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Piperazine based antimicrobial polymers: a review

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Microbial infections are a life threatening concern in several areas, which include the biomedical sector, healthcare products, water purification systems, and food packaging. Polymers with low molecular weight bioactive agents or disinfectants help the scientific community to reduce the lethality rate caused by pathogenic microbes. Antimicrobial polymeric approach is one of the advanced approaches made by researchers in concern with the problems associated with small molecules that restrict their applications in broad spectrum. History reveals the synthesis of numerous antimicrobial polymers using various antimicrobial agents but lacks the use of piperazine molecule, which is of pharmaceutical importance. This review gives an insight into the current and future perspective for the development of piperazine-based antimicrobial polymers.

1. Introduction

The piperazine molecule has been classified as a privileged structural motif in drug discovery.¹ It is a six-membered heterocyclic compound with the chemical formula $C_4H_{10}N_2$ and is also called hexahydropyrazine. Hexahydropyrazine was named as piperazine because of its chemical similarity with piperidine, which is a part of the piperine structure isolated from the black pepper plant (*Piper nigrum*), and it contains two reactive secondary amine groups at the first and fourth positions.^{2,3} Piperazine was first used in the treatment of gout disease in 19th century, and later on molecules obtained by modifying the piperazine moiety were used in the treatment of intestinal infections.^{4–6} In the early 20th century, numerous researchers synthesized piperazine and substituted piperazine molecules, which were important pharmacophores found in numerous marketed drugs such as antibiotics, anticancer, antimicrobial, antipsychotics, and antidepressants.⁷ Piperazine was majorly found in the second generation antibiotic drugs and was extended up to sixth generation antibiotics.^{8,9} A recent statistical analysis of the substructure has shown that piperazine is the third most frequently used N-heterocycle (ranked right behind piperidine and pyridine) in pharmaceutical small molecule drugs. Several drugs containing the piperazine moiety are amongst the top 100 best-selling pharmaceutical products and are listed in Table 1.^{1,8–10}

Small-molecule drugs containing the piperazine moiety have substitutes on either both or single nitrogen atoms and are predominantly used as a linker for different molecules/macromolecules to adjust the physico-chemical properties of a macromolecule. Piperazine, a six-membered heterocyclic ring

with two opposing nitrogen atoms, provides a large polar surface area, structural rigidity, and hydrogen-bond acceptors and donors, which often lead to enhanced target affinity, specificity, water solubility, oral bioavailability, and ADME (*i.e.*, absorption, distribution, metabolism, and excretion) properties.^{2,77–82} The absence of vinyl groups and multifunctional groups in the piperazine molecule restricts their use in the synthesis of polymers though piperazine and substituted piperazine derivatives are extensively used as antibiotic, anticancer, antimicrobial, antipsychotic, antidepressant drugs and so forth.

Polymeric materials are one among those materials used in combating pathogenic microorganisms to prevent infectious diseases. The growth of pathogenic microorganisms in the surroundings can be inhibited or killed by the macromolecules with the antimicrobial property. The polymer molecules provide promise for escalating the efficacy of some existing low-molecular-weight antimicrobial agents and minimize environmental issues by reducing their residual toxicity. The applications of antimicrobial polymers can be found in water purification systems, fibers, food packaging, surfactants, detergents, surgical, pharmaceutical industries, and so forth.^{83–89} Some of the disadvantages of antimicrobial polymers are as follows: (i) macromolecules are very large and thus may not act as fast as small molecule agents, (ii) short half-life, and (iii) degradation issues.^{90,91} This review article gives an insight into the recent advancements in the synthesis, applications and development of novel piperazine-based antimicrobial monomers and polymers and is classified into two sub-sections based on their composition, *i.e.*, homo-/co-/tripolymers and grafted polymers.

1.1 Piperazine-based homo-/co-/tripolymers

In 2003, norfloxacin-containing quinolone moieties were converted to monomer (Scheme 1) and polymers and further

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Table 1 List of commercialized drugs containing the piperazine moiety in pharmaceutical applications

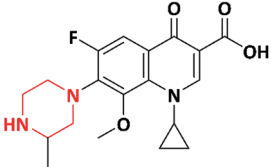
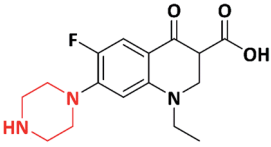
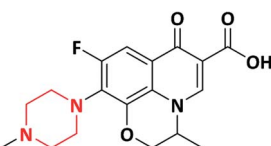
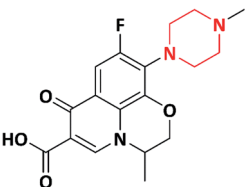
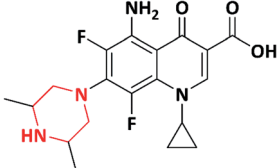
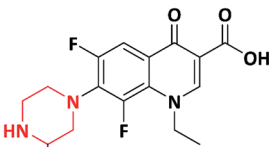
S. no.	Drug	Activity	Product name	Company	Ref.
1	 <p>Gatifloxacin</p>		Gatiflo, Tequin and Zymar	Kyorin Pharmaceut-icals, Japan	11–13
2	 <p>Norfloxacin</p>	Antibiotic	Noroxin	Merck Co., USA	14–16
3	 <p>Ofloxacin</p>		Floxin, Ocuflox	Daiichi Sankyo, Japan	17–19
4	 <p>Levofloxacin</p>		Levaquin	Sanofi-Aventis, France	20 and 21
5	 <p>Sparofloxacin</p>	Antibiotic	Spacin, Zagam	Torrent pharmaceuticals, India	22–24
6	 <p>Lomefloxacin</p>		Maxaquin, Okacyn, Uniquin	Wockhardt, India	25 and 26



Table 1 (Contd.)

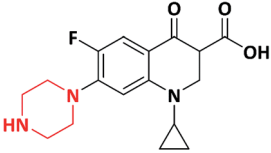
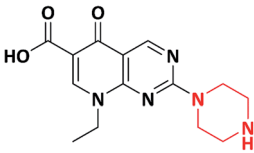
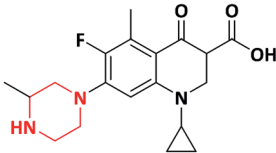
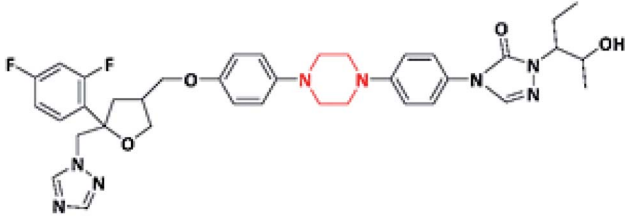
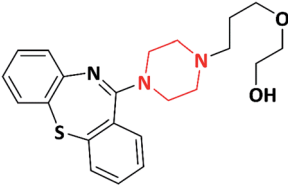
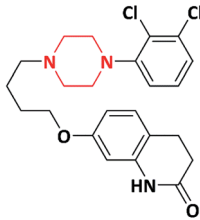
S. no.	Drug	Activity	Product name	Company	Ref.
7	 Ciprofloxacin		Cipro, Ciproxifan	Bayer AG, Germany	27–31
8	 Pipemidic acid	Antibacterial	Pipemidic acid	Yoshindo, Japan	32–34
9	 Grepafloxacin		Raxar, Glaxo Wellcome	GlaxoSmithKline, UK	35–37
10	 Posaconazole	Antifungal	Noxafil	Schering-Plough, USA	38–42
11	 Quetiapine		Seroquel	Biovail Corporation, Canada	43–45
12	 Aripiprazole	Antipsychotic	Abilify	Otsuka pharmaceuticals, Japan	46–48



Table 1 (Contd.)

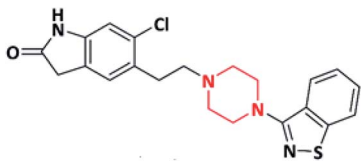
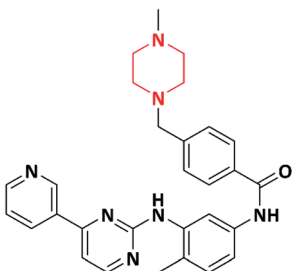
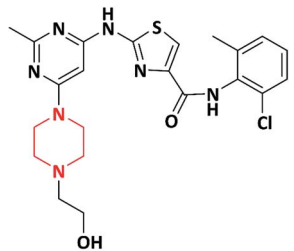
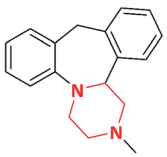
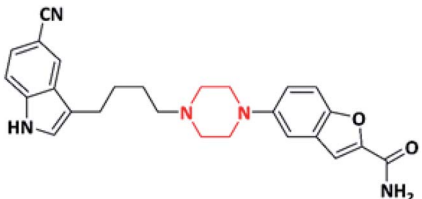
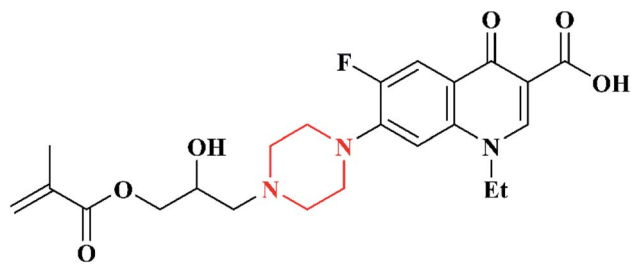
S. no.	Drug	Activity	Product name	Company	Ref.
13	 <p>Ziprasidone</p>		Geodon	Pfizer, USA	49–51
14	 <p>Imatinib</p>	Anticancer	Gleevec	Ciba-Geigy (Novartis), Switzerland	52–54
15	 <p>Dasatinib</p>		Sprycel	Bristol-Myers Squibb, USA	55–57
16	 <p>Mirtazapine</p>	Antidepressant	Remeron	Adcock Ingram pharmaceuticals, South Africa	58
17	 <p>Vilazodone</p>		Viibryd	Merck co., USA	59–61



Table 1 (Contd.)

S. no.	Drug	Activity	Product name	Company	Ref.
18	 <chem>CC(C)(C)NC(=O)N1CCN(CC1Cc2cccnc2)CC(O)CC(=O)Nc3c4ccccc4c5ccccc35</chem>	Antiretroviral	Crixivan	Merck co., USA	62–64
19	 <chem>CC1(C)N2C(=O)N(C1)CC(C2)C(=O)CC(N)Cc3cc(F)c(F)c(F)c3</chem>	Antidiabetic	Januvia, Tesavel, Xelevia	Merck co., USA	65–67
20	 <chem>CC(C)N(C)C(=O)N1CCN(C1Cc2cc(F)c(C(F)(F)F)cc2)C(=O)N3CCN(C3Cc4cc(F)c(C(F)(F)F)cc4)</chem>	Anxiolytic	Vestipitant	GlaxoSmithKline, UK	68–70
21	 <chem>CC1CN(C1)C(=O)Oc2nc3cc(Cl)ccn3c2=O</chem>	To treat insomnia Lunesta		GlaxoSmithKline, UK	71–73
22	 <chem>CC1=NC2=C(N1)N(=C2C(=O)N3C=CC=C3C(=O)N4C=CC=C4S(=O)(=O)N5CCN(C5)C6=CC=CC=C6C7=CC=CC=C7OCC)C8=CC=CC=C8</chem>	To treat erectile dysfunction	Viagra	Pfizer, USA	74–76

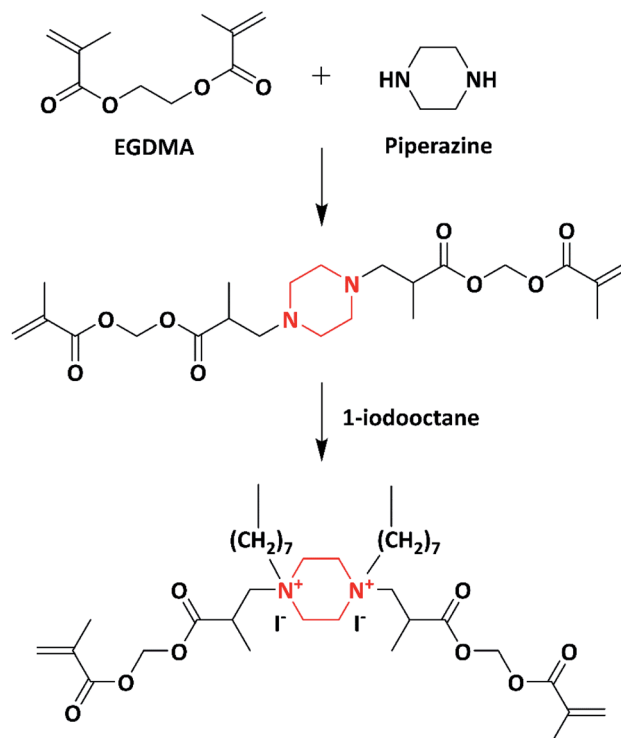




Scheme 1 Acrylic monomer-containing quinolone moiety.

blended with numerous synthetic polymers and were tested for their antimicrobial activity, thermal stability and mechanical properties by Moon *et al.* The as-synthesized monomer, polymer and polymer blends exhibited potential activity against *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis*) and *Micrococcus luteus* (*M. luteus*). Quinolones were chosen for the synthesis of monomer, polymer and polymer blends in food packaging due to their high thermal stability. The moulding of the quinolone polymer was practically impossible because the polymer was brittle and rigid in nature. To reduce the rigidity, the quinolone polymer was blended with numerous synthetic polymers such as low-density polyethylene (LDPE), poly(methyl methacrylate) (PMMA), poly(butylene succinate) (PBS), polycaprolactone (PCL) and maleated polypropylene (PPMA) with varying concentrations of polymer quinolone from 1 wt% to 5 wt%. The quinolone polymer exhibited a potent antimicrobial activity even at the concentration of 1 wt% in the polymer blends. Due to the increase in the concentration of quinolone polymers to the polymer blends, there was a decrease in the tensile property. The decrease in the tensile property was due to the incompatibility between polymer quinolone and synthetic polymers. The decrease in the tensile properties due to compounding with polymer quinolone was less significant in the PCL/PQ blend compared to those in LDPE/PQ, PMMA/PQ, PBS/PQ, and PMMA/PQ blends. This indicated that PQ is more compatible with PCL compared to other polymers. Henceforth, the PCL/PQ blend was expected to have application in food packaging materials due to their antimicrobial activity, high thermal and mechanical properties.⁹²

An efficient non-leaching contact-killing polymer was developed by Supriya *et al.* in 2006. First, piperazine was reacted with ethylene glycol dimethacrylate (EGDMA), followed by its quaternization using an alkyl iodide (1-iodooctane) to yield a quaternary monomer (Scheme 2). Further, the quaternized monomer was copolymerized with 2-hydroxyethyl methacrylate (HEMA) using redox initiators (ammonium persulphate (APS) and *N,N,N',N'*-tetramethyl ethylenediamine (TEMED)). The copolymers with varying quaternized monomer (QAMA) percentages (0 to 40%) were synthesized. Decline in the thermal properties was observed as the concentration of the monomer increased in the copolymer system, which was due to increase in the hydrocarbon chain length of alkyl iodide. The copolymer with a high monomer ratio exhibited increased activity against *E. coli* and *S. aureus* compared to other copolymers with a lower

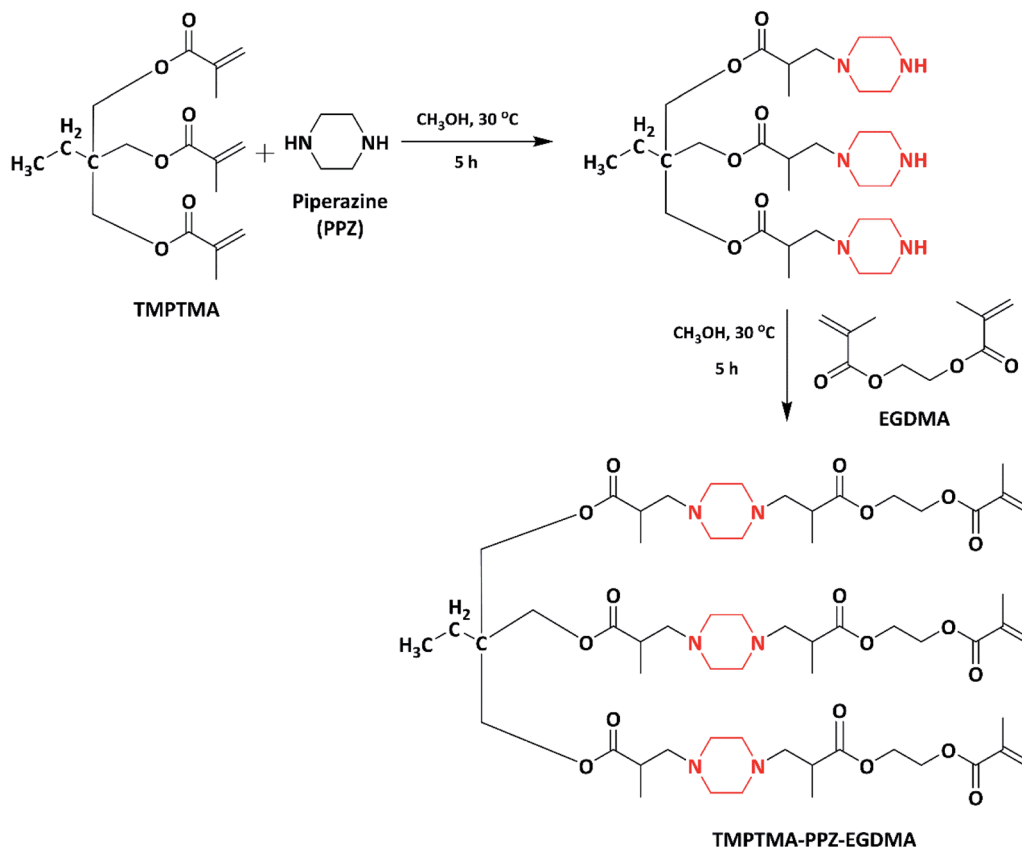


Scheme 2 Synthesis of the quaternary amine methacrylate monomer.

monomer concentration. The copolymer with 40% of the monomer concentration displayed 100% contact-killing activity in a time span of just 10 min.⁹³

Based on their previous study, the same authors in 2007 made an attempt to develop piperazine copolymers with non-leaching, contact-killing properties. Initially the methacrylate monomer, trimethylolpropane trimethacrylate–piperazine–ethyleneglycol dimethacrylate (TMPTMA–PPZ–EGDMA) (Scheme 3), was synthesized by the amination of trimethylolpropane trimethacrylate (TMPTMA) with piperazine (PPZ), followed by its reaction with ethyleneglycol dimethacrylate (EGDMA). The methacrylate monomer (TMPTMA–PPZ–EGDMA) was further copolymerized with 2-hydroxyethyl methacrylate (HEMA) using redox initiators (ammonium persulfate (APS) and *N,N,N',N'*-tetramethyl ethylenediamine (TEMED)). The copolymers with varying monomer (TMPTMA–PPZ–EGDMA) percentages (0 to 100%) were synthesized, but after varying monomer (TMPTMA–PPZ–EGDMA) beyond 60% incomplete in the polymerization was observed. Further the obtained copolymers with different monomer ratios were quaternized with 1-iodooctane. Due to increase in the hydrocarbon chain length of the alkyl iodide, depletion in the decomposition temperature was observed as the concentration of the monomer (TMPTMA–PPZ–EGDMA) increased from 0 to 60% in the copolymer system. The quaternized copolymer with variable percentages of TMPTMA–PPZ–EGDMA from 5% to 60% was tested against *E. coli* and *S. aureus*. The site of quaternization increases as the monomer ratio increases; hence, the bacterial growth percentage decreases. The contact-killing microbiocidal role of the copolymer can be attributed to the hydrophobic interaction of the alkyl chain with

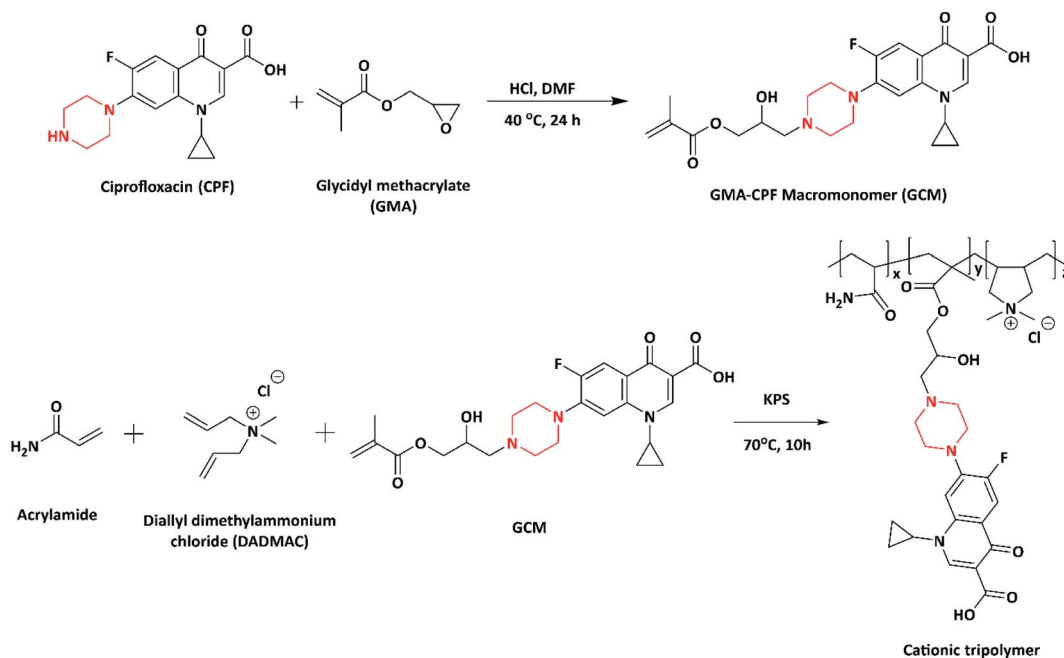




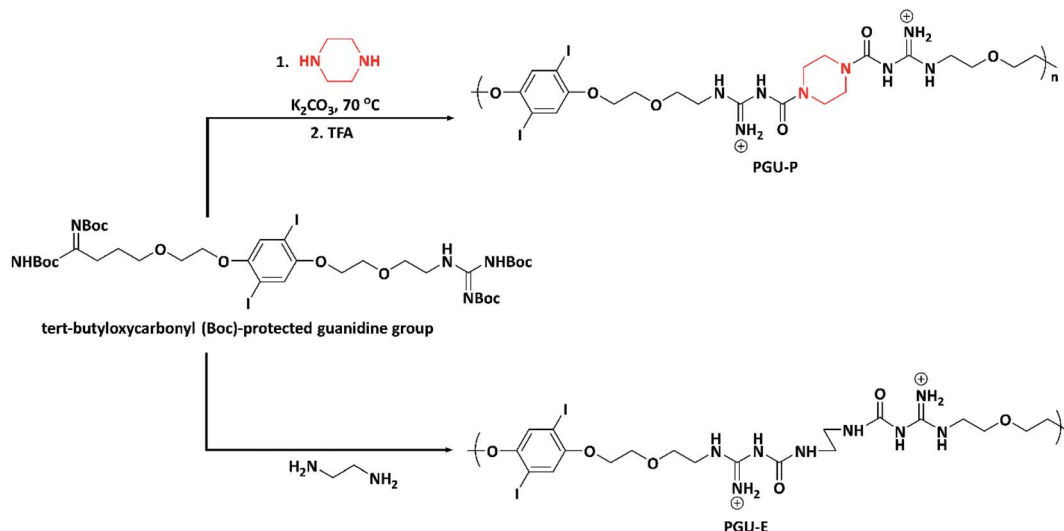
Scheme 3 Synthesis of the trimethylolpropane trimethacrylate–piperazine–ethyleneglycol dimethacrylate monomer.

the bilipid layer of the cell wall and the amphiphilic nature of the copolymer, which disrupts the cell membrane and leads to the leakage of K^+ ions and cytoplasmic fluid. This mechanism

was studied *via* scanning electron microscopy (SEM). The copolymer showed broad spectrum contact-killing antimicrobial properties without releasing any bioactive agents. Hence,



Scheme 4 Synthesis of the ciprofloxacin pendant polymer (cationic tripolymer).



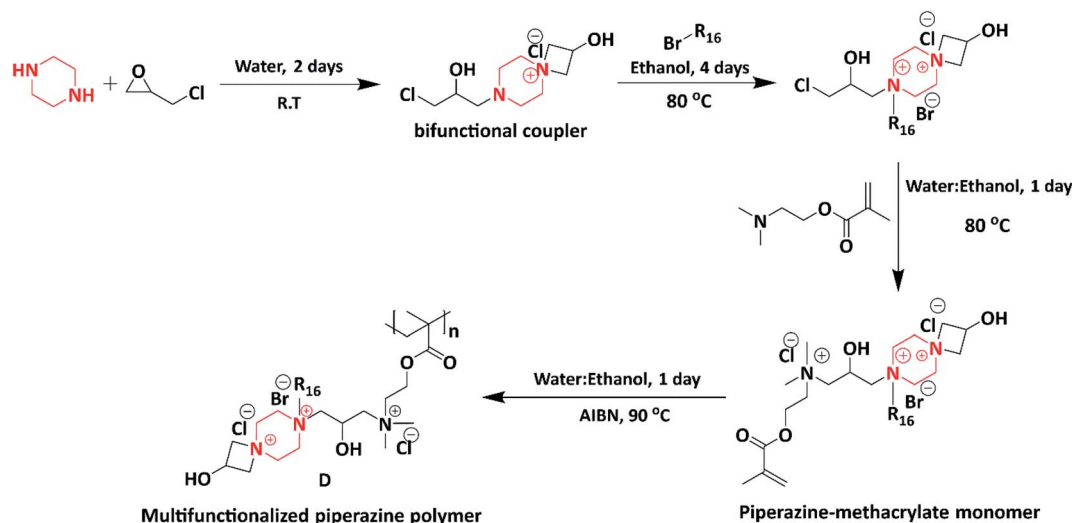
Scheme 5 Synthesis of poly(guanylurea)-piperazine (PGU-P) and poly(guanylurea)-ethylenediamines (PGU-E).

the synthesized copolymer is used as contact-killing antimicrobial polymer for numerous biomedical applications.⁹⁴

In 2012, a well-known second generation antibiotic drug, ciprofloxacin containing piperazine moiety, was converted to a novel methacrylate monomer and cationic tripolymers by Xue *et al.* The macromonomer (GCM) was synthesized by reacting ciprofloxacin (CPF) with glycidyl methacrylate. Further, the copolymerization of macromonomer (GCM) with acrylamide and diallyl dimethyl ammonium chloride (DADMAC) at different molar ratios was carried out *via* free radical polymerization using KPS as the initiator, which resulted in the formation of a cationic tripolymer (Scheme 4). The antimicrobial activity of the synthesized cationic tripolymers was screened against *E. coli*. As the macromonomer (GCM) concentration increased, the antimicrobial activity of the tripolymers also increased. The authors designed these CPF

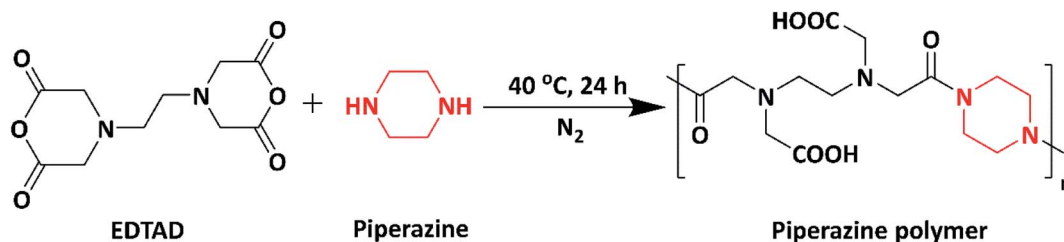
pendant cationic tripolymers for the purpose of antimicrobial paper products (such as tissues, paper towels, kitchen paper, food wrapper and bank notes) and for numerous hygiene products including cellulose based fibres.⁹⁵

In 2018, Ahmed *et al.* designed cationic poly(guanylurea)s (PGUs) using piperazine and ethylenediamine for the development of biocompatible, specific, and selective antimicrobial polymers. Poly(guanylurea)-piperazine (PGU-P) and poly(guanylurea)-ethylenediamines (PGU-E) (Scheme 5) were synthesized by reacting piperazine and ethylenediamine with a monomer containing *tert*-butyloxycarbonyl (Boc)-protected guanidine groups at the end of short ethylene oxide side chains. The as-synthesized PGU-P exhibited broader antimicrobial activity compared to PGU-E with high selectivity to target against *Mycobacterium smegmatis* (*M. smegmatis*), *S. aureus*, methicillin resistant *Staphylococcus aureus* (MRSA), and



Scheme 6 Synthesis of the piperazine-methacrylate monomer and its homopolymer.





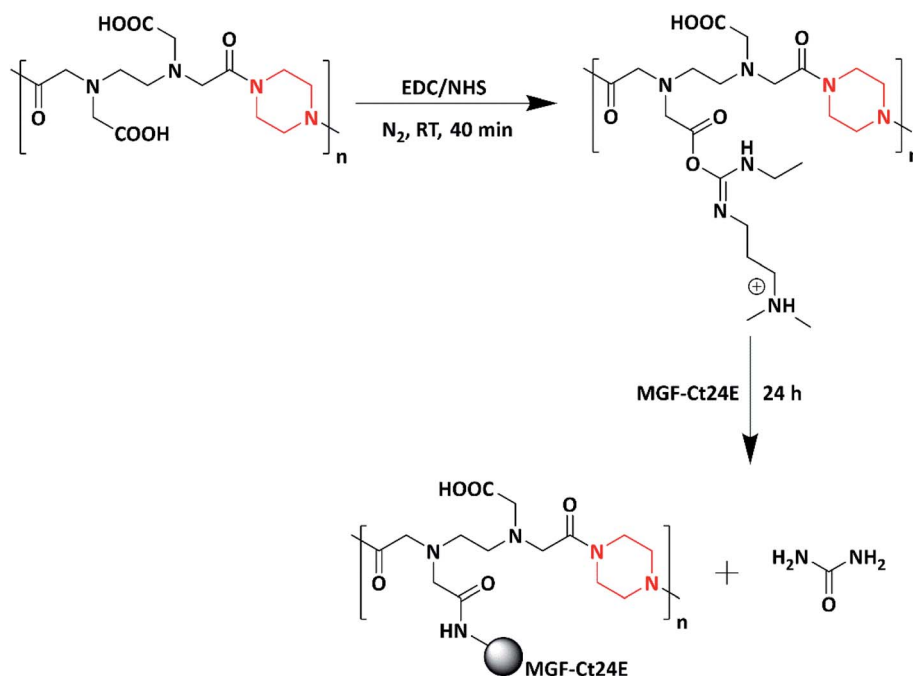
Scheme 7 Synthesis of the biocompatible piperazine polymer.

Shigella flexneri (*S. flexneri*). The PGU-P polymer has key functional characteristics *i.e.*, piperazine moiety, positive charge, H-bonding, and the lipophilicity, which help kill the bacteria *via* interacting with the cell membrane, followed by its disruption; the mechanism was studied *via* transmission electron microscopy (TEM).⁹⁶

In 2019, a novel piperazine-methacrylate monomer and its homopolymer were synthesized by Jalageri *et al.* Initially, piperazine and epichlorohydrin were used to react with each other to prepare a bifunctional coupler (piperazine-bearing aminochlorohydrin and azetidinium group). To increase the functionalities, the bifunctional coupler was quaternized with bromohexadecane and *N,N'*-dimethylaminoethyl methacrylate (DMAEMA) to yield a piperazine-methacrylate monomer. Further, the quaternized piperazine-methacrylate monomer was homopolymerized using an azobis(2-methylpropionitrile) (AIBN) initiator (thermal) yielding a multifunctionalized piperazine polymer (Scheme 6). The multifunctionalized piperazine polymer exhibited efficient antimicrobial activity against *E. coli*, *M. smegmatis*, *S. aureus* and *Candida albicans* (*C. albicans*) in comparison with standard drugs ciprofloxacin (antibacterial)

and fluconazole (antifungal). The mode of action is as follows: the electrostatic interaction occurs between a negatively charged microbial cell wall and positively charged quaternary ammonium group that leads to cell lysis. The authors concluded that the as-synthesized piperazine-based polymer could be applicable in wound dressing, textile industry, biomedical field, water purification system, and so forth.⁷⁴

In 2019, novel biocompatible piperazine polymer (PE) (Scheme 7) for bacterial repellence on biomedical materials was designed and synthesized *via* green synthetic route by Zhang *et al.* The piperazine polymer was prepared by the straightforward reaction of piperazine with ethylenediaminetetraacetic dianhydride (EDTAD). The piperazine polymer exhibited significant antimicrobial activity against *E. coli* and *S. aureus* in comparison with standard antibacterial ciprofloxacin. Piperazine targets the cytoplasmic membrane of the bacteria, resulting in the leakage of intercellular components leading to cell death. Based on their antibacterial activity and biocompatibility, the authors reported that the polymer could be applicable in biomedical field.^{97,98}



Scheme 8 Synthesis of the MGF-Ct24E-modified piperazine polymer.

Table 2 List of piperazine-based homo/co/tripolymers synthesized by researchers against numerous pathogenic microorganisms

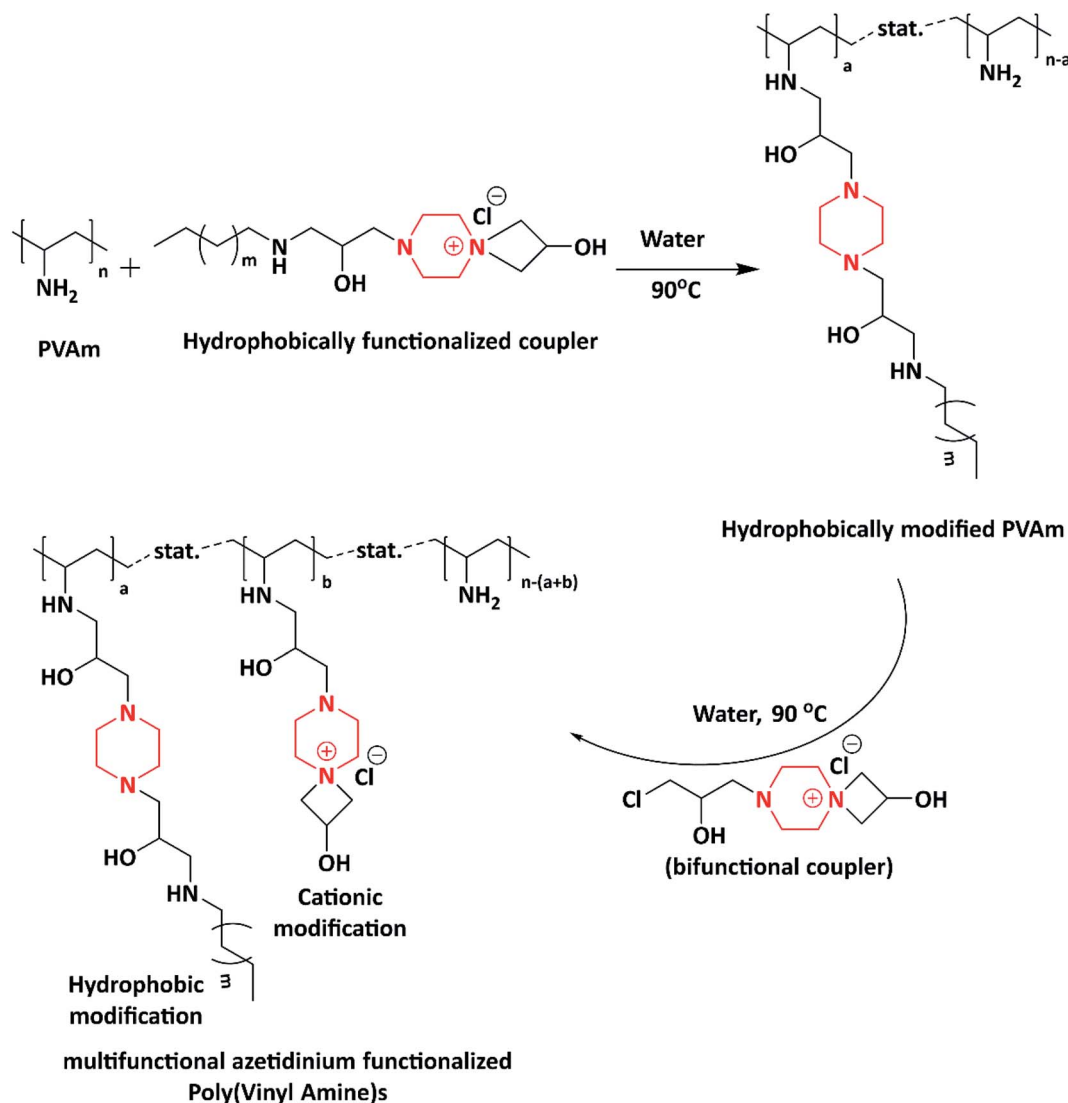
S. no.	Year	Author	Monomer/Polymer	Antimicrobial activity	Applications	Ref.
1	2003	Woong sig moon <i>et al.</i>		<i>E. coli</i> , <i>S. aureus</i> , <i>B. subtilis</i> , and <i>M. luteus</i>	Food packaging	92
2	2006	Supriya <i>et al.</i>		<i>E. coli</i> and <i>S. aureus</i>	Biomedical	93
3	2007	Supriya <i>et al.</i>		<i>E. coli</i> and <i>S. aureus</i>	Biomedical	94
4	2012	Xue <i>et al.</i>		<i>E. coli</i>	Paper products	95
5	2018	Ahmed <i>et al.</i>		<i>M. smegmatis</i> , <i>S. aureus</i> , MRSA, and <i>S. flexneri</i>	Biomedical	96



S. no.	Year	Author	Monomer/Polymer	Antimicrobial activity	Applications	Ref.
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Mechano-growth factor and its 24 amino acid peptide (MGF-Ct24E)-modified piperazine polymer (PEM) for biomedical applications was designed and synthesized by the same author in 2019. First, the piperazine polymer (PE) was synthesized by reacting piperazine with ethylenediaminetetraacetic dianhydride (EDTAD) *via* the condensation polymerization method. Further, the MGF-Ct24E peptide polymer was grafted to the as-synthesized piperazine polymer (PE) yielding a piperazine-modified polymer (PEM) (Scheme 8). The antimicrobial activity of PE and PEM was tested against *E. coli* and *S. aureus*, in which PE showed better antibacterial activity against *E. coli* compared to PEM. In case of *S. aureus*, both PE and PEM





Scheme 10 Step-wise synthesis of multifunctional azetidinium-functionalized Poly(vinyl amine) by reacting PVAm with the functionalized coupler and the bifunctional coupler.

showed similar activity. After the insertion of MGF-Ct24E to PE, the as-synthesized polymeric material not only maintained the physical and chemical properties but also reduced the biological toxicity of PE and produced the balance between the antibacterial and biological toxicity. Piperazine and amino peptides target the cell wall and cytoplasmic membrane of the bacteria, eventually leading to the leakage of cytoplasmic fluid and cell death; the mechanism was studied *via* scanning electron microscopy (SEM). The authors stated that the as-synthesized polymer could be applicable in biomedical field for the repair of bone, muscle and neuronal tissues.^{97,99} Numerous piperazine-based homo/co/tripolymers are listed in Table 2.

1.2 Piperazine grafted polymers

In 2014, Subrata *et al.* developed non-leaching antimicrobial surfaces in a solution by synthesizing azetidinium-functionalized polytetrahydrofurans. Initially, they prepared

a bifunctional coupler (piperazine-bearing amino chlorohydrin and azetidinium group) using piperazine and epichlorohydrin. The as-synthesized bifunctional coupler was further post-polymerized with synthetic polymer aminotelechelic polytetrahydrofuran (PTHF) [XTJ-548], resulting in the formation of azetidinium-functionalized polytetrahydrofuran polymers (Scheme 9). The authors concluded that the as-synthesized functional polymer could be applicable to solve the problems associated with hospital environment because of its excellent activity exhibited (>9.99–100%) in both solution and on the surfaces of textiles against *E. coli* and *S. aureus*. Azetidinium-functionalized polymers possess cationic nature, ionic interaction and covalent linkage, which helps to inhibit the bacterial growth *via* interacting with cell wall, followed by its death.^{100,101}

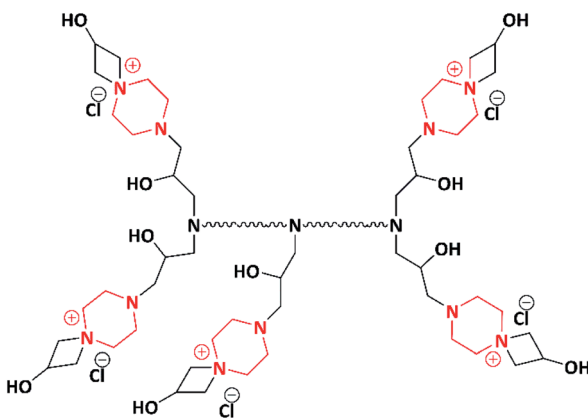
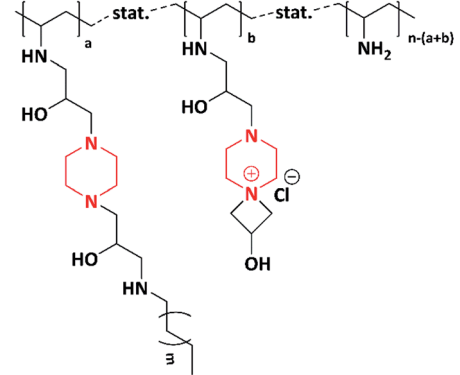
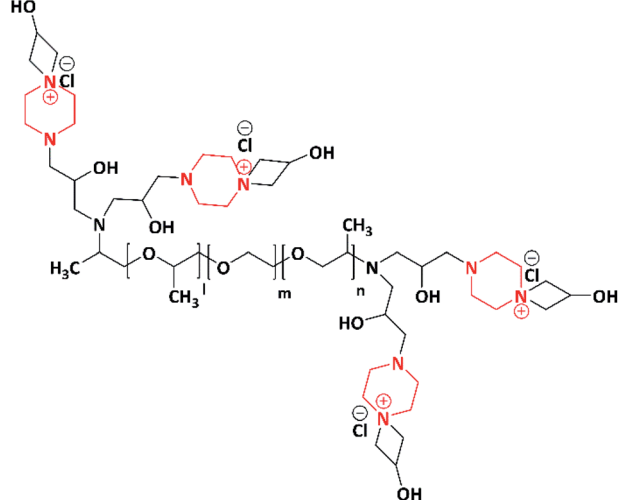
The same author in 2014 fabricated antimicrobial fabrics by coating synthesized multifunctional polymers induced with piperazine on to cotton fibre. A one pot synthesis method was adopted to synthesize multifunctional polymers. Piperazine was





aminochlorohydrin and azetidinium group) *via* a one-pot synthesis method. Because of the presence of the piperazine moiety, counter ions (Cl^-), hydroxyl ($-\text{OH}$), and quaternary ammonium groups, the functionalized Jeffamine polymer exhibited antimicrobial activity against *E. coli*, *M. smegmatis*, *S. aureus* and *C. albicans*. The antimicrobial action of the functionalized Jeffamine polymer is ascribed to the quaternary ammonium group, which leads to cell lysis where electrostatic interaction takes place between the positively charged Jeffamine polymer and negatively charged microbial cell wall. In addition, it also contains $-\text{OH}$ groups associated with azetidinium and amino-chlorohydrin, which are known for targeting the cytoplasmic membrane of microorganisms. This leads to leakage in intercellular components, followed by the death of microbes; the mechanism was studied *via* scanning electron microscopy (SEM). The author conveyed that the as-synthesized functionalized Jeffamine polymer having the piperazine moiety could be applicable in antimicrobial coatings, biomedical applications, textile industries, water purification system, and so forth.² Numerous piperazine-grafted polymers are listed in Table 3.

Table 3 List of piperazine grafted polymers synthesized by researchers against numerous pathogenic microorganisms

S. no.	Year	Author	Polymer	Antimicrobial activity	Applications	Ref.
1	2012	Subrata <i>et al.</i>		<i>E. coli</i> and <i>S. aureus</i>	Textile	100 and 101
2	2013	Subrata <i>et al.</i>		<i>E. coli</i> and <i>S. aureus</i>	Textile	102
3	2019	Jalageri <i>et al.</i>		<i>E. coli</i> , <i>S. aureus</i> , <i>M. smegmatis</i> and <i>C. albicans</i>	Biomedical, coatings, and textile	2

2. Conclusion

In summary, this review highlights the use of piperazine in the synthesis of antimicrobial polymers due to their wide range of pharmacological activities, which lead to the development of new therapeutic agents. In this aspect, piperazine-based antimicrobial polymers have gained interest from both academic and industrial researchers. The probable drawbacks and

challenges encountered in the synthesis of piperazine polymers are (i) difficulty in handling due to its hygroscopic nature that liquidifies by absorbing moisture from air, therefore interrupting in the polymerization process, (ii) it contains only two reactive sites: secondary amines that restrict the adaptability of conversion to monomer or limits itself in incorporating into polymer structures, (iii) synthesized polymers may encounter difficulty in maintaining physical stability due to the



hygroscopic nature of piperazine, (iv) polymer synthesis involves a multi-step synthetic procedure, which makes the purification of the polymer laborious. By considering the future perspectives of piperazine, a highly potential pharmacological interest can be used for the synthesis of antimicrobial polymers, which may have significant importance in sectors such as biomedical, food packaging and storage, textile, drug carriers, wound dressing, water purification system, and health care products.

Conflicts of interest

There are no conflicts to declare.

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