NCT02493764). Moreover, a phase III non-randomized, open label study for the efficacy and safety of imipenem–cilastatin/relebactam for the treatment of cIAI and cUTI is currently ongoing in Japan (https://clinicaltrials.gov/ct2/show/NCT03293485). The activity of this triple combination will be useful against organisms that harbor metallo-β-lactamase such as New Delhi metallo-β-lactamase-1 (NDM-1), imipenemase (IMP), and Verona integron-encoded metallo-β-lactamase (VIM) (Blizzard et al. 2014; Falagas et al. 2016).

18.8 Aspergillomarasmine A

The adjuvant aspergillomarasmine A (AMA) was recently discovered to resuscitate the biocidal activity of the carbapenem drug, meropenem, against metallo-β-lactamase-producing organisms (King et al. 2014). The fungal metabolite AMA was first isolated in the 1960s (Haenni et al. 1965) and was later evaluated for its antihypertensive properties (Arai et al. 1993; Matsuura et al. 1993). In an antibiotic era where enzymes capable of degrading even the most powerful β-lactam (e.g. carbapenems) are abundant, it is promising to find AMA able to inhibit metallo-β-lactamases such as the NDM-1 enzyme. AMA was found to sequester zinc cations (King et al. 2014) that are essential for the hydrolytic activity of metallo-β-lactamases (Karsisiotis et al. 2014; Meini et al. 2015). In a mouse model of NDM-1-positive *Klebsiella pneumoniae* infection, a single dose of meropenem ($10\,mg\,kg^{-1}$) and AMA ($30\,mg\,kg^{-1}$) combination led to >95% survival after five days post-infection (King et al. 2014). Meropenem alone ($10\,mg\,kg^{-1}$) or AMA alone ($30\,mg\,kg^{-1}$) resulted in 0% survival (King et al. 2014). These promising results stimulate the need for an optimized dosing regimen of AMA in combination with carbapenems for the treatment of metallo-β-lactamase-producing pathogens. Currently, AMA is undergoing preclinical optimization (Albu et al. 2016; Koteva et al. 2016; Liao et al. 2016).

18.9 Intrinsic Resistance Challenges and Strategies to Overcome Them

Poor outer membrane permeability and overexpression of multidrug efflux pumps, the hallmarks of intrinsic resistance in GNB, prevent many classes of antibiotics from achieving the required intracellular or periplasmic concentrations to elicit their antibacterial effect (Li et al. 2015; Tommasi et al. 2015; Zygurskaya et al. 2015; The Pew Charitable Trusts 2016; Brown and Wright 2016; Silver 2016; Domalaon et al. 2018c). One pathogen that uses intrinsic resistance at near perfection is *P. aeruginosa*. *Pseudomonas aeruginosa*