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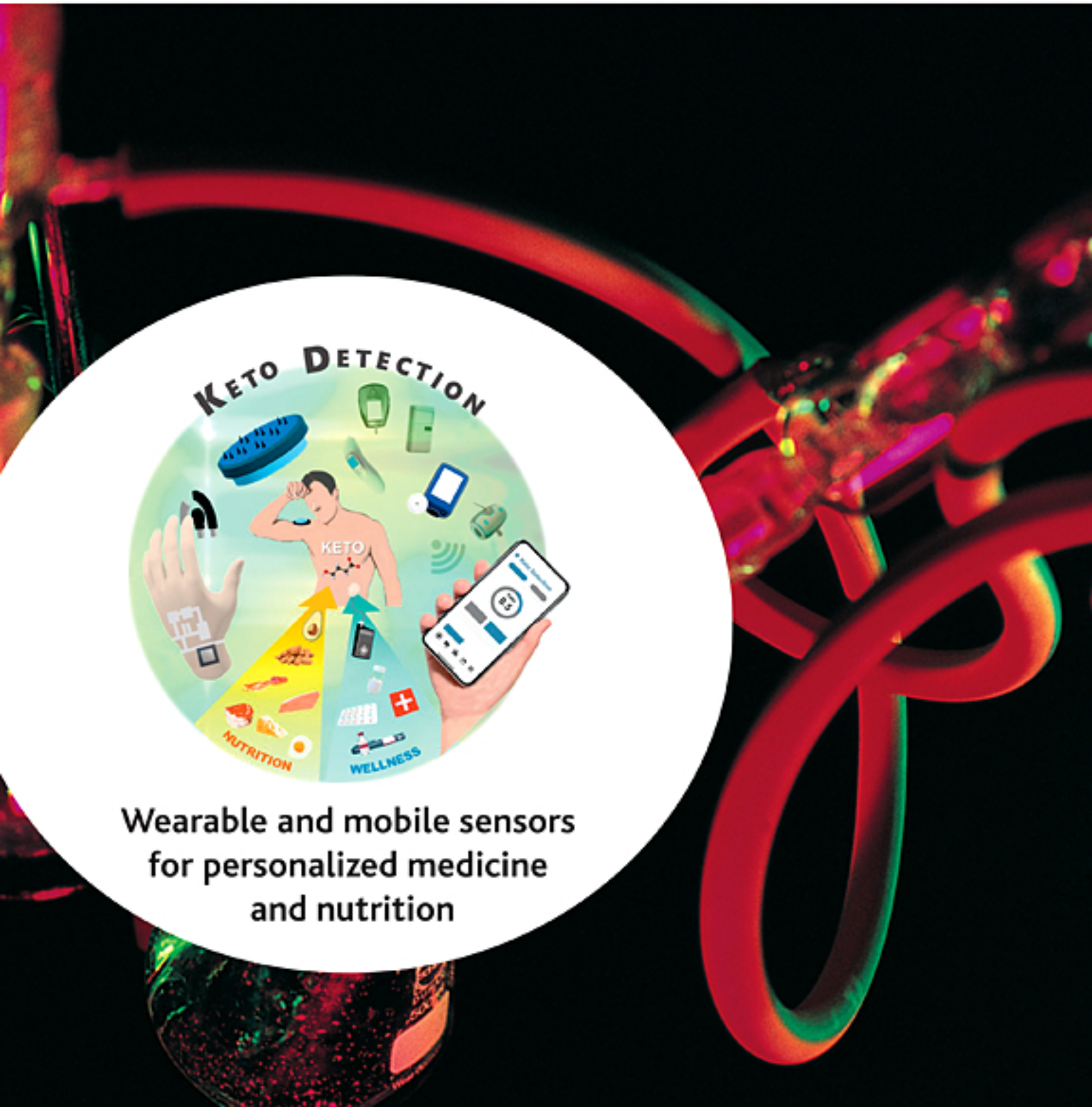

Wearable and mobile sensors for personalized medicine and nutrition

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Microbial metabolites diversity and their potential as molecular template for the discovery of new fluorescent and radiopharmaceutical probes

Hendris Wongso [a, b, *], Rudi Hendra [c], Ari S. Nugraha [d], Rien Ritawidya [a, b], Indra Saptiama [a], Christerra E. Kusumaningrum [a]

[a] Research Center for Radioisotope, Radiopharmaceutical, and Biodosimetry Technology, Research Organization for Nuclear Energy, National Research and Innovation Agency, Puspiptek Area Serpong, Banten, 15314, Indonesia
[b] Research Collaboration Center for Theranostic Radiopharmaceuticals, National Research and Innovation Agency, Jl. Raya Bandung-Sumedang KM 21, Sumedang, 45363, Indonesia
[c] Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Riau, Riau, 28293, Indonesia
[d] Drug Utilisation and Discovery Research Group, Faculty of Pharmacy, University of Jember, Jember, East Java, 68121, Indonesia

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ABSTRACT

Microbial metabolites have tremendous roles on human life, with a wide variety of applications in pharmaceutical sciences. Given their ability to interact with a diverse array of biological macromolecules-typically in a highly selective fashion, bioactive compounds from microbes may also serve as an advantageous molecular template for the development of sensitive and selective molecular probes, such as fluorescent and radiopharmaceutical probes. Despite numerous chemical probes have made significant contributions in clinical settings, there were only a few fluorescent and radiopharmaceutical probes derived from microbial metabolites available until recently. Those probes are being investigated for their potential to diagnose diseases associated with biomarkers, detect overexpression of proteins, and navigate the presence of pathogens, most notably bacterial and fungal infections. This review summarizes recent advances in the development of molecular probes derived from microbial metabolites, discusses selected applications, and identifies key opportunities.

1. Introduction

Microbes are capable of producing a wide variety of therapeutically significant bioactive molecules and are therefore critical in the process of drug discovery and development [1]. These bioactive molecules have played an important role in human life for many years, as evidenced by their unique biological activities, including antimicrobial (e.g., antibacterial, antifungal, antiviral, and antiprotozoal) and anticancer properties [2]. Alexander Fleming's 1929 discovery of penicillin initiated the antibiotic era and fundamentally altered the study of natural products, establishing naturally occurring microbial metabolites as a fundamental platform for drug discovery [1,3]. Since then, products derived from microorganisms have been applied to a variety of fields, including medicine [4]. As a result, the majority of antibiotics are originated from bioactive microbial products or their semi-synthetic derivatives [5].

The study of secondary bioactive compounds produced by microbes is a challenging endeavor. The quest to discover naturally occurring microbial bioactive constituents becomes more appealing as screening, isolation, and separation techniques advance [6]. Indeed, with a growing number of newly isolated molecules exhibiting a diverse range of pharmacological activities, microbial metabolites are gaining prominence in natural product research and related fields. Secondary metabolites isolated from various microorganisms, including bacteria, actinomycetes, and fungi have undoubtedly aided in the discovery of new drugs over the last few centuries [3,7,8]. Until recently, bioactive constituents derived from microbes and plants were the primary agents used to cure a wide array of diseases [2].

* Corresponding author. Research Center for Radioisotope, Radiopharmaceutical, and Biodosimetry Technology, Research Organization for Nuclear Energy, National Research and Innovation Agency, Jl. Tamansari No.71, Lb. Siliwangi, Bandung, West Java 40132, Indonesia.
E-mail addresses: hend042@brin.go.id, hendriswongso@batan.go.id (H. Wongso).

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Abbreviations

ADME	absorption, distribution, metabolism, and excretion
ASTM	diacetyl-bis (N^4-methylthiosemicarbazone)
ATCC	American Type Culture Collection
BLB	blood-labyrinth barrier
Boc-FL	BOCILLIN FL
BODIPY	boron-dipyrromethene
Ceph C-T	cephalosporin-carboxytetramethylrhodamine conjugates
CT	computed tomography
CYP	cytochrome P-450
d	day (s)
Df-Bz-NCS	p-isothiocyanatobenzyl-desferriox amine B
DFO	desferrioxamine
DHFR	dihydrofolate reductase
DIPEA	*N*,*N*-diisopropylethylamine
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA-TOC	1,4,7,10-tetraazacyclododecane-N′,N″,N‴,N⁗-tetraacetic acid (D)-Phe^1-Tyr^3-octreotide
EDANS	5-((2-aminoethyl)amino)naphthalene-1-sulfonic acid
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FITC	fluorescein isothiocyanate
FSC	fusarinine C
GTTR	gentamicin-Texas Red
h	hour (s)
ICG	indocyanine green
IVIS	in vivo imaging system
keV	kiloelectron volt
MAbs	monoclonal antibodies
MB	methylene blue
MBC	minimum bactericidal concentration
MeV	Megaelectron volt
MIC	minimum inhibitory concentrations
min	minute (s)
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
nm	nanometer
NBD	4-nitrobenzo-2-oxa-1,3-diazole
NETs	neuroendocrine tumours
NIR	near-infrared
NOTA	1,4,7-triazacyclononane-1,4,7-trisacetic acid
PET	positron emission tomography
PRRT	peptide receptor radionuclide therapy
PSMA	prostate specific membrane antigen
SPECT	single photon emission tomography
TETA	1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid
TMP	trimethoprim
UV	ultraviolet.

Although microbial metabolites have contributed significantly to human history [9], there is still room for advancement and innovation in the way to address today's health problems. Natural metabolites have increasingly been used as a chemical template for the discovery of potent drugs over the last few decades. Bioactive compounds isolated from plants and microbes are not only being used to cure and control a variety of ailments, but they have also served as a starting point for the generation of natural product-based chemical probes [10]. Several active molecules derived from synthetic chemistry have been labeled with fluorophores, resulting in fluorescent probes for in vitro and in vivo investigations of various diseases [11,12]. Additionally, there are numerous examples of synthetic-based radiopharmaceuticals that are suitable for either diagnosis or therapy of human diseases in nuclear medicine, encompassing a diverse range of active molecules, such as small organic molecules, peptides, monoclonal antibodies, proteins, and nanoparticles [13,14]. Despite this, the number of fluorescent and radiopharmaceutical probes derived from microbial metabolite templates is surprisingly small.

Molecular imaging using fluorescent probes offers several key advantages, including inexpensive procedure due to the low cost of instrumentations [15], the utilization of nonionizing radiations, portability and real-time capabilities. However, due to light scattering, fluorescence molecules suffer from low tissue penetration which limits their applications in in vivo settings [16]. Light scattering could lead to the loss of light directionality, resulting the loss in resolution, and consequently blurring the image. In addition, the presence of melanin and blood in tissue may reduce light intensity, leading to a low signal to noise ratio [17]. To address this issue, several near-infrared (NIR) fluorophores have been developed, allowing adequate in-depth tissue penetration, reduce interferences from tissue autofluorescence, and better images quality [18,19].

On the other hand, radioctive probes provide high tissue penetration, low signal attenuation [20], and high-sensitivity imaging [21]. Their widespread applications is strengthened by the fact that radioimaging modalities can be complemented with other anatomical imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI) [22]. Nevertheless, the routine use of radiopharmaceuticals is often associated with high cost procedure due to the need for expensive instrumentations and equipment (e.g., expensive imaging modalities and cyclotrons for producing the radionuclides), and controlled facilities. More recently, the use of combined fluorescence-radioactive imaging probes can provide complementary molecular information, thus may be valuable for many biomedical purposes, such as cancer detection dan localization using PET, and subsequent surgical intervention with intraoperative optical imaging during image-guided surgery procedures [23].

It is obvious that microbial metabolites have a tremendous effect on our society. Developing chemical probes based on microbial metabolites, on the other hand, has proven challenging and will require further technological advancement. For example, developing chemical probes from microbial metabolites is not only challenging synthetically, but also takes into account the steric effect of conjugating the radionuclide or relatively large fluorescent dye on the agent's binding and pharmacological profiles toward the biological target. Nevertheless, advances in chemical synthesis and associated methodologies (i.e., isolation, elucidation, and purification) enable the conjugation of a microbial metabolite with a fluorophore or a radionuclide without altering their initial biological activities. This review summarizes recent advances in the development of molecular probes based on secondary microbial metabolites and emphasizes the potential of secondary microbial metabolites as molecular templates for the synthesis of chemical probes, most notably fluorescent and radiopharmaceutical probes.

2. Diversity of microbial metabolites

Microbes such as bacteria, actinomycetes (also known as actinobacteria), and fungi have developed into important sources of a large number of pharmacologically active compounds. Due to advances in screening, separation, and isolation techniques, as well as the rapid growth of biotechnology research, the total number of natural products discovered to date exceeds one million. Around 5% of them were derived from microorganisms [2]. Secondary metabolites produced by microorganisms come in a variety of forms, including antibiotics, pigments, anticancer agents, and growth hormones. Although these bioactive compounds are not required for microorganisms' growth and development, they have been shown to have various health benefits for humans and animals [24]. Bacteria, actinomycetes, and fungi are the most common microorganisms that produce secondary metabolites. Their metabolites are known to display a wide spectrum of pharmacological properties and are of interest to numerous disciplines, including food sciences, agrochemicals, and pharmaceuticals [25,26]. Nonetheless, some purified microbial natural products may be ineligible for use as drugs. This is because the produced metabolites are not selected to act as drugs but rather for their ability to perform normal roles and survive in the ecosystem. As a result, a large number of microbial metabolites serve only as parent compounds for further modification by drug developers to achieve more appropriate drug-like properties (e.g., widened antimicrobial activities and enhanced pharmacological profiles) [27].

Until recently, the majority of antibiotics used in clinical practice were either isolated from microbial metabolites or were semi-synthetic derivatives of these molecules [28]. Regrettably, the dramatic increase in antibiotic-resistant infections has exacerbated societal health crises. Around 700,000 people die each year due to drug-resistant infections on a global scale [29]. This clearly demonstrates that efforts in the discovery of new antibiotics for modern medicine are urgently needed [30]. With the addition of new and innovative technologies, such as genome mining and editing [31], the discovery of new antibiotics can be more efficient than ever before. The ability of high resolution spectroscopic and spectrometric instrumentation to generate high-quality molecular fingerprints, in conjunction with statistical data analysis techniques, have increased the significance of metabolomics studies and enabled the correlation of molecular spectral attributes with dependent factors, such as pharmacological activities. Additionally, these techniques have made dereplication procedures for commonly occurring natural complex mixtures more feasible, thereby avoiding research redundancy [32–34].

Actinomycetes accounted for 65% of all known natural antibiotics, while fungi and bacteria accounted for the remaining 35%. It is worth noting that naturally occurring antibiotics possess a high degree of structural diversity and complexity compared to synthetic antibiotics [27]. The structural complexity of these bioactive compounds also presents challenges for drug discovery, including unsuccessful reaction, low yield, and the presence of impurities. In this case, structural modification (s) of a bioactive compound is necessary, which can include the transformation of a specific group into a functional unit that serve as a conjugation site with a fluorophore or a radionuclide, protection-deprotection of reactive groups (e.g., NH_2 and OH) to prevent undesired side reaction (s), and the introduction of a linker or functional chelator between bioactive molecule and a fluorophore or a radionuclide to minimize the steric impact on binding to the protein biomarker or targeted receptor [13]. These challenges have been attributed to a dearth of research aimed at developing chemical probes based on microbial metabolites. Recent technological advancements in the field of natural products, however, are addressing these issues and creating new opportunities. Numerous secondary bioactive metabolites derived from microorganisms are described below, along with their potential use as active molecules in the design and synthesis of fluorescent and radiopharmaceutical probes.

2.1. Fungal metabolites

Historically, fungi have been critical in the production of several essential human products, including alcohol, bread, and medicine (e.g., penicillin). Since the discovery of penicillin, the fungi kingdom has piqued scientists' worldwide interest and has been recognized as a valuable source of diverse therapeutic molecules [35]. As a consequence, several naturally occurring antibiotics with biological activity against pathogens have been discovered (Fig. 1). Given that approximately 38% of active microbial metabolites originate from fungi and only about 10% of fungi species have been identified so far, fungi represent an enormous opportunity for new drug development efforts [36,37]. Specifically, filamentous fungi groups, including the Pezizomycotina Ascomycete class and some Basidiomycete classes (e.g., Agaricomycetes and Exobasidiomycetes) have been recognized as a significant group of microorganisms capable of producing a large variety of bioactive secondary metabolites [35,38]. Additionally, many reports have demonstrated that numerous compounds isolated from fungi possess pharmacologically significant properties, including antibacterial, antitumor, antifungal, antiparasitic, anti-inflammatory, antiviral, and antioxidant properties [38–40].

The abundance and diversity of fungal species have long been regarded with the terrestrial ecosystem. Recent studies, however, estimate that over 10,000 fungal species live in marine environments, ranging from the surface of the waters to deep-sea sediments and even arctic ice [36,41]. In addition, some marine fungi thrive in harsh and stressful environments (i.e., under cold, lack of sunlight, and high water pressure) [42]. Thus, fungi, particularly endophytic fungal species, are the main producers of bioactive compounds with diverse chemical structures, resulting in a broad range of biological properties [1].

Numerous natural product classes, including alkaloids, polyketides, peptides, terpenes, sesquiterpenoids, and sugar, have been elucidated from fungi, and several have been used as molecular scaffolds and lead compounds for the production of semisynthetic antibiotics [29,43,44]. Table 1 summarizes representative pharmacologically significant fungal secondary metabolites and their biological activities. These metabolites could potentially be used to treat numerous diseases and serve as lead structures for the development of molecular probes for the diagnosis and therapy of a variety of disorders.

2.2. Bacterial and actinomycetes metabolites

As with fungal secondary metabolites, bacteria and actinomycetes excrete bioactive compounds that are not essential for growth and development, but are highly beneficial for their survival and intercellular communication (Fig. 2). Additionally, the compounds have been a significant source of novel therapeutic agents with a variety of pharmacological properties, including antimicrobial, antitumor, antiparasitic, anti-fowling, and insecticidal activity [65,66]. Secondary metabolites produced by bacteria are primarily low molecular weight, uncharged, and non-polar compounds typically produced during the late-exponential and stationary phases of life cycles [67].

Almost three-quarters of bioactive molecules produced by microbes come from actinomycetes, with genus *Streptomyces* accounting for the majority (i.e., each strain produced between 10 and 20 bioactive molecules). It is estimated that among 23,000

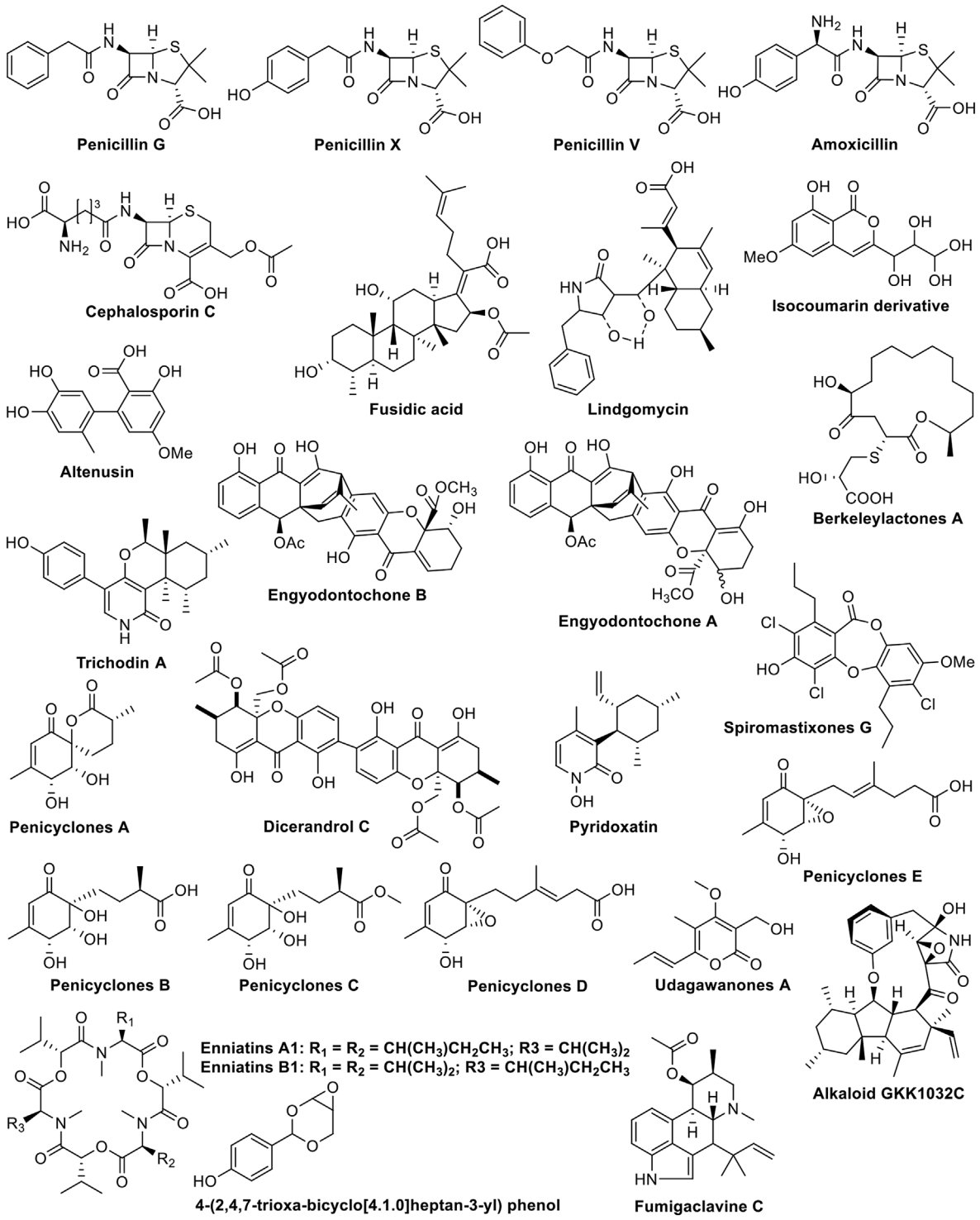

Fig. 1. The structures of several natural antibiotics isolated from fungi.

bioactive products from microorganisms, about 10,000 compounds are reported from actinomycetes [7,68,69], and several types/classes of natural antibiotics have been identified, for instance, beta-lactams, tetracyclines, peptides/glycopeptides, anthracyclines, benzoxazolophenanthridines, lactones, and polyenes [1].

Subsequently, marine bacteria are a significant producer of a variety of pharmaceutically significant molecules with a diverse range of biological properties ranging from antiviral to antimalarial activity. Hence, numerous bioactive constituents have been applied to the food industry, cosmetics, medicine, and agriculture [70]. Bacteria in marine habitats face constant pressures from physico-chemical factors (i.e., high salinity, high hydrostatic pressure, and low oxygen), predation, and biotic competition from nematodes and protozoans [71]. These unfavorable conditions have resulted in the synthesis of fascinating and structurally diverse secondary metabolites [42,71]. Table 2 highlights selected examples of

Table 1
Natural product antibiotics isolated from fungi.

No	Secondary Metabolite	Fungi	Biological Activity	Reference
1	Penicillin G	*Penicillium chrysogenum*	Penicillin G (benzylpenicillin) is potent against Gram-positive bacteria, in particular cocci (e.g., *Pneumococci, Staphylococci*, and *streptococci*), and *bacilli* (e.g., *Clostridium perfringens*, *Bacillus anthracis*, and *Corynebacterium diphtheriae*).	[45]
2	Amoxicillin (semisynthetic derivative of penicillin)	*Penicillium chrysogenum*	A beta-lactam antibiotic used to combat a broad range of diseases, such as genitourinary tract infections and *Helicobacter pylori* infections.	[31,46]
3	Cephalosporins	*Cephalosporium acremonium*	Fifth-generation cephalosporins, including ceftaroline and ceftobiprole show good activities against Gram-positive cocci (e.g., methicillin-sensitive *Staphylococcus aureus*, anti-methicillin-resistant *S. aureus*, and *Streptococcus* spp.), and some enteric Gram-negative rods.	[47,48]
4	Fusidic acid	*Fusidium coccineum*	A natural tetracyclic triterpene used against anaerobic Gram-negative and most Gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA) and coagulase-negative staphylococci.	[43,49,50]
5	Lindgomycin	*Lindgomycetaceae*	Antimicrobial activity against *Staphylococcus epidermidis, S. aureus*, MRSA, and *Propionibacterium acnes* was significant, with IC_{50} values ranging from 2 to 18 μM.	[51]
6	Berkeleylactone A	*Coculture fermentation of Penicillium fuscum and Penicillium camembertii*	It had potent antimicrobial activity against four MRSA strains, *B. anthracis*, *Streptococcus pyogenes*, at low micromolar concentrations (MIC = 1−2 μg/mL). It did not restrict the protein synthesis or target the ribosome, indicating a new mode of action.	[52]
7	Altenusin	*Alternaria* sp. isolated from mangrove (*Sonneratia alba*)	It possessed antibacterial activity against MRSA and *S. pneumonia* with MIC values of 31.25−62.5 μM.	[53]
8	Isocoumarin	*Trichoderma harzianum* isolated from Rubber Tree *Ficus elastica leaves*	The compound exhibited inhibitory activity against *Escherichia coli* with MIC values of 32 μM.	[54]
9	Engyodontochone A and B	*Engyodontium album strain* LF069	The compounds had a 10-fold greater inhibitory activity against MRSA than chloramphenicol.	[55]
10	Trichodin A and Pyridoxatin	*Trichoderma* sp. strain MF106	It was discovered that these compounds had antibiotic activity against *Staphylococcus epidermidis*, a clinically relevant microorganism, with inhibitory concentrations (IC_{50}) of 24 and 4 μM, respectively.	[56]
11	Spiromastixones G	Deep-sea *Spiromastix* sp. fungus	It displayed potent inhibitory effects against Gram-positive bacteria, including *S. aureus, Bacillus thuringiensis*, and *Bacillus subtilis* with MIC values of 0.25−0.5 μg/mL.	[57]
12	Penicyclones A−E	Deep-sea-derived fungus *Penicillium* sp. F23-2.	Antimicrobial activity was observed against Gram-positive bacterium *S. aureus* at MIC values ranging from 0.3 to 1.0 μg/mL.	[58]
13	4-(2,4,7-trioxa-bicyclo [4.1.0]heptan-3-yl) phenol	*Pestalotiopsis mangiferae*	The compound showed potent antibacterial activity against *B. subtilis, Klebsiella pneumoniae, E. coli, Micrococcus luteus,* and *Pseudomonas aeruginosa* at MICs of 5.0 −10.0 μg/mL.	[59]
14	Dicerandrol C	*Phomopsis longicolla* isolated from red seaweed *Bostrychia radicans*	It displayed strong antimicrobial activity against *S. aureus* (ATCC6538) and *Staphylococcus saprophyticus* (ATCC 15305), with MIC of 1.33 and 2.66 μM, respectively.	[60]
15	Fumigaclavine C	*Aspergillus* sp. EJC08 isolated from *Bauhinia guianensis*	The alkaloid showed strong activity against *B. subtilis* and *S. aureus* with MIC of 7.81 and 15.62 μg/mL, respectively.	[61]
16	Enniatin A1 and B1	Coculturing the fungal endophyte *Fusarium tricinctum* with the bacterium *B. subtilis 168 trpC2*	The compounds suppressed the growth of the cocultivated *B. subtilis* strain with MICs of 16 and 8 μg/mL, respectively, and were also effective against *S. aureus*, *S. pneumoniae*, and *Enterococcus faecalis* with MIC values of 2−8 μg/mL	[62]
17	Udagawanones A	*Neurospora udagawae*	Udagawanone A had a mild antibacterial effect on *S. aureus* (MIC = 66 μg/mL).	[63]
18	Alkaloid GKK1032C	*Penicillium* sp. CPCC 400817	It displayed effective antibacterial activity against MRSA with an MIC value of 1.6 μg/mL.	[64]

pharmacologically active natural products from bacteria and actinomycetes, with an emphasis on their structural potential for the development of new molecular probes.

3. Fluorophores

A variety of fluorophores have been synthesized, but only a few have been approved by the Food and Drug Administration (FDA) for biomedical applications, including NIR dyes indocyanine green (ICG) and methylene blue (MB) (Fig. 3) [95]. Fluorophores enable noninvasive imaging of various biological samples in real-time by probing their structure and mechanisms [96]. The term of fluorescence analysis was first introduced in 1868 by F. Göppelsröder when he reported the fluorescence phenomenon as a result of complexation of morin with aluminum. Later, fluorescence techniques have been used extensively for a diversity of applications [97]. Nowadays, fluorophore agents are a primary driving force for the recent success of fluorescence-based imaging strategies [98]. However, significant room for improvement remains. The success of in vivo imaging with fluorescently labeled molecules is dependent on several optical properties, including low proton scattering, negligible autofluorescence, and high deep-tissue penetration. There are two primary strategies for increasing deep tissue penetration and thereby improving imaging results: developing new or optimizing existing imaging modalities/instruments, and synthesizing new fluorophores and fluorescent probes with improved quantum yield, spectral characteristics, photostability, and biocompatibility [99].

Apart from fluorophores approved by the FDA, various organic synthetic molecules are used as fluorophores in preclinical and clinical studies (Fig. 3). Fluorophores can be broadly classified based on their spectral properties: (1). Fluorophores that emit light in the ultraviolet and blue spectral ranges (e.g., pyrene and pyranine). While these fluorophores can be used to study biological systems, their applications are limited due to UV light's toxicity. (2). Fluorophore with a green-yellow emission spectrum. Borodifluorodipyrromethene-based molecules, also known as BODIPY is one of the examples of green fluorophores which have long been used for biomedical research. The presence of substituents at the BODIPY core could tune both the electronic

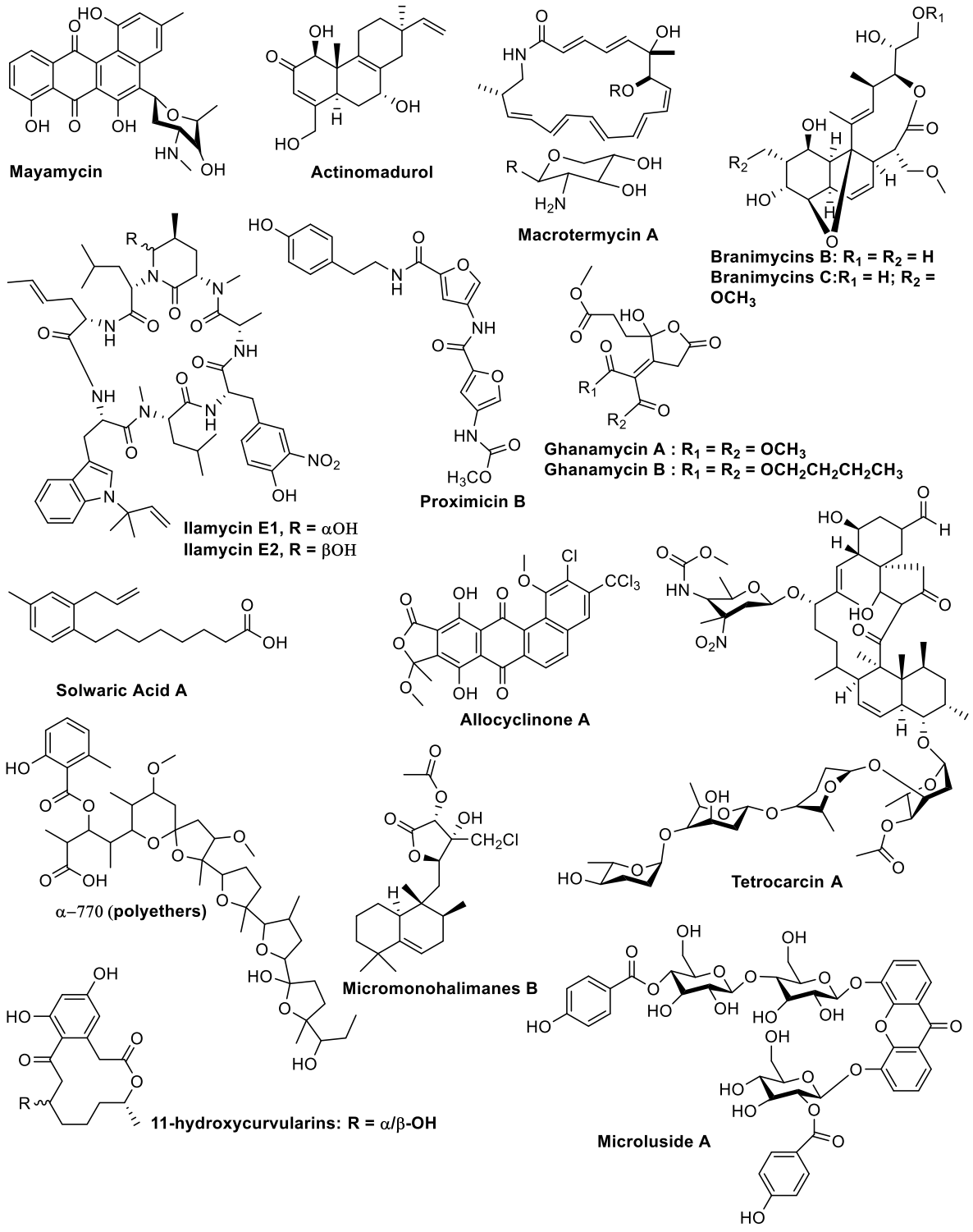

Fig. 2. The structure of several natural antibiotics from bacteria and actinomycetes.

properties and color of BODIPY dyes [100,101]. The 4-nitrobenzo-2-oxa-1,3-diazole (NBD), dansyl chloride, 5-[(2-aminoethyl)amino] naphthalene-1-sulfonic acid (EDANS), rhodamine 110, and lucifer yellow are all other examples of these types of fluorophores. (3). Fluorophores with NIR emissions. These fluorophores are of particular interest in pharmacology because they enable the detection of signals at depths of several millimeters beneath the tissues, minimize photodamage to living organisms, and mitigate the effects of tissue autofluorescence; thus, near-infrared may offer advantages for optical in vivo applications [100,102–104]. Examples of infrared fluorophores are carbocyanine dyes (cyanins), including Cy3, Cy5, and Cy5.5 [100].

NIR fluorophores are primarily used in biomedical research, where they have revolutionized the visualization and detection of biomolecules. Nowadays, NIR fluorescent probes synthesized in the laboratory are used to visualize proteins, metal ions, signaling

Table 2
Natural product antibiotics from bacteria and actinomycetes.

No	Secondary Metabolite	Bacteria/Actinomycetes	Biological Activity	Reference
1	Clindamycin	Semi-synthetic derivative of lincomycin (*Streptomyces lincolnensis*)	Clindamycin is commonly used to combat Gram-positive streptococci, MRSA, and *Clostridium* species.	[31,72,73]
2	Tetracycline	*Streptomyces aureofaciens*	Effective against various gram-positive and gram-negative bacteria, protozoan parasites, and atypical organisms (e.g., chlamydiae, mycoplasmas, and rickettsiae).	[74,75]
3	Erythromycin	*Saccharopolyspora erythraea*	Potent against a wide number of microorganisms, such as pneumococci, *S. aureus* cocci, streptococcal group A, *Mycoplasma pneumoniae*, *Legionellae pneumophilae*, and Chlamydiae.	[76]
4	Vancomycin	*Amycolatopsis orientalis*	Effective against the majority strains of *Clostridia*, MRSA, coagulase-negative Staphylococci, and drug-resistant *Enterococcus* species.	[77,78]
5	Gentamycin	Micromonospora	Clinically used to treat many types of bacterial infections caused by *Staphylococcus*, *K. pneumoniae*, *Serratia marcescens*, and *E. coli*.	[79]
6	Kanamycin A	*Streptomyces kanamyceticus*	Kanamycin A is a class of aminoglycoside antibiotic which used clinically to combat a broad spectrum of bacteria, including *Mycobacterium tuberculosis*.	[80]
7	Mayamycin	*Streptomyces venezuelae*	Effective to inhibit *Pseudomonas aeruginosa,* MRSA, *Dermabacter hominis, Brevibacterium epidermidis*, with MIC less than 10 μM	[81]
8	Branimycins B & C	*Pseudonocardia carboxydivorans M-227,* isolated from deep seawater of the Avilés submarine Canyon	Both compounds exhibited strong antibacterial against *C. perfringens*, *Corynebacterium urealyticum*, and *Micrococcus luteus* at MIC values of 1−32 μg/mL.	[82]
9	Ghanamycin A & B	*Streptomyces ghanaensis*	These compounds exhibited promising antimicrobial activities against *Pseudomonas syringae* and *Erwinia* sp.	[83]
10	Ilamycin E1 and E2	Deep sea-derived *Streptomyces atratus* SCSIO ZH16	Antituberculosis activity against *M. tuberculosis* H37Rv with an MIC of 9.8 nM.	[84]
11	Macrotermycin A	*Amycolatopsis* sp.	It had antibacterial activity against human-pathogenic *B. subtilis* and *S. aureus* at MIC values of 1.0 and 1.5 μg/mL, respectively.	[85]
12	Actinomadurol	*Actinomadura* sp. strain KC 191	It exhibited potent antibacterial activity against *S. aureus, Kocuria rhizophila*, and *Proteus hauseri* (MIC = 0.39−0.78 μg/mL).	[86]
13	Solwaric acid A	*Solwaraspora* sp.	The compound demonstrated antibacterial activity against MRSA.	[87]
14	Proximicin B	*Verrucosispora* sp.	Proximicin B exhibited strong anti-MRSA (MIC = 3.125 μg/mL), anti-Bacille Calmette-Guérin (MIC = 6.25 μg/mL), and anti-tuberculosis (MIC = 25 μg/mL) activities.	[88]
15	Tetrocarcin A	*Micromonospora carbonacea* LS276	The compound exhibited significant antibacterial activity against *B. subtilis* ATCC 63501 with MIC = < 0.048 μg/mL.	[89]
16	α-770 (polyethers)	*Actinoallomurus* spp.	It exhibited antibacterial activity against *S. pneumoniae*, *S. pyogenes*, *E. faecalis*, *B. subtilis* with MIC ≤ 0.03 μg/mL.	[90]
17	Allocyclinone A	*Actinoallomurus* spp.	It demonstrated antibacterial activity against *S. pyogenes, S. aureus, E. faecalis* with MIC 0.25−0.5 μg/mL.	[91]
18	Micromonohalimanes B	Marine Micromonospora sp.	It has a MIC of 40 μg/mL against MRSA.	[92]
19	11-hydroxycurvularins	Marine *actinomycete Pseudonocardia* sp. HS7	It possessed good activity against *E. coli* with an MIC value of 20 μg/mL and a minimum bactericidal concentration (MBC) value of 30 μg/mL.	[93]
20	Microluside A	*Micrococcus* sp. EG45	It exhibited antibacterial properties against *E. faecalis* and *S. aureus* with MIC values of 10 and 13 μM, respectively.	[94]

molecules, nucleic acids, enzymes, and reactive species [104]. Numerous biotechnology companies have developed several modern and low molecular weight fluorophores in recent years, including IRDye, Alexa dyes, VivoTag, and HylitePlus dyes. In comparison to previous fluorophores, these fluorophores have relatively high extinction coefficients and superior optical properties (e.g., low photobleaching and limited non-specific binding) [105].

4. Radionuclides

George de Havesy introduced the tracer approach in nuclear medicine in 1913, using radionuclides as tracers to track the biodistribution of a native element or molecule containing the element in plants and animals. This was dubbed the “tracer principle” at the time. Later, Paul Enhrlich developed the “magic bullet” concept, emphasizing the potential for biomolecules, particularly antibodies, to be used as targeting molecules for the delivery of toxins to tumor tissues [106]. He hypothesized that if a biomolecule could selectively target a disease, it could be combined with a therapeutic agent to cure the disease. This approach has inspired drug developers to develop highly effective agents for the therapy and diagnosis of a diverse array of diseases, including cancer [107]. With the advancement of radiopharmaceutical probes that specifically target specific diseases, several radionuclides have gained popularity in recent years. Radiopharmaceuticals are defined as drugs that contain two common components: a radionuclide that conveys its function via its decay energy (s) and an organic ligand or biomolecule that controls the radiopharmaceuticals' localization and biodistribution [106]. Several radionuclides that potentially be used for labeling microbial metabolites (antibiotics), including technetium-99m, gallium-68, lutetium-177, copper-64, scandium-44, zirconium-89, fluorine-18, and radioiodines (i.e., iodine-131, iodine-123, iodine-124, and iodine-125) are briefly discussed below.

4.1. Technetium-99m

Technetium-99m (^{99m}Tc) is one of the most commonly used radionuclides worldwide for diagnostic imaging procedures with single-photon emission tomography (SPECT)-the “m” denotes a metastable state [108,109]. Today, this radionuclide still gains popularity due to its ideal nuclear properties, such as its ideal half-life (6.06 h), convenient supply method through the transportable ^{99}Mo/^{99m}Tc generator system, low-cost production, and easy preparation and administration of ^{99m}Tc radiopharmaceuticals to the patients. During its decay, technetium-99m emits a 140 keV γ-rays (89% abundance), making it an ideal choice for bioimaging

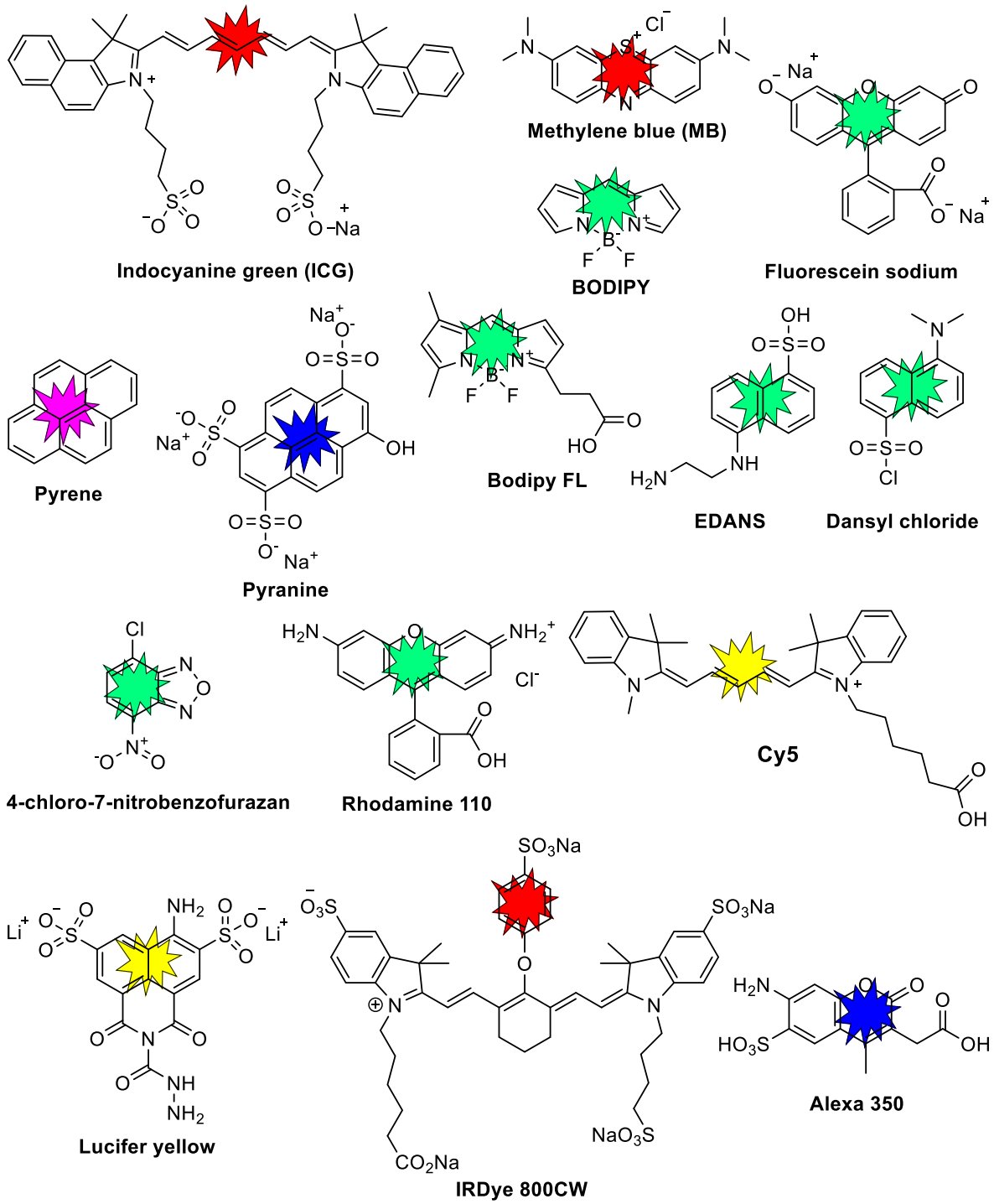

Fig. 3. The structure of several synthetic fluorophores. Colours indicate the typical fluorophores wavelength regions (UV = 300–400 nm, blue = 450–500 nm, green = 500–570 nm, yellow = 570–590 nm, red (infrared) = > 620 nm).

with medical gamma cameras [110]. Technetium-99m can be produced through the decay of the parent molybdenum-99 by eluting the ^{99}Mo/^{99m}Tc generator system. The generator is composed of an alumina column in which the ^{99}Mo is absorbed in the chemical form of molybdate ($[^{99}Mo]MoO_4^{2-}$). During its decay, ^{99}Mo leads to the generation of pertechnetate ($[^{99m}Tc]TcO_4^-$). Finally, the obtained sodium ^{99m}Tc-pertechnetate ($[^{99m}Tc]NaTcO_4$) can be easily eluted from the column with a saline solution, and is ready for use in nuclear medicine facilities [110–112]. A broad range of ^{99m}Tc-based imaging agents have been developed and approved by FDA for the localization and determination of organ functionality and disease progression [113]. Although its wide applications in medical practices, account for 76,000 scans per day [114], technetium-99m possesses some limitations and challenges for drug developers. For instance, technetium is a transition metal, and therefore can not be substituted with a hydrogen or a carbon atom in the targeting compound, limiting the choices for radiolabeling with active molecules. Additionally, it is always assumed that the introduction of a

radioactive does not alter the parent molecule's native biological activity. Thus, radiolabeling with technetium requires a thorough understanding of inorganic chemistry (coordination chemistry) as well as familiarity with the design of suitable ligands that enable robust molecular imaging [110].

4.2. Gallium-68

Gallium-68 is the family member of post-transition metals with a half-life of 67.8 min. It decays to 89% by positron emission and to 11% through electron capture, with an average positron energy per disintegration of 740 keV. Over the past decades, gallium-68 has been used for labeling small organic compounds, peptides, oligonucleotides, particles, and antibody fragments [115,116]. Gallium-68 can be easily produced by a germanium-68/gallium-68 (^{68}Ge/^{68}Ga) generator, which can continuously be used for ~1 year in the preclinical and clinical environments thanks to the long half-life of its parent element (germanium-68 = 270.8 d). The availability of such generators has eliminated the need for a cyclotron, and therefore made the development of ^{68}Ga-based radiopharmaceuticals more attractive [115,117]. Interestingly, gallium-68 is compatible to be combined with other radionuclides, such as yttrium-90, lutetium-177, and actinium-225 to form a theranostic pair [115]. The majority of ^{68}Ga-based imaging agents are produced using tagging methods where a vector molecule is first attached to a chelator unit for the subsequent complexation with gallium-68. Some chelators that can be used mostly the derivatives of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), providing stable gallium-68(III) complex [116].

4.3. Lutetium-177

Lutetium-177 is a radiometal that belongs to the lanthanide group with +3 oxidation state and a coordination number of 9. Due to its capability to emit γ rays (208 keV (11%) and 113 keV (6.6%) as well as a low energy of β^- (0.49 MeV)), this radiometal can be used as both imaging and therapeutic agents [106]. Recently, the utility of lutetium-177 has expanded beyond cancer treatment to a broad range of diseases, including bone pain palliation, radiation synovectomy, and radioimmunotherapy. Thus, it is expected that the number of ^{177}Lu-radiopharmaceutical applications (e.g., personalized patient therapy) and regulatory approvals will grow rapidly in the near future [106,118]. In recent years, its medical applications have grown significantly in nuclear medicine area, especially for peptide receptor radionuclide therapy (PRRT) of prostate cancer and neuroendocrine tumours (NETs) [119]. Several ^{177}Lu-based radiopharmaceuticals have been developed, covering some bioactive molecules, such as small molecules, steroids, phosphonate ligands, peptides, monoclonal antibodies, and particulates. Lutetium-177 production by neutron irradiation in a nuclear reactor is the most efficient and cost-effective method, although it can also be prepared by a cyclotron [120].

4.4. Radioiodines

There are 38 isotopes of iodine. All of these, except iodine-127 undergo radioactive decay [121]. Four isotopes of iodine (i.e., iodine-131, iodine-123, iodine-124, and iodine-125) are isotopes of choice, used widely for radioiodine labeling of chemical compounds and biomolecules, depending on the intended applications in nuclear medicine. For example, iodine-123 (half-life = 13.1 h) and iodine-124 (half-life = 4.17 d) have long been applied for the assessment of a molecule or a biomolecule for its SPECT and positron emission tomography (PET) imaging procedures, respectively [122]. Iodine-123 with the main gamma emission (159 keV) is suitable for the study of molecules that exhibit rapid radiolabeling procedures, fast clearance in the body, and short metabolic processes. Since the mid-1970s, iodine-123 has been utilized for thyroid research, especially for imaging thyroid diseases [121]. Initially, iodine-124 was considered as an impurity during iodine-123 production. However, due to its positron decay (22.7%) with maximum and mean positron energies of 2.14 and 0.98 MeV, respectively, this radionuclide has found its application for PET imaging [123]. Owing to its convenient half-life of 4.2 d, it can be used in PET imaging facilities apart from the radionuclide production location [124]. Iodine-125 (half-life = 59.9 d) with the main X-ray energy emission at 27 keV and low gamma emission at 35.5 keV could be used for labeling a molecule and a biomolecule for its absorption, distribution, metabolism, and excretion (ADME) studies in living systems [122,123]. Moreover, molecules bearing iodine-131 with a half-life of 8.02 d, beta energy of 606 keV (90%), and mean energy of 191 keV are often used for radiation therapy. Some medical applications of iodine-131 include thyroid remnant ablation, cancer therapy, including locoregional recurrences and metastases, and surgical navigation of residual diseases [125]. The literature is replete with radioiodination methods for the synthesis of radioiodine-based radiolabeled compounds ranging from small molecules to peptides and antibodies. Several different types of reactions have been used to label radioiodine, including nucleophilic aromatic substitutions, electrophilic aromatic substitutions, and transition-metal-mediated reactions [123,126,127].

4.5. Copper-64

Copper-64 is a ubiquitous radionuclide of great importance for PET imaging due to its interesting chemical and physical characteristics. This radionuclide generates a low positron yield (17.5%, 0.65 MeV), beta particles (38.5%, 0.57 MeV), and Auger electron emission [128,129]. The combination of these decay modes can potentially be explored to be used for both therapy and diagnosis. Copper-64 has an intermediate half-life of 12.7 h, relatively longer than carbon-11 (half-life = 20.4 min) and fluorine-18 (half-life = 110 min) [130]. Furthermore, copper-64 is a versatile coordination chemistry that can react with various chelating agents, such as DOTA, 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA), and NOTA, which can be linked to some biomolecules, including antibodies, protein, and peptides [131–136]. The reactor-based and cyclotron-based methods can produce copper-64. Production of copper-64 in a nuclear reactor requires a fast or highly energetic neutron via ^{64}Zn(n,p)^{64}Cu in order to obtain the high-specific activity. However, this process can produce some undesirable impurities, and affect the product quality. Hence, recently, copper-64 is mostly produced by cyclotron-based method via ^{64}Ni(p,n)^{64}Cu reaction [137–139]. The main limitation of this route is the low natural abundance of ^{64}Ni (0.926%), making the target material expensive [128]. Numerous radiotracers involving radionuclide copper-64 have been developed in nuclear medicine. For example, a combination of copper-64 with diacetyl-bis(N^4-methylthiosemicarbazone) (ASTM) ligand was utilized as a hypoxia-targeting PET tracer with application in cardiology and oncology [140–142]. Furthermore, the safety, biodistribution, and internal dosimetry of the [^{64}Cu]-DOTA-trastuzumab were investigated clinically for PET imaging in a patient with Her2-positive breast cancer [131].

4.6. Scandium-44

Scandium-44 is a versatile radionuclide for PET and an alternative to galium-68 due to its longer half-life (3.97 h), a greater

positron intensity ($\beta^+ = 94.3\%$), and a lower average positron energy ($E_{\beta+av} = 632$ keV) [143–145]. Moreover, scandium-44 is often utilized in preclinical and clinical PET investigations because the more tiny positron range in tissue creates better spatial image resolutions. Furthermore, the chemistry properties of scandium-44 resemble lutetium-177 and other lanthanides, where it could generate stable radio conjugates [146–148]. Titanium-44 (^{44}Ti)/scandium-44 (^{44}Sc) generator and biomedical cyclotron can be used to produce scandium-44 [143,148]. Due to the sophisticated purification process and safety requirement of the parent radionuclide, the applicability of the ^{44}Ti generator is an unfavorable option. Therefore, ^{44}Ti/^{44}Sc generator is only suitable for research centers and universities desiring to utilize scandium-44 without a cyclotron. On the other hand, the cyclotron route provides a more valuable method to yield significantly higher scandium-44 radioactivities due to the effective cross-sections and yields of ^{44}Ca (p,n) and ^{45}Sc(p,2n)^{44}Ti → ^{44}Sc schemes [145,149,150]. A number of in vitro and in vivo investigations have demonstrated the compatibility of scandium-44 with various bifunctional chelators. For example, [^{44}Sc]Sc-PSMA-617 showed comparable biological properties (e.g., binding affinity, lipophilicity, and internalization) with clinically used agents [^{68}Ga]Ga-PSMA-617 and [^{177}Lu]Lu-PSMA-617 [151]. In addition, the potential use of new scandium-44-based radiotracer, namely [^{44}Sc]Sc-DOTATOC is being extensively investigated in the clinical trial for PET imaging of metastatic neuroendocrine neoplasms [147].

4.7. Zirconium-89

Zirconium-89 (^{89}Zr) is a radiometal PET nuclide that belongs to the transition metal group [152]. This element is one of the ideal PET radionuclides for biomedical applications due to its favorable decay properties, including lower positron energy of 395.5 keV (23%) [153]. In addition, zirconium-89 decays with a low intensity (99%) gamma energy of 909 keV as a result of its electron capture (77%) decay [154]. These decay properties are beneficial for PET imaging, especially for generating high spatial resolution images which are not provided by another PET radionuclide, such as iodine-124 [155]. Unlike radioiodine-124, the γ emission of zirconium-89 does not disturb the PET scans. The other advantage of zirconium-89 is its relatively long half-life (3.3 days) which is suitable for the labeling biomolecules with relatively long circulation time in biological system, in particular, monoclonal antibodies (MAbs). Therefore, zirconium-89 has been a radionuclide of choice for labeling antibodies eligible for immuno-PET application [153]. The main route of zirconium-89 production is through irradiation of a highly pure natural yttrium-89 target in a biomedical cyclotron via ^{89}Y(p,n)^{89}Zr nuclear reaction [156]. After the bombardment in the biomedical cyclotron, zirconium-89 is separated and purified from its irradiated target by an anion exchange column chromatography using hydroxamate resin. The column elution using 1.0 M HCl recovers the yttrium-89 target material. Further elution with oxalic acid achieved a high yield with high purity and specific activity of zirconium-89 oxalate ([^{89}Zr]Zr(ox)$_2$) [157]. Similar to other radiopharmaceuticals based on radiometals, the labeling of zirconium-89 with targeting ligand involves the use of a chelating agent. Desferrioxamine (DFO, Desferral) is a type of hexadentate siderophore, and a commonly used chelator in the radiosynthesis of [^{89}Zr]-labeled antibodies [158,159]. Three hydroxamate groups of DFO can stabilize chelate zirconium-89 metals, and its primary amine can attach to target biomolecule [158]. Furthermore, various studies have reported the development of DFO derivatives and other novel promising chelators, such as fusarinine C (FSC) and *p*-isothiocyanatobenzyl-desferriox amine B (Df-Bz-NCS) that can potentially generate more stable bioconjugation towards targeting biomolecules with zirconium-89 [160,161].

4.8. Fluorine-18

In recent years, fluorine-18 is the most widely used positron-emitting radionuclide in nuclear molecular imaging. It has gained considerable attention for radiolabeling of biomolecules (e.g., peptides and small molecules) due to its suitable nuclear and physical properties, such as high positron emission (97%), and relatively low positron energy (maximum 635 keV) with a short tissue penetration of 2.4 mm [162,163]. Fluorine-18 has an ideal physical half-life of 109.7 min that allows for biochemistry investigation and radiochemistry studies. Labeling of active compounds with fluorine-18 typically requires a simple, rapid, and effective synthesis strategy. In addition, due to its relatively short half-life, it is preferable that the ^{18}F-radiolabeling is carried out in the last synthetic route. The fluorine atom has shown great interest in pharmaceuticals because it has a high electronegativity and small van der Waals radius [164,165]. Fluorine is a bioisostere of H (size and electron valence) and O (size and electronegativity) [166]. Consequently, the substitution of hydrogen or oxygen with fluorine results in a minimum effect on the biological activity of the biologically active compound [167]. Moreover, the carbon-fluorine (C–F) bond is much stronger than the carbon-hydrogen (C–H) bond (112 kcal/mol vs 98 kcal/mol), and therefore, fluorine insertion into biomolecules may modulate their metabolic stability towards cytochrome P-450 (CYP) as well as improving their binding affinity and selectivity to specific target [164,166,168]. The main production route of fluorine-18 is via proton bombardment of [^{18}O] target in a cyclotron with ^{18}O(p,n)^{18}F nuclear reaction. Two main synthetic strategies to introduce fluorine-18 into the biomolecule are nucleophilic radiofluorination and electrophilic radiofluorination [167]. The first approach has gained popularity since it allows the preparation of radiopharmaceuticals with high specific activities, as suggested by published literature so far [165,167]. ^{18}F-based radiopharmaceuticals have shown potential in biomedical fields since the discovery of [^{18}F]-fluorodeoxyglucose. [^{18}F]FDG has been the primadonna of PET tracers for imaging and early detection of cancers based on glucose uptake mechanism [162].

5. Microbial metabolites-inspired fluorescent probes

Fluorescence imaging has become an effective method for investigating biological phenomena in living systems due to its high spatiotemporal resolution, high selectivity, real-time imaging, and noninvasive properties [169,170]. This technique has a wide range of biomedical applications; for example, fluorescence imaging is a critical tool for studying the growth, division, transcription, and translation of microbes, particularly bacteria [171]. Additionally, this technique has the potential to differentiate live bacteria at the Gram-stain level, which is critical in microbiology [172]. Fluorophore-antibiotic conjugates also provide a valuable contribution to the study of antimicrobial resistance due to their superiority over other methods [173]. More importantly, certain fluorescent probes may be used to detect and diagnose specific bacteria infections [11]. Thus, over the past decades, several natural antibiotics have been used as lead compounds for the synthesis of fluorescent probes (Fig. 4).

Penicillin and vancomycin are two natural antibiotics that are frequently used as fluorescent probes for the specific recognition of target bacteria [174]. Antibiotics commonly act on three primary sites within bacteria cells, which include the inhibition of peptidoglycan (cell wall) synthesis, the inhibition of protein synthesis, and the inhibition of nucleic acid synthesis [175]. Penicillin and vancomycin are both antibiotics that inhibit peptidoglycan

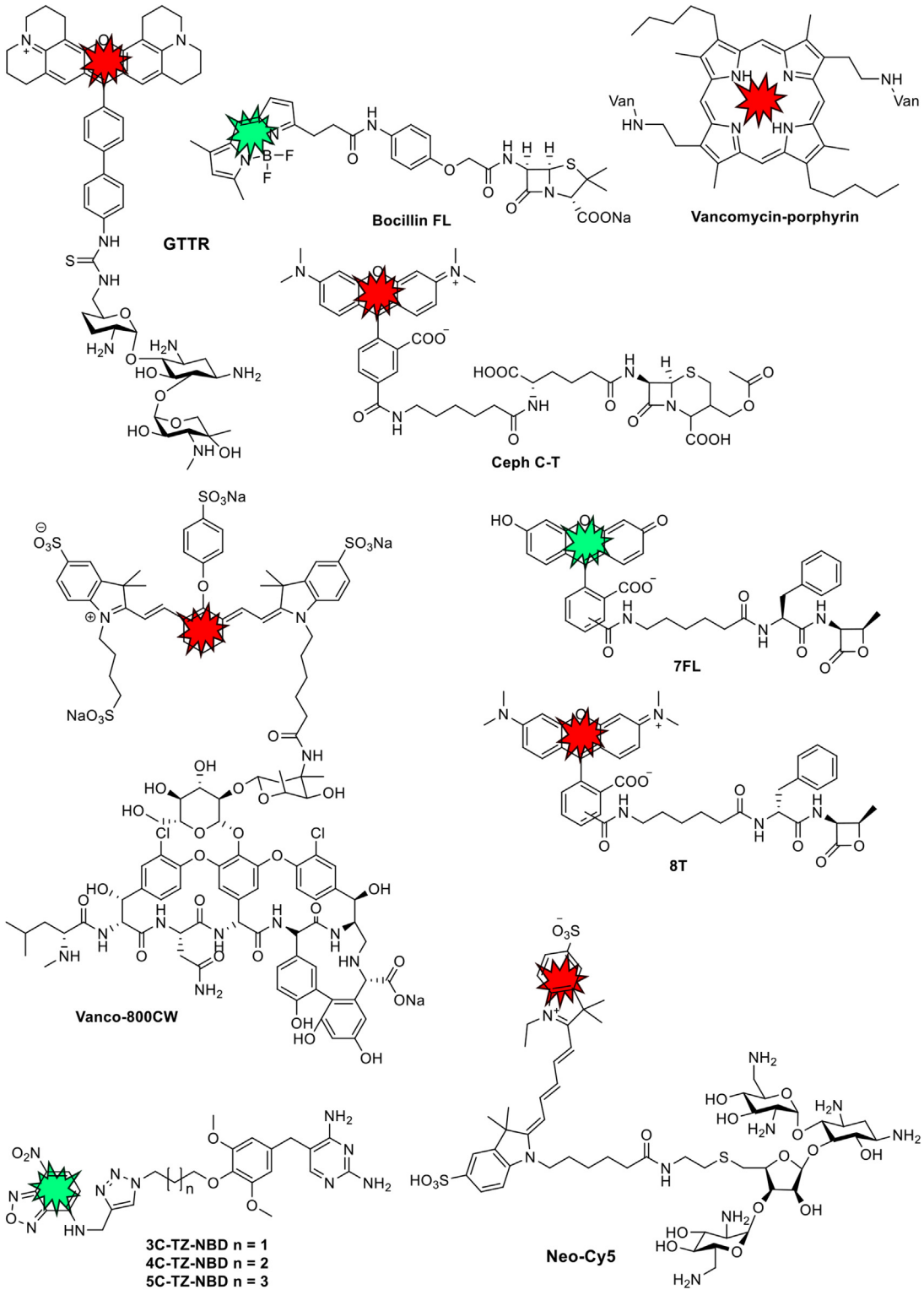

Fig. 4. Structure of microbial metabolite-based fluorescent probes. Colours indicate the typical fluorophores wavelength regions (green = 500–570 nm, red (infrared) = > 620 nm).

synthesis [30]. Penicillin is a widely known antibiotic class derived from the bacterium *Penicillium notatum*. It is potent in inhibiting the growth of Gram-positive bacteria by interfering with the transpeptidation cross-linking step of peptidoglycan (the precursor to the cell wall) and, as a result, preventing cell reproduction. On the other hand, a strong hydrogen-bonding arrangement is formed between vancomycin and the terminal D-alanine peptidyl tail of the precursor peptidoglycan subunit, resulting in an inhibition of cell wall formation [4,30,176].

The development of fluorescent molecules based on antibiotics

has resulted in the discovery of some highly effective fluorescent probes that can be employed to investigate bacterial and fungal infections. PBPs (peptidoglycan-binding proteins) are membrane-associated proteins that have been identified as primary targets for β-lactam antibiotics because they are involved in the final step of peptidoglycan synthesis [171,177]. These proteins continue to be the main focus of interest for drug design, as exemplified by several antibiotic-based fluorescent probes (i.e., BOCILLIN FL (Boc-FL) [178], cephalosporin-carboxytetramethylrhodamine conjugates (Ceph C-T) [171], 2*R*,3*S*-β-lactone-L-Phe-fluorescein (7FL), and (2*R*,3*S*)-β-lactone-D-Phe-(5(6)-carboxytetramethylrhodamine (TAMRA) (8T)) [179]. Other fluorophore-tagged natural and semisynthetic antibiotics include vancomycin-IRDye 800CW (vanco-800CW) [180], gentamicin-Texas Red (GTTR) [181], and neomycin-Cy5 (Neo-Cy5) [182].

Boc-FL (Fig. 4), also known as FL-penicillin, is a highly sensitive and commercially available fluorescence-labeled antibiotic that has been extensively used to recognize PBPs [178]. Structurally, the probe consists of the penicillin V structure, with the BODIPY unit attached to the para position of the phenyl moiety [183]. Similarly, a fluorescent probe based on cephalosporin, Ceph C-T (Fig. 4), was used to target a PBP subset. The probe labeled a small subset of PBPs in *S. pneumoniae* and *B. subtilis* selectively. In both bacteria, fluorescent imaging using 3D-structured-illumination microscopy (3D-SIM) revealed that tagged PBPs were localized to the division region [171]. Moreover, a study revealed that Boc-FL and Ceph C-T might be potentially used for dual imaging of PBP in *S. pneumoniae* (Fig. 5A) [184].

In addition, fluorophore-tagged natural antibiotics, such as GTTR conjugate (Fig. 4), has been developed for the purpose of determining drug routes across the blood-labyrinth barrier (BLB) and into hair cells [181,185]. Neo-Cy5 (Fig. 4) is another fluorescent probe created by conjugating the natural antibiotic neomycin with the yellow cyanine fluorophore Cy5. The probe was designed to assess bacteria's uptake of aminoglycosides [182]. β-lactones-based probes, 7FL and 8T are PBP-selective compounds developed by Sharifzadeh et al. for imaging PBP2x and PBP2b in *S. pneumoniae*. The synthesized probes exhibited interaction with the PBPs, in which the PBP2x and PBP2b show clear patterns of localization during constriction [186].

Vanco-800CW was synthesized by van Oosten et al. by covalently linking the IRdye800CW-NHS ester to the antibiotic vancomycin hydrochloride hydrate in DMSO in the presence of a base, namely *N*,*N*-diisopropylethylamine (DIPEA). The probe was used to specifically recognize and detect Gram-positive bacterial infections. The authors revealed that vanco-800CW could specifically identify Gram-positive bacterial infections in a mouse model of myositis, distinguish sterile inflammation from bacterial infection in vivo, and detect infections induced by biomaterial [180]. Xing et al. conjugated vancomycin with a porphyrin molecule to create a divalent vancomycin fluorescent probe for in vitro imaging of bacteria. As indicated by the fluorescence intensity, the divalent

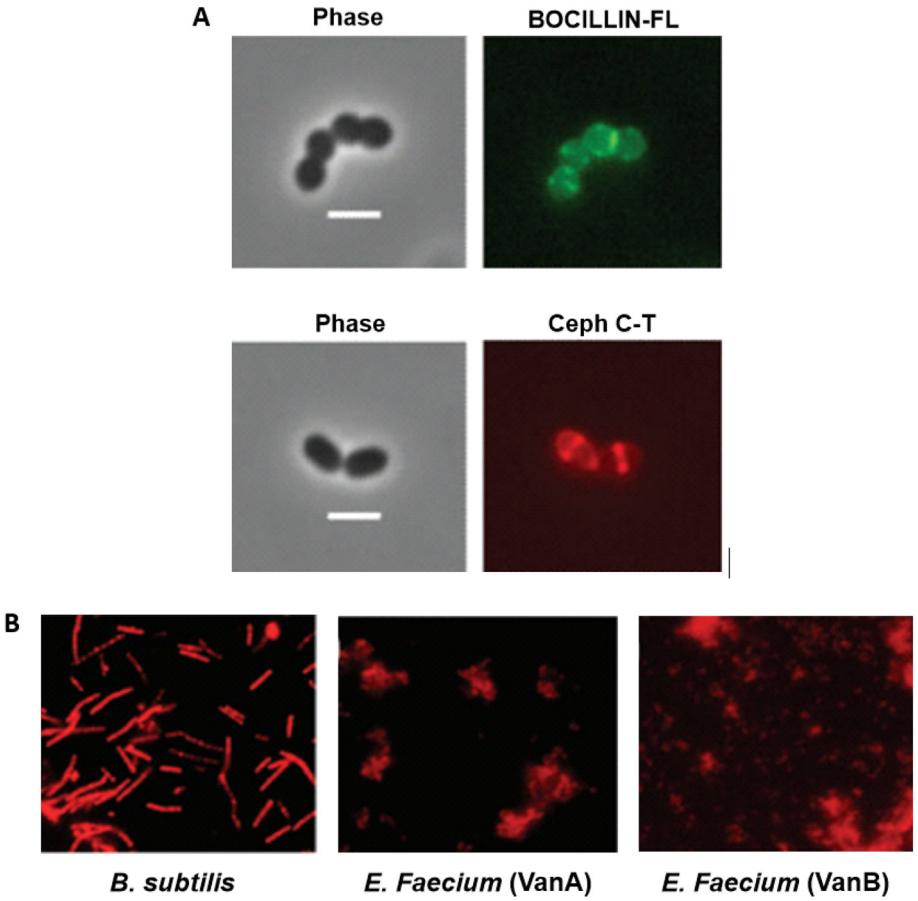

Fig. 5. Examples of the use of natural antibiotics-based fluorescent probes targeting bacteria. (A) Dual imaging of PBP in *S. pneumoniae* with fluorescent probes Boc-FL (green) and Ceph C-T (red), as captured by wide-field fluorescence microscopy (scale bar = 2 μm) (Reprint from Ref. [184] with permission); (B). Fluorescent imaging of *B. subtilis*, and vancomycin-resistant *E. faecium* (VanA) and *E. faecium* (VanB) with divalent vancomycin-porphyrin probe (Reprint from Ref. [187] with permission).

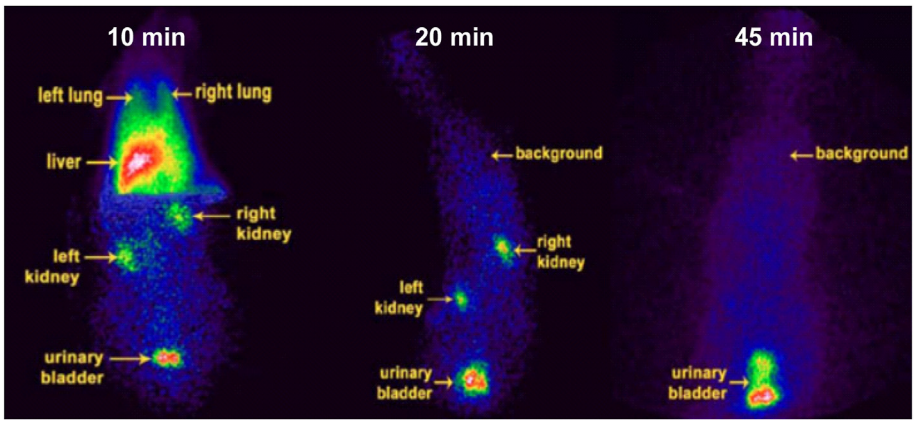

Fig. 6. Whole-body gamma camera of normal rabbit after 10, 20, and 45 min of [^{177}Lu]-kanamycin injection (Reprint from Ref. [204] with permission).

vancomycin-porphyrin conjugate was found to strongly attach to the surface of *B. subtilis*. In contrast, imaging of two enterococci resistant to vancomycin (*Enterococcus faecium* (VanA genotype) and *E. faecalis* (VanB genotype)) revealed relatively weak fluorescence signals (Fig. 5B) [187].

Along with fluorescent probes based on natural antibiotics, several fluorescently labeled synthetic antibiotics have been developed. For example, Phetsang et al. synthesized fluorescent probes 3C-TZ-NBD, 4C-TZ-NBD, and 5C-TZ-NBD based on the trimethoprim (TMP) scaffold, a broad-spectrum antibiotic primarily used to inhibit an intracellular enzyme called dihydrofolate reductase (DHFR). TMP is typically used to treat and prevent a variety of infections, including lower urinary tract infections, cystic fibrosis-related respiratory infections, and *Pneumocystis carinii* infection. TZ-NBD derivatives are composed of a TMP and an NBD fluorophore that are connected via a carbon linker and a triazole moiety (Fig. 4). These probes exhibited comparable antimicrobial activity to TMP against *E.coli* mutants deficient in tolC. When *S. aureus*, *E. coli*, and *E. coli* (ΔtolC) were imaged live, probe 4C-TZ-NBD colocalized predominantly within the bacterial membrane, in contrast to the location of the red FM4-64FX staining [188,189].

Until recently, a number of strategies have been utilized for the synthesis of fluorescent probes, most notably involving some straightforward chemical reactions. For example, vanco-800CW was synthesized by a direct conjugation of a primary amine on the sugar moiety of vancomycin structure with NHS ester on the IRDye800CW to create amide linkage. This reaction was accomplished under mild conditions in the presence of DIPEA in DMF [180]. However, more recent report suggest that the dye was coupled to a secondary amine at the peptide N-terminus instead of the primary amine [190]. Similarly, Neo-Cy5 was synthesized via the conjugation of fluorophore cyanine NHS-ester with free amine on neomycin structure at room temperature for 2h, assisted by DIPEA. To avoid unwanted side reactions, the amine groups on the neomycin was previously protected by di-*tert*-butyl dicarbonate (Boc anhydride) [182]. Furthermore, aryl amination reaction can also be used for the synthesis of fluorescent probes, as reported by Keller and colleagues. The authors synthesized a series of fluorescent probes by conjugating the free amines with fluorophore NBD-Cl in DMF in the presence of DIPEA in the dark [12].

In general, the design of fluorescent probes can be varied to ensure several desired properties, such as suitable excitation and emission wavelengths, appropriate chemical reactivity, excellent binding affinity to molecular targets, and good subcellular localization [191]. Accordingly, a fluorescent probe is commonly built by three chemical entities, i.e., an active molecule (recognition group), a fluorophore (reporting group), and a linker (connecting group). The active molecule is the core unit and is responsible for the binding of the fluorescent probe to target receptor. The fluorophore unit provides the fluorescent signal as well as determines the fluorescence properties of the probe. In particular, the fluorophores based on NIR-I window (650−950 nm) has attracted great attention due to their high quantum yield and great biocompatibility [192]. However, more recent studies have suggested that bioimaging in the NIR-II window (1000−1700 nm) could achieve higher tissue penetration depth (up to 20 mm) and spatial temporal resolution, leading to a better image quality [193]. The connecting group is also important in the probe design as this unit could affect the specificity, selectivity, and binding affinity of the probe to corresponding receptor [194].

6. Microbial metabolites-inspired radiopharmaceutical probes

Numerous antibiotics, including those derived from natural sources, have been reported to be radiolabeled. Due to the antibiotics' specific binding to receptors or biological components in bacteria, radiolabeled antibiotics are rapidly becoming a convenient diagnostic test for detecting infectious tissues in the modern era [195]. However, detecting bacterial infections continues to be a significant medical challenge. This has been attributed to the high global mortality and morbidity rates. To date, several radiolabeled antibiotics and antimicrobial peptides have shown promise in nuclear medicine for identifying physiological and biochemical changes associated with pathogen invasion [196]. Some examples of the radiolabeled natural antibiotics include [^{99m}Tc]-HYNIC-tetrazine-TCO-vancomycin [197], [^{201}Tl]III-vancomycin [198], [^{99m}Tc]-vancomycin [199], [^{99m}Tc]-amoxicillin [195,200], [^{99m}Tc]-clindamycin [201], [^{99m}Tc]-erythromycin [202], [^{99m}Tc]-kanamycin [203], [^{177}Lu-kanamycin] [204], [^{125}I]-penicillin X [205], and [^{125}I]-penicillin V [206] (Table 3).

A number of bioactive molecules have been successfully radiolabeled with technetium-99m, without losing or decreasing their biological activities, as exemplified by radiolabeled antibiotics. It is noteworthy that some radiolabeled antibiotics were simply obtained by the direct conjugation between antibiotic and radionuclide. For example, [^{99m}Tc]-amoxicillin was synthesized by direct labeling method, employing the presence of the various electron donor species in the amoxicillin structure (i.e., oxygen and nitrogen). These species could interact and form a stable complex with technetium-99m [195]. Moreover, [^{99m}Tc]-kanamycin has also been prepared by direct labeling method by Widyasari et al. The labeling

Table 3
Radiolabeled natural antibiotics and their applications.

No	Radiolabeled Natural Antibiotic	Application	Reference
1	[^{99m}Tc]-HYNIC-tetrazine-TCO-vancomycin	Targeting *S. aureus* infection in the animal model. The results suggest that the radiolabeled antibiotic accumulation was higher in the infected calf muscle than in those in the non-infected calf muscle.	[197]
2	[^{201}Tl]III-vancomycin	*S. aureus* binding study showed that the radiolabeled vancomycin could retain its biological activity after radiolabeling. In vivo imaging study in normal rats revealed a low accumulation in the liver.	[198]
3	[^{99m}Tc]-vancomycin	[^{99m}Tc]-vancomycin showed high accumulation in the *S. aureus* infection sites of Sprague-Dawley rats. In contrast, the radiolabeled compound exhibited low uptake in turpentine-inflamed rats.	[199]
4	[^{99m}Tc]-amoxicillin	A biodistribution study revealed that [^{99m}Tc]-amoxicillin has higher uptake in *E.coli*-infected and turpentine-inflamed thigh muscle compared to healthy muscle. From scintigraphic study, it was found that the radiolabeled amoxicillin remained at the infection and inflammation foci until 5 h post-injection.	[200]
		Another study demonstrated that [^{99m}Tc]-amoxicillin could target *S. pneumoniae* both in vitro and in vivo. However, the binding capacity of the radiolabeled amoxicillin was highly dependent on incubation time and concentration. Furthermore, it exhibited high uptake in infected thigh muscle within 1 h post-injection.	[195]
5	[^{99m}Tc]-clindamycin	A biodistribution study on Sprague Dawley rats bearing *S.aureus* infection revealed that [^{99m}Tc]-clindamycin has a high accumulation at the infection site. Scintigraphic images from infected rabbit suggest an increase of [^{99m}Tc]-clindamycin accummulation in the infection site (rabbit's left thigh) at 3 h post-injection.	[201]
6	[^{99m}Tc]-erythromycin	The maximum accumulation of [^{99m}Tc]-erythromycin at the infection site of the animal model was observed 0.5 h post-injection. However, the radiolabeled erythromycin could not distinguish between the septic (*S. aureus*) and sterile inflammation.	[202]
7	[^{99m}Tc]-kanamycin	A biodistribution study in *S.aureus* infected rats and rabbits demonstrated that the radiolabeled kanamycin can be accumulated at the infection sites. In addition, whole-body images of infected rabbit reveal high accumulation of [^{99m}Tc]-kanamycin at the infection foci 15 min post-administration.	[203]
8	[^{177}Lu]-kanamycin	Biodistribution and scintigraphic studies in normal animals showed that the radiolabeled kanamycin has rapid clearance from the body (Fig. 6).	[204]
9	[^{125}I]-penicillin X	[^{125}I]-penicillin X labels all the PBPs of *E.coli* in a manner very similar to those reported for [^{14}C]-penicillin G.	[205]
10	[^{125}I]-penicillin V	[^{125}I]-penicillin V could recognize bacterial PBPs of *Bacteroides fragilis*, *E. coli*, *Providencia rettgeri*, *S. aureus*, *S. pyogenes*, *E. faecalis*, and *Enterococcus faecium*.	[206]

was accomplished in quantitative yield using $SnCl_2.2H_2O$ as a reducing agent [207]. Despite their exact structures have not been elucidated yet, the proposed structures of [^{99m}Tc]-amoxicillin [195] and [^{99m}Tc]-kanamycin are shown in Fig. 7 [207].

In addition to technetium-99m, other radiometals from elements, such as Ga, Zr, Y, and Cu are widely used for radiolabeling of bioactive materials, both for diagnostic SPECT and PET imaging and radio theranostic applications [208]. In some cases, the use of technetium-99m can be substituted with other radiometals to yield new radiolabeled antibiotics, as exemplified by [^{99m}Tc]-kanamycin-[^{177}Lu]-kanamycin.

Several labeling strategies have been employed for the synthesis of radiopharmaceuticals, covering direct labeling and indirect labeling methods [13]. Direct labeling methods are those in which the radionuclide is reacted directly with an active molecule to form a radiopharmaceutical complex. Examples of this approach includes [^{99m}Tc]-amoxicillin, [^{99m}Tc]-kanamycin, [^{125}I]-penicillin V, and [^{125}I]-penicillin X (Fig. 7). Direct labeling using technetium-99m via the reduction of pertechnetate with stannous chloride in acidic condition has been widely used strategy for many applications [209]. Additionally, direct labeling with radioiodines requires the use of oxidizing agents to convert radioactive iodide into iodine or

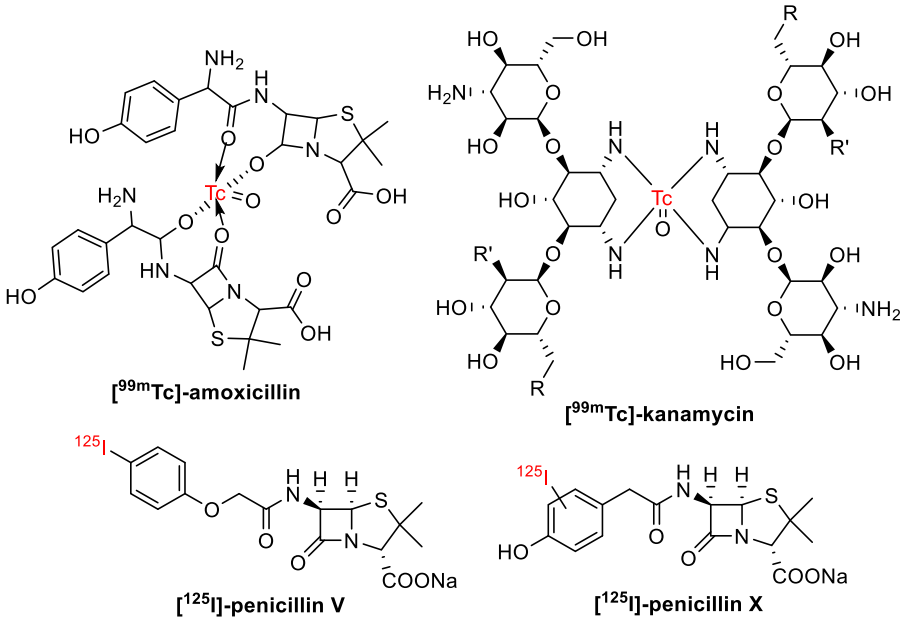

Fig. 7. Representative natural antibiotic-based radiolabeled probes.

iodine monochloride, which can be further facilitate the introduction of iodine to a bioactive molecule via electrophilic substitution reactions [126]. In contrast, indirect labeling methods require prior attachment of a bifunctional chelator or prosthetic group into a bioactive molecule for subsequent conjugation with a radionuclide [167,210]. Over the past decades, several chelators have been developed for radiolabeling active compounds with suitable radiometals (copper-64, gallium-68, scandium-44, yttrium-86, zirconium-89, etc.) [211]. Furthermore, labeling approach using prosthetic groups have been increasingly studied in recent years for the production of therapeutic or diagnostic radiopharmaceuticals, especially halogen-based agents (i.e., radioiodines, and ^{18}F-labeled bioactive molecules) [212–214].

7. Conclusions

Numerous human ailments, including infection-related diseases, have altered historical patterns. This has compelled drug developers to seek new sources of funding in order to develop effective and safe medications to meet the world population's growing needs. Secondary metabolites isolated from microbes have long been recognized as critical pharmacophores for disease control, but their full potential remains largely untapped. Microbes contain an abundance and diversity of bioactive molecules that can be used not only to treat diseases, but also to develop imaging probes for a variety of diseases, particularly infections. In biomedical applications, the developed fluorescent and radiopharmaceutical probes derived from microbial active molecules have demonstrated encouraging results. With the massive diversity of microbial metabolites found in nature, the potential for developing additional imaging probes for detecting and studying human pathogens is enormous. Additionally, advancements in analytical tools, genome mining, and engineering, as well as synthetic chemistry, have been associated with the ease and efficiency with which microbial metabolites can be extracted from nature. When combined, microbial metabolites can be used as viable molecular templates for the development of novel fluorescent and radiopharmaceutical probes capable of detecting a broad spectrum of infections.

8. CRediT authorship contribution statement

H.W contributed as the main contributor of this paper, with the order reflecting the contributions by H.W., R.H., A.S.N., R.R., I.S., and C.E.K. Conceptualization, H.W.; methodology, H.W., R.H., and A.S.N.; software, H.W., and R.H.; investigation, all authors.; writing-original draft preparation, all authors; writing-review and editing, H.W., R.H., and A.S.N.; visualization, C.E.K.; supervision, H.W. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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