ELSEVIER

Archives of Medical Research ■ (2017) ■

Archives of Medical Research

ORIGINAL ARTICLE

Synthesis and Anticancer Activity of Novel Ureas and Sulfamides Incorporating 1-Aminotetralins

Bünyamin Özgeriş,[a] Yusuf Akbaba,[a] Özlem Özdemir,[b] Hasan Türkez,[b] and Süleyman Göksu[c]

[a]*Department of Basic Sciences,* [b]*Department of Molecular Biology and Genetics, Erzurum Technical University, Faculty of Science, Erzurum, Turkey*
[c]*Department of Chemistry, Atatürk University, Faculty of Science, Erzurum, Turkey*

Received for publication May 22, 2017; accepted December 6, 2017 (ARCMED-D-17-00321).

Background and Aims. In the present study, a series of ureas and sulfamides derived from 1-aminotetralins were synthesized. For this purpose, urea and sulfamide analogues were synthesized from the reactions of substituted 1-aminotetralins with N,N-dimethylcarbamoyl chloride and N,N-dimethylsulfamoyl chloride. The anticancer activity of newly synthesized compounds was tested against human U-87MG glioblastoma and PC-3 prostate cancer cell lines. Cytotoxicity was examined using MTT and LDH release assays.

Results. The obtained data revealed that tested compounds showed a variable degree of cytotoxic activity against the tested cell lines. 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1,1-dimethylurea (9) and 3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1,1-dimethylurea (10) proved to be the most active cytotoxic members in this study.

Conclusions. These two compounds could be considered as possible anticancer agents.

Key Words: Sulfamide, Urea, Aminotetralin, Anticancer activity, PC-3 cell line, U-87MG cell line.

Introduction

Substituted ureas and their derivatives have numerous important applications. They are widely used in all the chemical process such as in agricultural field as plant growth regulators and agricultural herbicides, in medicinal chemistry as abirritant, anticonvulsant, and HIV-1 protease inhibitors, etc., and in organic chemistry as starting materials for the synthesis of carbamates, isocyanates, etc. (1). Sulfamides and their analogues have also very important biological activity such as anticonvulsant, anti-inflammatory, antidepressant, antitumor, norovirus and renin inhibitory (2). Aminotetralins are the precursors for the synthesis of biologically active benzylamine derivatives. For instance, sulfamide compound 1 is an anticonvulsant (3). Aminotetralin 2 has been reported to show highly potent inhibition against HDAC6 and HDAC8 (4). Another aminotetralin 3 known as SR 59230 is used as a common β_3-adrenoceptor antagonist (5). Tametraline (CP-24,441, 4) is a norepinephrine-dopamine reuptake inhibitor, as well (6). Urea compound 5 has been reported to exhibit significant inhibitory activity against HT-29 cell line (7) (Figure 1). In our earlier studies, we reported the synthesis and biological properties of urea and sulfamide derivatives relating to the 2-aminotetralins and also 1-aminoindanes (8−10). All of these reported compounds have shown excellent inhibitory effects in the micro-submicromolar, and low nanomolar range against hCA I, hCA II isoenzymes, and AChE enzyme (2,8,10). In continuation of our studies, we aimed to synthesize some novel urea and sulfamide derivatives 9−14 starting from 1-aminoteralins. In addition, the anticancer activity of the title compound will be very important for the synthesis of novel drug candidates. In this context, we also aimed to investigate the anticancer activity of the synthesized compounds 9−14 against human U-87MG glioblastoma and PC-3 prostate cancer cell lines.

Cytotoxicity assays are widely used in *in vitro* toxicology studies. The 3-(4,5-dimethyl-thiazol-2-yl) 2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) leakage assays are the most common methods to evaluate the cell viability and cell death, respectively (11,12). Based on these described properties, in this

Address reprint requests to: Bünyamin Özgeriş, Asst. Prof. Dr., Department of Basic Sciences, Erzurum Technical University, Faculty of Science, Erzurum, Turkey; Phone: +90 442 6662525; FAX: +90 442 2812526; E-mail: bunyamin.ozgeris@erzurum.edu.tr

0188-4409/$ - see front matter.
https://doi.org/10.1016/j.arcmed.2017.12.002

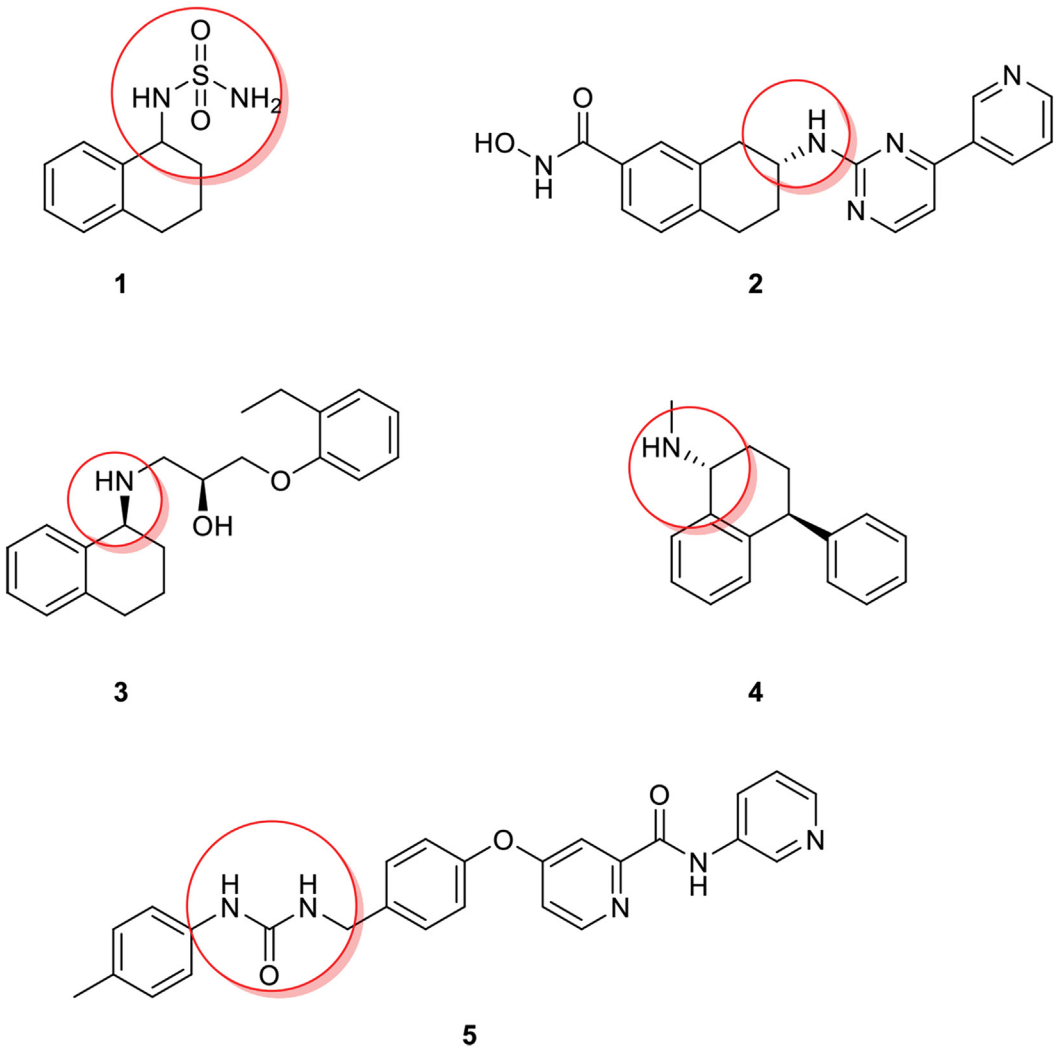

Figure 1. Some aminotetralin, urea and sulfamide compounds 1−5.

study it was aimed to determine the anticancer potential of newly synthesized urea and sulfamide compounds in cultured human glioblastoma and prostate cancer cell lines for the first time. In the current study, MTT and LDH release assays were performed on U-87 MG and PC-3 cells for evaluating anticarcinogenic potential.

Material and Methods

General Methods

All chemicals and solvents are commercially available and were used without purification or after distillation and treatment with drying agents. Melting points are uncorrected and they were determined on a capillary melting apparatus (BUCHI 530). IR spectra were obtained from solutions in 0.1 mm cells with a Perkin-Elmer spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a 400 (100)-MHz Varian and 400 (100)-MHz Bruker spectrometer; δ in ppm, Me_4Si as the internal standard. Elemental analyses were performed on a Leco CHNS-932 apparatus. All column chromatography was performed on silica gel (60-mesh, Merck). PLC is preparative thick-layer chromatography: 1 mm of silica gel 60 PF (Merck) on glass plates. All biologically evaluated compounds were demonstrated to exist in $>95\%$ purity by elemental analysis.

The Synthesis of 1-Aminotetralins

1-Aminotetralins 6 (13), 7 (14) and 8 (14) were synthesized as describes previously.

General procedure for the synthesis of ureas: 3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1, 1-dimethylurea (9). Amine hydrochloride salt 6 (1.00 g, 4.68 mmol) was dissolved in CH_2Cl_2 (10 mL). NEt_3 (0.78 mL, 5.62 mmol) was added to this solution and stirred in a salt-ice bath for 30 min. After 30 min, N,N-