González-Sabin and Morís, Biochem & Pharmacol 2013, 2:1
DOI: 10.4172/2167-0501.1000e140

Biochemistry & Pharmacology: Open Access

Editorial Open Access

Exploring Novel Opportunities for Aureolic Acids as Anticancer Drugs

Javier González-Sabín* and Francisco Morís

Entrechem SL and Oviedo Spain Campus The Christ, Spain

The aureolic acids are a family of polyglycosylated aromatic polyketides bearing a tricyclic core that includes mithramycin A, chromomycin A_3, olivomycin A, UCH9 and durhamycin A (Figure 1) [1]. They are all antineoplastic antibiotics against Gram-positive bacteria and also stop the proliferation of tumor cells. Several studies have pointed out that the basis for the antitumor properties of mithramycin and its analogs (Mithralogs) is the inhibition of replication and transcription processes during macromolecular biosynthesis by interacting, in the presence of Mg^{2+}, with GC-rich nucleotide sequences, especially the site of union of Sp1 transcription factor [2-4]. Mithramycin A (MTM) and chromomycin A_3 (CRM) are the most representative members of the family, MTM being approved as an anticancer drug in 1970, and used originally for the treatment of several types of cancer, Paget's bone disease and hypercalcemia [5-7]. However, the use of mithramycin in humans has been limited because its side effects, to the point commercial clinical batches have not been reported since 2000. Regarding CRM, despite being 10 times more active than MTM against several tumor cell lines, it has been limited clinically due to severe toxicity [8].

Not withstanding, in recent years has been a renewed interest in aureolic acids, as new uses and activities has been described to MTM, including inhibition of apoptosis or antiangiogenic activity, in both cancer and noncancer related processes [9,10]. For example, MTM selectively blocks expression of cell proliferation and transforming growth factor β (TGF-β) signaling clusters in human gingival fibroblasts, and in glioma cells it was found to suppress and delay tumor cell migration [11]. On the other hand, the combination of MTM and betulinic acid has led to a novel antiangiogenic therapy for pancreatic cancer [12] and has also revealed to be a neuroprotective drug with potential application as neurological therapeutics [13]. Likewise, CRM was identified through *in silico* analysis of the publicly available drug profiles from the NIH (National Cancer Institute) as an agent suitable to selectively targeting the loss of the von Hippel-Lindau (VHL) tumor suppressor gene in clear cell renal carcinoma [14].

More recently, MTM has just been identified as the top candidate from a high-throughput screening of over 50,000 compounds to inhibit the aberrant EWS-FLI1 fusion transcription factor, associated to the malignant transformation and progression of Ewing sarcoma family of tumors (ESFTs) [15]. Similarly, it has been shown that MTM is able to downregulate ABCG2, a xenobiotic pump, a knockdown effect that inhibits proliferation and migration in lung and esophageal cancer cells [16]. Importantly, both findings have provided the basis for starting clinical trials of MTM in cancer for the first time in decades [17,18].

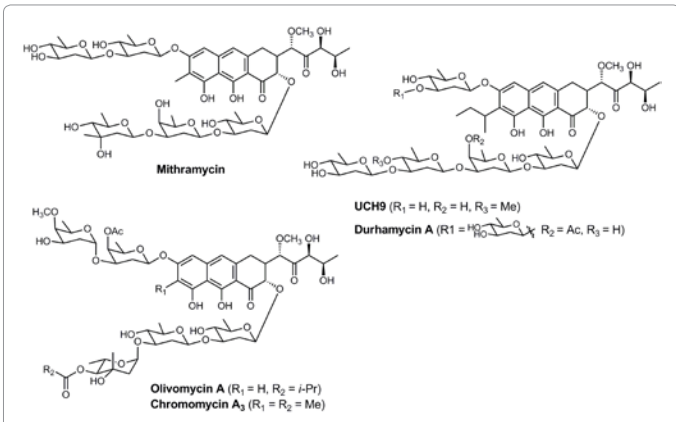

Figure 1: Chemical structures of selected aureolic acids.

These promising applications have triggered the development of several synthetic approaches in order to discover novel aureolic acid analogs with an improved therapeutic index [1,19,20]. In the field of combinatorial biosynthesis, modifications achieved by genetic engineering have allowed to modify the MTM molecule in the 3-side chain (aglycone), the sugar profile or both. Particularly, the mithralogs SK (MTM-SK), and SDK (MTM-SDK) [21], which bear a shorter side chain, showed higher antitumor activities and lower toxicity than the parental compound and were particularly effective in treating ovarian and advanced prostate cancers [22-24]. Likewise, the gene cluster involved in the biosynthesis of CRM has been cloned and characterized, showing that the CmmA gene encodes the acetyltransferase responsible for transferring both acetyl groups to the sugar moiety. Further employment of the CmmA acetyl transferase as a biosynthetic enzyme enabled to prepare novel mono-, di- and triacetyl derivatives of aureolic acids with improved antitumor activities [25]. Moreover, a biocatalytic approach based on a lipase-catalyzed regioselective acylation led to a plethora of mono- and diacetyl derivatives of MTM and CRM [26,27]. Recently the complexation of aureolic acids with metal ions has been studied as well as the activity of the resulting complexes. All the MTM and CRM complexes with divalent metal ions exhibited a 2:1 drug-metal complex stoichiometry. The antitumor activity of the CRM-complexes with Ni(II), Fe(II) and Co(II) were significantly higher than the uncomplexed drug due to higher DNA-acting affinity meanwhile the association with Cu(II) disfavored DNA binding [28]. Similarly, the dimer complex of MTM with Ni(II) exhibited a greater cytotoxicity than free MTM in several cancer cell lines [29].

One major problem to address with the aureolic acid family of drugs is the low bioavailability, short plasma retention time and low tumor accumulation. Previous attempts to address this issue with liposomal formulations as controlled delivery systems turned out to be not effective. Recently, two nanoparticle formulations of MTM analogs, poly(ethylene glycol)-poly(aspartatehydrazide) self-assembled

***Corresponding author:** Javier González-Sabin, EntreChem SL, Campus El Cristo, Oviedo, Spain, Tel: 34-985-259-021; Fax: 34-985-103-686; E-mail: jgsabin@entrechem.com

Received November 29, 2012; **Accepted** December 03, 2012; **Published** December 06, 2012

Citation: González-Sabin J, Morís F (2013) Exploring Novel Opportunities for Aureolic Acids as Anticancer Drugs. Biochem & Pharmacol 2:e140. doi:10.4172/2167-0501.1000e140

and cross-linked polymer micelles have been developed in order to achieve a pH-dependent release of the drug. To a pH of 7.4 both self-assembled and cross-linked micelles retained 40-50% of the drug after 24 hours meanwhile drug release was accelerated at pH 5.0, especially in the cross-linked micelles. Interestingly, both formulations retained the antitumor activity of the mithralogs, the cross-linked micelles being even more potent against the A549 human non-small cell lung cancer cell line [30].

Olivomycin A was discovered more than forty years ago at the Gause Institute of New Antibiotics [31]. Despite having shown great activity in clinical trials as anticancer drug, its use was also limited due to the high toxicity. Regarding synthetic approaches, the Roush's group accomplished after ten years of impressive work the total synthesis of olivomycin A by preparing the aglycone unit (olivin), the di- and trisaccharide appendages and final assembly [32]. More recently, some synthetic analogs has been prepared by chemical modification of the aglycone moiety. For example, the attachment of amide groups to the 2'-keto group of the side chain led to a novel derivative with higher antitumor activity in *in vivo* experiments on mice bearing leukemia P-388 and lower toxicity than the parent drug as well as a marked inhibitory activity against topoisomerase I (Topo-I) [33]. Similarly, the shortening of the side chain of olivomycin to a methoxyacetic residue and further functionalization as an amide provided a novel derivative with improved DNA binding constant and antitumor effect against lymphoma and melanoma [34]. Durhamycin A was discovered in 1966 as an antifungal antibiotic from *Streptomyces durhamensis* sp. [35]. Although by far much less studied, in contrast to the well-established antitumor activity of all the other aureolic acids, durhamycin A exhibited excellent activity as a potent inhibitor (IC50=4.8 nM) of Tat, a small protein essential for both viral replication and progression of HIV disease [36]. Recently, the tetra- and trisaccharide units of the sugar moiety as well as an advanced precursor for the aglycone core have been synthesized which opens the door to new analogs [37]. Similarly, UCH9 with a structure close related durhamycin A, was isolated from *Streptomyces sp*. from a soil sample collected in Iwakuni city (Japan) in 1998. UCH9 showed cytotoxic activity against HeLa S3 cells with an IC50 value of 13 nM and significant antitumor activity in a murine syngenic model [38].

In the immediate future, and in light of the promising applications highlighted above, it is almost certainly that novel aureolic acid analogs will be developed, especially taking advantage of the combinatorial biosynthesis and biocatalysis, as well as chemical synthesis. The launch of new clinical trials with MTM is re-opening the clinical interest in mithralogs. The viability of new analogs will be enabled by improvements in therapeutic window, a critical issue in many cancer therapeutics, especially those of natural origin. Overall, it is likely we will see new opportunities to this neglected class of compounds, long stigmatized since they address the activity of generally regarded undruggable targets.

References

1. Lombó F, Menéndez N, Salas JA, Méndez C (2006) The aureolic acid family of antitumor compounds: structure, mode of action, biosynthesis, and novel derivatives. Appl Microbiol Biotechnol 73: 1-14.
2. Bataller M, Méndez C, Salas JA, Portugal J (2010) Cellular response and activation of apoptosis by mithramycin SK in p21WAF1-deficient HCT116 human colon carcinoma cells. Cancer Lett 292: 80-90.
3. Mansilla S, Garcia-Ferrer I, Mendez C, Salas JA, Portugal J (2010) Differential inhibition of restriction enzyme cleavage by chromophore-modified analogues of the antitumour antibiotics mithramycin and chromomycin reveals structure-activity relationships. Biochem Pharmacol 79: 1418-1427.
4. Vizcaíno C, Mansilla S, Núñez LE, Méndez C, Salas JA, et al. (2012) Novel mithramycins abrogate the involvement of protein factors in the transcription of cell cycle control genes. Biochem Pharmacol 84: 1133-1142.
5. Kennedy BJ (1970) Metabolic and toxic effects of mithramycin during tumor therapy. Am J Med 49: 494-503.
6. Brown JW, Kennedy BJ (1965) Mithramycin in the treatment of disseminated testicular neoplasms. N Engl J Med 272: 111-118.
7. Ryan WG, Schwartz TB, Northrop G (1970) Experiences in the treatment of Paget's disease of bone with mithramycin. JAMA 213: 1153-1157.
8. Davis HL Jr, von Hoff DD, Henney JE, Rozencweig M (1978) The role of antitumor antibiotics in current oncologic practice. Cancer Chemother Pharmacol 1: 83-90.
9. Chatterjee S, Zaman K, Ryu H, Conforto A, Ratan, RR (2001) Sequence-selective DNA binding drugs mithramycin A and chromomycin A3 are potent inhibitors of neuronal apoptosis induced by oxidative stress and DNA damage in cortical neurons. Ann Neurol 49: 345-354.
10. Jia, Z, Gao Y, Wang L, Li Q, Zhang J, et al. (2010) Treatment with Combination of Mithramycin A And Tolfenamic Acid Promotes Degradation of Sp1 Protein And Synergistic Antitumor Activity In Pancreatic Cancer. Cancer Res 70: 1111-1119.
11. Fajardo OA, Thompson K, Parapuram SK, Liu S, Leask A (2011) Mithramycin reduces expression of fibro-proliferative mRNAs in human gingival fibroblasts. Cell Prolif 44: 166-173.
12. Gao Y, Jia Z, Kong X, Li Q, Chang DZ, et al. (2011) Combining betulinic acid and mithramycin a effectively suppresses pancreatic cancer by inhibiting proliferation, invasion, and angiogenesis. Cancer Res 71: 5182-5193.
13. Osada N, Kosuge Y, Oguchi S, Miyagishi H, Ishige K, et al. (2012) Protective action of mithramycin against neurodegeneration and impairment of synaptic plasticity in the hippocampal CA1 area after transient global ischemia. Neurochem Int 60: 47-54.
14. Sutphin PD, Chan DA, Li JM, Turcotte S, Krieg AJ, et al. (2007) Targeting the loss of the von Hippel-Lindau tumor suppressor gene in renal cell carcinoma cells. Cancer Res 67: 5896-5905.
15. Grohar PJ, Woldemichael GM, Griffin LB, Mendoza A, Chen QR, et al. (2011) Identification of an inhibitor of the EWS-FLI1 oncogenic transcription factor by high-throughput screening. J Natl Cancer Inst 103: 962-978.
16. Zhang M, Mathur A, Zhang Y, Xi S, Atay S, et al. (2012) Mithramycin represses basal and cigarette smoke-induced expression of ABCG2 and inhibits stem cell signaling in lung and esophageal cancer cells. Cancer Res 72: 4178-4192.
17. Mithramycin for Children and Adults with Solid Tumors or Ewing Sarcoma.
18. Mithramycin for Lung, Esophagus, and Other Chest Cancers.
19. Baig I, Perez M, Braña AF, Gomathinayagam R, Damodaran C, et al. (2008) Mithramycin analogues generated by combinatorial biosynthesis show improved bioactivity. J Nat Prod 71: 199-207.
20. Núñez LE, Nybo SE, González-Sabín J, Pérez M, Menéndez N, et al. (2012) A novel mithramycin analogue with high antitumor activity and less toxicity generated by combinatorial biosynthesis. J Med Chem 55: 5813-5825.
21. Remsing LL, González AM, Nur-e-Alam M, Fernández-Lozano MJ, Braña AF, et al. (2003) Mithramycin SK, a novel antitumor drug with improved therapeutic index, mithramycin SA, and demycarosyl-mithramycin SK: three new products generated in the mithramycin producer Streptomyces argillaceus through combinatorial biosynthesis. J Am Chem Soc 125: 5745-5753.
22. Albertini V, Jain A, Vignati S, Napoli S, Rinaldi A, et al. (2006) Novel GC-rich DNA-binding compound produced by a genetically engineered mutant of the mithramycin producer Streptomyces argillaceus exhibits improved transcriptional repressor activity: implications for cancer therapy. Nucleic Acids Res 34: 1721-1734.
23. Previdi S, Malek A, Albertini V, Riva C, Capella C, etal. (2010) Inhibition of Sp1-dependent transcription and antitumor activity of the new aureolic acid analogues mithramycin SDK and SK in human ovarian cancer xenografts. Gynecol Oncol 118: 182-188.
24. Malek A, Núñez LE, Magistri M, Brambilla L, Jovic S, et al. (2012) Modulation of the activity of Sp transcription factors by mithramycin analogues as a new strategy for treatment of metastatic prostate cancer. PLoS One 7: e35130

25. García B, González-Sabín J, Menéndez N, Braña AF, Núñez LE, et al. (2011) The chromomycin CmmA acetyltransferase: a membrane-bound enzyme as a tool for increasing structural diversity of the antitumour mithramycin. Microb Biotechnol 4: 226-238.

26. González-Sabín J, Núñez LE, Braña AF, Méndez C, Salas JA, et al. (2012) Regioselective enzymatic acylation of aureolic acids to obtain novel analogues with improved antitumor activity. Adv Synth Catal 354: 1500-1508.

27. González-Sabín J, Núñez LE, Menéndez N, Braña AF, Méndez C, et al. (2012) Lipase-catalyzed preparation of chromomycin A3 analogues and biological evaluation for anticancer activity. Bioorg Med Chem Lett 22: 4310-4313.

28. Hsu CW, Chuang SM, Wu WL, Hou MH (2012) The crucial role of divalent metal ions in the DNA-acting efficacy and inhibition of the transcription of dimeric chromomycin A3. PLoS One 7: e43792.

29. Hsu CW, Kuo CF, Chuang SM, Hou MH (2012) Elucidation of the DNA-interacting properties and anticancer activity of a Ni(II)-coordinated mithramycin dimer complex. Biometals [Epub ahead of print].

30. Scott D, Rohr J, Bae Y (2011) Nanoparticulate formulations of mithramycin analogs for enhanced cytotoxicity. Int J Nanomedicine 6: 2757-2767.

31. Berlin YU, Kiseleva OA, Kolosov MN, Shemyakin MM, Soifer VS (1968) Aureolic acid group of anti-tumour antibiotics. Nature 218: 193-194.

32. Roush WR, Hartz RA, Gustin DJ (1999) Total synthesis of olivomycin. A J Am Chem Soc 121: 1990-1991.

33. Tevyashova AN, Olsufyeva EN, Balzarini J, Shtil AA, Dezhenkova LG, et al. (2009) Modification of the antibiotic olivomycin I at the 2'-keto group of the side chain. Novel derivatives, antitumor and topoisomerase I-poisoning activity. J Antibiot (Tokyo) 62: 37-41.

34. Tevyashova AN, Shtil AA, Olsufyeva EN, Luzikov YN, Reznikova MI, et al. (2011) Modification of olivomycin A at the side chain of the aglycon yields the derivative with perspective antitumor characteristics. Bioorg Med Chem 19: 7387-7393.

35. Gordon MA, Lapa EW (1966) Durhamycin, a Pentaene Antifungal Antibiotic from Streptomyces durhamensis sp. n. Appl Microbiol 14: 754-760.

36. Jayasuriya H, Lingham RB, Graham P, Quamina D, Herranz L, et al. (2002) Durhamycin A, a potent inhibitor of HIV Tat transactivation. J Nat Prod 65: 1091-1095.

37. Pragani R, Roush WR (2008) Studies on the synthesis of durhamycin A: stereoselective synthesis of a model aglycone. Org Lett 10: 4613-4616.

38. Ogawa H, Yamashita Y, Katahira R, Chiba S, Iwasaki T, et al. (1998) UCH9, a new antitumor antibiotic produced by Streptomyces: I. Producing organism, fermentation, isolation and biological activities. J Antibiot (Tokyo) 51: 261-266.