NEW BENZOTRIAZOLE-BASED DERIVATIVES

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Abstract. Several human diseases are caused by enteroviruses and are currently clinically untreatable, pushing the research to identify new antivirals. A notable number of benzo[*d*][1,2,3]triazol-1(2)-yl derivatives were designed, synthesized, and in vitro evaluated for cytotoxicity and antiviral activity against a wide spectrum of RNA positive- and negative-sense viruses.

Keywords: benzotriazoles, enterovirus, acrylonitrile, RNA-virus.

For centuries, infectious diseases have been the leading cause of death. Unfortunately, this sad record is still upheld today, primarily in the poorest countries; however, it was sadly proved that the pandemic risk was not negligible even in the most advanced countries and viral diseases must be considered a threat that we should not underestimate. Within the past century, multiple viruses caused pandemics across the word. It is worth mentioning the Spanish flu (1918-19), which was due to the H1N1 virus, which caused 50 million deaths [1], the Asian flu (1957), caused by the H2N2 virus [2,3], and the Hong Kong avian flu (1968), which originated from the H3N2 virus [4]. In recent history, HIV infection, causing AIDS, was arguably the most important huge viral infection, that claimed more than 36 million deaths, according to the World Health Organization (WHO) [5]. Therefore, the structural modifications were mainly focused on a) the

introduction of a methylene spacer between the benzotriazole moiety and the para-substituted benzene ring and b) the position variation of the substitution on the aromatic ring, as exemplified in figure 1. The structural manipulations were rationally designed to allow a greater degree of molecule flexibility to evaluate the effects induced by different molecular conformations.

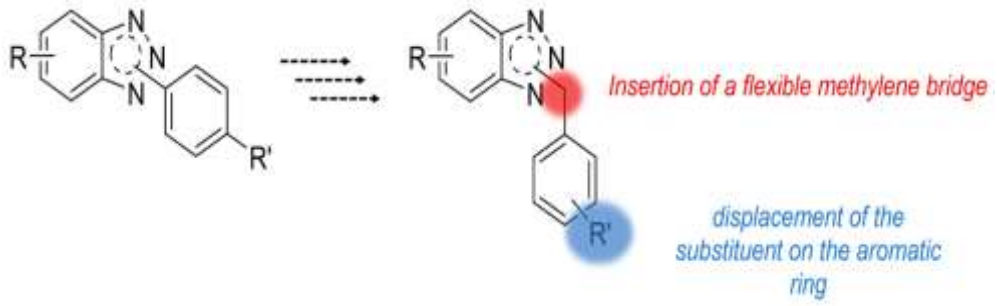

Figure 1. Structural modifications on our hit compounds: introduction of a methylene bridge (red) and displacement of the substituent on the benzene ring (blue).

Three series of derivatives were obtained starting from the plain benzotriazole scaffold, substituted in position 4, or disubstituted in positions 5 and 6 with methyl groups or halogens. Then, a 3′ or 4′ benzylamine moiety was inserted on N1 or N2 of the triazole ring. The subsequent *N*-functionalization of the benzylamine portion led to aliphatic amides, aromatic amides, and urea-derivatives. Benzotriazol-1ylphenylamino and 2-ylphenylamino intermediates were, respectively, condensed with:

1.The proper anhydride **1** (acetic anhydride, propionic anhydride, butyric anhydride and pivalic anhydride) at room temperature or for 1–72 h. The crude products were in turn obtained pure or required purification by flash chromatography;

2.The required benzoyl chloride derivatives **2** in N,N-dimethylacetamide (DMA) or N,N-dimethylformamide (DMF) at 80 °C from 3 h to 7 days. The

purification of the compounds was carried out by recrystallization from ethanol or by flash chromatography;

3.The appropriate isocyanate $R_2N=C=O$ **3** in DMF, stirring the mixture at 100 °C from 2 to 9 days. The crude products were triturated with diethyl ether to obtain solids that were purified through recrystallization from ethanol or by flash chromatography.

Among the whole series of synthesized compounds, only about 15% of which showed antiviral activity. The non-active compounds were withheld to simplify the table readability. Most of the appealing compounds were found selectively active against CVB5 with EC_{50} values ranging between 6 and 52 μM, when non-inhibitory activity against the remaining virus replication was detected. Non-substituted benzotriazole-based compound **86c** was selectively active against BVDV (EC_{50} = 3 μM), while compound **21e** preferentially inhibited RSV (EC_{50} = 20 μM). Overall, the most promising and effective derivatives are **18e** and **43a**, whose EC_{50} values were 12.4 and 9 μM, respectively, when tested against CVB5. To further outline the structure–activity relationships (SARs), Figure 2 reported the structures of the most active compounds together with precursors and the corresponding EC_{50} values. Favorable chemical manipulations are indicated with a blue arrow, while unfavorable modifications are indicated with a red one. The intermediate 6a, bearing the side chain on position C-3′, presented moderate activity towards CVB5, with an EC_{50} of 52 μM. Notably, the substitution of the amine group with 3,4,5-trimethoxybenzoyl or *p*-chlorobenzoyl groups increased the antiviral activity against the same virus, with EC_{50} values decreased to 18.5 and 9 μM for compounds 41a and 43a, respectively.

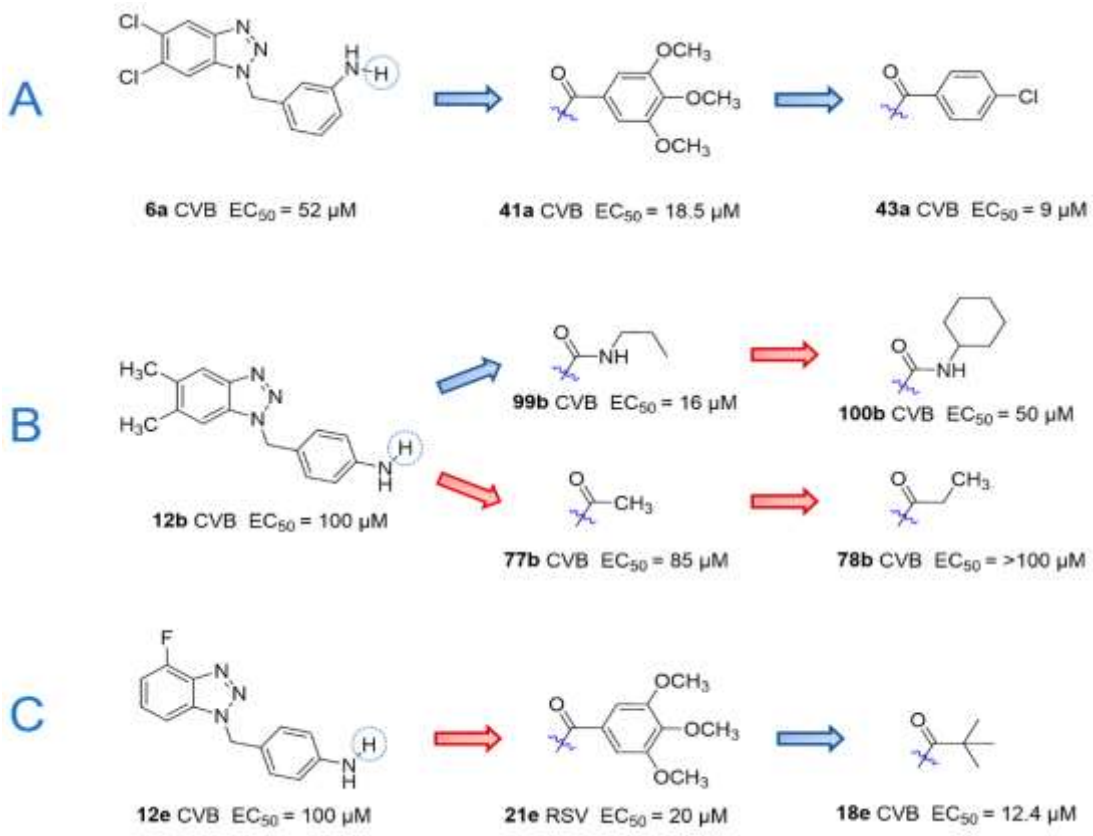

Figure 5. (**A**–**C**) SARs analysis from the synthetized compounds

The latter compounds bore two chlorine atoms on C-4 and C-5 of the benzotriazole scaffold (in Figure 2A). The chlorine atoms seemed to be responsible for the greater activity, since their replacement with methyl groups led to inactive derivatives 51b and 53b (data not shown). Aliphatic amides (35a and 36a) and urea derivatives (58a–62a) obtained from chlorinated intermediate 6a showed no antiviral activity (data not shown). Aromatic amide moiety is allegedly required for anti-CVB5 activity. Concerning the C-4′-aminobenzyl derivatives, dimethyl benzotriazole-based aliphatic-urea compounds 99b and 100b showed a moderate anti-CVB5 activity resulting in EC_{50} values of 16 and 50 µM, while corresponding aliphatic amides 77b and 78b were revealed to be inactive (in Figure 2B, data not shown). When aliphatic-urea steric hindrance was increased from 99b to 100b, activity decreased. A remarkable SAR analysis may be described when compound 21e is compared with 18e derivative. The former was active against RSV, while the latter inhibited the CVB5 viral replication. The two derivatives

both shared the 4-F benzotriazole intermediate 12e, but derivative 21e carried on a trimethoxy-phenyl amide moiety, while 18e was the simplest pivalamide (in Figure 2C).

References

1. Johnson, N.P.A.S.; Mueller, J. Updating the Accounts: Global Mortality of the 1918-1920 "Spanish" Influenza Pandemic. *Bull. Hist. Med.* **2002**, *76*, 105–115.

2. Rajagopal, S.; Treanor, J. Pandemic (Avian) Influenza. *Semin. Respir. Crit. Care Med.* **2007**, *28*, 159–170.

3. Viboud, C.; Simonsen, L.; Fuentes, R.; Flores, J.; Miller, M.A.; Chowell, G. Global Mortality Impact of the 1957–1959 Influenza Pandemic. *J. Infect. Dis.* **2016**, *213*, 738–745.

4. Ruan, L.; Zeng, G. SARS Epidemic: SARS Outbreaks in Inner-Land of China. In Emerging Infections in Asia; Springer US: Boston, MA, USA, 2008; pp. 75–96.

5. Ruan, L.; Zeng, G. SARS Epidemic: SARS Outbreaks in Inner-Land of China. In Emerging Infections in Asia; Springer US: Boston, MA, USA, 2008; pp. 75–96.

6. Toshpo'latovich, Y. O. (2022). INTERPRETATION OF SMART TECHNOLOGY IN TECHNOLOGY LESSONS. *Open Access Repository*, *9*(11), 23-31.