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# Synthesis and haemolytic activity of novel salts made of nicotine alkaloids and bile acids

Beata Jasiewicz [a,*], Lucyna Mrówczyńska [b,*], Karolina Malczewska-Jaskóła [a]

[a] Faculty of Chemistry, Adam Mickiewicz University, Umultowska 89b, 61-614 Poznań, Poland
[b] Department of Cell Biology, Faculty of Biology, Adam Mickiewicz University, Umultowska 89, 61-614 Poznań, Poland

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ABSTRACT

A series of novel salts made of nicotine alkaloids and bile acids were synthesized and their haemolytic activity was examined in vitro using human erythrocytes. All compounds were characterized by spectroscopic methods. The novel salts show membrane-perturbing properties inducing the erythrocyte shape alterations and haemolysis in dose-dependent manner. Nicotine decreases the membrane interacting potential of bile acids in the novel compounds. The presence of sulfur or selenium atom in the nicotine molecule affects the haemolytic activity of its novel salts depending on the hydrophobicity of bile acids.
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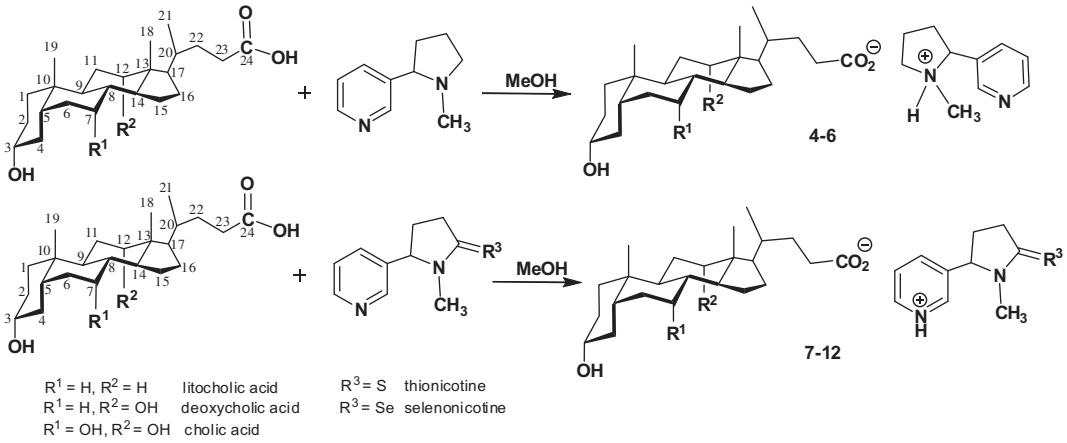
(*S*)-Nicotine (**1**) is the most abundant alkaloid isolated from the genus *Nicotiana* plant. It has a long history of being produced and used by humans for pharmacological purposes because of its numerous biological properties. Nicotine displays numerous effects on the central nervous system: enhancement of the working memory and attention, increase in arousal and alertness. Those many effects are due to the interaction of nicotine with the nicotinic acetylcholine receptors (nAChRs). Recent studies have shown




**Scheme 1.** Synthesis of salts **4**–**12**.

* Corresponding authors. Tel.: +48 61 8291354; fax: +48 61 8291555.
*E-mail addresses:* beatakoz@amu.edu.pl (B. Jasiewicz), lumro@amu.edu.pl (L. Mrówczyńska).

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**Table 1**
Composition and yields of salts **4**–**12**

| Compound | $R^1$ | $R^2$ | $R^3$ | Molecular formula | mp (°C) | Yields (%) |
|---|---|---|---|---|---|---|
| **4** | H | H | — | $C_{34}H_{54}N_2O_3$ | 142–144 | 80 |
| **5** | H | OH | — | $C_{34}H_{54}N_2O_4$ | Oil | 89 |
| **6** | OH | OH | — | $C_{34}H_{54}N_2O_5$ | 180–182 | 70 |
| **7** | H | H | S | $C_{34}H_{52}N_2O_3S$ | 146–149 | 83 |
| **8** | H | OH | S | $C_{34}H_{52}N_2O_4S$ | Oil | 88 |
| **9** | OH | OH | S | $C_{34}H_{52}N_2O_5S$ | 143–145 | 74 |
| **10** | H | H | Se | $C_{34}H_{52}N_2O_3Se$ | 99–107 | 88 |
| **11** | H | OH | Se | $C_{34}H_{52}N_2O_4Se$ | Yellow oil | 84 |
| **12** | OH | OH | Se | $C_{34}H_{52}N_2O_5Se$ | Yellow oil | 78 |

that nicotine displays beneficial effects on patients suffering from Parkinson's disease, anxiety, schizophrenia, Alzheimer's disease, ulcerative colitis, and other CNS disorders.[1–5]

Introduction of different functional groups or heteroatoms such as sulfur or selenium to the parent molecule of nicotine can lead to new potentially biologically active compounds. The presence of thiolactam (or selenolactam) group can significantly change the pharmacological properties of compounds through interaction with different cellular receptors. As a part of our structural and spectroscopic studies on nicotine alkaloids, we have reported recently the structure and spectroscopic properties of nicotine thio-[6] and seleno-analog.[7] Preliminary toxicity analysis showed that the (*S*)-thionicotine has at least about 80 times less toxicity in comparison to (*S*)-nicotine. It also interacts with nicotinic acetylcholine receptor (nAChR) α7 type.[8]

It has been reported that apoptosis induced by deoxycholic acid is stimulated by nicotine in HCT-116 cells.[9] As a continuation of our program in nicotine research, we have focused our attention on the influence of nicotine and its thio- or seleno-analogues on the membrane-perturbing and haemolytic properties of bile acids.

Bile acids are natural amphiphilic compounds present commonly in human bile and blood that play important role in the metabolism of lipids. Moreover, bile acids are used therapeutically to correct deficiency states, to decrease the cholesterol saturation of bile, or to decrease the cytotoxicity of retained bile acids in cholestatic liver disease.[10] As amphiphilic molecules, bile acids can form micelles or mixed complexes with different molecules/drugs, for example hydrogen-bonded complexes with lidocaine[11] or morphine,[12] to facilitate their transport through the cell membrane. Recently, the antiparasitic activity of novel hybrids of *Cinchona* alkaloids and bile acids has been shown in vitro.[13] On

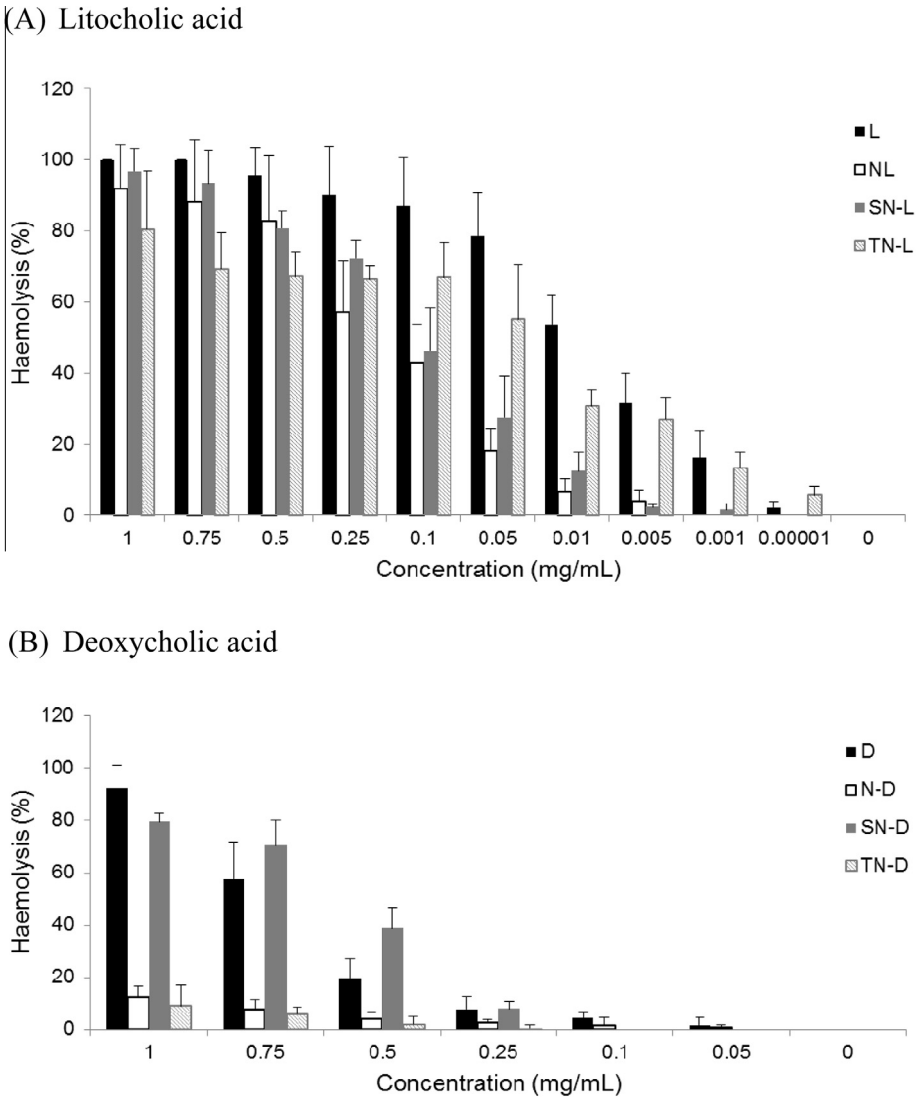


**Figure 1.** (A and B) Haemolysis (%) of erythrocytes under nicotine (N), selenonicotine (SN) and thionicotine (TN) and deoxycholic (D) and litocholic (L) acid salts after 60 min at 37 °C. (A) Lithocholic acid series, (B) deoxycholic acid series. Means values ± SD from 4 to 6 independent experiments are presented.

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