Journal of Biosciences and Medicines, 2023, 11, 208-218
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Triphenylmethanol Conjugates of Triptorelin as Cell-Penetrating Anti-Cancer Prodrugs

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How to cite this paper: Alnakhli, J., Alhamed, S., Boadi, W. and Beni, R. (2023) Triphenylmethanol Conjugates of Triptorelin as Cell-Penetrating Anti-Cancer Prodrugs. *Journal of Biosciences and Medicines*, **11**, 208-218.
https://doi.org/10.4236/jbm.2023.1111018

Received: October 3, 2023
Accepted: November 17, 2023
Published: November 20, 2023

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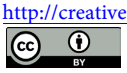

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Abstract

Some Triptorelin® (TRP) conjugates of triphenylmethanol derivatives (TPMs) with optimized hydrophobicity were synthesized by reacting 2-substituted methoxy benzenes with 1,3,5-trioxane, followed by the conjugation with TRP and sebacic acid to produce TRP-TPMs derivatives. Comparative antiproliferative assays between TRP-TPMs conjugates and the corresponding non-covalent physical mixtures of the TPMs derivatives and TRP were used to treat human acute lymphoblastic leukemia (CCRF-CEM), human ovarian adenocarcinoma (SK-OV-3) and mouse preadipocytes (3T3-L1) cells. TRP-TPMs conjugates at the 50 μM inhibited cell proliferation in CCRF-CEM, SK-OV-3 and 3T3-L1 cells by 21% - 37%, 24% - 73%, 37% - 56%, respectively following incubation for 72 h. These findings indicate that TRP-TPMs derivatives have the potential to enhance the biological activity of TRP.

Keywords

Prodrugs, Triptorelin, Polyphenols, Prostate Cancer, Triphenylmethanol

1. Introduction

Triptorelin® (TRP) is a synthetic analogue of the gonadotropin-releasing hormone (GnRH), first reported in 1976. The structure of TRP consists of ten amino acids (5-*oxo*Pro-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-GlyNH_2) and is used to treat advanced prostate cancer and endometriosis. TRP has been reported to stimulate the pituitary gland resulting in the secretion of FSH and LH [1]. However, prolonged stimulation (*i.e.*, with constant concentration of TRP in the blood) of the pituitary causes, insensitivity to the action of GnRH [1]. This reduces the level of gonadotropin in the blood, resulting in decreased levels of sex hormones to post-castration or menopausal levels. These effects are however, reversible. In addition to the usual side effects of the agonist analogs of LH-RH,

other reported adverse effects include transient hypertension, dry mouth, excessive salivation, para-esthesia and increased dysuria [1].

LHRH analogues are found in a variety of formulations and depending on the medication, can be administered every 1 to 12 months. Medications currently available in the United States include different formulations of triptorelin® leuprolide®, goserelin® and histrelin® in a variety of dosing intervals ranging from monthly to yearly. The associated side effects include hot flashes, decreased libido, erectile dysfunction, loss of bone mineral density, anemia and mood changes [2].

Efficacy and toxicity of anticancer drugs can be modified by using drug delivery systems and adjusting the physicochemical properties such as lipophilicity, cellular uptake and prolonging activity through chemical conjugation with various chemical moieties. Drug delivery systems avoid the P-glycoprotein and other multidrug resistance proteins (MRPs) that are involved in drug efflux to overcome the resistance problem and P-glycoprotein-mediated drug efflux [3] [4] [5].

Prodrug strategy is a drug delivery system through which chemical conjugation with the parent drug [6] [7] has been widely used in the delivery of anticancer drugs such as Doxorubicin® [8] [9]. For example, several conjugation methods have been used to improve the delivery of Doxorubicin®, including using gold nanoparticles [10], gold nanospheres [11], liposomes [12], peptides [13]-[18], and dendrimers [19]. The conjugation of TRP with agents that have optimal lipophilicity has yet to be explored. Therefore, the development of efficient and safe prodrug carriers to enhance the delivery and retention of TRP into drug-resistant tumor cells remains less explored.

Polyphenols are naturally occurring compounds found largely in fruits, vegetables, cereals and beverages. Fruits like grapes, apples, pears, cherries and berries contain up to 200 - 300 mg of polyphenols per 100 grams fresh weight [20] [21] [22]. In the last decade, there has been much interest in the potential health benefits of dietary plant polyphenols as antioxidants. The effect of polyphenols on human cancer cell lines is most often protective and induces a reduction in the number of tumors or growth rate. These effects have been observed at various sites including the mouth, stomach, duodenum, colon, liver, lungs, mammary glands and skin. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol and curcumin have been tested; all of them showed protective effects in some models although their mechanisms of action were found to be different [23] [24]. Polyphenols influence the metabolism of pro-carcinogens by modulating the expression of cytochrome P450 enzymes involved in their activation of carcinogens [25] [26].

To take advantage of the anticancer properties of polyphenolic antioxidants, several polyphenolic derivatives were chosen for the chemical modification of TRP. Sebacic acid has been chosen as a lipophilic linker to attach TRP to polyphenolic derivatives. In this study, we first report the synthesis of the antioxidant

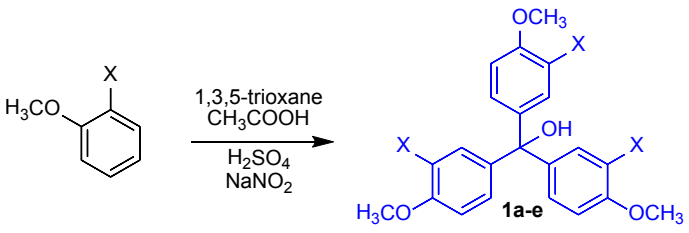
triphenylmethanol (TPMs) derivatives of TRP through the covalent conjugation with sebacic acid as the linker. Second, we report the evaluation and efficacy of the TPMs in *in vitro* cell antiproliferation activities using multiple cell lines. Prodrug conjugates were designed to improve cellular uptake, prolong biological activity and reduce therapeutic dosage of TRP.

Antiproliferative studies of the TPMs in cells were carried out using three cell lines, namely: human leukemia carcinoma (CCRF-CEM); human ovarian adenocarcinoma (SK-OV-3); and preadipocytes (3T3-L1). Obesity is a serious problem which heightens the risk of several chronic illnesses including cancer development [27] [28] [29] [30]. It has been estimated that about 20% of all cancers are caused by excess weight [31]. Therefore, and in addition to the use of the above cancer cell lines, the anti-obesity effect of our synthesized compounds was also tested in 3T3-L1.

2. Experimental

2.1. Preparation of TPMs 1a-e

The TPMs were synthesized using a modified method as reported in the literature [32] [33] (see **Scheme 1** below). Accordingly, 1,3,5-trioxane (15 mmole) was added to 2-chloroanisole, 2-nitroanisole, 2-methylanisole 1,2-dimethoxybenzene or methyl 2-methoxybenzoate (100 mmole) in 10 mL glacial acetic acid. The mixture was heated to 90˚C - 95˚C and 1 mL mixture of sulfuric acid and glacial acetic acid (1:5, v/v) was added to the solution. The mixture was stirred for 5 h at 90˚C - 96˚C. The reaction mixture was cooled to 0˚C using an ice bath and a homogenous solution of sodium nitrite (1.0 g, 15 mmole) and 2-chloroanisole, 2-nitroanisole, 2-methylanisole, 1,2-dimethoxybenzene or methyl 2-methoxybenzoate (15 mmole) in 10 ml concentrated sulfuric acid was added to the reaction mixture. The ice bath was removed and stirring of the reaction mixture was continued at room temperature for an additional 24 hr. The mixture was then poured into crushed ice (100 g) while stirring. The precipitate was filtered off and dried under vacuum and further purified on C_{18} column and hexanes/ethyl acetate as solvent using a TeledyneCombiFlash® Rf-200 chromatography machine with the gradient system set at a constant flow rate of 25 ml/min to yield pure products in 63% - 87% yield.



(**1a**) X=Cl, (**1b**) X=NO_2, (**1c**) X=CH_3, (**1d**) X=OCH_3, (**1e**) X=CO_2CH_3

Scheme 1. Preparation of triphenylmethanol (TPMs) derivatives 1a-e.

Tris(3-chloro-4-methoxyphenyl)methanol (**1a**), (4.51 g, 66%), MS (ESI-TOF) (*m/z*) for $C_{22}H_{19}C_{l3}O_4$: calcd., 453.0, found 453.0 $[M + H]^+$; tris(3-nitro-4-methoxyphenyl)methanol (**1b**), (4.52 g, 63%), MS (ESI-TOF) (m/z) for $C_{22}H_{19}N_3O_{10}$: calcd. 485.1, found 485.4 $[M]^+$; tris(3-methyl-4-methoxyphenyl)methanol (**1c**), (4.77 g, 81%), MS (ESI-TOF) (m/z) calcd. 415.2, found 415.2 $[M + Na]^+$; tris(3,4-dimethoxyphenyl)methanol (**1d**), (5.75 g, 87%), MS (ESI-TOF) (*m/z*) for $C_{25}H_{28}O_7$: calcd, 441.2, found 441.4 $[M + H]^+$; trimethyl 5,5',5''-(hydroxymethanetriyl) tris(2-hydroxybenzoate) (**1e**), (5.57 g, 77%), MS (ESI-TOF) (m/z) for $C_{28}H_{28}O_{10}$: calcd. 525.2, found 525.4 $[M + H]^+$.

2.2. Preparation of Tris(2-(Hydroxymethyl)Phenol) Conjugates of TRP 2a-e

Tris(4-methoxyphenyl)methanol derivatives **1a-e** (0.05 mmol), TRP acetate (0.05 mmol), sebacic acid, 10 mg, 0.05 mmol) and HBTU (19 mg, 0.05 mmol) were dissolved in dry NMP (3 mL). N,N'-diisopropylcarbodiimide (DIC, 8 µL, 0.05 mmol) and N,N-Diisopropylethylamine (DIPEA, 21 µL, 0.12 mmol) were added to the reaction mixture.

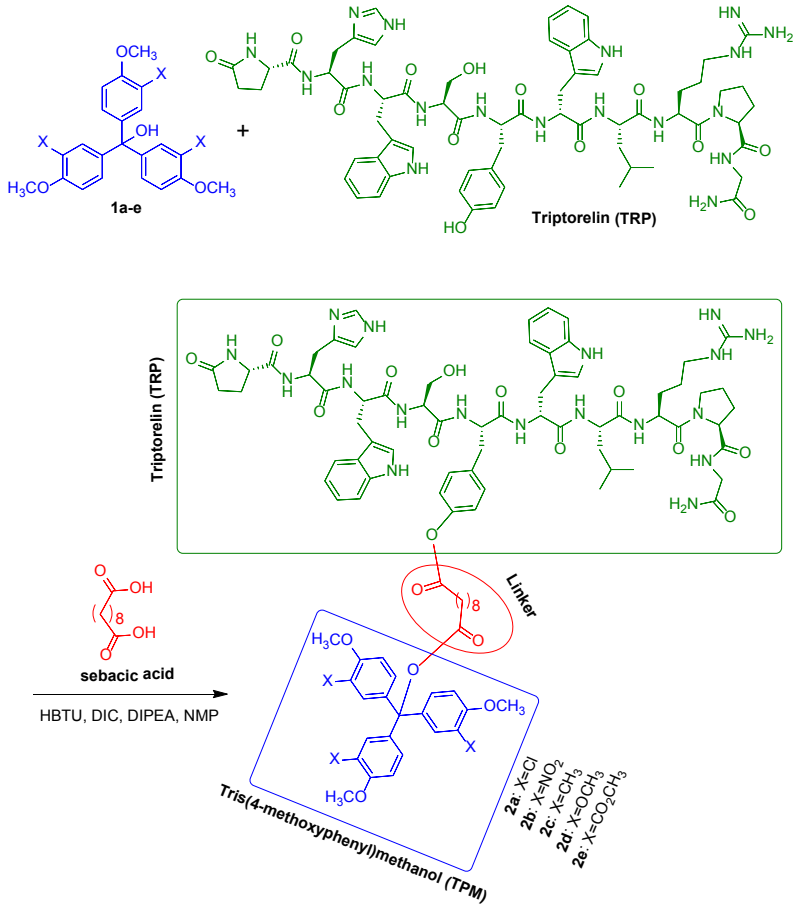
The mixture was stirred at room temperature for 24 h. Afterwards, the solvent was evaporated and dried under vacuum. The final product was purified with a C_{18} column and hexanes/ethyl acetate as solvents using a TeledyneCombiFlash® Rf-200 chromatography machine. The gradient system is set at a constant flow rate of 25 ml/min to yield pure TRP-TPMs conjugates **2a-e** (Scheme 2). TRP-TPMs conjugate (**2a**), (64 mg, 66%), MS (ESI-TOF) (*m/z*) for $C_{96}H_{116}Cl_3N_{18}O_{19}$: calcd, 1929.8, found 1929.8 $[M + H]^+$; TRP-TPMs conjugate (**2b**), (71 mg, 72%), MS (ESI-TOF) (*m/z*) for $C_{96}H_{115}N_{21}O_{25}$: calcd, 1961.9, found 1978.9 $[M + OH]^+$; TRP-TPMs conjugate (**2c**), (64 mg, 68%), MS (ESI-TOF) (*m/z*) for $C_{99}H_{122}N_{18}O_{18}$: calcd, 1850.9, found 1850.9 $[M - H_2O]^+$; TRP-TPMs conjugate (**2d**), (84 mg, 87%), MS (ESI-TOF) (*m/z*) for $C_{99}H_{124}N_{18}O_{22}$: calcd, 1917.9, found 1917.9 $[M + H]^+$; TRP-TPMs conjugate (**2e**), (77 mg, 77%), MS (ESI-TOF) (*m/z*) for $C_{102}H_{125}N_{18}O_{25}$: calcd, 2001.9, found 2001.9 $[M + H]^+$.

3. Cell Culture

Human leukemia carcinoma CCRF-CEM (ATCC no. CCL-119), human ovarian adenocarcinoma SK-OV-3 (ATCC no. HTB-77) and mouse pre-adipocyte fibroblast cells (3T3-L1) cell lines were obtained from American Type Culture Collection. The cells were grown on 75 cm^2 cell culture flasks with RPMI-1460 medium for leukemia cell line, McCoy's 5A medium for ovarian cell line and Dulbecco's Modified Eagle's Medium (DMEM) (GIBCO, Grand Island, NY) for pre adipocytes cell line and supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin solution (10,000 units of penicillin and 10 mg of streptomycin in 0.9% NaCl) in a humidified atmosphere of 5% CO_2, 95% air at 37˚C for 24 hr.

3.1. Cell Antiproliferation Assay

Antiproliferative activities of synthesized TRP-TPMs **2a-e** (see Scheme 2) and



Scheme 2. Synthesis of triphenylmethanol conjugates of TRP 2a-e.

physical mixtures of TPMs **1a-e** + TRP were evaluated in CCRF-CEM, SK-OV-3 and 3T3-L1 cells and the results compared with cells treated alone with TRP. The use of TRP-TPMs as opposed to that of TRP alone was based on the findings in our previous studies where lipid peroxides measured as thiobarbituric reactive substances (TBARS) decreased between 20% - 30% for the TRP-TPMs samples in comparison to those of TRP (5% - 10%) [34]. The assay was carried out using the CellTiter 96 aqueous one solution cell proliferation assay kit (Promega, USA). Briefly, 100 µL each of SK-OV-3 cells in suspension at 5000/mL, CCRF-CEM at 50,000/mL and 3T3-L1 at 10,000/mL were placed in 96 well culture plate. After seeding for 24 h, the cells were treated with 50 µM of compounds **2a-e** in 2% DMSO in triplicate. TRP (50 µM) was used as the positive control. For the physical mixtures, an appropriate volume of TRP stock solution was mixed with an appropriate volume of an aqueous solution of compounds **1a-e** to obtain a final concentration of 50 µM respectively for TPMs and TRP. The mixtures were vortexed until the solutions became homogeneous. Subsequently, the mixtures were incubated for 30 min at 37˚C before treating the cells with it. The cells were incubated at 37˚C with 5% CO_2 for 72 h. Following the incubation, 20 µL CellTiter 96 aqueous solution was added to the samples and incubated for a further I h. under the same conditions. The absorbance of the

formazan product was measured at 490 nm using a microplate reader. The percentage of cell survival was calculated as the OD value of cells treated with the test compound – OD value of culture medium/(OD value of control cells – OD value of culture medium) × 100%.

3.2. Cell Cytotoxicity Assay

The cytotoxicity of TRP, TPMs **1a-e** and TRP-TPMs **2a-e** treated with CCRF-CEM, SK-OV-3 and 3T3-L1 cells was determined by the MTT assay using the CellTiter 96 aqueous one solution cell proliferation assay kit (Promega, USA). The respective cells were cultured overnight in 96 well plates at a density of 5000 cells per well in 0.1 mL of the appropriate growth medium at 37˚C. Different concentrations of TRP, TPMs **1a-e** and TRP-TPMs **2a-e** (up to a maximum of 100 μM) were used to treat the cells and incubated for 2 h. Following the treatments, the media was aspirated and replaced with fresh medium and incubated for another 72 h. Samples without the above compounds served as controls and treated under the same conditions as the treated samples. The absorbance of the formazan product was measured at 490 nm using microplate reader. The percentage of cytotoxicity was calculated as (OD value of untreated cells – OD value of treated cells)/OD value of untreated cells × 100%.

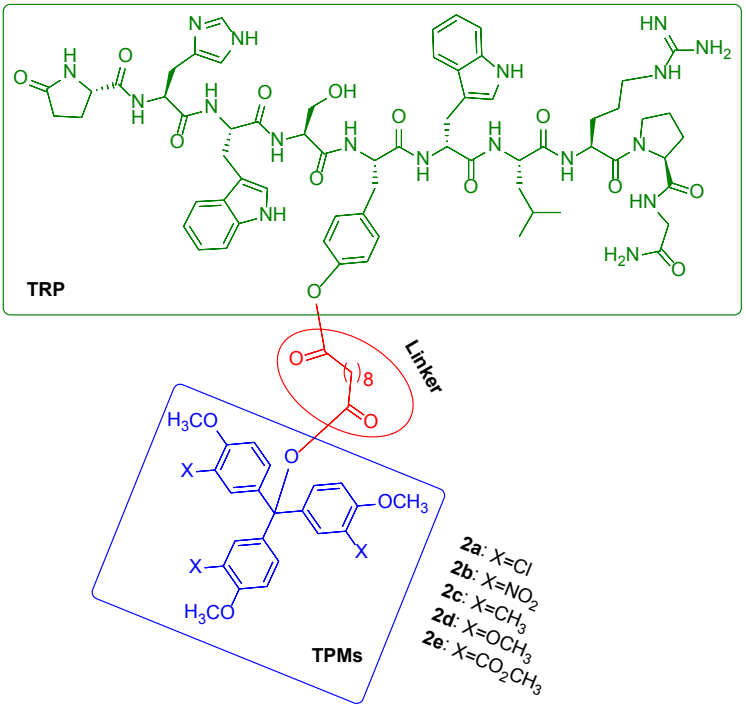
4. Results and Discussion

4.1. Chemistry

TRP, DMSO and other chemicals and reagents were purchased from Fisher Scientific or Sigma-Aldrich Chemical Co. All coupling reactions (Scheme 2) were carried out in Bio-Rad polypropylene columns by shaking and mixing using a Glass Col® small tube rotator in dry conditions at room temperature. TPMs **1a-e**, which mimic the naturally occurring poly phenolic antioxidants, were synthesized in moderate yields (Scheme 1) through covalent attachment to TRP via the hydrophobic linker, sebacic acid. Tris(2-(hydroxymethyl)phenol) conjugates of TRP (**2a-e**) with optimal hydrophobicity were synthesized to transport TRP into the cells (see Scheme 2). All products were purified (≤95%) by a flash chromatography system (TeledyneCombiFlash® Rf-200) and the structures of all the final compounds were confirmed by ESI/TOF mass spectrometry. Scheme 3 shows the structures of the final TRP-TPMs conjugates **2a-e**.

4.2. Cytotoxicity and Antiproliferative Activity of TRP-TPMs 2a-e

TRP, TPMs **1a-e** and TRP-TPMs **2a-e** did not show any significant toxicity in CCRF-CEM, SK-OV-3 and 3T3-L1 cells at the 100 μM dose following treatment for 72 h. Thus, a non-cytotoxic concentration of 50 μM was selected for cell-based studies of TRP-TPMs **2a-e** and the physical mixture of TPMs **1a-e** + TRP. The effects of the said compounds on cell proliferation for the cell lines were also investigated at the 50 μM for 72 h. The 72 h, incubation was selected because the antiproliferative activity of the compounds was apparent following



Scheme 3. Structure of synthesized TRP-TPMs derivatives 2a-e.

exposure as early as the 24 with the maximum at the 50 μM for the 72 h. incubation. The activity of synthesized compounds **2a-e** was evaluated and in comparison, to the noncovalent physical mixtures of (TPMs **1a-e** + TRP) and TRP alone respectively (Figure 1).

TRP-TPMs **2a-e** showed higher antiproliferative activity compared to the TRP alone for all cell lines with the highest activity observed following the 72 h, incubation. The effects of compounds on the cells were found to be time dependent. The cell proliferation inhibitory effects of compounds were enhanced at longer incubation period. The observed inhibitory effects of the compounds in the cells may probably be attributed to the hydrolysis of the conjugate to TRP and TPMs. The derivatives **2a-e** inhibited the cell proliferation of CCRF-CEM (21% - 37%), SK-OV-3 (24% - 73%) and 3T3-L1 (37% - 56%) at a concentration of 50 μM after 72 h. These data suggest that covalent conjugation of TRP-TPMs provided a more effective transporter for TRP. The antiproliferative activity of TRP-TPMs **2a-e** was in order of CCRF-CEM > SK-OV-3 > 3T3-L1.

In general, the physical mixtures of TPMs **1a-e** + TRP showed less antiproliferative activity in comparison to the covalent TRP-TPMs **2a-e** after 72 h incubation with the following respective percentages for CCRF-CEM (51% - 69%), SK-OV-3 (79% - 87%) and 3T3-L1 and showed slightly better or comparable activity against 3T3-L1 (62% - 73%). TRP exhibited similar antiproliferative activity in comparison to the physical mixture against CCRF-CEM (54%), SK-OV-3 (82%) and 3T3-L1 (68%) after 72 h of incubation, indicating that conjugation of the TRP with TPMs in compounds **2a-e** improved the antiproliferative activity of TRP in some of the tested cells.

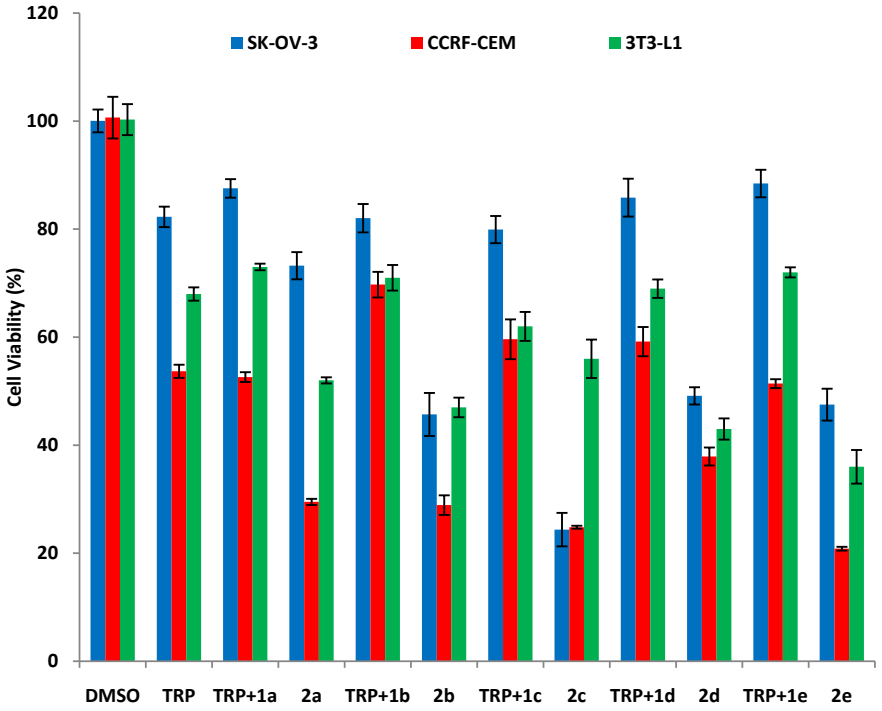


Figure 1. Inhibition of (a) CCRF-CEM, (b) SK-OV-3 and (c) 3T3-L1 cells by compounds (50 μM) after 72 h incubation. The results are shown as the percentage of the control DMSO that has no compound (set at 100%). All the experiments were performed in triplicate (±SD).

5. Conclusions

In summary, TRP-TPMs derivatives were synthesized as prodrugs, and evaluated for their antiproliferative activities in two cancer cell lines and in preadipocytes, 3T3-L1, and in comparison, to their corresponding physical mixtures. The conjugation of TRP with a specific TPMs derivative improved the antiproliferative activity compared to the corresponding physical mixtures in all tested cell lines. TRP-TPMs showed comparable antiproliferative activity against CCRF-CEM, SK-OV-3 and 3T3-l1 cells when compared to TRP alone.

Since the system was designed as a prodrug, we did not detect any huge significant differences between TRP and TRP-TPMs in cytotoxicity over time. These data suggest that TRP-TPMs can be used as a potential prodrug for improving the biological profile and cellular delivery of TRP.

With regards to any future studies based on the current findings, normal cells such as human fibroblasts or HeK293 from kidneys may be included and to elucidate the potential effects and benefits of TRP-TPMs in the said cells in comparison to cancer.

Acknowledgements

We acknowledge the financial support from the National Cancer Institute, MMC-Vanderbilt-TSU Partners in Eliminating Cancer Disparities (MVTCP), Grant Number 5U54CA163066-03. We thank US Department of Education,

Title III Part B, grant number P031B090214 for partial financial support. The financial support of the Novartis TMCF I HBCU is also acknowledged. Jawzah Alnakhli and Samiyah Alhamed acknowledge the scholarship provided by the Saudi Arabian Cultural Mission to the US (SACM).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

CCRF-CEM, human leukemia carcinoma cell line; SK-OV-3, human ovarian adenocarcinoma; TRP, Triptorelin; TPMs, Triphenylmethanols; DCM, dichloromethane; NMP, N-Methyl-2-pyrrolidone; HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; DIC, N,N'-Diisopropylcarbodiimide; DIPEA, N,N-Diisopropylethylamine; GnRH, gonadotropin-releasing hormone; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; LHRH, luteinizing hormone-releasing hormone.