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Design and synthesis of novel 5-aminosalicylate (5-ASA)–4-thiazolinone hybrid derivatives with promising antiproliferative activity

Hajjaj H. M. Abdu-Allah [a,*], Samia G. Abdel-Moty [a], Raafat El-Awady [b,c], Abdel-Nasser A. El-Shorbagi [a,c]

[a] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt
[b] Cancer Biology Department, National Cancer Institute, Cairo University, Cairo, Egypt
[c] Sharjah Institute for Medical Research and College of Pharmacy, University of Sharjah, Sharjah 27272, United Arab Emirates

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ABSTRACT

Two privileged pharmacophores were assembled in one molecular frame involving 5-aminosalicylate and 4-thiazolinones that can be found in different stereochemical features. The compounds were fully characterized and evaluated for antiproliferative activity against four human cancer cell lines and some are equipotent to doxorubicin with lower cytotoxicity to normal cells. The most interesting finding relates to compound **10**, which shows an IC_{50} value of 70 nM against MCF-7 cells, while the IC_{50} against human fibroblasts is 10 μM. The results of this study indicate that the new compounds are optimal anti-cancer leading compounds and merit further studies to optimize their structure, detect their biotargets and in vivo activity.

Although a range of treatment options are available for cancer, chemotherapy is fraught with significant levels of toxicity to healthy cells, and drug resistance develops in some treatment regimes. To decrease the current cancer burden, drug discovery is directed at the development of highly effective and potent medications with reduced side effects. 5-Aminosalicylic acid (5-ASA), as well as its prodrugs that are currently used in the management of inflammatory bowel diseases have been shown recently to possess cancer chemopreventive and chemotherapeutic properties.[1] The mechanism of this activity is attributed to improved maintenance of genomic stability that counteracts carcinogenesis,[2] thus contributing to its chemopreventive and chemotherapeutic properties, in particular, against colorectal cancer.[3,4] 1,2,3-Triazolyl-salicylamides exhibited antiproliferative activity as lavendustin mimetics and potent aurora kinase inhibitors.[5] Recently, it was suggested that the antioxidant properties of salicylate derivatives is a possible mechanism of anti-inflammatory activity.[6]

On the other hand, 2-arylaminothiazolidin-4-ones having 5-un/substituted benzylidenes were the most promising in inhibiting growth of several human cancer cell lines but not normal fibroblasts in a dose dependent manner.[7–13] Several mechanisms were suggested for these effects involving reversible blockage of cell cycle progression at the G2/M phase border, induction of apoptosis,[14] antagonizing stimulatory effect of free fatty acids at cell proliferation,[15] inhibition of translation initiation,[16] interaction with Sphingosine Kinase and non-membrane protein tyrosine phosphatase (SHP-2).[17]

For complex diseases like cancer; a balanced modulation of several targets can provide advanced therapeutic effects and a favorable side effects profile compared to the action of selective ligand. Accordingly, it is thought of interest to accommodate thiazolin-4-one and 5-ASA moieties in a single molecular framework as the key pharmacophore and screen the antiproliferative activity. Interestingly, the target compounds can be considered as lavendustin analogs.[18] Our design is based, also, on an interesting SAR study in 2-amino-4-thiazolinones which allowed to identify optimal H-bond donating OH substituent at *para* position of arylamino fragment, as well as small lipophilic substituents of the benzylidene moiety at positions 3 and 4 are favored.[19] Several studies revealed that the presence and the nature of the moiety at position 5 of thiazolidinone play the key role in realization of the pharmacological effects.[19–22] Accordingly, the structural variations were selected by introducing different benzylidenes at that position.

* Corresponding author. Tel.: +20 01010211566, +20 088 241594; fax: +20 088 2332776.
E-mail address: hagag.abdallah@pharm.au.edu.eg (H.H.M. Abdu-Allah).

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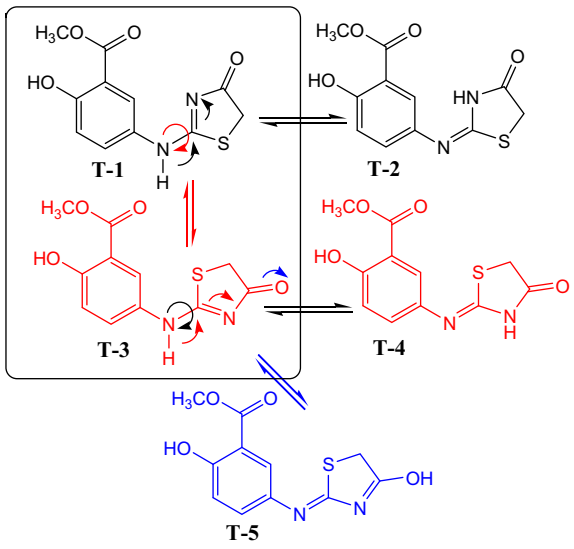
The target compounds were synthesized as shown in Scheme 1 (see ESI for Experimental details). 5-ASA was chloroacetylated by heating with chloroacetyl chloride in dry benzene.[23] Heterocyclization of the product in the presence of ammonium thiocyanate in refluxing ethanol efficiently produced methyl 2-hydroxy-5-[(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-amino]benzoate (**1**).[24] The two active methylene protons appear as separate doublets at $\delta = 4.00$ and 3.96 ppm. The target compounds (**2**–**19**) were obtained by refluxing **1** with commercially available aromatic aldehydes using a Knoevenagel condensation procedure in the presence of sodium acetate, in glacial acetic acid. The purity of the synthesized compounds has been checked by TLC. The structures of the synthesized compounds were confirmed by analytical and spectral data (IR, ^{1}H, ^{13}C NMR and ESI-HRMS).[25] In ^{1}H NMR spectra of compounds **1**–**19** characteristic doubling of the signals is seen that corresponds to the presence of tautomerism or *syn*/*anti* arrangement rotamers. On the basis of spectra the correlation of the two isomers in the solution make approximately 1:1 mixture. For example, NH proton appears as two singlets at about ~11.60 ppm and ~12.45 ppm. The 5-ASA moiety forms subspectrum of multiplets at ~7.05–7.55 ppm. Only *Z*-isomers were obtained as in the Knoevenagel reaction, because it is thermodynamically stable.[26]

2-Arylamino-2-thiazolin-4-ones and their 5-substituted derivatives can primarily display amino/imino due to prototropic tautomerism. Additionally, both tautomeric forms may exist as a mixture of two conformers (T-1, T-2 and T-3, T-4; Scheme 2), which are particularly stabilized by the formation of intramolecular hydrogen bonds. It is worth noting that amino/imino tautomerism in 2-amino(imino)-1,3-thiazolidin-4-one derivatives have been extensively investigated. Results from these studies showed that the tautomer with the carbonyl–imine group in the five-membered heterocyclic ring and an exocyclic amine N atom is predominant.[27]

Similarly, X-ray single crystal analysis of **1** revealed that the amino form is predominant and the compound is crystallized with two independent molecules in the asymmetric unit that differ primarily in the rotational orientation of the five-membered heterocyclic ring (Fig. 1).[24] This finding was also studied by computational chemistry.

The possible conformational (*S-trans* and *S-cis*, such as T-1 and T-3, respectively) and the configurational (*E* and *Z* such as T2 and T4, respectively) isomers are shown in Scheme 2. The structures and the vibrational frequencies of all stable rotamers and tautomers have been calculated. Final energies have been obtained and recorded in Table 1. The results show that the rotamers T1 and T3 are almost of equal heat of formation and both are much more stable than their corresponding tautomers T-2 and T-4, respectively. This finding explains why this precursor **1** is found as inseparable 1:1 mixture of conformers (T-1 and T-3). To our knowledge this is the 1st crystal structure shows conformers (not tautomers) and in equal ratio. Systematic investigation of the reported X-ray structure shows that the two rotamers are stacked together oppositely and face to face via the amino-thiazoline entities.



Scheme 2. Tautomers and conformational isomers of compound **1**.

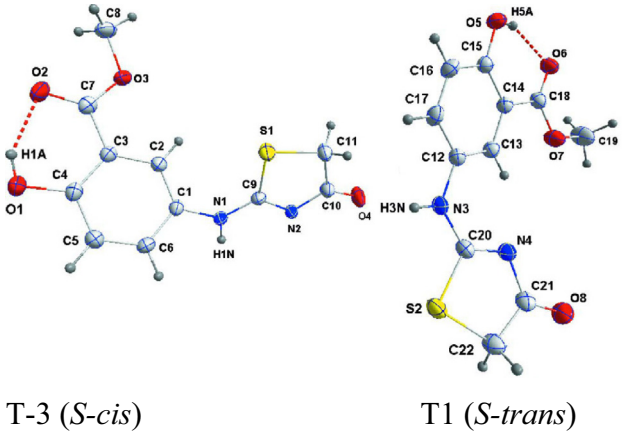
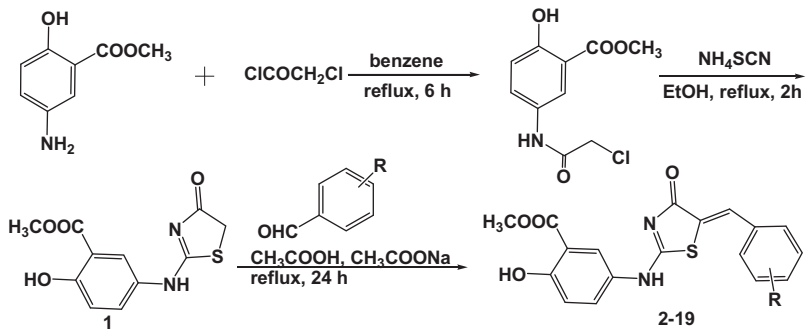


Figure 1. The structures of the rotamers of compound **1**. The asymmetric unit with labeling scheme and 50% probability ellipsoids.[24]



2: R = H; **3**: R = 4-Me; **4**: R = 4-OMe; **5**: R = 4-NO_2; **6**: R = 4-Cl; **7**: R = 2-OH; **8**: R = 3-Cl; **9**: R = 2-OMe; **10**: R = 4-Br; **11**: R = 2-Cl; **12**: R = 3-Br; **13**: R = 4-NMe_2; **14**: R = 3,4-OCH_2O-; **15**: R = 3,4-di-OMe; **16**: R = 4-OH; **17**: R = 3-NO_2; **18**: R = 3,4,5-tri-OMe; **19**: R = 4-F

Scheme 1. Synthesis of methyl 2-hydroxy-5-[(5-benzylidene-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-amino]benzoates **2**–**19**.