Bachelor's project

NTNU
Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

Robin Verkerk

KJ2900 Bachelor Project in Chemistry

The anti-cancer potential of sulfoquinovosyl-derivatives from marine sources

Bachelor's project in Natural Science with Teacher Education

Supervisor: Nebojsa Simic

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Summary

Cancer is among the deadliest diseases known to man. What makes cancer more challenging to treat than other diseases is the fact that it, by its very nature, undergoes rapid and frequent mutations, making every case – to greater or lesser extent – unique. As a result, treatment that may prove effective in one patient may not be as effective in other patients. Cancer may also develop in virtually any part of the human body, often rendering surgical options infeasible. Consequently, it is desirable to have as many different available treatments as possible, not only in order to have contingencies should a specific treatment prove ineffective, but also in order to treat cancer more efficiently by using various treatments in conjunction with one another. Many anti-cancer drugs have been derived or extracted from natural sources, and nature remains a field of focus for finding new cytotoxic drugs or inhibitors that can help in the fight against cancer. Recently a group of sulfoquinovosyl-derivatives from marine sources have been found to have anti-cancer properties in a number of ways, and could potentially make effective new anti-cancer drugs [1].

Content

Introduction

This bachelor will concern a group of sulfoquinovosyl-derivatives that have been found to have anti-cancer properties. These compounds either have been, or could potentially be, extracted from marine sources such as algae.

Firstly, I will elaborate on the working mechanisms behind cancer generally in the theory section of this paper. Without going too deeply in the complex details of cancer I will attempt to lay out the essentials in layman's terms where possible, and introduce the required nomenclature and terminology where necessary about what sulfoquinovosyl-derivatives actually are. In the discussion part I will move on to how the sulfoquinovosyl-derivatives have been found to inhibit cancer, and by what means they may be extracted and/or synthesized. Whether extraction from natural sources or a pure chemical synthesis is more feasible in terms of yield, cost-effectiveness etc. is however beyond the scope of this project. Lastly, I will make a conclusion based on the aforementioned research on whether sulfoquinovosyl-derivatives present a promising new avenue that warrants further research.

Theory

Cancer and how it works

Common for all cancers is the uncontrolled proliferation of cells, in the form of tumours or other growths, called neoplasms. It is important to note, however, that while tumours are ostensibly similar as symptoms, there exist more than one kind that may appear, and not all tumours are considered cancerous. Here the distinction is drawn between malignant and benign tumours: Malignant tumours are considered cancerous and will spread to other parts of the body in time – this process is called metastasis [2]. They often grow rapidly and also invade surrounding tissue, readily crossing across tissue boundaries. Benign tumours are considered non-cancerous in the sense that they will not spread to other areas of the body and usually have clear boundaries. They can however still grow to large sizes and can be life-threatening if pressing against surrounding tissue or organs. Benign tumours are not always dangerous and subsequently don't require treatment. In the cases where they do, they can fortunately often be removed surgically if the need arises, given that the location of the tumour is accessible. This procedure is rarely successful with malignant tumours unless the cancer is detected early, as the cancer will often have started to metastasize. At this point the cancer will often resurface even after removal of existing tumours.

At the very root of all cell division, including the growth of neoplasms, is the replication of DNA from a parent cell [3]. This is done by a class of enzymes known as DNA polymerase, which thus form a particular point of interest in the pursuit of anti-cancer treatment. An elaborate walkthrough of DNA polymerase would warrant a thesis of its own and goes beyond the scope of our goal here. It suffices to say that inhibiting polymerase around neoplastic sites would reduce the replication of the DNA of the neoplasm(s) and prevent further growth. The obvious challenge in this particular avenue is how one would, if it is possible at all, direct inhibition towards damaged DNA exclusively without affecting surrounding, healthy tissue.

Closely related to the DNA replication process are telomeres. While not part of the "functional" DNA code itself, telomeres can be viewed as protecting "caps" that are added to the ends of DNA strands. This is because parent DNA strands are not replicated in their entirety; the daughter strand loses some of the parent's telomeres. When this daughter strand eventually would be replicated, its resulting daughter strand would be even shorter, and eventually, some generations later, the DNA itself would start to be affected. Cue telomerase, an enzyme that adds telomeres to DNA strands and thus protects succeeding generations of DNA. It has been

found that cancer cells rely heavily on telomerase to maintain their proliferative capacity, and by inhibiting telomerase the cancer would by virtue of its own hyperproliferation eliminate itself. Furthermore, the risk to healthy tissue by telomerase inhibition are thought to be relatively low. This is partly due to that telomeres on regular cells and that of cancer cells are of comparable length, so the cancer cells will be affected by telomerase inhibition much faster [4], as well as the fact that most cells in the human body don't express telomerase activity at all and are mostly limited to certain stem cells, and cancer cells [5].

Treating cancer is in and of itself a colossal challenge, and treating it without affecting surrounding tissue is an even greater one, because the ways in which cancer may be treated usually also affect regular cells. In normal, healthy tissue, there is a carefully maintained balance between cell growth, proliferation, and death in multi-celled organisms. This controlled cell death is called apoptosis and occurs naturally in organisms to ensure cells don't proliferate out of control, as is the case with cancer. In the case of tumour growth however, apoptosis is not always able to sufficiently retard the cell proliferation. Many cancer treatments therefor aim to increase the rate of apoptosis in tumours, and thusly eliminate the growth [6]. However, increasing apoptosis sufficiently to retard tumour growth would affect healthy tissue much more severely – underlining the need for treatments that specifically target cancer while sparing surrounding tissue.

Stimulating apoptosis is a way to inhibit tumour growth directly, but other approaches are also available. Malignant tumours are characterized by rapid, uncontrolled growth, which demands great amounts of energy. This is supplied by an every-expanding network of blood vessels in the tumour, providing oxygen to facilitate growth. The process by which these blood vessels form, is called cancer angiogenesis. Angiogenesis also occurs normally in healthy tissue, where new vessels form from pre-existing ones through "branching" from a mother-vessel. In malignant tumours, however, new vessels are formed drastically faster, allowing at times dramatic tumour growth [7]. Cancer angiogenesis produces vessels that share many traits with the tumour it sustains; they are often deformed and grow rapidly across tissue borders. By targeting angiogenesis, the basis of growth would be removed, without having to combat the tumour itself by for instance apoptosis.

What are sulfoquinovosyl derivatives?

Sulfoquinovosylacylglycerols (**1**) are a group of sulfolipids consisting of 3 main components: Sulfoquinovose (**2**) and glycerol (**3**) are found in most derivatives, see figure 1. The third component(s) are substituents on the remaining hydroxyl group of the glycerol moiety. For the sulfoquinovosyl derivatives we concern ourselves with, these are usually a fatty acid group of some kind, though in some cases the hydroxyl group remains unaltered or is even removed. Depending on whether the sulfoquinovosylacylglycerol has 1 or 2 fatty acid substituents, it is referred to as a sulfoquinovosylmonoacylglycerol (SQMC) or sulfoquinovosyldiacylglycerol (SQDG), respectively.

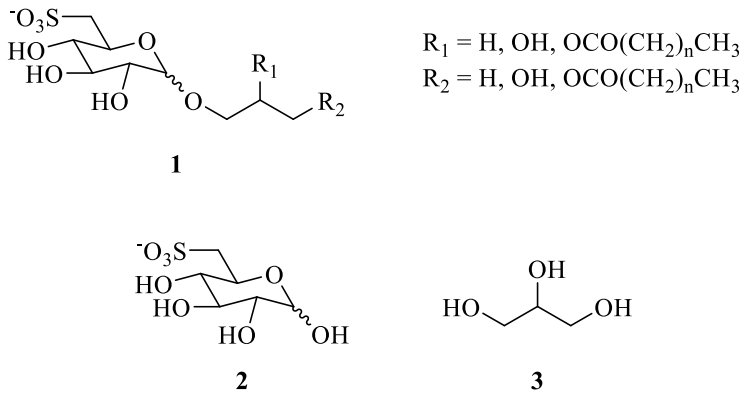


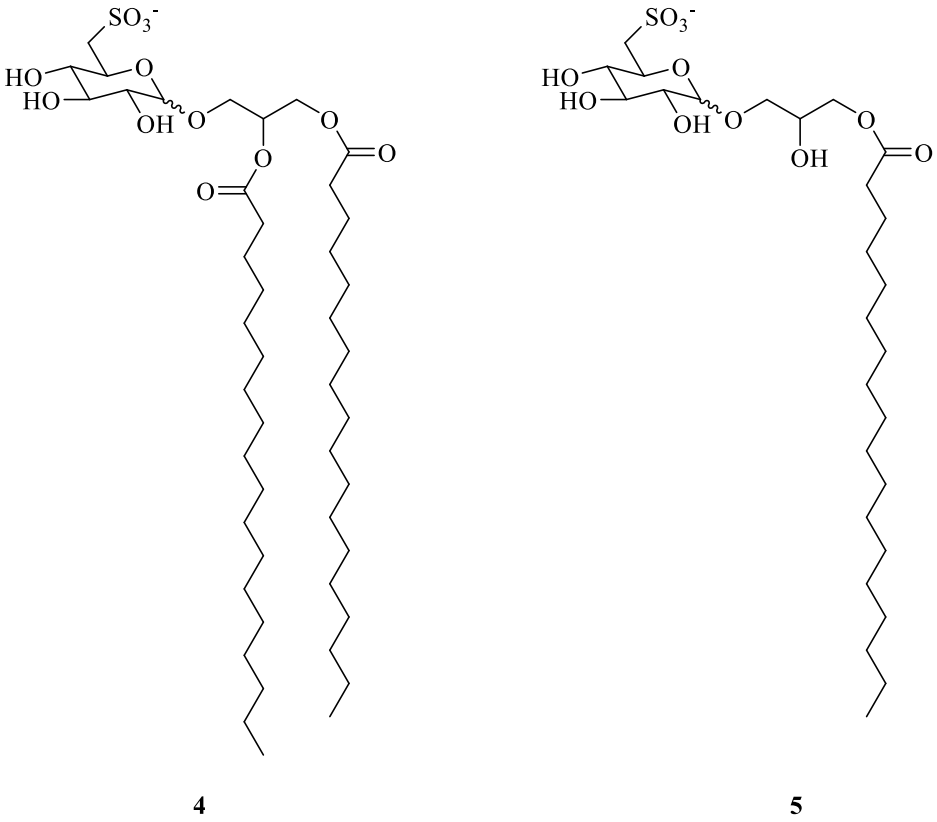
Figure 1: (**1**) illustrates the general structure of sulfoquinovosylacylglycerols, depending on the substituents R_1 and R_2 on the glycerol (**3**) moiety. Common for all derivatives are the presence of a sulfoquinovose (**2**) and glycerol (**3**) moiety.

Many of the processes just described, with the exception of apoptosis, represent biological processes that are desired reduced in the treatment of cancer. To assess the effectiveness of sulfoquinovosyl derivatives to inhibit the various processes enabling neoplastic growth, it is useful to introduce a way of measuring this. A common measure of a substance's ability to inhibit a given biological process is the half maximal inhibitory concentration, or IC_{50}, defined as the required concentration of the substance required to inhibit the process in question by 50%. The lower the IC_{50} value is, the more efficient the substance. In order to have an effective cancer drug, it is desirable to have a low IC_{50} value so as to make treatment effective while affordable for widescale production and use, but it should also be kept in mind that particularly effective agents that also target surrounding, healthy cells could present health risks of their own. With our foundation in place, it is high time to discuss the sulfoquinovosyl compounds and their anti-cancer properties.

Discussion

How sulfoquinovosyl derivatives can inhibit cancer

Sulfoquinovosyl's derivatives have been found to inhibit DNA polymerase significantly. The class of sulfo-glycolipids known as sulfoquinovosyl diacylglycerol (SQDG) is of particular interest here, as their properties as DNA polymerase inhibitors are well documented [8] [9] [10]. One of these compounds is 1,2-di-*O*-acyl-3-*O*-(α-D-sulfoquinovosyl)-glyceride with two stearic acid molecules, hereafter referred to as α-SQDG-$C_{18:0}$ (**4**), see figure 2. α-SQDG-$C_{18:0}$ (**4**) proved to be an effective inhibitor of mammalian DNA polymerase *in vitro* by Murakami *et al.* [8], but *in vivo* tests of its effectiveness against human stomach cancer cells (NUGC-3) demonstrated no effectiveness. A derivative however, 2-mono-*O*-acyl-3-*O*-(α-D-sulfoquinovosyl)-glyceride, α-SQMG-$C_{18:0}$ (**5**) for short (see figure 2), demonstrated efficient inhibition, and was also found to be a potent apoptosis inducer. The differences of effectiveness *in vivo* is believed to be due that α-SQDG-$C_{18:0}$ (**4**) was not cell permeable, whereas α-SQMG-$C_{18:0}$ (**5**) was [8].



4 **5**

Figure 2: (1,2-di-O-acyl-3-O-(α-D-sulfoquinovsyl)-glyceride with two stearic acids and (2-mono-O-acyl-3-O-(α-D-sulfoquinovsyl)-glyceride with stearic acid, or α-SQDG-$C_{18:0}$ (**4**) and α-SQMG-$C_{18:0}$ (**5**) respectively, for short.

α-SQMG-$C_{18:0}$ (**5**) has also been found to have effect against cancer angiogenesis. A problem often encountered with angiogenesis inhibitors is that they often cause undesirable side effects and are only effective in combination with radiotherapy. α-SQMG (**5**) however shows great effect in small dosages in combination with ionizing radiation, as shown in a study by Sakimoto *et al.* [11]. Multiple α-SQMG's, including α-SQMG-$C_{18:0}$ (**5**), were tested *in vitro*, and the latter was reported to inhibit capillary formation in bovine aortic endothelial cells grown on Matrigel at a concentration of 40 μM. The inhibitory effects of α-SQMG-$C_{18:0}$ (**5**) were further tested *in vivo* both with and without radiation present, and showed significant effect in combination with radiation on human umbilical vein endothelial cells grown on Matrigel. Neither α-SQMG-$C_{18:0}$ (**5**) nor radiation showed effect separately.

Similar results regarding angiogenesis inhibition have been found for Sulfoquinovosylacylpropanediol, or SQAP (**6**), see figure 3, as shown by Sawada *et al.* [12]. Their study involved the human prostate cancer cells DU145 and PC3, which were cultivated in athymic nude mice and subsequently extracted and treated with a combination of SQAP (**6**) and X-ray radiation. While SQAP (**6**) in combination with X-ray irradiation resulted in retardation of tumour growth from DU145 cells, SQAP (**6**) did not appear to have significant effect on tumours originating from the PC3 cells. Similar to α-SQMG-C_{18} (**5**), SQAP (**6**) showed no significant activity without accompanying X-ray radiation either. Another study on the antiangiogenetic properties of SQAP (**6**) performed by Iwamoto *et al*. [13] showed similar results, and proposed SQAP (**6**) as a possible candidate to induce angiogenic switch-off in hepatocellular carcinoma, a common type of liver cancer.

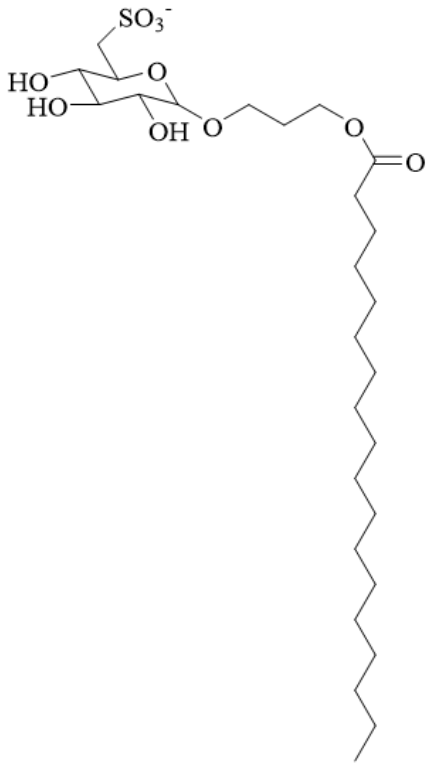


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Figure 3: Sulfoquinovosylacylpropanediol, or SQAP (**6**).

Another set of SDQG's, (**7.1-7.4**), seen in figure 4, were found to have considerable inhibitory effects on telomerase. The differences between these and α-SQDG-$C_{18:0}$ (**4**) are the length of their fatty acid chains and degree of saturation. These SDQG's were extracted from the

cyanobacteria *Microcystis aeruginosa* PCC 7806, and their inhibitory effects on telomerase were tested with Telospot assay in a study by Makhlouf Brahmi *et al.* [14]. However, the extracted mix of SQDG's proved to be inseparable due to entanglement of the fatty acid chains and overall similar properties of the molecules that complicated separation. In order to study the effectiveness of one of them, SQDG **7.2**, in better detail, it was chemically synthesized and studied separately, and an IC_{50} value of 17 μM was determined. A monoacylated derivative (**7.5**) of SQDG (**7.2**) was also synthesized, with a determined IC_{50} value of 40 μM. SAR studies were performed on these molecules by varying the fatty acid chains and observing inhibitory effects of the various derivatives, the most efficient one being (**7.6**) with an IC_{50} value of 11 μM, the lowest of the study. The general trend appeared to be that inhibition efficiency increases with fatty acid chain length ($C \geq 9$) as well as the introduction of lipophilic and bulky substituents. Whether a monoacylated analogue of (**7.6**) would be more effective still *in vivo*, as was the case with the study by Murakami *et al.* [8] is not known however, as its corresponding SQMG was not synthesized in this study.

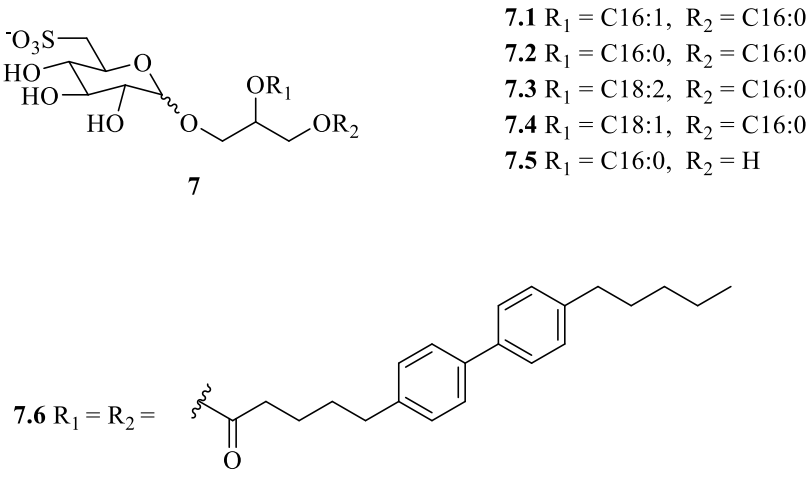


Figure 4: The SQDG's extracted and/or synthesized by Makhlouf Brahmi *et al*. [14]. The various substituents R = C*n*:*m* represent fatty acids with carbon chains of length *n* and degree of unsaturation *m*.

Other uses

While the anti-cancer properties of sulfoquinovosyl derivatives are cause for optimism, it should not be overlooked that these compounds have additional potential in the medicinal field as well. SQDG's have for instance been found to have some antiprotozoal effect [15]. Protozoa are a type of parasites, most of which cause a number of diseases in humans as well as animals [16], and have also shown effect against viral afflictions such as herpes [17] and even HIV [18]. Incidentally, protozoa are cause of infections that are particularly dangerous to immunosuppressed people [19]. Some may find it ironic then, that *β*-SQDG-$C_{18:0}$ (**4**) has shown

potential as an immunosuppressive drug. In addition to high effect it has low toxicity, an attractive combination slightly undermined by its low solubility in water, which presents a challenge in regards to medicinal application [20].

SQDG's have been shown to have uses outside the realm of cancer as potential medicine for a small host of other ailments, but their usefulness doesn't end there either. SQDG's might also serve as molecular adjuvants for vaccines as shown by Menzo *et al*. [21] [22]. A common present-day problem with vaccines is that they commonly utilize very pure synthetic macromolecules that, while safer, do not trigger the same response more traditional vaccines comprised of attenuated/inactivated biological molecules would. Therefor they need to be combined with adjuvants, compounds that enhance the immune response [21].

Sulfoquinovosyl derivatives, and particularly SQDG's and SQMG's appear to be promising avenues for producing new anti-cancer drugs. A clear advantage about these compounds is that they show anti-cancer activity through several pathways, having the potential to be a very versatile source of drugs. Additionally these compounds have shown to have beneficiary effects in other fields of medicine as well, such as vaccine adjuvants and potential drugs against other conditions. It is not the question then whether or not sulfoquinovosyl-derivatives have potential in medicine, but rather whether this potential can be utilized. One significant hurdle to overcome will be the feasibility of production, which brings us to our next point of discussion: synthesis

Extraction/Synthesis

In the early days of researching the anti-cancer properties of compounds from marine sources, it was usual to extract and purify these directly, and ways to extract sulfoglycolipids from various marine sources have been known for some time. For instance, Sahara *et al.* [23] used the following procedure to isolate SQMG's from the intestine of *Strongylocentrotus intermedius*, a sea urchin. Here, the intestines were immersed in acetone and dried. The sulfoglycolipids were extracted with a mixture of chloroform-methanol-water (CMW) with ratio 4:8:3 three times, and the extracts evaporated to dryness in vacuo. The crude product was then dissolved in CMW, 30:60:8 and separated with column chromatography [23].

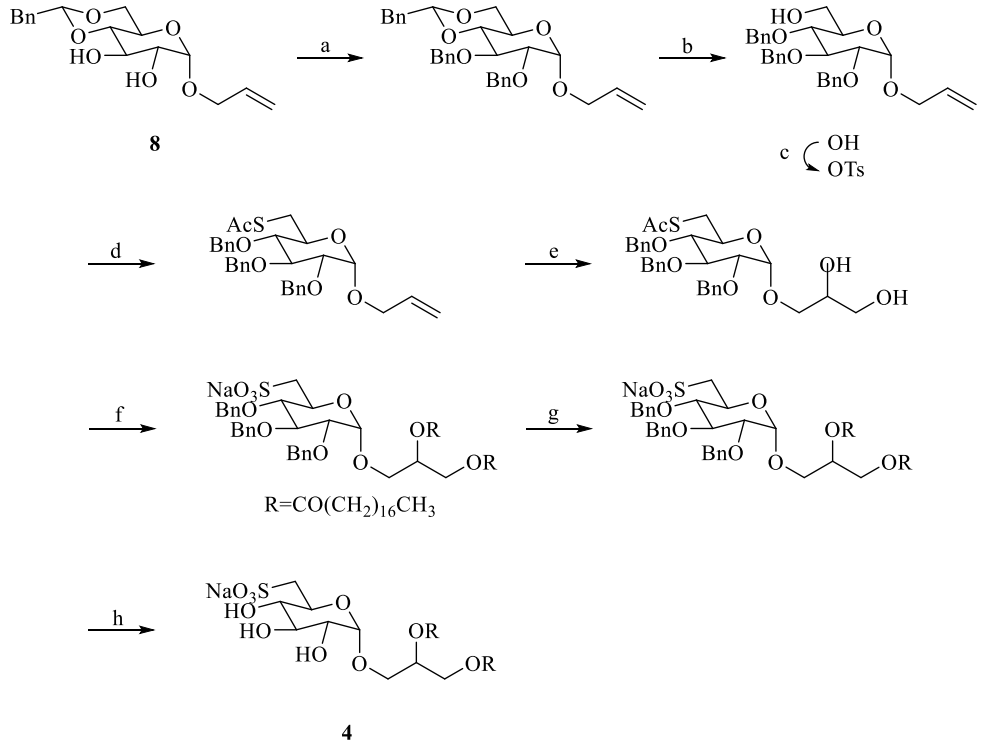
Makhlouf Brahmi *et al*. [14] also extracted a number of compounds from a variety of cyanobacteria in their study of telomerase inhibition. They cultured the different strains for 4 months, and harvested biomass via centrifugation. The products were extracted with MeOH (70 %) in an ultrasonic bath, and the extracts separated from the biomass again by means of

centrifugation, followed by evaporation on rotary evaporator. The dry extracts were dissolved in MeOH (70 %), filtered and prepared for the assay. In principle, the method of producing sulfoquinovosyl derivatives from their natural (marine) sources is simple; produce an extract and separate its components. Reality however is never simple, and a common issue is that the extracts often contain similar, but different, compounds of comparable size, molecular weight, polarity etc. that are difficult to separate. It is possible, as demonstrated by Sahara *et al*. [23], where they separated compounds by repeated column chromatography, but often tedious and time-consuming, and Sahara *et al*. [24] were among several who turned to chemical synthesis to produce compounds for further research.

Samples prepared from their natural sources have proven sufficient to determine that anti-cancer properties *exist* in sulfoquinovosyl derivatives, but the problem here is that (among others) SQDG's from their natural sources are difficult to separate from each other due to their highly similar characteristics and entanglement of fatty acid chains. Research performed on extracted SQDG's therefore often cannot make definite conclusions on exactly which fatty acid substituents make up the most efficient compounds, and makes it difficult to ascertain the SAR in regards to the fatty acids. This is problematic for a number of reasons; it makes it difficult to determine which compound shows the most effect, and also whether one or multiple compounds in the "mixture" have adverse effects. If the latter is found to be the case, it is important to be able to determine what compound causes it and how to eliminate the effect while not affecting the anti-cancer activity. For this reason it is necessary to synthesize the specific SQDG's in question to test their individual effectiveness. In more recent studies, synthetic pathways to synthesize SQDG's, SQMG's, and other derivatives have been devised and improved upon. Some of these methods were utilized by studies mentioned so far and will be discussed in order of mention in the previous part of our discussion.

Murakami *et al.* [8] synthetized both α and β SQDG-$C_{18:0}$ (**4**) in accordance to a procedure previously laid out by Hanashima *et al.* [25], in which the starting material is 1-*O*-allyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside (**8**). First, the secondary hydroxyl groups were protected as benzyl ethers and the benzyl group of the benzylidene acetal was cleaved reductively with $LiAlH_4$ and then treated with $AlCl_3$. The resulting hydroxyl group was tosylated with TsCl, and converted further into a thioacetyl group with potassium thioacetate. The next step was to convert the allyl group into the glycol moiety seen in the finished SQDG's by oxidation with OsO_4. This netted a diastereomeric diol that Hanashima *et al.* were not able to separate, and the isomerism was reported to not have effect for *in vitro* effects of DNA polymerase inhibition.

The glycerol moiety was subsequently acylated with (among others) stearic acid with EDCl and DMAP, which gave a mixture of mono- and diester. These were separated with silica gel chromatography. The thioacetal group was converted into the sulfonate group by oxidation with oxone, and finally the protecting benzyl ether groups were removed through Pd-C-catalyzed hydrogenation to yield the finished SQDG (**4**). A schematic overview of the synthesis can be seen in scheme 1.

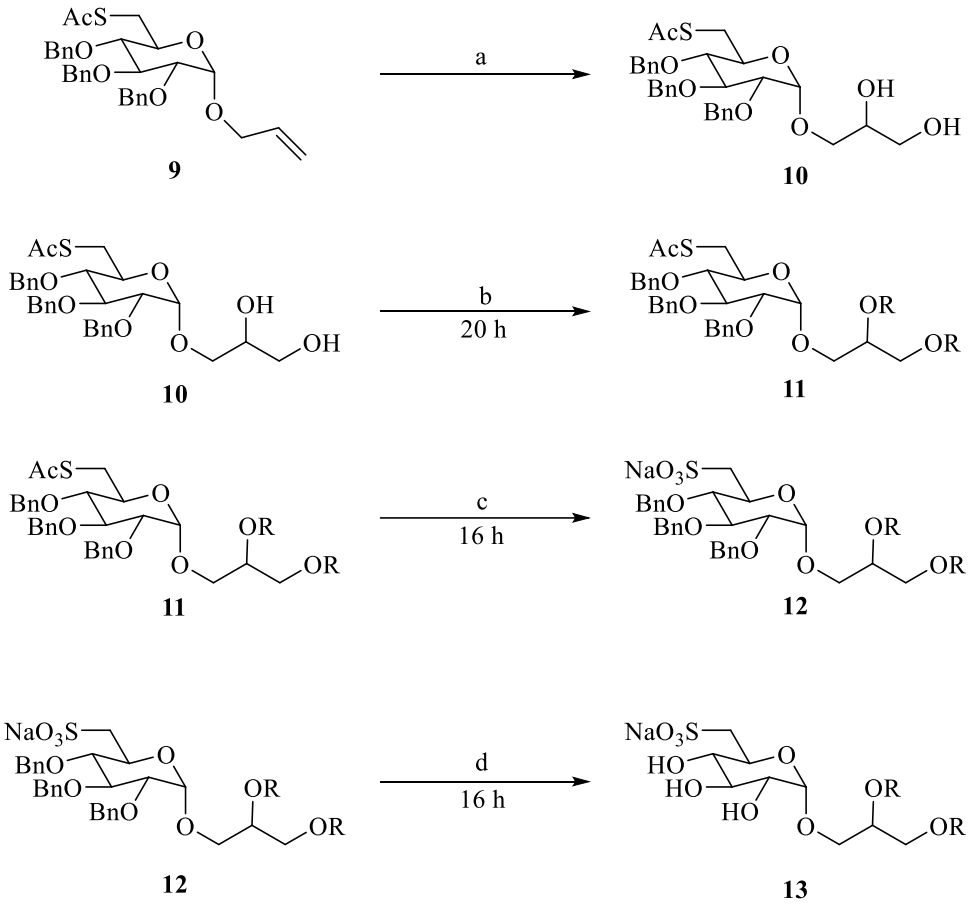


Scheme 1: Synthesis of SQDG-$C_{18:0}$, among other SQDG's. Synthesis as performed by and scheme based on Hanashima *et al.* [25]. **a**) BnBr, NaH, DMF, 68,2%; **b**) $LiAlH_4$, $AlCl_3$, Et_2O, CH_2Cl_2; **c**) TsCl, pyridine, DMAP, 72,3% ; **d**) AcSK, EtOH, reflux 88,2%; **e**) OsO_4, trimethylamine *N*-oxide, *t*-BuOH, H_2O, 56,9%; **f**) R (stearic acid), EDCl, DMAP, CH_2Cl_2, 72,9-95,9%; **g**) OXONE, AcOH, AcOK, 43,4-92,6%; **h**) 10% Pd-C, EtOH, H_2, 43,3-86,8%.

To produce SQMG-$C_{18:0}$ (**5**), SQDG-$C_{18:0}$ (**4**) can be hydrolyzed enzymatically. In this process, either α or β SQDG-$C_{18:0}$ (5 mg), depending on the desired SQMG, was suspended in Tris-HCl buffer (0,5 ml, 0,2 M), pH=7,6 that contained pancreatic lipase (5 mg) and $CaCl_2$ (5 mg, 0,25 M). This mixture was incubated (37 °C, 20 min), after which HCl (0,1 ml, 6 N), the hydrolyzed product was extracted with diethyl ether and separated with thin layer chromatography (CH_2Cl_2/MeOH 2:1, v/v). This procedure was also used by Sakimoto *et al.* [11] to synthesize SQMG's in their study.

The synthesis of the SQDG's performed by Makhlouf Brahmi *et al.* [14] is shown stepwise in scheme 2 and is near identical to the procedure described by Hanashima *et al.*[25], with the main difference being the starting material (**9**)**.** In step a), the allyl group of the starting

compound (**9**), prepared from *D*-glucose, was dihydroxylated to give the characteristic glycol moiety of SQDG's through oxidation with OsO_4. The amount of (**9**) used or obtained was not explicitly stated. Step b) introduced the desired fatty acid, R, through acylation of the glycol alcohol groups. EDCl (2,38 mmol), DMAP (1,52 mmol) and R (2 eq) were added to a solution of (**10**) (0,95 mmol) in dry CH_2Cl_2 (40 mL) and stirred at room temperature for 20 hours and subsequently diluted with H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 ml), and the organic layers were combined and washed with brine (1×20 mL), dried over Na_2SO_4, concentrated under reduced pressure and finally purified by flash column chromatography. Step c) featured introduction of the sulfonic group characteristic of sulfoquinovose through oxidation of the thioacetate group. Oxone (1,86 mmol) and AcOK (14,9 mmol) were added to a solution of (**11**) (0,75 mmol), in glacial AcOH and left at room temperature for 16 hours, after which the mixture was diluted with H_2O (40 ml) and extracted with EtOAc (3×80 ml). The organic layers were combined and washed with saturated $NaHCO_3$ solution (3×60 ml) and brine (1×40ml). It was then dried over Na_2SO_4 and concentrated under reduced pressure to give (**12**). Lastly, the protecting groups on the glycolic alcohols were finally removed in step d) by hydrogenation to generate the desired SQDG (**13**). The exact yields obtained for each separate fatty acid were not reported.

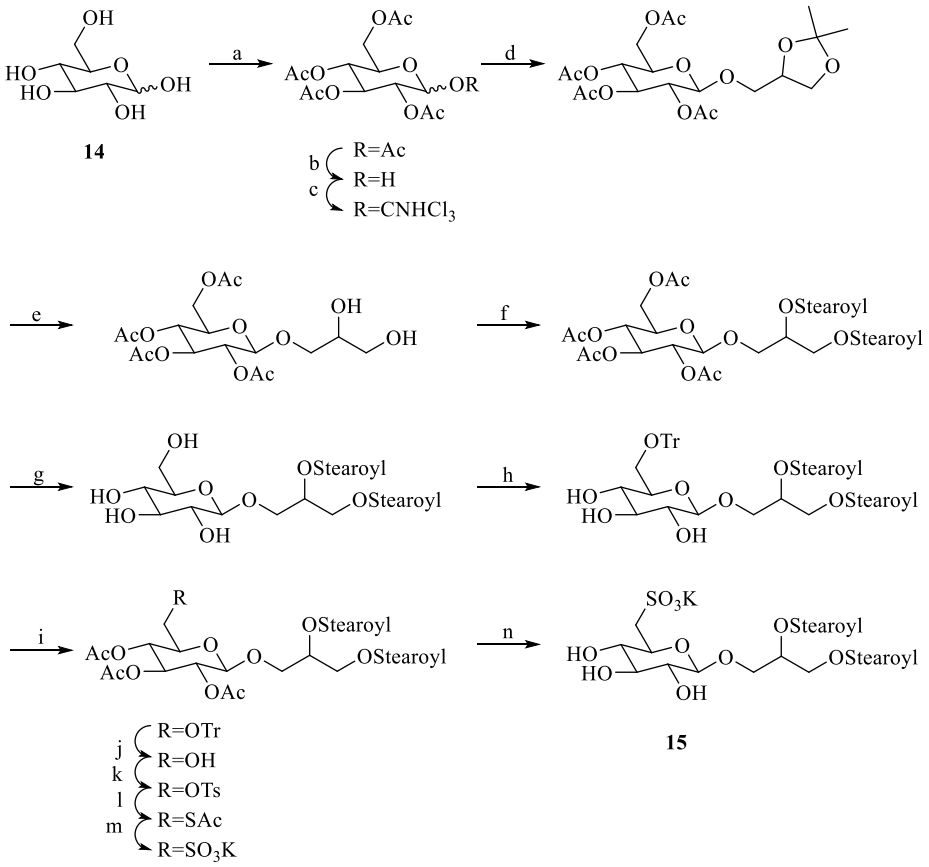


Scheme 2: Synthesis of SQDG's with fatty acids R on the glycol moiety, adapted from and performed by Makhlouf Brahmi *et al*. [14]. The reagents and conditions were as follow: **a**) OsO_4, trimethylamine *N*-oxide, *t*-BuOH, H_2O, RT, 75%; **b**) fatty acid R, EDCl, DMAP, dry CH_2Cl_2, RT; **c**) Oxone, AcOH, AcOK, RT; **d**) 10% Pd/C or 20% $Pd(OH)_2$/C, EtOH, H_2, RT (performed in 2 steps).

The previously described methods of synthesizing SQMG's and SQDG's share a common approach; starting out with *D*-glucose or a derivative hereof, a glycol moiety is added and subsequently acylated with the desired fatty acids. The same methods were applied by Sawada *et al*. [12] in their study regarding sulfoquinovosylacylpropanediol; the only aberration from literature procedure here would be that no fatty acids are added to the glycol moiety. This appears to be the preferred method of synthesizing SQMG's, SQDG's and similar derivatives.

A problem noted by Manzo *et al.* [22] however was that the use of benzyl as protecting groups of the sugar hydroxyl groups reduced the viability of adding unsaturated fatty acids to the glycerol moiety. They developed an improved version of the established synthesis pathway which they describe as "characterized by clean and efficient steps, along with a simple and easy workup, which makes the procedure suited for subsequent and crucial

scaling up". Furthermore, the procedure required no changes to produce product in greater quantities, and quantities of up to 400 mg were synthesized unproblematically. Additionally, the procedure can be easily modified to prepare a wide range of analogs. The synthesis, applied to produce β-SQDG-$C_{18:0}$, (**4**) is shown in scheme 3.



Scheme 3: Synthesis of β-SQDG-$C_{18:0}$ by the procedure of, and scheme based on, Menzo *et al.* [22]. **a**) Ac_2O/pyridine, 94%; **b**) $BnNH_2$, THF, 73%; **c**) Trichloroacetonitrile, DBU, CH_2Cl_2, 0 ℃, 82%, α/β 98/2; **d**) BF_3-Et_2O, glycerol acetonide, CH_2Cl_2, -10 ℃, 80%, α/β 95/5; **e**) $Zn(NO_3)_6$–$6H_2O$, acetonitrile, 50 ℃, 75%; **f**) Stearic acid, DCC, DMAP, CH_2Cl_2, 92%; **g**) hydrazine monohydrate, EtOH 85%, 45 ℃, 70; **h**) TrCl, pyridine, 70%; **i**) Ac_2O/pyridine, 90%; **j**) I_2-MeOH (1%), 60 ℃, 82%; **k**) Tosyl chloride, pyridine; 80%; **l**) Potassium thioacetate, 2-butenone, 80 ℃, 93%; **m**) Hydrogen peroxide, CH_3COOH, potassium acetate, 40 ℃, 65%; **n**) hydrazine monohydrate, EtOH, 85%, 44 ℃, 68%.

Conclusion

As has been seen, there are various reports of sulfoquinovosyl compounds demonstrating various degrees of effect against various cancers, and through several pathways. Both SQDG's and SQMG's have been proven to inhibit cancer polymerase, telomerase, angiogenesis as well as induce apoptosis, though effect *in vitro* and *in vivo* vary. Other sulfoquinovosyl derivatives such as SQAP have also demonstrated similar effects. However, these promising results come accompanied by significant hurdles to overcome; after all, a compound may be ever so effective, but in order to have value as a drug it must be able to be administered successfully. Two of the problems that have yet to be solved to achieve this, are the questions of cell permeability and water solubility.

As for how the compounds work, the reactivity of SQDG's and SQMG's appear to be correlated to the structure of the fatty acids. For instance, findings thus far seem to indicate that bulky and lipophilic acids increase telomerase inhibition effectively at low concentrations, with IC_{50} values as low as 11μM [14]. While this was achieved in idealized and simplified conditions, these initial results are cause for optimism.

Extraction of SQDG's and other sulfoquinovosyl derivatives have proven challenging to separate from their natural sources, but synthetic pathways exist and have been improved in recent year that allow straight-forward production of a wide array of analogues with various fatty acids and presumably other substituents. Production from natural sources may also become an option with ever improving methods of chromatographic separation, and if "mixtures" of SQDG/SQMG's from marine sources prove to have no adverse effects, separation may not even be necessary. While a finished drug is probably still some time off, there is a solid basis for future research, as sulfoquinovosyl derivatives have been demonstrated to have a variety of beneficiary effects, as well as their existing efficient and relatively straight-forward synthesis methods that are already shown to support production on a larger scale. All this considered, it is fair to assess that SQDG's and SQMG's present a medicinal potential we would be remiss not to investigate further.

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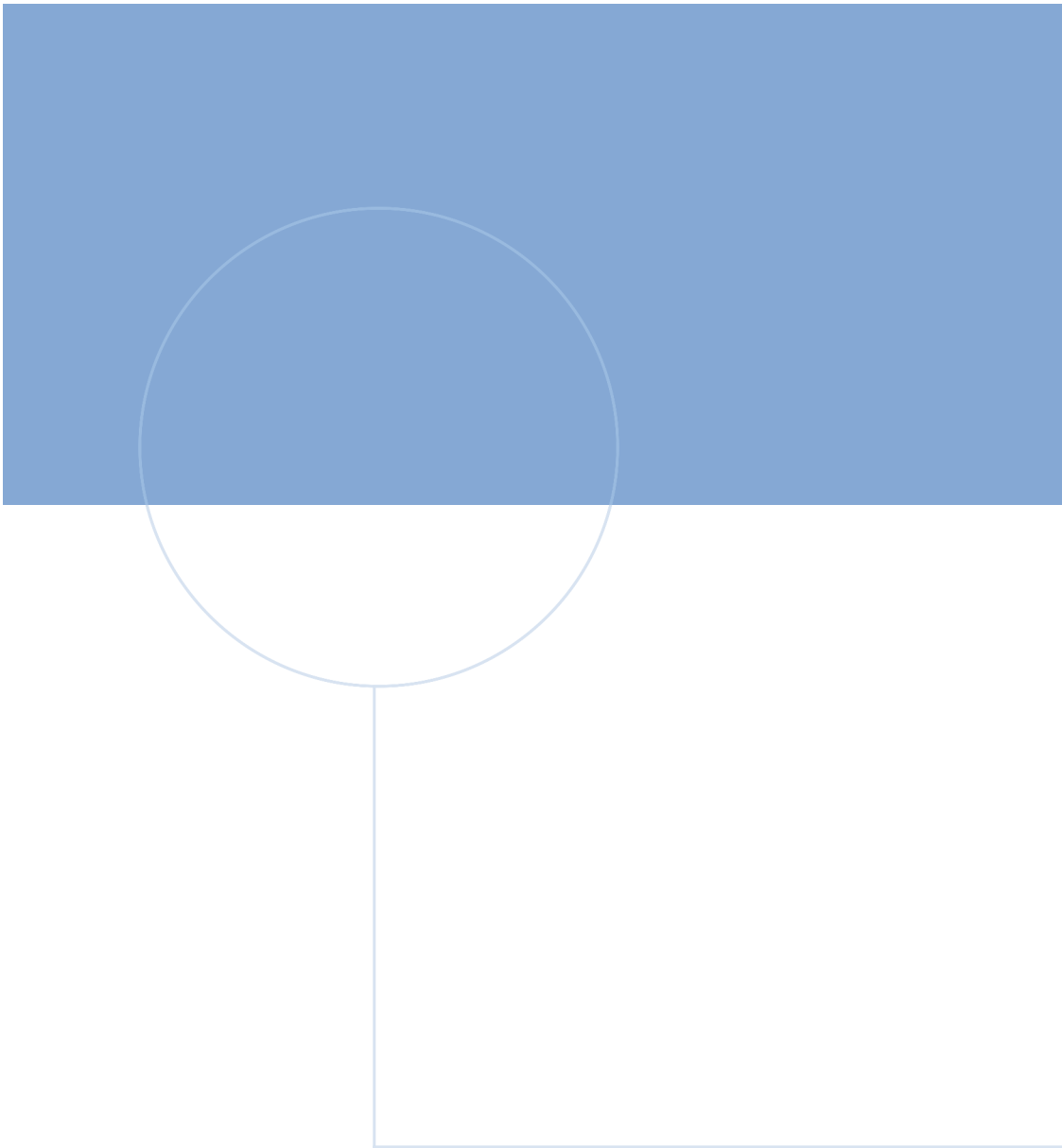

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