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A Short Overview on the Medicinal Chemistry of (—)-Shikimic Acid

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Abstract: Shikimic acid, a natural compound is a key intermediate in the biosynthesis of amino acids. Consequently, this derivative is widely present in many plants and has interesting biological properties. But besides the pharmacological relevance of shikimic acid itself, it is also an intermediate in the synthesis of many drugs, being the most relevant the antiviral agent oseltamivir (Tamiflu^{TM}). Here we present a short overview on recent natural, biotechnological and synthetical sources of shikimic acid, togheter with pharmacological applications of this compound and a selection of derivatives, including oseltamivir (Tamiflu^{TM}).

Keywords: Shikimic acid, natural products, biotechnology, Oseltamivir (TamifluTM), neuraminidase inhibitors.

1. INTRODUCTION

Shikimic acid (Fig. **1**) [1], first isolated in 1885 by Eykman from the fruit of *Illicium religiosum* [2], is a hydroaromatic intermediate in the common pathway of aromatic amino acid biosynthesis which is widely spread in leaves of fruit of many plants and also in microorganisms (bacteria and fungi), but in limited quantities [3].

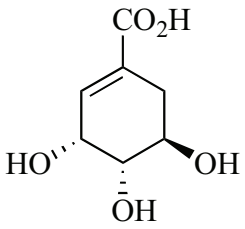

Fig. (1). (-)-Shikimic acid.

Shikimic acid is a key hydroaromatic intermediate in the biosynthetic shikimate pathway (Scheme 1) of essential aromatic amino acids (L-phenylalanine, L-tyrosine and L-tryptophan), lignin and most of the alkaloids of plants and microorganisms [4]. It plays also a principal role as precursor of cinnamic acids and flavonoids, such as flavones, antocyanidins, flavonols and tanins [5]. Moreover, it is also required for the assimilation of folic acid, alkaloids and vitamins in those organisms.

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Taking into account that the shikimate pathway is not present in mammals, there is great potential for the design and synthesis of enzyme inhibitors, which may selectively block specific enzyme-catalysed transformations along this pathway. Accordingly, intensive work was developed aimed at the design, synthesis and evaluation of antibacterial, herbicidal and antifungal agents of low environmental impact that may interfere specific transformations along this pathway, without a negative effect towards mammals [6]. An example is the commercial broad spectrum herbicide Roundup® which contains the active ingredient glyphosate (*N*-phosphonomethyl glycine), a specific inhibitor of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase in that pathway [7].

Shikimic acid has interesting biological properties, displaying activity as antioxidant, anticoagulant and antithrombotic, antibacterial, antiinflamatory and analgesic agent. However, besides being important itself from the pharmacological point of view, shikimic acid has also a key role in the synthesis of a number of relevant compounds in the pharmacological industry and there are reports on the shikimic acid-based synthesis of anticancer agents, antibacterials, hormones or herbicides.

But the reason why shikimic acid has found itself thrust under the spotlight in the recent years is because it is generally used as a starting material for industrial synthesis of the antiviral oseltamivir, a drug against the H5N1 influenza virus [8]. As fears spread about a potential flu pandemic, the current supply of of tamiflu is thought to cover just 2% of the world population. Health officials and researchers around the word are now working against the clock in creating enough supplies of shikimic acid to prepare large amounts of the antiviral drug, which could help to control an eventual outbreak of bird flu until a vaccine can be developed. Accordingly, studies on the presence of shikimic acid and new techniques for its isolation from

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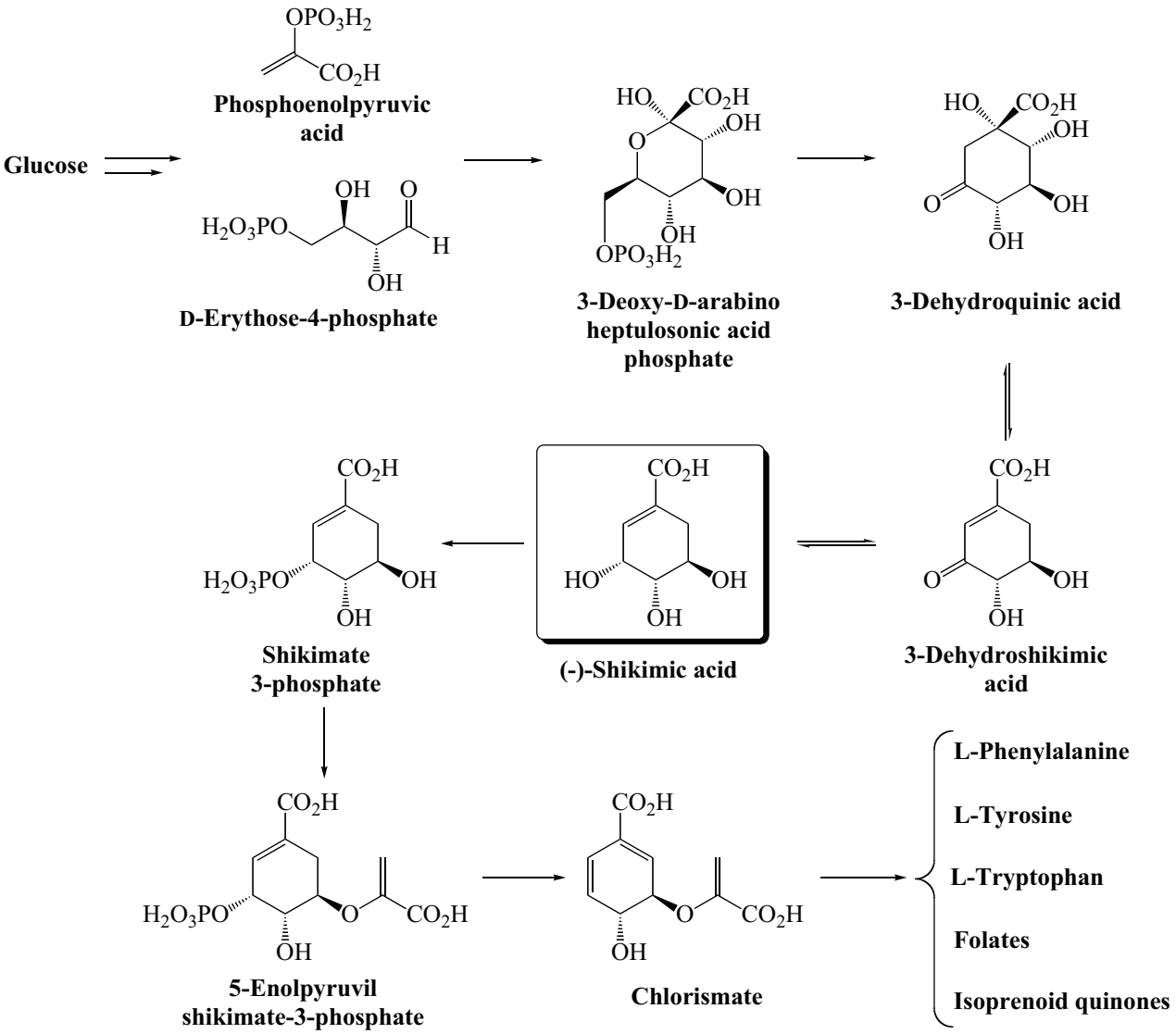

Scheme (1). The shikimate pathway.

known and novel sources are topics of current interest. However, limited availability from plants has led to the discovery of other synthetic and biosynthetic means to obtain shikimic acid. Many synthetic strategies have been developed for the multigram preparation of shikimic acid and recently it has been also reported the obtention of shikimic acid from microbial fermentation of glucose, using recombinant *Escherichia coli.*

To sum up, shikimic acid has become a compound of enormous interest in medicinal chemistry due to its key role in the preparation of antivirals. Different procedures have been employed for the access to shikimic acid: isolation from natural sources, biotecnological procedures or chemical synthesis.

The main aim of this review is to present a compendium on the recent approaches to obtain shikimic acid, as well as the most relevant aspects of the medical application of this compound and relevant derivatives.

2. ISOLATION OF SHIKIMIC ACID FROM NATURAL SOURCES.

Although shikimic acid is present in most autotrophic organisms, it is a biosynthetic intermediate generally found in very low concentrations.

Currently most of the shikimic acid required by the pharmaceutical industry for production of oseltamivir (Tamiflu™) arises from the chinese star anise (*Illicium verum*) [9]. The fruits of this tree are reported to yield 2 to 7% of shikimic acid, the higher concentration found in plants. But, as the cultivation of this tree is difficult, it is unlikely that *I. verum* source alone could satisfy its growing market demand. This is the reason why there is a continuous search for alternate plant sources of shikimic acid, as well as attempts to explore novel tecnologies for more efficient isolation [10]. Here we include a compendium of plants from where shikimic acid was isolated since 2005 and of different methods of extraction, which were subsequently developed.

Natural sources from which shikimic acid has been isolated include: seeds and pericarps from *Illiciun griffithii* (12-18%) [11], star anise (*Illicium verum*) (3-7%) [12], sweet gum (*Liquidambar Styraciflue*) (1-5%) [13], needles and branches from *Cedrus deodara* (From 1.66% to 4.11%) [14], Rhizoma Smilacis Glabrae (RSG) [15], leaves of the Malian medicinal tree *Terminalia macroptera* [16], ginkgo biloba leaves [17], stems and leaves of *I. Simonsii* [18], herbal plant *Dendrobium huoshanense* (traditional Chinese medicine) [19], fermentation broth and mycelia of strain PRE-5 (Strain PRE-5 was isolated from the root of the herbal plant *Panax notoginseng*) [20], needles of *Pinus densiflora* (a representative pinus species that grows in Korea) [21], *platycladus orientalis* [22], leaves of *Dipteronia dyeriana* [23], pine needles of *Pinus elliottii* [24], pericarp of *Illicium macranthum* [25], leaves of *Ficus carica* [26], *Pinus massoniana* [27], *Illicium simonsii* [28], *Linaria vulgaris* (Scrophulariaceae) infusion [29], bark of *Pseudolarix kaempferi* [30], stems and leaves of *Calophyllum inophyllum* L [31], young fronds of the bracken fern *Pteridium aquilinum* [32], leaves of *Taxodium distichum* L [33], leaves of *Sapium sebiferum* [34], leaves of *Alnus formosana* [35], *Schinus polygamus* [36], berries of *Juniperus phoenicea* [37], fruits of *Chaenomeles lagenaria* [38], seeds of *Cydonia oblonga* [39], leaves of the big tree from american tropical rain forests *Calophyllum brasiliense* (Clusiaceae) [40], plant *Rhus tripartitum* [41], *Selaginella tamariscina* (Beauv.) [42], aerial parts of *Hypericum monogynum* [43], fruits of T, chebula Retz [44], pine needles of *Pinus massoniana* [45], and roots of *Codonopsis lanceolada* [46] and *Cleistopholis patens* [47].

The extraction of shikimic acid from natural sources is a very complex process. Roche, the company that manufactures oseltamivir, starts with dried star anise (*Illicium verum)*. It is harvested by local farmers in four chinese provinces between March and May and the shikimic acid is extracted at the start of a 10-stage manufacturing process which takes a year. Moreover, huge amounts of seeds are needed to isolate shikimic acid and the 90% of the production is already used by Roche for the preparation of oseltamivir (Tamiflu^{TM}). In addition to the efforts made to find alternative sources for shikimic acid, many efforts have also been made for improved methods for its extraction. Some of the recent methods developed for the detection and isolation of shikimic acid are the following:

- Detection by spectrophotometric and high-pressure liquid chromatography (HPLC) methods [48].
- Capillary electrophoresis (DAD fingerprint method) [49].
- Methanol extraction [50].
- Extraction with the ionic liquid 1-butyl-3-methylimidazolium chloride ([bmim]Cl), which dissolves cellulose [51].
- Extraction with ethanol. Then, the ethanol extract was dispersed in water and extracted with petroleum, chloroform and butanol, successively. The organic fractions were isolated and purified by column chromatography [52].
- Fractionation of the water soluble part of *D. huoshanense* by repeated chromatography [53].
- Extraction of the dried pine needle of *Cedrus deodara* with ethanol. The alcohol is dispersed in water, followed by washing with petroleum ether. The remained aqueous solution is extracted with ethyl acetate, evaporated and mixed with silica gel. Elution afforded crude shikimic acid, which is dissolved in methanol and precipitated with dichloromethane to obtain the final pure product [54].
- Pulverization of *Illicium verum*, extraction with water, filtration through microporous filtering film and through hyperfiltration membrane, and purification of the filtrate *via* ion resin column chromatography, eluting with 5 % sodium hydroxide afforded, after crystallization in methanol, the pure product [55].
- Extraction at 100°C during of 80 min. with 10-folds water and precipitation with ethanol [56].
- Decompressing inner ebullition method [57].
- Ultrasonic extraction technology [58].
- Dilute acid pretreatment [59].
- Water extraction and ethanol precipitation, followed with macroporous adsorptive resin decolorization and ion-exchange resin purification [60].
- Extraction of aniseed oil from *Illicium verum* with supercritic CO_2 fluid, immersing the treated *Illicium verum* in water, concentrate *via* reverse osmosis membrane and crystallization [61].
- Microwave assisted extraction process of shikimic acid by response surface analisys methodology [62].
- Soaking raw material (*Illicium verum* fruit, *Illicium simonsii* fruit, or *Illicium lanceolatum* fruit) with water for 1-3 h, decocting twice each for 2-3 h under mildly boiling, merging the decoctions, cooling, filtering, adjusting the filtrate to pH 8-10 with base, purifying on macroporous adsorbent resin column eluting with diluted acid concentrate, crystallize at 0-4°C, dehydrate by high-speed centrifugation, dissolve with pure water, decolorize with macroporous adsorbent resin (such as AB-8) or activated carbon, concentrate, recrystallize at 0-4°C, dehydrate by high-speed centrifugation, and freeze dry to obtain shikimic acid [63].
- Recovery of the shikimic acid product from aqueous process streams utilizing membrane separation techniques [64].
- Rapid separation of shikimic acid from chinese star anise (*Illicium verum*) with hot water extraction [65].
- Isolation from *Illicium verum* by extraction with ethanol and water, basic anion resin chromatography and recrystallization [66].
- Extraction with n-butanol from the bark of *Pseudolarix kaempferi* [67].

- Extraction and purification by repeated silica gel and sephadex LH-20 chromatography [68].
- A simple and rapid capillary zone electrophoresis method using phosphate-borate mixture as running electrolyte with direct UV detection was developed for the analyzation of shikimic acid [69].
- Pulverizing dry *Illicium verum* fruit, desorbing with an apolar solvent, drying, extracting with industrial grade ethanol, combining the extracts and concentrating, dissolving with hot water, precipitating, blotter-treating, and filtering, concentrating, introducing to neutral macroporous absorbent resin to remove impurities, then introducing to a basic anion exchange resin to purify, volatilizing solvent, dissolving in hot water, adding acetone, freeze-crystallizing, and recrystallizing [70].
- Extraction from *Illicium verum* with organic solvent under reflux, filtering, concentrate, add water, decolorize with activated carbon, concentrate, centrifuge and filter to obtain crude solid. Crystallization to obtain pure shikimic acid [71].
- Response surface analisys methodology (RSM) was used for optimizing the extraction process of shikimic acid from *Illicium verum*. Based on single-factor experiments, three independent variables (extraction time, solvent-solid ratio and ultrasound power) were selected as affecting factors during extraction [72].
- Grinding *Illicium verum* fruit, extracting with alcohol twice under reflux, combining both extracts, concentrate, dissolve in water, filter, adsorb the supernatant on basic anionic resin column (D201-D296), wash with water, alcohol solution, elute with glacial acetic acid precipitate and recrystallize in alcohol twice to obtain pure shikimic acid as a white powdery crystal [73].
- Simultaneous extraction of shikimic acid and essential oil from *Illicium verum* fruit [74].
- Extraction from pine needles using water at relatively low temperature. After the subsequent evaporation, column adsorption/desorption and crystallization afforded shikimic acid crystals with a purity of over 98%. A total recovery of approx. 85 % is reached [75].
- Extraction from star anis seeds employing aqueous isopropanol. [12a]
- Pulverization of *Illicium verum* and extraction with water. Microfilter to remove water-soluble proteins, pectin and suspended substances, ultra-filter to separate shikimic acid, nano-filter to concentrate untill 1/10 the volume and recrystallize in acetone to obtain shikimic acid [76].
- Extraction with water, methanol, ethanol, acetone or n-butanol, removing impurity, purifying on ion exchange chromatography column, decoloring and recrystallizing [12b].
- Ultrasonic wave extraction of shikimic acid in *Illicium verum* was achieved using water as solvent in a solute ratio 1:15 and extracting twice 40 min [12c].
- Pulverization of *Illicium verum* dry fruits, extraction with supercrit. CO_2 at 40-45, 25-35 MPa, CO_2 flow speed of 15-20 kg/h for 1-2 h, reflux with methanol and extraction with ethyl acetate. Evaporation and crystallization of the crude product with chloroform and methanol [77].
- Solvent extraction using an extractant/diluent system was evaluated for the recovery of shikimic and quinic acids. Tridodecylamine (TDA) was used as the extractant, and 1-heptanol as the diluent [78].

3. BIOTECHNOLOGICAL PREPARATION OF SHIKIMIC ACID

Fermentation is an alternative way to produce shikimic acid and Roche already uses engineered *E. coli* bacteria to boost shikimic acid production [79]. Today, around two thirds of the shikimic acid used for oseltamivir are gained from star anise and the remaining shikimic acid is obtained through fermentation [80]. Fermentation is as an alternative to isolation that allows independece from events such as bad harvests and could also allow to ramp up production if needed.

There is another advantage to using fermentation: microbes could be engineered to make variations on the structure of shikimic acid and so allow production of analogues of Oseltamivir with slightly different pharmacological properties that could potentially target emerging strains other than H5N1. Should a pandemic hit, it might be valuable to focus on accelerating the biological evaluation of such analogues.

Some recent advances in the production of shikimic acid *via* biosynthetic pathways are the following:

- *Escherichia coli* for production of shikimic acid [81].
- Metabolic engineering approaches were employed to produce shikimic acid in *Escherichia coli* strains derived from an evolved strain (PB12) lacking the phosphoenolpyruvate [82].
- Biological fermentation method for expressing and manufacturing shikimic acid, and constructed engineering bacteria [83].
- Fermentation for producing shikimic acid using *Brevibacterium lactofermentu* [84].
- Method for constructing bacterial strain capable of producing shikimic acid [85].
- Production of shikimic acid from glyphosphate in recombinant microorganisms [86].
- Shikimate production from quinate with two enzymatic systems of acetic acid bacteria [87].
- Shikimic acid production by a modified strain of *E. coli* (W3110.shik1) under phosphate-limited and carbon limited conditions [88].

- Metabolic engineering for microbial production of shikimic acid [89].
- Shikimic acid production by a modified strain of *E. coli* K-12 upon increased availability of phosphoenolpyruvate [90].
- Shikimic acid is preparation with the coenzyme PQQ-and quinate dehydrogenase-producing acetic acid bacteria which has deficient TCA cycle [91].
- Bioengineered synthesis of shikimic acid from a carbon source [92].
- Increase in transketolase activity and production of shikimic acid from cloned *Citrobacter freundii* strain HSK10 [93].
- Low-cost extracellular manufacturation of shikimic acid using a mutant U-5 strain of *Citrobacter freundii* [94].
- Biocatalytic synthesis of shikimic acid in genetically engineered *Escherichia coli* [95].
- Shikimic acid is produced by cultivating a bacterium belonging to the genus *Bacillus* [96].
- Shikimic acid production by using a microorganism mutant, which belongs to the genus *Citrobacter* and is capable of secreting shikimic acid [97].
- Shikimic acid manufacturation with microorganism such as *Citrobacter freundii* that secretes extracellularly shikimic acid in the presence of a transition metal [98].
- A fed-batch fermentor cultivation of a genetically engineered *Escherichia coli* resulted in the synthesis of 27.2 g/L of shikimic acid [99].

4. SYNTHESIS OF SHIKIMIC ACID

There are several methods available for the chemical synthesis of shikimic acid and its analogues from simple starting materials, which have been revised in 1998 [100]. We include here a brief compilation of some of the methods developed since then.

- Regioselective transformation of (-)-quinic acid to (-)-shikimic acid *via* direct conversion of a 1,2-diol into allyl sulfide [101].
- Transformation of (-)-quinic acid into (-)-shikimic acid in a route involving dehydration with Martin's sulfurane [102].
- Synthesis of (-)-shikimic acid from carbohydrates in a route involving as key steps a Barbier allylation and a ring-closing metathesis reaction [103].
- Using a chiral building block having a 6,8-dioxabicyclo[3.2.1]octane framework as starting material for a diastereocontrolled synthesis of (-)-shikimic acid by employing a ring-closing metathesis as the key step [104].
- Synthesis of (-)-shikimic acid from a synthetic equivalent of (*R*)-4-hydroxycyclohex-2-enone *via* either a retro-Diels Alder reaction [105] or a palladium-mediated elimination reaction [106].

5. BIOLOGICAL ACTIVITY OF SHIKIMIC ACID

Shikimic acid and its derivatives displays a number of interesting biological properties. For example, shikimic acid presents high antioxidant activity [107]. It has been reported to be active against DPPH and nitric oxide radicals in a concentration-dependent way and presented capacity to scavenge superoxide radical [108]. Shikimic acid can decrease triglycerides (TG), total cholesterol (TC), low-d. lipoprotein (LDL), hemotocrit, and blood viscosity, and increase high-d. lipoprotein (HDL) of atherosclerosis suffering rats, thus being a promising candidate in the search for therapeutics for atherosclerosis [109] and for the control of biliary stone [110]. The application of shikimic acid to prepare medicines for treating ulcerative colitis was also described, obtaining promising results in animal tests [111]. Shikimic acid has inhibitory effects of on platelet aggregation and blood coagulation [112], and it shows antagonistic effects of shikimic acid against focal cerebral ischemia injury in rats subjected to middle cerebral artery thrombosis [113].

On other hand, it has been reported that shikimic acid displays antipyretic, antiinflammatory and analgesic activity [114], as well as antibacterial activity [115]. Some derivatives of shikimic acid also have interesting biological properties. For example, the triacyl derivatives of shikimic acid can inhibit blood platelet assembling and thrombosis by affecting the metabolism of arachidonic acid [116]. There are also data available on the synthesis of monopalmityloxy shikimic acid possessing anticoagulant activity and being capable of reducing blood coagulability when injected intramuscularly [117]. Other derivative, the 3,4-oxo-isopropylidene-shikimic acid (ISA), have an interesting biological profile. This derivative has anti-thrombosis effect, increasing the PGI2 release [118] and inhibiting anti-platelet-aggregation [119]. ISA have some protective effect on focal cerebral ischemia, decreasing the the size of cerebral infarction and the brain edema [120] and improving the abilities of learning and memory [121]. ISA also have significant antiinflammatory effects which might be related to reducing the production of PGE2 and inhibiting free radical oxidation [122].

6. SHIKIMIC ACID DERIVATIVES

Over recent years, there has been extensive interest in the efficient preparation of analogues of (-)-shikimic acid, which have been targeted as likely inhibitors of enzymes on the shikimic acid pathway and which are of relevance as potential antifungal, antibacterial and antiparasitic agents.

6.1. Oseltamivir (Tamiflu^{TM}) and Related Compounds

The arsenal of antiviral therapeutic agents is relatively modest, as compared to antibacterials and antifungals. In the recent years, the emergence and worldwide spread of the avian influenza A virus subtype H5N1 has raised concerns of possible easy human-to-human transmission, which calls for the need to develop more potent antiviral drugs to be used for the prophylaxis and treatment of influenza, a viral infection of the respiratoy system that affects around 20% of the worldwide poblation and results in ca. 500.000 deaths [123].

Neuraminidase (NA), a membrane glycoprotein of the influenza virus which is required for the release of budding virions from the host cell, is one of the potential drug targets of antiviral agents. Neuraminidase is an external glycoprotein that accelerates the breaking of the connection of sialic acid end and neighboring sugar half which causes subsequent respiratory infection *via* various mechanisms. Probably the discharge of virus from infected cells initiates and stimulates the penetration of virus into respiratory epithelial cells which was initially caused by neuraminidase. Neuraminidase inhibitors also cause cellular apoptosis by stimulating transforming growth factor beta and induce cytokines including interleukin-1 and tumor necrosis factor.

At present, research and development of anti-influenza drugs based on the inhibition of influenza virus neuraminidase (sialidase) is a very active research area. Several potent and specific inhibitors of NA have been developed through structure-based rational dessing. However only zanamivir (Relenza^{TM}) and oseltamivir phosphate (Tamiflu^{TM}) (Fig. **2**) have been approved for human use and, in practical terms, they constitute the current therapy for the treatment of influenza [124].

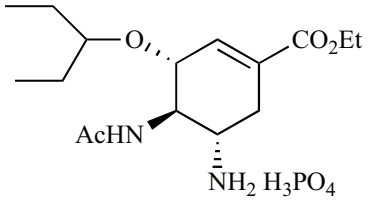

Fig. (2). Osealtamivir phosphate (Tamiflu^{TM}).

Tamiflu^{TM} prodrug is hydrolized in the liver by hepatic estearases to its active form oseltamivir carboxylate, a compound that acts as an inhibitor of neuraminidase, one of the proteins of the virus surface [125]. As a result of this inhibition, the virus is unable to infect other cells.

Tamiflu is most popular due to its oral administration, thus being the drug of reference for the therapy of avian influenze. This resulted in a high demand for this compound that cannot apparently be satisfied by the industrial production, which relies on a impresive semisynthesis from (-)-quinic acid or (-)shikimic acid, developed by Vilead and Roche chemists [126]. This stimulated extensive efforts of the synthetic community, with the aim of developing an efficient total synthesis applicable on a large scale [127]. The challenge resulted in quite a number of ingenious synthetic approaches to this small, but densely functionalized molecule, where a range of mechanistically different reactions were used as key steps in syntheses [128].

Different strategies for the preparation of Tamiflu in industrial scale have been subjected to extensive investigations [129]. The most recent synthetic approach to oseltamivir from (-)-shikimic acid is an efficient, nine-step route recently reported by Karpf and Trussardi at F. Hoffmann-La Roche Ltd. in Switzerland [129g] This and other preparations have been addressed in a recent review on synthetic approaches to oseltamivir phosphate reported in 2010 [127a]. Some ulterior methods include:

- A novel asymmetric synthesis from (-)-shikimic acid via a 3,4-cyclic sulfite intermediate [130].
- A eight-step synthesis of (-)-oseltamivir devolped by Barry Trost [131]. Key transformations include a novel palladium-catalyzed asymetric allylic alkylation reaction (Pd-AAA) as well as a rhodium-catalyzed chemo-, regio-, and stereoselective aziridination reaction.
- A enantioselective synthesis of oseltamivir phosphate [132], including as key steps an asymmetric Diels-Alder reaction, Mitsunobu inversion using Fukuyama modified Weinreb reagent and carbamate directed epoxidation.
- Four generations of chemoenzymatic approaches are surveyed [133]. The first two generations relied on the use of cyclohexadiene-*cis*-diol derived enzymically from bromobenzene. The third and fourth generation used the corresponding diol obtained from ethyl benzoate by fermentation with *E. coli* JM109 (pDTG601a). Both of these advanced approaches benefited from symmetry considerations and translocation of the acrylate double bond with concomitant elimination of the C-1 hydroxyl. The syntheses are evaluated for overall efficiency by the use of efficiency metrics and compared with other syntheses of oseltamivir (both academic and industrial).

Regarding pharmacological aspects of Tamiflu, a recent review on neuraminidase inhibitors is mainly dedicate to profile of oseltamivir: pamacokinetics, prophylasis, antiviral chemoprophylaxis, dose adjuntment, toxicity, resistance and drug interactions [134].

High mutation rate and emerging drug resistance to the commercially available drugs, especially to oseltamivir, have been widely reported [135]. Therefore, finding novel potent inhibitors of NA less affected by cross-resistance as well as identification of new drug targets is a vital goal.

Regarding resistance, as an alternative to oseltamivir, the novel neuraminidase inhibitor peramivir (RapiactaTM) was prepared. (Fig. **3**) [136]. It failed to show statistically significant viral inhibition due to the relatively low blood levels obtained after oral administration [137]. But it continues to progress through clinical trials as a potential injectable anti-influenza drug for treating patients with life-threatening strains of the influenza A viruses H1N1 (swine flu) and H5N1 (bird flu) [138]. It appears to act as the long-acting neuraminidase inhibitors, because only one injection is required, but it needs to be administered no later than 36–48 h after manifestation of the symptoms in order to be effective [139].

6.2. (-)-Zeylenone

(-)-Zeylenone (Fig. **4**) is a polyoxygenated cyclohexene isolated from *Uvaria grandiflora* [140], which shows antiviral, anticancer and antibiotic activities and is widely employed as a preparation for chemotherapy of cancerous

diseases [141]. It was prepared for the first time in a stereoselective synthesis from shikimic acid [142].

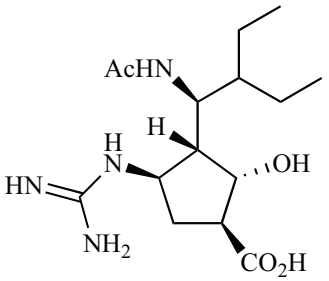

Fig. (3). Peramivir (Rapiacta™).

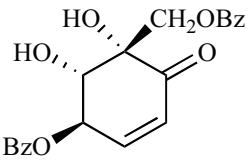

Fig. (4). Zeylenone.

6.3. Haloshikimic Acids

The plethora of derivatives of shikimic acid of interest as enzyme inhibitors include fluorinated analogues such as (*6S*)-6-fluoro-shikimic acid (Fig. **5**), a compound that display *in vitro* antibacterial activity against a range of *Escherichia coli* strains [143]. Furthermore, the 4-*epi*-shikimic acid skeleton [144] is present in numerous natural products with interesting biological properties. One example is the (*6S*)-6-chloro derivative pericosine A (Fig. **5**), an antitumour agent from *Periconia byssoid*.

Fig. (5). (6*R*)-6-Fluoro-shikimic acid and Pericosine A.

6.4. (-)-MK7607

Carbasugars are carbocycle monosaccharides in which the ring oxygen has been repalced by a methylene group. As carbohydrate mimics, they are stable to enzymatic hydrolysis in biological systems and often display a range of biological activities, particularly as glycosidase inhibitors. (-)-MK7607 is a carbasugar isolated from the fermentation broth of *Curvularia eragrostidis* D2452, which was found to have effective herbicidal activity [145]. It was prepared from shikimic acid in a seven-step sequence [146].

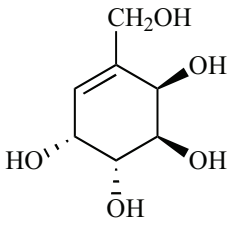

Fig. (6). (-)-MK7607.

7. CONCLUSIONS

The past several years have witnessed explosive developments in shikimic acid chemistry and biochemistry, targeting many biological applications. Particularly relevant is the use of shikimik acid in the preparation of antivirals as oseltamivir, drug or reference in the treatment of avian influenza. Revising the existent literature on shikimic acid and its derivatives, we can find many other pharmaceutical applications of shikimic acid and its derivatives, as antioxidants, antitumoral agents, antibacterials or hormones. Thus, looking to the future, the widespread and wide field of application of shikimic acid in medicinal chemistry, and the emergence of increasingly sophisticated methodologies for its synthesis and extraction, seems certain to ensure continued interest in this derivative. We thus hope that this review will provide a useful aid to medicinal chemists interested in the use of shikimic acid as a base for the development of novel pharmacologically relevant derivatives.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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