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A NEW PROFILE OF AZOMETHINES CONTAINING HALOGEN AND CYANOETHYL MOIETIES TOWARDS SYNTHETIC AND PHARMACOLOGICAL UTILITIES: A REVIEW

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ABSTRACT

Azomethines most widely used organic compounds are like carbonyl compounds in which the >C=O group is replaced by an imine or azomethine group, have been shown to exhibit a broad range of biological activities. Azomethine group is present in various natural-derived, natural and non-natural compounds. In the past years a number of innovations and new techniques have been reported. The biological activity of this class of compounds deserves further investigations. Although the research on this subject is incipient, a number of reports disclosing the effects of the azomethines on the pathogens of clinical interest have recently been increasing. Azomethines have been shown to be promising leads for the design of more efficient antimicrobial agents. Present communication is an attempt to review the reports on the pharmacologically active azomethines synthesized using halogens and cyano moieties.

KEYWORDS: Azomethines, Pharmacological activity, Halogen and Cyanoethyl group.

INTRODUCTION

The chemistry and biological science has produced a number of compounds that are now utilized as antibacterial agents. Azomethines revealed a great promise in the area of synthesis and medical fields.[1] The imine linkage has been found as an excellent bioactive and medicinally important moiety. Azomethines and their derivatives has been a research subject,[2,3] due to their pharmacological applications and striking complexometric behaviour. These properties allow it to play a pivotal role in various activities[4,5] *viz.* antibacterial[6-9], antiviral[10], antifungal[11-15], anticancer[16-19], anti-tubercular[20-22], anticonvulsant[23,24], anti-HIV[25], anthelmintic[26], anti-amoebic[27-30], anti-inflammatory[31], antinociceptive[32], antimouse hepatitis virus (MHV)[33], inhibition of herpes simplex virus type-1 (HSV-1), adenovirus type-5 (AD-5)[34] antimalarial[35,36], pesticidal[37] and herbicidal[38] activities. Azomethines have also been shown great potentials to be used in different areas such as electrochemistry, bioinorganic catalysis, metallic deactivators, separation processes and in environmental chemistry.[39]

SYNTHESIS OF AZOMETHINES

Since the first preparation of imines reported in the 19th century a variety of methods for the synthesis of imines have been described.[40] The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation.[41] In 2004 Chakraborti[42] *et al.* demonstrated that the efficiency of this method is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. In the past some years a number of innovations and new techniques have been reported, including solvent-free/clay/microwave irradiation, solid-state synthesis, K-10/microwave, water suspension medium, [bmim]BF_4/molecular sieves, infrared irradiation/no solvent, $NaHSO_4ESiO_2$/microwave/solvent free, solvent-free/CaO/microwave and silica/ultrasound irradiation,[43-51] among these innovations, microwave irradiation has been extensively used due to its operational simplicity, enhanced reaction rates, and great selectivity. The use of microwave irradiation commenced with the independent studies of Rousell and Majetich groups.[52,53] Microwave irradiation is less environmentally problematic than other methods because it abolishes the excessive use of aromatic solvents and the Dean-Stark apparatus for azeotropic removal of water. Another feature of this technique is that the reactions achieve high efficiency in a shorter period of time.

Azomethines have been known since 1864 when Hugo Schiff reported the condensation of primary amines with carbonyl compounds. The common structural feature of

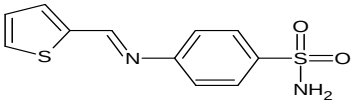
these compounds is the azomethine group (RHC=N-R^1, where R and R^1 are alkyl, aryl, cycloalkyl or heterocyclic groups) which may be substituted variously and are also known as azomethines, anils and imines. Studies showed that the presence of a lone pair of electrons in a sp^2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological interest.[54-60] These bases have been studied extensively because of the relative easiness of preparation, synthetic flexibility, structural similarities with natural biological substances and the special property of -C=N- group. The presence of hetero atoms such as oxygen and nitrogen are also helpful in the biological activity of the azomethines.[61]

They are widely used for industrial purposes and also exhibit a broad range of biological activities. Antimicrobial activities of azomethines are affected by the type of substituents at the aldehyde or amine fragment. Effects of substituent on antimicrobial activities have been investigated for azomethines derived from *o*-carboxymethyl chitosan (CMCh), *p*-substituted benzaldehydes[62], salicyl aldehyde and 2-aminophenol.[63] Structure-activity-relationship (SAR) of azomethines derived from 5-chloro salicylaldehyde showed that hydrophilicity and aromaticity are important parameters for antimicrobial activity and the electronic nature (electron withdrawing and donating) of the substituent affects the activity of azomethines significantly.[64-66] Azomethines derived from salicylaldehyde and *o*-, *m*- and *p*-COOH substituted amino benzoic acids have been investigated for the presence of antibacterial constituents. The *ortho*- and *meta*- substituted compounds exhibited better antibacterial activity against *P. aeruginosa*, *S. aureus* and *E. feacalis.*[67]

Mkpenie[68] *et al*. have synthesized *o*-, *m*- and *p*- methyl substituted azomethines by the condensation of appropriate aromatic amines (*o*-, *m*- and *p*-toluidine) with benzaldehydes and the sensitivity of bacteria and fungi was evaluated by the micro-organisms. Antifungal and antibacterial activities are affected by the position of substituents in the aryl ring of the azomethines. The results of the antimicrobial activity showed that the methyl group substituted at *meta*- and *para*- positions exhibited more antifungal and antibacterial activities compared to the *ortho*- or un substituted derivatives. The effect of substituents on biological activity of azomethines was investigated by Joshi[69] *et al*., using azomethines derived by the condensation of oxindol, with 4-methylanthranilic acid, 4-methoxyanthranilic acid, 4-nitroanthranilic acid, 4-chloroanthranilic acid and 4-hydroxyanthranilic acid, the *in-vitro* antifungal and antibacterial activity results showed that azomethines of 4-chloroanthranilic acid exhibited highest activity.

An interesting application of azomethines as effective corrosion inhibitors for mild steel and similarly copper, zinc and aluminium has been observed.[70] Many commercial inhibitors include aldehydes or amines but presumably due to the -C=N- bonds, the azomethines functions more efficiently in many cases[71] and have been found to posses more inhibitory efficiency than their constituent carbonyls and amines.[72-74] Due to the presence of the azomethine group, the electron cloud of the aromatic ring and electronegative nitrogen, oxygen and sulphur atoms in the azomethine molecules, these compounds effectively prevent corrosion of mild steel, copper, aluminium and zinc in acidic medium.[75]

Azomethines namely 4-((thiophene-2-yl)methylene-amino)phenyl-sulphonamide **(1)**, (2E)-2-((5-((E)-(2-hydroxyphenylimino)methyl)thiophene-2-yl)methylene-amino) phenol **(2)**, 2-(5-methoxy-2-hydroxybenzylidene-amino) phenol **(3)** and N'N-bis((thiophene-2yl)-methylene)benzene-1,2-diamine **(4)** were synthesized. These azomethines exhibited a good corrosion inhibition action as well as *in-vitro* antimicrobial activities.[76]



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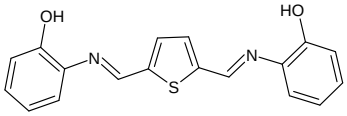

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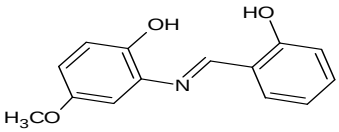

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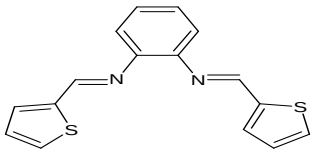

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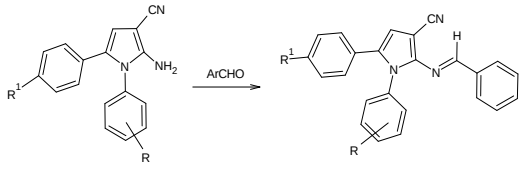
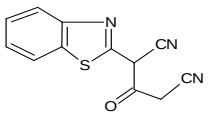
The novel synthesis of poly-N-alkyltrimethylene imines by a replacement of cyanoethyl group in poly-N-β-cyanoethyltrimethylene imine, poly-N-*p*-nitrobenzyltri-methy lene imine and poly-N-methyl-trimethylene imine by other alkyl group are reported by Yamashita.[77] Azomethines ligand Indal-4-aminoantipyrene), derived from indole-3-carboxaldehyde and 4-aminoantipyrine were synthesized by Shiva kumaran[78] *et al.* A series of C-cyanovinylpyrrole containing aroylhydrazones, derived from ethyl-2-cyano-3-(5-formyl-1H-pyrrol-2-yl)-acrylate and acid hydrazides: Salicylhydrazide, isoniazid and 3,5-dinitrobenzohydrazide.[79] A series of novel pyrrole azomethines was synthesized by reaction of 2-amino-1,5-diarylpyrrole-3-carbonitrile **(5)** with different aromatic aldehydes using P_2O_5 as a catalyst to obtain **(6)** (2-amino-3-cyano-1,5-diaryl-pyrroles) which have been tested against Herpes Simplex Virus type-1 by Hilmy[80] *et al.*



(5) **(6)**

Benzothiazoles with a cyanomethyl group at position-2 have been the subject of extensive study in the recent past. Numerous reports have been appeared in the literature, which highlights their chemistry and uses. However, heterocyclics containing cyanoacetyl group are relatively unexplored. In the last two decades, authors involved in aiming to develop new and simple or novel precursors for the synthesis of heterocyclic compounds of biological interest and also their evaluation as biodegradable agrochemicals.[81-85] Some heterocyclic compounds containing benzothiazole nucleus with cyano group, 2-(benzothiazol-2-yl)-3-oxopentanedinitrile **(7),** synthesised by Abdelrazek[86] *et al.*, for biological activities.



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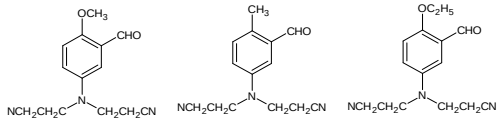
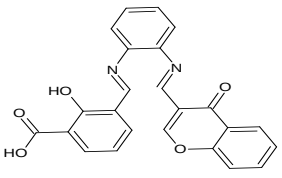
Reactions of *p*-N'N-diethylaminobenzaldehyde with substituted glycines, rhodanine, hydantoin, thiohydantoin, malonanilic acids, substituted malonanilic acid hydrazides, fluorine and cyanoacetamide have been reported by Saxena[87] *et al*. The substitution of formyl group in the *m*-position with respect to the cyanoethyl group of the benzene ring structure of aldehydes has been proposed as **(8), (9)** and **(10).**



(8) **(9)** **(10)**

An interest in azomethines derived from aromatic *o*-hydroxyl aldehyde has been increased significantly due to their structure[88-90] and applications.[91-94] Recently, new azomethine(-hydroxy-3-((E)-(2-((E)-(4-oxo-4H-chromen -3-yl)methylene-amino)phenyl-imino)methyl)benzoic acid) **(11)** has been reported as inhibitor of carbon steel corrosion.[95]



(11)

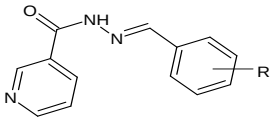
Azomethines also have importance in biological systems, an imine linkage between the aldehyde derived from vitamin A and the protein; Opsin in the retina of the eye plays an important role in the chemistry of vision. An example of a biologically important aldehyde is pyridoxalphosphate, which is the active form of vitamin B6. *o*-Phenylenediamine azomethines show clinical properties.[96] Azomethines derived from 4-dimethylamine and benzaldehyde shows antibacterial activity and also being used as antibodies and anti-inflammatory agents[97, 98] in medicines.

The antimicrobial drugs occupy a unique niche in the history of medicine. A series of vanillin substituted azomethines have been synthesized using vanillin and various aromatic amines in presence of a basic catalyst; triethylamine showed excellent biological activity.[99]

Recently, new biologically active amino substituted azomethines have been reported by Makwana[100] *et al*., derived from 2-aminophenol, vanillin and salicylaldehyde by the reaction of two different amino substituted compounds and substituted aldehydes. Considerable interest has attached with the chemistry of azomethines[101], obtained from heterocyclic aldehyde. Azomethines derived from substituted aromatic aldehydes *viz.* salicylaldehyde and amines gave the best quantitative structure anti-tumour activity relationship correlation.[102,103] Azomethines of salicylaldehyde have also been reported as plant growth regulator[104], antimicrobial[105] antimycotic[106] and some analytical applications.[107]

Azomethines derived from the reaction of the 3-hydroxybenzaldehyde and 5-nitrosalicylaldehyde, with the amines, aniline and *o*-aminothiophenol, were reported by Kolwalkar[108] *et al*. Azomethines derived from 5-nitro salicylaldehyde and amines, *o*- and *p*-amino phenols, *o*-amino thiophenol and sulfanilic acid were reported by Murthy[109] *et al*. Azomethines derived from ethylene-2,2'-(dioxydibenzenaldehyde) and 2-aminothiophenol have been reported by Zhau[110] *et al*. The deep studies on a new kind of chemotherapeutic azomethines are attracting the attention of biochemists.[111,112]

A new series of azomethine derivatives **(12)** containing pyridine moiety have been synthesized by Madhavi[113] *et al*. Substitution of 3,4,5-methoxy and 2,5-difluoro moiety exhibited good antibacterial activity on E-N'-(2-methoxy-6-pentadecyl-substituted-benzylidene) benzohydrazide **(13)** which were accomplished from the key inter mediate 2-methoxy-6-pentadecyl-benzaldehyde on evaluation for antimicrobial screening against Gram "-"ve strains by a study of Swami[114] *et al*.



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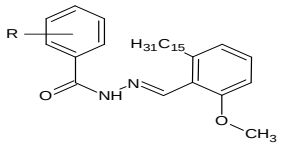

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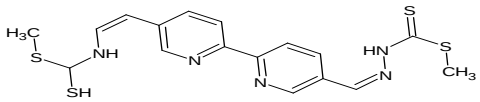
Karim[115] *et al.* have synthesized azomethines **(14)** by the condensation of 2,2'-bipyridyl-5,5'-dicarbaldehyde with O, S, N and F containing amines and studied their antibacterial properties.



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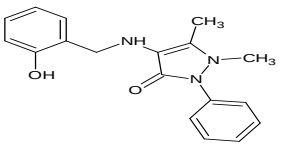
Tudor[116] *et al.* have reported the synthesis of azomethines **(15)** by the condensation of 2-hydroxy benzaldehyde or terephthalicaldehyde **(16)** with 4-amino antipyrine.



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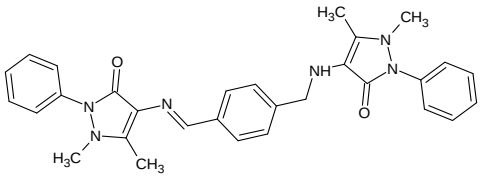
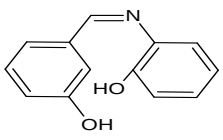


(16)

Synthesis and antimicrobial activity of the azomethines **(17)** derived by the condensation of *o*-hydroxybenzaldehyde with aminophenols and nitrogen donor amine bases were reported by Islam[117] *et al*. Salicylaldehyde azomethines derived from 1-amino-3-hydroxy guanidine tosylate are good material for the design of new antiviral agents.[118] Synthesis of new azomethine derivatives from 3-(amino)-3-*p*-tolyl-propanoicacid) and 2-hydroxybenzaldehyde have been reported by Wilson[119] and co-workers. Singh[120] *et al.* have synthesised substituted aniline (3-methoxy-4-substitued-acetyloxy)benzylidenes **(18)** which inhibited the *in-vitro* monoamino-oxidase activity of rat brain homogenates. The products also possessed anticonvulsant activity against pentylenetetrazole induced convulsion in mice.



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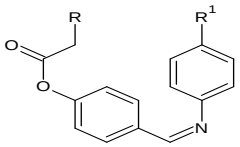
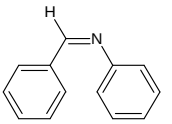


(18)

Azomethines derived from aromatic aldehydes are used in optical and electrochemical sensors in various chromatographic methods and to enhance selectivity and sensitivity of the organic reagents. Their preparation procedures are relatively simple and have synthetic flexibility that enables tuning of suitable structural properties.[121,122] Azomethines **(19)**, **(20)** and **(21)** have been synthesized from benzaldehyde and salicylaldehyde, some of them were tested for anti-inflammatory activity.[123] Environment friendly procedure for synthesis of azomethines (antimicrobial) has been reported by Yahyazadeh.[124]



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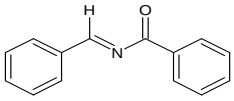

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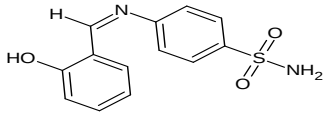


(21)

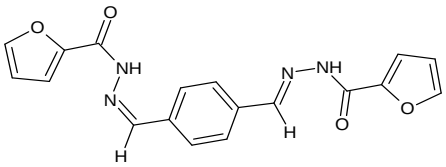
N-sulfamoyl azomethines continue to attract the attention of chemists because the sulfonyl moiety has proven to be powerful activating group of the -CH=N- bond.[125]

Literature is enriched with progressive findings about the synthesis and biological significance of fused heterocyclics. As a consequence, N-sulfonyl azomethines has been widely used in various transformations in organic synthesis to access biologically active compounds.[126] These are excellent substrates in nucleophilic additions [127], Aza Deils-Alder reaction[128], reductions[129], oxaziridine synthesis[130], asymmetric synthesis of β-amino acids derivatives[131] and reactive alkenes in Ene-reaction.[132] In addition, these are excellent precursors for the preparation of optically active 2-imidazolines.

Recently, Auf[133] *et al.* afforded the synthesis of N-sulfamoyl azomethine derivatives by the reaction of aldehydes with primary sulphonamides. In a study, azomethines were synthesized by condensation of 4-aminobenzene sulfonamide and carbonyl molecules, their biocidal activities also been evaluated against *S. aureus, B. subtilis E. coli, P. aeruginosa* and *C. albicans*, some compounds exhibited better biocidal effects.[134] Azomethines synthesized by Yousuf[135] *et al.*, by the condensation of primary amines with carbonyl groups have been reported. Synthesis and *in-vitro* antimicrobial activities of new azomethines obtained from

3-formylchromone with sulfapyridazine, 3-formyl-6-methylchromone with sulfamethoxypyridazine and 3-formyl-6-methylchromone with sulfaproxylene have been investigated by Hadi[136] *et al*.

In view of the immense significance of the pharmacological and biological activities associated with azomethines, synthesis and spectral characterization of hydrazone azomethines **(22)** derived from condensation of terephthalaldehyde and 2-furoicacidhydrazide were reported by Abbasi[137] *et al*. Fungicidal activity enhanced due to the presence of -OCH_3 (methoxy) and -$COCH_3$ (acetyloxy) groups in a series of azomethines **(23)** derived from 4-substituted and 4, 5-disubstitued-2-aminothiazole and 3-methoxy, 4-substituted-acetyloxy benzaldehydes.[138]



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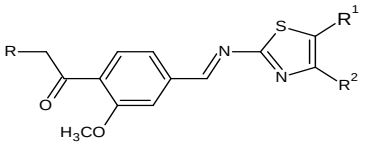
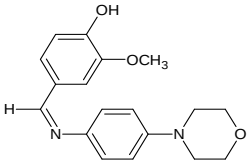


(23)

Azomethines **(24)** and **(25)** derived from vanillin showed marked inhibition against the investigated bacteria and appeared as promising antimicrobial agents.[139,140]



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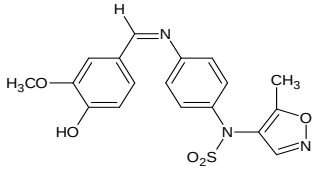
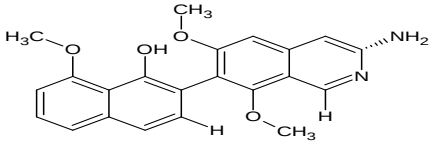


(25)

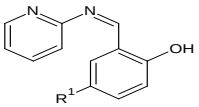
N-Substituted azomethines prepared by aliphatic and aromatic aldehydes on condensation with aliphatic and aromatic primary amines are used as polymer, analytical, medicinal and liquid crystalline materials.[141] The condensation reaction of benzaldehydes and anilines to benzylidene-anilines occurred in a water suspension medium[142] without using any acid catalyst and the products were isolated simply by filtration.[143] The condensation reactions of aliphatic and aromatic aldehydes and amines carried out efficiently in a water suspension medium by Gupta[144] *et al*. Several researchers have paid attention towards synthesis[145] and biological evaluation,[146,147] due to biological signifycance connected with azomethines. Several research groups have increased their interest in the development of newer synthetic methods.[148] Azomethines have been shown to be interesting moieties for the design of antimalarial agents[149]. Ancistrocladidine **(26)** a secondary metabolite produced by plants, bearing an azomethine linkage into its molecular scaffold has been shown active against *P. falciparum.*



(26)

The antibacterial activities of azomethines derived from chitosan and cinnamaldehyde were investigated by Xiao and co-workers.[150] Parekh[151] and co-workers synthesized azomethines and evaluated them as potential antibacterial agents, against bacterial strains. Srikar *et al.* used *p*-dimethylamino cinnamaldehyde to form desired azomethine, which is used for quantitative estimation of Sparfloxacin in bulk and pharmaceutical dosage forms.[152]

Azomethines **(27)** N-(2-hydroxylbenzylidene)pyridin-2-amine, **(28)** N-(5-nitro-2-hydroxylbenzylidene)pyridin-2-amine, **(29)** N-(5-bromo-2-hydroxylbenzylidene)pyridin-2-amine **(30)** and N-(5-methoxy-2-hydroxylbenzylidene)pyridin-2-amine have been prepared by Gupta[153] *et al.* these compounds were able to prevent the growth of *S. aureus* and *E. coli* in diverse concentrations. A series of 1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one containing azomethines were synthesized by Khan[154] *et al.* and antibacterial screening results revealed that compounds exhibited moderate to good antibacterial activity.



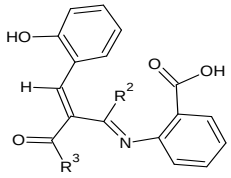
R^1 = -H **(27),** -NO_2 **(28),** -Br **(29)** and -OCH_3 **(30)**

The inherent electron withdrawing character of azomethines results in colourful materials that absorb intensely across the entire visible spectrum, especially when coupled with electron rich moieties.[155,156] Importantly, these can be prepared with straight forward protocols without stringent reaction conditions.[157] Siddiqui[158] *et al*. synthesized a series of azomethines by reacting 2-formylphenoxyacetic acid with aromatic amines. Among the compounds, 2-(4-acetamidophenyl-iminomethyl)phenoxyacetic acid, 2-(4-methyl pyridin-2-yl-iminomethyl)phenoxyacetic acid**,** 2-(2,3-dichlorophe nyliminomethyl)phenoxy acetic acid**,** (2-{[4-(2′-chloro phenyl)-thiazole-2-ylimino]methyl}phenoxy)acetic acid

and 2-{2-[(3-imida-zol-1-ylpropylimino)methyl]phenoxy}acetic acid exhibited good activity against *S. aureus* and *E. coli*. Aromatic poly azomethines have also attracted interest for their good thermal stability and interesting optoelectronic properties.[159, 160]

Isatin azomethines were reported to possess antiviral, anti-HIV, antiprotozoal and anthelmintic activities,[161] they also exhibit significant anticonvulsant activity, apart from other pharmacological properties.[162] However, in a number of studies azomethines are being used for the construction of various nanostructures.[163,164] Azomethines 2-[1-(4-chloro phenyl)ethylidene-amino]phenol and 2-[1-(4-hydroxyphenyl)ethylidene-amino]phenol were synthesized by Aslam[165] and co-workers and were screened for their biological activity. The azomethines 2-[1-(4-hydroxyphenyl)ethylidene amino]phenol showed potent antioxidant activity and *α*-glucosidase inhibitor. Azomethine ligands derivatives showing anti bacterial activity against Gram "-" ve *E. coli* and Gram "-" ve bacteria *S. aureus* have been synthesized[166] by the condensation of aromatic aldehydes *viz.* salicylaldehyde/ benzaldehyde/pyrrole-2-carboxaldehyde/*p*-hydroxybe benzaldehyde/isatin/*o*-hydroxyacetophenone with 1,3-diaminopropane. A family of azomethines were synthesized[167] **(31)** by the reactions of *o*-aminobenzoic acid and Knoevenagel condensate of β-ketoesters(2-[3-(2-hydr-oxy-phenyl)-1-methyl-2-phenoxycarbonylallylideneamino]benzoic acid, 2-[3-(3-hydroxy-nap-hthalen-2-yl)-1-methyl-2-phenoxycarbonylally-lideneamino]-benzoic acid) and were subjected to study for their biocidal efficacy against *S. epidermidis*, *E. coli*, *B. cinerea* and *A. niger*.

Recently, azomethines **(32)** were obtained by reaction of 4-aminobenzoic acid with substituted aldehydes in acetic acid by Kumbhar[168] *et al.*



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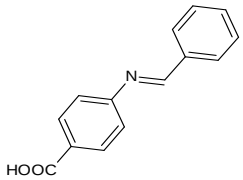
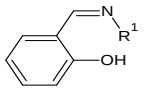


(32)

Recently, azomethines of salicylaldehyde **(33)** with different amines, have been synthesized including 2-{[(*Z*)-(2-hydroxyphenyl)methylidene]amino}benzoic acid, 4-{[(*Z*)-(2-hydroxyphenyl)methylidene]amino}benzoic acid, 2-[(naphthalene-2-ylimino)methyl]phenol, 2-2'-[benzene-1,4-diyl-bis-(nitrilomethylylide-ne)]diphenol, 2-2'-[benzene-1,2-diylbis(nitrile-(*E*)-methyllidene)]diphenol, 2-[(2-phenylhydrazineylidene)methyl]phenol, 2-2'-[ethene-1,2-diyl-bis-(iminomethanediyl)]diphenol and 2-[(*Z*)-(phenylimino)methyl]phenol and evaluation of their antimicrobial activities against different bacterial strains has been reported by Ahmed[169] *et al.* Investigation on the synthesis of azomethines **(34)** derived from 3-formylchromones and various aromatic anilines were reported by Shelke[170] *et al.*



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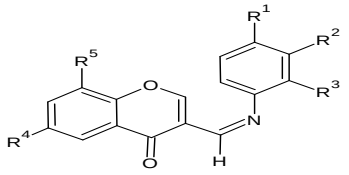
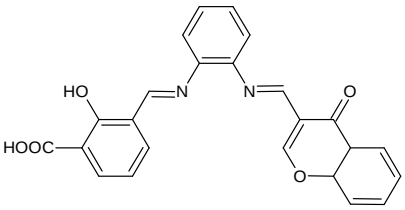


(34)

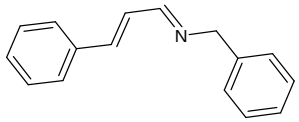
Recently, Hadi[171] *et al.* reported synthesis of new unsymmetrical azomethine namely (2-hydroxy-3-(E)-(2-(E)-(4-oxo-4H-chromen-3-yl)methylene-amino)phenyl imino)-methyl)benzoic acid **(35)** and the inhibition action on the corrosion of carbon steel in industrial water have been investigated.



(35)

Mathew[172] *et al*. concentrated a research on the synthesis of some azomethines of 5-phenyl-substituted-2-amino-1,3,4-thiadiazole derivatives by the reaction between various aryl carboxylic acids with thiosemicarbazide to form 5-phenyl-substituted, 2-amino-1,3,4-thiadiazole derivatives, which further on treatment with various aldehydes gave azomethines of anthelmintic activity. Parmar[173] *et al.* have synthesized some biologically active 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazole and their azomethines by condensing these 1,2,4-triazolo[3,4-b] [1 ,3,4]-thiadiazole with different substituted aromatic aldehydes. These azomethine ligands and their transition metal (II) complexes were found to exhibit varied activity against different strains of bacteria.

A series of biologically active amino substituted azomethines have been synthesized showing *in-vitro* bioactivities against bacteria, fungi and yeast.[174] The work is abundant on physico-chemical properties of various symmetrical azomethines and chelates with their pyridine, 2,2´bipyridine and 1,10-phenanthroline adducts.[175,176] Azomethines from 2-(diphenylphosphino) benzaldehydes are valuable ligands.[177,178] Recently, trans-cinnamaldehyde-(3-phenylpropenal) was used for the preparation of the biologically active[179] azomethine (1-phenyl-*N*-[(1E,2E)-3-phenylprop-2-en-1-ylidene]methanamine)cinnamaldehydebenzylamine **(36).**



(36)

REVIEW ON HALOGENATED AZO-METHINES

Fluorine has become an essential tool in drug discovery, including fluorine atom in potential medicines can have a variety of dramatic effects on the molecular properties perhaps making them more selective, increasing efficacy. 6-Fluoro-7-chloroaniline has been used as starting molecule to synthesize novel fluoro benzothiazole Schiff's bases in hope of getting molecule with biodynamic potentials which are known to exhibit anti-inflammatory activities.[180, 181] Sathe reported the synthesis of a series of novel fluoro benzothiazole azomethines with potent anti-inflammatory activity and good therapeutic values.[182]

Compounds containing halogen atoms are active ingredients in health care from blood extenders to anticancer drugs. Halogenated compounds have become particularly important in higher value added pharmaceutical and agrochemical products.[183] Presence of halogens in the biologically active molecules has shown to play a crucial role in their pharmacological properties. Fluorinated chemicals are of growing importance with applications in diverse fields, particularrly in medicine and agrochemicals. Fluorine containing drugs are used in medicine such as anaesthetics (*ie.* Halothane, Isoflurane), antibiotics (*ie.* Fluoroquinolones, Ciprofloxacin), anti-cancer, anti-inflammatory (*ie.* Niflumic acid), psychopharmaceuticals (*ie.* Fluoxetine, Citalopram) and are many other applications.[184]

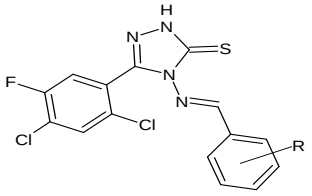
Fluorine substitution can alter the metabolic stability, hydrogen-bonding capacity, lipophilicity, solubility, conformation and even the fundamental structure of a molecule, alteration can profoundly influence biological activity.[185] Very high electro negativity of fluorine can modify electron distribution in the molecule, affecting its absorption, distribution and metabolism. The importance of fluorine substitution in pharmaceutical development is evident in the large number of fluorinated compounds that have been approved by the food and drug administration as drugs; fluorinated anticancer, antiviral, antibacterial, antidiabetic, antimalarial, antifungal, anti depressant, antipsychotic, anti-inflammatory and anaesthetic agents, among others, are represented.[186,187] Azomethines containing 2,4-dichloro-5-fluoro-phenyl moieties also take part in effective inhibition of bacterial growth.[188]

Fluorine containing compounds are the nerve centre of interest in modern medicinal chemistry and are ideal for use in drug design[189], because of the good biological activity and low toxicity of molecules. Now a day's vast number of compounds with fluoro benzene moiety features in diverse areas like antibacterial, antifungal, anti-inflammatory, psychoactive agents, pesticides, herbi cides[190] etc. Sulphonamides elicit wide varieties of anti-tubercular[191] and anti-microbial activity[192, 193] while quinazolines exhibited various activities.[194, 195] Based on these observations Shierke *et al.* have synthesized some fluoro-benzothiazolo-sulphonamidoquinazoline derivatives starting with fluoro/chloro aniline, getting pharmacological agents with broad-spectrum of anti-tubercular activity.[196]

Fluorine containing drugs such as Fluphenazine, Fipranavir, Oflaxacin, Trovafloxacin Halothane[197,198] and Fluoro-quinoline[199] are commonly used family. Recently, More and Rama reported fluorinated propane diones as anti-inflammatory[200] compounds.

Ha[201] and co-workers synthesized a series of azomethine esters possessing polar chloro group. Thermotropic and mesomorphic properties of azomethine esters (or alkano yloxy) with chloro terminal group were investigated.

Many compounds containing dichlorophenyl moiety are found to be biologically important. Dichloro fluoro phenyl containing congeners of triazole Schiff and Mannich bases synthesized to explore as better chemo therapeutic agents. A series of 2,4-dichloro-5-fluoro phenyl bearing Mannich base was prepared by Karthikeyan[202] *et al.* from triazole azomethines **(37)** by aminomethylation with formaldehyde and secondary/ substituted primary amines. All compounds were screened for their antimicrobial activity. A series of new azomethines derived from 2-aminopyridenes with various aromatic aldehydes have been synthesized by Najjar[203] *et al*. Recently the condensation of appropriate amines with 4-(*o*-chlorobenzyloxy)-3-methoxybenzal dehyde resulted in formation of corresponding novel azomethines (N-Aryl-4-(*o*-chloro-benzyl-oxy)-3-methoxyphenyl-1-yl-azomethines) **(38)** were also screened for their *in-vitro* antimicrobial activity.[204]



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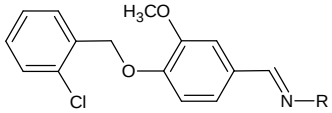
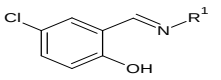


(38)

Aslam[205] and co-workers reported azomethines, {5-Chloro-2-[(2-chlorobenzylidene)-amino]phenyl}(phenyl) methanone and {2-[(3-bromobenzylidene)amino]-5-chlo rophenyl}(phenyl)methanone, by the condensation of halobenzaldehydes with 2-amino-5-chlorobenzophenone

with moderate antioxidant and urease inhibition activity results. Azomethine of 3-chloro-4-fluoro aniline with isatin were synthesized and screened displaying moderate to good antibacterial[206] and β-lactamase inhibitory activities.

The synthesis and antimicrobial activity of a series of azomethines **(39)** derived from the condensation of 5-chloro-salicylaldehyde and primary amines have been reported.[207] The 5-chlorosalicylaldehyde azomethines were most active against at least one of the evaluated bacterial species *P. fluorescence*. 4-Hydroxymethylbenzoate and 2-fluoro-6-(trifluoromethyl)pyridine were treated in DMF at given condition to get pyridine moiety, which was further treated with hydrazine to get benzohydrazide, which gave azomethines **(40)** containing trifluoromethylpyridine on reaction with different substituted aldehydes. These azomethines have been evaluated for their activity against Gram "+"ve and Gram"-"ve bacterial and fungal strains, most of the compounds showed significant activity.[208] Fluorine substituted azomethines were prepared by the condensation of different substituted benzaldehydes with 4-fluoroaniline and evaluated for their action against some bacteria and fungi.[209]



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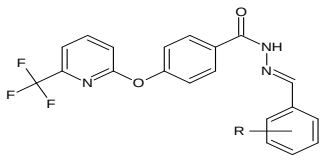
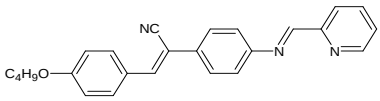


(40)

REVIEW ON CYANO SUBSTITUTED AZOMETHINES

The nitrile functionality (R-CN) is a key constituent of numerous natural products which have served as an important synthetic intermediate for pharmaceuticals[210], agricultural chemicals, dyes, material sciences[211] and as intermediates in microbial metabolism.[212] Nitriles are also products of the petrochemical industry and are widely used as solvents and recrystallizing agents. Nitriles are important synthons in preparative organic chemistry due to their conversion into carboxylic acids, aldehydes, amides, amines and ketones.[210, 213] Nitrile compounds are viable precursors for preparation of a variety of nitrogen-containing functional compounds. The presence of the >C=N- bond conjugated with the cyano group in N-cyanoimines affects their physicochemical properties considerably,[214] expanding the possibilities of their use as synthons.

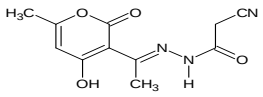
A series of 5-methyl-4-ethoxycarbonyl-3-cyano-2-furanamine azomethines were synthesized by substituted aromatic aldehydes.[215] Azomethines involving a pyridine ring have received considerable attention in literatures.[216,217] Diphenylacrylonitrile moiety has been widely used in various fluorescent materials due to its rigid structure of co planarity.[218-220] Ethylenic bond of diphenylacrylonitrile moiety gets activate because of the existence of cyano group with strong electron withdrawing character and two benzene rings. A novel pyridine contained *α*-cyanostilbenzene azomethine(*Z*)-3-(4-butoxyphenyl)-2-(4-(*E*)-pyridin-2-yl-methyleneamino)phenyl)acrylo-nitrile **(41),** has been synthesized and characterised by Lin[221] *et al*.



(41)

2-Amino-3-cyanopyridines have been identified to possess antimicrobial[222], anti fungal[223], cardiotonic[224], analgesic[225], anti-inflammatory[226] and antilung cancer[227] activities. Many synthetic methods have been used for the preparation of 2-amino-3-cyanopyridine derivatives.[228, 229] Synthesis of 4,6-bis[2′-amino-3′-cyano-4′-(substituted-phenyl)-6′-pyridyl]resorcinols were achieved, with biological screening for their *in-vitro* activity against *Pseudomonas, Bacillus, Streptococcus, Staphylococcus, E. coli, C. albicans* and *A. niger*.[230] 1-Amino-2-cyano-3-methyl-3-ethyl-1,2-dihydronaphthalene-aminonitrile was synthesized and converted to azomethines by Markosyan[231] *et al*.

A series of cyano derivatives of N-alkyl and N-arylpiperazine were synthesized by Chaudhary[232] *et al.* and their antimicrobial activities were evaluated as antibacterial and cytotoxic activity. A work involved in the preparation and testing of biological activity with kinds of bacteria of many azomethines derived from [5-cyano(1,3,4-thiadiazole-1-2-yl)thio]acetohydrazide by Abbas[233] *et al.* A one-pot procedure has been developed for the synthesis of 2-substituted-3-alkoxyisoindolin-1-imine derivatives *via* three-component condensation of 2-cyano benzaldehyde, amine and alcohol by Shen[234] *et al.* In search of some novel antibacterial agents, synthesis and antibacterial activity of 2-cyano-N'-(1-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-ethylidene)acetohydrazide,azomethine **(42)** has been reported by Saini[235] *et al.*



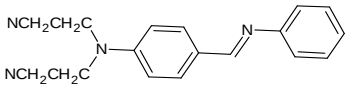
(42)

A series of cyano derivatives of N-alkyl and N-aryl piperazine were synthesized and their antimicrobial activities have been evaluated with results possessing anti bacterial activity and some of the compounds were reported for their cytotoxic activity.[236] The work by Abbas[237] *et al*. involved in preparation of [5-cyano (1,3,4-thiadiazole-1-2-yl)thio]acetohydrazides which were condensed with carbonyl compounds to give azomethines. The interest in various 3-cyano-4-(substituted-

phenyl)6-phenyl-2(1*H*)-pyridinone derivatives stems largely from their unique properties, which enable their use in the production of dyes, pigments, fuel and oil additives and development of medicinal products having broad-spectrum of biological activities.[238, 239]

REVIEW ON CYANOETHYLATED AZO METHINES

Azomethines formed by 4-N'N-bis-(2'-cyanoethyl)aminobenzaldehyde **(43)** have been reported by Arora[240] *et al*. to form stable complexes with metals. A new series of complexes of dioxouranium (IV) with the azomethines N-[(4-N'N-bis-(2'cyanoethylaminobenzylidene-amino] benzene derived from N-[(4-N'N-bis-(2'cyanoethyl amino-benzylidene-amino]benzaldehyde and aniline were prepared by Arora[241] *et al*. Azomethines containing chloro and cyano group display enhanced antibacterial effects.[242, 243]



(43)

CONCLUSION

The aim of the present study is to come with a review on work approached towards synthesis of pharmacologically active azomethines bearing halogen and cyano moieties. The synthetic versatility and pharmacological properties of azomethines has stemmed the interest in this study. Synthetic chemists are studying to find out the possibility of great therapeutic values associated with these active moieties and any people succeeded to find out the newer azomethines. The updated citation and literature is absolutely vital for researchers to find pioneering ideas and relevant information on progress and development of synthetic chemistry. This review would provide basic and advanced information pertaining to this area and encourage researchers of this field to overcome the challenges in developing newer significant bioactive compounds.

ACKNOWLEDGEMENT

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