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Synthesis and description of intermolecular interactions in new sulfonamide derivatives of tranexamic acid

Muhammad Ashfaq [a], Muhammad Nadeem Arshad [b, c, *], Muhammad Danish [a], Abdullah M. Asiri [b, c], Sadia Khatoon [a], Ghulam Mustafa [a], Pavel N. Zolotarev [d, e], Rabia Ayub Butt [a], Onur Şahin [f]

[a] Department of Chemistry, University of Gujrat, Gujrat 50700, Pakistan
[b] Chemistry Department, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia
[c] Centre of Excellence for Advanced Materials Research (CEAMR), King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia
[d] Samara Center for Theoretical Materials Science (SCTMS), Samara State University, Ac. Pavlov St. 1, Samara 443011, Russian Federation
[e] Samara State Aerospace University (National Research University), SSAU, 34, Moskovskoe Shosse Str., Samara 443086, Russian Federation
[f] Scientific and Technological Research Application and Research Center, Sinop University, 57010 Sinop, Turkey

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ABSTRACT

Tranexamic acid (4-aminomethyl-cyclohexanecarboxylic acid) was reacted with sulfonyl chlorides to produce structurally related four sulfonamide derivatives using simple and environmental friendly method to check out their three-dimensional behavior and van der Walls interactions. The molecules were crystallized in different possibilities, as it is/after alkylation at its O and N atoms/along with a co-molecule. All molecules were crystallized in monoclinic crystal system with space group $P2_1/n$, $P2_1/c$ and $P2_1/a$. X-ray studies reveal that the molecules stabilized themselves by different kinds of hydrogen bonding interactions. The molecules are getting connected through O–H···O hydrogen bonds to form inversion dimers which are further connected through N–H···O interactions. The molecules in which N and O atoms were alkylated showed non-classical interaction and generated centro-symmetric $R_2^2(24)$ ring motif. The co-crystallized host and guest molecules are connected to each other *via* O–H···O interactions to generate different ring motifs. By means of the ToposPro software an analysis of the topologies of underlying nets that correspond to molecular packings and hydrogen-bonded networks in structures under consideration was carried out.

1. Introduction

Plasminogen is a plasma protein which is present in an inactive form. Because of an activator, it is transformed into plasmin, which originates from tissues in case of injuries or damage to the body. Plasmin is an enzyme that breaks down proteins (fibrin and several different proteins) through its proteolytic activity [1]. Tranexamic acid performs its antifibrinolytic activity as it blocks competitively those sites of protein plasmin, plasminogen and plasminogen activator that bind lysine hence their interaction with fibrin is prevented. So plasminogen cannot be converted into plasmin and in this way proteolytic activity is prohibited [2]. It is a synthetic drug that causes antifibrinolytic activity by inhibiting the breakdown of protein fibrin hence leads towards the stabilization of blood clots [3]. Gastrointestinal tract is the place where its absorption takes place and after almost 3 h peak plasma concentration occurs. The drug has a bioavailability around 30–50% and is excreted from the body mostly in an unchanged form [4]. Almost 95% drug is removed through kidneys in unaltered form. Its half-life is approximately 3 h [5]. Owing to its antifibrinolytic nature, the drug is being given to "Coronary Artery Bypass Graft" (CABG) patients on a regular basis [6]. It is an adjuvant drug that enhances the efficacy of other medicines when administered together with them so it is being used for site specific laser therapy. It also prevents menstrual loss of blood and is substitute for operation in menorrhagia. Hemophilic patients also require this drug during extraction of tooth and blood loss disorders [7]. Tranexamic acid is applied on the knee joint during knee arthroplasty so as to reduce bleeding after operation and it has also been used for spine, cardiac and dental procedures [8].

* Corresponding author. Chemistry Department, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia.
E-mail address: mnachemist@hotmail.com (M.N. Arshad).

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Tranexamic acid does not have any π-electrons so it cannot act as fluorophore or chromophore and hence cannot be measured through UV spectroscopy. It is therefore imperative to derivatize this compound so as to quantify its UV-active derivative though HPLC-UV. A review of the literature resulted into many papers describing derivatization of this drug with different reagents followed by their HPLC determinations. Some of these methods utilized methanolic ninhydrin [9], phenylisothiocyanate [10], 2-hydroxynaphthaldehyde in aqueous ethanol [11] and sodium picrylsulfonate [12] followed by their determination through HPLC-UV. In addition to these, LC-fluorescence method utilizing naphthalene-2,3-dicarboxaldehyde plus cyanide [13], o-phthalaldehyde [14], an electrochemical method [15], a LC-MS method [16] and UPLC-MS/MS [17] has also been established for the determination of tranexamic acid. An RP-HPLC method for the determination of tranexamic acid along with its related substances and a GC method are also reported in the literature [18,19].

A number of scientists derivatized this drug, evaluated the activity and found that most derivatives were superior to the parent drug [20–24]. The present study is also in extension to our program for the synthesis and crystallographic studies of tranexamic acid [25,26]. Topological studies are also one of the area to explain the networks formed by the hydrogen bonds and other intermolecular interactions [27,28]. With the aim to study the structures of tranexamic acid sulfonamides, we reacted it with suitable sulfonyl chlorides to get these (Scheme 1), which further were crystalized as such, after alkylation or co-crystallized along with another guest molecule.

2. Experimental

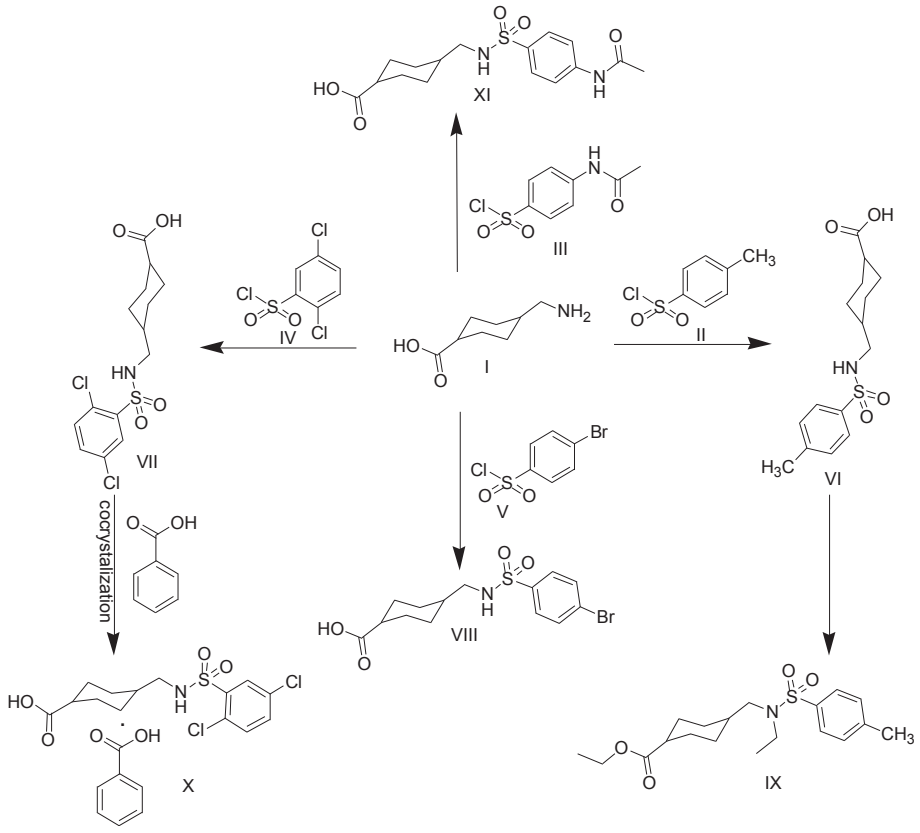
The sulfonamide syntheses (Scheme 1) were carried out at room temperature using distilled water as a media. Mixture of ethyl acetate and *n*-hexane was used as a solvent in TLC. Reactions were monitored using Merck patented aluminum-backed TLC plates coated with silica gel 60 or alumina (0.2 mm) containing a fluorescent indicator active at 254 nm. The chromatograms were visualized under UV light (254 nm and higher wavelength). Melting points were recorded using Stuart SMP 10 melting point apparatus and are reported as uncorrected. The experimental and theoretically calculated values of ^{1}H NMR are provided in Supplementary material.

2.1. Synthesis of 4-[(toluene-4-sulfonylamino)-methyl]-cyclohexanecarboxylic acid (VI)

Tranxemic acid (4 g, 25.4 mmol) was dissolved in water (50 mL). p-Toluenesulfonyl chloride (4.85 g, 25.4 mmol) was added to it under stirring at room temperature keeping the pH of a mixture about 8–9 using 1 M sodium carbonate solution until the completion of reaction. The dissolution of suspended sulfonyl chloride to clear solution indicates the progress of reaction. On completion the pH of solution was decreased to 2–3 by adding 1 M HCl. The precipitates produced were filtered, washed by distilled water and recrystallized from methanol [20] (Yield: 84%) mp 192–194 °C.

2.2. Synthesis of 4-({[(2,5-dichlorophenyl)sulfonyl]amino}methyl) cyclohexanecarboxylic acid (VII)

Tranxemic acid (2 g, 12.7 mmol) was dissolved in water (50 mL). 2,5-Dichlorobenzenesulfonyl chloride (3.11 g, 12.7 mmol) was added to it under stirring at room temperature keeping the pH of a mixture about 8–9 using 1 M sodium carbonate solution until the completion of reaction. The dissolution of suspended sulfonyl chloride to clear solution indicates the progress of reaction. On



Scheme 1. Synthesis of sulfonamide derivatives of tranexamic acid.