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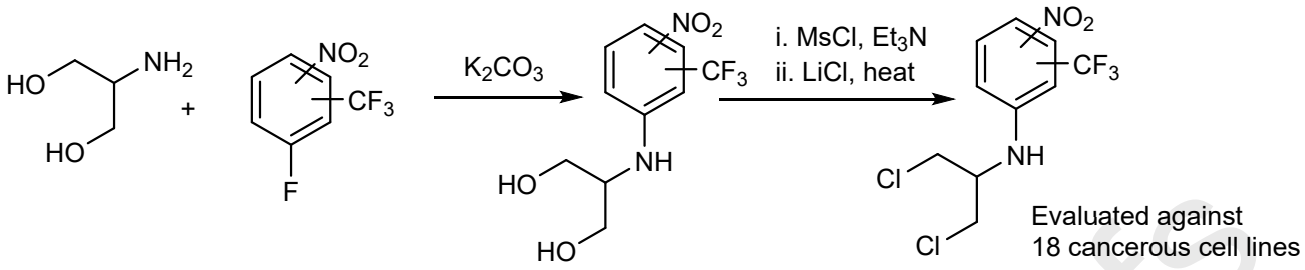

The synthesis of trifluoromethylated *N*-nitroaryl-2-amino-1,3-dichloropropane derivatives and their evaluation as potential anti-cancer agents

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Abstract: Six *N*-nitroaryl-2-amino-1,3-dichloropropane derivatives have been prepared and evaluated against 18 cancer cell lines and two non-cancerous cell lines. Analysis of cell viability data and IC_{50} values indicated that the presence of a trifluoromethyl group in the nitroaryl moiety is an important structural feature associated with the compounds' cytotoxicities.

Key words: nitroaromatic drugs; anti-cancer agents; trifluoromethylated drugs; nitrogen mustards.

The design, synthesis and therapeutic utility of nitroaromatic pro-drugs has attracted considerable interest and this area of medicinal chemistry has been recently reviewed.[1] Within this general class of pro-drugs, the nitrogen-mustards of general structure **1** have received particular attention as potential anti-cancer agents (Scheme 1).[2,3] In these compounds, the bioreduction of an appropriately positioned *ortho*- or *para*-nitro group produces the corresponding hydroxylamine/amine derivative **2** with a concomitant augmentation of the nucleophilic character of the mustard's nitrogen atom. An intramolecular nucleophilic substitution reaction subsequently follows producing a highly reactive aziridinium ion **3** which is believed to be responsible for DNA alkylation. The remaining chloroethyl group can then participate in a similar reaction forming a second aziridinium ion hence resulting in dialkylation.

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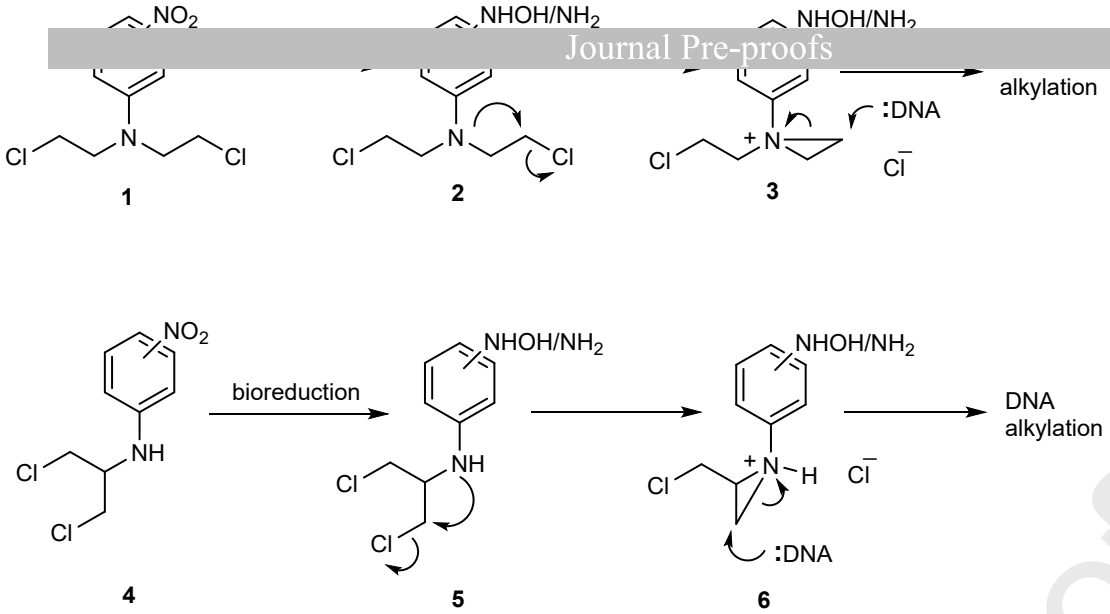
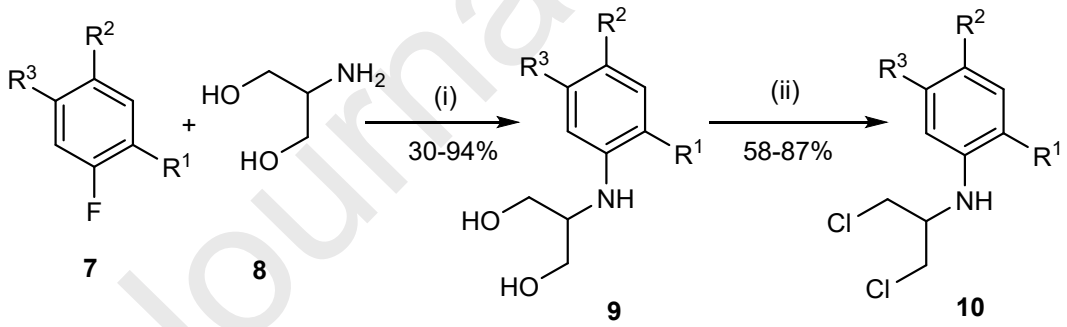


Scheme 1. Nitroaromatic pro-drugs acting as anti-cancer agents.

Compounds of general structure **4** appear to be under-represented in the literature and a similar mode of DNA alkylation might be feasible for these compounds via the hydroxylamine/amine **5** and the aziridinium ion **6** (Scheme 1). In view of the extensive interest in fluorinated drugs,[4-7] and our work in this area,[8] we were particularly interested in evaluating the anti-cancer properties of trifluoromethylated nitroaromatics and hence compounds **10d-f** were chosen as target molecules (Scheme 2). One potential benefit of the secondary amine group in compounds **10d-f** is the opportunity for the >NH group to participate in intramolecular hydrogen bonding with either an appositely located *ortho*-nitro or -trifluoromethyl group. The mono-nitro derivatives **10a** and **10b** were chosen as reference compounds and compound **10c** was also included in this study because the 2,4-di-nitro structural motif is a common feature of many known pro-drugs of general structure **1**.[3] The series of nitroaromatic compounds **10a-f** were prepared from their diol precursors **9a-f** respectively which in turn were synthesised from an appropriately substituted fluoroaromatic **7a-f** and serinol **8** (Scheme 2).



	R^1	R^2	R^3
a	NO_2	H	H
b	H	NO_2	H
c	NO_2	NO_2	H
d	NO_2	CF_3	H
e	CF_3	NO_2	H
f	H	NO_2	CF_3

Scheme 2. Reagents and conditions: (i) K_2CO_3, DMSO, heat 70-80 °C, 3 h; (ii) (a) $MeSO_2Cl$, Et_3N, rt, (b) LiCl, DMF, heat 70 °C, 2 h.

The cell viabilities (Table 1) and the IC_{50} values (Table 2) relating to a selection of 18 cancer cell lines and 2 non-cancerous cell lines were determined in the presence of the diols **9a-f** and the dichloro compounds **10a-f**. The ratio of the percentage cell viability **9** / percentage cell viability **10** is also reported in Table 1 as an indication of the efficacy of the dichloro compounds **10** compared to their diol counterparts **9**.

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Cancer type	Cell			ratio			ratio			ratio			ratio			ratio			ratio
Breast Cancer	MCF7	66.6 ± 2.4	37.7 ± 1.1	1.8	65.6 ± 1.2	38.8 ± 0.4	1.7	55.5 ± 4.4	25.1 ± 2.1	2.2	57.4 ± 1.9	21.4 ± 4.3	2.7	45.7 ± 1.9	10.5 ± 0.9	4.4	49.7 ± 2.1	20.5 ± 0.5	2.4
Breast Cancer	MDA-MB-231	91.8 ± 3.3	85.1 ± 2.1	1.1	87.7 ± 2.1	72.4 ± 1.1	1.2	79.4 ± 8.4	83.4 ± 2.5	1.0	67.3 ± 1.8	32.1 ± 0.5	2.1	93.1 ± 5.5	31.8 ± 3.9	2.9	65.7 ± 1.7	57.4 ± 2.7	1.1
Breast Cancer	MDA-MB-468	104.0 ± 5.0	63.6 ± 6.1	1.6	102.2 ± 5.5	45.1 ± 2.4	2.3	105.8 ± 7.1	61.3 ± 4.3	1.7	100.4 ± 4.1	65.1 ± 6.6	1.5	93.2 ± 3.2	20.4 ± 4.9	4.6	98.7 ± 2.7	58.6 ± 2.1	1.7
Breast Cancer	SKBR3	100.9 ± 7.9	79.9 ± 0.8	1.3	93.1 ± 1.1	73.1 ± 1.1	1.3	98.9 ± 3.4	71.6 ± 5.0	1.4	66.40 ± 5.1	38.5 ± 0.9	1.7	75.2 ± 3.5	55.6 ± 1.1	1.4	79.4 ± 2.1	52.7 ± 1.5	1.5
Breast Cancer	T47D	76.2 ± 5.9	69.8 ± 1.9	1.1	73.6 ± 1.0	65.2 ± 1.5	1.1	79.9 ± 2.2	58.7 ± 3.4	1.4	68.6 ± 2.0	25.6 ± 1.1	2.7	59.1 ± 2.2	24.3 ± 1.7	2.4	71.2 ± 5.5	33.2 ± 0.9	2.1
Colorectal Cancer	Caco2	95.1 ± 4.7	104.0 ± 0.4	0.9	100.6 ± 1.8	91.6 ± 5.7	1.1	102.2 ± 8.4	105.1 ± 2.5	1.0	89.5 ± 4.4	21.9 ± 0.8	4.1	100.9 ± 1.9	9.5 ± 0.4	10.6	96.1 ± 2.7	20.9 ± 3.9	4.6
Colorectal Cancer	HCT116	76.9 ± 4.9	64.9 ± 1.1	1.2	89.7 ± 3.0	79.4 ± 7.0	1.1	81.9 ± 2.2	73.1 ± 3.2	1.1	83.9 ± 4.9	45.1 ± 1.9	1.9	84.9 ± 2.1	24.5 ± 1.8	3.5	86.8 ± 2.1	45.0 ± 2.9	1.9
Colorectal Cancer	HT29	86.1 ± 5.2	65.3 ± 1.1	1.3	96.3 ± 2.0	60.9 ± 1.9	1.6	89.6 ± 3.4	89.1 ± 3.2	1.0	95.2 ± 5.1	47.1 ± 1.7	2.0	84.2 ± 3.3	45.3 ± 1.9	1.9	109.8 ± 2.3	38.4 ± 1.7	2.9
Colorectal Cancer	SW48	101.6 ± 4.2	62.6 ± 1.2	1.6	95.3 ± 2.2	58.8 ± 2.1	1.6	88.2 ± 6.6	55.2 ± 3.0	1.6	98.8 ± 3.1	32.8 ± 0.9	3.0	61.8 ± 2.2	26.5 ± 1.1	2.3	78.9 ± 0.5	29.1 ± 0.5	2.7
Lung Cancer	A549	74.9 ± 4.1	82.9 ± 0.1	0.9	96.7 ± 1.1	73.5 ± 3.1	1.3	77.4 ± 6.1	59.4 ± 3.2	1.3	57.9 ± 6.1	24.6 ± 1.7	2.4	99.6 ± 2.5	37.1 ± 1.1	2.7	61.9 ± 1.5	27.8 ± 0.9	2.2
Lung Cancer	H1299	96.7 ± 4.9	109.1 ± 5.1	0.9	92.7 ± 3.2	67.4 ± 6.4	1.4	89.8 ± 9.1	96.3 ± 0.9	0.9	91.3 ± 6.6	52.4 ± 4.1	1.7	93.1 ± 3.3	38.1 ± 0.8	2.4	72.3 ± 1.1	43.7 ± 0.8	1.7
Nasopharyngeal Cancer	CNE1	102.2 ± 3.1	72.5 ± 1.5	1.4	104.3 ± 2.4	88.1 ± 0.9	1.2	102.2 ± 6.5	70.5 ± 1.2	1.4	106.4 ± 5.5	27.1 ± 1.0	3.9	82.5 ± 2.1	12.4 ± 0.5	6.7	100.3 ± 2.2	32.6 ± 0.9	3.1
Nasopharyngeal Cancer	HK1	90.1 ± 1.3	101.3 ± 4.1	0.9	99.6 ± 1.2	76.9 ± 1.1	1.3	103.3 ± 5.1	88.9 ± 3.2	1.2	92.9 ± 1.1	59.7 ± 0.5	1.6	90.4 ± 2.5	61.4 ± 3.7	1.5	92.8 ± 1.1	59.7 ± 1.9	1.6
Nasopharyngeal Cancer	SUNE1	99.3 ± 1.0	80.5 ± 3.4	1.2	109.1 ± 1.2	109.6 ± 5.4	1.0	105.7 ± 5.4	68.6 ± 3.1	1.5	83.4 ± 5.0	42.3 ± 5.5	2.0	52.4 ± 1.5	38.6 ± 2.5	1.4	104.2 ± 2.7	44.9 ± 2.5	2.3
Neuroblastoma	SHSY5Y	89.7 ± 3.1	60.8 ± 1.2	1.5	99.9 ± 2.4	65.8 ± 3.3	1.5	86.1 ± 7.2	63.6 ± 0.9	1.4	84.9 ± 8.1	33.7 ± 0.7	2.5	74.7 ± 5.5	21.6 ± 2.9	3.5	70.8 ± 1.5	30.6 ± 2.9	2.3
Pancreatic Cancer	AsPC1	101.2 ± 0.9	75.2 ± 0.9	1.3	96.4 ± 1.1	67.7 ± 2.1	1.4	108.5 ± 3.3	106.2 ± 4.4	1.0	81.8 ± 1.7	51.1 ± 0.9	1.6	84.7 ± 2.2	40.2 ± 2.7	2.1	87.3 ± 1.1	58.7 ± 1.7	1.5
Pancreatic Cancer	BxPC3	101.9 ± 5.3	105.3 ± 5.4	1.0	100.1 ± 0.4	82.9 ± 7.0	1.2	103.6 ± 5.5	102.9 ± 3.3	1.0	108.2 ± 0.9	62.9 ± 1.7	1.7	108.8 ± 1.9	23.2 ± 2.1	4.7	107.8 ± 2.3	56.5 ± 1.0	1.9
Pancreatic Cancer	SW1990	91.9 ± 5.3	64.4 ± 8.1	1.4	87.5 ± 2.4	55.1 ± 5.2	1.6	65.8 ± 2.1	69.8 ± 3.2	0.9	68.5 ± 5.5	42.1 ± 1.9	1.6	72.4 ± 2.2	28.6 ± 1.6	2.5	71.5 ± 5.5	36.7 ± 2.3	1.9
Breast Cells (non-cancerous)	MCF10A	100.4 ± 0.3	88.7 ± 9.4	1.1	102.8 ± 1.4	82.7 ± 1.9	1.2	104.9 ± 5.2	78.8 ± 1.2	1.3	102.4 ± 8.1	77.1 ± 4.5	1.3	88.8 ± 0.9	47.5 ± 2.0	1.9	102.5 ± 3.5	59.7 ± 4.4	1.7
Lung Cells (non-cancerous)	MRC5	100.9 ± 9.1	54.8 ± 4.2	1.8	32.2 ± 3.5	44.9 ± 2.2	0.7	78.9 ± 4.5	24.3 ± 4.4	3.2	64.9 ± 6.1	29.9 ± 4.3	1.8	74.9 ± 4.5	22.2 ± 2.2	3.4	32.8 ± 2.1	22.1 ± 2.4	1.5

Table 1. Cell viabilities (%) of diols **9a-f** and dichlorides **10a-f** (all at 100 μM). Results are expressed as the average percentage of cell viability ± standard deviation from three independent experiments.

Examination of Table 1 reveals that in the majority of entries, the cell viabilities of the diols **9a-f** exceeds that of the corresponding dichloro derivatives **10a-f** and hence the ratio is greater than 1. This demonstrates that the presence of the mustard moiety is efficacious in reducing the cell viabilities in comparison to the diol substituents. The magnitude of this ratio is generally low (between 1 and 2) for the majority of the non-trifluoromethylated series of

compounds whereas the trifluoromethylated compounds exhibit significantly larger values across the majority of cell lines

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With the exception of the breast cancer MDA-MB-468 and the lung cell MRC5 cell lines, all of the other cell lines have their three lowest cell viabilities associated with the three trifluoromethylated compounds **10d-10f**. The magnitude of the difference between the cell viabilities of the trifluoromethylated and non-trifluoromethylated compounds is noteworthy; for example for the lung cancer A549 cell line the cell viabilities recorded for the trifluoromethylated derivatives **10d-10f** (24.6-37.1%) are lower than those displayed by the non-trifluoromethylated compounds **10a-10c** (59.4-82.9%). It is also evident from the data in Table 1 that some dichloro-compounds exhibit enhanced cytotoxicity towards the non-cancerous lung cell line MRC5. For example, in the presence of compounds **10d** and **10e**, 13 of the 18 cancerous cell lines are associated with higher cell viabilities compared to the MRC5 cell line.

Inspection of the IC_{50} data presented in Table 2 indicates that the majority of the IC_{50} values associated with the diols **9a**-**9f** are greater than 100 µM regardless of the presence/absence of a trifluoromethyl group in the aryl ring. Only the diols **9b** (MRC5 cell line), **9e** (MCF7 cell line) and **9f** (MCF7 and MRC5 cell lines) showed values less than 100 µM. Within the non-trifluoromethylated series of dichloro-compounds **10a-10c**, only six IC_{50} values below 100 µM are observed; these are associated with the MCF7 cell line (all three compounds), the MRC5 cell line (compounds **10b** and **10c**) and the T47D cell line (compound **10c** only). In contrast, the trifluoromethylated derivatives **10d-10f** exhibit IC_{50} values below 100 µM for the majority of the entries in Table 2 (14, 18 and 12 entries for each compound respectively) thus supporting the hypothesis that the trifluoromethyl group is an important factor associated with the cytotoxicity of these compounds. Compound **10e** displayed the lowest IC_{50} values and is the only compound associated with IC_{50} values below 20 µM in 3 cell-lines [MCF7 (12.1 µM), Caco2 (10.1 µM) and CNE1 (15.3 µM)].

It is also evident from the data in Table 2 that the five derivatives **10b-f** are cytotoxic towards the non-cancerous lung cell line MRC5 with IC_{50} values within the range 31.0-62.1 µM. The only compound to show an IC_{50} value under 100 µM against the other non-cancerous cell line studied (the MCF10A breast cell line) was the trifluoromethylated derivative **10e** (81 µM).

Cancer type	**Cell line**	**9a**	**10a**	**9b**	**10b**	**9c**	**10c**	**9d**	**10d**	**9e**	**10e**	**9f**	**10f**
Breast Cancer	MCF7	>100	50.9 ± 7.8	>100	70.2 ± 5.3	>100	44.3 ± 7.5	>100	34.3 ± 1.3	88.3 ± 1.1	12.1 ± 3.3	88.1 ± 0.9	33.1 ± 1.8
Breast Cancer	MDA-MB-231	>100	>100	>100	>100	>100	>100	>100	54.5 ± 2.3	>100	42.4 ± 4.6	>100	>100
Breast Cancer	MDA-MB-468	>100	>100	>100	>100	>100	>100	>100	>100	>100	52.1 ± 5.1	>100	>100
Breast Cancer	SKBR 3	>100	>100	>100	>100	>100	>100	>100	67.8 ± 1.9	>100	>100	>100	>100
Breast Cancer	T47D	>100	>100	>100	>100	>100	85.3 ± 2.1	>100	35.1 ± 0.9	>100	34.7 ± 1.2	>100	64.1 ± 2.1
Colorectal Cancer	Caco 2	>100	>100	>100	>100	>100	>100	>100	39.9 ± 1.7	>100	10.1 ± 1.8	>100	37.1 ± 0.8
Colorectal Cancer	HCT116	>100	>100	>100	>100	>100	>100	>100	82.1 ± 0.5	>100	33.1 ± 8.1	>100	83.8 ± 8.1
Colorectal Cancer	HT29	>100	>100	>100	>100	>100	>100	>100	87.8 ± 2.2	>100	92.1 ± 2.1	>100	63.1 ± 3.0
Colorectal Cancer	SW48	>100	>100	>100	>100	>100	>100	>100	62.3 ± 2.3	>100	33.4 ± 4.5	>100	43.4 ± 4.9
Lung Cancer	A549	>100	>100	>100	>100	>100	>100	>100	33.3 ± 1.9	>100	57.7 ± 1.7	>100	70.4 ± 1.1
Lung Cancer	H1299	>100	>100	>100	>100	>100	>100	>100	>100	>100	49.1 ± 2.1	>100	>100
Nasopharyngeal Cancer	CNE1	>100	>100	>100	>100	>100	>100	>100	32.1 ± 3.2	>100	15.3 ± 1.9	>100	33.2 ± 2.8
Nasopharyngeal Cancer	HK1	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100

Nasopharyngeal Cancer	SUNE	>100	>100	>100	>100	>100	>100	>100	92.9 ±	>100	55.1 ±	>100	93.1 ±
Neuroblastoma	SHSY 5Y	>100	>100	>100	>100	>100	>100	>100	62.5 ± 4.4	>100	33.7 ± 2.7	>100	56.4 ± 6.9
Pancreatic Cancer	AsPC 1	>100	>100	>100	>100	>100	>100	>100	>100	>100	85.1 ± 1.9	>100	>100
Pancreatic Cancer	BxPC 3	>100	>100	>100	>100	>100	>100	>100	>100	>100	52.1 ± 3.3	>100	>100
Pancreatic Cancer	SW1990	>100	>100	>100	>100	>100	>100	>100	92.1 ± 7.7	>100	33.3 ± 2.5	>100	55.8 ± 4.3
Breast Cells (non-cancerous)	MCF10A	>100	>100	>100	>100	>100	>100	>100	>100	>100	81.0 ± 0.7	>100	>100
Lung Cells (non-cancerous)	MRC 5	>100	>100	60.2 ± 3.7	58.3 ± 4.4	>100	54.1 ± 4.4	>100	62.1 ± 3.2	>100	31.0 ± 0.9	41.0 ± 0.9	33.9 ± 2.8

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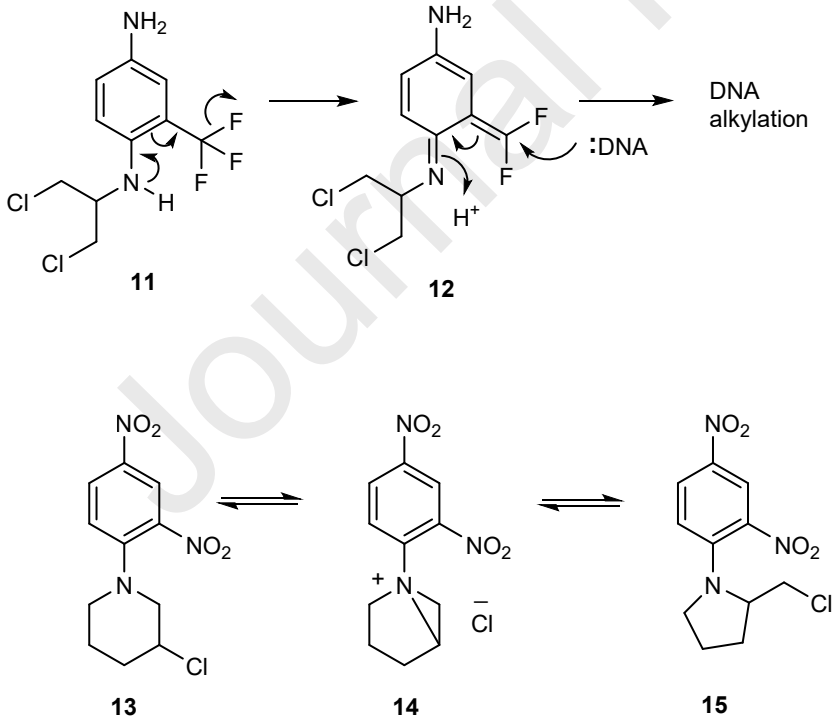
Table 2. IC_{50} values (μM) of diols **9a-f** and dichlorides **10a-f**. Results are expressed as the average IC_{50} value ± standard deviation from three independent experiments.

A commonly accepted mode of action of nitroaromatic pro-drugs is through bioreduction of a nitro group leading to highly reactive aziridinium ions as already illustrated in Scheme 1. A possible explanation of the mode of action of the trifluoromethylated compounds **10d-f** is that bioreduction of the nitro group in these compounds (eg compound **10e**, Scheme 3) would give the amine (or hydroxylamine) derivative **11** from which HF may be evolved resulting in the production of the difluoro derivative **12** as a potential alkylating agent.[9] The presence of the 1,3-dichloroproane moiety is important for biological activity suggesting that this group could also be a potential alkylating agent. Compounds **10a-f** may have the potential to act as alkylating reagents (rather than pro-drugs) without the prior reduction of a nitro group; our previously work demonstrated that compound **13** can be transformed into compound **15** presumably via an intermediate aziridinium ion **14** (Scheme 3).[10] However, this potential mode of alkylation would not account for the clear differences in biological activity shown between the non-trifluoromethylated compounds **10a-c** and the trifluoromethylated structures **10d-f**.



Scheme 3. Potential modes of DNA alkylation.

In conclusion, we have demonstrated that the elevated cytotoxicities of compounds **10d-f** compared to compounds **10a-c** can be attributed to the presence of a trifluoromethyl group. Of the three trifluoromethylated compounds

evaluated, compound **10e** appears to be the most cytotoxic to the majority of cell lines but it is also cytotoxic to non-canc

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Acknowledgements

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Cancer type	Cell line	9a	10a	ratio	9b	10b	ratio	9c	10c	ratio	9d	10d	ratio	9e	10e	ratio	9f	10f	ratio
Breast Cancer	MCF7	66.6 ± 2.4	37.7 ± 1.1	1.8	65.6 ± 1.2	38.8 ± 0.4	1.7	55.5 ± 4.4	25.1 ± 2.1	2.2	57.4 ± 1.9	21.4 ± 4.3	2.7	45.7 ± 1.9	10.5 ± 0.9	4.4	49.7 ± 2.1	20.5 ± 0.5	2.4
Breast Cancer	MDA-MB-231	91.8 ± 3.3	85.1 ± 2.1	1.1	87.7 ± 2.1	72.4 ± 1.1	1.2	79.4 ± 8.4	83.4 ± 2.5	1.0	67.3 ± 1.8	32.1 ± 0.5	2.1	93.1 ± 5.5	31.8 ± 3.9	2.9	65.7 ± 1.7	57.4 ± 2.7	1.1
Breast Cancer	MDA-MB-468	104.0 ± 5.0	63.6 ± 6.1	1.6	102.2 ± 5.5	45.1 ± 2.4	2.3	105.8 ± 7.1	61.3 ± 4.3	1.7	100.4 ± 4.1	65.1 ± 6.6	1.5	93.2 ± 3.2	20.4 ± 4.9	4.6	98.7 ± 2.7	58.6 ± 2.1	1.7
Breast Cancer	SKBR3	100.9 ± 7.9	79.9 ± 0.8	1.3	93.1 ± 1.1	73.1 ± 1.1	1.3	98.9 ± 3.4	71.6 ± 5.0	1.4	66.40 ± 5.1	38.5 ± 0.9	1.7	75.2 ± 3.5	55.6 ± 1.1	1.4	79.4 ± 2.1	52.7 ± 1.5	1.5
Breast Cancer	T47D	76.2 ± 5.9	69.8 ± 1.9	1.1	73.6 ± 1.0	65.2 ± 1.5	1.1	79.9 ± 2.2	58.7 ± 3.4	1.4	68.6 ± 2.0	25.6 ± 1.1	2.7	59.1 ± 2.2	24.3 ± 1.7	2.4	71.2 ± 5.5	33.2 ± 0.9	2.1
Colorectal Cancer	Caco2	95.1 ± 4.7	104.0 ± 0.4	0.9	100.6 ± 1.8	91.6 ± 5.7	1.1	102.2 ± 8.4	105.1 ± 2.5	1.0	89.5 ± 4.4	21.9 ± 0.8	4.1	100.9 ± 1.9	9.5 ± 0.4	10.6	96.1 ± 2.7	20.9 ± 3.9	4.6

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Colorectal Cancer	HCT	76.9	64.9	1	89.7	79.4	1	81.9 ±	73.1 ±	1	83.9	45.1	1	84.9	24.5	3	86.8	45.0	1.9
Colorectal Cancer	HT29	86.1 ± 5.2	65.3 ± 1.1	1.3	96.3 ± 2.0	60.9 ± 1.9	1.6	89.6 ± 3.4	89.1 ± 3.2	1.0	95.2 ± 5.1	47.1 ± 1.7	2.0	84.2 ± 3.3	45.3 ± 1.9	1.9	109.8 ± 2.3	38.4 ± 1.7	2.9
Colorectal Cancer	SW48	101.6 ± 4.2	62.6 ± 1.2	1.6	95.3 ± 2.2	58.8 ± 2.1	1.6	88.2 ± 6.6	55.2 ± 3.0	1.6	98.8 ± 3.1	32.8 ± 0.9	3.0	61.8 ± 2.2	26.5 ± 1.1	2.3	78.9 ± 0.5	29.1 ± 0.5	2.7
Lung Cancer	A549	74.9 ± 4.1	82.9 ± 0.1	0.9	96.7 ± 1.1	73.5 ± 3.1	1.3	77.4 ± 6.1	59.4 ± 3.2	1.3	57.9 ± 6.1	24.6 ± 1.7	2.4	99.6 ± 2.5	37.1 ± 1.1	2.7	61.9 ± 1.5	27.8 ± 0.9	2.2
Lung Cancer	H1299	96.7 ± 4.9	109.1 ± 5.1	0.9	92.7 ± 3.2	67.4 ± 6.4	1.4	89.8 ± 9.1	96.3 ± 0.9	0.9	91.3 ± 6.6	52.4 ± 4.1	1.7	93.1 ± 3.3	38.1 ± 0.8	2.4	72.3 ± 1.1	43.7 ± 0.8	1.7
Nasopharyngeal Cancer	CNE1	102.2 ± 3.1	72.5 ± 1.5	1.4	104.3 ± 2.4	88.1 ± 0.9	1.2	102.2 ± 6.5	70.5 ± 1.2	1.4	106.4 ± 5.5	27.1 ± 1.0	3.9	82.5 ± 2.1	12.4 ± 0.5	6.7	100.3 ± 2.2	32.6 ± 0.9	3.1
Nasopharyngeal Cancer	HK1	90.1 ± 1.3	101.3 ± 4.1	0.9	99.6 ± 1.2	76.9 ± 1.1	1.3	103.3 ± 5.1	88.9 ± 3.2	1.2	92.9 ± 1.1	59.7 ± 0.5	1.6	90.4 ± 2.5	61.4 ± 3.7	1.5	92.8 ± 1.1	59.7 ± 1.9	1.6
Nasopharyngeal Cancer	SUNE1	99.3 ± 1.0	80.5 ± 3.4	1.2	109.1 ± 1.2	109.6 ± 5.4	1.0	105.7 ± 5.4	68.6 ± 3.1	1.5	83.4 ± 5.0	42.3 ± 5.5	2.0	52.4 ± 1.5	38.6 ± 2.5	1.4	104.2 ± 2.7	44.9 ± 2.5	2.3
Neuroblastoma	SHSY5Y	89.7 ± 3.1	60.8 ± 1.2	1.5	99.9 ± 2.4	65.8 ± 3.3	1.5	86.1 ± 7.2	63.6 ± 0.9	1.4	84.9 ± 8.1	33.7 ± 0.7	2.5	74.7 ± 5.5	21.6 ± 2.9	3.5	70.8 ± 1.5	30.6 ± 2.9	2.3
Pancreatic Cancer	AsPC1	101.2 ± 0.9	75.2 ± 0.9	1.3	96.4 ± 1.1	67.7 ± 2.1	1.4	108.5 ± 3.3	106.2 ± 4.4	1.0	81.8 ± 1.7	51.1 ± 0.9	1.6	84.7 ± 2.2	40.2 ± 2.7	2.1	87.3 ± 1.1	58.7 ± 1.7	1.5
Pancreatic Cancer	BxPC3	101.9 ± 5.3	105.3 ± 5.4	1.0	100.1 ± 0.4	82.9 ± 7.0	1.2	103.6 ± 5.5	102.9 ± 3.3	1.0	108.2 ± 0.9	62.9 ± 1.7	1.7	108.8 ± 1.9	23.2 ± 2.1	4.7	107.8 ± 2.3	56.5 ± 1.0	1.9
Pancreatic Cancer	SW1990	91.9 ± 5.3	64.4 ± 8.1	1.4	87.5 ± 2.4	55.1 ± 5.2	1.6	65.8 ± 2.1	69.8 ± 3.2	0.9	68.5 ± 5.5	42.1 ± 1.9	1.6	72.4 ± 2.2	28.6 ± 1.6	2.5	71.5 ± 5.5	36.7 ± 2.3	1.9
Breast Cells (non-cancerous)	MCF10A	100.4 ± 0.3	88.7 ± 9.4	1.1	102.8 ± 1.4	82.7 ± 1.9	1.2	104.9 ± 5.2	78.8 ± 1.2	1.3	102.4 ± 8.1	77.1 ± 4.5	1.3	88.8 ± 0.9	47.5 ± 2.0	1.9	102.5 ± 3.5	59.7 ± 4.4	1.7
Lung Cells (non-cancerous)	MRC5	100.9 ± 9.1	54.8 ± 4.2	1.8	32.2 ± 3.5	44.9 ± 2.2	0.7	78.9 ± 4.5	24.3 ± 4.4	3.2	64.9 ± 6.1	29.9 ± 4.3	1.8	74.9 ± 4.5	22.2 ± 2.2	3.4	32.8 ± 2.1	22.1 ± 2.4	1.5

Cancer type	**Cell line**	**9a**	**10a**	**9b**	**10b**	**9c**	**10c**	**9d**	**10d**	**9e**	**10e**	**9f**	**10f**
Breast Cancer	MCF7	>100	50.9 ± 7.8	>100	70.2 ± 5.3	>100	44.3 ± 7.5	>100	34.3 ± 1.3	88.3 ± 1.1	12.1 ± 3.3	88.1 ± 0.9	33.1 ± 1.8
Breast Cancer	MDA-MB-231	>100	>100	>100	>100	>100	>100	>100	54.5 ± 2.3	>100	42.4 ± 4.6	>100	>100
Breast Cancer	MDA-MB-468	>100	>100	>100	>100	>100	>100	>100	>100	>100	52.1 ± 5.1	>100	>100
Breast Cancer	SKBR3	>100	>100	>100	>100	>100	>100	>100	67.8 ± 1.9	>100	>100	>100	>100
Breast Cancer	T47D	>100	>100	>100	>100	>100	85.3 ± 2.1	>100	35.1 ± 0.9	>100	34.7 ± 1.2	>100	64.1 ± 2.1
Colorectal Cancer	Caco2	>100	>100	>100	>100	>100	>100	>100	39.9 ± 1.7	>100	10.1 ± 1.8	>100	37.1 ± 0.8
Colorectal Cancer	HCT116	>100	>100	>100	>100	>100	>100	>100	82.1 ± 0.5	>100	33.1 ± 8.1	>100	83.8 ± 8.1
Colorectal Cancer	HT29	>100	>100	>100	>100	>100	>100	>100	87.8 ± 2.2	>100	92.1 ± 2.1	>100	63.1 ± 3.0
Colorectal Cancer	SW48	>100	>100	>100	>100	>100	>100	>100	62.3 ± 2.3	>100	33.4 ± 4.5	>100	43.4 ± 4.9
Lung Cancer	A549	>100	>100	>100	>100	>100	>100	>100	33.3 ± 1.9	>100	57.7 ± 1.7	>100	70.4 ± 1.1
Lung Cancer	H1299	>100	>100	>100	>100	>100	>100	>100	>100	>100	49.1 ± 2.1	>100	>100

Nasopharyngeal Cancer	CNE1	>100	>100	>100	>100	>100	>100	>100	32.1 ±	>100	15.3 ±	>100	33.2 ±
Nasopharyngeal Cancer	HK1	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Nasopharyngeal Cancer	SUNE1	>100	>100	>100	>100	>100	>100	>100	92.9 ± 5.2	>100	55.1 ± 2.5	>100	93.1 ± 1.9
Neuroblastoma	SHSY5Y	>100	>100	>100	>100	>100	>100	>100	62.5 ± 4.4	>100	33.7 ± 2.7	>100	56.4 ± 6.9
Pancreatic Cancer	AsPC1	>100	>100	>100	>100	>100	>100	>100	>100	>100	85.1 ± 1.9	>100	>100
Pancreatic Cancer	BxPC3	>100	>100	>100	>100	>100	>100	>100	>100	>100	52.1 ± 3.3	>100	>100
Pancreatic Cancer	SW1990	>100	>100	>100	>100	>100	>100	>100	92.1 ± 7.7	>100	33.3 ± 2.5	>100	55.8 ± 4.3
Breast Cells (non-cancerous)	MCF10A	>100	>100	>100	>100	>100	>100	>100	>100	>100	81.0 ± 0.7	>100	>100
Lung Cells (non-cancerous)	MRC5	>100	>100	60.2 ± 3.7	58.3 ± 4.4	>100	54.1 ± 4.4	>100	62.1 ± 3.2	>100	31.0 ± 0.9	41.0 ± 0.9	33.9 ± 2.8

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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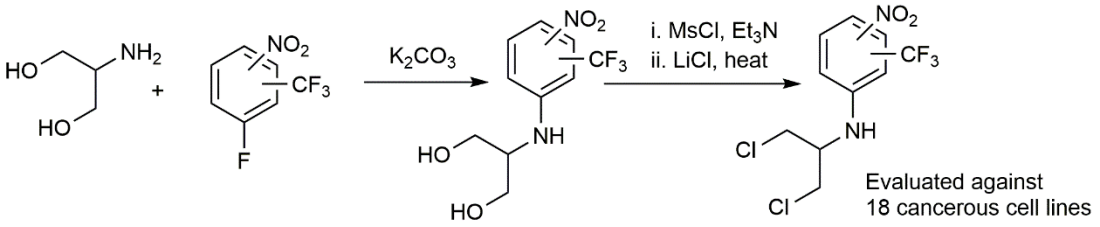

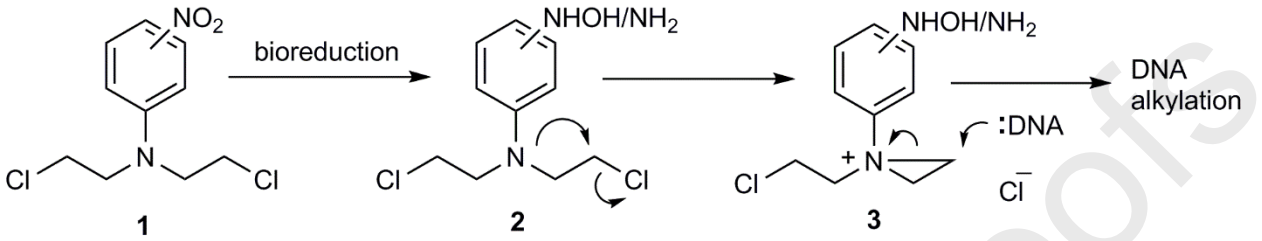

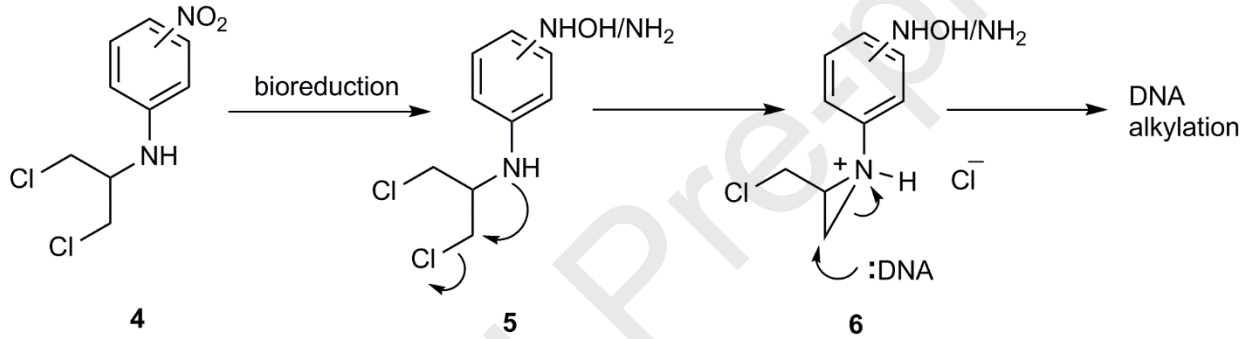

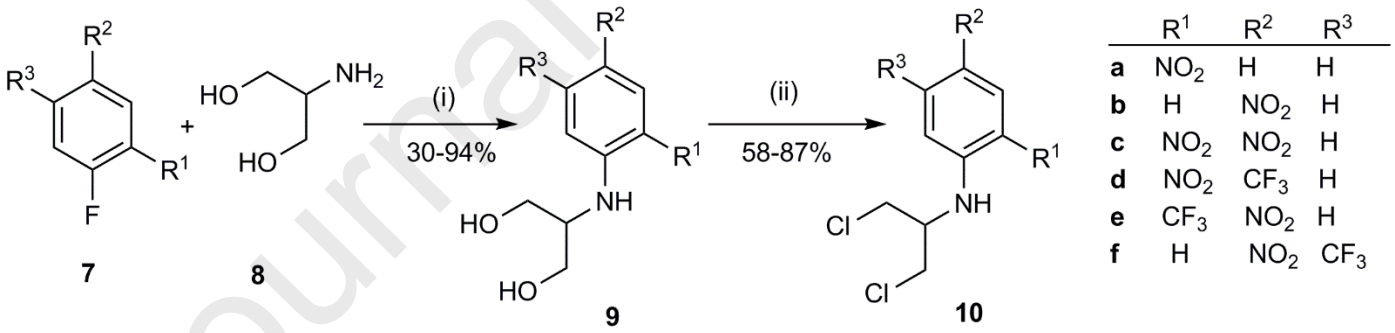

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b	H	NO_2	H
c	NO_2	NO_2	H
d	NO_2	CF_3	H
e	CF_3	NO_2	H
f	H	NO_2	CF_3

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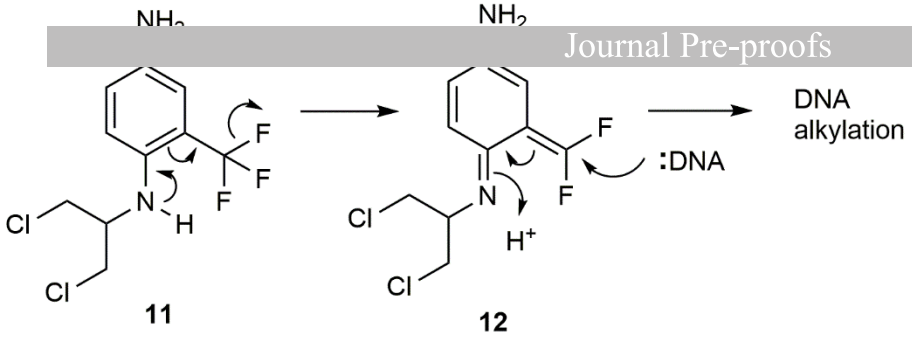

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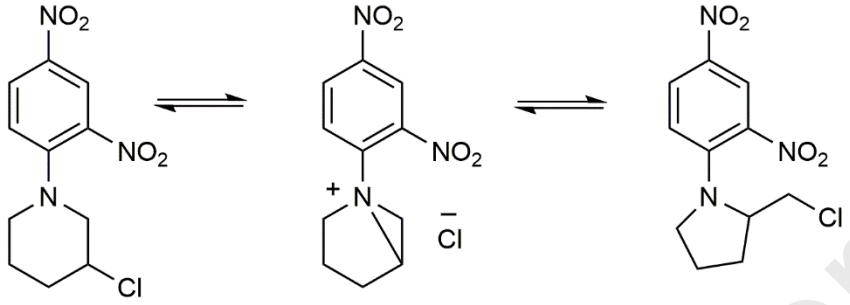

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