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Original article

Synthesis, stereochemistry and biological activity of some novel long alkyl chain substituted thiazolidin-4-ones and thiazan-4-one from 10-undecenoic acid hydrazide

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Abstract

The synthesis of four novel compounds, (i) [(11-{[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-11-oxoundecyl)sulfanyl]acetic acid (**4**), (ii) *N*-[5-methyl-2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]undec-10-enamide (**5**), (iii) 2-[(11-{[5-methyl-2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-11-oxoundecyl)sulfanyl]propanoic acid (**6**) and (iv) 3-[(11-{[2-(3-nitrophenyl)-4-oxo-1,3-thiazinan-3-yl]amino}-11-oxoundecenyl) sulfanyl]propanoic acid (**8**) from 10-undecenoic acid hydrazide (**1**) via *m*-nitrobenzaldehyde-10-undecenohydrazone (**2**) using mercaptoacetic acid in (i), 2-mercaptopropionic acid in (ii and iii) and 3-mercaptopropionic acid in (iv) is described. The uncyclized products, ({11-[(2*E*)-2-(3-nitrobenzylidene)hydrazino]-11-oxo-undecyl}sulfanyl)acetic acid (**3**) and 3-({11-[(2*E*)-2-(3-nitrobenzylidene)hydrazino]-11-oxoundecyl}sulfanyl)propanoic acid (**7**) are also obtained in (i) and (iv), respectively. The hydrazones (**2**), (**3**) and (**7**) exist in two conformers as synperiplanar and antiperiplanar. Structural assignment, stereochemistry and biological assays are discussed.

Keywords: Acylhydrazone; Thiazolidin-4-ones; Tetrahydro-1,3-thiazin-4-one; Terminal carboxymethyl/ethylthio acylhydrazones; Cytotoxic activity; Antimicrobial activity

1. Introduction

In recent years attention has been focussed on the synthesis of naturally occurring long alkyl chain substituted heterocycles and their analogues [1–3]. The interest in thiazolidin-4-ones and tetrahydro-1,3-thiazin-4-ones for medical applications is also increasing strongly. (–) 2-(5-Carboxypentyl) thiazolidin-4-one (actithiazic acid) isolated from the culture broth of a strain of streptomyces shows highly specific in vitro activity against *Mycobacterium tuberculosis* [4a,b]. Other substituted thiazolidin-4-ones exhibit diverse biological activities such as anticonvulsant [5], antidiarrheal [6], antiarthritic [7], anti-platelet activating factor activity [8,a,b,c], antihistaminic [9a,b,c], antimicrobial [10a,b,c], antidiabetic [11a,b], oxygenase inhibitory [12], K^+ channel inhibitory [13], calcium antagonist [14], cardioprotective [15], antiischemic activity [16a,b] and a promising agent for treating Alzheimer [11b], cancer [17], AIDS [18a,b] and hepatitis B [18a]. Among the tetrahydro-1,3-thiazin-4-ones, 2-(4-chlorophenyl)-3-methyl-tetrahydro-1,3-thiazin-4-one-1,1-dioxide (chloromezanone) is widely used as anticoagulant [19], tranquilizer and muscle spasm [20]. Other derivatives show wide range activities as antimicrobial [21a,b], antiarthritic [22], antirheumatic [23] and in the treatment of cardiac arrythimia [13], peptic ulcer [24] and occular inflammation [25]. Also a number of long chain alkyl thioethers has been reported for their antimicrobial [26a,b], tranquilizer [27], analgesic and antidepressant [28] activities. As part of our aim in search of biologically active nitrogen and sulfur containing heterocyclic compounds, we have recently reported [29,30] the synthesis and cytotoxic activity of two novel compounds, 2-[2-carboxymethylthio-2-(4-chlorophenyl) ethyl]-2-(4-chlorophenyl)-4-thiazolidinone and 2-[2,2-bis(4-chlorophenyl) ethyl]-2-(4-chlorophenyl)thiazo-

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lidin-4-one from *p*,*p*′-dichlorochalcone using mercaptoacetic acid in the presence of ammonium carbonate. Evaluation for cytotoxic activity was performed against 60 cell lines of nine types of human cancers leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. Noteworthy results are obtained in the case of melanoma, colon and renal cancers where the reduction in growth is 52%, 80% and 91%, respectively, at the concentration of 1.0×10^{-4} M.

Because 4-thiazolidinones and thiazanones substituted in the 2-position were proven to be biologically very potent and selective and in anticipation that the lipophilization by long alkyl chain thioether substitution in the ring may further enhance their activity, prompted us to undertake this problem. The present paper deals with the synthesis, stereochemistry and biological screening of four novel compounds, (i) [(11-{[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-11-oxoundecyl)sulfanyl]acetic acid (**4**) (ii) *N*-[5-methyl-2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]undec-10-enamide (**5**) (iii) 2-[(11-{[5-methyl-2-(3-nitro-phenyl)-4-oxo-1,3-thiazolidin-3-yl]amino}-11-oxoundecyl) sulfanyl]propanoic acid (**6**) and (iv) 3-[(11-{[2-(3-nitrophenyl)-4-oxo-1,3-thiazinan-3-yl]amino}-11-oxoundecenyl) sulfanyl]propanoic acid (**8**) along with two adducts (**3**) and (**7**), from 10-undecenoic acid hydrazide (**1**) via *m*-nitrobenzaldehyde-10-undecenohydrazone (**2**) using mercaptoacetic acid in (i), 2-mercaptopropionic acid in (ii and iii) and 3-mercaptopropionic acid in (iv). The uncyclized adducts, ({11-[(2*E*)-2-(3-nitrobenzylidene)hydrazino]-11-oxoundecyl}sulfanyl)-acetic acid (**3**) and 3-({11-[(2*E*)-2-(3-nitrobenzylidene) hydrazino]-11-oxoundecyl}sulfanyl)propanoic acid (**7**) are obtained in (i) and (iv), respectively. It is believed that the mercaptoacetic acid and 3-mercaptopropionic acid first undergo addition to the terminal olefinic bond giving the adducts (**3**) and (**7**) while 2-mercaptopropionic acid first undergoes cyclocondensation at the C=N double bond and thus no uncyclized adduct is formed in (ii) and (iii). The stereochemical investigation of the hydrazones (**2**), (**3**) and (**7**) confirm the existence of two conformers as synperiplanar (major) and antiperiplanar (minor). The hydrazone (**2**), thiazolidin-4-one derivatives (**4**) and (**5**) and thiazan-4-one derivative (**8**) are evaluated for cytotoxic activity first against three cell lines of three types of human cancers: lung, breast and CNS. The compound (**5**) found to be active in a panel of three cell lines is then screened on a full panel of 60 cell lines of nine types of human cancers: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. Screening results of seven compounds (**2**)–(**8**) are also summarized for antimicrobial activity against four bacteria, *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and one fungus, *Candida albicans*.

2. Results and discussion

2.1. Chemistry

The synthesis of compounds (**3**)–(**8**) has been performed in two steps: the hydrazone (**2**) as a precursor was first prepared following a published procedure [31] by refluxing a solution of 10-undecenoic acid hydrazide with *m*-nitrobenzaldehyde (molar ratio, 1:1) in anhydrous benzene for 5 h as yellow crystalline needles in 87.0% yield. The compound (**2**) was then separately reacted with mercaptoacetic acid, 2-mercaptopropionic acid and 3-mercaptopropionic acid (molar ratio, 1:3, in each case) in anhydrous benzene monitoring (TLC) and refluxing the reaction mixtures for 16, 22 and 26 h, respectively, with azeotropic removal of water. The products on chromatography over a silica gel column using pet. ether (60–80 °C)–diethylether (1:1) as eluent, yielded the respective compounds (Fig. 1). It is noteworthy that no uncyclized product is formed in the reaction of 2-mercaptopropionic acid with the hydrazone (**2**) while an uncyclized adduct is formed both in the case of mercaptoacetic acid and 3-mercaptopropionic acid. This is due to the fact that mercaptoacetic acid and 3-mercaptopropionic acid first undergo anti-Markovnikov's addition at the terminal olefinic bond and then cyclocondensation at the C=N double bond whereas 2-mercaptopropionic acid first undergoes cyclocondensation at the C=N double bond and then addition at the olefinic bond of the hydrazone (**2**) to give the respective products. The increased nucleophilicity of the mercapto group in the 2-mercaptopropionic acid probably facilitates cyclocondensation. The course of addition of mercapto acids to terminal olefinic bond is attributed to the free radical mechanism [32].

The structures and stereochemistry of (**2**), (**3**) and (**7**) have been established by a combined study of IR, DCI-MS, ^{1}H-NMR, NOE, ^{13}C-NMR and HETCOR spectra (spectral data of the representative compound (**2**) are shown in Tables 1 and 2 and that of (**3**) and (**7**) in Section 4). IR spectra exhibited characteristic absorption peaks corresponding to N–H/O–H, C=O, C=C, C=N and NO_2 groups. DCI-MS spectra showed characteristic $[M + 1]^+$ peaks corresponding to their molecular weights. The assignments of all the signals to individual H or C-atoms have been performed on the basis of typical δ-values, *J*-constants, a HETCOR spectrum and by comparing with the reference spectra (SDBS) [33] of 10-undecenoic acid, 10-undecenamide and *m*-nitrobenzaldehyd. The ^{1}H-NMR and ^{13}C-NMR spectra of these compounds dissolved in acetone-d_6 showed double signals especially of NH, H-7 and H-2′ and of C-7, C-2′, C-3′, C-2 and C-6 which indicated that these molecules are present in two stereoisomeric forms. The two forms were found to be in the ratio (3:1) as calculated from the integration values of the NH- and H-2′ signals. This can be thought of about *E*/*Z* isomers of the C=N bond or stabile conformers around single bond such as in the CO–NH group. To investigate this, we irradiated the NH-proton, which resulted in a NOE-enhancement of H-7 (both signals), showing that the NH-proton and H-7 (in both forms) are very near to each other. This can only be the case in *E*-isomers. Further, in case of H-2′ signals, a NOE-enhancement was observed only for the largest H-2′ signal (75%) and absolutely no NOE-enhancement was seen for the small H-2′ signal (25%) (Table 1). This showed that only in