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An efficient, three-component synthesis and molecular structure of derivatives of 2-amino-3-*R*-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine-5,5-dioxide spirocombined with a 2-oxindole nucleus

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ABSTRACT

Spiro[(2-amino-3-*R*-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-5,5-dioxide)-4,3′-(1′-*R*′-5′-*R*″-indolin-2′-one)] compounds were synthesized based on the three-component interaction of benzo[*c*][2,1]thiazin-4-on 2,2-dioxide with corresponding isatins and appropriate methylene active nitriles in the presence of a base as a catalyst. The molecular structures of the target compounds were proved uniquely by the X-ray diffraction analysis method.

1. Introduction

Currently, synthetic organic chemistry provides medicine with new and effective heterocyclic compounds for treating a variety of diseases. In this regard, derivatives of benzothiazinone *S*,*S*-dioxide occupy a special place, since they are very perspective compounds to create new drugs. This is associated with their fairly wide range of biological activities. Sedative, anticonvulsant, hypnotic, hypoglycemic, muscle relaxant, anti-arrhythmic hypotensive and other activities are the most typical for them.[1,2]

Among 10 possible structural isomers of benzothiazinone *S*,*S*-dioxide,[3,4] benzo[*c*][2,1]thiazin-4-on 2,2-dioxide attracted our attention, due to insufficient studies of the biological activity spectra for different derivatives of this benzothiazinone and insufficient studies of its chemical properties.

Derivatives of 3,4-dihydro-2,1-benzothiazine-2,2-dioxide are characterized by such biological activities as IL-8 receptor antagonism,[5] selective inhibition of focal adhesion kinase,[6] antiviral (reverse transcriptase inhibitory activities),[7] anticancer[8] and antibacterial activities.[9] Also, they demonstrate potent biological activities such as lipoxygenase inhibition and are applied as agents for heart diseases.[10] On the other hand, being structural isomers, the benzo[*c*][2,1]thiazine-4(3*H*)-on 2,2-dioxide core is bioisosteric to the benzo[*e*][1,2]thiazine one. It serves as a base for such drugs as piroxicam®, droxicam® and meloxicam® (Fig. 1), which one to efficient analgesic and anti-inflammatory agents.[11] Some of these compounds showed anti-bacterial activity.[12]

Benzo[*c*][2,1]thiazine-4(3*H*)-on 2,2-dioxide represents the methylene active CH-acid. Its structure is an analogue of a cyclic methyleneactive 1,3-dicarbonyl compound, which makes it a very convenient and promising intermediate for building new heterocyclic systems based on it. Although this compound, unlike its carbonyl analogue, exists entirely in the 4-oxo form,[13,14] it exhibits a number of specific properties that are not characteristic for carbonyl compounds. In particular, it is not reduced in 4-hydroxy derivatives by the direct route and does not form enamines with secondary amines. The carbonyl group of the given heterocycle is distinguished by a high propensity for enolization in when of

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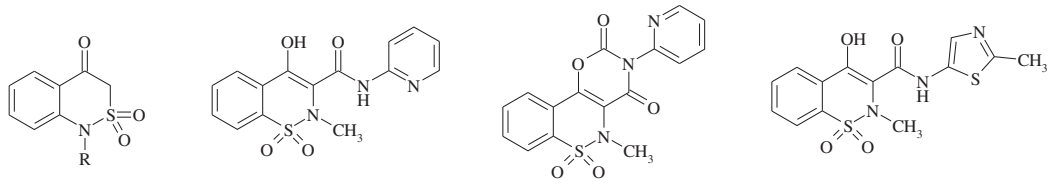


Fig. 1. Initial benzo[*c*][2,1]thiazin-4-on 2,2-dioxide and bioisosteric biologically active benzothiazine derivatives.

introducing alkyl or acyl groups into position 3.[15,16] This property opens up great opportunities for the synthesis of condensed heterocyclic systems using CH_2CO-group in this compound in particular using multi-component reactions.

Multicomponent reactions of enol-nucloephilic compounds, carbonyl compounds and the appropriate active nitriles have recently attracted the interest of the synthetic community, because the formation of diverse condensation products can be expected depending on the specific conditions and structure of the building blocks. This interaction is the direct route for construction of the 2-amino-4*H*-pyrane core.[17] The mechanism of this coupling is based on a domino Knoevenagel/Michael cyclization sequence between carbonyl compounds, appropriate nitriles and carbonyl CH-acids.[18] There are no data about these interactions for benzo[*c*][2,1]thiazine-4(3*H*)-on 2,2-dioxide. No information is available about the synthesis of the condensed heterocyclic systems including benzo[*c*][2,1]thiazine-4(3*H*)-on 2,2-dioxide and the 4H-pyranic ring as well.

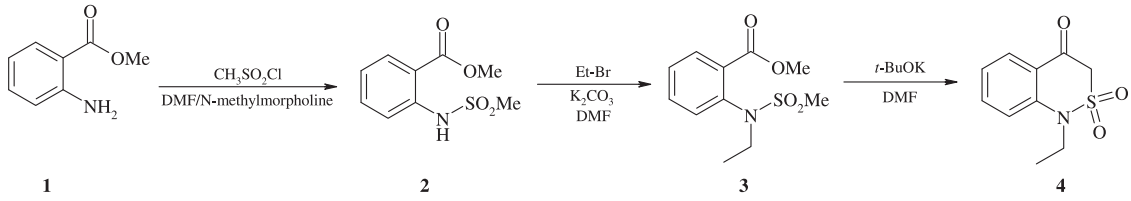
Using isatins in this reaction as the carbonyl component allows construction of the spiro[4*H*-pyran-oxindole] core[19] in a one-pot synthesis. For example, a three-component reaction of isatins, ethylcyanoacetate or malononitrile, and 3-methylpyrazol-5-one in the presence of base catalysts[20] or under ultrasound irradiation,[21] or in the presence of $NaHCO_3$ under grinding,[22] leads to the spiro[pyrano[2,3-*c*]pyrazolo-2-oxindoles] with good yields. The same principle was used by us in the preparation and study of the previously reported 4-hydroxy-2-quinolones annelated by a spiro[indole-3,4′-pyran] ring.[23]

In this aspect, *N*-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide is new synthon for the one-step three-component synthesis of condensed system of 2-amino-6-ethyl-3-*R*-4-*R*′-4-*R*″-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide.

This article is devoted to a new spirocyclic system of spiro[(2-amino-3-*R*-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-5,5-dioxide)-4,3′-(2′-oxindole)]. Experiments carried out by us have shown that exchange of the 4-hydroxycoumarin or 4-hydroxy-2-oxo-1,2-dihydroquinoline for heteroanalog, in particular, *N*-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide **4**, does not have any kind of effect on the course of the reaction and thus, it gives spiro[(2-amino-3-*R*-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-5,5-dioxide)-4,3′-(2′-oxindole)] **10**–**11**.

2. Results and discussion

The synthesis of the initial *N*-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide **4** was described in the literature,[24] and included esters of anthranilic acids **1** as initial compounds (Scheme 1). Different authors used different conditions for the synthesis of compound **2**, such as THF(dioxane)-triethylamine, methylenechloride/pyridine, pyridine, etc. We found that using the DMF/*N*-methylmorpholine system in this reaction allows pure compound **2** to be obtained with excellent yields in a short time. Moreover, all authors[21,24] used only NaH in DMF for heterocyclization of alkylated compound **3**. We also found that replacement of NaH with *t*BuOK increases the yield of compound **4**, obtaining it in analytically pure form, which did not need further purification.



Scheme 1. Synthesis of *N*-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide **4**.

The synthesis of target compounds **10a**–**e** and **11a**–**e** was carried out according to transformations presented on Scheme 2.

A three-component one-pot reaction of equimolar quantities of benzothiazinone **4**, malonodinitrile and the appropriate isatins **5a**–**e** in the presence of triethanolamine under reflux for 30 min in ethanol, gave to derivatives of 2-amino-3-*R*-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-5,5-dioxide **10a**–**e** spiricombined with a 2-oxindole core with the yields of 64–83% (Scheme 2, Table 1).

Using ethylcyanoacetate in the three-component condensation as the methyleneactive nitrile increases the time of interaction to about 2 h. The yields of target compounds **11a**–**e** were 46–63% (Scheme 2, Table 1).

It was possible to carry out a two-step synthesis of target compounds **10a**–**e** and **11a**–**e** using the corresponding Knoevenagel condensation products, namely 2-oxoindolinilidenes **8a**–**e** and **9a**–**e**, in accordance with the mechanism of the reaction. Synthesis of compounds **8a**–**e** and **9a**–**e** was carried out pursuant to a procedure presented in our previous work.[5] Interaction of benzothiazinone **4** with 3-cyanomethylidene-2-oxindoles **8a**–**e** and **9a**–**e** proceeded by reflux in ethanol in the presence of a base. In the case of compounds **8a**–**e**, heating continued for 1 h; as a result, compounds **10a**–**e** were formed with the yields of 53–77%. For 2-oxoindolinilidenes **9a**–**e**, the duration of heating was 3–4 h, and the yields of target compounds were 40–52% (Scheme 2, Table 1).