3-Cyano-2-oxa-pyridines: a promising template for diverse pharmacological activities

Amr K. A. Bass*, Elshimaa M. N. Abdelhafiez², Mona S. El-Zoghbi¹, Mamdouh F. A. Mohamed³, Mohamed Badr⁴, Gamal El-Din A. Abuo-Rahmab¹

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Menoufia University, Menoufia, Egypt.
²Department of Medicinal Chemistry, Faculty of Pharmacy, Minia University, Minia 61519, Egypt.
³Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sohag University, 82524 Sohag, Egypt.
⁴Department of Biochemistry, Faculty of Pharmacy, Menoufia University, Menoufia, Egypt.

Received: December 7, 2020; revised: December 29, 2020; accepted: December 31, 2020

Abstract

Pyridines have occupied a unique place in medicinal chemistry as it is widely profound as natural products and formed the integral backbone of great number of drugs in the market. In particular, 3-cyano-2-oxa-pyridines showed diverse biological and pharmacological activities such as cardiotonic, antimicrobial, antidepressant, and anticancer activity. 3-Cyano-2-oxa-pyridine derivatives have elevated importance for modern medicinal applications especially in cancer therapy. This article shed light on the general chemical synthetic approaches of 3-cyano-2-oxa-pyridines and summarized their various biological activities and pharmacological uses. This article may be helpful in the future to direct attention towards utilization of 3-cyano-2-oxa-pyridine template in the design of new molecules with enhanced biological properties such as PIM1 kinase, tubulin polymerase and survivin inhibitors for cancer therapy or new AMPK activator for diabetes and obesity control or cardiotonic agents.

Key words

Cyanopyridines; PIM-1 kinase inhibitors; Survivin inhibitors; AMPK activators

1. Introduction

A diversified and highly functionalized nitrogen-containing heterocyclic compounds are core structural units in several natural products and synthetic drugs. These natural products and synthetic molecules possess tremendous applications in drug discovery and useful functional materials [1-3]. This encouraged the synthesis of biologically active heterocyclic compounds such pyridine derivatives [4-7]. Furthermore, pyridine derivatives are one of the important heterocyclic compounds that possess medicinal and functional properties with attractive applications as pharmaceuticals as well as general synthetic building blocks [8-11]. The pyridine nucleus is an integral part of anti-inflammatory and anticancer agents [12-14]. Pyridine derivatives containing various groups such as streptonigrone, streptonigrin, and lavendamycin are reported as anticancer drugs, and cerivastatin is reported as the HMG-CoA reductase enzyme inhibitor [15]. Moreover, substituted pyridines are reported as leukotriene B-4 antagonists [16, 17]. On the other hand, cyanopyridine derivatives have shown to possess promising antimicrobial [18-20], antioxidant [21-23], antibiotic [24-26], anti-inflammatory [27, 28], analgesic [29], anticonvulsant [30] and anticancer [31-33] properties. In particular, 3-cyano-2-pyridones are known to have diverse biological and pharmacological activity, particularly antimicrobial [19, 34-36], antidepressant [37], cardiotonic [6, 38], and anticancer activity [33, 35, 39, 40]. There is much interest in the anticancer activity of these compounds owing to different types of biological targets they might interfere with for this effect to occur e.g. PIM1 Kinase [40-44], tubulin [45], PDE3 [10, 40, 46-49] and Survivin protein [33, 40, 50-53]. In this context, due to the great significance of 3-cyano-2-oxa-pyridines and the interest in further development of new routes in their synthesis, we focus on their reported pharmacological activities and the general different methods involved in their synthesis.

2. General methods for synthesis of 3-cyano-2-oxa-pyridines

Several synthetic methods for preparation of 3-cyano-2-oxa-pyridines were reported: herein we have stated the general methods for their synthesis.

2.1. From chalcones (α,β-unsaturated ketones)

Condensation of chalcone with ethyl cyanocetate and excess of ammonium acetate in ethanol (reflux) gave 3-cyano-2-oxo-1,2-dihydropyridines but in poor yield and consume time(yield about 60-70%, 2 steps more than 24 hours)[50,54-57], Scheme 1.

Scheme 1: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines from chalcones.

2.2. One-pot multi-component reaction

Synthesis of 3-cyano-2-substituted pyridines might be done via one-pot four component reaction of substituted acetophenone, ethyl cyanocetate or malononitrile, appropriate aldehyde and

* Correspondence: Amr K. A. Bass
Tel.: ++201002055099.
Email Address: amr_ph_80@yahoo.com
excess of ammonium acetate in various solvents e.g. ethanol, butanol and toluene, but also gave poor yield and consume time (yield about 60%, more than 12 hours) [38, 41, 58-60]. (Scheme 2)

The synthesis can be carried out without solvent through one-pot four component reaction of equal quantity of substituted acetophenone, ethyl cyanoacetate or malononitrile, appropriate aldehyde and ammonium acetate under strong stirring at 120-130 °C, for 10-15 min. the reaction consumed short time and good yield (yield up to 90%, 10-15 min.) [61]. (Scheme 2)

\[
\begin{align*}
\text{Scheme 2: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines via on-pot reaction with/ without solvent from substituted ketone and aldehyde} \\
\end{align*}
\]

2.3. One-pot multi-component reaction using piperidine as a base

This synthesis method is through one-pot reaction of equal quantity of 2-cyanoacetohydrazide, an activated nitrile, appropriate aldehyde in ethanol using catalytic amount of piperidine to afford 3-cyano-2-oxo-1,2-dihydropyridine [62-65]. (Scheme 3)

\[
\begin{align*}
\text{Scheme 3: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines via on-pot reaction using piperidine as catalyst.} \\
\end{align*}
\]

2.4. From β-dicarbonyl compounds

This synthetic method involves refluxing equimolar amount of the appropriate β-dicarbonyl compound with malononitrile and triethylamine in ethanol with stirring for 15 min [66, 67]. (Scheme 4)

\[
\begin{align*}
\text{Scheme 4: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines from β-dicarbonyl compound.} \\
\end{align*}
\]

3. Biological activity of 3-cyano-2-substituted pyridine

3-Cyano-2-substituted pyridines (particularly; 3-cyano-2-oxa-pyridine) and its derivatives have been showed well known significant role in various biological processes as well as, their pharmacological and chemical importance [68-71]. (Figure 1)

The pharmacophore 2-pyridone is noticeable in several therapeutic agents [72] that can be expanded into cardiotoxic agents [73-77], antimicrobial [78], HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) [79, 80], and sedatives [81]. Structural similarity to nucleosides [82-86], has attracted attention of researchers. Researches have also indicated that they were found to be a key precursor in building of complex natural products such as nitroguanidine insecticide Imidacloprid [87].

\[
\begin{align*}
\text{Figure 1: Various biological activities of 3-cyano-2-oxa-pyridine.} \\
\end{align*}
\]

3.1. 3-Cyano-2-oxa-pyridine as cardiotoxic agents

3-Cyano-2-oxa-pyridine derivatives exhibited potent cardiotoxic activity [6, 38]. One of these derivatives, Milrinone 1 was marketed in treatment of congestive heart failure. Moreover, compounds 2-6 showed cardiotoxic activities. The mechanism of their action includes inhibition of Phosphodiesterase-3 (PDE-3), resulted in prevention of cAMP degradation that followed by the decrease in Protein kinase A (PKA) amount in cells [73-77]. (Figure 2).

\[
\begin{align*}
\text{Figure 2: Structures of cardiotonics with 3-cyano-2-substituted-pyridine pharmacophore.} \\
\end{align*}
\]

J. Adv. Biomed. & Pharm. Sci.
3.2. 3-Cyano-2-oxa-pyridines as an AMPK activator in metabolic syndrome, diabetes, and obesity

Adenosine monophosphate-activated protein kinase "AMPK", a heterotrimeric serine/threonine kinase, has been found to be as a key sensor and regulator of intracellular and whole-body energy metabolism [88-91]. Its activation modifies the metabolism of carbohydrate and lipid via increase glucose uptake and fatty acid oxidation and decrease synthesis of fatty acid and cholesterol. Through its central role in the regulation of glucose and lipid metabolism, AMPK is emerging as an attractive molecular target for the treatment of diabetes, metabolic syndrome, and obesity [92-98]. Some 3-cyano-2-oxo-pyridine derivatives showed AMPK activation [58], (Figure 3). Compound 7, which exhibited modest AMPK activity (rat liver EC50, 38 µM), has been used as starting point to be optimized. The most potent one was compound 10 with more potent AMPK activity (rat liver EC50, 3.7 µM) than 11, 9 and 8 with AMPK activity (rat liver EC50 of 5.8, 8 and 20 µM), respectively.

Figure 3: Structure of AMPK activators with 3-cyano-2-oxa-pyridine pharmacophore.

3.3. 3-Cyano-2-oxa-pyridines with anticancer activity

Cancer, the second leading factor of death after cardiovascular diseases, is an abnormal uncontrollable cell cycle disease characterized by the rapid proliferation of normal cells [99]. Several 3-cyano-2-oxa-pyridine derivatives display promising potent anticancer activity [33, 35, 39, 40] against a wide range of cell lines [100-102]. There is much interest in the anticancer activity of these compounds as they might act on different types of biological targets via different mechanisms of action.

3.3.1. 3-Cyano-2-substituted pyridine as PIM-1 kinase inhibitor

Proto-oncogenic encodes for serine/threonine kinase (PIM-1 kinase) has been found to be overexpressed in various cancer cells [103-106], PIM-1 plays an important role in cancer cell survival, differentiation and proliferation [107-109]. Its inhibition resulted in cancer cell arrest and apoptosis [105, 110, 111]. Cheney et al., [44] developed a series of cyanopryidine derivatives (Figure 4) that showed potent PIM-1 kinase inhibition. Compound 12 was the most potent inhibitor (IC50 = 50 nM). Several recent studies reported different cyanopryidine derivatives as potent PIM-1 kinase inhibitors e.g.: compound 13 (PIM-1 kinase IC50 = 0.84 µM), compound 14 (PIM-1 kinase IC50 = 0.43 µM), compound 15 (PIM-1 kinase IC50 = 0.99 µM) and used 4,6-diaryl-3-cyano-2-substitutedpyridine motif as a template for this purpose [33, 41-43]. These compounds showed potent anticancer activity via inhibition for PIM-1 Kinase [40-44].

Figure 4: Structure of PIM-1 kinase inhibitors carrying 3-cyano-2-oxa-pyridine pharmacophore.

3.3.2. 3-Cyano-2-substituted pyridine as Survivin inhibitor

Survivin is an inhibitor of apoptosis family (IAP) [52]. It is encoded protein by the BIRC5 gene in human. Survivin has been found to be highly expressed in various cancer cells and fetal tissue and non-detectable in differentiated adult tissues [53]. Its inhibition resulted in cancer cell arrest and apoptosis. 3-Cyano-2-substituted pyridine derivatives with higher lipophilic properties as compounds 16-23 showed anticancer activity via inhibition of surviving protein. The affinity of the nominated compounds to survivin was enhanced by improving the lipophilicity through the introduction of halogen atom to the phenyl at position 4 of the pyridone ring [33, 40, 50-53]. (Figure 5).

Figure 5: Structures of survivin inhibitors with 3-cyano-2-substituted pyridine pharmacophore.

3.3.3. 3-Cyano-2-substituted pyridine as tubulin polymerization inhibitor

Some of 3-cyano-2-substituted pyridine derivatives showed potent cytotoxic activity higher than the combretastatin A4 (CA-4) via tubulin polymerization inhibition in sub-micromolar concentrations such as compounds 24-27 [45]. Their β-tubulin polymerization percentage inhibition assay indicates that the antimut activity of these compounds correlates well with their ability to inhibit β-tubulin polymerization. (Figure 6).

Figure 6: Structures of tubulin polymerization inhibitors carrying 3-cyano-2-substituted pyridine pharmacophore.
4. Structure activity relationship

The reported biological activities of 3-cyano-2-substituted pyridine nucleus seemed to be manipulated with structural variations (Figure 7). First of all, and in all cases, the presence of cyano group is essential for all previously reported activities in this review.

1- The presence of phenyl group Ring A and B either substituted or unsubstituted provides PIM-1 kinase inhibitors derivatives as in compounds 12-13. Replacement of ring A and/or Ring B with thienyl or benzocoumarin-2-one groups retain the PIM-1 kinase inhibitory activity as in compounds 14 and 15.

2- However, introducing of lipophilic groups such as Cl or F atoms on ring A produces derivatives with high survival inhibitory activity such as compounds 17-23.

3- Moreover, adding trimethoxy group to ring A and/or ring B yielded combrestatin analogues with high tubulin polymerization inhibitory activity such as compounds 24-27. Replacement of O at position 2 with S is also tolerated.

4- Notably, replacement of phenyl group (ring B) with pyridine ring gives derivatives with cardiotonic activity with O > NH2 > S at position 2 as in 1-6.

5- Additionally, When the pyridine acquires the aromaticity as in 2-NH2 substituted derivatives possesses available lone pair of electrons (not available in dihydropyridine derivatives) that can be participated in extra H-bond donating with the targeted enzymes.

6- Finally, fusion of thienyl group with 3-cyano-2-substituted pyridine nucleus produces thienopyridin-2-one with enhanced AMPK inhibitory activities as in 7-11. While replacing the thienyl group with other heterocyclic rings resulted in inactive derivatives.

Figure 7: Effects of substitution on biological activity of 3-cyano-2-substituted pyridine.

Conclusion

3-Cyano-2-oxa-pyridine is a potential molecular template for variable biological activities which attracts the attention of many chemists globally to synthesize different compounds carrying this scaffold via easily efficient synthetic methods to explore their biological activity and sometimes their molecular drug target. Based on our survey, we could conclude that altering the substitutions on the 3-Cyano-2-oxa-pyridine skeleton is noticed in various pharmacophores for different targets with diverse biological activities. Therefore, this article may be helpful in the future to direct attention towards utilization of this template in the design of new molecules with enhanced biological properties such as PIM1 kinase, tubulin polymerase and survivin inhibitors for cancer therapy or new AMPK activator for diabetes and obesity control or cardiotonic agents as well as ultimately leading to the development of new approaches in the synthesis of their skeleton.

References

[1] Wells JA, McClendon CL. Reaching for high-hanging fruit in drug discovery at protein–protein interfaces. Nature. 2007;450(7172):1001-1009.
[2] Feng Y, Mitchell J, Bender A, Young DW, Tallarico JA. Multi-parameter phenotypic profiling: using cellular effects to characterize small-molecule compounds. Nature Reviews Drug Discovery. 2009;8(7):567-578.
[3] Azzario V, Long K, Murphy NS, Wilson AJ. Inhibition of α-helix-mediated protein–protein interactions using designed molecules. Nature chemistry. 2013;5(3):161-173.
[4] Marzouk AA, Bass AK, Ahmed MS, Abdelhamid AA, Elshaier YA, Salaman AM, et al. Design, synthesis and anticonvulsant activity of new imidazololindione and imidazole derivatives. Bioorganic Chemistry. 2020;101:104020.
[5] Movassaghi M, Hill MD, Ahmad OK. Direct synthesis of pyridine derivatives. Journal of the American Chemical Society. 2007;129(33):10096-10097.
[6] Wilson CO, Gisvold O, Block JH, Beale JM, Wilson and Gisvold’s textbook of organic medicinal and pharmaceutical chemistry/edited by John H. Block. John M. Beale Jr. 11th ed: Philadelphia: Lippincott Williams & Wilkins; 2004.
[7] Henry GD. De novo synthesis of substituted pyridines. Tetrahedron. 2004;29(60):6043-6061.
[8] Li A-H, Moro S, Forsyth N, Melman N, Ji X-D, Jacobson KA. Synthesis, CoMFA analysis, and receptor docking of 3, 5-diacyl-2, 4-diacylpyridine derivatives as selective A3 adenosine receptor antagonists. Journal of medicinal chemistry. 1999;42(4):706-721.
[9] Vacher B, Bonnaud B, Funes P, Jubault N, Koek W, Assié M, et al. Novel derivatives of 2-pyrimidinemethanesulfonic as selective, potent, and orally active agonists at 5-HT1A receptors. Journal of medicinal chemistry. 1999;42(9):1648-1660.
[10] Murata T, Shimizu K, Narita M, Mangianneli VC, Tagawa T. Characterization of phosphodiesterase 3 in human malignant melanoma cell line. Anticancer research. 2002;22(6A):3171-3174.
[11] Teague SJ. Synthesis of heavily substituted 2-aminopyridines by displacement of a 6-methylsulfonyl group. The Journal of Organic Chemistry. 2008;73(24):9765-9766.
[12] Amr A-GE, Abdulla MM. Anti-inflammatory profile of some synthesized heterocyclic pyridine and pyridine derivatives fused with steroid structure. Bioorganic & medicinal chemistry. 2006;14(13):4341-4352.
[13] Son J-K, Zhao L-X, Basnet A, Thapa P, Karri R, Na Y, et al. Synthesis of 2, 6-dial substituted pyridines and their antitumor activities. European journal of medicinal chemistry. 2009;44(2):1648-1660.
[14] Bass AKA, Elzoghbi MS, Abdelhaleem EMN, Mohamed MF, Badr M, Abou-Rahma GE-DA. Comprehensive review for anticancer hybridized multitargeting HDAC inhibitors. European journal of medicinal chemistry. 2020;112904.
[15] Bringmann G, Reichert Y, Kane VV. The total synthesis of streptonigrin and related antitumor antibiotic natural products. Tetrahedron. 2004;16(60):3539-3574.
[16] Cooke MW, Hanan GS. Luminescent polynuclear assemblies. Chemical Society Reviews. 2007;36(9):1466-1476.
[17] Zhou Y, Kijima T, Kuwahara S, Watanabe M, Izuini T. Synthesis of ethyl 5-cyano-6-hydroxy-2-methyl-4-(1-naphthyl)-nicotinate. Tetrahedron Letters. 2008;49(23):3757-3761.
[18] Abou El farkoosh GH, Abd El-fazeza NA, Midurah WH, Mikolajczek M. Chemistry of seven-membered heterocycles, VI. Synthesis of novel bicyclic heterocyclic compounds as potential anticancer and anti-HIV agents. Zeitschrift Fur Naturforschung B. 2000;55(5):417-424.
[19] Faulahah HM, Rostom SA, Badr MH, Ismail AE, Almohammedi AM. Synthesis of 3-N-(3-Substituted-2-oxo-1, 2-dihydropyridine-3-carbonitriles and Their Biological Evaluation as Cytotoxic and Antimicrobial Agents. Archiv der Pharmazie. 2015;348(11):824-834.
[20] Kumar S, Das SK, Dey S, Maity P, Guha M, Choubey V, et al. Antiplasmodial activity of [aryl] arylsulfonylmethyl pyridine. Antimicrobial agents and chemotherapy. 2008;52(2):705-713.
[21] Sayed HH, Morsy EM, Fiefe EM. Synthesis and reactions of some novel nicotinonitrile, thiazolotriazole, and imidazolotriazole derivatives for antioxidant evaluation. Synthetic Communications. 2010;40(9):1360-1370.
[22] Kobt ER, Anwar MM, Abbas H-AS, Abd El-Moez SI. A concise synthesis and antimicrobial activity of a novel series of naphthylpyridine-3-carbonitrile compounds. Acta Pol Pharm. 2013;70:667-679.
[23] Al-Ethabi AM, El-Apasery MA. A comprehensive review on the synthesis and versatile applications of biologically active pyridine-based disperse dyes. International Journal of Environmental Research and Public Health. 2020;17(13):4714.
[24] Mukai A, Nagai A, Inaba S, Takagi M, Shin-ya K. JIBIR-54, a new 4-pyridine derivative isolated from Penicillium daeiae Zaleski IE50. The Journal of Antibiotics. 2009;62(12):705-706.

[25] Mamedov I, Naghiyev F, Maharramov A, Uwange O, Farewell A, Sunnerhagen P, et al. Antibacterial activity of 2-amino-3-cyano pyridine derivatives. Mendeleev Communications. 2020;30(4):498-499.

[26] Alrobaian M, Azwari SA, Belal A, Eldeeb HA. An eco-friendly technique: Solvent-free microwave synthesis and docking studies of some pyridine nucleosides and their pharmacological significance. Molecules. 2019;24(10):1986.

[27] Martin C, G Gregg D, Dal Piaz V, Vergelli C, Giovannoni M, Ernst M, et al. Airway relaxant and anti-inflammatory properties of a PDE4 inhibitor with low affinity for the high-affinity rolipram binding site. Naunyn-Schmiedeberg's archives of pharmacology. 2002;365(4):284-289.

[28] Albo-Ghalia MH, Amr AE-GE, Abdulla MM. Synthesis of some new (N′-diphenylacetyl-d-lysine)-yl) linear tetra and cyclic octa bridged peptides as new antiinflammatory agents. Zeitschrift für Naturforschung B. 2003;58(9):903-910.

[29] Al-Omar MA, Amr AE-GE, Al-Salah RA. Anti-inflammatory, analgesic, antiulcerant and antiparkinsonian activities of some pyridine derivatives using 2, 6-disubstituted nonionic acid hydrazides. Archiv der Pharmazie. 2010;343(11-12):648-656.

[30] Amr AE-GE, Sayed HH, Abdulla MM. Synthesis and reactions of some new substituted pyridine and pyrimidine derivatives as analgesic, antiulcerant and antiparkinsonian agents. Archiv der Pharmazie: An International Journal Pharmacological and Medical Chemical. 2003;358(9):433-440.

[31] Koth ER, El-lagany M, Salama MA, Kalf HS, Abdel Wahab NA. Synthesis and reactions of some novel nictinonitrile derivatives for anticancer and antiinflammatory evaluation. Acta Chim Slov. 2009;56:908-919.

[32] Al-Abdullah ES. Synthesis and anticancer activity of some novel tetralin-6-yl pyrazoline, 2-thioxopyridimine, 2-oxopyridine, 2-thiopyridine and 2-iminopyridine derivatives. Molecules. 2011;16(4):3410-3419.

[33] Ismail MM, Farrag AM, Harras MF, Ibrahim MH, Mehaney AB. Apoptosis: A target for anticancer therapy with novel pyridine cyclones. Bioorganic Chemistry. 2020;94:103481.

[34] Alaa A-M, El-Subbagh HI, Kuniida T. Lewis acid-promoted transformation of 2-alkoxyoxindoles into 2-aminoindoles and their antibacterial activities: Part 2: remarkably facile C-N bond formation. Bioorganic & medicinal chemistry. 2005;13(16):4929-4935.

[35] Attia MM, Khodair AI, Gendy EA, El-Magd MA, Elshayery YAMM. New 2-oxopyridine/2-thiopyridine derivatives tethered to a benzotriazole with cytotoxicity on MCF-7 cell lines and with antiviral activities. Letters in Drug Design & Discovery. 2020;17(2):124-137.

[36] Haggam R, El-Sayed H, Sain D, Ahmed M, Moustaafa A, Abd-El-Noor R. O-Glycosylation/Alkylation and Antimicrobial Activity of 4,6-Diaryl-2-Oxonicotinonitrile Derivatives. Journal of Heterocyclic Chemistry. 2017;54(1):375-383.

[37] Abdel-Latif NA. Synthesis and antidepressant activity of some new coumarin derivatives. Scientia Pharmaceutica. 2005;73(4):193-216.

[38] Mosti L, Menozzi G, Schenone P, Dorigo P, Gaion R, Belluco P. Synthesis and cardiototoxic activity of 2-substituted 5-cyano-1, 6-dihydro-6-oxo-3-pyridinecarboxylic acids and their methyl or ethyl esters. Farmaco (Societa Italiana Farmacologia). 2005;60(4):427-432.

[39] Thompson P, Manganillo V, Degerman E. Re-discovering PDE inhibitors—new opportunities for a long neglected target Cur Top Med Chem. 2007;7:421-436.

[40] Abadi AH, Abouel-Ella DA, Lehmann J, Tinsley HN, Gary BD, Piazza ME, et al. Discovery of colon tumor cell growth inhibitory agents through a combinatorial approach. European journal of medicinal chemistry. 2010;45(1):90-97.

[41] Abdelaziz MM, El-Miligy MM, Fahmy SM, Mahran MA, Hazzaa AA. Design, synthesis and docking study of pyridine and thieno [2, 3-b] pyridine derivatives as anticancer PIM-1 kinase inhibitors. Bioorganic chemistry. 2018;80:674-692.

[42] Abouzid KA, Al-Ansary GH, El-Naggar AM. Eco-friendly synthesis of novel cyanopyridine derivatives and their anticancer and PIM-1 kinase inhibitory activities. European journal of medicinal chemistry. 2017;134:357-366.

[43] Abnous K, Manavi H, Mehr S, Aibolandi L, Kamali H, Ghadandi M, et al. In vitro evaluation of dihydroxypropidine-3-carbonitriles as potential cytotoxic agents through PIM-1 protein kinase inhibition. Research in Pharmaceutical Sciences. 2017;12(3):196.

[44] Cheney IW, Yan S, Appleby T, Walker H, Vo T, Yao N, et al. Identification and structure-activity relationship of substituted pyridines as inhibitors of Pim-1 kinase. Bioorganic & medicinal chemistry letters. 2007;17(6):1679-1683.

[45] Ryad N, MY A-S, Ismail MM, El Meligie S. Design, Synthesis and Screening of 4, 6-Diaryl Pyridine and Pyrimidine Derivatives as Potential Cytotoxic Molecules. Chemical and Pharmaceutical Bulletin. 2018;66(8):00269.
[71] Kappe CO, Kappe T. Synthesis of substituted 3-pyridinecarboxamides with potential biological activity. Monatsh Chem 1989;120(12):1095-1100.

[72] Ghosh PS, Manna K, Banik U, Das M, Sarkar P. Synthetic strategies and pharmacology of 2-oxo-3-carboxyamide derivatives: A review. Int J Pharm Sci 2014;6:15-22.

[73] Robert N, Verrier C, Hoarau C, Célandre S, Marsais F. A convenient synthesis of cyclopentan [b] pyridin-2-yl, 5-dione as a non-glycosidic cardiotonic agent. Arkivoc 2008;7:92-100.

[74] Endoh M. Basic and clinical characteristics of 3DE 3 inhibitors as cardiotonic agents. Cardiovasc Drugs 2007.

[75] Endoh M, Honi M. Acute heart failure: Inotropic agents and their clinical uses. Expert opinion on pharmacotherapeutics. 2006;7(16):2179-2202.

[76] Presti EL, Boggia R, Feltrin A, Menozzi G, Dorigo A, Presti EL, Boggia R, Feltrin A, Menozzi G, Dorigo A. Facile synthesis and antiproliferative activity of new 3-carboxyamidines. BMC chemistry. 2019;13(1):1-10.

[77] Rostom SA, Faidallah HM, Al-Saadi MS. A facile synthesis of some 3-cyano-1, 4, 6-trisubstituted-2-(1H)-pyridinones and their biological evaluation as anticancer agents. Medicinal Chemistry Research. 2011;20(8):1260-1272.

[78] Makii A, Mohsen M, Aziz H, Riek O, Shaban O, El-Sayed M, et al. New 3-Cyano-2-substituted pyridines induce apoptosis in MCF-7 breast cancer cells. Molecules. 2016;21(2):230.

[79] Asati V, Mahapatra DK, Bhatti SK. PIM kinase inhibitors: Structural and pharmacological perspectives. European journal of medicinal chemistry. 2019;172:95-108.

[80] Markou A, Tzankou E, Strati A, Zavvndou M, Mostaraki S, Bournaakis E, et al. PIM-1 is Overexpressed at a High Frequency in Circulating Tumor Cells from Metastatic Castration-Resistant Prostate Cancer Patients. Cancers. 2020;12(5):1188.

[81] Keane N, Reidy M, Natoni A, Raab M, O’dwyer M. Targeting the PIM kinases in multiple myeloma. Blood cancer journal. 2015;5(7):e325-e325.

[82] Tursynbay Y, Zhang J, Li Z, Tokay T, Zhumadilov Z, Wu D, et al. Pim-1 kinase as cancer drug target: an update. Biomedical reports. 2016;4(2):140-146.

[83] Narlik-Grassow M, Blanco-Aparicio C, Carnero A. The PIM family of serine/threonine kinases in cancer. Medicinal research reviews. 2014;34(1):136-159.

[84] Warfel NA, Kraft AS. PIM kinase (and Akt) biology and signaling in tumors. Pharmacology & therapeutics. 2015;151:41-49.

[85] Szymdowski M, Prochorow-Sobieszek M, Szumera-Cieciwczek A, Derezinski E, Hoser G, Wasilewska D, et al. Expression of PIM kinases in Reed-Sternberg cells fosters immune privilege and tumor cell survival in Hodgkin lymphoma. Blood. The Journal of the American Society of Hematology. 2017;130(12):1418-1429.

[86] Le BT, Kamarasri M, Adams JR, Yu M, Milne R, Sykes MJ, et al. Targeting Pim kinases for cancer treatment: opportunities and challenges. Future Medicinal Chemistry. 2015;7(1):35-53.

[87] Nagub BH, El-Nassam HB, Abdelghany TM. Synthesis of new pyrido[3,4-b]pyrimidine derivatives as Pim-1 inhibitors. Journal of enzyme inhibition and medicinal chemistry. 2017;32(1):457-467.