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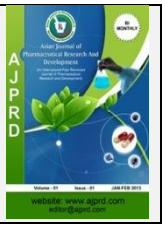

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Review Article

NSAID Carprofen Structure-Based Derivatives as Potential Antibacterial Agents

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A B S T R A C T

Drug repurposing (DR) is the use of existing drug in new alternative therapeutic role. Antibacterial perspective of non-antibiotic drugs includes NSAIDS are very useful to combat in a variety of infections in clinical practice. Carprofen (RS)2-(6-chloro-9H-carbazol 2-yl)propanoic acid), is a NSAIDS category drug based on potential pharmacophore tricyclic carbazole nucleus, now commonly used in veterinary medicine. This carprofen drug is used in osteoarthritis and postoperative pain in dogs. Around the worldwide, researchers' significantly revealed drug repurposing role of carprofen structure-based derivatives as antibacterial agents. These carprofen structure-based compounds displayed excellent antibacterial activities against gram positive as well as gram-negative bacterial strains in review literature. Some carprofen derivatives also displayed potential antibiofilm activity. Multi-target direct ligand (MTDLs) strategy also used to design novel carprofen integrated molecules tethered with potential bioactive pharmacophore like coumarin, 1,3,4-oxadiazole, hydrazide etc. also showed significant *in vitro* antibacterial activities. Articles related to carprofen as antibacterial agents collected on PubMed, Science direct and Google scholar mainly. However, less research works done on this topic. This review highlighted antibacterial potential of new carprofen derivatives based on carbazole structure tested against bacterial strains with their target mechanism based on literature.

Keyword- Drug Repurposing (DR), Carbazole, Antibacterial, Carprofen, NSAIDS (Nonsteroidal anti-inflammatory Drugs), Antibiofilm activity

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INTRODUCTION

Drug repurposing (DR) is the process of find out new therapeutic role of existing/old drug other than it was initially marketed[1]. Drug repurposing has many advantages; one of them is use as alternative medicine in other disease. This drug repositioning strategy can be work in faster way to achieve results with lower expenses [2,3]. Best current examples of drug repurposing are antiviral drugs because they have already played an important role for fighting against corona virus disease (COVID-19)[4]. However, we cannot ignore some regulatory and economic challenges associated with it [3].

Generally traditionally clinically approved medicines such as Beta-lactams, cephalosporins, aminoglycosides, tetracyclines, macrolides, quinolones and synthetic antibiotics are successfully used in a variety of infections[5,6]. However, use of traditionally antibiotics can be produce Antimicrobial resistance (AMR) due to resistant bacteria[6-8]. In the 21st century, AMR has been becoming threat associated to human health [7-9]. According to 2021 WHO report, 42 traditional and 32 non-traditional antibiotics were testing stage of preclinical and clinical development[5, 10]. Resistance may be associated with traditionally antibiotic when it enters in cell, it degraded either enzymatically or modification or changes of cell wall target due to resistant bacteria [11]. Another resistance mechanism can be occurs due to decreased influx or increased efflux of antibiotics into the cell wall[11,12]. Other may be increasing prevalence of pathogenic multidrug-resistant bacteria such as MRSA (*methicillin-resistant S. aureus*), VRE (vancomycin-resistant *Enterococci*), *Acinetobacter baumannii* etc. can be

difficult to treat[13, 14]. Drug repurposing (DR) can be an alternative strategy against multidrug resistant (MDR) microorganisms[15]. In recent years, antimicrobial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) well acknowledged [16]. E.M. Yimer et al. covers a review on topic role of NSAIDs against various bacterial strains with their proposed antibacterial mechanism[17]. NSAIDs drugs works as a drug repurposing strategy for biofilm related infections in literature[16, 18]. Claudia Leão et al. and others researchers covers the review on topic drug repurposing Strategy of some NSAIDs drugs for Biofilm Control in 5 years data against bacterial infections.[19-20]. Biofilms are communities of microorganisms embedded in an extracellular complex polymeric substance (EPS) and its formation starts with the attachment of bacteria to the surface[20]. Biofilm form are more resistant than planktonic forms of microorganisms[21,22]. A number of target specific strategies are being used to control bacterial biofilm formation[23]. However, no role of MIC to determine the efficacy of antimicrobial agents against infections involving biofilms[23]. Recently, Almeida et al. covers a review on topic antibacterial perspective of non-antibiotic drugs such as antihypertensive drugs, anti-inflammatory drugs mainly against some bacterial infection[2]**.** Synergistic effects of NSAIDs with other traditional antibiotics on antibacterial activity against resistant bacteria also well investigated by researchers[24].

Carprofen (**1**), (RS)2-(6-chloro-9H-carbazol-2-yl)propanoic acid (IUPAC) (**Fig. 1**) is a propionic acid derivative under the category of NSAIDS [25]. Carprofen exhibits strong anti-inflammatory and analgesic effects[26]. It mechanism of action is not clear, but carprofen is a COX-2 selective derivative, with relatively weak COX-1 activity[25-28]. Earlier, carprofen used in human medicine over 10 years (1985-1995)[28-29]. Now days, carprofen use for treatment of acute and chronic pain, rheumatoid arthritis and osteoarthritis in dogs and cats[28-31]. Carprofen (**1**, **Fig. 1**) structure is based on aromatic tricycle carbazole moiety which already displayed well established pharmacological activities like anticancer, antibacterial, anti-inflammatory, antiviral, antifungal, anti-Alzheimer, etc. in literature [31-40]. Introduction of diverse substituent like halogen or electron donating group and also linked to other pharmacophore in carbazolyl moiety makes it becomes a privilege scaffold in the areas of medicine, specially medicinal chemistry[37-38]. As an adjuvant, Carprofen is approved in antimicrobial therapy in European unions[31, 38-39]. Recently published review on topic drug repurposing strategy used as alternative medicine suggested that carprofen found as an inhibitor of SARS-CoV-2 main-protease (M-pro) enzyme, used in the treatment of COVID-19 virus infection[39]. In literature, carprofen and its derivatives showed potential *in vitro* antibacterial activities. Earlier, clinical efficacy of carprofen showed promising results as an adjunct therapy in bacterial infection of bovine respiratory disease[40-41].

Multitarget antibacterial drugs found effective design strategy with potential to reduce drug resistance[42]. Carprofen structure based hydrazone compounds found significant antibacterial activities in this review article. Carprofen hydrazones also reported potential tuberculostatic agents[21,42]. A. Maitra covers the drug repurposing role of various NSAIDS in tuberculosis treatment[43]. This review encouraged to scientists to investigate drug repurposing role of carprofen structure-based derivatives against various bacterial strains which not covered till now.

In Vitro Antibacterial activities of Carprofen and its derivatives

Some known NSAIDs based on propionic acid structure

In 2014, Zhou Yin et al. investigated antibacterial activities of the some known NSAIDs such as carprofen (**1**), bromfenac (**2**), vedaprofen (**3**), Flufenamic acid (**4**),Tolfenamic acid (**5**), evaluated against gram positive and gram negative bacterial strains (**Fig. 1**)[45]. MICs with varying concentration of these five NSAIDs were found significant antibacterial potential against four species: *E. coli*, *Acinetobacter baylyi*, *Staphylococcus aureus*, and *Bacillus subtilis*. All five NSAIDs (carprofen, bromfenac, vedaprofen, Flufenamic acid, Tolfenamic acid) found better antibacterial activities against tested gram-positive bacterial strains. Among five NSAIDS, carprofen showed lowest MIC value 85 µg/mL& 85 µg/mL against two bacterial strains *s. aureus,* and *b. subtilis,* respectively. *In vitro* DNA replication assay was carried to explore inhibition of the E. coli SC by all these five NSAIDs. Carprofen exhibit complete replication or inhibition at 1 mM concentration. However, only Ibuprofen found much weaker effects or no inhibition of DNA replication. This study supported that DNA replication is the major target of some reported NSAIDS drugs in this research work[45].

Synergistic effect of doxycycline with carprofen

In 2016**,** R. P. Brochmann et al. investigated synergistic effect of some antimicrobial drugs and non-antimicrobial drugs includes some NSAIDs against MRSP (methicillin-resistant Staphylococcus pseudintermedius)[46]. In study, a total of 216 antimicrobial/non-antimicrobial drug combinations were tested on clinical MRSP sequence type (ST) 71 strain. This MRSP strain was found resistant to reported six antibacterial drugs (ampicillin, ciprofloxacin, clindamycin, doxycycline, oxacillin, and trimethoprim/sulfamethoxazole). The objective of this work was to restore antimicrobial susceptibility of traditionally used antimicrobials drugs against *methicillin-resistant Staphylococcus pseudintermedius*. This study suggested that combination of doxycycline-carprofen (**6**&**1, Fig. 1**) found better results in terms of susceptibility to doxycycline in *MRSP strain* loading with *tetK* such as MRSP ST71[46].

Coumarin-carprofen hybrids

In vitro antibacterial activities of coumarin-carprofen derivatives**(Fig. 1**) evaluated against various bacterial strains [47]. Condensation reaction of substituted coumarin and carprofen drug in the presence of mild base gave new coumarin-carprofen hybrids (**7a-i**). In series, two compounds (**7a** and **7b)** found to be 0.90 and 1.0 µg/ml respectively against gram positive bacterial strain *S. aereus* (**Fig. 1)**. Compound **7a** and **7b** also found to be low MIC value of 1.3 and 1.35 µg/ml respectively with 12 mm zone of inhibition (ZOI) against gram negative Strain E. coli.. Another compound **7i** MIC was also found to be MIC value of 2.85 and 0.95 µg/ml for *S. aereus and B. cepacia* respectively with 11 mm of ZOI. Another two compounds, **7d** and **7f**was showed significant MIC value of 1.9 and 1.7 µg/ml for *E. coli*

with 12 mm of zone of inhibition compared to standard drug Ciprofloxacin MIC values of 3.8, 0.9, 1.0 and 4.55 µg/ml respectively against S. *aereus, B. cepacia, E. coli* and *B. cereus* respectively. *In vitro* anti-tubercular activity of these coumarin hybrids were evaluated against *M. tuberculosis* (H37Rv) strain (ATCC No- 27294) in BACTEC 12 B medium, using Microplate Alamar Blue Assay. In series, two compounds (**7c& 7f)** found more significant *in vitro* anti-tubercular activity with MIC of 1.56 µg/mL, better than clinically approved antibacterial drugs like pyrazinamide and ciprofloxacin (3.125 µg/mL). The study of coumarin carprofen hybrids found potential *in-vitro* antibacterial as well anti-tubercular activity[47].

N-phenylacetamide carprofen derivatives

Novel N-phenylacetamide-functionalized carbazole derivatives reported by Pattanashetty et al. **(Fig. 1**) (**8 a-i**) and investigated their antibacterial as well as anti-inflammatory, and antioxidant activities[48, 49]. Design of N-phenylacetamide derivatives based on carprofen structure and various amide groups were linked to carprofen structure based molecules prepared. Clinically available antibiotic drugs like Penicillin G, Cephalosporins, chloramphenicol contains amide linkage in their structures are successfully useful in various bacterial infections[6]. All designed compounds displayed excellent *in vitro* antibacterial activity with MIC ranges from 0.25–8.0 µg/mL against tested bacterial strains. Three carprofen amide derivatives (**8a**, **8g**, and **8i)** showed potent *in vitro* antibacterial activity with MIC value 0.50 µg/mL for *S. aureus*. Another derivatives (**8g** and **8i)** also found significant antibacterial activity with MIC of 0.25 and 0.50 µg/mL for E. coli, respectively, better than standard ciprofloxacin (MIC = 2.0 µg/mL). One compound **8h** showed excellent MIC value 0.25µg/mL against *B. subtilis*. SAR study showed that carprofen linked with amide linkage and donating substituent's like -CH_3, -OCH_3 on phenyl ring part was necessary required for best *in vitro* antibacterial results against tested bacterial strains**(Fig. 1**).

In docking study, three best antibacterial activity compounds (**8g**, **8**i, and **8h**) interacted with active site of the E. coli MurB enzyme receptor found lowest docking scores of 305.25, 303.43, and 281.31 kcal/mol, respectively comparable to standard drug ciprofloxacin (237.66 kcal/mol). Major binding interaction was hydrogen bonds, alkyl, pi-alkyl, vander walls mainly through or within the vicinity of receptors. The study of novel carbazole hybrids based on carprofen structure exhibit promising *in vitro* antibacterial activity against *S.aureus*, *B. subtilis*, *E.coli*, *P. aeruginosa* strain and also better binding affinity results with active site of the E. coli MurB enzyme receptor in docking study[48].

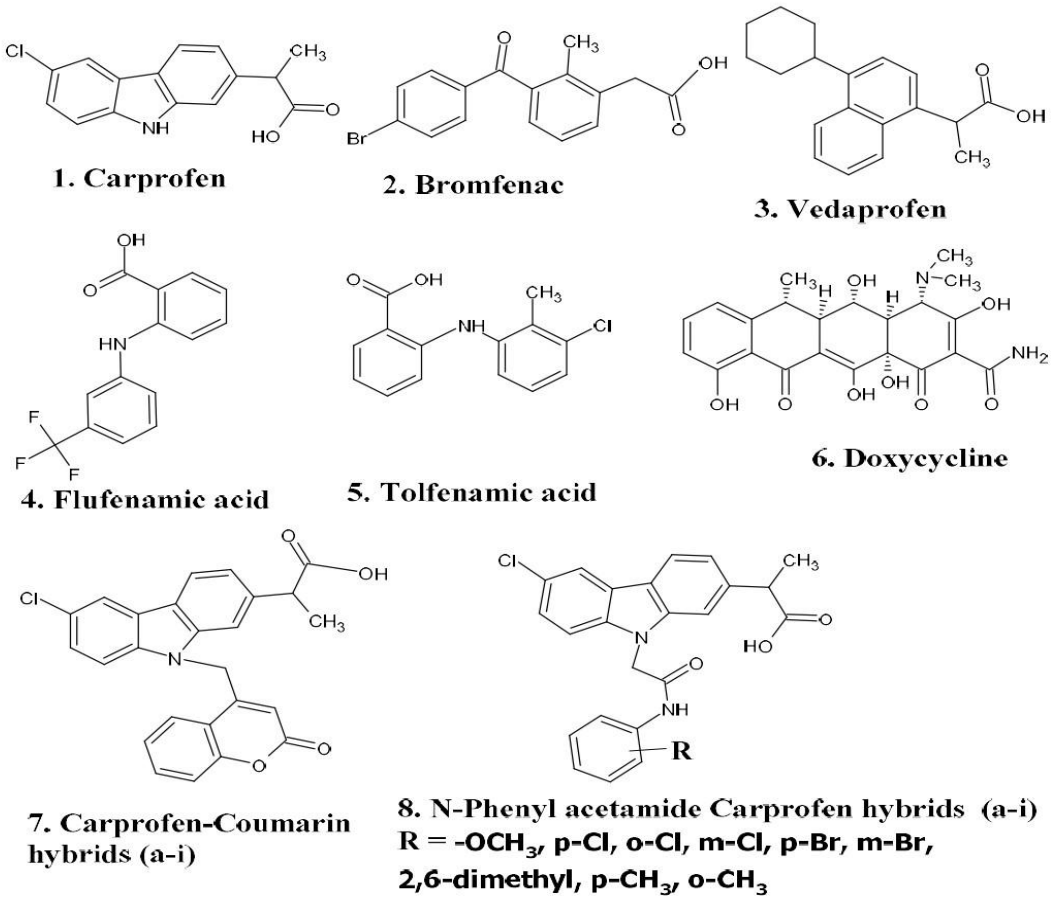

Figure 1: Structure of some NSAIDS like Carprofen (**1**), Bromfenac (**2**), Vedaprofen (**3**), Flufenamic acid (**4**), Tolfenamic acid **(5),** antibiotic Doxycycline **(6),** Carprofen-Coumarin hybrids **(7a-f),** N-Phenyl acetamide carprofen hybrids **(8a-8i)**

Carprofen hydrazide derivatives

In 2019, A.T. Bordei et al. reported novel Schiff based carprofen hydrazide derivatives[50]. All final carprofen structure based hydrazide (**(Fig. 2, 9a-i**) were prepared by the reaction of carbazole hydrazide with substituted aromatic aldehyde under microwave irradiation method. Hydrazides incorporated compounds showed potential in vitro antibacterial activities[51]. All carprofen hybrid derivatives were tested for *in vitro* antibacterial activity against S. aureus. All carprofen hydrazides reported significant antibacterial activity against *S. aureus*. However, they did not share any antibacterial data in paper[50].

Novel carprofen derivatives linked with or not 1,3,4-oxadiazole derivatives

Novel carprofen derivatives and also tethered with 1,3,4-oxadiazole based integrated molecules**(Fig. 2**, **10 a-c** and **11 a-c**) based on carprofen structure synthesized by Telehoiu et al. [52]. 1,3,4-Oxadiazoles based compounds exhibited various biological activities including antibacterial [53], antifungal [54]. They evaluated their *in vitro* antimicrobial activities against gram-positive bacteria (*E. faecalis* ATCC 29212, *S. aureus* ATCC 25923) and gram-negative bacteria (*P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922) as well as fungal species candida albicans. All carprofen oxadiazole derivatives displayed MIC values ranging from 0.625 to 10 mg/ml against bacterial strains. One carprofen derivative **11 c** found the lowest MIC value of 0.625 against Candida albicans species. All carprofen oxadiazole hybrids displayed good anti-biofilm activities against the bacterial and fungal species, with MBEC values ranging from 0.009 to 2.5 mg/mL. All designed carprofen compounds showed highest susceptibility to the *P. aeruginosa* biofilm. The study of carbazole hybrids based on carprofen structure found significant potential *in vitro* antibacterial activities[52].

Carprofen and its analogs elicits pleiotropic mechanisms in drug resistance mycobacterium tuberculosis

In this study, carprofen (**1**) inhibits efflux pump activity, affecting the mycobacterial biofilm phenotype and also disrupting the membrane potential in mycobacterium tuberculosis[55]. Further, they also synthesized and evaluation of novel series of novel carprofen analogues, in which one carprofen analog 2-(6-chloro-9H-carbazol3-yl)acetic acid (**12**) based on carbazole structure**(Fig. 2)** exhibits similar antimycobacterial activity to carprofen, This study supports that carprofen (**1**)and its chemical analogue (1**2**) exhibits pleiotropic mechanisms of action to reverse antimicrobial drug resistance in tuberculosis. This study promotes to clinical trials of new combinations of drugs especially carprofen based molecules or others in antimicrobial drug resistance in mycobacterium tuberculosis [55].

New carbazole derivatives

In 2022, Florea Dumitrascu et al. reported a series of novel carprofen derivatives '(**13a-j).** All novel carprofen derivatives were prepared by nitration, halogenation, N-alkylation, and esterification reactions **(Fig. 2)** [56]. *In vitro* antimicrobial activity of these carprofen compounds was evaluated on Gram-positive and Gram-negative strains through quantitative assay of minimal inhibitory/ bactericidal/biofilm concentrations (MIC/MBC /MBEC). One carprofen compound **13h** has two bromine atoms, found significant MIC values against *S. aureus*,

E. faecalis strains (0.090-0.019 mg/mL). In series, four compounds **13 b, 13i, 13c** and **13d** showed MIC values ranging from 0.6 to 1.3 mg/mL potential antibacterial activity against *E. coli, P. aeruginosa* and *E. faecalis* strains. These compounds (**13 b, 13i, 13c** and **13d)** also showed MBC values from 1.3 to 2.5 mg/mL and MBEC values from 0.6 to 1.3 mg/mL against *E. coli, P. aeruginosa* and *E. faecalis* strains. Another two compounds **13e** and **13f** showed lowest antibacterial activity against the planktonic growth of *E. coli, P. aeruginosa* and *E. faecalis* strains (MIC of 1.3 mg/mL). However, compound **13f** also found antibiofilm activity against *P. aeruginosa* (MBEC of 1.3 mg/mL). *In vitro* antibacterial data of carprofen based compounds suggested that halogen atoms like chlorine or bromine on carprofen nucleus required for better antibacterial activity against tested bacterial strains. However, alkylation of nitrogen atom at 9^{th} position with a methyl group diminishes the antibacterial activity. The study of novel carprofen derivatives possess potential in vitro antibacterial profile against bacterial strains[56].

(EZ)-N'-benzylidene-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propano hydrazide derivatives

In 2022, A. Teodora et al. reported (EZ)-N'-benzylidene-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanohydrazide(**14 a-i)** derivatives and well characterized by HR-MS and thermal analysis**(Fig. 2**) [21, 57]. Antibacterial profile of these novel carprofen compounds were evaluated against Gram-negative and gram positive bacteria such as *E. coli ATCC 25922, P. aeruginosa* ATCC 27853) and Gram-positive (*Staphylococcus aureus* ATCC 25923 and Enterococcus faecalis ATCC 29212). These compounds also tested on fungal strain (*C. albicans* ATCC 10231). The anti-biofilm activity of these carprofen structure-based compounds also investigated. In antibacterial activity results, three compounds (**14a**, **14d** and **14b)** *displayed significant* MIC value of 0.31 mg/mL, 0.31 mg/mL & 0.31 mg/mL respectively against tested two Gram-positive bacteria *(S. aureus* and E. faecalis) and fungal strain(Candida albicans), respectively. All carprofen derivatives(**14 a-i)** investigated antibiofilm activity at different MBIC values (5 - 0.009 mg/ mL). The study showed that carprofen derivatives has better inhibition against biofilms of Gram-positive bacteria and also fungal strain C. albicans rather than gram-negative ones.

At MBIC of 0.078 mg/mL, one compound 1**4b** showed very good antibiofilm effects against S. aureus ATCC 25923 and E. faecalis ATCC 29212. Another carprofen compound **14d** also found significant antibiofilm effect against C. albicans ATCC 10231 with the MBIC value of 0.009 mg/mL. Compound **14f** did not found any antibacterial and antifungal effect against tested strains. SAR study of these carprofen Schiff based molecules suggested that chloro at the 4-position of the benzene nucleus and hydroxy at the second position of the benzene nucleus in compounds **14 b** and **14 a** respectively was important for potent antibacterial activity against E. faecalis ATCC 29212, C. albicans ATCC 10231 and S. aureus ATCC 25923 respectively. The antibacterial data of these

carprofen hydrazides found potent antibacterial potential against tested bacterial strains and also inhibits microbial biofilms formation[21]**.**

Novel developed carprofen derivatives

In 2022, Florea Dumitrascu et al. [58] reported a series of some novel carprofen compounds (**15-23**) and evaluated for their antibacterial activity against planktonic cells and also biofilm inhibition activity, on Gram-positive strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212) and Gram-negative strains (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853)**(Fig. 2**). In series, three carprofen derivatives **15** (R_1 = Br, R= OH), **16** (R_1 = I, R= OH), **23** (R_1 = Br, R= $NHNH_2$) displayed excellent *in vitro* antibacterial activity with same MIC value 0.078 µg/mL on *S. aureus*. In series, compound **16** also possess excellent *in vitro* antibacterial activity with a same MIC value of 0.078 µg/mL on *E. faecalis* and *E. coli*. Another two compounds (**15** and **16**) also found same MIC values 0.625 µg/mL against *P. aeruginosa*. Compounds (**15**, **16**) also found significant antibiofilm activity with MBC values of 0.078 µg/mL and 0.078 µg/mL, respectively, against *S. aureus*. To predict their binding affinity of all designed carprofen derivatives (**15-23**), docking analysis carried out on penicillin-binding proteins (PBP) and Tyrosyl-tRNAsynthetase (TyrRS) from *S. aureus*. In docking analysis, two best compounds (**15** and **16)** interacted with protein PBP receptor site showed minimum binding energies of −8.21 kcal/mol and −8.41 kcal/mol respectively. In docking study results, one compound **23** interacted with the PBP target found lowest binding energy of -11.28 kcal/mol. The study of designed novel carprofen derivatives found excellent antibacterial profile against both gram-positive and gram-negative strains and also significant antibiofilm activity [58].

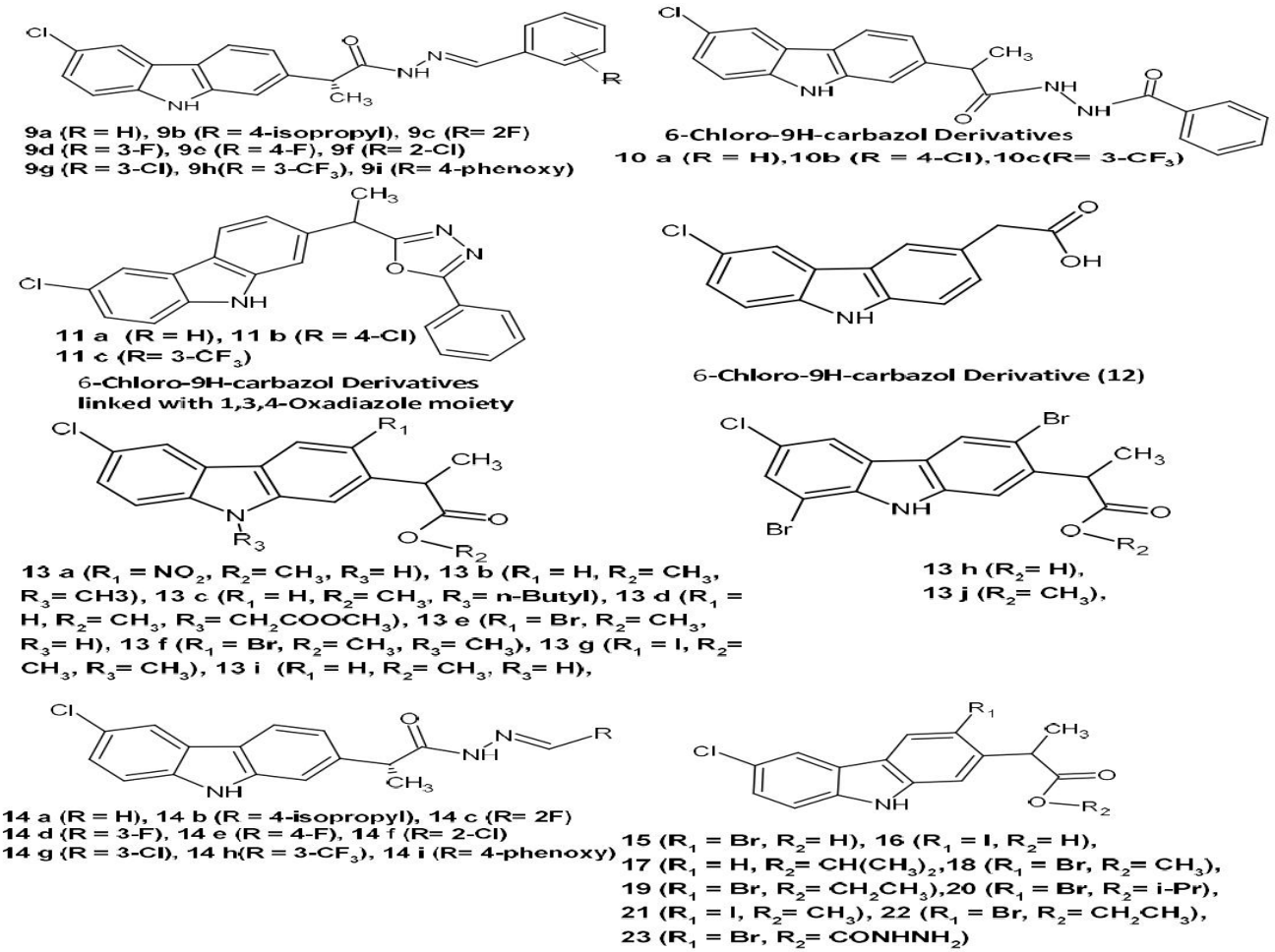

Figure 2: Structure of Carprofen hydrazide derivatives **9 (a-i),** carprofen derivatives linked with or not 1,3,4-oxadiazole derivatives (**10-a-c & 11 a-c),** Novel carprofen analog (**12**), some carprofen derivatives (**13 a-j**), Carprofen hydrazide derivatives (**14 a-j**), novel carprofen derivatives based on carbazole structure (**15-23**)

CONCLUSION

The review covers drug repurposing role of carprofen and its derivatives possesses potential antibacterial activities against a wide variety of bacterial strains. A lot of scientists designed new carprofen hybrids linked with other bioactive compounds like coumarin, 1,3,4-oxadiazole, hydrazide etc. found potential antibacterial activities against tested bacterial species. Novel Schiff bases of carprofen structure-based derivatives also significantly synthesized to combat bacterial infections in this literature survey. Design of Schiff based molecules found significant potential antibiofilm activity in reported literature. Carprofen structure-based molecules

showed significant antibiofilm effect on microbial growth and its can be a tactic to battle against biofilm-related infections due to bacteria species. Based on significant *in vitro* antibacterial activities of carprofen and its derivatives can be an effective strategy to combat a variety of bacterial strains. This study will also encourage to scientists to design novel carprofen derivatives against various bacterial strains and find out new proposed antibacterial mechanism to solve AMR problem. This review study encouraging role of drug repurposing strategy specially NSAIDS drugs-based derivatives against bacterial disease.

CONFLICT OF INTEREST

Review written content does not any conflict of interest declared by authors.

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