Chapter

Pyridine Heterocycles in the Therapy of Oncological Diseases

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Abstract

Oncological diseases pose a major challenge for modern medicine. Heterocyclic compounds play a vital role in modern medical and pharmaceutical science as most medicinal substances incorporate them. Nitrogen-containing heterocycles serve as the basis of numerous drugs and, therefore, are deeply involved in the design and synthesis of promising new therapeutic agents. Pyridine or pyrimidine scaffolds, with a number of substituents attached, comprise a large portion of FDA-approved drugs. They are chemically stable in the human body, manifest an affinity for DNA via hydrogen bonding, and present an opportunity for the development of novel anticancer agents. A large number of pyridine-based molecules are synthesized and tested for anticancer activity each year. The present chapter aims to introduce the most current synthetic approaches, published in scientific literature, and would also elaborate on structure-activity relationships described therein.

Keywords: pyridine, anticancer, biological activity, synthetic approaches, structure-activity relationship

1. Introduction

Oncological diseases pose a major problem worldwide in terms of societal, healthcare, financial, and economic impact with the number of cancer cases continually rising. The research for novel anticancer drugs comprises a significant portion of contemporary research and development in the field of medicine and pharmacy. Nitrogen heterocycles are a component of 59% of FDA-registered drugs [1] as of 2014. Among them, pyridine is the second most commonly incorporated nitrogen heterocycle. Pyridine-containing drugs are quite heterogeneous in terms of chemical structure, pharmacokinetics and pharmacodynamics – antihistamines (chlorpheniramine, brompheniramine), antiarrhythmic (disopyramide), antihypercholesterolaemic (cerivastatin), antitubercular (isoniazid, ethionamide), antibiotic (telithromycin), antiretroviral for AIDS treatment (indinavir), and anticancer (crizotinib, abiraterone) to name a few.

A multitude of natural substances contains pyridine. They tend to be involved in a number of physiological processes, among which is cancer pathogenesis. The pyridine ring is a chemically stable heterocyclic structure. Its nitrogen atom is able to participate in hydrogen bonding, which allows pyridines to bind to DNA and exhibit anticancer effects [2]. Pyridine can play the role of pharmacophore and can also serve

as a stable basis for the synthesis of novel anticancer drugs. The present chapter aims to inform the reader in a brief and concise manner on the latest developments in the search for pyridine-based anticancer drugs, their mechanisms of action, and the most utilized synthetic approaches. Herein are included the most common types of novel, pyridine-based compounds, found in the scientific literature that do not involve fused ring structures. They are represented by molecular hybrids that the authors have classified into the following groups in terms of structure:

- Coumarin-pyridine hybrids
- Chalcone-pyridine hybrids
- Combretastatin-pyridine hybrids
- Terpyridines and terpyridines isosteres

Additionally, the authors are also presenting data on biological activity, types of cancer cell lines being suppressed, and pharmacodynamic action of the molecules discussed, should such information be available.

2. Pyridine derivatives recently approved for anticancer treatment

A number of pyridines have recently been registered for anticancer treatment [3]. The list predominantly includes kinase inhibitors (apalutamide, pexidartinib, lorlatinib, acalabrutinib, abemaciclib, neratinib, and alpelisib) – drugs that inhibit cellular kinases. Kinases are a family of enzymes that participate in cellular metabolism, signaling, replication, and survival. Inhibiting them suppresses vital cellular functions, therefore, targeting cancer-specific kinases suppresses tumor growth. Ivosidenib and enasidenib serve as isocitrate dehydrogenase (IDH) inhibitors. IDH is involved in energy production and includes two subtypes (IDH1 and IDH2). Mutations in IDH1 and IDH2 can cause changes in DNA gene expression including expression of oncogenes [4]. Inhibition of these enzymes could impair cancer growth. Benetoclax is a Bcl-2 inhibitor. Bcl-2 is a protein that suppresses cell death (apoptosis) [4]. Overexpression of Bcl-2 can prevent or significantly delay cell death – a typical characteristic of cancer. These drugs have been approved by FDA within the period 2017–2019. Considering the extremely stringent approval process of novel medicinal molecules, such a large number of newly-approved anticancer agents underscores both the extreme intensity of scientific exploration for novel anticancer treatments as well as the important role of the pyridine structure plays in drug research.

3. Coumarin-pyridine hybrids

The coumarin (benzopyran-2-on) structure (**Figure 1**) is considered an important bioactive scaffold, included in numerous drugs currently in use [5].

Coumarins are derived both naturally and synthetically. The specific structure of the coumarin scaffold allows coumarin derivatives to interact with a large variety of receptors and enzymes. They are currently being clinically utilized as anticoagulants and antithrombotic agents with relatively low toxicity. Naturally occurring

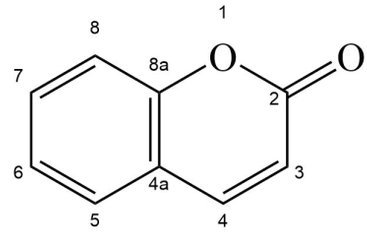


Figure 1.
Chemical structure of coumarin.

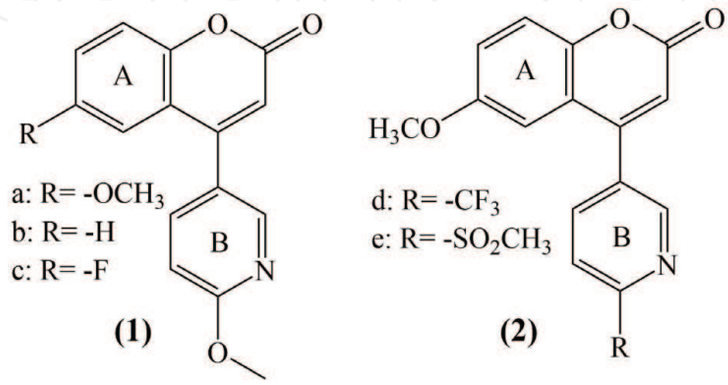


Figure 2.
Structure of the 4-arylcoumarin isosteres.

and synthetic derivatives have shown promise as antimicrobial, anti-inflammatory, anticancer, antioxidant, and MAO-B inhibitory agents [6]. They can exhibit cytostatic and cytotoxic activities against a significant number of cancer cell lines [7]. Adding a variety of functional groups and creating molecular hybrids is a promising direction for the development of novel medicinal molecules, aimed at alleviating a wide variety of maladies. Hybridization of coumarin derivatives with pyridines is a field of intense study in anticancer drug research [8–10].

4-Arylcoumarins are known for their cytotoxic and antiproliferative properties [11]. They can be viewed as structural analogs of the promising antiproliferative molecule combretastatin A-4 (CA-4), yielding very similar effects. For more information on CA-4 and its characteristics, please see Section 5. Pyridine isosteres of that class of compounds have been synthesized and tested for antiproliferative activity (**Figure 2**).

Pyridine derivatives manifest moderate activity against the A549 lung adenocarcinoma cell line [12]. Variants a and b significantly disrupt microtubule formation. Adding an electron-donating group in 6th place of ring A increases antiproliferative activity (**Figure 2**). Substituting with an electron-withdrawing group, such as a fluorine atom, in that same place decreases biological activity. Substituting the para-situated methoxy group in ring B only decreases the effect (**Figure 2**). The basics of the synthetic approach to yield 4-arylcoumarins are schematically presented in **Figure 3**.

Research and development of novel anticancer drugs are most often targeted toward a specific mechanism of action. A number of potential PI3K lipid kinase inhibitors have been synthesized by hybridization of coumarins and pyridines.

PI3K are enzymes, involved in the regulation of cellular growth, replication, and survival, as well as the mediation of protein kinase B (universally known as Akt). Upregulation of PI3K and Akt signaling is associated with tumor growth and tumor cell migration. The aforementioned substances have been tested for PI3K and Akt

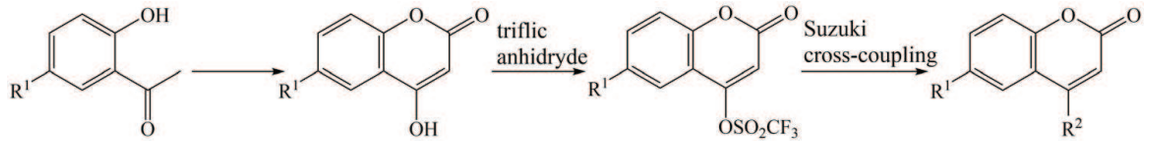


Figure 3.
Brief representation of the synthesis of 4-arylcoumarines.

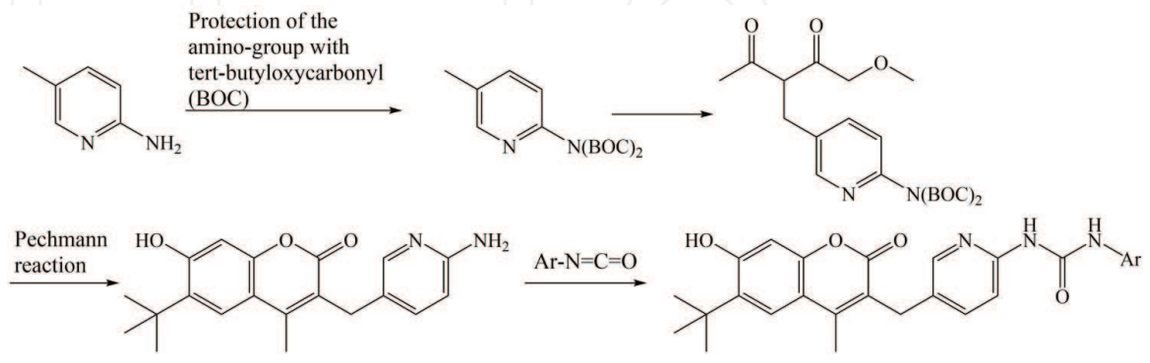


Figure 4.
Synthetic approach for generating some PI3K kinase inhibitors.

inhibition as well as antiproliferative activity against K562 (myelogenous leukemia), HeLa (cervical carcinoma), A549, and MCF-7 (adenocarcinoma) cancer strains [13]. A brief schematic of the synthesis is presented in **Figure 4**.

The member with difluoro-substituted phenyl ring (**Figure 5**) has the strongest effect on all observed cell lines.

All 3,4-disubstituted members exhibit a similar degree of antiproliferative effect. Another member, with monochloro substituted phenyl ring (**Figure 5**) has been found to significantly inhibit both PI3K and Akt and to initiate apoptosis in the K562 cell line.

A number of hybrid molecules have been synthesized using a novel approach [14]. The final step of the synthesis is conducted in two different media – in refluxing ethanol or under microwave heating. Microwave heating proves to be more energy-efficient, quicker, and produces significantly higher yields. **Figure 6** represents the basic synthesis of the most potent substance which exhibits promising activity against HCT-116 (colorectal carcinoma) and MCF-7 cell lines.

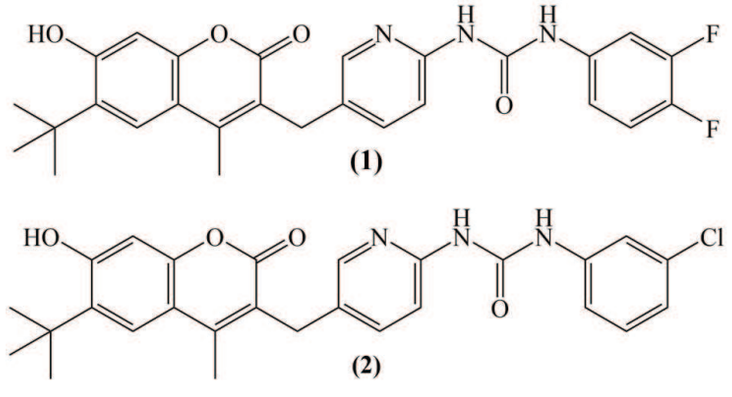


Figure 5.
The most active PI3K inhibitors against various cancer cell lines.

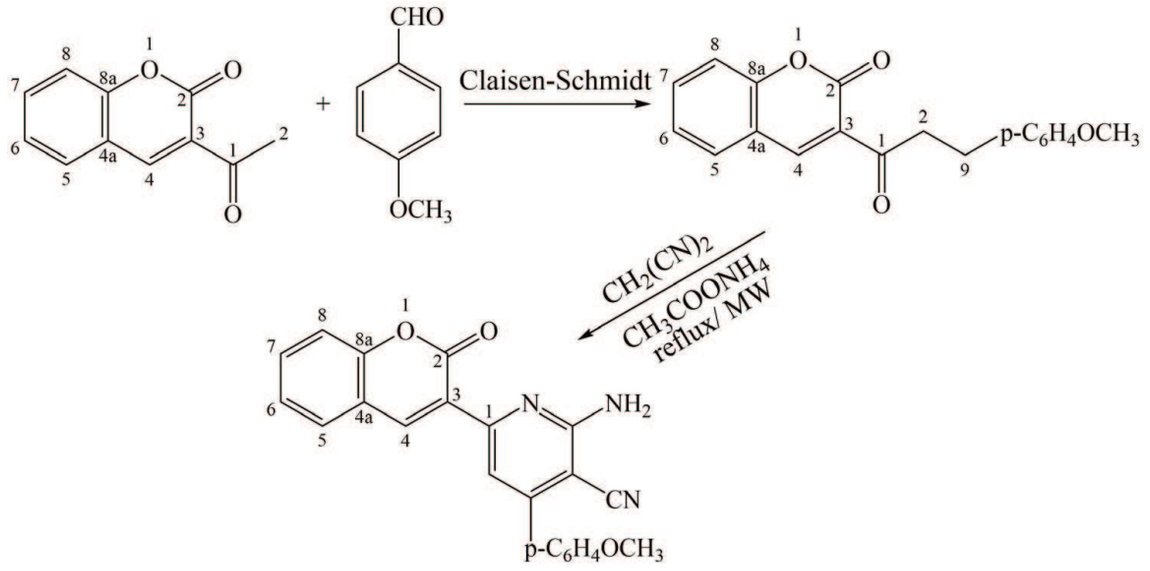


Figure 6.
Novel synthesis of coumarin-pyridine hybrid compounds.

4. Chalcone-pyridine hybrids

Chalcones are natural products from the flavonoid family, found in abundance in plants. Chalcone (**Figure 7**) is a molecular scaffold, characterized by uncomplicated chemistry, easy synthesis, and a large number of hydrogen atoms that, when substituted, can yield a huge selection of derivatives, exhibiting multiple physiological effects – antioxidant [15], antidiabetic [16], antihypertensive [17], anticancer [18], and many others.

They are known to inhibit cell proliferation, acting as antitumor agents both in vitro and in vivo. The antiproliferative properties of chalcones have been known for more than two decades [19]. Chalcones tend to bind to the so-called colchicine binding site in tubulin – a building block of microtubules. Microtubules are essential structures in all eukaryotic cells, responsible for keeping the structural integrity of cells, cell division, and many others [20]. Disrupting their synthesis is the mechanism of action of a number of antineoplastic drugs [21]. Attaching a pyridine moiety to the chalcone skeleton would be a way to complement the observed anticancer activity.

A promising design approach for the synthesis of chalcone-pyridine derivatives would be replacing one of the benzene rings with pyridine. A number of such molecules have been generated and then tested for antiproliferative activities and tubulin polymerization suppression [22]. α-(4-pyridyl) ketones and the necessary aldehydes undergo an aldol reaction to yield a number of chalcone-pyridine hybrids. The aforementioned step in the synthesis of the most potent member is presented in **Figure 8**.

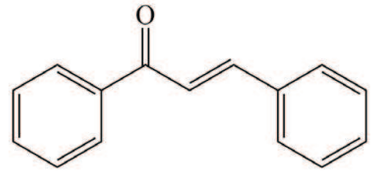


Figure 7.
The chalcone molecular scaffold.

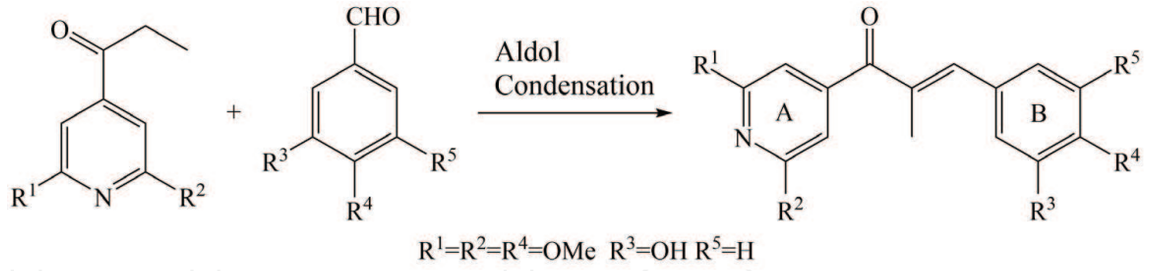


Figure 8.
Chalcone synthesis via aldol condensation.

All generated substances prove to be effective against K652 cells. The most potent one (**Figure 8**) is almost as effective as combretastatin A-4. It acts as a microtubule-destabilizing agent with an IC_{50} lower than that of CA-4. It connects with the colchicine binding site with 88% potency at 5 μM concentration, arresting the cell cycle of K562 at the G2/M phase and inducing apoptosis in a concentration-dependent manner.

The α-positioned methyl moiety to the carbonyl group tends to improve activity. The exposed hydroxyl at the meta-position of ring B (R^3) is important for the biological activity – changing it to methoxy decreases the observed effect. Adding electron-donating groups to ring A increases the effect, while adding electron-withdrawing groups (such as chlorine atoms) decreases the activity.

Aldol condensation has also been applied to generate a number of pyridinium bromide salts that have manifested promising antiproliferative activity against MCF-7, HeLa, U-87MG (malignant glioblastoma), and HEK293 (kidney) cell lines [23]. A brief summary of the synthesis of the two most active members is presented in **Figure 9**.

In terms of the structure-activity relationship, adding a strongly electron-donating functional group at the para-position of the phenyl radical R increases biological activity. Interestingly, adding the strongly electron-withdrawing nitro group also improves the antiproliferative properties. Replacing the radical R with a coumarin substituent (potentially anticancer-bearing) nullifies the anticancer effect.

Another class of substances that have been synthesized incorporates pyridine nucleus not as a substitute of one of the chalcone phenyl rings, but as a substituent [24]. They have been tested for their antiproliferative effect and colchicine-binding ability. The synthesis of the most active compounds is shown in **Figure 10**.

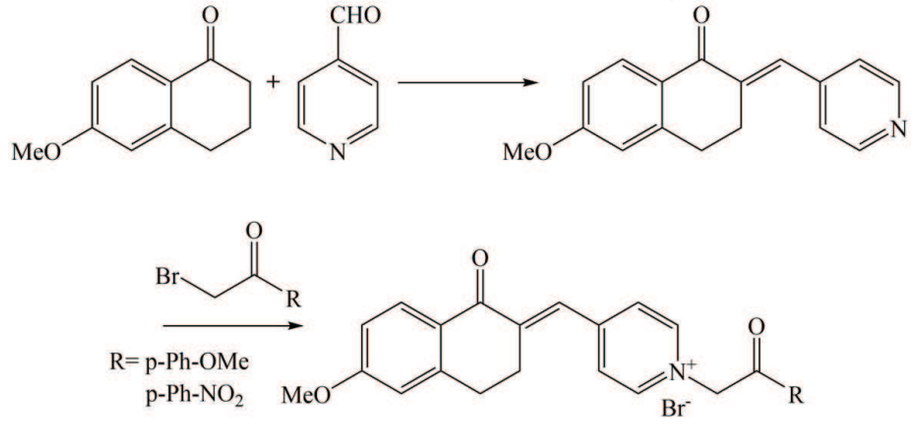
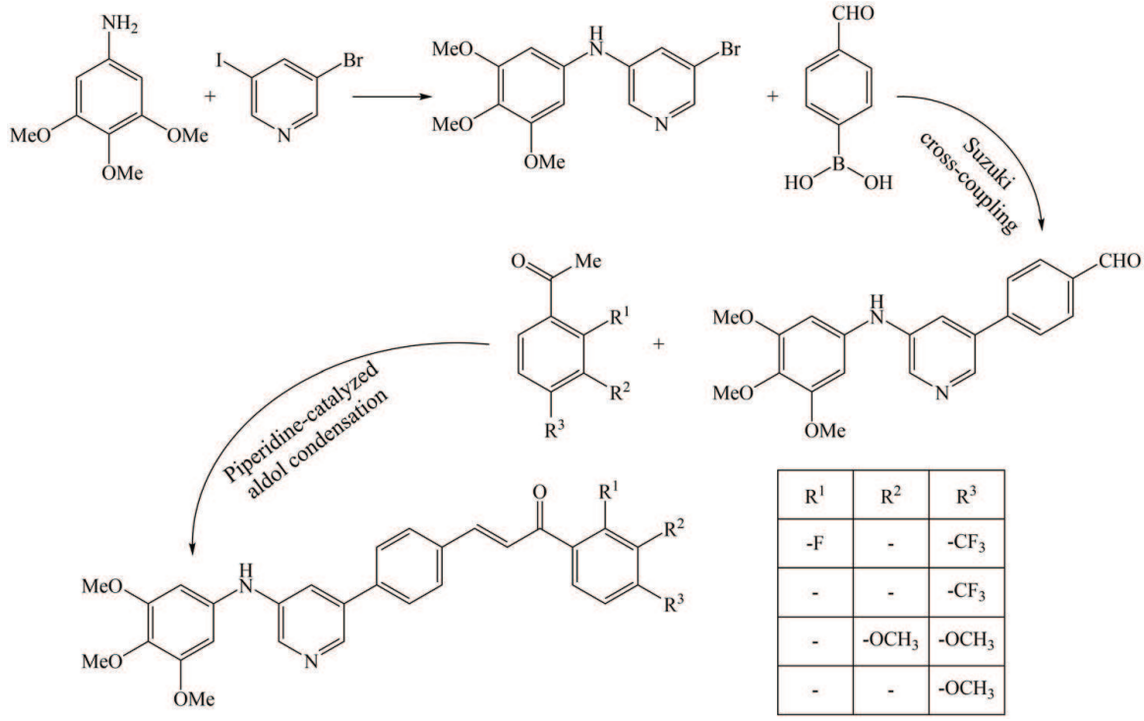


Figure 9.
Pyridinium bromide salts' synthesis.



R^1	R^2	R^3
-F	-	$-CF_3$
-	-	$-CF_3$
-	$-OCH_3$	$-OCH_3$
-	-	$-OCH_3$

Figure 10.
Synthesis of pyridine substituted chalcones.

As in the previous case, adding electron-withdrawing groups, particularly in para-position, to the chalcone phenyl ring increases biological activity. Adding electron-donating groups (methoxy) to the same position has the same effect on ACHN (renal adenocarcinoma), MCF-7, and A549 cancer cell lines. The novel compounds have been docked in silico to the tubulin receptor, yielding promising results in terms of microtubule disruption.

5. Combretastatin: Pyridine hybrids

Combretastatins are a family of stilbenes, derived from the bark of the African Willow tree [25]. Combretastatin A-4 (**Figure 11**) in particular is an effective, selective inhibitor of tubulin polymerization by binding to the colchicine binding site. Thus it inhibits microtubule growth and acts as an antivascular and antimitotic agent, preventing cellular multiplication, changing endothelial cell structure, and resulting in tumor necrosis [26].

The cis-orientation of rings A and B is crucial for combretastatin A-4's cytotoxicity [27]. CA-4's application has been limited by its low solubility in aqueous media.

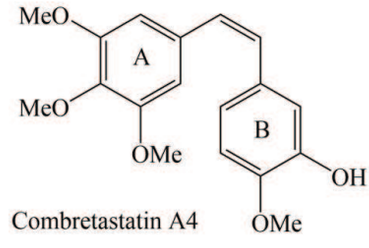


Figure 11.
Structure of combretastatin A4.

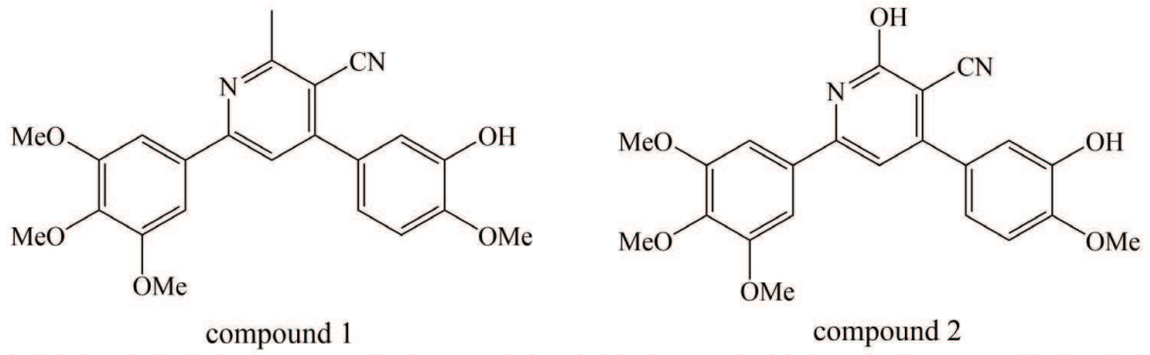


Figure 12.
CA-4 analogs – 2,4-diphenyl-substituted pyridines.

Modification of its molecular structure (changing the aromatic rings and replacing the stilbene bridge) to increase its bioavailability, while maintaining its physiological effect has been a source of numerous investigations [28–30].

A number of combretastatin A-4 analogs with pyridine aromatic rings as a linker have been synthesized [31]. Two examples are presented in **Figure 12**.

Compound 1 manifests moderate cytotoxicity against MCF-7 cancer cells. Replacing the methyl group in its pyridine cycle with a hydroxyl group causes negation of the observed effect (compound 2). The antiproliferative effect associated with these 2,4-diphenyl-substituted pyridine structures is not very clearly manifested.

Interesting observations have been made with similar compounds, utilizing a pyridine linker between the two phenyl rings [32]. Among dozens of substances, three exhibit notable anticancer activity (**Figure 13**).

In terms of the structure-activity relationship, when the phenyl rings are at a para position from each other in the pyridine linker, cytotoxicity is low. Meta-position improves biological activity. The best results are observed with a 2,6-diphenyl substituted pyridine linker. 3,4,5-trimetoxy substituted ring A does not contribute significantly to biological activity. Compound 3 is the only one from a multitude of members, bearing such substituent, that yields promising results. It is an almost full analog of CA-4 – the stilbene linker is replaced with a 2,6-disubstituted pyridine. On the other hand, a 2,4-dimethoxy substituted ring A causes significant suppression against several cell lines – MDA-MB-231 (breast cancer), A549, and HeLa. Any other

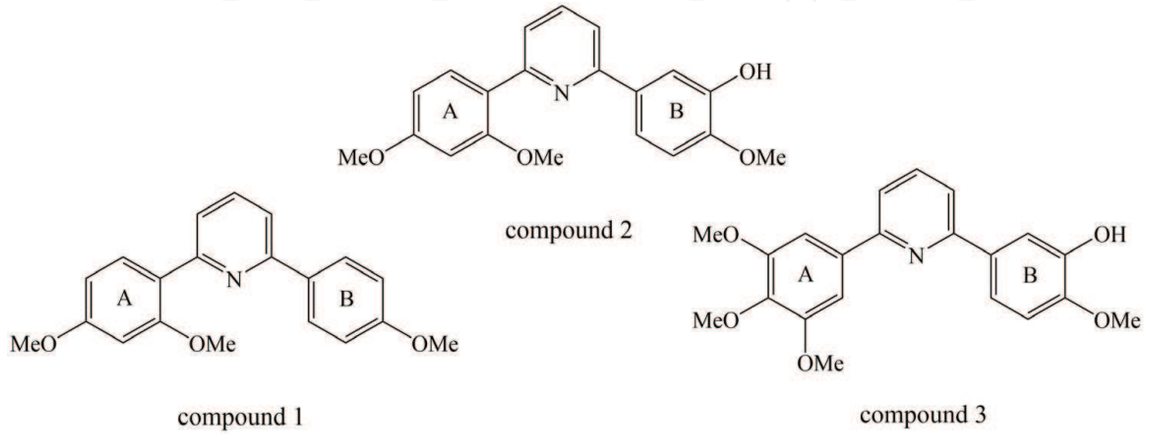


Figure 13.
CA-4 analogs - 2,6-diphenylsubstitited pyridines.

type of dimethoxy substitution (e.g., 3,4-; 2,5-, etc.) decreases the antiproliferative effect. 3,4,5-trimethoxy substitution in ring B also weakens the biological effect. With 2,4-dimethoxysusbtituted ring A, 3-monomethoxy and 4-monomethoxy substituted ring B offer high antiproliferative effect, while 2-monomethoxy offers lesser activity. Thus, compounds 1, 2, and 3 potently inhibit cell survival and growth, arrest the cell division cycle and bind to the colchicine site to a degree, similar to combretastatin A4.

6. Terpyridine derivatives

Terpyridine is a known ligand in a variety of complexes [33]. Its structural analogs tend to bind to and intercalate in nucleic acids [34, 35]. α-Terpyridine (**Figure 14**) and its isosteres have manifested significant topoisomerase I and II inhibitory activity as well as notable cytotoxicity against a variety of cancer cell lines [36, 37]. Topoisomerases are a family of enzymes that catalyze changes in the topological state of the DNA double helix. They are involved in DNA replication and transcription, hence impairment of their function inhibits cellular replication – a way to suppress rapid tumor growth.

Terpyridines can be derived by way of the Kröhnke pyridine synthesis [38], represented in **Figure 15**.

Two families of terpyridine isosteres have been synthesized and tested for topoisomerase inhibitory activity and cytotoxicity – molecules with four aryl groups (furyl, thienyl, and pyridyl) and molecules with three aryl groups (**Figure 16**).

Three-ringed terpyridine members manifest low topoisomerase inhibitory activity and cytotoxicity. Some 2,4,6-trisubstituted members exhibit significant biological activity (listed in **Table 1**).

Notably, topoisomerase I inhibiting substances do not suppress topoisomerase II and topoisomerase II inhibiting substances do not suppress topoisomerase I. Interestingly, topoisomerase inhibitors manifest low toxicity toward a variety of cancer cell lines – MCF-7, HeLa, DU145 (prostate cancer), and HCT15 (colorectal

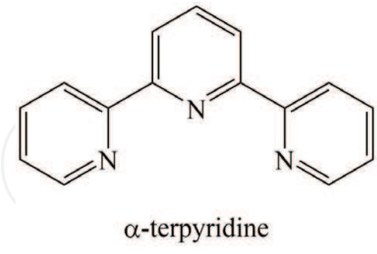


Figure 14.
Chemical structure of α-terpyridine.

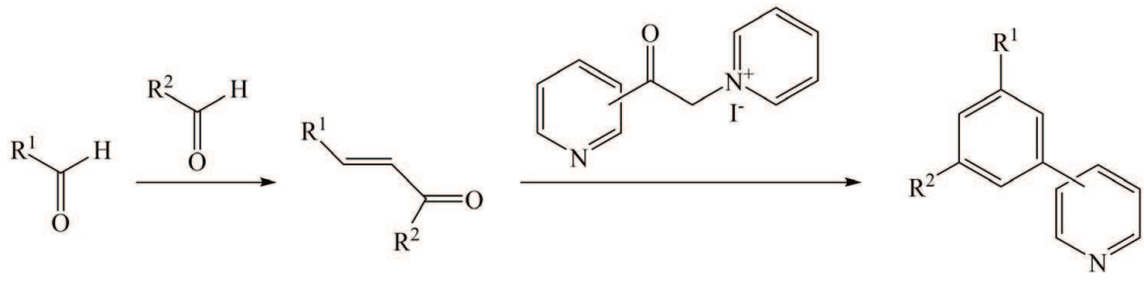


Figure 15.
Schematic representation of the synthesis of terpyridines and their isosteres.

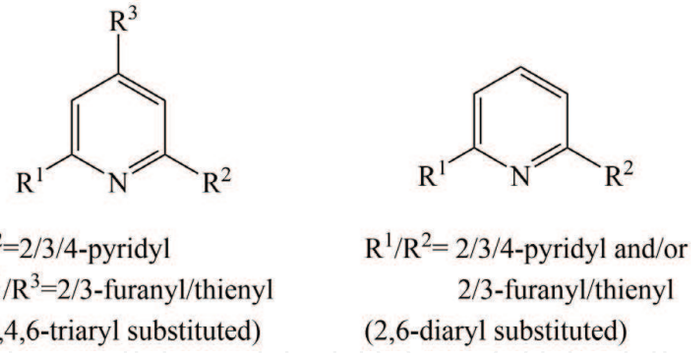


Figure 16.
Structures of the investigated terpyridines.

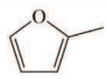
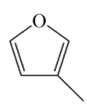
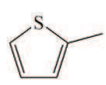
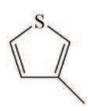
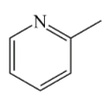
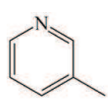
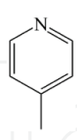
Moiety:	R^1	R^2	R^3	Biological activity
 = a	a	g	c	Topoisomerase I inhibitor
 = b	a	g	d	Topoisomerase I inhibitor
 = c	c	e	d	Topoisomerase I inhibitor
 = d	c	g	d	Topoisomerase I inhibitor
 = e	a	g	d	Topoisomerase II inhibitor
 = f	c	g	f	Topoisomerase II inhibitor
 = g	a	g	b	Topoisomerase II inhibitor
	c	g	c	High cytotoxicity
	c	g	a	High cytotoxicity
	c	f	d	High cytotoxicity
	c	f	a	High cytotoxicity
	d	g	c	High cytotoxicity
	d	g	d	High cytotoxicity

Table 1.
Biological effect of various terpyridine isosteres with four aryl groups.

cancer). At the same time, some trisubstituted terpyridines did not behave as enzyme inhibitors but despite that are highly cytotoxic. In terms of molecular structure 2-furyl and 2-thienyl moieties in 2nd place, 4-pyridyl in 6th place, and 2/3-thienyl in 4th place seem to have the greatest impact on biological activity.

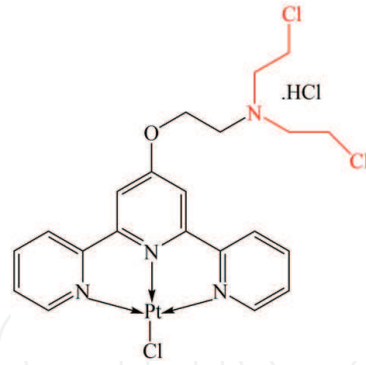


Figure 17.
An example of terpyridine-platinum complex. The ligand incorporates a "nitrogen mustard" moiety (in red), linked to the central pyridine ring. That molecular "tail" increases antiproliferative activity and DNA-binding of both the ligand itself and its platinum complex.

Terpyridines are being intensely studied in the field of oncology not so much for their intrinsic antiproliferative properties but for their ability to chelate metal ions. Recent data show that chelating copper ions with terpyridine ligands produce coordination compounds with high cytotoxicity and G0/G1 cell cycle phase inhibitory activity [39]. Experiments have demonstrated that complexes of terpyridines manifest antiproliferative activity in the nanomolar range against a large variety of cancer cell lines – MCF-7, A549, HCT-116, U-251 (glioblastoma), and PANC-1 (pancreatic carcinoma). At the same time, the observed IC_{50} doses against normal human fibroblasts (NHDF) are about 10–15 times higher, demonstrating good selectivity and potentially lower toxicity toward healthy human tissues. Numerous terpyridine complexes with platinum (**Figure 17**), palladium, and lanthanides have also recently been synthesized [40–43], bearing promising protein-binding, DNA-binding, and antiproliferative activities.

7. Conclusions

The pyridine heterocycle is an important chemical structure, ubiquitously utilized within the field of modern pharmaceutical science, research, and development. Its characteristic physicochemical properties (chemical stability, participation in hydrogen bonding, and numerous hydrogen atoms that can be substituted) make it an attractive molecular basis for synthesis of medicinal substances. Its nitrogen atom makes it a useful pharmacophore, imbuing potential drug molecules with novel pharmacological effects. Attaching it to extant compounds can modify their pharmacokinetics, pharmacodynamics, and physiological effect. The authors' aim is that the present chapter reveals to the reader the important role pyridine chemistry plays in the field of oncology. Pyridine-based compounds are being intensely researched in the hope of inventing novel oncological drugs that combine significant anticancer cytotoxicity with an improved safety profile and a targeted mechanism of action. Within the past several years a large number of novel pyridine anticancer molecules have been synthesized, yielding some very promising results. Substances of both natural and synthetic origin have been generated and/or modified, synthetic approaches have been refined and interesting and potentially important structure-activity relationships have been revealed. Hopefully, the authors have been able to present the subject of pyridines in oncology to the reader's satisfaction, both informing them as well as sparking an interest in this rapidly evolving area of research.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: Miniperspective. Journal of Medicinal Chemistry. 2014;**57**(24):10257-10274

[2] Özkay Y, Işıkdağ İ, İncesu Z, Akalın G. Synthesis of 2-substituted-N-[4-(1-methyl-4, 5-diphenyl-1H-imidazole-2-yl) phenyl] acetamide derivatives and evaluation of their anticancer activity. European Journal of Medicinal Chemistry. 2010;**45**(8):3320-3328

[3] Sahu R, Mishra R, Kumar R, Mazumder A, Kumar A. Pyridine moiety: Recent advances in cancer treatment. Indian Journal of Pharmaceutical Sciences. 2021;**83**(2):162-185

[4] Chao DT, Korsmeyer SJ. BCL-2 family: Regulators of cell death. Annual Review of Immunology. 1998;**16**

[5] Riveiro ME, De Kimpe N, Moglioni A, Vazquez R, Monczor F, Shayo C, et al. Coumarins: Old compounds with novel promising therapeutic perspectives. Current Medicinal Chemistry. 2010;**17**(13):1325-1338

[6] Sandhu S, Bansal Y, Silakari O, Bansal G. Coumarin hybrids as novel therapeutic agents. Bioorganic & Medicinal Chemistry. 2014;**22**(15):3806-3814

[7] Marshall M, Kervin K, Benefield C, Umerani A, Albainy-Jenei S, Zhao Q, et al. Growth-inhibitory effects of coumarin (1, 2-benzopyrone) and 7-hydroxycoumarin on human malignant cell lines in vitro. Journal of Cancer Research and Clinical Oncology. 1994;**120**(1):S3-S10

[8] Fayed EA, Sabour R, Harras MF, Mehany A. Design, synthesis, biological evaluation and molecular modeling of new coumarin derivatives as potent anticancer agents. Medicinal Chemistry Research. 2019;**28**(8):1284-1297

[9] Zhang L, Xu Z. Coumarin-containing hybrids and their anticancer activities. European Journal of Medicinal Chemistry. 2019;**181**:111587

[10] Rawat A, Reddy AVB. Recent advances on anticancer activity of coumarin derivatives. European Journal of Medicinal Chemistry Reports. 2022;**100038**

[11] Bailly C, Bal C, Barbier P, Combes S, Finet J-P, Hildebrand M-P, et al. Synthesis and biological evaluation of 4-arylcoumarin analogues of combretastatins. Journal of Medicinal Chemistry. 2003;**46**(25):5437-5444

[12] Mutai P, Breuzard G, Pagano A, Allegro D, Peyrot V, Chibale K. Synthesis and biological evaluation of 4 arylcoumarin analogues as tubulin-targeting antitumor agents. Bioorganic & Medicinal Chemistry. 2017;**25**(5):1652-1665

[13] Ma C-C, Liu Z-P. Design and synthesis of coumarin derivatives as novel PI3K inhibitors. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2017;**17**(3):395-403

[14] El-Naggar AM, Hemdan MM, Atta-Allah SR. An efficient one-pot synthesis of new Coumarin derivatives as potent anticancer agents under microwave irradiation. Journal of Heterocyclic Chemistry. 2017;**54**(6):3519-3526

[15] Iqbal H, Prabhakar V, Sangith A, Chandrika B, Balasubramanian R. Synthesis, anti-inflammatory and antioxidant activity of ring-A-monosubstituted chalcone derivatives. Medicinal Chemistry Research. 2014;**23**(10):4383-4394

[16] Kaushal R, Kaur M. Bio-medical potential of chalcone derivatives and their metal complexes as antidiabetic agents: A review. Journal of Coordination Chemistry. 2021;**74**(4-6):725-742

[17] Mahapatra DK, Bharti SK. Therapeutic potential of chalcones as cardiovascular agents. Life Sciences. 2016;**148**:154-172

[18] Modzelewska A, Pettit C, Achanta G, Davidson NE, Huang P, Khan SR. Anticancer activities of novel chalcone and bis-chalcone derivatives. Bioorganic & Medicinal Chemistry. 2006;**14**(10):3491-3495

[19] Ducki S, Forrest R, Hadfield JA, Kendall A, Lawrence NJ, McGown AT, et al. Potent antimitotic and cell growth inhibitory properties of substituted chalcones. Bioorganic & Medicinal Chemistry Letters. 1998;**8**(9):1051-1056

[20] Howard J, Hyman AA. Dynamics and mechanics of the microtubule plus end. Nature. 2003;**422**(6933):753-758

[21] Dumontet C, Jordan MA. Microtubule-binding agents: A dynamic field of cancer therapeutics. Nature Reviews Drug Discovery. 2010;**9**(10):790-803

[22] Xu F, Li W, Shuai W, Yang L, Bi Y, Ma C, et al. Design, synthesis and biological evaluation of pyridine-chalcone derivatives as novel microtubule-destabilizing agents. European Journal of Medicinal Chemistry. 2019;**173**:1-14

[23] Gondru R, Saini R, Vaarla K, Singh S, Sirassu N, Bavantula R, et al. Synthesis and characterization of chalcone-pyridinium hybrids as potential anti-cancer and anti-microbial agents. ChemistrySelect. 2018;**3**(5):1424-1431

[24] Madhavi S, Sreenivasulu R, Yousuf Ansari M, Jawed Ahsan M, Ramesh RR. Synthesis, biological evaluation and molecular docking studies of pyridine incorporated chalcone derivatives as anticancer agents. Letters in Organic Chemistry. 2016;**13**(9):682-692

[25] Pettit GR, Singh SB, Niven ML, Hamel E, Schmidt JM. Isolation, structure, and synthesis of combretastatins A-1 and B-1, potent new inhibitors of microtubule assembly, derived from Combretum caffrum. Journal of Natural Products. 1987;**50**(1):119-131

[26] Chaplin D, Pettit G, Hill S. Anti-vascular approaches to solid tumour therapy: Evaluation of combretastatin A4 phosphate. Anticancer Research. 1999;**19**(1A):189-195

[27] Woods J, Hadfield JA, Pettit G, Fox BW, McGown AT. The interaction with tubulin of a series of stilbenes based on combretastatin A-4. British Journal of Cancer. 1995;**71**(4):705-711

[28] Ohsumi K, Nakagawa R, Fukuda Y, Hatanaka T, Morinaga Y, Nihei Y, et al. Novel combretastatin analogues effective against murine solid tumors: Design and structure– activity relationships. Journal of Medicinal Chemistry. 1998;**41**(16):3022-3032

[29] Liou J-P, Chang Y-L, Kuo F-M, Chang C-W, Tseng H-Y, Wang C-C, et al. Concise synthesis and structure–activity relationships of combretastatin A-4 analogues, 1-aroylindoles and 3-aroylindoles, as novel classes of potent antitubulin agents. Journal of Medicinal Chemistry. 2004;**47**(17):4247-4257

[30] Jian X-E, Yang F, Jiang C-S, You W-W, Zhao P-L. Synthesis and biological evaluation of novel pyrazolo [3, 4-b] pyridines as cis-restricted combretastatin A-4 analogues. Bioorganic & Medicinal Chemistry Letters. 2020;**30**(8):127025

[31] Shringare SN, Chavan HV, Bhale PS, Dongare SB, Mule YB, Patil SB, et al. Synthesis and pharmacological evaluation of combretastatin-A4 analogs of pyrazoline and pyridine derivatives as anticancer, anti-inflammatory and antioxidant agents. Medicinal Chemistry Research. 2018;**27**(4):1226-1237

[32] Zheng S, Zhong Q, Mottamal M, Zhang Q, Zhang C, LeMelle E, et al. Design, synthesis, and biological evaluation of novel pyridine-bridged analogues of combretastatin-A4 as anticancer agents. Journal of Medicinal Chemistry. 2014;**57**(8):3369-3381

[33] Mukkala VM, Helenius M, Hemmilä I, Kankare J, Takalo H. Development of luminescent europium (III) and terbium (III) chelates of 2, 2′: 6′, 2 ″-terpyridine derivatives for protein labelling. Helvetica Chimica Acta. 1993;**76**(3):1361-1378

[34] Carter PJ, Cheng C-C, Thorp HH. Oxidation of DNA and RNA by oxoruthenium (IV) metallointercalators: Visualizing the recognition properties of dipyridophenazine by high-resolution electrophoresis. Journal of the American Chemical Society. 1998;**120**(4):632-642

[35] Jennette K, Lippard S, Vassiliades G, Bauer W. Metallointercalation reagents. 2-hydroxyethanethiolato (2, 2′, 2 ″-terpyridine)-platinum (II) monocation binds strongly to DNA by intercalation. Proceedings of the National Academy of Sciences. 1974;**71**(10):3839-3843

[36] Son J-K, Zhao L-X, Basnet A, Thapa P, Karki R, Na Y, et al. Synthesis of 2, 6-diaryl-substituted pyridines and their antitumor activities. European Journal of Medicinal Chemistry. 2008;**43**(4):675-682

[37] Basnet A, Thapa P, Karki R, Na Y, Jahng Y, Jeong B-S, et al. 2, 4, 6-Trisubstituted pyridines: Synthesis, topoisomerase I and II inhibitory activity, cytotoxicity, and structure–activity relationship. Bioorganic & Medicinal Chemistry. 2007;**15**(13):4351-4359

[38] Adib M, Tahermansouri H, Koloogani SA, Mohammadi B, Bijanzadeh HR. Kröhnke pyridines: An efficient solvent-free synthesis of 2, 4, 6-triarylpyridines. Tetrahedron Letters. 2006;**47**(33):5957-5960

[39] Malarz K, Zych D, Kuczak M, Musioł R, Mrozek-Wilczkiewicz A. Anticancer activity of 4′-phenyl-2, 2′: 6′, 2 ″-terpyridines–behind the metal complexation. European Journal of Medicinal Chemistry. 2020;**189**:112039

[40] Adams M, Sullivan MP, Tong KK, Goldstone DC, Hanif M, Jamieson SM, et al. Mustards-derived Terpyridine–platinum complexes as anticancer agents: DNA alkylation vs coordination. Inorganic Chemistry. 2021;**60**(4):2414-2424

[41] Kacar O, Adiguzel Z, Yilmaz VT, Cetin Y, Cevatemre B, Arda N, et al. Evaluation of the molecular mechanisms of a palladium (II) saccharinate complex with terpyridine as an anticancer agent. Anti-Cancer Drugs. 2014;**25**(1):17-29

[42] Li C, Xu F, Zhao Y, Zheng W, Zeng W, Luo Q, et al. Platinum (II) terpyridine anticancer complexes possessing multiple mode of DNA interaction and EGFR inhibiting activity. Frontiers in Chemistry. 2020;**8**:210

[43] Hussain A, Gadadhar S, Goswami TK, Karande AA, Chakravarty AR. Photoactivated DNA cleavage and anticancer activity of pyrenyl-terpyridine lanthanide complexes. European Journal of Medicinal Chemistry. 2012;**50**:319