Review

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Review

Synthesis and Beneficials Effects of Glycerol Derivatives

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Abstract: Glycerol conversion to valuable biomolecules has been a research avenue that has attracted a significant interest in recent years due to its increasing over production, with possibilities for chemical transformation for eco-friendly processes and distinct compounds with biological activities. Also, in the current climate change in which a major emphasis is being placed on the design of green processes, solvents are key factors from both an economic and environmental point of view. In this context, due to its abundance and low-price, glycerol represents an innovative solvent coming from biomass and produce in high amount. On the other hand, Epichlorydrin, Glycidol and Solketal have become useful intermediates in chemical transformations when using glycerol as a raw material. This review focuses on glycerol as a green solvent in the synthesis of complex molecules, Epichlorydrin, Glycidol, Solketal and Tosyl solketal as an efficient recycling process for glycerol, as well as building blocks in the synthesis of glycerol derivatives, which are undeniable new source of potentials drugs.

Keywords: Glycerol; Solketal; alkylglycerol; organochalcogen; green-solvent; glycidol

1. Introduction

The use of fossil resources on the petrochemical processes for the production of fine chemical, fuels, and polymers is a matter of great concern due to the climate change. Therefore, several correctives measures were implemented in order to reduce the environmental pollution while satisfying the energy need and the production of chemicals [1]. Bio-diesel is a green solvent compatible with diesel engines due to its properties such as biodegradability, lower emission and reduced toxicity [2–5].

The major by-product in biodiesel industry is glycerol, which is produced via trans-esterification reaction, while the focus it is still on ecologically friendly catalytic reactions in which waste (glycerol) is turned into commercial products [6]. Currently, the abundance of glycerol formed during biodiesel production as a waste provides a vast low-cost feedstock. In the other hand, in the current climate change in which a major emphasis is being placed on the design of green processes, solvents are a key factor from both an economic and environmental point of view. Therefore, researchers have shown a growing interest in using glycerol as a sustainable solvent for the preparation of complex molecules, as well as an undeniable raw material for the synthesis of potential drugs.

Glycerol as a raw material has versatile applications due to its distinct combination of physio-chemical properties and typical elemental analysis. It is easy to handle and compatible with other substances. It is nontoxic to human health, viscous and stable under different conditions [7,8]. This molecule with low molecular weight has wide applications in cosmetics, foods, polymer, paint, automotive, pulp and paper, plastic and pharmaceutical industries [9,10]. However, the increasing over production of glycerol [11] can turn to uncontrolled waste with the disposal and affect the economics of the biodiesel industries. One of the route to valorize glycerol involves its condensation

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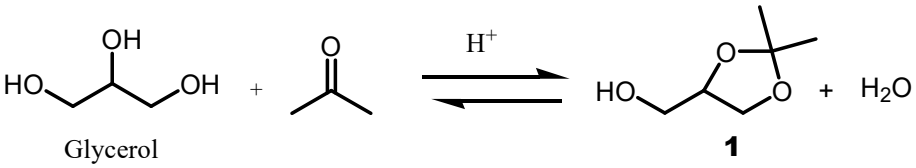
with acetone in the presence of acid as catalyst to provide Solketal **1** (2,2-dimethyl-1,3-dioxolane-4-methanol) [12–16] (Scheme **1**).

(*S*)-Solketal was used as a chiral precursor in the synthesis of medicinally active unnatural products, including the hypotensive *β*-adrenergic blockers, aryl-oxypropanolamines [17], while (*R*)-Solketal was used as a building block in the synthesis of Alkylglycerols and analogues found in the Greenland shark liver oil (SLO) mixture (*Centrophorus squamosus*), which displayed anti-tumor and anti-metastatic activities on a model of grafted tumor in mice (3LL cells), as well as the ability to inhibit the endothelial cell migration [18–21]. In the other hand, tosylsolketal was used as a starting material for the synthesis of several biologically active compounds [22]. Solketal was reported to control the emissions, to enhance the cold flow properties and decreases the gum formation [23]. It was also used as a plasticizer and versatile solvent in the polymer industry [24]

This review focuses on glycerol as a green solvent for the synthesis of complex molecules, and its conversion to Epichlorydrin, Glycidol, Solketal and Tosyl solketal as an efficient recycling process to avoid wastes, and key intermediates which were in turn used as building blocks in the preparation of glycerol derivatives, described as an undeniable new source of potentials drugs.



Scheme 1. Synthesis of Solketal from acetalization of glycerol with acetone.

2. Synthetic Approaches with Glycerol as a Green Solvent

Solvents are used in most of organic reactions as a contact surface between reactants or reagents. In some cases, they can determine the chemical mechanism and the transition states of the intermediates and target molecules, as well as the recycling or disposal strategies. It was reported that a green solvent should possess certain characteristics such as low toxicity, low flammability, biodegradability, functional group compatibility, low volatility organic compounds (VOC) emission, cheap, easy to handle and recyclable with a limited environmental impact coming from the consuming of these solvents in chemical production [25–27]. Conventional solvents such as halogenated, petroleum-based where suggested to be replaced by green solvent such as water, ethyl acetate and glycerol [28].

Glycerol is a sweet-tasting, clear, colorless, odorless and viscous liquid. It is a polar protic solvent with a dielectric constant of 42.5 (at 25°C), which is intermediate between that of water (78.5) and an ionic liquid such as 1-buyl-3-methylimidazolium hexafluorophosphate ([BMIm]PF6, 11.4) [29]. Its low-cost, non-toxicity, high boiling point (290.8°C), negligible vapor pressure (<1 mmHg at 293 K), highest solubility for organic and inorganic compounds, low miscibility with other organic solvents such as ethers and alkanes [30] have made glycerol a green solvent in the synthesis of pharmaceutically active ingredients or potential drugs in which the toxicity and residual solvents are attentively monitored.

2.1. Glycerol as a Viable Solvent in the Synthesis of Bis (Aryl) Ketones and Aryl Compounds

Organometallic compounds are generally prepared by Grignard reagent or lithium acetylides to yield carbon-lithium bonds, which are key intermediates in the synthesis of bioactives compounds. These reactions are carried out through nucleophilic addition or substitution. Due to the high reactivity associated with the Lithium-Carbon bond, constraining protocoles such as inert atmospheres, moisture and oxygen-free organic solvents, low temperatures are used in order to synthesize organolithium compounds [31]. Thus, performing organolithium chemistry under anhydrous conditions and oxygen free without the need of moistureless organic solvents, it is one of the resulting challenge for researchers working in this field. Therefore, glycerol (Gly), owing exceptional physicochemical properties (high boiling point and polarity, low toxicity and flammability) was used as a green solvent to achieve the synthesis of unknown bis (aryl) ketone **4**-**12**

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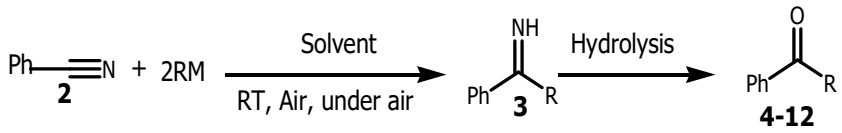
(Table **1**) [32] under air and ambiant temperature. In the meanwhile, the most remarkable aspect of this reaction is that, the use of inert-atmosphere Schlenk techniques or low temperatures that is standard reaction conditions for manipulating organolithium reagents was not required.

Furthermore, once Gly was replaced by others green solvents such as water, dichlomethylene, 2-methyl tetrahydrofuran (Me-THF) or methanol, the yield of these reactions decreased. When phenyllithium or phenylmagnesium bromide (RM) was added to benzonitrile **2** in the presence of Gly and without stirring, the yield was reduced from 83% to 51% (entry 6) compared to water, where the absence of stirring can completely affect the reaction [33].

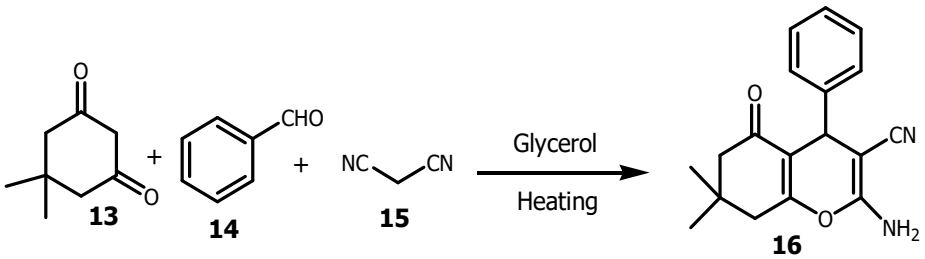
Table 1. Addiction of phenyllithium or phenylmagnesium bromide (RM) to benzonitrile **2** in different green solvents.



RM = PhLi, PhMgBr, R= Ph

Entry	RM	Solvent	Ketone	Yield[%]
1	PhLi	Gly	**4**	83
2	PhLi	1 $CHCl_2$ /2 Gly	**5**	71
3	PhLi	H2O	**6**	79
4	PhLi	Ethylene glycol	**7**	53
5	PhLi	MeOH	**8**	8
6	PhLi	Gly(without stirring)	**9**	51
7	PhLi	Me-THF	**10**	47
8	PhMgBr	Gly	11	traces
9	PhMgBr	Me-THF	12	3

Rodriguez-Alvarez et al. showed that Gly can function as an environmentally friendly reaction medium for the ultrafast and chemoselective addition of aryllithium reagents to nitriles like water under air and ambient temperature, which for almost a century was not mentioned in organometallic Chemistry [32]. Cost-effectiveness of glycerol made it also a good green solvent for the synthesis of 4H-pyrans **16** with catalyst-free (Scheme **2**). It was reported that, when Gly was replaced by water in this cyclization reaction (one-pot and three-component strategy), the yield of the reaction decreased down to 70% [34].



Scheme 2. One pot in three components strategy using glycerol as green solvent.

α,β-Unsaturated carbonyl compounds are important intermediates in organic synthesis. The general structure is (O=CR)−C^{α}=C^{β}-R. In these compounds, the carbonyl group is conjugated with an alkene (unsaturated). A variety of well-established methodologies make use of *α,β*-unsaturated carbonyl compounds to construct diverse building blocks used to prepare bio-active compounds including pharmaceuticals, precursors for materials flavors, fragrances, or optically important

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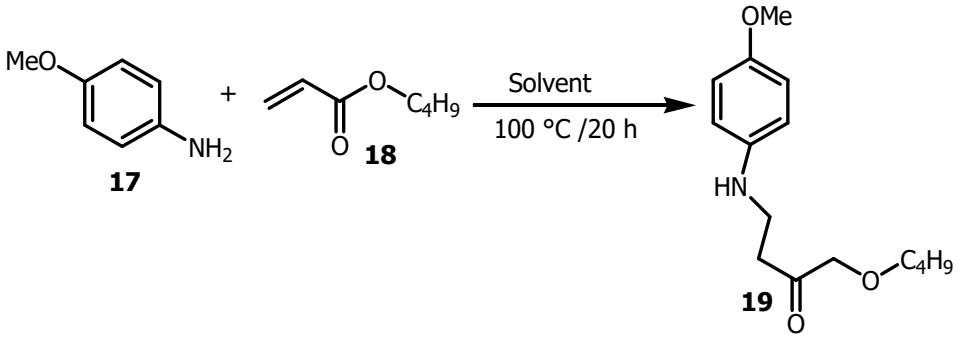
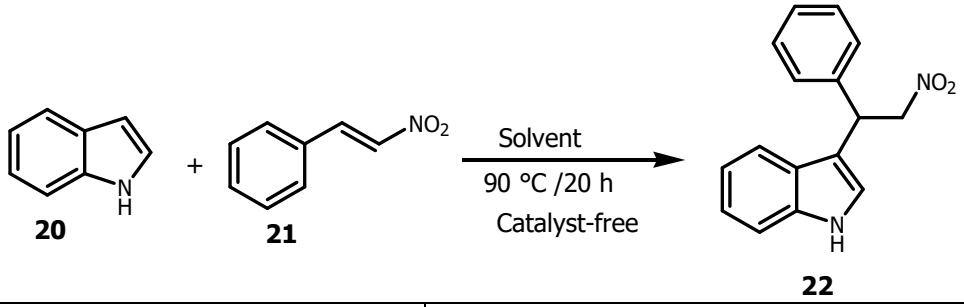
molecules [36–41]. Thus, the synthesis of *α,β* -unsaturated carbonyl compounds remains an actual interesting task in the development of improved synthetic methodologies. In this context, the reaction of a nucleophilic addition on the *β* position of *α,β*-unsaturated carbonyl compound was carried out in different green solvents such as Gly, DMF, toluene and DMSO. Furthermore, it was reported that an aza-Michael reaction between *p*-anisidine **17** and n-butyl acrylate **18** (Scheme **3**) was successfully proceeded under catalyst free conditions with 82% yield when Gly was used as a solvent, while 81% yield was obtained in technical grade glycerol, 30% in 1,2-propanediol, 5% in water and no desired product **19** was observed in toluene, DMSO, DMF or DCE [35].



Solvent	Yield %
Glycerol	82
No solvent	< 5
Toluene	0
DMF	0
DMSO	0
Water	< 5
1,2-propandiole	30

Scheme 3. Nucleophilic addition on *α,β*-unsaturated carbonyl compound in different solvents.

A comparable phenomena was observed in the Michael addition when reacting indole **20** with nitostyrene **21** (scheme **4**), in which only glycerol was found to be capable of providing the desired product **22** in 80% yield under catalyst-free conditions. The desired product was also isolated in liquid-liquid phase extraction with ethyl acetate allowing the recycling of glycerol.



Solvent	Yield %
Glycerol	80
Crude glycerol	78
Toluene	< 5
DMF	< 5
Water	55

Scheme 4. Michael reaction of indole in different solvents.

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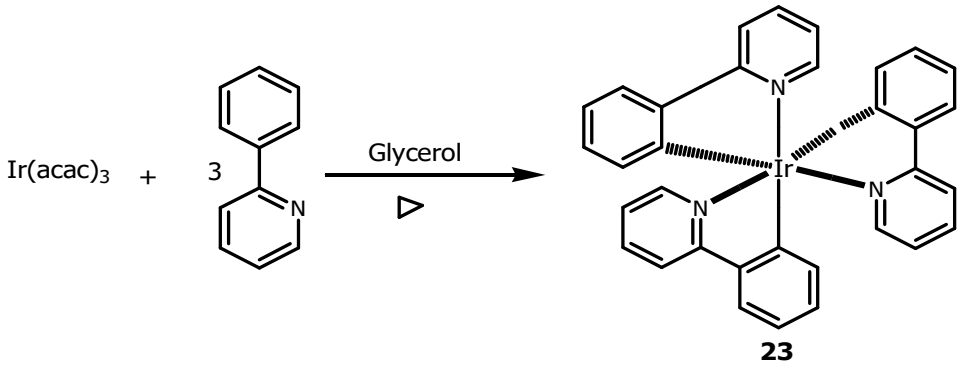
These experimental data accumulated so far displayed the importance of using glycerol as a green solvent free catalyst in organic reactions, thus simplifying the work-up procedure and consequently increasing the cost-effectiveness in the synthetic methodology.

2.2. Glycerol as a Suitable Solvent in the Synthesis of Metallic Complexes

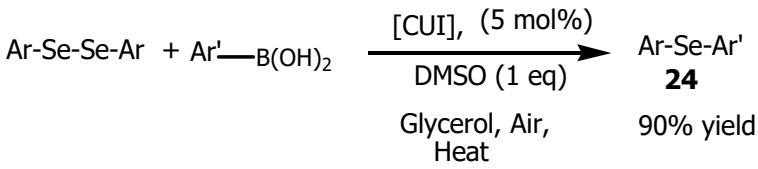
Metallic complexes have attracted huge interest in fields such as nanomaterials, optics, catalysis, molecular framework materials and biomedicine, due to their optical and electrochemical properties, and high specific surface areas [42–44]. Key to all these applications is the dependence of complex composition and structure on the metal ion, and its oxidation state. Glycerol was used as a green solvent in the synthesis of organometallic and coordination compounds due to its properties (viscosity, solubility and lower temperature), while some green solvent with high boiling point are often unsuitable for the synthesis of metal complexes [45]. It was also reported that the free hydroxyl group of Gly hindered the formation of C-H bond involved in cyclometallation reactions [46]. Homoleptic Ir^{III} complexes containing 2-arylpyridine-based ligands (L) of the general formula [Ir(k^2-*N*,*C*-L)$_3$] **23** have been efficiently prepared in glycerol at high temperature (Scheme **5**).



Scheme 5. Synthesis of [Ir{k^2-N,C-(2-phenylpyridine)}$_3$] in neat glycerol.

Following the synthesis of homoleptic Ir^{III} complexes, some metallic complexes other than iridium derivatives have been synthesized (mono- and polymetallic Ru^{II} complexes) containing conjugated N-donor ligands, bimetallic cyclometallated Rh^{III} complexes, and monometallic Zn^{II} and Cd^{II} complexes in glycerol, which have also found applications in different fields due to their optical or electrochemical properties [47–50].

Palladium and copper-based catalytic systems are the most used in catalysis reaction when Gly is used as solvent to form C-C and C-heteroatom bonds. The N-arylation of primary and secondary amines with aryl halides under basic conditions in glycerol were catalyzed by CU^{II} and CU^{I} to provide better yield than when DMF and DMSO were used as solvents [51]. Glycerol also provided an efficient catalyst immobilization allowing the catalytic phase to keep its properties and to be recycled up to six times. It was also reported that diaryl-diselenides cross-coupling reaction with aryl boronic acids in glycerol yielded corresponding diaryl-selenides **24** (Scheme **6**) when DMSO was added as an additive.



Scheme 6. Synthesis of diaryl-selenides catalyzed by Cu^{I} systems in glycerol.

Cyclometallated complexes of transition metals synthesized in glycerol had shown many applications due to their properties. Gly also displays enormous potential for both molecular and colloidal-based catalysts in metal-mediated reactions. Glycerol accelerates reactions, immobilizes the

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catalyst mainly in the case of nanoparticles systems, allowing the recycling of the catalytic phase and provides metal-free target compounds [45].

3. Glycerol as a key Synthetic Intermediate

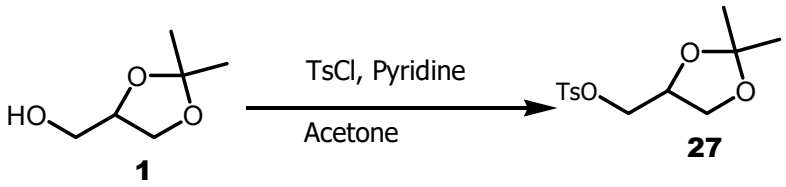
Nowadays, special attention is focused on the environmental health due to the climate change in which any chemical waste can be transformed into useful products. Glycerol is an industrial waste, and one of the trends is the comprehensive recycling of glycerol into valuable compounds for new applications, because it is produced in large amount as a by-product of biodiesel production, which is equivalent to approximately 10 wt% of the total biodiesel manufactured. Therefore, Gly was transformed into useful keys synthetic intermediate such as Epichlorydrin, Glycidol, Solketal or Tosyl solketal as its new recycling process.

3.1. Conversion of Glycerol to Solketal

Acetalization reaction has gained potential interest in applications for the better use of excess glycerol produced from the biodiesel process. Solketal can be synthesized from renewable resources such as glycerol and acetone (Scheme **1**). It is extracted from biomass and was reported to be a suitable approach for various applications such as fuel additives and in medicine industries. Gly was reacted with acetone in the presence of acid as a catalyst to provide a five membered heterocycle named Solketal (1,2-*O*-isopropylidene-glycerol) **2** almost exclusively, [52] along with the corresponding by-product 1,3-*O*-isopropylidenc derivative formed only in trace amount. Solketal can also be obtained from *D* and *L*-Serine, *D*-mannitol, (*L*)-ascorbic acid as well as (*S*)-and (*R*)-methyl benzylamine.

3.2. Conversion of Glycerol to Tosylsolketal

Glycerol has been used in a great number of common applications in cosmetics, pharmaceuticals, food industries and as a platform for bio-based polymers. Tosyl solketal **27** it is another key intermediate of glycerol. This compound was widely used in the preparation of bioactive lipopeptides, spiro heterocycles, pheromones, glyco-glycerolipids [53]. Tosyl-isopropylideneglycerol **27** was obtained by reacting compound **1** with *p*-toluenesulfonyl chloride in the presence of pyridine in acetone (Scheme **7**).



Scheme 7. Synthesis of Tosylsolketal **27.**

Racemic form of Solketal was first reported by Fischer in 1895 and was also prepared from glycerol many times [54]. (*R*)-Solketal is a precursor to alkylglycerol synthesis that naturally occurs in the S configuration. While (S)-Solketal is usually prepared from *D*-mannitol, it is not the same for *R* enantiomer, which access is much challenging. Several chiral precursors have been described to lead to (*R*)-Tosylsolketal **30** such as *L*-ascorbic acid (vitamin C), *L*-serine and *L*-tartaric acid, but the use of (*L*)-ascorbic acid as a starting material was put forward compared to others.

The saturated diol function of ascorbic acid **28** it is easily protected as acetonide by dissolving ascorbic acid in excess acetone containing a catalytic amount of acetyl chloride, which in turn crystallized directly from the reaction in 80-85% yields [55]. The powder obtained was treated with sodium borohydride followed by sodium hydroxide and the product obtained was then acidified to pH 7 to provide **29**, that was then oxidized in the presence of lead tetraacetate to afford **30**. Due to **30** instability, it was immediately reduced with an excess of sodium borohydride and basified to provide **26** in 50-60%, which in turn reacted with *p*-toluene sulfonyl chloride in the presence of triethylamine to provide **30** in 90% yield (Scheme **8**) [56].

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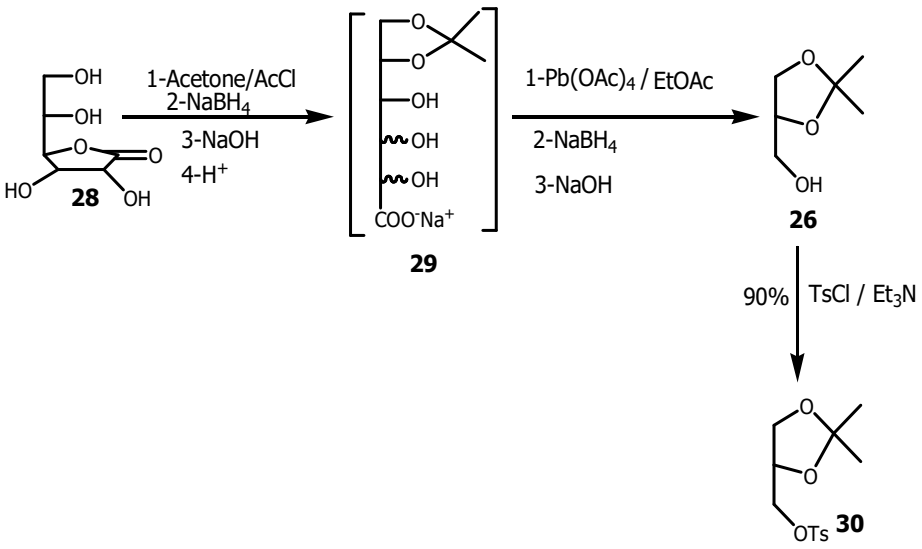
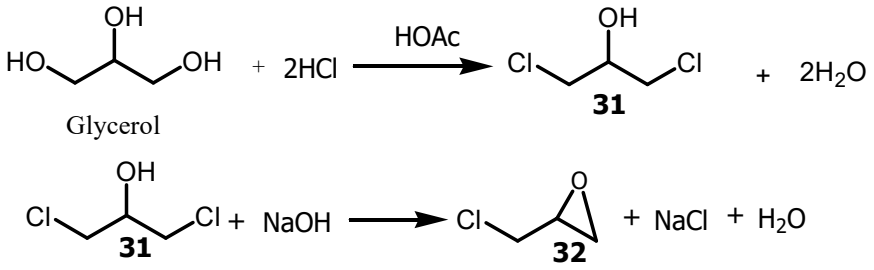


Scheme 8. Preparation of (*R*)-Tosylsolketal **30.**

Following this first synthesis, others less efficient methods for the preparation of **26** from inexpensive naturally occurring materials were also investigated.

3.3. Conversion of glycerol to Epichlorohydrin

Epichlorohydrin **32** is used in the production of epoxy resins, adhesives, elastomers, rubbers and plastics, paints, cellulose and pesticide formulation [57]. Epichlorohydrin was obtained when glycerol was reacted with hydrogen chloride in the presence of carboxylic acid as a catalyst to yield the intermediate **31**, which was then treated with a base to provide **32** (scheme **9**).



Scheme 9. Synthesis of Epichlorydrin from Glycerol.

3.4. Conversion of Glycerol to (R)-Glycidol

Oxiranes are a group of compounds used in organic synthesis as a building block because of their ring opening in the presence of nucleophilic group, reducing agents or lewis acid to form a new carbon-carbon bond. Several methods were also established to provide optically active epoxide in one spot step or two steps [58]. Glycidol **35** is one of the most important glycerol derivative generally used in the pharmaceutical industry, perfumes, paints and detergents. It was also used in the preparation of compounds such as glycidyl ethers, polyglycerols and polyurethanes [59]. Glycidol (GL) was prepared either via epoxidation of allyl alcohol, or of 3-chloro-1, 2-propanediol with bases [59–61]. But most of these reactions were challenged by multistep synthesis, the product cost and petrochmical derived raw materials, which impacting the environment from the viewpoint of sustainability. Therefore **35** was synthesized in one pot via the transesterification of Glycerol with Dimethyl carbonate (DMC) **33** using nanoparticulate KNO_3/Al_2O_3 as a solid base catalyst in almost 64% yield (Scheme **10**) [62]

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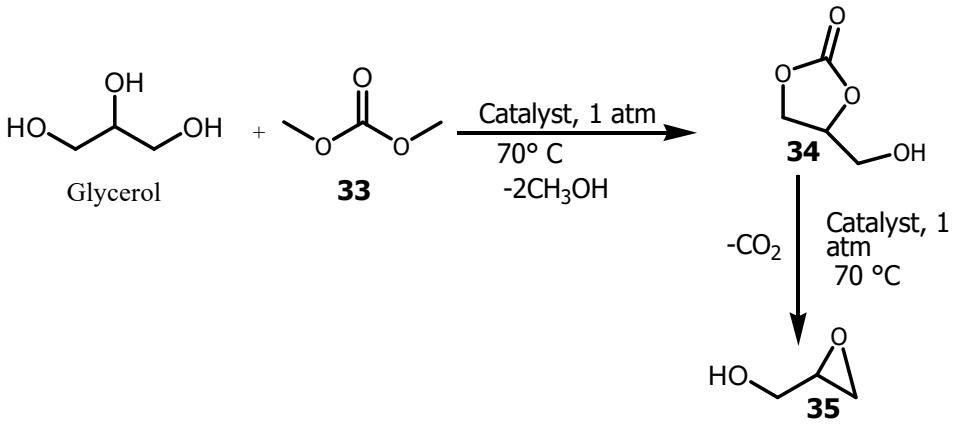
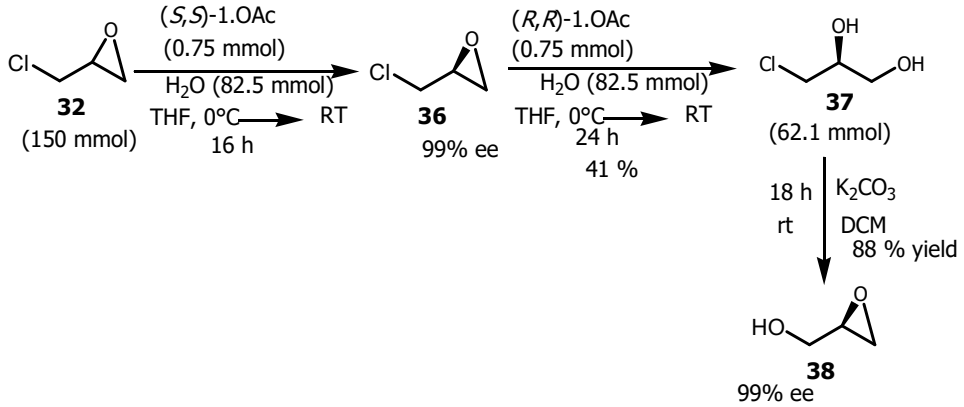


Scheme 10. Synthesis of Glycidol from Glycerol and DMC over the KNO_3/Al_2O_3 Solid Base Catalyst.

The rise of asymmetric synthesis is mainly due to the determining role of the absolute configuration of chiral compounds which provide different physiological or pharmacological properties. Indeed, the activity of these products essentially depends on their recognition by the specific chiral receptors which have different chemical behaviors with respect to the two enantiomers [63]. The difference in biological activity linked to the absolute configuration can be illustrated by the case of propranolol where the two enantiomers are used for different therapeutic purposes. The *S* antipode is a *β*-blocker involved in the treatment of heart disease, while the *R* configuration compound is used for contraceptive purposes. Enantiomeric purity is therefore essential for the clinical use of this molecule. Access to enantiomeric enriched molecules can currently be achieved in three ways: Creation from prochiral precursors, use of chiral pool materials, or disconnection of racemates. The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen) cobalt (III) complex affords both recovered unreacted epoxide and 1,2-diol products in highly enantioenriched form. Consequently, the HKR provides general access to useful, highly enantioenriched chiral building blocks (enantiomers terminal oxiranes and 1,2-diols). The reaction was reported to afford a higher enantioselectivity (generally ≥ 99%) within an enantiomeric ratio 50:50 of relative rates of the two enantiomers [64]. The HKR also provided practical access to a series of enantioenriched 1-halo-2,3-propane diol derivatives. Therefore, Epichlorohydrin **32** underwent ring opening to afford 1-chloro-2,3-propanediol **37** in 95% ee and 40% yield catalyzed by chiral (salen)Co^{III} complex (1.OAc), which in the presence of a base provided (*R*)-glycidol **38** (Scheme **11**).



Scheme 11. HKR of Epichlorydrin **32** to (*R*)-glycidol **38.**

Therefore, the development of efficient syntheses of enantiomerically pure chiral synthons is the subject of intense current study. Compound **38** was used as a starting material in the preparation of optically bioactive compounds (l-blockers centrally-acting antihypertensives, antiglaucoma agents, antitussive drug, alkylglycerols and glycerophospholipids).

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4. Synthesis of Glycerol Derivatives

The development of organic processes based on the use of glycerol as a safe organic building block is strongly limited by the physicochemical properties of glycerol (strong hydrophilicity, three unprotected hydroxy groups). Thus Gly was first converted into either Solketal, Glycidol or Tosylsolketal and then used as a building block in the synthesis of bioactives molecules.

4.1. Synthesis of 1-O-Alkylglycerol from Solketal

Shark liver oil (SLO) mixture was used in folk medicine in Scandinavian countries and in Japan, for its fortifying or healing properties. Its widespread use particularly in Europe, is now experiencing growing interest. Chemical studies carried out on the shark liver oil mixture have made it possible to characterize a certain type of etherlipids present in abundance named alkylglycerols (AKGs) **39**, in diacylated form: alkyldiacylglycerols (AKDAGs) **40** and phospholipids **41** [65]. It was also established that the alkyl chain of a 1-*O*-alkylglycerol was bound to the glycerol backbone at the *sn*-1 position, thus leading to an *S* configuration at the asymmetric carbon [66] (Figure **1**).

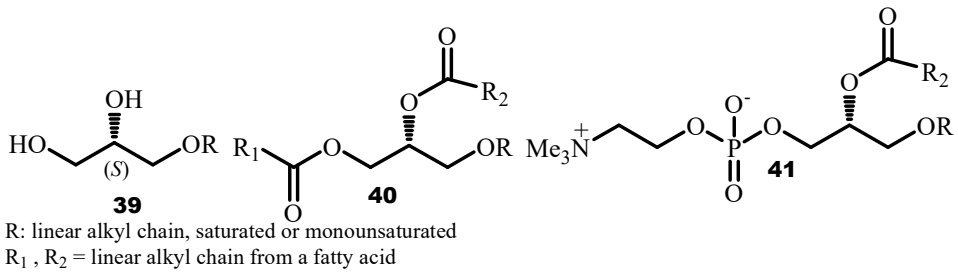

Figure 1. Natural shark liver oil mixture components.

1-*O*-alkylglycerols (AKGs) **39** are compounds derived from glycerol where one of the primary alcohol functions of glycerol is etherified by an alkyl chain. These compounds are present in many marine natural sources (sharks, rays, stars of sea, chimera, molluscs), but also in cattle and in humans. In the latter, AKGs were found in the liver, spleen, bone marrow, erythrocytes and in breast milk. It is particularly in the liver oil mixture of certain sharks that they are much more abundant and where they can represent more than 50% by weight of this oil. Beneficial effects of the SLO mixture on health were recognized in the traditional medicine of northern countries involved in fishing such as Japan, Norway and Iceland [67].

In these countries, the ancestral use of the SLO mixture was empirically as strengthening and wound healing medication. Later in the 20th century, beneficial effects on health of the SLO mixture were attributed to ether-linked glycerols known as 1-*O*-alkylglycerols (AKGs). Experimental studies were performed during the last century, aiming to demonstrate whether AKGs from the SLO mixture had biological properties and beneficial effects. Indeed, several studies did observe interesting effects such as hematopoiesis stimulation, lowering radiotherapy-induced injuries, reducing tumor growth, anti-microbial, antigiogenic, and improving vaccination efficiency [68–75].

In the SLO mixture from Greenland, small amounts (2-4%) of AKGs were also identified, possessing an additional methoxy group (methyl glyceryl ethers: MGE) at the 2 position in the alkyl chain and varying from C-14 to C-22 length alkyl chain [19]. It was further reported that a natural 2-methoxy alkyl glycerol ether owned the 2'R, 2S configuration, when the NMR spectra and optical rotation value of each synthesized stereoisomer of 1-O-(2'-methoxyhexadecyl)glycerol where compared. MGEs isolated from the Greenland SLO mixture were able to inhibit tumour growth and metastasis formation, and to stimulate the immunoreactivity in mice [75]. MGE **42** was first synthesized as a mixture of stereoisomers in racemic form (Scheme **12**) [76]. Palmitic acid **43** was converted to acid chloride by refluxing with thionyle chloride followed by bromine in methanol to provide methyl 2-bromohexadecanoate **44**, that was in turn treated with sodium methoxide in methanol to yield methyl 2-methoxylhexadecanoate **45**. Reduction of **45** with lithium aluminium hydride in ethyl ether afforded 2-methoxyhexadecanol **46**, which upon tosylation provided **46**,

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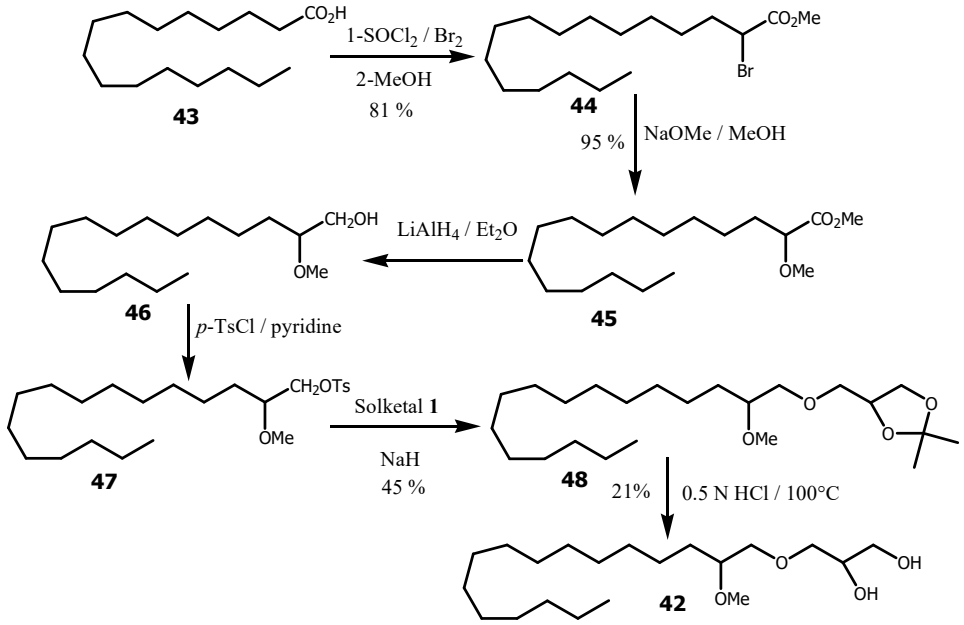
followed by its alkylation with solketal **1** in the presence of sodium hydride to provide **47**. Acetonide **47** cleavage in acidic conditions provided **42** in 21% yield.



Scheme 12. Synthesis of 1-*O*-(2-methoxyhexadecyl)-glycerol **42.**

4.2. Synthesis of Glycerol Derivatives from Glycidol

Glycidol is an organic compound that contains both epoxide and alcohol fonctional group. Being bifunctional, provides it with a variety of industrial uses. This compound is a slightly viscous liquid and slightly unstable. It is not often encountered in pure form.

The development of novel, selective and efficient chemical pathways towards application of glycerol-derived products remains a key scientific and industrial challenge. Very recently, because of this unique molecule structure, glycidol received a special attention as a valuable product in many applications such as the production of monomer and semi-product in the synthesis of surface-active agents. One of the most important applications of glycidol is the synthesis of analgesic and antiviral drugs, where the latter is the active compound fighting with the human immunodeficiency virus (HIV) [77,78]. Several syntheses of molecules have been reported for racemic glycidol **35** (Scheme **13**). For example, heating **35** with CH_2FCN in the presence of tetraethylammonium bromide gives oxazoline **49** [79]. Its reaction with phenyl isocyanate under similar conditions gives oxazolidinone **50** [80]. Treating also an aldehydes with **35** provide dioxolane **51**. Finally, esterification of **35** provided the α-toluenesulfonylacetate which when reacting with dicyclocarbodiimide and followed by lithium diisopropylamide resulted in ring closure, forming the lactone **52** [77].

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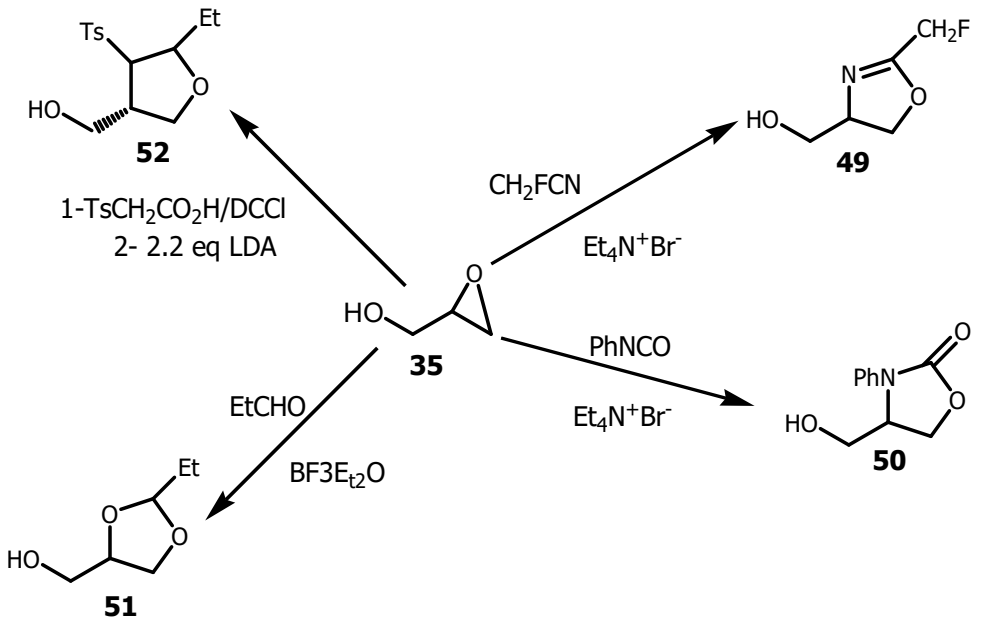
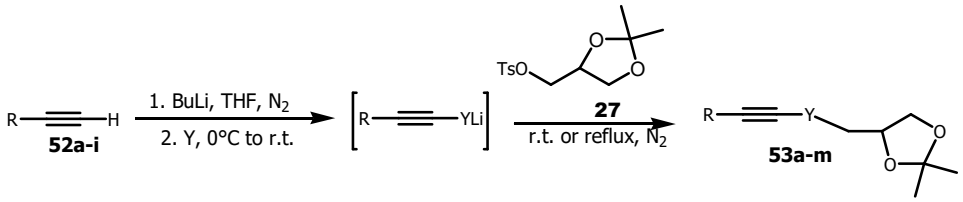
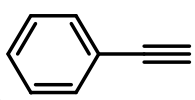
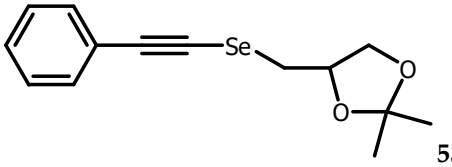


Scheme 13. Synthesis of Glycerol derivatives **49-52** from Glycidol **35.**

4.3. Synthesis of Organochalcogen from TosylSolketal

Organochalcogen compounds have attracted the interest of a multitude of studies to design potential therapeutic agents. For instance, organoselanyl and organotellanyl alkynes have become extensively studied due to their pharmacological and biological activities [81–83] and their use as starting material in organic synthesis [84,85]. Organotellanyl alkynes for example exhibited antidepressive-like activity [86], while alkyne-derived organotellanyl alkenes showed in vitro antioxidant activity with slight toxicity [87,88]. On the other hand, tosyl solketal **27** was used as a building block in the synthesis of several biologically active compounds. Chalcogenyl alkynes were selectively prepared from the reaction of glycerol-derived dichalcogenides with terminal alkynes in the presence of $NaBH_4$, using ethanol as the solvent. However, reaction times were in the range of 5 to 26 h and the scope of the reaction was limited to organoselanyl alkynes, and only the synthesis of one organotellanyl alkyne in 55% yield was reported [89]. To address these limitations, terminal alkyne **52** were first reacted with *n*-butyl lithium to provide lithium alkynylchalcogenolate (Se and Te), which in turn were reacted with tosyl solketal **27** to yield organoselanyl **53**a-h and organotellanyl alkynes **53**i-m (Scheme **12**).



Entry	Alkyne **52**	Y	Product **53**	Yield (%)
1	**52a** 	Se	 **53a**	80

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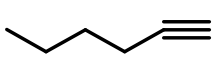
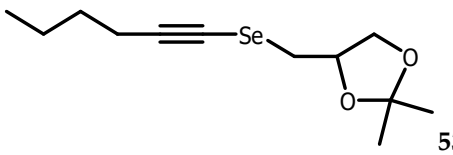
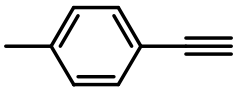
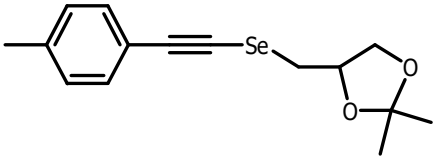
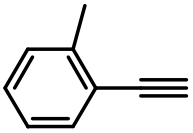
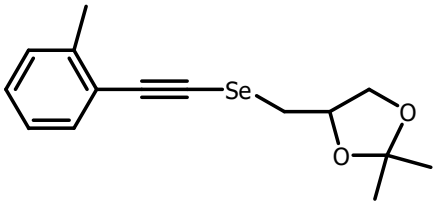
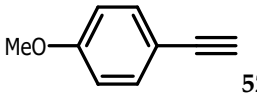
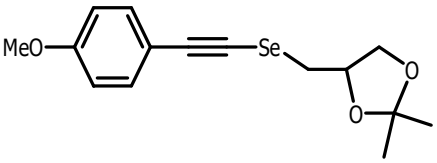
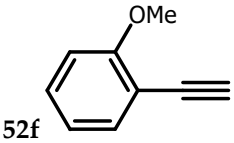
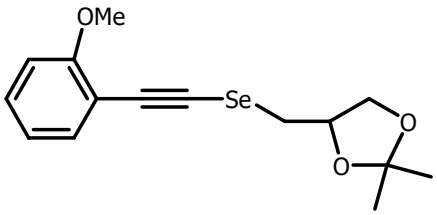
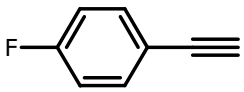
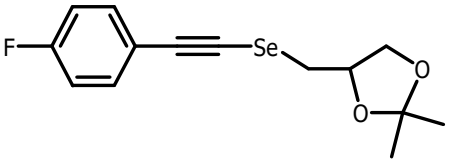
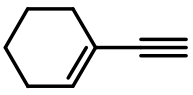
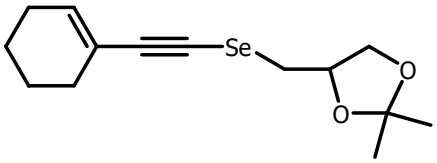
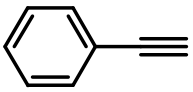
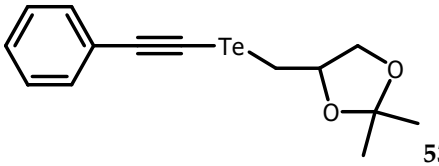
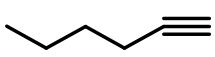
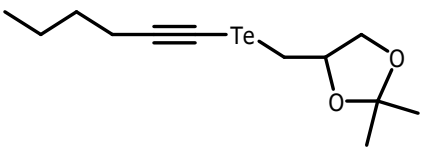
2	 **52b**	Se	 **53b**	63
3	 **52c**	Se	 **53c**	65
4	 **52d**	Se	 **53d**	70
5	 **52e**	Se	 **53e**	60
6	 **52f**	Se	 **53f**	60
7	 **52g**	Se	 **53g**	67
8	 **52h**	Se	 **53h**	52
9	 **52i**	Te	 **53i**	85
10	 **52j**	Te	 **53j**	63

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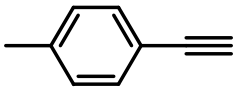
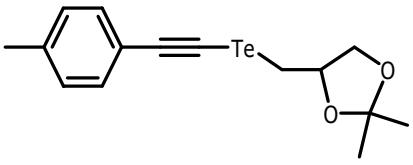
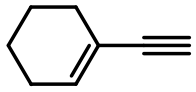
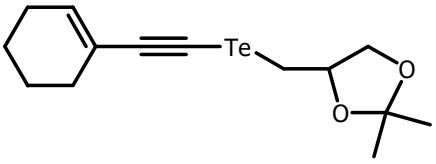
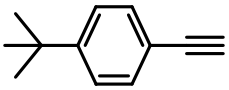
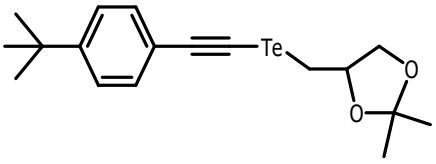
11	 **52k**	Te	 **53k**	55
12	 **52l**	Te	 **53l**	61
13	 **52m**	Te	 **53 m**	63

Scheme 12. Synthesis of organoselanyl **53**a-h and organotellanyl alkynes **53**i-m using Tosyl solketal **27** as a building block.

5. Conclusion

This review summarizes the chemistry of glycerol including some of its keys synthetic intermediates and derivatives, as the use of fossil resources for the petrochemical processes is a matter of great concern due to the climate change and the environmental pollution. Therefore, Glycerol was used as a green solvent for the preparation of 4H-pyrans, bis (aryl) ketones and aryl compounds, metallic complexes, as well as an undeniable raw material for the synthesis of potential drugs with eco-friendly processes.

It was shown that Glycerol possesses most characteristics of a green solvent: low toxicity, low flammability, biodegradability, functional group compatibility, low volatility organic compounds (VOC) emission, cheap, easy to handle and recyclable with a limited environmental impact. Nevertheless, the abundance of glycerol formed during biodiesel production as a waste provides a vast low-cost feedstock that can turn to uncontrolled waste with the disposal, and affect the economics of the biodiesel industries. Therefore, Glycerol was converted into Epichlorydrin, Glycidol, Solketal and Tosylsolketal as an efficient recycling process and useful keys synthetic intermediates, which were in turn used in the synthesis of glycerol derivatives such as Alkylglycerols, Organochalcogen and others molecules of potential beneficial effects. It was also noticed that Glycerol remains a green solvent of choice when compared to others green solvents in the synthesis of pharmaceutically active ingredients, where the toxicity and residual solvents are attentively monitored.

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