Tetrahedron 73 (2017) 5115–5121

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel quinoxaline derivative: Solubilization by surfactant solutions and membranotropic properties

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ARTICLE INFO

Article history:
Received 10 March 2017
Received in revised form
21 June 2017
Accepted 3 July 2017
Available online 4 July 2017

Keywords:
Quinoxaline
Solubility
Surfactant
Membranotropic properties

ABSTRACT

Novel compound, (*E*)-3-([1,2,4]triazolo[4,3-*a*]quinoxalin-4(5*H*)-on-1-yl)acrylic acid, containing triazole and quinoxaline moieties has been synthesized and characterized. The solubility of the compound in water and surfactant solutions has been estimated at different pH. It has been shown that the increase in solubility is due to hydrophobic effect as well as electrostatic interactions. The capability of this compound to integrate within dipalmitoylphosphocholine lipid bilayer has been evaluated. An increase in membranotropic properties after encapsulation of this compound in nanocontainers based on dicationic surfactant has been exhibited.

1. Introduction

Most of the compounds derived from quinoxalines[1] and 1,2,4-triazoles[2] have been shown to display a wide spectrum of biological activities. Moreover, a few fused triazoles to different heterocycles have been found to be significant anticonvulsant[3] and tranquillizing agents.[4] Also, 1,2,4-triazoloquinoxalines have been reported as antidepressant, cardiotonic and antifatigue agents.[5] Further, hydrazine quinoxalines and their cyclic analogues were reported as antimicrobial agents.[6] As for the (*E*)-3-*R*-acrylic moiety it can be found in numerous natural products of diverse structural complexity and biological properties.[7] Moreover, due to its dense functionality, compounds bearing the (*E*)-3-*R*-acrylic subunit exhibit interesting combinations of miscellaneous reactivities. These provide a multitude of synthetic options for further structural modifications.[8] A broad applicability of 3-acylacrylic building blocks came hand in hand with the development of several complementary synthetic routes to access them. Keeping this in view, it was thought worthwhile to design the synthesis of title compound wherein the biologically active (*E*)-3-R-acrylic and triazole moieties are fused to quinoxaline ring at *c* bond.

The design and synthesis of bioactive molecules is the primary important task, whereupon a variety of problems occurs before they can demonstrate therapeutic effect and clinical trials can be performed. Considering this, researchers need to address such challenges as (i) an increase in water solubility of potential drug; (ii) improvement of bioavailability; (iii) protection from biodegradation; penetration through cell membranes and biological barriers including nasal, skin and the mouth mucosa, brain-blood barrier and so on. To solve these problems supramolecular strategies are developed to fabricate nanosized carriers for drug molecules. Amphiphile-based nanocarriers are known to be successfully used for these purposes,[9] with micelles, microemulsions, vesicles and liposomes demonstrating excellent efficacy in both laboratory and clinical practice.

Herein, we report the synthesis of hitherto unknown (*E*)-3-([1,2,4]triazolo[4,3-*a*]quinoxalin-4(5*H*)-on-1-yl)acrylic acid (TQA, Fig. 1) starting from 1,2-diaminobenzene and oxalic acid via quinoxaline ring build-up.[10] The chemical structure of the compound studied is given below.

The solubility of this compound in water was quantitatively characterized at various pH values as well as in the presence of surfactants of different nature: a typical cationic surfactant

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http://dx.doi.org/10.1016/j.tet.2017.07.002
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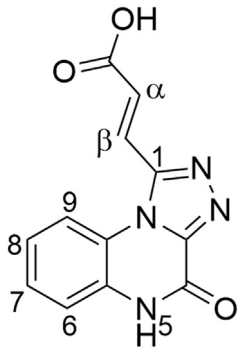

Fig. 1. Chemical structure of (*E*)-3-([1,2,4]triazolo[4,3-*a*]quinoxalin-4(5*H*)-on-1-yl) acrylic acid (TQA).

cetyltrimethylammonium bromide (CTAB) and its dicationic analogue hexanediyl-*α*,*ω*-bis(dimethyltetradecylammonium bromide (14-6-14), anionic surfactant sodium dodecyl sulphate (SDS) and nonionic surfactant Tween-80. In addition, the ability of free and formulated TQA molecules to penetrate through a lipid bilayer was explored.

2. Results and discussion

2.1. The approaches to increase in TQA solubility in water

The TQA molecule bears a polar fragment and is therefore capable of partially dissolving in water. We managed to obtain a solution with ~1 mM TQA concentration and pH ~3.5. Potentiometric titration of this solution using 0.01 M NaOH allows us to estimate the pK_a value of TQA to be 4.25, corresponding to dissociation of the carboxylic group. Importantly, the TQA transition to anionic form is accompanied by an increase in its solubility. Elimination of a proton from nitrogen atom can occur in highly alkaline media. Due to low TQA solubility in water, we were unable to obtain its higher concentration, that was necessary for the second pK_a value determination. However, this was possible using the mixed solvent – water/DMF (7:3). Under these conditions we prepared the TQA solution with 10 mM concentration. As a result of its titration by 0.1 M alkali potentiometry plot was obtained (Fig. S1), at which two stages of TQA ionization could be observed (determined pK_a values are 3.8 and 9.8).

Solubilization of organic compounds of low polarity in surfactant micellar solutions is a successfully used approach to increase water solubility, with the solubilization efficiency depending on the nature and hydrophilic-lipophilic properties of surfactants as well as on the structure of solubilizate. In this work CTAB, SDS and Tween-80 were used as solubilizers, which are typically applied for this purpose. Along with conventional monomeric surfactants, gemini 14-6-14 was also used. Geminis contain two alkyl radicals and two head groups connected by a spacer fragment. They demonstrate notably lower critical micelle concentration (cmc), higher surface potential and a considerable hydrophobic domain in comparison with their monocationic analogues, which allows them to exhibit significant solubilization activity at low concentrations.[11]

2.2. Quantitative evaluation of TQA solubilization effect

Electronic spectroscopy was used for quantitative determination of TQA content in solutions, possible due to the fact that this compound has characteristic absorption bands in the UV–visible region of spectrum. There is intense absorption in aqueous solution of TQA in the 220–250 nm range at pH from 2 to 7. However, a wide band with the maximum of optical density at 304 nm is more suitable for analysis (extinction coefficient $\varepsilon = 11020\ mol^{-1}\ L\ cm^{-1}$ (Fig. 2)). Transition to micellar solutions almost doesn't influence the location of absorption bands of the compound, nevertheless slightly changes its intensity. The λ and ε values of TQA in different media are listed in Table 1. Absorption spectra of this compound in CTAB micellar solutions are exemplified in Fig. 3. A decrease of extinction coefficient was observed for TQA in surfactant solution in comparison with aqueous solutions associated with the change of microenvironment at transition from polar bulk phase to nonpolar micellar pseudophase. An increase in pH results in widening of the absorption band, enhancing in its intensity and appearing of two bands with poor resolution at 295 nm and 320 nm. Due to the fact that the carboxylic group pK_a equals to 4.25, and spectra of the examined compound are almost identical in the pH region 2–7, their changes at further alkalization, probably related to deprotonization of amino group.

Spectral characteristics (Fig. 2, Fig. S2–S5) are the basis for quantitative analysis of TQA content in micellar solutions. Analysis of TQA solubility in surfactant solutions (Fig. 4) was performed through the determination of TQA maximum concentration at various amphiphile content from the region of surfactant monomeric form (the section of slight increase in TQA concentration) existence to the region of micellar solutions (the section of abrupt increase in TQA concentration). The inflection point at the plot corresponds to surfactants' cmc values. Noteworthy, that this approach is widely used for surfactants' cmc value determination.[12] Data listed in Table 1 indicate that the presence of SDS and Tween-80 in water has a little effect on TQA solubility, whereas CTAB and 14-6-14 induces a significant increase in solubility. Addition of this cationic surfactant (2 mM) increases the content of TQA approximately by 40%. A more pronounced effect was observed in the case of 14-6-14. More significant solubilization ability in micellar solutions of cationic surfactants allows to conclude, that the key role in increase of TQA solubility play attractive electrostatic forces between positively charged ammonium head groups of CTAB or 14-6-14 and negatively charged carboxylic group.

For instance, the concentration of 14-6-14 required for a 1.5-fold increase in solubility of TQA is one order of magnitude lower than in the case of CTAB. TQA is predominantly nonionized in aqueous solution, so pH 3.4–3.8 is maintained in the system. The TQA molecule switches to anionic form beyond a solution pH of 6.5 on the addition of alkali. It was shown by spectrophotometry that solubility of the anionic form in water is approximately 6 times higher than that of the neutral one. This tendency intensifies with transition to micellar solutions of cationic surfactants (inset in Fig. 4). It indicates on the fact, that electrostatic forces during TQA solubilization in micellar systems contributes significantly. Marked

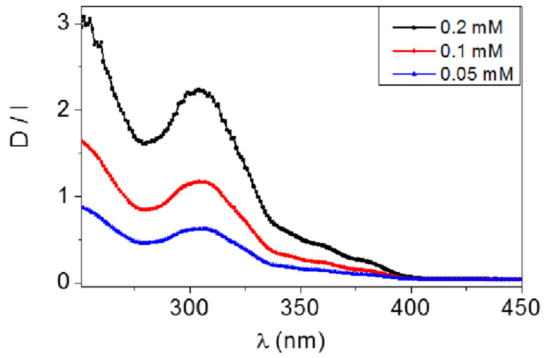

Fig. 2. Electronic absorption spectra of TQA at different TQA concentrations in water, pH 6.