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Review Article

MEDICINAL INTEREST OF AZO-BASED ORGANIC COMPOUNDS: A REVIEW

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ABSTRACT

The azo derived products are versatile building blocker organic compounds used in drug research. In this review, we include the synthetic strategy and medicinal utility of some new azo derived candidates in recent years, which must be a good source of information to the researchers. A number of research articles explored with the help of different electronic databases such as PubMed, Scopus, Science direct, Crossref, Orcid, and Google Scholar to study the various biological activities of azo compounds. A number of journals from last decades were surveyed and found to be observed that azo-linkage synthetic organic compounds have good therapeutic properties, *viz.,* antitumor, antioxidant, antiviral, antimicrobial, antidiabetic, anticonvulsant, and antidepressant activity. Keeping the medicinal utility included in the article, it can be concluded that the invention of new azo molecules and their complexes should be encouraged to present novel bioactive molecules.

Keywords: Diazotization, Antioxidant, Cytotoxic, Cholinesterase, Antitubercular.

INTRODUCTION

In an early 19th, the dyes were obtained from natural sources for coloring the fabrics. Mauveine was the first synthetic dye synthesized in 1856. By 1970, nearly 60% of the dyes were available in synthetic form. Azo compounds remain successful in drugs, dye, and cosmetics. These molecules are better stable in a wide range of pH and temperature [1]. They are synthesized by diazotization reaction of a primary aromatic amine and coupled with one or more nucleophiles, mostly an amino, active methylene, and hydroxyl group where the -N=N- represents as azo group.

Heterocyclic amines bearing dyes have pronounced bathochromic shift [2]. Not only for coloring properties but also azo molecules are popular for their therapeutic uses such as antiseptics [3], antimicrobial [4], antidiabetics [5], antineoplastics [6], transmissible spongiform encephalopathy [7], antiulcerative [8], antioxidant [9], analgesic [10], anti-inflammatory [11], antiviral [12], antitubercular [11], and antitumor [13] activities. Azo compounds are also involved in a number of biological reactions such as inhibition of DNA, RNA and protein synthesis, carcinogenesis, and nitrogen fixation [14].

Incorporation of suitable heterocyclic moieties enhances the biological potency of azo-linked compounds [15]. Azo dyes are more accepted in food processing units due to their low toxicity, no hyperactivity effect, and less allergic reactions (ex-tartrazine, azorubin, etc.) [16]. Azo molecules have their importance in various fields including textile, reprography, dye sensitizing solar cells, lasers, liquid crystalline displays, electro-optical devices, and metalochromic indicators [17]. It was found to be observed from a lot of literatures that azo bearing ligands have enhanced therapeutic effect when they were combined with transition metallic ions [18].

BIOLOGICAL ACTIVITIES

Antioxidant activity

At present researchers take more interest in searching of new antioxidant molecules both from synthetic and natural source. Synthetic antioxidants were often observed to be more effective than that of natural antioxidants [19]. Reactive oxygen species can react with various metabolic enzymes and cause diseases such as atherosclerosis, respiratory disease, and cancer. Antioxidants can terminate these chain reactions by removing free radical intermediates and prevent cell mortality [20].

A series of heterocyclic azo dyes were synthesized by coupling of various nucleophiles, viz., 8-hydroxyquinoline; 2,6-diaminopyridine, 2-naphthol, N, N-dimethyl aniline, resorcinol, and 4,6-dihydroxypyrimidine with 5-phenyl-1,3,4-thiadiazole-2-amine (Scheme 1). The synthesized compounds were subjected to evaluation of their *in vitro* antioxidant activity followed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and metal chelating model where butylated hydroxytoluene and ethylenediaminetetraacetic acid is taken as standard. The diazotized 5-phenyl-1,3,4-thiadiazole-2-amine was coupled with 8-hydroxyquinoline showed maximum antioxidant capacity than 1,3,4-thiadiazole azodye coupled 2-napthol [9].

A series of 3-heteroarylazo 4-hydroxy coumarin derivatives were synthesized by coupling of 4-hyroxy coumarin with various aryl and heteroaryl moieties (Scheme 2). These azo-based newly synthesized compounds were subjected to evaluate their free radical scavenging activity by DPPH model. The pyrazolone substituted compound 4-[(4-hydroxy-2-oxo-2H-chromen-3-yl) diazenyl]-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (4e) and 3-nitro phenyl substituted compound 4-hydroxy-3-((3-nitrophenyl) diazenyl)-2H-chromen-2-one (4iv) have been exhibited potential antioxidant activity among the other compounds included in the scheme [4].

Cytotoxic activity

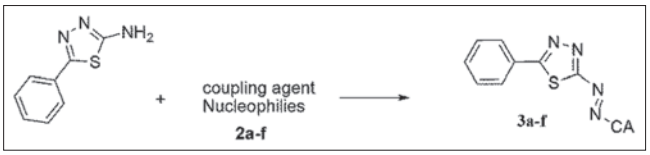
On the basis of reports of the World Health Organization (WHO) survey, cancer will be the first cause of death in the globe in future [21]. Nowadays, research is going on to develop novel compounds that can able to stop the growth of cancer cell.

Nine tautomeric azo hydrazone compounds of N-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)-2-aryl hydrazono-3- oxobutanamide derivatives were synthesized by coupling with diazotized aniline derivatives (Scheme 3). The *in vitro* cytotoxic study was conducted using Ehrlich ascites carcinoma (EAC) tumor cells. The compounds (3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*] thien-2-yl)-2-(4-methylphenyl hydrazono)-3-oxobutanamide (4b), (3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)-2-(4-chlorophenyl hydrazono)- 3-oxobutanamide (4e), (3-Ethoxycarbonyl-

4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)-2-(3-chlorophenyl hydrazono)-3-oxobutanamide (4f), *N*-(3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*] thien-2-yl)-2-(3-nitrophenyl hydrazono)-3-oxobut anamide (4g), and (3-Ethoxycarbonyl-4,5,6,7-tetrahydrobenzo [*b*]thien-2- (3) showed a high degree of antitumor activity against EAC tumor cells [13].

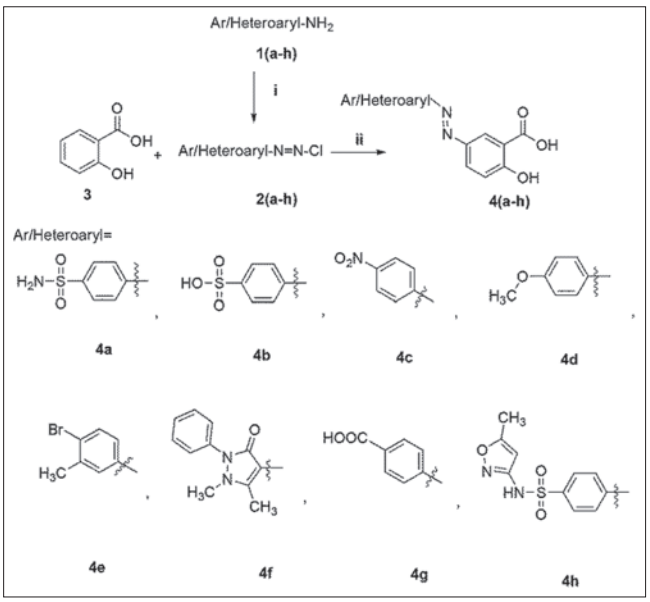
A series of new arylazothiophene and arylazopyrazole derivatives were synthesized using 1-phenylbutane-1,3-dione was as key intermediate (Scheme 4). The newly synthesized compounds were evaluated for *in vitro* cytotoxicity against ascites carcinoma tumor cells and *in vivo* cytotoxicity for compound 10d using EAC assay and 5-fluorouracil is used as reference drug. Compound 10d is the more effective and showed the highest cytotoxic activity [22].

By coupling compound 5c and 5d with benzenediazonium chloride, the compound 5,5'-Bis(phenylazo)-2-(2-hydroxybenzamido)ethyl-2-hydroxybenzoate (10c) and 5,5'-Bis(phenylazo)ethane-1,2-diyl-bis(2-hydroxybenzamide) (10d) were obtained (Scheme 5) subjected to evaluate their *in vitro* cytotoxicity activity against MCF7, human breast adenocarcinoma ER+, MDA-MB-231, human breast adenocarcinoma ER−, PC3, prostate cancer, HeLa S3, cervix epithelioid carcinoma, Hs 294T, human melanoma, K562, chronic myelogenous leukemia, as well as MRC-5, normal fetal lung fibroblasts by standard SRB assay method. The bis-derivatives with the phenylazo groups, 10c and 10d, showed strong cytotoxicity, especially against three cell lines: MCF7, MDA-MB-231 and PC3. However, compound 10c and 10d showed high cytotoxicity against MCF7 and K562 cells, respectively, [23].



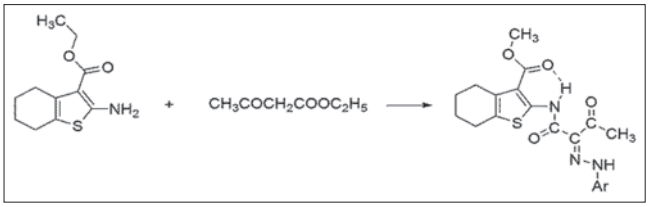
Comp.	CA
2a	8-hydroxyquinoline
2b	2,6-diaminopyridine
2c	2-naphthol
2d	N, N-dimethyl aniline
2e	resorcinol
2f	4,6-dihydroxypyrimidine

Scheme 1: Synthesis of 5-phenyl-1,3,4-thiadiazole-2-amine azo analogues



Comp.	R
4a	2-Thiazolyl-
4b	2-Pyridyl-
4c	1,2,4-triazol-3-yl-
4d	4-phenyl- thiazol-2-yl-
4e	4-(1,5 dimethyl-2-phenyl-pyrazol-3-one)
4f	N-(5-methylisoxazol-3-yl) benzene
4g	2-Benzothiazolyl-
4i	4-phenyl sulfonic acid-
4ii	2-methoxy phenyl-
4iii	4-carboxy phenyl
4iv	3-nitro phenyl-
4v	2-tolyl-

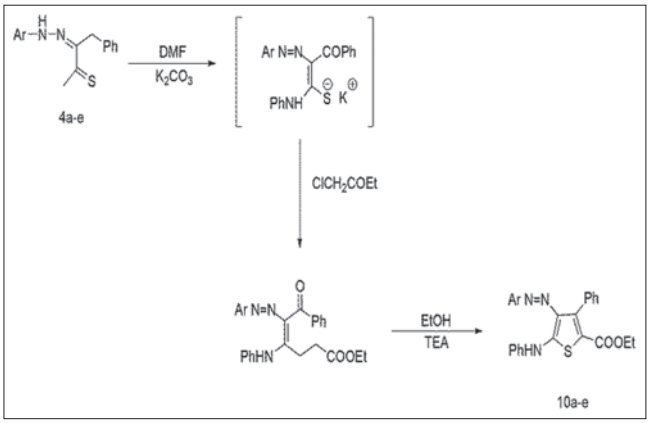
Scheme 2: Synthesis of 3-heteroaryl/arylazo 4-Hydroxy Coumarin analogues



Ar=XC_6H_4

Comp.	X
4a	4-OCH_3
4b	4-CH_3
4c	3-CH_3
4d	H
4e	4-Cl
4f	3-Cl
4g	3-NO_2
4h	4-NO_2
4i	$COCH_3$

Scheme 3: Synthesis of N-(3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)-2-aryl hydrazono-3-oxobutanamide derivatives



Comp.	Ar
10a	C_6H_5
10b	C_6H_4-CH_3-*p*
10c	C_6H_4-OCH_3-*p*
10d	C_6H_4-NO_2-*p*
10e	C_6H_4-Cl-*p*

Scheme 4: Synthesis of thiophene derivatives

Anthelmintic activity

The anthelmintics expel the helminths or intestinal parasites by killing or stunning them without causing any harm to the host. The infection due to helminths is called helminthiasis. The WHO report suggests that the annual death due to soil-transmitted helminthiasis is more than 1,35,000 [24]. Helminths harm the host by causing blood loss, injury to organs, intestinal or lymphatic obstruction and by secreting toxins.

A series of seven novel azo derivatives of dihydropyrimidinones were synthesized by coupling various aryl diazonium salts. The anthelmintic activity of the synthesized compounds was carried out on Indian earthworm, *Pheretima posthuma*. The compounds 4b: (2-napthol substituted dihydropyrimidinone) and 4c: (5-hydroxycoumarin substituted dihydropyrimidinone) showed good anthelmintic activity, whereas 8-hydroxy quinoline and 2,6-dichloro phenol substituted dihydropyrimidinones showed moderate anthelmintic activity (Fig. 1) [25].

Cholinesterase inhibitory effect

Acetylcholine is an important neurotransmitter for memory. The cholinesterase enzyme helps to break down acetylcholine in the brain. Anti cholinesterases prevent the hydrolysis of acetylcholine. Cholinesterase inhibitors result in higher concentrations of acetylcholine, leading to increased communication between nerve cells. Anticholinestereses are nowadays popular for the treatment of Alzheimer's disease, glaucoma, postural tachycardia syndrome, and cognitive impairments in patients with schizophrenia [26].

Two series of azo coumarin analogues were synthesized. In Series I, coupling of coumarin and 4-methyl coumarin was done with diazotized metoclopramide to obtain the azo compounds, and in Series II, coupling of 7-aminocoumarin and 7-amino 4-methyl coumarin was done with diazotized diphenhydramine to obtain the azo analogues. The newly synthesized azo analogues were subjected to investigation of their *in vitro* cholinesterase inhibitory effect and protection ability against chlorpyrifos by modified Elman electrometric method. Diphenhydramine derivatives with coumarin showed more protective ability for both plasma cholinesterase (BchE) and erythrocyte ChE (AchE) as the compound 3 (7-aminocoumarin conjugated diphenhydramine azo compound) (Fig. 2) showed the maximum protection for all concentration while metoclopramide derivatives (compound 1) with coumarin showed selectivity protection for ChE against chlorpyriphos inhibitory effect as one derivative protected BchE and increased the inhibition of the AchE [27].

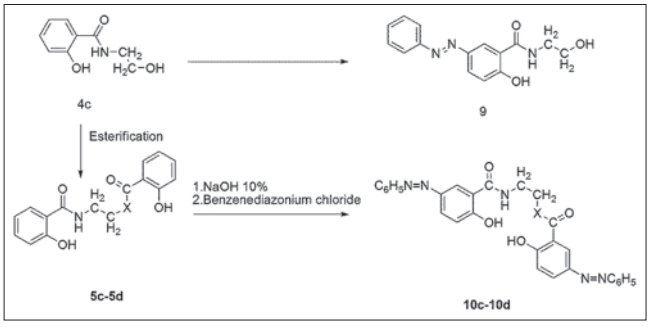
Antimicrobial activity

In recent years, fungal and bacterial infections have an important complication and a major cause of morbidity and mortality. The growing incidence of microbial resistance to existing antibiotics poses a serious medical problem in treating pathogenic infections. Antimicrobials are the agents that kill or inhibit the growth of microorganisms. Azo compounds are well known for their medicinal importance and are recognized as good antimicrobial [4].

A series of 5-aryl/heteroaryl azo bearing pyrimidine analogues (4i-4xii) were synthesized by the coupling of 2-thiobarbituric acid with different aryl/heteroaryl diazonium salts (Scheme 6). The preliminary antibacterial activity of the synthesized compounds was screened against different pathogenic bacterial strains by agar well diffusion method. The antibiogram pattern revealed that compound 4-nitro phenyl azo substituted thiobarbituric acid (4ii) exhibited broad spectrum antimicrobial activity including compounds 4-bromo,3-methyl, phenyl (4v) and 2-methoxy phenyl (4vii), and (5-methyl isoxazol-3-yl) benzene sulfonamido azo substituted thiobarbituric acid [28].

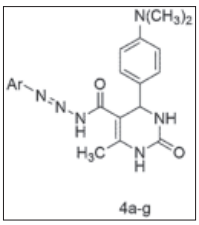
A series of 3-heteroarylazo 4-hydroxy coumarin derivatives were synthesized (Scheme 2) and evaluated for their *in vitro* antibacterial activities. Zone of inhibition and minimum inhibitory concentration revealed that all the products were exhibited greater antibacterial potential against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis,* and *Pseudomonas aeruginosa* except 4g, whereas the compound pyrazolone azo analog 4e having tremendous antibacterial activity [29].

A series of 4,4'Bisazo Dapsone analogues were synthesized by coupling various nucleophiles to the diazonium salts of dapsone (Scheme 7) and screened against different bacterial and fungal strains by well and plate method. Compound (4b) showed excellent antibacterial activities against *Bacillus circulans*, *Shigella flexneri, E. coli, Vibrio cholera,* and *Streptococcus mitis* in comparison to standard (ampicillin), whereas the same showed excellent antifungal activities against *Aspergillus niger*, *Trichophyton rubrum,* and *Candida glabrata* in comparison to standard (fluconazole) [30].



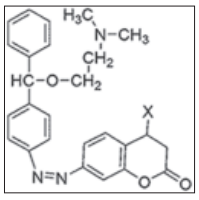
Comp	R	X
5c	H	O
5d	H	N
10c	-	O
10d	-	NH

Scheme 5: Synthesis of mono and bis salicyloyl azo derivatives



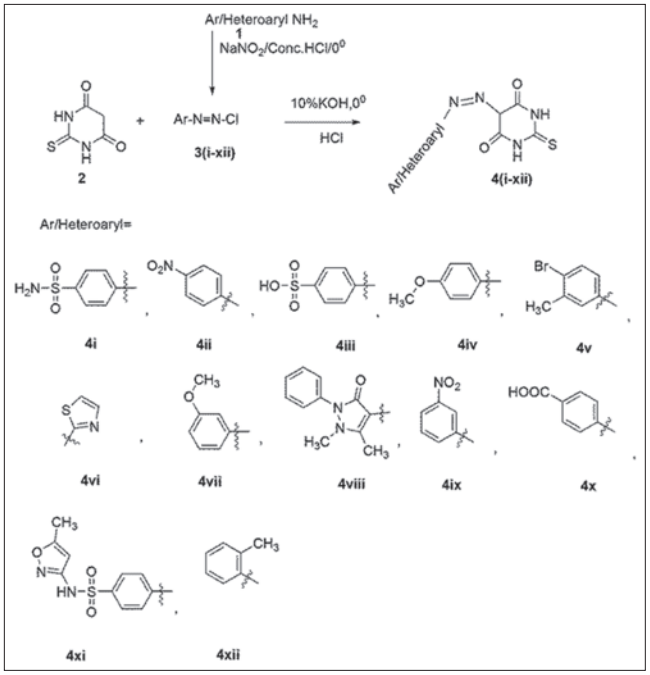
Comp	Ar
4a	1-naphthol
4b	2-naphthol
4c	5-hydroxy coumarin
4d	7-hydroxy coumarin
4e	2-hydroxy benzaldehyde
4f	8-hydroxy quinoline
4g	2,6-dichloro phenol

Fig. 1: Dihyropyrimidinone bearing azo derivatives



Comp.	X
3	H
4	CH_3

Fig. 2: 7-arylazo-chromen-2-one



Comp.	Ar/Heteroaryl
4i	4-benzenesulfoamido-
4ii	4- nitro phenyl-
4iii	4-Sulfonic phenyl-
4iv	4-methoxy phenyl-
4v	4-bromo, 3-methyl phenyl-
4vi	Thiazol-2-yl-
4vii	2-methoxy phenyl-
4viii	4-(1,5 dimethyl-2-phenyl)-pyrazol-3-one-
4ix	3- nitro phenyl-
4x	4-carboxy phenyl-
4xi	N-(5-methylisoxazol-3-yl) benzene sulfonamide-
4xii	2-methyl phenyl-

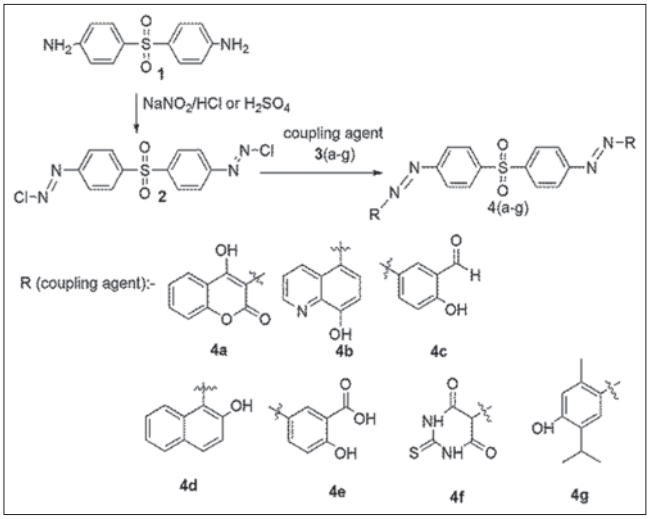
Scheme 6: Synthesis of 5-aryl/heteroaryl azo bearing pyrimidine analogues

A series of substituted heteroaryl/arylazo salicylaldehyde analogues and the metal complex of 2-((*E*)-(4-methoxyphenylimino) methyl)-4-((*E*)-(3-nitrophenyl) diazenyl) phenol were synthesized (Scheme 8) and their antimicrobial activity was evaluated by agar well diffusion method. The 3-nitrophenyl substituted azo-salicylaldehyde analogue (4d) showed significant antibacterial activity against *Salmonella ser. typhi, Salmonella typhimurium, S. flexneri, P. aeruginosa, Klebsiella pneumonia, B. circulans, S. mitis,* and *B. subtilis* in comparison to standard (ampicillin). The Bis(2-((E)-(4-methoxyphenylimino) methyl)-4-((E)-(3-nitrophenyl)diazenyl) phenoxy) cobalt showed significant antifungal activities against *T. rubrum* and *C. glabrata* in comparison to fluconazole [31].

Wound healing activity

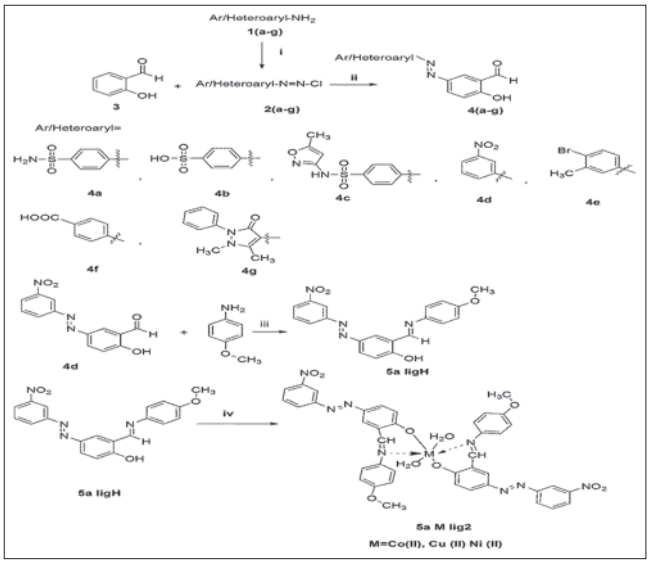
Specifically wound is a sharp injury which damages the epidermis and dermis of the skin by cutting or puncturing or by burning. Wound healing is a complex process. In normal skin the epidermis and dermis exist in steady-state equilibrium, forming a protective barrier against the external environment. Wound healing included hemostasis, inflammation, proliferation, and remodeling like the process to repair the damaged cell [32]. To promote accelerating skin repair, many clinicians have been focused on searching of novel pharmacological agents having a maximum efficiency of wound contraction and minimum toxicity.

A series of 5-heteroaryl/arylazo 8-hydroxy quinoline (8-HQ) congeners (Scheme 9) were synthesized by the reaction of different diazonium



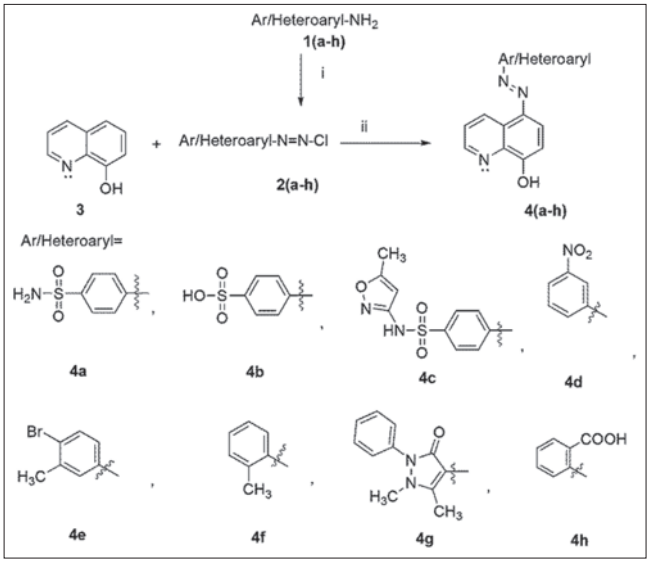
Comp.	R
4a	4-hydroxy coumarin
4b	8-hydroxy quinoline
4c	Salicylic acid
4d	2-Naphthol
4e	Salicylaldehyde
4f	Thiobarbituric acid
4g	Thymol

Scheme 7: Synthesis of 4, 4' Bisazo Dapsone analogues



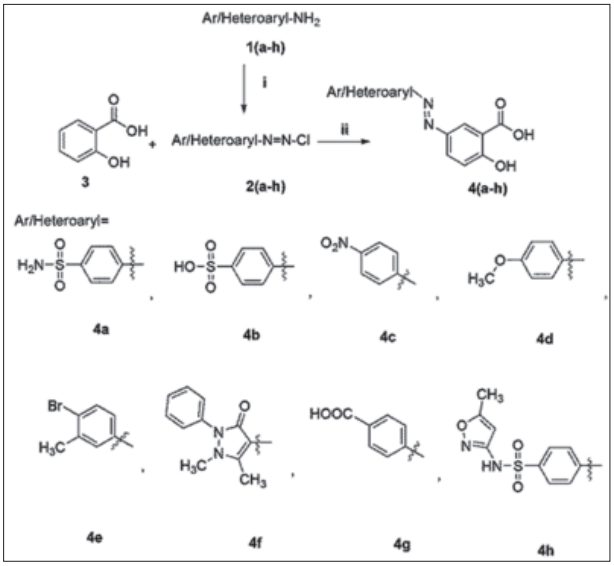
Comp.	Ar/Heteroaryl
4a	4-benzenesulfoamido-
4b	Phenyl 4-sulfonic acid-
4c	N- (5-methyl isoxazol-3-yl) benzene Sulfonamido-
4d	3-nitro phenyl-
4e	4-bromo, 3-methyl, phenyl-
4f	4-carboxy phenyl-
4g	4-antipyrinyl-
5a (Lig)	Schiff base of 4d
5a (Cu Lig_2)	Cupper complex of Schiff base of 4d
5a (Ni Lig_2)	Nickel complex of Schiff base of 4d
5a (Co Lig_2)	Cobalt complex of Schiff base of 4d

Scheme 8: Synthesis of 4-heteroaryl/arylazo salicylaldehyde analogues



Comp.	Ar/Heteroaryl
4a	4-sulfamoyl phenyl-
4b	Phenyl 2-sulfonic acid-
4c	N-(5-methylisoxazol-3-yl) benzene sulfonamide-
4d	3- nitro phenyl-
4e	2-methoxy phenyl-
4f	4-bromo, 3-methyl phenyl-
4g	4- (1, 5 - dimethyl-2-phenyl-pyrazol-3-one)
4h	2-carboxy phenyl-

Scheme 9: Synthesis of 5-heteroaryl/arylazo 8-hydroxy quinoline (8-HQ) congeners



Comp.	R
4a	4-benzenesulfoamido-
4b	4-Sulfonic phenyl
4c	4- nitro phenyl-
4d	4-methoxy phenyl -
4e	4-bromo, 3-methyl phenyl-
4f	4-(1,5 dimethyl-2-phenyl)-pyrazol-3-one-
4g	4-carboxy phenyl-
4h	N-(5-methylisoxazol-3-yl) benzene sulfonamide-

Scheme 10: Synthesis of 5-heteroaryl/arylazo salicylic acid congeners

salts of primary aryl and heteroaryl amines coupled with 8-HQ and were subjected to evaluation of their wound healing activity at different concentrations in a simple ointment form by wound excision and incision model. The compound (4g) (10%) showed highly significant wound healing activity [33].

Analgesic activity

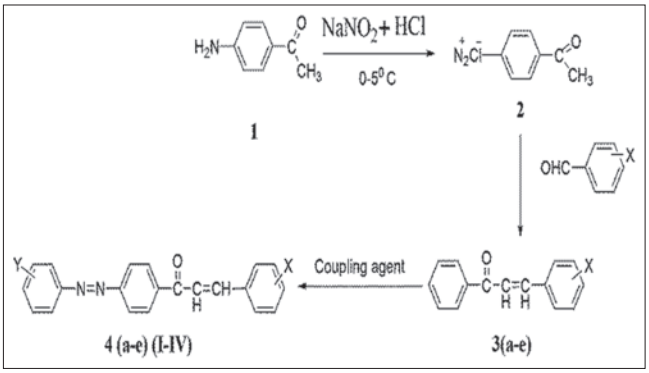
The state of reduced awareness to pain is defined as analgesia. Analgesics are the drugs which can reduce the pain sensation.

A series of novel azosalicylic acid analogues (Scheme 10) were synthesized by coupling various aryl and heteroarylamines with salicylic acid nucleus. The analgesic activity of the synthesized compounds was determined by acetic acid induced writhing method. Acetylsalicylic salicylic acid was used as standard (100 mg/kg body weight orally). The newly synthesized salicylic acid congeners 4e, 4f, 4g, and 4h showed satisfactory of inhibition of pain at a dose of 100 mg/kg body weight in comparison to control. The compound (4e) showed the highest significant analgesic activity 45±4.86 ($p<0.001$) at a dose of 100 mg/kg body weight [10].

Anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for the treatment of acute and chronic inflammation and to relieve pain and fever. Most of the NSAID those available in the market are in constitutive form COX-1 and inducible form COX-2 to offer therapeutic effect that is to inhibit COX-1 and COX-2, thereby the synthesis of prostaglandin and thromboxane can be blocked.

Novel phenyl azochalcone derivatives were prepared from 4-aminoacetophenone. Diazotization of the amino ketone followed



Comp.	X	Y
4a (1)	NO_2	NH_2
4a (II)	NO_2	OCH_3
4a (III)	NO_2	CH_3
4a (IV)	NO_2	C_6H_5-OH
4b (I)	OCH_3	NH_2
4b (II)	OCH_3	OCH_3
4b (III)	OCH_3	CH_3
4c (I)	OCH_3	C_6H_5-OH
4c (II)	CH_3	NH_2
4c (III)	CH_3	OCH_3
4c (IV)	CH_3	CH_3
4d (I)	OH	NH_2
4d (II)	OH	OCH_3
4d (III)	OH	CH_3
4d (IV)	OH	C_6H_5-OH

Scheme 11: Synthesis of novel phenyl azo chalcone derivatives

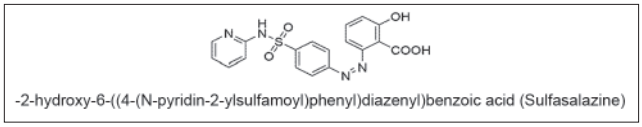


Fig. 3: 2-hydroxy-6-((4-(N-pyridin-2-ylsulfamoyl)phenyl) diazenyl)benzoic acid (Sulphasalazine)

by Claisen Schmidt condensation and finally coupled with various electrophiles gave phenylazochalcone derivatives (Scheme 11). The *in vitro* anti-inflammatory activity of the synthesized compounds were conducted by protein denaturation method using UV-spectrophotometer. The nitrochalcone coupled with aniline 4a (I), anisidine 4a (II) and methoxy chalcone coupled with anisidine 4b (II); hydroxyl chalcone coupled with aniline 4d (I) and anisidine 4d (II); and methyl chalcone coupled with toluidine 4c (III) have shown moderate to good anti-inflammatory activity [11].

Antitubercular activity

Tuberculosis (TB) is one of the most common infectious airborne disease caused by *Mycobacterium tuberculosis*. About 32% of the world's population is infected by tubercle bacillus. TB typically attacks the lungs but can also affect other parts of the body. Every year tentatively 8 million of infected people develop active TB and 2 millions of them face death [11].

Novel phenyl azochalcone derivatives were prepared from 4-aminoacetophenone. Diazotization of the amino ketone followed by Claisen Schmidt condensation and finally coupled with various electrophiles gave phenylazochalcone derivatives (Scheme 11). The antitubercular activity of compounds was assessed against *M. tuberculosis* using microplate alamar blue assay method. It was found to be observed that the chalcone derivatives showed the inhibition of growth of *M. tuberculosis* H37 RV at 50 and 100 µg/ml concentrations due to the presence of electron releasing substituent on different aryl rings 4(a-e) (I-IV) [11].

Antirheumatoidal activity

The 5-aminosalicylic acid and sulphapyridine coupled to form azo compound sulfasalazine (Fig. 3). Normally, it is given in enteric coated form as an antiulcerative drug. Sulfasalazine is an effective drug in the treatment of rheumatoid arthritis with an efficacy very similar to that of injectable gold, D-penicillamine and methotrexate [34].

CONCLUSION

This review article covered an up-to-date survey of various biological activities of azo compounds. It is expected that this review work will draw the attention of the researchers who have interest in the development of novel azo bearing molecules.

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