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Synthesis and microbiological evaluation of several benzocaine derivatives

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ABSTRACT

Starting from benzocaine, a well-known anaesthetic, ten derivatives were synthesized and characterized by UV–vis, IR, NMR, and elemental analysis. Most of the compounds contain residues with recognized biological activity, like nicotinic acid (vitamin B3 or PP), biotin (vitamin B7 or H), lipoic acid (thioctic acid), adamantine, as well as other residues of crown-ether type, benzofurazane, naphtylurea, di- and tri-nitrobenzene, and a nitroxide radical. The biological evaluation of the obtained compounds included hydrophobicity (lipophobicity) assay, total antioxidant and microbiological activity tests.

1. Introduction

In the quest for new medicines, drug design and synthesis play an important part. Many medicines loose their activity due to extensive use, requesting higher doses or the replacement of the active compound. Among medicines, anaesthetics are a separate class of compounds, because many of them can induce addiction and therefore, generate drug abuse [1–4].

Design and synthesis of novel medicines is a quite long and expensive process, requesting a tremendous amount of work. Besides, the chosen chemical as a prospective medicine has to pass a huge number of tests, in which all the aspects of the possible chemical and biological factors have to be carefully addressed [5].

Benzocaine, an anaesthetic, is a simple chemical compound that induces pain relief; it is used in topical, dermal and mucous formulations, but, because its low water solubility, benzocaine cannot be used in parenteral administration. As any medicine, benzocaine has advantages and weak issues; therefore, new derivatives containing as substructure the benzocaine moiety are always of interest. Previous studies have demonstrated that benzocain-containing local anaesthetics and novel derivatives exhibited antimicrobial activity against different species, either Gram-positive, or Gram-negative, or fungal strains [6,7].

This paper deals with the synthesis, structural characterization and the microbiological activity evaluation tests of several novel benzocaine derivatives.

2. Results and discussion

2.1. Synthesis and structural characterization

Starting from benzocaine, all the compounds **1**–**10** (Fig. 1) were obtained practically in a single step, coupling benzocaine with the desired compound. Although some of the compounds (like **1**, **3**, **6**, **7**, Fig. 1) are present in the literature [7–11], we synthesized them to cover a broader

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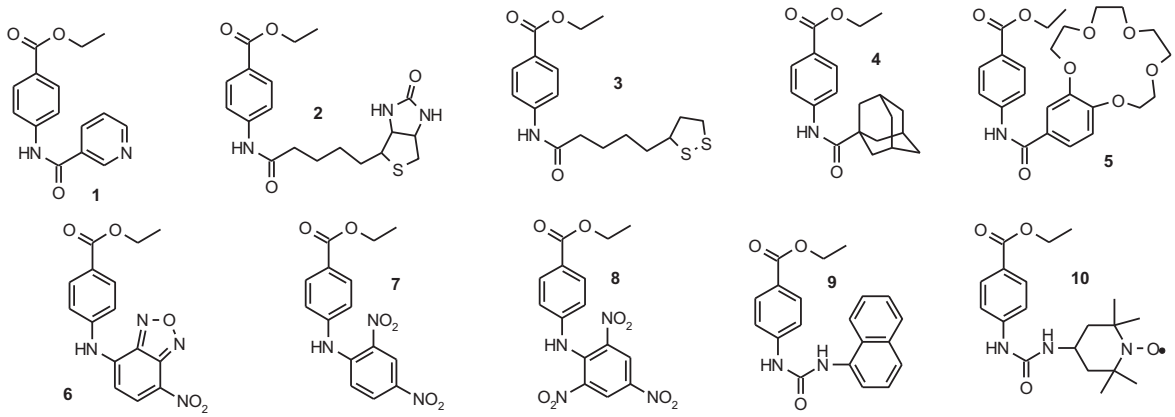

Fig. 1. Chemical structure of the synthesized compounds **1**–**10**.

range of chemicals with possible biological activity, and also to be compared with the new synthesized derivatives.

Thus, to obtain the desired compounds **1**–**5,** the coupling reactions between benzocaine and the required carboxylic acids have been tried in three different types of reactions, in order to get the highest yields:

- coupling using dicycloxexylcarbodiimide (DCC);
- coupling using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ);
- coupling using the corresponding acid chloride of the carboxylic acid.

It was shown that the higher yields were obtained by using the corresponding acid chloride of the carboxylic acid; between EEDQ and DCC, in our cases EEDQ was a better coupling agent. Compounds **6**–**8** were obtained by simple and effective nucleophilic aromatic substitution, while compounds **9** and **10** were synthesized by a coupling reaction between an amine and an isocyanate derivative. The general yields were between 40 and 95%.

Most of the obtained compounds required purification by column chromatography or preparative TLC; for analytical samples obtained in this way, structural characterization has been performed using current spectroscopic methods, like IR, UV–vis, NMR, and fluorescence and electron spin resonance (ESR), as necessarily (fluorescence for compound **6**, containing a benzofurazan moiety, and ESR for compound **10**, containing a free stable radical moiety).

All the analyses performed to characterize compounds **1**–**10** confirmed their chemical structure. Thus, in IR spectra, intense signals are noticed for the carbonyl groups, either from the ethyl ester moiety or from the amide or ureido moieties (around 1700 cm^{-1}). Amino groups appear between 3200 and 3500 cm^{-1} as broad signals. Aliphatic groups appear in IR at about 2900–3000 cm^{-1}, while the aromatic ones can be observed between 3000 and 3100 cm^{-1}. Nitro groups can easily be recognized by their values at about 1350 cm^{-1} and 1550 cm^{-1}, while the ether ones appear at about 1100–1200 cm^{-1}.

In UV–vis spectra (Table 1), the most bathochromic shift is noticed for compound **6** (472 nm, as an orange solid); this is accounted for by the nitrobenzofurazan (NBD) moiety, well known for its intense colour. Compounds **7** and **8**, containing nitro groups, are yellow solids, while all the others are white-grey solids.

In NMR spectra, amino groups are shifted under the influence of their chemical neighbours, and they appear between 7.5 and 10.5 ppm; all other ^{1}H and ^{13}C NMR values confirm the structure (see also Section 3).

Compound **6** exhibits the well-known fluorescence of the NBD moiety, with the emission value at 500 nm; compound **10**, containing a stable free radical moiety, shows the corresponding triplet in the ESR spectrum with a hyperfine coupling value of 15.5 G.

2.2. Biological evaluation

2.2.1. Lipophilicity

One of the most important properties of the medicines is their hydrophobicity or lipophilicity (usually noted log *P*, where *P* means the partitioning coefficient), which is correlated with the water or fat solubility, and therefore, with the capacity of crossing the cell membrane. The standard experimental methods used to determine the hydrophobicity values (log *P*) are the *n*-octanol/water repartition measurements [12] and the reverse-phase (RP) TLC [13], the latter being employed in this study; we

Table 1
UV–vis, lipophilicity and TAC values for compounds **1**–**10.**

Comp.	λ_{max} [a]	R_{M_0} [b]	b [b]	Log P [c]	SA [c]	TAC [d]
1	385	1.23	−2.82754	2.50	410	3.2
2	272	1.14	−2.91535	1.23	603	6.4
3	311	1.30	−2.76971	2.92	586	12
4	273	2.98	−4.31451	3.49	372	0.8
5	288	−0.36	−0.57627	1.70	485	8.8
6	472	1.51	−2.79154	3.05	515	10.4
7	341	2.42	−3.21055	3.28	549	8
8	378	2.39	−3.82341	3.23	580	3.2
9	292	2.91	−4.84119	3.74	518	43.2
10	317	1.57	−3.00695	1.69	607	22.3

[a] nm, in methanol.
[b] Experimental values from RP–TLC.
[c] Theoretical values.
[d] Experimental values.