Background: The ongoing threat of Antimicrobial Resistance (AMR) complicated by the rise of Multidrug-Resistant (MDR) pathogens calls for increased efforts in the search for novel treatment options. While deriving inspiration from antibacterial natural compounds, this study aimed: at using synthetic approaches to generate a series of glucovanillin derivatives and explore their antibacterial potentials. Among the synthesized derivatives, optimum antibacterial activities were exhibited by those containing 2, 4- and 3, 5-dichlorophenylamino group coupled to a glucovanillin moiety (compounds 6h and 8d respectively). In those compounds, the Minimum Inhibitory Concentrations (MIC) of 128–256 μg/mL were observed against reference and MDR strains of Klebsiella pneumonia, Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). Moreover, these findings emphasize the claims from previous reports on the essence of smaller molecular size, the presence of proton table amino groups and halogens in potential antibacterial agents. The observed moderate and broad-spectrum activities of the stated derivatives point to their suitability as potential leads towards further efforts to improve their activities. Graphical abstract Introduction: The ever-increasing rates of Antimicrobial Resistance (AMR) continue to pose a great threat to public health globally. Among others, the infections caused by Gram-negative bacteria need an urgent attention as they are more difficult to treat, and the rise of Multidrug-Resistant (MDR) bacteria have left very limited treatment options [1,2]. The World Health Organization (WHO) categorizes carbapenem-resistant and third generation cephalosporin-resistant Enterobacteriaceae among the critical priority pathogens against which new antibiotics are urgently needed [3]. This challenge is intensified by the increasing trends of resistance against the current antibiotic of the last resort for those pathogens, colistin [3, 4]. Furthermore, the slow entry rates of novel antibacterial agents into the antibiotic development pipeline have long led to an almost empty pipeline [5].In the face of these challenges, the necessity for constant efforts in the search for novel antibacterial agents is outstanding. Favorably, diverse approaches in the discovery and development of antibacterial agents are well established. Among them, the screening of natural products from plants, fungi, bacteria etc. for compounds with antibacterial activities has increasingly reported a good number of potential compounds [[6], [7], [8]]. Natural compounds are particularly attractive due to their higher likelihood of hosting novel bioactive

scaffolds beyond those from synthetic or computational approaches. Concerning antibacterial compounds, this attribute is essential towards the discovery of agents with novel targets and modes of action, hence lowering chances for their cross-resistance with the existing antibiotics [[6], [7], [8]]. Moreover, the chemical synthesis of natural compounds or their modifications stands as a valuable tool towards increased access and diversity of such compounds for different purposes. Here, compounds/scaffolds from natural compounds can potentially inspire synthetic approaches targeting increased potency, better pharmacokinetic and physicochemical profiles, as well as reduced toxicities [[9], [10], [11], [12]]. The development of feasible synthetic approaches to prepare natural compounds and their derivatives is therefore essential in optimizing the combined benefits from the ideal qualities of nature-derived compounds and their synthetic derivatives. Development of agents against the Gram-negative bacteria is challenged by the roles played several morphological features. These include the presence of outer and inner cell membranes, selective porins, as well as single- or multi-component efflux transporters [13, 14]. Apart from limiting the entry of antibacterial agents into the Gram-negative bacteria by the cell membranes and porin channels, the forced efflux of agents, which manage to enter the bacterial cells, hinder the exhibition of their targeted effect(s) [13, 14]. To account for such limitations, the development of small molecules with high globularity and lower flexibility due to e.g. lesser number of rotatable bonds, having amphiphilic characters, and which possess proton table amino group(s) are among the highly recommended strategies [13]. In line with those approaches, this study, aimed at identifying and profiling a potential natural compound, followed by its synthesis, derivatization, and assessment of antibacterial activities. Generally, the exploration of a wider chemical space around the selected natural product was hypothesized to possibly reveal other compounds with antibacterial potentials. Section snippets Selection of the natural hit compound From the review of literature, the compound vanilloloside (compound 4) was selected by virtue of having reported MIC values of 16–32 μg/mL against the Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella typhimurium* and *Pseudomonas aeruginosa* [15]. Moreover, vanilloloside was previously isolated from honeybee venom and several plant species, whereby it was associated with wound healing, neuroprotection, anti-inflammatory, antibacterial, ant mutagenic, and anticancer Conclusions: Nature-inspired synthesis of antibacterial

compounds is a promising way to maximize the benefits of chemical diversity, novelty, and biological potentials of nature-derived compounds. While well-studied natural hits might not be attractive for further studies, less explored hits are likely to be associated with limited reproducibility of their scarcely available data. This study has highlighted the usefulness of a surrogate approach to explore the biological profiles of natural hits with scarce.