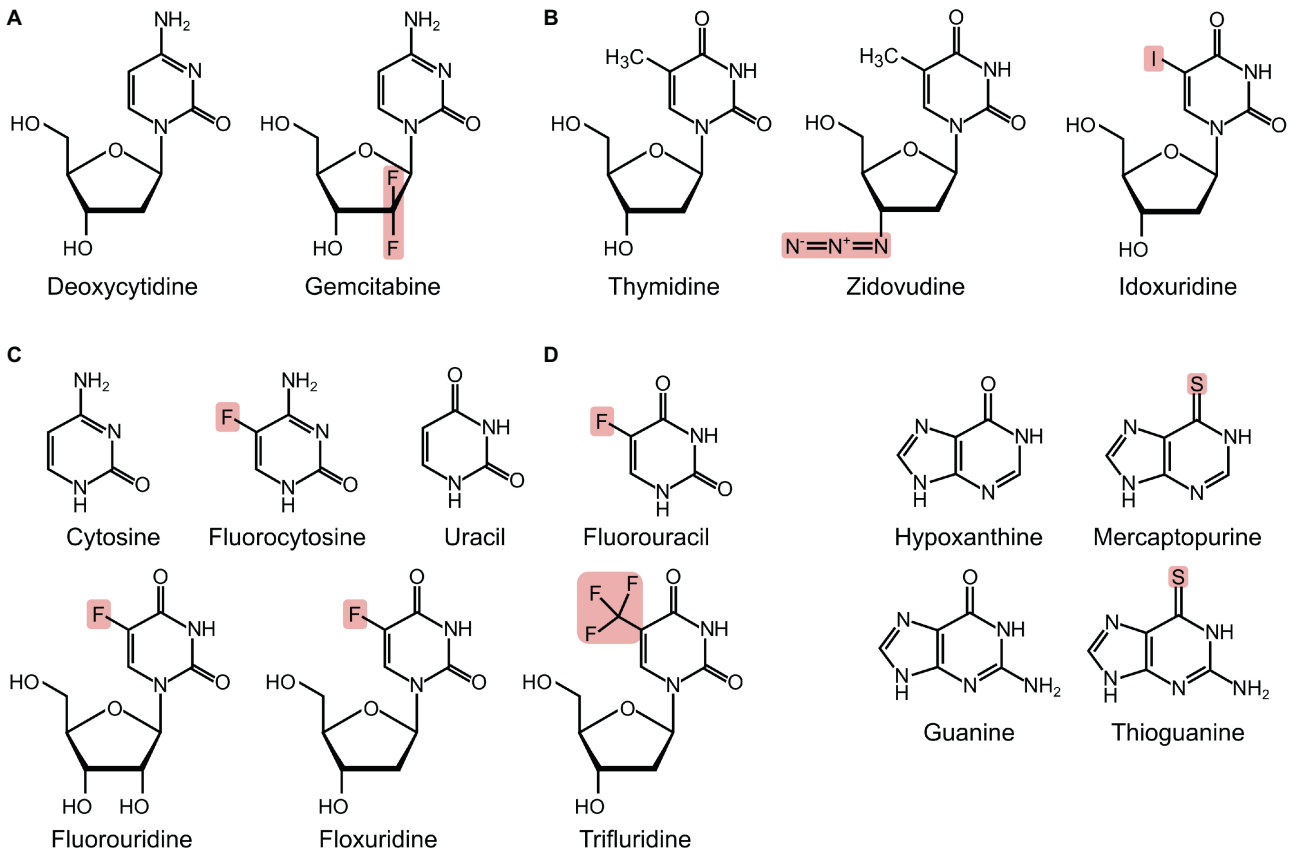

FIGURE 2 | Structures of pyrimidines, purines, and their analogues, with substituted atoms highlighted. **(A)** Deoxycytidine and its analogue. **(B)** Thymidine and its analogues. **(C)** Cytosine, uracil, and fluorinated pyrimidines. **(D)** Hypoxanthine, guanine, and their analogues.

Doleans-Jordheim et al., 2011; Peyclit et al., 2018). It also acts synergistically with conventional antibiotics, enhancing their effectiveness (Wambaugh et al., 2017; Ng et al., 2018; Falagas et al., 2019; Hu et al., 2019). Zidovudine is ineffective against Gram-positive bacteria such as *Listeria* species, *Bacillus* species, Staphylococci, and *Enterococcus faecalis* as well as against *Mycobacteria* species and *Pseudomonas aeruginosa* (Elwell et al., 1987; Sandrini et al., 2007a).

The antibacterial activity of zidovudine has been demonstrated both *in vitro* and *in vivo*. Herrmann and Lagrange (1992) used a macrophage cell line to demonstrate that zidovudine inhibited intracellular growth of *S. typhimurium*. Zidovudine had potent *in vivo* activity. Zidovudine prevented lethal infections in mice with pyelonephritis caused by *E. coli* infection, being as effective as either trimethoprim or ampicillin (Keith et al., 1989). It also inhibited growth of antibiotic-resistant *E. coli* and *K. pneumoniae* in a murine peritoneal infection model, acting synergistically with colistin (Hu et al., 2019). When administered subcutaneously, zidovudine also prevented lethal salmonellosis in calves infected with *S. dublin* (Keith et al., 1989). Zidovudine has therapeutic potential for humans as well; zidovudine given as an antiretroviral to HIV/AIDS patients also had the additional protective effect of lowering the recurrence of *Salmonella* bacteremia, a significant problem for HIV/AIDS patients (Casado et al., 1999). These *in vivo* findings suggest that zidovudine has potential application as an antibacterial agent. Zidovudine has also been the subject of modification studies, which aim to improve its therapeutic efficacy and resolve issues like short half-life of the drug. Research has gone into creating zidovudine derivatives that retain antiviral activity while having improved bactericidal activity (Moroni et al., 2002). Such derivatives may be particularly useful for HIV/AIDS patients; HIV/AIDS patients are susceptible to opportunistic bacterial infections, and improved bactericidal profile of these derivatives would be a beneficial side activity.

Fluorinated Pyrimidines

Originally synthesized as antitumor drugs (Heidelberger et al., 1957), fluorinated pyrimidines have also been used widely as antifungals (Vermes et al., 2003), have some use as antivirals (Wilhelmus, 2010), and show promise as antibacterials. The fluorinated pyrimidine family was first synthesized after the observation that tumor cells preferentially utilized uracil for nucleic acid biosynthesis (Rutman et al., 1954; Heidelberger et al., 1957). From this large family of compounds, the nucleobase 5-fluorouracil and the nucleoside floxuridine (5-fluoro-2′deoxyuridine, **Figure 2C**) are frequently used for the treatment of various cancers (Galmarini et al., 2002; Alvarez et al., 2012).