EXCLI Journal 2008;7:63-70 – ISSN 1611-2156
Received: January 18, 2008, accepted: March 07, 2008, published: March 10, 2008

Original article:

ANTIMICROBIAL AND ANTIOXIDATIVE ACTIVITIES OF 1-ADAMANTYLTHIO DERIVATIVES OF 3-SUBSTITUTED PYRIDINES

Supaluk Prachayasittikul[1*], Thummaruk Suksrichavalit[2], Chartchalerm Isarankura-Na-Ayudhya[2], Somsak Ruchirawat[3], Virapong Prachayasittikul[2*]

[1]Department of Chemistry, Faculty of Science, Srinakharinwirot University, Bangkok 10110 Thailand, [2]Department of Clinical Microbiology, Faculty of Medical Technology, Mahidol University, Bangkok 10700 Thailand, [3]Chulabhorn Research Institute, Bangkok 10210, Thailand
[1]Telephone: 662-664-1000 ext 8209, Fax: 662-259-2097,
[2]Telephone: 662-418-0227, Fax: 662-412-4110,
E-mail: supaluk@swu.ac.th, mtvpr@mahidol.ac.th ([*]corresponding authors)

ABSTRACT

Diverse biological activities of sulfur containing pyridines were reported. To investigate for new lead compounds, thus, 1-adamantylthiopyridines bearing 3-substituents (OEt, OAc, NAc_2, Br and OH) were prepared and evaluated for antimicrobial and antioxidative activities. The antimicrobial assay against 27 strains of microorganisms was performed using agar dilution method. The results show that all the tested 2-(1-adamantylthio)-3-ethoxypyridine **(4a)**, 2-(1-adamantylthio)-3-acetoxypyridine (**4b)**, *N*-acetyl-2-(1-adamantylthio)-3-acetamidopyridine **(4c)**, 2-(1-adamantylthio)-3-bromopyridine **(4d**), 2-(1-adamantylthio)-5-hydroxypyridine **(5)** and 3-(1-adamantylthio)-5-bromopyridine (**6**) exhibit antigrowth activity on *Streptococci* at 30 μg/mL. Particularly, the thiopyridines **4c, 5** and **6** are the most active compounds, displaying complete inhibition against β-hemolytic *Streptococcus* group A at 30 μg/mL. These pyridyl sulfides **4a-d, 5 and 6** represent a new group of antimicrobial agents. Antioxidative activity was analyzed using the DPPH assay. The sulfides **4a-d, 5 and 6** show only a weak antioxidative activity. In contrast the 2-(1-adamantylthio)-3-bromopyridine **(4d)** shows the highest radical scavenging activity.

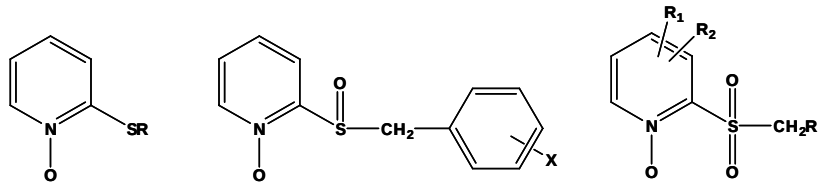
Keywords: 1-adamantylthiopyridines, antimicrobial and antioxidative activities

INTRODUCTION

A number of sulfur (Ballell et al., 2005; Scozzafava et al., 2001), sulfonyl (Scozzafava et al., 2001; Centrone and Lowary, 2004) and sulfonamide (Joshi et al., 2004) containing pyridines are active antimicrobial agents and herbicides (Parrish et al., 2001; Doweyko et al., 1983; Lee, 1981; Plant and Bell, 1976). For example, 2-alkyl- or 2-arylthiopyridines and *N*-oxides have been reported to possess diverse biological activities (Bauer and Prachayasittikul, 1987). Cyclic thionehydroxamic acids (**1**, R=H shown in the tautomeric form) are antibacterials (Shaw et al., 1950). The best known example is the zinc salt of 1-hydroxy-2-pyridthione which is the active ingredient in many popular shampoos. The oxidation products of pyridyl sulfides, such as *N*-oxides, sulfoxides **2** and sulfones **3** have proved to be herbicides (Doweyko et al., 1983; Lee, 1981; Plant and Bell, 1976) (Figure 1).

Methyl sulfide and sulfoxide of acetamidopyridines show antituberculous activity (Ozawa, 1957). 3,5-Diamino, 3,5-dialkylthio and 3,5-dialkoxypyridines and their pyridinium salts of cephalosporin are antibacterials (Yamazaki et al., 1986).

EXCLI Journal 2008;7:63-70 – ISSN 1611-2156
Received: January 18, 2008, accepted: March 07, 2008, published: March 10, 2008



1 2 3

R = H X = alkyl, aryl, NO_2 R = alkyl, aryl
R_1, R_2 = alkyl C_1-C_4

Figure 1: Sulfides, sulfoxides and sulfones of pyridine *N*-oxides

3-Alkoxysulfonylpyridine derivatives of carbapenem and their *N*-oxides are antibacterials (Guthikonda and Dininno, 1992). Furthermore, 3-hydroxypyridine analogs are antioxidants (Wijtmans et al., 2003). In addition, a number of 3-pyridthiol based com-pounds are theoretically proposed as novel antioxidants (Nam et al., 2006). To discover new lead compounds for medicinal uses, 1-adamantylthiopyridines have drawn much of our attentions. So far no bioactivities of 1-adamantylthiopyridines have been reported. Based on the reported bioactive pyridyl sulfides and the rational of drug design, thus, it prompted us to investigate on antimicrobial and antioxidative activities of 1-adamantylthio analogs of 3-substituted pyridines **4-6** as shown in Figure 2**.**

Generally, alkyl or arylthiopyridines are prepared by various methods (Bauer and Prachayasittikul, 1987) such as aromatic nucleophilic substitution (Abramovitch et al., 1969; Abramovitch and Newman, 1974) of halopyridines by thiolates, deoxydative substitution (Bauer and Prachayasittikul, 1986) of pyridine *N*-oxides by thiols, and *S*-alkylation (Bauer and Prachayasittikul, 1987) of pyridthiones with alkylating agents. In this study, the pyridyl sulfides **4**–**6** were prepared using the deoxydative substitution (Prachayasittikul et al., 1991) of pyridine *N*-oxides by thiol.

MATERIALS AND METHODS

The tested compounds 4-6

2-(1-adamantylthio)-3-ethoxypyridine **(4a)**, 2-(1-adamantylthio)-3-acetoxypyridine (**4b)**, *N*-acetyl-2-(1-adamantylthio)-3-acetamido-pyridine **(4c)**, 2-(1-adamantylthio)-3-bromopyridine **(4d**), 2-(1-adamantylthio)-5-hydroxypyridine (**5)** and 3-(1-adamantylthio)-5-bromopyridine **(6).**

These compounds **4-6** were prepared according to the literature (Prachayasittikul et al., 1991) using the reaction of 3-substituted pyridine *N*-oxides **7** with 1-adamantanethiol in refluxing acetic anhydride (Figure 2).

Microorganisms

Twenty seven strains of microorganisms (shown as follows) were used for antimicrobial activity assay:

- *Escherichia coli* ATCC 25922
- *Edwardsiella tarda*
- *Shigella dysenteriae*
- *Shigella flexneri*
- *Salmonella paratyphi* A
- *Salmonella typhi*
- *Salmonella enteritidis*
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Klebsiella pneumoniae* ATCC 700603
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Serratia marcescens* ATCC 8100
- *Serratia rubidaca*
- *Morganella morganii*
- *Providencia rettgeri*
- *Providencia alcalifaciens*
- *Pseudomonas aeruginosa* ATCC 27853
- *Vibrio cholera*
- *Vibrio parahaemolyticus*
- *Aeromonas hydrophila*
- *Bacillus subtilis* ATCC 6633

EXCLI Journal 2008;7:63-70 – ISSN 1611-2156
Received: January 18, 2008, accepted: March 07, 2008, published: March 10, 2008

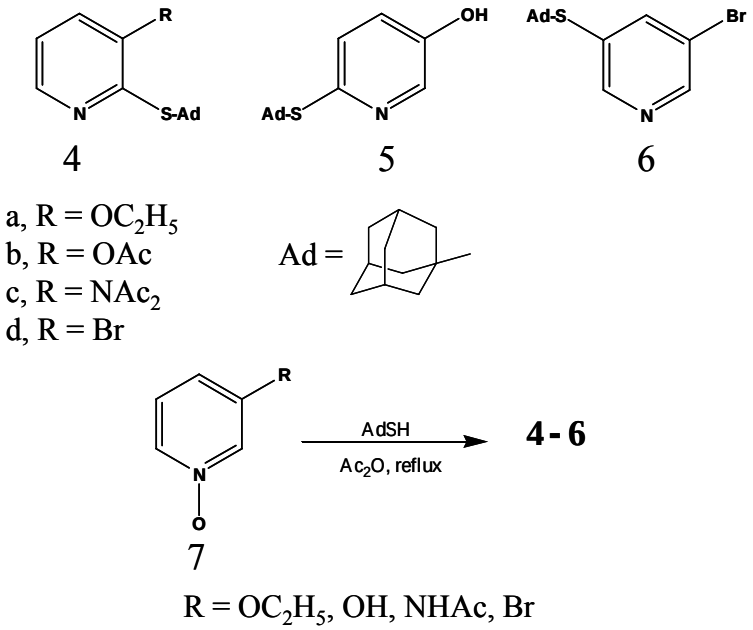


Figure 2: 1-Adamantylthiopyridines **4-6**

- *Staphylococcus aureus* ATCC 25923
- *Staphylococcus saprophyticus*
- β-hemolytic *Streptococcus* group A
- α-hemolytic *Streptococcus* spp.
- *Streptococcus* group D enterococcus

Antimicrobial assay *(Baron et al., 1994)*

Antimicrobial activity of 1-adamantylthiopyridine derivatives was investigated by using agar dilution method (Baron et al., 1994). Briefly, the tested compounds dissolved in DMSO were individually mixed with 1 mL Müller Hinton (MH) broth. The solution was then transferred to the MH agar solution to yield the final concentrations of 15 and 30 μg/mL. Twenty seven strains of microorganisms, cultured in MH broth at 37 °C for 24 h, were diluted with 0.9 % normal saline solution to adjust the cell density of 3×10^9 cell/mL. The organisms were inoculated onto each plate and further incubated at 37 °C for 18-48 h. Compounds which possessed high efficacy to inhibit bacterial cell growth were analyzed.

Antioxidative assay *(Yen and Hsieh, 1997)*

Antioxidative activity of 1-adamantylthio derivatives of 3-substituted pyridines was elucidated by DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay. When DPPH (a stable purple color) reacts with an antioxidant compound, it is reduced to yield a light-yellow color of diphenylpicrylhydrazine. Changes of the color can be spectrophotometrically measured. In this study, experiment was initiated by preparing 0.2 mM solution of DPPH in methanol. One millilitre of this solution was added into 0.5 mL of sample solution (1 mg/mL dissolved in methanol). After 30 min, absorbance was measured at 517 nm and the percentage of radical scavenging activity was calculated from the following equation:

$$\% \text{ Radical scavenging} = (1-\text{Abs. sample}/\text{Abs. cont})\times 100$$

where Abs. cont is the absorbance of the control reaction and Abs. sample is the absorbance in the presence of sample.

RESULTS AND DISCUSSION

Chemistry

As described in the literature (Prachayasittikul et al., 1991), the reaction of 3-substituted pyridine *N*-oxide **7** (R=OC_2H_5) with 1-adamantanethiol in boiling acetic anhydride gave 2-(1-adamantylthio)-3-ethoxypyridine **(4a)**. Similarly, the *N*-oxide

EXCLI Journal 2008;7:63-70 – ISSN 1611-2156
Received: January 18, 2008, accepted: March 07, 2008, published: March 10, 2008

7 (R=OH) afforded 2-(1-adamantylthio)-3-acetoxypyridine (**4b)** and 2-(1-adamantylthio)-5-hydroxypyridine **(5)**. *N*-acetyl-2-(1-adamantylthio)-3-acetamidopyridine **(4c)** was obtained from the reaction of *N*-oxide **7** (R=NHAc). 3-Bromopyridine *N*-oxide (**7**, R=Br) furnished a mixture of 2-(1-adamantylthio)-3-bromopyridine **(4d)** and 3-(1-adamantylthio)-5-bromopyridine (**6)**. The structures of pyridyl sulfides **4a-d**, **5** and **6** were confirmed by ^{1}H NMR and melting points.

Antimicrobial assay

The pyridyl sulfides **4-6** were tested for antimicrobial activity against 27 strains of microorganisms using agar dilution method (Baron et al., 1994). The results (Table 1) show that all the tested pyridyl sulfides **4-6** inhibit the growth of *Streptococci* at 30 μg/mL. The structures of these active sulfides **4-6** (Figure 2) constitute 1-adamantylthio group at various positions

Table1: Antimicrobial activity of 1-adamantylthiopyridines **4-6**

Compounds / Microorganisms	4a (μg/mL)		4b (μg/mL)		4c (μg/mL)		4d (μg/mL)		5 (μg/mL)		6 (μg/mL)	
	15	30	15	30	15	30	15	30	15	30	15	30
Escherichia coli ATCC 25922	4	4	4	4	4	4	4	4	4	4	4	4
Edwardsiella tarda	4	2	4	3	4	1	4	4	3	2	3	2
Shigella dysenteriae	4	4	4	4	4	4	4	4	4	4	4	4
Shigella flexneri	4	4	4	4	4	3	4	4	3	4	4	4
Salmonella paratyphi A	2	1	4	2	4	1	4	2	4	3	4	3
Salmonella typhi	4	3	4	4	4	2	4	3	4	4	4	4
Salmonella enteritidis	4	4	4	4	4	3	4	4	4	4	4	4
Citrobacter diversus	4	4	4	4	4	3	4	4	4	4	4	4
Citrobacter freundii	4	4	4	4	4	3	4	4	4	4	4	4
Klebsiella pneumoniae ATCC 700603	4	4	4	4	4	4	4	4	4	4	4	4
Enterobacter aerogenes	4	4	4	4	4	4	4	4	4	4	4	4
Enterobacter cloacae	4	4	4	4	4	2	4	4	4	4	4	4
Serratia marcescens ATCC 8100	4	4	4	4	4	3	4	4	4	4	4	4
Serratia rubidaca	4	4	4	4	4	2	4	3	4	4	4	4
Morganella morganii	4	4	4	4	4	3	4	4	4	4	4	4
Providencia rettgeri	4	4	4	4	4	3	4	4	4	4	4	4
Providencia alcalifaciens	4	3	4	3	4	2	4	4	4	4	4	4
Pseudomonas aeruginosa ATCC 27853	4	3	4	4	4	3	4	3	4	4	4	4
Vibrio cholerae	4	4	4	4	4	3	4	3	4	4	4	4
Vibrio parahaemolyticus	4	4	4	4	3	4	4	2	4	4	4	4
Aeromonas hydrophila	4	4	4	4	4	4	4	3	4	4	4	4
Bacillus subtilis ATCC 6633	4	4	4	4	4	4	4	3	4	4	4	4
Staphylococcus aureus ATCC 25923	4	2	4	3	4	3	4	3	3	2	3	2
Staphylococcus saprophyticus	4	3	4	3	4	3	4	3	4	2	4	2
β-hemolytic *Streptococcus* group A	2	2	2	2	2	0	2	2	1	0	1	0
α-hemolytic *Streptococcus*	2	2	2	2	2	2	2	2	1	1	1	1
Streptococcus group D enterococcus	2	2	2	2	2	2	2	2	1	1	1	1

Note: 4 = no inhibition of bacterial cell growth
3 = 25 % inhibition of bacterial cell growth,
2 = 50 % inhibition of bacterial cell growth
1 = 75 % inhibition of bacterial cell growth,
0 = 100 % inhibition of bacterial cell growth

EXCLI Journal 2008;7:63-70 – ISSN 1611-2156
Received: January 18, 2008, accepted: March 07, 2008, published: March 10, 2008

(2-, 5-, or 6-) on the rings of 3-substituted pyridines. The 3-substituted pyridines, **4c** (R=NAc_2), **5** (R=OH) and **6** (R=Br) having 1-adamantylthio group at 2-, 6- and 5- positions, respectively, exhibit complete inhibition against β-hemolytic *Streptococcus* group A at 30 μg/mL. Thus, the sulfides **4c**, **5** and **6** are more active than the other compounds **4a, 4b** and **4d**. However, the sulfide **4c** also displays antigrowth activity on *Edwardsiella tarda, Salmonella paratyphi* A, *Salmonella typhi*, *Enterobacter cloacae, Serratia rubidaca* and *Providencia alcalifaciens* at 30 μg/mL. The growth of *Salmonella paratyphi* A is also inhibited by the sulfides **4a, 4b** and **4d** at 30 μg/mL. In addition, the sulfides **4a**, **5** and **6** at 30 μg/mL are active against *Staphylococcus aureus* ATCC 25923. As a result, these pyridyl sulfides **4-6** represent a new group of antimicrobial agents.

It is interesting to note that *N*-acetyl-2-(1-adamantylthio)-3-acetamidopyridine **4c** exhibits activity against many microorganisms. However, bioactivity of sulfide of *N*-acetyl-3-acetamidopyridine has not been reported. Bioactivity of sulfur compounds of acetamidopyridines were reported, such as 2-methyl sulfide and sulfoxide of 3-acetamidopyridines showed antituberculous activity (Ozawa, 1957). In addition, 3-methyl sulfoxide of 2,6-diacetamidopyridine also produced antituberculous activity (Ozawa, 1957). Phenylthio analogs of aminopyridines such as 2-phenylthio-3- and 5-aminopyridines including 3-phenylthio-6-aminopyridine also showed antituberculous (Ozawa, 1957) activity. In the absence of thio moiety, *N*-acetyl-3-acetamidopyridine and its 2-isomer were reported to significantly inhibit the replication of influenza A virus (Pushkar-skaya et al., 1973) in a chick embryonic fibroblast culture at 200-300 μg/mL. Other structural related compounds e.g. 3-, and 4-formamidopyridines as well as 4-acetamidopyridine and 4-propionamidopyridine were used as controlling birds (Reinert and Williams, 1969), and were less toxic to mammals. Salt of 3-aminopyridine such as 1-dodecyl-methyl-3-dimethylamino pyridinium chloride showed strong antimicrobial activity and was a wide antimicrobial spectrum (Pernak and Branicka, 2003). When the 3-dimethylamino group was replaced by 3-hydroxy, the antimicrobial activity was loss. At this point, the sulfide **4c** is of interested target leads to be further developed in more details as therapeutic substances. Sulfides of 3-hydroxy, 3-acetoxy, 3-ethoxy and 3-bromopyridines have not been reported for any bioactivities. However, 3-acetoxy-2-pyridone was shown to be a potential antitumor agent (Hwang and Driscoll, 1979), displayed reproducible activity against murine P-388 lymphocytic leukemia. Antimicrobial activity of 3-hydroxypyridines has been reported. For example, 3-pyridinol is an active ingredient in antimicrobial composition (Tsuchida et al., 2007). 3-(2-Hydroxyphenyl) oxy-5-chloropyridine (Huang et al., 2007) is active against *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* and *Escherichia coli* with MIC value of 15.7, $\leq$ 0.5, 31.3 and 31.3 μg/mL, respectively. In addition, an aqueous bamboo grass *(Sasa senamensis)* (Higo et al., 2007; Endo et al., 2006) extracts containing 3-pyridinol, acetic, formic, coumaric and feruric acids (3.24, 18.62, 15.45, 2.74 and 0.97 mg/g, respectively) showed high antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* as well as antimutagenic activity.

Antioxidative assay

The sulfides **4-6** were evaluated for antioxidative activity using DPPH assay (Yen and Hsieh, 1997). The results (Table 2) show that the tested compounds **4-6** at 333.33 μg/mL display weak antioxidative activity using vitamin E as a control, percentages of radical scavenging are in the range of 0.3-21.08 %. Antioxidative activity of 3-bromo-, 3-ethoxy-, 3-acetoxy- and *N*-acetyl-3-acetamidopyridines has not been reported. In this study, the corresponding 1-adamantylthio derivatives of such pyridines are **4d** and **6, 4a**, **4b** and **4c**, respectively. Among the tested compounds, the 2-(1-

adamantylthio)-3-bromopyridine **4d** show highest activity, 21.08 % radical scavenging. The sulfide **5**, derivative of 3-pyridinol is almost inactive antioxidant (0.3 % radical scavenging). However, generally, 3-hydroxypyridines are active radical scavengers. For example, synthetic 3-hydroxypyridines bearing substituents at 2-, 4-, 5- and 6-positions showed antioxidative activity (Smirnov et al., 1999; Shabarchin et al., 1995; Lokhov et al., 1982) probably due to complexation of Fe^{2+} with ring N-atom or functional groups. 3-Hydroxypyridine derivatives (Tilekeeva et al., 1987) exhibited antihypoxic effect as active as sodium hydroxybutyrate, but less active than gutimine. This showed that 3-OH group was critical for activity, and substitution at 2-position was also important. From our results, it can be concluded that ring N-atom and 1-adamantylthio group may involve in the radical scavenging activity.

Table 2: Antioxidative activity of 1-adamantylthiopyridines **4-6**

Compounds (500 μg)	Radical scavenging (%)
4a	14.22
4b	7.03
4c	17.72
4d	21.08
5	0.30
6	17.07
α-Tocopherol (10 μg)	50.00

CONCLUSION

The investigated 1-adamantylthio analogs of 3-substituted (OEt, OAc, NAc_2, Br, OH) pyridines **4-6** have shown to inhibit the growth of *Streptococci* at 30 μg/mL. Particularly, the compounds **4c, 5** and **6** are the most active, displaying complete inhibition against β-hemolytic *Streptococcus* group A at very low concentration. The sulfide **4c** shows antigrowth activity against many microorganisms. Furthermore, 2-(1-adamantylthio)-3-substituted pyridines (OEt, OAc, NAc_2 and Br) **4a**, **4b**, **4c**, and **4d** selectively inhibit the growth of *Salmonella paratyphi* A at 30μg/mL. Additionally, the sulfides **4a**, **5** and **6** are active against *Staphylococcus aureus* ATCC 25923. All the tested sulfides show weak antioxidative activity. The sulfide **4d** is the most active antioxidant, 21.08 % radical scavenging activity. To evaluate for structure activity relationship, more derivatives are being made and tested for the antimicrobial and antioxidative activities. Other biological activities are under investigation.

Briefly, this study shows that 1-adamantylthio analogs of 3-substituted pyridines respresent a new group of antimicrobial agents. In particular, the sulfide **4c** which is of great interest leads to be further developed for therapeutic applications. This result also paves a way to explore the synthesis and bioactivities of other related 1-adamantylthio derivatives.

Acknowledgements: We thank the Faculty of Science, Srinakharinwirot University, and the Faculty of Medical Technology, Mahidol University for facilities and support. This project was partially supported by the annual budget grant of Mahidol University (B.E. 2551-2555).

REFERENCES

Abramovitch RA, Helmer F, Liveris M. Aromatic substitution. XXI. Kinetics of nucleophilic substitution of some bromopyridines and picolines with thiophenoxide ion. Nature of activation by ortho-methyl groups. J Org Chem 1969;34:1730-4.

Abramovitch RA, Newman AJ, Jr. Aromatic substitution. XXVI. Kinetics of nucleophilic substitution of some bromopyridines and picolines with methoxide, thiomethoxide, phenoxide, and thiophenoxide ions. J Org Chem 1974;39:2690-5.

Ballell L, Field RA, Duncan K, Young RJ. New small-molecule synthetic antimycobacterials. Antimicrob Agents Chemother 2005;49:2153-63.

Baron EJ, Peterson LR, Finegold SM. Methods for testing antimicrobial effectiveness. In: Bailey and Scott's diagnostic microbiology, 9th ed. (pp 168-193). St. Louis: Mosby-Year Book, Inc., 1994.

Bauer L, Prachayasittikul S. Deoxydative substitution of pyridine *N*-oxides by thiols. Heterocycles 1986;24:161-79.

Bauer L, Prachayasittikul S. Review of some recent syntheses, reactions and bioactivities of pyridyl sulfides. Sulfur Reports 1987;7:275-309.

Centrone CA, Lowary TL. Sulfone and phosphinic acid analogs of decaprenol-phosphoarabinose as potential antituberculosis agents. Bioorg Med Chem 2004; 12:5495-503.

Doweyko AM, Regis RR, Bell AR. Herbicidal 2-(chloromethylsulfonyl) pyridine 1-oxide. US Patent 4,360,477; Chem Abstr 1983;98:71951.

Endo A, Kawashima Y, Negishi H, Higo Y, Oyama T, Tsuchiko I et al. Pharmacologically active extracts from Sasa bamboo and their production. Jpn Patent 2006,036,731; Chem Abstr 2006;144: 198751.

Guthikonda RN, Dininno FP. Preparation of 2-(3-pyridyl) carbapenems as antibacterial agents. Eur Patent 1992,479,574; Chem Abstr 1992;117:111377.

Higo Y, Endo A, Negishi H, Oyama T, Tsuchiko I, Kawashima Y et al. Manufacture of bamboo grass extracts, and their use for physiologically active compositions, cosmetics, and foods. Jpn Patent 2007,204,423; Chem Abstr 2007;147: 242708.

Huang L, Clancy J, Taylor C, Pan W, Tomazic A, Jackson WJ. Preparation of 2-heteroaryloxyphenol derivatives as antibacterial agent. US Patent WO 2007,079,173; Chem Abstr 2007;147: 166334.

Hwang DR, Driscoll JS. Pyridones as potential antitumor agents. J Pharm Sci 1979;68:816-9.

Joshi S, Khosla N, Tiwari P. *In vitro* study of some medicinally important Mannich bases derived from antitubercular agent. Bioorg Med Chem 2004;12:571-6.

Lee KT. Herbicidal pyridine 1-oxides. US Patent 4,201,567; Chem Abstr 1981;94: 11637.

Lokhov RE, Marzoev AI, Chuchuk LV, Doroshenko TD. Inhibition of the chain peroxide oxidation of bilayer membrane lipids by monoazine derivatives. Deposited Doc. 1980, VINITI 3682-80; Chem Abstr 1982;96:47938.

Nam PC, Nguyen MT, Chandra AK. Theoretical study of the substituent effects on the S-H bond dissociation energy and ionization energy of 3-pyridinethiol: Prediction of novel antioxidant. J Phys Chem 2006;110: 10904-11.

Ozawa S. Antituberculous activity of heterocyclic compounds. IV. Pyridine, pyridothiazole, phenylpyridyl ether, nicotinoyl hydrazide and isonicotinoyl hydrazide derivatives. Kyoto Daigaku Kekkaku Kenkyusho Nempo 1956;4:284-94; Chem Abstr 1957;51:30395.

Parrish NM, Houston T, Jones PB, Townsend C, Dick JD. *In vitro* activity of a novel antimycobacterial compound, *N*-octanesulfonylacetamide, and its effects on lipid and mycolic acid synthesis. Antimicrob Agents Chemother 2001;45:1143-50.

Pernak J, Branicka M. The properties of 1-alkoxymethyl-3-hydroxypyridinium and 1-alkoxymethyl-3-dimethylaminopyridinium chlorides. J Surf Deterg 2003;6:119-23.

Plant HL, Bell AR. Herbicidal 2-sulfinyl and 2-sulfonyl pyridine 1-oxide derivatives. US Patent 3,960,542; Chem Abstr 1976;85: 108543.

Prachayasittikul S, Doss G, Bauer L. De-oxydative substitution of pyridine 1-oxides by thiols. Part XX. Reactions of (2,3 and 4-phenyl)-,3-acetamido-,3-bromo-,3-acetoxy-,3-ethoxypyridinel-Oxides with 1-adamantanethiol in acetic anhydride. J Heterocycl Chem 1991;28:1051-60.

Pushkarskaya NL, Ermolaev KM, Popova PA, Red' kin IA, Tochilkin AI. Inhibiting action of some cyclic *N*-diacetylamines on reproduction of influenza A virus in tissue culture. Vopr Med Virusol 1971;12:240-2; Chem Abstr 1973;78: 38512.

Reinert AJ, Williams RP. Compositions and methods for controlling birds. US Patent 3,433,873; Chem Abstr 1969;70:105442.

Scozzafava A, Mastrolorenzo A, Supuran CT. Antimycobacterial activity of 9-sulfonylated/sulfenylated-6-mercaptopurine derivatives. Bioorg Med Chem Lett 2001;11: 1675-8.

Shabarchin EI, Genten LY, Kruglyakova KE. Method for evaluating the action of synthetic antioxidants and other chemical compounds as inhibitors of the respiratory chain of mitochondria. Antioksidantov in vitro in vivo 1992:68-72; Chem Abstr 1995; 122:309971.

Shaw E, Bernstein J, Losee K, Lott WA. Analogs of aspergillic acid. IV. Substituted 2-bromopyridine *N*-oxides and their conversion to cyclic thiohydroxamic acid. J Am Chem Soc 1950;72:4362-4.

Smirnov LD, Stolyarova LG, Kesarev OG, Zhestkov VP. Pharmaceuticals based on synthetic antioxidants: pharmacology, chemistry, technology. Rossii Khimich Zhur 1998;42:114-9; Chem Abstr 1999;131: 78217.

Tilekeeva UM, Voronina TA, Kuz'min VI, Sopyev DA, Aliev AN. Characteristics of the antihypoxic activity of 3-hydroxypyridine antioxidants. Farmakol Toksikol 1987;50:74-7; Chem Abstr 1987;106: 188454.

Tsuchida Y, Tsuchida K, Watanabe K, Sakurai D, Koketsu M, Kawabe M et al. Antimicrobial agent and antimicrobial composition. Jpn Patent WO 2007,105,581; Chem Abstr 2007;147:336304.

Wijtmans M, Pratt DA, Valgimigli L, DiLabio GA, Pedulli GF, Porter NA. 6-Amino-3-pyridinols: Towards diffusion-controlled chain-breaking antioxidants. Angew Chem Int Ed 2003;42:4370-3.

Yamazaki A, Shibanuma T, Koda A, Nakano K, Maeda T, Nagano N et al. Cephalosporin compounds. Eur Patent 1985,160,546; Chem Abstr 1986;104: 207048.

Yen GC, Hsieh GC. Antioxidant effects on dopamine and related compounds. Biosci Biotech Biochem 1997;61:1646-9.