Available online on 15.07.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2023 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited

Open Access Full Text Article

Review Article

Therapeutic aspects of biologically potent vanillin derivatives: A critical review

Senthil Kumar Raju*, Naveena Sundhararajan, Praveen Sekar, Yogadharshini Nagalingam

Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode – 637 205, Tamilnadu, India.

Article Info:

Article History:

Received 23 May 2023
Reviewed 19 June 2023
Accepted 02 July 2023
Published 15 July 2023

Cite this article as:

Senthil Kumar R, Naveena S, Praveen S, Yogadharshini N, Therapeutic aspects of biologically potent vanillin derivatives: A critical review, Journal of Drug Delivery and Therapeutics. 2023; 13(7):177-189

DOI: http://dx.doi.org/10.22270/jddt.v13i7.6159

*Address for Correspondence:

Dr. R. Senthil Kumar, Professor & Head, Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamilnadu, India.

Abstract

4-hydroxy 3-methoxy benzaldehyde (Vanillin) is an aromatic phenolic aldehyde with unique chemical properties and pharmacological impact. Because of its potent nature, it acts as a lead for drug discovery and development techniques. Heterocyclic compounds with vanillin moiety were efficacious and thrive against many emerging infectious diseases, which can also lead to develop numerous fused heterocyclic vanillin derivatives and various heterocyclic compounds such as pyrimidines, quinoxalines, imidazoles or thiazoles. Greener-mediated synthesis is a sustained chemical reaction used to synthesize hazardless vanillin derivatives with a high yield of product in desired time. Due to its several reasonable modifications with high bioactivity, vanillin moiety can be used to develop various potent derivatives like vanillin-based ferrocenyl chalcone derivatives, vanillin-hydrazone derivatives, Schiff base and Mannich base-based derivatives, pyrazoline vanillin-based derivatives, triazole-based vanillin derivatives and vanillin hybrids plays a crucial role in the coordination chemistry. These derivatives exhibited plenty of biological applications, which include anticancer, antioxidant, antibacterial, antitubercular, antimalarial, antiviral, anti-inflammatory, anti-Alzheimer and anti-diabetic effects. Hence, this review focuses on the significance of vanillin derivatives responsible for biological activity.

Keywords: Vanillin; 4-hydroxy 3-methoxy benzaldehyde; Vanillin derivatives; Antimicrobial; Anticancer; Biological applications

Introduction

Vanillin (4-hydroxy 3-methoxy benzaldehyde), a white monoclinic crystalline phenolic aldehyde, has three functional groups, an aldehyde, hydroxy and ether groups located around an arene. The organic modifications in vanillin moiety can be achieved by altering the reactive groups namely, phenol and aldehyde for a good safety impact[1,2]. Vanillin can be synthesized naturally, synthetically and by means of biotechnological ways. Vanillin is obtained naturally from the seed pods of *Vanilla planifolia* orchid. Lignin, guaiacol, 4-hydroxybenzaldehyde and 3-methoxy-4-hydroxy benzyl alcohol are some of the substrates involved in the synthesis of vanillin. It acts as an intermediate substrate for the synthesis of various pharmaceuticals like papaverine, L-methyldopa and trimethoprim[3]. Vanillin can also be prepared by means of biotechnological ways using enzymes i.e., isoeugenol and 4-vinyl guaiacol were converted to vanillin by *oxygenase* which has a coenzyme-independent catalyst activity, while enoyl-CoA *hydratase/aldose* converts the ferulic acid to vanillin[4,5]. In the food and cosmetic industries, ethyl vanillin has been employed as a preservative because it has a remarkable protective effect against both bacteria and fungi. It significantly affects the cytoplasmic membrane of food-related bacteria and fungi such as *Escherichia coli, Lactobacillus plantarum, Listeria innocua, Pseudomonas aeruginosa* and *Aspergillus niger*. In contrast to more effective phenolic antimicrobials, the vanillin derivatives were found to be highly bacteriostatic[6,7]. Vanillin is a non-toxic and bioactive substance with a wide range of pharmacological activity including anticancer and antioxidant[6,8], antimicrobial[9], antimycobacterial[10], antiviral[11], antimalarial[12], anti-inflammatory[13], anti-Alzheimer[14], anti-sickling[15] and antidiabetic[16] activities.

Vanillin was highlighted as a very promising building block for the preparation of bio-based monomers, bio-based epoxy thermosets and cross-linked polymers. Eco-friendly, vanillin derivatives can be synthesized by various approaches such as one-pot multicomponent synthesis, oil bath-assisted synthesis, microwave-assisted synthesis, hot plate with magnetic stirring, grindstone method and solvent-free chemical reactions using a simple trituration technique[2,17]. In Schiff base derivatives, vanillin is used as an aromatic aldehyde with a primary aromatic or aliphatic amine in the presence of a basic catalyst resulting in the formation of azomethine (C=N) linkage which is responsible for various bio-activities. Mannich base is a deamination process used to generate α, β-unsaturated ketone moiety by reaction of the secondary amine with aldehyde and ketone[3,18]. Vanillin hybrids were synthesized by reacting vanillin with various organic compounds or with their derivatives. For consideration, the vanillin reacted with diaryl pyrazole and obtained a pyrazole-based hybrid compound that produced dual activity against oxidative stress and diabetes[19]. Through a conventional method, vanillin-based chalcones were formed by the Claisen-Schmidt condensation reaction by reacting vanillin with different acetophenone derivatives. The vanillin and isovanillin-based chalcones can be referred to as curcumin

mimics[20,21]. Vanillin can also act as a phase transfer catalyst in the conversion of peracetylated lactosyl bromide to vanillin-based lactoside[22]. The biologically potent vanillin Schiff base metal complexes were developed using various metals such as copper, cobalt, manganese, zinc, nickel and palladium[23-26].

In this review, various literature indexed in PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, Springer, Embase and ResearchGate databases were collected between the period of 2011 to 2023 by using the keywords vanillin and its derivatives, anticancer, antimicrobial, antioxidant and biological activities, individually and in combination. The collected literature was shortlisted and scrutinized based on their abstracts. Thus, this review focuses on the potential pharmacological applications of possible derivatives of vanillin and it will be useful for designing potent novel derivatives in the future.

Pharmacological Activity of Vanillin Derivatives

Anti-microbial activity

4-(((4-butylphenyl)amino)methyl)-2-methoxyphenol **(1)** was obtained by reacting vanillin with the aromatic amine. The synthesized compound tested against *E. coli*, *Micrococcus luteus* and *Bacillus subtilis* microorganisms, determined by the broth microdilution method. The better activity was due to the presence of butyl group and lengthy aliphatic chain, which enhanced the antimicrobial property of vanillin derivatives[6]. The novel acetyl vanillin derivatives, 4-(((4-Fluorobenzyl)-imino)-methyl)-2-methoxy-6-nitrophenyl acetate **(2)** and 2-Methoxy-6-nitro-4-(((2-(pyridin-2-yl)-ethyl)-imino)-methyl)-phenyl acetate **(3)** were synthesized by reacting acetyl nitro vanillin with various amines and found to be exhibiting potent antimicrobial agent against *E. coli*, evaluated by using well diffusion method. The presence of electron-withdrawing substituents at the para position of substituted amine in the compounds **(2)** and **(3)** were the reason for their potent antimicrobial effect[7].

Pyridyl substituted (3-methoxy benzylidene)-5-fluoroindolin-2-one derivatives, 5-Fluoro-3-(3-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methoxy)benzylidene)indolin-2-one **(4)** and 5-Fluoro-3-(3-methoxy-4-((4-methoxy-3,5-dimethyl pyridine-2-yl)methoxy) benzylidene)indolin-2-one **(5)** were synthesized by reacting vanillin derivatives, 5-Fluoro-3-(2-hydroxy-3-methoxybenzylidene)indolin-2-one and 5-Fluoro-3-(4-hydroxy-3-methoxybenzylidene)indolin-2-one with 2-chloromethyl pyridine and they were screened for *in vitro* and *in silico* antimicrobial studies. The *in vitro* antimicrobial effect was analyzed through the agar well diffusion method against fungal *(Candida albicans),* gram-positive bacterial *(Streptococcus pyogenes, Staphylococcus aureus)* and gram-negative bacterial *(P. aeruginosa, E. coli)* species. Thus, the vanillin pyridyl-based derivatives showed broad-spectrum antimicrobial activity against bacterial and fungal species with better DNA gyrase inhibition[9]. Vanillin chalcone derivatives, (E)-1-(4-Chlorophenyl)-3-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)prop-2-en-1-one **(6)** and (E)-3-(4-(2-(Dimethylamino)ethoxy)-3-methoxyphenyl)-1-(p-tolyl)prop-2-en-1-one **(7)** were synthesized by Claisen-Schmidt reaction and found to be having potent antifungal activity against three dermatophytes (*Trichophyton rubrum*, *T. mentagrophytes* and *Microsporum gypseum*). The potent activity was due to the presence of electron-withdrawing substituted chalcone with high electrophilic character[20].

Vanillin-derived Schiff bases, (E)-2-(4-hydroxy-3-methoxybenzylideneamino)-4-methoxybenzoic acid **(8)** and (E)-4-(4-hydroxy-3-methoxybenzylideneamino) benzoic acid **(9)** were obtained by reacting vanillin with various aromatic amines such as 2-amino-4-methoxy benzoic acid and *p*-amino benzoic acid in presence triethyl amine as a basic catalyst. These compounds exhibited excellent antibacterial activity against both gram-positive and gram-negative bacterial species (*B. subtilis, S. aureus, Klebsiella pneumonia* and *P. aeruginosa*), determined by the disc diffusion method[27]. Vanillin hydroxamic derivative, 2-[2-ethoxy-4-({[2-(pyridin-2-yl)ethyl]amino}methyl)phenoxy]-N-hydroxyacetamide **(10)** was synthesized by condensing vanillin derivative, ethyl 2-(2-ethoxy-4-(((2-(pyridin-2-yl)ethyl)amino)methyl)phenoxy) acetate with hydroxylamine and the obtained novel peptide *deformylase* inhibitor showed promising antibacterial activity against *E. coli*, *S. aureus*, *A. oryzae* and *A. foetidus* microorganisms, which was also utilized to treat drug-resistant pathogens[28]. The structures of the above discussed compounds are given in figure 1.

A novel chalcone and pyrazoline derivatives bearing substituted vanillin nucleus were screened for antibacterial and antifungal activity against gram-positive (*S. aureus* and *M. luteus*), gram-negative bacteria (*E. coli* and *Salmonella typhi*) and *C. albicans* as a fungal organism. The chalcone derivative, 3-(3-Methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-1-arylprop-2-en-1-one **(11)** and the corresponding pyrazoline derivative, 1-(5-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy) phenyl)-3-aryl-4,5-dihydro-1H-pyrazol-1-yl)ethanone **(12)** were designed and synthesized by reacting vanillin derivatives, 3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl)methoxy) benzaldehyde and 3-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy) phenyl)-1-arylprop-2-en-1-one with corresponding acetophenone and hydrazine hydrate. The result indicated that the synthesized compounds were found to be exhibiting better antibacterial activity against the tested species. Thus, the replacement of phenyl ring with heterocyclic rings demonstrated significant antibacterial activity against commercial drugs[29]. 3-chloro-4-(4-(dimethylamino)phenyl)-1-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one **(13)** and 2-(4-(dimethylamino)phenyl)-3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one **(14)** were synthesized by reaction carried out between the obtained vanillin derivative, 4-(5-((4-(substituted)benzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxy phenol with chloroacetyl chloride and mercaptoacetic acid. Thus, both compounds showed potent antibacterial and antifungal activity, determined by the cup plate method against *S. aureus, S. typhi, E. coli, K. pneumonia*, *C. albicans* and *A. niger*[30].

Vanillin-derived piperidin-4-one oxime esters with phenyl ester as a substituent, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-(4-fluorobenzoyl) oxime **(15)** and 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-(4-chlorobenzoyl) oxime **(16)** were synthesized by reacting a vanillin derivative, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one oxime with substituted benzoyl chlorides and found to be possessing considerable antimicrobial activity against bacterial and fungal species such as *E. coli*, *S. aureus*, *P. aeruginosa*, *A. flavus, C. albicans* and *Chrysosporium keratinophilum*. Hence, the presence of electron-withdrawing substituents such as fluoro and chloro group at the para position of aryl ester in both compounds has been found to be an essential part of the antimicrobial effect[31].

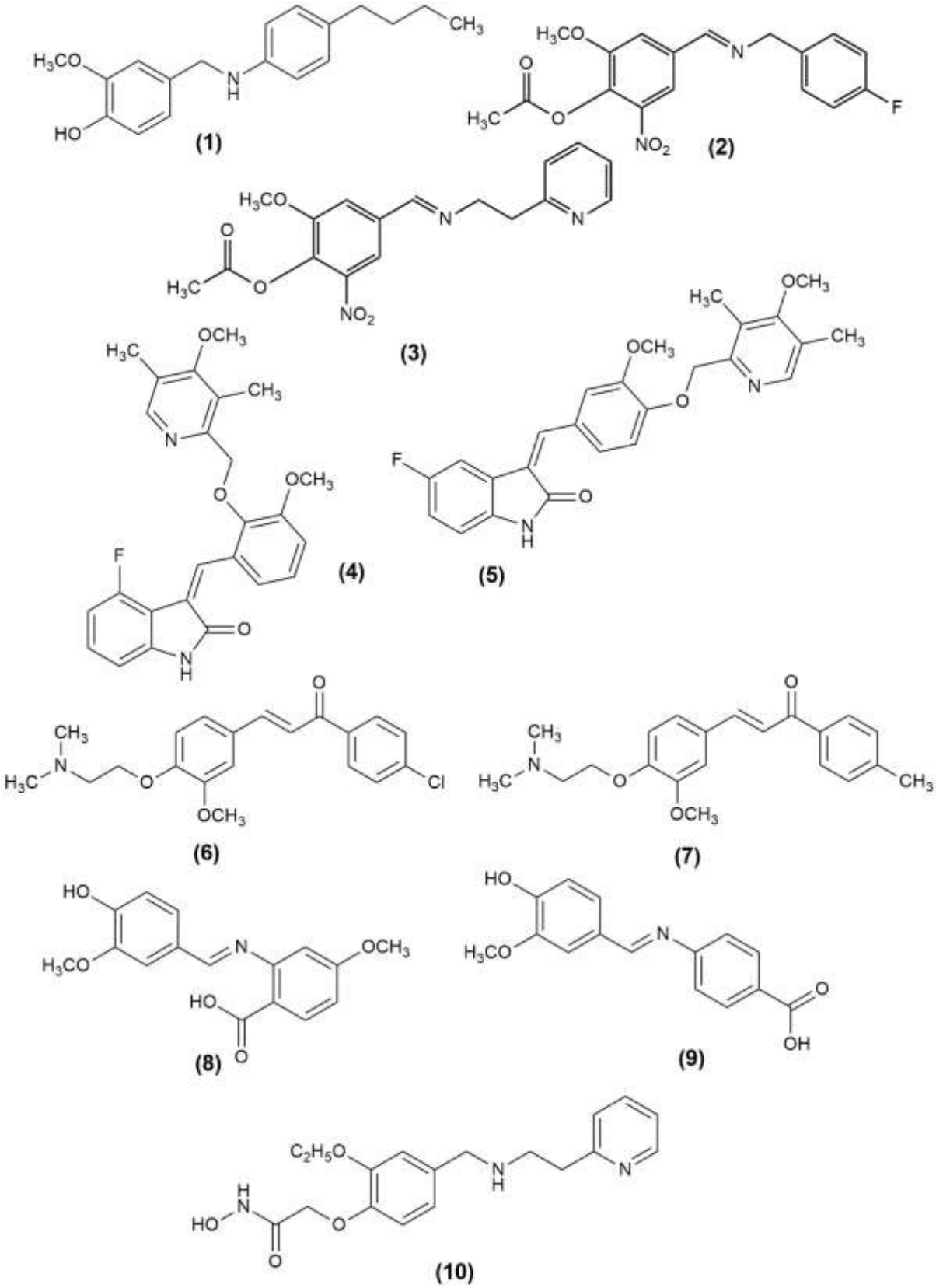

Figure 1: Compounds with antimicrobial activity

Using click reaction, 1,2,3-triazoles and Bis-1,2,3-triazoles derivatives were synthesised by reacting vanillin derivative, 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde with 1-(3-azidopropoxy)-3-nitrobenzene and 1,3-bis(3-azidopropoxy) benzene yield two bioactive compounds 3-methoxy-4-((1-(3-(3-nitrophenoxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde **(17)** and 4,4'-(((((1,3-phenylenebis(oxy)) bis(propane-3,1-diyl))bis(1H-1,2,3-triazole-1,4-diyl))bis (methylene))bis(oxy))bis(3-methoxybenzaldehyde) **(18)**. Both of them were evaluated for antimicrobial activity by the agar well diffusion method. The compound **(17)** bearing propoxy phenyl ring offers antibacterial activity against gram-negative bacteria such as *P. aeruginosa* and *Shigella dysenteriae* and the compound **(18)** with a benzene ring as an aromatic linker between both triazoles also showed promising antibacterial activity against *B. subtilis,* Methicillin-resistant *S.*

aureus, S. epidermidis, S. saprophyticus and Vancomycin-resistant *Enterococcus* organisms. The molecular docking studies were also correlated with the *in vitro* findings[32].

Vanillin-based ferrocenyl chalcone derivatives, 1-Ferrocenyl-3-(4-ethoxy-3-methoxyphenyl)prop-2-en-1-one **(19)** and 1-Ferrocenyl-3-(3-methoxy-4-propoxyphenyl)prop-2-en-1-one **(20)** were designed and synthesized by reacting o-alkylated vanillin derivatives with acetyl ferrocene using Claisen-Schmidt reaction. The obtained novel derivative showed significant antibacterial activity against various bacterial species such as *S. aureus*, *B. subtilis*, *B. cereus*, *E. coli* and *Proteus mirabilis* with better MIC (minimum inhibitory concentration) values indicating the presence of active ferrocene moiety, determined by the broth microdilution method. 1-Ferrocenyl-3-(4-isopropoxy-3-methoxyphenyl) prop-2-en-1-one **(21)** with the same active ferrocene moiety produced antifungal activity against five fungal species such as *A. niger*, *C. albicans*, *Penicillium italicum*, *Mucor mucedo* and *Trichoderma viride*[33]. The structures of the anti-microbial compounds are given in figure 2.

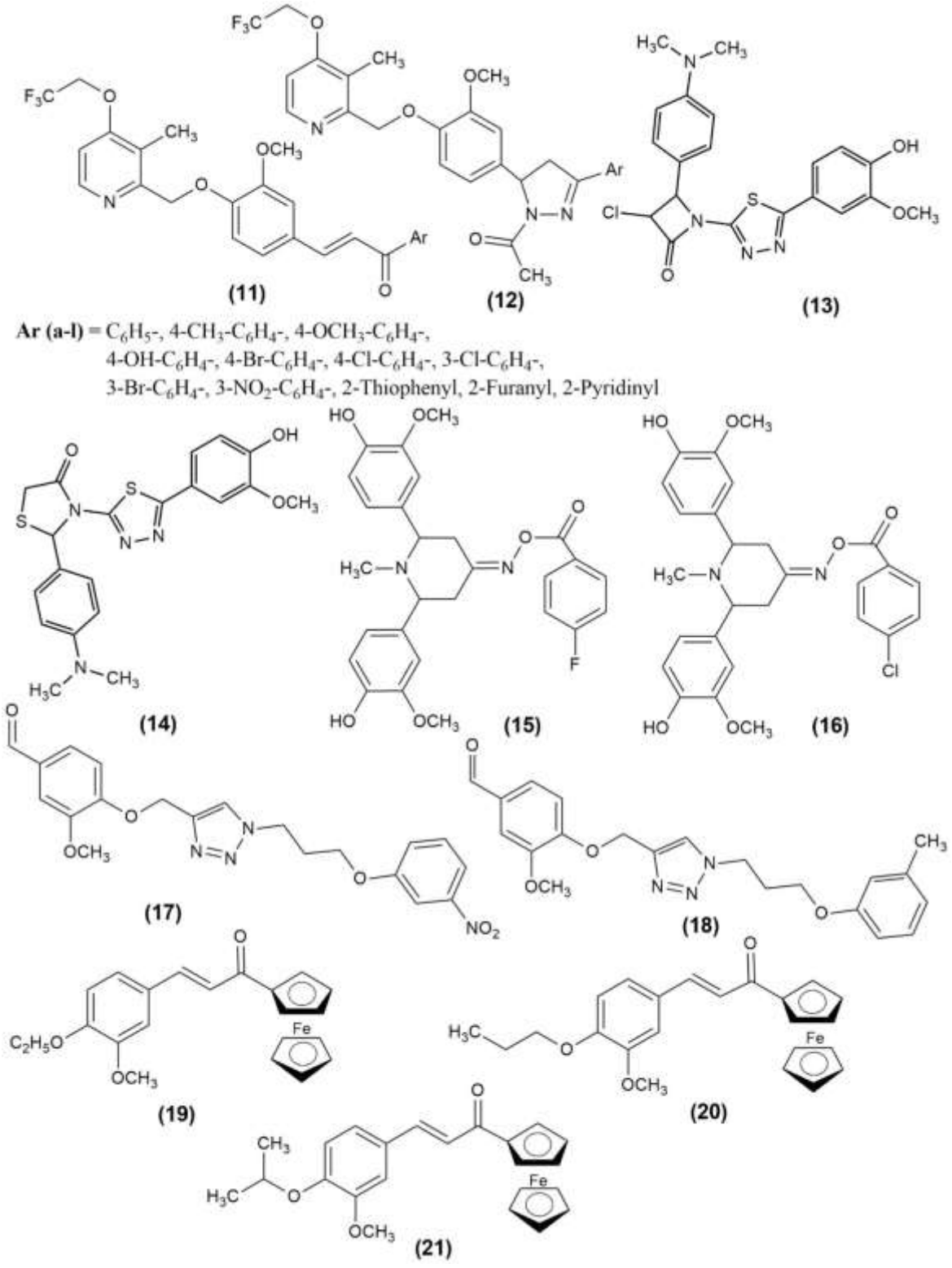

Figure 2: Compounds possessing antimicrobial activity

The reaction between dimedone with aromatic aldehyde resulted in 1,8-dioxo-octahydroxanthene derivative, 9-(3-ethoxy-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**22**) which had very strong antibacterial activity against *S. epidermidis.* Hence, the potent activity was due to the ethoxy substitution, determined by the agar well diffusion method[34]. The coupling of vanillin hydrazone derivatives, 4-[2-(4-Phenyl-1H-1,2,3-triazol-1-yl)ethoxy]-3-methoxybenzaldehyde and 4-[2-(4-(2,4,6-Trimethoxyphenyl)-1H-1,2,3-triazol-1-yl)ethoxy]-3-methoxy benzaldehyde with substituted benzohydrazides produced (E)-3,4,5-Trimethoxy-N'-{3-methoxy-4-[2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethoxy]benzylidene}benzohydrazide (**23**) and (E)-3,4,5-Trimethoxy-N'-{3-methoxy-4-[2-{4-(2,4,6-trimethoxyphenyl)-1H-1,2,3-triazol-1-yl}ethoxy]benzylidene} benzohydrazide **(24)** and they were screened for antibacterial activity using the agar well diffusion method. The presence of 3,4,5-trimethoxyphenyl and phenyl substituent in the compound **(23)** and 1,3,5-trimethoxyphenyl and 3,4,5-trimethoxyphenyl substituent in the compound **(24)** were responsible for increased activity against four bacterial strains such as *E. coli, P. aeruginosa, S. pyogenes* and *S. aureus*[35].

Vanillin derivatives with 1-Pyrimidin-2-yl piperidine-4-carboxylic acid hydrazide resulted in novel vanillin hydrazone derivatives, namely, 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid (4-butoxy-3-methoxy-benzylidene)-hydrazide **(25)** and 1-Pyrimidin-2-yl-piperidine-4-carboxylic acid [3-methoxy-4-(2-methoxy-ethoxy)-benzylidene] hydrazide **(26)**. The newly derived compounds were determined for antibacterial activity against both gram-positive and gram-negative bacterial strains (*S. aureus* and *P. aeruginosa*) by using the paper disc diffusion method and showed better antibacterial activity against the tested microorganisms. The better activity was due to the presence of butoxy, methoxy and methyl-ethoxy groups with a highly reactive azomethine group[36].

2-{[(4-fluorophenethyl)imino]methyl}-6-methoxyphenol **(27)** was derived simply by reacting ortho vanillin with aliphatic amine and examined for antifungal activity against *C. albicans* species. Due to the presence of azomethine moiety, it produced a good MIC value with a better radius of inhibition, determined by agar-well diffusion and broth microdilution techniques[37]. Vanillin hybrid derivative, (Z)-3-methoxy-4-(2-(4-((4-(3-oxoprop-1-en-1-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde **(28)** was synthesized by hybridization of alkyne with azomethine moiety produced vanillin connected triazole moiety acted as a potent inhibitor of LasR (Intracellular receptor-type transcription factor) and PqsR (PQS-binding response regulator) receptors by ameliorating the virulence of the gram-negative pathogen *P. aeruginosa*[38]. The structures of the above discussed molecules are given in figure 3.

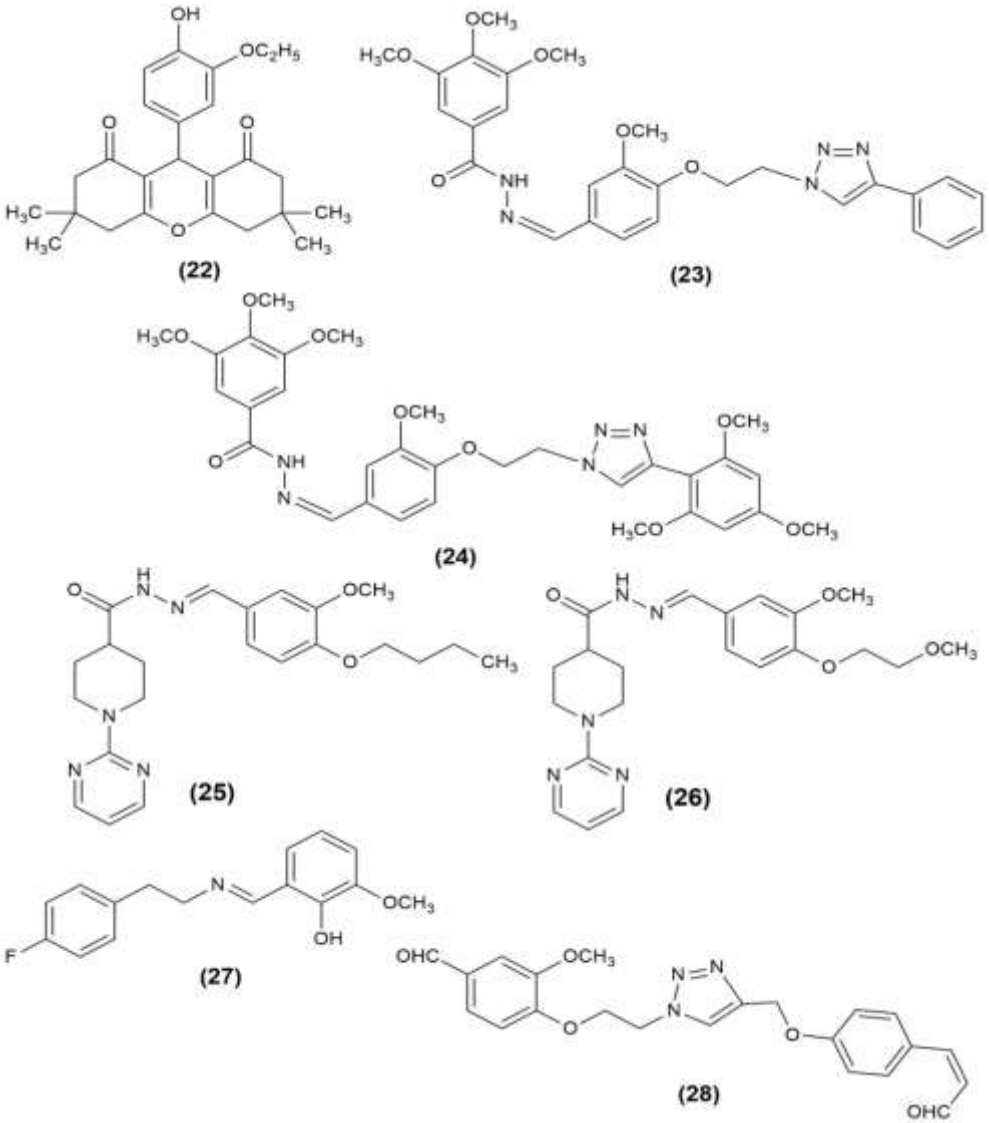

Figure 3: Compounds showed antimicrobial activity

Antitubercular activity

Tuberculosis was mainly due to *Mycobacterium tuberculosis,* a bacterial strain responsible for the leading cause of life-threatening lung infectious disease over a global population. Thus, a vanillin lipophilic amine derivative, 2-methoxy-4-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamino)methyl)phenol **(29)** was synthesized by reductive amination of vanillin with aromatic amine showed a promising degree of antimycobacterial activity against *M. tuberculosis* H37Ra strain, determined by the microplate resazurin assay. The range of bioactivity varied depending on the position of boron substitution in the aniline ring. Thus, the compound **(29)** bearing a boron moiety in the ortho position of the ring was responsible for the elevated potent activity[10].

A novel thiadiazole-based vanillin derivative, 4-(5-amino-1,3,4-thiadiazol-2-yl)-2-methoxyphenol **(30)** was obtained by reacting vanillin derivative, 2-(4-hydroxy-3-methoxybenzylidene) hydrazinecarbothioamide with two leading active moiety vanillin and thiosemicarbazide possessed significant antitubercular activity against *M. tuberculosis* H37Rv strain in Middlebrook 7H9 broth base i.e., a liquid growth medium used for *Mycobacterium* species, especially for *M. tuberculosis* adaptive growth[30]. A vanillin derivative, 7-methoxy-2-[4-(methoxy)phenyl)-l-benzofuran-5-carboxaldehyde undergoes reductive amination with 3-chloroaniline to form 3-Chloro-N-{[7-methoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline **(31)** which showed better antitubercular activity, determined by *in silico* molecular docking studies[39]. The structures of the above discussed compounds are given in figure 4.

Antimalarial activity

The infectious disorder transmitted by female mosquitoes belong to the genus of *Plasmodium* parasite leads to severe pathological conditions in the secondary host. The researchers developed some vanillin derivatives as a formidable antimalarial drug against the active parasite. A novel aminoalkylated chalcone derivative, (E)-1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxy-5-(piperidin-1-ylmethyl)phenyl)-prop-2-en-1-one **(32)** was synthesized by the reaction carried out between vanillin and chloroacetophenone through Claisen-Schmidt condensation and followed by addition of amine through Mannich base reaction. The obtained compound **(32)** showed significant antimalarial activity against chloroquine-resistant *Plasmodium falciparum,* determined by *in vitro* antimalarial studies and *in silico* docking studies. Hence, the addition of a secondary amine to this derivative resulted in increased antimalarial activity[12].

The i*n vitro* study of vanillin containing 9H-fluoren sulfone derivatives, (9H-fluoren-9-yl)methyl((2S)-1-((1-(4-ethoxy-3-methoxyphenyl)-2-(methylsulfonyl)ethyl)amino)-1-oxopropan-2-yl)carbamate **(33)** and (9H-fluoren-9-yl)methyl ((2R)-1-((1-(4-ethoxy-3-methoxyphenyl)-2-(methylsulfonly) ethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **(34)** showed better antimalarial activity against *P. falciparum* and both compounds were prepared by coupling 1-(4-ethoxy-3-methoxyphenyl)-2-(methylsulfonyl)ethan-1-amine with triethylamine and N, N-dimethylformamide. Thus, the compound containing methyl sulfone group, methoxy group at the third position and ethoxy group at the fourth position in the phenyl ring are responsible for the activity against *P. falciparum*[40]. The structures of the above discussed compounds are given in figure 4.

Antiviral activity

1-(3-formyl-5-methoxyphenyl)guanidine **(35)** was obtained by reacting vanillin with the guanidine and acted as a potential H1N1 *neuraminidase* inhibitor with the lowest EC_{50} (Half maximal effective concentration) value, determined by the enzymatic H1N1 *neuraminidase* inhibition assay. The antiviral activity was due to the presence of the guanidine group[11]. 1,2,3-triazoles vanillin derivative, 4-((1-(4-isopropylbenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde **(36)** was synthesized and found to be effective against Zika virus through *in vitro* and *in silico* docking studies[41]. The structures of the above discussed compounds are presented in figure 4.

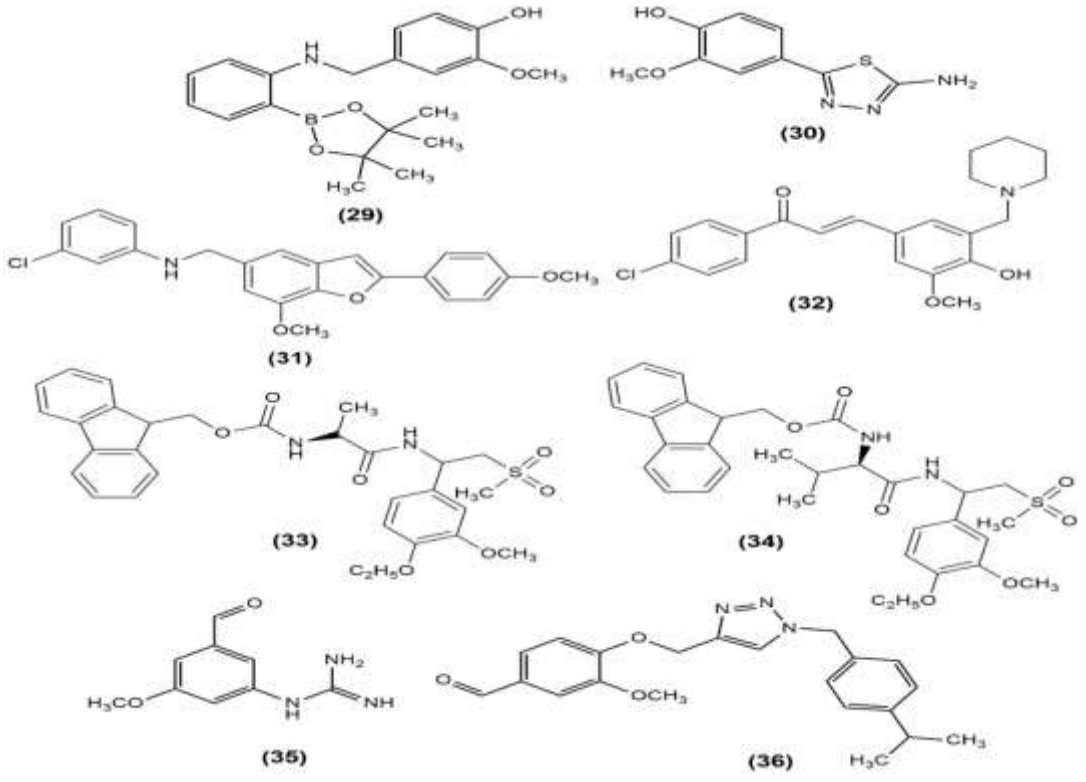

Figure 4**:** Compounds possessing antitubercular (29-31), antimalarial (32-34) and antiviral (35-36) activities

Anti-cancer activity

A vanillin derivative reacted with substituted sulfanilamide to synthesize *in vitro* cytotoxic potential compounds such as (E)-4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)-N-(pyridin-2-yl)benzenesulfonamide **(37),** (E)-2-methoxy-4-(((4-(N-(pyridin-2- yl)sulfamoyl)phenyl)imino)methyl)phenyl acetate **(38)** and (E)-2-methoxy-4-(((4-(N-(pyridin-2-yl) sulfamoyl)phenyl)imino)methyl)phenyl isobutyrate **(39)**. Then, these compounds were found to be significantly active against MCF-7 human breast cancer cell line. The *in silico* studies also correlated with the experimental outcomes and resulted in better interactions between the receptor and ligands. From the outcomes, it indicated that the compound containing azomethine group with sulfomoyl moiety and phenyl carboxylate system showed potent anticancer activity[3]. 4-(1H-imidazo[4,5-f][1,10]-phenanthrolin-2-yl)-2-methoxyphenol **(40)** was synthesized by reacting vanillin with 1,10-phenanthroline-5,6-dione and evaluated against human colorectal carcinogenic cell lines such as HT29 and HCT116 cells. The tested compound was found to be highly active against colorectal cancer, determined by the inhibition of Wnt/β-catenin signaling pathway. The molecular docking studies with better interactions confirmed that this compound had a significant effect against the colorectal cancer target[8].

A vanillin derivative, 2-(4-hydroxy-3-methoxy benzylidene)indan-1-one reacted with a secondary amine to synthesize 2-(4-hydroxy-3-dipropylaminomethyl-5-methoxy benzylidene)indan-1-one **(41)** and the obtained compound was studied against four human oral squamous cell carcinoma cell lines in the gingiva (Ca9–22), the tongue (HSC-2, HSC-3, HSC-4) and human normal oral cells namely, gingival fibroblasts (HGF), periodontal ligament fibroblasts (HPLF) and human pulp cells (HPC). The presence of dipropilamino moiety possesses potent anticancer activity against tested carcinoma cell lines with a good CC_{50} (50% Cytotoxicity concentrations) range[18]. (Z)-2-(4-hydroxy-3-methoxy benzylidene)hydrazinecarboxamide **(42)** showed prominent efficacy against Ehrlich-Lettre ascites carcinoma (EAC) cells in Swiss albino mice with an improved cell growth inhibition, tumour weight reduction and also resulted in the enhancement of survival time[42]. The structures of the above discussed compounds are given in figure 5.

Anti-oxidant activity

The spectrophotometric method was used for the determination of the antioxidant activity of vanillyl acetate **(43)** and *o*-methoxy-*p*-methyl cyclohexan-1-ol **(44)**. Both compounds were synthesized by reacting vanillin with acetic anhydride and tetrahydrofuran. The results revealed that the reduction and acetylation process of vanillin enhanced the antioxidant activity[1]. Vanillin reacted with aromatic amine and produced a potential antioxidant vanillin derivative, 4-(((4-butylphenyl)amino)methyl)-2-methoxyphenol **(45)**, determined by DPPH (2,2-diphenylpicrylhydrazyl), ($ABTS^{\bullet+}$) (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) and FRAP (Ferric reducing antioxidant power) assay. The phenyl group linked to the NH group was responsible for the potential antioxidant activity[6]. The vanillin-derived piperidine-4-one oxime ester derivatives, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *o*-(3,5-dihydroxy benzoyl) oxime **(46)** and 2,6-bis(4-hydroxy-3-methoxy phenyl)-1-methylpiperidin-4-one *o*-(3,4,5-trihydroxybenzoyl) oxime **(47)** were synthesized by reacting a vanillin derivative, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one oxime with substituted benzoyl chlorides and analyzed through DPPH and $ABTS^{\bullet+}$ radical scavenging activity. The compounds with the presence of a hydroxy group on phenyl ester in their structure were responsible for potent anti-oxidant activity[31]. 3-((3,4-dihydroxyphenethyl)amino)-3-(4-hydroxy-3-methoxyphenyl)-N-phenylpropanamide (**48)** and N-(4-bromophenyl)-3-((3,4-dihydroxyphenethyl)amino)-3-(4-hydroxy-3-methoxyphenyl) propanamide **(49)** were designed and synthesized by solvent-free method with simple trituration of reactive components such as dopamine, vanillin and N-methylacetamide. The obtained compounds were found to be better antioxidant potential with significant *antityrosinase* activity, determined by the ABTS, AAPH (2,2'-azobis (2-amidinopropane) dihydrochloride) free-radical assay, Nitric oxide (NO) scavenging activity and H_2O_2 scavenging activity. Hence, both compounds were commonly bearing a dopamine-connected vanillin substituent in their structure and showed elevated antioxidant activity with a better IC_{50} (Half-maximal inhibitory concentration) value[43]. The structures of the above discussed compounds are given in figure 5.

The novel vanillin derivatives, 4,4'-(((3-hydroxypropyl) azanediyl)bis(methylene))bis(2-methoxyphenol) **(50)** and 4, 4',4'',4'''-((1,4-phenylenebis (azanetriyl))tetrakis(methylene)) tetrakis(2-methoxyphenol) **(51)** were obtained by reacting vanillin with 3-amino-1-propanol and *p*-phenylenediamine. Both compounds exhibited strong antioxidant activity in DPPH, FRAP and ORAC (Oxygen radical absorbance capacity) assay. The presence of a tertiary amino group along with vanillin moiety in the molecule contributed to produce potent antioxidant activity[44]. Amino-alkylation of vanillin derivative, dehydrozingerone by Mannich base reaction produced 4-{3-[(dimethylamino)methyl]-4-hydroxy-5-methoxyphenyl}but-3-en-2-one **(52)** and the obtained novel compound was subjected to free-radical DPPH scavenging activity which has highest antioxidant activity due to the presence of tertiary amine, phenolic functionality, vanillin moiety and electronic delocalization[45]. The structures of the above discussed compounds are given in figure 6.

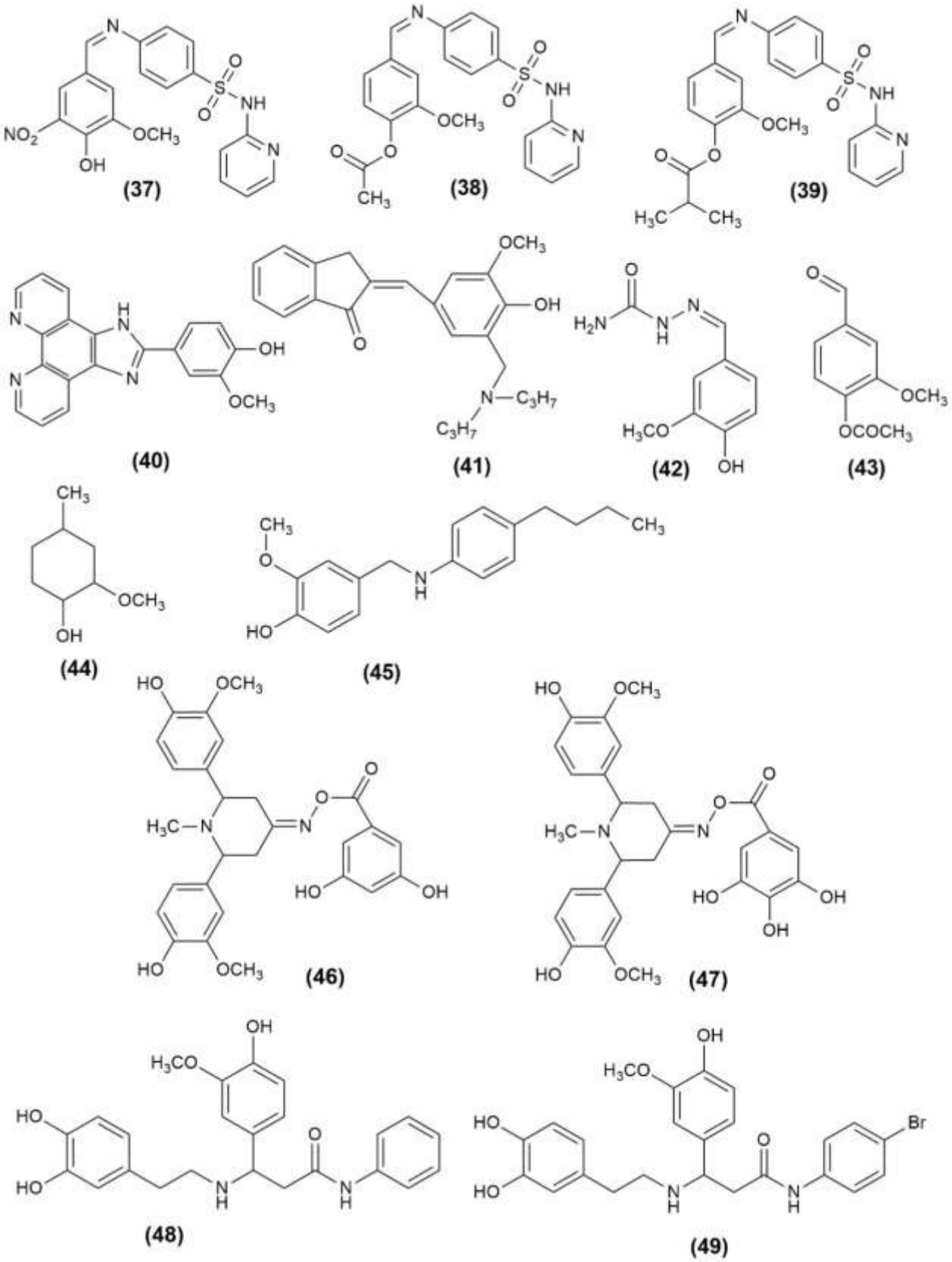

Figure 5: Compounds with anticancer (37-42) and antioxidant (43-49) activities

Anti-inflammatory activity

Vanillin-triazine derivative, 4-(4-(4-formyl-3-methoxy phenoxy)-6-chloro-1,3,5-triazin-2-ylamino)benzonitrile **(53)** was synthesized by the reaction carried out between 4,6-dichloro-1,3,5-triazine-2-ylphenylamine derivative with vanillin showed a significant anti-inflammatory effect due to the presence of three active substance triazine, vanillin, and phenylpyrazole, determined through *in vivo* animal studies and *in silico* docking studies with *cyclooxygenase*-1 and *cyclooxygenase*-2 isoenzymes[13]. A vanillin derivative, dehydrozingerone undergoes amino-alkylation through Mannich base reaction produced 4-{4-hydroxy-3-methoxy-5-[(4-methylpiperazin-1yl)methyl]phenyl}but-3-en-2-one **(54)**

which has N-methyl piperazine was a responsible moiety for potent anti-inflammatory effect, determined by the inhibitory of heat-induced albumin denaturation method with better IC_{50} range[45].

The anti-inflammatory effect of the synthesized derivatives, (4-nitro-phenyl)-acetic acid [4-(4'-fluoro-biphenyl-4-yl methoxy)-3-methoxy-benzylidene]-hydrazide **(55)** and (2,3-dihydro-benzofuran-5-yl)-acetic acid [4-(4'-fluoro-biphenyl-4-ylmethoxy)-3-methoxy-benzylidene]-hydrazide **(56)** were evaluated by using carrageenan-induced mice model. These compounds were synthesized by coupling vanillin with biphenyl moiety in the presence of various intermediates. The results revealed that the presence of 2-phenylacetohydrazides moiety in both compounds showed significant anti-inflammatory activity[46]. Vanillin derivative, 4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzaldehyde reacted with benzohydrazide derivative and yield a novel compound (E)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-hydroxybenzohydrazide **(57)** which has a hydroxy group at the fourth position in its structure showed effective anti-inflammatory activity in a carrageenan-induced rat model study[47]. Pyrazoline derivative of vanillin, 3-(4-aminophenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide **(58)** was synthesized by reacting a vanillin chalcone derivative, (2E)-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one with thiosemicarbazide produced a potent anti-inflammatory compound through *cyclooxygenase* assay[48]. The structures of the anti-inflammatory compounds are given in figure 6.

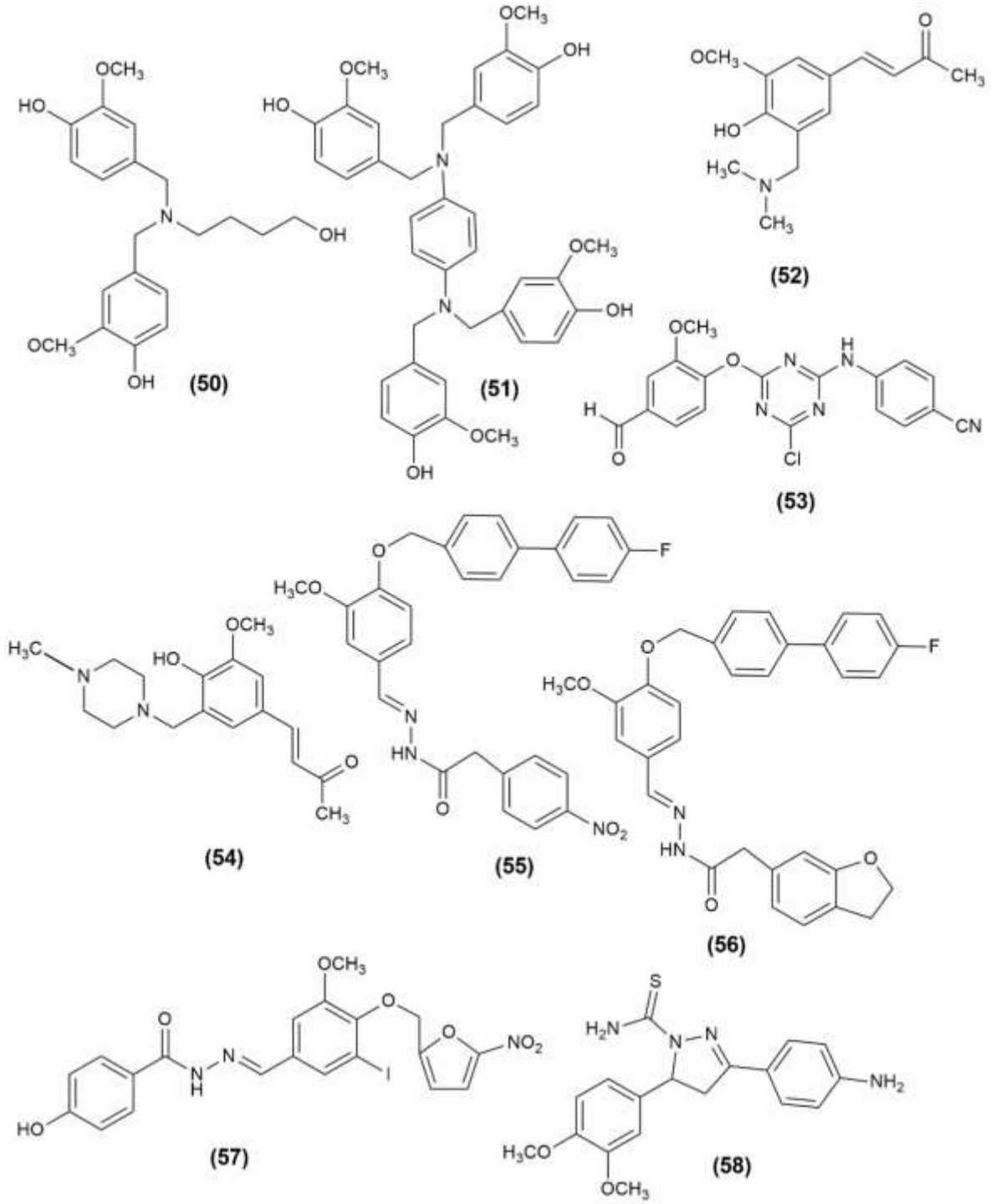

Figure 6: Compounds possessing antioxidant (50-52) and anti-inflammatory (53-58) activities

Anti-Alzheimer's activity

The accumulation of amyloid β peptide $A\beta_{(1-42)}$ in the extracellular as a plaque was one of the main pathological conditions that lead to the cause of Alzheimer's disease. Thus, (2-(3-(bis(4-hydroxy-3-methoxybenzyl)amino)propyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione) **(59)** was obtained by reacting di-vanillin derivative with naphthalimide exhibited potent *butyrylcholinesterase* (BuChE) selective inhibition activity with a better IC_{50} value, which was greater than the corresponding *acetylcholinesterase* (AChE) inhibitory activity. The synthesized compound was targeted to cross the BBB (Blood Brain Barrier) for potential activity. The computational study was carried out to predict the logP nature of the compound. Hence, the compound **(59)** with naphthalimide has a maximum ability to cross the BBB with a better logP range represented as a potential base for multi-target Alzheimer's disease (AD) therapeutic activity[14].

N1-(1,2,3,4-tetrahydroacridin-9-yl)benzene-1,4-diamin coupled with vanillin to form a new vanillin scaffold, 2-methoxy-4-(((4-((1,2,3,4-tetrahydroacridin-9-yl)amino) phenyl)amino)methyl)phenol **(60)** which inhibited the $A\beta_{(1-42)}$ peptide aggregation due to the presence of phenolic moiety with tacrine in their structure, determined by Thioflavin T (ThT) dye fluorescence assay[49]. Vanillin azomethine derivatives, 4-(4-Hydroxy-3-methoxybenzylideneamino) benzoic acid **(61)**, 4-(4-Hydroxyphenylimino) methyl)-2-methoxyphenol **(62)** and 2-Methoxy-4-(phenylimino) methyl)phenol **(63)** were obtained by reacting vanillin with aromatic amines. The existence of potent azomethine moiety showed considerable *in vitro acetylcholinesterase* inhibitory activity through AChE inhibition assay with a better IC_{50} range[50]. The structures of the above discussed compounds are given in figure 7.

Anti-sickling activity

Sickling is carried out when the hemoglobin inside the red blood cells clumps or sticks together and the cells lead to become fragile, rigid and sickle-shaped. These sickled cells are counteracted by a novel pyridyl vanillin derivative, 5-methoxy-2-[(pyridin-2-yl)methoxy]benzaldehyde **(64)** was synthesized by reacting vanillin derivative with 2-(bromomethyl)pyridine and exhibited a prominent antisickling activity due to the presence of methoxy group and also by stabilizing the R-state Hb complex by increasing O_2 affinity[15]. The structures of the above discussed compounds are given in figure 7.

Anti-diabetic activity

The morbid condition of the pancreas leads to the insufficiency of insulin production. Nowadays millions of populations were affected by diabetes mellitus. Thus, the vanillin-based acetohydrazide-hydrazone derivative, (2,3-dihydro-benzofuran-5-yl)-acetic acid [4-(4-cyano-benzyloxy)-3-methoxy-benzylidene]-hydrazide **(65)** was designed and synthesized by coupling a vanillin derivative, 4-((4-formyl-2-methoxyphenoxy)methyl)benzonitrile with 2-(2,3-dihydrobenzofuran-6-yl)acetohydrazide. The potent activity was due to the presence of 2,3-dihydrobenzofuran substituent in the synthesized compound, determined through *in vivo* study in alloxan-induced diabetic rats[16].

A vanillin hybrid, 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N'-[(Z)-(4-hydroxy-3-methoxyphenyl)methylidene]-4-methyl-1H-pyrazole-3-carbohydrazide **(66)** was synthesized by reacting 1,5-diarylpyrazole-3-carboxylic acids with vanillin and t-butyl carbazate. The hypoglycaemic activity was evaluated by using *in vivo* diabetes-induced rat model study. The presence of pyrazole moiety indicated a considerable anti-diabetic effect with a greater decrease in glycemia[19]. Thiazolidinedione vanillin derivative, (z)-5(4-hydroxy-3-methoxybenzylidine)-2,4-thiazolidinedione reacted in the presence of diazonium salt offered two novel compounds namely, 5-((E)-4-hydroxy-3-methoxy-5-((Z)-(4(methyl sulfonyl)phenyl)diazenyl)benzylidene) thiazolidine **(67)** and 5-((Z)-4-hydroxy-3-methoxy-5-((E)-(3,4,5-trimethoxyphenyl) diazenyl) benzylidene) thiazolidine-2,4-dione **(68)**. Both compounds showed effective hypoglycaemic activity by *in vivo* antidiabetic assay[51]. The structures of the anti-diabetic compounds are presented in figure 7.

Radioprotective activity

Before radiation therapy radioprotective drugs are utilized in order to ensure high protection to prevent radiation-induced damage. The vanillin derivative, 4-hydroxy-3,5-dimethoxybenzaldehyde **(69)** improved the survival of lethally irradiated mice by promoting intestinal regeneration by significantly increasing the number of $Lgr5^+$ intestinal stem cells (ISCs) with their daughter cells and the transient $Ki67^+$ proliferating cells. The appropriate level of activated p53 gene was maintained which triggered the cell cycle arrest but it does not sufficient to induce NOXA-mediated apoptosis, thus it ensured the DNA damage repair in the irradiated small intestinal crypt cells. Further, it restored the intestinal bacterial flora structures altered by TBI (Traumatic brain injury) exposure. Thus, compound **(69)** had excellent radio-protective activity by modulating the p53/NOXA signaling pathway and also restoring the balance of gut microbiota[52]. The structures of the above discussed compounds are given in figure 7.

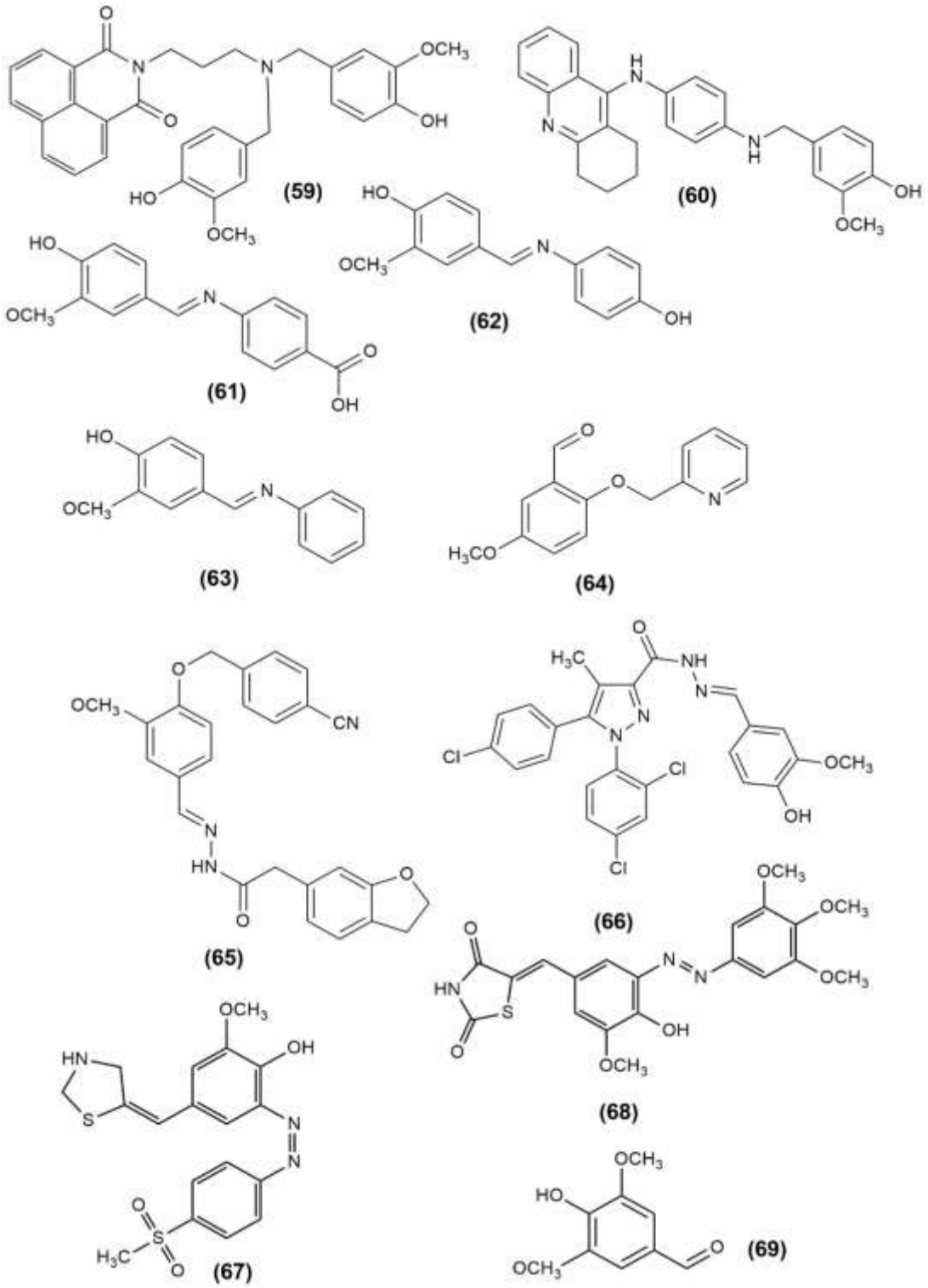

Figure 7: Compounds showed anti-Alzheimer (59-63), anti-sickling (64), antidiabetic (65-68) and Radioproductive (69) activities

Conclusion

This review summarized the medicinally potent vanillin derivatives synthesized through recent development techniques. Hence, the researchers developed novel potential antimicrobial agents against various microbial species from vanillin moiety with a better inhibition rate. These derivatives can also act as an anticancer agent with high efficacy against various carcinoma cell lines resulting in induced cellular apoptosis. Apart from these activities, vanillin derivatives have a more prominent and extensive role against diverse diseases than the comparative standard drugs by easily modulating severe pathological conditions. Some recently developed vanillin derivatives are chalcone-based derivatives, hydrazone-based derivatives, azomethine Schiff base derivatives, Mannich-base derivatives, pyrazoline-based derivatives, triazole-based derivatives, vanillin-based hybrid molecules and metal complexes. Because of its massive therapeutic effect, it is continuously involved in the recent development techniques and also sustain in the field of medicinal chemistry as a leading scaffold.

Acknowledgement

We thank the Management and Dr. G. Murugananthan, the Principal of our college for giving constant support and encouragement for writing this review.

Author's Contributions: All the authors have contributed equally.

Funding: Nil.

Conflicts of Interests: The authors declare no conflict of interest.

References

1. Oladimeji HO, Njinga S, Abdullahi ST. Evaluation of Antioxidant Activity of Obtained Derivatives of Vanillin. J Pharm Res Sci Technol. 2022; 6(1):17-26. https://doi.org/10.31531/jprst.1000157.
2. Breloy L, Negrell C, Mora AS, Li WSJ, Brezova V, Caillol S, et al. Vanillin Derivative as Performing Type I Photoinitiator. Eur Polym J. 2020; 132(3):109727. https://doi.org/10.1016/j.eurpolymj.2020.109727.
3. Sahoo CR, Paidesetty SK, Sarathbabu S, Dehury B, Kumar NS, Padhy RN. Molecular dynamics simulation, synthesis and topoisomerase inhibitory actions of vanillin derivatives: a systematic computational structural integument. J Biomol Struct Dyn. 2022; 40(22):11653-63. https://doi.org/10.1080/07391102.2021.1961867.
4. Furuya T, Kuroiwa M, Kino K. Biotechnological production of vanillin using immobilized enzymes. J Biotechnol. 2016; 243:25-28. https://doi.org/10.1016/j.jbiotec.2016.12.021.
5. Saito T, Aono R, Furuya T, Kino K. Efficient and long-term vanillin production from 4-vinylguaiacol using immobilized whole cells expressing Cso_2 protein. J Biosci Bioeng. 2020; 130(3):260-64. https://doi.org/10.1016/j.jbiosc.2020.04.012.
6. Fayeulle A, Trudel E, Damiens A, Josse A, Youssef NBH, Vigneron P, et al. Antimicrobial and antioxidant activities of amines derived from vanillin as potential preservatives: Impact of the substituent chain length and polarity. Sustain Chem Pharm. 2021; 22:100471. https://doi.org/10.1016/j.scp.2021.100471.
7. Yadav R, Saini D, Yadav D. Synthesis and Evaluation of Vanillin Derivatives as Antimicrobial Agents. Turkish J Pharm Sci. 2018; 15(1):57-62. https://doi.org/10.4274/tjps.97752.
8. Ma W, Li X, Song P, Zhang Q, Wu Z, Wang J, et al. A vanillin derivative suppresses the growth of HT29 cells through the Wnt/β-catenin signaling pathway. Eur J Pharmacol. 2019; 849:43-49. https://doi.org/10.1016/j.ejphar.2019.01.047.
9. Mohanraj DGR, Alagumuthu M, Subramaniam P, Bakthavachalam D, Arumugam S, Chellam S. Anti-microbial effects of vanillin-based pyridyl-benzylidene-5-fluoroindolins. J Heterocycl Chem. 2021; 58(7);1515-24. https://doi.org/10.1002/jhet.4277.
10. Patterson AE, Flewelling AJ, Clark TN, Geier SJ, Vogels CM, Masuda JD, et al. Anti-microbial and anti-mycobacterial activities of aliphatic amines derived from vanillin. Can J Chem. 2015; 93(11):1-26. https://doi.org/10.1139/cjc-2015-0400.
11. Hariono M, Abdullah N, Damodaran KV, Kamarulzaman EE, Mohamed N, Hassan SS, et al. Potential New H1N1 Neuraminidase Inhibitors from Ferulic Acid and Vanillin: Molecular Modelling, Synthesis and *in Vitro* Assay. Sci Rep. 2016; 6:38692. https://doi.org.10.1038/srep38692.
12. Syahri J, Nasution H, Nurohmah BA, Purwono B, Yuanita E. Novel aminoalkylated chalcone: Synthesis, biological evaluation, and docking simulation as potent antimalarial agents. J Appl Pharm Sci. 2020; 10(6):1-005. https://doi.org/10.7324/JAPS.2020.10601.
13. Asadi P, Alvani M, Hajhashemi V, Rostami M, Khodarahmi G. Design, synthesis, biological evaluation, and molecular docking study on triazine based derivatives as anti-inflammatory agents. J Mol Struct. 2021; 1243. https://doi.org/10.1016/j.molstruc.2021.130760.
14. Blaikie L, Kay G, Lin PKT. Synthesis and in vitro evaluation of vanillin derivatives as multi-target therapeutics for the treatment of Alzheimer's disease. Bioorg Med Chem Lett. 2020; 30(21):127505. https://doi.org/10.1016/j.bmcl.2020.127505.
15. Pagare PP, Ghatge MS, Musayev FN, Deshpande TM, Chen Q, Braxton C, et al. Rational design of pyridyl derivatives of vanillin for the treatment of sickle cell disease. Bioorg Med Chem. 2018; 26(9):2530-38. https://doi.org/10.1016/j.bmc.2018.04.015.
16. Upendar reddy M, Somasekhara Reddy MC. Synthesis, characterization and anti-diabetic activity of vanillin based acetohydrazide-hydrazone derivatives. World J Pharm Res. 2017; 6(11):814-25. https://doi.org/10.20959/wjpr201715-10115.
17. Deepam A, Jyothi V. Green Protocols for the One-Pot Synthesis of Vanillin Based aminoalkyl and Amidoalkyl Naphthols and their Antibacterial Activity. Orient J Chem. 2017; 33(3):1354-65. http://dx.doi.org/10.13005/ojc/330336.
18. Tugrak M, Gul HI, Sakagami H, Mete E. Synthesis and anticancer properties of mono Mannich bases containing vanillin moiety. Med Chem Res. 2017; 26(1). https://doi.org/10.1007/s00044-017-1833-x.
19. Hernandez-Vázquez E, Castaneda-Arriaga R, Ramirez-Espinosa JJ, Medina-Campos ON, Hernandez-Luis F, Chaverri JP, et al. 1,5-Diarylpyrazole and vanillin hybrids: Synthesis, biological activity and DFT studies. Eur J Med Chem. 2015; 100:106-18. https://doi.org/10.1016/j.ejmech.2015.06.010.
20. Illicachi LA, Montalvo-Acosta JJ, Insuasty A, Quiroga J, Abonia R, Sortino M, et al. Synthesis and DFT Calculations of Novel Vanillin-Chalcones and Their 3-Aryl-5-(4-(2-(dimethylamino)-ethoxy)-3-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde Derivatives as Antifungal Agents. Molecules. 2017; 22(9):1476. https://doi.org 10.3390/molecules22091476.
21. Raghavan S, Manogaran P, Kuppuswami BK, Venkatraman, G, Narasimha KKG. Synthesis and anticancer activity of chalcones derived from vanillin and isovanillin. Med Chem Res. 2015; 24(12):4157-165. https://doi.org/10.1007/s00044-015-1453-2.
22. Belkhadem K, Cao Y, Roy R. Synthesis of Galectin Inhibitors by Regioselective 3'-*O*-Sulfation of Vanillin Lactosides Obtained under Phase Transfer Catalysis. Molecules. 2020; 26(1):115. https://doi.org/10.3390/molecules26010115.
23. De A, Ray HP, Jain P, Kaur H, Singh N. Synthesis, characterization, molecular docking and DNA cleavage study of transition metal complexes of o-vanillin and glycine derived Schiff base ligand. J Mol Struct. 2020; 1199(8):12690. https://doi.org/10.1016/j.molstruc.2019.126901.
24. Tuna M, Ugur T. Investigation of The Effects of Diaminopyridine and o-Vanillin Derivative Schiff Base Complexes of Mn(II), Mn(III), Co(II) and Zn(II) Metals on The Oxidative Bleaching Performance of H_2O_2. Sakarya Univ J Sci. 2021; 25(4):984-94. https://doi.org/10.16984/saufenbilder.948657.
25. Fugu M.B, Ndahi1 N.P, Paul B.B, Mustapha A.N. Synthesis, characterization, and antimicrobial studies of some vanillin schiff base metal (II) complexes. J Chem Pharm Res. 2013; 5(4):22-28.
26. Muche S, Harms K, Biernasiuk A, Malm A, Popiołek L, Hordyjewska A, et al. New Pd(II) schiff base complexes derived from ortho-vanillin and l-tyrosine or l-glutamic acid: Synthesis, characterization, crystal structures and biological properties. Polyhedron. 2018; 151:465-77. https://doi.org/10.1016/j.poly.2018.05.056.
27. Chigurupati S. Designing New Vanillin Schiff Bases and their Antibacterial Studies. J Med Bioeng. 2015; 4(5):363-66. https://doi.org/10.12720/jomb.4.5.363-366.
28. Gao J, Qiu S, Liang L, Hao Z, Zhou Q, Wang F, et al. Design, Synthesis, and Biological Evaluation of Vanillin Hydroxamic Acid Derivatives as Novel Peptide Deformylase Inhibitors. Curr Comput Aided Drug Des. 2018; 14(1):95-101. https://doi.org/10.2174/1573409913666170613074601.

29. Patel PA, Bhadani VN, Bhatt PV, Purohit DM. Synthesis and Biological Evaluation of Novel Chalcone and Pyrazoline Derivatives Bearing Substituted Vanillin Nucleus. J Heterocycl Chem. 2014; 52(4):1119-125. https://doi.org/10.1002/jhet2215.

30. Swapna M, Basavaraja HS, Jayadevaiah KV, Nagina kumari DN, Bharathi DR. Synthesis, characterization and biological activities of some novel thiadiazole derivatives. J Pharm Sci Res. 2019; 11(6):2113-120.

31. Harini ST, Kumar HV, Rangaswamy J, Naik N. Synthesis, antioxidant and antimicrobial activity of novel vanillin derived piperidin-4-one oxime esters: preponderant role of the phenyl ester substituents on the piperidin-4-one oxime core. Bioorg Med Chem Lett. 2012; 22(24):7588-92. https://doi.org/10.1016/j.bmcl.2012.10.019.

32. Hussain M, Qadri T, Hussain Z, Saeed A, Channar PA, Shehzadi SA, et al. Synthesis, antibacterial activity and molecular docking study of vanillin derived 1,4-disubstituted 1,2,3-triazoles as inhibitors of bacterial DNA synthesis. Heliyon. 2019; 5(11):e02812. https://doi.org/10.1016/j.heliyon.2019.e02812.

33. Muskinja J, Burmudzija A, Ratkovic Z, Rankovic B, Kosanic M, Bogdanovic GA, et al. Ferrocenyl chalcones with O-alkylated vanillins: synthesis, spectral characterization, microbiological evaluation, and single-crystal X-ray analysis. Med Chem Res. 2016; 25(9):1744-53. https://doi.org/10.1007/s00044-016-1609-8.

34. Retnosari R, Rachman IB, Sutrisno S, Sari MEF, Sukarianingsih D, Rukayadi Y. The antibacterial activity of vanillin derivative compounds. AIP Conf Proc. 2021; 2349(1):020073. https://doi.org/10.1063/5.0051523.

35. Kiran K, Ashok D, Rao BA, Sarasija M, Rao AS. Synthesis, characterisation, and antibacterial activity of some novel vanillin related hydrazone derivatives bearing 1,2,3-triazole ring. Russ J Gen Chem. 2017; 87(6):1288-94. https://doi.org/10.1134/S1070363217060251.

36. Govindasami T, Pandey A, Palanivelu N, Pandey A. Synthesis, Characterization and Antibacterial Activity of Biologically Important Vanillin Related Hydrazone Derivatives. Int J Org Chem. 2011; 01(03):71-7. https://doi.org/10.4236/ijoc.2011.13012.

37. Berk B, Ertas M, Biltekin SN. Synthesis, Antimicrobial Activity Studies and Molecular Property Predictions of Schiff Bases Derived from ortho-Vanillin. Acta Pharm Sci. 2017; 55(1):83-96. https://doi.org/10.23893/1307-2080.APS.0556.

38. Dua T, Mangal S, Akshita G, Harshdeep, Atri AK, Sharma P, et al. Novel Vanillin-based hybrids inhibit quorum sensing and silences phenotypical expressions in Pseudomonas aeruginosa. Drug Dev Res. 2023; 84(1):45-61. https://doi.org/10.1002/ddr.22011.

39. Thorat BR, Yamgar RS, Kamat P, Thorat VB, More K. Synthesis, SAR Study, Molecular Docking, HPLC Method Development and Anti-TB study of Novel 3-Chloro-N-{[7-mehtoxy-2-(4-methoxyphenyl)-1-benzofuran-5-yl]methyl}aniline. Chem Sci Rev Lett. 2015; 4(16):1253-68.

40. Narode H, Gayke M, Bhosale RS, Eppa G, Gohil N, Bhattacharjee G, et al. Vanillin containing 9H-fluoren sulfone scaffolds: Synthesis, biological evaluation and molecular docking study. Results Chem. 2021; 4(6):100269. https://doi.org/10.1016/j.rechem.2021.100269.

41. da Silva Rodrigues JV, Rodrigues Gazolla PA, da Cruz Pereira I, Dias RS, Poly da Silva IE, Oliveira Prates JW, et al. Synthesis and virucide activity on zika virus of 1,2,3-triazole-containing vanillin derivatives. Antiviral Res. 2023; 105578. https://doi.org/10.1016/j.antiviral.2023.105578.

42. Mohsin Ali SM, Abdul Kalam Azad M, Jesmin M, Ahsan S, Mijanur Rahman M, Khanam JA, et al. *In vivo* anticancer activity of vanillin semicarbazone. Asian Pac J Trop Biomed. 2012; 2(6):438-42. https://doi.org.10.1016/S2221-1691(12)60072-0.

43. Mani A, Ahamed A, Ali D, Alarifi S, Akbar I. Dopamine-Mediated Vanillin Multicomponent Derivative Synthesis via Grindstone Method: Application of Antioxidant, Anti-Tyrosinase, and Cytotoxic Activities. Drug De Dev Ther. 2021; 15:787-02. https://doi.org/10.2147/DDDT.S288389.

44. Scipioni M, Kay G, Megson I, Lin PKT. Novel vanillin derivatives: Synthesis, anti-oxidant, DNA and cellular protection properties. Eur J Med Chem. 2018; 143:745-54. https://doi.org/10.1016/j.ejmech.2017.11.072.

45. Hayun H, Arrahman A, Purwati EM, Yanuar A, Fortunata F, Suhargo F, et al. Synthesis, anti-inflammatory and antioxidant activity of mannich bases of dehydrozingerone derivatives. J Young Pharm. 2018; 10(2):s6-s10. https://doi.org/10.5530/jyp.2018.2s.2.

46. Kumar Reddy ALV, Kathale NE. Synthesis and Anti-Inflammatory Activity of Hydrazones Bearing Biphenyl Moiety and Vanillin Based Hybrids. Orient J Chem. 2017; 33(2):971-78. https://doi.org/10.13005/ojc/330250.

47. Kumar Reddy ALV, Kathale NE. Synthesis, characterization and anti-inflammatory activity of hydrazones bearing 5-nitro-furan moiety and 5-iodo-vanillin hybrid. World J Pharm Res. 2017; 6(11):982-93. https://doi.org/10.20959/wjpr201711-9635.

48. Neethu MJ, Yusuf S. In-silico design, synthesis, anti-inflammatory and anticancer evaluation of pyrazoline analogues of vanillin. Int J Pharm Sci Drug Res. 2014; 6(2); 128-31. http://www.ijpsdr.com/index.php/ijpsdr/article/view/319.

49. Scipioni M, Kay G, Megson IL, Lin PPKT. Synthesis of novel vanillin derivatives: novel multi-targeted scaffold ligands against Alzheimer's disease. Med Chem Comm. 2019; 10(5):764-77. https://doi.org/10.1039/c9md00048h.

50. Chigurupati S, Selvaraj M, Mani V, Mohammad JI, Selvarajan KK, Akhtar SS, et al. Synthesis of azomethines derived from cinnamaldehyde and vanillin: *in vitro* aetylcholinesterase inhibitory, antioxidant and *in silico* molecular docking studies. Med Chem Res. 2018; 27(17):807-16. https://doi.org/10.1007/s00044-017-2104-6.

51. Kadium RT, Al-Hazam HA, Hameed BJ. Design, synthesis and characterization of some novel thiazolidine-2,4-dione derivatives as antidiabetic agents. Acta Pol Pharm Drug Res. 2022; 78:773-79. https://doi.org/10.32383/appdr/145368.

52. Li M, Gu MM, Lang Y, Shi J, Chen BPC, Guan H, et al. The vanillin derivative VND3207 protects intestine against radiation injury by modulating p53/NOXA signaling pathway and restoring the balance of gut microbiota. Free Radic Biol Med. 2019; 145:223-36. https://doi.org/10.1016/j.freeradbiomed.2019.09.035.