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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and preliminary evaluation of difluorinated 1,3-propanediones as potential agents in the treatment of breast cancer

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Abstract A series of difluorinated propanediones were synthesized and evaluated for in vitro cytotoxic activity by Sulforhodamine B (SRB) assay against a panel of four human cancer cell lines. Though the compounds showed varying degrees of cytotoxicity in the tested cell lines, most marked effect was observed in breast cancer cell line (MCF7), wherein nine of the ten synthesized chalcones showed good antiproliferative activity.

Keywords Difluorinated 1,3-propanediones · Sulforhodamine B assay · Breast cancer · Cytotoxicity

Introduction

Worldwide, breast cancer is the most common cancer among women after skin cancer, and it is also the second leading cause of cancer death (after lung cancer) in women (Hsu *et al.* 2006). In 2007, breast cancer caused 40,460 deaths worldwide and in 2008, an estimated 182,480 new cases of invasive breast cancer were diagnosed among women, as well as an estimated 67,770 additional cases of in situ breast cancer (Jemal *et al.*, 2008; Kaur *et al.*, 2010).

Breast cancer is currently controlled through surgery and/or radiotherapy, and is frequently supported by adjuvant chemo- or hormonotherapies. Unfortunately these classical treatments are hampered by unwanted side-effects and, most importantly, the development of tumor resistance. Therefore, there is an urgent need for novel and effective therapies against breast cancer (Chopin *et al.*, 2004).

It has long been recognized that infections and inflammation are related to cancer, and strong correlations between the presence of inflammation and development of precancerous lesions at various anatomic sites have been established (Rayburn *et al.*, 2009). As tumor develops, it expresses phenotypes similar to inflammatory cells (Arias *et al.* 2007). For example, numerous cancer cells express cytokines and chemokines and their receptors. These molecular mediators and their respective receptors have a significant impact on angiogenesis, cell migration and metastasis (Coussens and Werb, 2002). In a study conducted by (Chavey *et al.*, 2007), a number of cytokines, including IL-6, IL-8, G-CSF (Granulocyte colony stimulating factor), IFN-γ (interferon-γ), and MIP-1β (Macrophage inflammatory protein-1 β) were found to be more abundant in breast carcinoma than in normal breast tissue . Given its myriad pro-tumor effects, inflammation has become a target for cancer prevention and therapy. More than two decades ago, it was demonstrated that NSAIDs (non-steroidal anti-inflammatory drugs) have anti-colon cancer effects (Waddell and Loughry, 1983). Other clinical trials have indicated that long-term use of aspirin or other NSAIDs decreases the incidence of colorectal, esophageal, breast, lung, and bladder cancers (Wang and Dubois, 2006). By inhibiting cyclooxygenase-2, nonsteroidal anti-inflammatory drugs (NSAIDs) decrease aromatase activity and might reduce breast cancer risk by suppressing estrogen synthesis (Gierach *et al.*, 2008). Given that their toxicity is modest compared to conventional chemotherapeutic agents, various anti-inflammatory agents are being investigated for cancer therapy and prevention.

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Our laboratory has been actively involved in synthesis and evaluation of difluorinated chalcones and their propanedione derivatives as anti-inflammatory agents (Jadhav and Ramaa, 2007; More and Ramaa, 2010). The anticancer effects of the synthesized difluorinated chalcones has previously been reported (Ingale *et al.*, 2010). As a continuation of the efforts in developing newer antitumor agents, the authors report herein the results of preliminary cytotoxicity testing of difluorinated propanediones in a panel of four cancer cell lines viz., MCF7 (breast cancer), HOP62 (lung cancer), A498 (renal cancer), and MIAPACA2 (pancreatic cancer).

Results and discussion

Chemistry

Compounds **5a**–**5j** (Table 1) were synthesized according to the synthetic pathway depicted in Scheme 1 in accordance with previously standardized and reported procedure (More and Ramaa, 2010). Difluorinated chalcones **3a**–**3j** were prepared using the Claisen Schimdt condensation procedure by condensing 2,4-difluoroacetophenone **1** with variously substituted benzaldehydes **2a**–**2j**. These compounds were converted to dibromo derivatives **4a**–**4j**, which on treatment with methanolic KOH gave the difluorinated propanediones **5a**–**5j**.

All the synthesized compounds were identified by ^{1}H nuclear magnetic resonance (NMR) and infrared (FTIR) spectroscopy.

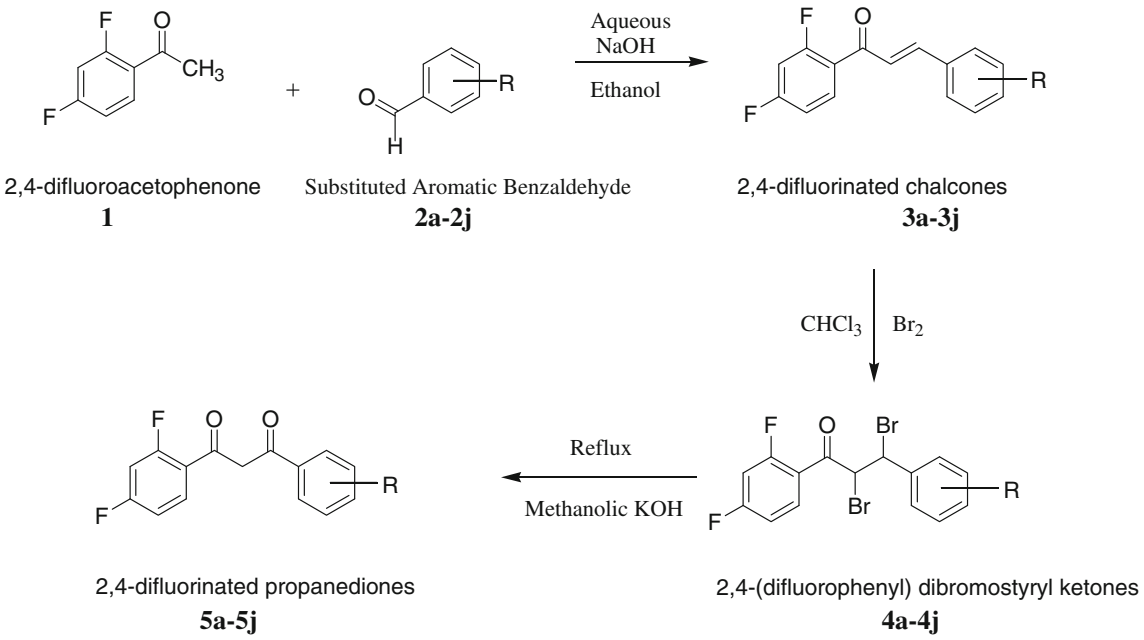
Biological evaluation

Anticancer evaluation

After successful synthesis of the derivatives of 2,4-difluorinated propanediones, their anticancer activity was evaluated in vitro on the 4-cell line panel consisting of MCF7 (breast cancer), HOP62 (lung cancer), A498 (renal cancer)

Table 1 Physical and spectral data for compounds **5a**–**5j**

Compound name	R	M.P(°C)	Yield (%)	^{1}H NMR (δ) ($CDCl_3$)
5a	3-NO_2	144	88.42	3.89 (s, 2H, CH_2), 6.45 (dd, J = 12.6 Hz, 2.4 Hz, 1H, aromatic proton); 6.83 (dd, J = 9 Hz, 2.7 Hz, 1H, aromatic proton), 6.98 (s, 1H, aromatic proton), 7.68 (t, J = 8.1 Hz, 1H, aromatic proton), 7.99–8.07 (m, 1H, aromatic proton), 8.27–8.41 (m, 1H, aromatic proton), 8.79 (s, 1H, aromatic proton)
5b	4-Cl	102	72.30	3.88 (s, 2H, CH_2), 6.67 (dd, J = 10.8 Hz, 2.4 Hz, 1H, aromatic proton), 6.81 (dd, 1H, J = 9 Hz, 2.4 Hz, aromatic proton), 6.90 (s, 1H, aromatic proton), 7.45 (d, J = 8.1 Hz, 2H, aromatic protons), 7.89 (d, J = 8.7 Hz, 1H, aromatic proton), 8.01 (t, 1H, J = 8.7 Hz, aromatic proton)
5c	4-F	93	78.13	3.88 (s, 2H, CH_2), 6.69 (dd, J = 13.6 Hz, 2.1 Hz, 1H, aromatic proton); 6.82 (dd, J = 8.8 Hz, 2.7 Hz, 1H, aromatic proton), 6.89 (s, 1H, aromatic proton),7.36 (t, J = 7.5 Hz, 1H, aromatic proton),7.67 (d, J = 6.9 Hz, 1H aromatic proton), 7.93 (d, J = 7.8 Hz, 1H, aromatic proton).7.98–8.10 (m, 1H, aromatic proton)
5d	3-Br	105	88.57	3.87 (s, 2H, CH_2), 6.65 (dd, J = 13.4 Hz, 2.1 Hz, 1H, aromatic proton); 6.80 (dd, J = 8.8 Hz, 2.1 Hz, 1H, aromatic proton), 6.86 (s, 1H, aromatic proton), 7.11–7.20 (m, 2H, aromatic protons), 7.94–8.07 (m, 2H, aromatic protons)
5e	4-OCH_3	153	76.13	3.88 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 6.67 (dd, J = 13.8 Hz, 2.4 Hz, 1H, aromatic proton), 6.81 (dd, J = 9 Hz, 2.7 Hz, 1H, aromatic proton), 6.85 (s, 1H, aromatic proton), 6.97 (d, J = 8.7 Hz, 1H, aromatic proton), 7.92–8.02 (m, 2H, aromatic protons), 8.18 (s, 1H, aromatic proton)
5f	2-Cl	89	58.00	3.90 (s, 2H, CH_2), 6.66 (dd, J = 13.8 Hz, 2.4 Hz, 1H, aromatic proton); 6.8 (d, J = 8.4 Hz, 2H, aromatic protons), 7.4 (m, 2H, aromatic protons), 7.68 (dd, J = 7.8 Hz, 2.4 Hz, 1H, aromatic proton), 8.0 (t, J = 8.7 Hz, 1H, aromatic proton)
5g	4-Br	114	80.00	3.90 (s, 2H, CH_2), 6.68 (dd, J = 13.5 Hz, 2.1 Hz, 1H, aromatic proton), 6.82 (dd, J = 9 Hz, 2.4 Hz, 1H, aromatic proton), 6.9 (s, 1H, aromatic proton), 7.6 (d, J = 8.7 Hz, 1H, aromatic proton), 7.82 (d, J = 9 Hz, 2H, aromatic protons), 8.0 (t, 1H, aromatic proton)
5h	4-CH_3	100	52.00	2.4 (s, 3H, CH_3); 3.90 (s, 2H, CH_2), 6.7 (dd, J = 13.5 Hz, 2.4 Hz, 1H, aromatic proton), 6.8 (dd, J = 9 Hz, 2.4 Hz, 1H, aromatic proton), 6.9 (s, 1H, aromatic proton), 7.3 (s, 1H, aromatic proton), 7.9 (d, J = 9.3 Hz, 2H, aromatic protons), 8.0 (t, J = 8.7 Hz, 1H, aromatic proton)
5i	2-NO_2	114	52.00	3.90 (s, 2H, CH_2), 6.60 (s, 1H, aromatic proton), 6.64 (dd, J = 13.8 Hz, 2.4 Hz, 1H, aromatic proton), 6.8 (m, 1H, aromatic proton), 7.7 (m, 3H, aromatic protons), 8.0 (m, 1H, aromatic proton)
5j	3,4,5-OCH_3	116	53.00	3.90 (s, 2H, CH_2), 3.98 (s, 9H, O-CH_3), 6.7 (dd, J = 13.8 Hz, 2.4 Hz, 1H, aromatic proton), 6.82 (dd, J = 9 Hz, 2.7 Hz, 1H, aromatic proton), 6.89 (s, 1H, aromatic proton), 7.67 (s, 1H, aromatic proton), 8.0 (t, J = 8.7 Hz, 1H, aromatic proton)



Scheme 1 Synthetic route for difluorinated propanedione derivatives

and MIAPACA2 (pancreatic cancer). Primary anticancer assay was performed in accordance with the US NCI protocol (Momose *et al.*, 1991; Monks *et al.*, 1991; Boyd and Paull, 1995).

The cytotoxic effects of synthesized compounds were tested in vitro against the panel of cell lines at ten-fold dilutions of four concentrations ranging from 10^{-4} to 10^{-7} M. The percentage growth was evaluated spectrophotometrically versus negative control not treated with test agents and positive control, treated with doxorubicin, a proven anticancer agent. A 48 h continuous drug exposure protocol was followed and an SRB protein assay was used to estimate cell viability or growth. For the compounds, the 50% growth inhibition (GI_{50}) and total growth inhibition (TGI) were obtained for each cell line. The $\log_{10}$ GI_{50} and $\log_{10}$ TGI were then determined, defined as the mean of the log10's of the individual GI_{50} and TGI values. Negative values indicated the most sensitive cell lines. Compounds having $\log_{10}$ GI_{50} value -4.0 and <-4.0 were declared to be active. The results obtained for anticancer evaluation have been tabulated in Table 2.

Amongst the various cell lines in which compounds were tested, MCF7 breast cancer cell line afforded maximum cytotoxicity, wherein nine of the ten synthesized propanediones showed good anti-proliferative activity.

Compounds **5c**, with 4-fluoro substitution, and **5f**, with 2-chloro substitution, showed favorable anti-proliferative activity in all of the four tested cancer cell lines.

Compounds **5c** ($\log_{10}GI_{50}$ value -5.56), **5g** ($\log_{10}GI_{50}$ value -5.58) exhibited good cytotoxicity on renal cancer cell line A498. Compounds **5b** ($\log_{10}GI_{50\ all}$value -4.42), **5d** ($\log_{10}GI_{50}$ value -4.49), **5f** ($\log_{10}GI_{50}$ value -4.49), **5h** ($\log_{10}GI_{50}$ value -4.47) were moderately active in the in vitro screen on renal cancer cell line (A498).

Compound **5c** ($\log_{10}GI_{50}$ value -5.54) yielded good anti-proliferative activity against pancreatic cancer cell line MIAPACA2 and compounds **5d** ($\log_{10}GI_{50}$ value -4.45), **5e** ($\log_{10}GI_{50}$ value -4.50), **5f** ($\log_{10}GI_{50}$ value -4.52) and **5h** ($\log_{10}GI_{50}$ value -4.44) were found to have moderate cytotoxicity in the same cell line.

Compound **5a** with a 3-nitro substitution was found to be inactive in all the tested cell lines with $\log_{10}GI_{50}$ values greater than -4.0.

In one of our earlier articles, we have reported the anti-proliferative prowess of difluorinated chalcones (Ingale *et al.*, 2010). A striking observation made was that both chalcones and their β diketone derivatives proved to be more cytotoxic in MCF7 breast cancer cell line than in other tested cell lines. A comparative profile of anti-proliferative evaluation of difluorinated chalcones and their corresponding propanediones have been described in Table 3 and Fig. 1.

Experimental section

Melting points were determined with a Veego melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded as KBr discs, using Shimadzu 8400S FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Varian Mercury Plus spectrometer at 300 MHz, with

Table 2 In vitro anticancer activity in four human tumor cell lines for **5a–5j**

Compound	Disease	Cancer cell line	Log_{10}GI50 (μM)	Log_{10}TG1 (μM)
5a	Renal cancer	A498	>−4	>−4
	Breast cancer	MCF7	>−4	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	>−4	>−4
5b	Renal cancer	A498	−4.42	>−4
	Breast cancer	MCF7	−4.46	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	>−4	>−4
5c	Renal cancer	A498	−5.56	>−4
	Breast cancer	MCF7	−4.52	>−4
	NSC lung cancer	HOP62	−4.44	>−4
	Pancreatic cancer	MIACAPA2	−5.54	>−4
5d	Renal cancer	A498	−4.49	>−4
	Breast cancer	MCF7	−5.65	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	−4.45	>−4
5e	Renal cancer	A498	>−4	>−4
	Breast cancer	MCF7	−4.51	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	−4.50	>−4
5f	Renal cancer	A498	−4.49	>−4
	Breast cancer	MCF7	−5.60	>−4
	NSC lung cancer	HOP62	−5.69	>−4
	Pancreatic cancer	MIACAPA2	−4.52	>−4
5g	Renal cancer	A498	−5.58	>−4
	Breast cancer	MCF7	−5.6	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	>−4	>−4
5h	Renal cancer	A498	−4.47	>−4
	Breast cancer	MCF7	−4.52	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	−4.44	>−4
5i	Renal cancer	A498	>−4	>−4
	Breast cancer	MCF7	−5.60	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	>−4	>−4
5j	Renal cancer	A498	>−4	>−4
	Breast cancer	MCF7	−5.64	>−4
	NSC lung cancer	HOP62	>−4	>−4
	Pancreatic cancer	MIACAPA2	>−4	>−4
Doxorubicin	Renal cancer	A498	−6.91	−5.63
	Breast cancer	MCF7	−6.92	−6.70
	NSC lung cancer	HOP62	−6.88	−5.68
	Pancreatic cancer	MIACAPA2	−6.95	−6.77

$CDCl_3$ as a solvent and TMS as an internal standard. All reactions as well as column chromatography were followed by TLC using Merck pre-coated silica gel 60 F_{254} plates and spots were visualized by observing in UV cabinet under short UV. All reagents were used as received unless otherwise stated.

Table 3 Comparison of anti-proliferative potential of chalcones with propanediones in MCF7 (breast cancer cell line)

R	Chalcones	Propanediones
3-nitro	−5.56	>−4
4-chloro	−4.48	−4.46
4-fluoro	−5.51	−4.52
3-bromo	−5.55	−5.65
4-methoxy	−4.42	−4.51
2-chloro	−5.60	−5.60
4-bromo	−5.55	−5.60
4-methyl	>−4	−4.52
2-nitro	−5.62	−5.60
3,4,5-trimethoxy	−5.61	−5.64

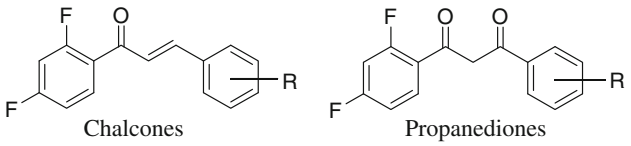


Fig. 1 General structure of chalcones and propanediones

General method for synthesis of difluorinated propanediones **5a–5j**

A series of 2′,4′-difluorinated chalcones **3a–3j** were prepared by condensing substituted benzaldehydes, **2a–2j** and 2,4-difluoroactophenone **1**, using sodium hydroxide in ethanol at RT. Their synthesis, physical constants and spectral characterization have been reported by us in an earlier article (Jadhav and Ramaa, 2007). 2,4-(difluorophenyl)dibromostyrylketones, **4a–4j**, were synthesized by reacting difluorinated chalcones with bromine in chloroform. Difluorinated propanediones (**5a–5j**) were synthesized by refluxing 2,4-(difluorophenyl) dibromostyrylketones with KOH in methanol for 3 h followed by reflux with concentrated HCl for further 2 h. Compounds **5a–5e** have been reported by us in an earlier article (More and Ramaa, 2010).

Cell culture and drug treatment

The cell lines were grown in RPMI 1640 medium containing 10% fetal bovine serum and 2 mM L-glutamine. For present screening experiment, cells were inoculated into 96-well microtiter plates in 90 µl at plating densities of 5,000 cells/well. After cell inoculation, the microtiter plates were incubated at 37°C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs.

After 24 h, one plate of each cell line was fixed in situ with trichloroacetic acid (TCA), to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Test compounds were solubilized in DMSO solvent at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of compound addition, an aliquot of frozen concentrate was thawed and diluted to ten times the desired final maximum test concentration with complete medium containing 1% gentamicin. Additional three, ten-fold serial dilutions were made to provide a total of four concentrations plus control. Aliquots of 10 µl of these different dilutions were added to the appropriate micro-titer wells already containing 90 µl of medium, resulting in the required final concentrations.

After compound addition, plates were incubated at standard conditions for 48 h at 37° C, 5% CO_2, 95% air, and 100% relative humidity and assay was terminated by the addition of cold TCA. Cells were fixed in situ by the gentle addition of 50 µl of cold 30% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4°C. The supernatant was discarded; the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (50 µl) at 0.4% (w/v) in 1% acetic acid was added to each of the wells, and plates were incubated for 20 min at room temperature. After staining, unbound dye was recovered and the residual dye was removed by washing five times with 1% acetic acid. The plates were air dried. Bound stain was subsequently eluted with 10 mM trizma base, and the absorbance was read on an Elisa plate reader at a wavelength of 540 with 690 nm reference wavelength.

Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells. Percent growth was expressed as the ratio of average absorbance of the test well to the average absorbance of the control wells *100.

Using the six absorbance measurements [time zero (Tz), control growth (C), and test growth in the presence of drug at the four concentration levels (Ti)], the percentage growth was calculated at each of the drug concentration levels. Percentage growth inhibition was calculated as:

$$[(\mathrm{Ti}-\mathrm{Tz})/(\mathrm{C}-\mathrm{Tz})] \times 100 \text{ for concentrations for which Ti} > / = \mathrm{Tz}\ (\mathrm{Ti}-\mathrm{Tz}) \text{ positive or zero}$$

$$[(\mathrm{Ti}-\mathrm{Tz})/\mathrm{Tz}] \times 100 \text{ for concentrations for which Ti} < \mathrm{Tz}. (\mathrm{Ti}-\mathrm{Tz}) \text{ negative}$$

The dose response parameters were calculated for each test article. Growth inhibition of 50% (GI_{50}) was calculated from [(Ti–Tz)/(C–Tz)] × 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control

cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz.

Values were calculated for each of these parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the values for that parameter were expressed as greater or less than the maximum or minimum concentration tested.

Conclusion

The results obtained in this study strongly suggest that difluorinated 1,3-propanediones have pronounced cytotoxic activity in MCF7 breast cancer cell line as compared with other tested cell lines. In an earlier study published by us, toxicity studies on β diketones established their safety in mice at doses up to 2,000 mg/kg (More and Ramaa, 2010). These findings indicate that difluorinated 1,3-propanediones may be used as lead molecules for development of agents in the treatment of breast cancer.

Further extensive studies need to be carried to determine the mechanism of action of the test compounds and to ascertain the cause for their greater specificity toward breast cancer cell line.

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