues were synthesised to explore the following hypotheses:

i. Whether potent antitumour activity could be maintained for benzimidazole congeners of PMX 610, with an accompanying increase in hydrophilicity/water solubility (estimated clogP for the direct benzimidazole analogue of PMX 610 = 2.8 [14]).
ii. The necessity for fluorination on the benzimidazole ring for optimal activity, since fluorine is essential for the antitumour activity of PMX 610.

Materials and methods

Melting points were measured on a Griffin apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE 500 MHz instrument; coupling constants (J values) are in Hz. Thin layer chromatography (TLC) was performed using pre-coated, aluminium backed silica gel plates (F_{254}-Merck) with UV visualisation. Merck silica gel 60 (40-60 μM) was used for column chromatography. All commercially available starting materials were used without further purification.

*General procedure for the synthesis of 2-phenylbenzimidazoles **3a-f***

Sodium metabisulfite (0.607 g, 3.16 mmol) was added to a stirring mixture of (substituted)-1,2-phenylenediamine **1a-c** (3.12 mmol) and substituted benzaldehyde **2a-b** (3.16 mmol) in DMF (10 mL), and the reaction mixture was heated under reflux for two hours. After completion of the reaction (monitored by TLC), the mixture was allowed to cool to room temperature. Addition of water (approximately 20 mL) caused precipitation of a solid, which was collected by vacuum filtration and dried. The crude product was further purified by recrystallization (aqueous methanol) to give the pure substituted 2-arylbenzimidazole as a solid in yields of 46-61%. The following compounds were prepared:

*2-(3,4-Dimethoxyphenyl)-1H-benzimidazole (**3a**)*. From 1,2-phenylenediamine and 3,4-dimethoxy benzaldehyde (55% yield), mp 231-233°C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6) δ 3.84 (3H, s, OMe), 3.88 (3H, s, OMe), 7.13 (1H, d, J 8.5 Hz, H-5′), 7.18 (2H, dt, J 3.7, 7.0 Hz, H-5, H-6), 7.57 (2H, dd, J 3.5, 5.0 Hz, H-4, H-7), 7.76 (1H, dd, J 2.0, 8.5 Hz, H-6′), 7.78 (1H, d, J 2.0 Hz, H-2′), 12.84 (1H, bs, NH). Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.01. Found: C, 70.56; H, 5.62; N, 10.75%.

*2-(3,4-Dimethoxyphenyl)-5-fluoro-1H-benzimidazole (**3b**)*. From 4-fluoro-1,2-phenylenediamine and 3,4-dimethoxybenzaldehyde (52% yield), mp 212-214°C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s, OMe), 3.88 (3H, s, OMe), 7.03 (1H, dt, J 2.5, 10.5 Hz, H-6), 7.13 (1H, d, J = 8.5 Hz, H-5′) 7.36 (1H, m, ArH) 7.55 (1H, m, ArH), 7.73 (1H, dd, J 1.5, 8.5 Hz, H-6′), 7.75 (1H, d, J 1.5 Hz, H-2′), 12.78 (1H, bs, NH). Anal. calcd. for $C_{15}H_{13}N_2O_2F$: C, 66.17; H, 4.81; N, 10.28. Found: C, 66.00; H, 4.86; N, 10.08%.

*2-(3,4-Dimethoxyphenyl)-1-methyl-1H-benzimidazole (**3c**)*. From *N*-methyl-1,2-phenylenediamine and 3,4-dimethoxybenzaldehyde (61% yield), mp 107-109°C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s, NMe), 3.95 (3H, s, OMe), 3.96 (3H, s, OMe), 6.98 (1H, d, J 8.0 Hz, H-5′), 7.24 (1H, dd, J = 1.8, 8.3 Hz, H-6′), 7.30 (2H, m, ArH), 7.36 (2H, m, ArH), 7.79 (1H, m, ArH). Anal. calcd. for $C_{16}H_{16}N_2O_2$:

C, 71.62; H, 6.01; N, 10.44. Found: C, 71.85; H, 6.02; N, 10.39%.

*2-(3,4,5-Trimethoxyphenyl)-1H-benzimidazole (**3d**)*. From 1,2-phenylenediamine and 3,4,5-trimethoxy benzaldehyde (46% yield), mp 254-255°C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6) δ 3.74 (3H, s, OMe), 3.91 (6H, s, 2 × OMe), 7.20 (2H, dd, *J* 3.0, 5.5 Hz, H-4, H-7), 7.53 (2H, s, H-2′, H-6′), 7.60 (2H, m, H-5, H-6), 12.83 (1H, bs, NH). Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.65; H, 5.71; N, 9.73%.

*5-Fluoro-2-(3,4,5-trimethoxyphenyl)-1H-benzimidazole (**3e**)*. From 4-fluoro-1,2-phenylenediamine and 3,4,5-trimethoxybenzaldehyde (57% yield), mp 243-245°C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6) δ 3.74 (3H, s, OMe), 3.91 (6H, s, 2 × OMe), 7.06 (1H, dt, *J* 2.5, 9.5 Hz, H-6), 7.40 (1H, d, *J* 9.0 Hz, ArH), 7.51 (2H, s, H-2′, H-6′), 7.59 (1H, m, Ar-H), 12.83 (1H, bs, NH). Anal. calcd. for $C_{16}H_{15}N_2O_3F$: C, 63.57; H, 5.00; N, 9.26. Found: C, 63.51; H, 5.03; N, 9.14%.

*1-Methyl-2-(3,4,5-trimethoxyphenyl)-1H-benzimidazole (**3f**)*. From *N*-methyl-1,2-phenylenediamine and 3,4,5-trimethoxybenzaldehyde (59% yield), mp 114-116°C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 3.89 (3H, s, NMe), 3.93 (3H, s, 4′-OMe), 3.94 (6H, s, 2 × OMe), 6.96 (2H, s, H-2′, H-6′), 7.31 (2H, m, ArH), 7.39 (1H, m, ArH), 7.82 (1H, m, ArH). Anal. calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.85; H, 6.19; N, 9.48%.

*General method for the synthesis of 2-phenylbenzimida zoles **3g-i***

Triethylamine (5.8 mL, 4 mmol) was added to a solution of (substituted)-1,2-phenylenediamine (0.291 g, 2.7 mmol) and piperonyloyl chloride (0.5 g, 2.7 mmol) in THF (10 mL) at 0°C with stirring. The reaction mixture was stirred at 0°C for around one hour (until reaction was complete by TLC), then the solution was concentrated *in vacuo*. The resulting residue was further heated under reflux in acetic acid (100°C) for 12 h. The solution was then neutralised (aqueous sodium hydroxide), and the product extracted using ethyl acetate (2 × 20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (60% CH_2Cl_2-40% EtOAc) afforded the title compound as a white solid.

*2-(Benzo[1,3]dioxol-5-yl)-1H-benzimidazole (**3g**)*. From 1,2-phenylenediamine and piperonyloyl chloride (46% yield), m.p. 242-244°C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6) δ 6.13 (2H, s, OCH_2), 7.10 (1H, d, *J* 8.8 Hz, H-5′), 7.18 (2H, m, Ar-H), 7.56 (1H, m, Ar-H) 7.65 (1H, m, Ar-H), 7.69 (1H, d, *J* 1.5 Hz, H-2′), 7.72 (1H, dd, *J* 1.5, 8.8 Hz, H-6′), 12.79 (1H, bs, NH). Anal. calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.75. Found: C, 70.31; H, 4.21; N, 11.66%.

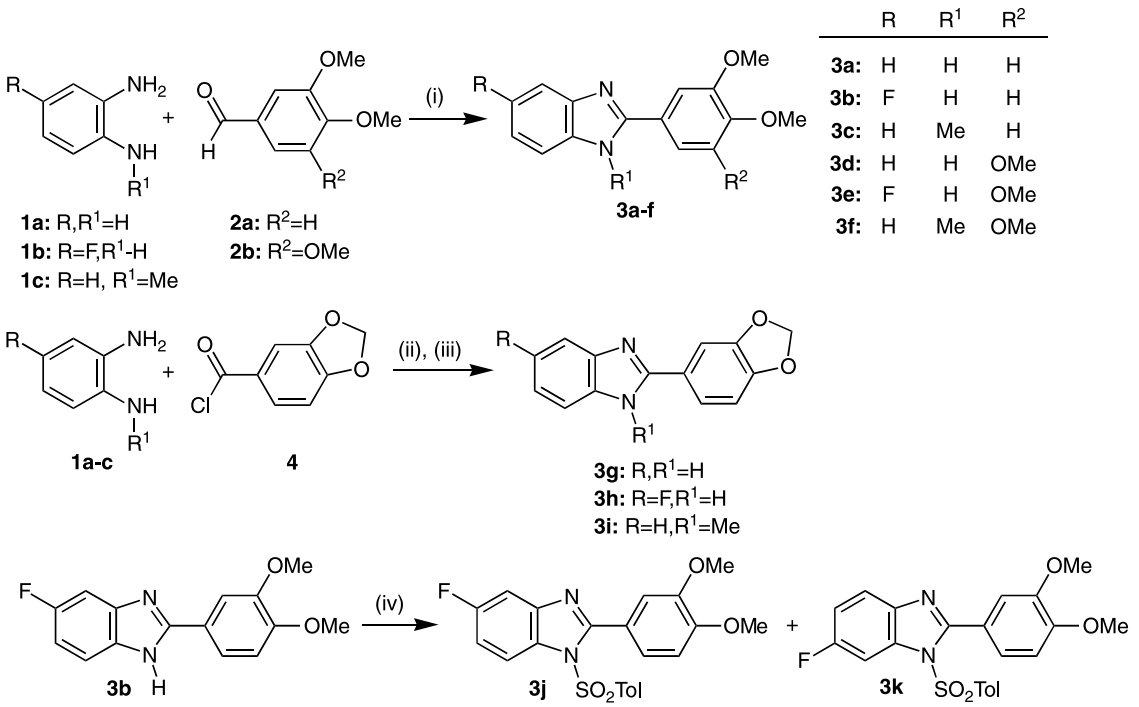
*2-(Benzo[1,3]dioxol-5-yl)-5-fluoro-1H-benzimidazole (**3h**)*. From 4-fluoro-1,2-phenylenediamine and piperonyloyl chloride (46% yield), mp 205-207°C (MeOH/H_2O); ^{1}H NMR (DMSO-d_6) δ 6.13 (2H, s, OCH_2), 7.04 (1H, dt, *J* 2.5, 10.0 Hz, H-6), 7.10 (1H, d, *J* 8.0 Hz, H-5′), 7.36 (1H, m, Ar-H), 7.55 (1H, m, Ar-H) 7.66 (1H, d, *J* 2.0 Hz, H-2′), 7.70 (1H, dd, *J* 2.0, 8.0 Hz, H-6′), 12.86 (1H, bs, NH). Anal. calcd. for $C_{14}H_9N_2O_2F$: C, 65.62; H, 3.54; N, 10.93. Found: C, 65.38; H, 3.56; N, 10.74%.

*2-(Benzo[1,3]dioxol-5-yl)-1-methyl-1H-benzimidazole (**3i**)*. From *N*-methyl-1,2- phenylenediamine and piperonyloyl chloride (59% yield), mp 149-151°C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 3.84 (3H, s, NCH_3), 6.05 (2H, s, OCH_2), 6.94 (1H, d, *J* 8.0 Hz, H-5′), 7.23 (2H, m, Ar-H), 7.29 (2H, m, Ar-H) 7.36 (1H, m, Ar-H), 7.77 (1H, m, Ar-H). Anal. calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.02; H, 4.75; N, 11.00%.

*General method for the synthesis of 2-phenylbenzimida zoles **3j-k***

p-Toluenesulfonylchloride (1.1 mmol) was added in small portions to a stirring solution of 2-(3,4-dimethoxyphenyl)-5-fluoro-1*H*-benzimidazole **3b** (0.73 mmol) in pyridine (10 mL) under nitrogen, and the reaction mixture was stirred for 24 h. The reaction mixture was then diluted with H_2O and extracted with dichloromethane (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The two regioisomeric products (**3j** and **3k**) were separated by column chromatography (DCM/EtOAc) to give the pure title compounds as solids.

*2-(3,4-Dimethoxyphenyl)-5-fluoro-1-toluenesulfonyl-1H-benzimidazole (**3j**)*. (21% yield), m.p.123-125°C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.88 (1H, d, *J* 8.0 Hz, H-5′), 7.01 (2H, d, *J* 8.5 Hz, H-3″, H-5″), 7.03 (1H, d, *J* 2.0 Hz, H-2′), 7.08 (1H, dt, *J* 2.5 Hz, 9.0 Hz, H-6), 7.17 (1H, dd, *J* 2.0 Hz, 8.0 Hz, H-6′), 7.18 (2H, d, *J* 8.5 Hz, H-2″,H-6″), 7.29 (1H, dd, *J* 2.5 Hz, 9.5 Hz, H-4), 8.08 (1H, dd, *J* 5.0 Hz, 9.5 Hz, H-7). Anal. calcd. for $C_{22}H_{19}N_2O_4FS$: C,



[a]Reagents: (i) $Na_2S_2O_5$, DMF, reflux, 2h; (ii) NEt_3, THF, 0°C, 1h; (iii) AcOH, 100°C, 12h; (iv) Tos-Cl, pyridine, 20°C, 24h

Scheme 1. Synthesis of 2-phenylbenzimidazole products **3a-k**.

61.96; H, 4.49; N, 6.57. Found: C, 61.64; H, 4.46; N, 6.38%.

*2-(3,4-Dimethoxyphenyl)-6-fluoro-1-toluenesulfonyl-1H-benzimidazole (**3k**)*. (16% yield), m.p.129-131°C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.87 (1H, d, *J* 8.5 Hz, H-5′), 7.00 (1H, d, *J* 2.0 Hz, H-2′), 7.04 (2H, d, *J* 8.5 Hz, H-3″, H-5″), 7.07 (1H, dt, *J* 2.5 Hz, 9.0 Hz, H-5), 7.15 (1H, dd, *J* 2.0 Hz, 8.5 Hz, H-6′), 7.22 (2H, d, *J* 8.5 Hz, H-2″, H-6″), 7.56 (1H, dd, *J* 5.0 Hz, 9.5 Hz, H-4), 7.88 (1H, dd, *J* 2.5 Hz, 9.5 Hz, H-7). Anal. calcd. for $C_{22}H_{19}N_2O_4FS$: C, 61.96; H, 4.49; N, 6.57. Found: C, 61.65; H, 4.48; N, 6.28%.

In vitro *antitumour evaluation in human tumour cell lines*

Compounds were prepared as 10 mM top stock solutions, dissolved in DMSO, and stored at 4°C, protected from light for a maximum period of 4 weeks. Human derived cell lines (MCF-7 (ER +), MDA 468 (ER-) breast carcinoma) were routinely cultivated at 37°C in an atmosphere of 5% CO_2 in RPMI 1640 medium supplemented with 2 mM L-glutamine and 10% fetal calf serum and subcultured twice weekly to maintain continuous logarithmic growth. Cells were seeded into 96-well microtiter plates at a density of 5×10^3 per well and allowed 24 h to adhere before drugs were introduced (final concentration 0.1 nM-100 μM, n = 8). Serial drug dilutions were prepared in medium immediately prior to each assay. At the time of drug addition and following 72 h exposure, 1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan (MTT) was added to each well (final concentration 400 μg/mL). Incubation at 37°C for 4 h allowed reduction of MTT by viable cells to an insoluble formazan product. Well contents were aspirated and formazan solubilized by addition of DMSO. Absorbance was read on an Anthos Labtec systems plate reader at 550 nm as a measure of cell viability; thus cell growth or drug toxicity was determined.

Results

Benzimidazole synthesis

The synthesis of substituted 2-phenylbenzimidazoles **3a-f** was accomplished in a single synthetic step from commercially available starting materials, as illustrated in Scheme 1. Following heating of (substituted) benzene-1,2-diamine and substituted benzaldehyde under reflux for two hours in the presence of sodium metabisulfite, addition of water produced a precipitate that was collected and recrystallized to give the pure 2-phenylbenzimidazole product in moderate yield (46-61%) without the need for chromatographic purification. A different route was employed to access the 2-phenylbenzimidazoles **3g-i** containing a

methylenedioxy bridge, due to the restricted commercial availability of piperonal. In these cases the benzenediamine **1a-c** was treated with piperonoyl chloride **4** in the presence of triethylamine at 0°C followed by heating in acetic acid. Neutralisation, extraction and purification using column chromatography gave the required pure 2-phenylbenzimidazole product **3g-i** in moderate yield (46-59%).

The fluorinated 2-phenylbenzimidazole products (**3b**, **3e**, **3h**) resulting from reaction of 4-fluoro-1,2-benzenediamine **1b**, although represented here as 5-fluorobenzimidazole products, are actually a rapidly equilibrating mixture of the formal 5- and 6-substituted products due to tautomerism of the benzimidazole N-proton on the NMR timescale (Figure 2). Deprotonation and substitution of the benzimidazole N-proton would prevent this rapid tautomerism and lead to a separable equimolar mixture of 5- and 6-substituted products. Hence the fluorinated 2-phenylbenzimidazole product **3b** was treated with *p*-toluenesulfonyl chloride (Tos-Cl) in pyridine, leading to the isolation of an equimolar mixture of products, which were separated using column chromatography to give the pure 5-fluoro- and 6-fluoro-benzimidazole products **3j** and **3k** respectively. Characterisation of the individual isomeric products was carried out by observation of a ^{1}H NMR nuclear Overhauser enhancements (nOe) between tolyl protons and the benzimidazole H-7, allowing the H-7 proton to be characterised and identified for each particular fluorinated isomer on the basis of its ^{1}H NMR splitting pattern (Figure 2, see Materials and Methods for details).

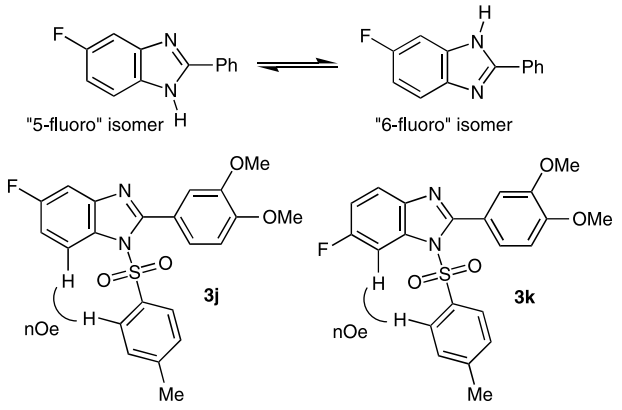


Figure 2. N-1/N-3 proton tautomerisation in compounds **3b**, **3e** and **3h**, and nOe effects in products **3j** and **3k**.

In vitro *antitumour activity*

New compounds were tested for *in vitro* antitumour activity in the human breast carcinoma cell lines MCF-7 (ER + ve) and MDA 468 (ER-ve) using the well-established MTT assay [11] following drug incubation over 72 h (see Materials and Methods for details). MCF-7 and MDA 468 cell lines were chosen here since they were previously shown to be exquisitely sensitive to the lead benzothiazole PMX 610. Table I lists the results (GI_{50} values) of our antitumour evaluation studies and includes the data previously obtained using the same method for PMX 610 [11].

Discussion

Inspection of Table I reveals that the new 2-phenylbenzimidazole derivatives prepared in this study do not display antitumour activity at the sub-nanomolar GI_{50} level seen for PMX 610, for the two breast cancer cell lines examined. In most cases growth inhibitory values were in the micromolar range. This point is illustrated by comparison of the lead benzothiazole (**PMX 610**; MCF-7 $GI_{50} = < 0.0001\,\mu M$) with its direct benzimidazole analogue (**3b** MCF-7 $GI_{50} = 85.7\,\mu M$). Notable observations were that the presence of a fluorine atom in the benzimidazole ring did not lead to substantial enhancement of antitumour activity (compare **3b** versus **3a**, or **3e** versus **3d** for example). Also noteworthy was that the N-methylated compounds **3c**, **3f** and **3i** were essentially inactive.

The most potent and interesting compounds from this new series were the 5-fluoro- and 6-fluoro-benzimidazoles **3j** and **3k** where the benzimidazole nitrogen bears an electron-withdrawing group (*p*-tolylsulfonyl). In these cases low micromolar GI_{50} values were obtained, suggesting that there is space for further drug design and potential for the installation of other electron-withdrawing groups in this position in order to further optimise activity. Clearly the synthesis of further agents of this type would be greatly assisted by identification of a

Table I. *In vitro* antitumour activity against the MCF-7 and MDA 468 breast cancer cell lines.

Compound	Mean $GI_{50}/\mu M$[1] MCF-7[2]	Mean $GI_{50}/\mu M$[1] MDA 468[3]
PMX 610[4]	<0.0001	<0.0001
3a	59.8	>100
3b	175.7 (15.6)	94.4 (6.9)
3c	90.3 (8.5)	84.2 (19.8)
3d	50.8 (0.2)	43.6 (7.9)
3e	53.4 (4.5)	39.8 (3.8)
3f	>100	>100
3g	70.6 (4.4)	43.2 (0.5)
3h	49.4 (8.4)	26.3 (21.4)
3i	72.4 (2.5)	79.3 (16.2)
3j	6.82 (0.07)	5.19 (1.09)
3k	6.40 (0.28)	4.55 (0.40)

[1] Mean GI_{50} (50% growth inhibition) values from experiments carried out in triplicate. Standard deviations are given in brackets; [2] MCF-7 = Estrogen receptor positive human breast carcinoma cell line; [3] MDA 468 = Estrogen receptor negative human breast carcinoma cell line; [4] see reference [11].

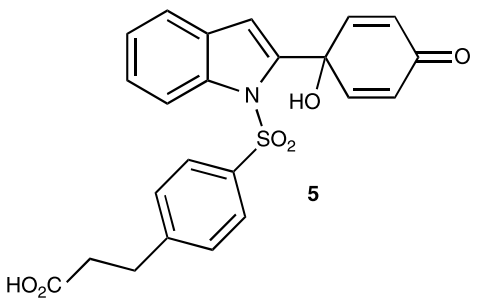


Figure 3. Structure of carboxylic acid linked (arylsulfonyl) indole-substituted antitumour quinol **5**.

molecular target responsible for the observed antitumour activity. Fortunately the tolylsulfonyl-substituted benzimidazole offers the potential for further derivatisation with a view to linking to a solid support followed by challenge with cellular lysate and identification of potential molecular targets using mass spectrometry. An analogous approach has been previously tested in our group to identify molecular targets of the arylsulfonyl-derived indole quinol **5** (Figure 3), through derivatisation with amino-terminal agarose beads [16]. This type of proteomic approach should also be achievable here provided that a carboxylic acid terminal group attached to the arylsulfonyl moiety does not compromise the antitumour activity.

Conclusions

The new series of substituted 2-phenylbenzimidazoles **3a-k** did not recapitulate the potent activity previously observed for the corresponding benzothiazole PMX 610; however the tolylsulfonyl-derived benzimidazoles **3j** and **3k** gave low micromolar GI_{50} values in both MCF-7 and MDA 468 human cancer cell lines and will be the focus of future studies. The search for a molecular target on which to base a rational drug design effort to optimise antitumour activity may be aided to the presence of the arylsulfonyl group, through installation of a synthetic handle for proteomic target identification studies.

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