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Original article

Synthesis and anti-HIV-1 integrase activities of 3-aroyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazines

Zdzisław Brzozowski [a], Franciszek Sączewski [a,*], Jarosław Sławiński [b], Tino Sanchez [c], Nouri Neamati [c]

[a] Department of Chemical Technology of Drugs, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland
[b] Department of Organic Chemistry, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland
[c] Department of Pharmaceutical Sciences, School of Pharmacy, University of Southern California, 1985 Zonal Avenue, PSC 304BA, Los Angeles, CA 90089, USA

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Abstract

A series of novel 3-aroyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazines **15**–**28** as potential HIV-1 integrase (IN) inhibitors have been synthesized by the reduction of 3-aroyl-1,1-dioxo-1,4,2-benzodithiazines **1**–**14** with benzenesulfonyl hydrazide. All the compounds **15**–**28** inhibited IN mediated strand transfer reaction with IC_{50} values ranging from 3 to 30 μM. The 3-(4-bromobenzoyl)-6-chloro-7-methyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazine **17** with the IC_{50} values of 4 ± 1 and 3 ± 1 μM for 3′-processing and strand transfer, respectively, was the most potent. Compound **17** as well its analogues were 5–20-fold less potent in Y99S and H114A mutants, implicating these residues as potential drug-binding site. This is a first report implicating Y99S and H114A of IN core domain in drug-binding interactions.

Keywords: 3-Aroyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazines; Synthesis; HIV-1 integrase inhibitors

1. Introduction

It is well known that compounds bearing arylsulfonamide moiety have been applied in various strategies aimed at discovery of novel antiviral agents [1–5]. HIV-1 integrase (IN) is an attractive target for selective blockade of viral infection since there are no known counterparts in the host cell [6]. Previously, we described the syntheses and anti-HIV activities of various 4-chloro-2-mercaptobenzenesulfonamide derivatives with the nitrogen atom of sulfonamide moiety attached to a variety heterocyclic ring systems (Fig. 1, structure **I**) [7–12]. Some of these compounds (**I**) [13,14], di(4-mercapto-3-nitrophenyl)sulfones (e.g., **II**) [15] and 1,2-di(2-mercaptobenzoyl)hydrazines (e.g., **III**) [16] were described as novel class of potent IN inhibitors (Fig. 1) [13–16]. In fact, among the recently reported dipyridine inhibitors, only compounds containing a free mercapto group showed antiviral activity and inhibited IN (e.g., **IV**, Fig. 1) [17]. A common theme in these leads is the requirement for a free mercaptoaryl group for antiviral activity as well as anti-IN potency (**I**–**IV**, Fig. 1) [10,12,13,15–17]. More recently, we found that cyclic analogues of 2-mercaptobenzenesulfonamides (Fig. 1, structure **V**) also showed anti-HIV and anti-IN properties [18]. This led us to an assumption that expansion of a series of candidate anti-IN agents of general formula **VI** (Fig. 1) may shed light on the structural features contributing to the IN inhibitors.

2. Results and discussion

2.1. Chemistry

The previously described methods were used to synthesize starting compounds, 3-aroyl-1,1-dioxo-1,4,2-benzodithiazines

* Corresponding author. Tel.: +48 58 3493250; fax: +48 58 3493257.
E-mail address: saczew@amg.gda.pl (F. Sączewski).

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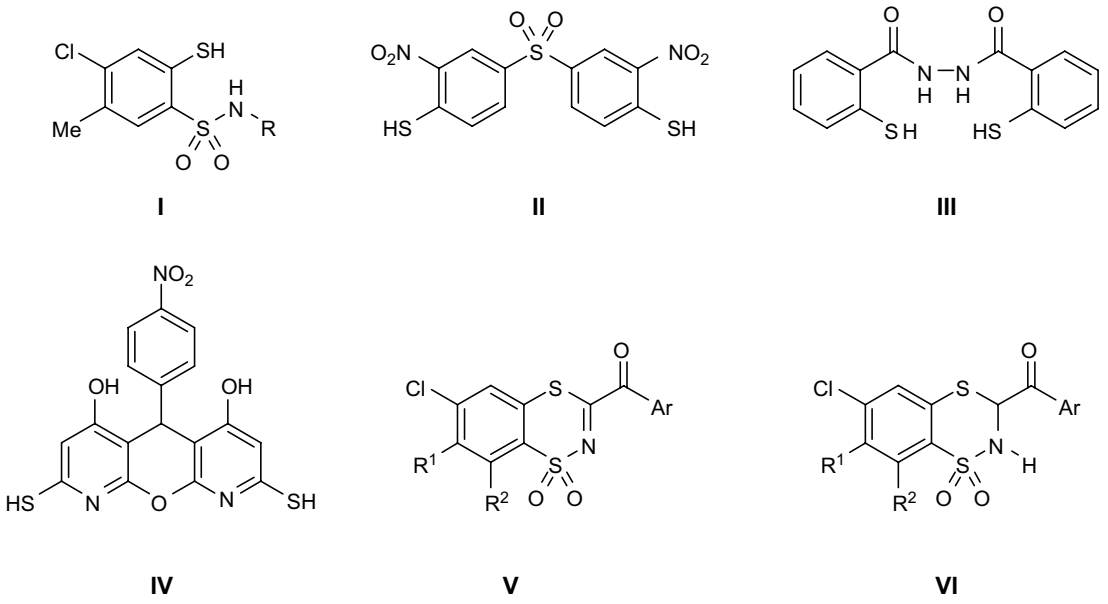

Fig. 1. Structures of HIV-1 integrase inhibitors.

1–**14** [18]. The synthesis of the target 3-aroyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazines **15**–**28** was achieved by reacting benzenesulfonyl hydrazide with the corresponding aroylbenzodithiazines **1**–**14** in methanol.

To our knowledge the above reaction is the first example of the reduction of C=N bond using arylsulfonylhydrazide. It has been well known that arylsulfonylhydrazides upon heating decompose to diimide which is convenient reducing agent for symmetrical double bonds such as C=C, N=N or C≡C. Under this conditions, however, polar C=N bond has not been reduced before [19]. Therefore, we propose two possible mechanisms A and B which can be operative for the reduction of compounds **1**–**14** incorporating formal α-imino-carbonyl moiety (Scheme 1). According to mechanism A, the initial step would consist in the formation of a spiro intermediate of type **A** by [2 + 2] cycloaddition of benzenesulfonyl hydrazide to the C3–C(=O)Ar bond of 3-aroyl-1,4,2-benzodithiazine 1,1-dioxides **1**–**14**, followed by the 1,2-diazetidine ring scission with subsequent loss of N_2 and benzenesulfinic acid. In the final stage of the reaction, the non-isolable enol **B** undergoes tautomerization to afford the corresponding ketones **15**–**28**. According to mechanism B, the addition of hydrazone NH_2 group to carbonyl C=O group of **1**–**14** may afford hemiaminal of type **C**, which undergoes a spontaneous retro-ene fragmentation with the formation of enol **B** (Scheme 1).

The ^{1}H NMR spectrum of the product **18** containing an aroyl group at position 3 of benzodithiazine ring showed two doublet signals attributed to the C3-H proton at δ 7.29 ppm and NH proton at δ 9.13 ppm with the coupling constant $J = 11.5$ Hz. Furthermore, the correlation between NH proton and both C-3 carbon atom at δ 64.04 and C=O carbon atom at δ 190.16 was found in the ^{1}H–^{13}C heterocorrelated spectrum (HMBC-heteronuclear multiple bond correlation), while the HSQC (heteronuclear single quantum coherence) spectrum showed the correlation between this C3-H proton and the C-3 carbon atom, and were fully consistent with the proposed structure.

2.2. Biology

The IN inhibitory activities of the newly prepared compounds **15**–**28** compared to those of parent benzodithiazines **1**–**14** are presented in Table 1. All tested compounds are significantly active against wild-type IN in the presences of Mg^{2+}, albeit less effective as compared to Mn^{2+}, when added as a co-factor. This is in agreement with our previous studies [16].

For a series of compounds **1**–**7** with methyl group at position 7 of benzodithiazine ring, partial hydrogenation leads to compounds **15**–**21**, inhibitory activity of which is equal (compound **16**, Ar = 4-MeOPh), higher (**15**, Ar = Ph; **17**, Ar = 4-BrPh; **18**, Ar = 4-ClPh and **19**, Ar = 3-O_2NPh) or lower (**20**, Ar = 3,4-diClPh and **21**, Ar = 2-naphthyl). Thus, electronic and steric effects brought about by the Ar substituents seem to be crucial for biological activity of these compounds. The above pattern, however, is not observed for benzodithiazines **8**–**10** with 8-Me substituent, which upon hydrogenation gave **22**–**24** with similar inhibitory activities.

Interestingly, upon hydrogenation of compounds **11**–**13** lacking the methyl group at both 7 and 8 position of benzodithiazine ring, a very considerable improvement of inhibitory activity is noted for **25** (Ar = 4-ClPh) and **26** (Ar = 3,4-diClPh) thus obtained, while hydrogenated compound **27** (Ar = 2-naphthyl) retains a relatively high potency of **13**.

Summing up, all newly prepared compounds showed significant inhibition of purified IN with IC_{50} values ranging from 3 to 30 μM for strand transfer. The most active 3-(4-bromobenzoyl)-6-chloro-7-methyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazine (**17**) with IC_{50} values of 4 ± 1 and 3 ± 1 μM for