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BIOLOGICALLY ACTIVE QUATERNARY AZAAROMATICS

Abstract: The paper concerns selected quaternary azaaromatics showing biological activities, promising for pharmaceutical applications as well as useful as NAD models and DNA intercalators.

Introduction

Quaternary azaaromatics are a topic of numerous reports^{1–4} due to their chemical^{5–8} and physicochemical^{9–13} properties as well as in view of their interesting application possibilities^{14–16}, e.g. as NLO (nonlinear optics) materials^{17,18}, catalysts^{19,20}, surfactants²¹, ionic liquids²², sensors²³ and components of supramolecular systems promising as molecular switches or machines^{24–30}.

It should be pointed out that a special attention is paid to viologens^{31–33} and porphyrins bearing quaternary azaaromatic moieties^{34–36}.

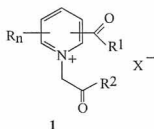
Studies of our laboratory concern quaternary salts of diazaphenanthrenes^{37–45}.

In the first part of the paper the biologically active quaternary azaaromatics suitable for pharmaceutical use are described, then NAD models and DNA intercalators are briefly characterized.

1. Quaternary azaaromatics showing biological activities

Quaternary azaaromatics exhibit various biological activities^{25, 46, 47}, e.g. antibacterial^{48–50}, antidiabetic⁵¹ and antineoplastic^{52,53}.

As examples may serve compounds **1** and **2**. Compounds **1** are useful in the treatment of diabetes, in neurovascular complications and in inflammatory and dermatological disorders⁵⁴, while compounds **2** show antineoplastic activities⁵⁵.



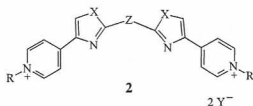
R = F, Cl, Br, SH

R¹ = alkyl, aryl, heteroaryl

R² = H, alkyl, aryl

X⁻ = Cl⁻, Br⁻, AcO⁻, BF₄⁻, ClO₄⁻

n = 0-2



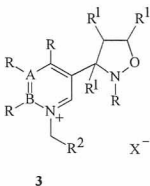
R = alkyl

X = O, S

Z = bond, -CH=CH-, , ,

Y⁻ = Cl⁻, NO₃⁻, AcO⁻, EtCOO⁻, PrCOO⁻, C₁₅H₃₁COO⁻

It was found that compounds **3** may be used in the treatment of addiction to psychostimulating drugs, addiction to opiates and to tobacco products⁵⁶, and **4** is a re-activator of tabun - inhibited acetylcholinesterase⁵⁷.

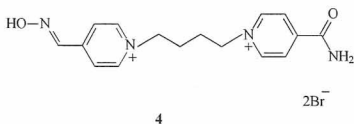


R¹ = H, alkyl, cycloalkyl, aryl

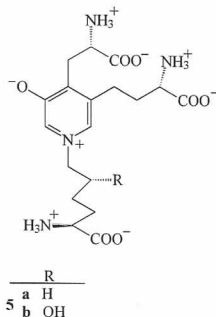
R² = H, alkyl, alkenyl

R = alkyl, cycloalkyl, aryl

X⁻ = Cl⁻, Br⁻, I⁻, HSO₄⁻, TsO⁻



Compounda **5a**, **b** are collagen cross-links used as biomarkers for the non-invasive assessment of bone degradation in osteoporosis, and in alteration of bone metabolism^{58,59}.

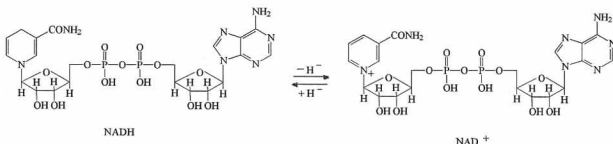


The synthetic procedure for **5b** was reported⁶⁰⁻⁶². It should be pointed out that the synthesis of **5b** is more difficult than that of **5a**, due to the presence in **5b** of the additional stereogenic centre at the carbon atom substituted by hydroxyl group.

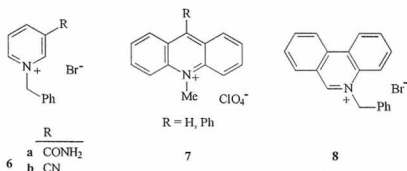
2. Quaternary salts as NAD models

Nicotinamide adenine dinucleotide coenzyme (NAD^+) plays an important role in enzyme-catalyzed oxido-reduction processes⁶³.

The reduced form of NAD^+ , *i.e.* NADH transfers a hydride ion or an electron to the surrounding substrate affording NAD^+ .



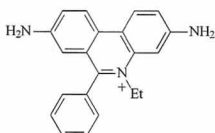
The mechanism of this process is a topic of a great interest, for this purpose numerous quaternary azaaromatics serving as NAD analogs are studied;⁶⁴⁻⁶⁶ examples are compounds **6-8**⁶⁷⁻⁷¹.



3. Quaternary azaaromatics as DNA intercalators

Quaternary azaaromatics bind nucleic acids ^{72,73}, this process often involves intercalation. The affinity of quaternary azaaromatics to DNA is useful for designing anti-neoplastic drugs.

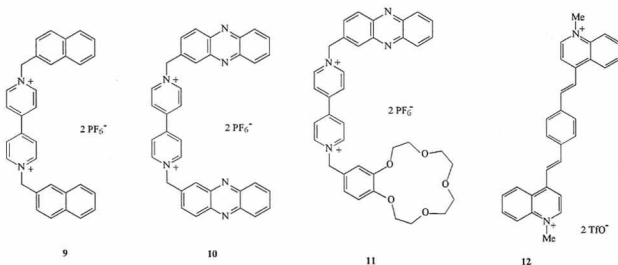
To investigate interactions between ethidium as intercalator and base pairs adenine-thymine and guanine-cytosine *ab initio* calculations were made ⁷⁴.

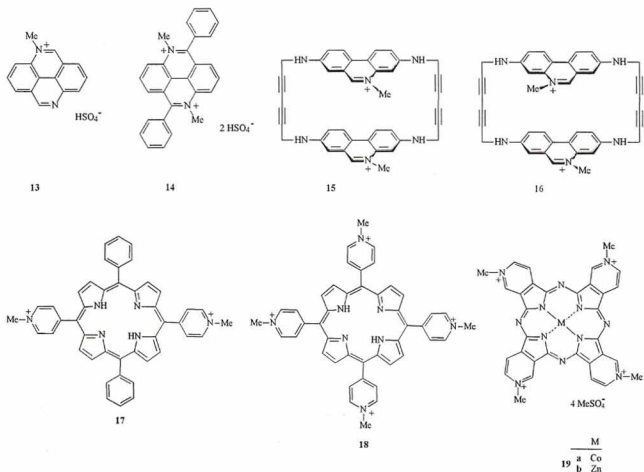


ethidium

Examples of DNA intercalators are compounds containing 4,4'-bipyridinium units **9–11**, ^{75,76} 1,4-bis(methylquinoliniumyl vinyl) benzene **12** ⁷⁷, 4,9-diazapyrenium – **13** and **14** ^{79–81} and phenanthridinium salts **15** and **16** ⁸², among porphyrinic DNA intercalators compounds **17** ⁸³ and **18** ⁸⁴ may be mentioned.

In the study of porphyrazine derivatives **19a,b** it was found that in the case of **19a** the intercalation and the external binding to calf thymus DNA coexist, whereas **19b** binds only externally ⁸⁵.





The above paper shows briefly a variety of biological activities of quaternary azaaromatics; the attention paid to this study has its reflection in the great number of reports⁸⁶⁻⁹⁰.

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CZWARTORZĘDOWE SOLE ZWIĄZKÓW AZAAROMATYCZNYCH WYKAZUJĄCE AKTYWNOŚĆ BIOLOGICZNĄ

Streszczenie: W artykule przedstawiono biologicznie aktywne czwartorzędowe sole związków azaaromatycznych jak również modelowe układy NAD oraz interkalatory kwasów nukleinowych.