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Natural and Synthetic Derivatives of the Steroidal Glycoalkaloids of *Solanum* Genus and Biological Activity

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ABSTRACT

Steroidal alkaloids are secondary metabolites mainly isolated from species of *Solanaceae* and *Liliaceae* families that occurs mostly as glycoalkaloids. α -chaconine, α -solanine, solamargine and solasonine are among the steroidal glycoalkaloids commonly isolated from *Solanum* species. A number of investigations have demonstrated that steroidal glycoalkaloids exhibit a variety of biological and pharmacological activities such as antitumor, teratogenic, antifungal, antiviral, among others. However, these are toxic to many organisms and are generally considered to be defensive allelochemicals. To date, over 200 alkaloids have been isolated from many *Solanum* species, all of these possess the C27 cholestane skeleton and have been divided into five structural types; solanidine, spirosolanes, solacongostidine, solanocapsine, and jurbidine. In this regard, the steroidal C27 solasodine type alkaloids are considered as significant target of synthetic derivatives and have been investigated for more than 10 years in order to obtain new physiologically active steroids. It is important to state that the wide range of biological activities and the low amount available from natural sources, make relevant to obtained these metabolites by synthetic pathway.

Keywords: Steroidal glycoalkaloids; Synthetic derivatives; *Solanum*; Biological activity

INTRODUCTION

Steroidal alkaloids are secondary metabolites holding a basic cholestane skeleton and have mainly been isolated from around 300 species of the *Solanaceae* and *Liliaceae* families [1,2]. This type of components mostly occurs as glycoalkaloids, a nitrogen-containing steroidal glycosides found in members of the *Solanum* genus, including crop species, such as, potato (*S. tuberosum*), tomato (*S. lycopersicum*) and eggplants (*S. melongena*, *S. macrocarpon* and *S. aethiopicum*). These are usually found as paired structures sharing a common aglycon but holding two different sugar moieties, chacotriose or solatriose [3].

α -chaconine and α -solanine are among the steroidal glycoalkaloids most commonly isolated from *Solanum* species (*S. tuberosum*, commonly known as potato), that contains solanidine as aglycon. Another pair of alkaloids frequently found in *Solanum* species are solamargine and solasonine, which have a spirosolane basic skeleton with chacotriose or solatriose as

carbohydrate moiety, respectively. Furthermore, *Solanum* species may also contain β -solamarine, which is the chacotriose glycoside of tomatidenol and α -solamarine whose aglycon is also tomatidenol, however, solatriose is the carbohydrate moiety. These glycoalkaloids confer *Solanum* plants resistance against pathogenic organisms and insects being the chacotriose containing glycoalkaloids the most active [4-7].

The large family of saponins has received considerable attention because of the diverse pharmaceutical properties [8]. Since ancient times, plant extract containing saponins have been used in traditional medicine and there has been a great interest for the study of the steroidal glycoalkaloids isolated from *Solanum* species [9,10]. Among these, chacotriose present in solamargine and chaconine, has caught the attention of researchers [11].

Chacotriose is a branched carbohydrate formed by one molecule of glucose and two molecules of rhamnose: α -L-rhamnopyranosyl-(1 \rightarrow 2)- α -L-rhamnopyranosyl-(1 \rightarrow 4)-D-

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glucopyranose. Solatriose is also a branched carbohydrate formed by galactose, rhamnose and glucose: α -L-rhamnopyranosyl-(1 \rightarrow 2)- β -D-glucopyranosyl-(1 \rightarrow 3)-D-galactopyranose. The structure of chacotriose and solatriose [12,13].

There are also oligosaccharide counterparts to chacotriose, in particular solatriose, \langle -L-rhamnopyranosyl-(1 \rightarrow 2)- β -D-glucopyranosyl-(1 \rightarrow 3)- β -D-galactopyranose [14-17]. However, glycosides-containing chacotriose are consistently more active than their solatriose-containing counterparts [16]. Diosgenin, the diosgenyl-3-O- β -chacotrioside isolated from oriental vegetables and traditional medicinal plants, displayed promising *in vitro* antitumor activities [16-18].

Furthermore, some investigations have indicated that glycoalkaloids must have evolved in nature to protect plants against bacteria, fungi, insects, and animals. They are toxic to a wide range of organisms and are generally considered to be defensive allelochemicals [19]. However, it has been reported that many of glycoalkaloids have important biological and pharmaceutical activities such as antitumor, teratogenic, antifungal, antiviral, anti-estrogen, among others [20-25]. Nevertheless, these compounds may cause toxicity if used over 2-5 mg/kg (body weight) since may promote systemic and gastrointestinal effects and also down-regulate acetylcholinesterase effect [26]. Glycoalkaloids might also disrupt cells by making a complex with sterol at cellular membranes [27]. Neurological signs and symptoms of toxicity due to glycoalkaloids include; weakness, depression, coma, convulsions, paralysis and mental confusion [28].

STEROIDAL ALKALOIDS/GLYCOALKALOIDS

Solanaceae family has yielded several types of steroidal bases, and over 200 alkaloids have been isolated from many species of *Solanum* and *Lycopersicon* [29-39]. All these alkaloids possess the C27 cholestane skeleton and may be divided into five structural types (Figure 1): Solanidine (1) Spirosolanines (2) Solacongestidine (3) Solanocapsine (4) and Jurbidine (5) [30].

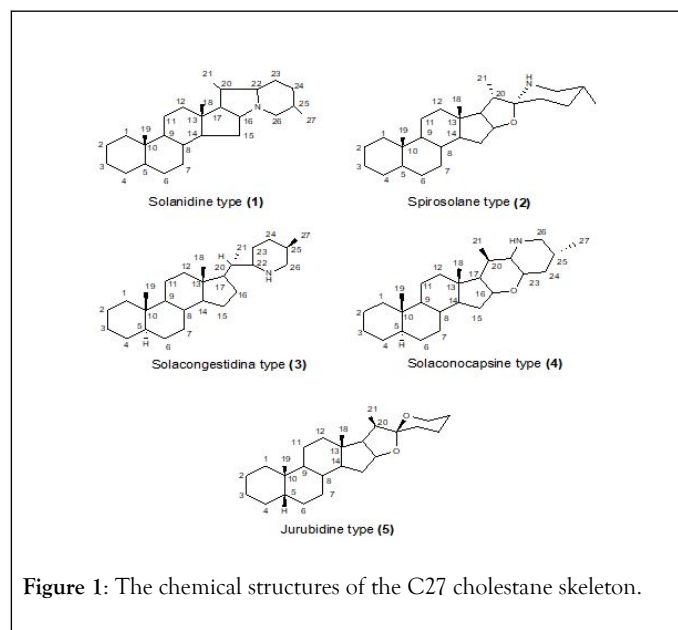


Figure 1: The chemical structures of the C27 cholestane skeleton.

In *Solanaceae* family the steroidal C27 type alkaloids jervaratum and cervaratum have not been found yet, while solasodine (7) has remained as an important target of synthetic studies over the last 10 years. A number of solasodine derivatives (7) (Figure 2), such as N-cyano and A-nor-3-aza derivatives and degradative products, were prepared in order to obtain new physiologically active steroids.

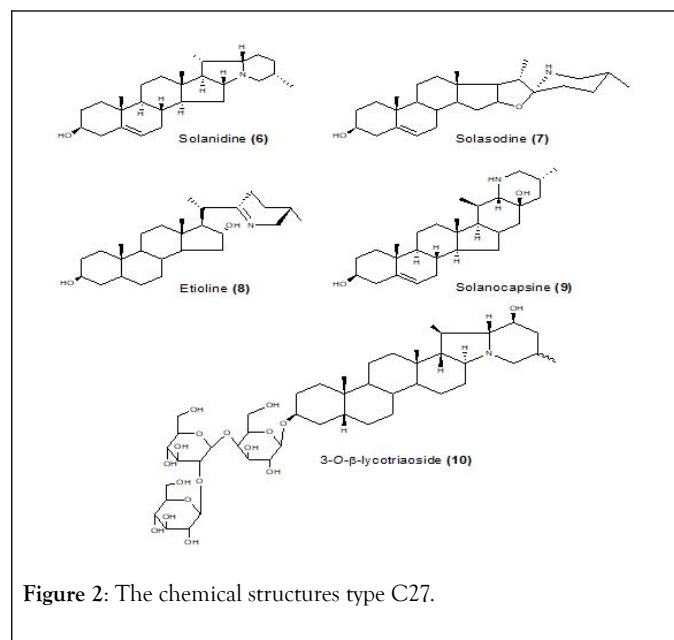


Figure 2: The chemical structures type C27.

Glyco-derivatives of solasodine, such as solaradixine, solashbanine, solaradine, robustine, and ravifoline, have also been isolated from species of *Solanum* genus [37,38]. In addition, over 50 members of the solacongestidine type steroidal alkaloids have also been obtained, mostly from *Solanum* and *Veratrum* species. A representative example is etioline (8), which was isolated from *Solanum capsicastrum* Link, *S. spirale*, *S. havanense*, *Veratrum lobelianum*, and *V. grandiporum* [39,40].

Leaves, roots, and stems of *Solanum havanense* Jacq. provided -solamarine and the glycoside etiolinine (8), while solanidine-type alkaloids (1) have been isolated mainly from *Solanum* species, however, these have also been found from species of the *Liliaceae* family specifically in *Veratrum*, *Rhinopetalum*, *Fritillaria*, and *Notholirion* genera. About 40 members of this class, including both alkalines (aglycone) and glycoalkaloids have been reported being solanidine (6) the most important member of this group [9,37,41,42].

Stems of *S. lyratum* have yielded a mixture of steroidal glycoalkaloids, including 3-O- β -lycotriaside (10). Only a few members of solanocapsine type (4) alkaloids are known, and have been isolated from *Solanum* species. Solanocapsine (9) is an important member of this class, isolated from *S. capsicastrum* L. *S. hendersonii* Hort, and *S. pseudocapsicon* L. [43].

From the roots of Taiybo Shinko No. 1 (a hybrid between *Lycopersicon esculentum* Mill. and *L. hirsutum* Humb. et Bonpl.), which is a tomato stock highly resistant to soil-borne pathogens, were isolated two solanocapsine-type alkaloids, 22,26-epi-imino-16 β ,23-epoxy-23 α -ethoxy-5 α ,25 α H-cholest-22-(N)-ene-3 β ,20 α -diol and 22,26-epi-imino-16 α ,23-epoxy-5 α ,

22 β H-cholestane-3 β , 23 α -diol. Jurubidine-type (5) bases are a small group of *Solanum* alkaloids, from which jurubidine is the most representative example [44].

BIOLOGICAL ACTIVITY OF NATURAL GLYCOALKALOIDS

A number of investigations carried out with steroidal glycoalkaloids isolated from different *Solanum* species have demonstrated that these type of secondary metabolites have antifungal [45-51], trypanolytic, trypanocidal [52], larvicidal, molluscicide, acaricidal [53-56], hepatoprotective [57-59], anti-ulcerogenic [60], anti-seizure [61], cytoprotective [62], neuropharmacological [63], antioxidative [64,65], antimicrobial [66] and embryotoxic activities [67]; as well as exhibit significant anticancer effect. In addition, glycosides containing chactriose are consistently more active than solatriose containing counterparts regarding antiviral [68-70] antiestrogen [71], anti-inflammatory [72-74], mastitis [75], antitumour [76-82]; teratogenic [83,84] and antibacterial activities [85,86].

Despite the wide range of reported pharmacological studies, anticancer activity seems to be considered as high priority to researchers who stated that glycosides from *Solanum* plants, showed potent antitumor activity, specifically chactriosyl steroids such as, α -L-rhamnopyranosyl-(1 \rightarrow 4)- β -D-glucopyranosyl, however, those compounds that contain an extra sugar on the side chain lack of activity [87,88]. The steroidal glycosides isolated from *S. dulcamara*, *S. lyratum* and *S. nigrum*, exhibit cytotoxicity towards human cancer cells and herpes simplex virus type 1 (HSV-1) [89]. According to traditional medicine in China and Japan, the entire plant of *Solanum nigrum* is used to treat different types of cancer such as liver, lungs, urinary bladder, larynx, and carcinoma of vocal cords [90].

Anticancer phytochemicals present in *Solanum nigrum* include glycoproteins, polysaccharides, steroidal alkaloids and glycoalkaloids [91]. Among these solanine, solamargine, solasonine and solasodine are the most common glycoalkaloids observed [92,93]. Solasodine exhibits potent antitumour activity both *in vitro* and *in vivo* [94,95], however, the solasodine glycosides are regularly more cytotoxic against a variety of tumour cell lines when compared with its aglycone [96,97]. Glycoalkaloid α -solamargine isolated from *Solanum incanum*, a chinese herb, triggers gene expression of human TNF 1 that may lead to cell apoptosis. Similarly, the anticarcinogenic action of solamargine on human hepatoma cells (Hep3B) has proved to induce cell death by apoptosis. Furthermore, α -solasonine from *S. crinitum* and *S. jabrense* has demonstrated cytotoxic activity against erlich carcinoma and human K562 leukemia cells as well as, chaconine, solanine, tomatine and their derivatives inhibit the growth of human colon (HT29) and liver (HepG2) cancer cells [98].

Glycoalkaloids solamargine and solasonine, isolated from *Solanum sodomaeum* have shown activity against malignant human tumors [99]. Tomatidine is able to reduce the resistance of cancer cells to drugs [100]. α -solamargine and α -solasonine, isolated from *S. melongena*, *S. macrocarpon* and *S. aethiopicum* have potential to treat different types of cancers, such as gastric cancer, leukemia [101], liver cancer, lung cancer, osteosarcoma

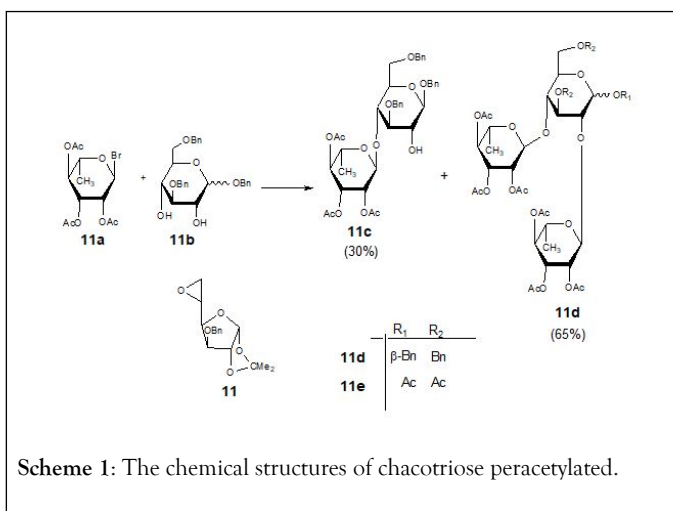
[102] and basal cell carcinoma [103]. In addition, antiparasitic activity on *Leishmania mexicana* [104], and *Trypanosoma cruzi* they has been reported in the literature for these type of components [105].

It is also important to mention the applications of these compounds in traditional medicine. In Australia a topical preparation that contains a mixture of solasodine glycosides (BEC) is used to treat cutaneous solar keratosis [106,107]. In Venezuela the juice obtained by expression of *Solanum americanum* Miller fruits are used to treat skin injuries caused by Herpes zoster, Herpes simplex and Herpes genitalis. The main steroidal glycoalkaloids found in the fruits of this species are α -solamargine and α -solasonine [108,109]. Leaves of *Solanum nigrum* is applied topically for the treatment of sores, carbuncles, swelling and injuries [110]. Likewise, it is used to treat stomachache, jaundice, liver problems, toothache and many skin diseases [111]. α -chaconine, the glycoside of solanidine with chactriose, is highly effective against Herpes simplex virus, whereas the corresponding aglycone is inactive. Despite the beneficial effects of glycoalkaloids these may be toxic to humans and might even cause death at high concentrations (3-5 mg/kg body mass) [112]. Several investigations have revealed that α -solanine, α -chaconine, as well as solanidine and other *solanum* steroidal alkaloids are responsible for the inhibition of acetylcholinesterase and may lead to central nervous system damage [113].

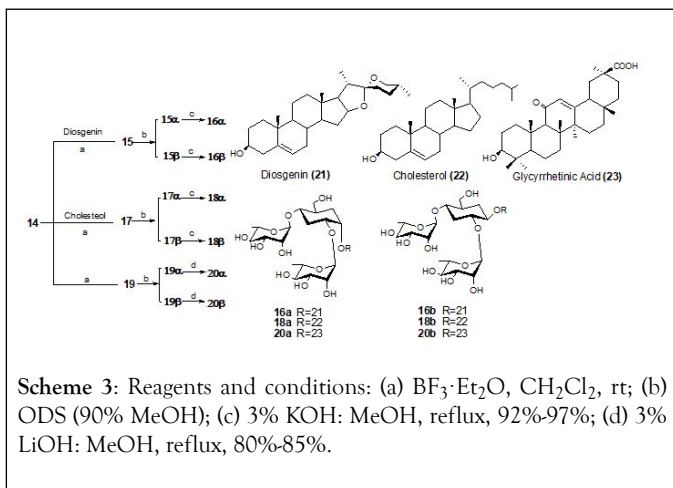
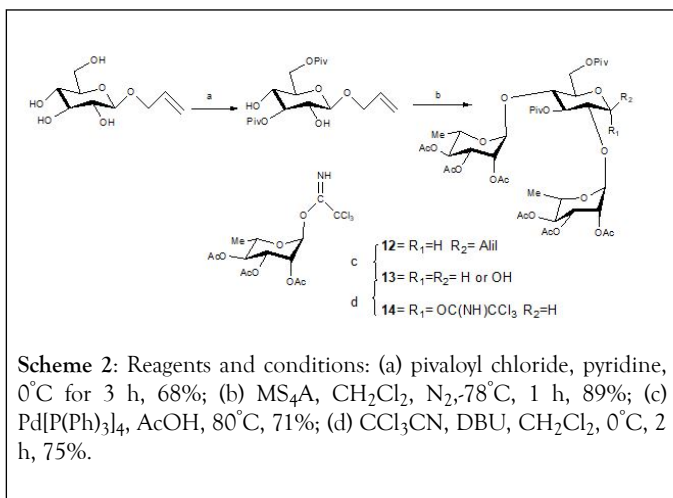
STUDIES ON SYNTHETIC DERIVATIVES OF SOLANUM ALKALOIDS AND THEIR BIOLOGICAL ACTIVITY PUBLISHED IN THE LAST 15 YEARS

According to literature consulted there are a number of investigations regarding the synthetic derivatives of *Solanum* alkaloids. In addition, the biological activity and the low amount available from natural sources, make relevant to obtained these metabolites by synthetic pathway. Thus, many researchers have carried out diverse synthetic pathways to obtain chactriose and its analogues [114-118].

They synthesized chactriose peracetylated from D-glucose as starting unit. The strategy adopted was to partially protect the glucose molecule leaving the 2-and 4-hydroxyl groups available for glycosidic bond formation with two L-rhamnopyranose units. The final reaction of peracetylated chactriose provided 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene- α -D-glucofuranose (11). On the other hand, L-Rhamnose was first peracetylated with $\text{Ac}_2\text{O}-\text{C}_5\text{H}_5\text{N}$ and treated with 4.5 equivalents of HBr (33% in glacial acetic acid) to obtain 2,3,4-tri-O-acetyl- α -L-rhamnopyranosyl bromide (11a). Compound (11b) was mixed with four equivalents of (11a) in dry CH_2Cl_2 at 0°C, in the presence of tetramethylurea and silver triflate to give benzyl 2,3,4-tri-O-acetyl- α -L-rhamnopyranosyl-(1 \rightarrow 4)-3,6-di-O-benzyl- β -D-glucopyranoside (11c) (30%) and benzyl 2,3,4-tri-O-acetyl- α -L-rhamnopyranosyl-(1 \rightarrow 2)-[(2,3,4-tri-O-acetyl- α -L-rhamnopyranosyl-(1 \rightarrow 4))-3,6-di-O-benzyl- β -D-glucopyranoside (11d) (65%). Compound (11d) was subjected to catalytic hydrogenolysis to remove the benzyl protecting groups and subsequently acetylated to obtain the desired peracetylated chactriose (11e) in 24% yield (Scheme 1).

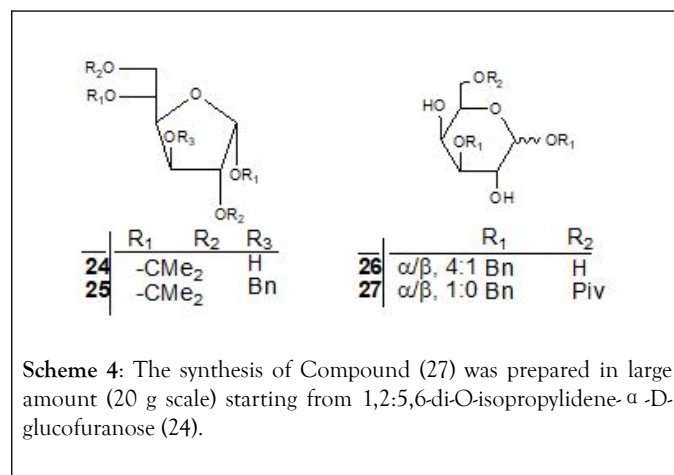


They synthesized α -L-rhamnopyranosyl-(1.4)- α -L-rhamnopyranosyl-(1.2)- α -D-glucopyranosyl (chactriosyl) trichloroacetimidate (6) from allyl glucoside as initial molecule to obtain (6), achieving 32% overall yield, even though the α -glycosides were predominant over β -glycosides in the oligoglycosylation. According to cytotoxic assays only 16 β isomer proved to be active, thus, both the β -chactrioside and the steroidal aglycone moiety are considered relevant for the cytotoxic activity (Schemes 2 and 3).

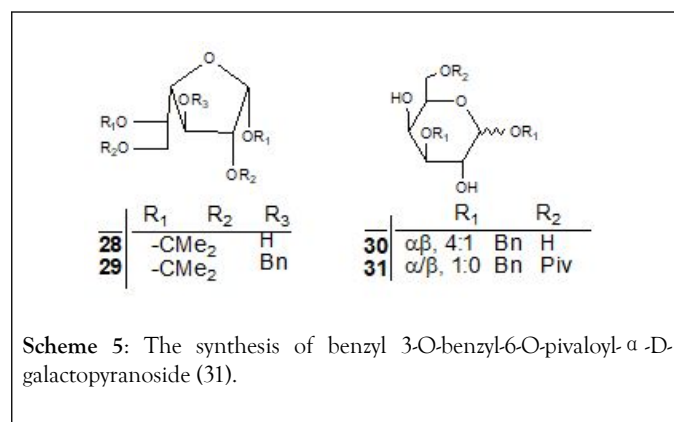


The synthesis of three chactriose analogues, β -L-fucopyranosyl-(1 \rightarrow 2)-[β -L-fucopyranosyl-(1 \rightarrow 4)]-D-glucopyranose, β -L-fucopyranosyl-(1 \rightarrow 2)-[β -L-fucopyranosyl-(1 \rightarrow 4)]-D-galactopyranose, and α -L-rhamnopyranosyl-(1 \rightarrow 2)-[α -L-rhamnopyranosyl-(1 \rightarrow 4)]- α -D-galactopyranose (Schemes 4-6) [11].

Compound (27) was readily prepared in large amount starting from 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (24). Compound (25) was prepared by condensing (24) with benzyl bromide in 83% yield. Removing the isopropylidene protection followed by selective protection of the anomeric hydroxyl with benzyl alcohol in the presence of acetyl chloride afforded compound (26), (Scheme 4).



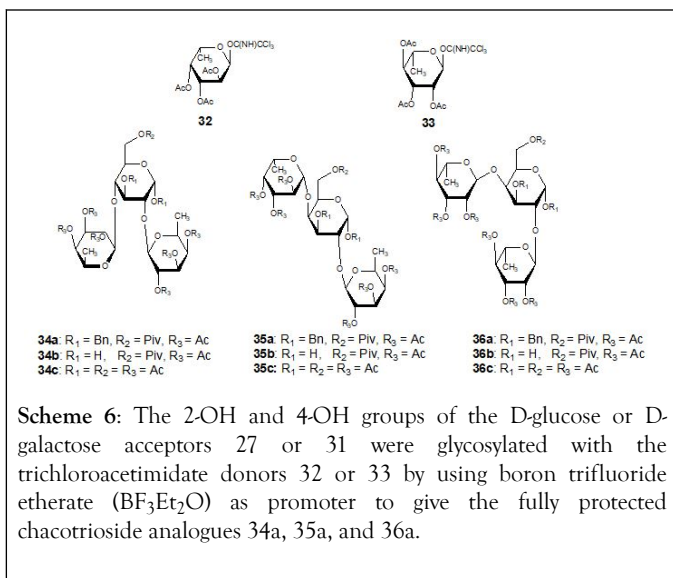
By the same method, we also prepared the galactosylated acceptor (31), starting from 1,2:5,6-di-O-isopropylidene- α -D-galactofuranose (28). Removing the isopropylidene protection of (29) with 3:2 HOAc-H₂O followed by selective protection of the anomeric hydroxyl with benzyl alcohol in the presence of acetyl chloride afforded compound (30) (65% yield). The anomeric mixture (30 α /30 β) ($\alpha = \beta$, 4:1) was separated by conventional work up: acetylation following by deacetylation. Position 6 of (30 α) was selectively protected with pivaloyl chloride in pyridine to give benzyl 3-O-benzyl-6-O-pivaloyl- α -D-galactopyranoside (31) in 76% yield, (Scheme 5).



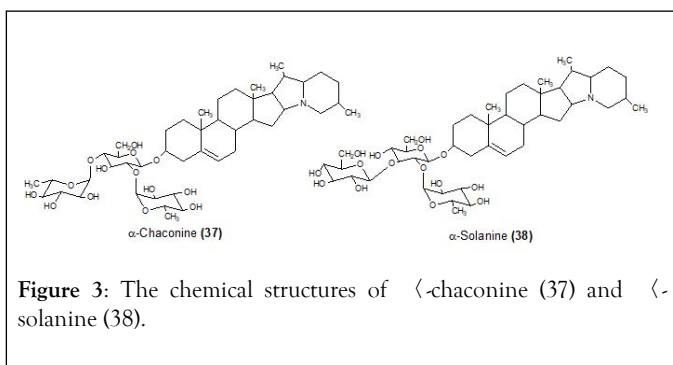
The 2-OH and 4-OH groups of the D-glucose or D-galactose acceptors (27) or (31) were glycosylated with the trichloroacetimidate donors (32) or (33) by using boron trifluoride etherate (BF₃·Et₂O) as promoter to give the fully

protected chacotrioxide analogues (34a, 35a, and 36a), (Scheme 6).

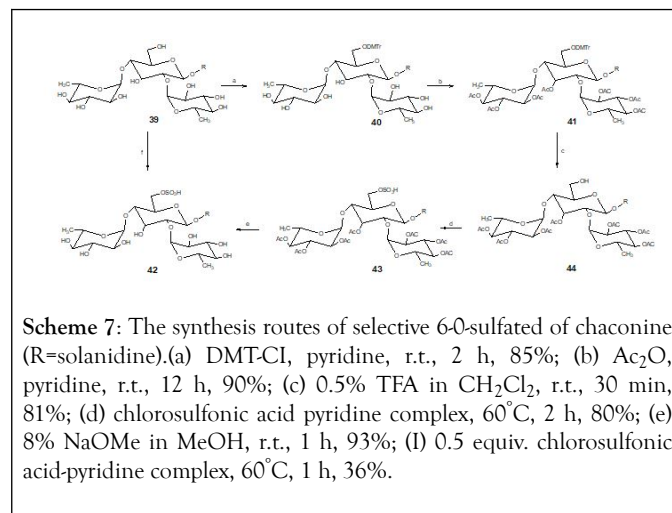
Trisaccharides (34a, 35a, and 36a) were then peracetylated. The protected trisaccharides were treated with hydrogen in the presence of Pd/C (10%) to give (34b-36b) and, then with NaOH to remove the pivaloyl and acetyl groups, and were subsequently acetylated to obtain the desired peracetylated chacotrioxide analogues (34c, 35c, and 36c), (Scheme 6).



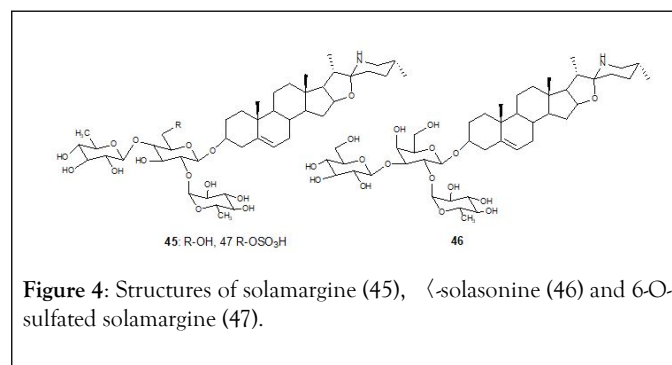
The isolation of two natural glycoalkaloids, α-solanine (37) and α-solanine (38), isolated from potato stems and leaves (*Solanum tuberosum* L.) (Figure 3) [118].



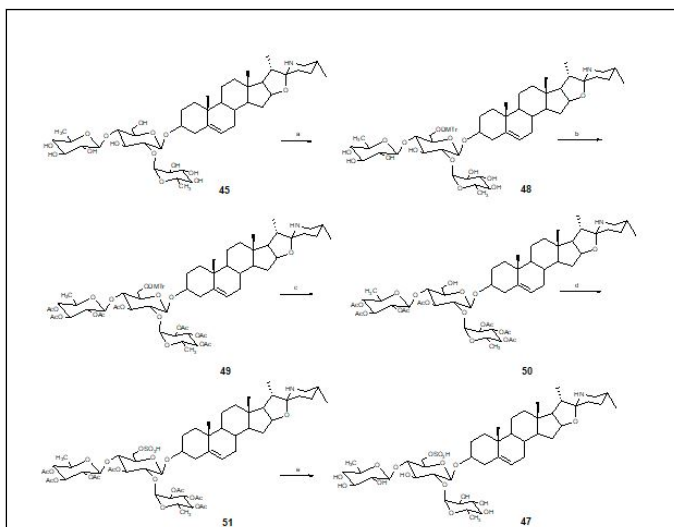
In order to obtain the synthetic analogues of these natural glycoalkaloids, D-galactose and L-fucose were used as starting molecules. The 6-hydroxyl groups of sugar moiety in chaconine and solanine were protected with 4,4'-dimethoxytrityl (DMT) while the additional hydroxyl groups were acetylated. The protective group DMT was removed by using 0.5% TFA in dichloromethane. The free 6-hydroxyl groups were treated with chlorosulfonic acid in pyridine to yield 6-O-sulfated derivatives. Finally, the acetyl groups were removed to obtain sulfated chaconine and sulfated solanine (Scheme 7).



The structures of two glycoalkaloids α-solanine (45) and α-solanine (46) are shown in (Figure 4) [119].

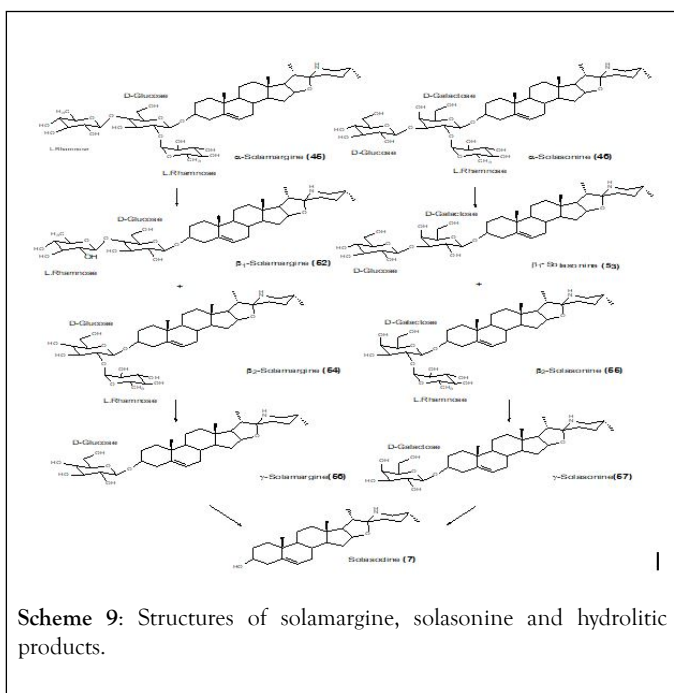


The possible effect of the sugar moiety present in glycoalkaloids against cancer cells. In this regard, 6-O-sulfated solamargine and catalyzed hydrolytic products of α-solanine and α-solanine were prepared. The sulfation at 6-O of solamargine was carried out by five steps. First stage was to selectively protect the 6-OH group with DMT, followed by the acetylation of secondary hydroxyl groups on the sugar ring. Once the protective group on the 6-OH was removed, a sulfonation was carried out to obtain the sulfate derivative. Finally, the acetyl groups on the sugar molecule were removed to yield 6-O-sulfated solamargine (51), (Scheme 8) [119].



Scheme 8: The synthetic routes of 6-O-sulfated solamargine (51) (a) DMT-Cl, pyridine, r.t., 3 h; (b) Ac₂O, pyridine, r.t., 10 h; (c) 0.5%TFA inCH₂Cl₂, r.t., 30 min; (d) chlorosulfonic and pyridine complex, 60°C, 2 h; (e) 8 mg/mL NaOMe in MeOH, r.t., 1 h.

The partial acidic hydrolysis of α -solamargine and α -solasonine lead to formation of disaccharides β 1 and β 2-solamargine as well as β 1 and β 2-solasonine. Similarly, monosaccharides \odot -solamargine, \odot -solasonine and aglycon solasodine were also obtained (Scheme 9). Results demonstrated that \odot -solamargine and aglycon solasodine were the main products observed while \odot -solasonine was achieved in low yield and β -solasonine could not be successfully obtained.

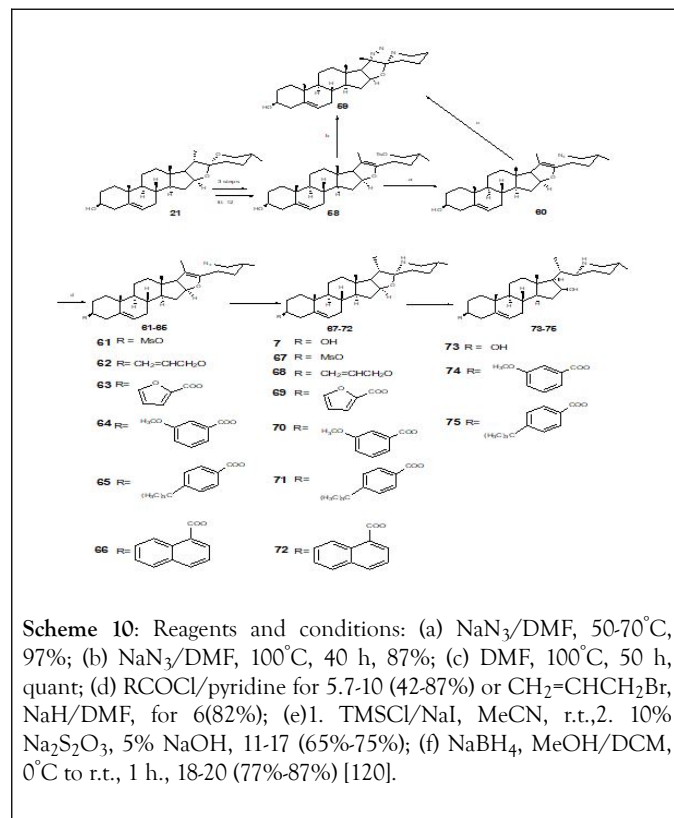


Scheme 9: Structures of solamargine, solasonine and hydrolytic products.

Glycoalkaloids have drawn scientific attention due to the significance of their biological activities. Some studies have revealed that differences in glycoalkaloids structure including the type and number of sugar moieties attached by a glycosidic bond at C-3 may be related to several biological activities. A study carried out by Li et al in 2007, showed the antiproliferative

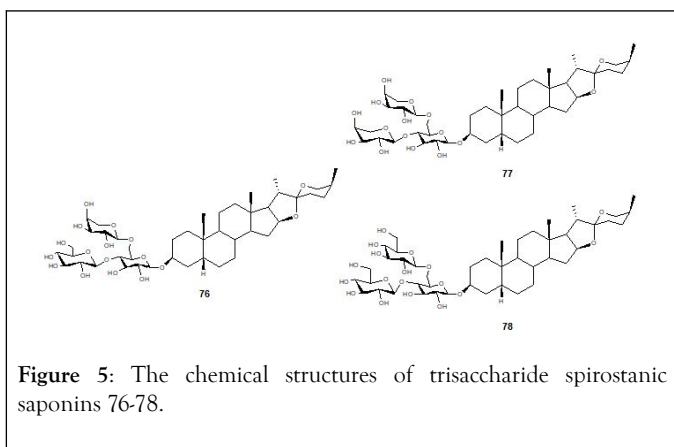
activities against HCT-8 cancer cells of α -solamargine, α -solasonine and their derivatives, including 6-O sulfated solamargine and partial acidic hydrolyzed products. Results showed that α -solamargine and α -solasonine exhibit strong cytotoxic activity with IC₅₀ values of 10.63 and 11.97 μ mol/L, respectively, whereas their derivatives proved to be less active. Authors concluded that sugar chains present in glycoalkaloids molecules might play an important role in this activity.

The synthesis of eight solasodine derivatives and their effect on prostate cancer cell proliferation was assessed *in vitro*. Significant improvement in antiproliferative activity was achieved among some of the synthetic analogs. In particular, (74) exhibited the most potent inhibitory effect against the proliferation of PC-3 cell line (IC₅₀: 3.91 μ mol/L). The cellular activity of (7,59,67-69), and (71-75) compounds (purity above 98%), was evaluated in a prostate gland adenocarcinoma cell line (PC-3). Solasodine (7) also showed inhibitory effect on the proliferation of PC-3 cell line with IC₅₀ value of 25 μ mol/L. Esterization and etherisation of solasodine at C-3 position (67-72), except for (72) (1-naphthoyl), did not enhance the inhibitory activity. In comparison to solasodine, analogs (59) and (74) significantly improved the cytotoxicity on PC-3 cell line. However, analogs (73) (3 β -hydroxyl) and (75) (3 β -p-tertbutylbenzoyl) exhibited a rather low activity suggesting that substitution at C-3 might be related to the *in vitro* anticancer activity observed (Scheme 10) [120].

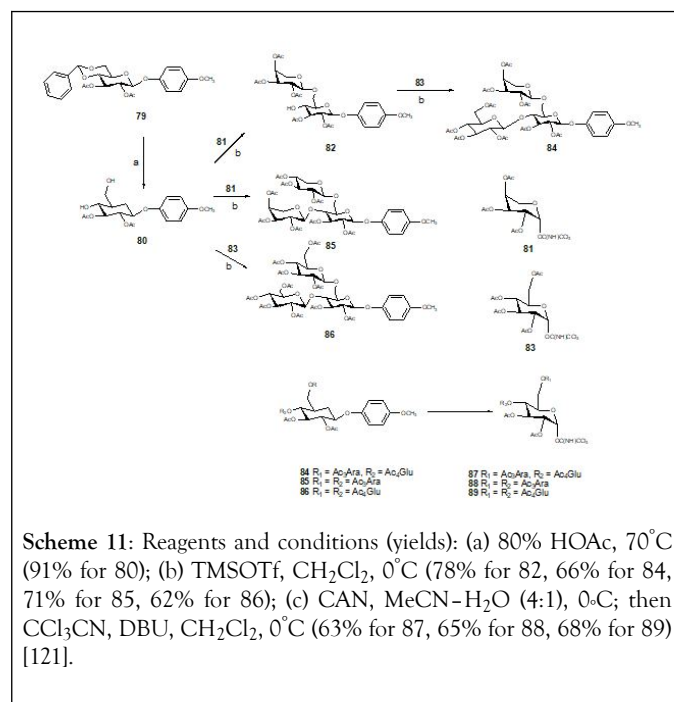


The synthesis of β -D-glucopyranosyl-(1 \rightarrow 4)-[α -L-arabinopyranosyl-(1 \rightarrow 6)]- β -D-glucopyranoside (sarsasapogenin), a trisaccharide spirostane saponin (76, Figure 5), through a direct transglycosylation strategy. In addition, two trisaccharide saponin derivatives (77) and (78), which contain a structurally

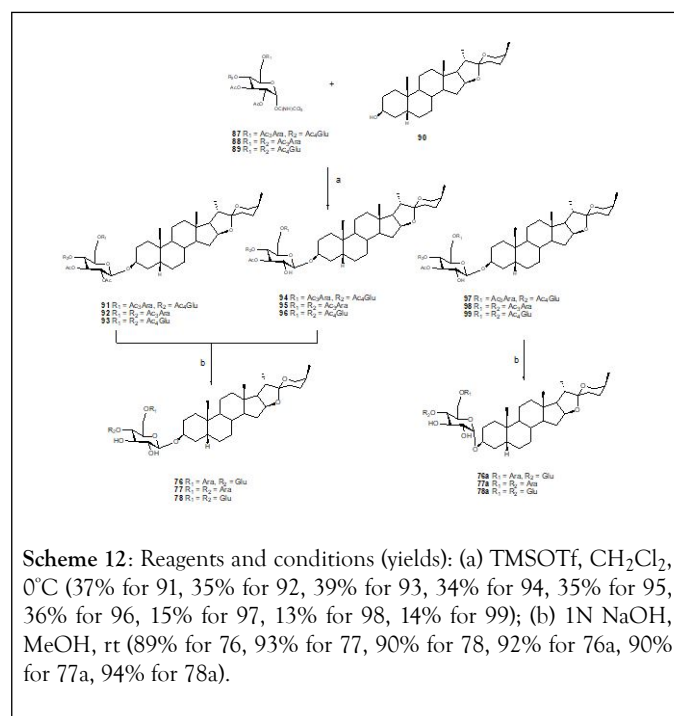
modified trisaccharide unit were also obtained as shown in Scheme 11 [121].



To complete the synthesis of molecules (76-78), a direct transglycosylation strategy using trisaccharide trichloroacetimidates as glycosyl donors was assessed. The first step of the synthesis was the preparation of 4,6-dibrached trisaccharide (Scheme 11). Acidic cleavage of the benzylidene group of 4-methoxyphenyl 2,3-di-O-acetyl-4,6-di-O-benzylidene- β -D-glucopyranoside (79) with 80% acetic acid at 70°C afforded 4,6-diol, 80 with 91% yield. Regioselective glycosylation of compound (80) and 2,3,4-tri-O-acetyl- β -L arabinopyranosyl trichloroacetimidate (81) in anhydrous CH_2Cl_2 at 0°C under the promotion of trimethylsilyl triflate (TMSOTf) gave the α - $(1\rightarrow 6)$ -linked disaccharide (82) in 78% yield. Coupling of disaccharide (82) and 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl trichloroacetimidate (83) in CH_2Cl_2 with TMSOTf as a catalyst lead to formation of trisaccharide (84). In addition, direct condensation of compound (80) along with arabinosyl donor (81) in dry CH_2Cl_2 in the presence of TMSOTf gave 4,6-diarabinosylated glucopyranoside (85) with 71% yield. Similarly, the trisaccharide (86) was obtained from 4,6-glucosylation (80) and glucosyl donor (83) catalyzed by TMSOTf under standard glycosylation condition. Furthermore, cerium ammonium nitrate (CAN)-promoted cleavage (86) of the anomeric 4-methoxyphenyl group of trisaccharides (84-86) in a 4:1 MeCN- H_2O solvent system, followed by trichloroacetimidate formation (87) with trichloroacetonitrile (Cl_3CCN) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), afforded the trisaccharide donors (87-89), (Scheme 11).

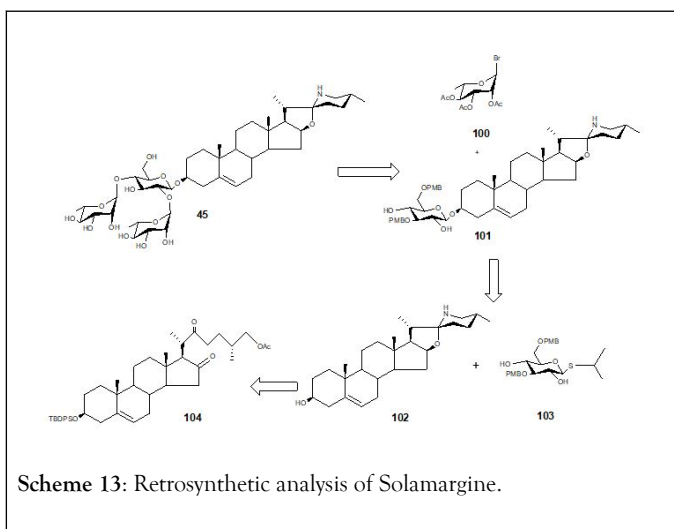


Direct condensation of the trisaccharide donors (87-89) and sarsasapogenin aglycon (90) in the presence of TMSOTf in CH_2Cl_2 at 0°C generated the fully protected trisaccharide saponins (91-93) (Scheme 12). The trisaccharide products (91-93) were obtained together with C-2 deacetylated trisaccharide products (94-96) and α -isomers of trisaccharide products (97-99). Finally, deacetylation of the trisaccharide saponins (91-93) and (94-96) in methanol with 1 N aqueous sodium hydroxide generated compounds (76-78). Similarly, the acetyl protecting groups of trisaccharide saponins (97-99) were removed by a solution of NaOH 1 N in methanol, giving the α -isomer products (76a-78a), (Scheme 12).

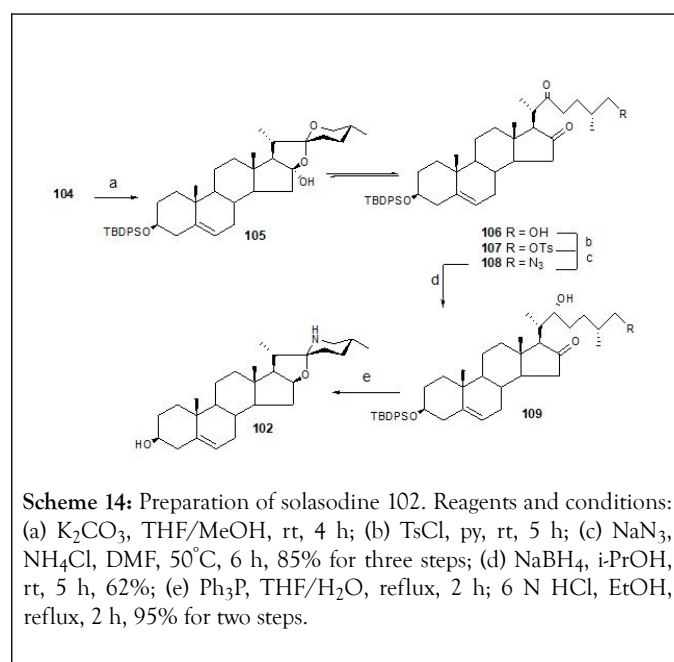


The anti-proliferative activity was evaluated for trisaccharide saponins (76-78) and (76a-78a) against MKN-45 and HeLa, two human tumor cell lines. Results showed that all the synthetic trisaccharide saponins exhibited moderate anti-proliferative activities (IC₅₀:11 μM) against MKN-45 and HeLa tumor cells. The structurally derived saponins 76 and 77 and their α-isomer saponins (76a-78a), revealed similar IC₅₀ values against both tumor cell lines as well as the natural saponin (76), which indicated that modification of sugar unit and conversion of glycosyl bond between the sugar chain and steroidal aglycon did not have any influence on the bioactivities displayed by these compounds. The results were compared with adriamycin, as a strong positive control [121-123].

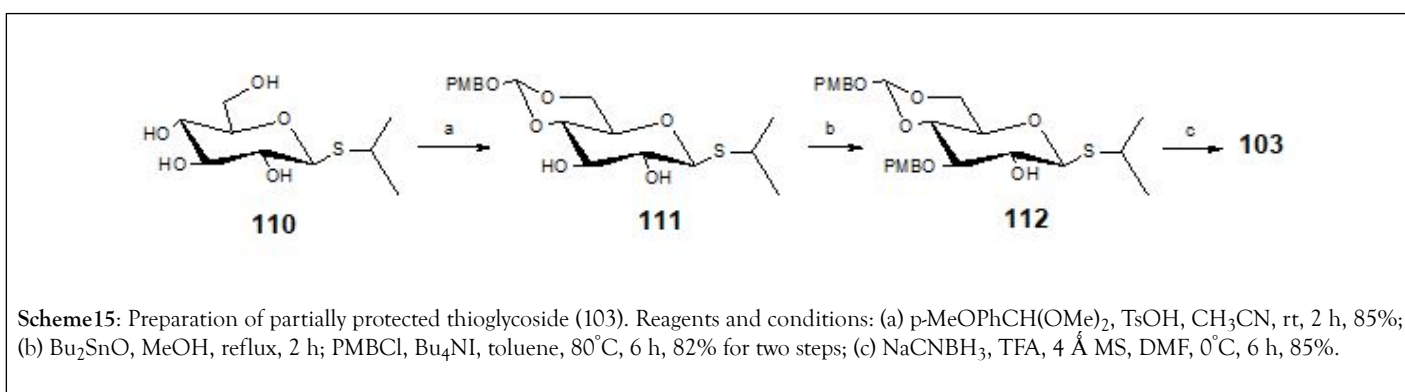
It synthesized solamargine (45), (25R)-3β-[(1→2)-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyloxy]-22-N-spirosol-5-ene following a 13 steps synthetic pathway starting from the secondary metabolite diosgenin with a 10.5% yield (Scheme 13). The cytotoxic activity of synthetic solamargine (45) on HeLa, A549, MCF-7, K562, HCT116, U87, and HepG2 tumour cell lines, as well as two normal cell lines (HL7702 and H9C2), was assessed following the standard MTT assay [124]. Results showed that synthetic solamargine 45 exhibit cytotoxic activity with IC₅₀ values ranging from 2.1 to 8.0 μM in all cell lines evaluated, but showed low cytotoxicity to the normal hepatocyte cell HL7702.



Treatment of (104) with K₂CO₃ in MeOH generated spiroketal (105) and its counterpart dione (106). These two compounds were found to be interconvertible in organic solution and consequently, the mixture of (105-106) was treated directly with p-toluenesulfonyl chloride/pyridine (→ 107), followed by azido-substitution with NaN₃, to give (108). It has been well documented that selective reduction of the 16-ketone of the cholestan-16,22-dione with NaBH₄ in i-PrOH provided the corresponding furostan through a concurrent intramolecular hemiketal formation. Applying the same idea, dione (108) was successfully converted into the hemiketal (109). The reductive-cyclization of compound (109) was carried out in the presence of Ph₃P under refluxing conditions, and followed by desilylation with 6N HCl to produce solasodine (102) (Scheme 14).



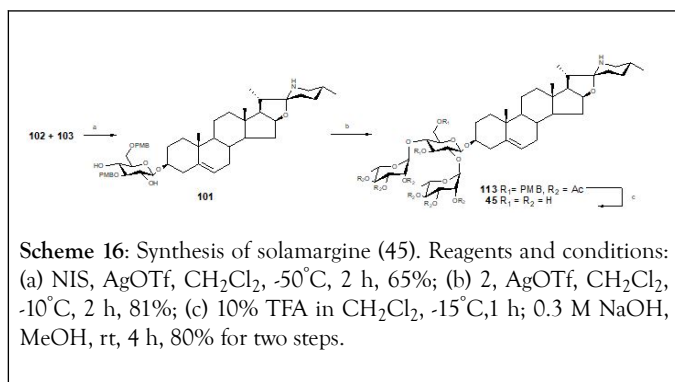
The partially protected thioglycoside donor (103) was prepared from compound (110) and p-methoxybenzylideneation of (110) with anisaldehyde dimethyl acetal (→ 111), followed by tin-assisted regioselective p-methoxybenzylation, provided (112) from (110). Selective ring opening of (112) with sodium cyanoborohydride and trifluoroacetic acid afforded (103) (Scheme 15).



Coupling of solasodine (102) and a partially protected glycosyl donor (103) was carried out in dry methylene dichloride in the presence of AgOTf and N-iodosuccinimide (NIS) at -50°C

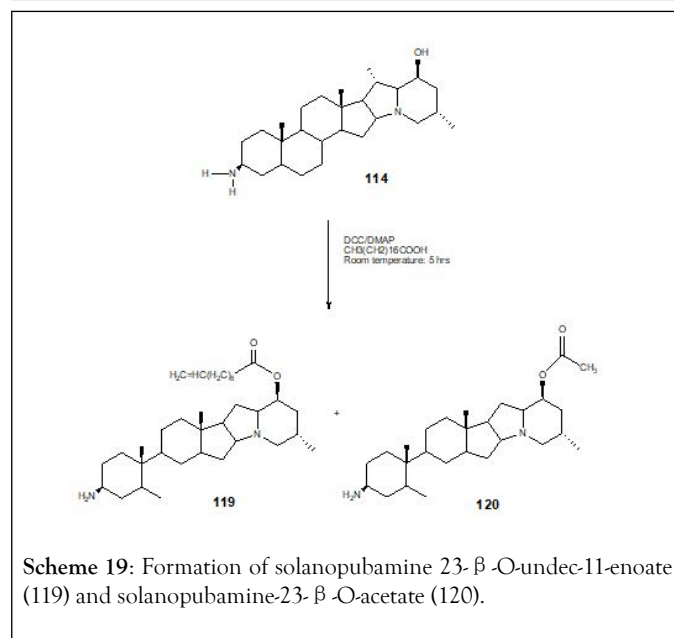
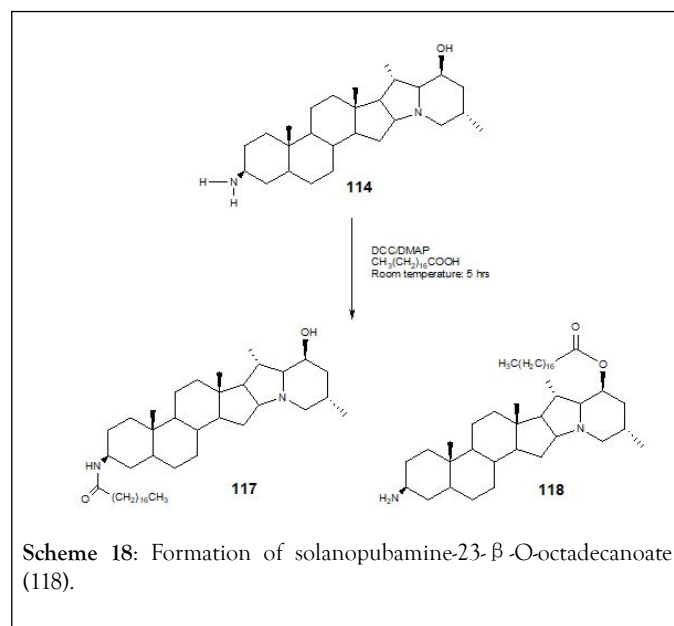
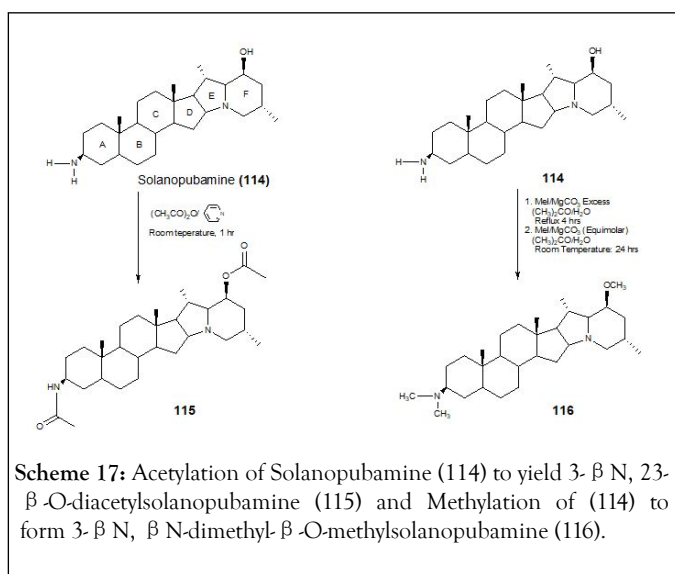
generating the saponin (101). Moreover, condensation of (101) with (100) generated saponin (113). Finally, removal of the PMB groups from compound (113) by using 10% TFA in CH₂Cl₂ at

-15°C, followed by deacylation with 0.3 M NaOH in MeOH afforded compound (45) (Scheme 16).

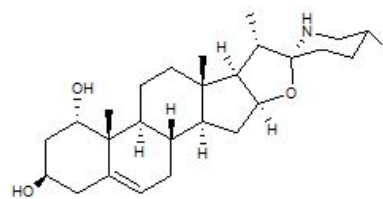
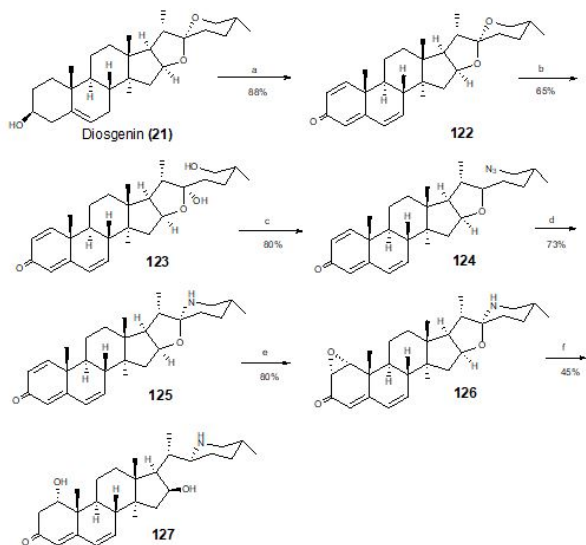


They were studied Solanopubamine (114) (3β-amino-5α, 22α-H, 25β-H-solanidan-23β-ol) a steroidal alkaloid isolated from *Solanum schimperianum*. IR, positive ESI-MS, 1D and 2D NMR techniques, established the structure. The presence of 3β-NH₂ and 23β-OH groups was achieved through methylation, acetylation or coupling with octadecanoic and undec-11-enoic acids to achieve six derivatives (115-120). Synthetic transformation of 3β-C-NH₂ and 23β-COH of solanopubamine (114) was carried out in order to provide new semi-natural compounds, such as (116, 117, 118, 119 and 120), (Schemes 17-19) [125].

Solanopubamine and semi-synthetic analogs were investigated for their *in vitro* cytotoxicity against several human cancer cell lines (SK-MEL, human malignant melanoma; KB human epidermal carcinoma; BT-549, human ductal carcinoma; SK-OV-3, human ovary carcinoma; HL-60, human leukemia; VERO, monkey kidney fibroblast) and also to evaluate anti-microbial activity. Solanopubamine showed antifungal activity only against *Candida albicans* and *Candida tenuis* with MIC value of 12.5 μg/mL. Semi-synthetic compounds (114-120) did not show neither anti-tumor nor anti-microbial activity.

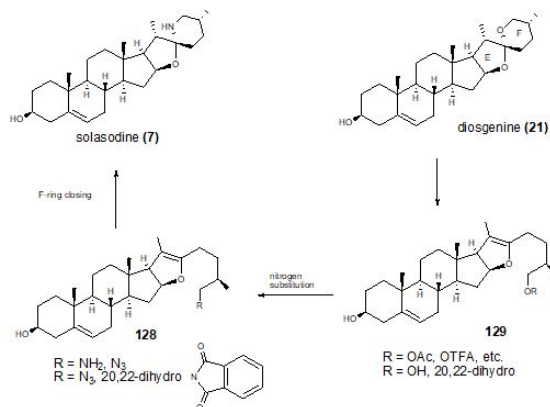


The search for new vitamin D analogues with a rigid side chain as a promising precursor containing a conformationally constrained spiro ring at the side chain is another topic of interest for researchers [126]. Thus, the synthesis of 1α-hydroxysolasodine (121, Figure 6) from diosgenin. In this investigation, all synthetic compounds as well as solasodine were evaluated for their cell growth inhibitory activity against human prostate cancer (PC3), human cervical carcinoma (Hela), and human hepatoma (HepG2) cell lines. During the process of synthesis, a Birch reduction of 1α, 2α-epoxy-4,6-dien-3-one analogue (126) led to an unexpected tetrahydrofuran ring opening product (127). The piperidine E-ring seems to have great impact on the chemical reactivity of solasodine. Regarding the cytotoxic activity only epoxide 126 displayed moderate inhibitory rates towards these cells (40%-54%) at the concentration of 10 μM (Scheme 20).

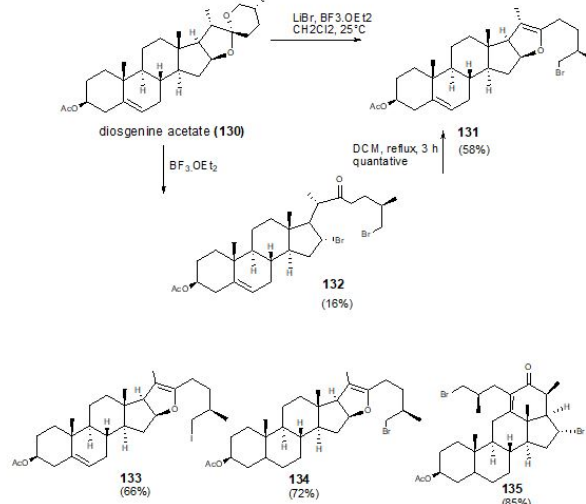
1- α -Hydroxysolasodine (**121**)Figure 6: The chemical structures of 1 α -Hydroxysolasodine (**121**).

Scheme 20 : Synthesis of solasodine analogues from diosgenin. Reagents and conditions: (a) 10% Pd/C, ADP, Na₂CO₃, DMF, reflux; (b) (i) Ac₂O, POCl₃, pyridine; (ii) KOH, H₂O, MeOH; (c) PPh₃, DIAD, DPPA, THF; (d) TMSCl, NaI, MeCN, reflux; (e) H₂O₂, NaOH, MeOH; (f) Li, NH₃ (l), -78°C.

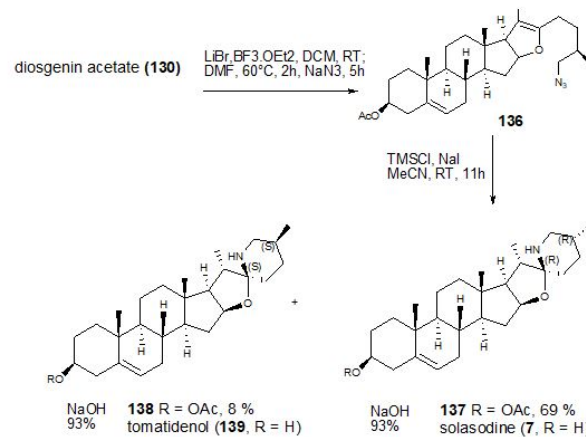
The halogenation-ring opening reaction of spiroketals in steroidal sapogenins at room temperature which provides α -halo enol ethers in high yields. Boosted by this method, solasodine known as an antitumor steroidal alkaloid was obtained from diosgenin acetate through three steps synthesis with an overall yield of 50%. In addition, the isomerization of C25 in steroidal alkaloids was observed and tomatidenol (**139**) was also prepared as side product. Authors were able to determine that configuration at C22 and C25 always appear in pairs (R,R or S,S) which might help to develop a stereoselective synthesis of tomatidenol (**139**), (Schemes 21-23) [127-130].



Scheme 21 : Synthesis strategies of solasodine (**7**) from diosgenin (**21**).



Scheme 22 : A mild halogenation-ring opening reaction of spiroketals.



Scheme 23: Facile synthesis of solasodine (**7**).

CONCLUSION

A number of investigations carried out with steroidal glycoalkaloids isolated from different *Solanum* species have demonstrated that these type of secondary metabolites have antifungal, trypanolytic, trypanocidal, larvicidal, molluscicide, acaricidal hepatoprotective, anti-ulcerogenic, anti-seizure, cytoprotective, neuro-pharmacological, antioxidative, antimicrobial and embryotoxic activities, as well as exhibit significant anticancer effect. In addition, studies have evidenced that steroidal glycoalkaloids, in particular, aglycones solanidine and solasodine have antitumor activity against many tumor cell lines. Thus, the increased interest of researchers to obtained these metabolites by synthetic pathway.

In this regard, eight solasodine derivatives have been obtained by synthesis revealing high antiproliferative activity. The possible effects of the sugar moiety present in glycoalkaloids have also been studied against cancer cells achieving promising results. Furthermore, solanopubamine and semi-synthetic analogs were investigated for their *in vitro* cytotoxicity against several human cancer cell lines exhibiting excellent cytotoxic activity. Due to the importance of these metabolites and their synthetic derivatives, research on this field should continue in order to obtain new compounds that might show a wide range of biological and pharmacological activities.

REFERENCES

- Roddick JG. Steroidal glycoalkaloids: natural and consequences of bioactivity, Plenum Press, New York, 1996; pp:277.
- Hameed A, Ijaz S, Mohammad IS, Muhammad KS, Akhtar N, Khan HMS. Aglycone solanidine and solasodine derivatives: A natural approach towards cancer. Biomed Pharmther. 2017;94:446-457.
- Roddick JG, Weissenberg M, Leonard AL. Membrane disruption and enzyme inhibition by naturally-occurring and modified chactriose containing *Solanum* steroidal glycoalkaloids. Phytochem. 2001;56(6):603-610.
- Tarlakovskii SA. Studies on sterol and sterol glycoalkaloids in potato leaves e relation to the problem of their field resistance to *Phytophthora infestans*. Vsesoiuznyi Nauchno-Issledovatel'skii Inst. Zashchity Rastenii, Trudy, Leningrad, 1981; pp:59-66.
- Tingey WM. Glycoalkaloids as pest resistance factors. Am Potato J. 1984;61:157-159.
- Fewell AM, Roddick JG, Weissenberg M. Interactions between the glycoalkaloids solasonine and solamargine in relation to inhibition of fungal growth. Phytochem. 1994;37(4):1007-1011.
- Johnston KA, Kershaw WJS, Pearce RS. Biological mechanism of resistance of potatoes to slug attack. Br Crop Protection Monogr. 1989;41:281-288.
- Hostettman K, Marston A. Saponins. Cambridge University Press: 2nd edn. Cambridge, UK, 1995;121-136.
- Ripperger H, Schreiber K. In The Alkaloids; 9th edn. Academic: New York, 1981;81-192.
- Weissenberg M. Isolation of solasodine and other steroidal alkaloids and saponins by direct hydrolysis-extraction of *Solanum* plants or glycosides. Phytochem. 2001;58(3):501-508.
- Lequart V, Goethals G, Usubillaga A, Villa P, Cecchelli R, Martin P. Synthesis of chactriose analogues. Carboh Res. 2004;339:1511-1516.
- Kuhn R, Loew I. The constitution of solanines. Chem Ber. 1955;88:1492-1507.
- Kuhn R, Loew I. The constitution of α -chaconines. Chem Ber. 1955;88:1690-1693.
- Kuo KW, Hsu SH, Li YP, Lin WL, Liu LF, Chang LC, et al. Anticancer activity evaluation of the *solanum* glycoalkaloid solamargine. Triggering apoptosis in human hepatoma cells. Biochem Pharmacol. 2000;60:1865-1873.
- Cham BE, Daunter B. Solasodine rhamnosyl glycosides cause apoptosis in cancer cells. do they also prime the immune system resulting in long-term protection against cancer? Cancer Lett. 1990;55:209.
- Nakamura T, Komori C, Lee YY, Hashimoto F, Yahara S, Nohara T, et al. Cytotoxic activity of steroidal glycosides from *solanum* plants. Biol Pharm Bull. 1996;19:564-566.
- Hu K, Dong AJ, Yao XS, Kobayashi H, Iwasaki S. Antineoplastic agents; I. Three spirostanol glycosides from rhizomes of *Dioscorea collettii* var. *hypoglauca*. Planta Med. 1996;62:573-575.
- Liu LF, Liang CH, Shiu LY, Lin WL, Lin C C, Kuo KW. Action of solamargine on human lung cancer cells: enhancement of the susceptibility of cancer cells to TNFs. Febs Letters. 2004;577:67-74.
- Fukuhara K, Shimizu K, Kubo I. Arudonine, an allelopathic steroidal glycoalkaloid from the root bark of *Solanum arundo* Mattei. Phytochem. 2004;65(9):1283-1286.
- Zha X, Sun H, Hao J, Zhang Y. Efficient synthesis of solasodine, O-Acetylsolasodine, and soladulcidine as anticancer steroidal alkaloids. Chem Biodivers. 2007;4(1):25-31.
- Sheikh NA, Attard GS, Rooijen N. Differential requirements for CTL generation by novel immunostimulants: APC tropism, use of the TAP-independent processing pathway, and dependency on CD80/CD86 costimulation. Vaccine. 2003;21(25):3775-3788.
- Bejarano L, Mignolet E, Devaux A, Espinola N, Carrasco E, Larondelle Y. Glycoalkaloids in potato tubers: the effect of variety and drought stress on the α -solanine and α -chaconine contents of potatoes. J Sci Food Agric. 2000;80(14):2096-2100.
- Kuo KW, Hsu SH, Li YP, Lin WL, Liu LF, Chang LC, et al. Anticancer activity evaluation of the *solanum* glycoalkaloid solamargine Triggering apoptosis in human hepatoma cells. Biochem Pharmacol. 2000;60:1865-1873.
- Sandrock RW, Vanetten H. Fungal sensitivity to and enzymatic degradation of the phytoanticipin α -tomatine. Phytochem. 1998;88:137-143.
- Blankemeyer JT, McWilliams ML, Rayburn JR, Weissenberg M, Friedman M. Developmental toxicology of solamargine and solasonine glycoalkaloids in frog embryos. Food Chem Toxicol. 1998;36(5):383-389.
- Langkilde S, Mandimika T, Schroder M, Meyer O, Slob W, Peijnenburg A, et al. A 28-day repeat dose toxicity study of steroidal glycoalkaloids, α -solanine and α -chaconine in the Syrian Golden hamster. Food Chem Toxicol. 2009;47(6):1099-1108.
- Roddick JG, Rijnenberg AL, Osman SF. Synergistic interaction between potato glycoalkaloids α -solanine and α -chaconine in relation to destabilization of cell membranes: ecological implications. J Chem Ecol. 1988;14(3):889-902.
- Smith BD, Roddick JG, Jones JL. Potato glycoalkaloids: some unanswered questions, Trends. Food Sci Technol. 1996;7(4):126-131.
- Prelog V, Jeger O. "Steroid alkaloids: The chemistry of *solanum* and *veratrum* alkaloids." in, the alkaloids chemistry and physiology, 3rd Edn. Academic Press Inc, New York, 1953; pp: 248-312.
- Prelog V, Jeger O. In "The Alkaloids" 7th Edn, Academic Press, New York, 1960; pp:343.
- Habermehl G. In: The Alkaloids. RHF Manske. 9th edn, Academic Press: New York, 1967; pp:147.

32. Schreiber VK, Ripperger HZ. Chapter 2 chemistry and biology of steroidal alkaloids. *Naturforsch.* 1962;17:217.
33. Wagner H, Seegert K, Sonnenbichler H, Ilyas M, Odenthal KP. Die steroidalalkaloide von *funtumia africana*. *Planta Med.* 1987;53(5):444-449.
34. Harrison DM. Steroidal alkaloids. *Nat Prod Rep.* 1990;7:139-147.
35. Schakirov R, Yunusov MS. Steroidal Alkaloids. *Nat Prod Rep.* 1990;7:557.
36. Rahman A. Diterpenoid and Steroidal Alkaloids. Elsevi Sci Publ. Amsterdam. 1990.
37. Rahman A, Choudhary MI. Diterpenoid and steroidal alkaloids. *Nat Prod Rep.* 1995;4:361-379.
38. Rahman A, Choudhary MI. Diterpenoid and steroidal alkaloids. *Nat Prod Rep.* 1997;14(2):191.
39. Rahman A, Nisa MS, Farhi S. Some recent isolation structural and synthetic studies on the constituents of indigenous medicinal plants. *Nat Prod Chem.* 1984;39:330-357.
40. Lin CN, Chung MI, Lin SY. Steroidal alkaloids from *Solanum capsicastrum*. *Phytochem.* 1987;26:305-307.
41. Basterrechea MJ, Mola JL, Coll F, Verez V. Chapter two pyridine and piperidine alkaloids: an update. *rev cubana quim.* 1987;2(71):155-299.
42. Murakami K, Ezima H, Takaishi Y, Takeda Y, Fujita T, Sato A, et al. Pre-germinated brown rice could enhance maternal mental health and immunity during lactation. *Chem Pharm Bull.* 1985;33:67.
43. Schreiber VK, Ripperger HZ. Synthesis of cyclopentadienyl metal compounds. *Naturforsch.* 1962;17:217.
44. Chakravarty AK, Das B, Pakrashi SC. Juripidine. A 3-amino steroidal alkaloid from roots of *Solanum hispidum*. *Phytochem.* 1983;22:2843.
45. Fewell AM, Roddick JG. Interactive antifungal activity of the glycoalkaloids α -solanine and chaconine. *Phytochem.* 1993;33:323-328.
46. Alison MF, Roddick JC, Weissenberg M. Interactions between the glycoalkaloids solasonine and solamargine in relation to inhibition of fungal growth. *Phytochem.* 1994;37(4):1007-1011.
47. Alison MF, Roddick JC. The glycoalkaloids solasonine and solamargine in relation to inhibition of fungal growth. *Phytochem.* 1993;33(2):323.
48. Chen YH, Zhou QT, Bai DL. Synthesis of several analogues of antifungal steroid alkaloids. *Acta Pharm Sin.* 1998;33:436-441.
49. Lee HS, Seo Y, Rho JR, Shin J, Paul VJ. New steroidal alkaloids from an undescribed sponge of the genus *Corticium*. *J Nat Prod.* (2001;64:1474-1476.
50. Zhou CX, Liu JY, Ye WC, Liu CH, Tan RX. Neoverataline A and B, two antifungal alkaloids with a novel carbon skeleton from *Veratrum taliense*. *Tetrahedron.* 2003;59:5743-5747.
51. Shamim S, Ahmed SW, Azhar I. Antifungal activity of allium, aloe, and *Solanum* species. *Pharm Biol.* 2004;42(7):491-498.
52. Chataing B, Concepción JL, Lobatón R, Usubillaga A. Inhibition of *Trypanosoma cruzi* growth *in vitro* by *Solanum* alkaloids: a comparison with ketoconazole. *Planta Medica.* 1998;64:31-36.
53. Ahmed A, Kamal I, Ramzy R. Studies on the molluscicidal and larvicidal properties of *Solanum nigrum* L. leaves ethanol extract. *J Egypt Soc Parasitol.* 2001;31(3):843-852.
54. Wanyonyi AW, Chhabra SC, Mkoji G, Njue W, Tarus PK. Molluscicidal and antimicrobial activity of *Solanum aculeastrum*. *Fitoterapia.* 2003;74(3):298-301.
55. Ahmed A, Rifaat M. Molluscicidal and cercaricidal efficacy of *Acanthus mollis* and its binary and tertiary combinations with *Solanum nigrum* and *Iris pseudacorus* against *Biomphalaria alexandrina*. *J Egypt Soc Parasitol.* 2004;34(3):1041-1050.
56. Ahmed A, Rifaat M. Effects of *Solanum nigrum* leaves water extract on the penetration and infectivity of *Schistosoma mansoni* cercariae. *J Egypt Soc Parasitol.* 2005;35(1):33-40.
57. Sultana S, Perwaiz S, Iqbal M, Athar M. Crude extracts of hepatoprotective plants, *Solanum nigrum* and *Cichorium intybus* inhibit free radical-mediated DNA damage. *J Ethnopharmacol.* 1995;45(3):189-192.
58. Raju K, Anbuganapathi G, Gokulakrishnan V, Rajkapoor B, Jayakar S. Manian Effect of dried fruits of *Solanum nigrum* LINN against CCl4-induced hepatic damage in rats. *Biol Pharm Bull.* 2003;26(11):1618-1619.
59. Lin HM, Tseng HC, Wang CJ, Lin JJ, Lo CW, Chou FP. Hepatoprotective effects of *Solanum nigrum* Linn extract against CCl 4-induced oxidative damage in rats. *Chem Biol Interact.* 2008;171(3):283-293.
60. Jainu M, Devi CSS. Antiulcerogenic and ulcer healing effects of *Solanum nigrum* (L.) on experimental ulcer models: possible mechanism for the inhibition of acid formation. *J Ethnopharmacol.* 2006;104(1):156-163.
61. Wannang NN, Anuka JA, Kwanashie HO, Gyang S, Auta A. Anti-seizure activity of the aqueous leaf extract of *Solanum nigrum* Linn (solanaceae) in experimental animals. *Afr Health Sci.* 2008;8(2):74-79.
62. Kumar VP, Shashidhara S, Kumar M, Sridhara B. Cytoprotective role of *Solanum nigrum* against gentamicin-induced kidney cell (Vero cells) damage *in vitro*. *Fitoterapia.* 2001;72(5):481-486.
63. Perez RM, Perez JA, Garcia LM, Sossa H. Neuropharmacological activity of *Solanum nigrum* fruit. *J Ethnopharmacol.* 1998;62(1):43-48.
64. Heo KS, Lim KT. Antioxidative effects of glycoprotein isolated from *Solanum nigrum* L. *J Med Food.* 2004;7(3):349-357.
65. Abas F, Lajis NH, Israf D, Khozirah S, Kalsom YU. Antioxidant and nitric oxide inhibition activities of selected Malay traditional vegetables. *Food Chem.* 2006;95(4):566-573.
66. Rani P, Khullar N. Antimicrobial evaluation of some medicinal plants for their anti-enteric potential against multi-drug resistant *Salmonella typhi*. *Phytother Res.* 2003;18 (2):670-673.
67. Raybum JR, Friedman M, Bantle JA. Synergistic interaction of glycoalkaloids alpha-chaconine and alpha-solanine on developmental toxicity in *Xenopus* embryos. *Food Chem Toxicol.* 1995;33(12):1013-1019.
68. Thome HV, Clarke CF. The inactivation of herpes simplex virus by some *Solanaceae* glycoalkaloids. *Antiviral Res.* 1985;5(6):335-342.
69. Samuel B, Switz S. Concentrations of mercury, copper, cadmium and lead in fruiting bodies of edible mushrooms in the vicinity of amercury smelter and a copper smelter. *Dtsch Apoth.* 1996;136(19):251-258.
70. Marino SD, Iorizzi M, Zollo F, Roussakis C, Debitus C, Plakinamines C. Dand three other new steroidal alkaloids from the sponge *Corticium* sp. *Eur J Org Chem.* 1999;3:697-701.
71. Chang LC, Bhat KPL, Pisha E, Kennelly EJ, Fong HHS, Pezzuto JM, et al. Activity-guided isolation of steroidal alkaloid antiestrogen-binding site inhibitors from *Pachysandra procumbens*. *J Nat Prod.* 1998;61:1257-1262.
72. Emmanuel S, Ignacimuthu S, Perumalsamy R, Amalraj T. Antiinflammatory activity of *Solanum trilobatum*. *Fitoterapia.* 2006;77:611-612.
73. Ding X, Zhu FS, Li M, Gao SG. Induction of apoptosis in human hepatoma SMMC-7721 cells by solamargine from *Solanum nigrum* L. *J Ethnopharmacol.* 2012;139(2):599-604.

74. Hossain MB, Tiwari BK, Gangopadhyay N, O'Donnell CP, Brunton NP, Rai DK. Ultrasonic extraction of steroidal alkaloids from potato peel waste. *Ultrason Sonochem.* 2014;21:1470-1476.
75. Li J, Li Q, Feng T, Li K. Aqueous extract of *Solanum nigrum* inhibit growth of cervical carcinoma (U14) via modulating immune response of tumor bearing mice and inducing apoptosis of tumor cells. *Fitoterapia.* 2008;79(7):548-556.
76. Kupchan SM, Barboutis SJ, Knox JR, Lau Cam CA. Betasolamarine: tumor inhibitor isolated from *Solanum dulcamara*. *Science.* 1965;150:1827-1828.
77. Lee KR, Kozukue N, Han JS. Glycoalkaloids and metabolites inhibit the growth of human colon (HT29) and liver (HepG2) cancer cells. *J Agric Food Chem.* 2004;52(10): 2832-2839.
78. Lee ST, Welch KD, Panter KE, Gardner DR, Garrossian M, Chang CWT. Cyclopamine: from cyclops lambs to cancer treatment. *J Agric Food Chem.* 2014;62:7355-7362.
79. Sunassee SN, Ransom T, Henrich CJ, Beutler JA, Covell DG, McMahon JB, et al. Steroidal alkaloids from the marine sponge *Corticium niger* that inhibit growth of human colon carcinoma cells. *J Nat Prod.* 2014;77:2475-2480.
80. Prakash O, Kumar A, Kumar P, Ajeet. Anticancer potential of plants and natural products: A review. *Am J Pharmacol Sci.* 2013;6:104-115.
81. Phi TD, Pham VC, Thi Mai HD, Litaudon M, Guéritte F, Nguyen VH, et al. Cytotoxic steroidal alkaloids from *Kibatalia laurifolia*. *J Nat Prod.* 2011;74:1236-1240.
82. Zhang ZQ, Luo JG, Wang JS, Kong LY. Five new steroidal alkaloid glycosides from *Solanum tuberosum*. *Helv Chim Acta.* 1996;96:931-940.
83. Gaffield W, Keeler RF. Structure and stereochemistry of steroidal amine teratogens. *Adv Exp Med Biol.* 1984;177:241-251.
84. Gaffield W, Keeler RF. Induction of terata in hamsters by Solanidane alkaloids derived from *Solanum tuberosum*. *Chem Res Toxicol.* 1996;9:426-433.
85. Vaz NP, Costa EV, Santos EL, Mikich SB, Marques FA, Braga RM, et al. Caavuranamide, a novel steroidal alkaloid from the ripe fruits of *Solanum caavurana* Vell. (Solanaceae). *J Braz Chem Soc.* 2012;23:361-366.
86. Devkota KP, Lenta BN, Wansi JD, Choudhary MI, Kisangau DP, Naz Q, et al. Bioactive 5 α -pregnane-type steroidal alkaloids from *Sarcococca hookeriana*. *J Nat Prod.* 2008;71:1481-1484.
87. Zakaria ZA, Gopalan HK, Zainal H, Mohd Pojan NH, Morsid NA, Aris A, et al. Antinociceptive, anti-inflammatory and antipyretic effects of *Solanum nigrum* chloroform extract in animal models. *Pharm Soc Jap.* 2006;126(11):1171-1178.
88. Ikeda T, Miyashita H, Kajimoto T, Nohara T. Synthesis of neosaponins having an α -L-rhamnopyranosyl-(1 \rightarrow 4)- β -L-rhamnopyranosyl-(1 \rightarrow 2)-D-glucopyranosyl glyco-linkage. *Tetrahedron Lett.* 2001;42:2353-2356.
89. Ikeda T, Kinjo J, Kajimoto T, Nohara T. Synthesis of Neosaponins Carrying Oligosaccharides from Natural Products. *Heterocycles.* 2000;52(2):775-798.
90. Hu K, Kobayashi H, Dong A, Jing Y, Iwasaki S, Yao X. Antineoplastic agents. III: steroidal glycosides from *Solanum nigrum*. *Planta Med.* 1999;65(1):35-38.
91. Ding X, Zhu F, Yang Y, Li M. Purification, antitumor activity *in vitro* of steroidal glycoalkaloids from black nightshade (*Solanum nigrum* L.) *Food Chemistry.* 2013;141: 1181-1186.
92. Saijo R, Murakami K, Nohara T, Tomimatsu T, Sato A, Matsuoka K. Studies on the constituents of *Solanum* plants. II. On the constituents of the immature berries of *Solanum nigrum* L. (author's transl), *Yakugaku zasshi.* *J Pharm Soc Jap.* 1982;102(3): 300-305.
93. Eltayeb EA, Al-Ansari AS, Roddick JG. Changes in the steroidal alkaloid solasodine during development of *Solanum nigrum* and *Solanum incanum*. *Phytochem.* 1997;46(3):489-494.
94. Shabana MM, Salama MM, Ezzat SM, Ismail LR. *In vitro* and *in vivo* anticancer activity of the fruit peels of *Solanum melongena* L. against hepatocellular carcinoma. *J Carcinog Mutagen.* 2013;4(3): 1-6.
95. Aoki S, Watanabe Y, Tanabe D, Arai M, Suna H, Miyamoto K, et al. Structure - activity relationship and biological property of cortistatins, anti-angiogenic spongean steroidal alkaloids. *Bioorg Med Chem.* 2007;15:6758-6762.
96. Cham BE. Solasodine rhamnosyl glycosides specifically bind cancer cell receptors and induce apoptosis and necrosis. Treatment for skin cancer and hope for internal cancers. *Res J Biol Sci.* 2007;2:503-514.
97. Cui C, When X, Cui M, Gao J, Sun B, Lou H. Synthesis of solasodine glycoside derivatives and evaluation of their cytotoxic effects on human cancer cells. *Drug Discov Ther.* 2012;6(1):9-17.
98. Esteves SA, Smento da Silva TM, Alves CCF. Leptospirose pulmonary Pulmonary leptospirosis. *J Bra Chem Soc.* 2002;13(6): 838.
99. Liu MJ, Wang Z, Ju Y, Zhou JB, Wang Y, Wong RNS. The mitotic-arresting and apoptosis-inducing effects of diosgenyl saponins on human leukemia cell lines. *Biol Pharm Bull.* 2004;27:1059-1065.
100. Yang YW, Wu CA, Moirou WJW. Immunobiology of the tomatine adjuvant. *Vaccine.* 2004;22(17):2380-2384.
101. Sun L, Zhao Y, Yuan H, Li X, Cheng A, Lou H. Solamargine, a steroidal alkaloid glycoside, induces oncosis in human K562 leukemia and squamous cel carcinoma KB cells. *Can Chemother Pharmacol.* 2011;67:813-821.
102. Li X, Zhao Y, Ji M, Liu SS, Cui M, Lou HX. Induction of actin disruption and downregulation of P-glycoprotein expression by solamargine in multidrug-resistant K562/A02 cells. *Chin Med J.* 2011;124:2038-2044.
103. Punjabi S, Cook LJ, Kersey P, Marks R, Cerio R. Solasodine glycoalkaloids: A novel topical therapy for basal cell carcinoma. A double-blind, randomized, placebo-controlled, parallel group, multicenter study. *Intern J Dermatol.* 2008;47:78-82.
104. Lezama-Dávila CM, McChesney JD, Bastos JK, Miranda MA, Tioosi RF, da Costa JC, et al. A new antileishmanial preparation of combined solamargine and solasonine heals cutaneous leishmaniasis through different immunochemical pathways. *Antimicrob Agents Chemother.* 2016;60:2732-2738.
105. Hall CA, Hobby T, Cipollini M. Efficacy and mechanisms of α -solasonine and α -solamargine-induced cytolysis on two strains of *Trypanosoma cruzi*. *J Chem Ecol.* 2006;32:2405-2416.
106. Cham BE, Meares HM. Glycoalkaloids from *Solanum sodomeum* are effective in the treatment of skin cancer in man. *Can Lett.* 1987;36:111-1918.
107. Cham BE, Daunter B, Evans RA. Topical treatment of malignant and pre-malignant skin lesions by very low concentrations of a standard mixture (BEC) of solasodine glycosides. *Can Lett.* 1991;59:183-192.
108. Lobatón R. Estudio de los Glicoalcaloides del *Solanum americanum* Miller, Universidad de Los Andes, Mérida, Venezuela. 1995.
109. Rojas BDC. The Biology of Canadian Weeds: 155. *Panicum miliaceum* L. *Rev Facult Agronom.* 1991;49:67-76.
110. Ji Y, Gao S, Ji C, Zou X. Induction of apoptosis in HepG 2 cells by solanine and Bcl-2 protein. *J Ethnopharmacol.* 2008;115(2): 194-202.
111. Gogoi P, Islam M. Phytochemical screening of *Solanum nigrum* L. and *S. myriacanthus* dunal from districts of upper assam, India. *IOSR J Pharm.* 2012;23(2):455-459.

112. Bagheri M, Bushehri AAS, Hassandokht MR, Naghavi MR. Evaluation of solasonine content and expression patterns of SGT1 gene in different tissues of two Iranian eggplant (*Solanum melongena* L.) genotypes. *Food Technol Biotechnol*. 2017;55:236-242.
113. Duan GM. Inhibition of potato glycoalkaloids to human blood cholinesterase. *Chin Biochem J*. 1994;10:575-578.
114. Lahmann M, Gyback H, Garegg PJ, Oscarson S, Suhr R, Thiem T. A facile approach to diosgenin and furostan type saponins bearing a 3 β -chacotriose moiety. *J Carbohydr Res*. 2002;337(21):2153-2159.
115. Suhr R, Pfefferkorn P, Weingarten S, Thiem. Synthesis of rhamnosylated diosgenyl glucosides as mimetics of cytostatic steroidal saponins from *Ornithogalum saundersiae* and *Galtonia candicans*. *J Org Biomol Chem*. 2003;5(24):4373-4379.
116. Du Y, Gu G, Wei G, Hua Y, Linhardt R. Synthesis of Saponins Using Partially Protected Glycosyl Donors. *Org Lett*. 2003;5(20):3627-3630.
117. Morillo M, Lequart V, Grand E, Goethals G, Usubillaga A, Villa Pierre, et al. Synthesis of peracetylated chacotriose. *Carb Res*. 2001;334:281-287.
118. Zhao JM, Li SY, Zhou YF, Zhang LP, Zhou DW. 6-o-sulfated modification of natural glycoalkaloids chaconine and solanine. *Chem Res Chinese*. 2006;22(2):189-192.
119. Li S, He D, Zhang X, Ni W, Zhou Y, Zhang I. Modification of sugar chains in glycoalkaloids and variation of anticancer activity. *Chem Res Chin*. 2007;23(3):303-309.
120. Zha XM, Zhang FR, Shan JQ, Zhang YH, Liu JO, Sun HB. Synthesis and evaluation of *in vitro* anticancer activity of novel solasodine derivatives. *Chin Chem Lett*. 2010;21:1087-1090.
121. Gu G, Fang M, Liu J, Gu Li. Concise synthesis and antitumor activities of trisaccharide steroidal saponins. *Carb Res*. 2011;346:2406-2413.
122. Shi CS, Kehrl JH. Pyk2 amplifies epidermal growth factor and c-src-induced stat3 activation. *J Biol Chem*. 2004;279:17224-17231.
123. Wei G, Wang J, Du Y. Total synthesis of solamargine. *Bioorg Med Chem Lett*. 2011;21:2930-2933.
124. Kuroda M, Mimaki Y, Sashida Y, Hirano T, Oka K, Dobashi A, et al. Novel cholestane glycosides from the bulbs *Ornithogalum saundersiae* and their cytostatic activity on leukemia HL60 and MOLT-4 cells. *Tetrahedron*. 1997;53:11549.
125. Al-Rehaily AJ, Ahmad MS, Mustafa J, Al-Oqail MM, Hassan WH, Khan SI, et al. Solanopubamine, a rare steroidal alkaloid from *Solanum schimperianum*: Synthesis of some new alkyl and acyl derivatives, their anticancer and antimicrobial evaluation. *J of Saudi Chem Soc*. 2013;17:67-76.
126. Liu Ch, Xie F, Zhao DG, Wang DF, Lou HX, Liu ZP. Synthetic studies towards 1 α -hydroxysolasodine from diosgenin and the unexpected tetrahydrofuran ring opening in the Birch reduction process. *Steroids*. 2015;51:2231-2243.
127. Wu JJ, Shi Y, Tian WS. Facile synthesis of solasodine based on a mild halogenation-ring opening reaction of spiroketals in steroidal saponins. *Tetrahedron Lett*. 2015;56:1215-1217.
128. Jeger O, Prelog, V. In: *The Alkaloids* (R. H. F. Manske) 2nd edn, Academic Press, New York, 1960;pp:247.
129. Gaffield W, Keeler RF. Induction of terata in hamsters by Solanidane alkaloids derived from *Solanum tuberosum*. *Chem Res Toxicol*. 1996;9:426-433.
130. Du Y, Gu G, Wei G, Hua Y, Linhardt R. Synthesis of saponins using partially protected glycosyl donors. *J Org Lett*. 2003;5:3627-3629.