# SALTS OF *spiro*-DERIVATIVES OF BENZO[*f*]QUINOLINE AND SEVERAL NATURAL CARBOXYLIC ACIDS

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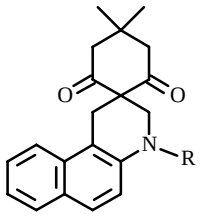
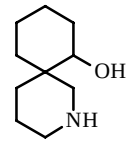
Derivatives of benzo[*f*]quinoline (4′,4′-dimethyl-*spiro*-1,2,3,4-tetrahydrobenzo[*f*]quinolin-[2;1′]-cyclohexan-2′,6′-dione) **1a** and **b** were prepared by a three-component cascade heterocyclization of 2-naphthylamine, formaldehyde, and dimedone [1] and contained structural features of the alkaloid nitramine (**2**) [2, 3], which is found in the aerial part of *Nitraria sibirica* Pall.



**1a, b**

**a:** R = H
**b:** R = $CH_2OMe$



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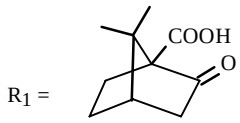
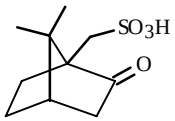
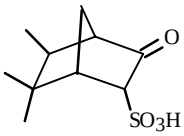


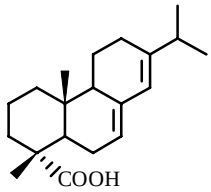
**4a, b**



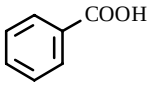
**5a, b**



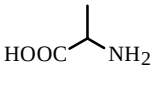
**6a, b**



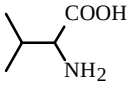
**7a, b**



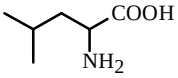
**8a, b**



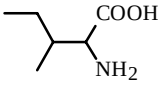
**9a, b**



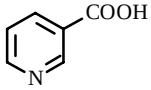
**10a, b**



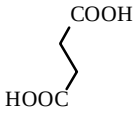
**11a, b**



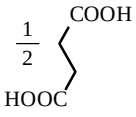
**12a, b**



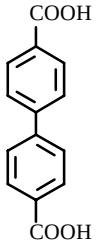
**13a, b**



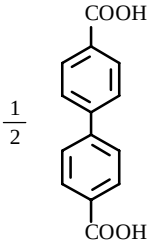
**14b**



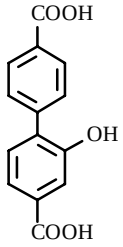
**15b**



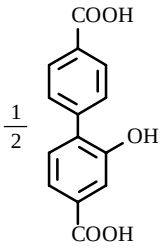
**16a, b**



**17a, b**



**18b**



**19b**

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TABLE 1. Antitumor Activity of **1a**, **b**, **4a**, and **b-19b** *in vitro*; Concentration of Compound Completely Suppressing Growth of Tumor Cells, mmol/L

| Compound | Tumor type | | | | | Compound | Tumor type | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | | I | II | III | IV | V |
| **1a** | 10 | >10 | >10 | >10 | >10 | **10b** | 7 | 8 | 8 | 8 | 9 |
| **1b** | 10 | >10 | >10 | >10 | >10 | **11a** | 8 | 8 | 8 | 8 | 9 |
| **4a** | 10 | 10 | 10 | 9 | 9 | **11b** | 7 | 8 | 9 | 9 | 9 |
| **4b** | 9 | 9 | 9 | 9 | 9 | **12a** | 8 | 8 | 9 | 9 | 9 |
| **5a** | 8 | 8 | 8 | 8 | 8 | **12b** | 7 | 8 | 8 | 9 | 8 |
| **5b** | 7 | 7 | 8 | 8 | 9 | **13a** | 6 | 8 | 8 | 7 | 8 |
| **6a** | 7 | 8 | 9 | 8 | 8 | **13b** | 5 | 7 | 7 | 7 | 7 |
| **6b** | 7 | 8 | 8 | 8 | 7 | **14b** | 6 | 8 | 8 | 7 | 8 |
| **7a** | 7 | 8 | 8 | 7 | 7 | **15b** | 3 | 5 | 5 | 4 | 5 |
| **7b** | 6 | 7 | 8 | 8 | 8 | **16a** | 5 | 6 | 6 | 7 | 6 |
| **8a** | 6 | 6 | 7 | 7 | 8 | **16b** | 4 | 5 | 5 | 5 | 5 |
| **8b** | 5 | 6 | 7 | 6 | 6 | **17a** | 2 | 3 | 3 | 4 | 3 |
| **9a** | 8 | 9 | 8 | 10 | 10 | **17b** | 1 | 2 | 1 | 1 | 1 |
| **9b** | 8 | 8 | 8 | 9 | 8 | **18b** | 0.8 | 1 | 2 | 1 | 1 |
| **10a** | 8 | 8 | 8 | 9 | 8 | **19b** | 0.3 | 0.4 | 1 | 0.5 | 0.8 |

The goal of the present work was to develop a preparative synthesis of new biologically active salts of *spiro*-derivatives of benzo[*f*]quinoline **1a** and **b** with several natural carboxylic acids **3** (ketopinic, 10-camphorsulfonic, 3-*exo*-isocamphanonesulfonic, abietic, benzoic, L-alanine, L-valine, L-leucine, L-isoleucine, nicotinic, succinic, 4,4′-biphenyldicarboxylic, and 2-hydroxy-4,4′-biphenyldicarboxylic). The optimal conditions were selected for preparing the previously unknown salts **4a** and **b-19b** by reacting **1a** and **b** with **3** in stoichiometric ratios 1:1 (salts **4a**, **b-13a**, **b**, **14b**, **16b**, and **18b**) or 2:1 (**15b**, **17a**, **b**, **19b**) in absolute MeOH. The reaction was carried out with boiling for 2-3 h. After removing MeOH over 4-5 h with heating at less than 40°C, the yields of **4a** and **b-19b** were 91-96%.

The products had the following melting points (°C) and compositions: **1a**, 196, $C_{20}H_{21}NO_2$; **1b**, 168, $C_{22}H_{25}NO_3$; **4a**, 91, $C_{30}H_{35}NO_5$; **4b**, 103, $C_{32}H_{39}NO_6$; **5a**, 125, $C_{30}H_{37}NSO_6$; **5b**, 87, $C_{32}H_{41}NSO_7$; **6a**, 163, $C_{30}H_{37}NSO_6$; **6b**, 133, $C_{32}H_{41}NSO_7$; **7a**, 141, $C_{40}H_{51}NO_4$; **7b**, 118, $C_{42}H_{55}NO_5$; **8a**, 107, $C_{27}H_{27}NO_4$; **8b**, 87, $C_{29}H_{31}NO_5$; **9a**, 194, $C_{23}H_{28}N_2O_4$; **9b**, 136, $C_{25}H_{32}N_2O_5$; **10a**, 192, $C_{25}H_{32}N_2O_4$; **10b**, 147, $C_{27}H_{36}N_2O_5$; **11a**, 188, $C_{26}H_{34}N_2O_4$; **11b**, 156, $C_{28}H_{38}N_2O_5$; **12a**, 197, $C_{26}H_{34}N_2O_4$; **12b**, 139, $C_{28}H_{38}N_2O_5$; **13a**, 184, $C_{26}H_{26}N_2O_4$; **13b**, 134, $C_{28}H_{30}N_2O_5$; **14b**, 127, $C_{26}H_{31}NO_7$; **15b**, 131, $C_{48}H_{56}N_2O_{10}$; **16a**, 198, $C_{34}H_{31}NO_6$; **16b**, 142, $C_{36}H_{35}NO_7$; **17a**, 182, $C_{54}H_{52}N_2O_8$; **17b**, 131, $C_{58}H_{60}N_2O_{10}$; **18b**, 193, $C_{36}H_{35}NO_8$; **19b**, 215, $C_{58}H_{60}N_2O_{11}$.

The salts **4a** and **b-19b** are colorless or weakly colored crystalline compounds that are soluble in acetone, $C_{1-4}$ alcohols, and DMSO and poorly soluble in water. They are not hygroscopic. The purity of the products was 98±1%.

Compounds **1a**, **b**, **4a**, and **b-19b** are promising for studies of their antitumor properties [4].

The antitumor activity of the synthesized compounds (**1a**, **b**, **4a**, **b-19b**) was studied against five cancer types in various cell cultures: leukemia (I), melanoma (II), cancer of the colon (III), kidney (IV), and breast (V) (Table 1). After an initial computerized structure—activity analysis of the products, they were tested *in vitro*.

All studied compounds exhibited very good cytostatic activity toward leukemia (I). Changing the NH moiety to $NCH_2OMe$ increased the activity toward all five cancer types. All studied salts (**4a** and **b-19b**) were more highly active than the starting compounds (**1a** and **b**). The aromatic carboxylic acids (**13a**, **b**, **16a**, **b-19b**) had the highest antitumor activity. The activity did not increase if salts of natural amino acids were used (**9a**, **b-12a**, **b**).

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**REFERENCES**


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