Ibn Al Haitham Journal for Pure and Applied Science

Journal homepage: http://jih.uobaghdad.edu.iq/index.php/j/index

A Review: Saccharin Discovery, Synthesis, and Applications

Ammar A. Razzak Mahmood
Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
kubbaammar1963@gmail.com

Sahar B. Al-Juboori
Department of Pharmacy, College of Al-Rafidain University, Baghdad-Iraq.

Article history: Received 2 October 2019, Accepted 13 January 2020, Published in April 2020.

Doi: 10.30526/33.2.2442

Abstract

Saccharin is firstly synthesized in 1879. It is a very well-known as an inexpensive substitute for sugar as it is a non-caloric sweetener. The article shows the properties, use, metabolism and various synthesis and reactions of saccharine. Moreover, the toxicological reports explain that saccharin is mostly responsible for the bladder tumors observed in the male rats, the relationship between the consumption of saccharin and bladder cancer is afforded by epidemiological studies. The benefit-risk evaluation for saccharin is hardly to indicate. Saccharin is a sugar substitute, frequently used either in food industry, or in pharmaceutical formulations and even in tobacco products. The chemistry of saccharin is interesting because of it suspected carcinogenous character and the possible use as an antidote for metal poisoning. It appears prudent to evaluate their main properties and applications further.

Keywords: Saccharin, Carcinogen, Artificial sweetener, Toxicity, Safety and Photo isomerization

1. Introduction

1.1. Saccharin

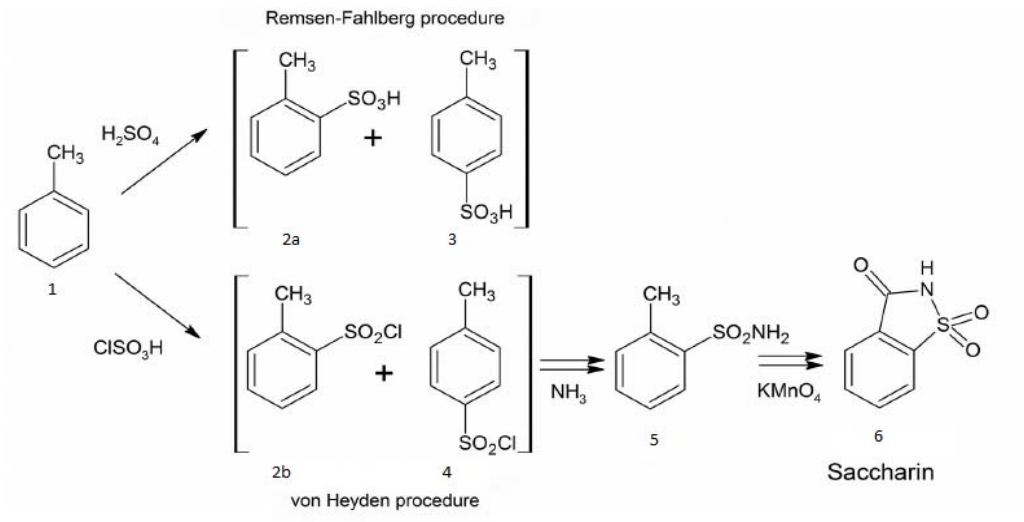
Saccharin is an artificial sweetener with no food energy. It is chemically identified as *o*-sulfabenzamide (2,3-dihydro-3-oxobenzisosulfonazole). It is about 400 times as sweet as sucrose. It is a sulphonamide derivative of toluene, existing as acid saccharin, sodium saccharin and calcium saccharin [1]. Saccharin is a week organic acid, slightly soluble in water, with a *p*Ka of 1.6 and chemical formula $C_7H_5NO_3S$. It has a molar mass of 183.2 g/mol and a specific gravity of 0.83 g/cm^3[2]. Sodium saccharin has high solubility in water and because of its ease production, it is the most generally used salt. Also, calcium saccharin is used in different food applications. It is remarkable to know that there is no relation between

saccharin form and its sweetness intensity. Saccharin and its salts are stable in a solid form, while in solution it is high hydrolytic thermal, and photo stability. Stability is not affected by pH and temperatures, usually encountered in food and beverage manufacturing, contain table-top sweeteners, yogurt, desserts, ice-cream, baked goods, jam, preserves, marmalade, soft drinks, sweets, mustard and sauces, saccharin can be used in cooking, baking and canning due to its stability, The acceptable levels of use differ from a hundred to five hundred mg/kg, based on the food category [3].

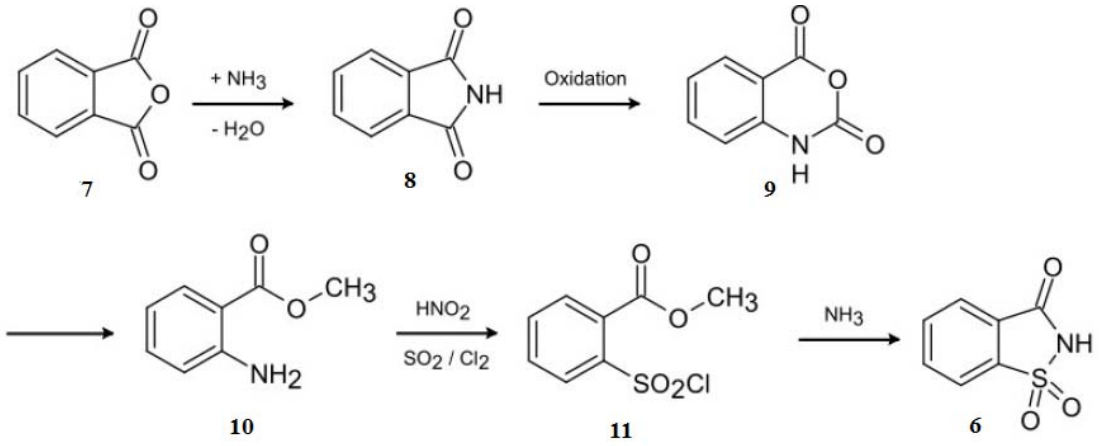
Saccharin is decomposed when heated to 380 °C, and all three forms of saccharin emit toxic fumes of nitrogen oxides and sulfur oxides. During a typical food process, saccharin does not decompose; however, some hydrolysis happens after prolonged exposure to excessive conditions pH or temperature when the pH is less than 2.0 and at particularly high temperatures. The hydrolytic decomposed products of saccharin are (2-sulfobenzoic acid and 2-sulfamoyl benzoic acid). Neither of these compounds displays a sweetener taste [4].

1.2. History of Discovery

Saccharin was discovered in 1878 by a Russian chemist named "Constantine Fahlberg. During his lab work, he tried to oxidize toluene sulfonamides [5]. **Scheme 1.** was the first commercially recognized as a sweet-tasting agent, which was significantly more potent than sucrose. The first story of saccharin commercial development and its use as a non-caloric sweetener was reviewed in 2001 by Pearson [6]. (PMC Specialties Group, Inc.), a company long concerned in the production of saccharin, and more recently by Hicks (Pennsylvania State University). Today, major companies were involved in saccharin production including Kaifeng and Shanghai Fortune of China and JMC of South Korea.



Scheme 1. The saccharin production by Remsen–Fahlberg process**.**

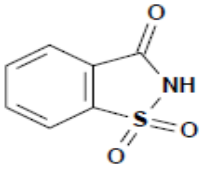


Scheme 2. Maumee-Synthesis for saccharin manufacture [6].

1.3. Forms of saccharin

1.3.1. Neutral saccharin

IUPAC Name: 1,2-Benzisothiazolin-3-one

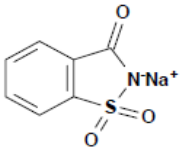


Saccharin

6

1.3.2. Sodium saccharin

IUPAC Name: 1,2-Benzisothiazolin-3-one, 1,1-dioxide, sodium salt [7].

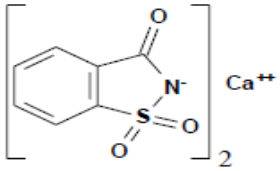


Sodium saccharin

6a

1.3.3. Calcium Saccharin

IUPAC Name: 1,2-Benzisothiazolin-3-one, 1,1-dioxide, calcium salt [7].



Calcium saccharin

6b

1.4. Regulatory Aspects

Food ingredients are evaluated and/or regulated by several national and international organizations. There are various international groups which they assess the use of sweeteners in the market, including expert scientific committees for example the Scientific Committee on Food (SCF) of the European Commission (EC), the Joint Expert Committee of Food Additions (JECFA) of the United Nations Food and Agricultural Organization (FAO) and the World Health Organization (WHO) [8]. In India Saccharin, Aspartame, Acesulfame k, Sucralose are allowed under FSSAI, 2011.

Sucrose is generally known as table sugar, and is considered as standard material, to which all other sweeteners are compared. Sucrose in solution has sweetness perception rating 1, and other substances are rated relative to this. There are many other alternative sweeteners present in the market; all with somewhat different sweetness compared to sucrose. Each high-intensity sweetener has its feature. Manufacturer's use of an ingredient of sweetener or combination of elements is the key to product success. The potency of an intense sweetener is an essential basic characteristic, due to its impact on a diversity of issues involving relative cost and amounts consumed (the latter impacting safety considerations). Sweetness potency (more times compared to sucrose) of saccharin is equal 300 [9].

1.5. Physio-chemical Properties

Saccharin is generally found in acid, sodium and calcium forms. All of these are white solids. Saccharin is considered as a strong acid with pKa of 2.32 [10]. Normally a non-caloric sweetener should be sufficiently soluble to be utilized in beverages and foods, but, not all non-caloric sweeteners meet this requirement. It must be mentioned that sweetness intensity corresponding to 10% sucrose are required, and in several systems (e.g., frozen desserts), sweetener levels equivalent the sweetness of 15–20% sucrose are desirable. Also, it's (it is) observed for many food systems, rapid dissolution is critical to satisfying) with manufacturing needs. For example, concentrates of the sweetener-flavor system complex are prepared in carbonated soft drinks, and it is essential that all components quickly dissolve. Thus, for non-nutritive sweeteners, must display rapid dissolution rates which are very desirable properties. Besides, a non-caloric sweetener must be stable to hydrolysis plus, to photochemical and thermal and breakdown to be used in beverages, baked goods, and confectionery [11].

A commercial non-caloric sweetener must have sufficient resistance upon degradation during hydrolytic, pyrolytic or photochemical processes that may be encountered in food or beverage applications. Stability is critical for three reasons. First, the product shelf life, during degradation rate must not be affected. Second, degradation must not produce any unpleasant taste or odor. And third, any degradation product produced from the use of a non-caloric

sweeteners that used as food additives, should be safe. In the USA for any food or beverage application, the safety assessment work for the sweeteners is necessary to carry out if exposure to the degradation product may exceed 12.5µg/kg, to ensure regulatory approval for the sweeteners [12]. **Table 1.** shows the physical properties of saccharin.

Table 1. The physical properties of saccharin.

IUPAC	**2-benzothiazol-1,1,3-trione**
Other name	Benzoic sulfimide
Chemical formula	C7H5NO3S
Appearance	White cristalline solid
Molar mass	182,999014 g/mol
Density [3]	0,828 g/cm³
Melting Point	(228,8-229,7)°C
Solubility in water	3,448 g/L
Solubility in ethanol	32,258 g/L
Solubility in acetone	83,333 g/L
Solubility in glycerol	20 g/L
Uv (vis) Spectroscopy maximum	267,3 nm

1.6. Uses of Saccharin

Saccharin is in the form of an acid and also as calcium-or sodium salt, used in food manufacturing, mainly the salt, due to its high solubility in water [13]. There is no considerable difference in the sweetness of the various forms; the intensity of sweetness for each derivative is ranging about 300-800 times greater than that of sucrose and dependent on concentration and other factors. As with most other sweeteners, there is an inverse relationship between sweetening intensity and concentration, compared to a sucrose-solution. For example, a 1%-saccharin-solution is approximately eight hundred times sweeter, while a 3%- sucrose solution is only five hundred times as sweet as a sucrose-solution. The sweetening intensity of saccharin depends on concentration and also on the composition of the solution [14]. A great value of sweetening intensity can be noticed in a combination of saccharin and other sweeteners, more than just the additive values of every component. In addition, mixing up various sweeteners will lead to the taste modification; even small amounts of additional sweeteners can reduce the slight bitter metallic aftertaste of saccharin considerably [14]. For that, the food industry often uses saccharin combined with aspartame, cyclamate, thaumatine or xylit [15]. Since saccharin is excreted unchanged mostly through urine, it is most–appropriate for diabetic persons or overweight individuals as a sugar substitute [13]. The recommended maximum everyday dose is equal 5mg/kg body weight [15]. Even though saccharin is surely most well-liked as food additive E954, it also presents in other sectors: in cosmetics, toothpaste and mouthwash, pharmaceuticals, cigarettes, as a flavoring agent in pig feed and even as a brightener in anticorrosive nickel coatings. [14].

1.7 Ingestion

Saccharin, when ingested, actually goes through the human GIT without being digested. The experimental models revealed that the saccharin is not absorbed or metabolized [16−18]. It is excreted and unmoved via the kidneys. Saccharin has zero energy. It was banned in the United States by the US FDA. It can stimulate the release of insulin in humans. It was only artificial sweetener presented in the rats because of its taste [19].

1.8. Absorption

Saccharin's absorption depends on different factors including the pKa and the pH values of the animal. The absorption of saccharin occurs with a pKa of about 2.0- 2.2. The unionized species found in acidic media which is completely absorbed form in many of animal species. While, in the stomach of the rabbit and guinea-pig, saccharin is absorbed completely when the pH come to 1.9 and 1.4, respectively. as it is compared to the stomach of rat, the pH equal to 4.2. The pH of the stomach and extent of absorption in monkeys and man are in-between those of the rabbit and guinea-pig on one side, and the rat on the other. The extent of saccharin absorption depends mainly on food intake that affects the acidity of the stomach contents [20].

1.9. Distribution and Excretion

Researchers used radioactivity to observe the distribution of radioactive-saccharin in organs and tissues of rats at different time intervals (one, two, four, eight, twenty-four, forty eight and seventy-two h), following a single oral administration of labeled saccharin ($^{3\text{-}14}C$) ,(0.2 mg/kg), nearly 1 h after dosing, a trace of radioactivity was found in approximately all organs. Small quantities of ^{14}C was found in spleen and brain. While the highest amount of ^{14}C was established in urinary bladder, liver, and kidney, which reached a maximum at four and eighth. In the next research, bladders of the treated rats were washed with 8, 0.5 ml portions of a 0.9% saline solution, a significant portion of the labeled ^{14}C activity was found to be concentrated in the bladder tissue [21].

1.10. Metabolism of Saccharin

A research work carried out in metabolism of saccharin has shown that saccharin, an efficient sweet taste agonist, does not undergo detectable metabolism in each animal or human being. Whereas, saccharin (84%) principally was excreted within the urine and about 40% of the dose was recovered from the feces after dosing 24h, traces of administered saccharin radioactivity stayed in different tissue after 3 days including heart, liver, pancreas, adrenals, thymus, and testes. Previous metabolic studies have shown that activating either sweet taste receptors (taste receptors family 1 [T1Rs]), or bitter taste receptors (taste receptors family [T2Rs]) on taste receptor cells (TRCs) by sweet, umami, or sour compounds initiates a common signaling cascade. Saccharin can stimulate signaling cascade associated with taste receptors (sweet, T1R2 þ T1R3; bitter, T2R43/T2R44) and their heterotrimeric G protein gustducin (consisting of Ga and Gbc subunits), to trigger Ca2þ signaling pathways and affect cAMP levels in taste cells. T1R3 or Ga knockout mice indicated a distinctly reduced preference for saccharin. New T1Rs and their downstream protein Ga are detected beyond the taste buds [22].

1.11. Toxicity Study of Saccharin

Saccharine is similar to aspartame, acesulfame K, and cyclamates. Saccharine -300 times sweeter than sucrose- is normally used in many foods like soft drinks, baked goods, jams, canned fruits, candy, salad dressings, dessert, etc, since saccharin is utilized by a lot of people. Safety of saccharin is essential for public health. Also, many works have been done to ensure the safety of saccharin [23]. Carried out since patients with serious diabetes, cancer, and liver damage, who consume artificial sweeteners with drugs. Such interaction may have an effect on drug metabolism. The research work showed the effects of the possible saccharin, and medication interaction on the activities of five cytochrome P450 enzymes (CYPs) in male ICR mice. Another research work examined the significant effects of saccharin dose, equal 4,000 mg/kg using the medication bupropion after pretreatment of mice within saccharin for seven days, and after simultaneous administration of both bupropion and saccharin. The results established that saccharin did not have a considerable effect on the five CYPs in the S9 fractions obtained from the liver of mice. Also, there were no obvious differences in the pharmacokinetics factors of bupropion between the control and the pretreated groups with saccharin, and that receiving associated administration of saccharin. Thus, the results documented the safety of saccharin, and it has very low hazard of saccharin-drug interaction [24].

1.11.1. Carcinogenicity Study

Saccharin is still considered as a diabetic and carcinogen inducer in several parts of the world. In 1977, after the publication work a high rate of bladder cancer was reported in rats administered with large doses of saccharin. Canada banned saccharin however US-FDA also suggested a ban. All saccharin-containing foods showed a warning label alerting that saccharin can be carcinogenic. The teratological, hepatotoxicity, genotoxicity and carcinogenicity studies of saccharin in animals containing humans were conducted by the most profoundly important global health and credible science organizations worldwide. Their results showed no evidence to prove a causal association among saccharin consumption and health risks in humans at usual dosage. The US-FDA officially withdrew its 1977 suggestion to prohibit the saccharin's use, and the National Toxicity Program advertised the unsafe of saccharin as a carcinogen.

Therefore, saccharin can be used safely and results in a good physical shape lifestyle without accumulation of calories, or the risk of obesity due its associated cardiovascular problems [25].

Urinary bladder carcinogenesis can be promoted by sodium saccharin and sodium ascorbate in rats when they fed at high doses of sodium saccharin. It increases epithelial proliferation in short-term assays. While the free acid forms lack either promoting or cell proliferating inducing activity. When the researcher set up an experiment to compare the tumor-promoting activity of various types of saccharin, and to estimate the role in urinary sodium, pH, and calcium promotion, in addition to other factors [26].

Saccharin does not increase the risk of bladder cancer in humans. [24]. It was considered in all literature about saccharine safety. Work on saccharin carcinogenicity appears to be mystifying, as shown in **Table 2.**

Table 2. Shows the Carcinogenicity of saccharin happening in animals' models.

Test material	Carcinogenicity model	Results	References
Male and female Charles River rats	Bladder tumors	-	Munro *et al.* [25]
Male and female Charles River	Bladder tumors	+	Howe *et al*. [26]
rats	Bladder tumors	+	Reuber [27]
Rats and mice	Bladder tumors	-	Risch *et al.* [28]
Rats and mice	Bladder tumors	-	Morgan and Wong [29]
Rats and mice	Bladder tumors	+	Zurlo and Squire [30]
Rats & Monkey	Bladder tumors	-	Takayama *et al*. [31]

Footnote: + (Positive), - (Negative)

1.11.2. Toxicological Study

Saccharin has the possibility to induce cancer in rats and dogs, therefore, in1911, there was the first attempt to ban saccharin, when a group of researchers identified it, for example, an "adulterant" not appropriate for common use in foods. Later on, the same group workers permitted its use in products for patients. At the time of Arnold's publication, there were only three studies of saccharin, used a two-generation model. The investigations established that when rats were exposed to diets containing 5% or 7.5% saccharin from the time of conception to death, a significantly increased frequency of urinary bladder cancers was shown, generally in males. The fact that saccharin is considered to be as a nucleophilic agent, and cannot bind DNA. Therefore, saccharin is not metabolized, but it does destroy humeral antibody production in rats. Using a dose of 5% or more, saccharin does not function as a distinctive harmful carcinogen. Theoretically, all carcinogens are considered as a strong electrophilic agent [32].

1.11.3. Genotoxicity Study

Induction of chromosomal aberrations in Chinese hamster cells and human lymphocytes, *in-vitro* studies for sodium saccharin was found weakly positive.

Weak responses were noticed in some in-vitro assays at the chromosomal level. While elevated concentrations maybe due to ionic imbalances that are well believed to cause non-specific effects. There are also conflicting reports from in vitro work , but in certain cases, the materials used were found to contain impurities raised from the manufacture of saccharin.[33]. It was studied that all literature about saccharine safety. As said by the research, genotoxicity is displayed in **Table 3.**

Table 3. Sum of the genotoxicity of saccharin.

Test material	Genotoxic end- point	Results	References
Human	lymphocytes Sister chromatid exchanges	+	Zhang *et al.* [34]
Plant	Sister chromatid exchanges	+	Zhang *et al*. [34]
F344 and Sprague-Dawley rats	Rat hepatocyte DNA repair assay	-	Jeffrey and Williams [35]
Male ddY mice	glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow comet assay	+(glandular stomach and colon)	Sasaki *et al.* [36]
Salmonella typhimurium	Ames	-	Bandyopadhyay *et al.* [37]
Swiss albino mice	Comet assay	+	Bandyopadhyay *et al*. [37]
Fish sperm DNA	DNA binding affinity	+/-	Icsel and Yılmaz [38]
Human leukocytes	Alkaline and neutral comet assays	-	Frenzilli *et al* [39]

Footnote: + (Positive), - (Negative)

1.11.4. Epidemiological Study

The epidemiological studies showing a proof concerning on saccharin, indicated there was no noticeable relationship among artificial sweetener consumption mostly known saccharin, and bladder cancer in humans. Diverse epidemiological studies designated no increase in the frequency of bladder tumors in human from the consumption of saccharin, including in persons with the elevated use of artificially sweetened beverages and persons using saccharin. [22] The literature carcinogenicity of saccharine in epidemiological studies was still confusing, as displayed in **Table 4.**

Table 4. Sum of the carcinogenicity of saccharin in epidemiological studies.

Study design	Carcinogenicity model	Results	References
Human	Bladder	-	Armstrong and Doll [40]
Human	Bladder	-	Jensen and Kamby [41]
1953 cases and 4154 controls	Colorectum	-	Francheschi et al. [42]
254 bladder cancer patients and254 Controls	Bladder	+	Yu *et al.* [43]
598 cases and 1491 controls	Oral cavity and pharynx	-	Francheschi *et al*. [44]
304 cases and 743 controls	Oesophagus	-	Bosetti *et al.* [45]
1031 cases and 2411 controls	Ovary]	-	Bosetti *et al*. [46]
460 cases and 1088 controls	Larynx	-	Bosetti *et al.* [47]
2569 cases and 2588 controls	Female breast	-	Tavani *et al*. [48]
1294 cases and 1451 controls	Prostate	-	Bosetti *et al*. [49]
767 cases and 1534 controls	Renal cell	-	Bravi *et al*. [50]
51 patients and 87 controls	Urinary tract	+	Andreatta *et al*. [51]
230 patients and 547 controls	stomach	-	Bosetti *et al*. [52]
326 patients and 652 controls	pancreas	-	Bosetti *et al*. [52]
454 patients and 908 controls	endometrium	-	Bosetti *et al*. [52]

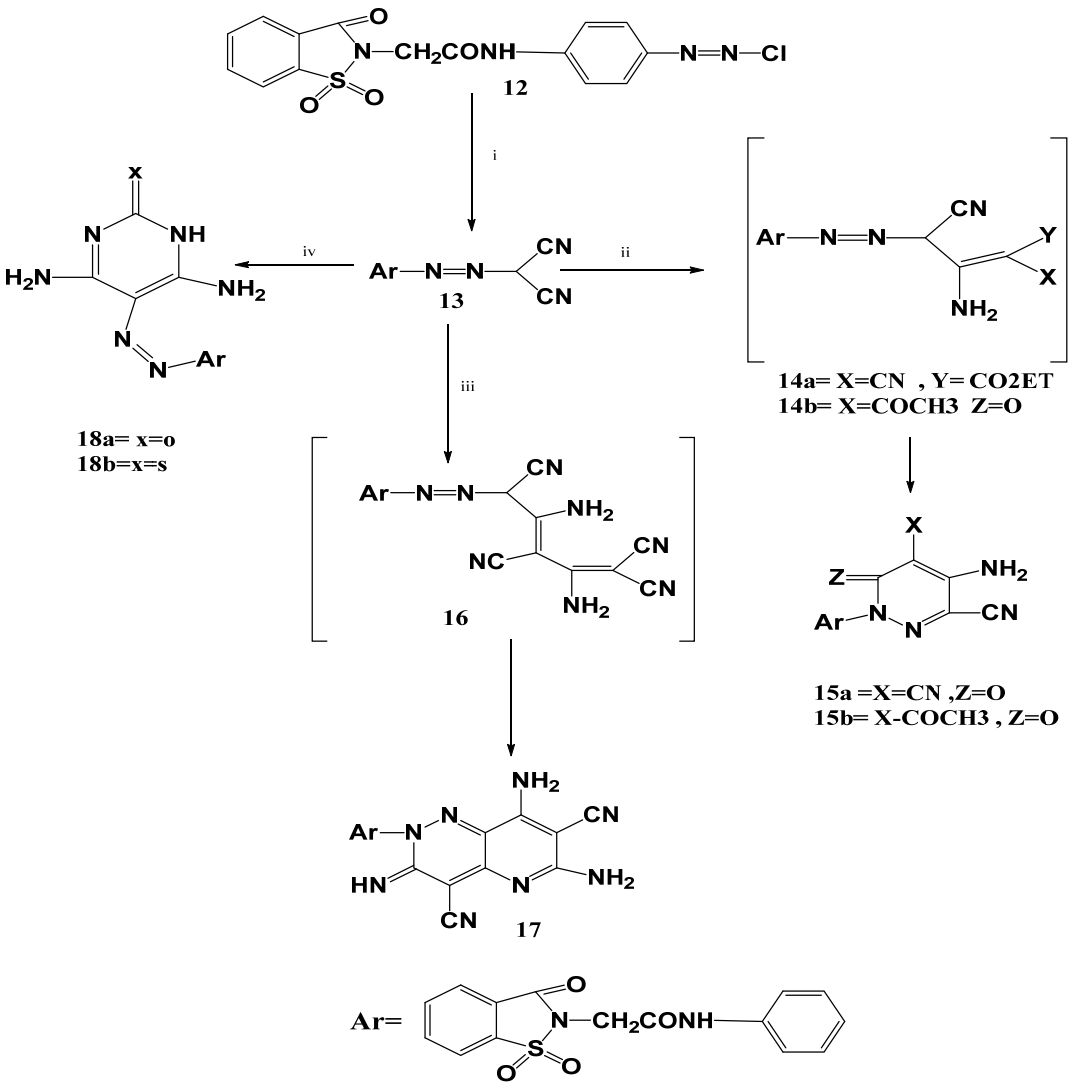
Footnote: + (Positive), - (Negative)

1.11.5. Hepatotoxicity Study

In 1992, Kumar *et al*. documented the favorable use of saccharin. It is reported that saccharin is safe to liver function [53]. Several generations of Americans have made the use of saccharin, supporting its role in the pathogenesis of liver damage. an essential part of their everyday lifestyle in the united patients. Saccharin is not metabolized in any number of healthy consumers to support the use of a non- vivo, being almost unchanged in the urine, and its caloric sweetener similar to saccharin for weight reduction, and doesn't accumulate in the liver. The small amount of diabetic persons, saccharin (never exceeding sixteen mg/day) were taken by patients marks the idiosyncratic reaction [54].

1.12. Synthesis of Saccharin Derivatives

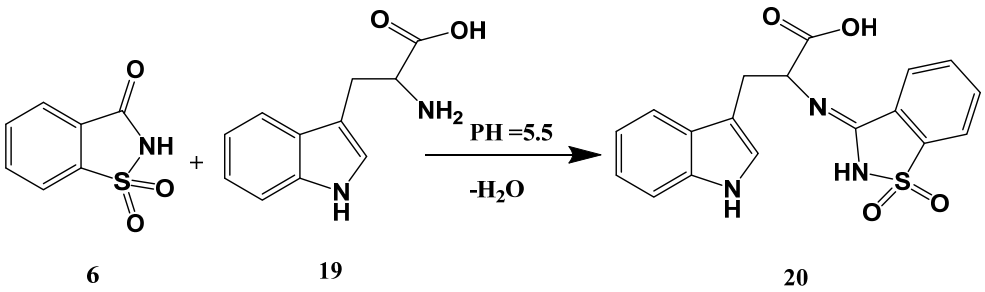
N-[4-(Dicyanomethylazo) phenyl]-2- saccharin-2-ylacetamide **(13)** showed to be a suitable precursor for the preparation of different pyridazine and pyrimidine derivatives**15a**, **b**, **17** and 18 as depicted in the **Scheme 3.** [55].



Scheme 3. Synthesis of different saccharin derivatives.

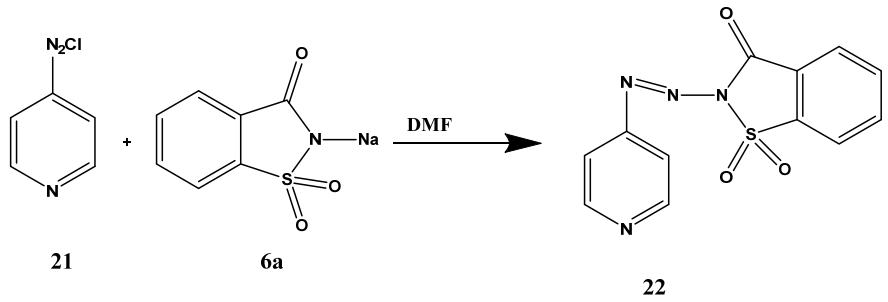
Reagents and conditions: (i) $CH_2(CN)_2$, Ethyl alcohol, Sod. acetate; (ii) XCH_2Y, Ethyl alcohol, Et_3N; (iii) $2CH_2(CN)_2$, EtOH, Et_3N; (iv) H_2NCXNH_2, Sod.ethoxide.

The reaction of saccharin and tryptophan occurred readily at room temperature in aqueous solution to produce a compound separated at pH 5.5 in a 1:1 ratio as shown in **Scheme 4.** [56].



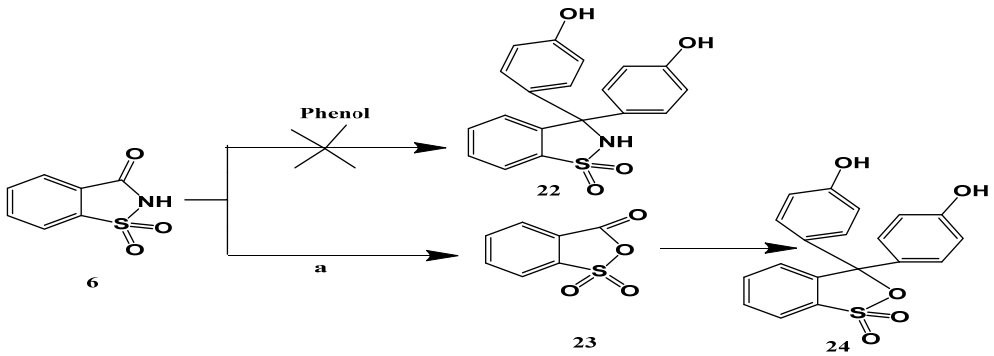
Scheme 4. Schiff-base formation from the reaction of tryptophan and saccharin.

2-(Pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide (**22**) resulted from the coupling reaction of 4-(chloridediazeayl) pyridine (**21**) with sodium saccharin(**6a**) in DMF, Scheme **5.** [57].



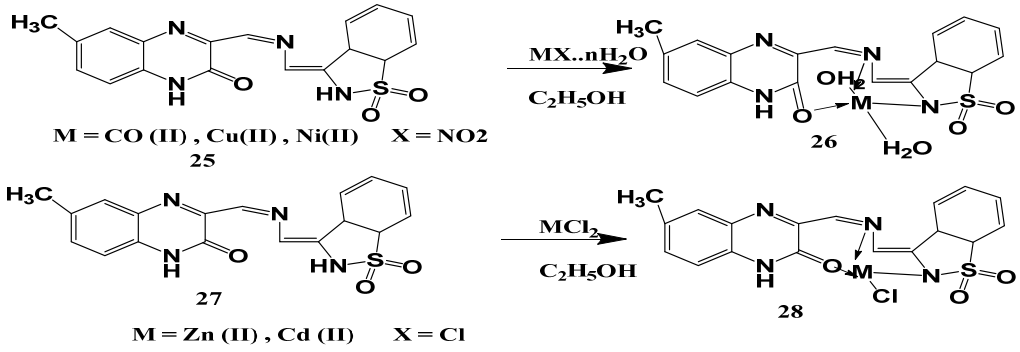
Scheme 5. Synthesis of 2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide.

Sulfonphthalein can be synthesized in a single pot by treatment of saccharin and phenol through the *in-situ* preparation of 2-sulfobenzoic anhydride, subsequently its reaction with phenol by using H_2SO_4 as the condensing agent, in the absence of any solvent, **Scheme 6.** [58].



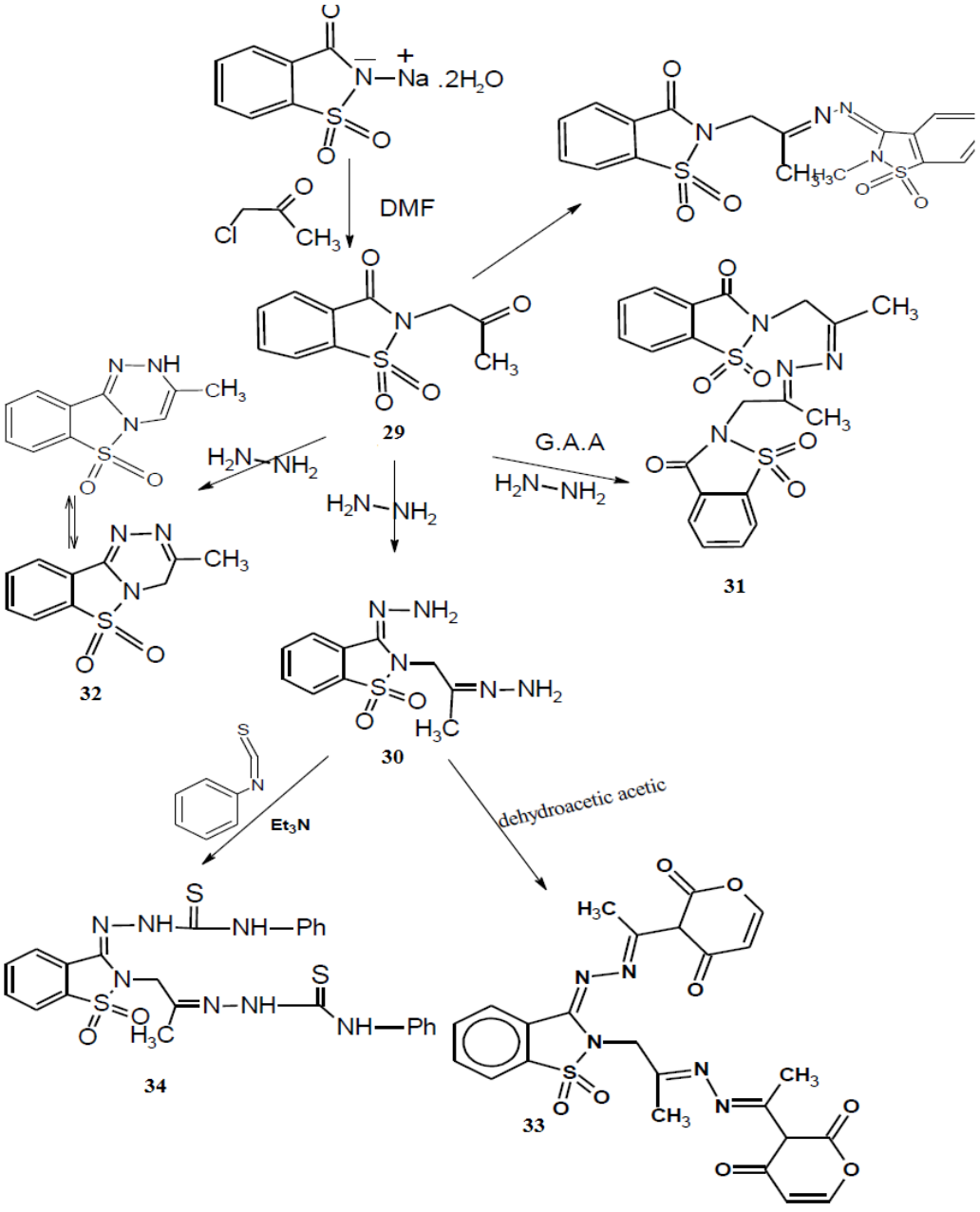
Scheme 6. Synthesis of phenol sulfonephthalein from saccharin and phenol: (a) conc. H_2SO_4 = oleum, 140 °C, 3 h; (b) phenol, conc. H_2SO_4, 140 °C, 3 h.

A new Schiff base was produced by the reaction of the transition metal complexes of Cobalt (II), Nickel (II), Copper (II), Zinc (II) and Cadmium(II) with (3E)-3-{(2E)-[(3-hydroxy-6-methyl-3, 4,6,8atetrahydroquinoxalin-2-yl) methylidene]hydrazinylidene}-3*H*-1,2-benziothiazol-2-ide1,1-dioxide were prepared, as shown in **Scheme 7.** [59].



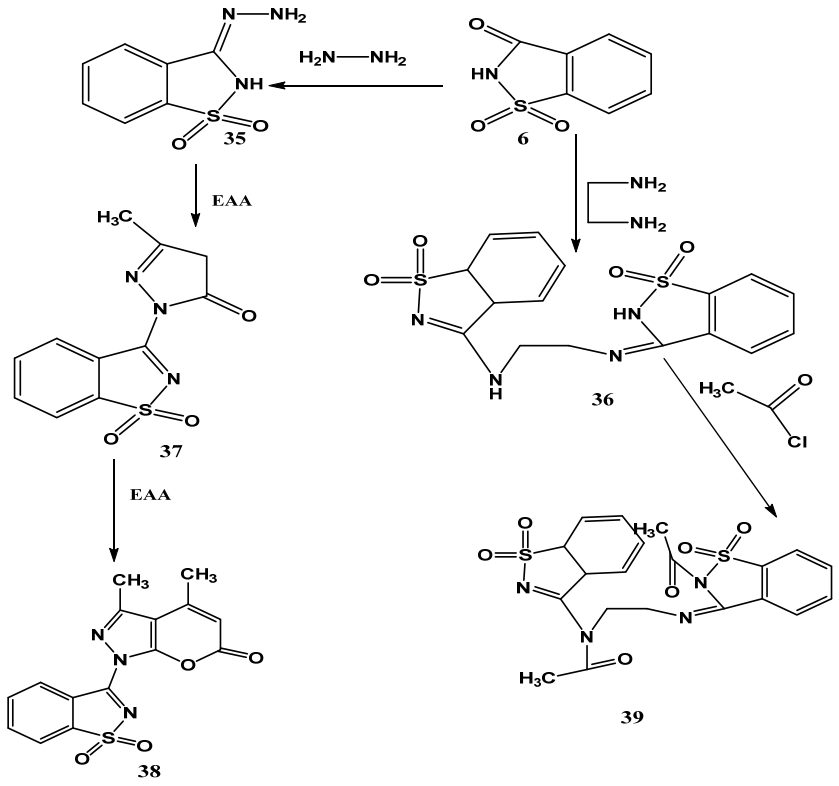
Scheme7. Synthesis of new Schiff base from metal complexes.

Schiff bases (**30, 31** and**33**) can be synthesized by reaction of a compound **(29**) with $NH_2NH_2.H_2O$, and glacial acetic acid. Compound (**34**) has been produced by a reaction of a compound (**29**) with phenyl isothiocyanate by using triethylamine as catalyst. Finally, compound (**32**) can be obtained by the reaction of a compound (**29**) with $NH_2NH_2.H_2O$ in the presence of NaOAc or, NaOH, as shown in the **Scheme 8.** [60].



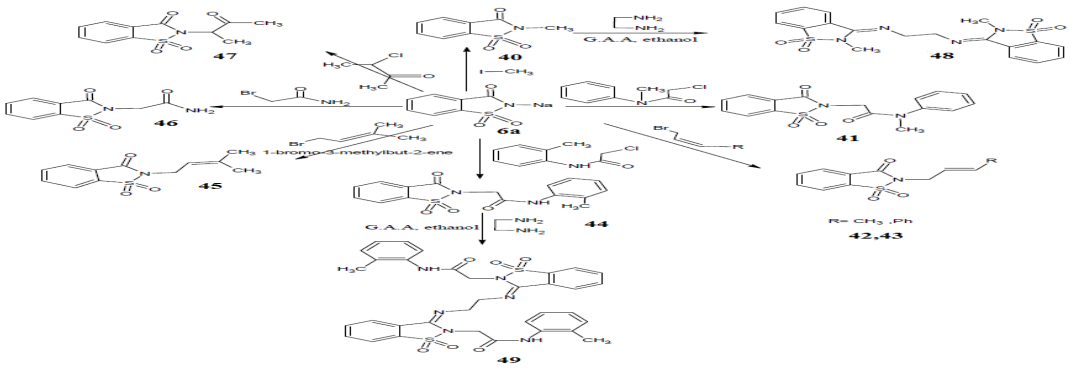
Scheme 8. Synthesis of saccharin derivatives (30-34) by reaction N-1,3-benzothiazole-2-yl-2-chloroacetamide-2-amimobezothiazo with different compounds**.**

The reaction of saccharin with ethylene diamine in presence few drops glacial acetic acid, produced compound (**35**). Acetylation of compound (**36)** produced a compound (**39**). Reaction of compound **(35**) with ethyl acetoacetate afforded pyrazole, and pyranopyrazole derivatives (**37, 38**), respectively, as shown in **Scheme 9.**



Scheme 9. Synthesis of saccharin derivatives (36-39) by reaction of saccharin with different reagents.

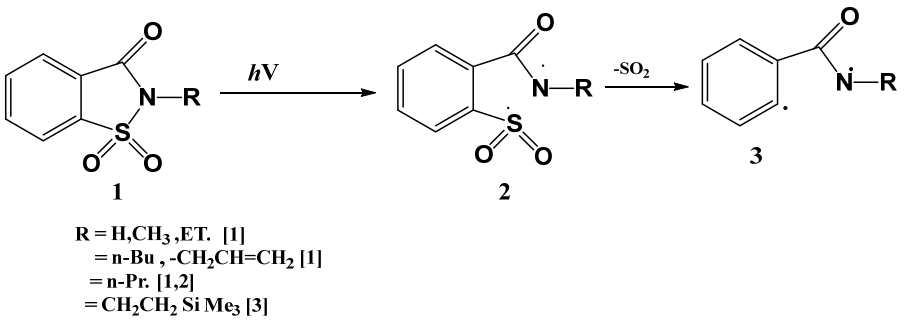
Also, the reaction of sodium saccharin with halo compounds afforded some of N-alkyl saccharin derivatives **(40-47**). Condensation of ethylene diamine with compounds **(40,44**) in presence few drops glacial acetic acid (GAA) produced compounds (**48,49**) as shown in **Scheme 10.** [61]



Scheme10. Synthesis of N-alkyl saccharin derivatives (40-49) by reaction of sodium saccharin with halo compounds**.**

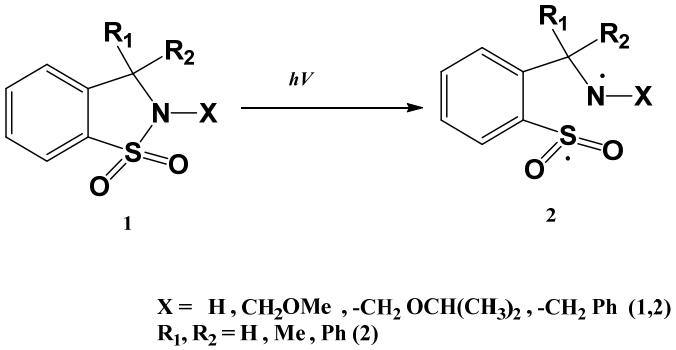
1.13.1. Photo isomerization of Saccharin

Regarding the photochemistry of benzisothiazoles, a literature survey reveals that the information available is restricted to photolysis in solution. Previous work on the photochemistry of N-propylsaccharin **(2, 3**) confirmed that photolysis led to cleavage of the S−N bond, eventually leading to the formation of benzamide through extrusion of SO_2, as shown in **Scheme 11.**



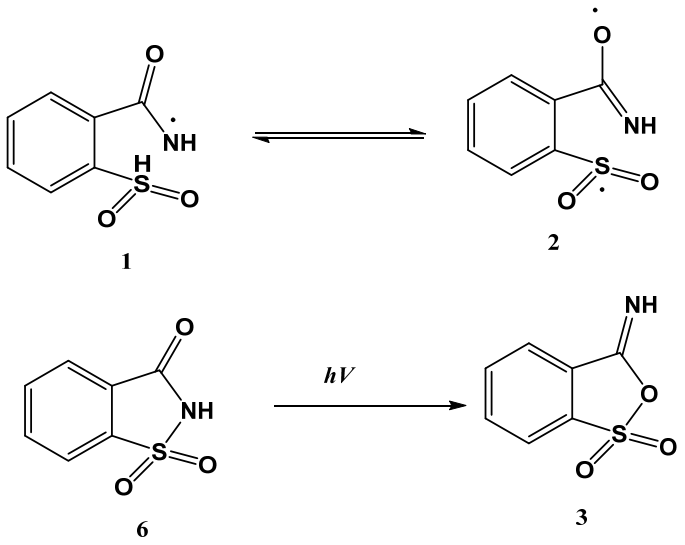
Scheme 11. Synthesis of benzamide.

Photochemistry of 3,3-di-substituted 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides in methanol and acetonitrile. Three reaction routes were detected in two cases: an initial S−N hemolysis, as shown in **Scheme 12.**



Scheme 12. Photochemistry of 3,3- substituted 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides.

Saccharyl system photo isomerization implies photo induced hemolysis of the S−N bond, then a delocalized bi radical is produced in the amide moiety, upon rotation around the exocyclic C−C bond, furnished the iso-saccharin through ring closure, as shown in **Scheme 13.** [62].



Scheme 13. Photoisomerization reaction observed for saccharin.

2. Conclusion

Saccharin safety has been reviewed and certified by the Joint Expert Committee on Food Additives (JECFA) of the World Health Organization and the Scientific Committee for Food of the European Union. Saccharin is permitted in many hundred countries around the world. It can be advocated as one of the very best choices for diabetic person and those dieting. The use of saccharin as it is free of calorie, safe and brings a well physical shape lifestyle state. While accumulation and the hazard of obesity within its related cardiovascular aggravations literature reports on genotoxicity and carcinogenicity of saccharine is still confusing. Therefore, persons should be careful to the consumption of this artificial sweetener.

References

1. Martínez-Cervera, S.; Sanz, T.; Salvador, A.; Fiszman, S.M. Rheological, textural and sensorial properties of low-sucrose muffins reformulated with sucralose/polydextrose. *LWT, (JFST)*. **2012**, *45*, 213-220.
2. Walters, E. 1. **2013**, the Sweetener Book.
3. Kapadiya Dhartiben, B.; Aparnathi, K.D. Chemistry and use of artificial intense, sweeteners *Int.J.Curr.Microbiol.App.Sci*.**2017**, *6*, *6*, 1283-1296.
4. Mortensen, A. Sweeteners permitted in European Union: Safety aspects. *Scandinavian J. Food Nutr.* **2006**, *50*, 104-116.
5. Otabe, A.; Fujieda, T.; Masuyama, T. A two-generation reproductive toxicity study of the high-intensity sweetener. advantame in CD rats. *Food Chem. Toxicol*.**2011**, *49*, 70-75.
6. Klaus Roth, Erich Lück: Ein Molekülschicksal – Die Saccharin-Saga, *Chemie in Unserer Zeit*. **2011**, *45*, 406-423.
7. Akram Arianfar, Aghdas Sadeghi, Zahra Hejri, Physical and chemical properties of high-potency sweeteners: *A Review, Chemistry Research Journal*.**2017**, *2*, *6*, 70-8.
8. Chemical Information Services, International Directory of Pharmaceutical Ingredients1995/96 Edition, *Dallas, TX*. **1995**, 860–867.

9. Nabors, L.Y. Alternative sweeteners: An overview. In alternative sweeteners" (Lyn O‟ Brien Nabors Ed.) CRC Press, *Taylor and Francis Group, Broken Sound Parkway NW*. **2001**, 1-12.
10. *Abe Bakal and Penny Cash, ABIC,* Sweetening the Pot. Prepared Foods, *International Consultants Inc*. **2006**, 55-58.
11. Dean, J.A. Lange's Handbook of Chemistry, 13th edn, McGraw-Hill Book Company, *New York*. **1985**, *5*, 56.
12. DuBois, G.E.; Prakash, I. Non-caloric sweeteners, sweetness modulators, and sweetener enhancers. *Annu. Rev. Food Sci. Technol*. **2012**, *3*, 353-380.
13. Hugh, A.; Tilson, R.M.A.; Jaspers, L.M.W. Kornet Toxicological principles for the safety assessment of direct food additives and color additives used in food, *U.S. Food and Drug Administration, Bureau of Foods*. **1982**, 1–19.
14. Salant, A. Handbook of Food Additives, Auflage, Furia, T.F. (Ed), Cleveland, OH: *CRC Press*. **1972**, 523.
15. Lyn O'Brien Nabors: Alternative Sweeteners,. Auflage, *CRC Press*. **2012**, *4*, 151-157.
16. Klaus Roth, Erich Lück: Ein Molekülschicksal – Die Saccharin-Saga, Chemie in Unserer Zeit, *Wiley VCH-Verlag, Weinheim*.**2011**, *45*, 406- 423.
17. Robert, A. Weinberg: The biology of cancer, New York, NY: Garland Science, *Taylor & Francis Group, LLC*.**2007**, 456.
18. Whitehouse, C.R.; Boullata. J.; McCauley, L.A. The potential toxicity of artificial sweeteners. *AAOHN Journal*. **2008**, *56*, *6*, 251-59.
19. Weihrauch, M.R.; Diehl, V. Artificial sweetener-do 30. Chapel CL. A review and biological risk assessment of the bear a carcinogenic risk? *Annals of Oncology, sodium saccharin. Regulatory Toxicology and Pharmacology*. **2004**, *15 10*, 1460-1465.
20. Samuel, M.; Cohen Leon, B. Ellwein Takehiko Okamura, Tsuneo Masui, Sonny L. Johansson, Raymond A. Smith, Jan M. Wehner, Mohamad Khachab, Clifford I. Chappel, Gerald P. Schoenig, James L. Emerson, and Emily M. Garland , Comparative bladder tumor-promoting activity of sodium saccharin, sodium ascorbate, related acids, and calcium salts in rats , *C.R.J*.**1991**, *51*, 1766-1777.
21. Noah, L.; Merrill, R.A. Starting from Scratch: sweeteners_factsheet. A reinventing the food additive approval process, *B.U. L. Rev*.**1998**, *329*, 336-401.
22. Ting Gong, Quan-Wei Wei, Da-Gan Mao, Kentaro Nagaoka, Gen Watanabe,4 Kazuyoshi Taya, and Fang-Xiong Shi, Effects of daily exposure to saccharin and sucrose on testicular biologic functions in mice. *Biol. of Reprod.2016*, *95*, *6*, 116, 1–13.
23. Jun Hyeon Jo, Sunjoo Kim, Tae Won Jeon, Tae Cheon Jeong, and Sangkyu Lee, Investigation of the regulatory effects of saccharin on cytochrome p450s in male ICR mice, *Toxicol. Res*.**2017**, *33*, *1*, 25-30.
24. Serkan Yilmaz, Aslı Uçar, Sacchrain genotoxicity & carcinogenicity: A review, *Advances in Food Sciences*.**2015**, 37, *3*, 213-216.
25. Munro, I.C.; Moodie, C.A.; Krewski, D.; Grice, H.C. A carcinogenicity study of commercial saccharin in the rat. *Toxicology and Applied Pharmacology*.**1975**, *32*, *3*, 513–526.
26. Howe, G.R.; Burch, J.D.; Miller, A.B.; Morrison, B.; Gordon, P.; Weldon, L.; Chambers, L.W.; Fodor, G.; Winsor, G.M. *Artificial sweeteners and human bladder cancer. Lancet*.**1977**, *2*, 578–581.

27. Reuber, M.D. Carcinogenicity of saccharin. *Environ Health Perspect*.**1978**, *25*, 173–200.
28. Risch, H.A.; Burch, J.D.; Miller, A.B.; Hill, G.B.; Steele, R.; Howe, G.R. Dietary factors and the incidence of cancer of the urinary bladder. *Am J Epidemiol*.**1988**, *127*, 1179-1191.
29. Morgan, R.W.; Wong, O. A review of epidemiological studies on artificial sweeteners and bladder cancer. *Food Chem. Toxicol*.**1985**, *23*, 529-33.
30. Zurlo, J.; Squire, R.A. Is saccharin safe? Animal testing revisited. *J Natl Cancer Inst*. **1998**, *90*, 2–3.
31. Takayama, S.; Sieber, S.M.; Adamson, R.H. et al. Longterm feeding of sodium saccharin to nonhuman primates: implications for urinary tract cancer. *J Natl Cancer Inst*.**1998**, *90*, 19– 25.
32. Sharma, A.; Amarnath, S.; Thulasimani, M.; Ramaswamy, S. Artificial sweeteners as a sugar substitute: Are they really safe*, Indian J Pharmacol*.**2016**, *48*, *3*, 237-240.
33. Leonard, A.; Leonard, E.D. Mutagenicity test with saccharin in the male mouse. *Journal of Environmental Pathology and Toxicology*.**1979**, *2*, 1047-1053.
34. Zhang, Z.L.; Yang, J.; Zhang, Q.A.; Cao, X.S. Studies on the utilization of a plant SCE test in detecting potential mutagenic agents. *Mutat Res*.**1991**, *261*, 69.
35. Jeffrey, A.M.; Williams, G.M. Lack of DNA-damaging activity of five non-nutritive sweeteners in the rat hepatocyte/ DNA repair assay. *(F CTJ)*.**2000**, *38*, *4*, 335–38.
36. Sasaki, Y.F.; Kawaguchi, S.; Kamaya, A.; Ohshita, M.; Kabasawa, K.; Iwama, K.; Taniguchi, K.; Tsuda, S. The comet assay with 8 mouse organs: results with 39 currently used food additives. *Mutat Res*.**2002**, *26*, 103-119.
37. Bandyopadhyay, A.; Ghoshal, S.; Mukherjee, A. Genotoxicity testing of low-calorie Sweeteners: Aspartame, Acesulfame-K, and Saccharin*. Drug Chem. Toxicol*.**2008**, *31*, 447–457.
38. Icsel, C.; Yilmaz, V.T. *In vitro* DNA binding studies of the sweetening agent saccharin and its copper (II) and zinc (II) complexes*. J Photo chem Photobiol Biol*.**2014**, *130*, 115-121.
39. Frenzilli, G.M.; Bernardeschi, R.; Barale. Alkaline versus Neutral Version of Comet Assay in Human Leukocytes Using, *Compounds Journal of Translational Toxicology*. **2014**, *1*, 60–71.
40. Armstrong, B.; Doll, R. Bladder cancer mortality in diabetics in relation to saccharin consumption and smoking habits. *Br J Prev Soc Med*.**1975**, *2*, 73–81.
41. Jensen, O.M.; Kamby, C. Intra-uterine exposure to saccharin and risk of bladder cancer in man. *Int J Cancer*.**1982**, *29*, 507–509.
42. Franceschi, S.; Favero, A.; La Vecchia, C. Food groups and risk of colorectal cancer in Italy. *Int J Cancer*.**1997**, *72*, 56-61.
43. YuY, Hu J, Wang PP. Risk factors for bladder cancer: a case-control study in northeast China, *Eur J Cancer Prev*.**1997**, *6*, 363–69.
44. Franceschi, S.; Favero, A.; Conti, E. Food groups, oils and butter, and cancer of the oral cavity and pharynx. *Br J Cancer*.**1999**, *80*, 614-620.
45. Bosetti, C.; La Vecchia, C.; Talamini, R. Food groups and risk of squamous cell esophageal cancer in northern Italy. *Int J Cancer*.**2000**, *87*, 289-294.

46. Bosetti, C.; Negri, E.; Franceschi, S. Diet and ovarian cancer risk: a case-control study in Italy. *Int J Cancer*.**2001**, *93*, 911- 915.
47. Bosetti, C.; La Vecchia, C.; Talamini, R. Food groups and laryngeal cancer risk: a case-control study from Italy and Switzerland. *Int J Cancer*.**2002**, *100*, 355-360.
48. Tavani, A.; Giordano, L.; Gallus, S. Consumption of sweet foods and breast cancer risk in Italy. *Ann. Oncol*.**2006**, *17*, 341- 345.
49. Bosetti, C.; Micelotta, S.; Dal Maso, L. Food group and risk of prostate cancer in Italy. *Int J Cancer*.**2004**, *10*, 424-428.
50. Bravi, F.; Bosetti, C.; Scotti, L. Food groups and renal cell carcinoma: a case-control study from Italy. *Int J Cancer*.**2007**, *120*, 681-685.
51. Andreatta, M.M.; Muñoz, S.E.; Lantieri, M.J.; Eynard, A.R.; Navarro, A. Artificial sweetener consumption and urinary tract tumors in Cordoba, *Argentina J Prev Med*. **2008**, *47*, 136–139.
52. Bosetti, C.; Gallus, S.; Talamini, R.; Montella, M.; Franceschi, S.; Negri, E.; La Vecchia, C. Artificial sweeteners and the risk of gastric, pancreatic, and endometrial cancers in Italy. *Cancer Epidemiol. Biomarkers Prev*.**2009**, *18*, 2235-2238.
53. Kumar, A.; Weatherly, M.R.; Beaman, D.C. Sweeteners, and dyes in antibiotics preparations. *Pediatrics*.**1992**, *87*, 352-360.
54. Elcock, M.; Morgan, R.W. Update on artificial Sweetness and Lite, FDA consumer, revised, sweeteners and bladder cancer. *Reg. Toxi*.**2006**, *6*, *3*.
55. Berthoud, H.R.; Trimble, E.R.; Siegel, E.G.; Bereiter, D.A.; Jeanrenaud, B. Cephalic-phase insulin secretion in normal and pancreatic islet-transplanted rats, *AJP –End. and Metab*.**1980**, *238*, *4*, 336-340.
56. Ionescu, E.; Rohner-Jeanrenaud, F.; Proietto, J.; Rivest, R.W.; Jeanrenaud, B. Taste-induced changes in plasma insulin and glucose turnover in lean and genetically obese rats. *Diabetes*.**1988**, *37*, 773–79.
57. Just, T.; Pau, H.W.; Engel, U.; Hummel, T. Cephalic phase insulin release in healthy humans after taste stimulation? *Appetite*.**2008**, *238*, *4*, 622–627.
58. Okoduwa, S.I.R.; Ebiloma, G.U.; Baba, J.; Ajide. S. the Metabolism and toxicology of saccharin, *Info health Awareness Article*. **2013**, *1*, 14-19.
59. Lethco, E.J.; Wallace, W.C. The metabolism of saccharin in animals, *Toxicology*. **1975**, *3*, 287-300.
60. Aly, A.A.; Nassar, S.A. *N*-[4-(Dicyanomethylazo) phenyl]-2- saccharin-2-ylacetamide in the Synthesis of pyridazine and pyrimidine derivatives, *Heter.Chem*.**2004**, *15*, *1*, 210-215.
61. Çakra, S.; Biçerb, E. Synthesis, spectroscopic and electrochemical characteristics of a novel Schiff-base from saccharin and tryptophan, *J. Iran. Chem. Soc*. **2010**, *7*, *2*, 394-404.
62. Tillu, V. H.; Dumbre, D.K.; Borate, H.B.; Wakharkar, R.D.; Choudhary, V.R. Solvent-free one-pot synthesis of sulfonephthaleins from saccharin and phenols, *Synthetic Communications*. **2012**, *42*, *8*,1101-1107.