The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design

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Abstract: Pyridine-based ring systems are one of the most extensively used heterocycles in the field of drug design, primarily due to their profound effect on pharmacological activity, which has led to the discovery of numerous broad-spectrum therapeutic agents. In the US FDA database, there are 95 approved pharmaceuticals that stem from pyridine or dihydropyridine, including isoniazid and ethionamide (tuberculosis), delavirdine (HIV/AIDS), abiraterone acetate (prostate cancer), tacrine (Alzheimer's), cilestropriox (ringworm and athlete's foot), crizotinib (cancer), nifedipine (Raynaud's disease and premature birth), piroxicam (NSAID for arthritis), nilvadipine (hypertension), roflumilast (COPD), pyridostigmine (myasthenia gravis), and many more. Their remarkable therapeutic applications have encouraged researchers to prepare a larger number of biologically active compounds decorated with pyridine or dihydropyridine, expanding the scope of finding a cure for other ailments. It is thus anticipated that myriad new pharmaceuticals containing the two heterocycles will be available in the forthcoming decade. This review examines the prospects of highly potent bioactive molecules to emphasize the advantages of using pyridine and dihydropyridine in drug design. We cover the most recent developments from 2010 to date, highlighting the ever-expanding role of both scaffolds in the field of medicinal chemistry and drug development.

Keywords: nitrogen heterocycles, pharmaceuticals, bioactive compounds, current trend, substituent effect

Introduction

Heterocycles are intricately woven into basic processes of life and play a crucial role in the pharmaceutical and agrochemical industries. In terms of pharmacological, physicochemical, pharmacokinetic, and toxicological properties, heterocyclic structures are found in >90% of newly synthesized and marketed drugs. Medicinal chemistry has evolved from an empirical practice involving the synthesis of novel substances and then gauging their biological activity. A plethora of synthetic compounds with heterocyclic structural frameworks have been identified — with privileged six-membered N-containing pyridine and dihydropyridine rings — linked to a diverse range of bioactivity. In the realm of six-membered heterocyclic structures, they have unique and interesting characteristics. Owing to their therapeutic potential, medicinal chemists have recently become drawn toward scaffolds in order to synthesize a wide range of novel bioactive molecules.

In pharmaceutical targets, pyridine and its precursor molecule dihydropyridine are among the most prevalent structural units. In plants, they are mostly found in the alkaloids. In biological systems, redox reactions of nicotinamide adenine dinucleotide
(NAD) reduces its pyridine ring into dihydropyridine, rendering NADH. Similar redox reactions are also present in anabolic reactions involving NAD phosphate (NADP+/NADPH) interconversion. A glance at the US Food and Drug Administration (FDA) database reveals that pyridine- and dihydropyridine-containing drugs constitute nearly 14% and 4% of N-heterocyclic drugs approved by the agency (Figure 1). For these 18% of drugs, the major therapeutic areas of focus are infectious diseases, inflammation, the nervous system, and oncology.

Substitution-type analysis of pyridine-containing drugs revealed that the ring is mostly monosubstituted (60%) in the database, whereas di-, tri-, and tetrasubstitution represented 22%, 12%, and 6%, respectively (Figure 2A). For dihydropyridine-containing drugs, neither mono- nor disubstitution was observed for the N-heterocyclic ring. However, trisubstitution of the dihydropyridine ring was the most abundant substitution type for this class of drugs. Tetra-, penta-, and hexasubstitution on the N-heterocyclic ring were 11%, 21%, and 5%, respectively (Figure 2B).

In recent years, synthetic chemists have been focusing on developing new analogues that employ pyridine or dihydropyridine templates in their molecular design, in order to study their mechanisms of action to discover new pharmaceutical leads. The importance of the two heterocycles in medicinal chemistry and chemical sciences can be seen by the sheer number of publications appearing between 2010 and 2020 (Figure 3).

Most reviews on this topic have concerned synthetic strategies to prepare pyridine- or dihydropyridine-containing compounds. For either of the two scaffolds, one can also find many reviews delineating their therapeutic potential concerning a specific malady. Most reviews on pyridine-containing compounds have examined only their anticancer potential. Likewise, several reviews on dihydropyridine-containing compounds typically scrutinized their calcium

![Figure 1](https://doi.org/10.2147/DDDT.S329547) Distribution of N-heterocyclic drugs in the FDA database.
channel–blocking abilities for the treatment of hypertension and associated ailments.\(^{19,24,26–28}\) The neuroprotective ability of dihydropyridine derivatives has also been examined.\(^{23}\) Lapidot et al summarized the antibacterial activity of dihydropyridine-containing peptidomimetics.\(^{25}\) For substituted 1,4-dihydropyridine, medicinal versatility and anticipable therapeutic effects have been the focus of past reviews,\(^{29–31}\) eg, Khedkar et al briefly discussed the pharmacological importance of this type of molecule.\(^{30}\) To the best of our knowledge, a review focusing on the therapeutic potential of pyridine- and dihydropyridine-containing compounds has never been published. Herein, we present commercially available drugs while discussing the major therapeutic potential of synthetic bioactive molecules with either of the two scaffolds. The review covers a sizable period in the scientific literature, including the publications from 2010 to date, thereby providing a broad picture of approved drugs and bioactivity reported for pyridine- or dihydropyridine-containing compounds, and is valuable material for those interested in exploring this class of compounds for further medicinal and clinical applications.

**Figure 2** Substitution-type analysis of pyridine- (A) and dihydropyridine (B)-containing FDA-approved drugs.

**Figure 3** Publications on pyridine- and dihydropyridine-containing compounds, 2010–2020 (source: Scopus and SciFinder).
Pyridine and Dihydropyridine Scaffolds in Natural Products and Commercially Available Drugs

Pyridine and dihydropyridine generate a suite of versatility when it comes to creating libraries of compounds with different functional groups for screening against different biological targets. Many natural products contain pyridine-based rings (Figure 4), including the vitamins (niacin and vitamin B₃), coenzymes (NAD, NADP), alkaloids (trigomelline, [−]-oxirene, [+]-anabasine, huperzine A, paecilomide, cystine), antibiotics (nikkomycin, collismycin), and many more compounds.¹¹

In pharmaceuticals, nitrogen-containing heterocycles are considered instrumental structural constituents.³² The presence of pyridine or dihydropyridine ring systems can have a substantial impact on pharmacological profiles of drugs and bioactive molecules.³³ For example, a pyridine motif in a drug improves its biochemical potency and metabolic stability, enhances permeability, and fixes protein-binding issues.³³ Some interesting examples of the pyridine effect are highlighted in Figure 5: Vanotti et al were able to develop the potent Cdc7 kinase inhibitor 2 by substituting the phenyl group of 1 with pyridine.³⁴ Similarly, metabolic stability of thiourea-based nicotinamide phosphoribosyltransferase inhibitor 3 is improved 160-fold when its terminal phenyl ring is replaced with pyridine in 4.³⁵ A heterocyclic pyridine ring in a molecule is also capable of enhancing its cellular permeability. For example, Doller et al identified a pyridine-containing positive allosteric modulator 6 with 190-fold the cellular permeability of 5.³⁶ For the treatment of schizophrenia, protein-binding issues of positive allosteric modulator 7 were resolved by the introduction of an additional pyridine ring in 8.³⁷ It is thus pertinent to say that substitution of nitrogen-containing heterocyclic rings profoundly affects the physicochemical properties of the bioactive molecule.³³

There is a plethora of commercially available drugs in the market which contain pyridine rings, such as abiraterone for prostate cancer,³⁸ enpiroline for malaria,³⁹ nicotinamide for pellagra,⁴⁰ nikethamide as a respiratory stimulant,⁴¹ piroxicam for arthritis,⁴² isoniazid for tuberculosis,⁴³ pyridostigmine for myasthenia gravis,⁴⁴ tropicamide as an antiguscarcinic,⁴⁵ doxylamine for allergies,⁴⁶ omeprazole for ulcers,⁴⁷ delavirdine as an antiviral against HIV/AIDS,⁴⁸ enisamium iodide for influenza,⁴⁹ and tacrine as an inhibitor of the AChE enzyme⁵⁰ for Alzheimer’s disease prevention (Figure 6).

Dihydropyridine ring–containing drugs mostly act as calcium-channel blockers,⁵¹ and are frequently employed for the treatment of hypertension and heart-related problems.⁵² Such drugs include nilvadipine, nifedipine, amlodipine, azelnidipine, clevidipine, felodipine, and pranidipine. Some of these drugs are also used to cure many other therapeutic conditions.⁵³ For example, nifedipine is being used for Raynaud’s syndrome and premature birth.⁵⁴ Dihydropyridine-containing huperzine, a natural product, acts as an AChE inhibitor and is employed in the treatment of Alzheimer’s disease, whereas ciclopirox is widely used as an antifungal agent to cure ringworm and athlete’s foot disease (Figure 7).

Milrinone and amrinone are the two commercially available vasodilators,⁵⁵ and contain both pyridine and dihydropyridine ring systems in their structures (Figure 8). In general, pyridine- and dihydropyridine-containing drugs are mostly used as antimicrobial, antiviral, anticancer, antioxidant, antihypertensive, antidiabetic, antimalarial, and anti-inflammatory agents, psychopharmacological antagonists, and antiamebic agents.⁵⁶–⁶² A comprehensive list of commercially available drugs containing pyridine and/or dihydropyridine scaffolds and their mechanism of action is summarized in Table 1.

Analysis of the substitution pattern in FDA-approved drugs has revealed that the 1,4-dihydropyridine ring in the drugs was mostly substituted at the para-position (4). Disubstitution at both ortho-positions (2 and 6) were observed in eleven drugs, while one drug had monosubstitution at the ortho-position (2). Similarly, three drugs had monosubstitution at the meta-position (3), whereas ten drugs had disubstitution at meta-positions (3 and 5) of the 1,4-dihydropyridine ring. For brevity, the substitution patterns of pyridine and dihydropyridine ring systems in FDA-approved drugs are illustrated in Figure 9.

Pharmacological Activity

On the therapeutic front, pyridine- and dihydropyridine-containing compounds possess versatile bioactivity, due to which they are the integral in numerous drugs. The literature revealed many examples wherein this class of compounds demonstrated promising pharmacological properties.

Cardiovascular Drugs and Bioactive Compounds

Hypertension is among the main risk factors of cardiovascular disease. Many different types of antihypertensive
drugs are employed to treat the problem. Main classes of such drugs include α- and β-adrenergic inhibitors, renin inhibitors, vasodilators, diuretics, calcium-channel blockers, angiotensin converting–enzyme inhibitors, and many more (Figure 10). Pyridine-containing torsemide is an FDA-approved drug that promotes diuresis, thereby lowering the blood pressure of the patient. Pyridine- and dihydropyridine-containing amrinone and milrinone are beta-adrenergic blockers, also called β-blockers, to help manage hypertension via vasodilation and ultimately save
the patient from a second heart attack. Disruption of calcium movement through cellular channels is another strategy to lower blood pressure. Most of the calcium antagonists in the FDA database contain dihydropyridine scaffolds, with penta-substitution pattern observed for the ring (Figure 11).

In 2014, N-propargyl–substituted derivatives of 1,4-DHP derivatives were synthesized by Rucins et al, who incorporated pharmacophore moieties into their structures and investigated their calcium channel–blocking activity. In SH-SY5Y–type neuroblastoma cells (which contain Ca\textsuperscript{2+} channels of L-and N-type) and A7r5 cells (which are rat aortic muscle cells expressing L-type Ca\textsuperscript{2+} channels), and impact of newly synthesized compounds on intracellular concentration of calcium [Ca\textsuperscript{2+}] was studied. Among the series, compounds 9 and 10 with n-dodecyl pyridinium moiety as an amphiphilic group exhibited the strongest calcium antagonistic activity in SH-SY5Y neuroblastoma cells (IC\textsubscript{50} = 5–14 mM), and A7r5 type lines (IC\textsubscript{50} = 0.6–0.7 mM). These compounds demonstrated moderately effective antioxidant activity. Compound 10 had no effect on mitochondrial function at dosages comparable to that used to block L-type calcium channels, and no damage was seen in vivo. As a consequence, this compound can be regarded as safe up to 100 mg/kg, with no toxicity. It was observed that the 1,4-DHP ring–bearing propargyl group at position 1 did not significantly influence the bioactivity of the tested derivatives. Therefore, compounds with n-dodecyl pyridinium moiety at the para-position (Figure 11) might be the lead molecules for subsequent modifications and in vivo studies of cardiovascular and neurological disorders.\textsuperscript{176}

Nitrendipine 11 is a DHP-type calcium antagonist with a simple structure, but low potency. Antihypertensive actions of nitrendipine analogues can be improved by increasing the alkyl-chain length at the 3 or 5 position.\textsuperscript{177,178} Zhou et al synthesized nitrendipine analogues, and their antihypertensive properties were assessed in spontaneously hypertensive rats by means of intravenous immunoglobulin administration. S- and R-enantiomers had different calcium antagonistic activity in various studies.\textsuperscript{179} It was found that the S-enantiomer had 100-fold the antihypertensive properties of the R-enantiomer (Figure 12). Moreover, the efficacy of nitrendipine analogues was further enhanced by elongating carbon chain-length. These findings suggest that alkyl-chain length at position 5 is closely linked to the antihypertensive effects of nitrendipine analogues. DHP's antihypertensive effects

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**Figure 5** Effect of pyridine on key pharmacological parameters.

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were attenuated by extra-long or extra-short alkyl chains at position 5. On position 5 of DHP, an alkyl chain containing seven carbon atoms is the most appropriate length. Therefore, the strongest antihypertensive effect was observed for 5-(n-heptyl-3-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [(±)-12]. Antihypertensive effects of (±)-12 and +-iso-mer were compared, with +-isomer being 1.79 times more potent at a dosage of 2 mg/kg than the raceme.\(^{180}\)

Calcium channel–antagonistic activity of phenyl amino imidazolyl–bearing 1,4-dihydropyridines were also investigated by Zarghi et al. His research group replaced the ortho-nitrophenyl group at the para-position of nifedipine with a 2-methylthio-1-phenylamino-5-imidazolyl substituent. Then, calcium channel–antagonist activity (IC\(_{50}\)) were determined in guinea pigs, which revealed that the contractile responses elicited by these novel dihydropyridine-containing compounds inhibited higher K\(^+\) concentrations.

**Figure 6** Some commercially available drugs containing the pyridine scaffold.

- Pyridostigmine (myasthenia gravis)
- Isoniazid (tuberculosis)
- Nikethamide (respiratory stimulant)
- Nicotinamide (pellagra)
- Piroxicam (arthritis)
- Bromazepam (anxiety)
- Enpirolone (malaria)
- Abiraterone (prostate cancer)
- Tacrine (Alzheimer's disease)
- Omeprazole (ulcer)
- Phenazopyridine (urinary tract analgesic)
- Metrapone (NSAID)
- Delavirdine (HIV/AIDS)
- Nicorandil (vasodilator)
- Doxylamine (allergy)
- Tropicamide (antimuscarinic)
in a dose-dependent manner. In the muscular membrane, these effects were comparable to those shown by nifedipine and might be attributed to the suppression of Ca\(^{2+}\) entry via voltage-dependent calcium channels. However, it should be noted that the gut features a complex network of tissue, and we cannot rule out the potential of these compounds acting differently on distinct muscular and neuronal sites. A comparison of the activity of alkyl ester series in these compounds shows that by increasing the chain length of methylene at C\(_3\) and C\(_5\) ester substituents, activity reduces. For example, the t-butyl ester–containing compound was the least active among the series. Overall results suggested that most of the compounds had activity comparable to those of nifedipine, with the exception of two compounds, 13 and 14, being more active than nifedipine (Figure 13). As such, they can be potential leads for the design of calcium-channel blockers.  

Kumar et al reported anticoagulant activity for dihydropyridine-containing compounds, which was assessed using activated partial thromboplastin time and prothrombin time coagulation assays. Compound 15 (Figure 14) had a coagulation time of 720.35 seconds at 30 mg/mL. The standard drug heparin was used at a similar concentration.  

Figure 7 Some commercially available drugs containing the dihydropyridine scaffold.

Figure 8 FDA-approved vasodilators containing both pyridine and dihydropyridine scaffolds.
Table 1 Commercially available pyridine- and/or dihydropyridine-containing drugs and their applications

| Number | Drug      | Scaffold | Indication                          | Mechanism                                                                 | Ref   |
|--------|-----------|----------|-------------------------------------|---------------------------------------------------------------------------|-------|
| 1      | Pyridostigmine | Pyridine | Myasthenia gravis                   | AChE inhibition                                                           | [63]  |
| 2      | Piroxicam  | Pyridine | Arthritis                           | COX inhibition, leading to the peripheral inhibition of prostaglandin synthesis | [64]  |
| 3      | Ampiroxicam | Pyridine | Anti-inflammatory                    | COX inhibition                                                            | [65]  |
| 4      | Tenoxicam  | Pyridine | Rheumatoid arthritis and osteoarthritis | COX inhibition, leading to the peripheral inhibition of prostaglandin synthesis | [66]  |
| 5      | Droxican   | Pyridine | Rheumatoid arthritis and osteoarthritis | COX inhibition, leading to the peripheral inhibition of prostaglandin synthesis | [67]  |
| 6      | Loroxican  | Pyridine | Rheumatoid arthritis                | Inhibition of both COX1 and COX2 enzymes                                  | [68]  |
| 7      | Clonixin   | Pyridine | NSAID for arthritis, migraine, and tissue disorders | COX inhibition, leading to the peripheral inhibition of prostaglandin synthesis | [69]  |
| 8      | Etoricoxib | Pyridine | NSAID (relieves postsurgical dental pain) | Selective inhibition of isoform 2 of COX2, by preventing production of prostaglandins (PGs) from arachidonic acid | [70]  |
| 9      | Bromazepam | Pyridine | Anxiety                             | Binds to the GABA-A receptor, producing a conformational change and potentiating its inhibitory effects. | [71]  |
| 10     | Nikethamide| Pyridine | Respiratory stimulant               | Increases the development of tension of a muscle stimulated indirectly at low frequencies and produces a depression of muscular contraction when stimuli are of higher frequency | [72]  |
| 11     | Isoniazid  | Pyridine | Tuberculosis                        | Reduction in mycobacterial ferric KatG catalase peroxidase by hydrazine and reaction with oxygen to form an oxyferrous enzyme complex | [73]  |
| 12     | Nicotinamide | Pyridine | Pellagra                            | NFκB-mediated transcription of signaling molecules by inhibiting the nuclear PARP1 | [74]  |
| 13     | Enpiroline | Pyridine | Malaria                             | Inhibition of β-hematin formation and hemin peroxidation                   | [75]  |
| 14     | Abiraterone | Pyridine | Prostate cancer                     | Inhibition of the steroidal enzyme CYP17A1 in a selective and irreversible manner | [76]  |
| 15     | Tacrine    | Pyridine | Alzheimer's disease                 | Inhibition of the hydrolysis of acetylcholine released from functioning cholinergic neurons, thus leading to an accumulation of acetylcholine at cholinergic synapses | [77]  |
| 16     | Delavirdine| Pyridine | HIV/AIDS                            | Through disruption of the enzyme's catalytic site, it blocks RNA-dependent and DNA-dependent DNA polymerase activity via binding directly to viral reverse transcriptase (RT) | [78]  |
| 17     | Omeprazole | Pyridine | Ulcer                               | Regulates H⁺/K⁺-ATPase of the proton pump, expressed in high quantities by the parietal cells of the stomach | [79]  |

(Continued)
| Number | Drug          | Scaffold | Indication                  | Mechanism                                                                 | Ref   |
|--------|---------------|----------|-----------------------------|---------------------------------------------------------------------------|-------|
| 18     | Nicorandil    | Pyridine | Vasodilator                 | Two main mechanisms: an activator, and as an opener of ATP-sensitive (ATP-dependent) potassium channels | [79]  |
| 19     | Doxylamine    | Pyridine | Allergy                     | Competitive inhibition of histamine at H₁ receptors                       | [80]  |
| 20     | Metoxsalen    | Pyridine | Antimuscarinic               | Inhibition of voltage-gated sodium channels                               | [81]  |
| 21     | Methympiperazine | Pyridine | NSAID                       | Bending to all subtypes of muscarinic receptors as non-selective muscarinic antagonist | [82]  |
| 22     | Tropicamide   | Pyridine | Antimuscarinic              | Inhibition of the 11β-hydroxylase reaction in the adrenal cortex          | [83]  |
| 23     | Metyrapone    | Pyridine | NSAID                       | Inhibition of the enzyme 11β-hydroxylase by physically plugging the channel | [84]  |
| 24     | Azelnidipine  | DHP      | Hypertension                | Inhibition of the extracellular influx of calcium by physically plugging the channel | [85]  |
| 25     | Nifedipine    | DHP      | Raynaud's syndrome, premature birth | Blocking voltage-gated L-type calcium channels in myocardial and vascular smooth-muscle cells | [86]  |
| 26     | Nisoldipine   | DHP      | Hypertension                | Calcium-channel blockers                                                  | [87]  |
| 27     | Levalodipine  | DHP      | Hypertension                | Calcium-channel blockers                                                  | [88]  |
| 28     | Isradipine    | DHP      | Hypertension                | Calcium-channel blockers                                                  | [89]  |
| 29     | Felodipine    | DHP      | Hypertension                | Calcium-channel blockers                                                  | [90]  |
| 30     | Nisoldipine   | DHP      | Hypertension                | Calcium-channel blockers                                                  | [91]  |
| 31     | Nimodipine    | DHP      | Hypertension                | Calcium-channel blockers                                                  | [92]  |
| 32     | Nitrendipine  | DHP      | Hypertension                | Calcium-channel blockers                                                  | [93]  |
| 33     | Clevidipine   | DHP      | Hypertension                | Calcium-channel blockers                                                  | [94]  |
| 34     | Ciclopirox    | DHP      | Hypertension                | Calcium-channel blockers                                                  | [95]  |
| 35     | Levalodipine  | DHP      | Hypertension                | Calcium-channel blockers                                                  | [96]  |
| 36     | Efonidipine   | DHP      | Hypertension, angina         | Calcium-channel blockers                                                  | [97]  |
| 37     | Ciclopirox    | DHP      | Raynaud's syndrome, premature birth | Calcium-channel blockers                                                  | [98]  |
| No. | Drug Name     | Structural Class | Indication                                                                 | Mechanism of Action                                                                 |
|-----|---------------|------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| 39  | Milrinone     | Pyridine/ Pyridine/ DHP | Pulmonary vasodilator                                                      | Partial competitive inhibitor of phosphodiesterase 3                                |
| 40  | Amrinone      | Pyridine/ Pyridine/ DHP | Chronic congestive heart failure                                            | Phosphodiesterase 3 inhibition                                                     |
| 41  | Torsemide     | Pyridine          | Antihypertensive                                                            | Diuretic                                                                            |
| 42  | Pitavastatin  | Pyridine          | Dyslipidemia                                                                | Cholesterol-lowering                                                                |
| 43  | Ceftaroline   | Pyridine          | Antibiotic                                                                  | Antibacterial                                                                       |
| 44  | Tedizolid     | Pyridine          | Antibiotic                                                                  | Bacterial protein–synthesis inhibitor                                               |
| 45  | Ceftazidime   | Pyridine          | Antibiotic                                                                  | Inhibits PonA1, PonA2, and PbpA at intermediate concentrations                       |
| 46  | Delafloxacin  | Pyridine          | Antibiotic                                                                  | Inhibits the activity of bacterial DNA topoisomerase IV and DNA gyrase (topoisomerase II) |
| 47  | Ethionamide   | Pyridine          | Tuberculosis                                                                | Binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activity by causing a disruption of the enzyme's catalytic site. |
| 48  | Nevirapine    | Pyridine          | HIV/AIDS                                                                    | A non-peptidic protease inhibitor (PI) of HIV.                                      |
| 49  | Tipranavir    | Pyridine          | HIV/AIDS                                                                    | Inhibits the HIV viral protease enzyme, which prevents cleavage of the gag-pol polyprotein, resulting in noninfectious, immature viral particles. |
| 50  | Doravirine    | Pyridine          | HIV/AIDS                                                                    | Doravirine is a pyridine non-nucleoside reverse transcriptase inhibitor of HIV1.     |
| 51  | Indinavir     | Pyridine          | HIV/AIDS                                                                    | Inhibition of multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-β) |
| 52  | Axitinib      | Pyridine          | Cancer                                                                      | Oral VEGFR and kinase inhibitor                                                    |
| 53  | Imatinib      | Pyridine          | Cancer                                                                      | Inhibition of protein-tyrosine kinase                                               |
| 54  | Sorafenib     | Pyridine          | Cancer                                                                      | Inhibition of multiple membrane-bound and intracellular kinases                     |
| 55  | Regorafenib   | Pyridine          | Cancer                                                                      | Inhibition of multiple membrane-bound and intracellular kinases                     |
| 56  | Pexidartinib  | Pyridine          | Tenosynovial giant cell tumors (TGCT)                                       | Kinase Inhibition                                                                   |
| 57  | Alpelisib     | Pyridine          | Cancer                                                                      | Kinase Inhibition                                                                   |
| 58  | Lorlatinib    | Pyridine          | Lung cancer                                                                 | Kinase Inhibition                                                                   |

(Continued)
| Number | Drug | Scaffold | Indication | Mechanism | Ref |
|--------|------|----------|------------|-----------|-----|
| 59     | Acalabrutinib | Pyridine | Lung cancer | Kinase Inhibition | [118] |
| 60     | Abemaciclib | Pyridine | Breast cancer | Kinase Inhibition | [119] |
| 61     | Neratinib | Pyridine | Breast cancer | Kinase Inhibition | [120] |
| 62     | Enasidenib | Pyridine | Leukemia | Enasidenib is a selective inhibitor of IDH2, a mitochondria-localized enzyme involved in diverse cellular processes including adaptation to hypoxia, histone demethylation and DNA modification | [121] |
| 63     | Ivosidenib | Pyridine | Leukemia | Reversible inhibitor of IDH1 which is non-competitive with respect to the cofactor NADH | [122] |
| 64     | Phenazopyridine | Pyridine | Lower urinary tract infection | Inhibition of voltage-gated sodium channels | [121] |
| 65     | Betahistine | Pyridine | Ménière's disease | Adaptive mechanisms of the CNS | [123] |
| 66     | Felodipine | DHP | High blood pressure (hypertension) | Calcium-channel blocker | [124] |
| 67     | Amifampridine | Pyridine | Lambert-Eaton myasthenic syndrome (LEMS) | Calcium-channel blocker | [125] |
| 68     | Torasemide | Pyridine | Hypertension and edema | Known to have an effect in the renin-angiotensin-aldosterone system by inhibiting the downstream cascade after the activation of angiotensin II | [126] |
| 69     | Nimodipine | DHP | Subarachnoid hemorrhage | Blocks intracellular influx of calcium through voltage-dependent and receptor-operated slow calcium channels across the membranes of myocardi, vascular smooth muscle, and neuronal cells | [127] |
| 70     | Chlorpheniramine | Pyridine | Upper respiratory allergies | Analgesic and antipyretic effects | [128] |
| 71     | Flunixin | Pyridine | Musculoskeletal and ocular pain. | Anti-inflammatory and analgesic effects | [129] |
| 72     | Pyridoxal phosphate | Pyridine | Vitamin B6 deficiency and to treat nausea | Acts as a coenzyme in all transamination reactions, and in some oxidation and decarboxylation reactions of amino acids. | [130] |
| 73     | Pyridoxine | Pyridine | Vitamin B6 deficiency | Targets the Raf/Mek/Erk pathway via inhibition of these kinases, genetic transcription involving cell proliferation and angiogenesis is also inhibited. | [131] |
| 74     | Scrambled | Pyridine | Liver carcinoma and advanced renal carcinoma | Carboxinamide competes with free histamine for binding at HA-receptor sites. | [132] |
| 75     | Carboxinamide | Pyridine | Allergic rhinitis, vasomotor rhinitis | Allergic asthma and rhinitis | [133] |

Table 1 (Continued).
| 77  | Etoricoxib | Pyridine  | Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, | Selectively inhibits isoform 2 of cyclooxygenase enzyme (COX2), preventing production of prostaglandins (PGs) from arachidonic acid. |
| 78  | Doxylamine | Pyridine  | Allergies | |
| 79  | Brompheniramine | Pyridine  | Coughs, upper respiratory symptoms, and nasal congestion | An antagonist of the H1 histamine receptors with moderate antimuscarinic actions, as with other common antihistamines such as diphenhydramine |
| 80  | Topiroxostat | Pyridine  | Hyperuricemia and gout | Xanthine oxidase inhibitor |
| 81  | Methyl nicotinate | Pyridine  | Interim relief of pains and aches in joints, tendons and muscles. | Prostaglandin D2 release |
| 82  | Niacin | Pyridine  | To treat pellagra and hypertriglyceridemia | Inhibition of hepatocyte diacylglycerol acyltransferase 2 |
| 83  | Pyrithione | Pyridine  | Seborrheic dermatitis and dandruff | Makes a CuPT complex. Copper deactivates iron-sulfur (Fe-S) and inhibit Fe-S proteins activity |
| 84  | Nicotine | Pyridine  | To reprieve of withdrawal symptoms of nicotine and helps in smoking cessation. | Initiates a response at nicotinic acetylcholine receptors |
| 85  | Torasemide | Pyridine  | To cure edema related to failure of heart, renal or liver disease and hypertension | It reduces the demand of oxygen by preventing the Na+, K+, Cl- pump |
| 86  | Desloradine | Pyridine  | To cure seasonal and unseasonal pruritus, allergic rhinitis and urticaria. | Obstruct the action of endogenous histamine |
| 87  | Dapiprazole | DHP  | Used to inverse mydriasis following the examination of an eye | Blocks alpha 1-adrenergic receptors |
| 88  | Zolpidem | Pyridine  | A short-term cure of insomnia | Bind the receptor |
| 89  | Amlodipine | DHP  | Angina and hypertension | Suspend calcium ion influx |
| 90  | Triprolidine | Pyridine  | To ease fever, cold and allergy symptoms and helps in sleep. | Binds to the histamine H1 receptor. |
| 91  | Nifedipine | DHP  | Manage pectoris, angina and hypertension. | Calcium-channel blocker |

(Continued)
Table 1 (Continued).

| Number | Drug            | Scaffold | Indication                     | Mechanism                                                                 | Ref  |
|--------|-----------------|----------|--------------------------------|---------------------------------------------------------------------------|------|
| 92     | Chromium picolinate | Pyridine | Use for proper function of insulin | Glucose level regulation                                                  | [148] |
| 93     | Chromium nicotinate | Pyridine | Treats chromium deficiency    | Increases the activity of kinase insulin receptor β                      | [149] |
| 94     | Ubrogepant       | Pyridine | To cure migraine              | Initiation of the trigeminal ganglion                                     | [150] |
| 95     | Nedocromil       | DHP      | To cure allergic conjunctivitis | Inhibition of axon reflexes and release of sensory neuropeptides          | [151] |
| 96     | Vemurafenib      | Pyridine | To cure Erdheim-Chester disease | A mutated BRAF-serine-threonine kinase inhibitor                          | [152] |
| 97     | Imiquimod        | Pyridine | Warts                         | Unknown                                                                   | [153] |
| 98     | Trovafoxacin     | Pyridine | To cure chlamydia and gonorrhea | Inhibits topoisomerase IV and DNA gyrase                                 | [154,155] |
| 99     | Chlorquinaldol   | Pyridine | To cure bacterial vaginosis    | Unknown                                                                   | [156] |
| 100    | Oxyquinoline     | Pyridine | Disinfectant, antiseptic and pesticide properties | Unknown                                                                 | [157] |
| 101    | Rupatadine       | Pyridine | Remedy for allergic rhinitis.  | Blocks H1 receptor                                                        | [158] |
| 102    | Diiodohydroxyquinoline | Pyridine | Amoebiasis                   | Unknown                                                                   | [159] |
| 103    | Papaverine       | Pyridine | To cure visceral spasms and muscle spasms | Inhibits nonxanthine phosphodiesterase                                   | [160] |
| 104    | NADH             | DHP      | Neutraceutical                | Participates in many enzymatic reactions in which it oxidized in to (NAD+) and reduced in to (NADH) | [161] |
| 105    | Chloroquine      | Pyridine | Malaria                       | Inhibition of heme polymerase enzymatic action                           | [162] |
| 106    | Bisacodyl        | Pyridine | Constipation                  | Converted into the active form bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) | [163] |
| 107    | Florbetapir<sup>18F</sup> | Pyridine | Used to find out the cognitive impairment causes | It binds to florbetapir                                                  | [164] |
| 108    | Quinine          | Pyridine | Malaria                       | Breaks parasitic hemoglobin                                              | [165] |
| 109    | Quinidine        | Pyridine | Treats atrial fibrillation and flutter | On the neuronal cell membrane, the compound acts on sodium channel     | [166] |
| 110    | Acrivastine      | Pyridine | Rhinitis                      | Blocks histamine                                                          | [167] |
Dyslipidemia is a complex disease that promotes atherosclerosis and cardiovascular problems. In 2001, the pyridine-containing drug cerivastatin was withdrawn from the market due to rhabdomyolysis risk. Later, another drug in the statin class, pitavastatin, was developed for lowering blood cholesterol (Figure 15).

In 2016, antihyperlipidemic compounds of type (benzoylphenyl)pyridine-3-carboxamide were reported (Figure 16), and demonstrated excellent in vivo activity. The antidyslipidemic activity of the compounds was tested in vivo. These compounds were able to lower total cholesterol (TC) from 11.0% to 24.8%. The compounds showed plasma phospholipid–lowering (PL) activity ranging from 5.7% to 28.5%. The most active compound in the series was (−28.5%), whereas gemfibrozil (39.1% PL-decreasing activity) was the least active. The scavenging capability of compounds was also tested against the production of superoxide ions (O$_2^-$) using 100 and 200 mg/mL allopurinol. Antioxidant activity of the compounds in the series was substantial, and those with tert-butyl ester functionality were found to be the most active. Compounds demonstrated potential antidyslipidemic potential, but compounds exhibited considerable antioxidant activity (Figure 17). It can tentatively be assumed that the ester group plays a key role in differentiating antidyslipidemic and antioxidant activity. Antidyslipidemic potential was shown by those compounds that contained methyl/ethyl ester groups, whereas antioxidant activity was displayed by compounds with tert-butyl ester functionality.

Although many dihydropyridine-containing drugs are commercially available to manage hypertension, we, believe that further research in the pyridine–dihydropyridine class of compounds will lead to the discovery of new pharmaceuticals to handle complications associated with cardiovascular diseases.

**Anti-Infectious Drugs and Bioactive Compounds**

**Antibacterial Agents**

Antibiotic resistance is a serious threat to public health, driving the search for novel inhibitors of bacteria. Most antibiotics are being resisted by bacterial pathogens, rendering the development of novel, more effective antibacterial drug candidates a critical requirement. In the last 10 years, the FDA has approved many pyridine-containing...
antibiotics, such as ceftaroline fosamil, tedizolid, ceftazidime, and delafloxacin (Figure 18).

Jo et al synthesized oxazolidinone-bearing pyridine derivatives, which had potent antibacterial activity. In vitro and in vivo antibacterial studies were performed against troublesome Gram-negative and Gram-positive strains of bacteria and two antibiotic-resistant strains. Several substituted (hetero)aromatic rings were tolerated on the pyridine moiety, and the presence or orientation of the methyl group in the (hetero)aromatic rings had a profound effect on antibacterial activity. The most active derivatives, 23–25 (Figure 19), displayed potent activity against a wide range of drug-resistant bacteria, as well as Moraxella catarrhalis and Haemophilus influenzae, and had longer half-lives in vivo than linezolid. They had 4–16 fold the in vitro activity of linezolid, and double the in vivo efficacy.186

In another study, oxazolo[4,5-b]pyridine derivatives were synthesized to derive antimicrobial agents. These compounds had excellent activity against methicillin-resistant Staphylococcus aureus, which is responsible for widespread hospital-acquired infections. Compounds 28 and 31 were the most potent, with MIC values of 1.56–25 µg/mL, while 26, 27, 29, 30, 32, and 33 showed moderate activity (6.25–50 µg/mL) in comparison to the conventional drugs streptomycin and ampicillin (Figure 20). Further studies revealed that oxazolo[4,5-b]pyridine analogues were more active against Gram-positive bacteria than Gram-negative bacteria. Compounds 28 and 31 had potent activity against S. aureus methicillin-resistant strains, with activity of 1.56–3.12 µg/mL, while standard drugs (ampicillin and streptomycin) had MIC values of 6.25–12.5 µg/mL. These compounds were also found to be active against other bacterial strains. Furthermore, the synthesized compounds were docked in the enterotoxin protein of S. aureus, which is a type A staphylococcal enterotoxin. Significant antibacterial activity for 28 and 31 in comparison to the standard drugs ampicillin and streptomycin was further validated by in vitro and in silico studies. The compounds were then tested for ligand–protein binding (MRSA protein) affinity toward S. aureus, wherein the compounds had higher ligand–protein binding affinity than the standard drugs.187

Novel pyrazolo[3,4-b]pyridine derivatives of 4-thiazolidinone Schiff bases, and azetidin-2-ones have also been synthesized and screened for antimicrobial activity.188 Most compounds exhibited moderate–high activity at 0.12–62.5 µg/mL, wherein amphotericin B, ampicillin, and gentamicin were used as standard antimicrobial agents. Against the Fusarium oxysporum fungal strain, compound 37 had an MIC of 0.98 µg/mL, comparable to that of the standard antimicrobial drug amphotericin B. Significant cytotoxic activity was observed for these compounds against the HepG2 cell line, with IC50 of 0.0158–71.3 µM in comparison to doxorubicin (IC50 = 0.008 µM). Compounds 34–38 also had antiproliferative activity (IC50 = 0.0001–0.0211 µM) against the MCF7 cell line (Figure 21). Specifically, highly significant antiproliferative efficacy was displayed by compound 37 against MCF7 cells and HepG2, with IC50 of 0.0001 µM and 0.0158 µM, respectively. These results suggest that these compounds might lead toward the development of promising and novel antimicrobial and antiproliferative drug candidates. These compounds undoubtedly hold great potential in the quest to develop novel antiproliferative and antimicrobial agents.188

Dihydropyridines bearing thiazole derivatives were initially assessed with in silico molecular docking simulations to investigate their possible DNA gyrase inhibitory activity. Antibacterial activity was then assessed to validate the results of computational studies, wherein compound 39 demonstrated the highest efficacy against Aspergillus flavus and compound 40 had significant potency against C. albicans and A. flavus (Figure 22).
Because of the phenyl ring’s size and inductive impact, the presence of an electron-withdrawing group might be responsible for excellent activity.\textsuperscript{189} Pyridine rings containing 1,3,4-oxadiazole derivatives were explored by Lak et al.\textsuperscript{190} All synthesized compounds were evaluated for their antibacterial activity against...
Figure 11 FDA-approved drugs containing pyridine or dihydropyridine scaffolds for the treatment of hypertension.

Figure 12 Highly potent calcium-channel antagonists.

Figure 13 Calcium-channel antagonists.
Pseudomonas aeruginosa, S. aureus, Staphylococcus epidermidis, Escherichia coli, Bacillus cereus, and Gram-positive bacteria showed greater inhibitory activity than Gram-negative bacteria. Most of the synthesized compounds were highly potent against S. aureus and S. epidermidis. Compounds 41 and 42 had strong antibacterial effects with excellent MIC and selectivity-index values (Figure 23). The key point in this study was the single-step synthesis of oxadiazole-pyridine derivative. This approach with sufficient molecular modification could be adopted as a cost-effective strategy to produce potent antimicrobial agents. In another study, 1,3,4-oxadiazole derivatives containing indole and pyridine were synthesized and evaluated against two strains of Mycobacterium tuberculosis — H37Ra and BCG — both in dormant and active conditions. Compound 43–45 showed remarkable antitubercular activity (Figure 24). Antiproliferative activity of the synthesized compounds was also tested on HeLa, PANC1, and A549 cell lines using modified MTT assays. Most were acytotoxic. Based on MIC values and cytotoxicity results, the selectivity-index values determined for 43–45, which were highly potent against Mycobacterium bovis BCG, while the compounds had index values ≥10. In addition, molecular docking studies were performed at the active site of enoyl reductase (InhA) for compounds 43–45. The encouraging results substantiated by selectivity, potency, and low cytotoxicity indicate these derivatives as potential antitubercular lead agents.

In the FDA database, one can find many pyridine-containing drugs, such as isoniazid, ethionamide, and prothionamide, that are highly effective against mycobacteria for the treatment of tuberculosis (Figure 25). Further efforts to discover new bioactive compounds resulted in the synthesis of 2-(1-adamantylthio) pyridine...
Figure 18 Pyridine-containing antibiotics approved by the FDA during the last decade.

Figure 17 Cholesterol-lowering compounds (18–22) containing dihydropyridine rings.
derivatives, which were screened for antibacterial activity against 27 strains, antimalarial activity against *Plasmodium falciparum*, and anticancer activity against HepG2, A549, HuCCA1, and MOLT3 cell lines. The results suggested that 2-(1-adamantylthio)pyridine–type compounds constituted a new class of antibacterial, antimalarial, and anticancer agent with potential therapeutic applications. All the compounds were highly active against streptococci, showing antigrowth activity of 15–30 µg/mL. Compounds 46–49 were potent antimalarial, anticancer, and antibacterial agents (Figure 26). Surprisingly, 6-(1-adamantylthio)nicotinonitrile 49 had selective antimicrobial activity against β-hemolytic streptococcus, *Edwardsiella tarda*, *Vibrio parahaemolyticus*, and *Vibrio cholerae*. These findings suggest that compound 49 could be a promising antibacterial agent with potential for further improvement in its therapeutic properties.\(^{191}\)

In summary, pyridine-containing compounds hold great promise for the development of pharmaceuticals against drug-resistant bacteria, since they exert

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**Figure 19** Oxazolidinone–pyridine-substituted antibacterial agents.

| m-position | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 |
|------------|----|----|----|----|----|----|----|----|
| R          | 2-Cl | 2-Me | 2-OMe | 3-Br | 3-Cl | 3-NO₂ | 3-OMe | 4-NO₂ |
|           |     |     |     |     |     |     |     |     |
| MIC (µg/mL) | S. aureus = 3.12 | 1.56 | B. subtilis = 6.25 | 3.12 |

**Figure 20** Oxazolo[4,5-b]pyridines containing antibacterial agents with remarkable activity.
significant inhibitory effects on pathogens. However, more research is needed to find a viable solution to drug-resistant pathogens.

Antifungal Agents

The recent rise in multidrug-resistant (MDR) fungal infections has led researchers to find new antifungal agents.
Pyridine-containing triazole derivatives demonstrate remarkable antifungal properties. For example, thiadiazole-containing triazolopyridines have been found to display antifungal activity against *Pseudoperonospora cubensis*, *Pseudomonas syringae* pv. *Lachrymans*, and *Corynespora cassiicola*. 

In 2016, Mu et al reported a series of hydrazone-containing triazolopyridine derivatives with significant antifungal activity against *Stemphylium lycopersici*, *Botrytis cinerea*, and *F. oxysporum*. 

In 2019, Wei et al designed inulineSchiff bases bearing pyridine rings and evaluated their in vitro antifungal properties against *Phomopsis asparagi*, *F. oxysporum* f. sp. *niveum*, and *Botrytis cinerea*. Pyridine-grafted chitosan polymers have also been reported with improved antifungal properties. Pyridine has been grafted onto starch to control different fungi. In summary, fusing triazole and pyridine derivatives may lead to the development of broad-spectrum antifungal agents against MDR fungal infections.

### Antimalarial Agents

A series of novel pyridyl–indole hybrids were described by Heba et al, which were designed using a fragment-based strategy. The compounds were tested for antimalarial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum*. Compounds 50–55 (Figure 27) displayed the most potent antimalarial activity (IC50 =1.47–9.23 μM for D6 and IC50 =1.16–7.66 μM for W2). Selectivity-index values were 1.47–8.3 for D6 and 1.7–10 for W2. Compounds 50, 51, and 54 demonstrated antimalarial activity against D6 and W2. The distinctive feature of these compounds was the absence of substitution at the C2 position of the pyridine ring.

| Entry | R      | Active (μM) | Dormant (μM) |
|-------|--------|-------------|--------------|
| 43    | 2-OH   | 0.94        | 1.19         |
| 44    | 2-NO2  | 1.03        | 0.85         |
| 45    | 4-NO2  | 2.50        | 2.37         |

Figure 24 Highly potent antitubercular compounds (43–45) with MIC values (μg/mL) against *M. bovis BCG*.

Figure 25 Pyridine-containing drugs against mycobacteria.

Figure 26 2(1-adamantylthio) pyridine derivatives with potent antimicrobial activity.
Furthermore, binding interactions of these compounds with quadruple mutant *P. falciparum* dihydrofolate reductase enzyme were investigated via molecular docking studies. Compounds 50–52 were the most active at the binding cavities of quadruple-mutant Pf DHFR-TS–active sites, indicating suitable binding associations that might be the mechanism influencing their activity as antimalarial agents.197

Xue et al reported fosmidomycin derivatives containing the pyridine scaffold that inhibited *P. falciparum* DXR with *K_i* values of 1.9–13 nM. The most potent compound (Figure 28) was elevenfold as active as fosmidomycin.198

We believe that pyridine-based compounds have immense potential for the development of antimalarial drugs, since they exhibit antimalarial effects due to hydrogen-bond interactions between pyridine nitrogen and cysteine of target proteins in the pathogen, thereby rendering such compounds highly effective against chloroquine-resistant strains.198

**Antiviral Agents**

For the treatment of HIV infection, the FDA database contains many pyridine- and dihydropyridine-containing drugs, such as nevirapine, tipranavir, doravirine, and indinavir (Figure 29).

In the last decade, research into new antiviral agents has resulted in the synthesis of pyridotriazines, furopyridines, and pyridothiadiazepinhiones.199 Among the synthesized ones, a few molecules had appreciable efficacy against adenovirus type 7 and the rotavirus Wa strain. Compound 56 suppressed viral titers by 60% and 53.3% for the rotavirus Wa strain and adenovirus type 7, respectively, and compound 57 demonstrated 50% and 53.3% reductions, respectively. These compounds (Figure 30) can potentially be used as therapies for rotavirus and adenovirus type 7, which currently have no adequate treatment options.199

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**Figure 27** Highly active antimalarial pyridyl–indole hybrids.

**Figure 28** Highly potent antimalarial pyridine-containing fosmidomycin derivative.

**Figure 29** Highly active antimalarial pyridyl–indole hybrids.
In recent years, antiviral drugs have been developed as a result of the search for viable viral therapeutic approaches. Click chemistry is one of the most effective ways for producing bioorganic molecules, such as antiviral therapeutics. In a recent study, pyridine derivatives were acquainted with propargyl group by $O$-propargylation $^{58-59}$ (Figure 31). Cu-catalyzed cycloaddition of azido-sugars with substituted (propargyl)oxypyridines or propargyl sugars with azidoethoxy-pyridine derivatives resulted in high yields of desired 1,2,3-triazoles. MTT and plaque-reduction assays were performed against the H5N1 influenza strain to evaluate antiviral activity. High activity and low toxicity were demonstrated by triazolyl glycoside $^{58}$. The effect of pyridinyl fragment binding to glycosyl triazole moieties on antiviral activity was studied using SAR correlations. Most of the compounds had weakly active to moderately active inhibitory profiles at different concentrations, with the exception of compound $^{59}$, which had the strongest activity. All tested compounds showed dose-dependent inhibitory behavior. Low cytotoxicity was observed for compounds $^{58}$ and $^{59}$. $^{200}$
Auxilin 2, also known as cyclin G–associated kinase (GAK), has been demonstrated to impact both the initial and late phases of the viral life cycle, thereby functioning as the master regulator against viral infection. This host-specific strategy offers many advantages, such as development of broad-spectrum antiviral agents and high barriers to resistance. Asquith et al initially discovered SGC-GAK-1, which has excellent GAK affinity with a $K_D$ value of 1.9 nm. Later, Jonghe et al developed potent and selective GAK inhibitors that were basically isothiazolopyridine-type compounds with morpholine residue (Figure 32). These compounds had high GAK affinity, but were moderately active against dengue and hepatitis C viruses. Subsequent research showed that the introduction of dimethyl groups to the morpholine residue of 62 had favorable antiviral effects, which led to the discovery of 63. The compound was active against chikungunya, dengue, and Zika viruses. However, replacing the morpholine residue with carboxamides, alkoxides, and amines resulted in weak antiviral effects.

Further modifications to the pyridine core of 63 were done to further improve the antiviral effect. The new compounds were highly active against dengue, with GAK-binding affinity

![Figure 32](https://doi.org/10.2147/DDDT.S329547) Antiviral GAK inhibitors containing isothiazolopyridine scaffold.

![Figure 33](https://doi.org/10.2147/DDDT.S329547) Antiviral compounds capable of targeting cyclin G–associated kinase of dengue virus.

![Figure 34](https://doi.org/10.2147/DDDT.S329547) Antiviral compounds with high GAK-binding affinity.
in the nanomolar range. For example, compound 64 inhibited GAK strongly (Figure 33) and was equally potent against dengue.\textsuperscript{206}

A novel series of isothiazolopyridines containing 3,4-dimethoxyphenyl residue was also synthesized,\textsuperscript{206} wherein GAK IC\textsubscript{50} values were 0.1–0.5 \(\mu\text{M}\). Compound 65 had the highest GAK affinity (IC\textsubscript{50} = 0.124 \(\mu\text{M}\)), whereas compound 66 containing N-morpholinyl residue was fivefold less active (Figure 34). Diverse structural modifications at the active site of the 6-phenyl moiety’s position 4 can, however, be employed to alter antiviral activity.\textsuperscript{206}

Although many pyridine-containing drugs are commercially available to manage HIV/AIDS, further research on the isothiazolopyridine class of compounds could lead to a viable solution for other types of viral infections, such as dengue.

**Anti-inflammatory Drugs and Active Compounds**

Oxicam compounds are used to treat musculoskeletal disorders: acute and chronic inflammation via inhibition of the cyclooxygenase isoforms COX1 and COX2.\textsuperscript{207} The FDA-approved oxicam NSAIDs containing the pyridine moiety are shown in Figure 35. These drugs are mainly used to treat musculoskeletal disorders, such as osteoarthritis and rheumatoid arthritis, by relieving painful inflammatory conditions.\textsuperscript{208}

Clonixin (Figure 36) is another FDA-approved drug and has analgesic and antipyretic effects in chronic arthritic conditions.\textsuperscript{69} For etoricoxib, the FDA needs additional safety data for the approval. It is, however, licensed in >80 countries worldwide. The drug, which is a COX2 inhibitor, is mainly used for the treatment of gout, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, and rheumatoid arthritis.\textsuperscript{209}

Recently, many bioactive molecules have been reported to deal with inflammatory markers.\textsuperscript{210,211} Thirumurugan et al synthesized indole-bearing pyridine derivatives and evaluated their anti-inflammatory activity against rat-paw edema. All compounds had remarkable anti-inflammatory activity, particularly 67–68, which demonstrated significantly higher activity than the standard drug indomethacin (Figure 37). The analgesic activity of dihydropyridine derivatives was also compared with aspirin. Compounds 68–70 had considerably higher analgesic activity.\textsuperscript{212}

In an attempt to broaden the scope of anti-inflammatory research, Liu et al designed thienopyridine derivatives (Figure 38). When subjected to NO-production assays, most of the compounds were able to inhibit NO production. The most effective analogue, 72, substantially reduced NO production at lower doses (IC\textsubscript{50} = 3.30 \(\mu\text{M}\)). Anti-inflammatory profiles were further investigated by evaluating TNF\textalpha-inhibitory activity of the most potent compound —

**Figure 35** FDA-approved oxicam-class NSAIDs for musculoskeletal disorders, such as osteoarthritis and rheumatoid arthritis.

**Figure 36** Commercially available NSAIDs containing the pyridine ring.
Figure 37 Indolyl pyridines (67–68) and dihydropyridine-containing compounds (69–71) with remarkable anti-inflammatory activity in animal models.

Figure 38 Thienopyridine derivatives (72–75) with anti-inflammatory and immunomodulatory profiles. IC50 values correspond to inhibition of NO production on murine RAW264.7 macrophages.

Figure 39 Highly potent anti-inflammatory compounds.
Interestingly, compounds with piperazine residue — 74 and 75 — demonstrated comparable effectiveness. These results indicated that thienopyridine-containing compounds of 72–75 may represent a new class of anti-inflammatory drugs that necessitated more attention.213

Yaqoob et al recently reported on highly potent anti-inflammatory compounds designed by employing pyridine-containing isonicotinic acid (Figure 39). Remarkable ROS-inhibitory activity was observed for compounds 76–79. Compound 76 was one of the most potent anti-inflammatory agents, with IC_{50} of 1.42±0.1 µg/mL.214

The antagonizing hormone glucocorticoid stimulates hepatic glucose synthesis while inhibiting insulin-assisted glucose absorption in skeletal muscles and adipose tissue.215 Glucocorticoidal stimulation, which is coordinated by 11β-HSD2 and 11β-HSD1 enzymes, is often used to measure glucocorticoid target–tissue activity.216 Enzyme 11-HSD1 is considered to play a crucial role during lipid and glucose metabolism in adipose tissue. Therefore, inhibitors of 11-HSD1 are a family of drugs that are being developed to address diabetic complications. The role of 11-HSD1 in the development of insulin resistance and obesity has been shown in several preclinical investigations. Recently, α-glucosidase–inhibitory activity was tested in vitro using a new set of triazole-containing dihydropyridine derivatives. When compared to the acarbose standard (IC_{50} = 395.17 µM), these compounds showed considerable α-glucosidase–inhibitory activity (IC_{50} = 72.71–283.41 µM). Compounds 80–82 (Figure 40) seemed to have the highest inhibitory action against the enzyme, with IC_{50} values of 72.71±1.09, 73.83±1.17, and 85.96±1.84 µM, respectively. To understand the mechanism of action, the most efficient compounds (80 and 81) of the series were evaluated using in vitro enzymatic tests to assess their 11β-HSD1 enzyme–inhibitory activity. The mechanism of action of 80 and 81 was further confirmed using molecular docking analysis, which showed that both compounds bound strongly in the cavity of 11β-HSD1 receptors, resulting in appreciable dock scores, electrostatic energy, and hydrogen-bond interactions for the desired molecular complex (both sides and back chain). Overall, compounds 80 (–9.758) and 81 (–8.959) demonstrated highly stable binding patterns for 11β-HSD1 in molecular docking studies.217

Larijani et al reported excellent α-glucosidase activity for coumarin-fused pyridines (Figure 41). Most of their compounds had IC_{50} values in the range of 101.0±2.0 to 227.3±1.4 µM, whereas the standard drug acarbose had an IC_{50} value of 750.0±1.5 µM. Compounds 83–85 were the most potent, with IC_{50} values of 101.0±2.0, 111.3±1.5 and 114.3±1.8 µM, respectively.218

Although many pyridine-containing NSAIDs are commercially available for musculoskeletal disorders, such as osteoarthritis and rheumatoid arthritis, further research on

![Figure 40](https://www.dovepress.com/)

% inhibition of α-glucosidase activity

**Figure 40** 11β-HSD1 inhibitors against diabetes mellitus.
and dihydroxypyridine have been synthesized and evaluated for their anti-Alzheimer’s activity. León et al developed a series of tacrine–dihydropyridine hybrids decorated with pyrin scaffolds. The series was evaluated for inhibitory potential against acetylcholinesterase. Compound 86 had tenfold the activity (IC<sub>50</sub> = 0.0048±0.001) of the donepezil standard (0.049±0.005; Figure 44).

Huperzine A 94 (Figure 45) is well recognized for its neuroprotective properties, which result in enhanced NGF production and expression, which are involved in the functional enhancement of neurons, their survival, and protection against damage in neurodegenerative illnesses (such as Alzheimer’s). It protects neurons from glutamate toxicity by decreasing glutamate-induced calcium mobilization. It also protects rat pheochromocytoma cells from oxidative stress caused by hydrogen peroxide. Because oxidative stress exacerbates Alzheimer’s neurodegeneration, huperzine A 94 is widely used to treat Alzheimer’s complications.

Recently, a dihydropyridine derivative with pyridinium moiety 87 was found to be highly active as a gene-transfection agent and displayed excellent mitochondrion-targeted antioxidant activity. It was found to play an important role in protection against neural injury (Figure 46), and caused increased expression of proteins in the hippocampus and cerebral cortex. It was found that increased expression of the GAD67 enzyme in hippocampus converted the glutamate to GABA, and GABA was found to protect the brain from neural injury. It regulated the development of spatial memory, and via synthesis of GABA it balanced neurotransmitters, consolidation, and stability of memory. Owing to its memory-improvement and neural protection abilities, it can be used in the treatment of Alzheimer’s disease.

Dihydropyridine derivatives with pyridinium moiety can be a viable solution for the cure Alzheimer’s, since they are able to enhance the expression of crucial proteins in the hippocampus and cerebral cortex. In coming years, extensive research in this type of compound is anticipated.

**Parkinson’s Disease**

Pyrazoline-containing pyridine derivatives have been reported to display antiparkinsonian activity. For example, compounds 88 and 89 have significant antiparkinsonian activity, with 0.8 relative potency compared to the reference drugs benzatropine and voltaren (Figure 47).

Several dihydropyridines have amino acids in their structure and are peptidomimetic in nature. The most

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**Neurogenic Drugs and Bioactive Compounds**

Neuroprotection may be defined as the maintenance, preservation, and stability of neuronal functions and structures. It is a mechanism for smooth working of the nervous system and prevention of neural damage. The brain is a very sensitive part of the body, so remains highly vulnerable to pathogens and damage causing neurodegenerative disorders, such as Parkinson’s disease, amyotrophic lateral sclerosis, epilepsy, brain tumors, and Alzheimer’s disease. These illnesses are main cause of neuronal death, including neural strokes, which are a result of different complications like calcium-homeostasis loss, cytotoxicity, metabolic failure, and oxidative stress. Many pyridine- or dihydropyridine-containing drugs are being evaluated for the treatment of neurodegenerative disorders (Figure 42).

**Alzheimer’s Disease**

Nimodipine is a wide-spectrum neuroprotective drug that is widely used in Alzheimer’s disease, migraine, and post-hemorrhagic vasospasm as an anti-ischemic agent. Nimodipine (Figure 43) is well known for its relaxing potential for cerebral vasculature.

Alzheimer’s disease is a neurodegenerative disorder characterized by memory dysfunction and cognitive impairment. A number of compounds based on pyridine- or dihydropyridine-containing oxicams may lead to the development of effective drugs for the cure of acute and chronic inflammation.

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**Figure 41** Coumarin-fused pyridines with potent α-glucosidase activity.
studied are glutapyrone 90 and tauropyone 91 (Figure 48). Both these compounds protect cerebellar granule cells from damage by lowering lactate dehydrogenase, thus avoiding ischemia/hypoxia (lack of oxygen and glucose) and glutamate excitotoxicity. Tauropyone 91 can be used for the treatment of Parkinson’s disease, as it suppresses the inflammatory process in rats in a Parkinson’s 6-hydroxydopamine model at 6.25 g/L per day for 7 and 14 days. Tauropyone 91 (1 mg/kg) shows dual actions in the brain. In some cases, it shows inflammatory and proapoptotic effects, but in azidothymidine toxicity, it acts as anti-inflammatory and antiapoptotic agent. The amino acid–containing monocyclic dihydropyridines represent a new atypical group of DHPs, and data have shown their neuromodulatory potential and normalizing effect on protein expression in the brain. 230–233

Although pyrazoline-containing pyridine derivatives have been reported to display antiparkinsonian activity,
many reports in the literature have suggested that non–calcium agonistic 1,4-dihydropyridine derivatives demonstrate remarkable neuroprotective effects, thus holding great potential for future drug design against Parkinson’s disease.

Cerebral Ischemia
Cerebral ischemia is also a neuronal disorder in which many noxious by-products and free radicals are generated, resulting in enzymatic activity being altered, which results in a breakdown of cellular phospholipids, proteins, and nucleic acids. Cerebral edema is a complication that occurs due to the overexpression of AQP4 whereby abundant water enters the brain and the swollen brain is compressed against the skull. This increased pressure in the cranium causes herniation and brain ischemia, leading to death. This condition is treated with piroxicam (Figure 49), which has inhibitory effects on AQP4 (the most abundant water channel in the brain). Pyridine ring–containing piroxicam 92 binds with AQP4, and in this way regulates it in brain to avoid cerebral ischemia and edema.234

Schizophrenia
Schizophrenia is a mental condition marked by behavioral, neurochemical, and morphological disorders. Antipsychotics that operate on molecular targets other than monoaminergic receptors have not yet been produced, despite significant progress in medication development for schizophrenia. GABAergic dysfunction may be implicated in this disease.235 Marcinkowska et al recently discovered the imidazopyridine-type neuroprotective agent 93 (Figure 50), which shows potential affinity for serotonin 5HT₂ and 5HT₃ receptors and antipsychotic-like activity. Compound 93 also shows positive allosteric modulator properties, high metabolic stability, and no hepatotoxicity.235

Senna spp. are a celebrated source of natural alkaloids of the piperidine and pyridine classes.236,237 Francisco et al isolated five new pyridine-containing alkaloids (Figure 51) from Senna and Cassia spp.: 8′-multijuguinol 95, 7′-multijuguinol 96, methyl multijuguinate 97, 12′-hydroxy-8′-multijuguinol 98, and 12′-hydroxy-7′-multijuguinol 99, which were isolated from Senna multijuga leaves. All these compounds had acetylcholinesterase-inhibitory activity comparable to the standard drug physostigmine. SAR studies have suggested that hydroxypyridine moiety is the key interaction site responsible for this activity, whereas the alkyl side chain also influences the acetylcholinesterase-inhibitory effect of the alkaloids.236 A summary of the neuroprotective compounds with their
potential applications and tentative mechanisms is presented in Table 2.

Anticancer Drugs and Bioactive Compounds

Cancer is considered a major challenge to public health. There are many pyridine-containing drugs in the FDA database (Figure 52), eg, axitinib — a tyrosine kinase inhibitor — developed by Pfizer. For the treatment of cancer, other kinase inhibitors containing the pyridine-ring system are shown in Figure 53.

Recently, the effectiveness of chemotherapeutic agents has been severely limited by tumor resistance.\(^{238,239}\) In a very recent study, pyridine–thiazole hybrid compounds were studied by Alqahtani et al. These hybrids contained (hydrazonomethyl)phenoxy-acetamide spacers, and novel compounds were evaluated for their cytotoxicity potential against normal fibroblast cells (WI38), breast cancer (MCF7), laryngeal carcinoma (Hep2), prostate cancer (PC3), and liver carcinoma (HepG2). The drug 5-fluorouracil (5-Fu) was employed as the standard during these experiments. Promising anticancer activity against the HepG2 and MCF7 cell lines was reported for compounds...
with IC\textsubscript{50} values of 5.36 and 8.76 µM, respectively (Figure 54). Interestingly, both compounds had weak cytotoxic effects on normal cell lines (WI38). Docking analysis revealed valuable information about the binding sites, wherein the synthesized compounds interacted with ROCK1 protein–kinase cavity. It can be safely assumed that combining pyridine and thiazole moieties in one molecular platform via a phenoxyacetamide spacer potentially results in novel compounds with considerable synergistic anticancer effects.

Table 2  
Summary of neurogenic/neuroprotective compounds with pyridine or dihydropyridine scaffolds

| Compound ID | Scaffold type | Potential application | Tentative mechanism |
|-------------|---------------|-----------------------|---------------------|
| 86          | Pyridine      | Alzheimer’s           | AChE inhibition     |
| 87          | Pyridine and dihydropyridine | Alzheimer’s           | Increase expression of GAD67 enzyme in hippocampus converts glutamate to GABA |
| 88          | Pyridine      | Parkinson’s           | ND                  |
| 89          | Pyridine      | Parkinson’s           | ND                  |
| 90          | DHP           | Parkinson’s           | Enhances caspase 3+ cells in the brain |
| 91          | DHP           | Parkinson’s           | Enhances caspase 3+ cells in the brain |
| 92          | Pyridine      | Cerebral ischemia     | Binds with water-channel AQP4 to prevent cerebral ischemia |
| 93          | Pyridine      | Schizophrenia         | Potential affinity for serotonin 5HT\textsubscript{2} and 5HT\textsubscript{x} receptors |
| 94          | DHP           | Alzheimer’s           | AChE inhibition     |
| 95          | Pyridine      | Schizophrenia         | AChE inhibition     |
| 96          | Pyridine      | Schizophrenia         | AChE inhibition     |
| 97          | Pyridine      | Schizophrenia         | AChE inhibition     |
| 98          | Pyridine      | Schizophrenia         | AChE inhibition     |
| 99          | Pyridine      | Schizophrenia         | AChE inhibition     |

Abbreviation: ND, not determined.

Schiff-based pyridine derivatives containing 4-thiazolidinones and azetidin-2-ones bearing pyrazolo[3,4-b]pyridine moiety have also been prepared. Their antiproliferative activity was tested using sulforhodamine B assays. In hepatocellular carcinoma (HB8065) cells, the compounds exhibited remarkable cytotoxic effects. Among the compounds assayed, 102–106 had exceptionally high antiproliferative activity (IC\textsubscript{50} = 0.0091–0.0211 µM) against breast carcinoma cells (MCF7), whereas the standard drug doxorubicin had an IC\textsubscript{50} of 0.099 µM. Compound 102 displayed significantly high antiproliferative effects against MCF7 and HB8065, with IC\textsubscript{50} of 0.0211 µM and 1.65 µM, respectively. These findings imply that these compounds (Figure 55) are highly promising leads in the pursuit of new antiproliferative agents.\textsuperscript{240}

![Figure 51 Neurogenically active pyridine alkaloids isolated from Senna and Cassia spp.](https://www.dovepress.com/10.2147/DDDT.S329547-DovePress)

\textsuperscript{240}
Enasidenib and ivosidenib (Figure 56) were recently approved by the FDA for leukemia. Both are pyridine-containing first-in-class drugs.

In 2015, Sailaja et al studied pyridine–indole hybrids and had promising cytotoxicity results, wherein compounds 107–109 had promising activity against K562 leukemia cells (Figure 57).

Viradiya et al synthesized a series of benzylpyridinium-bearing dihydropyridines (Figure 58). In MTT assays, these compounds had excellent anticancer activity against colorectal adenocarcinoma Caco2, lung cancer A549, and glioblastoma U87MG cell lines. For these cell lines, compounds 110–113 showed better anticancer activity than the widely used drugs carboplatin, gemcitabine, and daunorubicin. Compound 112 was the most potent in the series, 3.6-fold as potent as carboplatin and 4.2-fold as active than gemcitabine. The mechanisms of action showed that the tested compounds induced cell death via
Figure 54 Pyridine–thiazole hybrids with remarkable anticancer effect in MCF7 breast adenocarcinoma.

Figure 55 Pyrazolo[3,4-b] pyridine- and dihydropyridine-derived compounds.

Figure 56 Oncology drugs for leukemia recently approved by the FDA.
Figure 57 Substituent effect on cytotoxicity by pyridine-indole hybrid compounds.

Figure 58 1,4-Dihydropyridine-containing benzylpyridinium moieties with remarkable anticancer activity.

Figure 59 Fused heterocyclic derivatives containing pyridine moieties.
apoptosis. The excellent anticancer capabilities of benzyl-pyridinium-bearing dihydropyridines might be helpful against MDR cancer strains. However, to gain better knowledge of their mode of action, further in-depth mechanistic validation is still needed for these types of compounds.\textsuperscript{243}

Naglaa et al recently designed a series of pyridine-containing anticancer agents (Figure 59). The newly synthesized compounds were investigated for in vitro growth activity against mammary-gland carcinoma (MCF7) and human hepatocellular carcinoma (HepG2) cell lines. Doxorubicin, an anticancer drug, was employed as a comparative standard under the same conditions. Against HepG2 and MCF7, most of the newly synthesized compounds showed significantly potent anticancer activity. The derivatives 114–116 displayed remarkable activity. To further confirm the hypothesized mechanism, molecular docking studies were conducted to evaluate affinity between the compounds and their binding energy with the enzyme. For potent compounds, the calculated binding energies were in good agreement with their activity against the MCF7 and HepG2 cell lines.\textsuperscript{244}

Recently, Eman et al reported an important contribution toward new anticancer agents by developing a series of tetralin–pyridine hybrids, starting from 2-(pyridin-2-yl [oxy])acetohydrazide in appreciable yields (Figure 60). MTT assays were employed to evaluate the cytotoxic activity of these compounds against human MCF7 and HCT116 cells. IC\textsubscript{50} values were 7.7–9.0 µM against HCT116 cancer cells, comparable to the standard drug doxorubicin (IC\textsubscript{50} = 8 µM). The derivative 117–119 showed IC\textsubscript{50} values of 21.0, 33.3, and 60.3 µM, respectively, against MCF7 cells. It can tentatively be assumed that a tetralin–pyridine backbone is an effective antitumor pharmacophoric moiety against MCF7 cells. These findings suggest that all the tested compounds are more active against human colon cancer cells than human breast cancer cells.\textsuperscript{245}

Phosphodiesterases (PDEs) have been recognized as important targets in cancer therapy, due to their critical role in apoptosis induction and inhibition of tumor-cell growth.
growth. Some nonselective PDE inhibitors, eg, aminophylline and theophylline, have been recognized as growth regulators in various carcinoma cell lines, suggesting a potential role as anticancer drugs for PDE inhibition. A range of imidazoaryl-containing dihydropyridine compounds and their 2-oxo isostere derivatives was synthesized and evaluated as PDE inhibitors by Atieh et al. The cytotoxic effect was also checked for the HeLa and MCF7 cell lines. An extraordinarily high PDE3A inhibitory effect was demonstrated by compound 120, with IC\textsubscript{50} of 3.76 ±1.03 nM (Figure 61). Compound 89 also displayed significantly high cytotoxicity effects against MCF7 and HeLa cells (IC\textsubscript{50} 50.18±1.11 and 34.3±2.6 µM, respectively). The strong association between IC\textsubscript{50} values of cytotoxicity and PDE3A inhibition support the notion that PDE3 inhibitors could be used as cytotoxic entities. According to SAR investigations and docking studies, hydrophobic interactions were found to be equally important in the formation of hydrogen bonds intended for PDE3 inhibition and cytotoxic effects of proposed derivatives.\textsuperscript{246}

The crucial role of telomerase in tumor growth makes it a promising target for cancer treatment and other age-related illnesses. Telomere and telomerase are known to be linked to the progression of gastric cancer. Xin-Hua and others synthesized flavone containing 2-chloro-pyridine derivatives for telomerase inhibition (Figure 62). Modified telomeric repeat-amplification protocol assays were used to evaluated the telomerase-inhibitory effect of the compounds, and 121 and 122 showed significant activity against the SGC7901 gastric cancer cell line, with IC\textsubscript{50} of 18.45±2.79 µg/mL and 22.28±6.26 µg/mL, respectively. In order to determine the probable binding mode, docking-simulation studies were performed at 3DU6-active sites. Compound 122 was a more effective inhibitor of telomerase by binding with the telomerase-active site.\textsuperscript{247}

Fatma et al also reported disubstituted pyridines (Figure 63) and studied their anticancer activity against the HepG2 cells. Compounds 123–125 were found to have promising activity comparable to standard drugs and 5-fluorouracil.\textsuperscript{248}

In 2016, pyridine–pyrimidine hybrid ring system–containing compounds were screened at 10 µM against various cancer-cell lines,\textsuperscript{249} and compound 126 (Figure 64) showed promising inhibitory effects against the NCI60 cell lines, with IC\textsubscript{50} of 1.40 µM for UO31, 1.55 µM for

![Figure 62](https://www.dovepress.com/) Antitumor agents with telomerase-inhibitory effects.

![Figure 63](https://www.dovepress.com/) Compounds with remarkable activity against HepG2 liver cancer cells.
SNB75, 1.60 µM for M14, 1.62 µM for SKMEL5 and 1.77 µM for Colo205 cells.

Süss-Fink et al reported highly potent pyridine-based compounds [14] and evaluated their anticancer potential in A2780 (ovarian cancer) and A2780cisR (cisplatin-resistant cancer) cells. Pyridine-4-carboxylate containing a lipophilic chain of ten carbon atoms 127 was highly cytotoxic, with IC$_{50}$ values of 5 µM and 11 µM for A2780 and A2780cisR cell lines, respectively (Figure 65). Surprisingly, the arene ruthenium complex of 127 had remarkably high anticancer activity against both lines, the IC$_{50}$ (2 µM for A2780) of 128 being fivefold that of 127.

Interestingly, introduction of an OH group to 127 renders the new compound 129, which is almost inactive (IC$_{50}$ = 162 µM for A2780 and IC$_{50}$ = 208 µM for A2780cisR; Figure 66). However, the p-cymene ruthenium complex 130 shows very high anticancer activity in the submicromolar range, with IC$_{50}$ of 0.18 µM.

Pyridine hybrids of isatin have been found to demonstrate antiproliferative effects in MCF7, HT29, and HepG2 cells, wherein compounds 131–133 had noteworthy activity (Figure 67).

Higher activity in MCF7, U87MG, and HCT116 cells have recently been studied with [1,2,4]triazolo

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**Figure 64** Pyridine–pyrimidine hybrid ring system containing compound 126 with inhibitory effects against NCI60 cell lines.

**Figure 65** Isonicotinic ester containing compounds 127 and 128.

**Figure 66** p-cymene–ruthenium complex 130 with submicromolar anticancer activity against ovarian cancer cell lines.
Compound 134 had remarkably high anticancer effects in these cell lines (Figure 68).

In diphenyl-l-(pyridin-3-yl)ethylphosphonates,254 the compounds 135 and 136 also demonstrated cytotoxic effect against MCF7 and HepG2 cells (Figure 69).

Pyridine and dihydropyridine are considered attractive scaffolds for anticancer drug development, since many drugs containing these moieties are already in the market, having shown remarkable results. Rational design of new anticancer drugs can be achieved by incorporating these scaffolds into the backbone of bioactive molecules, followed by their analysis with computational methods to predict highly potent candidates. Drug repurposing of existing pyridine- and dihydropyridine-containing pharmaceuticals should also be explored to accelerate the discovery of new anticancer drugs.

**Conclusion**

The present review is a critical analysis of various drugs and research on the design and development of assorted derivatives of pyridine- and dihydropyridine-based compounds. They have been characterized on the basis of their pharmacological activity. Specific structural features pertinent to particular activity have also been discussed. The pyridine core has far greater tractability to produce anti-infectious and anticancer agents. This is evident from the fact that the FDA has recently

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**Figure 67** Structure simplification in pyridine–isatin hybrids resulted in better IC₅₀ values.

**Figure 68** [1,2,4]Triazolo[1,5-a]pyridinylpyridine–containing highly potent anticancer agent.

**Figure 69** Diphenyl l-(pyridin-3-yl)ethylphosphonate–containing anticancer agents.
approved many pyridine-containing antibiotics, such as cef-taroline fosamil (2010), tedizolid (2014), ceftazidine (2015), and delafloxacin (2017). In the database, one can also find isoniazid, ethionamide, and prothionamide, which are highly effective against mycobacteria for the treatment of tuberculosis. Combination of pyridine scaffolds with oxazolidinone hold great promise in this regard, since many such compounds have recently appeared in contemporary literature with remarkable antibacterial effects. For example, the compounds 23–25 have potent activity against a wide range of drug-resistant bacteria, as well as M. catarrhalis and H. influenzae, both in in vitro and in vivo evaluations. The FDA database also contains many pyridine-containing antiviral drugs, such as nevirapine, tipranavir, doravirine, and indinavir, which are being employed to manage HIV infection. During the last 10 years, many isothiazolopyridine-based compounds, such as 61–66, were developed as selective GAK inhibitors to thwart the initial and late-stage viral life cycle. Pyridine-containing oximac compounds were also found to be promising against musculoskeletal disorders, such as osteoarthritis and rheumatoid arthritis. For the treatment of cancer, pyridine was the integral part of numerous FDA-approved kinase inhibitors, such as acalabrutinib, neratinib, abemaciclib, alpelisib, lorlatinib, and pexidartinib, whereas many pyrazolo[3,4-b]pyridine-containing compounds (102–106), ha exceptionally high antiproliferative activity (IC50 = 0.0091–0.0211 µM) against MCF7 cells, while the standard drug doxorubicin had an IC50 of 0.099 µM. In arene–ruthenium complexes with pyridine scaffolds, Süss-Fink et al found highly potent anticancer effects, with IC50 values being in the submicromolar range. Pyridine-containing ruthenium compounds hold great promise for the replacement of cisplatin-based anticancer drugs. Dihydropyridine ring–containing drugs mostly act as calcium-channel blockers and were frequently employed for the treatment of hypertension and heart-related problems. Such drugs include nimodipine, ciclopirox, efondipine, nifedipine, milrinone, and amrinone. Cholesterol-lowering compounds (18–22) containing dihydropyridine rings were developed due to different antidiyslipidemic and antioxidant effects of such a scaffold. Dihydropyridine-containing 80–82 were able to inhibit 11β-HSD1 for the potential cure of diabetes mellitus. In the literature, one can also find numerous pyridine- or dihydropyridine-containing compounds (86–94) for the potential treatment of neurodegenerative disorders, along with many drugs-repurposing examples, such as dolutegravir, mastinitib, nilvadipine, nilotinib, clioquinol, imatinibs. Despite years of research, further work is still warranted to optimize their effects and understand their mechanisms of action. In summary, pyridine- and dihydropyridine-containing compounds combined with broadened chemical space will help medicinal chemists to design bioactive molecules for specific targets. Briefly, in view of the colossal structural diversity of pyridine- and dihydropyridine-containing compounds, the existing literature barely scratches the surface of possibilities for their pharmacological application. Therefore, the interest in them is unlikely to die out anytime soon. We will see an increase in the structure, application, and diversity of pyridine- and dihydropyridine-containing compounds, with great potential for new cardiovascular, anti-inflammatory, anti-infectious, neurogenic, and anticancer drugs containing the two heterocycles in the forthcoming decade.

**Abbreviations**

AChE, acetylcholinesterase; COX, cyclooxygenase; DHP, dihydropyridine; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GAK, G-associated kinase; HepG2, Hepatocellular carcinoma; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NAD, nicotinamide adenine dinucleotide; NADP, NAD phosphate; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PDE, phosphodiesterase; PL, phospholipid-lowering; ROS, reactive oxygen species.

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**Author Contributions**

All authors made substantial contributions to 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.
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