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Coumarin based-histone deactylace HADC inhibitors

Sarah Sattar Jabbar * Mohamed Hassan Mohammed

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad/Iraq

Abstract

Coumarins have been recognized as anticancer competitors. HDACis are one of the interesting issues in the field of antitumor research. In order to achieve an increased anticancer efficacy, a series of hybrid compounds bearing coumarin scaffolds have been designed and synthesized as novel HDACis, In this review we present a series of novel HDAC inhibitors comprising coumarin as a core e of cap group of HDAC inhibitors that have been designed, synthesized and assessed for their enzyme inhibitory activity as well as antiproliferative activity. Most of them exhibited potent HDAC inhibitory activity and significant cytotoxicity

Keywords: coumarin ; Histone deacetylase; anti-proliferative activity; Histone deacetylase inhibitors.

Introduction

Cancer is quite possibly the most well-known reasons for illness related death around the world. Regardless of the disclosure of numerous chemotherapeutic medications that restrain uncontrolled cell division measures for the therapy of different malignant growths, genuine symptoms and resistance of these medications are a urgent disadvantage [1].numerous investigations are being directed to find and develop effective anticancer medications. Epigenetic therapeutics are the new generation of chemotherapeutics for treatment of cancer, and histone deacetylase inhibitors have been effectively found in this classification .They target the biological processes including the cell cycle, apoptosis, DNA repair, cell cycle control, autophagy, metabolism, senescence and chaperone function. Several groups of histone deacetylase (HDAC) inhibitors have been synthesized and evaluated for their inhibitory activity . Their positive effects on the cell cycle have been shown in biological models and in clinical preliminaries [2].

Histone deacetylase (HDAC) is an amidohydrolase which deacetylates the histone lysine residues for chromatin remodeling and thus in this manner accepts an essential part in the epigenetic regulation of gene expression. As now eighteen human enzymes have been recognized to have deacetylase activity. depend on cofactor required for their catalytic activity. These eighteen HDACs have been grouped into two general categories. Greater part of HDACs (11) being metallo-enzymes require zinc for their activity and are known as zinc-dependent HDACs. the rest (7) HDACs requiring NAD^+ for their effect are known as NAD^+-dependent HDACs [3]. While based on likeness to yeast HDACs classifies HDACs into four fundamental classes from Class I to Class IV. Class I compising of four members, HDAC1, 2, 3 and 8[4]. While Class IIa includes HDAC4, 5, 7 and 9, Class IIb includes HDAC6 and HDAC10[5] .Class III HDACs also known as Sirtuins and act primarily as NAD^+ - dependent deacetylases. Class IV, has HDAC11[6] .

In spite of the huge structural variety , HDACis in general have a typical pharmacophore model : zinc binding group (ZBG), a linker and a surface recognition group (CAP group) [7-10]. The selectivity and potency in these different inhibitors rely upon varieties in any or every one of the three domains. The CAP region is viewed as a critical part for distinguishing diverse subtypes of HDACs, which interacts with the surface edge of the enzyme. The cap region contains hydrophobic and bulky cap groups such as benzene, pyridine and several fused bicyclic heterocycles Similarly, that bind to the surface region in the HDAC can increase the inhibitor potency. As a rule, lipophilicity assumes a significant part in deciding the anticancer action of HDAC inhibitors [11] . Molecular docking studies showed that the coumarin could be well accommodated in

*Corresponding author e-mail: ph.sarahsattar@gmail.com

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the active site of HDAC through interacting with the residues at the entrance of the protein [12].

A combination of docking, molecular dynamics simulations, structure activity relationships and pharamacophore models enormously help with growing more potent and enzyme specific HDAC inhibitors. Scaffold replacement method is another highly suitable approach by which different pharmacophore regions, such as the zinc binding domain, linker and cap region, in known HDAC inhibitors including those in clinical studies can be modified to synthesize more potent and specific HDAC inhibitors[13] .

Many compounds containing coumarin were found to exhibit potent anticancer activity by inducing cell apoptosis, arresting cell cycle, inhibiting DNA-associated enzymes, or suppressing angiogenesis [14-16] . references indicated that several compounds designed as HDAC inhibitors by taking advantage of coumarin scaffold as cap group.

Coumarin (2H-1-benzopyran-2-one, Fig.1) is universal in nature, and its derivatives display an entrancing exhibit of pharmacological properties such as antibacterial [17,18] , antifungal [19,20] , antimalarial [21-23] and anticancer [24,25] activities which might be credited to that coumarin moiety has the ability to exert non covalent interactions like π-π, hydrophobic, electrostatic interactions, hydrogen bonds, metal coordination and van der Waals force with the various active sites in organisms [26] . demonstrating coumarin is considering as a profoundly favored moiety for the advancement of novel anticancer medications.

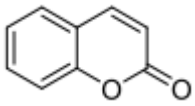


Fig. 1 . Structure of coumarin

In this review we presenta series of novel HDAC inhibitors comprising coumarin as a core e of cap group of HDAC inhibitors that have been designed, synthesized and assessed for their enzyme inhibitory activity .

A series of chalconoid coumarin analogs as HDACs inhibitors (1-3) (Fig. 2) were designed and synthesized (scheme 1) by Seidel et al. The activity of title compounds 1-3 on in vitro total HDAC activity exhibited that compound 1 and compound 3 (R1 = R2 = R3 = OMe) from prototype 3 containing 4-methoxyphenylor 3,4-dimethoxyphenyl moieties had 20% and 50% of inhibition at100 mM. The in vitro inhibition assay of compound 3 against seven HDAC isoenzymes showed a pan-HDAC inhibition. Particularly, this compound showed IC50 of 12 mM against HDAC3 isoenzyme[27].

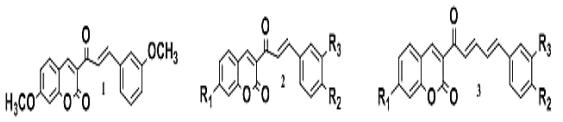
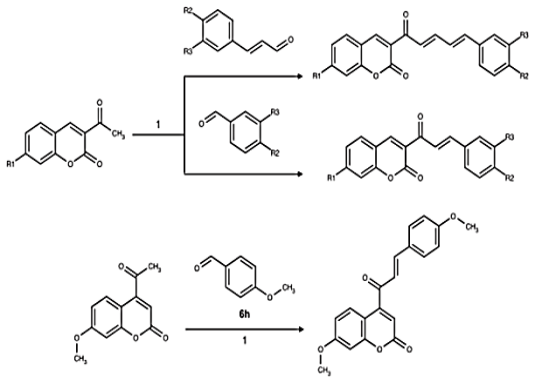


Fig. 2 . Structure of several coumarinic chalconoids (1-3) as HDACs inhibitors



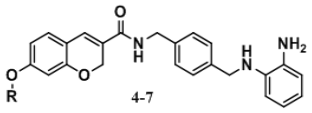
Reagent and conditions: (1) Pyrrolidine, ethanol, 80 C, 1–3 h.

Scheme1. Synthesis of of several coumarinic chalconoids(1-3) as HDACs inhibitors

A novel series of coumarin-based benzamides as HDACs inhibitors (Fig.3) were designed , synthesized (scheme 2) by Abdizadeh et al. and evaluated for their HDACs inhibitory activity. Almost all the synthesized coumarins showed good to excellent effect against the chosen cancer cell lines (MCF-7, PC3, A2780, HL60 HCT-116 and A549) in the cellular assay. Four compounds(4-7) had the most potent activity against the six cell lines with IC50 range of 0.53 – 57.59 μM, in addition they showed potent pan-HDAC inhibitory activity toward both pan HDAC and HDAC1 isozyme with IC50 ranging from 0.80 to 14.81 μM and 0.47 to 0.87 μM, respectively. Interestingly, compound 4 displayed an excellent potency againstHDAC1 with (IC50 value = 0.47 ± 0.02 mM) nearly equal to the reference drug Entinost (IC50 = 0.41 ± 0.06 μM) [28] .

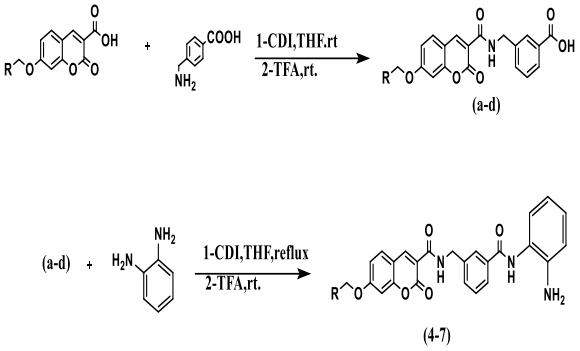
A new series of coumarin-based hydroxamate as anticancer HDAC inhibitors were designed and synthesized (scheme 3)by Na Zhao et al. among which compounds 8 and 9 (Fig.4) showed promising activities against cancer growth. Depending on a molecular docking simulation ,additional analogues further developed . Among them, compounds 10a and 10b were two to three times more effective than SAHA, and additional experimental tests were accomplished, Cell migration and colony formation assays displayed that the two compounds showed anti-metastatic and anti-

proliferative activities. 10a and Furthermore 10b arrest
ed MDA-MB-231 cells at G2/M phase and induced cell apoptosis. Moreover, Immunoblot analysis exhibited that 1a and 10b increased the acetylation of histone H3 and H4 in dose-dependent manner confirming their HDAC1 inhibitory activities[29] .

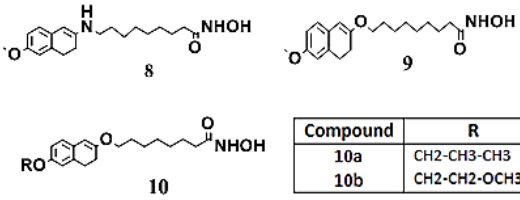


Compound	R
4	CH2-CH3
5	4-BrC6H4
6	4-CH3OC6H4
7	3,4-Cl2C6H3

Fig. 3 . Structure of coumarin-based benzamides(4-7) as HDACs inhibitors

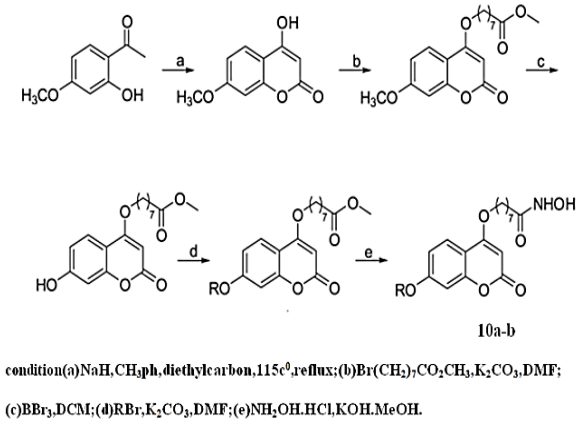


Scheme 2. Synthesis of coumarin-based benzamides (4-7) as HDACs inhibitors



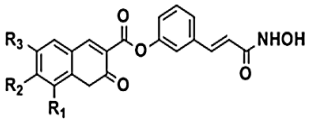
Compound	R
10a	CH2-CH3-CH3
10b	CH2-CH2-OCH3

Fig. 4 . Structure of several coumarin-based hydroxamate HDAC inhibitors



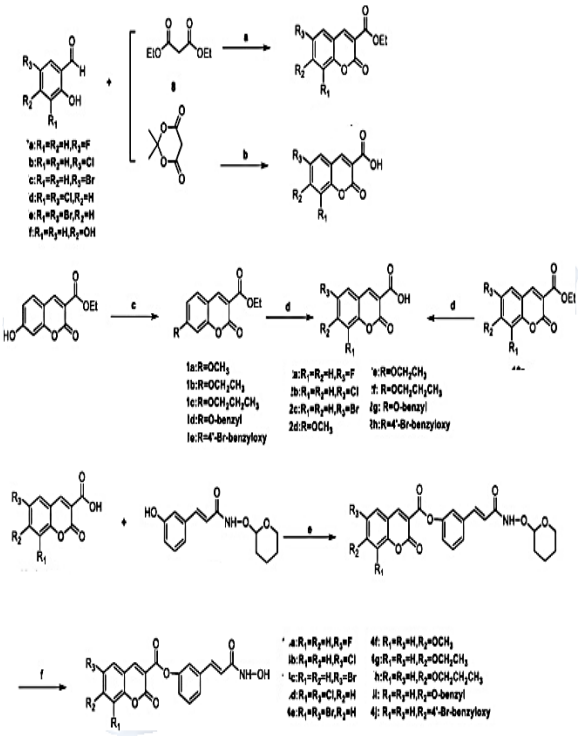
Scheme 3. Synthesis of several coumarin-based hydroxamate HDAC inhibitors

A novel series of coumarin based HDAC inhibitors (Fig.5) were designed, synthesized (scheme 4) by Jiaoli Ding et al. comprising coumarin as a cap group and N-hydroxycinnamamide as ZBG and linker group and evaluated for their enzyme inhibitory activity. Most of them displayed potent HDAC inhibitory effect and significant cytotoxicity against(HeLa, HepG2, HCT-116 and MCF-7). Among them, compound 11f was known as the most potent HDAC inhibitor in this series with(IC50 = 0.32 μM), which was more effective than that of SAHA (IC50 = 0.48 μM). HDAC isozyme inhibitory assay indicated that 11f exhibited better inhibitory activity against HDAC1 (IC50 = 0.19 μM) than SAHA (IC50 = 0.23 μM), and more than 25-fold selective inhibition for HDAC1 over HDAC6. Molecular docking studies exhibited the possible binding modes of compound 11f into HDAC1 and HDAC6, and gave a rationality for the high isozyme selectivity. As well as, compound 11f could decreased the colony formation and raised the acetylation of histone H3 in a dose-dependent manner, and it could also induce apoptosis and cell cycle arrest at G2/M phase in HeLa cells. Overall, all these findings supposed that compound 11f was a novel promising moiety as HDAC inhibitor with anticancer activity[12] .



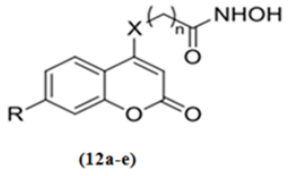
R1	R2	R3
H	H,CH3O	H
Cl	CH3CH2O,CH3CH2CH2O	Cl
Br	C8H10O,C8H9Bro	Br

Fig. 5 . Structure of several coumarin-based hydroxamate HDAC inhibitors (11a-j)



Scheme 4.Synthesis of several coumarin-based hydroxamate HDAC inhibitors (11a-j)

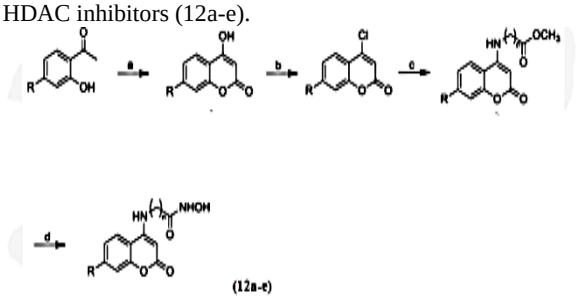
A novel series of coumarin-based hydroxamate derivatives as as HDACs inhibitors (Fig. 6) were designed and synthesized (scheme 5) by Feifei Yang et al. Selective compounds displayed a potent HDAC inhibition with nM IC50 values, with the best compound 10e showed the most potent inhibitory activity against HDAC1, with IC50 of 0.24 nM, which was almost 90 times lower than SAHA (IC50 = 21.10 nM). Compounds 12e and 12d showed a higher potency toward the human lung cancer cell line A549 and cervical cancer cell line Hela than against the hepatocellular carcinoma cell line HepG2 compared with SAHA. furthermore , Compounds 12e and 12d also upregulate the levels of acetylated histone H3 and H4, which is agreed with their strong HDAC inhibition. , Moreover, 12e and 12d significantly arrested A549 cells at the G2/M phase and induced apoptosis. Molecular docking studies revealed the possible mode of interaction of compounds 12e and 12a with HDAC1.All these results suggest that these novel coumarin-based HDAC inhibitors provide a promising scaffold for the development of new potential anticancer agents[30].



(12a-e)

compound	R	X	n
12a	H	NH	2
12b	H	NH	5
12c	OCH_3	NH	5
12d	OCH_3	NH	6
12e	OCH_3	NH	7
SAHA	-	-	-

Fig.6. Structure of several coumarin-based hydroxamate HDAC inhibitors (12a-e).

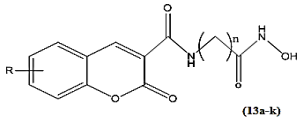


(12a-e)

Reagents and conditions: (a) Diethyl carbonate, NaH, CH_3Ph, 0 °C to reflux; (b) $POCl_3$, TEBAC, CH_3CN, reflux; (c) $NH_2(CH_2)_nCO_2CH_3$, Et_3N, EtOH, reflux; and (d) $NH_2OH{\cdot}HCl$, KOH, MeOH.

Scheme 5.Synthesis of several coumarin-based hydroxamate HDAC inhibitors (12a-e)

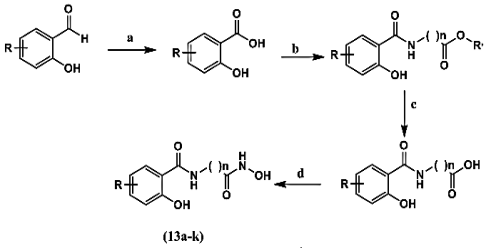
A new class of coumarin-based hydroxamate derivatives as HDACs inhibitors (Fig.7) were designed and synthesized (scheme 6) by Santiago García et al. The compounds displayed an important antiproliferative effects on two cell lines of breast cancer and one of prostate cancer. both 13i and SAHA exhibited a high percentage of antiproliferative effects at a concentration of 10 µM.as well as, this effect agrees with the gene regulation detected in two human cancer cell lines. The experiment with propidium iodide revealed the location of compound 13j in cancer cells, evidenced by the huge change in the color of the nucleus in BT-474 cells and to a lesser limit in MDA-MB-231 and PC3 cells. The findings gained presently should certainly be useful suggestion for designing derivatives as inhibitors of HDAC enzym**es** and better fluorescent prob[31].



(13a-k)

product	R	n
13a	H-	1
13b	H-	2
13c	H-	5
13d	6-ME-O-	3
13e	6-ME-O-	5
13f	8-EtO-	5
13g	6-Br-	1
13h	6-Br-	2
13i	6-Br-	5
13j	7-Et_2N-	2
13k	7-Et_2N-	5

Fig. 7. Structure of several coumarin-based hydroxamate HDAC inhibitors (13a-k).



(13a-k)

Reagent and reaction conditions. (a) Aldehyde , Meldrum's acid , H_2O reflux, 5–6 h. (b)amine hydrochloride , DMAP , CDI , DMF, rt, overnight (c) LiOH , THF/H_2O (1/2), rt, 12 h(d) NH_2OH/HCl , DMAP , CDI , DMF, rt, overnight

Scheme 6.Synthesis of of several coumarin-based hydroxamate HDAC inhibitors (13a-k

A novel series of thiazolyl-coumarins derivatives (Fig.8)were designed and synthesized (scheme 7) by Viviana Pardo-Jiménez et al. substituted at position 6 (R=H,Br,OCH3), linked to zinc binding groups (ZBGs), such as hydroxamic and carboxylic acid moieties and alternative zinc binding groups such as disulfide and catechol. evaluated for their in vitro inhibitory activities against HDACs. Disulfide and hydroxamic acid derivatives 14a-c and 15a-c derivatives are potent HDAC inhibitors. the advantage of thiazolyl–coumarin disulfide over hydroxamic acid derivatives is their low cytotoxicity and better ADMET parameters.All compounds at low concentration showed decreased cytotoxicity. Regarding the parameters associated to cardiac fibrosis development, the compounds showed antiproliferative effects, and enhanced a strong decrease on the expression levels of both α-SMA and procollagen I. these results suggesting that the thiazolyl–coumarin group is an effective surface recognition CAP inhibit HDAC activity and decrease profibrotic effects on cardiac fibroblasts[32].

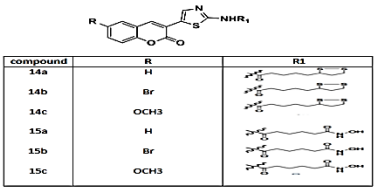
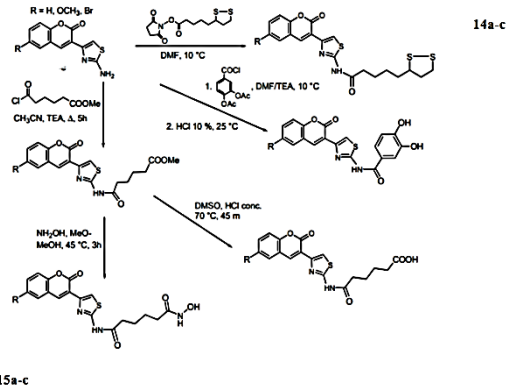


Fig. 8 .Structure of coumarin-based HDAC inhibitors



Scheme 7.Synthesis of coumarin-based HDAC inhibitors.

Conclusion

In this article we reviewed and focused on a series of novel HDAC inhibitors comprising coumarin as a core of cap group of HDAC inhibitors that have been designed, synthesized and assessed for their HDAC inhibitory activity as well as antiproliferative activity. Most of them exhibited potent HDAC inhibitory activity and significant cytotoxicity.All these findings suggested that coumarin derivatives could be promising lead compounds for further development of anticancer agents through HDACs inhibition

Reference

[1] Akko, E. K.; Genç, Y.; Karpuz, B .et al. Coumarins andCoumarin-RelateCompounds in Pharmacotherapy of Cancer . *Cancers* 2020, 12, 1959.

[2]Gharia, B. K.; Upadhyay, J.; Suhagia, B. N . et al. ,Current perspective of histone deacetylase inhibitors: A review *International Journal of Pharmaceutical Chemistry and Analysis (IJPCA)*. 2018;5(3),108-122

[3] Gregoretti, I.V.; Lee, Y.M.; Goodson, H.V., Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. *J Mol Biol*, 2004,338 , 17-31.

[4] Bertrand, P. Inside HDAC with HDAC inhibitors, *Eur J Med Chem*,2010, 45 ,2095-2116.

[5] Roche, J.; Bertrand, P.; Inside HDACs with more selective HDAC inhibitors. *Eur J Med Chem*. 2016, 121, 451-483.

[6] Yuan, H.; Marmorstein, R. Structural basis for sirtuin activity and inhibition, *J Biol Chem*. 2012, 287, 42428-42435.

[7] Taddei, M.; Cini, E.; Giannotti, L.et al. Lactam based 7-amino suberoylamide hydroxamic acids as potent HDAC inhibitors. *Bioorganic Med. Chem*. 2014, 24, 61–64.

[8] Huang, M.L.; Zhang, J.;Yan, C.J. et al. Small molecule HDAC inhibitors: promising agents for breast cancer treatment. *Bioorganic Chem*. 2019, 91, 103184.

[9] Jin, P.; Chen, X. Current status of epigenetics and anticancer drug discovery. *Anti-Cancer Agents Med. Chem.* 2016, 16, 699–712.

[10] Al-Amily, D., Mohammed, H. M. Design, Synthesis and Cytotoxicity Study of Primary Amides as Histone Deacetylase Inhibitors. *Iraqi J Pharm Sci*, 2019,28(2),(151-158).

[11] Zhan, P.; Wang, X.; Liu, X. et al. Medicinal chemistry insights into novel HDAC inhibitors:An updated patent review (2012–2016). Recent pat. *Anti-Cancer Drug Discov.* 2017, 12, 16–34.

[12] Ding, J.; Liu, J.; Zhang, Z. et al. Design, synthesis and biological evaluation of coumarin-based N-hydroxycinnamamide derivatives as novel histone deacetylase inhibitors with anticancer activities .*Bioorganic Chemistry*, 2020

[13] Mottamal , M; Zheng , S; Huang, T.L et al. Histone Deacetylase Inhibitors in Clinical Studies as Templates for New Anticancer Agents, *Molecules* 2015, 20, 3898-3941

[14] Ramdani, L.H. O.; Talhi, C.; Decombat et al. Bis(4-hydroxy-2H-chromen-2- one) Coumarin Induces Apoptosis in MCF-7 Human Breast Cancer Cells Through Aromatase Inhibition. *Anticancer Res*, 2019,39 , 6107-6114.

[15] Wang, J.; Lu, M.L.; Dai, H.L. et al . Esculetin, a coumarin derivative, exerts in vitro and in vivo antiproliferative activity against hepatocellular carcinoma by initiating a mitochondrial-dependent apoptosis pathway. *Braz J Med Biol Res*, 2015,48 ,245-253.

[16] Chuang,J.Y.; Huang,Y.F.; Lu,H.F. et al. Coumarin induces cell cycle arrest and apoptosis in human cervical cancer HeLa cells through a mitochondria- and caspase-3 dependent mechanism and NFkappaB down-regulation. In Vivo, 2007 ,21, 1003-1009.

[17] Zhang, L. , Zhi, X. Coumarin-containing hybrids and their anticancer activities. European Journal of *Medicinal Chemistry* ,2019, 181,111587

[18] Hu,Y.; Shen,Y.; Wu,X. et al. Synthesis and biological evaluation of coumarin derivatives containing imidazole skeleton as potential antibacterial agents. *Eur. J. Med. Chem*.2018, 143, 958-969.

[19] Kumar, S.; Mukesh,K. K.; Harjai, V. et al. Synthesis of coumarin based Knoevenagel Ugi adducts by a sequential one pot five-component reaction and their biological evaluation as anti-bacterial agents. *Tetrahedron Lett*.2019, 60, 8-12.

[20] Hu, X.L,; Xu, Z.; Liu, M.L. et al., Recent developments of coumarin hybrids as anti-fungal agents, *Curr. Top. Med. Chem*., 2017, 17 ,3219-3231.

[21] Fan,Y.L.; Ke,X.; Liu, M. Coumarin-1,2,3-triazole hybrids and their biological activities. *J. Heterocycl. Chem.* 2018,55,791-802.

[22] Hu,X.L.; Gao,C.; Xu Z. et al. Recent development of coumarin derivatives as potential antiplasmodial and

antimalarial agents. *Curr. Top. Med. Chem*.2018, 18,114-123.

[23] Singh, D.; Pathak, D.; Dharam P. et al. Coumarins, An overview of medicinalchemistry. Potential for new drug molecules. *Int. J. Pharmaceut. Sci. Res.* 2016,7, 482-504.

[24] Thakur, A.; Singla, R.; Jaitak ,V. Coumarins as anticancer agents: a review on synthetic strategies, mechanism of action and SAR studies. *Eur. J. Med. Chem*.2015, 101,476-495.

[25] Dandriyal,J. ; Singla,R.; Kumar M. et al., Recent developments of C-4 substituted coumarin derivatives as anticancer agents. *Eur. J. Med. Chem.* 2016,119 ,141-168.

[26] Ren,Q.C.; Gao,C.; Xu, Z. et al. Bis-coumarin derivatives and their biological activities, *Curr. Top. Med. Chem.* 2018,18 ,101-113.

[27] C. Seidel, M. Schnekenburger, C. Zwergel et al. *Bioorg. Med. Chem. Lett*.2014, 24,3797-3801.

[28] Abdizadeh,T.; Kalani , M. R.; Abnous, Kh. at al. Design, synthesis and biological evaluation of novel coumarin-based benzamides as potent histone deacetylase inhibitors and anticancer agents .*European Journal of Medicinal Chemistry* 2017,132, 42-62

[29] Zhao, N.; Yang , F.; Han, L, ,et al. Development of Coumarin-Based Hydroxamates as Histone Deacetylase Inhibitors with Antitumor Activities. *Molecules* 2020, 25, 717 2.

[30] Yang ,F.; Zhao,N.; Song, J. et al. Design, Synthesis and Biological Evaluation of Novel Coumarin-Based Hydroxamate Derivatives as Histone Deacetylase (Hdac) Inhibitors with Antitumor Activities.*molcules.* 2019 , 24(14), 2569.

[31] García ,S.; Sánchez, I. M.; Bahena, L. et al. *Molecules* 2020, 25, 5134

[32] Jiménez , V. P.; Encina P. N.; and Araya G. D. . Synthesis and Biological Evaluation of Novel Thiazolyl-Coumarin Derivatives as Potent Histone Deacetylase Inhibitors with Antifibrotic Activity. *Molecules* 2019, 24, 739.