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Review

Azo Dyes and the Microbial World: Synthesis, Breakdown, and Bioactivity

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Abstract: This review discusses natural and synthetic azo compounds found in bacteria, fungal endophytes, fungi, plants, and invertebrates. More than 100 of these compounds have demonstrated significant pharmacological activity, including antitumor, antimicrobial, and antibacterial effects. Using mathematical algorithms and the PASS program, researchers predict new potential applications based on their structure–activity relationships. This review emphasizes the importance of natural azo compounds as promising drug prototypes and key players in drug discovery. It also explores the synthesis and degradation of azo dyes and their potential uses in medicine, food, cosmetics, and related fields. Additionally, the role of microorganisms in producing natural azo compounds and their synthetic counterparts is examined, showcasing their potential in drug development and human health advancements.

Keywords: microorganisms; bacteria; azo dyes; azo compounds; activity; breakdown; fungal endophytes

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1. Introduction

Azo compounds, whether natural or synthetic, contain one or more azo groups (-N=N-), a functional group where two nitrogen atoms are joined by a double bond. Their general formula is R-N=N-R', with R and R' being either aryl or alkyl groups. The azo group plays a key role in determining their chemical properties, which are also influenced by other attached groups [1–3]. Azo ligands significantly affect the color of these compounds, creating bright and intense shades. These colors may change depending on pH, which may cause changes in the properties of the molecules, probably due to changes in the protonation state, which may lead to changes in electron density [4–6].

Azoxy metabolites, in contrast, feature an azoxy functional group, where two nitrogen atoms are linked by a double bond, with one also bonded to an oxygen atom. Their general formula is R-N(O)=N-R', where R and R' represent organic groups [7–9].

Some bacteria might be capable of producing azo or azoxy compounds, either as part of their metabolism or as secondary metabolites. If so, this ability would be specific to certain strains. Bacteria can also transform or break down synthetic compounds, including azoxy compounds, which may contribute to environmental cleanup processes like bioremediation [1,2,10–13].

Bacteria are often genetically engineered in biotechnology to produce useful chemical compounds. It is possible that bacteria could also be modified to synthesize azo or azoxy compounds for industrial purposes [14–16].

This review explores the structures and biological activities of natural azo and azoxy compounds, particularly those produced by microorganisms, as potential sources for drug

discovery. It also discusses how microorganisms degrade azo dyes. The presented data allow us to understand the role of microorganisms in the biosynthesis and degradation of these unusual natural metabolites. The findings on azo compounds are particularly relevant to pharmacologists, chemists, and biologists.

2. Microorganisms as Producers of Azo and Azoxy Compounds

A well-known example of a natural azoxy antibiotic is valanimicin (**1**), which is derived from the fermentation broth of *Streptomyces viridifaciens* MG456-hF10. Recent research has identified the genes responsible for valanimicin biosynthesis. The VlmF protein, part of the major facilitator superfamily, provides resistance to valanimicin. Meanwhile, VlmD, VlmH, and VlmR convert L-valine into isobutyl-hydroxylamine, and VlmL facilitates the formation of L-seryl-tRNA from L-serine (see Figure 1) [17,18].

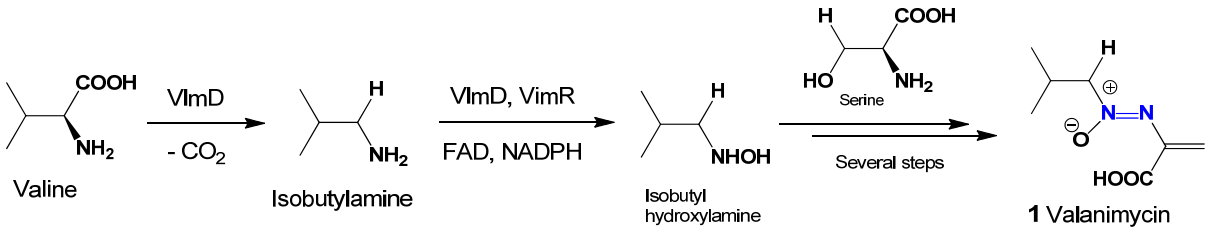


Figure 1. Common biosynthetic pathway for valanimycin by *Streptomyces* species, showing structures of the primary precursors l-valine and l-serine and structures of known intermediates. The pathway proceeds from L-valine and L-serine through the intermediacy of isobutylhydroxylamine.

Valanimicin is effective against both Gram-positive and Gram-negative bacteria, particularly *E. coli* BE1121, a mutant strain of *E. coli* K12 that is deficient in DNA repair. It has also shown toxicity against L1210, P388/S (doxorubicin-sensitive) and P388/ADR (doxorubicin-resistant) murine leukemia cells, with IC_{50} values of 0.8, 2.7, and 1.4 pg/mL, respectively. In animal studies, valanimicin extended the survival of mice with Ehrlich carcinoma or L1210 leukemia cells [19].

Several valinomycin derivatives have been discovered from different sources. A valanimicin derivative (**2**, see structure in Figure 2) was found in the culture broth of *Streptomyces viridifaciens* MG456-hF10 during valanimicin biosynthesis [20], with its structure confirmed using a more stable ammonia adduct (**3**) [21]. Table 1 summarizes the biological activities of compounds (**1**–**27**). The antibiotic LL-BH872α (4), which contains an α,β-unsaturated azoxy group, was isolated from *Streptomyces hinnulinis* [22]. More recently, LL-BH872a, 2z-OH (**5**), produced by *Actinomadura* sp., was found in apricot (*Prunus armeniaca*) roots [21], along with LL-BH872a, 2z-OH, 4′z-OH (**6**), produced by *Streptomyces misionensis* FERM 10459 [23].

Several microorganisms produce antifungal antibiotics. For example, manivamycins A (**7**) and B (**8**), isolated from *Streptomyces prasinopilosus*, showed broad antifungal and antibacterial activity against multiple *Candida* and *Trichophyton* species, *Cryptococcus neoformans*, and *Staphylococcus aureus* [24]. Another antifungal agent, azoxybacillin (**9**), was isolated from *Bacillus cereus* NR2991 and was particularly effective against *Aspergillus fumigatus* and *Trichophyton mentagrophytes* [25,26]. Azoxyalkene (**10**), an unstable azoxy compound, was discovered in *Actinomadura* sp. (strain A7), which grows in apricot roots, though it only displayed weak antifungal activity against *Rhodotorula* sp. [21].

Elaiomycin (**11**), an azoxy antibiotic isolated from *Streptomyces hepaticus*, was found to strongly inhibit *Mycobacterium tuberculosis* growth [27–30]. Elaomycins D–G (**12**–**15**), produced by *Streptomyces* sp. HKI0708, exhibit antimicrobial, anti-mycobacterial, and cytotoxic activities [31,32]. Additionally, elaomycins K (**16**), L (**17**), and elaomycin K amide (**18**), azoxy-type antibiotics found in *Streptomyces* sp. Tü 6399, showed weak antibacte-

rial effects against *Bacillus subtilis*, *Staphylococcus lentus*, and *Xanthomonas campestris*, a plant pathogen [33].

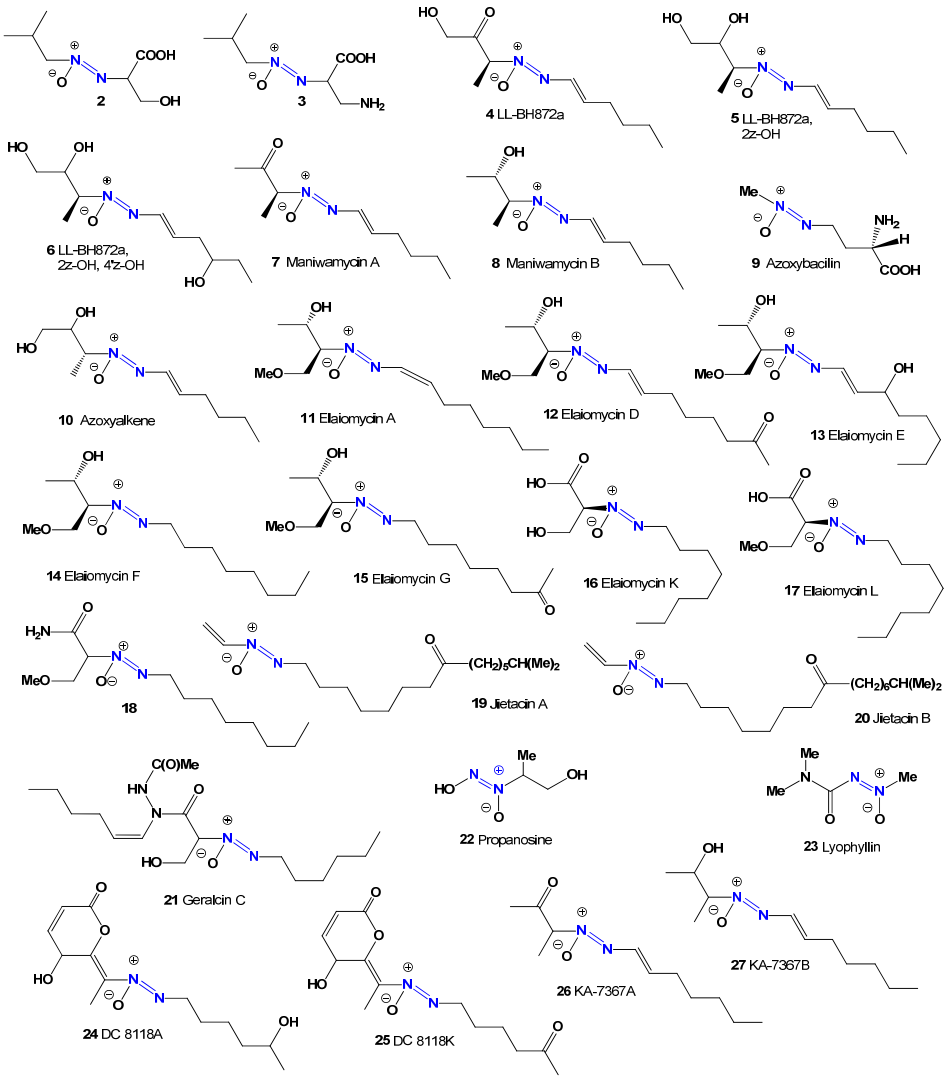


Figure 2. Bioactive azo and azoxy compounds derived from microorganisms. The presented natural metabolites demonstrate strong or moderate antineoplastic, antiviral, or antifungal activities.

Antiparasitic antibiotics, particularly those targeting nematodes, are rare. Jietacins A (**19**) and B (**20**), isolated from *Streptomyces* sp. [34,35], showed ten-times the activity of avermectin Bla, a veterinary nematicidal agent, against the pine wood nematode *Bursaphelenchus hylocomi* [36,37]. Additionally, geralcin C (**21**), D, and E, isolated from *Streptomyces* sp. LMA-545, exhibited anticancer properties, with geralcin C showing an IC_{50} of 0.8 µM against KB and HCT116 cell lines. It also inhibited *E. coli* DnaG primase, a Gram-negative antimicrobial target, with an IC_{50} of 0.7 µM [38]. Lastly, propanosine (K-76, **22**), identified in *Micromonospora chalcea* 671-AV2 extracts, inhibited *Valsa ceratosperma* growth [39].

Lyophylline (**23**) is an antibiotic obtained from the mushroom *Lyophyllum shimeji* or its fungal endophytes. It has been found to prevent forebrain blister formation in the cranial mesenchyme at a concentration of 50 µg/mL [40].

The antitumor antibiotics DC1881A (**24**) and DC1881B (**25**) are produced by *Streptomyces* sp. DO-118 [41]. Additionally, the azoxy compounds KA-7367A (**26**) and KA-7367B (**27**, activity see in Table 2), which have antifungal properties, were discovered in *Streptomyces* sp. (KC-7367, FERM BP-1277). KA-7367A (**26**) showed activity against *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton mentagrophytes*, and *T. rubrum* [42].

Calvacic acid (also called alvacic acid or calvatinic acid, **28**) and its methyl derivatives (**29**, see structure in Figure 3, and Table 3) belong to a group of antitumor antibiotics with a diazene N-oxide structure. These compounds are produced by the fungi *Calvatia craniformis* (Agaricaceae) [43], *Calvatia lilacina* [44], and *Lycoperdon pyriforme* [45]. Another antibiotic, clavulanic acid, inhibits the growth of Gram-positive and Gram-negative bacteria at concentrations of 3–6 μg/mL [44]. It has cytotoxic effects, preventing the growth of Yoshida sarcoma cells [43], and has shown carcinostatic activity against hepatoma and leukemia K562 cells [46]. Clavulanic acid is also effective against *Helicobacter pylori*, a Gram-negative bacterium associated with gastric infections [47].

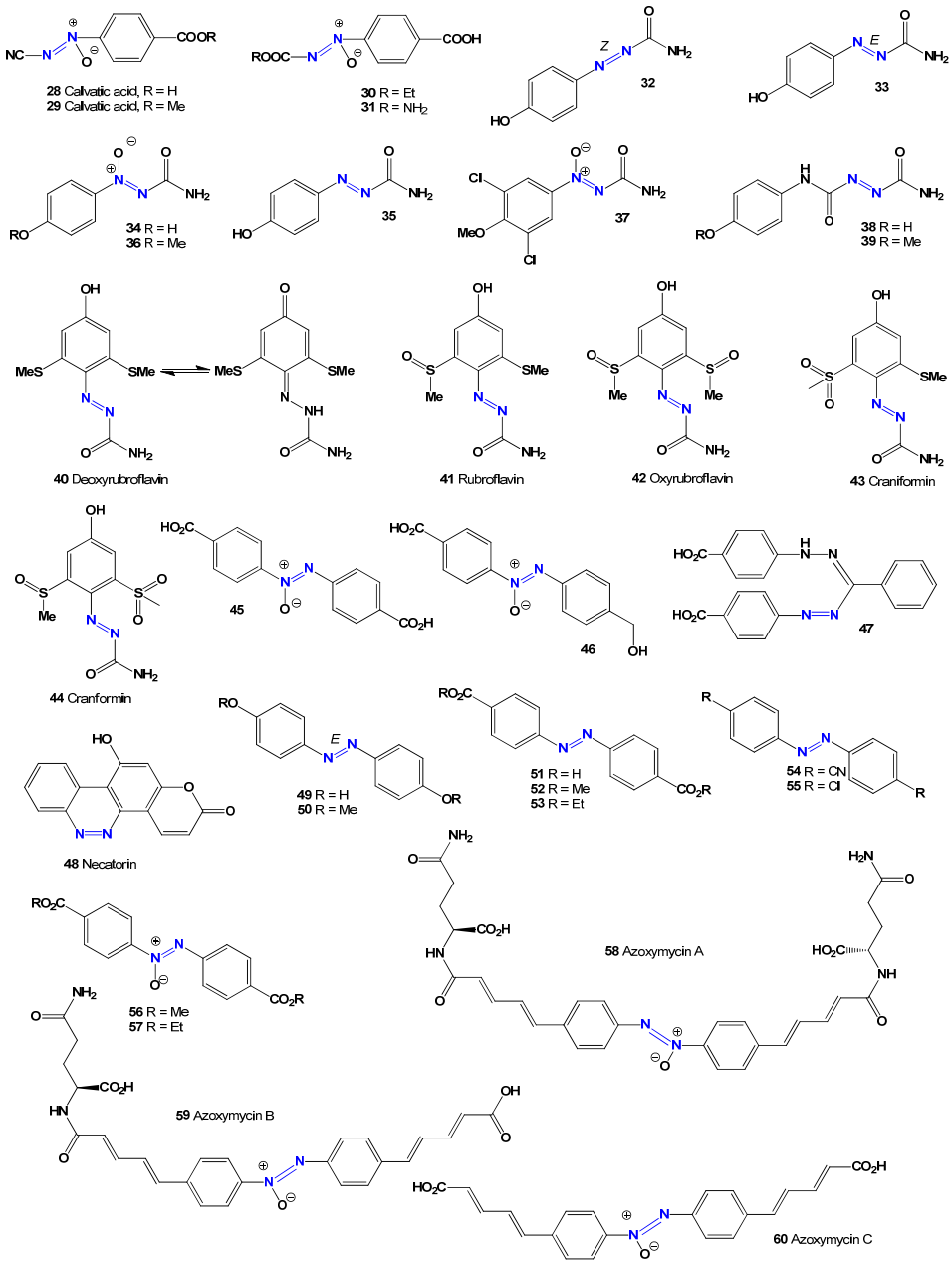


Figure 3. Bioactive azo compounds are produced by fungi and fungal endophytes. The presented natural metabolites demonstrate strong or moderate antineoplastic, anti-inflammatory, anti-Helicobacter pylori or antifungal activities.

Amoxicillin–clavulanic acid is frequently used to treat many of the World Health Organization's Priority Infectious Syndromes in adults and children. However, in some cases, a delayed antibiotic prescription or amoxicillin alone could be sufficient, reducing

unnecessary use [48,49]. Additionally, clavulanic acid is being investigated for its potential in preventing and treating scopolamine-induced Alzheimer's disease [50]. Some of its analogues (**30** and **31**) have been found to exhibit anti-microtubule activity [51].

Azoformamide (**32**), its (*E*)-form (**33** and **35**), and its azoxy derivatives (**34** and **36**) have been isolated from the puffball fungus *Lycoperdon pyriforme* [52,53] and have also been found in *Calvatia craniformis* [54]. A detection method for azoformamide in food additives has been developed [55].

Table 1. Biological activity of azo dyes produced by microorganisms (**1**–**13**) [13,24,34].

No.	Dominated Activity	Rank	Additional Activity	Rank
1	Antineoplastic	Strong	Antibiotic	Strong
2	Antineoplastic	Strong	Hepatic disorders treatment	Strong
3	Antineoplastic	Strong		
4	Antineoplastic	Moderate		
5	Antiviral (Arbovirus)	Moderate	Antineoplastic	Moderate
6	Antineoplastic	Moderate	Antifungal	Weak
7	Antineoplastic	Moderate	Antifungal	Moderate
8	Mucositis treatment	Moderate	Antiviral (Arbovirus)	Moderate
9	Antifungal	Moderate	Antiviral (Arbovirus)	Moderate
10	Antiviral (Arbovirus)	Moderate	Antifungal	Moderate
11	Vasodilator	Moderate	Antifungal	Moderate
12	Antifungal	Moderate	Antiviral (Arbovirus)	Moderate
13	Antifungal	Moderate	Natural killer cell stimulant	Weak

Extracts from the fungus *Lycoperdon pyriforme* yielded two compounds, 4-methoxybenzene-1-azoformamide (**33**) and 4-methoxybenzene-1-OH N-azoxyformamide (**34**), both of which were found to be effective against the parasitic nematode *Meloidogyne incognita*. A related compound, 3,5-dichloro- 4-methoxybenzene-1-OH-azoxyformamide (**37**), showed weaker nematicidal effects but higher cytotoxicity than compounds (**33**) and (**34**) [56].

Azoxyformamides (**34** and **36**) and two azoformamide derivatives (**38** and **39**) were isolated from the fruiting bodies of *Calvatia craniiformis* and *Lycoperdon hiemale*, respectively. Compounds (**34**) and (**39**) inhibited rootlet growth in lettuce seedlings, suggesting that their azoxy structure contributes to this effect. Additionally, compounds (**34**, **36**, and **39**) also inhibited the growth of pearl millet seedlings [57,58].

Fungi and their endophytes are known to produce colored pigments that contain azo groups. One such pigment, the red minor compound deoxyrubroflavin (**40**), was isolated from the lump fungus *Calvatia rubro-flava* [59,60]. Another pigment, the orange-colored rubroflavin (**41**), was found in the dried fruiting bodies of *Calvatia rubro-flava* and *Calvatia craniformis* [60,61]. Additional pigments, including oxyrubroflavin (**42**), craniformin (**43**), and cranformin (**44**, activity see in Table 4), were also identified in *Calvatia rubro-flava* [60–62].

The insect-pathogenic fungus *Entomophthora virulenta* produces a mixture of 4,4′-azoxybenzenedicarboxylic acid (**45**) and 4,4′-hydroxymethylazoxybenzene carboxylic acid (**46**), both of which have insecticidal properties [63,64]. A formazan derivative (**47**) was isolated from *Agaricus silvicola* [64]. Another notable fungal compound, necatorin (**48**), was discovered in *Lactarius necator*. This mutagenic alkaloid contains an azo group within a polycyclic aromatic structure that includes a 1-benzopyran moiety and a ketone group at carbon C2 [65–68].

Table 2. Biological activity of azo dyes produced by microorganisms (**14**–**27**) [13,36,37,41].

No.	Dominated Activity	Rank	Additional Activity	Rank
14	Antifungal	Moderate	Natural killer cell stimulant	Weak
15	Vasodilator, peripheral	Weak	Antineoplastic	Weak
16	Antiviral (Arbovirus)	Strong	Mucositis treatment	Moderate
17	Pre-neoplastic	Strong	Mucositis treatment	Moderate
18	Mucositis treatment	Moderate	Natural killer cell stimulant	Weak
19	Hepatic disorders treatment	Strong	Antifungal	Weak
20	Hepatic disorders treatment	Strong	Antifungal	Weak
21	Antineoplastic	Strong	Antibiotic	Moderate
22	Antineoplastic	Strong	Antiviral (Picornavirus)	Moderate
23	Antineoplastic	Strong	Antiviral (Arbovirus)	Weak
24	Antineoplastic	Strong	Antibacterial	Moderate
25	Antineoplastic	Strong	Antibacterial	Moderate
26	Hepatic disorders treatment	Moderate	Antifungal	Moderate
27	Hepatic disorders treatment	Strong	Antibacterial	Moderate

The azo dyes 4,4′-dihydroxyazobenzene (**49**) and its methyl derivative (**50**) were detected in fresh sporophores of *Agaricus xanthodermus* and exhibited antimicrobial activity against *Staphylococcus* species [69–71]. Several fungi, including *Beauveria bassiana*, *Beauveria brongniartii*, *Metarhizium anisopliae*, and *Verticillium lecanii*, produce azo dye toxins (**51**–**57**) [72–76].

Additionally, three aromatic azoxy compounds—azoxymycins A (**58**), B (**59**), and C (**60**)—were discovered in *Streptomyces chattanoogensis* L10 and *Streptomyces* sp. strain P8-A2 [77–79]. Azoxymycin B demonstrated cytotoxicity against human leukemia HL-60 cells, with an IC_{50} value of 2.2 μM [78].

Asterionellins A (**61**), B (**62**), and C (**63**) are eight-membered compounds with an azoxy-like structure, discovered in the microalga *Asterionella* sp. [80–82]. In the fruiting bodies of *Agaricus xanthoderma*, researchers identified an unstable agaritine derivative (**64**) and a metabolite (**65**) [83]. Another compound, glutamylase phenol (**62**), was also found in *Agaricus* sp. [84]. Among these, compound (**65**) displayed strong antibiotic and anticancer properties [84,85].

Table 3. Biological activity of azo dyes produced by microorganisms (**28**–**41**) [13,44,47].

No.	Dominated Activity	Rank	Additional Activity	Rank
28	Anti-Helicobacter pylori	Strong		
29	Anti-Helicobacter pylori	Strong		
30	Anti-Helicobacter pylori	Strong	Fibrinolytic	Weak
31	Anti-Helicobacter pylori	Strong	Pre-neoplastic conditions treatment	Weak
32	Anti-inflammatory	Strong	Hemostatic	Weak
33	Anti-inflammatory	Strong	Hemostatic	Weak
34	Anti-Helicobacter pylori	Strong		
35	Anti-Helicobacter pylori	Strong	Pre-neoplastic conditions treatment	Weak
36	Anti-Helicobacter pylori	Strong		

Table 3. *Cont.*

No.	Dominated Activity	Rank	Additional Activity	Rank
37	Anti-Helicobacter pylori	Strong	Pre-neoplastic conditions treatment	Weak
38	Apoptosis agonist	Strong	Antineoplastic	Strong
39	Apoptosis agonist	Strong	Antineoplastic	Strong
40	Anti-inflammatory	Strong	Antineoplastic	Strong
41	Hemostatic	Strong	Anti-inflammatory	Strong

Azamerone, an anti-infective meroterpenoid obtained from marine *Streptomyces* sp. grown in salt culture, features a unique chloropyranphthalazinone core with a distinctive side chain. It showed mild cytotoxic effects on mouse T-cell splenocytes and macrophages in laboratory tests. Additionally, the biosynthetic precursor of its azo-containing derivative (**66**, 3D structure see in Figure 4) was also detected in the same *Streptomyces* sp. strain [86,87]. The Gram-positive bacterium *Streptomyces* sp. Ank75 produces azoxy antibiotics **67** and **68**, which have antifungal properties against *Candida albicans* and *Mucor miehei* [88].

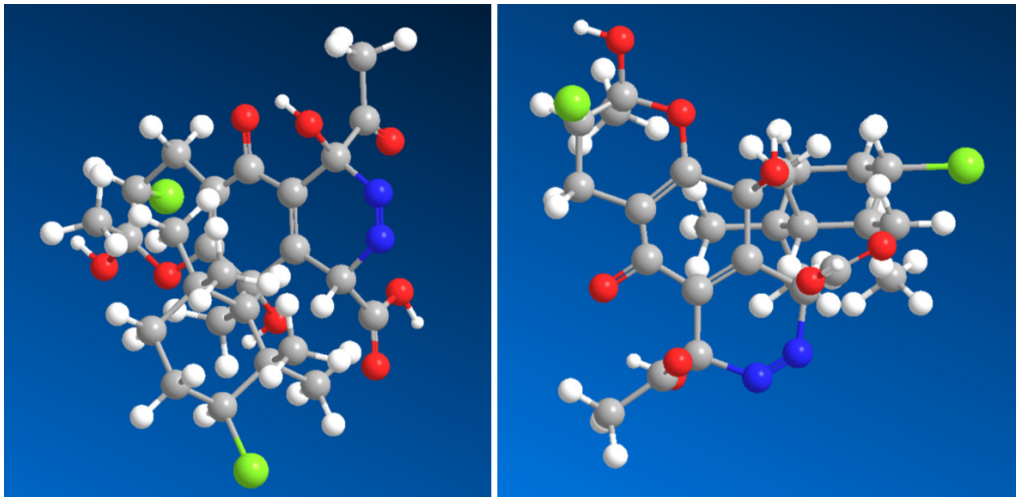


Figure 4. 3D Chemical structure of azo-containing derivative (**66**) produced by *Streptomyces* sp. The (-N=N-) bond is shown in blue, oxygen is shown in red, and chlorine atoms are shown in green. The chemical formula is shown from different directions to better view the structure.

Researchers identified two vasodilators, WS-1228 A (triaxin C, **69**) and WS-1228 B (triaxin D, **70**), in the culture filtrate of *Streptomyces aureofaciens* [89,90]. A few years later, Omura and colleagues [91] discovered triaxins A (**69**) and B (**70**) in *Streptomyces* sp. SK-1894 and found that they function as acyl-CoA synthetase inhibitors. These compounds, along with WS-1228 A and B, share a unique N-hydroxytriazene structure and are known for their vasodilatory effects. Additionally, they inhibit acyl-CoA synthetase, with IC_{50} values of 5.5 µg/mL for triaxin A and 3.6 µg/mL for WS-1228 A. The triaxins (A, B, C, and D) differ in their inhibition levels, with triaxin C (**71**) being the most potent, followed by triaxin A, triaxin D (**72**), and triaxin B [92,93].

A rare compound, citreoazopyrone (**73**), was isolated from a hybrid strain of *Penicillium citreo-viride* and was found to inhibit lettuce seedling growth [94]. The fluviol groups of antibiotics (**74**–**77**) and pseudoiodine (**78**), produced by *Pseudomonas fluorescens* and *Nostoc spongiaeforme*, exhibit antimicrobial, antiviral, and antitumor effects [95–98]. The activities of compounds **78**–**98** are detailed in Table 5. Additionally, schizocommunin (**79**), isolated from the fungus *Schizophyllum commune*, showed strong cytotoxic effects against mouse lymphoma cells [99].

Table 4. Biological activity of azo dyes produced by microorganisms (**42–60**) [13,72–78].

No.	Dominated Activity	Rank	Additional Activity	Rank
42	Anti-inflammatory	Strong	Hemostatic	Strong
43	Anti-inflammatory	Strong	Hemostatic	Strong
44	Anti-inflammatory	Strong	Hemostatic	Strong
45	Kidney function stimulant	Weak	Pre-neoplastic conditions	Weak
46	Immunosuppressant	Weak	Fibrinolytic	Weak
47	Pre-neoplastic conditions	Weak	Kidney function stimulant	Weak
48	Anti-mutagenic	Strong	Spasmolytic, urinary	Weak
49	Anti-seborrheic	Strong		
50	Carminative	Strong	Anti-microbial	Moderate
51	Phobic disorders treatment	Strong	Kidney function stimulant (0.786)	Moderate
52	Fibrinolytic	Moderate	Pre-neoplastic conditions	Moderate
53	Acaricide	Strong	Anti-seborrheic	Strong
54	Alopecia treatment	Moderate	Anti-inflammatory, intestinal	Weak
55	Anti-seborrheic	Strong	Acaricide	Moderate
56	Pre-neoplastic conditions treatment	Weak	Immunosuppressant	Weak
57	Fibrinolytic	Moderate	Acaricide	Weak
58	Mucositis treatment	Strong	Immunosuppressant	Weak
59	Mucositis treatment	Moderate	Immunosuppressant	Weak
60	Antiviral(Arbovirus)	Weak	Immunosuppressant	Weak

Table 5. Biological activity of azo dyes produced by microorganisms (**61–78**) [13,89,90,95].

No.	Dominated Activity	Rank	Additional Activity	Rank
61	Genital warts treatment	Moderate	Antineoplastic	Weak
62	Genital warts treatment	Moderate	Antineoplastic	Weak
63	Genital warts treatment	Moderate	Antineoplastic	Weak
64	Mucositis treatment	Strong	Antiviral (Arbovirus)	Moderate
65	Alopecia treatment	Weak	Vascular (peripheral) disease treatment	Weak
66	Antineoplastic	Strong	Antibacterial	Weak
67	Hepatic disorders treatment	Strong	Hepatoprotectant	Strong
68	Hepatic disorders treatment	Strong	Antineoplastic	Moderate
69	Vasodilator	Strong	Vasodilator, peripheral	Moderate
70	Vasodilator	Strong	Vasodilator, peripheral	Moderate
71	Vasodilator	Strong	Spasmolytic	Moderate
72	Vasodilator	Strong	Spasmolytic	Moderate
73	Anti-ischemic, cerebral	Moderate	Antimicrobial	Moderate
74	Antineoplastic (solid tumors)	Moderate	Antineoplastic (renal cancer)	Moderate
75	Gout treatment	Strong		
76	Guanyl-specific ribonuclease T1 inhibitor	Moderate		
77	Anxiolytic	Strong	Psychotropic	Moderate
78	Atherosclerosis treatment	Strong		

Researchers identified 3- and 4-methylcinnolines (**80** and **81**) in the volatile components of *Hibiscus esculentus* pods [100], while azoxy compounds (**82** and **83**) were found in yeast extract [101]. Two cinnoline derivatives, compound **84** and 4849F (**85**), were isolated from *Streptomyces* sp. 4849.171. Compound **84** functions as an IL-4 receptor inhibitor, while 4849F (**85**) shows antibacterial properties [102].

Pyridazomycin (**86**), an antifungal antibiotic from *Streptomyces violaceoniger* sp. *griseofuscus*, inhibits *Mucor hiemalis* [103,104]. Both pyridazomycin (**86**) and its chloride salt analogue (**87**) exhibit antimicrobial activity [105]. The compound 5-amino-1,4-dihydro-7H-1,2,3-triazolo [4,5-d]-pyrimidin-7-one (**88** or **89**), also called 8-azaguanine, is produced from guanine by *Streptomyces albus* [106]. Its cytotoxic effects on various cancers, including carcinoma and sarcoma, were first reported over 70 years ago [107].

Another form of 8-azaguanine, known as pathocidin (**89**), is an antifungal antibiotic obtained from Actinomycetes [108–110], which effectively inhibits fungal growth, including *Penicillium chrysogenum*. Two related natural metabolites, 8-azaguanine-3N-β-D-ribofuranosyl (**90**) and its 5′-phosphate version (**91**, see structure in Figure 5), have demonstrated anticancer effects against lymphoid leukemia and adenocarcinoma [111].

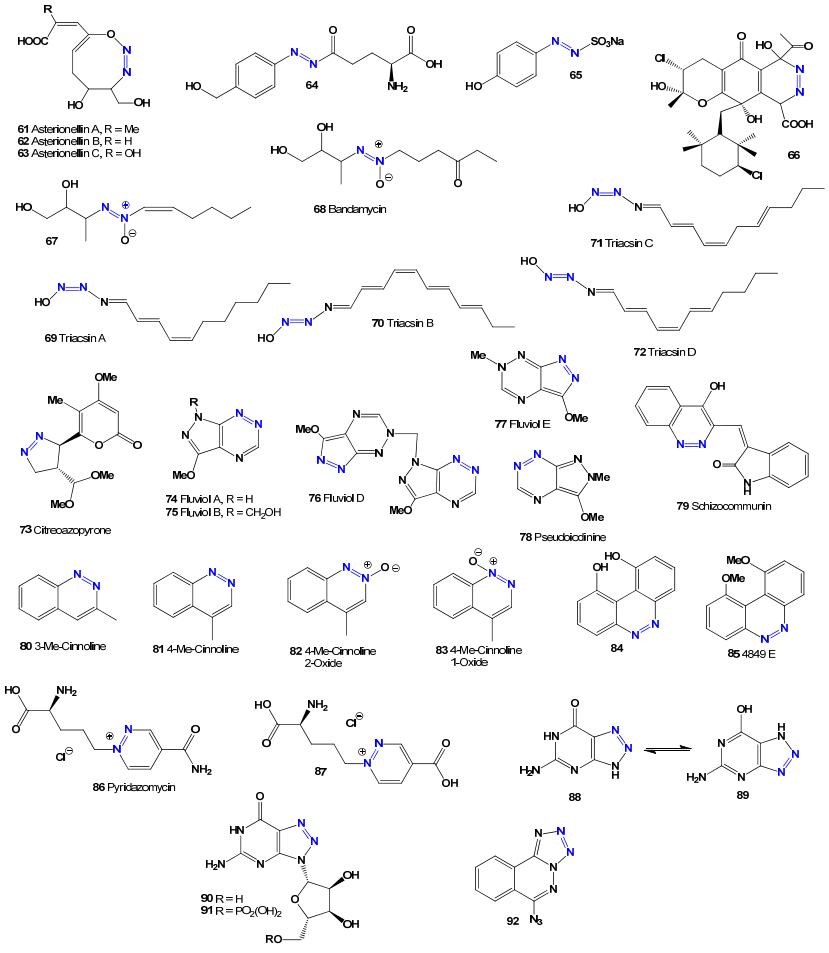


Figure 5. Bioactive azo compounds are produced by bacteria, fungi, and fungal endophytes. The azo compounds shown exhibit strong or moderate antineurotic, anti-allergic, antifungal, antineurotic or analgesic activity, and are also DNA synthesis inhibitor, and Lysase stimulant.

The red dinoflagellate *Gymnodinium breve* (syn. *Ptychodiscus brevis*) produces the antibiotic 6-azidotetrazolo [5,1-a]phthalazine (**92**) [112]. Additionally, the pathogenic Gram-negative *Burkholderia* species secretes extracellular enzymes involved in various biological processes, as well as toxins, antibiotics, and siderophores [113]. A rare dimeric siderophore,

malleobactin D (**93**, see structure in Figure 6, and activity shown in Table 6), was identified in *Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*) [114].

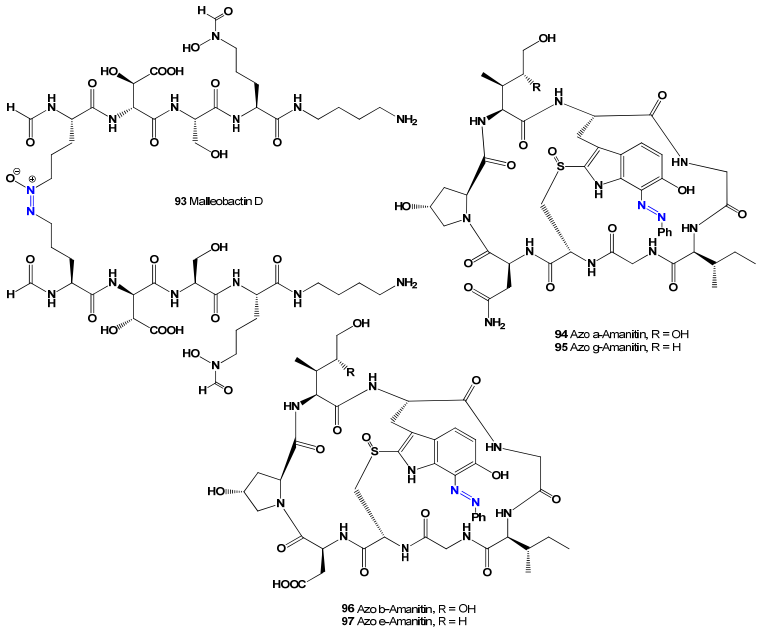


Figure 6. Bioactive azo dyes produced by the bacterium *Pseudomonas pseudomallei.* The presented natural metabolites demonstrate strong or moderate antiviral, antineoplastic, anti-ischemic, anxiolytic or anti-Helicobacter activities, and also demonstrate properties for the prevention of guanyl-specific ribonuclease T1 inhibitor, hepatic disorders treatment, gout treatment.

Table 6. Biological activity of azo dyes produced by microorganisms (**79**–**97**) [13,102,105].

No.	Dominated Activity	Rank	Additional Activity	Rank
79	Endothelial growth factor antagonist	Strong		
80	Phobic disorders treatment	Moderate	Antineurotic	Moderate
81	Antineurotic	Moderate	Phobic disorders treatment	Weak
82	Lysase stimulant	Strong		
83	Lysase stimulant	Strong		
84	Interleukin 4 antagonist	Moderate		
85	Antineurotic	Strong	Phobic disorders treatment	Moderate
86	Antifungal	Strong	Antimicrobial	Moderate
87	Antifungal	Moderate	Antimicrobial	Moderate
88	Pterin deaminase inhibitor	Strong		
89	Anti-allergic	Moderate	Cytostatic	Moderate
90	DNA synthesis inhibitor	Strong	Cytostatic	Moderate
91	DNA synthesis inhibitor	Strong	Neuroprotector	Strong
92	Antineoplastic (sarcoma)	Strong		
93	Antineoplastic	Strong	Antibacterial	Moderate
94	Analgesic	Moderate	Glycopeptide-like antibiotic	Weak
95	Glycopeptide-like antibiotic	Moderate	Analgesic	Weak
96	Glycopeptide-like antibiotic	Moderate	Analgesic	Weak
97	Glycopeptide-like antibiotic	Moderate	Analgesic	Weak

Amatoxins are toxic bicyclic octapeptides found in several fungi from the Agaricales family, including *Amanita phalloides*, *A. ocreata*, *A. verna*, *A. bisporigera*, *Conocybe filaris*, and *Galerina marginata* (syn. *G. autumnalis*), among others. These toxins are known for their

harmful effects, including heat-induced toxicity, gastrointestinal issues, and the ability to inhibit RNA polymerase II [115–118]. Azoamanitins (**94**–**97**), which are semi-synthetic versions of amatoxins, have been studied for their potential in antiviral, antimicrobial, and anticancer treatments [119–121].

3. Azo Dyes Derived from Terrestrial and Marine Sources

Azo dyes have been found in both terrestrial and marine environments, but it remains unclear whether bacteria or fungal endophytes played a role in their production, as these microorganisms often act as symbionts in plants and invertebrates [1–4,8,13,79]. Some key compounds isolated from terrestrial and marine sources include the following:

Geleganidin D (**98**, see structure in Figure 7 and activity in Table 7): A dimeric monoterpenoid indole alkaloid from *Gelsemium elegans* with moderate cytotoxic activity against MCF-7 and PC-12 cells [122]. *G. elegans* is used in clinical applications due to its indole alkaloids, which have antitumor, anti-inflammatory, analgesic, and immune-modulatory effects, though its therapeutic dose is close to toxic levels [122].

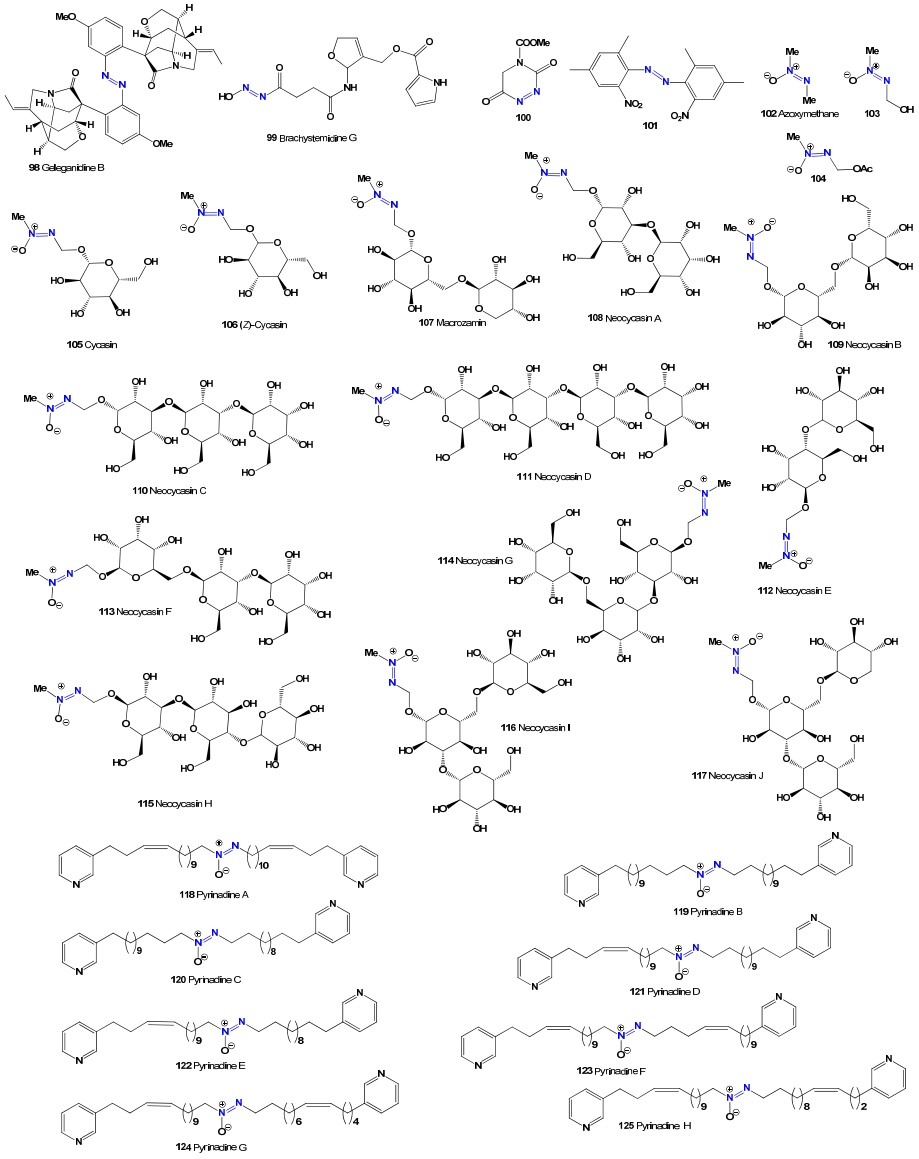


Figure 7. Bioactive azo compounds isolated from various sources. The presented natural metabolites demonstrate moderate or strong cytotoxic, antineoplastic, anti-parkinsonian activity, and also demonstrate strong properties for neurodegenerative diseases treatment.

Brachystemidin G (**99**): An alkaloid from *Brachystemma calycinum* with potent immunosuppressant properties, inhibiting murine T- and B-lymphocyte proliferation (IC50 = 5.6 μg/mL) [123].

1,2,4-Triazine derivative (**100**): Extracted from *Butea monosperma* (family Caryophyllaceae) [124]. This plant's odor repels mosquitoes, its flowers are used as a dye, and its gum, known as kamarkas in Hindi, is used in traditional cooking [125].

bis-(2,4-Dimethyl-6-nitrophenyl)-diazene (**101**): Isolated from the leaves of *Aconitum sungpanense* [126]. Azoxyglycosides, which contain the aglycone methylazoxymethanol (MAM), have been found in Cycadaceae plants, with all known glycosides having β-glycosidic linkages [127]. Metabolites, such as methylazoxymethane (**102**), MAM (**103**), methylazoxymethanol acetate (**104**), and cycasins (**105**,**106**), have been extracted from Cycadaceae, Stangeriaceae, and Zamiaceae, which are coniferous trees found in tropical and subtropical regions [127–132]. MAM (**103**) has been linked to liver and kidney carcinomas [133], while cycasins (**105**,**106**) and macrosamine (**107**) are highly toxic azoxyglycosides. Various insects, including caterpillars and weevils, feed on cycads' roots, stems, leaves, and reproductive parts [127,132].

Azoxyglycosides are believed to function as natural herbivore deterrents [134–136]. Cycasin, the primary azoxyglycoside found in cycads, has been shown to cause effects similar to those seen in carcinogenicity, mutagenicity, and neurotoxicity tests. The first isolation of neocycasin A (**108**) was recorded in 1959 [137], and, more recently, neocycasins B–J (**109**–**117**) have been identified from different plant species [138–146].

The first cytotoxic *bis*-3-alkylpyridine alkaloid with an azoxy moiety, pyrinadine A (**118**), was discovered in the Okinawan marine sponge *Cribrochalina* sp. [147,148]. Further cytotoxic *bis*-3-alkylpyridine alkaloids, pyrinadines B–H (**118**–**125**), were later extracted from the same sponge, demonstrating cytotoxicity against P388 murine leukemia cells [147–149]. The activities of these compounds (**118**–**125**) are summarized in Table 7.

Table 7. Biological activity of azo dyes produced by microorganisms (**98**–**125**) [13,122,137,144].

No.	Dominated Activity	Rank	Additional Activity	Rank
98	Antineoplastic	Moderate	Antiprotozoal (Plasmodium)	Weak
99	β-1,3-Galactosyl-O-glycosyl-glycoprotein	Strong	β-1,6-N-acetylglucosaminyl transferase inhibitor	Strong
100	Neurodegenerative diseases treatment	Strong		
101	Antiparkinsonian	Strong	Anxiolytic	Strong
102	Acaricide	Moderate	Antiviral (Arbovirus)	Weak
103	Antineoplastic	Strong		
104	Antineoplastic	Moderate		
105	Antineoplastic	Moderate		
106	Anti-infertility, female	Strong	Antineoplastic	Strong
107	Carcinogenic	Strong	Embryotoxic	Strong
108	Carcinogenic	Strong	Embryotoxic	Strong
109	Antineoplastic	Strong		
110	Carcinogenic	Strong	Embryotoxic	Strong
111	Antineoplastic	Strong		
112	Antineoplastic	Strong	Anti-infective	Strong
113	Antineoplastic	Strong	Anti-infective	Strong
114	Antineoplastic	Strong	Anti-infective	Strong

Table 7. *Cont.*

No.	Dominated Activity	Rank	Additional Activity	Rank
115	Antineoplastic	Strong	Anti-infective	Strong
116	Antineoplastic	Strong	Anti-infective	Strong
117	Antineoplastic	Strong	Anti-infective	Strong
118	Cytotoxic	Moderate	Anti-inflammatory	Weak
119	Cytotoxic	Moderate	Anti-inflammatory	Weak
120	Cytotoxic	Moderate	Anti-inflammatory	Weak
121	Cytotoxic	Moderate	Anti-inflammatory	Weak
122	Cytotoxic	Moderate	Anti-inflammatory	Weak
123	Cytotoxic	Moderate	Anti-inflammatory	Weak
124	Cytotoxic	Moderate	Anti-inflammatory	Weak
125	Cytotoxic	Moderate	Anti-inflammatory	Weak

4. Microbial Degradation of Textile Azo Dyes

The textile industry relies heavily on both natural and synthetic azo dyes [150–152]. Natural dyes have been used since ancient times and vary in color and chemical structure. Among synthetic azo dyes, commonly used examples include Orange II (**126**, see 3D structure in Figure 8 and activity in Table 8), Methyl Orange (**127**), Congo Red (**128**), Evans Blue (**129**), Bismarck Brown (**130**), Xylidine Ponceau (**131**), and Eriochrome Black (**132**). These dyes are widely applied in the textile and leather industries but contribute to environmental pollution, particularly through wastewater discharge. This contamination affects ecosystems, microbial communities in the soil, and the natural balance of certain species.

Azo dyes are aromatic compounds containing azo (-N=N-) and sulfonic (-SO_3-) groups. They are produced through the diazotization of aromatic amines, followed by a coupling reaction, creating a range of colors from yellow to red and orange [150–152].

Every year, inefficient dyeing processes result in the release of hundreds of thousands of tons of textile dyes into wastewater. This improper disposal has severe environmental consequences and poses health risks to humans and animals. Many azo dyes are known to be carcinogenic and mutagenic [153–156]. While various wastewater treatment methods exist, one promising approach is the use of microorganisms capable of degrading azo dyes naturally [157–160].

Extensive research has been conducted in this field, with numerous studies published annually. However, in this discussion, we will focus on how Actinomyces and other microbes contribute to azo dye degradation [161–163]. Several species of *Streptomyces* have been found to completely break down azo pigments (**128**–**133**) (see structures in Figure 9). These include *S. chromofuscus*, *S. coelicolor*, *S. viridosporus*, *S. rochei*, *S. psammoticus*, *S. diastaticus*, *S. ipomoeae*, *S. sviceus*, *S. ardesiacus*, and *S. cyaneus* [164–167]. In addition, a mixed culture of two *Pseudomonas strains* has shown effective degradation of azo dyes. Microbial enzymes known as azoreductases play a crucial role in this process by cleaving azo bonds (-N=N-) under mild conditions (see Figure 10). These enzymes are valuable for developing environmentally friendly dye removal methods [168,169].

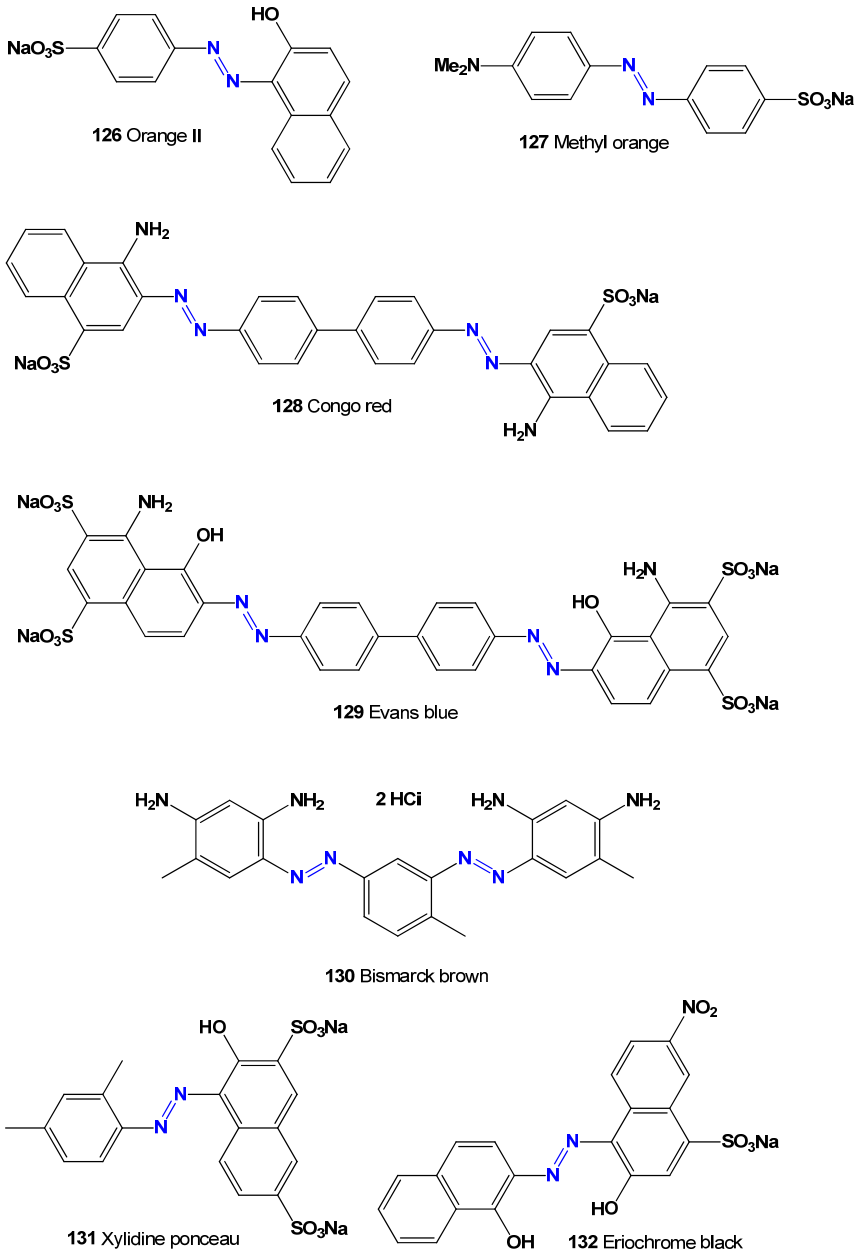


Figure 8. Azo dyes used in the textile industry. The presented synthesized compounds demonstrate strong carcinogenic activity and are dangerous to human health. Degradation using various microorganisms is important. Details are described in the text.

Table 8. Biological activity of textile azo dyes [164–169].

No.	Dominated Activity	Rank	Additional Activity	Rank
126	Embryotoxic	Strong		
127	Carcinogenic	Strong	Mutagenic	Strong
128	Carcinogenic	Strong	Mutagenic	Strong
129	Antineoplastic	Strong		
130	Antiviral	Strong		
131	Antibacterial	Moderate	Antifungal	Moderate
132	Antimicrobial	Moderate	Antibacterial	Moderate

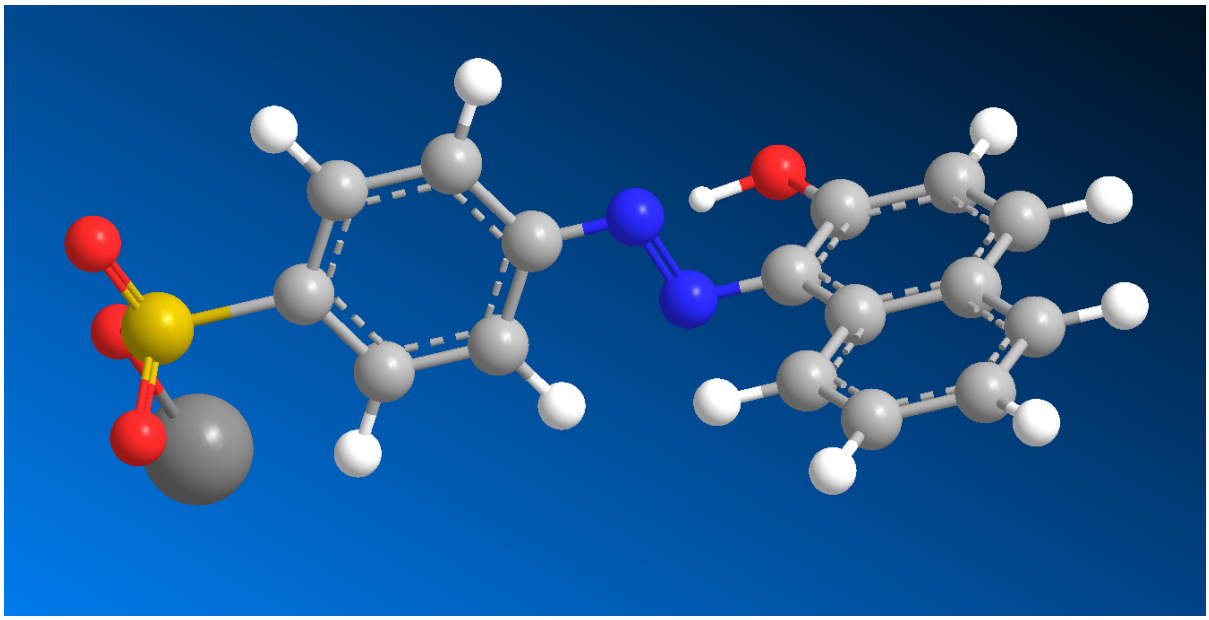


Figure 9. 3D structure of bioactive synthetic azo dye Orange II (**126**). Orange II or other azo dyes from the food industry are ingested via digestion and are metabolized to aromatic amines by intestinal microorganisms. Reductive enzymes in the liver can also catalyze the reductive cleavage of the azo bond to produce aromatic amines. However, evidence suggests that intestinal microbial azo reductase may be more important than liver enzymes in azo reduction. Azoreductase activity in various intestinal preparations was dependent on various dietary factors such as cellulose, proteins, fibers, antibiotics, or the addition of live Lactobacilli cultures.

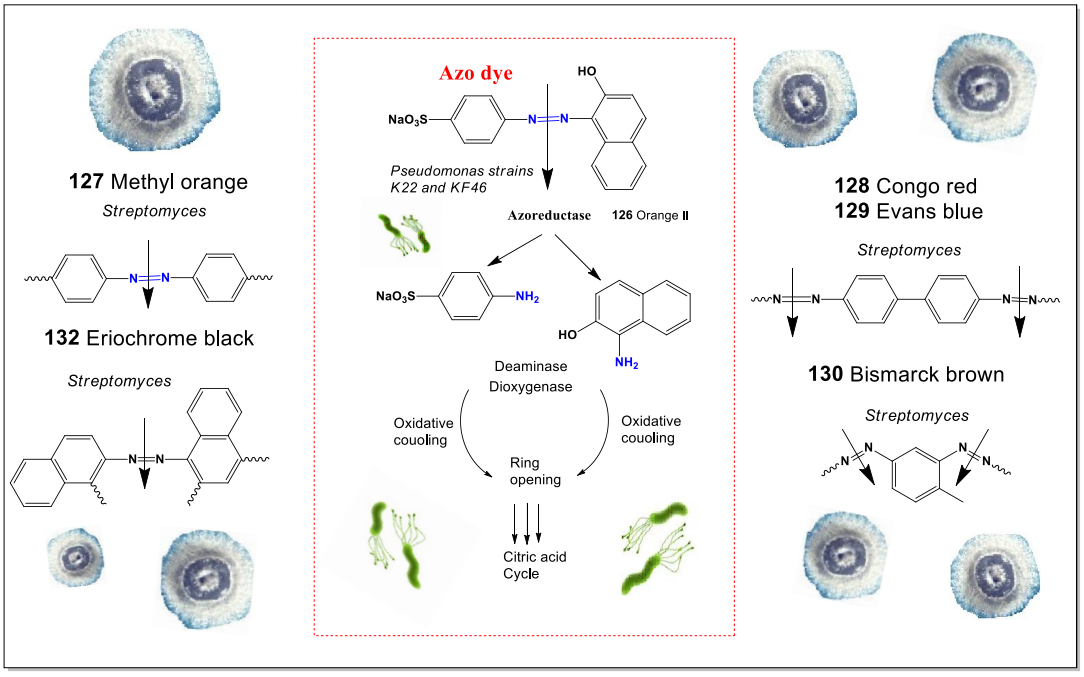


Figure 10. Summarizing the articles describing the degradation of azo dyes by various bacteria *Pseudomonas* strains or *Streptomyces* strains, we can conclude that bacteria adsorb azo dyes and with the help of azoreductase enzyme the (-N=N-) bond is cleaved. Aromatic hydrolysis products undergo oxidative coupling with subsequent opening of the aromatic ring. And at the final stage, the oxidation products of the aromatic ring are included in the citric acid cycle. The figure shows images *Pseudomonas* and *Streptomyces* strains that may be involved in the degradation of azo dyes and the cleavage of the azo bond.

5. Microbial Degradation of Food Azo Dyes

Azo dyes are widely used in the food industry as color additives in products, such as soft drinks, jams, candies, and pickles (azo dye coloring in Figure 11) [170]. Their popularity comes from their ability to produce bright, vibrant colors while being inexpensive, stable, and free from unwanted tastes or odors.



Figure 11. Food azo dyes coloring: Sunset Yellow (**1**), Carmoisine (**2**), Amaranth (**3**), Ponceau 4R (**4**), Brown HT (**5**), and Allura Red (**6**). The azo dyes mentioned above are added to foods to impart color, but they have no nutritional, food preservation, or health benefits. Because of their availability, accessibility, stability, and low cost, and because they provide intense color to the product without introducing undesirable flavors, the food industry often prefers to use synthetic azo dyes instead of natural dyes.

However, while azo dyes make food visually appealing, they may also pose health risks. Consuming them within the acceptable daily intake is generally considered safe, but higher doses—especially in children—have been linked to various health issues. These include allergies, ADHD, asthma, anxiety, and even potential cytotoxic and genotoxic effects, which may contribute to cancer development. Additionally, azo dyes are highly stable and do not break down easily under aerobic conditions [171–173].

Several synthetic azo dyes, such as Sunset Yellow (**133**, see structure in Figure 12, and activity see in Table 9), Carmoisine (**134**), Amaranth (**135**), Ponceau 4R (**136**), Brown HT (**137**), and Allura Red (**138**), are commonly added to food [170]. They enhance color but offer no nutritional benefits, preservation properties, or health advantages. Because they are cost-effective, chemically stable, and provide intense coloration without altering taste, the food industry often prefers them over natural dyes.

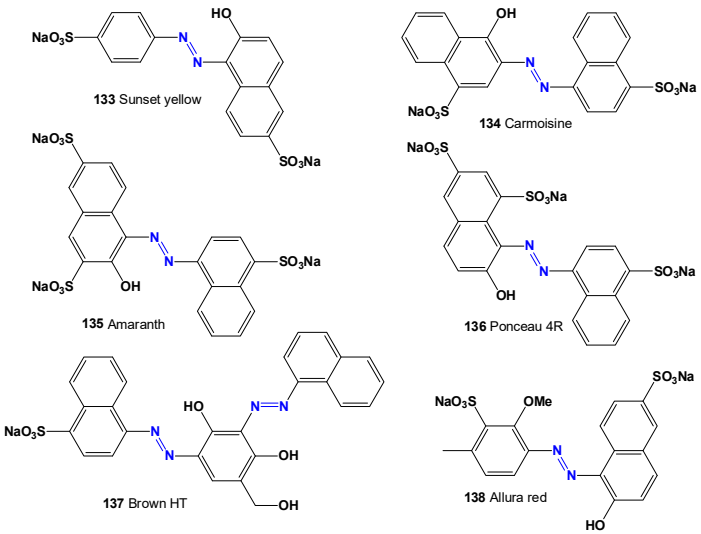


Figure 12. Azo dyes, as an important part of food additives, can not only improve the sensory properties of food products, but also increase appetite. They cannot provide the human body with any nutrients and even have toxicity, carcinogenic or mutagenic effects, which can cause serious harm to the health of consumers.

Table 9. Biological activity of food azo dyes.

No.	Dominated Activity	Rank	Additional Activity	Rank
133	Embryotoxic	Strong		
134	Carcinogenic	Strong	Mutagenic	Strong
135	Carcinogenic	Strong	Mutagenic	Strong
136	Antineoplastic	Strong		
137	Antiviral	Strong		
138	Antibacterial	Moderate	Antifungal	Moderate

Although food dyes are regularly tested for safety, their health effects remain controversial. Some studies suggest that the breakdown of azo dyes can produce harmful byproducts, raising concerns about their long-term safety [174,175].

Food azo dyes may have potential health risks, primarily due to their breakdown by intestinal bacteria after ingestion. When these dyes are reduced by gut microflora, their azo bonds are cleaved, producing aromatic amines. These amines can then undergo further chemical modifications, such as N-hydroxylation or N-acetylation. In mammals, azo dye reduction mainly takes place in the anaerobic environment of the lower gastrointestinal tract, where bacterial azoreductase enzymes are responsible for the process. While mammalian enzymes in the liver and kidney also contribute to azo dye metabolism, their exact role is not yet fully understood [176,177].

Many anaerobic bacteria found in the cecal contents of both humans and experimental animals have been shown to break down azo dyes into aromatic amines. This reaction is facilitated by azoreductases, which require flavins for optimal activity and are highly sensitive to oxygen [172–177].

Aromatic amines and their derivatives are a major class of chemicals formed when azo dyes are broken down by azoreductases, which cleave the azo bond. Different microorganisms produce azoreductases with varying kinetic properties and substrate specificities. Research shows that flavin-containing azoreductases follow a Ping-Pong bi-bi reaction mechanism, where the enzyme's activity depends on the substrate concentration. Many azoreductases show a higher affinity for NADPH over NADH, although they can utilize either as an electron source, with or without flavin [178–180].

Not all bacteria produce azoreductases, but several known species do. These include strains from both animals and humans, such as *Aquiflexum* sp., *Bacillus* sp., *Clostridium perfringens*, *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Rhodobacter sphaeroides*, *Shewanella oneidensis*, *Staphylococcus aureus*, and *Xenophilus azovorans* KF46F [178,181]. Several azo dyes are commonly used in food production:

Sunset Yellow (**133**) is an artificial dye used to enhance food appearance and shelf life. It has antioxidant properties, which increase with concentration, but also exhibits phytotoxicity [182–184].

Carmoisine (**134**) is a red azo dye used in foods that undergo heat treatment after fermentation. While azo dyes have been linked to carcinogenicity, especially bladder cancer, carmoisine itself has not been proven carcinogenic. Interestingly, its copper complex has demonstrated anticancer activity against colon cancer cells (HT-29), making it a potential candidate for future treatments [185–187].

Amaranth (**135**) is a red food dye used worldwide, although its use is banned in India due to concerns about its safety. Despite this, illegal production continues, with India contributing 2% of global output. Some studies suggest that amaranth may be carcinogenic under certain conditions [188,189].

Ponceau 4R (**136**) is widely used in pharmaceuticals and food products. It is stable in light, heat, and acidic conditions but breaks down when exposed to ascorbic acid. While approved in Europe, Asia, and Australia, the US FDA has not approved it due to concerns about its potential to form non-sulfone aromatic amines, which may be carcinogenic [190,191].

Brown HT (**137**), also called "food brown 3" or "chocolate brown HT", is a pigment with antioxidant properties. It is found in small amounts in coal tar [192–194].

Allura Red (**138**) is a widely used food dye, commonly found in sweets, beverages, and processed foods. It dissolves in water but poorly in 50% ethanol. Long-term consumption may cause liver and kidney toxicity [195–197]. Degradation of azo dyes and the cleavage of the (-N=N-) bond are shown in Figure 13.

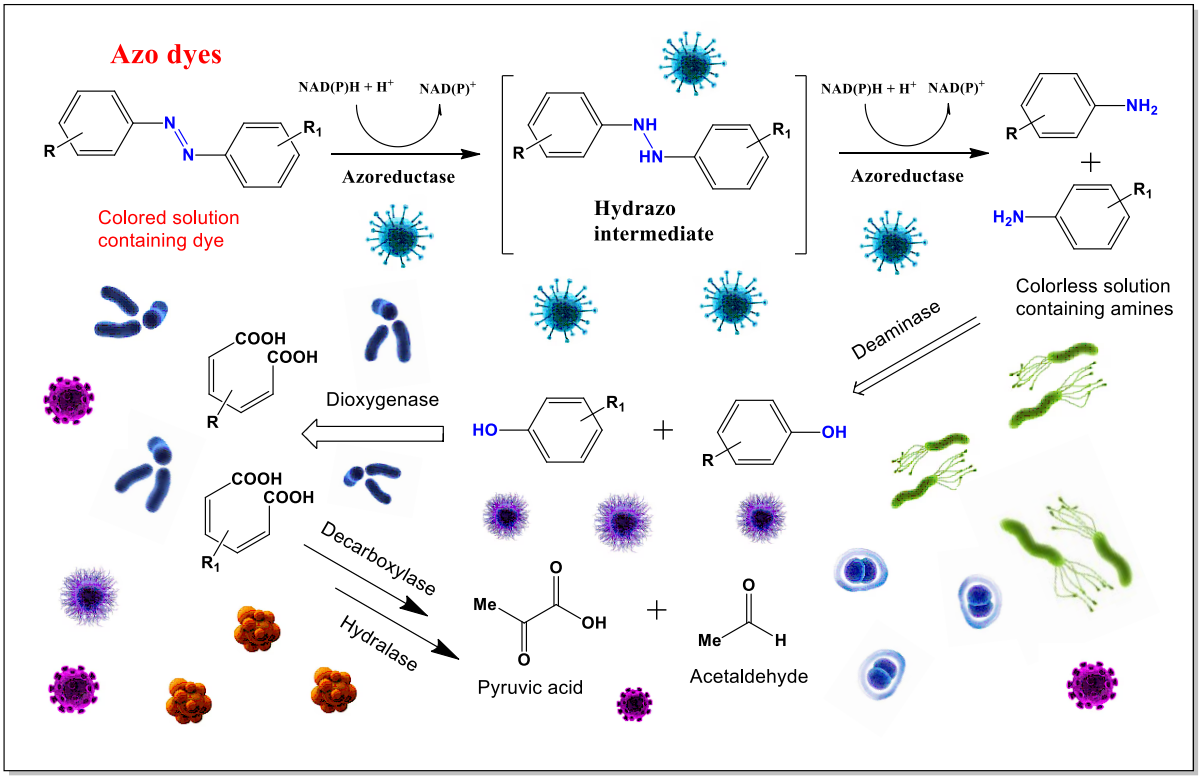


Figure 13. General scheme degradation of azo dyes which occurs in several stages when using microorganisms. In the first stage, azoreductases cleave the azo bond using NADH or NADPH, forming an intermediate product, hydrazo intermediate, which, when cleaved, forms aromatic amines. Microorganisms producing azoreductases participate in this process. In the second stage, aromatic amines are converted into the corresponding phenols and their derivatives, under the action of deaminase. Dioxygenase breaks down aromatic phenols into the corresponding dicarboxylic acids and their derivatives. And in the last stage, the enzymes decarboxylase and then hydrolase convert dicarboxylic acids into pyruvic acid and acetaldehyde, and the latter metabolites can be converted into water and carbon dioxide. The figure shows images of various bacteria that may be involved in the degradation and utilization of azo dyes.

6. Conclusions

Natural and/or synthetic azo compounds represent a valuable class of bioactive molecules with diverse pharmacological applications. Their confirmed antitumor, antimicrobial, and antibacterial properties, along with predicted novel activities, highlight their potential as drug prototypes and leads in pharmaceutical development. The role of microorganisms in the biosynthesis of natural azo compounds and their synthetic analogs further expands opportunities for drug discovery and therapeutic advancements. Additionally, the synthesis and degradation pathways of azo dyes present promising applications in

medicine, food, cosmetics, and related industries. Continued research into the structure–activity relationships and biological mechanisms of azo compounds will be essential for unlocking their full potential in improving human health.

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