

REVIEW ARTICLE

Preparations methods of tizanidine (API) and related compounds: A review

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ABSTRACT

Tizanidine is an imidazoline derivative with the agonistic activity of central alpha 2 receptors at both the spinal and supra-spinal levels. It was prepared for the first time in 1978 and approved for use in 1996. The present review focuses on all methods used for the synthesis of tizanidine, related compounds and intermediates. This review article covers all the methods that have been used in the preparation of tizanidine since its discovery until now. Methods used for the preparation of tizanidine-related compounds are also covered. This review gives those interested in drug synthesis and designs the ability to form a complete picture of the preparation of this drug, as well as providing the opportunity for the synthesis of other drugs developed from this drug to increase activity and/or reduce side effects.

Keywords: Tizanidine; Drug Intermediates; Imidazoline Derivative; Drugs Synthesis

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1. Introduction

Tizanidine, 5-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine (**Figure 1**) is an imidazoline central alpha(2)-adrenoceptor agonist drug used to relieve spasms and treat muscle tension caused by spinal cord injury or multiple sclerosis^[1]. In multiple sclerosis; nerves do not function properly and patients experience weakness, numbness, loss of muscle coordination, and problems with vision, speech, and bladder control^[2]. The efficacy of tizanidine is comparable to that of baclofen or diazepam^[3].

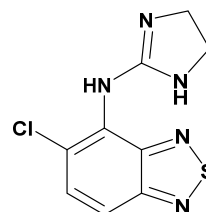


Figure 1. Tizanidine structure.

Tizanidine is a member of skeletal muscle relaxant drugs. It functions by reducing the rate that the brain and neurological system are acting so that the muscles may relax. In addition to other drugs, it is marketed under the brand name Zanaflex. Tizanidine was accepted for medicinal usage in the US in 1996^[4] and is now available as a generic drug^[2,5]. In 2018, the drug was registered as the most common prescription drug in the United States, with more than 8 million prescriptions^[6,7].

Tizanidine works by enhancing the inhibition of motor neurons, the nerve cells in the brain that instruct muscles to contract. Although the

drug doesn't directly affect muscles, it indirectly relaxes them by inhibiting motor neurons^[3,8].

Tizanidine usually causes dry mouth, sleepiness, lethargy, and dizziness as adverse effects. The drug's primary warnings are the possibility of low blood pressure and liver damage^[3,8].

There are a large number of review articles that have been done on the different uses of tizanidine as well as the possible side effects in addition to the use of drug delivery techniques^[3,8-10]. So far, to our knowledge, there is no article review on the chemical methods used in preparing the active substance (API) to prepare tizanidine drug, so it was important to prepare this article review, which focuses on the different methods used in the manufacture of this drug at the industrial and research level in order to benefit researchers interested in this point.

2. Preparation methods of the tizanidine base

2.1 Preparation tizanidine base using 1-(5-chlorobenzo[*c*][1,2,5]thiadiazol-4-yl)thiourea derivatives

There are several methods of preparation that used to prepare tizanidine since 1978, the year in which it was first prepared by Neumann, and the method of preparation was registered in US Patent No. 3,843,668^[11]. According to the US Patent

3,843,668 tizanidine was prepared using 1-(5-chlorobenzo[*c*][1,2,5]thiadiazol-4-yl)thiourea derivatives with the general formula (I) (**Figure 2**).

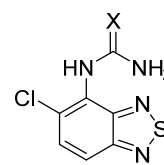
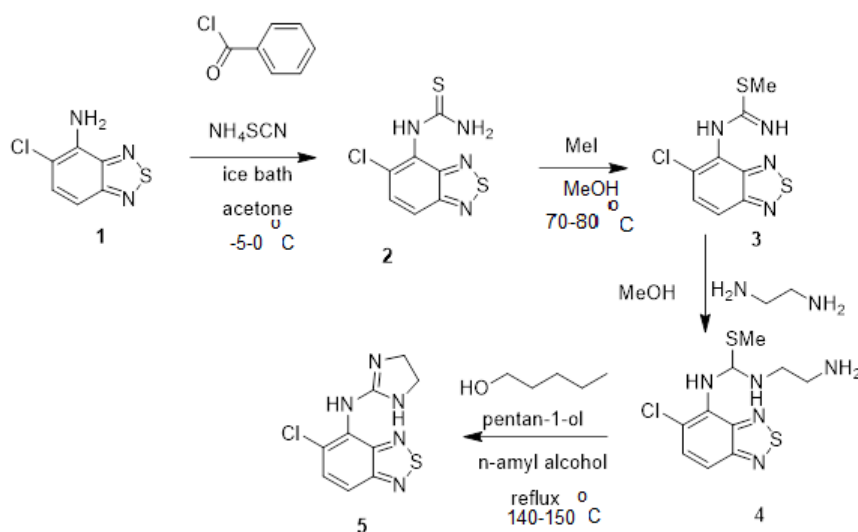


Figure 2. Formula of starting material for tizanidine preparation.

The 1st derivative of this series is 1-(5-chlorobenzo[*c*][1,2,5]thiadiazol-4-yl)thiourea (2) that was prepared from the reaction of 5-chlorobenzo[*c*][1,2,5]thiadiazol-4-amine (1) with ammonium thiocyanate, in the presence of benzoyl chloride in an ice bath, followed by heating under reflux temperature. To produce the thiourea derivative, the precipitate was refluxed with 2N NaOH solution and then acidified with acetic acid (2). After that, the preparation process was achieved in 3 steps starting from 1-(5-chlorobenzo[*c*][1,2,5]thiadiazol-4-yl)thiourea (2). The latter compound was reacted with methyl iodide to give methyl (5-chlorobenzo[*c*][1,2,5]thiadiazol-4-yl)carbamimidothioate (3). The *S*-methylated derivative (3) was reacted with ethylenediamine in refluxing methanol to afford the intermediate (4) that undergoes intermolecular cyclization when refluxed with amyl alcohol to afford tizanidine base (5) (**Scheme 1**)^[11].



Scheme 1

2.2 Preparation of tizanidine starting from 7-chloro-4-isothiocyano-

2,1,3-benzothiadiazole

The 2nd method for tizanidine preparation was

reported by the Swiss patent CH 579,565^[12]. In this method, the preparation process of tizanidine depends on the cyclization of the compound with the general formula II (**Figure 3**).

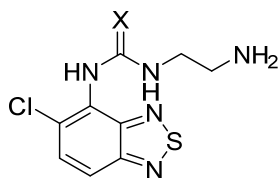
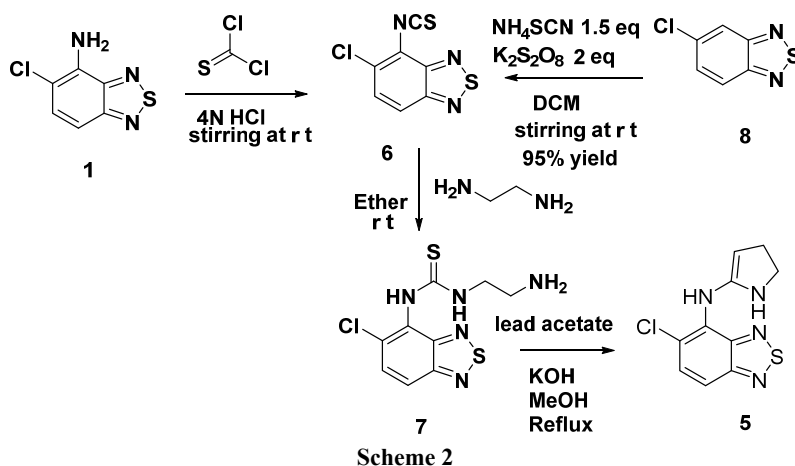


Figure 3. Formula II of starting material for tizanidine preparation.

The preparation process of tizanidine by the Swiss patent can be outlined in (**Scheme 2**). The reaction of 5-chlorobenzo[*c*][1,2,5]thiadiazol-4-amine

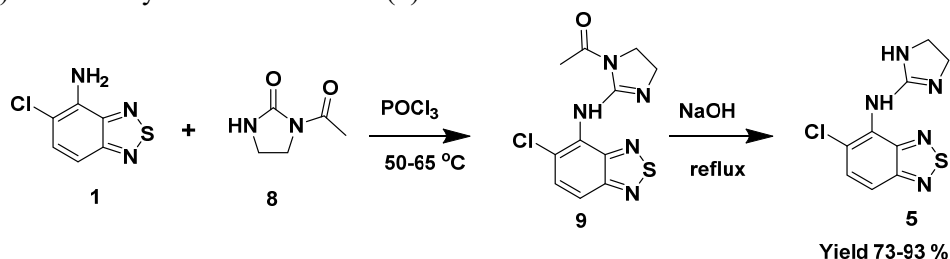
(1) with thiophosgene afforded the thiocyanate derivative (6) (**Scheme 2**).

In another approach, 5-chlorobenzo[*c*][1,2,5]thiadiazol-4-amine (1) was treated with ammonium thiocyanate and potassium persulphate in DCM at room temperature for three hours to produce the isocyanate (6) with a 95% yield. The compound of formula II, compound 7 as an example, was synthesized by a reaction of 7-chloro-4-isothiocyano-2,1,3-benzothiadiazole, with ethylenediamine. The cyclization process was achieved under reflux temperature in the presence of bases such as alkali metal or alkaline earth hydroxide and of certain compounds of lead acetate to afford the tizanidine.



2.3 Preparation of tizanidine from the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and 1-acetyl imidazolin-2-one (8)

The reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and 1-acetyl imidazolin-2-one (8) in



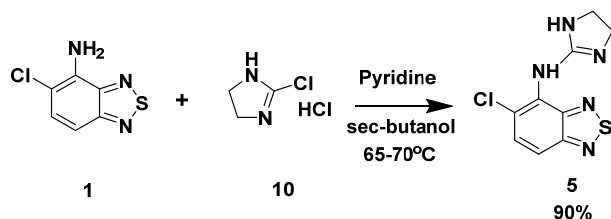
Scheme 3

2.4 Preparation of tizanidine from the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and 2-chloro-2-imidazoline hydrochloride (10)

Tizanidine was prepared with high purity

the presence of phosphorus oxychloride followed by treatment with NaOH was applied to prepare tizanidine (**Scheme 3**) with yield 85%^[13], 93.6 %^[14], 73%^[15], and 70%^[16].

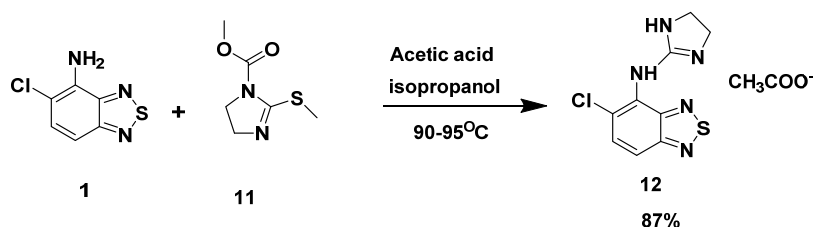
(99.18%) and high yield of 90.5%, by the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and 2-chloro-2-imidazoline hydrochloride (10) in pyridine followed by treatment with NaOH solution (**Scheme 4**)^[17].



Scheme 4

2.5 Preparation of tizanidine from the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) with *N*-methyl-2-methylthio-2-imidazoline (11)

Direct preparation of tizanidine salts of organic acids were prepared from the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and *N*-methyl-2-methylthio-2-imidazoline (11) (Scheme 5) the

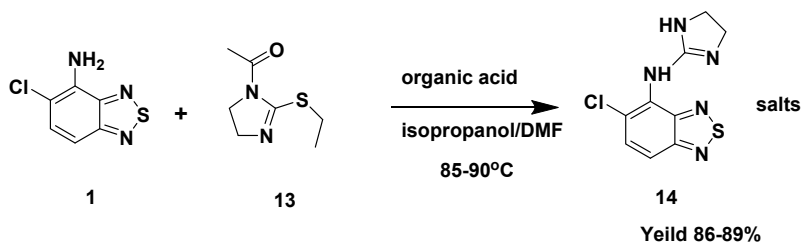


Scheme 5

2.6 Preparation of tizanidine from the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) with *N*-acetyl-2-ethylthio-2-imidazoline (13)

Several series of tizanidine salts of organic acids were prepared in the same manner as the previous reaction by the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and *N*-acetyl-2-ethylthio-

2-imidazoline (13) in the presence of organic acid to afford the corresponding tizanidine salts (14) (Scheme 6)^[18]. 10 examples of tizanidine salts of organic acid were prepared by this method that includes acetic acid, malic acid, citric acid, oxalic acid, 2-hydroxypropionic acid, butyric acid, glycolic acid, caproic acid, ethoxy acetic acid and malonic acid^[18].



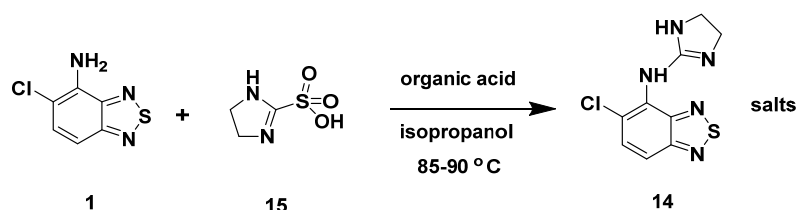
Scheme 6

Table 1. organic acid salts of tizanidine and the reaction conditions used

Acid	Solvent	Time	Temperature	Yield
Hexanoic acid	EtOH/DMF	8 h	75–80 °C	87.5%
3-oxapentanoic acid	MeOH/DMF	10 h	65–70 °C	86.5%
Glycolic Acid	Isopropanol/DMF	12 h	85–90 °C	86.2%
Malic acid	Isopropanol/DMF	13 h	85–90 °C	87.5%
Malonic acid	Isopropanol/DMF	9 h	85–90 °C	86.8%
butyric acid	EtOH/DMF	10 h	75–80 °C	86.0%
Lactic acid	Isopropanol/DMF	12 h	85–90 °C	88.3%
Xalic acid	MeOH/DMF	12 h	65–70 °C	86.9%
Citric acid	EtOH/DMF	12 h	75–80 °C	86.1%
Acetic acid	Isopropanol	15 h	90–95 °C	88.5%

The following table (**Table 1**) includes the organic acids that were used in these reactions, as well as the reaction conditions and time, in addition to the solvents that were used.

2.7 Preparation of tizanidine from the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) with imidazoline-2-sulfonic acid (15)



Another method for the preparation of tizanidine organic acid salts was achieved by the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) with imidazoline-2-sulfonic acid (15) under reflux temperature in isopropanol, as a solvent in the presence of a series of organic acid and afforded the corresponding tizanidine salts (**Scheme 7**)^[18].

The following table includes the organic acids that were used in these reactions, as well as the

reaction conditions and time, in addition to the solvents that were used.

Table 2. Organic acid salts of tizanidine and the reaction conditions used

Acid	Solvent	Time	Temperature	Yield
Hexanoic acid	DMF	10 h	120–125 °C	88.4%
Fumaric acid	Isopropanol	12 h	85–90 °C	85.6%
Tartaric acid	Sec-butanol	8 h	95–100 °C	87.3%
Malic acid	Isopropanol	10 h	85–90 °C	59.2%

3. Preparation of tizanidine starting material and related compounds

Drug-related compounds are the compounds that are present with the active pharmaceutical ingredient (API) in very few amounts, and they are often formed during the manufacture of the drugs as one of the starting materials that enter into the manufacturing process or as a by-product formed during the process.

All drugs sold in the market are determined by their drug-related compounds and the permissible percentages for the presence of these substances with the drugs. This information that includes; the methods of analyzing these substances, methods of

identifying them, and their percentages in the drugs is recorded in what is known as pharmacopeia. This information is continuously updated to keep up with both modern preparation and analysis methods. There are three related compounds to tizanidine that are registered in pharmacopoeia in the United States USP (**Figure 4**). These substances are tizanidine A, tizanidine B and tizanidine C related compounds, which must be identified and separated for many reasons, the most important of which is to avoid the side effects that may cause, which may be harmful, and the other reason is to determine the correct dose of the API. Therefore, identifying and analyzing these compounds and knowing the preparation separating methods in a pure form is one of the most important applications in the field of pharmaceutical chemistry.

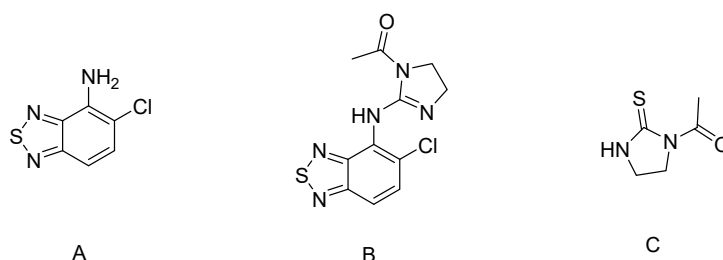


Figure 4. Structure of USP tizanidine related compounds A, B and C.

3.1 Preparation of tizanidine related compounds A

5-Chlorobenzo[*c*][1,2,5]thiadiazol-4-amine (1) is the tizanidine-related compound A that consider the main starting material for the preparation process of tizanidine. The preparation process of 5-

chlorobenzo[*c*][1,2,5]thiadiazol-4-amine (1) was achieved in 8 reaction steps starting with aniline and is outlined in **Figure 5**. We will report herein the preparation process starting from the commercially available 4-chloro-*o*-phenylenediamine.

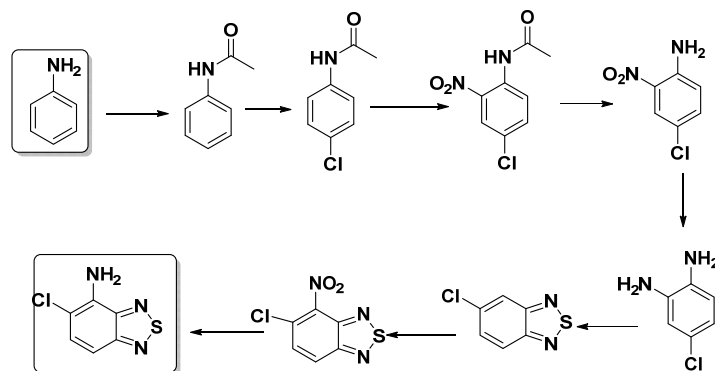
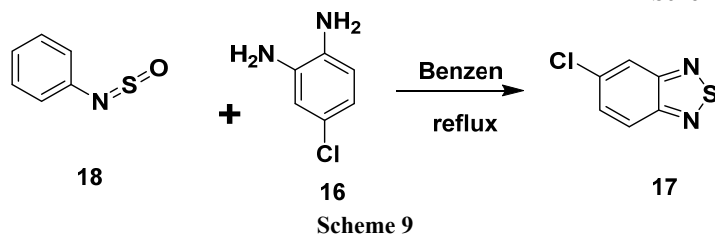
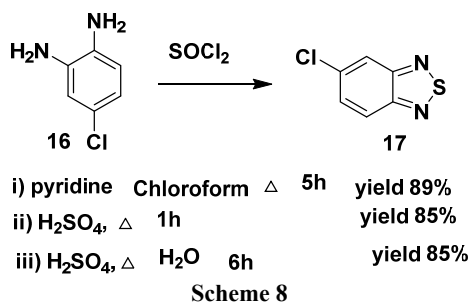


Figure 5. Preparation process of 5-chlorobenzo[*c*][1,2,5]thiadiazol-4-amine (1).

3.1.1 Preparation of 5-chlorobenzo[*c*][1,2,5]thiadiazole (17)

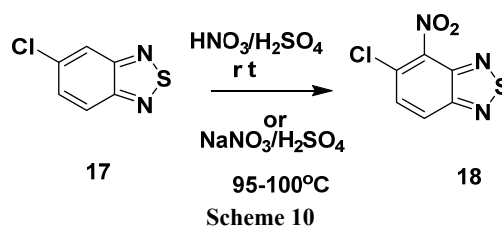
5-chlorobenzo[*c*][1,2,5]thiadiazole (17) was prepared by several methods mainly depending on the reaction of thionyl chloride with 4-chloro-*o*-phenylenediamine in basic media (pyridine)^[19] or acidic media (sulfuric acid)^[20,21].



N-Phenylsulfnylamine (18) was used also for the preparation of compound 17 by the reaction with 4-chlorobenzene-1,2-diamine (16) (**Scheme 9**)^[22].

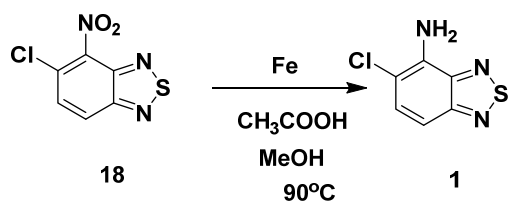
3.1.2 Preparation of 5-chloro-4-nitrobenzo[*c*][1,2,5]thiadiazole (18)

Nitration mixture from nitric and sulfuric acid was used for the nitration process under reflux temperature to afford 5-chloro-4-nitrobenzo[*c*][1,2,5]thiadiazole (18) with good to excellent yield^[21]. Another nitration mixture from NaNO₃, H₂SO₄ was used for the process at reflux temperature 95–100 °C (**Scheme 10**)^[21].



3.1.3 Preparation of 5-chlorobenzo[*c*][1,2,5]thiadiazol-4-amine (1)

The reduction reaction of 5-chloro-4-nitrobenzo[*c*][1,2,5]thiadiazole (18) to the corresponding amine (1) was achieved by treatment of 5-chloro-4-nitrobenzo[*c*][1,2,5]thiadiazole (18) reduction mixture from an iron-acetic acid mixture in MeOH (**Scheme 11**)^[21].



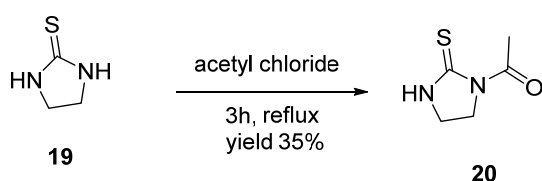
Scheme 11

3.2 Preparation of tizanidine-related compound B

1-Acetyl-*N*-(5-chloro-2,1,3-benzothiadiazol-4-yl)-4,5-dihydro-1*H*-imidazol-2-amine (9) consider as the tizanidine related compound B that was prepared by the reaction of 4-amino-5-chloro-2,1,3-benzothiadiazole (1) and 1-acetyl imidazolin-2-one (8) in the presence of phosphorus oxychloride. The reaction process stopped at this step without going to the alkaline hydrolysis step with NaOH (Scheme 3)^[13–15].

3.3 Preparation of tizanidine related compound C

USP tizanidine-related compound C; 1-Acetylimidazolidine-2-thione (20) was prepared by acetylation of *N,N'*-ethylenethiourea (19) using acetyl chloride or acetic anhydride under reflux condition^[23,24]. The reaction of acetyl chloride and *N,N'*-ethylenethiourea (19) under low temperature affords *S*-acetylated products that undergo intramolecular rearrangement with heating for several hours to afford the *N*-acetylated products (20) (Scheme 12)^[23].



Scheme 12

4. Conclusions

This review scoped all of the reported methods used for the preparation of tizanidine base starting from 4-amino-5-chloro-2,1,3-benzothiadiazole (1). 7 methods were reported for the tizanidine preparation starting from the first one that was achieved by Neumann. The importance of this article review is that it gives researchers and those interested in tizanidine drug the ability to form a complete picture of the preparation of this drug, as well as providing the

opportunity, in the future, for those interested in developing this drug and the synthesis of other drugs that are developed from this drug to increase activity and/or reduce side effects. Furthermore, we have also reported the reported methods for the preparation of tizanidine-related compounds and the starting materials used in the preparation process.

Acknowledgements

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Conflict of interest

The authors declare that there is no conflict of interest.

Dedication

We dedicate this work to our Prof. Dr Ahmed Frag, Professor of Organic Chemistry, on the occasion of his fiftieth year at the Faculty of Science, Cairo University.

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