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Review Article

A review on microwave-assisted synthesis and biomedical applications of Schiff bases

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Abstract

Schiff bases are versatile organic compounds widely used and synthesized by the condensation reaction of a different amino compound with aldehydes or ketones known as imine (-C=N-). Schiff base ligands are considered preferential ligands as they are simply synthesized by condensation. The Schiff base facilitates coordination with transition metal ions due to the presence of an azomethine group. These compounds have a wide range of applications in the chemical and pharmaceutical industries. Schiff bases form a new class of drugs that can strengthen the immune system and also be used in the treatment of various ailments. The electrophilic carbon and nucleophilic nitrogen of the C=N imine bond provide excellent binding opportunities with a variety of nucleophiles and electrophiles, which can be exploited to inhibit particular diseases, enzymes, or DNA replication. These compounds exhibit various biological activities including antifungal, antibacterial, antitubercular, antiviral, antimalarial, antidiabetic, anticancer, antioxidant, antidiuretic, anti-inflammatory, antipyretic and anti-HIV agents. In this review, synthesis and biological applications of Schiff bases synthesised using microwave irradiation are discussed.

Keywords: Schiff bases, Imines, Azomethine, Microwave irradiation, Green Chemistry, Coordination chemistry

Introduction

Hugo Schiff, a German scientist, first used the phrase "Schiff base" to describe the products developed when primary amines were combined with carbonyl compounds in 1864. Even a decade after its invention in coordination chemistry, Schiff bases play an important role as ligands. Schiff bases are a crucial class of compounds identified by the presence of a double bond (-C=N-) between the carbon and nitrogen atoms. The diversity of these substances is produced in a variety of ways by combining various alkyl or aryl substituents (Figure 1). To determine if Schiff bases can form complexes with transition metal ions, azo-methine is a crucial component of the Schiff base (Raju et al., 2022; Raczuk et al., 2022).

A hydrogen bond is formed between the nitrogen atom in azomethine and the active centres of cell components, which interferes with normal cell function. Schiff bases are crucial in the field of biology due to their structural resemblance to naturally occurring biological molecules. Antibacterial, antifungal, antiviral, anticancer, anti-tuberculosis, antipyretic, anti-inflammatory, antimalarial, and anti-HIV medicines were among the biological uses of Schiff base metal complexes (Uddin et al., 2020). They have a wide variety of pharmacological effects in addition to chemosensory, electroluminescence, optical, fluorescence, non-linear, cosmetic, material science, agricultural, and polymer industries, as well as being employed as O_2 detectors (Raju et al., 2022). According to the literature, the hydrogen bonding between the active centres of cell components and the imino group of Schiff bases is related to therapeutic efficacy (Dalia et al., 2018).

In comparison to traditional synthetic procedures, the utilisation of microwave-assisted Schiff base synthesis is recognised as a critical way for accelerating the process, increasing yield, consuming less energy, and reducing setup time. It is recognised as a great method for sustainable and green chemistry because of its eco-friendly properties. Microwave heating as an alternative energy source facilitates the use of eco-friendly solvents or solvent-free conditions and enhances catalytic reactions due to its rapid heating and energy transmission to the

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reaction medium. These techniques are frequently used to synthesise Schiff bases, which are then used to treat a variety of diseases (Gabano and Ravera, 2022).

In this review, only the literature indexed in ScienceDirect, PubMed, Springer, Google Scholar, ResearchGate and Research square databases were surveyed. The keywords for this survey include green synthesis, microwave irradiation, Schiff bases, azomethine, pharmacological actions, anti-microbial and cytotoxic activity, both individually and in combination were applied and shortlisted according to the purpose of this study. This review focuses on the Schiff base and its derivatives prepared using microwave-assisted synthetic approaches along with their pharmacological actions.

Microwave-assisted synthesis of Schiff bases and its derivatives with biological applications

The tetradentate Schiff bases were synthesised under catalyst-free and solvent-free conditions using microwave-assisted synthesis. The tetradentate Schiff bases **1a-d** were synthesised by adding an equimolar amount of various diamines including ethylenediamine, phenylenediamine, 4-chlorophenylenediamine and 2,3-diaminopyridine as reagents to an equimolar amount of salicylaldehyde and 2'-hydroxy acetophenone supported on silica gel and the reaction was accelerated by the microwave exposure (Mirza-Aghayan et al., 2003) (**Scheme 1**).

Naphthalene substituted Schiff base derivatives were synthesised using 2,2'-(naphthalene-2,7-diylbis(oxy)) diacetohydrazide and aromatic hetero aldehyde in presence of glacial acetic acid as catalyst were taken in DMSO and it was exposed to microwave irradiation at 180 W for 1-2 mins. Microwave-assisted synthesis resulted in high product yield with simple reaction steps, short reaction time and a small amount or no solvents. The synthesised naphthalene substituted Schiff bases **(2a-m)** was evaluated for their antibacterial potential against *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* using the agar well diffusion method. The compounds (**2h)** and (**2i)** showed potent activity against *E. coli, S. aureus* and *P. aeruginosa* due to the substitution of 3-ethoxy-4-hydroxybenzylidene and 3-methoxy-4-hydroxybenzylidene ring, compounds (**2d)** and (**2l)** showed least activity towards *E. coli, S. aureus* and *P. aeruginosa* due to the substitution of 3-nitro benzylidene and cinnamyl ring, compounds (**2a), (2b), (2c), (2f)** and (**2m)** exhibited good antibacterial potential against *E. coli, S. aureus* and *P. aeruginosa* and compound (**2e)** exhibited good antibacterial activity against *E. coli* and possessed

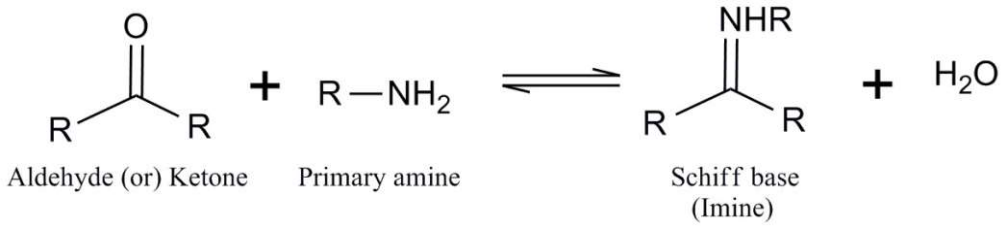
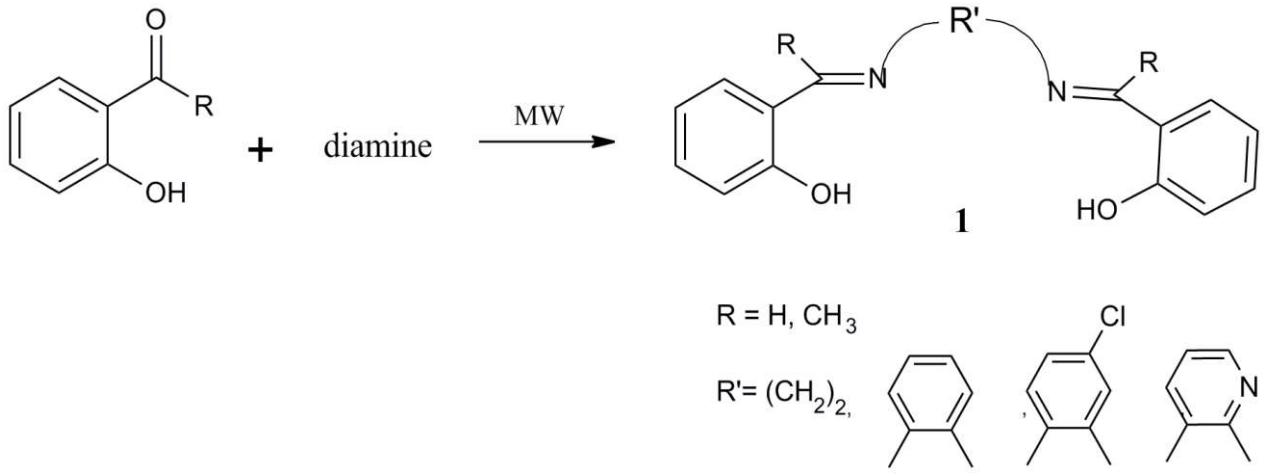


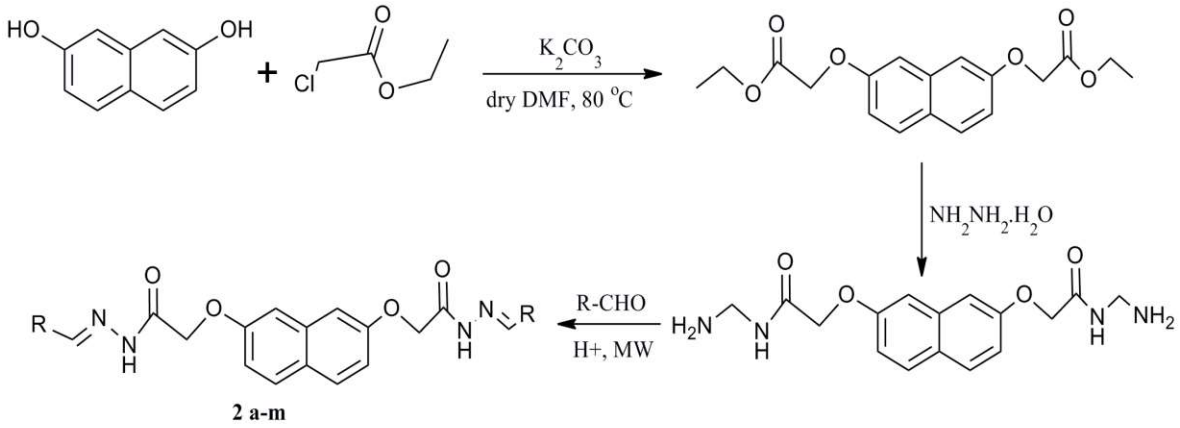
Figure 1: General synthesis of Schiff base



Scheme 1: Synthesis of tetradentate Schiff bases

moderate activity against *S. aureus* and *P. aeruginosa.* The results revealed that the compounds with electron donating group exhibited good activity than the compounds with electron-withdrawing drops (Venkatesan et al., 2012) **(Scheme 2).**

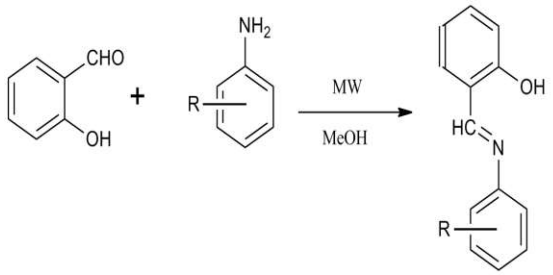
Chakraborty and co-workers synthesised various Schiff bases (**3a-e)** using different substituted aromatic amines and salicylaldehyde with methanol at 300 W from 30 secs to 2 mins. As a result, yellow-coloured amorphous products were obtained (Chakraborty et al., 2012) **(Scheme 3)**. A series of β-Isatin aldehyde-N,N'-thiocarbohydrazone Schiff base derivatives (**4a-n**) synthesised using thiocarbohydrazide and substituted aldehyde with glacial acetic acid as a catalyst at 160 W for 2 mins. The anti-microbial potential of the synthesised compounds was determined against the bacterial strains including *E. coli, S. aureus*, *P. aeruginosa* and *Bacillus subtilis* and fungal strains including using two-fold serial dilution technique. The results revealed that the compounds (**4j)** and (**4n)** showed potent antibacterial activity against *B. subtilis* at 12.5 µg/ml concentration. All the compounds exhibited potent antibacterial potential against *S. aureus* at 25 and 100 µg/ml concentration and for *E. coli* and *P. aeruginosa,* all the compounds exhibited potent activity at 25 and 400 µg/ml concentration. All the compounds exhibited potent antifungal activity against *C. albicans, P. notatum* and *A. niger* at 12.5 and 200 µg/ml and the compounds (**4e), (4j)** and (**4n)** showed high antifungal potential against all the fungal strains. The antioxidant potential of the synthesised Schiff bases was evaluated using DPPH and H_2O_2 method. Among all the compounds, compounds **(4e), (4j), (4l), (4m)** and (**4n)** exhibited greater antioxidant potential against



2 a-m

2a R= Phenyl
2b R= 4-ClPh
2c R= 4-CH_3OPh
2d R= 2,4-ClPh
2e R= 4-N(CH_3)$_2$ Ph
2f R= 4-OEt,3-CH_3OPh
2g R= 3-NO_2Ph
2h R= 3-OEt,4-OHPh
2i R= 4-OH,3-CH_3OPh
2j R= 3-CH_3Ph
2k R= 4-EtOPh
2l R= Cinnamyl
2mR= 2-Thiophenyl

Scheme 2: Synthesis of 2,2'-(naphthalene-2,7-diylbis(oxy))bis(n'-substituted acetohydrazide) derivatives



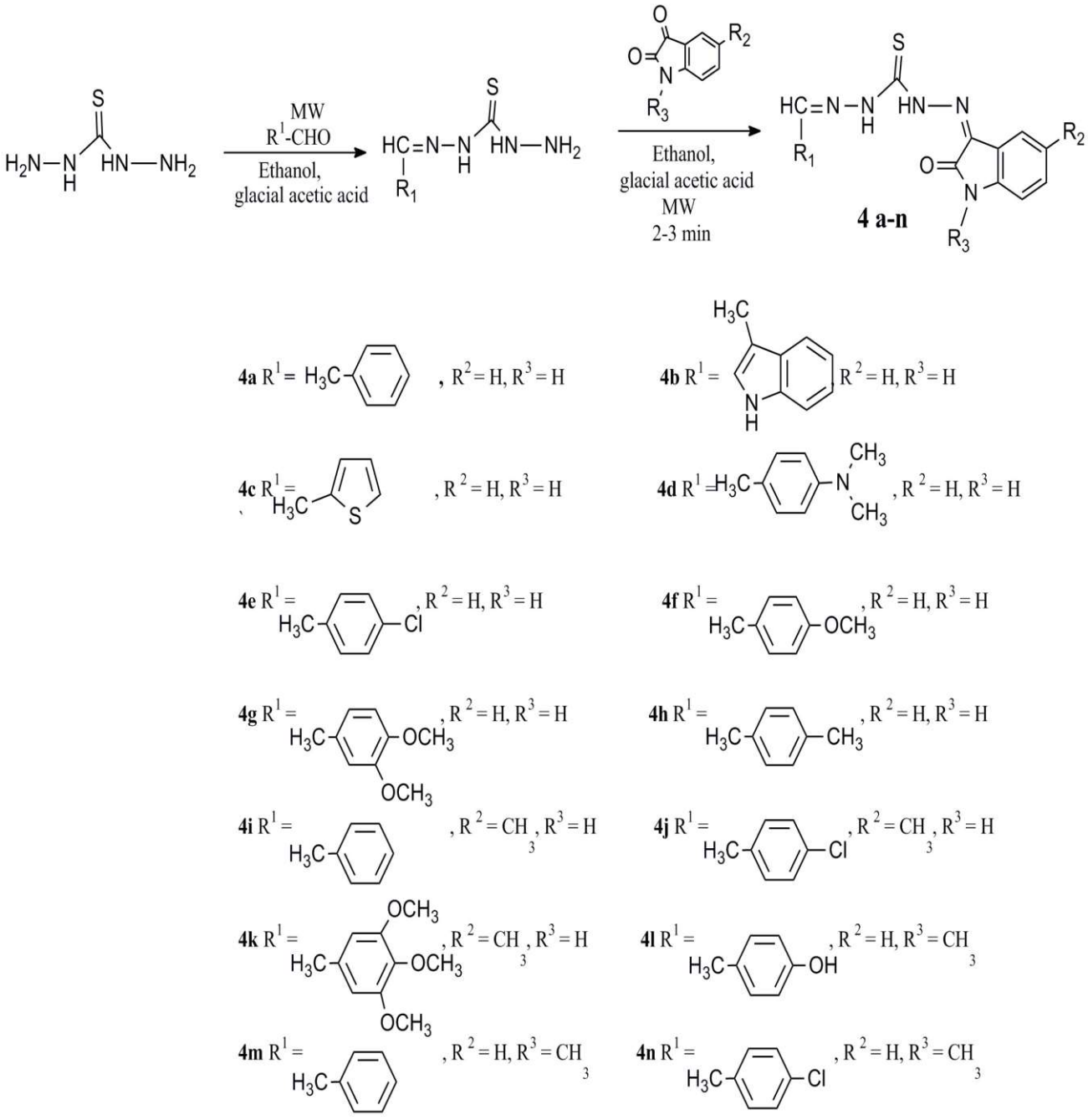
3 a-e
3a R= 2,4-Difluoro
3b R= 4-Chloro
3c R= 2,3,4,5-Tetrafluoro
3d R= 4-Bromo
3e R= 2-Amino

Scheme 3: Synthesis of substituted aromatic amine Schiff base derivatives

DPPH and H_2O_2 free radicals (Kiran et al., 2013) **(Scheme 4)**.

Novel steroidal 1,2,4-triazole Schiff base derivatives (**5a-j**) were synthesised by mixing Methyl 3α-(2-(4-amino-3-(4-fluorophenyl)-5-thioxo-4,5-dihydro-1,2,4-triazol-1-yl)-acetoxy)-12α-hydroxy-cholanate, aldehyde and glacial acetic acid thoroughly and the reaction mixture was irradiated at 300W for 3-7 mins using a microwave oven and its antibacterial potential was evaluated against *E. coli, S. aureus*, *P. aeruginosa* and *B. subtilis* using double dilution method. The results revealed that the compounds showed greater activity against *S. aureus* and *P. aeruginosa* and none of the compounds showed antibacterial activity against *E. coli* and *B. subtilis* (Xingli et al., 2014) **(Scheme 5).**

The microwave assisted Schiff bases with ethyl 4-aminobenzoate and aldehyde derivatives such as salicylaldehyde (**6a**), 3,5-dibromosalicylaldehyde (**6b**), 3,5-diiodo salicylaldehyde (**6c**), 5-chlorosalicylaldehyde(**6d**), 3,4-dimethoxy benzaldehyde (**6e**), 5-methoxybenzaldehyde(**6f**), 3,4,5-Trimethoxy benzaldehyde (**6g**) 3-nitrobenzaldehyde (**6h**), 4-nitrobenzaldehyde (**6j**), 3-bromo-4-hydroxy-5-

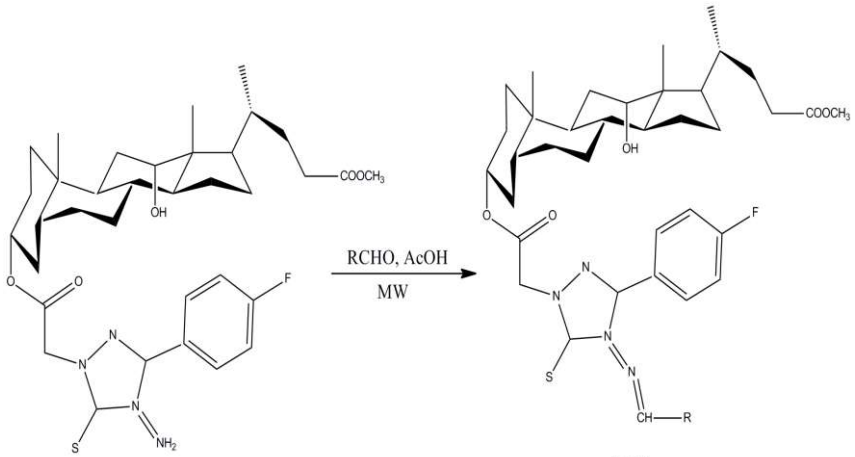


Scheme 4: Synthesis of β-Isatin aldehyde-N,N'-thiocarbohydrazone Schiff base derivatives

methoxybenzaldehyde (**6j**), 3-iodo-4-hydroxy-5-methoxy benzaldehyde (**6k**), 4-N,N-dimethyl benzaldehyde (**6l**) were synthesised using β-ethoxyethanol as a wetting agent. All the compounds were synthesised using microwave irradiation within 10-180 secs. The usage of wetting agents played a greater role in improving the yield of the product, reducing the by-products and also reducing the overall process time (Bhusnure et al., 2015) **(Scheme 6).**

(E)-N'-(4methylbenzylidene) hydrazinecarbothiohydrazide Schiff base **(7)** by reacting Thiocarbohydrazide and 4-methyl benzaldehyde without catalyst under solvent-free condition using green chemistry approach. The antibacterial potential of the Schiff base was evaluated against *S. aureus* and *E. coli* and its antifungal potential was evaluated against *A. niger* and *Rhizopus* sp. The compound showed better activity against all the micro-organisms, particularly, the compound exhibited better antifungal potential than the antibacterial potential (Nalawade et al., 2015) **(Scheme 7)**.

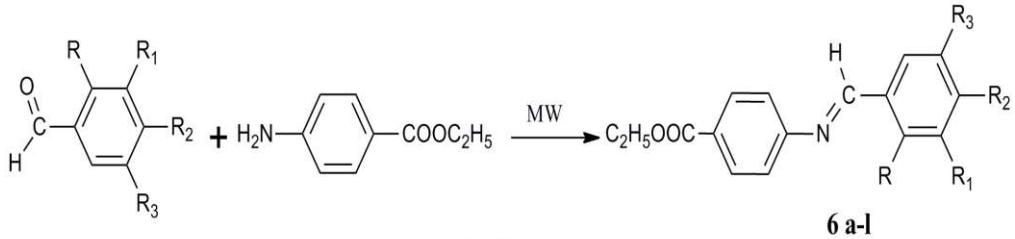
Symmetric double Schiff bases (**8a-k)** were synthesised with 1,1'-bis(4-amino-3-methylphenyl) cyclohexane and aromatic aldehydes in presence of ethanol using microwave irradiation for 2 mins and its antimicrobial activity were screened against *E. coli, Enterobacter aerogenes, Bacillus megaterium* and *A. niger* using Disc diffusion method. The results revealed that compounds exhibited mild antimicrobial potential against the standard drugs including Ciprofloxacin, Cephalexin, Gentamycin and Gentamicin (Aghera et al., 2015) **(Scheme 8)**.



5 a-j

5a R= C_6H_5 **5b** R= 4-FC_6H_4
5c R= 3-C_6H_4 **5d** R= 2,4-$F_2C_6H_3$
5e R= ClC_6H_4 **5f** R= 2-ClC_6H_4
5g R= 4-BrC_6H_4 **5h** R= 2-BrC_6H_4
5i R= 4-$CH_3OC_6H_4$ **5j** R= 4-$NO_2C_6H_4$

Scheme 5: Synthesis of 1,2,4-triazole Schiff base derivatives



6 a-l

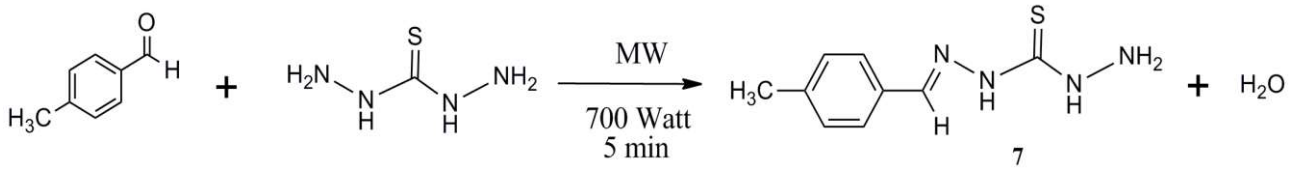
6a R= OH, R^1=H, R^2=H, R^3=H **6b** R= OH, R^1=Br, R^2=H, R^3=Br
6c R= OH, R^1=I, R^2=H, R^3=I **6d** R= OH, R^1=H, R^2=H, R^3=Cl
6e R= H, R^1=OCH_3, R^2=OCH_3, R^3=H **6f** R= OCH_3, R^1=H, R^2=H, R^3=OCH_3
6g R= H, R^1=OCH_3, R^2=OCH_3, R^3=OCH_3 **6h** R= H, R^1=NO_2, R^2=H, R^3=H
6i R= H, R^1=H, R^2=NO_2, R^3=H **6j** R= H, R^1=Br, R^2=OH, R^3=OCH_3
6k R= H, R^1=I, R^2=OH, R^3=OCH_3 **6l** R= H, R^1=H, R^2=$N(CH_3)_2$, R^3=H

Scheme 6: Synthesis of ethyl 4-aminobenzoate and substituted aldehyde Schiff base derivatives

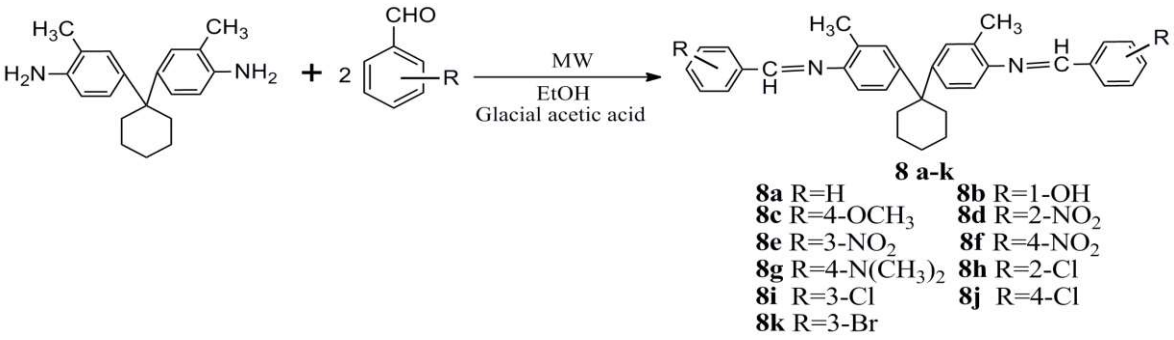
(E)-3-(4-or3-Aminophenylimino) quinoxaline-2(3H)-one oxime Schiff base derivatives (**9a-f)** and **(10a-f**) were prepared using (E)-3-(4-Aminophenylimino)-3,4-dihydroquinoxaline-2(3H)-one oxime / (E)-3-(3-Aminophenylimino)-3,4-dihydroquinoxaline-2(3H)-one oxime was dissolved in 10 mL of ethanol in presence of glacial acetic acid. To the reaction mixture, aldehyde was added and it was allowed to stir for 30 mins using a magnetic stirrer and exposed to microwave irradiation at 400W for 45 secs. After that, the hot solution was transferred to ice cold water resulting in the separation of solid products. The spirocidal activity of the compounds against *Leptospira icterohaemorrhagiae* was screened by using *in vitro* and *in vivo* method. The results revealed that the compounds showed considerable activity against *Leptospira icterohaemorrhagiae*, particularly, compound **(10c)** exhibited remarkable spirocidal activity than the standard, Penicillin G (Gopi et al., 2017) **(Scheme 9).**

5-Rimino-[4-trialkylsilyl(germyl)]-1*H*-1,2,3-triazoles Schiff bases were prepared from Si/Ge-substituted propynals, trimethylsilyl azide and functionalized primary amines using a high efficient catalyst and solvent free microwave assisted synthetic approach (Medvedeva et al., 2017) **(Scheme 10)**.

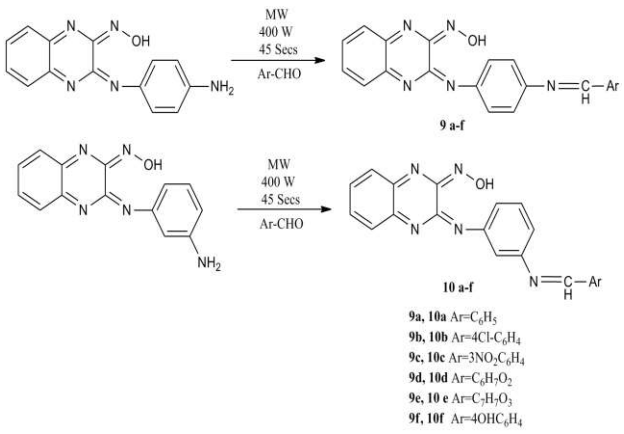
A series of isatin-β-thiocarbohydrazones Schiff bases (**11a-k** and **12a-j**) were synthesised by reacting isatin-β-thiocarbohydrazones with aryl aldehydes in ethanol using microwave irradiation resulted in the formation of β-isatin



Scheme 7: Synthesis of (E)-N'-(4methylbenzylidene) hydrazinecarbothiohydrazide Schiff base



Scheme 8: Synthesis of 1,1'-bis(4-amino-3-methylphenyl) cyclohexane and aromatic aldehydes derivatives

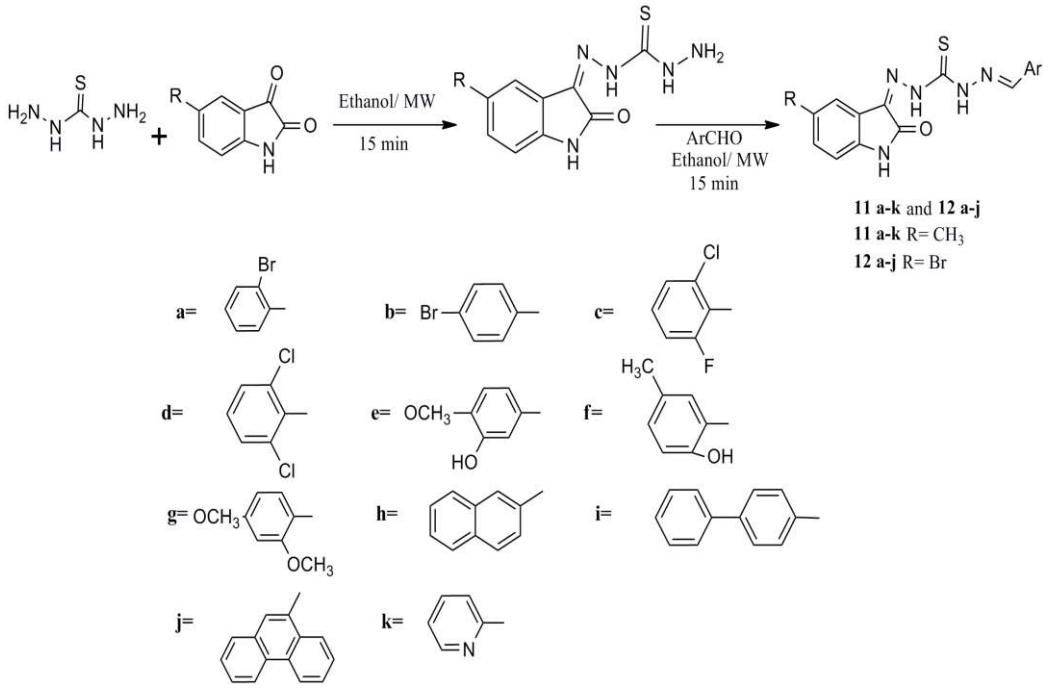


Scheme 9: Synthesis of (E)-3-(4-or3-Aminophenylimino) quinoxaline-2(3H)-one oxime Schiff base derivatives

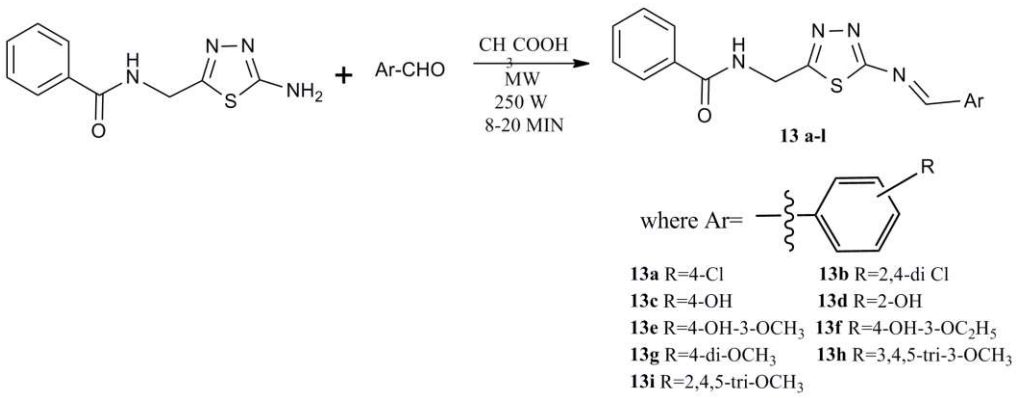
aldehyde-*N,N*^{1}-thiocarbohydrazones and its anticancer potential were screened against cervical cancer (HeLa) and kidney fibroblast (COS-7) cancer cell lines. The results revealed that compounds (**11c), (11d)** and **(11e)** exhibited better efficacy against HeLa cell line and compounds (**11c,) (11e), (11k), (12c)** and (**12e)** exhibited better efficacy against COS-7 cell line (Gabr et al., 2017) **(Scheme 10)**.

A series of novel N-((5-substituted methylene amino)-1,3,4-thiadiazol-2-yl)methyl) benzamide Schiff bases (**13a-i**) were synthesised from N-((5-amino-1,3,4-thiadiazol-2-yl)methyl benzamide and various suitable aldehydes in ethanol using microwave-assisted synthetic approach and their antitumor efficacy were screened against melanoma (SK-MEL-2), leukaemia (HL-60), cervical cancer (HeLa), breast cancer (MCF-7) and normal breast epithelial (MCF-10A) cell lines. The results revealed that the compounds (**13a), (13b), (13k)** and (**13i)** exhibited the most promising antitumor efficacy against all the cell lines and they are subjected to molecular docking and computational studies using QikProp v3.5 (Schrodinger LLC) which revealed better oral drug-like behaviour of the compounds (Tiwari et al., 2017) **(Scheme 11)**.

Isatin and salicylSchiff bases of 5-nitrosubstituted benzimidazole and 6-nitro substituted benzimidazole derivatives were synthesized by reacting iminoester hydrochloride, 4-nitro-*o*-phenylenediamine and ethanol in presence of a small amount of glacial acetic acid at 120-130 °C for 8-10 mins under microwave irradiation (Yilmaz et



Scheme 10: Synthesis of series of isatin-β-thiocarbohydrazones Schiff base derivatives



Scheme 11: Synthesis of N-((5-substituted methylene amino)-1,3,4-thiadiazol-2-yl)methyl) benzamide derivatives

al., 2017) **(Scheme 12)**.

2-(4-Methoxyphenyl) acetohydrazide and various substituted aldehydes were reacted in presence of methanol under microwave irradiation for 10 mins resulting in the formation of a series of Schiff bases and their *in vivo* anti-inflammatory and *in vitro* antioxidant activities were screened using carrageenan induced rat paw edema test and DPPH free radical scavenging assay. The results revealed that the compounds (**14a), (14c), (15a)** and (**15c)** exhibited potent anti-inflammatory action which results in a significant reduction of rat paw edema and compound (**15a)** exhibited potent antioxidant efficacy with the IC_{50} value of 7.2 ± 2.7 µg/ml (Hanif et al., 2018) **(Scheme 13)**.

Symmetrical 1,2-Phenylenediamine Schiff's base derivatives (**16a-g**) were prepared by reacting phenylene diamines and substituted aromatic aldehydes dissolved in ethanol and exposed to microwave irradiation at 350 W for 2-3 mins and their anti-microbial efficacy were screened against *E. coli*, *S. aureus* and *C. albicans* using the standard drugs namely ciprofloxacin and ketoconazole. The results revealed that compound (**16d)** exhibited excellent efficacy against *E. coli*, *S. aureus* and *C. albicans,* whereas compound (**16c)** exhibited moderate efficacy against *C. albicans* (Mohamed et al., 2018) **(Scheme 14)**.

The novel thiophene-benzothiazole derivative azomethine compounds [(2-

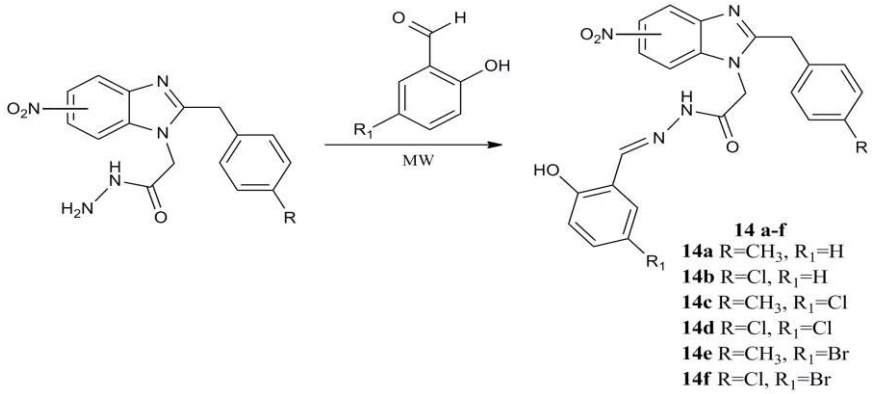
((Benzo[d]thiazol-2-ylimino)methyl)-4-(thiophen-2-yl)phenol **(17a),** 2-(((6-

Methylbenzo[d]thiazol-2-yl)imino)methyl)-4-(thiophen-2-yl)phenol **(17b)** and 2-(((6-

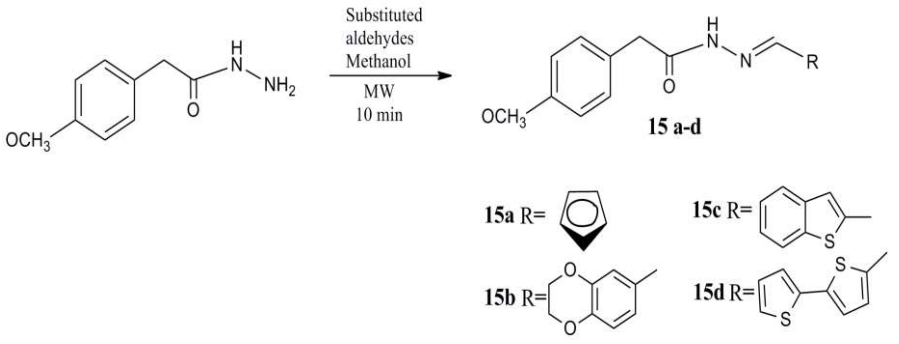
Methoxybenzo[d]thiazol-2-yl)imino)methyl)-4-(thiophen-2-yl)phenol **(17c)**] were successfully synthesized in excellent yields by using microwave-assisted synthesis methods. In addition, the new thiophene-benzothiazole derivative amine compounds [(2-((Benzo[d]thiazol-2-ylamino)methyl)-4-(thiophen-2-yl)phenol **(18a),** 2-(((6-

Methylbenzo[d]thiazol-2-yl)amino)methyl)-4-(thiophen-2-yl)phenol **(18b)** and 2-(((6-

Methoxybenzo[d]thiazol-2-yl)amino)methyl)-4-(thiophen-2-yl)phenol **(18c)**] were obtained in good yields by reduction



Scheme 12: Synthesis of 5-nitrosubstituted benzimidazole and 6-nitro substituted benzimidazole derivatives

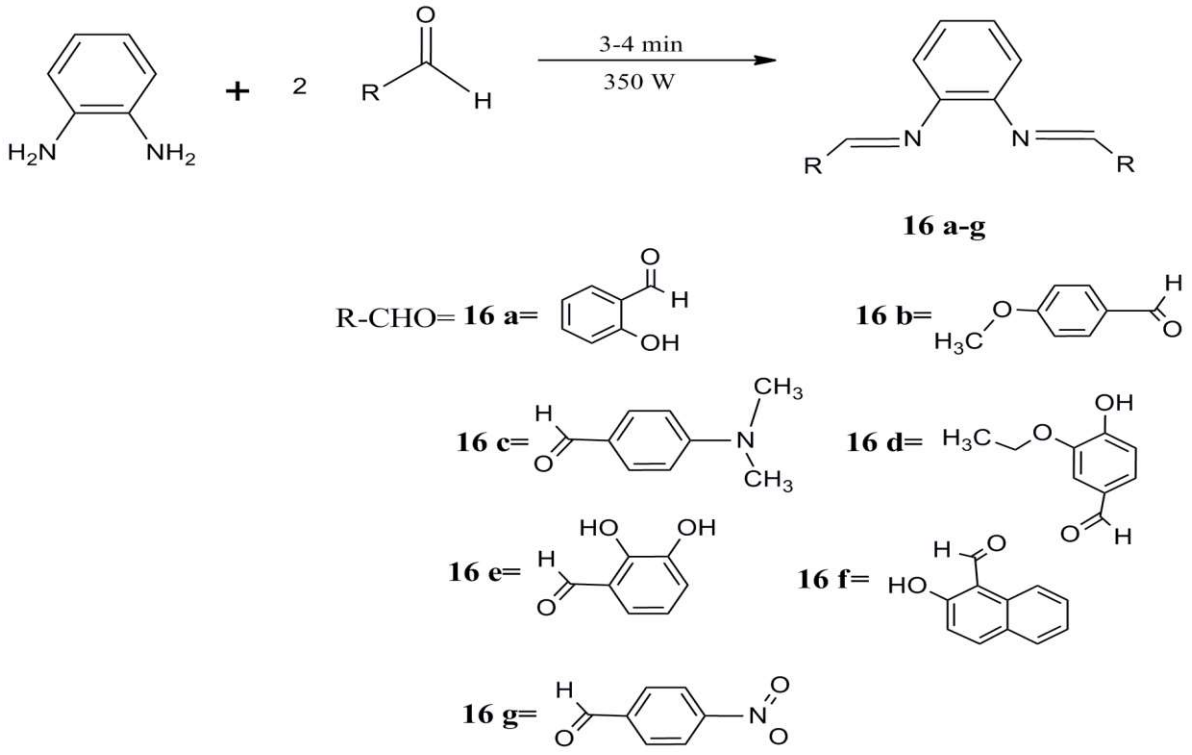


Scheme 13: Synthesis of 2-(4-Methoxyphenyl) acetohydrazide derivatives

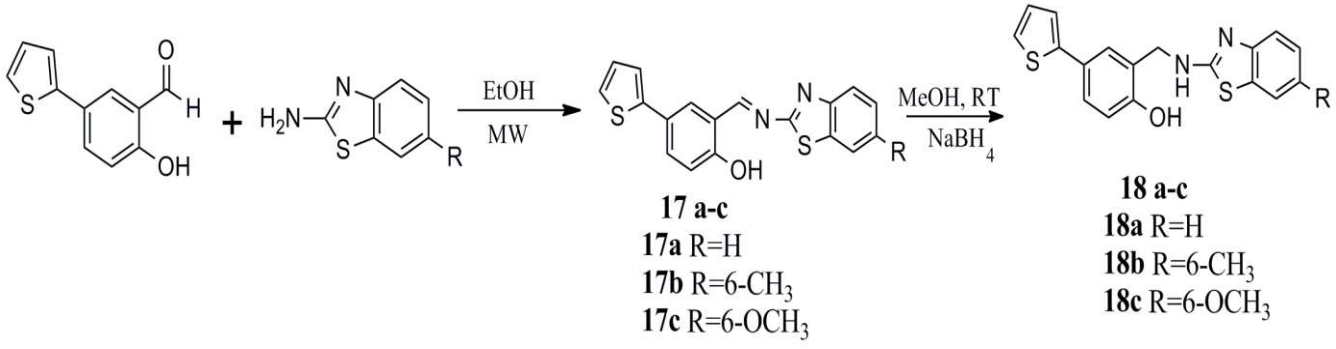
reaction of (**17a-c)** using microwave irradiation (Ermis and Durmus, 2020) **(Scheme 15)**.

Three novel isoniazid Schiff bases (**19, 20, 21**) were synthesised by reacting isoniazid with various aldehydes dissolved in ethanol and glacial acetic acid was added dropwise with shaking and the reaction was introduced to microwave irradiation at 85 °C for 10-20 mins. The synthesised compounds exhibited potent anti-proliferative efficacy against breast cancer (MCF-7) cell line with the IC_{50} value of 125-276 µM. The synthesised compounds exhibited greater *in vitro* antibacterial potential against *E. coli* and *S. aureus* with an inhibition value of 13-18 mm (Al-Hiyari et al., 2021) **(Scheme 16)**.

Schiff bases of Resorcin[4]arenes were synthesised by reacting resorcinol with various aldehydes dissolved in ethanol in presence of con. Hydrochloric acid under microwave irradiation for 3 h at 300 W. Resorcin[4]arene methyl ester was synthesised by reacting Resorcin[4]arenes with methyl 2-bromoacetate in presence of K_2CO_3 in acetonitrile at 300W for 2 h under microwave irradiation. After that, hydrazide derivatized resorcin[4]arenes were prepared by the reaction of Resorcin[4]arene methyl ester and hydrazine hydride under microwave irradiation at 300W for 1 h. Finally, the benzaldehyde was treated with hydrazide-derivatized resorcin [4] arenes in ethanol: DMF as a dual solvent media in the presence of acetic acid as catalyst under



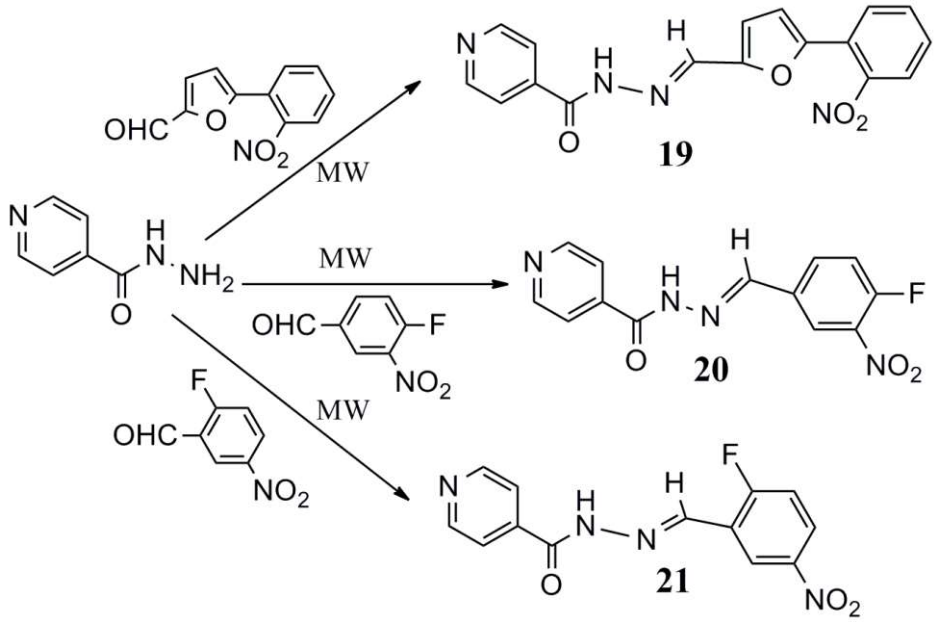
Scheme 14: Synthesis of Symmetrical 1,2-Phenylenediamine Schiff base derivatives



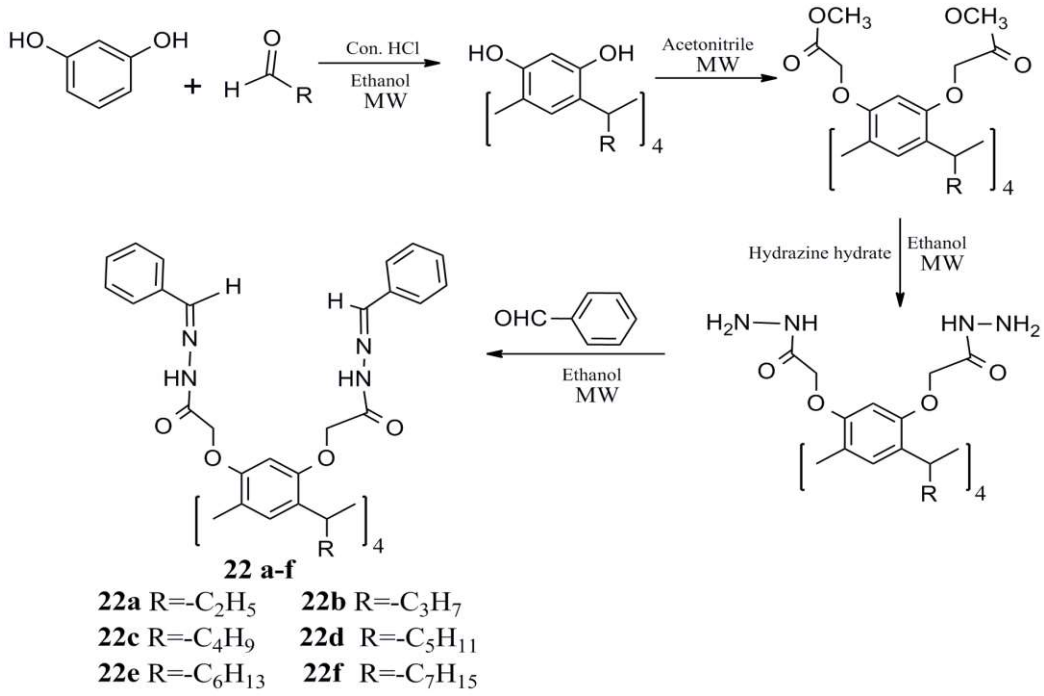
Scheme 15: Synthesis of novel thiophene-benzothiazole derivatives

microwave irradiation at 300W for 2 h to obtain the different Schiff base derivatives (**22a-f**). The antibacterial activity of the synthesised compounds was screened against *P. aeruginosa, Streptococcus pyogenus, E. coli* and *S. aureus* and the antifungal activity of the synthesised compounds were screened against *C. albicans.* The results revealed that the synthesised compounds exhibited potent antibacterial efficacy against all the bacterial strains as compared to the standard, Ampicillin. The synthesised Schiff bases exhibited potent antifungal efficacy against *C. albicans* as compared to the standard drug, Griseofulvin (Gajjar et al., 2021) **(Scheme 17)**.

Novel imines namely N-octadecyl-2-hydroxyacetophenonimine (**23a**), N-octadecyl-2-hydroxypropiophenonimine (**23b**), N-hexadecyl-2-hydroxyacetophenonimine (**23c**), N-hexadecyl-2-



Scheme 16: Synthesis of novel isoniazid azomethine derivatives

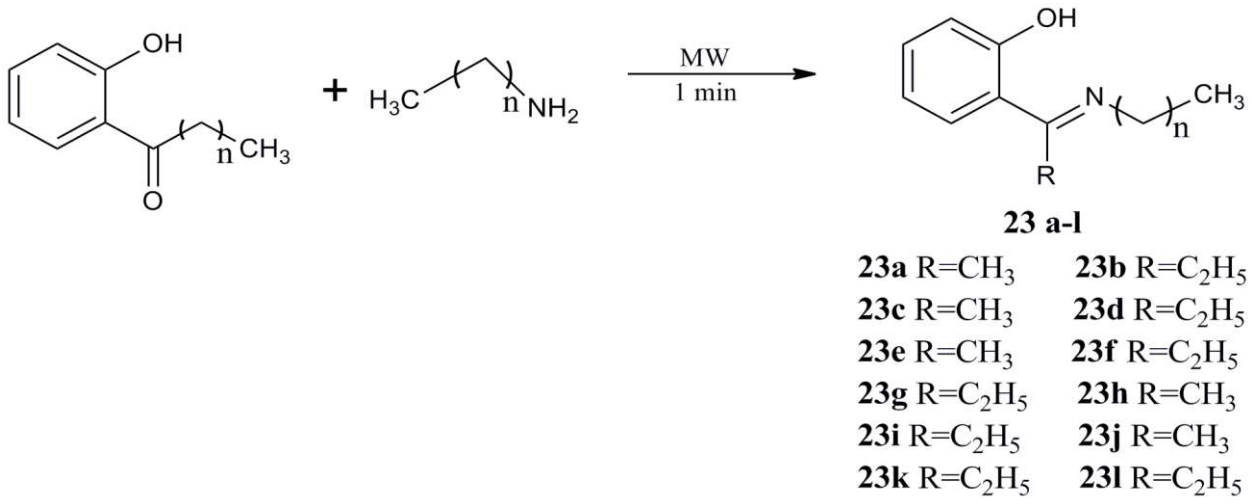


Scheme 17: Synthesis of hydrazide derivatized resorcin[4]arenes derivatives

hydroxypropiophenonimine (**23d**), N-pentadecyl-2-hydroxyacetophenonimine (**23e**), N-undecyl-2-hydroxypropiophenonimine (**23f**), N-nonyl-2-hydroxypropiophenonimine (**23g**), N-heptyl-2-hydroxyacetophenonimine (**23h**), N-heptyl-2-hydroxypropiophenonimine (**23i**), N-hexyl-2-hydroxyacetophenonimine (**23j**), N-hexyl-2-hydroxypropiophenonimine (**23k**) and N-propyl-2-hydroxypropiophenonimine (**23l**) were prepared by reacting o-hydroxy acetophenone/o-hydroxy propiophenone with different alkyl amines. The results of the bioassay revealed the promising nematicidal efficacy of the synthesised compounds, particularly, the compound (**23l**) being the most effective with an LC50 value of 74.46 mgL^{-1} followed by the compound (**23k**) with an LC50 value of 99.60 mgL^{-1} after 72 h of exposure (Kundu et al., 2009) **(Scheme 18)**.

A series of novel benzimidazole Schiff bases (**24a-l**) were synthesised in greater yields by using one step sequence from the reaction of 2-aminobenzimidazole under a green chemistry approach. The compounds (**24a-l**) were evaluated as potent inhibitors of lipoxygenase (LOX) and lipid peroxidation (LPO). The compounds (**24e), (24h)** and **(24i)** were found to be more potent. The compounds (**24d)** and **(24i)** were found to be more cytotoxic (Neochoritis et al., 2011) **(Scheme 19)**.

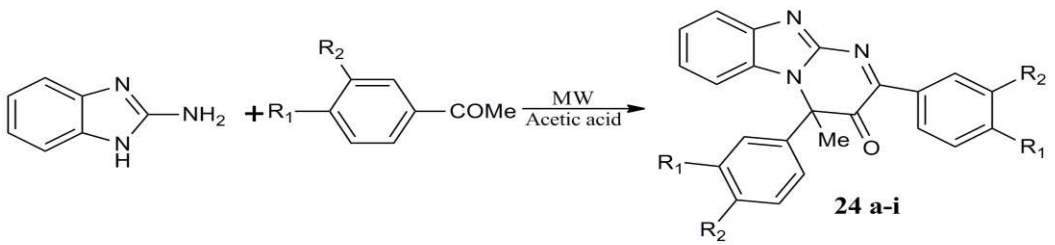
A series of novel sulphanilamide Schiff bases (**25a-h**) were synthesised by the condensation of sulphanilamide with different substituted aromatic aldehydes in presence of ethanol at 400 W for 0.5-1 min under microwave irradiation. The synthesis resulted in the formation of 4-[(Furan-2-



23 a-l

23a R=CH_3 **23b** R=C_2H_5
23c R=CH_3 **23d** R=C_2H_5
23e R=CH_3 **23f** R=C_2H_5
23g R=C_2H_5 **23h** R=CH_3
23i R=C_2H_5 **23j** R=CH_3
23k R=C_2H_5 **23l** R=C_2H_5

Scheme 18: Synthesis of o-hydroxy acetophenone/o-hydroxy propiophenone derivatives



24 a-i

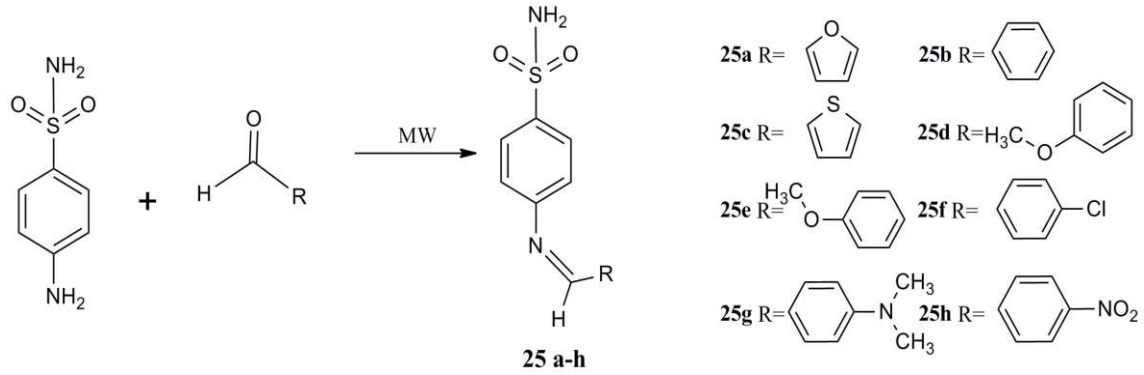
24a R_1=H, R_2=H **24b** R_1=Me, R_2=H
24c R_1=H, R_2=Me **24d** R_1=OMe, R_2=H
24e R_1=H, R_2=OMe **24f** R_1=Cl, R_2=H
24g R_1=Br, R_2=H **24h** R_1=H, R_2=Br
24i R_1=$(-CH=)_4$, R_2=$(-CH=)_4$

Scheme 19: Synthesis of benzimidazole Schiff base derivatives

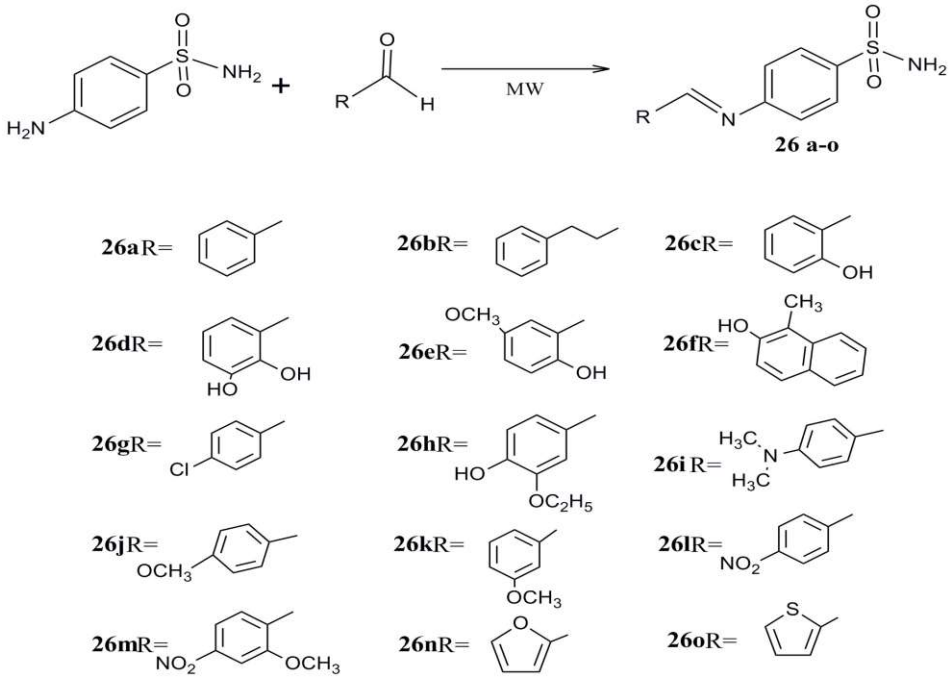
ylmethylene)-amino]-benzenesulfonamide (**25a**), 4-(Benzylidene-amino)-benzenesulfonamide (**25b**), 4-[(Thiophen-2-ylmethylene)-amino]-benzene sulphonamide (**25c**), 4-[(3-Methoxy-benzylidene)-amino]-benzene sulphonamide (**25d**), 4-[(4-Methoxy-benzylidene)-amino]-benzene sulphonamide (**25e**), 4-[(4-Chloro-benzylidene)-amino]-benzene sulphonamide (**25f**), 4-[(4-Dimethylamino-benzylidene)-amino]-benzene sulphonamide (**25g**) and 4-[(4-Nitro-benzylidene)-amino]-benzene sulphonamide (**25h**). The antimicrobial potential of the synthesised Schiff bases was screened against *E. coli, S. aureus* and *C. albicans* using the agar diffusion method. the results revealed that the compounds (**25e)** and **(25g)** showed greater efficacy against *C. albicans* whereas the compounds (**25b)** and (**25h)** showed moderate activity when compared with the standard drug Ketoconazole (Mohamed et al., 2012) **(Scheme 20)**.

The sulphanilamide Schiff bases (**26a-o**) were synthesised by the condensation of sulphanilamide and substituted aldehydes with a minimum amount of ethanol under microwave irradiation at 350-400 W for 0.5-1 min. The antitumor potential of the synthesised Schiff bases revealed as a promising cytotoxic agent against breast cancer (MCF-7) cell line with the IC_{50} value ranging from 90-166 µM. Based on the broad spectrum activity, the compounds (**26d), (26h)** and (**26m)** exhibited excellent cytotoxic efficacy against human breast and lung cancer cells with the IC_{50} value ranging from 96-140 µM (Mohamed et al., 2013) **(Scheme 21).**

Steroidal thiazoles were prepared by reacting steroidal ketones, thiosemicarbazide and phenacyl bromide in ethanol under microwave irradiation at 60 °C for 35-45 mins. The synthesised steroidal thiazoles were evaluated for DNA cleavage activity, genotoxicity, RBC haemolysis and reactive oxygen species



Scheme 20: Synthesis of 4-amino benzene sulphonamide Schiff base derivatives

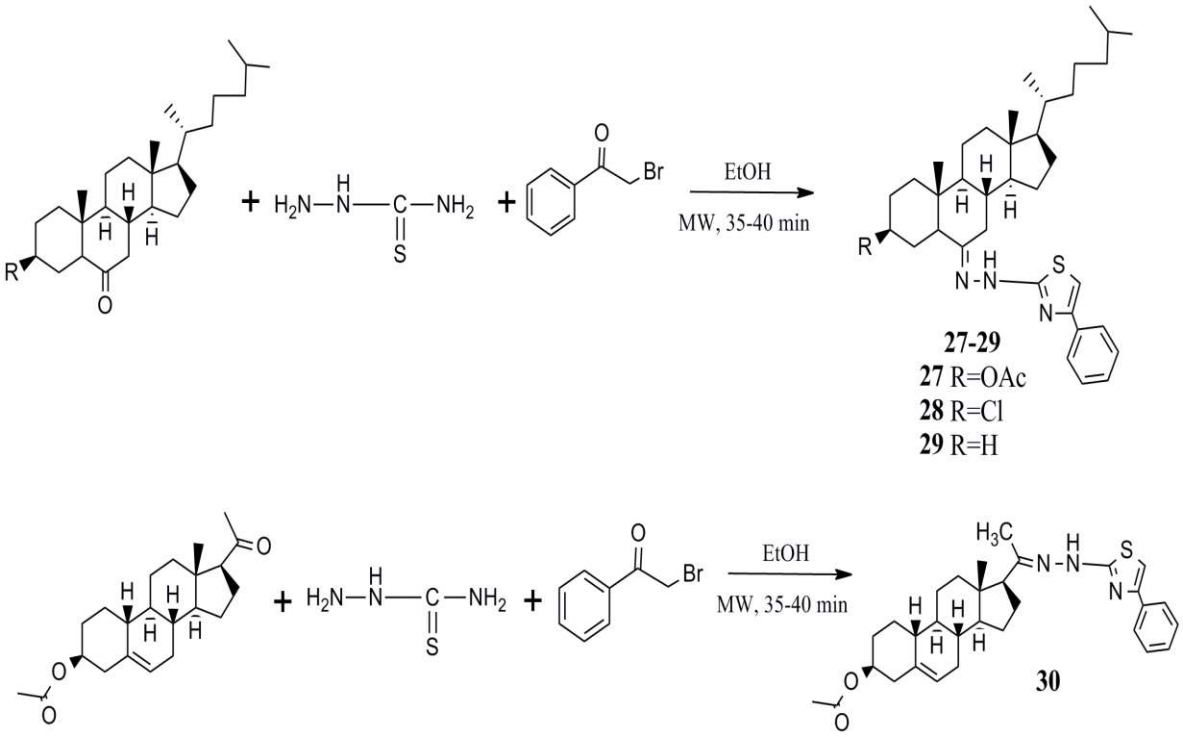


Scheme 21: Synthesis of sulphonamide and substituted aldehyde Schiff base derivatives

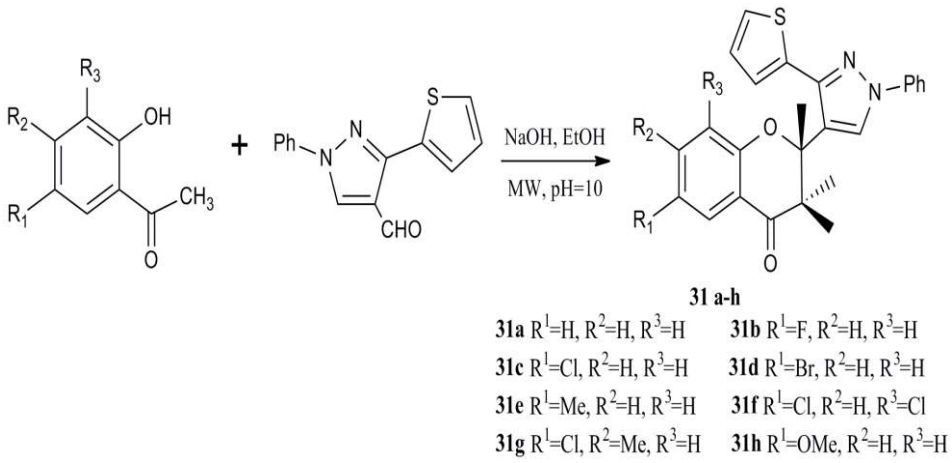
(ROS) production. Molecular docking results revealed potential biological agents, especially compounds **(27)** and **(30)** showed -8.1 and -8 kcal/mol (Asif et al., 2016) **(Scheme 22)**.

2-(1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl)chroman-4-one Schiff base derivatives (**31a-h**) were prepared by reacting substituted 2-hydroxyacetophenone **(31a–h)** and 1-phenyl-3-(2-thienyl)-1*H*-pyrazole-4-carbaldehyde at 180 W for 10-15 mins using microwave-assisted synthesis. For the synthesised compounds, the antibacterial activity was determined against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* using ampicillin as the standard and the antifungal activity were determined against *A. niger*, *Penicillium italicum* and *Fusarium oxysporum* using griseofulvin as standard. The results revealed that compounds **(31e), (31g)** and **(31h)** exhibited potential antibacterial efficacy, compounds **(31a), (31g)** and **(31h)** exhibited potential antifungal efficacy and compound **(31c)** exhibited excellent activity than the –chloro and –fluoro substituted compounds (Dongamanti et al., 2016) **(Scheme 23)**.

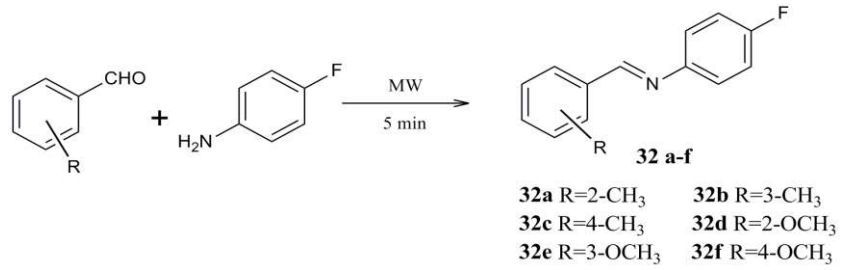
N-(methyl and methoxy) benzylidene 4-fluoroaniline derivatives (**32a-f**) were synthesised by reacting 4-fluoroaniline with 2-methylbenzaldehyde, 3-methylbenzaldehyde, 4-methylbenzaldehyde, 2-methoxybenzaldehyde, 3-methoxybenzaldehyde or 4-



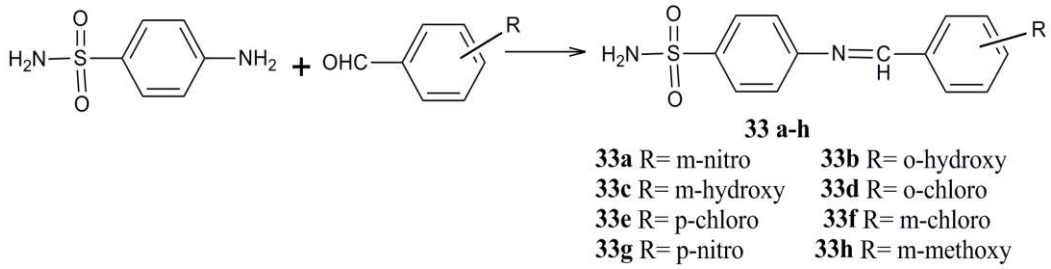
Scheme 22: Synthesis of thiosemicarbazide and phenacyl bromide derivatives



Scheme 23: Synthesis of 2-(1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl)chroman-4-one Schiff base derivatives



Scheme 24: Synthesis of N-(methyl and methoxy) benzylidene 4-fluoroaniline derivatives



Scheme 25: Synthesis of Sulphanilamide based Schiff base derivatives

methoxybenzaldehyde and irradiated at 900 W using microwave irradiation. The inhibitory actions of the synthesised Schiff bases were evaluated using carbonic anhydrase isoenzymes (hCA I and II). The results revealed that compounds **(32b), (32c)** and **(32d)** showed moderate inhibitory effects (Celik and Kuzu, 2019) **(Scheme 24)**.

Sulphanilamide-based Schiff bases (**33a-h**) were prepared by triturating Sulfanilamide with substituted aromatic aldehydes in a dry mortar to make a homogenous mixture. Then the reaction mixture was transferred to a beaker containing 2 g of activated silica gel in a 100 mL volume and exposed to microwave irradiation at 1000 W for around 8 minutes. After every 60 seconds of microwave irradiation, intermittent cooling was performed. The reaction mixtures were stirred well during intermittent cooling resulting in the formation of sulphanilamide-based Schiff bases (Saxena et al., 2021) **(Scheme 25)**.

Conclusion

Schiff bases are an important class of ligands for co-ordination chemistry because of the presence of azomethine nitrogen and can be easily synthesised with inexpensive catalysts. Schiff base ligands have been extensively studied in the field of coordination chemistry mainly because of their easy availability, facile synthesis and electronic properties. Besides synthetic chemistry, we can employ green chemistry concepts to enhance the compound's pharmacological and synthetic accessibility. The discovery of different Schiff base derivatives in pharmaceutical chemistry is constantly progressing, with several uses in coordination chemistry. In this review, the synthesis and biological applications of Schiff bases and their derivatives are discussed. The development of Schiff bases using green chemistry approaches has attracted chemists by improving the rate of reaction and yield with more efficient heating and these compounds exhibited potent pharmacological applications in treating various ailments. Therefore, it would be beneficial to consider using Microwave irradiation while designing novel organic compounds.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

Source of interest: Nil

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