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REVIEW ARTICLE

Perillyl alcohol and its synthetic derivatives: the rising of a novel class of selective and potent antitumoral compounds

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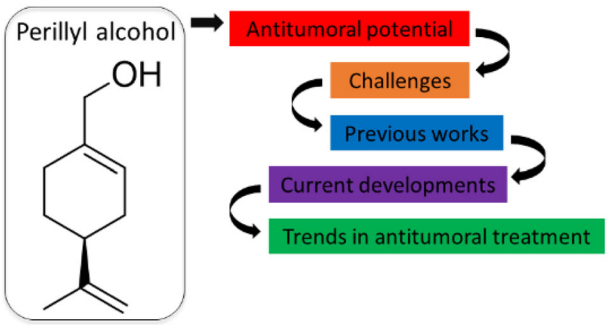
Abstract

(S)-(-)-perillyl alcohol (POH) is a natural occurrence monoterpene that can be found in specific plants' essential oil. Despite its poor bioavailability when orally administered, due to fast metabolization through P450 enzyme oxidation, inhalation unveiled its selective cytotoxicity for glioma cells. Actually, under phase I/II clinical trial for glioblastoma multiforme (GBM) treatment at Hospital Universitário Antônio Pedro (HUAP) in Brazil, POH became a potential lead compound for developing novel antitumoral drugs. Recent reports highlight POH potential as a chemosensitizing agent, describes efficient novel derivatives for topical administration in multiple myeloma treatment and unveils its effectivity against different chemoresistant cancer cell lines. In this review, POH and its synthetical derivatives will be presented reporting its potential as a valuable scaffold to develop novel selective antitumoral agents. A summarized biological and mechanistic approach is also discussed. Only selected synthetic procedures are presented to keep the article in a reader-friendly fashion.

Graphical abstract



Keywords Anticancer activity · Drug delivery strategies · Drug design · Multitarget drug · Bioactive natural product · Hybrid compound

Abbreviations

BBB	blood-brain barrier
BEC	brain endothelial cells
BF_3OEt_2	boron trifluoride diethyl etherate
BPA3	bromopyruvic acid
CuAAC	copper-catalyzed azide-alkyne cycloaddition
CYP450	cytochrome P450
Cys	cysteine
DHPM	dihydropyrimidinones
DMC	dimethyl celecoxib
ER	endoplasmic reticulum
FTase	farnesyltransferase
FTIs	FTase inhibitors
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GBM	glioblastoma multiforme
GI	growth inhibition

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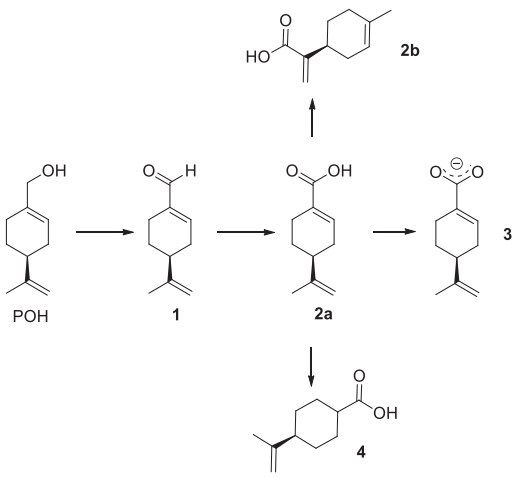
HSV-1	herpes simplex type-1 virus
POH	perillyl alcohol
ROS	reactive oxygen species
SAR	structure-activity relationship
TGF-β	transforming growth factor-beta
TMZ	temozolomide
MCT1	monocarboxylate transporter 1
-MCT1	down regulated MCT1
MGMT	O6-methylguanine DNA methyltransferase
MM	multiple myeloma

Introduction

(S)-(-)-perillyl alcohol (POH, Scheme 1) is a cyclic monoterpene of natural occurrence [1]. It can be obtained from lavender, caraway, cherries, cranberries, sage, peppermint and other plants' essential oil [2, 3]. This natural product detains many potential medicinal applications, like: anti-herpes simplex type-1 virus (HSV-1) [4], ischemia treatment [5], anticandidal activity [6–8], Parkinson's [9] and Alzheimer [10] Disease treatment, orofacial antinociceptive [11], asthma treatment [12], breast [13, 14], lung [15], and pancreatic [16, 17] cancers treatment.

However, major research interest in POH resides in its outstanding potential to selectively induce apoptosis in neoplastic cells through many specific mechanisms at transmembrane targets such as angiogenesis inhibition [18]; induction of transforming growth factor-beta (TGF-β) signaling pathway [19]; inhibition of nuclear factor kappa B [20] Jun N-terminal kinase pathway activation [21]; translational and post-translational inhibition of telomerase activity [22–25]; Na/K-ATPase inhibition [26, 27]; G0/G1 cell cycle arrest [28–33]; inhibition of small G-protein post-translational isoprenylation [13, 34, 35]; inhibition of reactive oxygen species (ROS) action; inducing endoplasmic reticulum (ER) stress [36].



Scheme 1 POH metabolic products: perillyl aldehyde **(1)**, perillic acid **(2a)**, iso-perillic acid **(2b)**, deprotonated perillic acid **(3)** and dihydroperillic acid **(4)** produced by CYP450 in the liver

Such characteristic is especially desirable in the search for new chemotherapy drugs for glioblastoma multiforme (GBM) treatment, a high vascularized and aggressive form of brain cancer, which mutability and metastasis characteristics make it a challenging disease to treat [37]. Typical treatment procedures involve temozolomide chemotherapy, radiotherapy and surgery. However, GBM has a high capacity for chemoresistance, making it one of the tumors with the highest mortality rate. The cellular heterogeneity of this tumor type makes treatment inefficient in most cases [38].

Due to its amphipathic structure, POH can modify the structure and dynamics of the plasma membrane [39–41], enabling drug delivery in the central nervous system. The first attempts of using POH as a therapeutic agent involved oral administration. However, the monoterpene was readily converted to its oxidized metabolites, perillyl aldehyde **(1)**, regioisomers perillic acid **(2a)** and iso-perillic acid **(2b)**, deprotonated perillic acid **(3)** and dihydroperillic acid **(4)** by cytochrome P450 (CYP450), present in the liver, and excreted in urine (Scheme 1) [3, 42]. This rapid metabolization in vivo reduces biodisponibility of POH at the brain, which justifies the use of high daily doses, such as 8400 mg/m^2, needed to evidence significant therapeutic results. Such high doses lead to collateral effects as nausea, headache, fatigue, stomatitis, diarrhea and vomiting [43, 44].

Another downside in the metabolization of the monoterpene, when orally administered, is the modified phospholipidic bilayer diffusion behavior due to the different polarities compounds formed. A molecular dynamic study pointed that POH, perillyl aldehyde **(1)** and deprotonated perillic acid **(3)** were capable of one, seventy-four and zero flip-flop events, respectively, during a 220 nanoseconds interval (Fig. 1) [40]. The reduced polarity and weaker "non-traditional" intramolecular hydrogen bond [45, 46] of **(1)** allows more liberty to diffuse between the hydrophilic heads. This results in more flip-flop events with the maintenance of some interactions with different transmembrane pharmacophoric sites [47], justifying it's biological activities being similar to the ones of POH [29]. Metabolite **(3)** otherwise, due to its strong polarity derived from its ionic structure and absence of a hydrogen bond donor is chemically unable to experiment flip-flop events, impairing proper interactions with pharmacophoric sites and being readily excreted. Hence, the presence of intracellular **(3)** is resultant from the metabolization of its precursors. So, this flip-flop-like mechanism also justifies the various and complex ways of POH acting on cancer cells, specifically on GBM, ensuring a pleiotropic behavior as described by Gomes and coworkers [2, 36, 47].

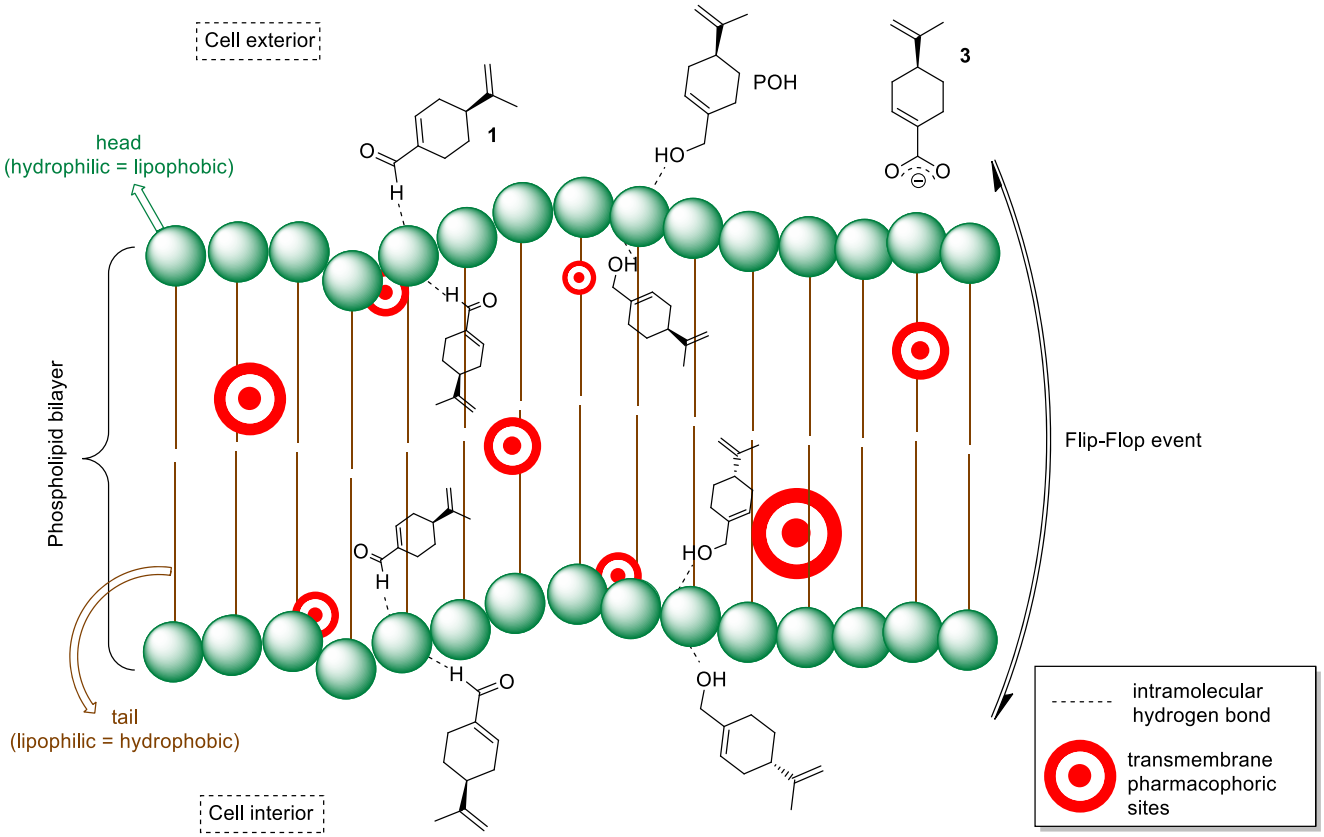


Fig. 1 Flip-flop-like mechanism illustrating the monoterpene and its metabolites **1** and **3** diffusions through the lipid bilayer

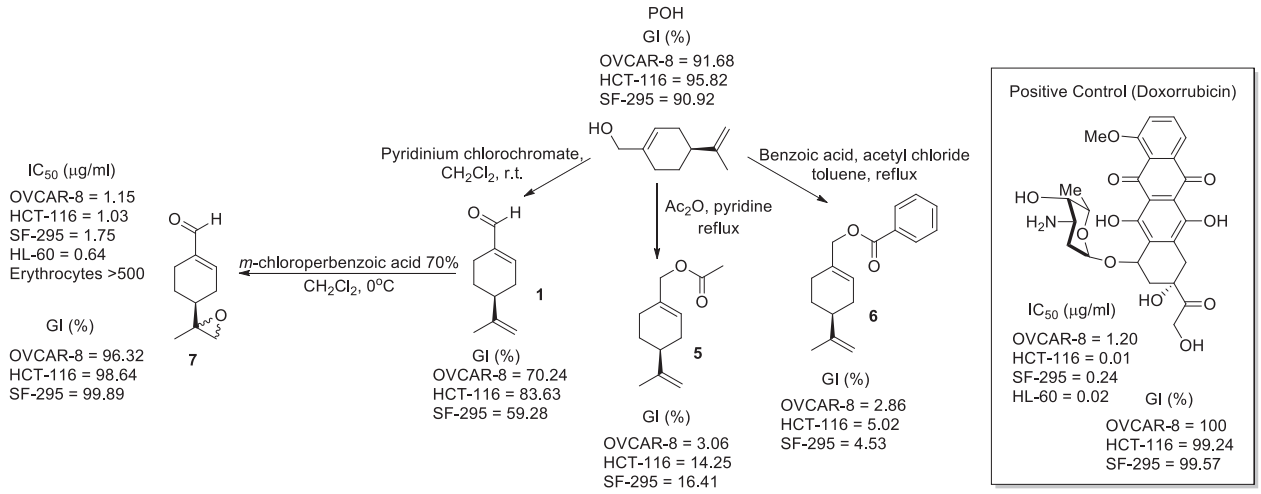
To effectively use POH in GBM treatment, the phytochemical has been successfully administered intranasally, in a phase I/II clinical trial in Brazil [48–52]. Different from the previous oral administration, inhalation allows direct and efficient transportation from the nasal cavity to the brain tissue via the olfactory and trigeminal nerves, consequently increasing bioavailability while avoiding undesired metabolization reactions [53–55]. Even for a compound that can permeate through the blood-brain barrier (BBB), like POH, another exclusive feature of intranasal delivery is bypassing the BBB. The BBB is an obstacle to the entrance of toxic substances or pathogens in the brain, working as a natural defense for the central nervous system [56, 57]. So, the strategy solved the two problems encountered when previously oral administered: biodisponibility and metabolization, in addition to being a non-invasive and very well tolerated delivery method.

Results of a clinical trial show that the use of POH increases the survival of patients with primary or secondary glioblastoma, especially in patients with tumors localized in brain deep regions. These studies also indicate that POH associated with temozolomide (TMZ) is capable of reducing tumor mass and delaying tumor recurrence, being a viable treatment alternative for patients who currently do not have effective therapies [50, 52]. Those data reveal POH as a potential chemotherapeutic agent of continuous use in the treatment of GBM.

So, POH is a biologically active compound that shows promising efficiency in the treatment of different tumor cells, especially GBM, and is safe for in vivo continuous long-term use. Moreover, the knowledge of the POH mechanism of action makes it possible to handle the monoterpene as a lead compound ready to be optimized to achieve novel antitumoral drugs candidates with increased potency, broader biological application and high selectivity [58–61]. In this review, molecular modifications in the POH structure will be presented to discuss this monoterpene potential as a lead compound for the development of novel patient-friendly antitumoral drugs.

Oxygenated derivatives

To achieve a better understanding of structure-activity relationship (SAR) comprising POH and cancer, important molecular structure deviations in POH were explored by Andrade and coworkers (Scheme 2) [62]. The investigated compounds **1**, **5**–**7** efficiency was preliminarily tested measuring the in vitro growth inhibition (GI) with a 25 µg/mL dose administration in ovarian adenocarcinoma (OVCAR-8), colon carcinoma (HCT-116) and human glioblastoma (SF-295) cell lines. Doxorubicin was used as the positive control.



Scheme 2 POH derivatives **1**, **5**–**7** and their biological activity assays against OVCAR-8 (ovarian adenocarcinoma), HCT-116 (colon carcinoma), SF-295 (human glioblastoma) and HL-60 (human leukemia) cell lines. All compounds were tested for in vitro GI essay at a concentration of 25 μg/ml and in a 72 h incubation period [62]

Derivatives **1**, **5** and **6** showed significative loss of activity against all cancer cell lines compared to POH, indicating the important role of a hydrogen bond donor for the monoterpene bioactivity. The epoxide one **7** presented better GI values than POH against all cancer cell lines and better GI value (GI = 99.89%) than Doxorubicin (GI = 99.57%) against SF-295. Therefore, **7** was also tested for IC50 against the same cell lines and human leukemia (HL-60). Surprisingly, it was more potent (IC50 = 1.15 μg/ml) than Doxorubicin (IC50 = 1.20 μg/ml) against OVCAR-8 and exhibited promising cytotoxicity against HCT-116, SF-295 and HL-60 compared to the positive control. Moreover, with concentrations of 500 μg/ml not being cytotoxic for erythrocytes, the hemolytic assays indicated high selectivity and specific mechanism for **7** against cancer cells. Further in-depth in vivo studies proved compound **7** low cytotoxicity and high selectivity, similar to the POH behavior in the tumor microenvironment [63].

Amino derivatives

Aiming antitumor activity improvement via exchanging oxygen atoms for nitrogen ones and gathering more information regarding SAR comprising POH and cancer, Hui and coworkers [64] proposed the synthesis of a great number of different POH amino derivatives, discovering fourteen novel compounds with potentialized antiproliferative effects in human lung adenocarcinoma cells (A549), human melanoma cells (A375-S2) and human fibrosarcoma cells (HT1080). Selected examples **8a-b** and **9a-d** are highlighted in Scheme 3.

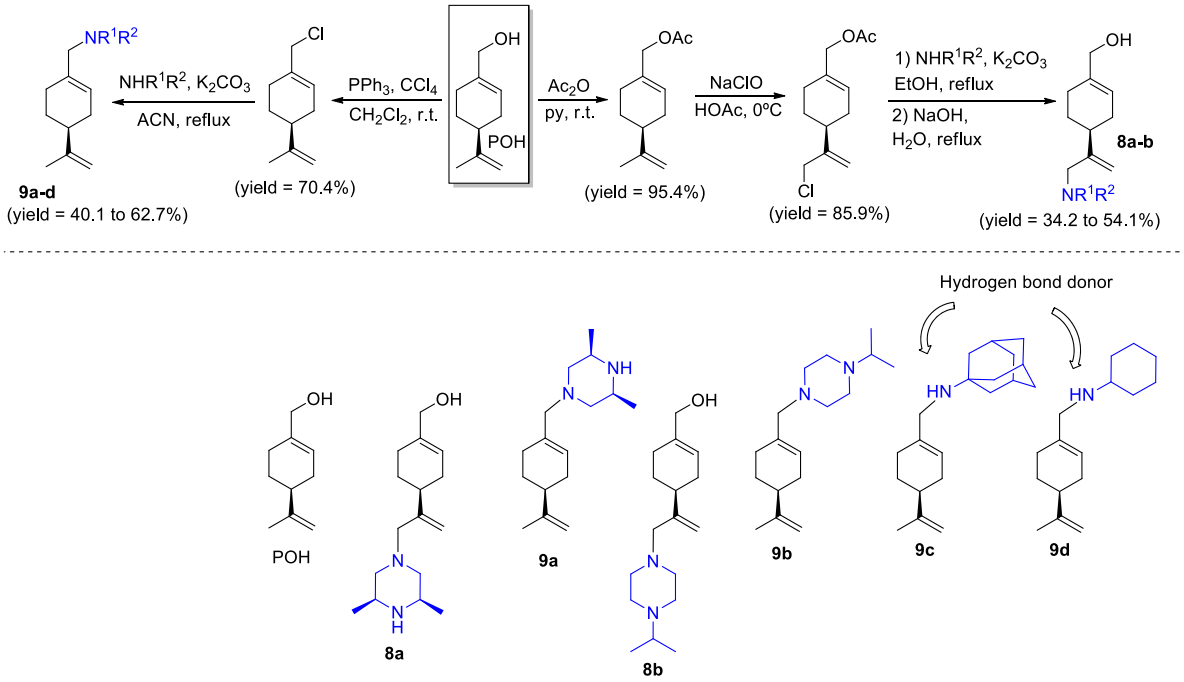
According to the in vitro biological assays, the majority of POH amino derivatives presented a considerable increase in potency to all cancer cell lines tested [64]. The comparative analysis points that compounds whose terminal isoprene units were not modified **9a-b** presented overall more promising results with lower IC_{50} values, indicating that its integrity is also important for the antitumoral activity. Moreover, **9c-d** outstanding increase in antitumoral activity of almost twenty times against A549, A375-S2 and HT1080 cancer cell lines illustrated the importance of an intramolecular hydrogen bond donor (N—H bond).

Phosphonate derivatives

Aiming to explore POH potential to selectively induce apoptosis in tumor cells through the mammalian protein farnesyltransferase (FTase) inhibition [35, 42, 65], Eummer and coworkers [66] proposed structural modifications to produce novel POH based phosphonates **10**–**12** as potential mammalian FTase inhibitors (FTIs) analogs by mimicking known promising FTIs structures **13**–**16** (Scheme 4). Comparing the in vitro biological assays results of derivatives **10**–**12** to the promising FTIs **13**–**16** IC50 values, it is possible to observe that POH might exert only a small part of its cytotoxicity via post-translational modulation in levels or modifications of small G-proteins. Hence, for this case, not being an adequate path for its antitumoral activity as pointed out in previous literature [67–71].

POH-glycoside hybrids

Some types of tumor cells have altered glucose metabolism and, despite the availability of oxygen for conversion of glucose into CO_2 (oxidative metabolism), which in terms of energy is much more productive, these cells with a high



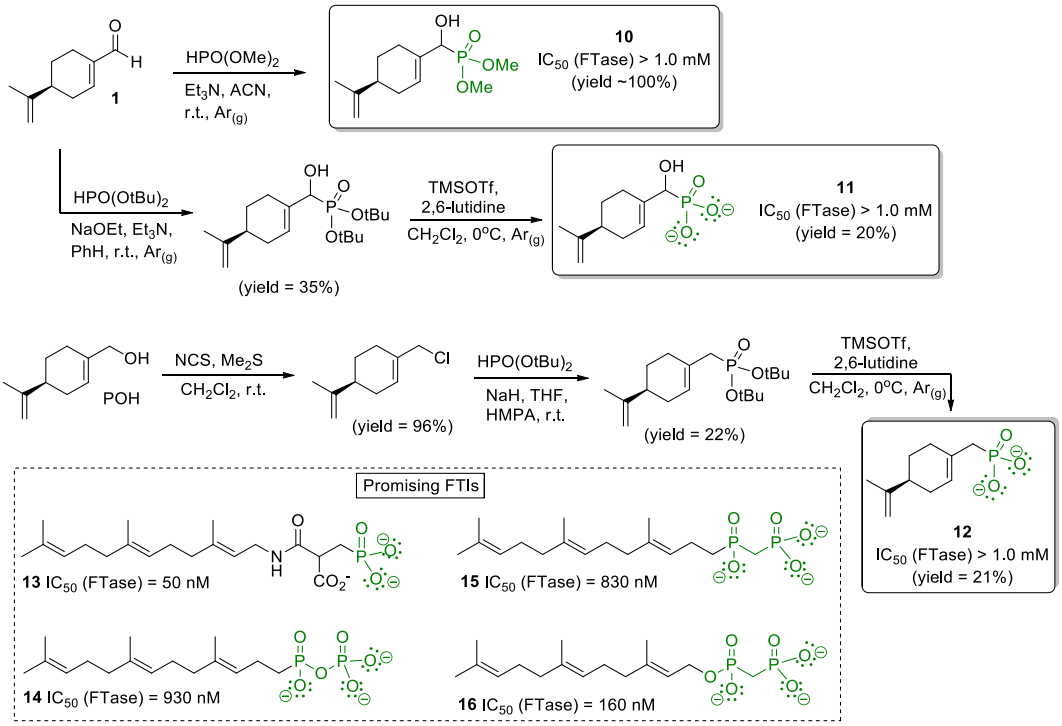
IC_{50} (μM)								
	A549	>1000	437.76	270.11	948.35	427.52	53.80	69.50
	A375-S2	>1000	309.61	359.23	501.32	463.80	53.80	72.77
	HT1080	>1000	556.38	426.01	>1000	409.16	56.17	69.37

Scheme 3 Selected examples of POH amino derivatives **8a-b** and **9a-d** and their in vitro antiproliferative activities against A549, A375-S2 and HT1080 cells [64]

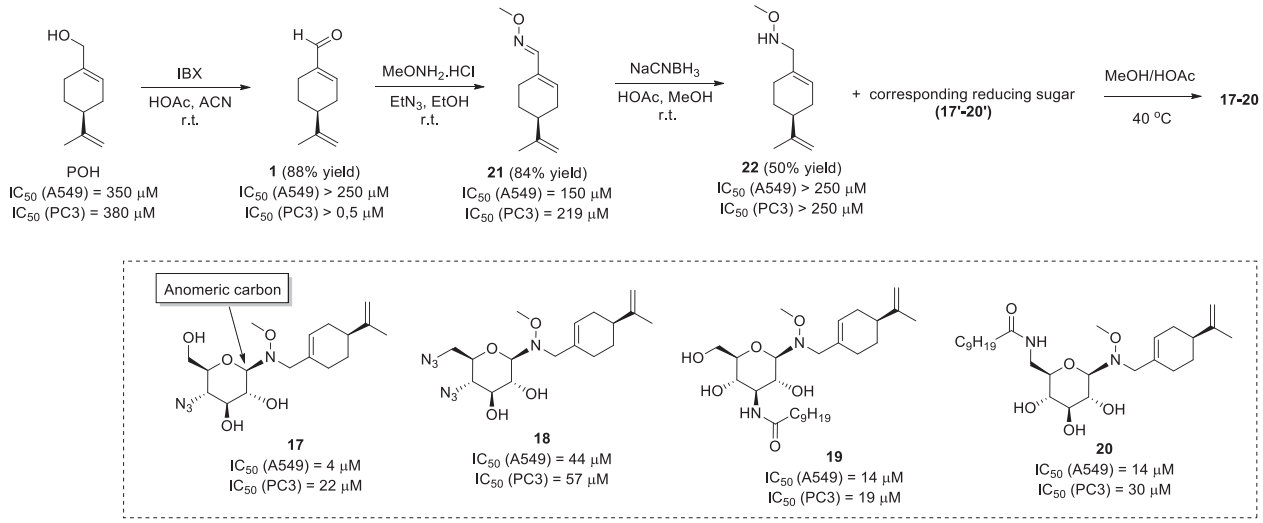
proliferative rate prioritize the exaggerated use of glucose for conversion and high levels secretion of lactate (aerobic glycolysis). The rapid consumption of glucose allows the feeding of several non-mitochondrial pathways of macromolecular synthesis that are often already active in response to oncogenic signaling [72, 73]. This phenomenon is known as Warburg Effect and can be explored as a viable pathway to produce novel selective chemotherapeutic agents for cancer treatment. So, the addition of carbohydrates to cytotoxic entities can furnish glycoside hybrids that have potentialized cytotoxicity through better solubility in a biological medium, increasing biodisponibility, and/or acting as a Trojan Horse, selectively luring the cytotoxic entity into the cancer cells using a masked fundamental survival component [72, 74, 75].

Based on the above-explained, carbohydrates role in cancer cells metabolism, Nandukar and coworkers synthesized thirty-four novel perillyl neoglycosides hybrids through a covalent bound at different (D)-(+)-glucose derivatives anomeric carbon [76]. In this review, we will focus on the four most promising ones **17**–**20** (Scheme 5). With an in vitro IC_{50} of 4 μM, hybrid **17** presented an improvement of 87.5-fold in cytotoxicity when compared to POH ($IC_{50} = 350$ μM) against lung cancer cell line (A549). And, with an in vitro IC_{50} of 19 μM, hybrid **19** presented an improvement of 20-fold in cytotoxicity when compared to POH ($IC_{50} = 380$ μM) against prostate cancer cell line (PC3). Western blot tests with **18** and **19** were able to point that phosphorylation inhibition of S6 ribosomal protein was the possible cause of cytotoxicity toward A549 cells. Moreover, SAR studies pointed that the azide (N_3) and *N*-acyl groups lipophilic character added to the hybrids played a key role in its promising cytotoxicity in the cancer cell lines. Moreover, the synthetic precursors oxime **21** and neo aglycon **22** also presented promising biological activity (Scheme 5). The synthetic procedure for obtainment of derivatives **17**–**20** involved the reaction between **22** with previously prepared corresponding reducing sugars **17'**–**20'** (Schemes 6–8) in methanol and acetic acid medium (Scheme 5).

In the same work, Nandukar and coworkers [76] further expanded the perillyl neoglycosides series by exploring the viability of a derivative containing a terminal azido **23** undergoing copper-catalyzed alkyne–azide cycloaddition (CuAAC) reaction (Scheme 9). The hybrid **23** was reacted with 4-pentin-1-ol **(24)** in a CuAAC reaction, furnishing the 1,2,3-triazolic derivative **25** in 82% yield. Albeit 1,2,3-triazolic nucleus have a well-established potential in medicinal chemistry [77–82] by producing derivatives with improved resistance against biological degradation, potentialized biological



Scheme 4 POH-based phosphonate derivatives **10**–**12** and their in vitro IC_{50} values for mammalian FTase inhibition. Promising FTIs **13**–**16** and their IC_{50} values for mammalian FTase inhibition are given inside the dotted rectangle [66]



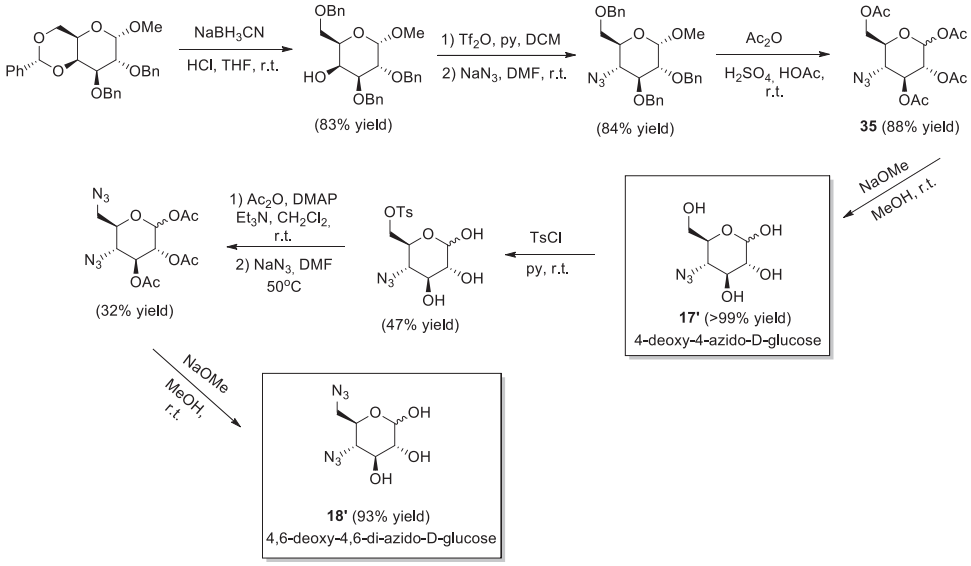
Scheme 5 Perillyl neoglycosides hybrids **17**–**20**, synthetic precursors **21**–**22** and their respective in vitro cytotoxicities against A549 and PC3 cells lines [76]

activities and under simple reactional conditions, its addition to **23** molecular structure did not show further improvements. In vitro cytotoxicity against A549 and PC3 cells decreased, as observed by the increase in IC_{50} values. The possible justification might lay in the introduction of two chemical entities capable of making intramolecular hydrogen bonds (triazolic ring and hydroxyl group) and also increasing the molecule overall polarity with strong dipole moments, leading to a less lipophilic compound. Thus, impairing cellular membrane diffusion and reducing transmembrane biodisponibility.

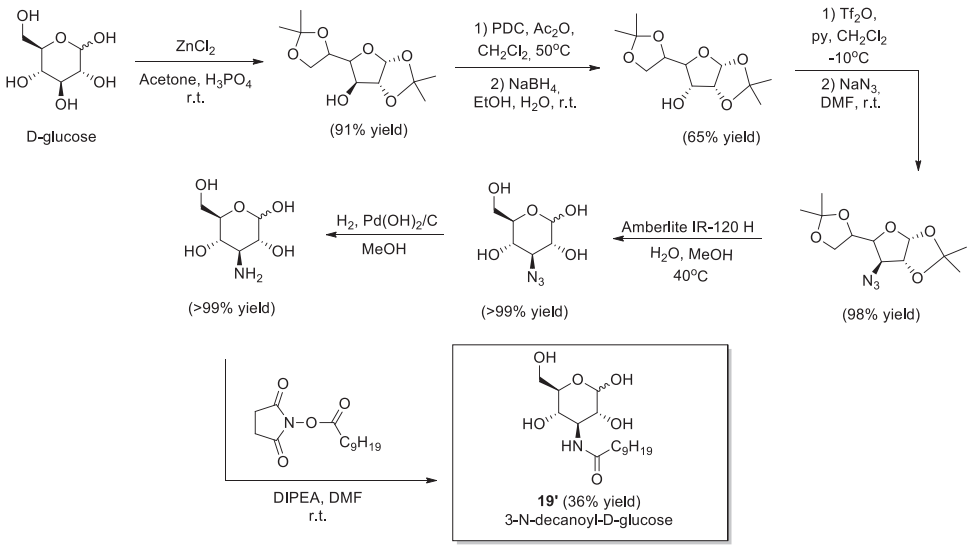
POH-dihydropyrimidinone hybrids

Recently, 1,2,3-triazole nucleus have been once more investigated with POH. However, used as a linker,

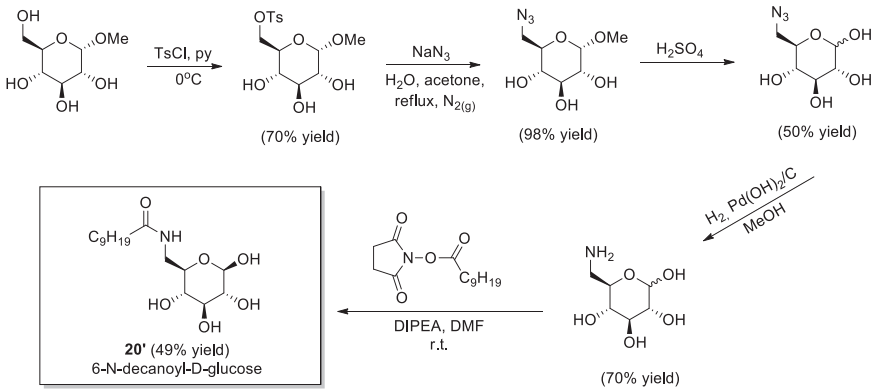
Scheme 6 Preparation of reducing sugars **17'** and **18'** [76]



Scheme 7 Preparation of reducing sugar **19'** [76]



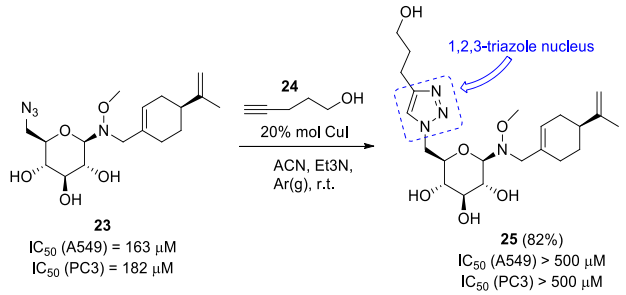
Scheme 8 Preparation of reducing sugar **20'** [76]



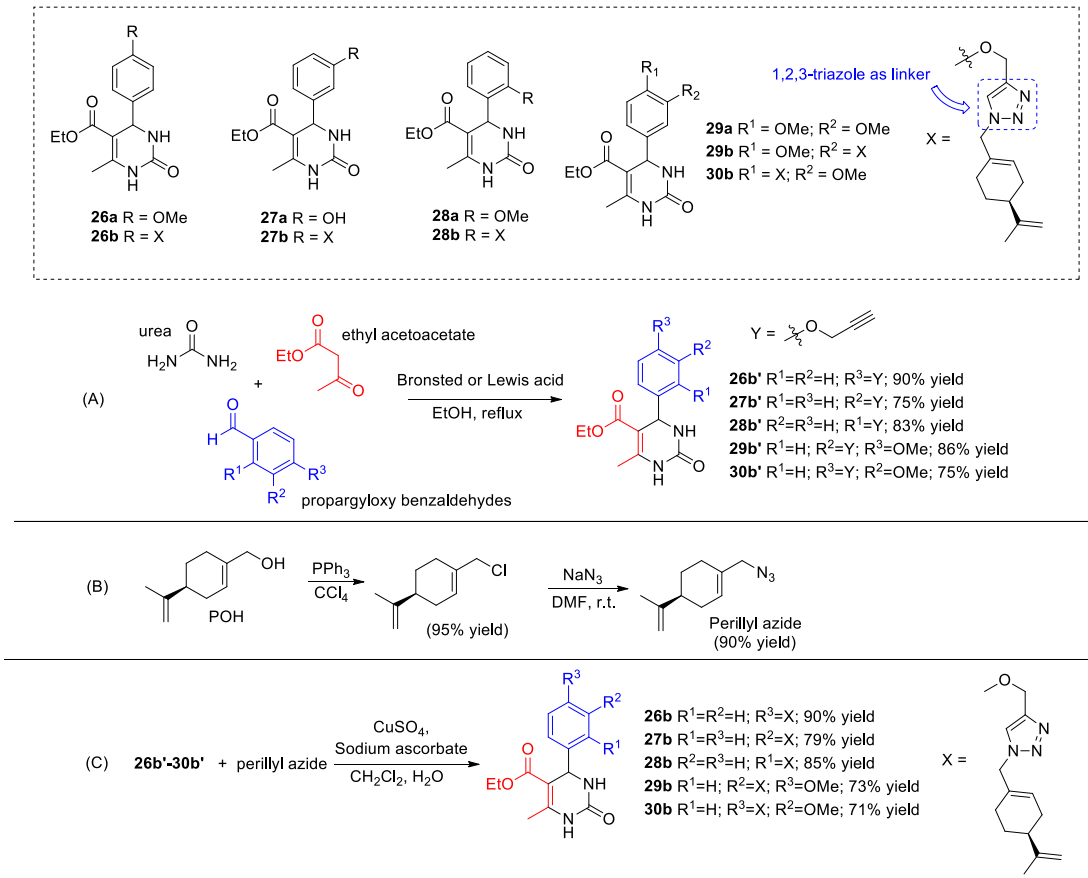
Vendrusculo and coworkers hybridized POH with different dihydropyrimidinones (DHPM) **26a**–**29a**, producing derivatives POH-DHPM **26b**–**30b** (Scheme 10) [83].

Compared to previous literature data [84], the biological assays pointed that incorporation of POH to DHPM molecular skeleton strongly enhanced their overall in vitro antiproliferative profile against melanoma (UACC-62), kidney (786-0), prostate (PC-3), multidrug-resistant breast (NCI/ADR-RES), colon (HT-29), breast (MCF-7) and ovarian (OVCAR-3) human cancer cell lines (Table 1). For example, **26a** presents almost no GI against MCF-7 cells, with only 2% at 861 µM against MCF-7 cells. However, after hybridization, corresponding derivative **26b** presented 100% GI at 43.14 µM. An increase of fifty times in antiproliferative activity together with a decrease of twenty times in the administrated dose to achieve total growth inhibition.

Interestingly, one of the hybrids **26b**, **27b** and **30b** most promising in vitro cytotoxicity were against glioma (U251) cell line, which might be attributed to POH presence. Otherwise, **28b** poor overall antiproliferative activity demonstrated that the spatial disposition (regioisomerism) of the hybridized chemical entities also plays an important role in cancer cell lines cytotoxicity. Moreover, POH and DHPM detain cytotoxic activity against *Plasmodium falciparium* [85, 86]. So, it would be interesting to investigate POH-DHPM hybrids potential antimalarial application.



Scheme 9 Perillyl neoglycosides hybrid **25** containing a 1,2,3-triazole nucleus synthesis strategy and antitumoral activities against A549 and PC3 cells lines [76]



Scheme 10 DHPM **26a**–**29a** and corresponding 1,2,3-triazole linked POH-DHPM hybrids **26b**–**30b** synthesized by Vendrusculo and coworkers. A Multi-component Bignelli reaction employed to obtain propargylated DHPMs **26b'**–**30b'**. B Preparation of perillyl azide intermediary. C CuAAC between **26b'**–**30b'** and perillyl azide furnishing POH-DHPM hybrids **26b**–**30b** [83]

Scheme 11 POH-TMZ hybrid, NEO212, synthesis procedure [88]

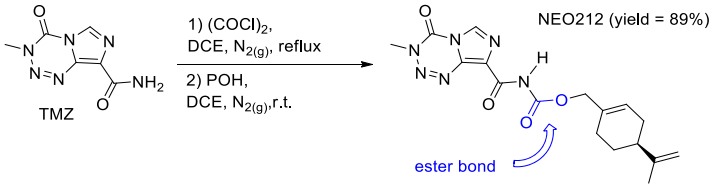


Table 1 In vitro GI of different cancer cell lines as a consequence of DHPM 26a–29a and corresponding PA-DHPM hybrids 26b–30b antiproliferative activity

Compound	GI (%) [dose (μM)][a]							
	UACC-62[b]	786-0[c]	PC-3[d]	NCI/ADR-RES[e]	HT-29[f]	MCF-7[g]	OVCAR-3[h]	U251[i]
26a[j]	67 [861]	30 [861]	17 [861]	30 [861]	30 [861]	2 [861]	24 [861]	n.c.[l]
26b[k]	100 [19.18]	100 [97.08]	100 [92.21]	100 [>100]	100 [77.13]	100 [43.14]	100 [6.90]	100 [12.43]
27a[j]	85 [905]	86 [905]	85 [905]	73 [905]	82 [905]	80 [905]	91 [905]	n.c.[l]
27b[k]	100 [22.92]	100 [39.67]	100 [>100]	100 [>100]	100 [73.42]	100 [42.52]	100 [18.45]	100 [12.19]
28a[j]	90 [861]	74 [861]	31 [861]	−2 [861]	89 [861]	72 [861]	−50 [861]	n.c.[l]
28b[k]	100 [>100]	100 [>100]	100 [>100]	100 [>100]	100 [>100]	100 [>100]	100 [81.19]	100 [>100]
29a[j]	57 [780]	16 [780]	30 [780]	16 [780]	8 [780]	27 [780]	22 [780]	n.c.[l]
29b[k]	100 [37.75]	100 [>100]	100 [>100]	100 [>100]	100 [>100]	100 [>100]	100 [13.45]	100 [98.09]
30b[k]	100 [26.73]	100 [87.34]	100 [54.39]	100 [>100]	100 [>100]	100 [82.50]	100 [53.76]	100 [11.34]

[a]In vitro assay values

[b]Human melanoma cell line

[c]Kidney cancer cell line

[d]Prostate cancer cell line

[e]Multidrug resistant breast cancer cell line

[f]Colon cancer cell line

[g]Breast cancer cell line

[h]Ovarian cancer cell line

[i]Human glioma cell line

[j]Reference [84]

[k]Reference [83]

[l]Not cited

POH-temozolomide hybrid (NEO212)

In vitro tests demonstrated that POH at a non-cytotoxic concentration of 1 mM was able to reduce the invasiveness of TMZ resistant glioma cells (U251TR) and sensitive TMZ glioma cells (U251) by almost 50%. Moreover, U251 cells showed approximately 50% survival rate in concentrations of 40 μM TMZ alone and approximately 10% survival rate in a mix of 40 μM TMZ with 0.6 mM POH, demonstrating POH potential as a chemosensitizing drug [87]. Based on those isolated drugs data, Chen (NeOnc CEO) and coworkers, at NeOnc Technologies GBM treatment research program comprising POH, managed to unite TMZ and POH through an ester covalent bound, creating NEO212 (Scheme 11) [88].

The biological assays (Table 2) showed that NEO212 was two times more potent than TMZ against sensitive TMZ glioma cells (U251 and LN229) and also presented cytotoxicity against TMZ resistant glioma cells (U251TR, LN229212 and TG98G) [89]. Moreover, comparative MTT assays with glioma cell lines (U87, A172 and U251) showed that at 200 μM NEO212 reduced glioma cells

Table 2 NEO212 and TMZ in vitro IC50 values against sensitive TMZ glioma cell lines (U251 and LN229) and resistant TMZ cell lines (U251TR, LN229TR and TG98G) [89]

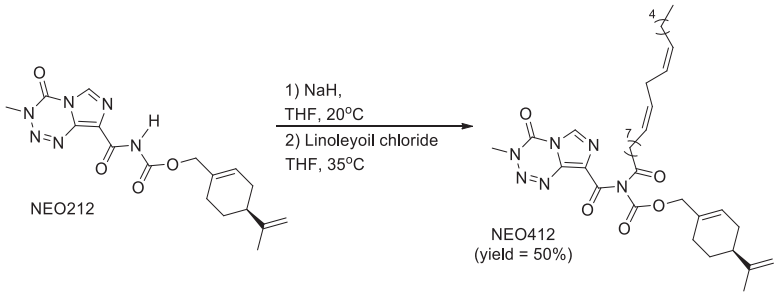
Compound	IC_{50} (μM)				
	U251[a]	LN229[a]	U251TR[b]	LN229TR2[b]	TG98G[b]
NEO212	8	5	40	45	50
TMZ	18	10	n.r.[c]	n.r.[c]	n.r.[c]

[a]Glioma TMZ sensitive cell lines

[b]Glioma TMZ resistant cell lines

[c]Not reached, IC_{50} was not observable in concentrations of 100 μM

Scheme 12 NEO212 structural modification synthetical procedure furnishing the linoleate hybrid derivative NEO412 for topical administration purposes [88]



survival rates below 20%, while TMZ alone didn't reach 60% at the same concentration [90]. NEO212 promising cytotoxicity for GBM treatment comes specifically from DNA alkylation of different TMZ resistant glioma cell lines, enhanced by ER stress and surpassing DNA repair enzyme *O*6-methylguanine DNA methyltransferase (MGMT) action that is responsible for TMZ resistance. Yet, in vivo studies on mice showed no abnormality or damage on normal tissues at an effective dose of 37.2 mg/kg and the hybrid was capable of crossing BBB, once it was subcutaneously administered [89]. Recent data also demonstrated that NEO212 great clinical potential in GBM treatment might also reside in its: **(i)** antiangiogenic capacity via Notch and TGF-β pathways regulation [91]; **(ii)** high selectivity for brain tumor tissues over normal ones followed by in situ hydrolysis products of NEO212 (TMZ and POH) that additively exerts different anti-tumoral mechanism, DNA alkylation for TMZ and ER stress for POH [92].

A further structural modification in NEO212 was done reacting it with sodium hydride (NaH) and then with linoleoyl chloride, furnishing the more lipophilic triple conjugated hybrid POH-TMZ-Linoleate (NEO412) in 50% yield (Scheme 12) [90]. Designed for transdermal application, NEO412 topical administration to treat melanoma in situ might allow a non-invasive and localized tumor treatment [93].

TMZ, NEO212 and NEO412 in vitro efficacies against MGMT negative (A2058) and positive (A375) human melanoma cell lines were verified and compared in the function of cell colonies control (Table 3). It was observed that in absence of MGMT enzyme, NEO212 colonies population control efficiency was twice of TMZ at 10 µM. And NEO412 reduced colonies to zero at the same concentration. TMZ and NEO212 didn't achieve such results before 25 µM. In presence of MGMT enzyme, both NEO212 and NEO412 achieved colonies population reduction to zero at 100 µM, while TMZ didn't go further than 50% colonies control even at 200 µM [88]. An in vivo essay pointed out that daily topic administration of NEO412 effectively controlled tumor growth in mice without damaging normal skin cells. The cytotoxicity was observed to be via DNA alkylation [93].

Table 3 In vitro cytotoxicity of TMZ, NEO212 and NEO412 in MGMT negative (A2058) and positive (A375) human melanoma cell lines survival rates [88]

Cell	Survival rate (%)		
	TMZ	NEO212	NEO412
A2058[a]	18	9	0
A375[b]	75	54	16

[a]Approximated values for a drug concentration of 10 µM and 48 h treatment

[b]Approximated values for a drug concentration of 50 µM and 48 h treatment

POH-dimethyl celecoxib hybrid

Based that POH is capable of potentializing brain tumor drugs chemotherapeutic potential through synergic ER stress, its mutual administration with Nelfinavir **(31)** and Dimethyl celecoxib (DMC), two ER stress-inducing drugs [94, 95], was investigated. It was found that, just as observed in the previously cited TMZ case, POH dramatically increased both drugs in vitro cytotoxicity against TMZ sensitive glioma cell line (U251) and TMZ resistant glioma cell line (U251TR) (Table 4) [87].

Those results encouraged the synthesis of POH-DMC hybrid **32**, where compounds were united by an ester bond (Scheme 13). Comparative in vitro assays involving different glioma cell lines (U87, A172 and U251) pointed that DMC alone reduced cell lines survival rate below 10% at 80 µM, while hybrid compound **32** could induce the same survival rate at a lower concentration of 40 µM [90].

POH-rolipram hybrid (NEO214)

Differently from NEO212 and **32**, the POH-Rolipram hybrid (NEO214, Scheme 14) was idealized to be a chimera drug [96]. Characterized as one hybrid compound

that is capable of acting in different diseases because it can exert cytotoxicity through different mechanisms. From POH, it should detain the ER stress potential. From Rolipram, it should detain the type IV phosphodiesterase inhibition potential, responsible for cell cycle arrest in glioma cells [97].

Due to drug resistance, multiple myeloma (MM) is still reported in many cases as an incurable disease [98]. But its reliance on ER signaling pathways to survive creates opportunities for the development of new chemotherapeutic agents that specifically target that MM Achilles heel, like POH-based derivatives [99]. In this scenario, four biological assays pointed out NEO214 as a promising multitarget antitumoral drug for clinical use in MM and glioma treatment.

Table 4 Mutual and isolated in vitro administration of POH/Nelfinavir and POH/DMC effects in different glioma cell lines survival rates [87]

Cell	Survival rate (%)[d]			
	DMC	DMC + POH	31	31 + POH
U251[a]	100	20	75	20
U251TR[b]	100	<5	100	20
U87[c]	80	10	n.t.[e]	n.t.[e]
U87TR[d]	70	<20	n.t.[e]	n.t.[e]

[a]Glioma TMZ sensitive cell lines survival rates with DMC (40 µM), **31** (30 µM) and POH (0.6 mM)

[b]Glioma TMZ resistant cell lines survival rates with DMC (40 µM), **31** (15 µM) and POH (1 mM)

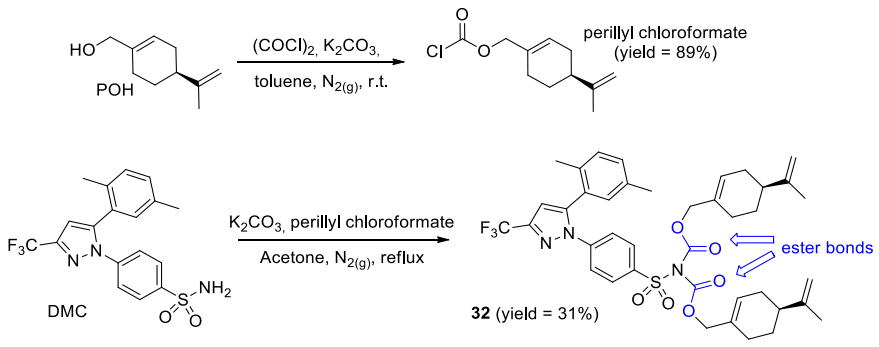
[c]Glioma TMZ sensitive cell lines survival rates with DMC (50 µM) and POH (0.6 mM)

[d]Glioma TMZ resistant cell lines survival rates with DMC (40 µM) and POH (1 mM). [d] approximated values

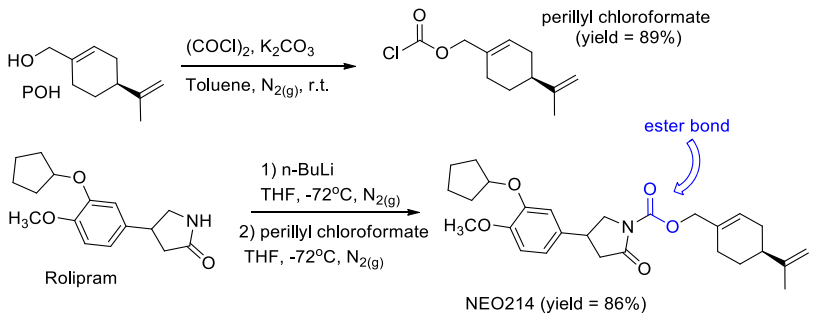
[e]Not tested

In the first one (Table 5), the in vitro IC_{50} values against six different human MM cell lines (U266, ARH-77, RPMI/8226, 8228/Dox40, H929 and Hs-Sultan) showed that "the whole was greater than the sum of the parts", with NEO214 being more cytotoxic than any of its isolated or mixture entities (Rolipram or POH) against all MM cell lines tested. Also, it was effective on 8228/Dox40 ($IC_{50} = 59$ µM), a multidrug-resistant strain where none of "the parts", isolated or combined, presented relevant cytotoxicity. Lastly, it showed no significant cytotoxicity in normal cell lines as Astrocytes and brain endothelial cells (BEC) presented $IC_{50} > 200$ µM and approximately halved overall cytotoxicity against immortalized human mammary gland epithelial cells (ME16C) with an IC_{50} of 118 µM, meaning that POH selectivity was carried over the hybridization process. NEO214 cytotoxicity against MM was derived from strong ER stress-inducing potential, capable of starting apoptotic process after 4 hours of exposition [96].

A second biological assay (Table 6) tested NEO214 cytotoxicity against TMZ sensitive glioma cell lines (A172, U87, U251 and LN229). The results pointed that, in comparison to Rolipram, NEO214 was approximately 17 times more potent against A172; 4.7 times more potent against U87; 14 times more potent against U251 and 9 times more potent against LN229 [100]. Hence being a promising chimera drug, just as planned.



Scheme 13 Preparation of hybrid compound POH-DMC **32** [100]



Scheme 14 POH-Rolipram hybrid (NEO214) synthesis with an ester bond uniting the compounds [100]

Table 5 Hybridized, isolated and mutual equimolar in vitro administration of POH/Rolipram IC50 values against many different human MM cell lines [96]

Cell	IC_{50} (μM)[a]			
	NEO214	POH	Rolipram	POH + Rolipram[h]
U266	56	>1000	>1000	606
ARH-77	52	>1000	>1000	783
RPMI/8226	50	>1000	551	482
8228/Dox40[b]	59	n.d.[g]	n.d.[g]	n.d.[g]
H929	50	>1000	578	486
Hs-Sultan	55	>1000	>1000	789
Astrocytes[c]	>200[f]	n.d.[g]	n.d.[g]	n.d.[g]
BEC[d]	>200[f]	n.d.[g]	n.d.[g]	n.d.[g]
ME16C[e]	118	n.d.[g]	n.d.[g]	n.d.[g]

[a]In vitro values corresponding to 48 h treatment

[b]Multidrug-resistant variant of RPMI/8226

[c]Human normal brain cells

[d]Human brain endothelial cells

[e]Immortalized human mammary gland epithelial cells

[f]Highest concentration tested and no cytotoxicity was found

[g]Not determined

[h]Equimolar concentration mixture

Table 6 Rolipram and NEO214 effects in different TMZ sensitive glioma cell lines in vitro survival rates after short exposure time [100]

Cell	Survival rate (%)[a]	
	Rolipram	NEO214
A172[a]	85	<5
U87[b]	70	15
U251[c]	70	<5
LN229[d]	90	10

[a]In vitro approximated values for 48 h exposure

[b]Rolipram (500 μM); NEO214 (500 μM)

[c]Rolipram (100 μM); NEO214 (100 μM)

[d]Rolipram (500 μM); NEO214 (500 μM)

[e]Rolipram (500 μM); NEO214 (500 μM)

A third biological assay (Table 7) confirmed that NEO214 was also effective in TMZ resistant glioma cell lines (T98G, U251TR and LN229TR), especially against LN229TR where none of its isolated or mixed parts (POH and Rolipram) were capable of effectively presenting cytotoxicity. The long-term in vitro studies also showed that NEO214 detains high stability. With a half life time of 48 h, it implies in reduced dose level administrations over long-term treatment. Those long-term in vitro results were also complemented by a fourth biological assay comprising an in vivo assay in mice where treatment with 50 mg/kg doses

Table 7 In vitro Rolipram, POH and NEO214 cytotoxic effects in different TMZ sensitive (U251) and resistant (T98G, U251TR, and LN229TR) glioma cell lines survival rates after long-term treatment [101]

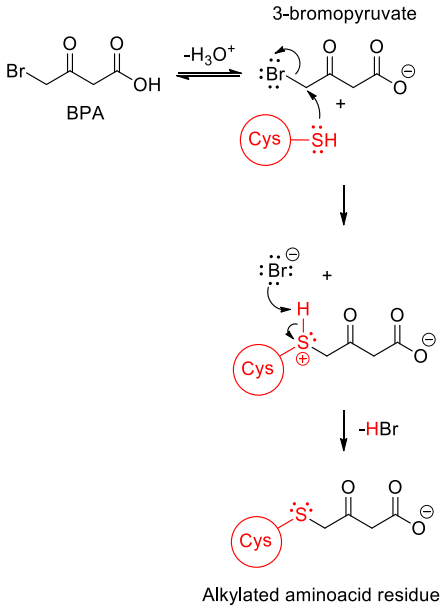
Cell	Survival rate (%)[a]			
	POH	Rolipram	Rolipram + POH[b]	NEO214
T98G[a]	85	64	73	0
U251[b]	78	86	86	0
U251TR[a]	92	72	72	0
LN229TR[a]	139	105	124	0

[a]Approximated values for 9–12 days treatment

[b]Equimolar mixture

[c]Compounds in vitro cytotoxicity given at 80 μM

[d]Compounds in vitro cytotoxicity given at 60 μM



Scheme 15 Alkylation of a cysteine residue (Cys) through a covalent bond between the nucleophilic thiol group with the electrophile BPA. Adapted from reference [102]

was capable of significatively reducing tumor growth, resulting in 52 days survival increase average compared to the control group. NEO214 cytotoxicity was once more verified to occur from apoptosis induction by ER [101].

POH-Bromopyruvic acid hybrid (NEO218)

Topic 5 presented the strategy involving cancer cells' metabolism and carbohydrates-based antitumoral derivatives to take advantage of the glycolytic energetic pathway. In the same fashion, 3-bromopyruvic acid (BPA) is an alkylating agent (Scheme 15) with promising specific antitumoral activity that resolves around shutting down

Table 8 NEO218 and BPA in vitro IC_{50} values in normal MCT1 levels (+MCT1) cells and down-regulated MCT1 levels (-MCT1) cells [112]

Cell[a]	IC_{50} (μM)[b]	
	BPA	NEO218
+MCT1		
HCT116[a]	20	17
U251[b]	50	23
ME16C[c]	57	27
MDA-MB-468[d]	43	17
-MCT1		
LN229[b]	151	28
T98G[b]	154	25
MCF7[d]	210	27
MDA-MB-231[d]	255	18
T47D[d]	291	18
BTM-12[e]	255	27
HCT116[g]	67	15

[a]Colon carcinoma cell line

[b]In vitro values corresponding to a 24 h treatment

[c]Normal breast epithelial cells line

[d]Breast cancer cell line

[e]Primary breast cancer cells

[f]Glioblastoma cell line

[g]Knocked down MCT1 expression colon carcinoma cell line

the survival strategy of cancer cells by inhibiting glycolytic pathway targets, like: glyceraldehyde-3-phosphate dehydrogenase (GAPDH), hexokinase 2, lactate dehydrogenase, succinate dehydrogenase, aldolase and pyruvate kinase [102–109]. An in vitro assay reported that BPA was capable of inducing rat C6 glioma cells to apoptosis via oxidative stress-energy depletion and an in vivo assay revelated that BPA significantly reduced C6 glioma cells growth and migration in Sprague-Dawley rats [110]. Another fundamental in vitro assay pointed out that a 100 μM dose of BPA totally reduced cell viability of human chemoresistant and radioresistant GBM U373MG cell line within 24 h [111].

The chimera compound NEO218 was able to enter tumor cells independently of MCT1 transportation, as observed by the high cytotoxicity perpetuated in different down-regulated MCT1 (-MCT1) cancer cell lines. Different from BPA, which presented an average 3-to-5-fold increase in in vitro IC_{50} values compared to the ones in normal MCT1 levels (+MCT1) cells (Table 8). Additional data about MCT1 independence was obtained treating an MCT1 expression suppressed colon carcinoma cell line HCT116 with BPA and NEO218. While NEO218 retained its potency ($IC_{50} = 17\mu M$ in +MCT1; $IC_{50} = 15$ μM in -MCT1), BPA presented an over three folded increased IC_{50} value ($IC_{50} = 20$ μM in +MCT1; $IC_{50} = 67$ μM in -MCT1).

Table 9 Different NEO218, BPA, POH and BPA + POH administrations concentrations in vitro cytotoxic effects comparison in down-regulated MCT1 levels MDA-MB-231 breast cancer cells line [112]

Concentration (μM)	MDA-MB-231 Cell Viability (%)[a]			
	NEO218	BPA	POH	BPA + POH[b]
70	0	95	100	95
80	n.r.[c]	88	>100	83
160	n.r.[c]	75	100	62
320	n.r.[c]	25	87	20

[a]MTT assay performed after 24 h of exposition

[b]equimolar concentration mixture

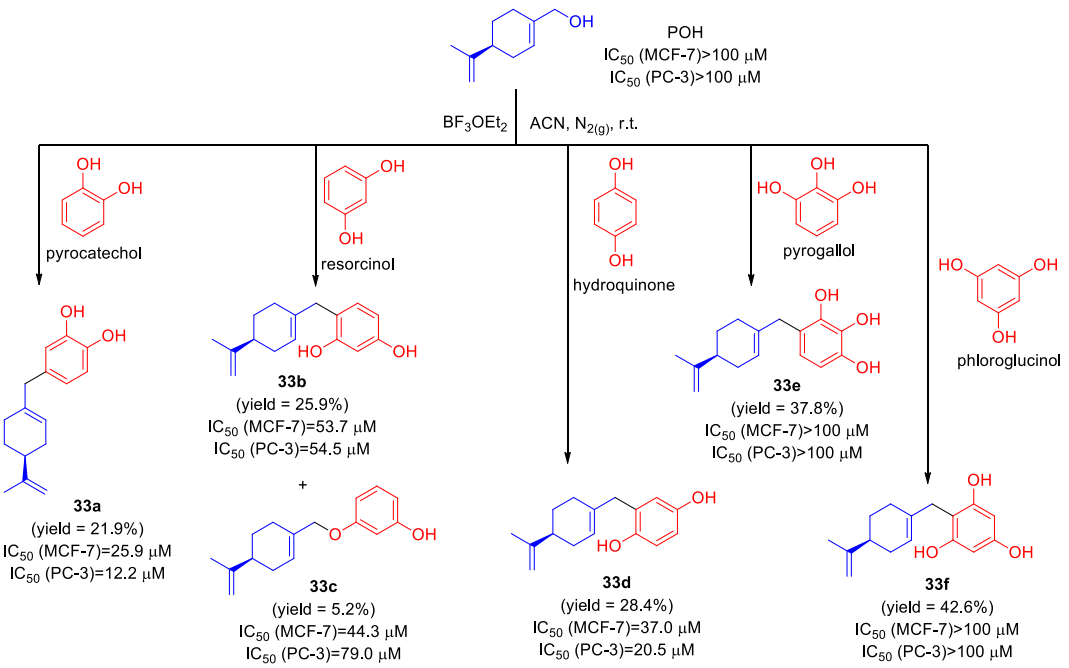
[c]*n.r.* not reported

A viable justification might reside in a NEO218 cell interaction mechanism through an independent lipid bilayer diffusion affeered by the intrinsic lipophilic characteristics derived from POH, once that in vitro mutual administration of POH and BPA showed little to no difference from BPA isolated administration in MDA-MB-231, a down-regulated MCT1 cancer cell line (Table 9). Lastly, NEO218 antitumoral activity was verified to occur via the retained BPA tumor cells energy depletion through GAPDH cysteine residues alkylation (Scheme 15), where total GADPH activity inhibition was achieved at a 100 μ μM dose for both NEO218 and BPA [112].

POH-Aryl hybrids

Meroterpenes are natural compounds formed by quinones, or hydroquinones, conjugated with terpenes fragments, resulting in a vast diversity of molecular frames. Originated by a complex mix of biosynthetic pathways, they can be found in marine organisms like algae and sponges. Together with their cytotoxicity through ROS production, the variated biological activities (antitumoral, antiproliferative, antimicrobial, antileukemic, anti-malarial, immunomodulatory and anti-HIV) attract medicinal chemistry researchers interest [113, 114]. Based on that, Said and coworkers synthesized six POH-Aryl hybrids **33a-f** (Scheme 16) via a single step Friedel-Crafts direct alkylation [115]. Pyrocatechol, resorcinol, hydroquinone, pyrogallol and phloroglucinol were reacted with POH, using boron trifluoride diethyl etherate (BF_3OEt_2) as a catalyst, furnishing the respective products **33a-f** in yields of 5.2–42.6%. Hybrid **33c** was obtained as a byproduct through retro Friedel-Crafts reaction, hence the lower yield of 5.2%.

In vitro essays presented promising antiproliferative activity against breast cancer cell line MCF-7 and prostate cancer cell line PC-3. Hybrids **33a** and **33d** presented lower IC_{50} values (12.2 μM and 20.5 μM, respectively) for PC-3

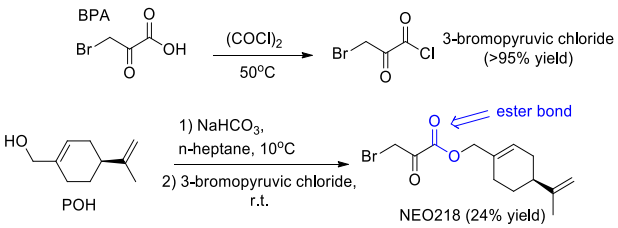


Scheme 16 Synthesis of POH-Aryl hybrids **33a-f** and their respective in vitro antitumoral activities against breast cancer cells (MCF-7) and prostate cancer cells (PC-3) [117]

than the control drug dunnione (IC_{50} of 14.56 μM and 26.51 μM for MCF-7 and PC-3, respectively) used for the in vitro antiproliferative effect essays. Daunorubicin with an IC_{50} of 0.21 μM and 0.39 μM for MCF-7 and PC-3, respectively, was also used as a control drug [115].

The results indicating higher IC_{50} values for the trisubstituted hybrids **33e-f**, were according to literature data where the arrangement of hydroxyl groups plays a greater role in biological activity than its number, especially when an intramolecular hydrogen bond can contribute to lower the bond dissociation enthalpy and increase the compound overall free radical scavenging potential [116, 117]. Justifying the lower IC_{50} values presented by **33a**. Compounds **33a-c** cytotoxicities were observed to proceed via up-regulation of caspase activity, which led to a mitochondrial membrane permeability loss and consequently produced a pro-apoptotic condition. Confirming the ROS cytotoxicity pathway found in meroterpenes. Compound **33d** was not identified as a pro-apoptotic condition inductor to cancer cells, hence its antitumoral activity mechanism needs further investigation.

Interestingly, just as POH, BPA can be inhaled to achieve better bioavailability [105]. However, the limitation of BPA activity in cancer treatment lies in its dependence on monocarboxylate transporter 1 (MCT1), a transmembrane transport protein, as some cancer cell lines might express down-regulated MCT1 levels [106, 111, 118, 119]. Based on those points, Chen and coworkers hybridized POH and BPA through an ester bond synthesizing NEO218 (Scheme 17) [120].



Scheme 17 POH-BPA hybrid compound NEO218 [120]

Conclusion

The growing impact of POH in medicinal chemistry slowly unveils its potential as a versatile scaffold for novel drugs development. The natural occurrence monoterpene had demonstrated promising effectivity in polychemotherapeutic approaches as a chemosensitizing agent, opening opportunities for more friendly chemotherapeutic treatments with reduced drugs administered doses. Also, outstanding results have been reported after molecular hybridization, expanding chemotherapy frontiers with promising quality potential drugs, especially for the challenging GBM treatment. Moreover, the new promising multitarget POH derivative drugs might allow administration protocols that are not limited to inhalation for GBM treatment, like topical administration for MM treatment. Lastly, it is notable that polarity sensibility, solubility and regioisomerism (when applicable) play a key role in overall hybrids cytotoxicity, making POH a challenging, but rewarding, lead compound for synthetic medicinal chemistry.

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Compliance with ethical standards

Conflict of interest NEO212, NEO412, POH-DMC, NEO214, and NEO218 are under patent protection for NEONC TECHNOLOGIES, INC., Los Angeles, CA (US), which were properly cited.

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