THIOSEMICARBAZONES OF ACETYLPYRAZINES AS POTENTIAL DRUGS


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Thiosemicarbazones are relatively toxic compounds. In spite of their toxicity, some of them have been used as chemotherapeutic agents for life-threatening infections. Currently, thiosemicarbazones and their complexes with various metals have been studied as potential anti-viral, anti-bacterial, anti-mycobacterial, antiprotozoal, anti-fungal, and anti-neoplastic agents. Their anti-convulsant and neurotropic effects were reported as well [1]. Examining biologically-active derivatives of pyrazine, a series of thiosemicarbazones derived from acetylpyrazines 1-10 (R1 = H, alkyl, CN; R2 = H, CN; R3 = H, alkyl) was prepared. Acetophenone thiosemicarbazone 11 was prepared for comparison. The purity of the compounds was checked by HPLC, and their identity corroborated by spectral data (IR, NMR). Their lipophilicity (log K) was also determined by means of RP-HPLC.

Compounds 1-10 exhibited good or moderate activity (MIC = 1.95 – 125 μmol.l⁻¹) in antifungal susceptibility test (Candida spp., Trichosporon beigeli, Aspergillus fumigatus, Absidia corymbifera, Trichophyton mentagrophytes), while compound 11 was inactive. In an anti-mycobacterial bioassay using M. tuberculosis H₃7Rv, the highest potency was displayed by compound 4 (R₁ = butyl; R², R³ = H). The presence of the cyano group on the pyrazine ring influenced antimicrobial potency negatively. Anti-proliferation assays on SK-N-MC neuroepithelioma cell line revealed that more hydrophobic analogues, namely 2 (R₁ = tert-butyl; R², R³ = H) and 4 (R₁ = butyl; R², R³ = H), showed highest anti-tumor effects. More polar analogues, such as 1 (R₁, R₂, R³ = H) and 9 (R₁ = CN; R², R³ = H), illustrated decreased anti-proliferative effects with IC₅₀ values of > 6.25 μmol.l⁻¹.

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