3,4-disubstituted benzoic acids as coformers in the salts and cocrystals of pyrimethamine

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2,4-diaminopyrimidine antifolate drugs [*e.g.* pyrimethamine (PYR, Fig. 1a), and trimethoprim(TMP)] are mainly used for the treatment of parasitic diseases, such as toxoplasmosis and malaria. They work by inhibiting plasma dihydrofolate reductase (DHFR). In their protonated form, they inhibit DHFR by generating hydrogen bonds between the aminopyrimidine group and the hydroxyl group of the enzyme [1].

Based on our previous studies on the formation of cocrystals and salts of pyrimethamine with isomeric monohydroxybenzoic acids [2], we decided to study the influence of small structural changes in acidic coformer on the formation of specific adducts (cocrystals and salts) of pyrimethamine.

In our studies, we used vanillic acid (VANA) and its analogues – 3,4-dihydroxybenzoic acid (34DHBA), and 3,4-dimetoxybenzoic acid (3,4DMBA), Fig. 1b. All of the adducts were characterized by SC-XRD (Fig. 1c) and thermal analysis (TGA and DSC).

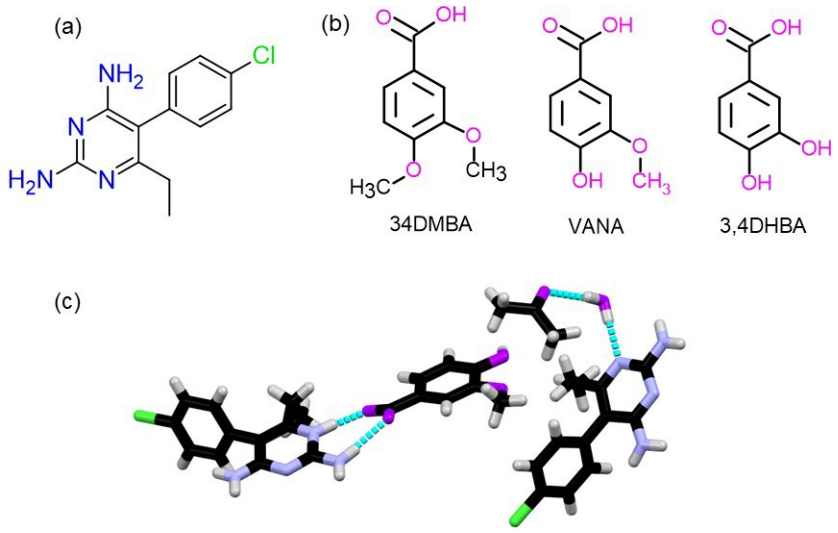

Figure 1. (a) Pyrimethamine (b) Acidic coformers: vanillic acid, 3-4-dihydroxybenzoic acid, and 3,4-dimetoxybenzoic acid (c) Exemplary associate of pyrimethamine with vanillic acid.

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