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REVIEW

Exploring the Potential of Pyridine Carboxylic Acid Isomers to Discover New Enzyme Inhibitors

Sana Yaqoob[1–3,*], Farooq-Ahmad Khan[1–3,*], Nimra Tanveer[2,3], Shujaat Ali[2,3], Abdul Hameed[4], Hesham El-Seedi[5], Zi-Hua Jiang[6], Yan Wang[1,3]

[1]Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources (Ministry of Education of China), Guangxi Key Laboratory of Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences, Guangxi Normal University, Guilin, Guangxi, People's Republic of China; [2]Third World Center for Science and Technology, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Sindh, Pakistan; [3]H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Sindh, Pakistan; [4]Department of Chemistry, University of Sahiwal, Sahiwal, Punjab, Pakistan; [5]Department of Chemistry, Faculty of Science, Islamic University of Madinah, Madinah, 42351, Saudi Arabia; [6]Department of Chemistry, Lakehead University, Thunder Bay, ON, Canada

*These authors contributed equally to this work

Correspondence: Farooq-Ahmad Khan; Yan Wang, Email farooq.khan@iccs.edu; yan.wang@iccs.edu

Abstract: Pyridine carboxylic acid isomers — picolinic acid, nicotinic acid, and isonicotinic acid — have historically resulted in a plethora of drugs against tuberculosis, cancer, diabetes, Alzheimer's, angina, dementia, depression, allergy, respiratory acidosis, psoriasis, acne, hypertension, hyperlipidemia, HIV/AIDS (specifically HIV-1), among others. Despite the large number of therapeutic agents derived from these isomers, the research involving these scaffolds is still exceptionally active. The current surge in enzyme inhibitory activities by the compounds derived from them has further created space for the discovery of new drug candidates. This review focuses on the medicinal relevance of these isomers by analyzing structure-activity relationships (SARs) and highlighting emerging trends from patents filed over the last decade. Notably, pharmaceutical giants like Bayer, Bristol-Myers Squibb, Novartis, Curis, and Aurigene have developed enzyme inhibitors based on these scaffolds with nanomolar potency. The role of these isomers in the development of antiviral agents, including protease inhibitors, is also discussed. Overall, this review brings to the readers, a pragmatic opportunity to comprehend the recent literature, highlighting the scaffolds' importance in the design of new enzyme inhibitors. Furthermore, it discusses the structure-activity relationship of pyridine carboxylic acid-derived compounds and highlights the current patenting trends in medicinal chemistry.

Keywords: pyridine, enzyme inhibitors, nitrogen heterocycles, patents, pharmaceuticals, current trend, substituent effect

Introduction

Heterocyclic chemistry is a rich source of unique and innovative drug formulations.[1–3] Among various nitrogen-containing heterocycles, pyridine has found extensive use in contemporary drug design due to its ability to accommodate diverse substitution patterns on the ring, thereby allowing its incorporation into countless molecules with a wide range of biological activities.[4–9] Pyridine stands out as the second most widely utilized nitrogen heterocycle in FDA-approved pharmaceuticals, securing the leading position among aromatic compounds.[10–12] Pyridine continues to fascinate researchers, as shown by our database analysis.[9,13–17] Throughout the last decade from 2013 to 2023, there was a consistent stream of research papers and patents featuring the word "pyridine" in their titles (Figure 1). These numbers not only highlight the enduring fascination of the scientific community but are also a testament to pyridine's relevance in technological patents.

Analysis of the United States FDA database reveals a notable presence of pyridine, as 14% of the total drugs contain this moiety (Figure 2). Pyridine's substantial representation in the database not only highlights its key role in the pharmaceutical landscape but also the potential of this heterocyclic moiety in shaping the future of therapeutics development.

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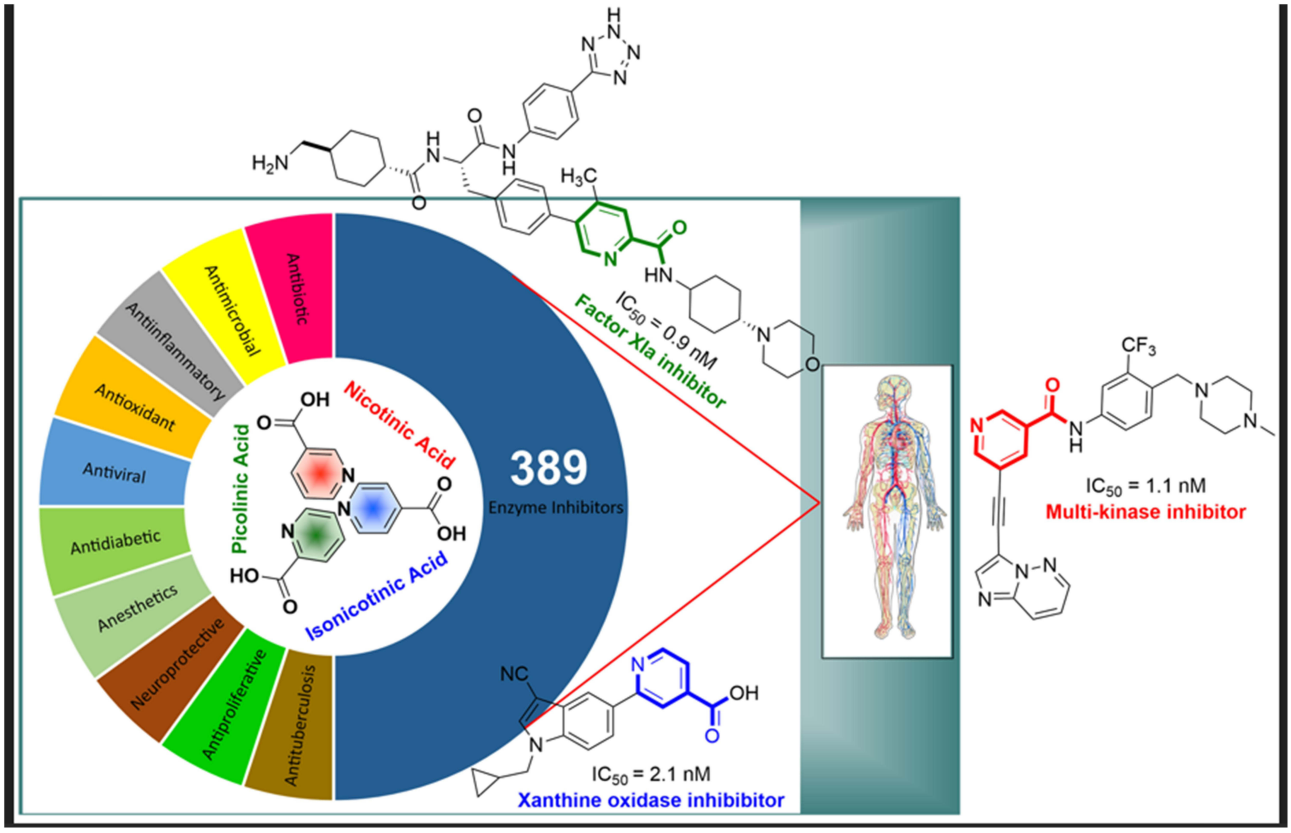
Graphical Abstract



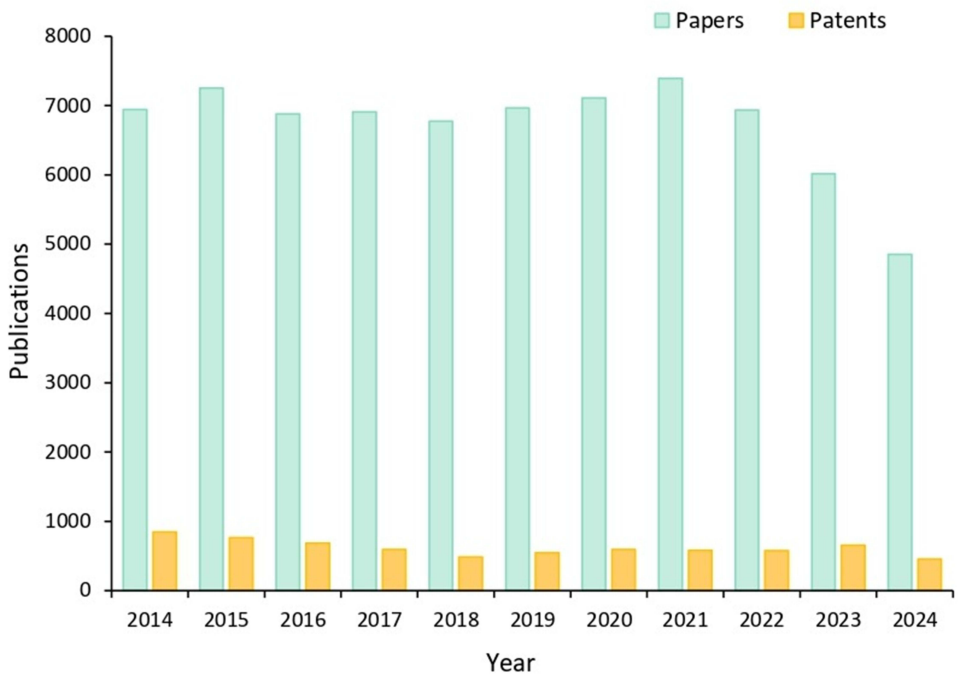


Figure 1 Number of research papers and patents featuring the word "pyridine" in their titles over the past one decade (2014–2024); Source: SciFinder[n].

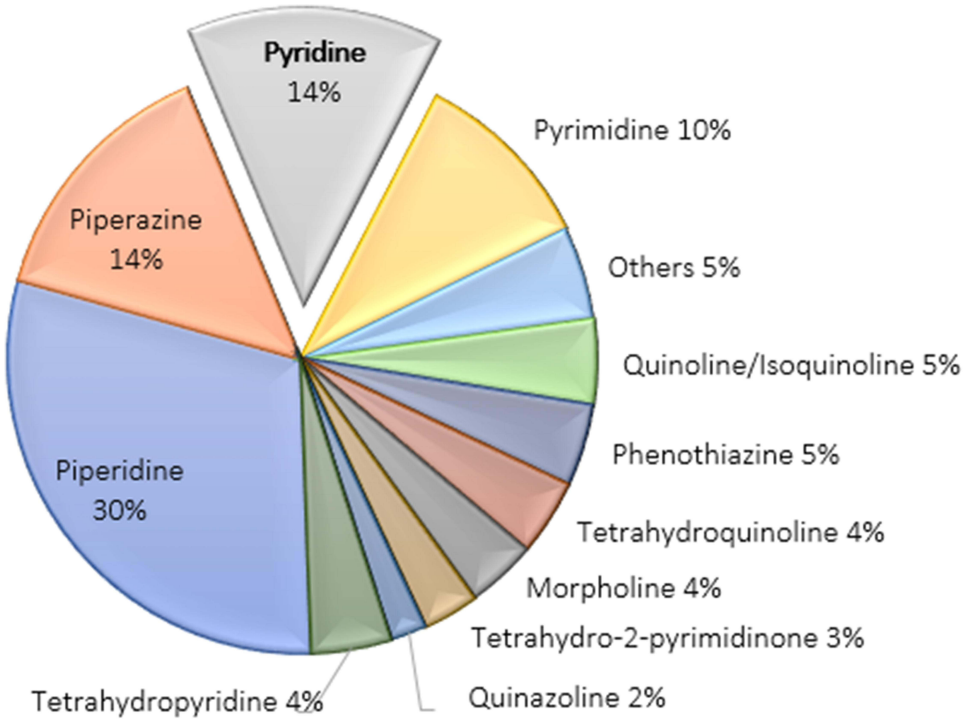


Figure 2 *N*-Heterocyclic drugs distribution in FDA database.

Center for Drug Evaluation and Research (CDER) is a vital part of the FDA and plays a crucial role in ensuring the safety and efficacy of drugs in the United States. Over the past decade (2013–2023), CDER has approved a myriad of New Molecular Entities (NMEs) with a marked presence of pyridine-containing NMEs in the annual approvals (Figure 3). Year after year, this continued inclusion of pyridine-containing NMEs emphasizes the integral role of this heterocyclic moiety in the pharmaceutical landscape, thereby emphasizing its potential and value in the realms of therapeutic advancements.[18]

Figure 4 offers an in-depth analysis of the FDA database, which gives a remarkable insight into the substitution patterns of pyridine-containing drugs approved during the last decade. In terms of substitution types, a substantial proportion of these drugs contain di-substituted pyridine, closely followed by tri-substituted and mono-substituted pyridines. While some drugs contained tetra-substituted and hexa-substituted pyridine, penta-substituted variants were notably absent from the database (Figure 4a).

Upon careful examination of substitution patterns within pyridine-containing pharmaceuticals approved between 2013 and 2023, a distinct trend emerges. There is a notable inclination towards substitution at position 2 of the pyridine ring, followed by significant instances of substitution at positions 5 and 3, especially when multiple substituents are present. Interestingly, some drugs feature direct substitution on the nitrogen atom within the ring structure (Figure 4b). These observations highlight the dynamic nature of the drug design and the adaptability of this heterocyclic moiety in pharmaceutical developments over the years.

In this comprehensive review, we delve into the intricate realm of pharmaceuticals derived from pyridine carboxylic acid isomers—an exploration critical to the contemporary understanding of medicinal chemistry. Through meticulous analysis, this study unveils the therapeutic significance and diverse applications of these compounds within the realm of approved drugs as well as patent communications. Pyridine carboxylic acid derivatives display a broad spectrum of biological activities and many of them have been approved for use in the clinic to treat various conditions including infections, inflammation, and cancers. This broad therapeutic potential is closely linked with their structural features. For example, the pyridine ring, which is aromatic in nature and electron deficient, facilitates π-π stacking and hydrogen bond interactions with biological targets, thereby enhancing the binding affinity. The carboxylic group contributes additional polarity and can co-ordinate with metal ions, a property particularly useful in enzyme inhibition. Moreover, the ease of

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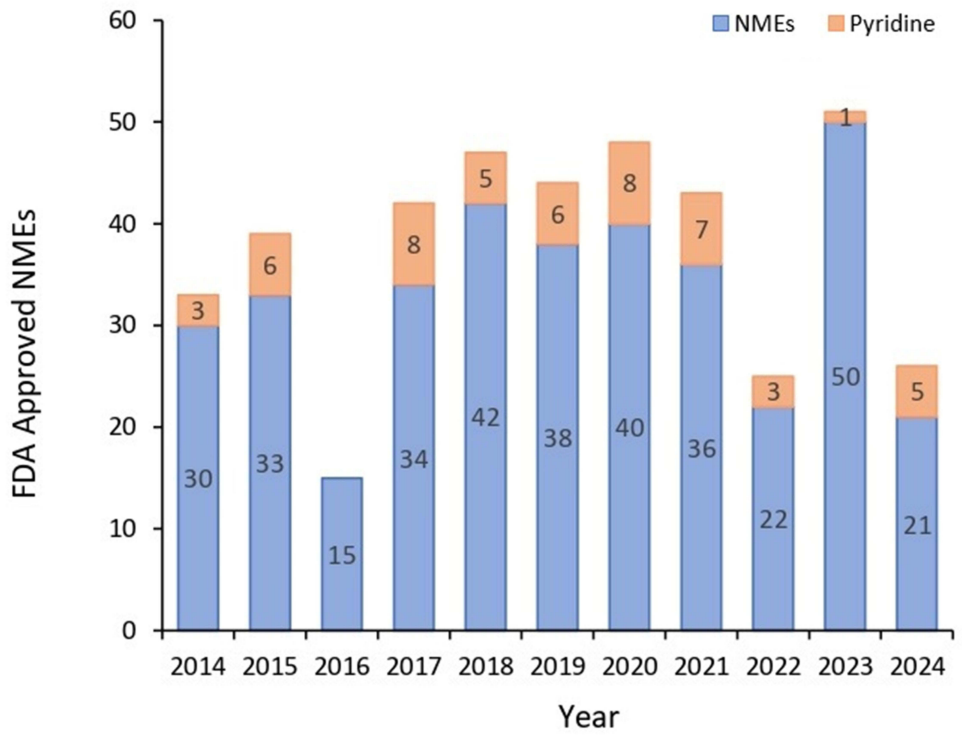

Figure 3 New molecular entities (NMEs) containing pyridine moiety, which were approved by FDA over the past one decade (2013–2023).

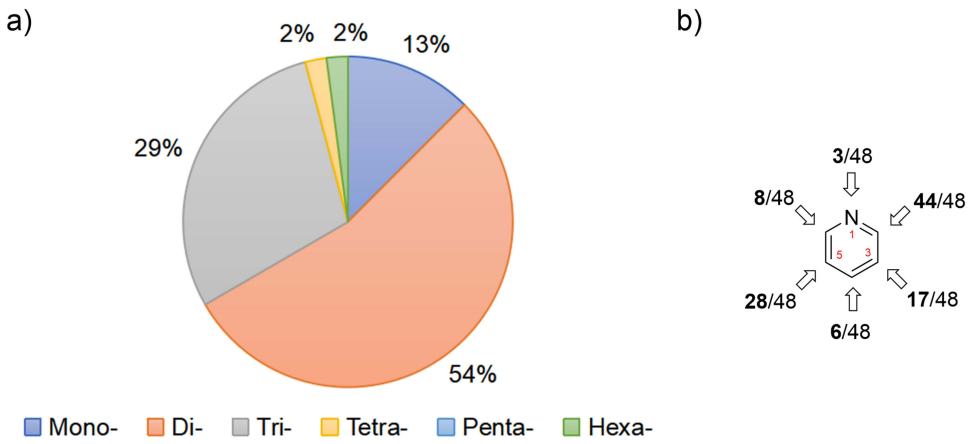

Figure 4 (**a**) Analysis of substitution type; and (**b**) examination of substitution pattern in pyridine containing drugs approved by FDA over the past one decade (2013–2023).

substitution at various positions of pyridine ring allows for structural flexibility and fine-tuning of activity and selectivity. Together, these features make pyridine carboxylic acid derivatives highly versatile scaffolds in medicinal chemistry. In recent years, there have been a good number of patents communicating the role of various pyridine carboxylic acid derivatives in this area of enzyme inhibition. Despite the significant impact of pyridine carboxylic acid-containing compounds on the pharmaceutical industry, there have been no review articles published specifically based on pyridine carboxylic acid derivatives. In the following sections, we provide a comprehensive review of approved drugs derived from pyridine carboxylic acid isomers and highlights of patents published in the last decade (2013–2023) which have disclosed a great number of pyridine carboxylic acid derivatives as potent enzyme inhibitors and potential therapeutic agents to treat various diseases.

Approved Drugs Derived from Pyridine Carboxylic Acid Isomers

The intricate interplay between molecular structures and pharmacological effects underscores the pivotal role played by pyridine carboxylic acid isomers in shaping the landscape of modern pharmaceuticals. The compounds stemming from pyridine carboxylic acids hold potential; likely due to the presence of nitrogen in the aromatic ring. The core is famous for its three isomers: picolinic acid (**1**), nicotinic acid (**2**), and isonicotinic acid (**3**) with carboxylic acid substitution at 2nd, 3rd, and 4th positions on the pyridine, respectively (Figure 5a). A detailed representation of natural products, which are categorized based on specific pyridine carboxylic acid isomers is also shown in Figure 5b. Many of them have garnered recognition as approved therapeutics by the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) of the United States. This includes natural drugs containing the picolinic acid moiety, like streptonigrin (**4**) with notable antitumor and antibacterial properties, along with antibiotics like fusaric acid (**5**) and its derivative, (+)-*S*-fusarnolic acid, both obtained from *Fusarium heterosporium*.[19,20] In this category, another group of antibiotics, promothiocin (**6**) isolated from *Streptomyces sp*. SF2741, and pyridomycin (**7**) obtained from *Dactylosporangium fulvum* were found promising against tuberculosis.[21,22] Nicotinic acid-derived natural products include several noteworthy examples, like Ilicifoliunine A (**8**), sourced from *Maytenus ilicifolia*, plagiochianin B (**9**) from *Plagiochila duthiana*, and clivimine (**10**) from *Clivia miniate*, all contributing towards the arsenal of natural

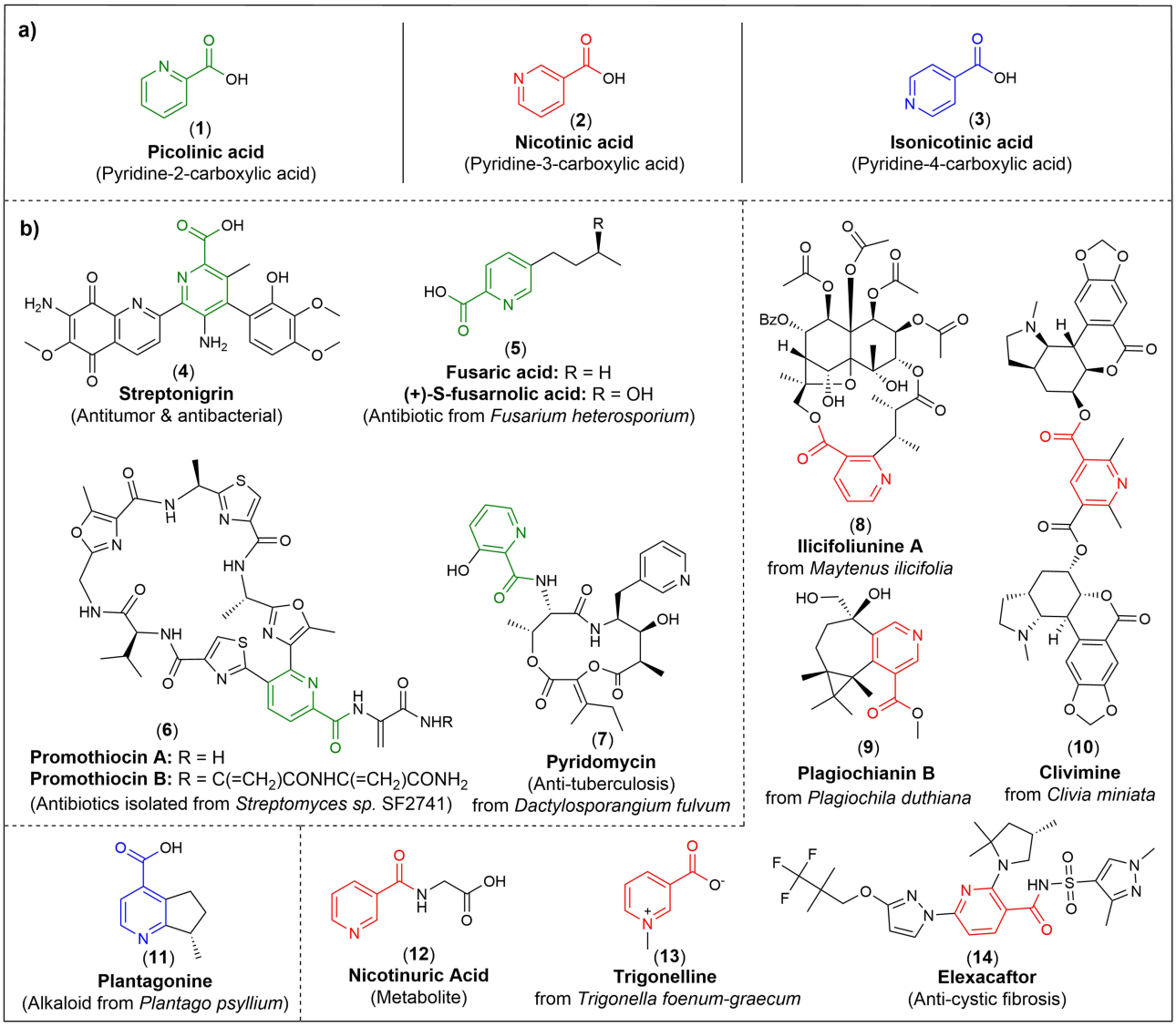

Figure 5 (**a**) Isomeric variants of pyridine carboxylic acid; (**b**) Representative examples of natural products and EMA/FDA approved natural product drugs.

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pharmacological agents.[23–25] It's worth noting that the figure presented in this context highlights plantagonine (**11**) from *Plantago psyllium*, which is a unique alkaloid containing the isonicotinic acid structure.[26] Notably, the ubiquitous niacin (vitamin B) is part of nicotinuric acid (**12**), trigonelline (**13**) sourced from *Trigonella foenumgraecum*, and elexacaftor (**14**) having anti-cystic fibrosis properties.[27–30] All these examples highlight the importance of isomeric variations of pyridine carboxylic acids, their derivatives, and related natural products in the pursuit of pharmacologically active agents.

Representative FDA-approved drugs stemming from different isomers of pyridine carboxylic acids are shown in Figure 6. Regorafenib (**15**) can tackle certain cancers as well.[31] Sorafenib (**16**) was approved in 2005 to help with liver, kidney, and thyroid cancers.[32] Lasmiditan (**17**) marked a milestone in migraine management, securing approval in 2019.[33] Picolinic acid-derived Quinupristin (**18**) emerged in 1999 as a new antibiotic for tough infections.[34] Nevirapine (**19**) combated the challenges of HIV with a significant impact in 2016.[35] Ubrogepant (**20**) was sanctioned in 2019 as a CGRP and 5HT1F antagonist to tackle migraines.[36] Flotufolastat F-18 (**21**) with cutting-edge imaging capabilities aligned with the dynamic needs of prostate cancer diagnostics.[37] Tazarotene (**22**) got approval for treating skin issues in 2017.[38] Serdexmethylphenidate (**23**) signified a breakthrough in addressing attention deficit hyperactivity disorder (ADHD).[39] By 2019, elexacaftor (**24**) was approved to target cystic fibrosis.[29] In 1983, Nicotinamide (**25**) gained recognition as a nutraceutical, sanctioned for the treatment of pellagra, highlighting its vital role in nutritional therapy.[40] Avatrombopag (**26**) received approval for treating blood issues in 2018.[41] Asciminib (**27**) as a tyrosine kinase inhibitor (TKI) was approved in 2021 to handle leukemia.[42] The nicotinic acid-derived FDA-approved drugs include Metyrapone (**28**), used to treat a hormone-related condition. Isoniazid (**29**) initially emerged as an anti-tuberculosis agent, along with protionamide (**30**) and ethionamide (**31**), to fight hard-to-treat tuberculosis.[43–46]

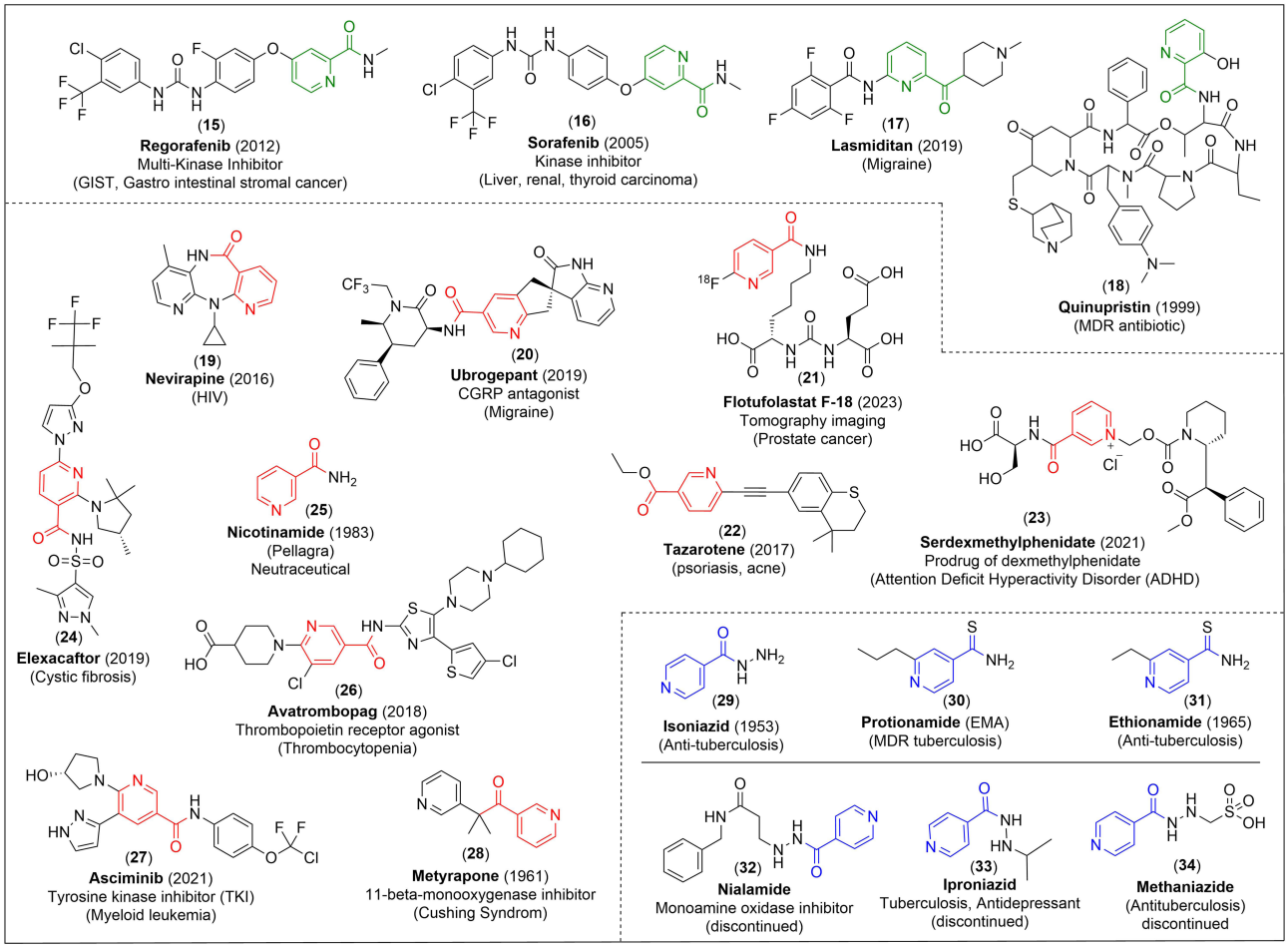

Figure 6 FDA approved drugs derived from the isomers of pyridine carboxylic acid, their indication and year of approval.

Ethionamide (**31**), a second-line tuberculosis treatment, is only used in combination therapy or the treatment of drug-resistant tuberculosis.[47] Nialamide (**32**) is a drug with anti-thrombotic properties. Its effects on the rabbit ear were observed when the internal surface of the arteries and veins were damaged, and a powerful thrombotic effect was observed by preventing intravascular thrombosis without inhibition of extravascular clotting.[48] Nialamide also had antidepressant properties, but it was withdrawn by the US, Canada, and UK in the 1960s due to serious side effects caused by tyrosine-containing foods.[49] Before 1950, Iproniazid (**33**), a medication renowned for its anti-tuberculosis properties, demonstrated significant improvements over earlier treatments.[50] Notably, it proved more effective than isoniazid in the treatment of bone and joint lesions, leading to its widespread recognition and safe usage during that era.[51,52] An experiment at Sea View Hospital Staten, Island N.Y., in 1951 revealed that iproniazid caused certain toxic side effects in patients when compared to the other two tuberculosis medications, including isoniazid. Despite this, the use of iproniazid continued by controlling and encountering its toxicity, and benefits exhibited in the case of osseous-tuberculous, were transferred to use in other lesions.[53] Iproniazid was originally developed to treat tuberculosis, but its mood-relaxing properties were discovered in 1952, making it the first commercialized antidepressant drug. This drug was used for decades for antidepressant treatment but was withdrawn in several countries, including the USA, due to hepatotoxic side effects. The drug has been replaced by other medication but it has an assigned place in therapy.[54,55] The discontinuation of nialamide (**32**), iproniazid (**33**), and methaniazide (**34**) reflects the dynamic nature of pyridine-4-carboxylic acid in pharmaceutical evolution.

The compounds **35**–**48** presented in Figure 7 comprehend a spectrum of analgesic effects, accentuating their significance across diverse inflammatory conditions. Nicomorphine (**35**), a potent opioid analgesic, and nicocodeine (**36**), an opioid receptor agonist, offer robust pain relief.[56] Dexamethasone isonicotinate (**37**) stands out as a notable anti-inflammatory agent, while the 2021-introduced CGRP antagonist,[57] (**38**), demonstrates promise in inhibiting neurogenic inflammation. Clonixin (**39**) and morniflumate (**40**), both COX-1 and COX-2 inhibitors, exemplify the NSAID class, displaying their prowess in alleviating inflammation.[58,59] Menthyl nicotinate (**41**) serves to foster circulation and relief in musculoskeletal conditions.[60] Noteworthy is niflumic acid (**42**) selectivity in addressing rheumatoid arthritis-associated inflammation through COX-2 inhibition.[61] Other

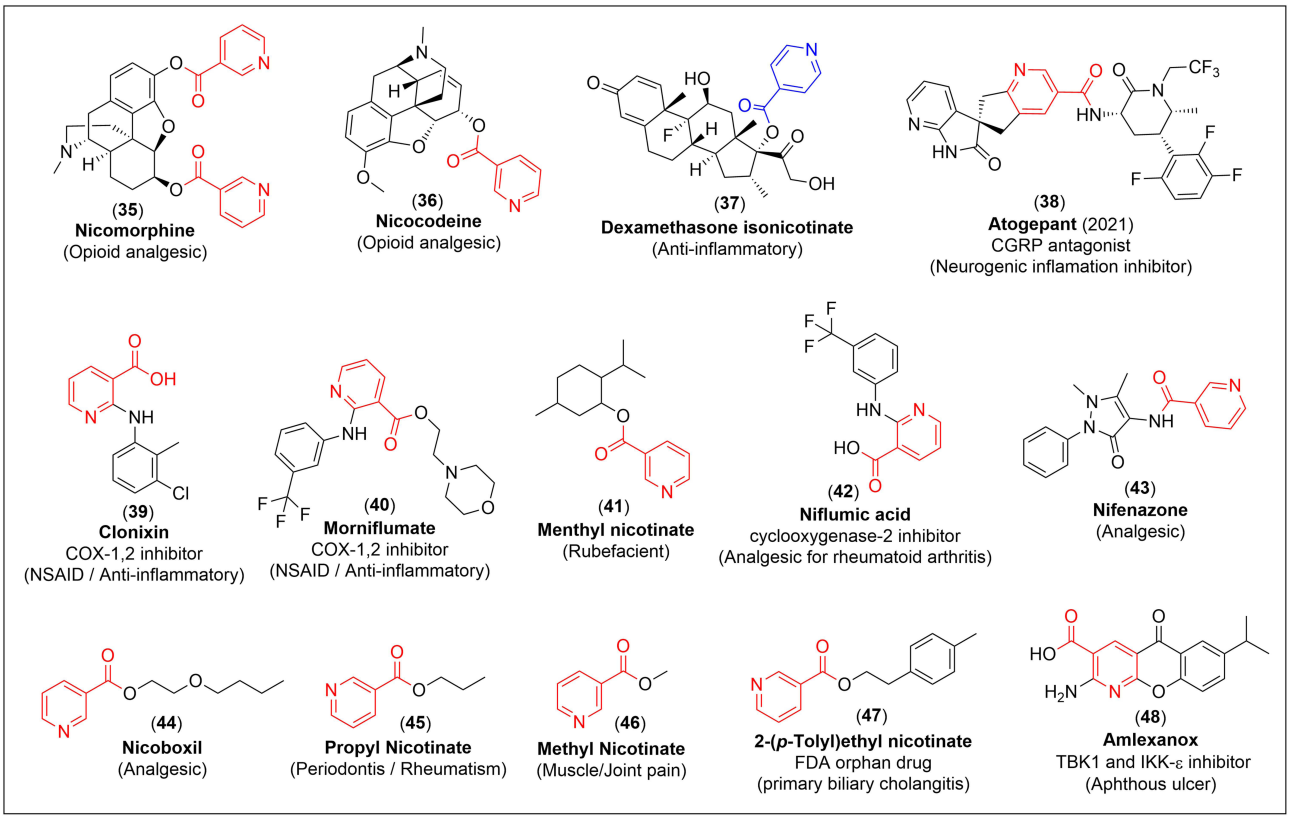

Figure 7 Pyridine carboxylic acid derived anti-inflammatory drugs.

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compounds, including nifenazone (**43**), a broad-spectrum analgesic, and derivatives like nicoboxil (**44**), propyl nicotinate (**45**), and methyl nicotinate (**46**), contribute distinct pain management perspectives. Particularly, 2-(*p*-tolyl)ethyl nicotinate (**47**) — an FDA orphan drug — offers promise against primary biliary cholangitis.[62–64] Finally, amlexanox (**48**), an inhibitor of TBK1 and IKK-e, exhibits potential in modulating inflammatory responses for aphthous ulcer treatment.[65]

Figure 8 encapsulates a compilation of antimicrobial agents, originating from different pyridine carboxylic acid isomers. Among antibiotics derived from picolinic acid, streptonigrin (**49**) is a noteworthy representative. Recent studies suggest that this isomer has the potential to block the release of free fatty acids from fat cells and increase the activity of lipoprotein lipase, offering promise as both a combination therapy and an economical standalone treatment for lowering lipid levels.[66–68] Notably, saquinavir (**50**), approved by the FDA in 1997, exhibited protease inhibition activity against HIV.[69] Further, pristinamycin (**51**) is another significant antibiotic in this context.[70] In the domain of antibiotics featuring a nicotinic scaffold, the array includes cefpiramide (**52**), a third-generation antibiotic, and the well-established nalidixic acid (**53**), introduced in 1986 by FDA.[71,72] Concurrently, enoxacin (**54**), approved by FDA in 2017, demonstrates broad-spectrum antibacterial potential.[73] Additionally, Gemifloxacin (**55**), established in 2003, further enriches this spectrum.[74] Finally, the category of antibiotics incorporating an isonicotinoyl moiety includes cefalonium (**56**), as a first-generation antibiotic.[75] Equally, cefsulodin (**57**) exhibits specificity against *Pseudomonas aeruginosa*. In addressing tuberculosis, aconiazide (**58**) assumes a pivotal role.[76–79] Notably, enisamium (**59**), a Russian introduction, offers antiviral efficacy against influenza.[80] Thus, the figure illuminates the extensive repertoire of antibiotic drugs emerging from pyridine carboxylic acid derivatives, delineating their expansive therapeutic potential across diverse infectious conditions.

Figure 9 provides a comprehensive assemblage of antidyslipidemic agents derived from pyridine carboxylic acid isomers, thereby revealing innovative therapeutic interventions to treat dyslipidemia. Notably, niceritrol (**60**) and nicofuranose (**61**) function as cholesterol reducers, contributing to lipid management.[81,82] The introduction of inositol nicotinate (**62**) in 2005 adds a vasodilatory agent to the spectrum, while etofibrate (**63**) serves as a dyslipidemic agent.[83–85] Furthermore, the recognition of nicorandil (**64**) by the EMA in 2015 underscores its vasodilatory properties.[86,87] In contrast, within the domain

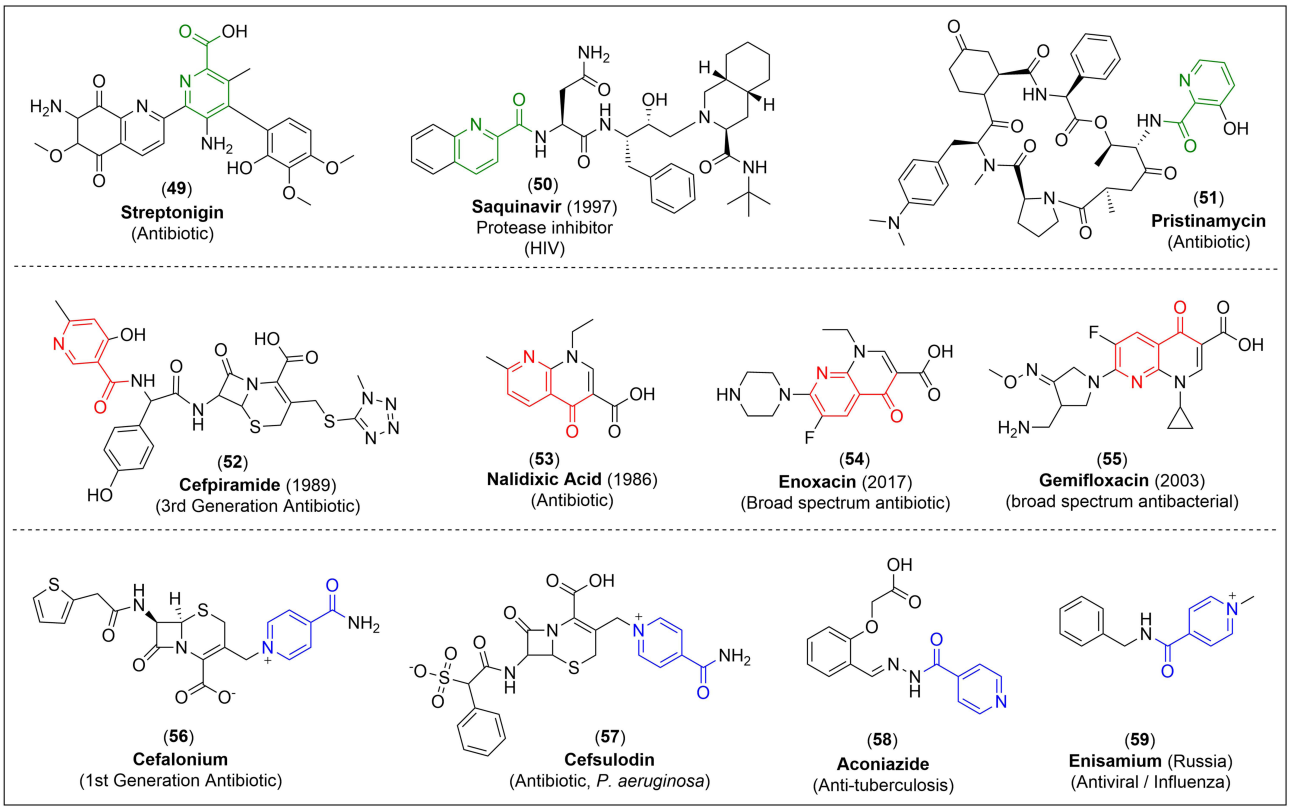

Figure 8 Antimicrobial drugs originating from pyridine carboxylic acid isomers.

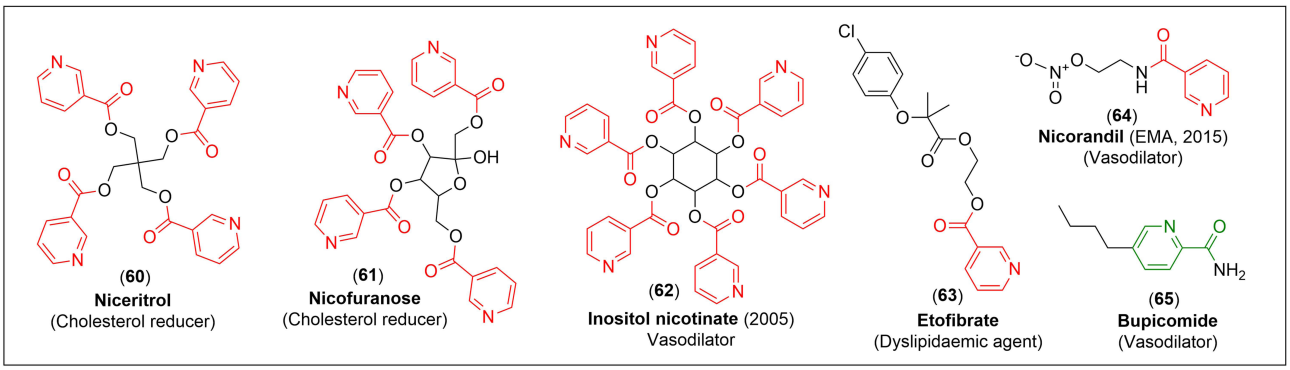

Figure 9 Antidyslipidemic drugs derived from pyridine carboxylic acids.

of picolinic acid derivatives, bupicomide (**65**) is a singular example of an antidyslipidemic agent enriching the repertoire of antidyslipidemic options.[88,89]

The vibrant potential of pyridine carboxylic acid-derived drug candidates is highlighted in Figure 10, which shows their clinical trial stages. For instance, picolinic acid-derived drug candidates include verubecestat (**66**) — a BACE2 inhibitor with

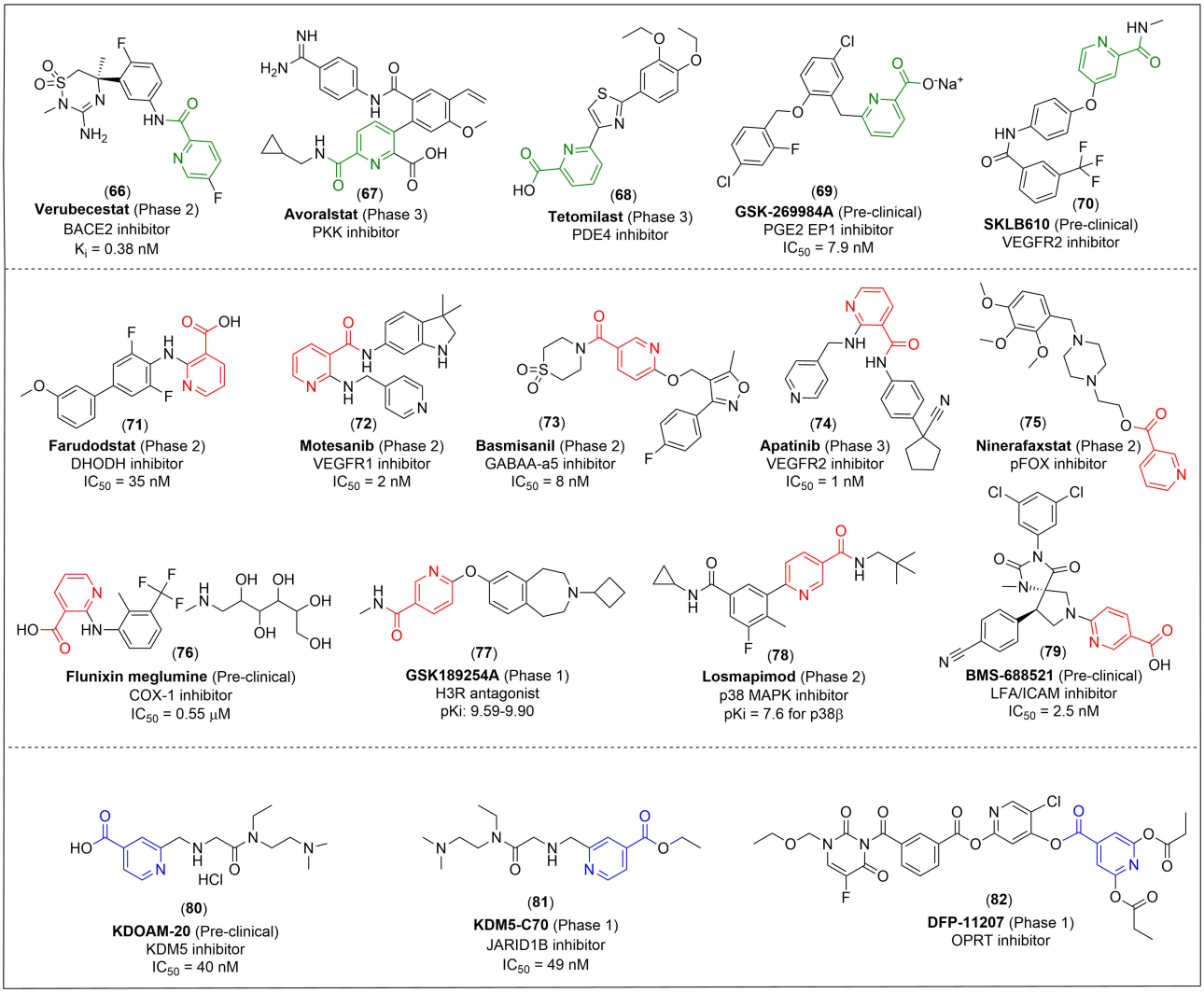

Figure 10 Pyridine carboxylic acid derivatives in drug development pipeline.

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a Ki of 0.38 nM — which is in Phase 2 of clinical trials.[90] Avoralstat (**67**) — a PKK inhibitor, and tetomilast (**68**), a PDE4 inhibitor are in Phase 3 trials.[91,92] GSK-269984A (**69**), a PGE2 EP1 inhibitor with an IC_{50} of 7.9 nM, and SKLB610 (**70**), a VEGFR2 inhibitor, have demonstrated their potential in pre-clinical stages.[93,94] Similarly, the spectrum of nicotinic acid-derived drugs under development presents a cohort of candidates with distinct attributes. Farudodstat (**71**), a DHODH inhibitor with an IC_{50} of 35 nM, and Motesanib (**72**), a VEGFR1 inhibitor with an IC_{50} of 2 nM, are undergoing phase 2 trials.[95,96] Basmisanil (**73**), a GABAA-a5 inhibitor (IC_{50} = 8 nM) is also in phase 2, while apatinib (**74**), a VEGFR2 inhibitor with an IC_{50} of 1 nM is undergoing phase 3 trials.[97,98] Ninerafaxstat (**75**), a pFOX inhibitor, is in Phase 2, while flunixin meglumine (**76**), a COX-1 inhibitor with an IC_{50} of 0.55 mm, is in the pre-clinical stage.[99,100] Moreover, GSK189254A (**77**), an H3R antagonist with a pKi range of 9.59–9.90, is in Phase 1, and losmapimod (**78**), a p38 MAPK inhibitor with a pKi of 7.6 for p38β, is progressing through phase 2 trials.[101,102] BMS-688521 (**79**), an LFA/ICAM inhibitor with an IC_{50} of 2.5 nM, has shown promise in the pre-clinical stage.[103] Notably, the isonicotinic acid-derived drug candidates include KDOAM-20 (**80**), which is a KDM5 inhibitor (IC_{50} = 40 nM) and is in pre-clinical stage.[104] Furthermore, KDM5-C70 (**81**) — a JARID1B inhibitor with an IC_{50} of 49 nM, and OPRT inhibitor DFP11207 (**82**) are in phase 1 of clinical trials.[105,106]

The Effect of Pyridine Substitution on Key Pharmacological Parameters

The physicochemical properties of molecules are significantly impacted by replacing the phenyl group with a ring-containing nitrogen atom, which can translate into improved pharmacological parameters.[107] Herein, we describe some key parameters, such as biochemical potency, target selectivity, cellular potency, and binding affinity by comparing the results of pyridine and non-pyridine ring-containing analogues. Figure 11 summarizes exciting examples of the pyridine effect on improving some key pharmacological parameters. For example, Dandapani et al evaluated nearly 100,000 different chemical structures and found that compound **83** could effectively stop the growth of *Trypanosoma cruzi* — a parasite responsible for Chagas disease. However, its isonicotinoyl analogue was 500-fold more potent than the parent molecule (*T. cruzi* IC_{50} = 1.0 nM for **84**). Likewise, ponatinib (**85**) — a multikinase inhibitor — is used to treat a type of highly resistant blood cancer by blocking some proteins that help in the growth of cancer cells. Ponatinib is also being evaluated for other types of cancers, such as lung and bile duct cancers. However, this drug has many side effects because it blocks many other proteins. By adding nitrogen to the structure of ponatinib, the new version (**86**) of this drug was 28-fold more potent by effectively blocking MNK1 and MNK2 proteins that make some cancers resistant to treatments. Naltrexone (**87**) is a drug with an antagonistic effect on the μ-opioid receptor (μ-OR) in our body. In 2013, Zhang et al made changes to naltrexone to help it fit into the receptor cavity and discovered that the addition of nitrogen to the drug improved its receptor binding. The docking study for compound **88** showed 880-fold improved binding affinity in comparison to **87** (μ-OR K_i = 120 nM). This new version of naltrexone did not activate the receptor, which is desirable for its intended purpose. When 6-substituted pyrrolo[2,3-d]pyrimidine containing compound **89** was modified by the addition of a nitrogen atom in the phenyl side-chain structure, compound **90** was obtained (Figure 12).

Upon testing this compound on isogenic Chinese hamster ovary (CHO) cells expressing folate receptors (FRs) α and β, it had superior anti-proliferative activity due to its competitively binding with [3H] folic acid. In further assays involving KB tumor cells, compound **90** exhibited an IC_{50} value of 0.37 nM, making it 3 times more potent than the original compound **89**. The findings suggest that compound **90** is potentially a powerful antitumor agent having reduced toxicity to normal cells.[108]

Le et al reported inhibitors of matrix metalloproteinase-13 (MMP-13) — an enzyme involved in osteoarthritis. To block MMP-13, the active compound **91** and its pyridine carboxylic acid derivative **92** were discovered by high-throughput screening (HTS) followed by structure-activity relationship (SAR) studies (Figure 13). It was found that compound **92** could be much more effectively absorbed and remained in the body for a longer period compared to **91**. Bioavailability (%F) of **92** in the animal model was 73%, which was significantly higher than that of **91** having 9% only. Similarly, **91** had a clearance rate (CL) of 20 mL/min/kg, while **92** had a slower rate of 7.6 mL/min/kg, meaning **92** stayed in the body longer. Furthermore, compound **91** had an AUC (the area under the plasma drug concentration-time curve) of 380 ng/h/mL, while **92** had a much higher AUC of 13,000 ng/h/mL, indicating a greater exposure of the body to pyridine carboxylic acid derived **92** over time.[107,109]

Overall, these examples identify the pyridine carboxylic acid isomers as important constituents of drug design for multiparameter optimization. Beyond all of the above-mentioned properties, pyridine derivatives are receiving interest for

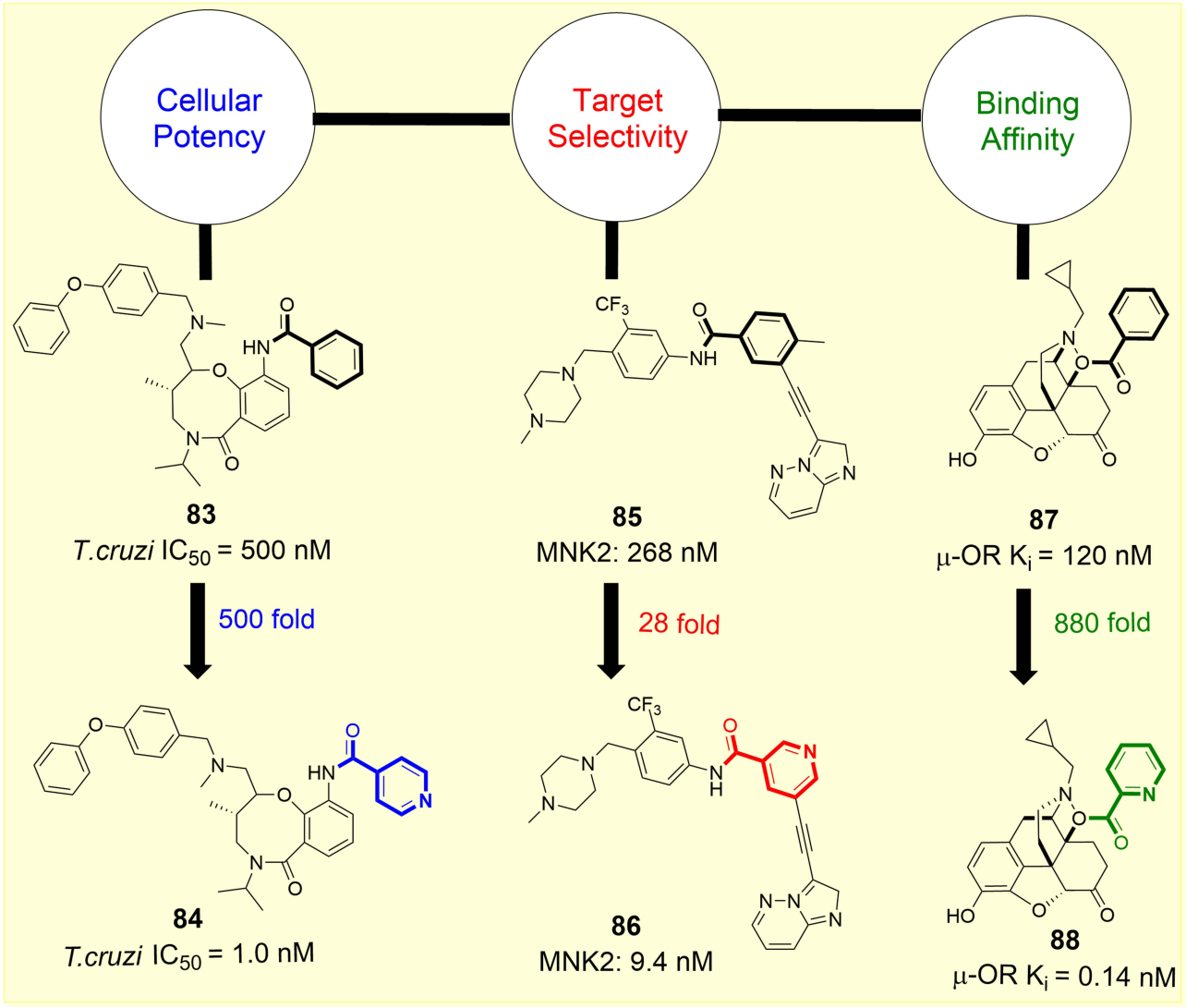

Figure 11 Effect of pyridine ring on pharmacology of bioactive molecules.

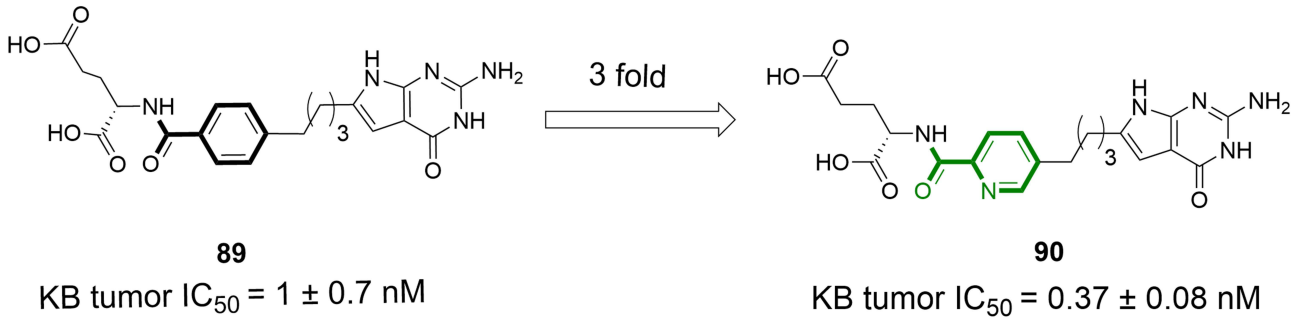

Figure 12 Enhancement of antitumor effect by the addition of nitrogen atom.

their ability to act as enzyme inhibitors.[110] Pyridine carboxylic acid-derived compounds function as enzyme inhibitors against a wide range of enzymes such as urease,[111] synthase,[112] tyrosinase,[113] myeloperoxidase (MPO), and acetylcholinesterase,[114] cyclooxygenase-2 (COX-2),[115] histone demethylase,[116,117] calpain (calcium-activated protease),[118] Bcr-Abl tyrosine

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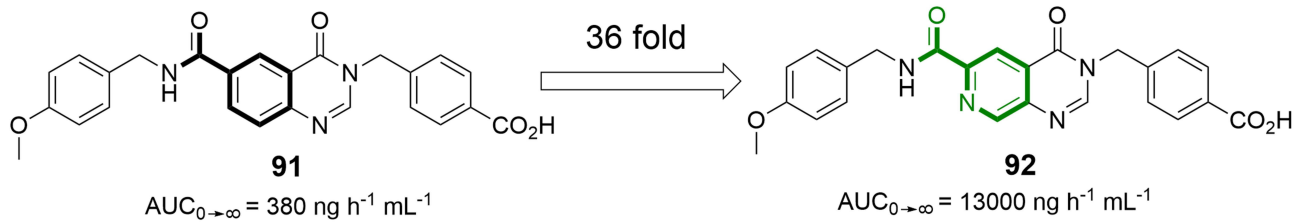

Figure 13 Effect of nitrogen atom substitution on in vivo pharmacological profiles.

kinase,[119] and c-Met kinase.[120–122] Hence in this perspective, there have been a large number of patents published in recent years communicating the role of various pyridine carboxylic acid derivatives in this area of enzyme inhibition.

Patent Literature Review (2013–2023)

Many enzyme inhibitors are well known for their function as drugs in clinical settings.[123] Interestingly, most of the patents unveiled herein depicted the enzyme-inhibitory activity of pyridine carboxylic acid derivatives. Within the diverse range of inhibitors emanating from pyridine carboxylic acid, the focus of this section will be on the patents and papers from 2013 to 2023, as shown in Table 1. These are categorized, depending on the proposed target when specified. The molecular structures of the notable biologically active inhibitors can be seen in Figure 14.

Table 1 Patents Published on Pyridine Carboxylic Acid Derivatives in Different Therapeutic Areas *from* 2013 to 2023

Patent No	Compound Nature	Applicants/ Assignees	Type of Inhibitor/Claims	Year	Reference
WO2023018643A1	Pyridine-3-carboxylic acid	AbbVie Inc.	Receptor-interacting protein kinase 1 (RIPK1) inhibitors for the treatment of diseases/These inhibitors alleviate neurodegenerative processes by reducing RIPK1 activity, which in turn mitigates neuroinflammation and cell necroptosis.	2023	[124]
WO 2016/174183	Pyridine-2-carboxylic acid	Bayer	Inhibitors of IRAK4 (Interleukin-1 receptor-associated kinase 4)/For treatment of lymphoma, psoriasis, macular degeneration, endometriosis COPD, and neoplastic disorders.	2016	[125]
WO 2019/099703 A1	Pyridine-2-carboxylic acid	Sidecar Therapeutics, Inc.	Inhibitors of ASK1(Apoptosis Signal-regulating Kinase 1)/ ASK1 has been found to be active for the treatment of fibrosis, cancer, diabetes, cardiovascular and neurodegenerative diseases, fibrosis, cancer, autoimmune disease, inflammatory disease or condition, cardiovascular disease, neurodegenerative disease or condition, or combinations thereof.	2019	[126]
WO2019081637	Pyridine-2-carboxylic acid	Boehringer Ingelheim International GMBH.	Transient Receptor Potential C6 Ion Channel (TRPC6) inhibitors/For the treatment of hypertension and other cardiac and vascular conditions, muscular dystrophy, fibrotic disorders, preeclampsia restenosis, liver disease, pain, ischemia and ischemic reperfusion injury, and certain forms of cancer.	2019	[127]
US 2020/0055824 A1	Pyridine-2-carboxylic acid	Vanderbilt University	Inhibitors of WD Repeat-containing protein 5 (WDR5) / These inhibitors efficiently modulate the interaction of WDR5 with chromatin, cognate transcription, and other regulatory factors ie, histone methyltransferase MLL1, proliferative activity, tumor formation, and tumor maintenance.	2020	[128]

(*Continued*)

Table 1 (Continued).

Patent No	Compound Nature	Applicants/ Assignees	Type of Inhibitor/Claims	Year	Reference
WO2022/047230A1	Pyridine-2-carboxylic acid Pyridine-4-carboxylic acid	Fibrogen. Inc	Histone lysine demethylase 5 (KDM5) inhibitors/For effective treatment of cancer such as colon cancer, breast cancer, neuroblastoma, cervical cancer, kidney cancer, liver cancer, lung cancer, leukemia, HIV, Hepatitis B infections, diabetes, and cardiovascular diseases.	2022	[129]
WO 2018/149986 Al	Pyridine-4-carboxylic acid	Oryzon Genomics, S.A.	Histone Demethylase inhibitors/For treating a disease associated with a JmjC- KDM, cancer, or viral infections.	2018	[130]
WO 2014/053491 Al	Pyridine-4-carboxylic acid	Epithera-peutics APS.	Histone Demethylase Inhibitors/For the prevention and/or the treatment of diseases where genomic dysregulation plays a role in pathogenesis, such as eg cancer	2014	[131]
WO 2014/100463 Al	Pyridine-4-carboxylic acid	Quanticel Pharma-ceuticals, Inc.	Histone Demethylase inhibitors/For the treatment of carcinoma, such as breast carcinoma, lung carcinoma, prostate carcinoma, bladder carcinoma, and/or melanoma.	2014	[132]
WO 2015/200709 Al	Pyridine-4-carboxylic acid	Quanticel Pharma-ceuticals, Inc.	Histone Demethylase inhibitors/For the treatment of cancer, such as breast carcinoma, lung carcinoma, prostate carcinoma, bladder carcinoma, and/or melanoma.	2015	[133]
US2022/0226292 A1	Pyridine-2-carboxylic acid	Indian Institute of Science, Bangalore	Effective against SARS-Cov-2, herpes simplex virus, influenza A virus, Japanese encephalitis virus, flavivirus, and zika viral infections.	2022	[134]
WO 2014/132220 A1	Pyridine-3-carboxylic acid	Novartis	Selective (Platelet Derived Growth Factor Receptor) PDGFR inhibitors/These are active pharmaceutical agents useful in the treatment of fibrotic diseases and conditions such as pulmonary arterial hypertension (PAH), respiratory and inflammatory infections.	2014	[135]
WO 2015/092610 Al	Pyridine-3-carboxylic acid	Pfizer	Tropomyosin Receptor Kinase (Trk) inhibitors offer targeted treatments for conditions such as atopic dermatitis, psoriasis, cancer and pain, acute and chronic itch, pruritus, eczema, and prurigo nodularis, inflammation, restenosis, atherosclerosis, thrombosis, lower urinary tract disorder, inflammatory lung diseases, inflammatory bowel diseases, fibrosis, neurodegenerative disease, infectious diseases such as *Trypanosoma cruzi* infection (Chagas disease), papillary thyroid carcinoma and adult myeloid leukaemia.	2015	[136]
US 8.450,316 B2	Pyridine-3-carboxylic acid	Trustees of Tufts College, Arisaph Pharmaceuticals, Inc.	Potential fatty Acid Binding Protein (FABP) inhibitors/For the treatment of conditions associated with hyperlipidemia and hypercholesterolemia that have been linked to an increased risk of other conditions, such as atherosclerosis, deleterious ailments, and heart attack.	2013	[137]
US 8,937,063 B2	Pyridine-3-carboxylic acid	Tufts College Trustees, Arisaph Pharmaceuticals, Inc.	Potential fatty Acid Binding Protein (FABP) inhibitors/For the treatment of conditions associated with hyperlipidemia and hypercholesterolemia that have been linked to an increased risk of other conditions, such as atherosclerosis, deleterious ailments, and heart attack.	2015	[137]
WO 2015/044174 Al	Pyridine-3-carboxylic acid	Bayer Pharma.	Factor XIa Inhibitors/FXIa inhibitors can be used to treat and/ or prevent diseases, particularly thrombotic or thromboembolic diseases, perioperative heavy blood loss, and/or cardiovascular diseases.	2015	[138]

(*Continued*)

Table 1 (Continued).

Patent No	Compound Nature	Applicants/ Assignees	Type of Inhibitor/Claims	Year	Reference
WO 2020/128850 A1	Pyridine-3-carboxylic acid	Pfizer Inc.	Selective Transforming Growth Factor-Beta (TFGβ) inhibitors/For the treatment of fibroproliferative diseases. Many forms of cancer, such as colorectal skin and lung cancer. In particular, to treat cancers of the pancreas, breast, and brain including glioma.	2020	[139]
WO 2020/092667 A1	Pyridine-3-carboxylic acid	Merck Sharp and Dohme Corp.	$Na_v1.8$ inhibitors/disease prevention, amelioration, or suppression mediated by $Na_v1.8$ channel activity The compounds of the current invention may be useful in the treatment of acute itch, chronic itch, pain, and cough disorders.	2020	[140]
US 8,691,852 B2	Pyridine-3-carboxylic acid	Almirall, S.A.	Dihydroorotate Dehydrogenase (DHODH) inhibitors/For the prevention or suppression of diseases and disorders known to be amenable to improvement through inhibition of dihydroorotate dehydrogenases, such as, immune and inflammatory diseases, autoimmune diseases, malignant neoplastic diseases, angiogenic-related disorders, viral and infectious diseases, and destructive bone disorders.	2014	[141]
US 8,729,273 B2	Pyridine-4-carboxylic acid	LG Life Sciences Ltd.	Xanthine Oxidase inhibitors/Provide methods for the treatment and/or prevention of the diseases associated with xanthine oxidase, such as hypertension, heart failure, hyperuricemia, kidney disease, cardiovascular disease, gout, diabetes, inflammatory bowel disease, inflammation, and articular disease.	2014	[142]
WO 2015/069594 Al	Pyridine-4-carboxylic acid	Bristol-Myers Squibb Company.	Inhibitors of Glycogen Synthase Kinase 3 (GSK-3)/Found effective for the treatment of both the symptomatic and neuropathologic aspects of Alzheimer's disease, as well as other neurodegenerative diseases ie Huntington's disease, Parkinson's disease, stroke, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord trauma, peripheral neuropathies, and vascular dementias.	2015	[143]
WO 2016/011209 Al	Pyridine-4-carboxylic acid	LifeSci Pharmaceuticals, Inc.	Plasma Kallikrein (Pkal) inhibitors/For the effective treatment of vascular system diseases and disorders. Angioedema, brain edema, and macular edema, are examples of such diseases and disorders.	2016	[144]
WO 2021/021933 A1	Pyridine-4-carboxylic acid	The Wistar Institute	IsPH inhibitors/IsPH is an enzyme involved in the methyl erythritol phosphate pathway of isoprenoid synthesis/used to treat bacterial infections.	2021	[145]
US11,382,907B2	Pyridine-4-carboxylic acid	Alkahest, Inc	Chemo kinase receptor 3 (CCR3) inhibitors/Methods for the improvement of neurodegenerative diseases including aging-associated-neuronal loss, aging-associated-loss of motor coordination, and aging-associated-memory impairment.	2022	[146]
WO2020/053812A1	Pyridine-3-carboxylic acid	Purdue Research Foundation.	Kinase inhibitor/These inhibitors target a wide range of cancer-driver kinases such as FGFR1-4, FLT3, ABL1, and RET including AML, CML, various RET and FGFR-driven cancers. In addition, for disease treatment such as cancer and, in particular, acute myeloid leukemia.	2020	[147]
WO 2015/089220 Al	Pyridine-3-carboxylic acid	Allergan, Inc.	Kinase inhibitor/This invention describes methods for modulating, regulating, or inhibiting tyrosine kinases, whether receptor or non-receptor, for the prevention and/or treatment of disorders caused by unregulated tyrosine kinase signal transduction, such as metabolic, and blood vessel proliferative disorders and abnormal cell proliferation.	2015	[148]

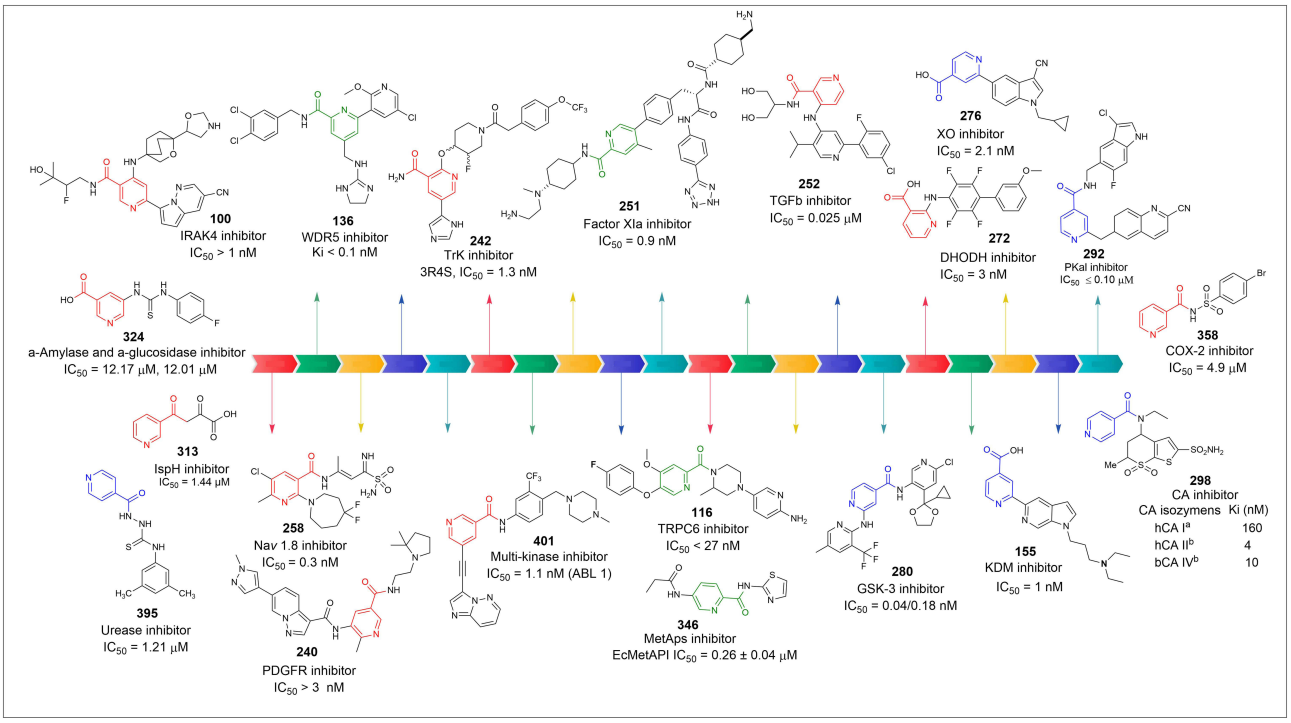

Figure 14 Biologically active pyridine carboxylic acid derived enzyme inhibitors reported in recently published literature.

IRAK4 Inhibitors

Interleukin-1 receptor-associated kinase 4 (IRAK4) is the most proximal kinase in the Toll-like receptor (TLR)/interleukin (IL)-1 receptor (TLR/IL-1R) signaling cascade, which is associated with autoimmune diseases, inflammation, and cancers.[149–151] TLR assembles the MyDDosome complex during signal transduction, which then activates transcriptional factors and the downstream pro-inflammatory cytokines production. Human and rodent genetics support the role of IRAK4 in immunological response. Moreover, clinical trials are ongoing for the evaluation of IRAK4 inhibition for non-Hodgkin lymphoma.[151] Bryan et al reported an IRAK4 inhibitor **93** with a clinical code CA-4948 having IC_{50} less than 50 nM (Figure 15).[152] Similarly, Bayer[125] and Bristol-Myers Squibb (BMS) have disclosed some noteworthy IRAK4 inhibitors such as **94**[153,154] with an IC_{50} value of 3.4 nM. BMS also discovered some potent IRAK4 inhibitors such as **95** and **96** with IC_{50} values of 3 and 2 nM, respectively. Gilead reported even more potent IRAK4 inhibitors **97–100** with IC_{50} values being less than 1 nM.[151,155] Remarkably, the compounds **93–100** are built around a substituted pyridine core, which facilitates hydrogen bonding and π-π stacking interactions within the kinase active site. The presence of electron-deficient nitrogen-containing rings enhance binding affinity, whereas rigid linkers like amides or ureas help maintain optimal geometry for target engagement. Together, these features support a strong and selective binding to IRAK4, with several inhibitors demonstrating IC_{50} values in nanomolar range.

ASK1 Inhibitors

Apoptosis signal-regulating kinase 1 (ASK1) is a serine-threonine kinase that activates other kinases in response to a range of stresses like calcium overload, ROS (reactive oxygen species) stress, lipopolysaccharides and endoplasmic reticulum stress[156,157] ASK1 has been found to engage in the development of cancer, diabetes, fibrosis, neurodegenerative, and cardiovascular diseases.[158–162]

Rowbottom disclosed a group of compounds as ASK1 inhibitors. The ability of ASK1 inhibition of 141 compounds was tested using the luminescent ADP-Glo™ Kinase Assay and Myelin Basic Protein (MBP) as a substrate (Promega Corporation, Madison, WI). It was found that the picolinic acid derivatives having different R groups did not show any activity but when the nitrogen atom in the picolinic acid moiety is replaced with a C-F group together with an R group modifications (Figure 16), all of the compounds showed significant inhibitory effect with an IC_{50} < 300 nM for most compounds.[126]

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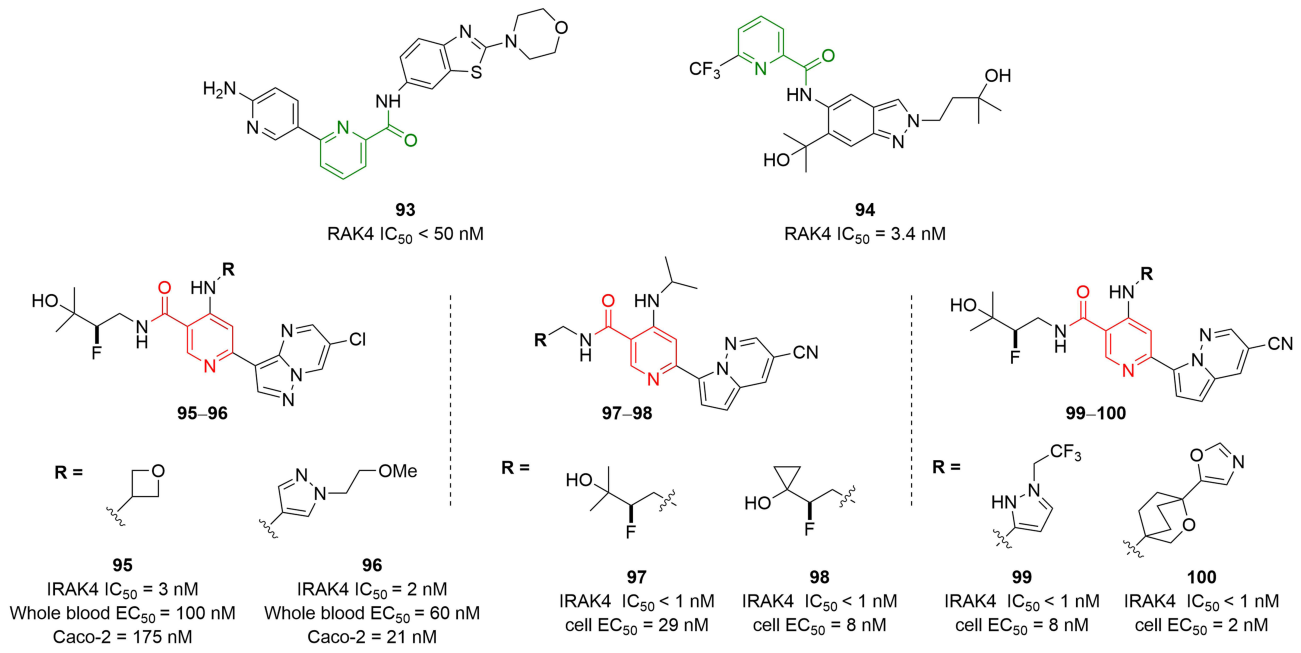

Figure 15 Structures of IRAK4 inhibitors **93**–**100**.

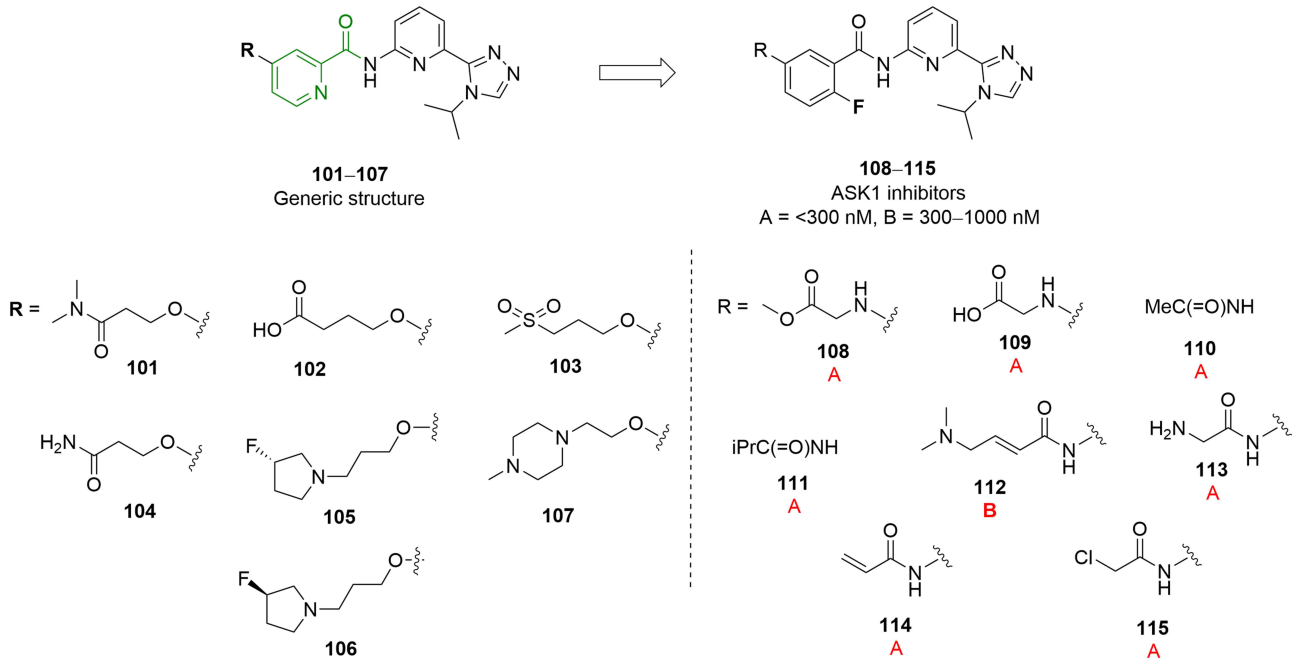

Figure 16 Structures of ASK1 inhibitors **108**–**115**.

TRPC6 Inhibitors

The superfamily of transient receptor potential (TRP) channels comprises over 28 members, which are categorized into seven subfamilies.[163,164] The transient receptor potential cation channel, subfamily C, member 6 (TRPC6) plays a multifaceted role in neuroprotection, particularly in Alzheimer's disease (AD) and cerebral ischemia. It has the potential to enhance dendritic spine formation, protect neurons from ischemic damage, and promote synaptic growth and cognitive functions.[165] However, excessive TRPC6 activity can be detrimental to various body systems, possibly contributing to conditions like breast cancer and glomerular sclerosis. The precise function of TRPC6 in AD and

ischemia is debated, with conflicting reports of reduced and increased activity.[166,167] The extensive TRP gene family is responsible for encoding transient receptor potential (TRP) proteins, which assemble into unique ion channels selectively permeable to cations. Striking a balance in TRPC6 activity is crucial for brain function preservation, emphasizing the need to investigate molecular irregularities and develop targeted pharmacological treatments.[168,169] Applications of pyridine carboxylic acid derivatives as transient receptor potential C6 (TRPC6) ion channel inhibitors for the treatment of pain, cardiac and respiratory conditions, renal disease, liver disease, ischemia or ischemic reperfusion injury, fibrotic disorders, cancer, and muscular dystrophy, have been patented (WO2019081637). To the best of our knowledge, this patent represents the only available report in the patented literature specifically describing pyridine carboxylic acid-based compounds as TRPC6 inhibitors. Considering the important role of ion channels in modulating the capacity for membrane and ion flux in cells, it is of great interest to identify agents that can promote or inhibit specific ion channels as diagnostic tools as well as potential therapeutic agents.[168] TRPC6 is one of these channels, which is part of the TRP ion channel family. It is a calcium-permeable channel, more specifically a calcium-permeable cation channel that is non-selective.[170] A range of pyridine carboxylic acid derivatives were synthesized via a multistep synthetic route and tested as TRPC6 inhibitors. The generic structure **116–129** comprising of pyridine carbonyl core is represented in Figure 17.

As described in the referenced patent (WO2019081637A1), a total of 95 pyridine carbonyl derivatives were synthesized and evaluated using Fluorescence Imagining Plate Reader (FLIPR) assay in a cell-based system that measures calcium influx as proxy for TRPC6 activity. Among these compounds **116, 117, 125, 126**, and **127** demonstrated high potency with IC_{50} values below 27 nM, while compounds **118–124, 128**, and **129** showed moderate potency (~27 Nm). Notably, these compounds displayed excellent selectivity, showing significantly weaker or no inhibitory activity against related TRP channels, including TRPC3, TRPC5 and TRPC7 as indicated in the patent's comparative selectivity profiling. These compounds can be used in a lower dosage form either alone or in combination with adjuvants that enhance the inhibitor stability, thus reducing the potential cytotoxicity and adverse side effects when used as a monotherapy. Compared to other TRP channels like TRPC3, TRPC5, and TRPC7; these pyridine carboxylic acid derivatives have very strong potency and selectivity for the TRPC6 channel and can be a good starting point for the pharmacological modulation of TRPC6.[127]

WDR5-MLL1 Inhibitors and Modulators

The protein-protein interaction between WDR5 (WD40 repeat protein 5) and MLL1 (mixed-lineage leukemia 1) is important for maintaining optimal H3K4 methyltransferase activity of MLL1.[171,172] Dysregulation of MLL1 catalytic function is relevant to mixed-lineage leukemia, and targeting WDR5-MLL1 interaction could be a promising therapeutic

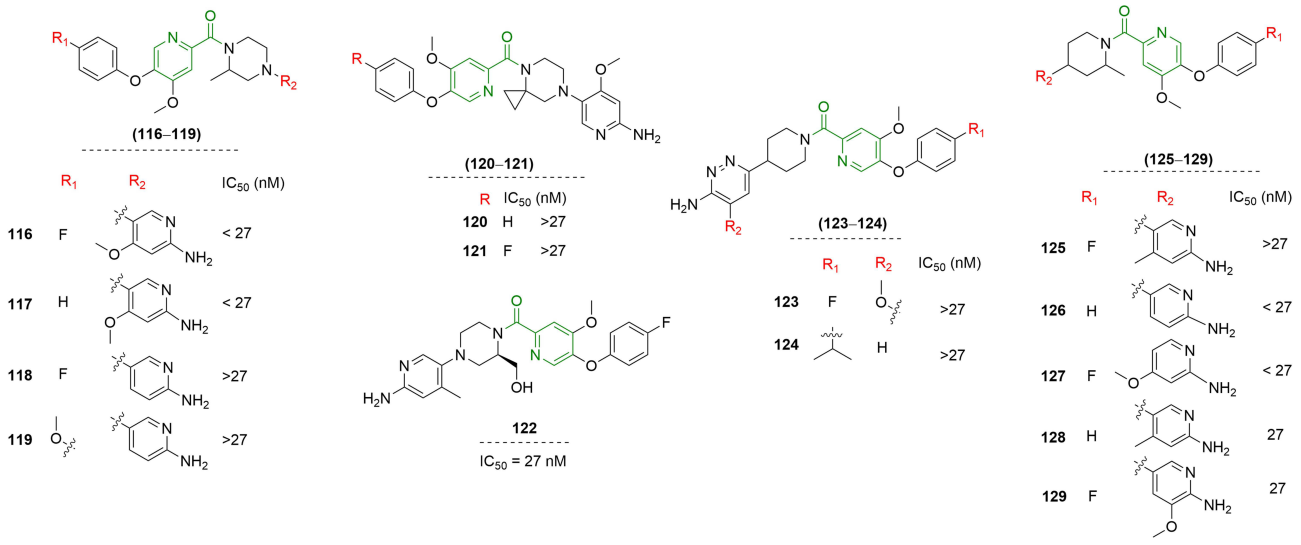

Figure 17 Structures of TRPC6 inhibitors **116–129**.

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strategy for leukemia harboring MLL1 fusion proteins.[172] In cancer research, the dysregulation of histone methylation pathways is a well-established contributor to tumorigenesis.[173–176] WDR5-MLL1 inhibitors and modulators offer a promising avenue for intervention by disrupting this crucial interaction, thereby potentially reestablishing normal epigenetic patterns and suppressing cancer progression.[174,177] Gogliotti et al disclosed an invention in a patent US 2020/0055824 A1 that relates generally to compositions comprising benzamides and picolinamides to modulate the interaction of WD repeat-containing protein 5 (WDR5) with chromatin, cognate transcription, and other regulatory factors for the treatment of solid cancers, leukemia, and other WDR5 dependent diseases. Mixed lineage leukemia (MLL) is a gene involved in the translocation of chromosomes in acute leukemia subtypes such as acute myeloid leukemia (2.8%) and acute lymphoblastic leukemia (10%).[178] Intrinsic histone methyl transferase (HMT) activity of MLL1 is extremely low and requires a complex assembly of WDR5, RbBP5, ASH2L, and DPY30 protein partners for effective H3K4 trimethylation, the so-called WRAD complex. The invention being discussed describes benzamide and picolinamides having guanidino-, imino-, or heterocycle-containing groups as their meta substituents. These compounds disrupt the WDR5-MLL1 protein-protein interaction and are extensively employed in pharmaceutical compositions, treating proliferative disorders and conditions such as cancer. Different assays such as time-resolved fluorescence resonance energy transfer (TR-FRET) assay and fluorescence polarization assay (FPA) were performed to evaluate the potential of the synthesized picolinamide derivatives **130–139** as inhibitors of WDR5. The data presented in Figure 18 demonstrates the utility of the representative compounds as selective inhibitors of the WDR5 protein to bind peptides from the relevant MLL domain. As described in the supporting patent (US10807959B2), compound **136** and **138** demonstrated strong inhibitory activity values of 0.1 nM and 0.15 nM, respectively, in the TR-FRET assay. Furthermore, the cellular viability of human tumor cell lines was determined for compounds **140–142** by examining the anti-proliferative activity using MLL harboring cell lines. Concisely, picolinamide derivatives can be an excellent choice in treating proliferative disorders and cancer, especially leukemia.[128]

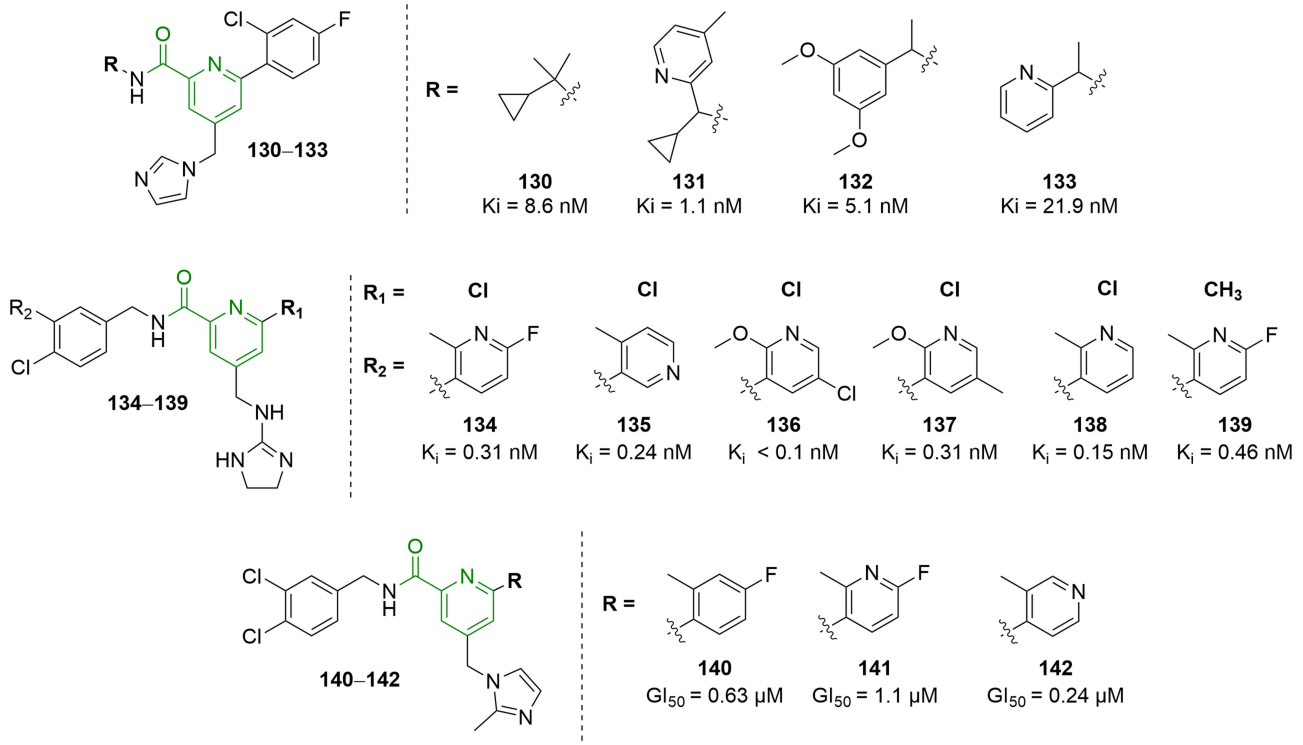

Figure 18 Structures of WDR5-MLL1 inhibitors and modulators **130–142**.

KDM4 Inhibitors

KDM4 inhibitors, a class of compounds gaining increasing attention in the field of epigenetics, target a group of enzymes known as lysine-specific demethylase 4 (KDM4), which play a crucial role in regulating gene expression by removing specific methyl groups from histone proteins.[179,180] The significance of KDM4 inhibitors extends into the field of cancer research, as dysregulated histone methylation is a hallmark of many cancer types. These inhibitors offer a promising avenue for therapeutic intervention, potentially reprogramming the epigenetic landscape to suppress tumor growth and metastasis.[181,182] Beyond cancer, KDM4 inhibitors hold promise in addressing other diseases linked to aberrant epigenetic modifications, such as neurological disorders and cardiovascular conditions.[183] As our understanding of epigenetics continues to expand, KDM4 inhibitors represent a valuable tool in the quest for targeted therapies and precision medicine, offering new possibilities for treating a wide range of complex diseases.[184]

Pyridine carboxylic acid-derived compounds are also investigated as histone demethylase inhibitors.[116,185,186] Histone lysine demethylase 4 (KDM4) catalyzes the removal of methyl marks from histone lysine residues to control chromatin structure and gene expression epigenetically.[187,188] Histone demethylase activity can be inhibited by methyllysine histone substrate mimics (Figure 19).[189] Epitherapeutics APS filed a patent disclosing histone demethylase inhibitors.[131] In AlphaLISA assays, the pyridine-4-carboxylic acid analogues **143–150** presented in Figure 20 demonstrated inhibitory activities against one or more of KDM4A, KDM4B, and KDM4C. Several of these compounds were tested in immunofluorescence assays using U2OS cells, and the representative compounds **143** and **144** were found to be potent KDM4C inhibitors (IC_{50} < 1 μM).[190] Moreover, the histone lysine-demethylase inhibitory effect of the compounds under

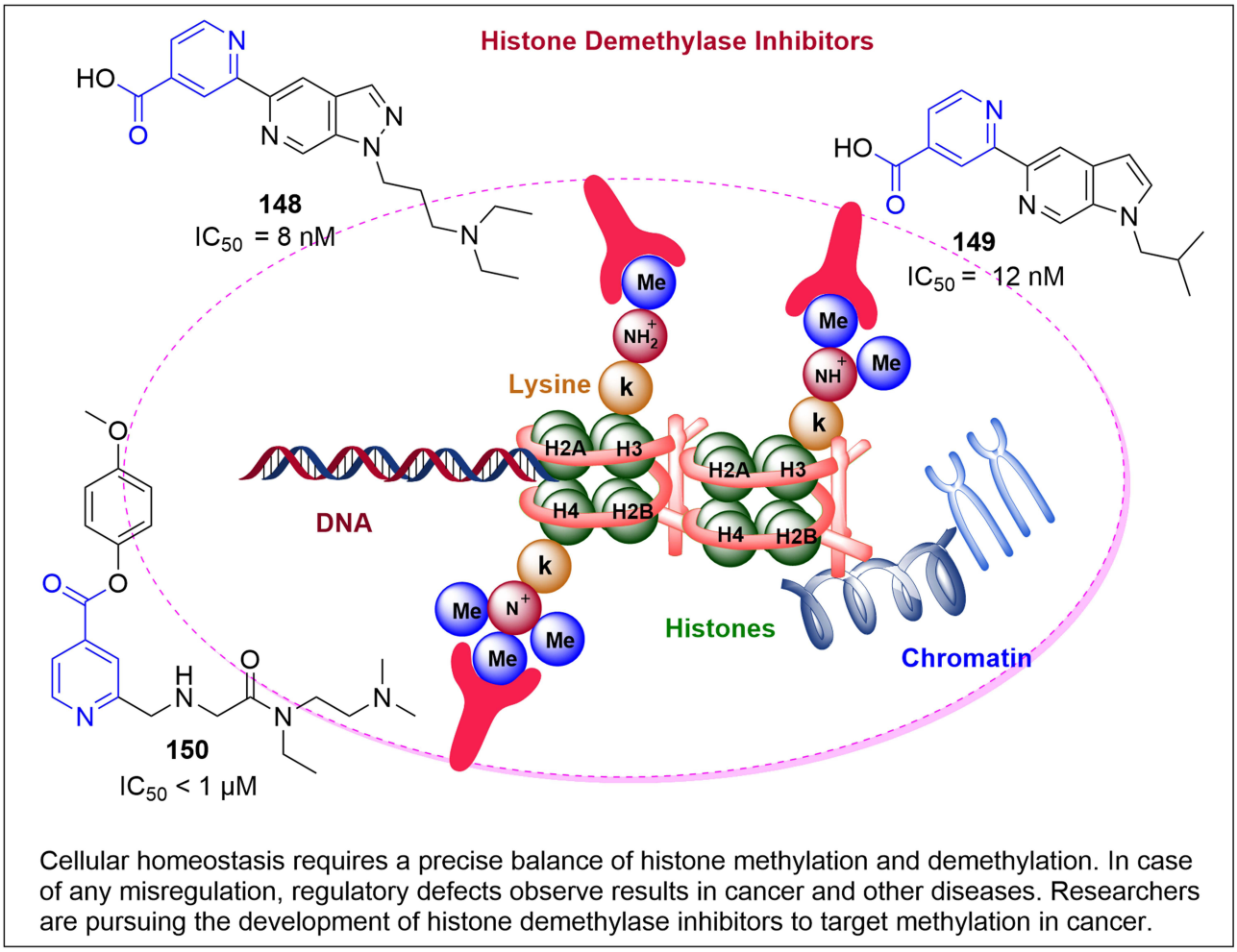

Figure 19 Mechanistic pathway of histone demethylases.

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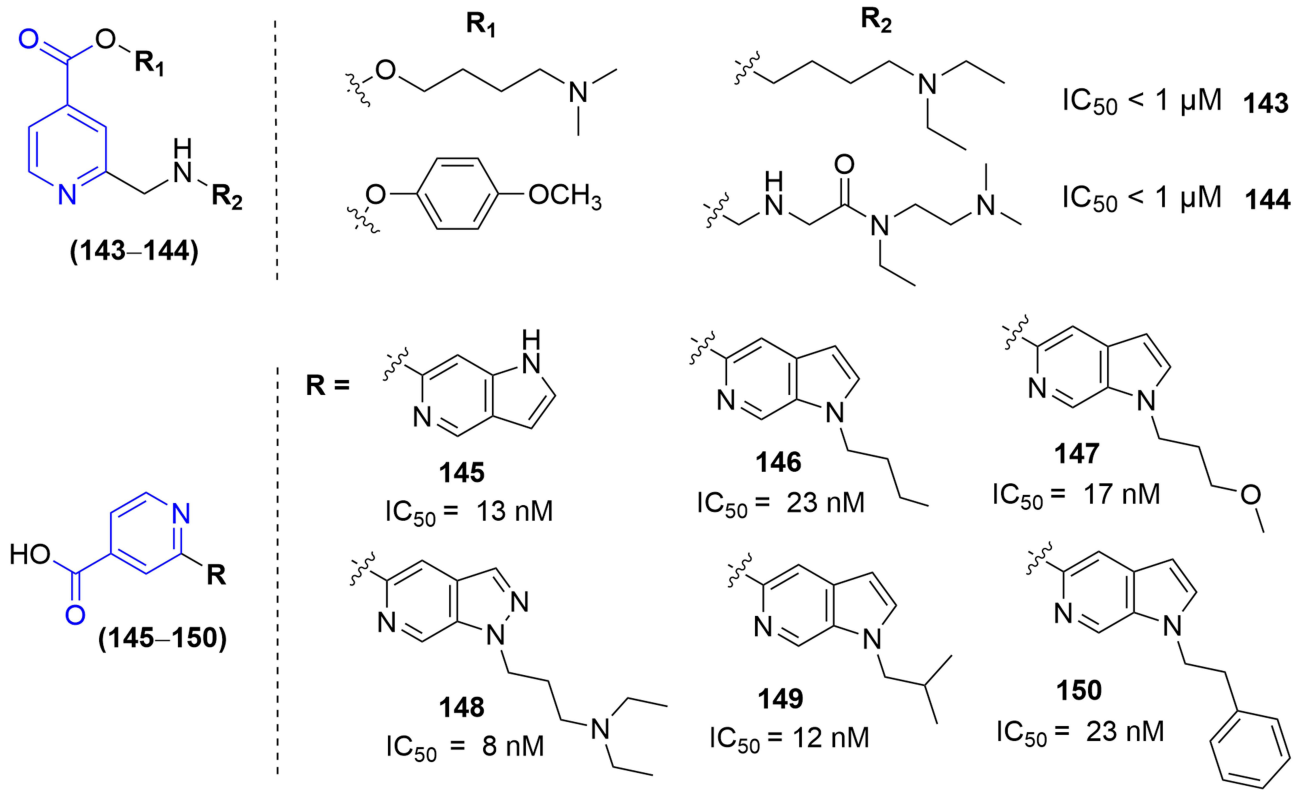

Figure 20 Structures of KDM inhibitors and modulators **143**–**150**.

discussion was tested within the cell, and global levels of tri-methylation on lysine 4 of histone 3 (H3K4me3) were assessed by Western blot in the breast cancer BT474 cell line. Compounds with different R groups exhibited strong biochemical KDM inhibitory as well as cellular activity against all cell lines tested below 100 nM concentration. The structures of the most potent JmjC-KDM inhibitors are displayed in Figure 20. In brief, it is suggested that the use of compounds **145–150** in therapeutically effective amounts, may help treat diseases associated with JmjC-KDM inhibitors as anticancer and antiviral agents.[130]

The ability of pyridine carboxylic acid-derived compounds enclosed in patent WO 2018/149986 A1 to inhibit the activity of KDM5B was determined by employing AlphaLISA technology in vitro using human recombinant proteins. For the determination of IC_{50} values, the patented inhibitors were tested at eight logarithmic serial dilutions. The invention also relates to pharmaceutical compositions comprising these compounds and to use in cancer therapy. The tested compounds **151**–**159** showed IC_{50} in the range of 1–3 nM, see Figure 21. [130]

A patent application WO2010043866 disclosed a series of pyridine-2,4-dicarboxylic acids for their inhibitory activities against JMJD2E in the FDH-coupled demethylase assay. Among the tested compounds, pyridine-2,4-dicarboxylic acid (**160**), 3-(4-methoxybenzylamino)pyridine-2,4-dicarboxylic acid (**161**), 3-(2-fluorophenyl amino)pyridine-2,4-dicarboxylic acid (**162**), 3-(o-tolylamino)pyridine-2,4-dicarboxylic acid (**163**), and 3-(2-aminophenylamino)pyridine-2,4-dicarboxylic acid (**164**) (Figure 22) showed quite potent inhibition with IC_{50} values of 1.4, 0.3, 1.1, 7.9, and 0.6 μM, respectively. Another test was conducted on 2,2-bipyridyl derivatives (heteroaryl derivatives, cofactor disruptor) in the FDH coupled inhibition assay and the non-denaturing MS binding assay. The compounds (**165**–**170**) in Figure 22, showed strong binding affinity and IC_{50} values of 6.6, 1.5, 3.6, 3.8, 4.5, and 8.0 μM, respectively.[190]

In 2014, Quanticel Pharmaceuticals, Inc. filed a patent application WO 2014/100463A1 that described the substituted aminopyridine derivatives (**171–176**) and their pharmaceutical compositions as inhibitors of histone demethylase for treating cancer and neoplastic diseases are shown in Figure 23. Most of these compounds induced complete tumor regression via an in vivo approach. The compounds were tested to inhibit JARID1A, JARIDlB, and JMJD2C

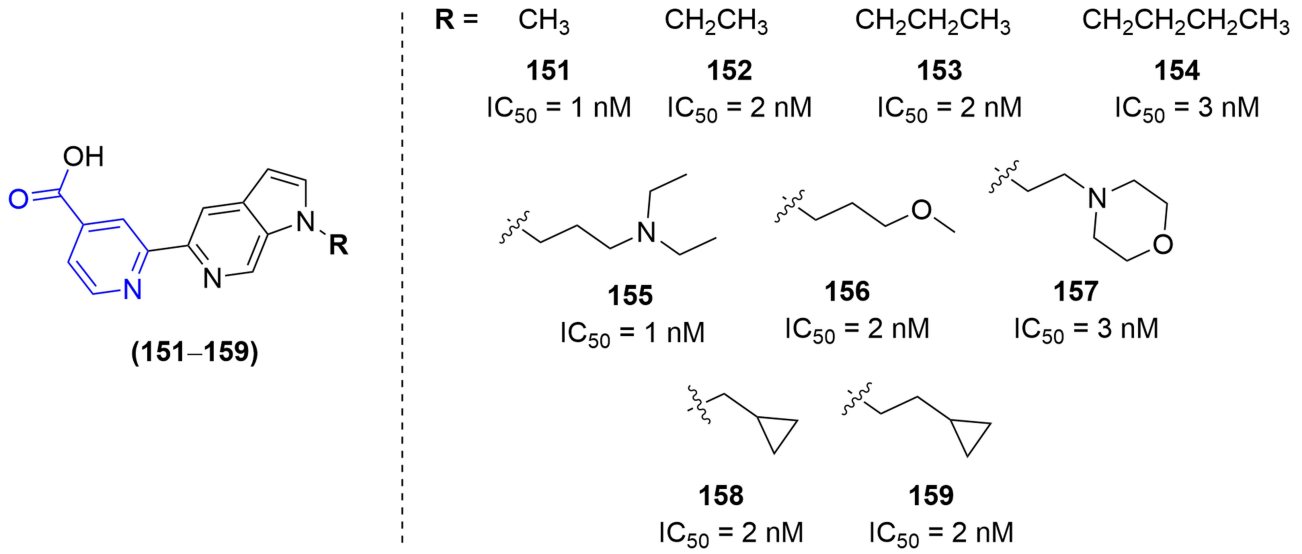

Figure 21 Structures of KDM 5 inhibitors and modulators **151**–**159**.

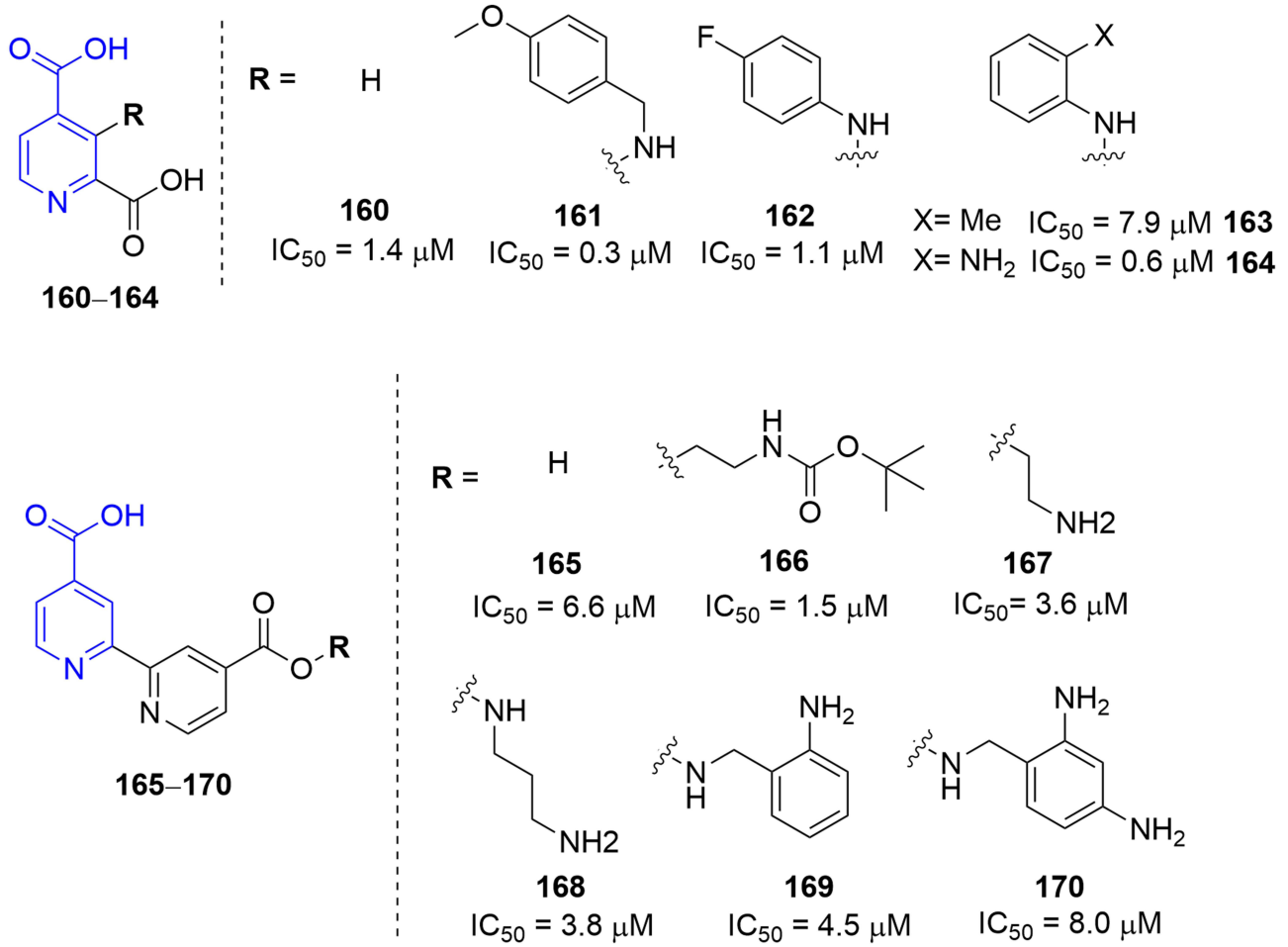

Figure 22 Structures of KDM inhibitors and modulators **160**–**170**.

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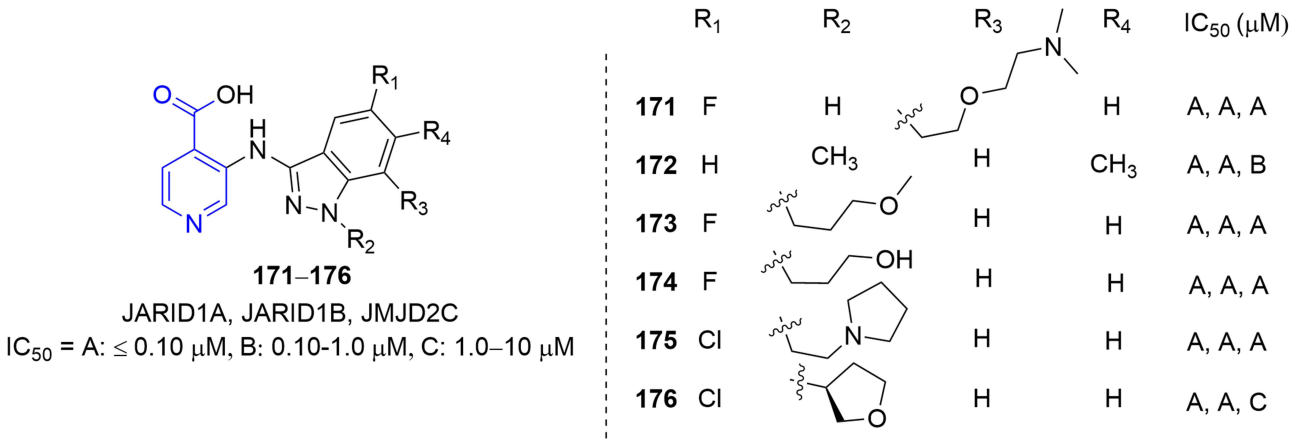

Figure 23 Structures of KDM (JARID 1A, JARID 1B, JMJD2C) inhibitors and modulators **171–176**.

demethylase activity in vitro employing time-resolved-fluorescence resonance energy transfer (TR-FRET) detection method. Most of the compounds were found to be active and inhibited the activity of a demethylase comprising of a JmjC domain (eg, a histone demethylase such as a JHDM protein) with low IC_{50} values (≤ 0.10 μM). The decrease in JARID1B is connected to a rise in tri-methylated H3K4 levels within tumor suppressor genes. The quantification of tri-methylated histone H3 and cellular inhibition of KDM5A and 5B, was done on ZR-75-1 breast cancer cell line via immuno-blotting assay. The subsequent IC_{50} values from these cellular assays revealed a correlation between the degree of inhibition of these enzymes in cancer cell lines and the degree of inhibition of these enzymes in a biochemical assay. To further support this claim, the most active compounds were subjected towards in vivo xenographic evaluation into nu/nu mice model. Most of the compounds had an overall favorable profile. In addition, such compounds have the advantage of being fairly soluble in water as well as stable in vivo; a characteristic not frequently shared by most synthetic derivatives. Since they exhibited specific inhibitory potential toward histone demethylases; it has been suggested that they can serve as an effective tool to regulate the modulation of demethylation in a cell, either generally or with respect to one or more specific target genes.[132]

Quanticel Pharmaceuticals, Inc. submitted a follow-up patent application WO 2015/200709A1 to their 2014 patent application WO 2014/100463A1. The generic structure for compounds **177–194** is given in Figure 24. Screening of these compounds for histone demethylase inhibitory activity was carried out using enzymatic and cellular inhibition assays. The results disclosed a number of substituted pyridine carboxylic acid derivatives as in vitro selective histone demethylase enzyme inhibitors with IC_{50} values in the sub-nanomolar range for cancer prevention and treatment of neoplastic disease. The enzymatic assays were performed to inhibit JMJD2C activity based upon time resolved-fluorescence resonance energy transfer (TR-FRET) detection. The human KYSE-150 (SMAD4 mut, TP53 mut) esophageal carcinoma cell line was used to test cell proliferation by in vitro cell-based assay. The IC_{50} values of cellular proliferation were found typically lower than 0.10 μM. The most potent inventive compounds were further evaluated for in vivo xenograft study using MCF-7 cells. The subsequent results provided the compounds with good to excellent oral bioavailability and pharmacokinetic profiles as highly active and selective histone demethylase inhibitors.[133]

WO2022/047230A1 patented by Fibrogen. Inc included 142 pyridine carboxylic acid derivatives (see representative structures of **195**–**227**, Figure 25). Among them, 139 compounds are pyridine-2-carboxylic acid derivatives with different R groups and the remaining three compounds (**199**–**201**) are pyridine-4-carboxylic acid derivatives. All these derivatives were tested for the inhibition of KDM5B and KDM4A. All pyridine-2-carboxylic acid derivatives showed pronounced inhibition against KDM5B with IC_{50} < 1.0 μM. Three pyridine-4-carboxylic acid derivatives showed weaker inhibition with IC_{50} of 1.4 and 2.0 μM. Among all compounds, only some of them displayed moderate inhibition against KDM4A with IC_{50} < 40 μM.

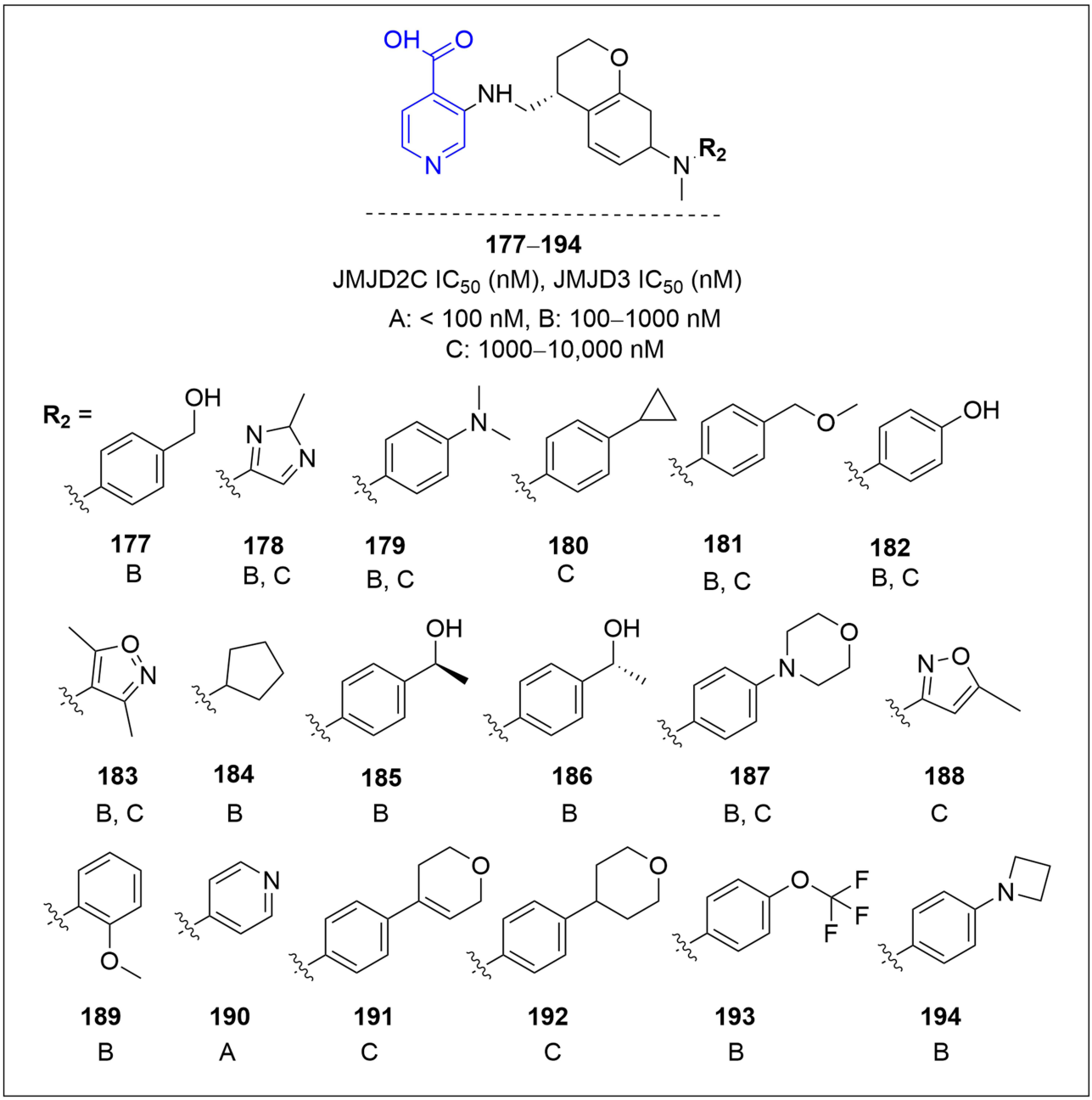

Figure 24 Structures of KDM inhibitors and modulators **177–194**.

Gilead Sciences, Inc. filed a patent (US 2018/0042905A1) disclosing an invention that relates to novel methods of treating Hepatitis B virus (HBV) by administering KDM5 inhibitors. The most auspicious compounds **228–235** (Figure 26) mentioned in the invention are listed in Table 2 with a summary of their HBV antiviral activity. The data in the patent leads us to the conclusion that pyridine carboxylic acid derivatives can be considered promising lead molecules for the development of new antiviral drug candidates for lifelong therapy of HBV.[191]

High concentrations of sub-viral particles (SVPs) with HBV surface antigen (HBsAg) in chronic HBV infection are a significant obstacle to effective immune responses. Despite significant advances in HBV treatment, only a small percentage of patients achieve the ideal goal of "functional cure", which is characterized by hepatitis B surface antigen (HBsAg) loss. More specifically, sustained loss of HBsAg is significant because it is linked to better long-term outcomes.

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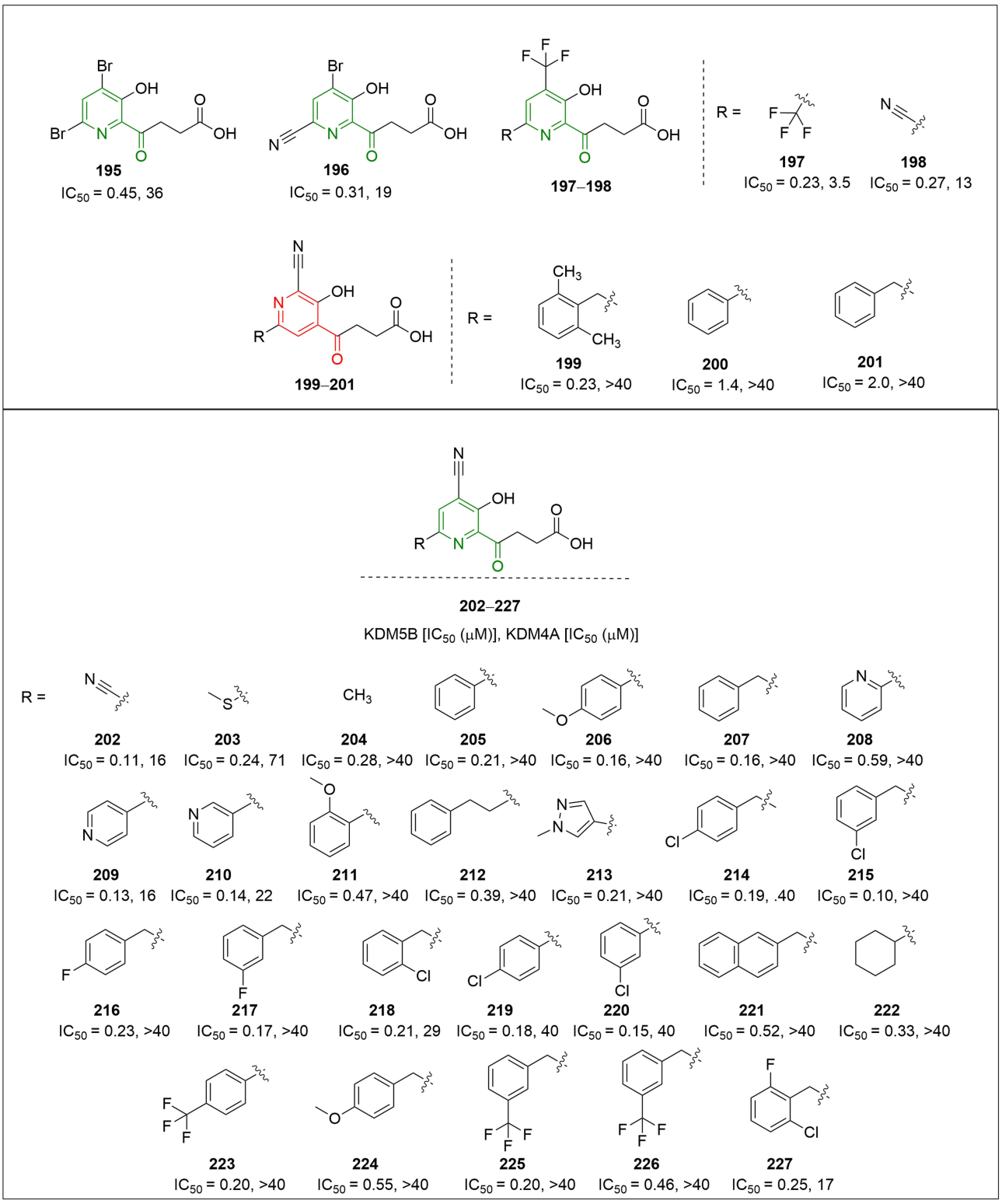

Figure 25 Structures of KDM inhibitors and modulators from WO2022/047230A1 (**195**–**227**).

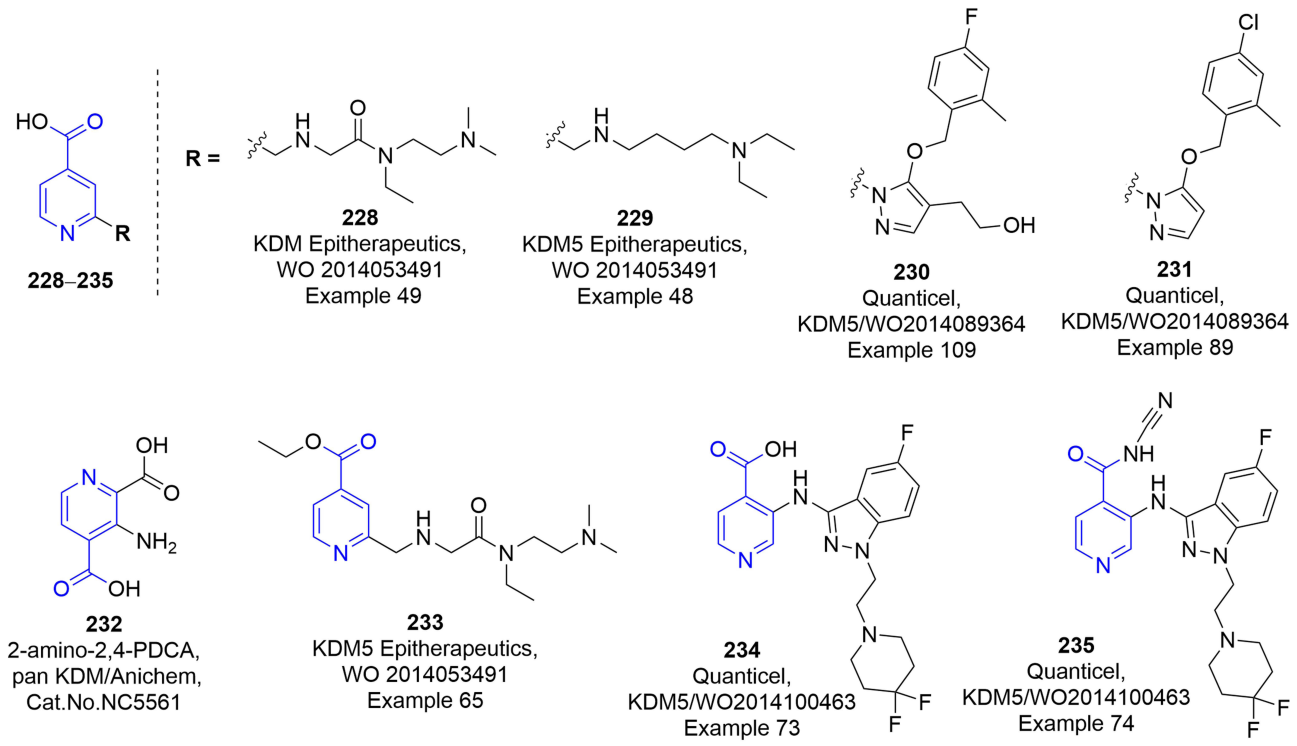

Figure 26 Structures of KDM inhibitors from US 2018/0042905 A1 (**228**–**235**).

HBV surface antigen (HBsAg) is a major obstacle that provides direct evidence in the timing of the decision to discontinue treatment and start off-therapy retreatment during antiviral therapies.[192,193]

3HAO Inhibitors

As an enzyme of the kynurenine pathway, which is directly responsible for the conversion of 3-hydroxyanthranilic acid into quinolinic acid (QUIN), through the intermediate formation of a semimuconic aldehyde and its subsequent non-enzymatic cyclization, 3-hydroxyanthranilate-3,4-dioxygenase (3HAO) is potentially involved in a series of neurodegenerative disorders and diseases, such as Huntington's disease, Alzheimer's disease, HIV-related dementia, and cerebral ischemia. As reported in the supporting patent (WO2012097869A1), compounds **236**–**238** (Figure 27) demonstrated 3HAO inhibition in rat brain homogenates, showing inhibition of 49%, 22%, and 78% at 10 μM, and 90%, 76%, and 97% at 100 μM, respectively. In human brain homogenates, the same compounds showed 66%, 42%, and 80% inhibition at 10 μM, and 93%, 100%, and 100% at 100 μM, respectively.

Table 2 HBV Antiviral Activity (EC_{50}, μm) of Compounds 228–235

Compounds	HBsAg	HBeAg	HBV RNA	PHH
228	2.024	1.631	–	50.00
229	1.298	1.090	–	50.00
230	0.481	0.642	0.224	100.00
231	4.049	5.771	–	50.00
232	19.502	22.632	–	–
233	0.0667	0.188	0.100	28.231
234	50.00	50.00	–	50.00
235	3.984	5.968	–	50

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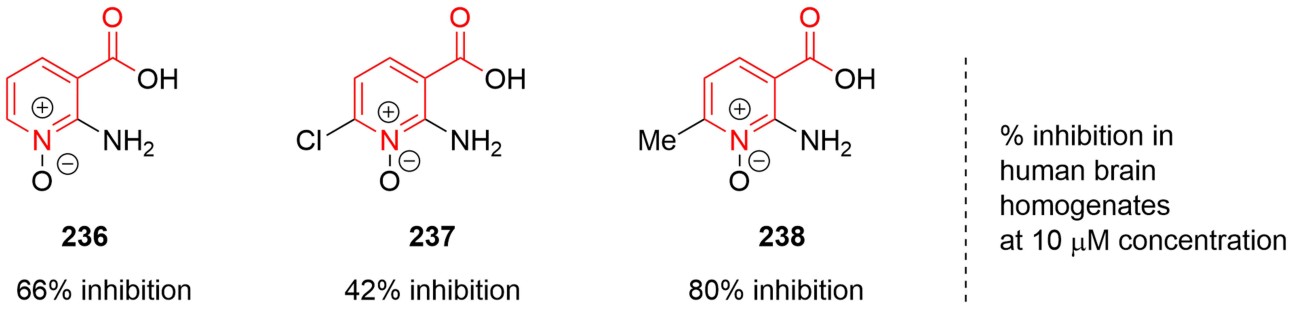

Figure 27 Structures of 3HAO inhibitors **236**–**238**.

PDGFR Selective Inhibitors

Pyridine carboxylic acid derivatives have also been reported as selective platelet-derived growth factor receptor (PDGFR) inhibitors to treat pulmonary arterial hypertension (PAH). Studies in animal models have revealed that PDGF appears to play a significant role in vascular remodeling.[194] Both PDGFRα and PDGFRβ receptors are associated with specific receptor tyrosine kinases. Inhibiting PDGFR kinase has been proposed as an additional therapeutic modality, and this hypothesis appears to be validated by clinical studies with the non-selective PDGFR inhibitor imatinib.[195] However, the adverse effects linked to a lack of selectivity imply that clinical utility requires the identification and development of selective PDGFR inhibitors.[196] Recently compound **239**[197] (PK-10453) has been described as a non-selective PDGFR inhibitor. PK-10453 inhibits PDGFRα and PDGFRβ with respective IC_{50} values of 10.1 and 35 nM. On the other hand, NOVARTIS AG specifically claims the crystalline form of PDGFR inhibitor **240** which is also a pyridine carboxylic acid-derived compound and is considered even more potent and selective than either imatinib or PK-10453 with IC_{50} of 3.0 nM.[135] It is possible that Novartis intends to develop compound **240**[196,198] for the treatment of PAH.[196] The structures of **239** and **240** are given in Figure 28.

Trk Inhibitors

Activation of the Tropomyosin-receptor-kinase (Trk) A/B/C receptor promotes growth, survival, and differentiation of discrete neuronal populations during development, adult life, and aging. It also plays a role in the emergence and progression of human disease. Trk-specific inhibitors have therapeutic applications in cancer and pain, making them a burgeoning field of study in oncology and neurology. Pyridine carboxylic acid core-containing compounds are reported as Trk Inhibitors. The compounds **241**–**243**[199,200] with fluorination at position 3 of the piperidine ring are prominent and showed marked potency with IC_{50} values of 1.7, 1.3, and 1.5 nM respectively, except compound **244** having 3R,4R stereo configuration with adjacent ether, decreases potency depicted from IC_{50} value (12.3 nM) (Bailey, Schirrmacher, Farrell, and Bernard-Gauthier, 2017; WO 2015/092610 Al, 2015). In another short publication, pyrrolidine analogs were

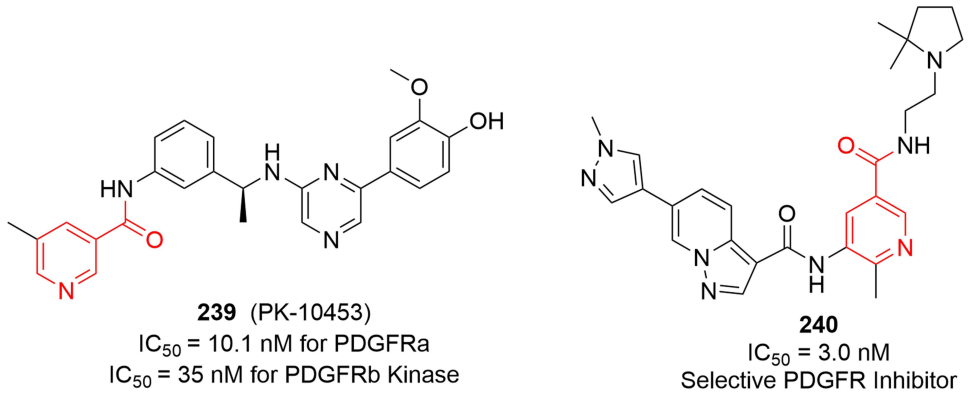

Figure 28 Structures of PDGFR inhibitors **239** and **240**.

described, which utilized a 6-aminonicotinamide hinge binder adorned with a variety of amide substitutions. Compounds **245** and **246** in this series are presented as sets of enantiomers and trend for a preference of the (R)-enantiomer **245** with IC_{50} of 11.6 nM.[201] The compounds **241–246** are illustrated in Figure 29.

FABP Inhibitors

Numerous studies show that excessive free fatty acid (FFA) is the pathogenic factor for a wide range of disorders such as atherosclerosis, obesity, hypertension, and metabolic syndrome. These are diseases that synergistically compromise human health. Fatty acid binding proteins (FABPs) are in charge of transporting FFA from cytoplasm to different cellular organelles like mitochondria, nucleus, peroxisomes, lipid droplets, and ER (endoplasmic reticulum), and thus play a pertinent role in cellular functions as depicted in (Figure 30). As a result, developing and employing FABP inhibitors could be a viable strategy for controlling atherosclerosis, obesity, diabetes, and metabolic syndrome in humans.[68] William W. Bachovchin et al disclosed pyridine-3-carboxylic acid derivatives (niacin) as FABP inhibitors in their two patents.[68,137] The derivatives included the representative compound **247** as shown in Figure 31. Compound

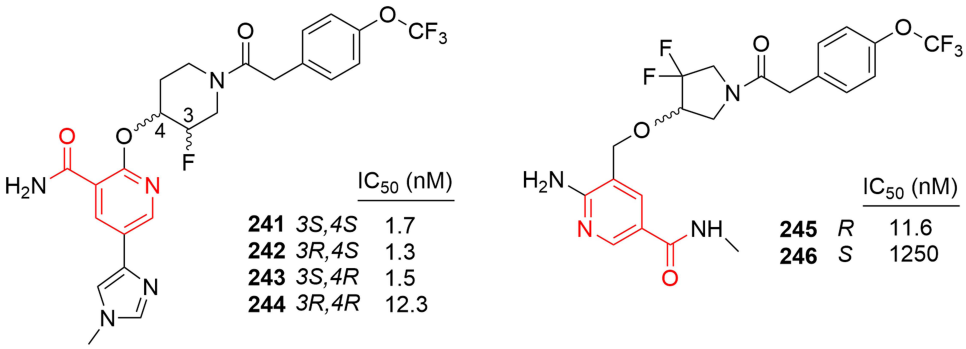

Figure 29 Structures of Trk inhibitors **241–246**.

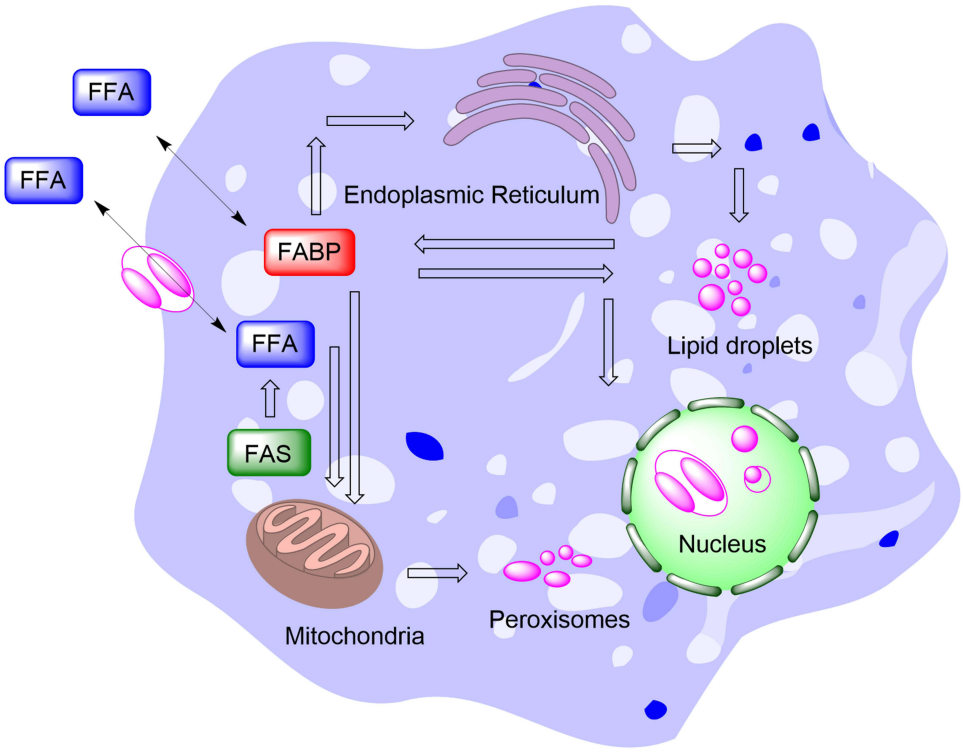

Figure 30 Intracellular transport of free fatty acid (FFA).

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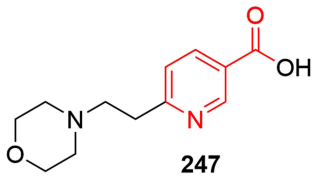

247

	TC (mg/dL) ± SD	HDL (mg/dL) ± SD	LDL (mg/dL) ± SD
Niacin (1200 mg/Kg)	552 ± 183	79 ± 26	170 ± 52
272 (1120 mg/Kg)	653 ± 194	142 ± 34	253 ± 91

Liver	ABCA1	Liver Apo AI
vehicle	1.02 ± 0.18	1.04 ± 0.28
Niacin (1200 mg/Kg)	0.80 ± 0.18	1.17 ± 0.19
272 (2240 mg/Kg)	1.54 ± 0.48	1.72 ± 0.24

Figure 31 Structure of FABP inhibitor **247**.

247 displayed a significant effect on lipid modulation by chronic administration of compounds compared to niacin in a hamster model. The concentrations of LDL (low-density lipoprotein) and total cholesterol in compound 272-treated trials are at least 1.67 and 1.54 times greater than those in the niacin trials. Additionally, the HDL (high-density lipoprotein) is noticeably higher in the compound 40 trace, in addition to the VLDL and LDL being significantly reduced. Meanwhile, when treated with compound **247**, both ABCA1 and ApoAI mRNA levels were higher in the compound **247**-treated animals relative to vehicle control animals. Therefore, Compound **247** could be used to develop new drugs to treat FABP-related disorders and metabolic syndrome. Because of their significant impact on the liver, niacin derivatives are also thought to target FABP4.[68] Although niacin has been linked to liver toxicity[202] and glucose intolerance in chronic dose settings, certain chemical modifications could avoid these side effects. In brief, pyridine-3-carboxylic acid derived-compounds could be good candidates for the development of new FABP inhibitors to treat various ailments.[10,203,204]

FXIa Inhibitors

The most common medications used to prevent and treat thrombotic disorders are anticoagulants. Each anticoagulant used in clinical practice is linked to serious adverse effects, particularly bleeding. It has been proposed that Factor XIa (FXIa), a crucial factor involved in the amplification of the procoagulation signal, is a primary target for the development of anticoagulant drugs.[138] The importance of pyridine carboxylic acid derived compound as FXIa inhibitor can be estimated from the fact that aryl boronic acid **249** (IC_{50} = 1.4 μM) having pyridine carboxylic acid core reported to show better FXIa active site inhibition as compared to its precursor **248** (IC_{50} = 7.3 μM) deprived of pyridine carboxylic acid core. The compound **249** has also much better selectivity than **248**. It was observed that S enantiomer of compound **249** was bound in active site assuming that only S enantiomer was found active against FXIa.[138,205] A review by Al Horani also discusses FXIa inhibitors in detail. Among these compounds was pyridine carboxylic acid derivative **250** with FXIa IC_{50} of 20 nM.[206] Furthermore, Bayer Pharma, Germany, filed several patent applications in 2015, disclosing phenyl alanine derivatives as FXIa inhibitors for the prophylaxis of various ailments related to cardiovascular disorders and thrombotic diseases. One of the interesting phenyl alanine derivative **251** having pyridine carboxyl moiety is reported as FXIa inhibitor with IC_{50} of 0.9 nM and the concentration required to double the clotting time was reported as 0.08 μM in APTT assay.[138] The structures of compounds **248–251** are shown in Figure 32.

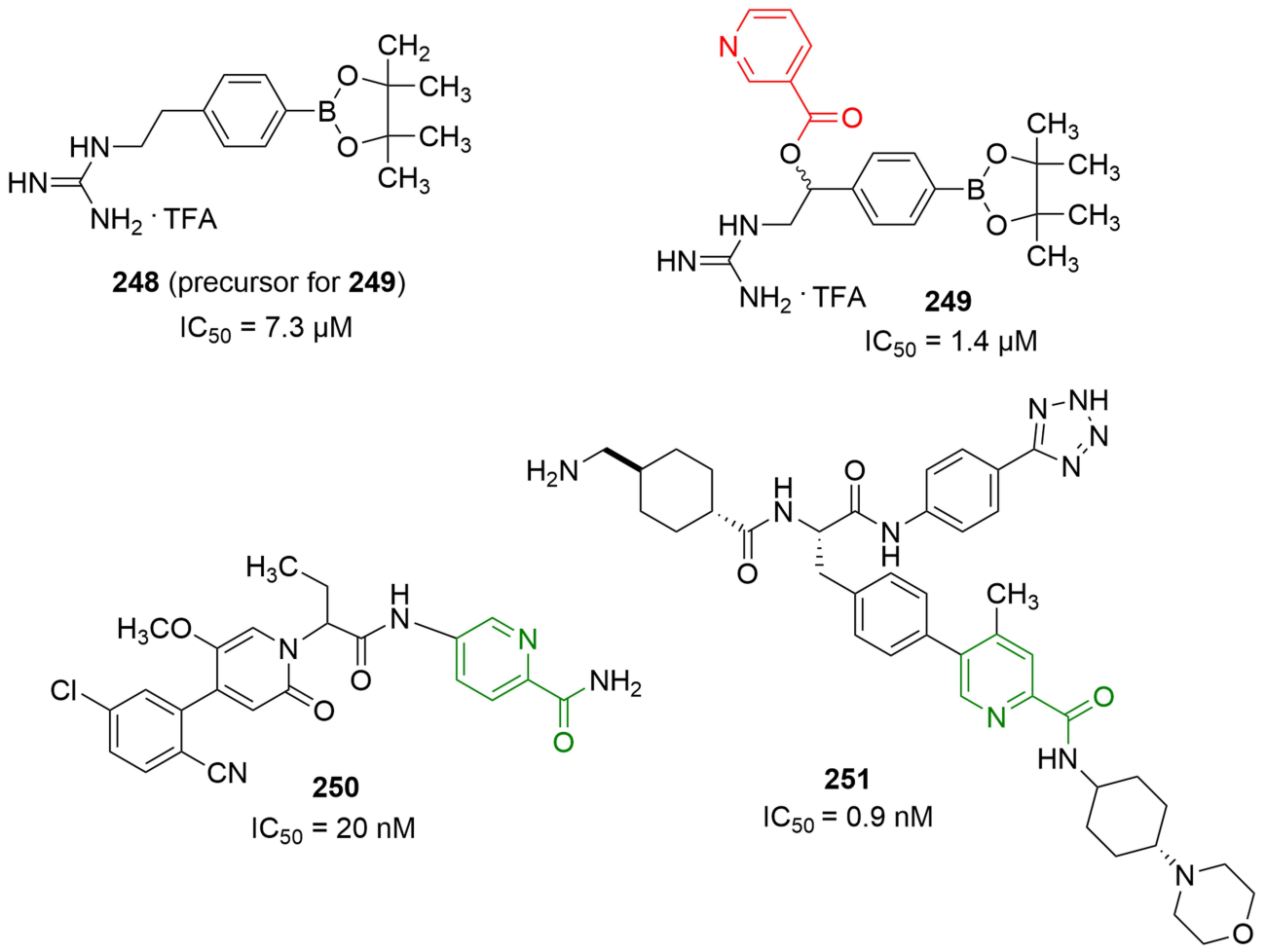

Figure 32 Structures of FXIa inhibitors **248**–**251**.

TGFβ Inhibitor

Transforming Growth Factor Beta (TGFβ) is a multi-functional cytokine, which is involved in numerous biological processes including cell growth, differentiation, immune regulation, fibrosis, and cancer progression. TGFβ inhibitors are being explored for cancer, fibrotic diseases, autoimmune and inflammatory conditions. Sistla et al disclose a patent unveiling novel crystalline polymorphic and amorphous form of 4-(2-(5-chloro-2-fluorophenyl)-5-isopropylpyridin-4-ylamino)-N-(l,3-dihydroxypropan-2-yl) nicotinamide **252**[207,208] (Figure 33) known for treating abnormal cell growth, such as cancer, in mammals by acting as a potent and selective TGFβ inhibitor.[139]

$Na_v1.8$ Inhibitors

Novel derivatives of 2-Amino-N-heteroaryl-nicotinamides as $Na_v1.8$ inhibitors were disclosed in patent WO 2020/092667 A1. Voltage-gated sodium ion channel ($Na_v1.8$) is thought to be involved in a variety of diseases such as inflammatory pain, neuropathic pain, chronic itch disorders, etc. The importance of $Na_v1.8$ is summarized in Figure 34.

The potency of the patented compounds was assayed using a patch clamp assay, and human $Na_v1.8$ and $Na_v1.5$ channels were stably expressed in human embryonic kidney (HEK) 293, and their inhibition was measured as a function of drug concentration by an offline analysis. Finally, 218 compounds were evaluated for their $Na_v1.8$ channel activity, the majority of which inhibited the flow of sodium through human $Na_v1.8$ and $Na_v1.5$ channels with IC_{50} values in the single-digit nanomolar range. The presence of a halogen substituent plays an important role in the $Na_v1.8$ activities of this series, particularly when it is located in an ortho-position. The compound **258** 5-chloro-2-(4.4-difluoroazepan-l-yl)-

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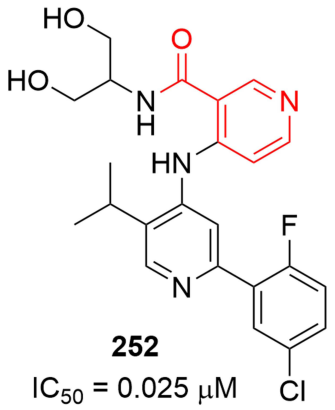

252

IC_{50} = 0.025 μM

Figure 33 Structures of TGFβ inhibitor **252**.

Figure 34 Importance of $Na_v1.8$ inhibitors.

6-methyl-N-(2-sulfamoylpyridin-4-yl) nicotinamide having chloro and methyl substitution at the nicotinamide moiety, exhibited an IC_{50} of 0.3 nM against $Na_v1.8$ channels employing a 1 hertz pulse train stimulation. Compounds **253**–**257** and **259**–**264** also showed significant activity (Figure 35). It is speculated that these compounds may be beneficial in the prevention, treatment, or management of cough, pain, acute itch, and chronic itch disorders. It was suggested by the

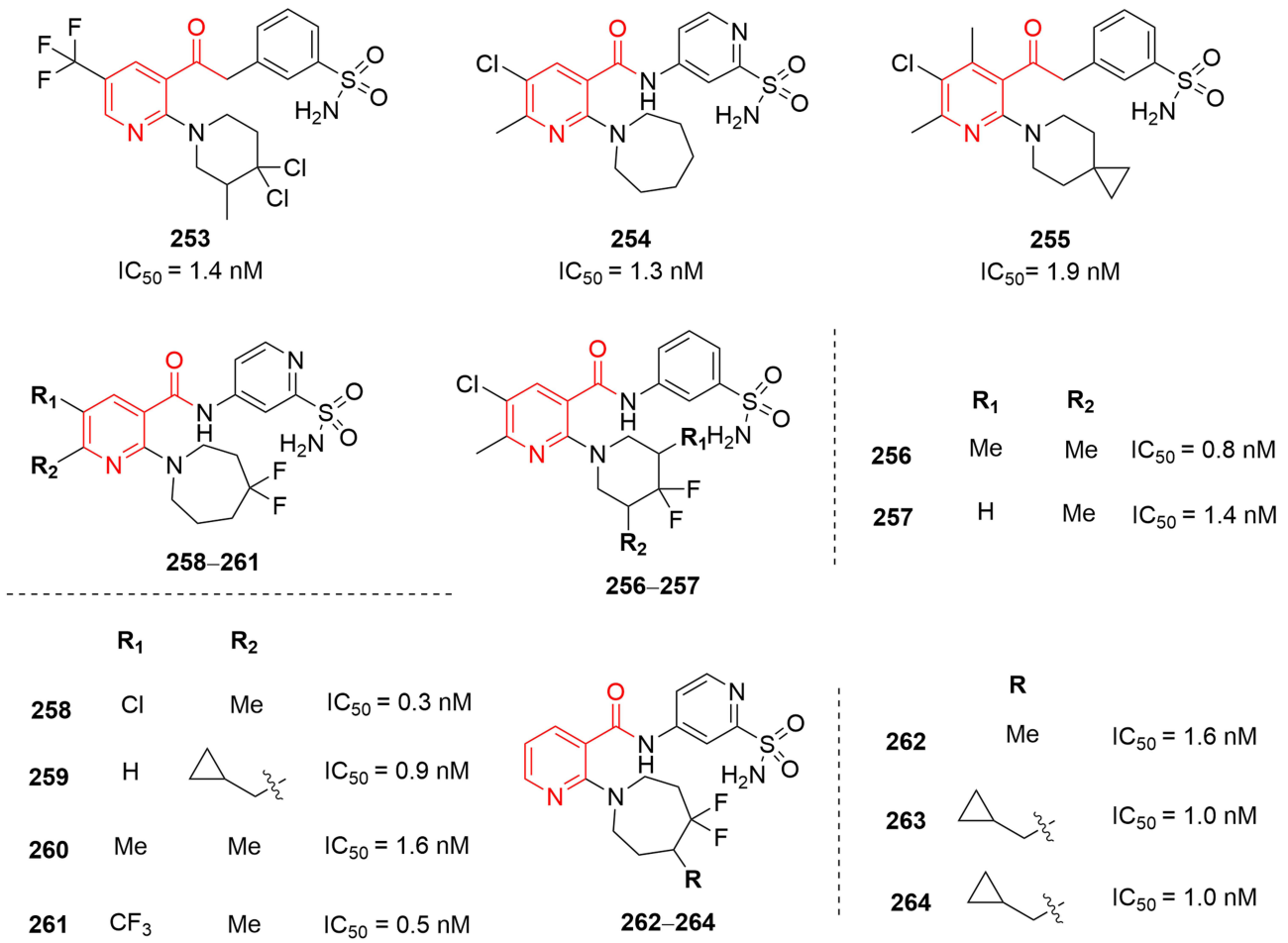

Figure 35 Structures of Nav1.8 inhibitor **253–264**.

inventor that the inhibitory effect of these compounds is dependent on halogen substituents; particularly, the presence of a fluoro group increases the activity in comparison to other groups. As part of a pharmaceutical preparation, these compounds can be used alone or in conjunction with a well-known analgesic.[140]

DHODH Inhibitors

Dihydroorotate dehydrogenase (DHODH) inhibitors act upon dihydroorotate dehydrogenase, thereby hindering pyrimidine biosynthesis.[209] This inhibition disrupts DNA and RNA synthesis in rapidly dividing cells, making them promising for cancer and autoimmune disease therapies by suppressing immune cell proliferation.[210,211] Pyridine carboxylic acid derivatives are also known for their dihydroorotate dehydrogenase (DHODH) inhibitory activity. DHODH inhibitors have demonstrated their effectiveness in treating a variety of diseases.[209] Despite extensive efforts to develop DHODH inhibitors, no FDA approval has yet been obtained.[212] Julio Cesar et al described the use of new amino derivatives of nicotinic and isonicotinic acid as inhibitors of the DHODH. The amino(iso)nicotinic acid derivatives were conveniently synthesized as described in Scheme 1. These compounds were subjected to human DHODH activity using a chromogen reduction assay with DCIP (2,6-dichlorophenol indophenol) to observe the inhibition effect.

The most significant feature observed for effective DHODH inhibitory activity is their substitution pattern on phenyl ring with flouro or trifluoromethyl group. These compounds **265–272**[213] were proved as potent DHODH inhibitors with IC_{50} values in a range of 3–8 nM (Figure 36). In addition to efficient inhibition of DHODH, the amino derivative of nicotinic and isonicotinic acid in the patent being discussed, also inhibits the proliferation of cells with a high turnover rate, particularly in lymphocyte cells. In conclusion, these patented amino (iso)nicotinic acid derivatives and their

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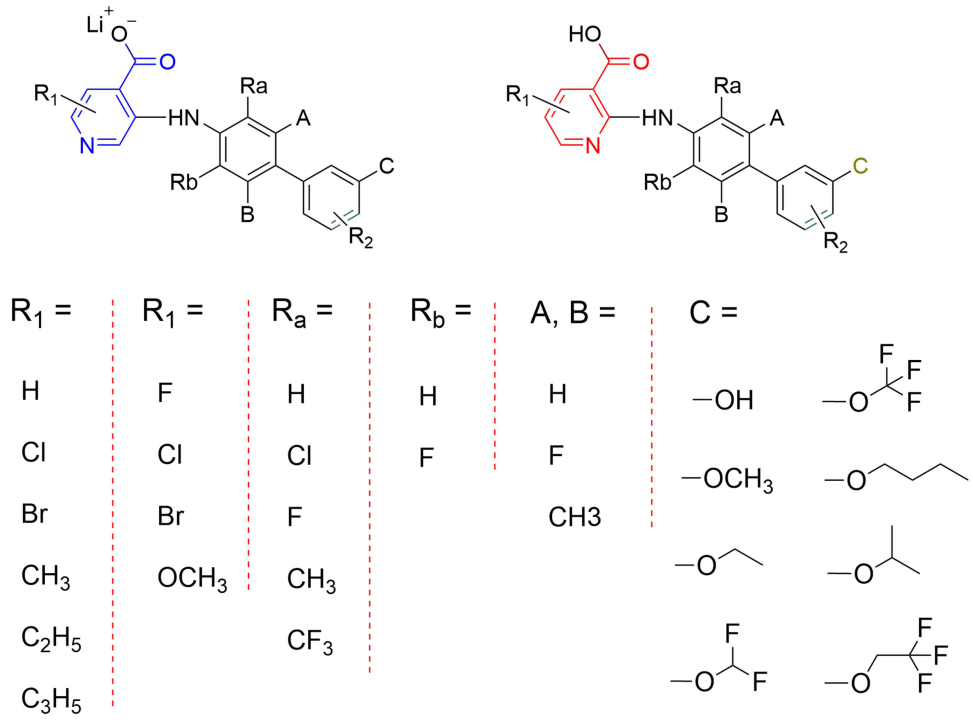

Scheme 1 General structures of amino nicotinic and isonicotinic acid derivatives as DHODH inhibitors.

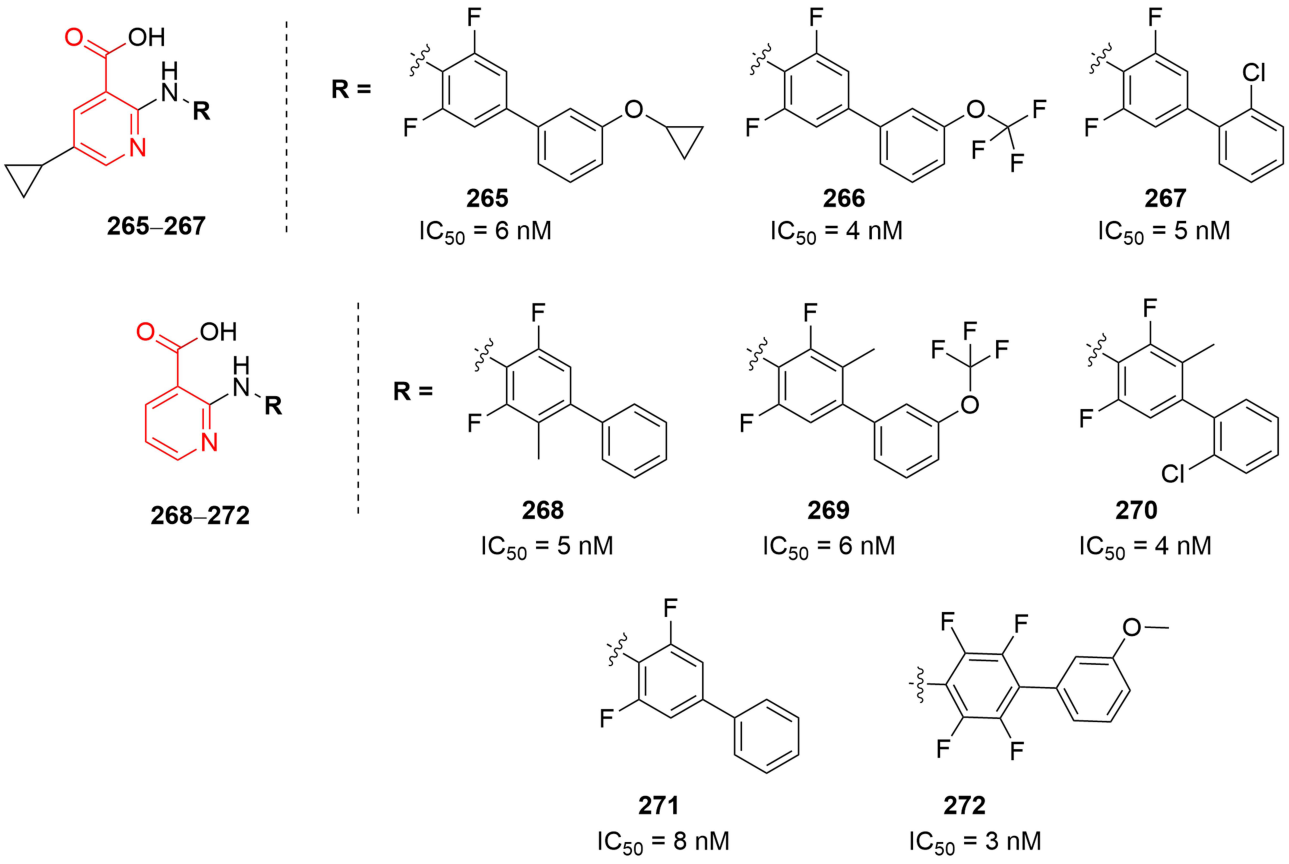

Figure 36 Structures of DHODH inhibitor **265**–**272**.

pharmaceutical compositions have been found useful for the diagnosis, prevention, or suppression of diseases and disorders that are susceptible to improvement by treatment with inhibitors of dihydroorotate dehydrogenase. Such diseases include autoimmune diseases, immune diseases, malignant neoplastic diseases, destructive bone disorders, angiogenic-related disorders, infectious, inflammatory, and viral diseases. This discloser also describes the dosage formation and pharmaceutical preparation methods of these amino(iso)nicotinic acid derivatives as potent DHODH inhibitors. These findings suggest new approaches towards the development of DHODH inhibitors involving pyridine carboxylic acid moieties. It highlighted their importance as a target for drug discovery and chemotherapeutics.[141]

XO Inhibitors

Xanthine oxidase (XO) is a multipurpose molybdoflavoprotein that can produce uric acid and reactive oxygen species via catalysis and thus can lead to various diseases like hyperuricemia, gout, heart failure, cardiovascular diseases, hypertension, diabetes, inflammation, cancers, kidney diseases, and articular diseases.[211,214–218] A number of patent publications have reported xanthine oxidase inhibitors (WO 1998/018765, WO 2007/043457, WO 1992/009279, WO 2008/126770, WO 2007/004688, WO 2008/126899, and WO 2008/126,898). Among these, WO 1998/018765 exhibits the inhibitory effects of pyrazoles and phenyl derivatives against xanthine oxidase, and WO 2008/126898 describes the inhibitory effects of indole compounds against xanthine oxidase. In 2014, Soga et al published a patent for deciphering novel compounds that act as xanthine oxidase inhibitors. A total of thirty compounds were reported in this invention, out of which seven compounds **273–279** were having a pyridine carboxylic acid core (Figure 37). The best XO inhibitory activity was shown by compound **276** with an IC_{50} of 2.1 nM. The ability to lower uric acid in plasma and the liver was also determined in vivo in a xanthine oxidase assay using an oxonic acid-induced hyperuricemic model, albeit moderate to poor activity was observed for pyridine-derived compounds.[142,219]

GSK-3 Inhibitors

Glycogen synthase kinase-3 (GSK-3) inhibitors have gained substantial attention in biomedical research and drug development.[220] These compounds, designed to target GSK-3, a key enzyme in cellular processes, hold promise for treating various diseases.[221,222] In neurological disorders like Alzheimer's, they may mitigate neurodegeneration.[223,224] GSK-3 inhibitors also show potential in cancer therapy, influencing cell cycle regulation and promoting apoptosis in cancer cells. Moreover, they have applications in regenerative medicine and diabetes research. Their versatility and central role in cellular pathways make them valuable tools for understanding and potentially addressing a wide range of medical conditions, offering prospects for novel therapeutic interventions.[225]

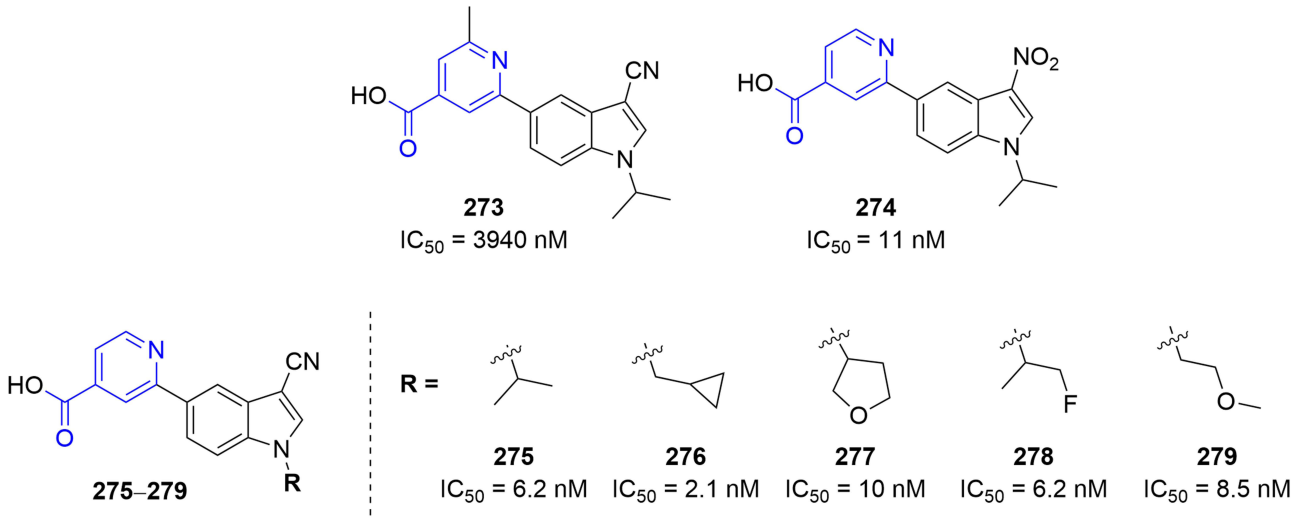

Figure 37 Structures of XO inhibitors **273–279**.

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In 2015, Bristol-Myers Squibb disclosed a series of aromatic and heterocyclic derivatives of isonicotinic acid (WO 2015/069594 Al) as inhibitors of glycogen synthase kinase 3 (GSK-3). In the patent under discussion, nicotinamide derivatives were conveniently synthesized by direct amination. To measure GSK-3 inhibitory activity, a kinase assay was developed using fluoresceinated peptide and a β-glycerol phosphate buffer system. A dose-response curve was generated to evaluate the ability to inhibit > 50% of the kinase activity (IC_{50}) at eleven varying concentrations. Their IC_{50} values ranged from subnanomolar to nanomolar concentrations, depending on the substitution pattern. Hundreds of compounds were prepared inhibiting GSK-3. The most potent activity (IC_{50} value < 1.0 nM for GSK-3β and < 5 nM for GSK-3α, respectively) was observed for compounds **280–284**, while other compounds displayed moderate activity. The structures of compounds with significant inhibitory potential are given in Figure 38 along with their IC_{50} values. These findings suggest that the regulation of GSK-3 modulators can also be useful for the treatment of neuropathological and symptomatic aspects of Alzheimer's disease and other neurodegenerative disorders.[143]

PKal Inhibitors

A number of plasma kallikrein (PKal) inhibitors have been identified so far, but only a few of them have entered clinical trials or have been marketed.[226,227] Lifesci Pharmaceuticals, Inc. reported a novel series of heterocyclic derivatives with a pyridine carboxylic acid core and their pharmaceutical compositions, which strongly inhibited PKal. Screening of the compounds was carried out using human plasma kallikrein (hPK) (Abeam) in an enzymatic assay. The resultant data showed that 136 among the tested 146 compounds were able to inhibit hPK with $IC_{50} \leq 1.0$ μM. Besides, the series were subjected to in vitro cellular assay. The majority of the compounds had EC_{50} values less than 1.0 μM, making them suitable candidates for the treatment of plasma kallikrein-related metabolic disorders, such as angioedema. The structures of **285–292** are depicted in Figure 39.[144]

CA Inhibitors

Carbonic anhydrase (CA) inhibitors suppress the conversion of CO_2 and H_2O into bicarbonate and block the reabsorption of bicarbonate from the proximal tubules (Figure 40) in the kidneys.[228,229] Studies revealed that CA inhibitors reduce aqueous humor secretion, which is found between the lens and cornea of the eyeball, and decrease intraocular pressure.[230] The

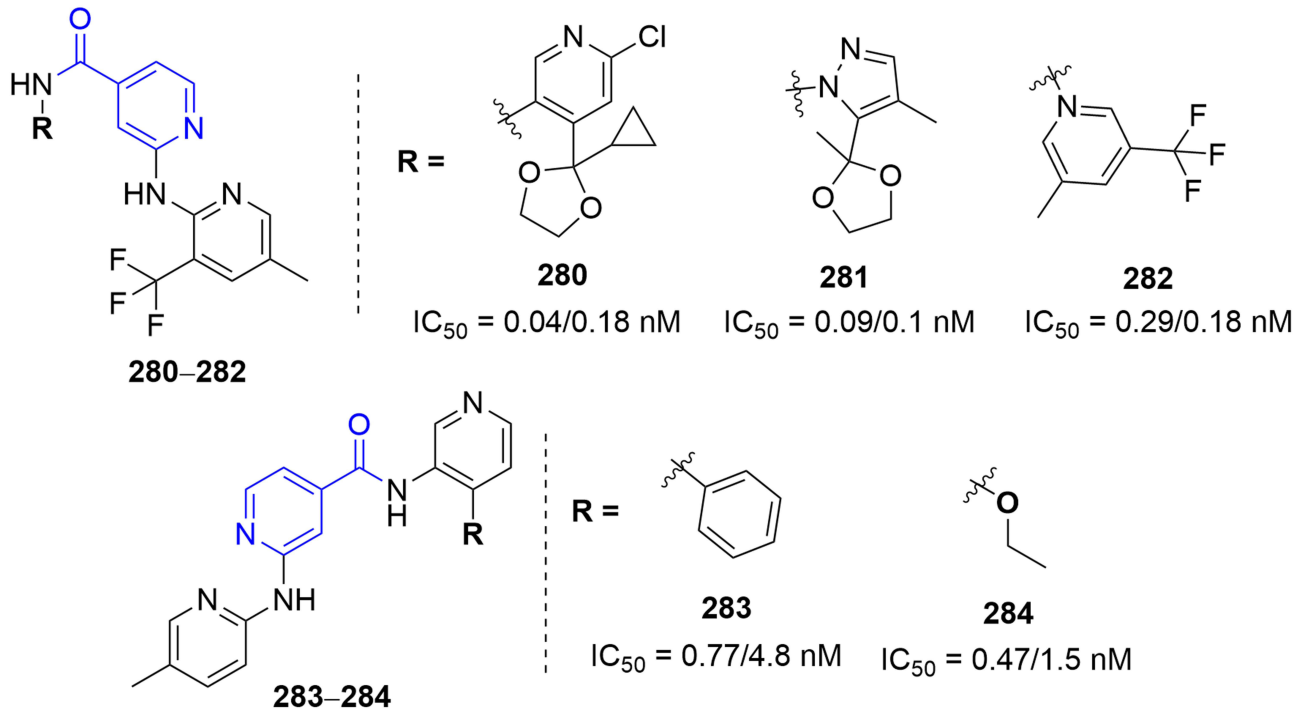


Figure 38 Structures of GSK-3 inhibitors **280–284**.

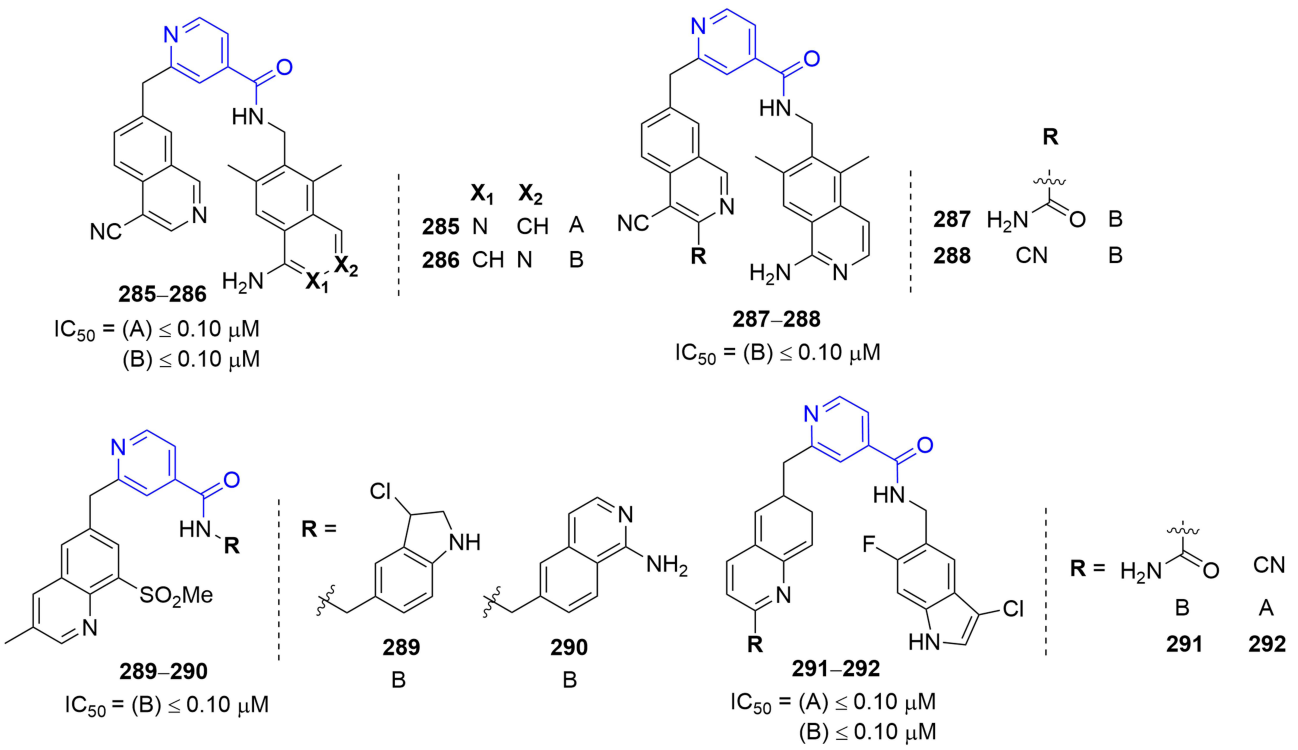


Figure 39 Structures of PKal inhibitors **285–292**.

inhibitors have greater use in edema, altitude sickness, glaucoma, and some adjuvant treatment for epilepsies.[231] Pyridine carboxylic acid derivatives inhibit the enzyme carbonic anhydrase more effectively. Some novel pyridine carboxamide derivatives **293–297** showed a CA inhibitory profile against various isoforms such as acetylcholinesterase (AChE) (K_{IS} 3.07–87.26 nM), human carbonic anhydrase I and II isoforms (hCA I and II) (K_{IS} 1.47–10.06 nM and K_{IS} 3.55–7.66 nM), respectively.[232] Another heterocyclic sulfonamide derivative **298**, exhibited CA inhibition activity against three forms of CA isozymes, CA I, II (cytosolic forms), and IV (membrane-bound) form. CA (II) (Ki = 4 nM) and (IV) (Ki = 10 nM) showed inhibitory effects in the lower nanomolar range.[233] Nicotinic acid-containing 6-substituted scaffolds **299–312** were developed and evaluated for CA inhibition activity (Figure 41). The activity was profound against isoenzyme CA (III). The docking studies and chromatographic data of nicotinic acid derivatives demonstrated the binding of the carboxylic part to the Zn^{2+} ion of the enzyme active site. Moreover, a hydrophobic part at position 6 enhanced activity, such as 6-(hexyloxy) pyridine-3-carboxylic acid (Ki = 41.6 μM).[234]

IspH Inhibitors

IspH is a crucial enzyme for isoprenoid biosynthesis in pathogenic bacteria. This enzyme is absent in humans, which makes it an attractive and selective target for antibacterial drug development. Additionally, IspH inhibition may interfere with tumor cell metabolism, highlighting its potential in cancer therapy. 4-Hydroxy-3-methylbut-2-enyl diphosphate reductase (IspH) inhibitors can play a role in bacterial infections and cancer. The Wistar Institute patented a series of compounds having inhibition against IspH in 2021. Among them, a pyridine-4-carboxylic acid derivative (**313**, Figure 42) was able to inhibit IspH with an IC_{50} of 1.44 μM.[145]

CCR3 Inhibitors

Alkahest, Inc. patented a pyridine-4-carboxylic acid derivative[235] (**314**, Figure 43) as a C-C motif chemokine receptor 3 (CCR3) inhibitor, which can be used for neurodegenerative disease. The compound **314** acted as an antagonist of CCR3, the receptor for Eotaxin-1 (CCL11). CCL11 is a protein increasing in blood by age, and the negative correlation between CCL11 and cognitive function has been proved.[236] Chronic inhibition against CCR3 was evaluated in vivo by several

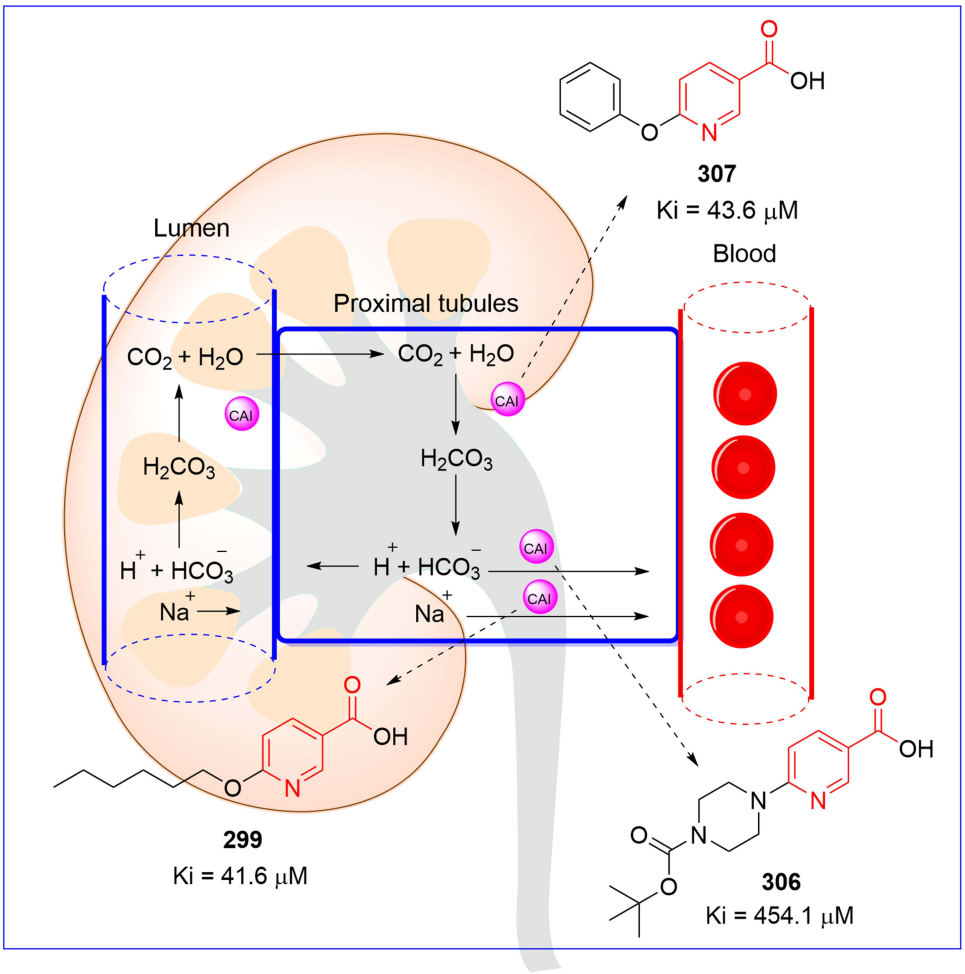


Figure 40 Pyridine carboxylic acid derivatives with inhibitory effects against carbonic anhydrase.

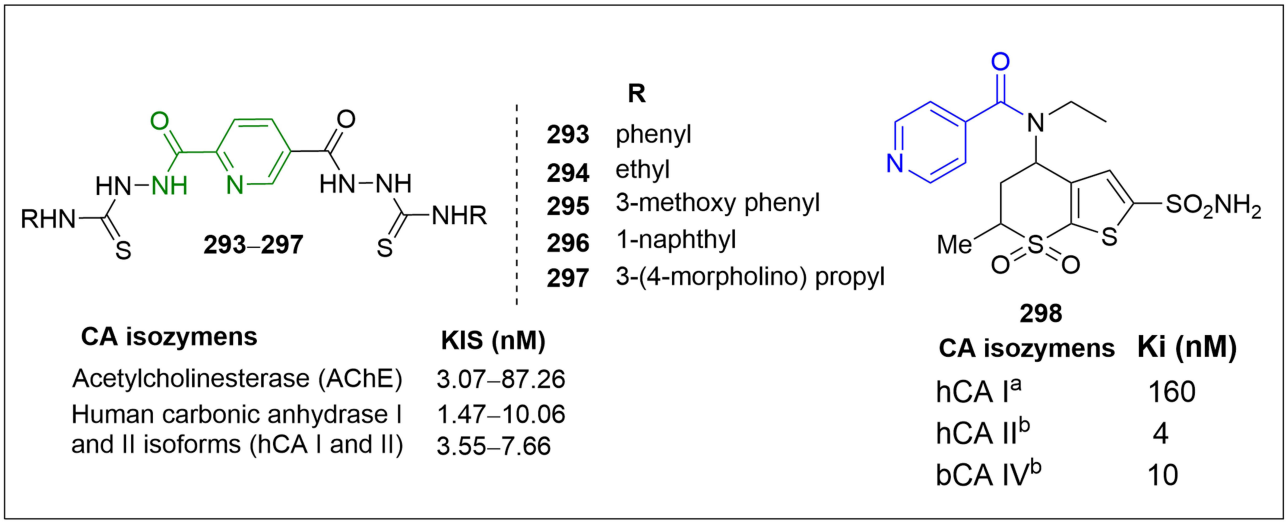
neurodegenerative animal models, such as the mouse MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's Disease, the Alzet mini-pump, model 2002, the oxazolone-induced model of eosinophilia, the synuclein transgenic mouse model of Parkinson's Disease, etc., and indicated a dose-dependent effect.

α-Amylase and α-Glucosidase Inhibitors

Diabetes mellitus disrupts carbohydrate homeostasis and lipid metabolism due to defects in pancreatic functions and can lead to organ failure, stroke, heart arrest, loss of vision, limb amputation, and damage to the nervous system. The two major enzymes, α-amylase and α-glucosidase, are involved in antidiabetic treatment. Pancreatic inhibition of carbohydrate digestive enzymes such as α-amylase and α-glucosidase inhibitors in the intestine can help in combating secondary diabetes and postprandial hyperglycemia (PPHG). In a recent study, 5-amino nicotinic acid derivatives **315–326**, summarized in Figure 44, have been synthesized and evaluated for inhibition activity against α-amylase and α-glucosidase with IC_{50} values in the range of 12.17–37.33 μg/mL for α-amylase and 12.01–38.01 μg/mL for α-glucosidase; see Table 3 for the inhibitory profile.[237]

Type I MetAPs Inhibitors

Methionine aminopeptidases (MetAPs) cleave *N*-terminal methionine from newly synthesized proteins and peptides distributed in both prokaryotes and eukaryotes, the inhibition of which is important for biological processes, subcellular location, and eventual degradation of proteins. MetAPs serve important physiological functions and disrupting the MetAPs gene in *Escherichia coli* (Ec MetAP1) or *Salmonella typhimurium* is a noxious phenomenon. In *Saccharomyces cerevisiae*, the inhibitor



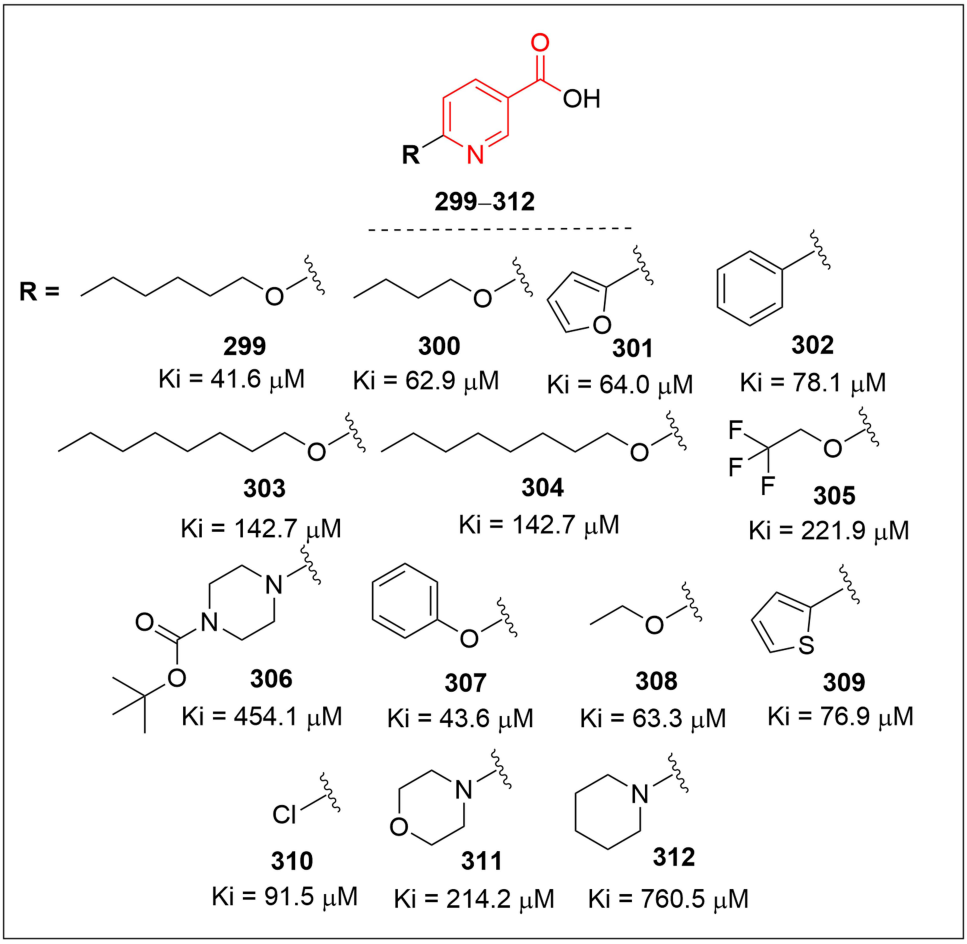


Figure 41 Structures of Carbonic anhydrase inhibitors **293–312**.

slows the bacterial growth, either hampering *map1* or *map2*. Therefore, MetAPs are potential targets for antibacterial and antifungal drug development. Inhibitors of the enzyme provide more effective treatment for bacterial and fungal infections. Recently, pyridine-2-carboxylic acid thiazol-2-ylamide (PACT) analogues **327–347** (Figure 45) were checked against type I MetAPs inhibition activity. It is found that substitutions at position 3 of pyridine were found more effective than position 2

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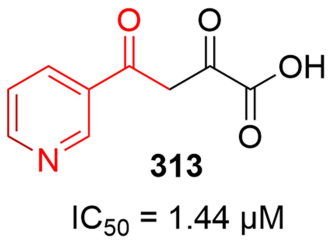

Figure 42 Structure of IspH inhibitor **313**.

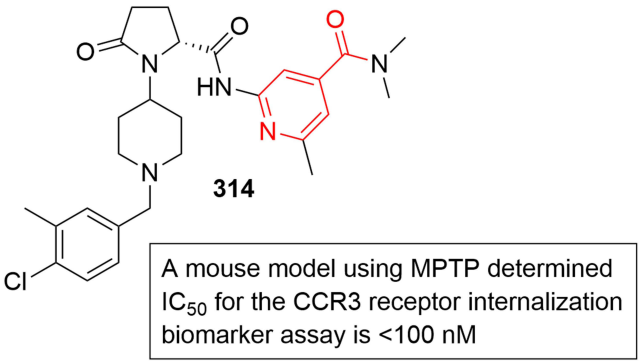

Figure 43 Structures of CCR3 inhibitor **314**.

substitutions and inhibition activity was enhanced when N and O atoms were connected to the pyridine ring directly, see Table 4.[238]

KMO Inhibitors

The Kynurenine pathway (KP) has multiple functions including the generation of cellular energy in the form of nicotinamide adenine dinucleotide (NAD^+) and catabolize tryptophan. In case of inflammation, KP enzymes, such as kynurenine 3-monooxygenase (KMO), upregulate and produce toxic substances that may cause disorders, such as neurodegenerative diseases.[239,240] Diclofenac (**348)** is known as a human KMO protein binder and inhibitor in cell lysate with low micromolar KD 64.8 μM and IC_{50} 13.6 μM, respectively, and low millimolar cellular IC_{50} 1.35 mm. (Figure 46).[241,242]

Table 3 Inhibition Study of α-Amylase and α-Glucosidase Compounds 315–326

Compounds	α-Amylase Inhibition μg/mL ± SEM	α-Glucosidase Inhibition μg/mL ± SEM
315	28.89 ± 0.102	28.09 ± 0.09
316	12.91 ± 0.04	12.72 ± 0.12
317	28.84 ± 0.03	28.61 ± 0.01
318	12.17 ± 0.14	12.01 ± 0.09
319	13.01 ± 0.07	13.11 ± 0.15
320	12.91 ± 0.08	12.79 ± 0.17
321	13.04 ± 0.02	12.99 ± 0.09
322	26.53 ± 0.08	26.27 ± 0.18
323	26.70 ± 0.06	25.97 ± 0.19
324	26.94 ± 0.02	27.02 ± 0.11
325	37.33 ± 0.02	38.01 ± 0.12
326	36.65 ± 0.03	37.47 ± 0.13
Acarbose	10.98 ± 0.03	10.79 ± 0.17

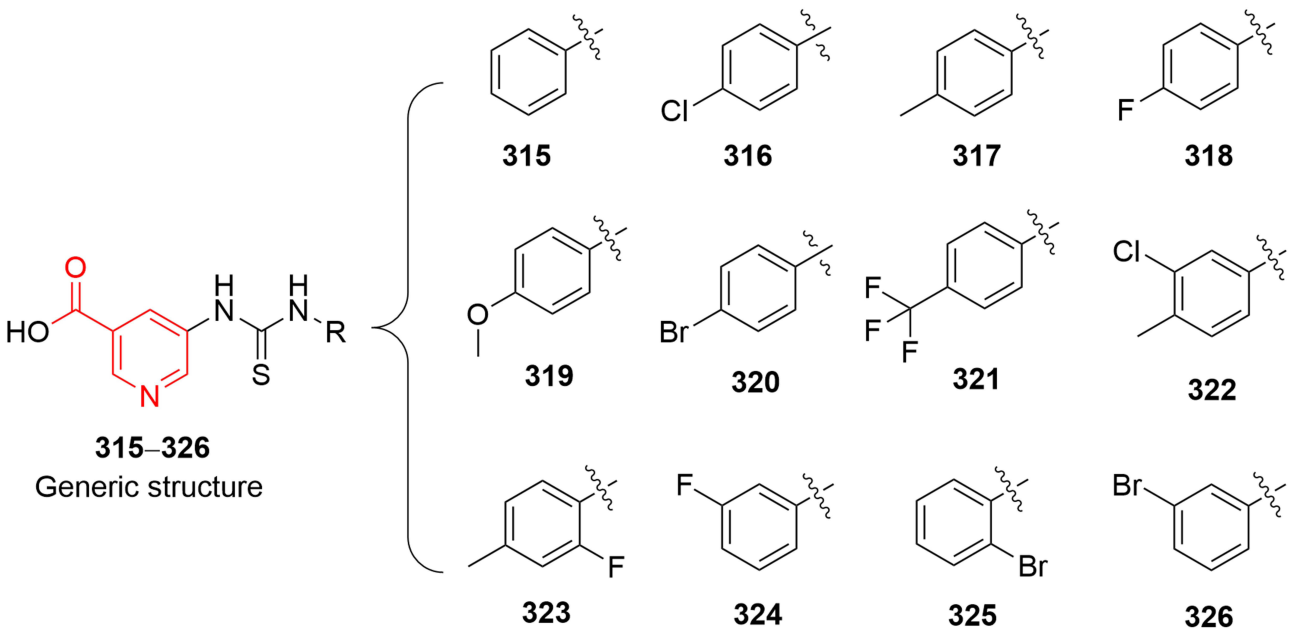

Figure 44 Structures of α-amylase and α-glucosidase inhibitors **315–326**.

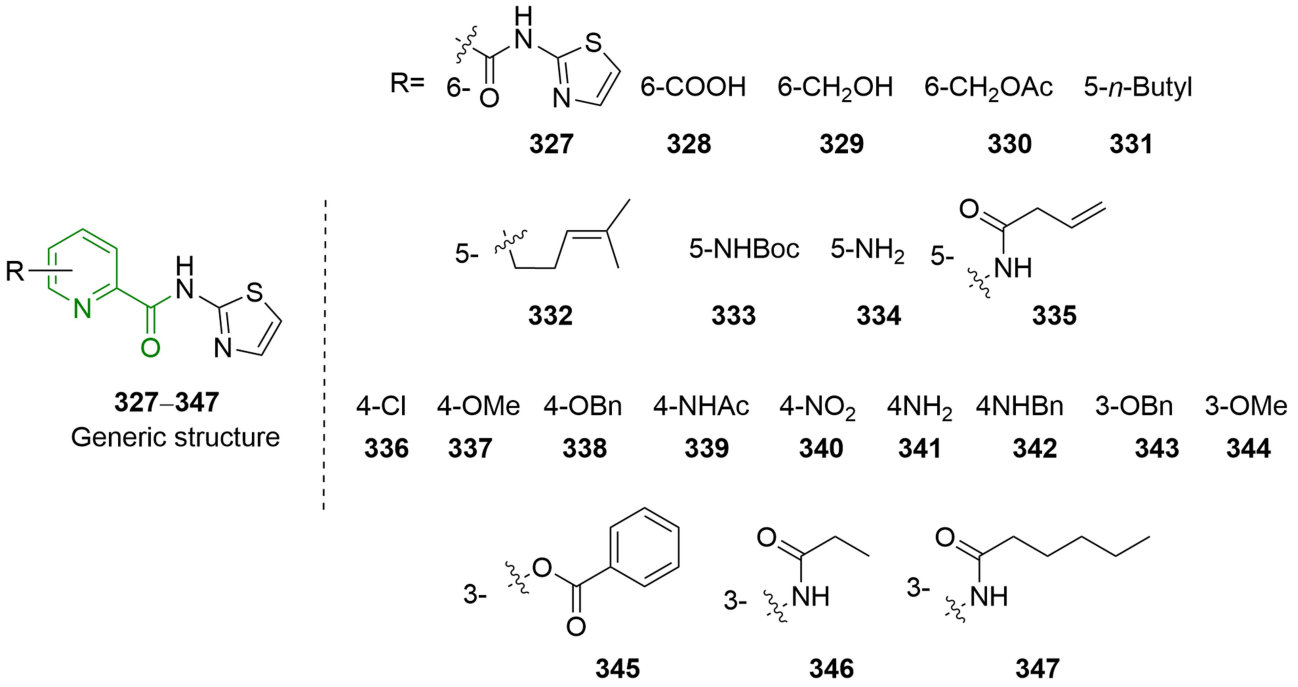

Figure 45 Structures of Type I MetAPs inhibitors **327–347**.

COX-1 and COX-2 Inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) are used against inflammation, pyrexia, and pain. Many of them follow their action by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, which are involved in the biosynthesis of prostaglandins from arachidonic acid through a catalytic reaction. However, toxicity related to NSAIDs, such as ulceration, bleeding, and perforation, limits their use as anti-inflammatory drugs. Nicotinic acid (pyridine-3-carboxylic acid) derivatives have been demonstrated as good options for COX-1 and COX-2 inhibitors, such as drug Niflumic acid (**349**), and

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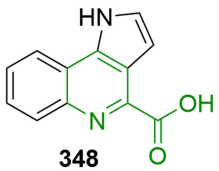
Table 4 Inhibitory Activity of Type I MetAPs Inhibitors 327–347

Compounds	EcMetAPI IC_{50} (μM)	ScMetAPI IC_{50} (μM)
327	> 100	> 100
328	> 100	> 100
329	5.82 ± 0.58	ND
330	> 100	ND
331	> 100	> 100
332	> 100	> 100
333	12.78 ± 0.97	62.86 ± 1.18
334	2.09 ± 0.01	2.43 ± 0.01
335	1.01 ± 0.02	> 100
336	> 100	> 100
337	9.22 ± 0.04	> 100
338	> 100	> 100
339	1.98 ± 0.01	17.04 ± 1.94
340	4.51 ± 0.36	> 100
341	6.71 ± 0.64	> 100
342	2.32 ± 0.03	> 100
343	1.41 ± 0.30	0.77 ± 0.28
344	4.49 ± 0.28	ND
345	1.22 ± 0.12	1.03 ± 0.09
346	0.26 ± 0.04	0.35 ± 0.03
347	0.38 ± 0.03	0.62 ± 0.06

prodrugs Flunixin (**350**) and Talniflumate (**351**). It was reported compounds including nicotinic acid portion **352**–**358** (Figure 47) showed reduced gastric toxicity with potent activities. Some novel nicotinic acid derivatives **359**–**373** (Figure 47) exhibited COX-2 inhibitory activity with greater selectivity as compared to COX-1 inhibition. Compounds **361** and **364** have shown highly potent anti-inflammatory activity compared to diclofenac and indomethacin and are as potent as celecoxib. The selectivity was 1.8–1.9-fold greater than the reference drug, celecoxib, see Table 5. Histopathological studies on nicotinic acid derivatives were also carried out. The results showed that there was no ulceration and that the gastric profile was safe.[243]

Urease Inhibitors

Urease is a nickel-containing metalloenzyme that is involved in the catalytic reaction of urea into ammonia and carbamate. Carbamate further hydrolyzes into bicarbonate and another molecule of ammonia is produced. This pH increase is associated with alkalinity and results in gastric ulcers, kidney stones, pyelonephritis, and hepatic coma. Urease inhibitors are required to regulate urease activity. Nicotinic and isonicotinic thiosemicarbazide derivatives **374**–**399** illustrated in Figure 48 possess highly potent urease inhibitory activity, showing IC_{50} values of 1.13 to 19.74 μM.[111]



348
(Diclofenac)

assay	protein source	protein/assay	parameter
kinetic	HEK-KMO cell lysate	200 mG of total protein	IC_{50} = 13.6 mM
kinetic	HEK-KMO whole cells	20, 000 cells	IC_{50} = 1.35 mM
microdialysis	enriched HEK-KMO lysate	10 mM KMO protein	KD = 64.8 mM

Figure 46 Structure of KMO inhibitor **348**.

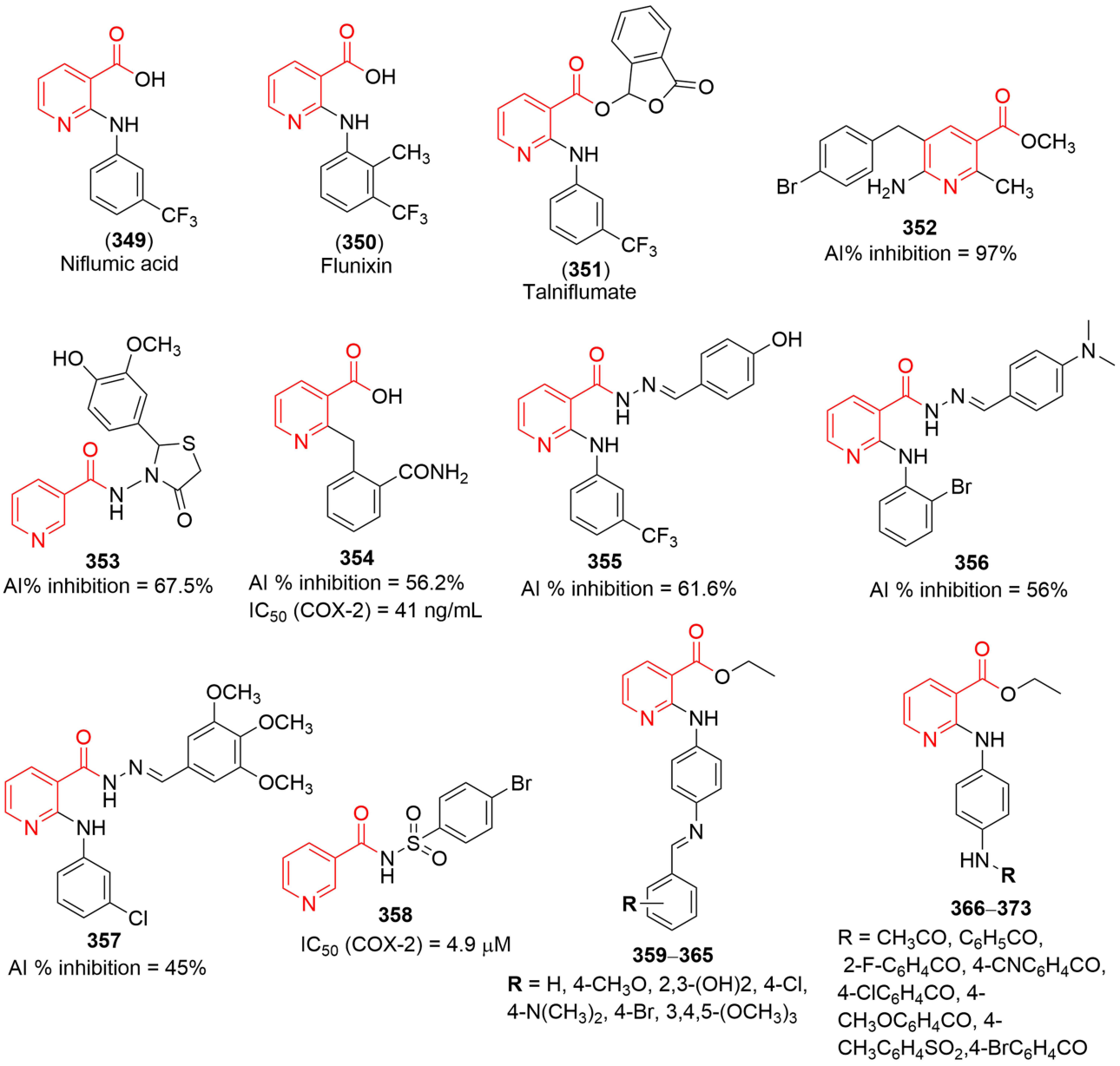


Figure 47 Structures of COX-1 and COX-2 inhibitors **349–373**.

Multi-Kinase Inhibitors

The FDA approved Ponatinib (**400**), a multi-kinase inhibitor developed by Ariad Pharmaceuticals, in 2012. It currently targets a wide range of cancer-driver kinases. Among these are the kinases FGFR1-4, FLT3, ABL1, and RET. Inspired by this, the

Table 5 COX-1 and COX-2 Inhibitory Activity of Compounds 359–373

Compounds	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	SI
359	0.1357 ± 0.003	0.1580 ± 0.004	0.85
360	0.2794 ± 0.007	0.0495 ± 0.001	5.64
361	0.1506 ± 0.004	0.0809 ± 0.002	1.86
362	0.8378 ± 0.023	0.2690 ± 0.007	3.11
363	0.2997 ± 0.008	0.0544 ± 0.001	5.51
364	0.7909 ± 0.022	0.0973 ± 0.002	8.13

(*Continued*)

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Table 5 (Continued).

Compounds	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	SI
365	1.5640 ± 0.044	0.1200 ± 0.003	13.00
366	0.3447 ± 0.009	0.1370 ± 0.003	2.52
367	0.6905 ± 0.019	0.1170 ± 0.003	5.90
368	0.2390 ± 0.006	0.1700 ± 0.004	1.41
369	0.7533 ± 0.021	0.0409 ± 0.001	18.41
370	1.4350 ± 0.040	0.1370 ± 0.003	10.47
371	0.2860 ± 0.008	0.1600 ± 0.004	1.79
372	0.7873 ± 0.022	0.0461 ± 0.001	17.07
373	0.5313 ± 0.015	0.1100 ± 0.003	4.83
Indomethacin	0.0891 ± 0.002	0.2240 ± 0.006	0.39
Diclofenac	0.4880 ± 0.019	0.4090 ± 0.013	1.19
Celecoxib	0.5120 ± 0.014	0.0553 ± 0.001	9.26

discussed patent outlines a variation of Ponatinib, where the original benzimide moiety is swapped with a nicotinamide moiety. This change is considered a potentially more efficient and less harmful alternative to Ponatinib, especially in its application for treating diseases like cancer, notably acute myeloid leukemia (AML). Ponatinib (**400**)[244,245] and HSN748

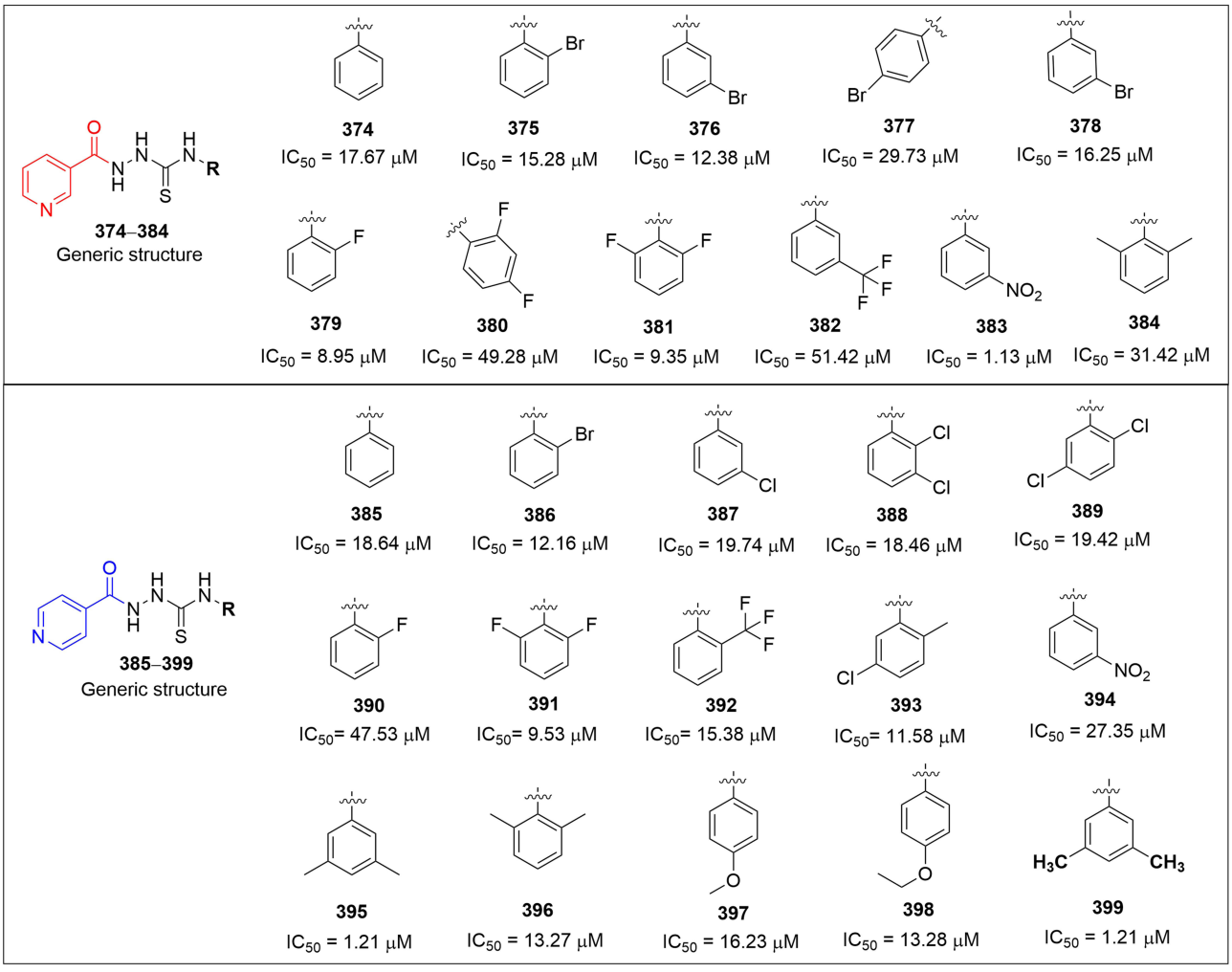

Figure 48 Structures of urease inhibitors **374–399**.

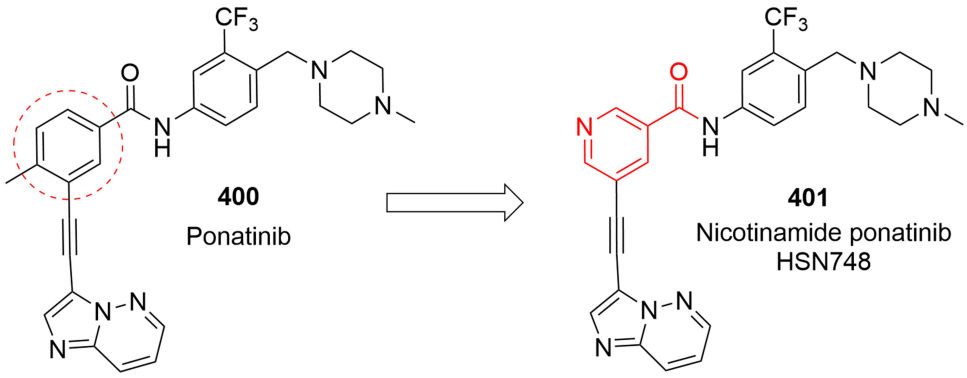

Figure 49 Structures of multi-kinase inhibitor **400** and **401**.

(**401**)[246] shown in Figure 49, were tested against a panel of disease-associated kinases, that have been demonstrated to be inhibited by Ponatinib. Though there were some noticeable discrepancies with some other kinases, the inhibitory profile of HSN748 against ABLl (T3l5I) and FLT3-ITD was interestingly similar to that of Ponatinib. ABL1 and FLT3 are mutated in chronic and acute myeloid leukemias, respectively. Ponatinib and HSN748 have similar activities against ABL1, ABLl (T3l5I). Interestingly HSN748 has a significantly lower IC_{50} against FLT3 (D835Y) kinase than Ponatinib (compare IC_{50} of 13.8 nM for HSN748 versus 176 nM for Ponatinib, as shown in Table 6.

Most FLT3 inhibitors initially worked well but within a few months, patients relapsed due to kinase mutation, which decreased the treatment's effectiveness. Therefore, HSN748 may be a more effective treatment option for drug-resistant AML (due to kinase mutation) compared to Ponatinib.[147]

Both vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor (PDGFRβ) are important receptor-type tyrosine kinases (RTKs) involved in vascular disease.[247] It was demonstrated that compounds inhibiting both kinases are more effective.[248] Allergan Inc. patented two series of compounds synthesized based on Formula I and Formula II (Figure 50). In the series of Formula 1, the most preferred compounds **402**–**406** have the greatest potency against both VEGFR2 and PDGFRβ. In the series of Formula II, compounds **407**–**410** show activity

Table 6 Ponatinib and HSN748 IC_{50} Against Several Kinases

Kinases	HSN748	Ponatinib
	IC_{50} (nM)[a]	
ABL1	1.1	0.87
ABL1 (T3151)	11.1	2.5
c-SRC	> 1000	4.6
FGFR1	24.4	6.9
FGFR2	11.7	6.0
FGFR3	96.4	25.0
FGFR4	125.1	46.8
FLT3 (D835Y)	13.8	176
FLT3 (ITD)	1.5	10.03
P38a/MAPK14	382.7	86.6
P70S6K/PRS6KBI	273.1	200.1
PDGFRα	10.7	3.8
PDGFRβ	10.2	7.01
RET	0.65	0.88
MNK1	202	3930
MNK2	9.36	268

Note: [a]IC_{50} was determined at Reaction Biology (Malvern, PA). [ATP] = 100 μM.

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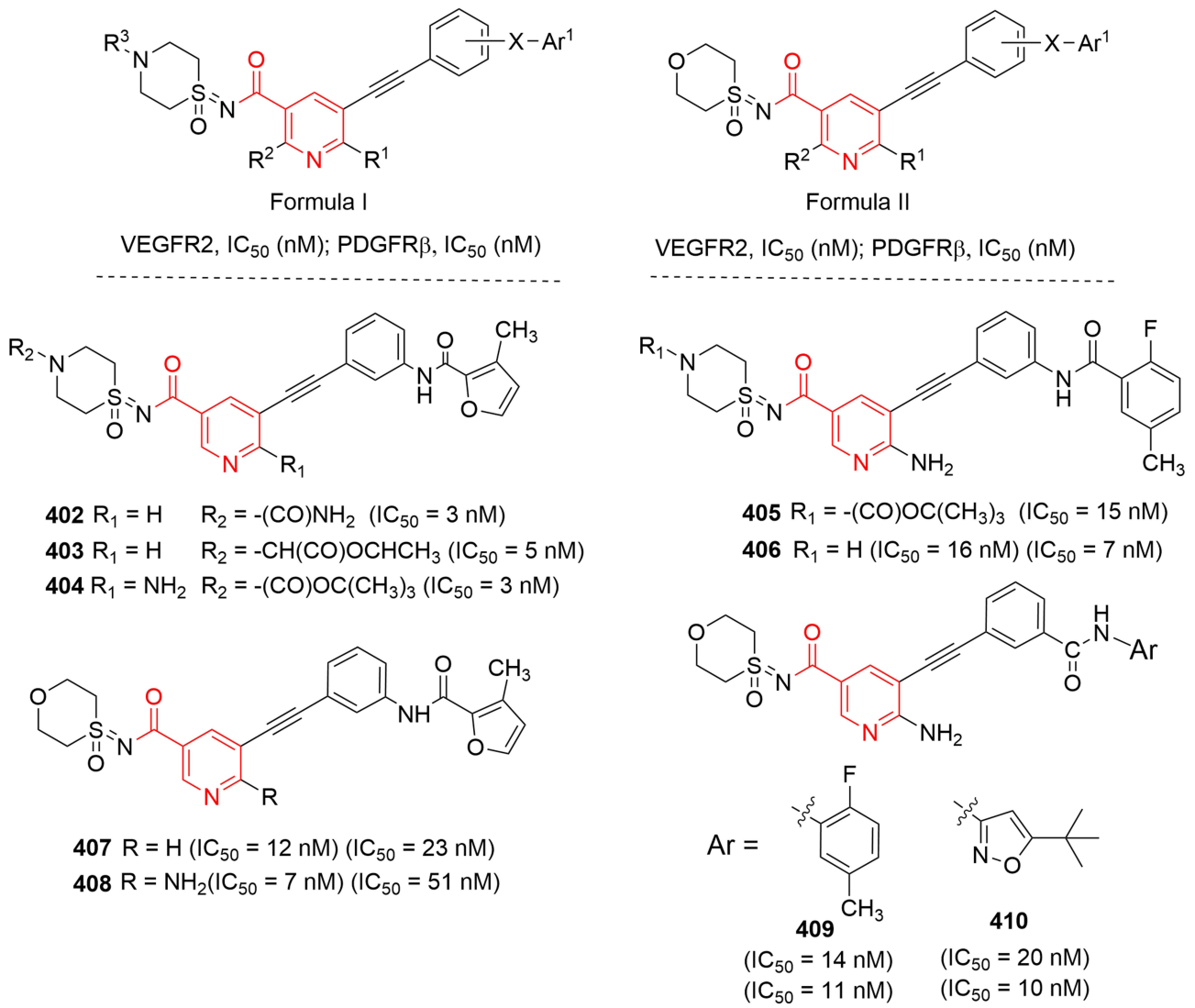

Figure 50 Structures of multi-kinase inhibitors **402–410**.

against both the VEGF and PDGF receptors. Compounds **407** and **408** have the highest activity against the VEGFR2 receptor; while compounds **409** and **410** had the best activity against the PDGFRβ receptor (Figure 50).[148]

Conclusion

Pyridine is a therapeutically active moiety, which is found in innumerable compounds, of both synthetic and natural origin. While there is a plethora of pyridine derivatives known to date, pyridine carboxylic acid isomers and its derivatives hold a special place in medicinal and pharmaceutical chemistry. This is mainly due to their renowned biological activities, and ease of syntheses. They can be further derivatized into numerous other interesting compounds using well-known and well-established synthetic strategies. Hence, pyridine carboxylic acid and its derivatives can be easily fused to other aryl or heteroaryl moieties, thereby bringing together active pharmacophores and thus opening up new avenues for drug discovery.

This review has highlighted a range of patented pyridine carboxylic acid derivatives with promising activity profile against key biological targets. These include IRAK4 and ASK1 inhibitors with anti-inflammatory and anti-cancer potential, WDR5 inhibitors targeting oncogenic MYC interaction, and selective PDGFR inhibitors for the treatment of pulmonary arterial hypertension (PAH). Other notable applications include inhibitors of Trk, FABPs, FXIa, TGFβ,

DHODH, TRPC6, KDM4, XO, GSK-3, PKaI, carbonic anhydrase, α-amylase, α-glucosidase, MetAPs, COX-1/COX-2, urease, and antiviral agents against hepatitis B. Several of these compounds are currently in various phases of clinical trials, and the hopes remain high regarding their success. A comprehensive summary of the enzyme targets, abbreviations, and their disease relevance is provided in supporting information.

Despite this encouraging progress, several challenges remain. Many pyridine carboxylic acid derivatives suffer from suboptimal pharmacokinetic properties, limited target selectivity, or insufficient in vivo validations. Furthermore, the patented literature often lack detailed mechanistic or structural biology data, making it difficult to fully assess therapeutic viability. Future research should focus on enhancing the metabolic stability, improving selectivity via structure-guided designs, and expanding biological validations in relevant disease model. In addition, more integrated studies combining computational modellings, SAR optimizations, and in vivo pharmacology will be essential to translate these compounds into clinically successful therapies. In conclusion, pyridine carboxylic acid isomers represent a class of privileged scaffolds with broad therapeutic potential. This review offers a unique patent-based perspective, capturing a decade of industry efforts and emerging trends that may inform and inspire future academic and translational research.

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Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

Supporting Information

Supporting information contains enzymes abbreviation, full version, and disease relevance.

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