Azo dyes – biological activity and synthetic strategy

Ewelina WĘGLARZ-TOMCZAK, Łukasz GÓRECKI – Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology

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Introduction

Azo dyes – a fatal threat or a new generation of drugs?

In 1858 Griss developed the azo coupling reaction and obtained first azo dye – Aniline Yellow. Nowadays, around 10 thousands of these compounds are described and more than 2 thousands are applied to color various materials. Azo dyes are characterized by the presence of the azo moiety (–N=N–) in their structure, conjugated with two, distinct or identical, mono- or polycyclic aromatic systems. Because of their specific physico-chemical properties and biological activities, they have found a broad application in pharmaceutical, cosmetic, food, dyeing/textile industry and analytical chemistry. However, the most typical and popular field of utility remains their coloring function. Azo dyes are the largest and the most versatile class of dyes. They possess intense bright colors, in particular oranges, reds and yellows. In addition, azo dyes exhibit a variety of interesting biological activities. Medical importance of these compounds is well known for their antibiotic, antifungal and anti-HIV properties. On the other hand they bring a certain danger for health and environment because of cancero- and mutagenicity. In this review, selected synthetic strategies and biological activities of azo dyes are presented, the latter in the context of a therapeutic potential and a hazard connected with their production and application.

Biological Activity

Biological activity of azo colorants mostly results from the specific pathway of their metabolism. An enzyme-mediated reduction of the azo bond occurs *in vivo* [1, 2]. In mammalian organisms it has found in liver [3], in digestive tract bacteria [4-6] and in skin bacteria such as *Staphylococcus aureus* [7]. The result of this reaction is cleavage of the azo bond and the release of the corresponding aromatic amines originating from the azo dye [8]. The products can be more or less toxic than the parent molecules, so this process can decrease or increase any toxic or carcinogenic effects of the dyes [9, 10]. Nevertheless, in most cases the products, in particular benzidine-based derivatives, demonstrate an increased toxicity [3,6,7]. For example, the azo dye Direct Black 38 is metabolized to the mutagen benzidine by human intestinal microflora [6].

Several independent research groups showed in 70-ies that benzidine-based dyes increased the risk of cancer of the bladder and other organs in humans [11]. It was proved that benzidine was the major factor responsible for mutagenesis [12]. Further studies also confirmed the mutagenicity of its analogs [13,14].

Methyl Yellow (4-dimethylaminoazobenzene) is one of azo dyes that exhibits carcinogenicity through highly reactive metabolic intermediates that can interact with DNA and cause mutations [10]. It was suggested that this dye is converted by demethylation followed by *N*-hydroxylation to *N*-hydroxy-*N*-methyl-4-aminoazobenzene which reacts covalently with a nucleic base of DNA (Fig. 1), thus, being the exact carcinogen [15].

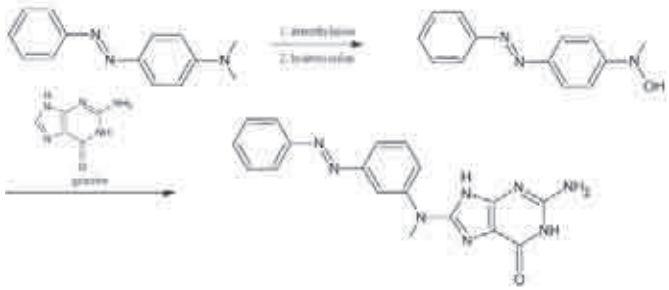

Fig. 1. Mechanism of a nucleic base (guanine) modification by Methyl Yellow

The main source of azo dyes in human organism is food. Groundwater can be a secondary source of contamination as 3 thousand tons of organic dyes are released into the surface water in the United States each year [16]. Because of such a considerable hazard, many research groups have recently focused on the area of biodegradation of these dyes [17,18]. It has been demonstrated that several microorganisms like lignolytic fungi or bacteria are able, under certain environmental conditions, to transform azo dyes to non-colored products or even to completely mineralize them [17]. Lignolytic fungi, using lignin and manganese peroxidases or laccases, decolorize azo dyes. Degradation of dyes by bacteria is mostly based on reduction of the azo bond, which results in formation of usually colorless amines [19÷21]. This process can be done under aerobic condition by bacteria like *Bacillus subtilis* [22], *Pseudomonas stutzeri* [23], *Streptomyces* [24], or in more common and less specific anaerobic way by bacteria such as *Bacteroides*, *Eubacterium* or *Clostridium* species [24, 25].

Despite the above described negative features of azo dyes, there are numerous biological activities which make them medically attractive compounds. One of the positive pharmaceutical application of azo dyes and their specific azoreduction *in vivo* is polymeric azo compound for site specific drug delivery in the colon diseases such as colitis and irritable bowel syndrome [26]. Reductive degradation and subsequent splitting of the azo bond occur in colon, and therefore they are highly site-specific [27], what gives an opportunity to prepare a targeted therapy. Pro-drug is reduced to the corresponding amines that are exact therapeutics [28]. Using of such pro-drug can be exemplified by low-molecular or polymeric (immobilized on a polyethylene glycol matrix, Fig. 2.) 5-aminosalicylic acid derivatives that exhibit anti-inflammatory and cytoprotective potency [29].

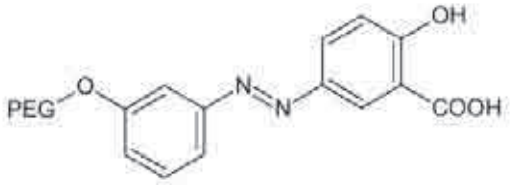

Fig. 2. Azo derivative of 5-aminosalicylic acid immobilized on polyethylene glycol

Another positive property of azo dyes is their antimicrobial activity. For example, 4-phenylazophenoxyacetic acids revealed antimicrobial activity against two gram-positive bacteria, *Staphylococcus ureus* (bacterium that can causes several serious illnesses such as skin infections, pneumonia, meningitis, osteomyelitis or endocarditis) and *Streptococcus pyogenes* (the causative agent in streptococcal infections, including strep throat) as well as three gram-negative bacteria (*Pseudomonas aeruginosa*, *Proteus vulgaris* and *Escherichia coli*) and one fungi species (*Candida albicans*) [30,31]. Azo Schiff bases exhibited antibacterial activity against *Bacillus subtilis* (bacterium responsible for causing ropiness in spoiled bread dough) and antifungal against several fungi including *Candida albicans*, *Cryptococus neoformans*, *Tricophyton mentagrophytes* [32].

Biomedical potential has been also reported for the bisazo compound known in the literature as FP-21399 (Fig. 3). It exhibits anti h***uman immunodeficiency virus*** (HIV) potency by inhibition HIV envelope glycoprotein-mediated membrane fusion what precedes virus infiltration into cell. FP-21399 appeared to inhibit the fusion of CD4+ cells (T helper lymphocytes) with cells that express gp160 (glycoprotein found on the outer surface, or envelope, of the human immunodeficiency virus) [33]. Further studies included clinical trials and confirmed the activity toward HIV virus [34].

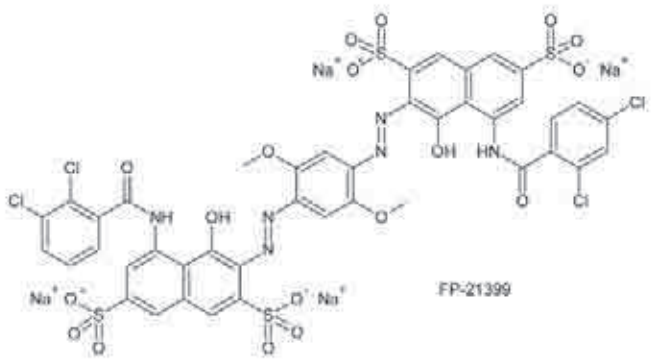

Fig. 3. Bisazo compound with anti-HIV activity

Azobenzene can exist in two forms, namely *cis* and *trans* isomers, which can interconvert under photochemical or thermal induction. Accordingly, compounds with azobenzene moiety show photo-switching properties which open new perspectives for their biological applications. Recently, this potential has been widely used to photoregulate protein conformation, enzyme activity and nucleic acid function [35]. Activation of the biomolecular functions can be switched "on" and "off" by reversible photoisomerization of the azobenzene moiety, increasing or decreasing the affinity of ligand and receptor interactions. Transition state analogue inhibitors of papain (a cysteine endopeptidase, isolated from *Carica papaya,* that catalyzes the breakdown of proteins, used to tenderize meat and as a clarifying agent in food industry) and -chymotrypsin (a serine exopeptidase produced by pancreas that cleaves amide bond on carboxylic side of amino acids) are interesting examples that use the photo-switching prosperities of compounds with azobenzene chromophore [36, 37].

Synthesis Strategy

Aromatic azo compounds are intermediates in the reduction of the nitro group to the amino, or reverse reactions – the oxidation of the amino group to the nitro one (Fig. 4). In both cases, an excess of a reducer or oxidant agent is used and the conditions are appropriately chosen to receive the product in the shortest time, with the best yield, and at minimum work and costs consumption. Thus, stopping the reaction sequence at the corresponding transition product (azo) as the main target and then its isolation conditions must be accurately selected.

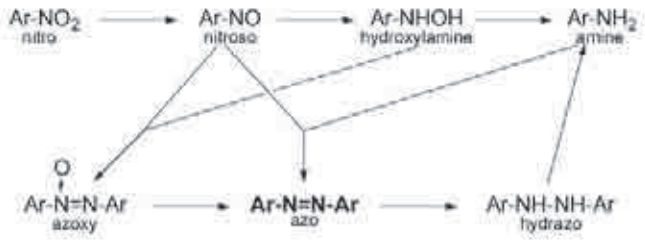

Fig. 4. General scheme of reduction reaction of the nitro compounds to the amino derivatives [38÷40]

In this context, five synthetic strategies leading to azo dyes are particularly useful (Fig. 5). The first four (I-IV) directly follow the diagram presented in Figure 4. The last one is a diazotization/coupling reaction. Each of them has certain restrictions mostly associated with substrates availability. This fact limits the pool of products that can be obtained with the use of a particular method.

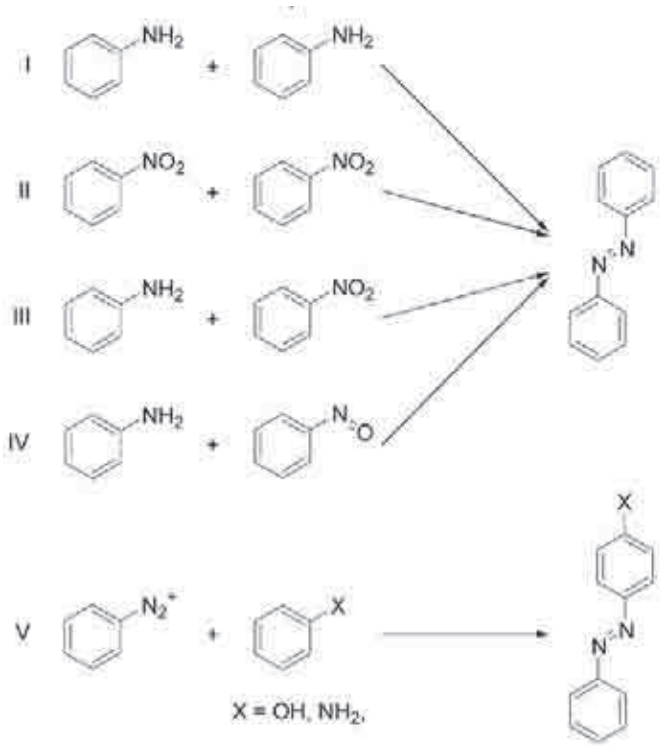

Fig. 5. Synthetic pathways leading to azo compounds (the phenyl ring represents an aromatic portion)

The first two synthetic pathways are dedicated to the preparation of symmetrical azo compounds. If two different substrates are used a mixture of three azo products is obtained: two symmetric and one asymmetric. Oxidative coupling of two amine components can be performed using: oxygen in the presence of a catalyst (CuCl/pyridine) [41], under photo-catalytic conditions promoted by TiO_2 [42], Fe_2O_3 [43], HgO [44] or under the action of oxidants such as: $KMnO_4$ [45], MnO_2 [46], $NaBO_3$ [47], KO_2 [48], K_2FeO_4 [49], AgO [50], $Pb(OAc)_4$ [51]. Moreover, a phase-transfer or enzymatic systems exemplified by Galvinoxyl (PTC)/$K_3Fe(CN)_6$/KOH [52] and peroxidase-H_2O_2 [53], respectively, can be used. There is no such a broad range of possibilities among the reducing agents applied for the preparation of azo derivatives from the nitro compounds as in the case of oxidation. Nevertheless, several publications describe the obtaining of complex molecules containing the azo group starting from *p*-nitrobenzoic acid. The procedure begins with reaction of the nitro substrate with reducing sugar (glucose) in alkaline conditions to obtain azobenzenedicarboxylic acid [54]. Another simple reducing reagents are zinc or $SnCl_2$ in alkaline conditions [55,56], $LiAlH_4$ [57],

ethylenediamine [58], Na_2Te [59] or lead with either triethylammonium formate or ammonium acetate [60,61]. An interesting method was published in 1906 and it has been used up to date – the reaction of *p*-nitrophenol in a strongly basic medium at 200°C [62].

The third and fourth of the proposed pathways can also be used for the preparation of symmetrical azo dyes, but it is more rational to apply them to obtain asymmetric compounds. The method III has gained the importance in recent years [63, 64], when harsh conditions of substrates heating in a KOH/DMF solution for 12 to 48 hours at 150°C under nitrogen atmosphere gave reasonable yields of the azo compounds. Previously, a shorter time and lower temperature allowed for only less than 20% of productivity [65, 66]. Reaction IV is the simplest in execution but prior to it the nitrosyl starting material must be obtained. This can be performed in three different ways (Fig. 6).

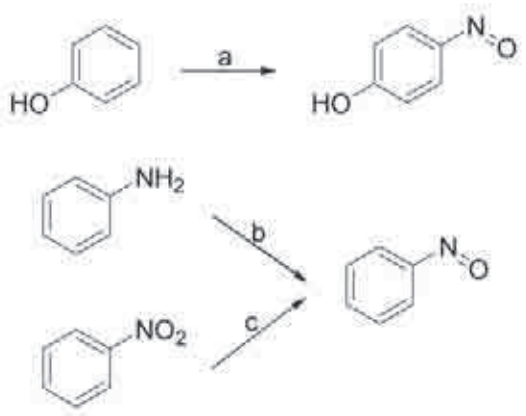

Fig. 6. Synthesis of nitroso derivatives: a) $NaNO_2$, acetic acid [67]; b) Oxone®, K_2CO_3 [68]; c) 1. NH_4Cl, Zn; 2. $FeCl_3 \times 6H_2O$ [69]

Then, the amino and nitroso substrates are just mixed in glacial acetic acid at room or slightly elevated temperature [70]. A modification of this method, involving generation *in situ* the nitroso derivative from starting amine under action of H_2O_2 and its subsequent reaction with non-oxidized reactant, can lead to the symmetric product [71].

Since its discovery the final presented reaction (V, Fig. 5) has been closely related to azo dyes. This reaction proceeds according to the mechanism of electrophilic aromatic substitution, in which the diazonium salt formed from aniline is the electrophilic reagent, while an aromatic system substituted with electron donating group (OH, NH_2, or their derivatives) is the corresponding nucleophile [56,72]. In rare cases, the coupling reaction takes place when an aromatic derivative substituted by alkyl groups is the nucleophilic reactant, but then the electrophile must contain electron withdrawing substituent e.g. nitro groups, that increase an electron deficit of the diazonium group. This allows coupling of 2,4,6-trinitroaniline with 1,3,5-trimethylbenzene, 1,2,3,5-tetramethylbenzene or pentamethylbenzene [73,74]. Typically, the received diazonium salt is immediately subjected to the coupling reaction, because after separation and drying it is explosive [75]. In reaction of diazonium salts with phenols, the product is substituted at the *para* position to the hydroxyl group. If this site is occupied the *ortho* isomer is obtained. In the case of non- substituted aniline, azoaminobenzene compound is preliminarily formed (-N=N-NH-) and subsequently rearranges to the mixture of *para* and *ortho* isomers of the aminoazobenzene product [76]. To avoid this inconvenience, a protection of the amino group can be applied for coupling and removed after the reaction, e.g. by hydrolysis [77]. The direct method of obtaining the aminoazobenzene structure (avoiding the rearrangement) is performing the reaction in formic acid and sodium formate [78].

A variety of reagents that generate a –N=N– bond is wide enough to choose easily the reaction conditions appropriate for available substrates. The situation becomes more complex when aromatic systems are substituted with groups sensitive to oxidation or reduction, acidic or basic conditions. In these cases, the design of a multistep synthesis becomes a real challenge for a chemist.

Conclusion and perspective

Azo dyes are synthetic compounds (it is known only one occurs in environment) containing azo bond –N=N–, are obtained mainly from the aromatic amine, nitro and nitroso substrate. Methods of their synthesis rely on the use of a suitable oxidative/reductive reactions or diazotization/coupling reaction. Historically, the last one procedure must be regarded as one of the most important achievements in the development of industrial organic chemistry. These methods have made them widely available. Through color, resulting from the presence of the characteristic system of conjugated bonds exhibiting absorption in the visible light range, they have found wide application in various industries. Based on huge amount of azo dyes released to environment and theirs toxicity, it is necessary to improve and develop new methods of biodegradation. Despite of the toxicity a lot of these compounds appear biomedical potency. As it is presented, they display various properties such as antibacterial and antifungal, are inhibitors of proteases (enzymes that play functions in many pathological disorders) or have anti-HIV potency. The challenge for scientists is also development of azopolymeric system for new generation targeted therapy of colon and liver.

Acknowledgments

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Ewelina WĘGLARZ-TOMCZAK – M.Sc. is a graduate in medicinal chemistry of the Faculty of Chemistry, Wrocław University of Technology. After graduating studies she served internship at Faculty of Chemistry and Biochemistry, Ruhr-University of Bochum. Since 2009 she is a Ph.D. student in Department of Bioorganic Chemistry, Wroclaw University of Technology. The subject of her study is synthesis and biological activity of inhibitors of aminopeptidase. She is the author of a book chapter and article, co-author of five scientific articles, 14 communications and posters presented at national and international conferences. She is scholarship holder of *"Enterprising Ph.D. student – investment in the innovative development of the region"(Operational Programme Human Capital)*, project co-financed by the European Union from the European Social Fund.

e-mail: ewelina.weglarz@pwr.wroc.pl; phone: +48 71 320 33 54

Łukasz GÓRECKI – M.Sc. is a graduate of the Faculty of Chemistry of the Opole University (2007). Currently, he is last year Ph.D. student at the Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology. He is scholarship holder of *"Enterprising Ph. D. student – investment in the innovative development of the region" (Operational Programme Human Capital)*, project

co-financed by the European Union from the European Social Fund.

Scientific interests: synthesis of phosphoroorganic derivatives of quinine alkaloids and azobenzenephosphonates. He is the author of a book chapter, co-author of a patent application, 2 articles in the scientific press, 17 communications and posters presented at national and international conferences.

e-mail: lukasz.gorecki@pwr.wroc.pl; phone: +48 71 320 29 77

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