European Journal of Medicinal Chemistry 186 (2020) 111911

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Molecules with versatile biological activities bearing antipyrinyl nucleus as pharmacophore

Jyotirmaya Sahoo [a, d, **], Chita Ranjan Sahoo [b, c], Priyambada Kshiroda Nandini Sarangi [d], Shakti Ketan Prusty [e], Rabindra Nath Padhy [c], Sudhir Kumar Paidesetty [b, *]

[a] School of Pharmacy, ARKA Jain University, Gamharia, Seraikela, Kharsawan, Jameshedpur, Jharkand, 832108, India
[b] Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to Be University), Bhubaneswar, 751003, Odisha, India
[c] Central Research Laboratory, Institute of Medical Sciences & Sum Hospital, Siksha 'O' Anusandhan (Deemed to Be University), Bhubaneswar, 751003, Odisha, India
[d] Department of Pharmaceutical Chemistry, Sri Jayadev College of Pharmaceutical Sciences, Bhubaneswar, 752101, Odisha, India
[e] Department of Pharmaceutical Pharmacology, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to Be University), Bhubaneswar, 751003, Odisha, India

ARTICLE INFO

Article history:
Received 17 September 2019
Received in revised form
6 November 2019
Accepted 24 November 2019
Available online 26 November 2019

Keywords:
Antipyrine
Pyrazolone
Schiffbase
Synthesis

ABSTRACT

Antipyrine (1,2-dihydro-1,5-dimethyl-2-phenylpyrazole-3-one) in a structural frame consists of a five membered lactam pyrazolone heterocyclic ring as a pharmacophore moiety. It is evident from literature that the molecules having nitrogen bearing heterocyclic nuclei clearly exhibit several biological actions. Commercially available pyrazolone derivatives as drugs, analgin and metamizol are an established chemical class of analgesics. Recent trends of synthetic routes and several biological actions of antipyrine analogues are considered in this review. Indeed, the synthesized derivatives possess antipyrine moiety having versatile biological properties, antimicrobial, antitubercular, anthelmintic, antioxidant, analgesic, anti-inflammatory, cytotoxic and antiviral activities.

Contents

* Corresponding author.
** Corresponding author. School of Pharmacy, ARKA Jain University, Gamharia, Seraikela, Kharsawan, Jameshedpur, Jharkand, 832108, India.
E-mail addresses: jjyotisahoo@rediffmail.com (J. Sahoo), sairampaidesetty@gmail.com (S.K. Paidesetty).

https://doi.org/10.1016/j.ejmech.2019.111911
0223-5234/

1. Introduction

Pyrazole, a five-membered unsaturated heterocyclic ring, contains nitrogen 1, 2 positions (Fig. 1). It occupies as an important place in medicinal chemistry and its derivatives are known having a wide range of biological actions namely, antimicrobial [1–3], anticancer [4], anti-inflammatory [5,6], antidepressant [7], anticonvulsant [8] and antipyretic [9] mainly due to substituted at C-4 position of the pyrazole ring; some derivatives have inhibitory actions on selected enzymes [10]. On computational analysis, it was discernible that pyrazole-based ligands have displayed with complex and coordinating behaviour with transitional metals [11]. The objective of the work is to focus on published synthetic and biological aspects of antipyrine analogues and to compile a review report regarding conjugation and alteration of their structure which could be benefited for new drug development. Outline of synthetic routes, schematic drug design and related information on biological activities of antipyrine derivatives are discussed.

Antipyrine (1,2-dihydro–1,5-dimethyl-2-phenylpyrazole-3-one) with the pyrazole heterocyclic ring with ketone in structure is known as a non-steriodal anti-inflammatory drug (NSAID) (Fig. 2).

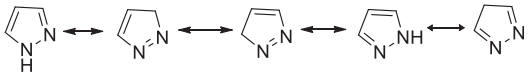


Fig. 1. Tautomeric structures of pyrazole.

In 1887, the molecule first investigated experimentally by Ludwig Knorr [12]. Furthermore, the above cited pharmacological properties of antipyrine were ascertained by several works [13–18].

Apart from use for relieving pain, inflammation and fever, it is used for evaluation of therapeutic activities of other drugs, through inhibition of metabolizing enzymes in liver [19]. These heterocyclic compounds are used as precursors for synthesis of novel hybrid molecules with critical biological activities [20,21]. The pyrazole structure of antipyrine in any derivative synthesized with both pyrazole nucleus and antipyrine moiety in structure render one or other potent pharmacological action. Blithely, this rationalisation helped researchers to explore a range of antipyrine derivatives in last decades for use of the synthesized molecules with a range of biological activities [22–24]. Some molecules remain effective as biomarkers in the experimental studies of metabolism of drugs in the body [25]. Moreover, demethylated hydroxylated metabolites of antipyrine were reported to have a positive correlation with plasma fibronectin level in monitoring patients with hepatic

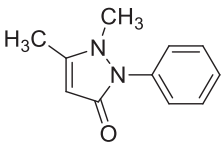


Fig. 2. Chemical structure of Antipyrine.

diseases [26]. Metals coordinated with organic compounds have been found the drastic change in biological action in comparison to their ligands and also the metals [27–29]. The metal complexes of antipyrine have been reported with interesting biological activity [30–32].

1.1. Chemistry in a nutshell

Antipyrine 4 can be synthesized by mixing of phenylhydrazine **1** and ethyl acetoacetate **2** under condesation for an intermediate product **3**, which by further methylation in dimethyl sulphate or methyl iodide in acetonitrile. The resulting product was re-crystallized to produce needle shaped crystals of antipyrine with melting point 156 °C (Scheme 1) [33,34].

2. Synthesis and biological activities of the antipyrine analogues

The broad spectrum biological activities of antipyrine analogues may be classified on basis of literature with the following several actions: 1. antioxidant (free radical scavenging) 2. antimicrobial 3. analgesic 4. anti-inflammatory 5. cytotoxic activity 6. anthelmintic action 7. antitubercular 8. antiviral.

3. Antioxidant activity

The research on antioxidant action has been started since nineteenth century [35]; the generation of free radical within the body system as well as due to environmental pollution causes oxidative stress and leads to various diseases such as, atherosclerosis [36], respiratory disease [37], cancer [38], liver injury [39], CNS disorders [40,41] cardiovascular diseases [42,43]. As against free radicals, a living system has its own immunity, this may not be sufficient to quench the requirements for which a demand for supplementary antioxidants is always there. Synthetic antioxidants in combination with dietary ones can help to prevent the diseases related to oxidative stress [44] Synthetic antioxidants were often observed to be more effective than natural antioxidating compounds [45].

3.1. Synthesis and antioxidant action of 3-heteroaryl/arylazo 4-hydroxy coumarin bearing antipyrinyl ring

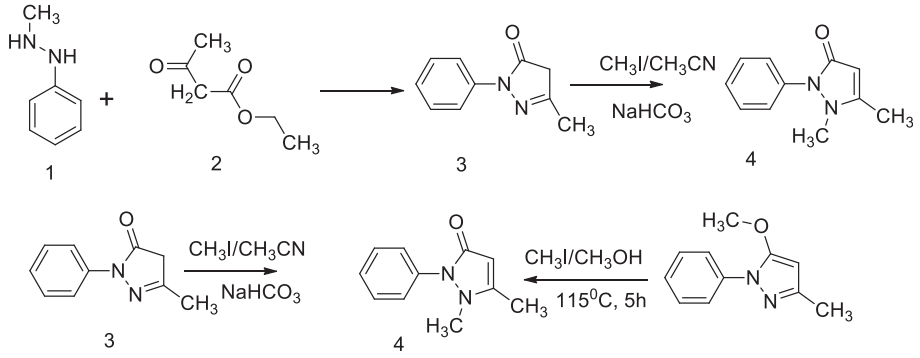
A series of 3-heteroaryl/arylazo-4-hydroxy coumarin (4-HC) 4a-4j analogues was synthesized by azo coupling reaction (Scheme 2) and the analogues were evaluated for *in vitro* radical scavenging activity by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay method. The diazonium salts of primary aromatic amines 2a-2j, coupled with the 4-hydroxy coumarin 3 the desired molecules were obtained. The 2-methoxy phenyl, 4-carboxy phenyl, 3-nitro phenyl, 2-thiazolyl, 2-pyridyl, 1,2,4-triazol-3-yl, 4-antipyrinyl- and 2-benzothiazolyl diazenyl substitution in 4-hydroxy coumarin analogues were subjected for evaluation of their antioxidant activity. The 4-diazenyl antipyrine conjugated 4-hydroxy coumarin molecule had IC_{50} at the lowest concentration 9 ± 0.87 μg/mL, in comparison to other synthesized analogues, whereas the standard butylated hydroxytoluene (BHT) had at IC_{50} 32 ± 0.4 μg/mL The inhibition of free radical in compound, which may be comes good results due to attachment of 4-diazenyl antipyrine at C-3 position of 4-hydroxy coumarin(4-HC) in compound 4d. In other hands, the hybrid molecule possesses both enolic −OH system and heterocyclic nitrogen bearing pyrazolone nucleus may be responsible for exhibiting a satisfactory radical scavenging activity [46].

3.2. Synthesis and antioxidant action of 5-heteroaryl/arylazo 8-hydroxy quinoline bearing antipyrinyl ring

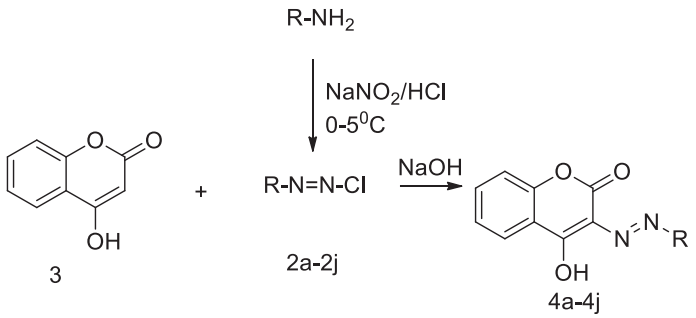
In another study (Scheme 3), a series of eight numbers of 5-heteroaryl/arylazo-8-hydroxyquinoline (8-HQ) analogues 4a-4h had been synthesized by coupling of diazotised primary aromatic amines 2a-2h with 8-hydroxyquinoline 3 under mild conditions. The obtained products were re-crystallized from ethanol. The radical scavenging activity of the synthesized 8-quinol derivatives were evaluated by *in-vitro* DPPH assay method, out of which synthesized molecules, the compounds 4-((8-hydroxyquinolin-5-yl) diazenyl)-*N*-(5-methylisoxazol-3-yl) benzene sulphonamide **(4c)**, 5-((2-methoxyphenyl) diazenyl) quinolin-8-ol **(4d)**, 4-((8-hydroxyquinolin-5-yl) diazenyl)-1, 5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **(4h)** and standard butylated hydroxytoluene (BHT) were reported with IC_{50} value at levels of 52 ± 1.13, 72 ± 1.4, 36 ± 0.56, 46 ± 0.98 and 31 ± 0.07 μg/mL, respectively. However, it was found that the antipyrinyl diazenyl analogue was reported with potential free radical scavenging effect among other molecules, and slightly chemical modification of the molecule may give better antioxidant activity in comparison to the standard. Structural hybridization of 4-aminoantipyrine with 8-hydroxy quinoline through azocoupling at its C-5 position may indicate the presence of phenolic −OH group as well as, nitrogen bearing heterocyclic quinoline nucleus in the concerned structure for exhibiting the reported excellent antioxidant activity [47].

3.3. Synthesis and antioxidant action of 4-(4-aryl. subst.benzylideneamino)-2, 3-dimethyl-1-phenyl-1,2-dihydro pyrazol-5-one

A series of antipyrine schiff base analogues 3a-3g were

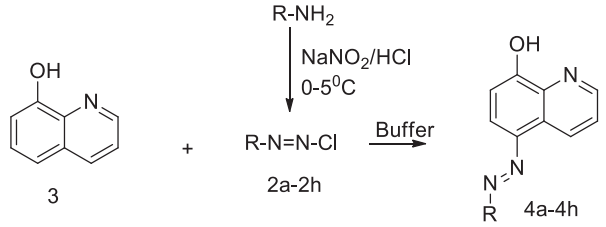


Scheme 1. Synthesis of antipyrine.



R= 2-Thiazolyl-(4a); 2-pyridyl-(4b); 1,2,4-triazol-3-yl-(4c); 4-antipyrinyl-(4d); N-(5-methyl isoxazolyl benzosulfamido)-(4f);2-benzothiazolyl-(4e); 4-sulfanic-(4f); 2-methoxy phenyl-(4g); 4-carboxy phenyl-(4h); 3-nitro phenyl-(4i) ;2-methyl phenyl-(4j)

Scheme 2. Synthesis of 3-heteroaryl/arylazo 4-hydroxy coumarin bearing antipyrinyl ring.



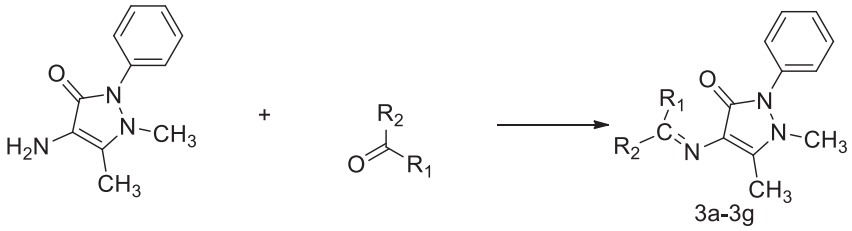
R= Benzenesulfonamido- (4a); 2-sulfanic-(4b); N-(5-methyl isoxazolyl benzosulfamido)- (4c); 2-methoxy phenyl- (4d); 4-bromo 3-methyl phenyl- (4e) ; 2-methyl phenyl- (4f); 4-phenyl thiazol-2-yl (4g); 4-antipyrinyl-(4h)

Scheme 3. Synthesis of 5-heteroaryl/arylazo 8-hydroxy quinoline bearing antipyrinyl ring.

synthesized by the Grinding method (Scheme-4). Using a mortar and pestle, solid carbonyls were ground to fine particles and further 4-aminoantipyrine was poured and ground up to 30 min at room temperature without any solvent. The free radical scavenging activity of the resulting molecules was monitored by DPPH assay method. Indeed, incorporation of electron releasing groups to benzylidene ring of the 4-aminoantipyrine schiff base analogues (*Z*)-4-(4-hydroxy-3-methoxybenzylideneamino)-2, 3-dimethyl-1-phenyl-1,2-dihydro pyrazol-5-one (3b) and (*Z*)-4-(4-dimethylamino) benzylideneamino)-2,3-dimethyl-1-phenyl-1-2-dihydro pyrazol-5-one (3g) were responsible for the antioxidant action. The recorded IC_{50} values showed by the said compounds are 1.13 and 2.4 μg/mL, respectively. Conjugation of 4-aminoantipyrine with several carbonyl compounds to produce schiff base analogues could produce compounds with potent radical scavenging action [48].

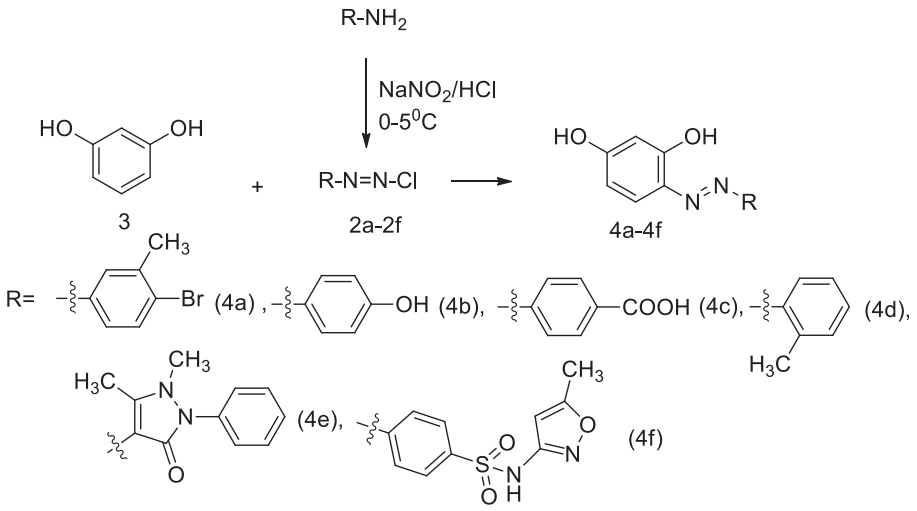
3.4. Synthesis and antioxidant action of heteroaryl/arylazo benzene 1,3-diol bearing antipyrinyl moiety

A series of benzene-1,3-diol analogues, 4a-4f were synthesized by coupling of benzene 1,3-diol 3 with diazotised aryl and heteroaryl amines 2a-2f in the mild condition (Scheme 5). The free radical scavenging activity of synthesized novel benzene-1,3-diol analogues were monitored by DPPH method. All these molecules had satisfactory levels of scavenging activity when compared to BHT. The analogues 4-((4-hydroxyphenyl) diazenyl) benzene-1, 3-diol (**4b)** and 4-((2, 4-dihydroxyphenyl) diazenyl)-1, 5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**4e**) had IC_{50} values at levels of 38 ± 1.4 and 48 ± 0.89 μg/mL, respectively; whereas the IC_{50} value of the standard BHT was 32 ± 0.80 μg/mL. The 4-aminoantipyrine conjugated with benzene-1,3-diol analogue (**4e**) had significant IC_{50} value 79.97% at 70 μg/mL, in comparison to standard BHT. The study revealed that the presence of pyrazolone nucleus and the increased numbers of hydroxyl group of resorcinol associated with



R_2=H, R_1=phenyl 3a-,4-hydroxy-3-methoxy phenyl-3b, 2-nitrophenyl-3c, 2-hydoxyphenyl-3d, 3-nitrophenyl-3e, 4-nitrophenyl-3f, 4-dimethylamino phenyl-3g

Scheme 4. Synthesis of 4-(4-aryl. subst.benzylideneamino)-2, 3-dimethyl-1-phenyl-1,2-dihydro pyrazol-5-one.



Scheme 5. Synthesis of Heteroaryl/arylazo benzene 1,3-diol bearing antiprinyl ring.

negative inductive effect of these groups in compound 4-((2, 4-dihydroxyphenyl) diazenyl)-1, 5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**4e)** that may be responsible for enhancing the antioxidant activity [49].

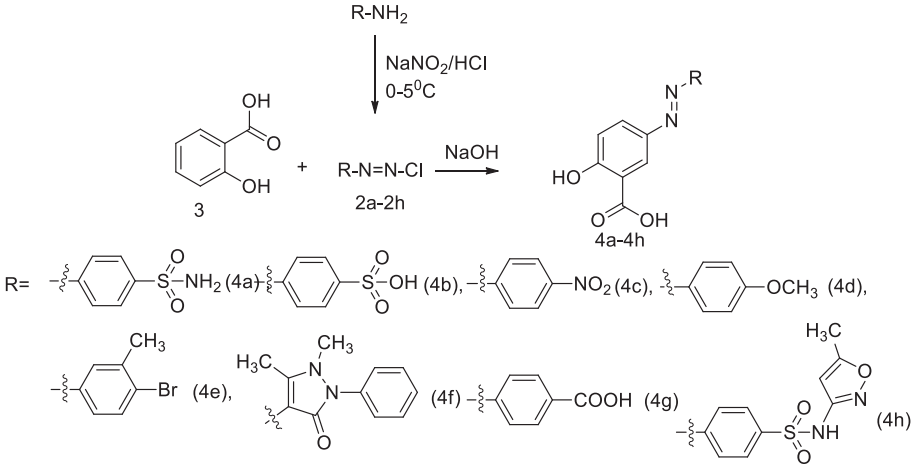
3.5. Synthesis and antioxidant action of 5-heteroaryl/arylazo salicylic acid bearing antipyrinyl ring

A series of azo salicylic acid, 4a-4h congeners were synthesized by coupling of salicylic acid 3 with diazotised primary aryl and heteroaryl amines **2a-2h** in mild condition. The antioxidant activity of selected molecules out of the newly synthesized azo salicylic acid congeners (Scheme 6) was monitored by *in-vitro* assay method. The radical scavenging activity of the synthesized analogues was compared with standard BHT. All these compounds had potential scavenging activity, whereas the 4-amino antipyrine conjugated salicylic acid *via*, azocoupled reaction the analogue 5-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)azo)-2-hydroxybenzoic acid (**4f**) had significant IC_{50} value ($p < 0.05$) at 60 μg/mL. However, the IC_{50} value showed by the antipyrinyl bearing salicylic acid analogue (**4f**) was 37.3 ± 0.02 μg/mL, among other salicylic acid analogues. The structural presence of phenolic −OH and attachment of pyrazolone moiety in the derived compound (**4f**) may attribute for showing potential antioxidant activity [50].

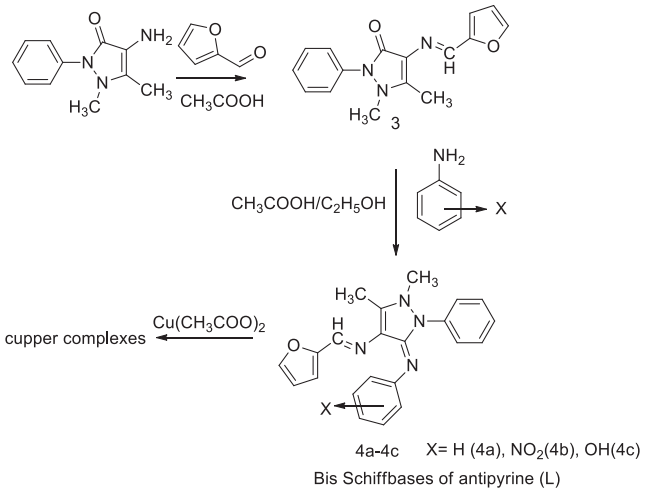
3.6. Synthesis and antioxidant action of 4-aminoantipyrin-furfuraldehyde schiff base bearing antiprinyl ring and transitional complexes

Moreover, 4-aminoantipyrine-furfuraldehyde schiff base 3 was synthesized by condensation of 4-amino antipyrine with ethanolic solution of furan 2-carboxaldehyde in glacial acetic acid medium. These intermediate product 3 was further treated with aniline derivatives to produce ligand (L) bearing 3,4-bis azomethine compounds 4a-4c, which act as a source of electron donor and these liberated products give moderate yield that are capable to complexing with copper(II) acetate in the presence of ethanol to produce complexes, 3,4-bis azomethine antipyinyl of copper (CuL^2) (Scheme 7).

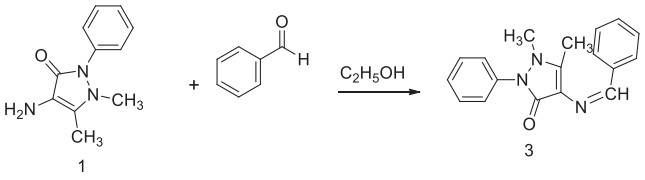
The antioxidant action of the synthesized complexes was monitored with superoxide dismutase (SOD) reducing power assay method, using DMSO as the source of superoxide radical (O_2^-) and nitrobluetetrazolium (NBT) as O_2^- scavenger. All complexes had comparatively higher SOD activity among which $CuL^2(OAc)_2$ had the activity with IC_{50} value 98 mol/dm. From the reducing power



Scheme 6. Synthesis of 5-heteroaryl/arylazo salicylic acid bearing antipyrinyl moiety.



Scheme 7. Synthesis of 4-aminoantipyrin-furfuraldehyde schiff base bearing antipyrinyl moiety and transitional complexes.



Scheme 8. Synthesis of 4-aminoantipyrin-benzaldehyde schiff base bearing antipyrinyl.

assay, it could be suggested that the complex $CuL^2(OAc)_2$ executed less reducing power with a greater antioxidant ability [51].

3.7. Synthesis and antioxidant action of 4-aminoantipyrin-benzaldehyde schiff base bearing antipyrinyl ring

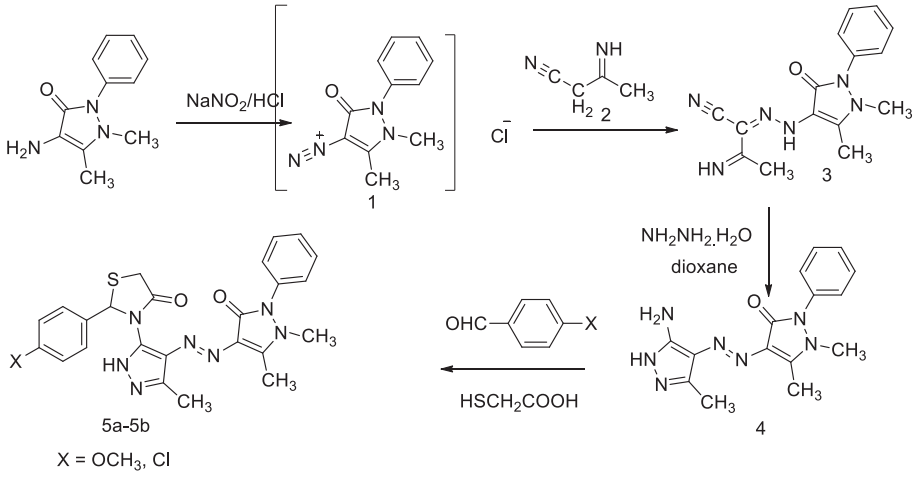
The (*E*)-4-[benzylideneamino]-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **3** was synthesized, by adding anhydrous ethanolic solution of 4-amino antipyrine **1** to benzaldehyde and the mixture was refluxed. The obtained precipitate product was re-crystallized from ethanol (Scheme 8). The free radical scavenging activity of the ligand was monitored by DPPH assay method and compare with the standard ascorbic acid. The antioxidant activity of the ligand reported with IC_{50} at the level, 31.26 μM. From the Mulliken charges (e) for the ligand, it was suggested that the carbons of two methyl groups, C11 (−0.584) and −C7−(-0.394) bear a high electron density and may produce proton free radicals to neutralize the DPPH. Additionally, the nitrogen bearing pyrazolone heterocyclic moiety also had exhibited free radical scavenging activity [52].

3.8. Synthesis and antioxidant action of antipyrinyl clubed with thiazolidinone and pyrazole

A series of novel schiff base antipyrine derivatives was synthesized (Scheme 9). A mixture of concentrated solution of HCl and water were added to 4-aminoantipyrine and further diazotised with sodium nitrite and obtained product **1**, which further was added to ethanolic solution of sodium acetate and 3-iminobutanenitrile 2; the mixture was stirred and *N*'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-iminopropane-hydrazonoyl cyanide 3 was obtained. To the dioxanic solution of intermediate product **3**, was added in hydrazine hydrate solution and refluxed to obtain 4-((3-amino-5-methyl-1*H*-pyrazol-4-yl) diazenyl)-1, 5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one 4. The target compound 4-((3-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-5-methyl-1*H*-pyrazol-4-yl)diazenyl)-2,3-dimethyl-1-phenyl-1,2-dihydropyrazol-5-one **5a** and 4-((3-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-5-methyl-1*H*-pyrazol-4-yl) diazenyl)-2,3-dimethyl-1-phenyl-1,2-dihydropyrazol-5-one **5b** were further obtained by refluxing the dimethyl formamide (DMF) made solution of an intermediate **4** with 4-methoxybenzaldehyde, 4-chlorobenzaldehyde and 2-mercaptoacetic acid. The activity of these compounds was investigated from the bleaching action of 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) derived radical cations. Ascorbic acid was used as the standard. **Started**. The compounds, commonly the pyrazolone moiety connected with 2-iminopropane hydrazonoyl cyanide in **3**, 3-amino-5-methyl pyrazole **4** and substiuted aryl thiazolidinone-pyrazole moiety **5a-5b** had good to moderate antioxidant activities [53].

4. Antimicrobial activity

Multidrug resistance is a commonplace event in clinics during the treatment with the existing antibiotics; consequently, serious health problems creep into in community and hospitals. Indeed, antimicrobials remain effective against pathogenic microorganisms



Scheme 9. Synthesis of antipyrinyl clubed with thiazolidinone and pyrazole.

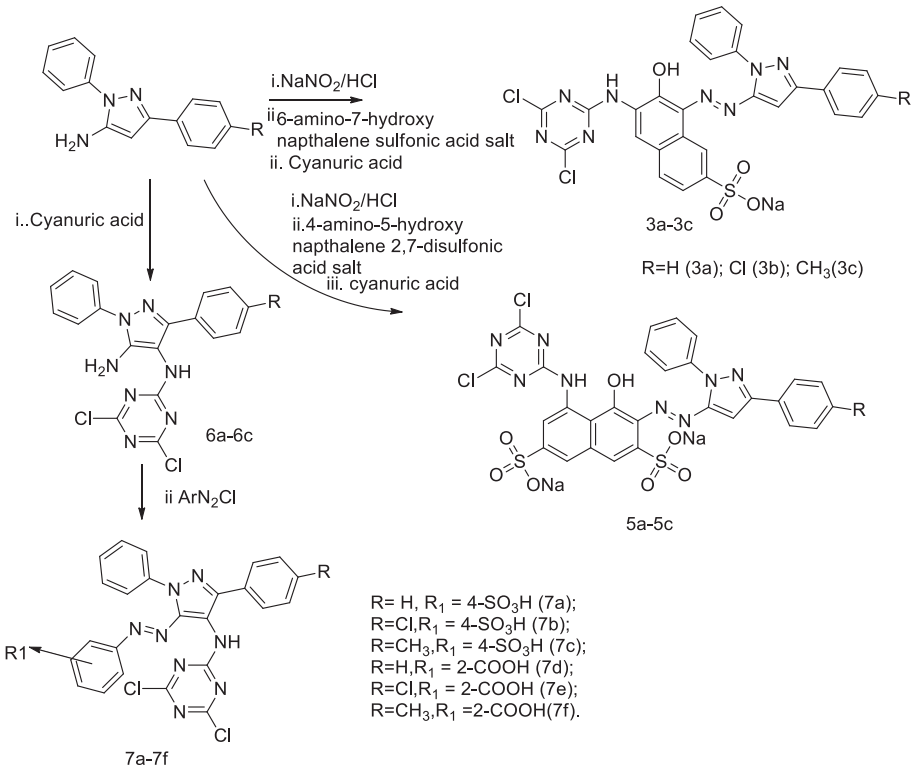
for a limited period till pathogens evolve drug resistant forms [54]. Thus, additions of new antimicrobials or chemical modifications of obsolete ones are the need of the hour in clinics against the plethora of drug resistant pathogens, bacteria and fungi.

4.1. Synthesis and antimicrobial action of 4-aminoantipyrin-furfuraldehyde schiff base and their transitional complexes

A series of copper complexes was synthesized from schiff base (3,4-bis azomethine) compunds, 4a-4c derived from furfurlylidene-4-aminoantipyrine and aniline, p-nitroaniline and p-hydroxyaniline, respectively (Scheme 7). The *in vitro* lethal concentration50 (LC_{50}) value of these compounds were determined against bacterial pathogens, *S. aureus*, *E.coli*, *K. pneumoniae*, *P. vulgaris* and *P. aeruginosa*, and pathogenic fungi, *A. niger*, *R. stolonifer*, *A. flavus*, *Rhizoctonia bataicola* and *C. albicans,* within a concentration range of 25–200 μg/mL with some standard antibiotic/antifungal agent. It was observed that all the ligands and with their complexes bearing antipyrinyl moiety had the MIC at a level of 16–72 μg/mL for bacterial strains and 6–80 μg/mL for fungal strains used; which may be due to in the structure the incorporation of pyrazolone in all the synthesized molecules [51].

4.2. Synthesis and antimicrobial activity of pyrazolyl bearing naphyl sulfonates derivative

Sodium 6-(4,6-dichloro-1,3,5-triazin-2-ylamino)-8-((1-phenyl-3-substituted-1*H*-pyrazol-4-yl)diazenyl)-7-hydroxynaphthalene-2-sulfonates, **3a**-3**c** and sodium 5-(4,6-dichloro-1,3,5-triazin-2-ylamino)-3-((1-phenyl-3-substituted-1*H* pyrazol-5-yl)diazenyl)-4-hydroxynaphthalene-2,7-disulfonates, **5a**-5**c** were synthesized by dissolving sodium nitrite in sulphuric acid at a suitable condition (Scheme 10). Furthermore, 5-amino-3-substituted-1-phenyl pyrazoles, **2a**-2**c** were dissolved in hot glacial acetic acid on an ice bath and thereafter the mixture was transferred to nitrosylsulphuric acid with portions was added and stirred to obtain the diazonium salt. The resulting diazonium salt was added to the alkaline solution of 6-(4,6-dichloro-1,3,5-triazin-2-ylamino)-7-hydroxynaphthalene-2-sulfonic acid and 4-(4,6-dichloro-1,3,5-triazin-2-ylamino)-5-hydroxynaphthalene-2,7-disulfonic acid. The product was precipitated by the addition of solution of disodium hydrogen phosphate and potassium dihydrogen phosphate with a sufficient addition of sodium chloride. The obtained precipitates were re-crystallized from ethanol for getting the desire final products, **3a**-3**c** and **5a**-5**c**. The compounds, 4-((5-(4, 6-dichloro-1,3,5-triazin-2-ylamino)-1-phenyl-3-substituted-1*H*-pyrazol-4-yl) diazenyl)benzensulfonic acids (**7a**-7**c**) and 2-((5-(4,6-dichloro-1,3,5-triazin-2-ylamino)-1-phenyl-3-substituted-1*H*-pyrazol-4-yl) diazenyl)benzoic acids (**7d**-7**f**) were synthesized by stirring the mixture of cynuric chloride and 3-(subst.phenyl)-*N*-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1-phenyl-1H-pyrazole-4,5-diamine **6a-6c;** which further were reacted with diazotised anthranilic salts in mild condition. The resulting obtained **7a-7f** precipitated, and those were washed with diethyl ether and were re-crystallized from ethanol. The *in vitro* antimicrobial activity of synthesized compounds were investigated against *S. aureus*, *Serratia marcescens*, *Shigella dysenteriae*, *Enterobacter cloacae, E. coli* and *C. albicans* by the agar cup method. Compounds, 4-((5-(4,6-dichloro-1,3,5-triazin-2-ylamino)-1,3-diphenyl-1H-pyrazol-4-yl)diazenyl)benzensulfonic acid (**7a**), 4-((3-(4-chlorophenyl)-5-(4,6-dichloro-1,3,5-triazin-2-ylamino)-1-phenyl-1*H*-pyrazol-4-yl)diazenyl) benzenesulfonic acid (**7b**), 4-((5-(4,6-Dichloro-1,3,5-triazin-2-ylamino)-1-phenyl-3-ptolyl-1*H*-pyrazol-4-yl)diazenyl) benzenesulfonic acid (**7c**), 2-((5-(4,6-dichloro-1,3,5-triazin-2-ylamino)-1,3-diphenyl-1*H*-pyrazol-4-yl)diazenyl)benzoic acid (**7d**) and 2-((5-(4,6-dichloro-1,3,5-triazin-2-ylamino)-1-phenyl-3-ptolyl-1*H*-pyrazol-4-yl)- diazenyl)benzoic acid (**7f**) had strong antimicrobial activity against all the pathogenic bacterial strains included in the test; and



Scheme 10. Synthesis of pyrazolyl bearing naphyl sulfonates derivative.

the compounds **7a**-7**c** exhibited antifungal activity against *C. albicans,* which may be due to the azo group in the pyrazole moiety and sulphonic group [55].

4.3. Synthesis and antimicrobial activity of trisubstuted of pyrazole derivatives

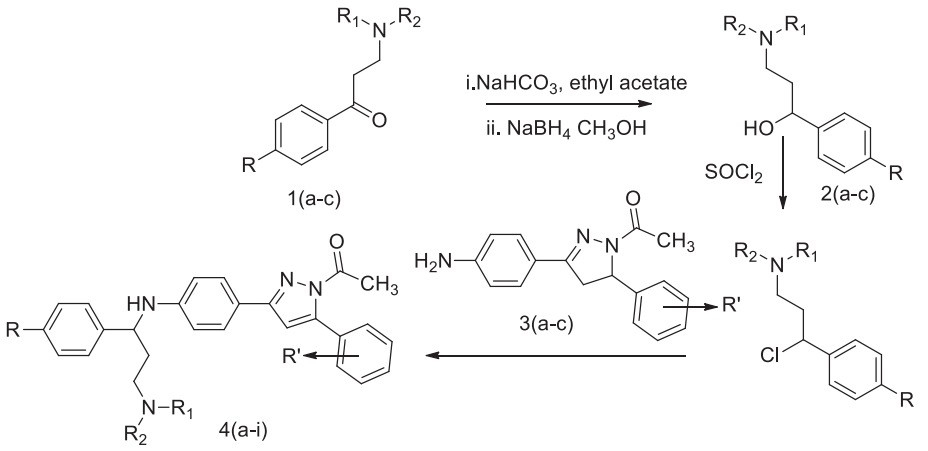
Some pyrazole derivatives were synthesized by Tiwari et al. [56], as shown (Scheme 11). Compounds, 1-(3-(4-(1-(4-substitutedphenyl)-3-morpholino propylaminophenyl)-5-(3/4-substituted phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone **4a**-4**c** and 1-(3-(4-(3-(benzyl (methyl)amino)-1-(4-substituted phenyl) propylamino)phenyl)-5-(3/4-substituted phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone **4d-4e** were synthesized by adding thionyl chloride in benzene solution to 3-*N*- substituted amino-1-phenyl propanol **2a**-**c**, as indicated. The excess amount of thionyl chloride was removed by azeotropic distillation. The chloride derivatives of **2a**-**c** were mixed with 1–3(4-aminophenyl)-5-(3/4-substituted phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone **3a**-**c** in ethanol and were refluxed. The obtained mixture was concentrated under reduced pressure and finally re-crystallized from ethanol. The antimicrobial activity of novel synthesized pyrazole derivatives **4a**-**e** was monitored against several bacterial strains, *S. aureus, Bacillus subtilis, P. aeruginosa, E. coli, Klebisiella pneumoniae,* fungal strains *C. albicans, A. fumigatus, P. chrysogenum* and the helminth *Trycophyton rubrum* by disc diffusion method using standard drugs, ciprofloxacin, ampicillin, gentamicin, fluconazole and miconazole. All these pyrazole analogues had significant antimicrobial activities. The compounds, 1-(3-(4-(3-(Benzyl(methyl) amino)-1-(4-chloro phenyl)propylamino)phenyl)-5-(3-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4d)** and 1-(3-(4-(3-(benzyl(methyl)amino)-1-(4-bromophenyl)propylamino) phenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone **4i** had significant antibacterial activity against *S. aureus, P. aeruginosa* and *E. coli;* which could be attributed to the presence of electron withdrawing groups. The compounds **4d**, **4i** and 1-(3-(4-(3-(benzyl(methyl)amino)-1-(4-bromophenyl)propylamino) phenyl)-5-(3-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone **4g** had promising antifungal activity against *A. fumigates* and *P. chrysogenum* [56].

4.4. Synthesis and antimicrobial action of schiff base of antipyrin derivatives

A compound of 4-amino antipyrine analogues, (*E*)-4-(2-methoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **3** was prepared by mixing 4-amino-1,5-dimethyl-2-phenyl pyrazol-3-one **1** with anhydrous ethanolic solution of 2-methoxy benzaldehyde **2**. The obtained precipitates were purified from ethanol (Scheme 12). The antimicrobial activities of the obtained products were investigated by disc diffusion method against *B. cereus* and *S. typhimurium, Listeria monocytogenes, K. pneumoniae* and *E. coli.* The compound (*E*)-4-(2-Methoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **3** showed highest activity against *B. cereus* (MIC = 12.5 μg/mL) and *S. typhimurium* (MIC = 50 μg/mL). However, it had significant antibacterial activity against Gram negative bacterial strains [57].

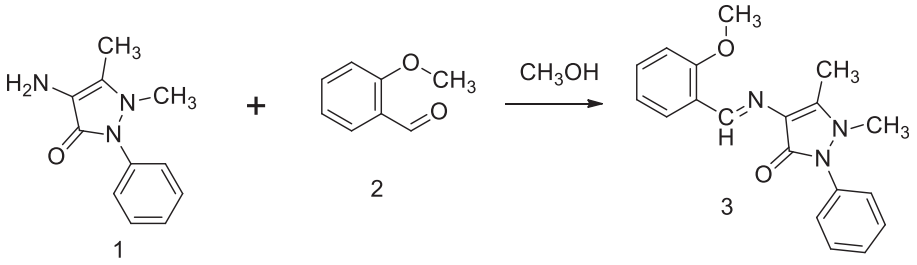
4.5. Synthesis and antibacterial action of metal complexes of antipyrin-hydroxy nathoic acid

The diazonium salt of 4-aminoantipyrin 2 was coupled with 3-hydroxy-2-napthoic acid **2** and to produce 4-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)diazenyl)-3-hydroxy-2-naphthoic acid **3**. Furthermore, the azo ligand and respective metals in the mixture of acetone and water in an equiproportion were mixed together and refluxed individually to obtain the respective metal complexes, **4a-4e** (Scheme 13). The antipyrine derived azo ligand **3** and the corresponding metal complexes were monitored for antimicrobial activity against *B. subtilis, S. aureus, E. coli*, *P aeruginosa*, fungi, *C. albicans, Nigrospora* sp. and *A. niger* by the disc diffusion method. The results of the antimicrobial activity of the synthesized ligand and their complexes revealed that the Cu^{2+} complex had significant antimicrobial activity against all the used strains, may be due to the structural presence of antipyrine nucleus [58] (see Scheme 14).

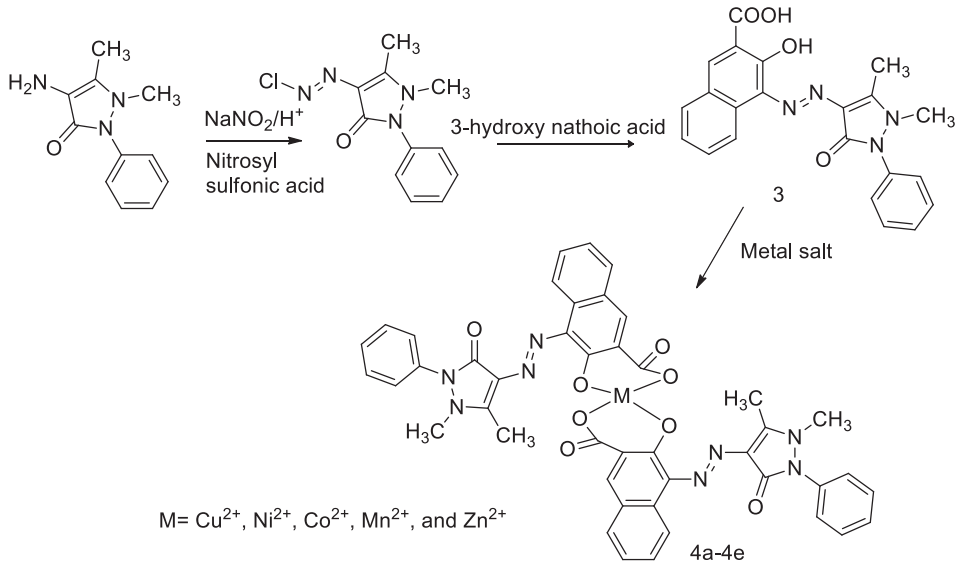


R= Cl, R_1 and R_2= morpholinyl (1a);R= Cl, R_1=CH_3 R_2= benzyl (1b);R= Br, R_1=CH_3 R_2= benzyl (1c);R'=3-nitro (3a),4-chloro(3b),4-methoxy(3c); R=Cl, R_1=R_2=morpholinyl,R'=3-nitro(4a);R=Cl, R_1=R_2=morpholinyl,R'=4-chloro(4b);R=Cl, R_1=R_2=morpholinyl,R'=4-methoxy(4c);R=Cl, R_1=CH_3 R_2=benzyl,R'=3-nitro(4d);R=Cl, R_1=methyl, R_2=benzyl,R'=4-chloro(4e),R=Cl, R_1=methyl, R_2=benzyl,R'=methoxy(4f);R=Br, R_1=methyl, R_2=benzyl,R'=3-nitro(4g);R=Br, R_1=methyl, R_2=benzyl,R'=4-chloro(4h);R=Cl, R_1=methyl, R_2=benzyl,R'=4-methoxy(4i)

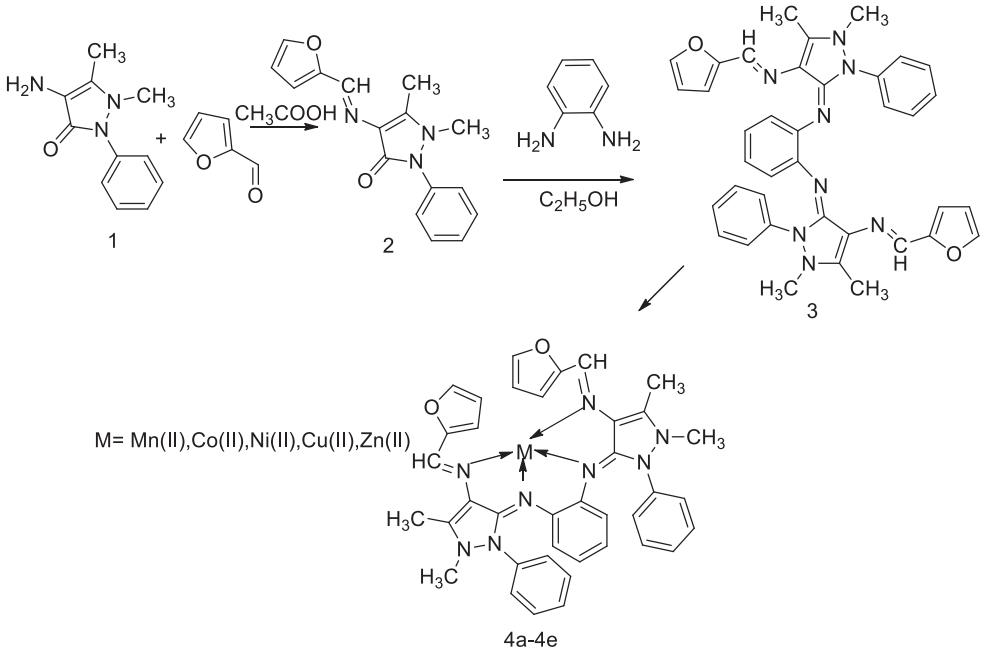
Scheme 11. Synthesis of triasubstuted of pyrazole derivatives.



Scheme 12. Synthesis of schiff base of antipyrine derivative.



Scheme 13. Synthesis of metal complexes of antipyrin-hydroxy nathoic acid.



Scheme 14. Synthesis of metal complexes of antipyrin-furfuryaldehyde and OPD.

4.6. Synthesis and antibacterial actions of metal complexes of antipyrin-schiffbase

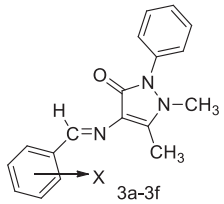
A series of antipyrine was synthesized and subjected for evaluation of antibacterial activities against *E. coli*, *Proteus mirabilis, S. aureus* and *B. cereus* by agar well diffusion method in comparison to ceftriaxone as the standard (Scheme 4). All the synthesized 4-amino antipyrine derived schiff bases (3a-3f) had potential antibacterial activities against *S. aureus*, *P. mirabilis*, *B. cereus* and *E. coli.* The bacterial susceptibility to (*Z*)-4-(2-hydroxybenzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5-one **(3c)**, (*Z*)-4-(3-nitrobenzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5-one **(3d)** (Fig. 3) may be due to inclusion of benzylidene phenyl ring and nitro substituent with 4-aminoantipyrine nucleus [48].

4.7. Synthesis and antibacterial action of metal complexes of antipyrin-furfuryaldehyde and o-phenylenediamine

A new series of transition metal complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) was synthesized from the schiff base ligand, derived from 4-aminoantipyrine. The obtained precipitates were recrystallized from ethanol. In this reaction an intermediate schiffbase **2** was further added to the ethanolic solution of *o*-phenylenediamine (OPD) and the mixture was refluxed and the products were recrystallized from ethanol. The obtained product contained OPD-antipyrinyl-schiff base ligand **3** refluxed with ethanolic solution of respective metal salts to obtain the corresponding metal complexes **4a-4e** (Scheme14). The antimicrobial activity of the obtained molecules was investigated against *S. aureus*, *E. coli, B. subtilis* and *P. aeruginosa*. The metal complexes exhibited stronger antibacterial activity than the ligand that may be due to the coordination of metals to an antipyrine derived schiff base analogue [59].

4.8. Synthesis and antibacterial action of metal complexes of antipyrin-thiophene 2,5-dicarbaldehyde

A new schiff base ligand (L) 4,4'-((1E,1′E)-(thiophene-2,5-diylbis(methanylylidene))bis(azanylylidene))bis(1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one) **3** was synthesized by adding ethanolic solution of thiophene 2,5-dicarboxaldehyde **2** to hot ethanolic solution of 4-aminoantipyrine **1**. The resulting mixture was refluxed and obtained precipitates were washed with cold ethanol to get an intermediate. Furthermore, the hot ethanolic solution of the desired ligand mixing with ethanolic solution of the corresponding metal salts (chloride, sulphate and nitrate of copper and nickel) and the mixtures were refluxed to obtain the respective metal complexes, **4a-4f** (Scheme 15). The MIC of the synthesized metals and their ligands were screened for antifungal properties against *Phoma sorghina, A. niger* and *F. oxysporum* by serial dilution assay procedure; bavistin was used as the standard antifungal. For the synthesized products, the $[Cu(L)SO_4]$: $CuC_{28}H_{26}N_6S_2O_6$ had significant antifungal activity at a quite low concentration against all the fungal strains included in the experiment may be due to the binding of metal copper with antipyrine derived schiff base [60].



X=4-OH,3-OCH_3 3a; 2-NO_2 3b; 2-OH 3c; 3-$NO_2$3d; 4-NO_2 3e; 4-$N(CH_3)_2$ 3f

Fig. 3. *N*-benzylideno substituted Antipyrine.

4.9. Synthesis and antibacterial action antipyrin-benzaldehyde derivatives

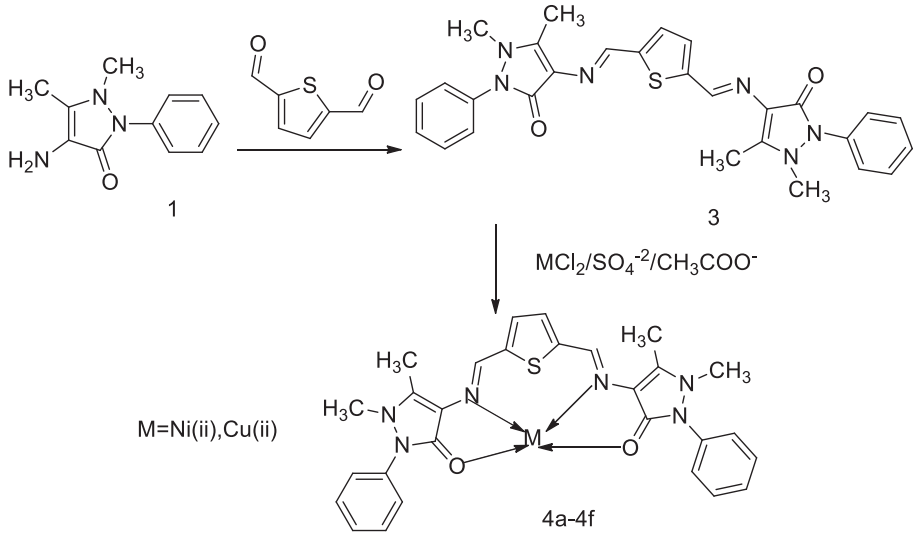
In the present study, the schiff base analogues of 4-aminoantipyrine (**3a**-**3m**) were synthesized as in Scheme-16. A mixture of ethanolic solution of 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one **1** and substituted benzaldehyde **2a-2m** was refluxed and the obtained precipitates were re-crystallized from ethanol. The obtained schiff base analogues of 4-aminoantipyrine were subjected to evaluate their *in vitro* antibacterial activities against *S. aureus*, *Cronobacter sakazakii*, *Citrobacter freundii*, *Salmonella enterica*, *K. pneumoniae* and *E. coli* by the disc diffusion method. Nalidixic acid was used as positive control. The results revealed that among the synthesized compounds, the compound (*E*)-4-(4-methoxy-3-methylbenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**3m**) was the most potential compound remains effective against *K. pneumoniae, S. aureus, C. sakazakii* and *E. coli* [61].

4.10. Synthesis and antibacterial action of metal complexes of antipyrin -1-diazenyl napthol

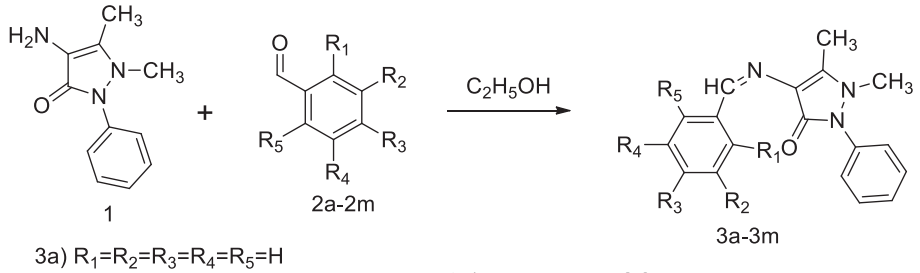
Synthesis of antipyrinyl azo analogue 4-((2-hydroxynaphthalen-1-yl) diazenyl)-1, 5-dimethyl-2-phenyl-1H-pyrazol-3(2*H*)-one (**3**) was done (Sahoo et al. 2016) (Scheme 17). Furthermore, the mixing of corresponding metal chlorides with ethanol and water (1:1) was prepared and was added to the solution of antipyrine azoanalogue **3** in equal proportion and refluxed. The obtained complexes precipitates were re-crystallized from diethyl ether. The antimicrobial activity of the ligand 3 and the synthesized metal complexes **3a-3c** were investigated against *S. flexneri, B. circulans, S. mitis* and *S. aureus* by agar well diffusion method with Ampicillin was used as standard. The conjugated of antipyrine azo analogue, cobalt complex of 4-((2-hydroxynaphthalen-1-yl) diazenyl)-1, 5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **4a** exhibited a significant antimicrobial activity [62].

4.11. Synthesis and antibacterial action of antipyrine derivative

A series of (*E*)-3-(subst.phenyldiazenyl)subst.benzaldehyde analogues (**4a**-**4f**), 1,5-dimethyl-4-((*E*)-(subst.-3-((*Z*)-subst.phenyldiazenyl)benzylidene)amino)-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**6a**-**6f**) was synthesized. These azo anil analogues were prepared by the mixing 4-aminophenazone and anhydrous sodium sulphate to the solution of azo benzaldehyde compounds with dichloromethane (DCM) under microwave oven at 360 W for different time intervals. The obtained azo anils were re-crystallized from ethanol (Scheme 18). The novel azo anils were screened by bacterial sensitivity filter paper disc method against *Mesorhizobium* sp, *Bacillus* sp. and *Pseudomonas* sp. by using CRYEMA, nutrient agar and King's B media, respectively, while *Ascochyta blight* was tested by using potato dextrose agar (PDA) media and *Sacchromyces cerevisiae* by filter paper disc method using glucose yeast extract media to evaluate their antimicrobial activity. Streptomycin was used as the standard drug. Due to antipyrinyl subsituted in compound (**6c**) 4-((*E*)-4-methoxy-3-((*E*)-(4-nitrophenyl)diazenyl) benzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2H)-one had antibacterial activity against *Bacillus* species [63].

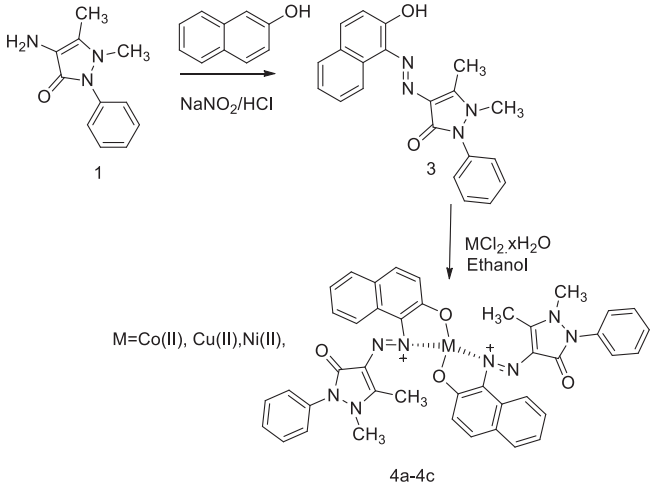


Scheme 15. Synthesis of metal complexes of antipyrin-thiophene 2,5-dicarbaldehyde.



3a) $R_1=R_2=R_3=R_4=R_5=H$
3b) $R_1=R_2=H,R_3=Cl,R_4=R_5=H$
3c) $R_1=R_2=H,R_3=N(C_2H_5)_2,R_4=R_5=H$
3d) $R_1=R_2=H,R_3=OH,R_4=R_5=H$
3e) $R_1=R_2=H,R_3=OCH_3,R_4=R_5=H$
3f) $R_1=H,R_2=R_3=OH,R_4=R_5=H$
3g) $R_1=H,R_2=OCH_3R_3=OH,R_4=R_5=H$
3h) $R_1=H,R_2=R_3=OCH_3,R_4=R_5=H$
3i) $R_1=H,R_2=R_3=OH,R_4=R_5=H$
3j) $R_1=OCH_3,R_2=H,R_3=OCH_3,R_4=R_5=H$
3k) $R_1=OH,R_2=H,R_3=OH,R_4=H,R_5=OH$
3l) $R_1=H,R_2=OCH_3,R_3=OH,R_4=OCH_3,R_5=H$
3m) $R_1=H,R_2=CH_3,R_3=OCH_3,R_4=R_5=H$

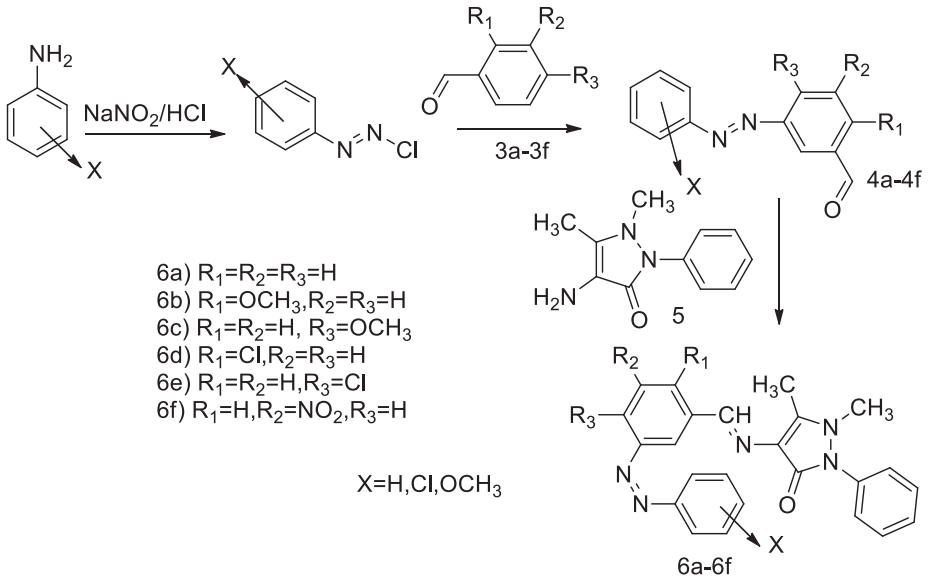
Scheme 16. Synthesis of antipyrin-benzaldehyde derivatives.



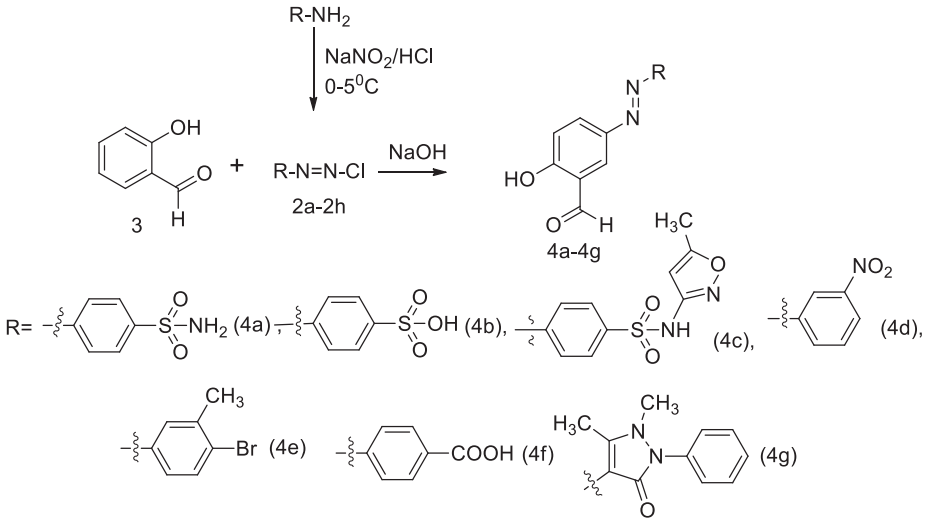
Scheme 17. Synthesis of metal complexes of antipyrin -1-diazenyl napthol.

4.12. Synthesis and antibacterial action of azosalicylaldehyde bearing antipyrinyl moiety

A series of azosalicylaldehyde analogues (**4a**-**4g**) were synthesized in Scheme 19 by Sahoo et al. on 2016. All the synthesized analogues were prepared by coupling of salicylaldehyde with various diazonium salts at mild condition. The azo salicylaldehyde analogues were screened to investigate their antimicrobial activity against *Escherichia coli*, *Salmonella enterica ser. typhi*, *Salmonella enterica typhimurium*, *Salmonella enterica paratyphi*, *Shigella flexneri*, *P. aeruginosa*, *Vibrio cholera*, *K. pneumoniae*, *Bacillus circulans*, *Streptococcus mitis*, *S. aureus*, *B. subtilis* by agar well diffusion method; ampicillin was used as the reference antibiotic. The compound 5-((1, 5-dimethyl-3-oxo-2-phenyl-2,3- dihydro-1H-pyrazol-4-yl)diazenyl)-2- hydroxybenzaldehyde (**4g**) remained significantly effective against *Salmonella enterica typhimurium* however it also showed good antibacterial activity against *P. aeruginosa*, *V. cholera*, *Bacillus circulans* and *S. aureus* may be due to the attachment of pyrazolone at C-5 position of salicylaldehyde [64].



Scheme 18. Synthesis of antipyrin derivatives.



Scheme 19. Synthesis of azosalicylaldehyde bearing antipyrinyl moiety.

4.13. Synthesis and antibacterial action of metal complexes of 4-aminoantipyrin-furfuraldehyde schiff base

A series of copper complexes synthesized from Schiff base (L) derived from furfurlylidene-4-aminoantipyrine and aniline, p-nitroaniline and 4-aminophenol, respectively (Scheme 7). The *in vitro* minimum inhibition concentration of the investigated compounds were determined against *S. aureus*, *E. coli*, *K. pneumoniae*, *Proteus vulgaris*, *P. aeruginosa*, *A. niger*, *Rhizopus stolonifer*, *A. flavus*, *Rhizoctonia bataicola* and *C. albicans* by serial dilution method within a concentration range of 25–200 μg/mL and compared to standard antibiotics. It was found that all the ligands with their complexes bearing antipyrinyl moiety had the MIC at a concentration level of 16–72 μg/mL for bacterial strains and 6–80 μg/mL for fungal strains [51].

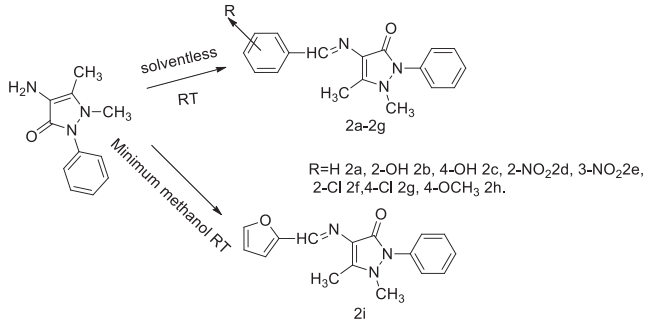
4.14. Synthesis and antibacterial action of antipyrinylazo subst. dimedone

The attempt of coupling of diazonium salt of 4-aminoantipyrine with dimedone to give 2,3-dimethyl-4-[2-(5,5-dimethyl-2,6-dioxocyclohex-2-ylidene)-hydrazino]-5-oxo-1-phenylpyrazoline **3** by azo coupling reaction was pursued. Further, the hot solution of 2,3-dimethyl-4-[2-(5,5-dimethyl-2,6-dioxocyclohex-2-ylidend)-hydrazino]-5-oxo-1-phenylpyrazoline **3** was treated with methanolic solution of phenylhydrazine hydrochloride in presence of acetic acid, sodium acetate and the mixture was refluxed to get 4-{2-[2,6-bis(phenylhydrazono)-5,5-dimethylcyclohex-2-ylidene] hydrazino}-2,3-dimethyl-5-oxo-1-phenylpyrazoline **4.** The ethanolic solution of 2,3-dimethyl-4-[2-(5,5-dimethyl-2,6-dioxocyclohex-2-ylidend)-hydrazino]-5-oxo-1-phenylpyrazoline treated with mixture of hydroxylamine hydrochloride and sodium acetate was refluxed to obtain 4-{2-[2,6-bis(hydroxyimino)-5,5-dimethylcyclohex-2-ylidene]hydrazino}-2,3-dimethyl-5-oxo-1-phenylpyrazoline **5**. The mixture of 2,3-dimethyl-4-[2-(5,5-dimethyl-2,6-dioxocyclohex-2-ylidend)-hydrazino]-5-oxo-1-phenylpyrazoline **4** and hydroxylamine hydrochloride in acetic anhydride was heated after re-crystallization the final product 4-acetoxyimino-6,6-dimethyl-2-(2,3-dimethyl-1-phenylpyrazolin-5-on-4-yl)-4,5,6,7-tetrahydrobenzo-[*d*] [1–3]triazole **7** was obtained

by heating the mixture of product **6** and acetic anhydride (Scheme 20). The antimicrobial activity of antipyrine derivatives was evaluated against *S. aureus*, *E. coli* and *C. albicans* by agar diffusion method. Ampicillin and clotrimazole was used as standard. The compound 2,3-Dimethyl-4-[2-(5,5-dimethyl-2,6-dioxocyclohex-2-ylidene)hydrazino]-5-oxo-1-phenylpyrazoline **3** showed better antifungal activity against *C. albicans* than the standard control, whereas the compound 2,3-dimethyl-4-[2-(5,5-dimethyl-2,6-dioxocyclohex-2-ylidene)-hydrazino]-5-oxo-1-phenylpyrazoline **4**, 4-{2-[2,6-Bis(hydroxyimino)-5,5-dimethylcyclohex-2-ylidene] hydrazino}-2,3-dimethyl-5-oxo-1-phenylpyrazoline **5** and 4-acetoxyimino-6,6-dimethyl-2-(2,3-dimethyl-1-phenylpyrazolin-5-on-4-yl)-4,5,6,7-tetrahydrobenzo-[*d*] [1–3]triazole **7** had moderate antibacterial activity against *S. aureus* [16].

4.15. Synthesis and antibacterial action of antipyrin schiff base by without any solvent

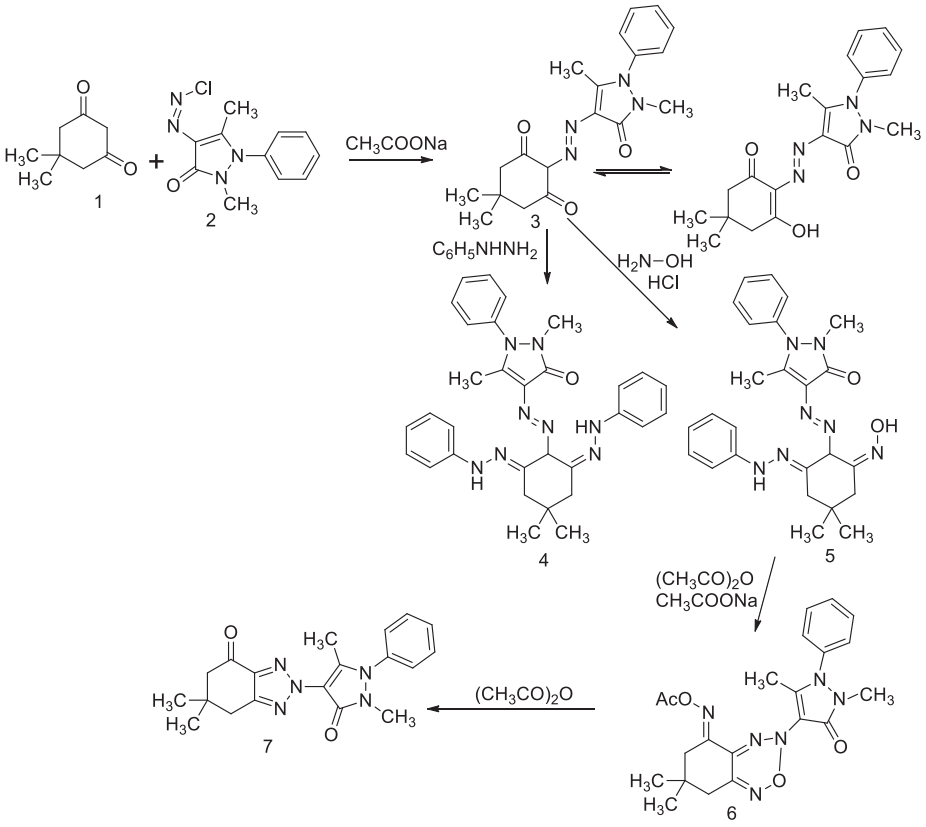
Some antipyrine derivatives (**2a**, **2b**, **2f**, **2h** and **2i**) were synthesized by a solvent free procedure by adding furfuraldehyde with 4-aminoantipyrine. Similarly, additional azomethines (**2c**, **2d**, **2e** and **2g**) were synthesized in the same way with a minimum addition of ethanol (Scheme 21). Agar cup method was evaluated for antimicrobial activity against *S. aureus, P. vulgaris, P. aeruginosa* and *E. coli*. Ampicillin and Streptomycin were used as standard drugs. The compounds 4-((benzylidineamino-2-yl) methyl-eneamino)-1,2-dihydro-2,3-dimethyl-1-phenylpyrazol-5-one **2a**, 4-((4-hydroxybenzylidineamino-2-yl)methyleneamino)-1,2-dihydro-2,3-dimethyl-1-phenylpyrazol-5-one **2c** and (*E*)-4-(furan-2-ylmethyleneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **2i** had a broad spectrum antibacterial activity may be due to the hybridisation of 4-aminoantipyrine [65].



Scheme 21. Synthesis of antipyrine Schiff base by without any solvent.

4.16. Synthesis and antibacterial action of metal complexes of bis-schiff base of antipyrin-terepthaldehyde

The mixture of methanolic solution of 4-aminoantipyrine and 2-hydroxybenzaldehyde was refluxed to synthesize the schiff base 1-phenyl-2,3-dimethyl-4-(*N*-salicylidene)-3-pyrazolin-5-one **3a**. Similarly, a mixture of methanolic solution of 4-aminoantipyrine and terephthalic aldehyde was refluxed to produce schiff base bis(1-phenyl-2,3-dimethyl-3-pyrazolin-5-one-4-imino) terephthalic aldehyde **3b**. The methanolic solution of both the schiff base ligands were added with aqueous solution copper chloride and copper sulphate, respectively and the lot was refluxed to obtain the desired metal complexes (Scheme 22). The synthesized ligands and complexes were subjected to evaluate antimicrobial activity against *E. coli*, *K. pneumoniae*, *Acinetobacter boumanii*, *P. aeruginosa*, *S. aureus,* and fungi *C. albicans* and *Candida tropicalis* by agar-cup diffusion method; gentamycin was used as the reference



Scheme 20. Synthesis of antipyrinylazo subst. Dimedone.

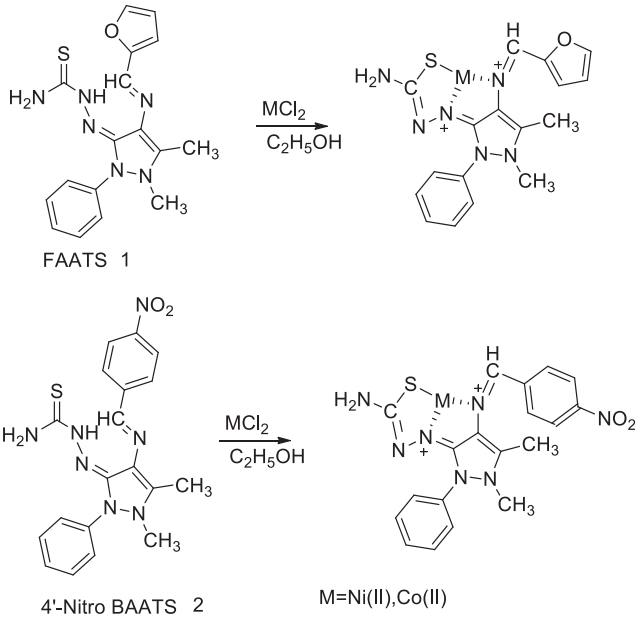
standard. All the synthesized molecules in this series remain effective against *P. aeruginosa,* whereas the schiff base 1-phenyl-2,3-dimethyl-4-(*N*-salicylidene)-3-pyrazolin-5-one **3a** and its metal complex **4a** had potential antibacterial activity against *E. coli* and *A. boumanii* and the schiff base bis(1-phenyl-2,3-dimethyl-3-pyrazolin-5-one-4-imino) terephthalic aldehyde **3b** and its metal complex **4b** remains effective against *E. coli*, *P. aeruginosa* and *S. aureus* [66].

4.17. Synthesis and antibacterial action of metal complexes of schiff base of antipyrin-thiosemicarbazone

This work comprises the synthesis of two schiff base ligands 4-[*N*-(furan-2′-aldimine)amino]antipyrine thiosemicarbazone **1** and 4-[*N*-(4′-nitrobenzalidene) amino]antipyrine thiosemicarbazone **2** and their metal complexes. The ethanolic solution of 4-[*N*-(furan-2′-aldimine)amino]antipyrine thiosemicarbazone and 4-[*N*-(4′-nitrobenzalidene) amino]antipyrine thiosemicarbazone individually was mixed with cobalt and nickel chloride and thiocyanate in ethanol and each mixture was refluxed to obtain corresponding cobalt/nickel complexes of 4[*N*-(furan-2′-aldimine)amino]antipyrine thiosemicarbazone FAATS and 4-[*N*-(4′-nitrobenzalidene) amino]antipyrine thiosemicarbazone 4′-nitro BAATS, respectively (Scheme 23). The synthesized ligands and complexes were screened against *S. enterica* ser.*typhi, E. coli, B. subtilis, S. aureus, A. niger* and *C. albicans* by agar well diffusion method. Ampicillin and Tetracycline were used as reference standard drugs. The Co(II) complexes of both the thiosemicarbazone bearing 4-aminoantipyrine derivatives had moderate antibacterial activities against *E.coli* and *S. typhi*. However, the complexes of 4-[*N*-(furan-2′-aldimine)amino]antipyrine thiosemicarbazone exhibited significant antifungal activity [67].

4.18. Synthesis and antibacterial action of metal complexes of schiff base of antipyrin-pyrrole carboxaldehyde

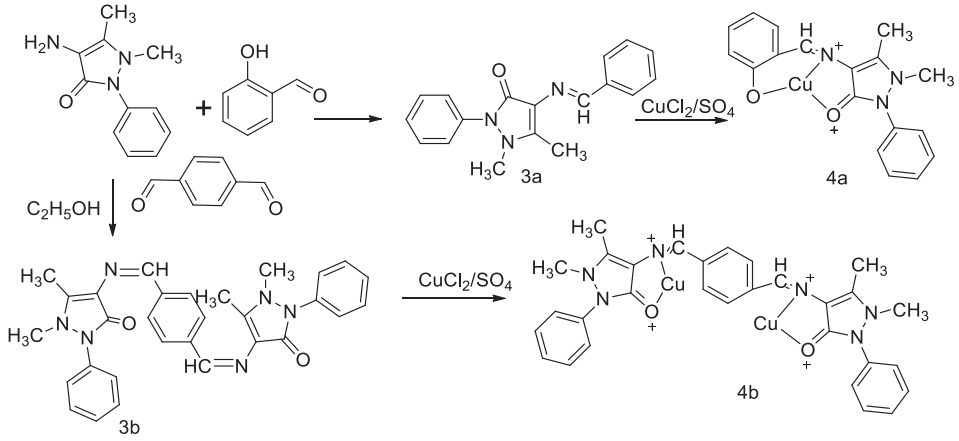
A series of copper complexes was synthesized by mixing of the ethanolic solution of pyrrole-2-carboxalde-hyde and 4-aminoantipyrine, refluxed. Finally, schiff base derivatives of the obtained (*Z*)-4-(((1*H*-pyrrol-2-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2H)-one **3** (HPAP) were re-crystallized from ethanol. Furthermore, the ethanolic solution of schiff base ligand **3** and the corresponding copper (II) salts were refluxed; the obtained precipitates were washed with a mixture of ethanol and diethyl ether to obtain the respective copper complexes (Scheme 24). The resulting ligand and complexes were tested with microbial strains, *B. subtilis, Sarci-na lutea, S. aureus, E. coli, K. pneumoniae, P. aeruginosa, S. typhi, S. marcescens, Shigella sonnie, P. mirabilis, Aspergillus arus, P. chrysogenum* and *C. albicans* to ascertain antimicrobial activity by disc diffusion method. A blank DMSO solution was the negative control. The complexes $[(PAP)Cu]_2Cl_2$, $[(PAP)Cu]_2Br_2$ and $[(HPAP)_2Cu](NO_3)_2$ had potential antimicrobial activity [68].



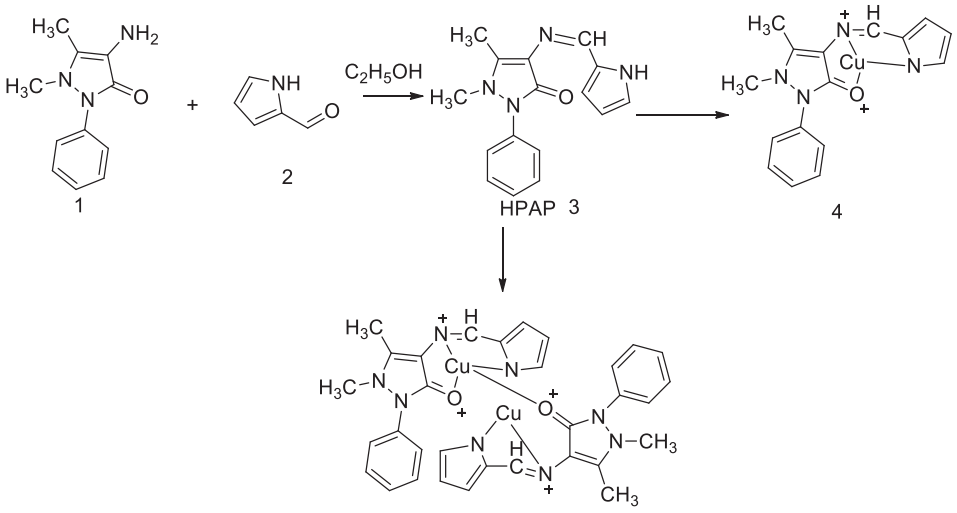
Scheme 23. Synthesis of metal complexes of Schiff base of antipyrin-thiosemicarbazone.

4.19. Synthesis and antibacterial action of scafolds [1,2,4]triazolo [5,1-c][1,2,4]triazine linked to antiprinyl with carboxamide

A series of antipyrine based molecules was synthesized by S. M. Riyadh et al. (2013) through incorporating antipyrin-4-yl or antipyrin-4-yl carboxamide moiety *via*. the readily accessible 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl) acetamide **1**. An intermediate product 1 was mixing with an equimolar concentration of different derivatives of diazonium salts 2a-2f to produce 3a-3f. Among these products the compound 2-cyano-



Scheme 22. Synthesis metal complexes of bis Schiff base of antipyrin-terepthaldehyde.



Scheme 24. Synthesis of metal complexes of Schiff base of antipyrin-pyrrole carboxaldehyde.

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-[2-(4-aminosulfonyl) phenylhydrazono]acetamide 3d was mixed with anhydrous sodium acetate and hydroxylamine hydrochloride and refluxed to obtain 5-amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*pyrazol-4-yl)-2-(4-sulfamoylphenyl)-2*H*-[1,2,3]triazole-4-carboxamide 4d. The cold solution of compound 1 was coupled with diazotised 5-amino- 1*H* -[1,2,4] triazole in pyridine solution to produce 4-amino-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)pyrazolo[5,1-c][1,2,4]triazine-3-carboxamide 5 (Scheme 25). An *in vitro* antimicrobial activity of the synthesized molecules were assessed by agar well diffusion method against *S. aureus*, *B. subtilis*, *P. aeruginosa*, *E. coli*, *A. fumigatus*, *Geotrichum candidum*, *C. albicans* and *Syncephalastrum racemosum*. The standard antimicrobials, itraconazole, clotrimazole, penicillin G and streptomycin were used to reference controls. The results revealed that the compound *N*-[4-[2-[1-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-2-oxoethylidene]hydrazinyl] biphenyl-4-yl]-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-2-oxoacetohydrazonoyl cyanide **3g** and compound 5 had significant antimicrobial activity against *G. candidum, C. albicans* and *S. aureus*, *B. subtilis* in comparison to standard drugs clotrimazole and streptomycin, respectively. This novelty might be due to the presence of antipyrin-4-yl or antipyrin-4-yl-carboxamide moiety in the synthesized molecules [69].

5. Analgesic activity

Analgesics are the substances used for inhibition of pain sensation by increasing the threshold to painful stimuli [70]. Most of the analgesic drugs include NSAIDs, salicylates derivatives and opoids are non-selective cycloxgenase inhibitors.

The analgesic activity of a series of newly synthesized azo analogues bearing 8-hydroxy quinoline (8HQ) nucleus was screened (Scheme 3) in acetic acid induced writhing model, using Diclofenac sodium as the standard drug. Albino mice of appropriate weight were used for the investigation. The pain percentile of inhibition (analgesic activity) showed by the different compounds suggested that though all the compounds showed significant writhing responses, the pain percentile inhibition showed by the compound of 4-((8-hydroxyquinolin-5-yl) diazenyl)-1, 5-dimethyl-2-phenyl-1H-pyrazol-3(2*H*)-one (**4g**) was 32.62% at a concentration of 50 mg/kg body weight may be due to linked of 4-antipyrinylazo at C-5 position of 8-hydroxy quinoline [47].

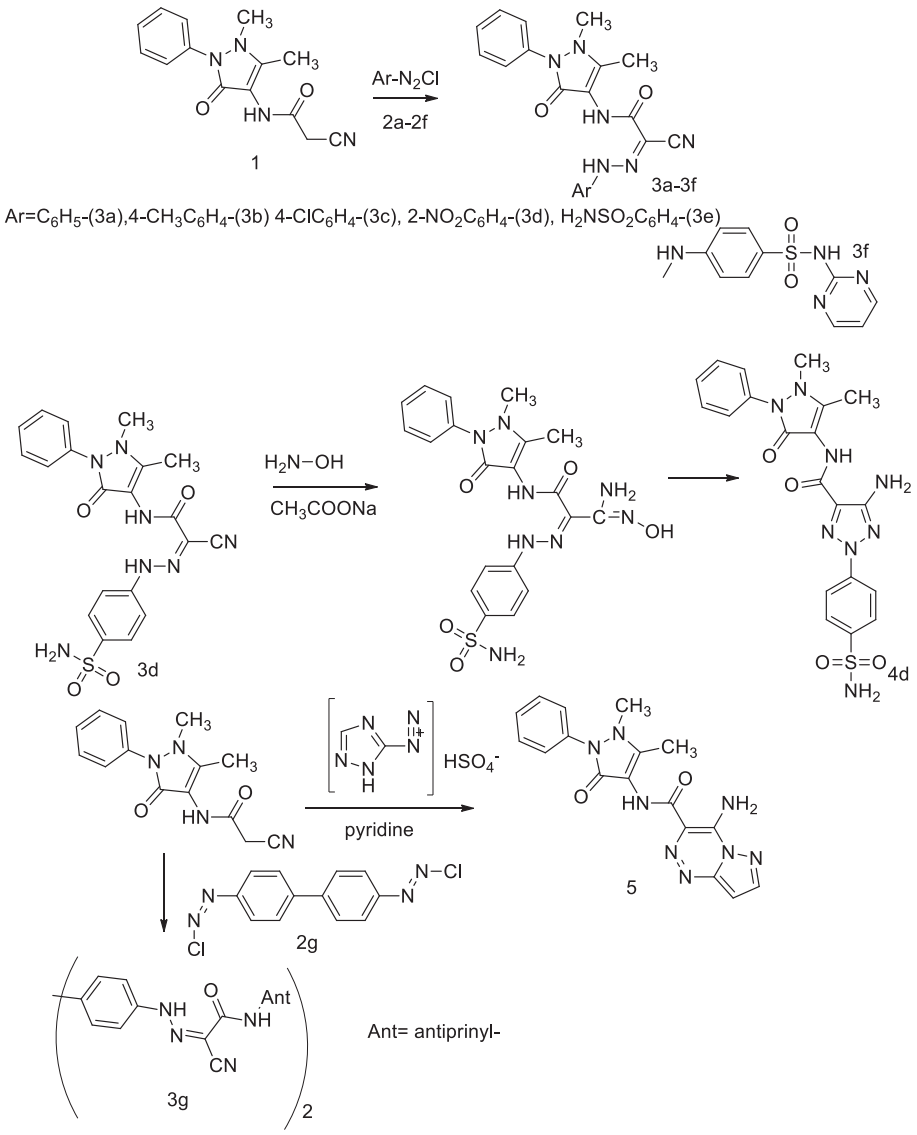
Moreover, a series of azo analogues conjugated salicylic acid were synthesized by azo coupling reaction (Scheme 6) and the analogues were investigated for analgesic activity by acetic acid induced writhing model, using albino mice in appropriate weight. Acetyl salicylic acid (ASA) was used as the standard drug. Among the included compounds, the 4-bromo-3-methyl phenylazo (**4e**) and 4-carboxy phenylazo (**4g**) substituted 5-azo salicylic acid congeners had significant analgesic activity, whereas the pyrazolylazo salicylic acid congener 5-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)azo)-2- hydroxybenzoic acid (**4f**) was less significant analgesic activity as 4-antipyrinylazo moiety [50].

6. Anti-inflammatory activity

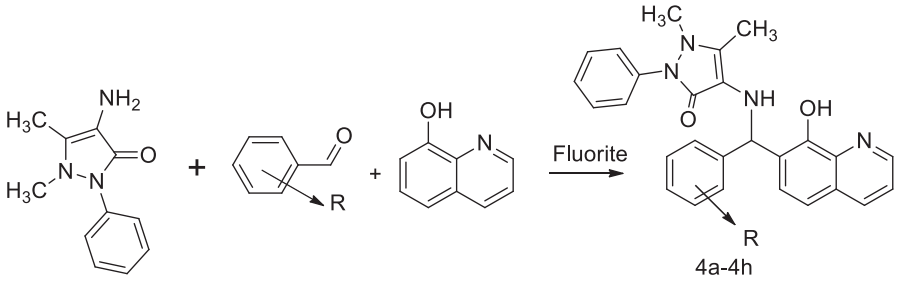
Anti-inflammatory agents are used for the treatment of acute and chronic inflammations to relieve pain and fever. Several tissue factors involved in inflammatory reactions are due to releasing of histamine, bradykinin, prostaglandin and thromboxane [70]. These drugs are acts by inhibitions inflammatory mediators in the body.

6.1. Synthesis and anti-inflammatory action of derivatives of chiralamino bearing antipyrin moiety

In the series of eight 4-aminoantipyrine derivatives (**4a**-**4h**) were synthesized by mixing the ethanolic mixture of 4-aminoantipyrine **1**, substituted aromatic aldehyde **2a-2h** and 8-hydroxyquinoline **3** (8-HQ) in presence of fluorite (Betti reaction). The reaction mixture was transferred into crushed ice. Consequently, the precipitates were re-crystallized from ethanol to obtain the pure 4-aminoantipyrine derivatives (Scheme 26). *In vivo* anti-inflammatory activity of the synthesized antipyrinyl analogues was evaluated using Wister albino rats by carrageenin induced acute paw oedema model. Diclofenac was used as the standard drug. The paw volume was measured using plethysmometer at an interval of 0, 1, 2, 3 and 4 h of administration of carrageenin injection. *In vivo* anti-inflammatory results revealed that, the compounds 4-[(4-methoxyphenyl) (8-hydroxyquinolinyl) methylamino]-1,5-dimethyl-2-phenylpyrazol-3-one (**4c**),4-[(4-(dimethylamino)phenyl)(8-hydroxyquinolinyl)methylamino]-1,5-dimethyl-2-phenylpyrazol-3-one (**4d**), 4-[(2-hydroxyphenyl) (8-hydroxyquinolinyl)methylamino]-1,5-dimethyl-2-phenylpyrazol-3-one(**4e**) and 4-[(2−chlorophenyl) (8-hydroxyquinolinyl)



Scheme 25. Synthesis of scafolds [1,2,4]triazolo[5,1-c][1,2,4]triazine linked to antiprinyl with carboxamide.



Scheme 26. Synthesis of derivatives of chiralamino bearing antipyrin moiety.

methylamino]-1,5-dimethyl-2-phenylpyrazol-3-one (**4h**) had significant anti-inflammatory activity due to several substitutions in the structure of 8-hydroxyquinolinyl)methylamino)-1,5-dimethyl-2-phenylpyrazol-3-one. Similarly, antipyrinyl derivatives exhibited anti-inflammatory activity in-comparison to the standard diclofenac [71].

6.2. Synthesis and anti-inflammatory action of N- sulfoamido antipyrine and N-succinamido antipyrine

A series of substituted antipyrinyl succcinamides, 3a-3c were synthesized by aminolysis of β-carbomethoxypropionamide 1 with ethanolic solution of morphine/amino alcohols, under the alkali

solution in ethanol; the compound II was prepared from compound I. Furthermore, XII was synthesized by the interaction of p-acetaminobezene sulfonyl chloride with 4-aminoantipyrine in the presence of acetonitrile. The obtained compound XII under the action of an alkali solution with ethanol was converted to the compound XIII. Finally, by the condensation of compound XIII with succinic anhydride with acetone, the compound XIV was prepared (Scheme 27). Anti-inflammatory activity of the synthesized analogues was studied on white male mongrel rats by adjuvant arthritis model. The compound, N^1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-4-(3-hydroxypropyl)succinamide **IV** had significant anti-inflammatory activity at the oral dose of 500 mg/kg body weight over the period of 17−18 days in comparison to standard drug Butadion [13].

7. Cytotoxic activity

On the basis of reports of WHO survey, cancer will be the first cause of death in the world in future [72]. Therefore, potentially bioactive molecules having cytotoxic activity are required for the treatment of cancer [73,74].

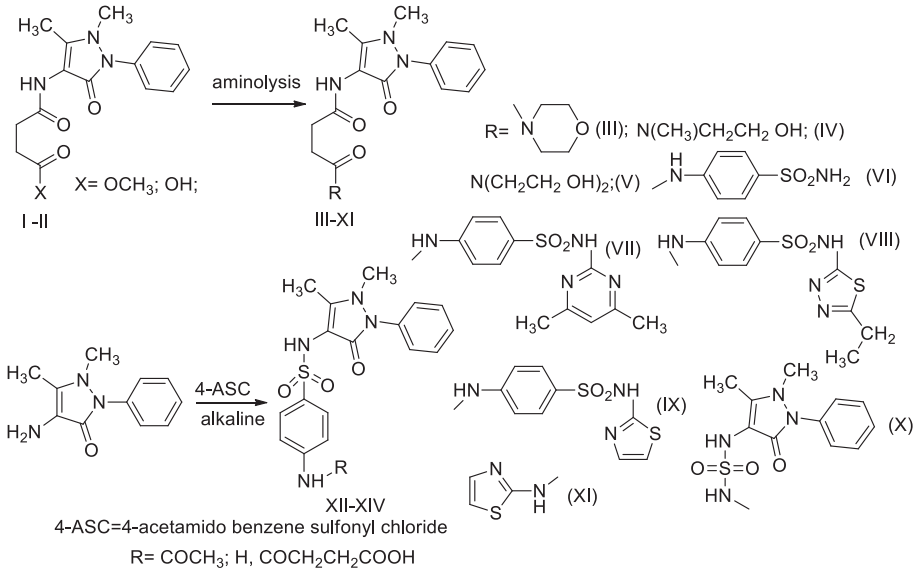
7.1. Synthesis and cytotoxicity action of vanillin-antipyrin schiff bases derivatives

The *in vitro* cytotoxic activity of newly synthesized antipyrine derivatives (Scheme 4) was investigated over nauplii of brine shrimp (*Artemia salina*). Antipyinyl schiff compounds such as, vanillin-antipyrin conjugate (*Z*)-4-(4-hydroxy-3-methoxybenzylideneamino)-2, 3-dimethyl-1-phenyl-1, 2 dihydropyrazol-5-one **3b**, 2-nitro benzaldehyde conjugate with antipyrin (*Z*)-4-(2-nitrobenzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5-one (**3c**), salicylaldehyde conjugate with antipyrin (*Z*)-4-(2-hydroxybenzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5-one **(3d)**, 3-nitro benzaldehyde conjugated with antipyrin (*Z*)-4-(3-nitrobenzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5-one (**3e**), 4-chloro benzaldehyde conjugate with antipyrin (*Z*)-4-(4-chlorobenzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5-one (**3f**), 4-dimethylamino benzaldehyde conjugate with antipyrin (*Z*)-4-(4-dimethylamino)benzylideneamino)-2, 3-dimethyl-1-phenyl-1-2-dihydropyrazol-5 one (**3g**) had significant cytotoxic effect with LC_{50} values below 20 μg/mL. The tested compounds showing good cytotoxic activity may be due to attachment of benzylidene phenyl ring to 4-aminoantipyrine [48].

Similarly, a new series of thirteen schiff base analogues of 4-aminoantipyrine (**3a**-**3m**) were synthesized (Scheme 16). The synthesized compounds were subjected for evaluation *in vivo* cytotoxic activity against nauplii of brine shrimp (*Artemia salina*). Cytotoxicity assay using the napulii of brine shrimp (*Artemia salina*) is an excellent method for screening synthesized molecules to evaluate the potentiality of treating cancer cells in comparison to the standard Gallic acid. The compounds, (*E*)-4-(4-chlorobenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**3b)**, (*E*)-4-(2,4-dihydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**3i)** and (*E*)-4-(3,4-dihydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**3f**) were recorded having brine shrimp toxicity with lC_{50} values 225, 481 and 581 ppm, respectively; whereas, gallic acid had lC_{50} value at 78 ppm. The cytotoxicity results of synthesized 4-aminoantipyrine analogues suggested that the potential cytotoxic activity exhibited by the compounds **3b, 3i** and **3f** could be due to the attachment of 4-chlorobenzylideneamino, 2,4-dihydroxybenzylideneamino and 3,4-dihydroxybenzylideneamino at C4 position of 4-amino antipyrine [61].

7.2. Synthesis and antibacterial action of metal complexes of aldehyde-antipyrin schiff bases derivatives

An equimolar mixture of methonolic solution of aminoantipyrin with salicylaldehyde, 4-hydroxy-5-methoxyisophthalaldehyde, 4,5-dihydroxyisophthalaldehyde and terephthalic aldehyde was refluxed individually to produce 4-(2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1*H*pyrazol-3(2*H*)-one:**L^1**;4,4'-(4-hydroxy-5-methoxy-1,3-phenylenebis(iminomethyl)-bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one): **L^2**; 4,4'-(4,5-dihydroxy-1,3-phenylenebis(iminomethyl)-bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-(2*H*)-one): **L^3** and bis(1-phenyl-2,3-dimethyl-3-pyrazolin-5-one-4-imino) terephthalicaldehyde: **L^4**, respectively. The an aqueous solution, respective metals salts was added with methanolic solution of the corresponding ligands and refluxed to obtain the desired metal complexes (Scheme 28) [73] The synthesized



Scheme 27. Synthesis of *N*- sulfoamido antipyrine and *N*-succinamido antipyrine.

analogues were tested over human promyelocytic leukemia cells HL-60. The cell proliferation assay was performed in 96- well microtitre plates using 3-(4,5-dimethyl-thiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) in comparison to the standard Doxorubicin drug. The complexes $[Cu(L^2)]SO_4C_{31}H_{30}CuN_6O_8S$, $[Cu(L^3)]SO_4C_{30}H_{28}CuN_6O_8S$ and $[VO(L^3)]SO_4C_{30}H_{28}VN_6O_9S$ exhibited significant cytotoxic effect at a level of 10 μM [66,75].

7.3. Synthesis and cytotoxicity action of scafolds [1,2,4]triazolo[5,1-c][1,2,4]triazine linked to antipyrinyl with carboxamide

A series of scaffolds [1,2,4],triazolo[5,1-*c*] [1,2,4] triazine, and pyrazolo[5,1- *c*] [1,2,4]triazine derivatives was synthesized by using antipyrin-4-yl or antipyrin-4-ylcarboxamide moiety *via* the readily accessible 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide **1,** as mentioned (Scheme 25). Out of the synthesized compounds, a selected ones were screened for anti-cancer activity against the colon carcinoma cell line (HCT-116) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay procedure. Vinblastine is used as the standard drug. The compounds 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H* pyrazol-4-yl)-2-[2-(4-aminosulfonyl)phenyl-hydrazono]-acetamide 3d, *N*'-[4-[2-[1-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-2-oxoethylidene]hydrazinyl]biphenyl-4-yl]-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-2-oxoacetohydrazonoyl cyanide 3g and 5-amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H* pyrazol-4-yl)-2-(4-sulfamoylphenyl)-2*H*- [1−3]triazole-4-

Carboxamide 4d had excellent to moderate anticancer activity that might be due to the presence of antipyrinyl moieties [69].

In Scheme 9, aliquots of different concentrations of antipyrine derived analogues were prepared using DMSO. Ehrlich cells from Ascites fluid was isolated and aseptically grown in a suspension culture of RPMI 1660 medium, supplemented with foetal bovine serum. The viability of cell in comparison to the negative control was determined microscopically using haemocytometer and trypan blue stain. The compound *N*'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-iminopropane- hydrazonoyl cyanide 3 and 4-[(3-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-5-methyl-1*H*-pyrazol-4-yl) diazenyl]-2,3-dimethyl-1-phenyl-1,2-dihydropyrazol-5-one **4a** had potential antitumor activity among all the synthesized antpyrinyl analogues.

8. Anthelmintic activity

The infection due to helminths is called helminthiasis. Anthelmintics expel helminths or intestinal parasites by killing or stunning them without causing any harm to the host. The report of WHO expert committee suggested that the annual death due to soil transmitted helminthiasis is more than 135,000 per annum [76].

Using three component Betti reaction procedures, 4-aminoantipyrine derivatives (**4a**-**4h**) were synthesized (Scheme 26). The obtained products were screened for *in vivo* anthelmintic activity against *Pheretima posthuma* (earth worm); Albendazole was the reference drug. The compound 4-((3-nitrophenyl)(8-hydroxyquinolinyl)methylamino)-1,5-dimethyl-2-phenylpyrazol-3-one (**4a**) had the highest significant action for time taken to paralysis and death may be due to conjugation of 3-nitrophenyl with 8-hydroxyquinolinyl)methylamino)-1,5-dimethyl-2-phenylpyrazol-3-one. However, other antipyrine derivatives in the series also exhibited potential anthelmintic activity at a minimum dose 12.5 mg/mL [71].

8.1. Synthesis and anhelminthetic activity of metal complexes of antipyrin-formyl 7- hydroxy coumarin schiff base

A mixture of hot ethanolic solution of 4-aminoantipyrine and 8-formyl-7-hydroxy-4- methylcoumarin was prepared in presence of hydrochloric acid and refluxed. Finally obtained precipitates were re-crystallized from ethanol to obtain 4-((7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)methyleneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2*H*)-one (schiff base I). Following the same procedure, (*E*)-4-((6-hydroxy-2-oxo-2H-chromen-5-yl)methyleneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2*H*)-one (schiff base II) was synthesized using 5-formyl-6-hydroxycoumarin. The alcoholic solution of schiff base ligand (I and II) was added with the corresponding metal chlorides, individually and refluxed. Sodium acetate was added to the obtained individual reaction mixtures, refluxed and the developed complexes (Scheme 29). The anthelmintic activity of the antipyrine derived schiff bases and complexes were investigated against *Pheretima posthuma,* in comparison to Albendazole. Though, the complexes had good anthelmintic activity [77].

9. Antitubercular activity

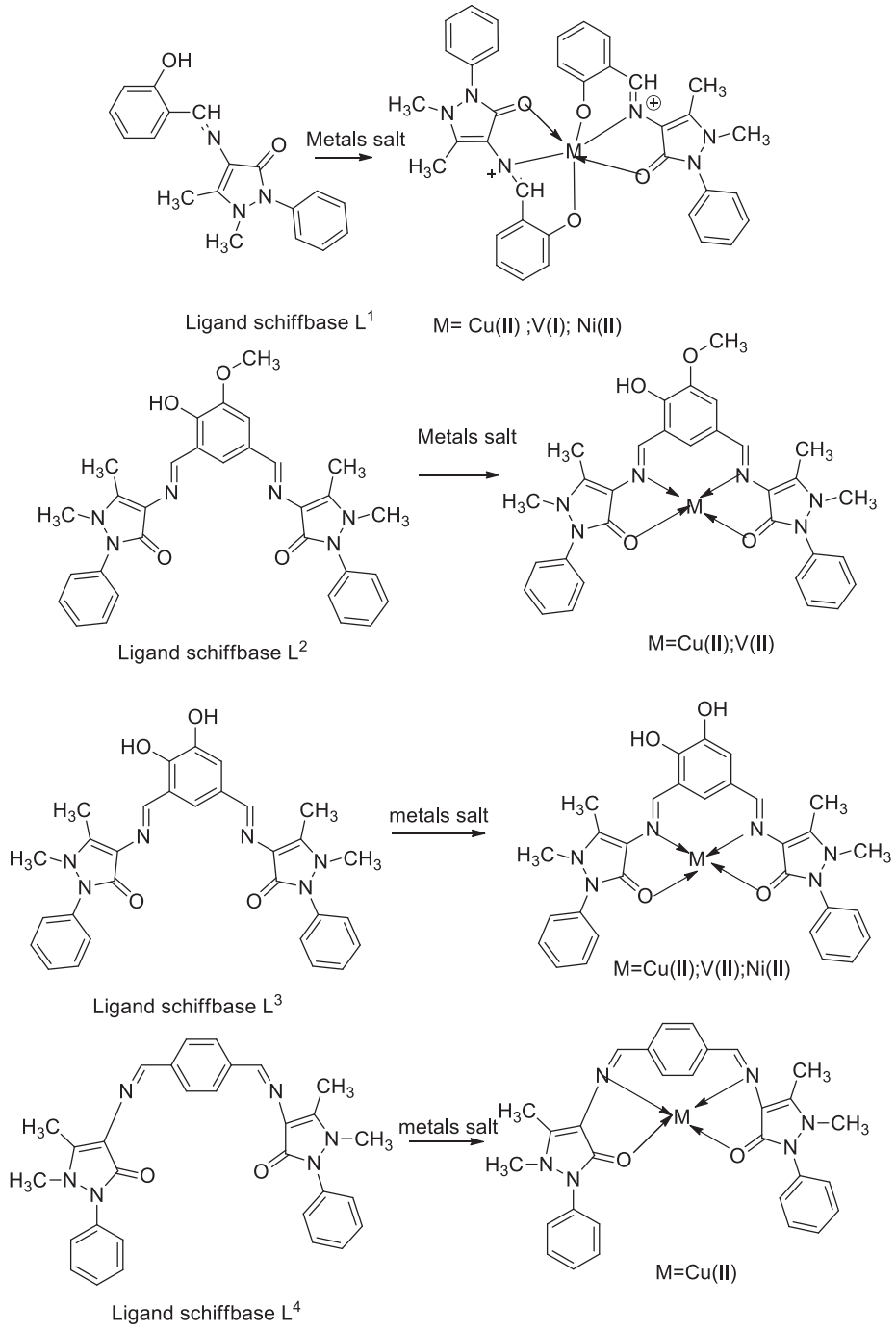
A combination therapy with isoniazid, ethambutol hydrochloride, streptomycin sulphate, and rifampicin are the established antitubercular molecules, against tuberculosis, caused by *Mycobacterium tuberculosis.* However today, drug resistant TB bacilli have come up in developing countries causing a threat to public health. Thus, suitable antitubercular drugs are a dire necessity to control isoniazid resistant TB [[78]].

9.1. Synthesis and antitubercular action of antipyrine analgues

A mixture of 3-amino-1-phenyl-4-[2-(4-phenyl-1,3-thiazol-2-yl) hydrazin-1-ylidene]-4,5-dihydro-1*H* pyrazol-5-one **1** (TZP4) and the corresponding aldehydes 2a-2l with ethanol in presence of glacial acetic acid was refluxed to synthesize a series of schiff bases of 3-amino-1-phenyl-4-[2-(4-phenyl-1,3-thiazol-2-yl) hydrazin-1-ylidene]-4,5-dihydro-1*H*-pyrazol-5-one **(4a-4l)** (Scheme 30). The preliminary, *in-vitro* antimycobacterial activity of the synthesized compounds were investigated against *M. smegmatis* (MTCC99) by the two fold serial dilution assay procedure using Middle brook 7H9 broth medium at a concentration range of 100−1.56 μg/mL. The above compounds were had 90% inhibition in a preliminary investigation against *M. tuberculosis* H37Rv (MTB) at a concentration range of 100−1.56 μg/mL with Alamar blue in a broth by the micro dilution assay procedure. Pyrazinamide and streptomycin were used as standards. All the test compounds had good *in vitro* anti-tubercular (antimycobacterial) activity against *M. tuberculosis* at a concentration range of 06.48−53.59 μM. The various substituents on the phenyl ring of schiff based pyrazolones in compounds TZP 4a-4l showed antitubercular activity. However, the compounds 3-[[(2,4-dihydroxyphenyl) methylidene] amino]-1-phenyl-4-[2-(4-phenyl-1,3-thiazol-2-yl) hydrazin-1-ylidene]-4,5-dihydro-1*H*-pyrazol-5-one (TZP 4g) were potent than standard drugs, and had MIC 0.648×10^{-3} μM mL^{-1}; whereas the other synthesized TZP schiff base bearing hydrazine pyrazolone with substituted 4-chlorophenyl and 3,4-disubstituted dihydroxyphenyl had moderate antitubercular activity [79].

10. Antiviral activity

Broad spectrum antivirals could remain effective against the infections due to different range of viruses; nevertheless, several antivirals are in clinical use.



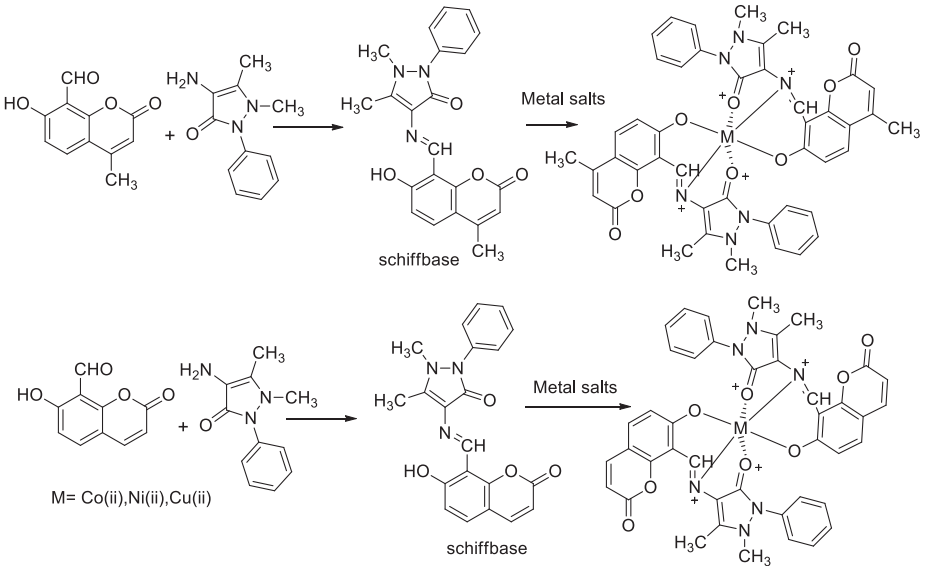
Scheme 28. Synthesis of metal complexes of aldehyde-antipyrin schiff bases derivatives.

10.1. Synthesis and antiviral action of pyrazolone analogues

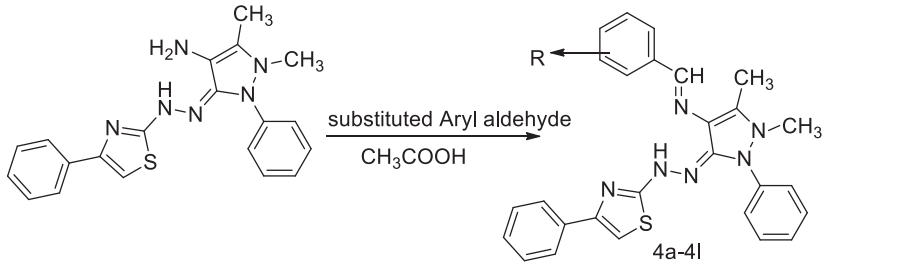
A series of antipyrinyl molecules was synthesized by Rusinov et al. (2005) (Scheme 31). An equimolar concentrations of pyrazine-1-oxide and antipyrine with dimethyl formamide (DMF) were mixed in the presence of benzoyl chloride. The obtained precipitates were re-crystallized from DMF. The synthesized antipyrinyl derivatives was screened by the 'neutral red dye inclusion procedure' against a series of pathogenic *ortho*-pox viruses *viz.,* variolovaccine (LIVP strain), cowpox (Grishak strain), monkeypox (Zair-599), Marburg (Rorr strain) and measles virus (L-16 vaccine strain). No molecule was found to have any significant antiviral activity [80].

11. Conclusion

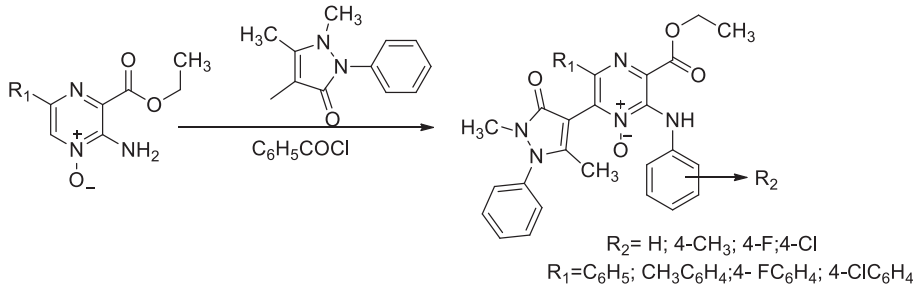
This review included exploring steps of synthetic antipyrinyl analogues and biological actions described so for, during last three decades; thus, this article gives up-to-date images on antipyrinyl analogues. The article focused on several *in vivo* and *in vitro* pharmacological screening models, for various biological activities exhibited by the newly synthesized molecules bearing antipyrine nucleus. Most of the new antipyrine derived molecules are able to exhibit potential antimicrobial activity along with other



Scheme 29. Synthesis of metal complexes of antipyrin-formyl 7- hydroxy coumarin schiff base.



Scheme 30. Synthesis of antipyrine analgues.



Scheme 31. Synthesis of pyrazolone analogues.

pharmacological activities. The control of multidrug resistant microbial pathogens creating havocs as emerging staggering infectious diseases require novel, rather emulating antimicrobials for microbial infections, such as TB. Thus this work is an addition to antimicrobial drug-research.

Declaration of competing interest

The authors declare that they do not have any conflict of interest.

Acknowledgements

The authors are thankful to the Dean, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University).

References

[1] T.J. Sullivan, J.J. Truglio, M.E. Boyne, P. Novichenok, X. Zhang, C.F. Stratton, H.J. Li, T. Kaur, A. Amin, F. Johnson, R.A. Stayden, C. Kisker, P.J. Tonge, High affinity InhA inhibitors with activity against drug-resistant strains of Mycobacterium tuberculosis, ACS Chem. Biol. 1 (2006) 43–53.
[2] A.M. Gilbert, A. Failli, J. Shumsky, Y. Yang, A. Severin, G. Singh, W. Hu, D. Keeney, P.J. Petersen, A.H. Katz, Pyrazolidine-3,5-Diones and 5-Hydroxy-

1H-Pyrazol-3(2H)-Ones, inhibitors of UDP-N-acetylenolpyruvyl glucosamine reductase, J. Med. Chem. 49 (2006) 6027–6036.
[3] A.M. Isloor, B. Kalluraya, P. Shetty, Regioselective reaction: synthesis, characterization and pharmacological studies of some new Mannich base derived from 1,2,4-triazoles, Eur. J. Med. Chem. 44 (2009) 3784–3787.
[4] I.V. Magedov, M. Manpadi, S.V. Slambrouck, W.F.A. Steelant, E. Rozhkova, N.M. Przheval'skii, S. Ogelj, A. Kornienko, Discovery and investigation of antiproliferative and apoptosis-inducing properties of new heterocyclic podophyllotoxin analogues accessible by a one-Step multi component synthesis, J. Med. Chem. 50 (2007) 5183–5192.
[5] G. Szabo, J. Fischer, A. Kis-Varga, K. Gyires, New celecoxib derivatives as anti-inflammatory agents, J. Med. Chem. 51 (1) (2008) 142–147.
[6] N. Benaamane, B. Nedjar-Kolli, Y. Bentarzi, L. Hammal, A. Geronikaki, P. Eleftheriou, A. Langunin, Synthesis and *in silico* biological activity evaluation of new N-substituted pyrazolo-oxazin-2-one systems, Bioorg. Med. Chem. 16 (2008) 3059–3066.
[7] Y.R. Prasad, A. Lakshmana Rao, L. Prasoona, K. Murali, K.P. Ravi, Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines, Bioorg. Med. Chem. Lett 15 (2005) 5030–5034.
[8] Z. Ozdemir, H.B. Kandilici, B. Gumusel, U. Calis, A.A. Bilgin, Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives, Eur. J. Med. Chem. 42 (2007) 373–379.
[9] A. Sener, M.K. Sener, I. Bildmci, R. Kasimogullari, Y. Akcamur, Studies on the reactions of cyclic oxalyl compounds with hydrazines or hydrazones: synthesis and reactions of 4-benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid, J. Heterocycl. Chem. 39 (2002) 869–875.
[10] G.A. Wachter, R.W. Hartmann, T. Sergejew, G.L. Grun, D. Ledergerber, Tetrahydronaphthalenes: influence of heterocyclic substituents on inhibition of steroidogenic enzymes P450 arom and P450 17, J. Med. Chem. 39 (1996) 834–841.
[11] A. Iqbal, H.L. Siddiqui, C.M. Ashraf, M.H. Bukhari, C.M. Akram, Synthesis, spectroscopic and cytotoxic studies of biologically active new Schiff bases derived from p-nitrobenzaldehyde, Chem. Pharm. Bull. 55 (2007) 1070–1072.
[12] K. Brune, The early history of non-opioid analgesics, Acute Pain 1 (1997) 33–40.
[13] D. Burdulene, A. Palaima, Z. Stumbryavichyute, Z. Talaikite, Synthesis and anti-inflammatory activity of 4-aminoantipyrine derivatives of succinamides, Pharm. Chem. J. 33 (1999) 20–22.
[14] N.V. Bashkatova, E.I. Korotkova, Y.A. Karbainov, A.Y. Yagovkin, A.A. Bakibaev, Electrochemical, quantum-chemical and antioxidant properties of antipyrine and its derivatives, J. Pharm. Biomed. Anal. 37 (2005) 1143–1147.
[15] D. Costa, A.P. Marques, R.L. Reis, J.L.F.C. Lima, E. Fernandes, Inhibition of human neutrophil oxidative burst by pyrazolone derivatives, Free Radical Biol. Med. 40 (2006) 632–640.
[16] E.S.H.E.L. Ashry, L.F. Awad, E.I. Ibrahim, O.K. Bdeewy, Synthesis of antipyrine derivatives derived from dimedone, Chin. J. Chem. 25 (2007) 570–573.
[17] P.M.P. Santos, A.M.M. Antunes, J. Noronha, E. Fernandes, A.J.S.C. Vieira, Scavenging activity of aminoantipyrines against hydroxyl radical, Eur. J. Med. Chem. 45 (2010) 2258–2264.
[18] K.L. Kees, J.J. Fitzgerald, K.E. Steiner, J.F. Mattes, B. Mihan, T. Tosi, D. Mondoro, M.L. McCalebr, New potent antihyperglycemic agents in db/db mice: synthesis and structure-activity relationship studies of (4-substituted benzyl) (trifluoromethyl)pyrazoles and -pyrazolones, J. Med. Chem. 39 (1996) 3920–3928.
[19] Martindale, The Extra Pharmacopoeia, 30th ed, 29.
[20] S. Bondock, R. Rabie, H.A. Etman, A.A. Fadda, Synthesis and antimicrobial activity of some new heterocycles incorporating antipyrine moiety, Eur. J. Med. Chem. 43 (2008) 2122–2129.
[21] S. Bondock, A. El-Gaber Tarhoni, A.A. Fadda, Heterocyclic Synthesis with 4-Benzoyl-1-cyanoacetylthiosemicarbazide: selective synthesis of some thiazole, triazole, thiadiazine, pyrrylthiazole, and pyrazolo[1,5-a]triazine derivatives, Monatshefte fur Chemie 139 (2008) 153–159.
[22] J. Hosler, C. Tschanz, C.E. Hignite, D.L. Azarnoff, Topical application of lindane cream (K well) and antipyrine metabolism, J. Investig. Dermatol. 74 (1980) 51–53.
[23] K.Z. Ismail, A. El-Dissouky, A.Z. Shehada, Spectroscopic and magnetic studies on some copper (II) complexes of antipyrine Schiff base derivatives, Polyhedron 16 (2009) 2909–2916.
[24] A.M. Farghaly, A. Hozza, A.B. Ali, M.S. Abu-Zeit Hart, F.A. Sharabi, Non-steroidal anti-inflammatory agents. 4-[1-(3, 5-disubstituted-2-thio-thio-1,3,5-perhydrotriazinyl)]-2,3-dimethyl-1-phenyl-5-pyrazolones, Die Pharmazie 35 (1980) 596–598.
[25] R.N. Patel, S. Kumar, K.B.E.s.r. Pandeya, Visible and SOD studies of imidazolate bridged $Cu^{II,II}_2$, $Cu^{II}Zn^{II}$ and $Cu^{II}Ni^{II}$ complexes with pentamethyldiethylenetriamine as capping ligand: a plausible model for superoxide dismutase, J. Inorg. Biochem. 89 (2002) 61–68.
[26] A. Grieco, A. Matera, P. Di-Rocco, S. Marcoccia, A. Giancaterini, B. Alfei, G. Addolorato, F. Varlese, G. Gasbarrini, Plasma levels of fibronectin in patients with chronic viral and alcoholic liver disease, Heparogastroenterol 45 (1998) 1731–1736.
[27] R.J.R. Sorenson, Biology of Copper Complexes, 1ed., Human Press, Clifton, New Jersey, 1987, pp. 533–540.
[28] B. Macias, I. Garcia, M.V. Villa, J. Borras, M. Gonzalez-Alvarez, A. Castineiras, Oxidative DNA damage of mixed copper(II) complexes with sulfonamides and 1,10-phenanthroline: crystal structure of [Cu(*N*-quinolin-8-yl-*p*-toluenesulfonamidate)2(1,10-phenanthroline)], J. Inorg. Biochem. 96 (2003) 367–374.
[29] S. Chandra, L.K. Gupta, EPR, mass, IR, electronic, and magnetic studies on copper (II) complexes of semicarbazones and thiosemicarbazones, Spectrochim. Acta, Part A 61 (2005) 269–275.
[30] A. El-Dissouky, A.Z. Shehada, G. El-Mahdy, Synthesis and characterization of oxovanadium(IV) and dichlorovanadium(IV) complexes of biologically active 4-aminoantipyrine derivatives, Polyhedron 16 (1997) 1247–1253.
[31] G.G. Mohamed, M.M. Qmar, A.M.M. Hindy, Synthesis, characterization and biological activity of some transition metals with Schiff base derived from 2-thiophene carboxaldehyde and aminobenzoic acid, Spectrochim. Acta A Mol. Biomol. Spectrosc. 62 (2005) 1140–1150.
[32] P. Eleni, H.-L. Dimitra, L. Konstantinos, N. Orazio, C. Angelo, Design, synthesis and pharmacobiological evaluation of novel acrylic acid derivatives acting as lipoxygenase and cyclooxygenase-1 inhibitors with antioxidant and anti-inflammatory activities, Eur. J. Med. Chem. 46 (2011) 191–200.
[33] A. Kar, Medicinal Chemistry, 3 ed., New Age International Publishers, New Delhi, 2005.
[34] E.M. Khaled, F.A. Ahmed, Chemistry of antipyrine. Synth. Commun. Rev. 46 (2016) 1567–1594.
[35] History of Antioxidants-Antiaging Club, 2018 https://m.antiagingclub.it>News>.
[36] F. Bonomini, S. Tengattini, A. Fabiano, R. Bianchi, R. Rezzani, Reactive oxygen species, antioxidant enzymes, Histol. Histopathol. 23 (2008) 381–390.
[37] O. Yasemin, A. Kubra, Oxidative stress related diseases in newborns, Oxi. Med. Cell. Long. (2016) 1–9, 2016.
[38] B. Halliwell, Oxidative stress and cancer: have we moved forward, Biochem. J. 401 (2007) 1–11.
[39] R. Vuppalanchi, R. Juluri, L.N. Bell, M. Ghabril, L. Kamendulis, J.E. Klaunig, R. Saxena, D. Agarwal, M.S. Johnson, N. Chalasani, Oxidative stress in chronic liver disease: relationship between peripheral and hepatic measurements, Am. J. Med. Sci. 342 (2011) 314–317.
[40] L. Haider, T.M. Fischer, J.M. Fischer, B. Jan, H. Romana, B. Gergo, E. Harald, C.J. Binder, J.L. Witztum, L. Hans, Oxidative damage in multiple sclerosis lesions, Brain 134 (2011) 1914–1924.
[41] V.P. Patel, C.T. Charleen, Nuclear transport, oxidative stress, and neurodegeneration, Int. J. Clin. Exp. Pathol. 4 (2011) 215–229.
[42] K.L. Liao, M.C. Yin, Individual and combined antioxidant effects of seven phenolic agents in human erythrocyte membrane ghosts and phosphatidylcholine liposome systems: importance of the partition coefficient, J. Agric. Food Chem. 48 (2000) 2266–2270.
[43] M.R. Saha, S.M.R. Hasan, R. Akter, M.M. Hossain, M.S. Alam, M.A. Alam, M.E.H. Mazumder, In vitro free radical scavenging activity of methanol extract of the leaves of *Mimusops elengi* Linn, Bangladesh J. Vet. Med. 6 (2008) 197–202.
[44] P.D. Shelke, A.S. Rajbhoj, M.S. Nimase, S.J. Takate, B.H. Zaware, S.S. Jadhav, Electrochemical synthesis, characterization and evaluation of antioxidant activity of copper oxide nanoparticles, Res. J. Chem. Sci. 6 (2016) 43–48.
[45] M.B. Ningappa, R. Dinesh, L. Srinivas, Antioxidant and free radical scavenging activities of polyphenol- enriched curry leaf extract (Murraya koenigii L.), Food Chem. 106 (2008) 720–728.
[46] J. Sahoo, S.K. Paidesetty, Biological evaluation and spectral characterization of 4-hydroxy coumarin analogues, J. Taibah Univ. Med. Sci. 10 (2015) 306–319.
[47] J. Sahoo, S.K. Paidesetty, Study of antimicrobial, analgesic wound healing and antioxidant activities of some newly synthesized oxychinolin derivatives and their characterization, Beni-suef Univ. J. Basic Appl. Sci. 4 (2015) 232–245.
[48] S. Mohammad, G. Rahman, S.W. Ali Shah, M.N. Umar, Synthesis of 4-aminoantipyrine derived Schiff bases and their evaluation for antibacterial, cytotoxic and free radical scavenging activity, Bangladesh J. Pharmacol. 10 (2015) 332–336.
[49] S.K. Paidesetty, S.K. Rout, J. Sahoo, Antimicrobial and antioxidant activities of some newly synthesized benzene-1, 3-diol congeners and their characterization, Int. J. Pharm. Pharm. Sci. 7 (2015) 427–433.
[50] S.K. Paidesetty, J. Sahoo, Antimicrobial, analgesic, antioxidant and in silico study of synthesized salicylic acid congeners and their structural interpretation. Egypt, J. Basic Appl. Sci. 2 (2015) 268–280.
[51] J. Joseph, K. Nagashri, G. Ayisha Bibin Rani, Synthesis, characterization and antimicrobial activities of copper complexes derived from 4-aminoantipyrine derivatives, J. Saudi Chem. Societ. 17 (2013) 285–294.
[52] S.A. Mohammad, L. Dong-Ung, Synthesis, molecular structure and antioxidant activity of (E)-4-[Benzylideneamino]-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one, a schiff base ligand of 4-aminoantipyrine, J. Chem. Crystallogr. 42 (2012) 93–102.
[53] M.A. Metwally, Y.A. Suleiman, M.A. Gouda, A.N. Harmal, A.M. Khalil, Synthesis, antitumor and antioxidant evaluation of some new antipyrine based azo dyes incorporating pyrazolone moiety, Int. J. Mod. Org. Chem. 1 (2012) 213–225.
[54] A.H. Shridhar, J. Keshavayya, H.H. Joy, Synthesis of 1,3,4-oxadiazole incorporated azo dye derivatives as potent biological activity molecules, Int. Res. J. Pharm. Pharm. Sc. 4 (2012) 386–390.
[55] H.F. Rizk, S.A. Ibrahim, M.A. El-Borai, Synthesis, fastness properties, color assessment and antimicrobial activity of some azo reactive dyes having pyrazole moiety, Dyes Pigments 112 (2015) 86–92.
[56] A.K. Tiwari, S. Fatma, A. Bishnoi, A. Srivastava, C.M. Tripathi, B. Banerjee, Synthesis, characterization and in vitro antimicrobial activity of some novel

4,5- dihydro-1 H-pyrazoline derivatives, Indian J. Chem. 56 (2017) 317–324.
[57] S.A. Mohammad, L. Dong-Ung, Physicochemical analyses of a bioactive 4-aminoantipyrine analogue-synthesis, crystal structure, solid state interactions, antibacterial, conformational and docking studies, EXCLI J 15 (2016) 614–629.
[58] K.K. Mehta, A.D. Patel, Synthesis, characterization, biological and chelating properties of new antipyrine derived azo dyes and its transition metal complexes, Acta Chim. Pharm. Indica. 6 (2016) 26–31.
[59] M.S. Suresh, V. Prakash, Preparation characterization and antibacterial studies of chelates of schiff base derived from 4-aminoantipyrine, furfural and o-phenylenediamine, E-J. Chem. 8 (2011) 1408–1416.
[60] M. Tyagi, S. Chandra, P. Tyagi, J. Akhtar, A. Kandan, B. Singh, Synthesis, characterization and anti-fungal evaluation of Ni(II) and Cu(II) complexes with a derivative of 4-aminoantipyrine, J. Taibah Univ. Scie. 11 (2017) 110–120.
[61] MdS. Alam, L. Dong-Ung, MdL. Bari, Antibacterial and cytotoxic activities of schiff base analogues of 4-aminoantipyrine, J. Korean Soc. Appl. Biol. Chem. 57 (2014) 613–619.
[62] J. Sahoo, S. Sahoo, S.K. Paidesetty, Biological evaluation of novel a-heteroaryl/arylazo 2-naphthol analogs and the transitional metal complexes derived from 4-((2-hydroxynaphthalen-1-yl) diazenyl)-1, 5-dimethyl-2-phenyl-1h-pyrazol-3(2h)-one, Indian Drugs 53 (2016) 15–24.
[63] S. Sharma, J. Kaur, S. Kaur, P. Sharma, Synthesis, antibacterial and antifungal activities of some new azo anils containing pyrazole moiety, Indian J. Chem. 53B (2014) 227–237.
[64] J. Sahoo, G. Parween, S. Sahoo, S.K. Mekap, S. Sahoo, S.K. Paidesetty, Synthesis, spectral characterization, in silico and in vitro antimicrobial investigations of some Schiff base metal complexes derived from azo salicylaldehyde analogues, Indian J. Chem. 55B (2016) 1267–1276.
[65] P. Ali, J. Meshram, J. Sheikh, V. Tiwari, R. Dongre, T.B. Hadda, Predictions and correlations of structure activity relationship of some aminoantipyrine derivatives on the basis of theoretical and experimental ground, Med. Chem. Res. 2 (2012) 157–164.
[66] T. Rosu, S. Pasculescu, V. Lazar, C. Chifiriuc, R. Cernat, Copper (II) complexes with ligands derived from 4-Amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one: synthesis and biological activity, Molecules 11 (2006) 904–914.
[67] R.K. Agarwal, S. Prasad, Synthesis, spectroscopic and physicochemical characterization and biological activity of Co(II) and Ni(II) coordination compounds with 4- aminoantipyrine thiosemicarbazone, Bio. Inorg. Chem. Appl. 3 (2005) 271–288.
[68] K.Z. Ismail, Synthesis, spectroscopic, magnetic and biological activity studies of copper (II) complexes of an antipyrine Schief base, Trans. Met. Chem. 25 (2000) 522–528.
[69] S.M. Riyadh, N.A. Kheder, A.M. Asiry, Synthesis, anticancer and antimicrobial activities of some new antipyrine based heterocycles, Chem. Mon. 144 (2013) 1559–1567.
[70] S.K. Kulkarni, Hand Book of Experimental Pharmacology, 2 ed., Vallabh Prakashan, Delhi, 1993.
[71] I. Mohanram, J. Meshram, Synthesis and biological activities of 4-aminoantipyrine derivatives derived from betti-type reaction, ISRN Org. Chem. 2014 (2014) 1–7.
[72] R.M. Hoffman, J.G. Elmore, K.M. Fairfield, B.S. Gerstein, C.A. Levin, M.P. Pignone, Lack of shared decision making in cancer screening discussions: results from a national survey, Am. J. Prev. Med. 47 (2014) 251–259.
[73] C.R. Sahoo, S.K. Paidesetty, R.N. Padhy, Norharmane as a potential chemical entity for development of anticancer drugs, Eur. J. Med. Chem. 162 (2019) 752–764.
[74] C.R. Sahoo, S.K. Paidesetty, R.N. Padhy, Nornostocine congeners as potential anticancer drugs: an overview, Drug Dev. Res. (2019), https://doi.org/10.1002/ddr.21577.
[75] T. Rosu, M. Negoiu, S. Pasculescu, E. Pahontu, D. Poirier, A. Gulea, Metal-based biologically active agents: synthesis, characterization, antibacterial and antileukemia activity evaluation of Cu(II), V(IV) and Ni(II) complexes with antipyrine-derived compounds, Eur. J. Med. Chem. 45 (2010) 774–781.
[76] P. Yap, T. Furst, I. Muller, S. Kriemler, J. Utzinger, P. Steinmann, Determining soil-transmitted helminth infection status and physical fitness of school-aged children, J. Vis. Exp. 66 (2012) 3966.
[77] M. Manjunath, A.D. Kulkarni, G.B. Bagihalli, S. Malladi, S.A. Patil, Bio-important antipyrine derived Schiff bases and their transition metal complexes: synthesis, spectroscopic characterization, antimicrobial, anthelmintic and DNA cleavage investigation, J. Mol. Struct. 1127 (2017) 314–321.
[78] S.S. Shasank, S.K. Paidesetty, R.N. Padhy, Antibacterial, antifungal and antimycobacterial compounds from cyanobacteria, Biomed. Pharmacother. 90 (2017) 760–776.
[79] K.K. Sivakumar, A. Rajasekaran, Synthesis, in-vitro antimicrobial and antitubercular screening of Schiff bases of 3-amino-1-phenyl-4- [2-(4-phenyl-1,3-thiazol-2-yl) hydrazin-1-ylidene]-4,5-dihydro-1H-pyrazol-5-one, Pharm. Bioallied. Sci. 5 (2013) 126–135.
[80] V.L. Rusinov, I.S. Kovalev, D.N. Kozhevnikov, M.M. Ustinova, O.N. Chupakhin, A.G. Pokrovskii, T.N. Ilicheva, E.F. Belanov, N.I. Bormotov, O.A. Serova, G.N. Volkov, Synthesis and antiviral activity of 2-amino-3-ethoxycarbonylpyrazine derivatives, Pharm. Chem. J. 39 (2005) 630–635.