Bioorganic & Medicinal Chemistry 21 (2013) 4951–4957

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

1-Hydroxypyrazole as a bioisostere of the acetic acid moiety in a series of aldose reductase inhibitors

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ARTICLE INFO

Article history:
Received 17 May 2013
Revised 22 June 2013
Accepted 26 June 2013
Available online 9 July 2013

Keywords:
Aldose reductase inhibitors
Bioisosterism
Inflammatory pathologies
Long-term diabetic complications
Molecular obesity

ABSTRACT

Therapeutic intervention with aldose reductase inhibitors appears to be promising for major pathological conditions (i.e., long-term diabetic complications and inflammatory pathologies). So far, however, clinical candidates have failed due to adverse side-effects (spiroimides) or poor bioavailability (carboxylic acids). In this work, we succeeded in the bioisosteric replacement of an acetic acid moiety with that of 1-hydroxypyrazole. This new scaffold appears to have a superior physicochemical profile, while attaining inhibitory activity in the submicromolar range.

1. Introduction

Aldose reductase (ALR2) is a cytosolic enzyme, which plays a pivotal role in a variety of pathologies.[1] It first gained attention for its implication in the onset and progression of diabetes mellitus' long-term complications[2] through the 'polyol pathway', where ALR2 acts as an alternative route to glucose metabolism. ALR2 catalyzes the first and rate-limiting reaction of this pathway, the NADPH dependent reduction of glucose to sorbitol, which is subsequently oxidized by sorbitol dehydronase (SDH) in the presence of NAD^+. Excessive flow through this pathway triggers a chain of reactions leading to high levels of osmotic and especially oxidative stress that damage the cells.[3,4] More recently, though, ALR2 has been identified as a key mediator of various inflammatory diseases and cancer.[5–7] Mechanistic studies show that ALR2 reduces glutathione conjugates with lipid-derived aldehydes, which in turn through a cascade of events induce several inflammatory signals. Therefore, ALR2 remains a compelling target for therapeutic intervention.

Over the years, continuous efforts on the development of aldose reductase inhibitors (ARIs) afforded mainly two chemical classes, spiroimids (e.g., sorbinil, fidarestat) and carboxylic acid derivatives (e.g., epalrestat, tolrestat). However, adverse side-effects and poor bioavailability, mainly due to low pK_a values, respectively, led few of their representatives to advanced clinical trials and just one, epalrestat, is currently commercially available in Japan, whereas its efficiency is considered marginal.[8] Thus, the need for potent and selective ARIs remains a problem to be solved.

In our previous work, effective ARIs have been synthesized, which are derivatives of the pyrrolyl acetic acid moiety.[9,10] In order to overcome the disadvantages of carboxylic acid derivatives mentioned above, we have successfully introduced the 2,6-difluorophenol and tetrazole rings as bioisosteres of the acetic acid moiety.[11,12] On this basis, in this study we introduce the 1-hydroxypyrazole ring as a new acetic acid bioisostere (Fig. 1). The 1-hydroxypyrazole moiety has been used as a carboxylic acid bioisostere of glutamic acid and aspartic acid resulting in analogues of the glutamate ligands.[13] The advantage of the 1-hydroxypyrazole derivatives in comparison to the carboxylic acid and tetrazole is the higher pK_a values, which can lead to more efficient tissue permeation. Thus, a series of pyrrol-1-yl-1-hydroxypyrazole derivatives (compounds **4a–c** and **8a–c**, Fig. 2) were designed, synthesized, and tested for their inhibitory potency towards the ALR2 enzyme. Additionally, carboxylic acids **IIb–c** were synthesized and evaluated on ALR2 in the scope of a more wholesome comparison. The selectivity index of all the compounds towards the closely related aldehyde reductase (ALR1) enzyme was then determined. Structure–activity relationships and comparison with

Abbreviations: AGEs, advanced glycation end-products; ALR1, aldehyde reductase; ALR2, aldose reductase; ARI, aldose reductase inhibitor; BEI, binding efficiency index; DHN, 1,4-dihydroxynonene; GSH, glutathione; HNE, 4-hydroxynonenal; LE, ligand efficiency; LELP, ligand efficiency-dependent lipophilicity; LLE, lipophilic ligand efficiency; ROS, reactive oxygen species; SDH, sorbitol dehydrogenase.

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http://dx.doi.org/10.1016/j.bmc.2013.06.062

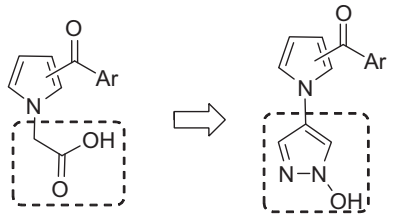


Figure 1. Bioisosteric replacement of the acetic acid moiety with 1-hydroxypyrazole.

the corresponding acetic acid derivatives (Fig. 2) are discussed, along with a computer-based physicochemical profiling of the compounds, and calculations of molecular obesity indices.

2. Results and discussion

2.1. Chemistry

Two different synthetic routes were followed for the synthesis of compounds **4a–c** and **8a–c**, as depicted in Schemes 1 and 2, respectively. The starting material in both routes was 1-(benzyloxy)-4-iodo-1*H*-pyrazole (**1**), which was prepared via a three-step procedure from commercially available pyrazole, according to a known method.[13]

In the first synthetic pathway (Scheme 1) compounds **1** and **2a–c** reacted in a modified Ullman type coupling reaction, as used in our previous work,[14] giving the respective benzyl ethers, **3a–c**. The benzyl group was, then, reductively removed by hydrogenolysis under mild conditions to selectively afford target compounds **4a–c**.

The same pathway was also used in an unsuccessful effort to synthesize compounds **8a–c**. Coupling reactions between **1** and the respective α-substituted pyrroles gave no product after 24 h, possibly due to steric hindrance. Thus, an alternative synthetic route (Scheme 2) was followed. The first step involved a coupling reaction between **1** and the sterically accessible pyrrole, which gave compound **5**. A regiospecific Friedel–Crafts reaction, described in a relative work,[15] was, then, employed for the preparation of compounds **7a–c**. Treatment of **5** with the appropriate aroyl chlorides (**6a–c**) afforded both the α-(**7a–c**) and β-isomers (**3a–c**) in various ratios, all however favoring the α-isomeric products. In the final stage, the desired compounds **8a–c** were obtained after deprotection of compounds **7a–c** by hydrogenolysis.

The α-substituted pyrrole **10c** synthesis was based on the already published method used for compound **10b**.[9,16] Both compounds reacted further to give the corresponding acetic acid derivatives **IIb–c**, according to our previously reported work[9] (Scheme 3).

2.2. ALR2/ALR1 inhibitory activity

ALR2 inhibitory activity was evaluated on partially purified rat lens ALR2. It has been shown that human ALR2 exhibits 85% sequence homology to rat ALR2,[17] while the catalytic active sites of both enzymes are considered identical.[18] ALR2 inhibitory activity is expressed as IC_{50} values and the results are shown in Table 1. Listed in Table 1 are also the IC_{50} values of the respective acetic acid analogues, for comparison's sake, along with sorbinil that was used as the reference compound.

From the obtained results it becomes apparent that all the compounds are potent ARIs in the micro- or submicromolar range. Substitution on the β-position of the pyrrole ring appears favored both in the 1-hydroxypyrazole (**4a–c**) and in the acetic acid series (**Ia–c**). However, this pattern was not observed in our previous works on bioisosteric replacement of the acetic acid moiety with a tetrazole and a 2,6-difluorophenol ring.[11,14] In the tetrazole series the same inhibitory activity was exhibited for both α- and β-regioisomers,[11] though the limited number of compounds (**2**) disallows a definitive conclusion. On the other hand, in a series of substituted 1-(3,5-difluoro-4-hydroxyphenyl)-1*H*-pyrrol-3-yl]phenylmethanones the most active derivative bore a 4-methoxyphenylacetyl substituent on the α-position of the pyrrole ring.[14] Supposedly, in the latter

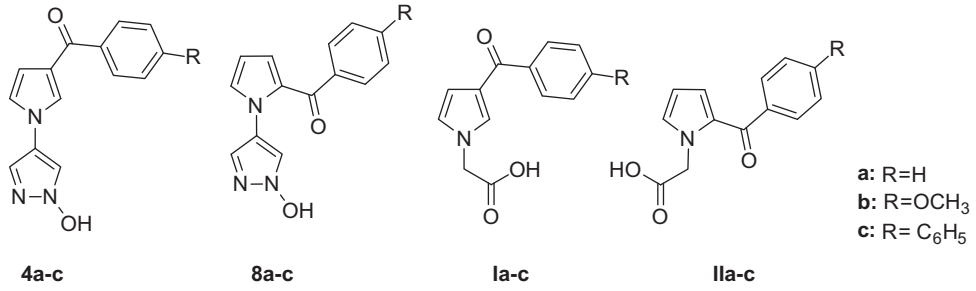
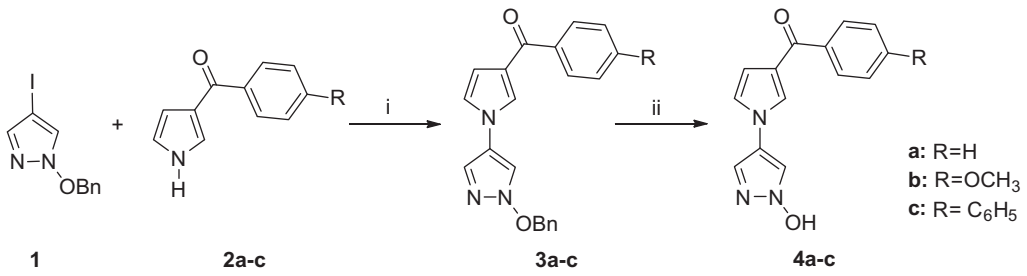


Figure 2. Chemical structures of the studied 1-hydrozypyrazole derivatives and the respective acetic acid derivatives.



Scheme 1. Synthesis of the β-substituted 4-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-1-ol derivatives **4a–c**.