BIOLOGICAL ACTIVITY OF 2-HYDROXYTHIOBENZANILIDES AND RELATED COMPOUNDS

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SUMMARY

Thiobenzanilides substituted in thioacyl moiety with one or more hydroxy groups are interesting for their biological effects depending on the substitution pattern. New findings in mechanisms of action of 2-hydroxybenzanilides insert 2-hydroxybenzanilides and their analogues, e.g. substituted thiobenzanilides, among interesting compounds in the development of new potential antimicrobial drugs. The present review paper with 32 references links up with our previous communications which reviewed biological activity of 2-hydroxybenzanilides and related compounds, and includes the research of mono-, di-, and trihydroxythiobenzanilides carried out in the last period.

Key words: thiobenzanilides, mycobacteria, fungi, alga, photosynthesis-inhibiting activity, toxicity

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INTRODUCTION

Search for novel drugs against dangerous fungal and bacterial infections including tuberculosis and other mycobacterioses is one of goals of the present-day pharmaceutical chemistry. New discoveries in the area of microbial regulatory mechanisms playing an important role in the process of infection have offered the opportunity for a totally new class of antimicrobial agents. Such targets are represented for example by the bacterial two-component signal transduction systems (TCS) or type III secretion in virulent Gram-negative bacteria. Both of these systems have been newly identified as mechanisms of action of 2-hydroxybenzanilides (1, 2). These findings insert 2-hydroxybenzanilides and their analogues among interesting compounds for the development of new potential antimicrobial drugs. Thiobenzanilides belong to groups of biologically active compounds characterized by a wide spectrum of biological activities depending on the substitution pattern (3, 4). Especially, the substitution with one or more hydroxy groups in thioacyl moiety of the molecule leads to strong active compounds.

RESULTS AND DISCUSSION

2-Hydroxythiobenzanilides

Antimycobacterial activity of 2-hydroxythiobenzanilides was described by Waisser et al. in 1998 (5). The presence of hydroxy group in position 2 is important for *in vitro* antimycobacterial effect which is evident from the comparison with less active 2-unsubstituted thiobenzanilides (6) or 2-aminothiobenzanilides (7). Chlorine atom in position 5 of the molecule increases the efficacy of 2-hydroxythiobenzanilides whereas 3,5-dichloro substitution causes a decrease of antimycobacterial activity (8, 9). However, the presence of thiocarbonyl group does not appear to be important for the activity against atypical strains which results from the comparison with 2-hydroxybenzanilides (10). The interest in 2-hydroxythiobenzanilides as potential systemic antimycotics increased in the connection with their specific effect on *Absidia corymbifera* from the order Mucorales which was not observed in the case of their oxo analogues. The presence of chlorine atom in the position 5, and especially, contrary to antimycobacterial activity, 3,5-dichloro disubstitution are connected with extremely high *in vitro* activity of 2-hydroxythiobenzanilides against *A. corymbifera* (8, 11). 3-Formylamino-2-hydroxythiobenzanilides are active against various phytopathogenic fungi (12). Analogous to antimycobacterial activity, 2-unsubstituted or 2-aminothiobenzanilides are weakly active or inactive against fungi (13). 2-Hydroxythiobenzanilides interact with chlorophyll *a* present mainly in pigment-protein complexes on the donor side of photosystem II and they show a significant photosynthesis-inhibiting and antialgal activity. Similarly to the above effects, the importance of 2-hydroxy group has been confirmed (13-15).

2,4-Dihydroxythiobenzanilides

2,4-Dihydroxythiobenzanilides variously substituted in anilide moiety are active against Gram-positive but completely inactive against Gram-negative bacteria (16). These compounds are developed as potential antimycotic agents with a broad spectrum against dermatophytes (17), yeasts (18), moulds (19), and phytopathogenic fungi (20). QSAR analyses showed that the antifungal activity of 2,4-dihydroxythiobenzanilides depended mainly on the hydrophobicity of molecule (17, 21). The molecular topology was successfully used to optimize the antifungal activity of 2,4-dihydroxythiobenzanilides (22). Some changes in the functional group were performed but, with the exception of amide group, they led to a decrease or loss of the *in vitro* activity against phytopa-

thogenic fungi (20). On the other hand, various *N*-heterocyclic derivatives of 2,4-dihydroxythiobenzamide were found *in vitro* active against dermatophytes, yeasts, and moulds (23). *N*-Azolyl-2,4-dihydroxythiobenzamides exhibited comparable or higher *in vitro* activity than itraconazole and fluconazole against *Candida albicans* and non-*C. albicans* spp. (24). Toxicological studies were carried out in the connection with preclinical evaluation of 2,4-dihydroxythiobenzanilides. LD_{50} of selected 2,4-dihydroxythiobenzanilides in mice were in the range from 239 (2,4-dihydroxy-4´-trifluoromethylthiobenzanilide) to 840.5 mg/kg (3´-chloro-2,4-dihydroxy-2´-methylthiobenzanilide) (25). Cytotoxicity of selected derivatives on clone 81 cat cells was lower than that of imaverol and thiuram used as standards (26). 4´-[(*N*-B enzoyl)aminomethanocarboxy/]-2,4-dihydroxybenzcarbothioamide does not exhibit toxic action against blood lymphocytes (27).

2,4,6-Trihydroxythiobenzanilides

N-substituted 2,4,6-trihydroxy(thio)benzamides were studied for their photosynthesis-inhibiting activity (28-31) as analogues of phloroglucinol derivatives grandinol and homograndinol from *Eucalyptus grandis* Hill ex Maiden. They acts as photosystem II inhibitors (30). QSAR analyses of 2,4,6-trihydroxy-3-nitrobenzamides and -thiobenzamides showed a dependence on total lipophilicity of molecule (31). *N*-alkyl mono-, di-, and trihydroxybenzamides and -thiobenzamides were tested as inhibitors of Epstein-Barr virus activation by 12-*O*-tetradecanoylphorbol-13-acetate which is primary *in vitro* screening for anti-tumour promoters. Only 2,4,6-trihydroxy derivatives were active. *N*-alkyl thioamides were more active and less cytotoxic than the corresponding amides. *N-sec*-Butyl-2,4,6-trihydroxy-3-propanoylthiobenzamide was active at in vivo two-stage mouse skin carcinogenesis test (32).

CONCLUSION

The present review paper with 32 references deals with the research carried out in recent years on the area of biologically active thiobenzanilides containing one or more hydroxy groups in thioacyl moiety of the molecule. In the last period, a number of articles contributing to the knowledge about their antimycobacterial, antibacterial, antifungal, anti-neoplastic, and photosynthesis inhibiting effects have been published. Since new mechanisms of action of 2-hydroxybenzanilides have been recently found it is possible that 2-hydroxybenzanilides and their analogs, e.g. substituted thiobenzanilides, could play a role in the development of new potential antimicrobial drugs.

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