ejpmr, 2017,4(7), 305-310

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF SUBSTITUTED THIETES - A REVIEW

Yogesh Waghmare*, Vilas Kamble and Sonali Mahaparale

Department of Quality Assurance Technique, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India.

***Corresponding Author: Yogesh Waghmare**

Department of Quality Assurance Technique, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India.

Article Received on 30/04/2017 **Article Revised on 20/05/2017** **Article Accepted on 10/06/2017**

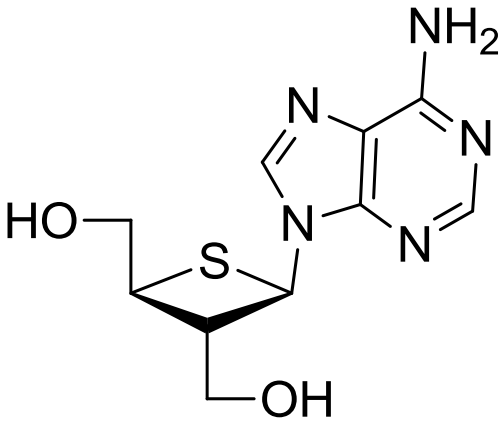
ABSTRACT

This chapter describes all the aspects of chemistry of mono cyclic Thietanes and Thietes. It is based on the literature, which appeared within the period 1996–2005. Thiete is a hetero cyclic compound containing an unsaturated four-member ed ring with three carbon atoms and one sulphur atom. The next three sections deal with the synthesis of mono cyclic Thietanes and Thiete rings. One of them describes syntheses from a cyclic compounds classified by number of ring atoms contributed by each component, the second the ring synthesized by transformation the act of changing in form or shape of other ring systems. The last section is about the biological and synthetic applications of mono cyclic Thietanes and Thietes.

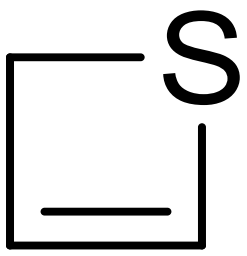
KEYWORDS: Thaitane, biological activities, lead molecules, synthetic schemes.

INTRODUCTION

Thiete is a hetero cyclic compound containing an unsaturated four-member ed ring with three carbon atoms and one sulphur atom. It is more commonly encountered not on its own, but in crenellated derivatives, several of which have been synthesized. Thietes are generally not very stable (CH2=CHCH. Thiete is a the phenomenon of forming chemical bond valence isomer of the unknown compound thioacrolein =S) Thiete has been shown to be planar, with a C-S-C angle of 76.8 degrees Benzothietes are Thietes annulled to benzo group. Such species are prepared by flash vacuum pyrolysis of 2-mercaptobenzyl alcohols. They are precursors to other S-hetero cyclic Most of these methods have been reviewed.29,30 Therefore, this review will cover the recent advances in the construction of this four member ed hetero cyclic reported in the Thiete 1,1-dioxides are sulfones, the parent being C3H4SO2. They are more stable than the parent Thietes. changeability by virtue of being replaceable Substituted thiete-1, 1-dioxides can also be prepared by [2+2] cyclo addition of sulfenes and ynamines. Synthesis of enantiomerically ether one of a pair of compound (crystals or molecules) pure 9 [(1′R, 2′R, 3′S)-bis (hydroxymethyl) thietan-1′-yl] adenine, 3′-thio analogue of oxetanocin A The enantiomerically pure synthesis of 9 [(1′R, 2′R, 3′S)-bis (hydroxymethyl) thietan-1′-yl] adenine 2, 3′-thio analogue of oxetanocin A, was achieved via coupling with sulfoxides 17 and 6-chloropurine in the presence of TMSOTf and Et3N under the Pummerer reaction conditions.



CHEMISTRY



Name: Thietes
IUPAC Name: 2H-thiete

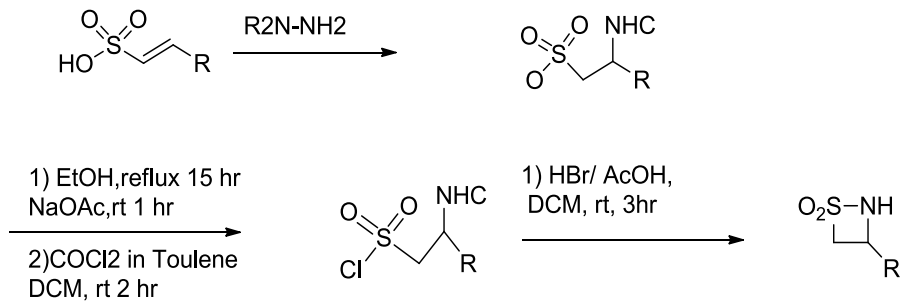
PROPERTIES

Chemical Formula: C_3H_4S
Molar Mass: 72.12886.

SYNTHESIS OF THIETES

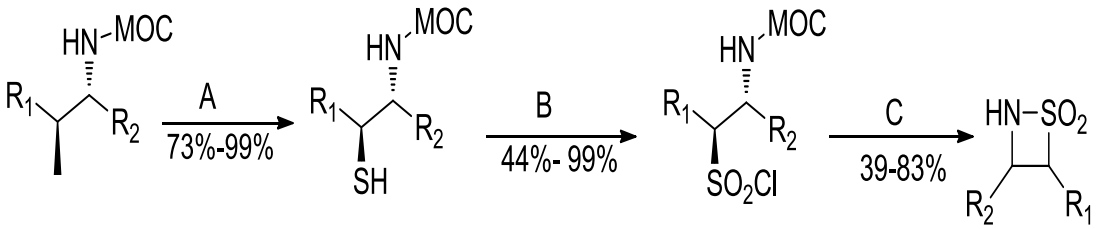
Scheme 1

One of the most reliable approaches to synthesize diastereomerically or enantiomerically pure heterocyclic is to introduce the chirality in an open chain precursor and subsequently close the ring in an intermolecular fashion. Enders et al. developed an asymmetric synthesis of 3-substituted β-sultams using this approach. The key step is the chiral synthesis of taurine derivatives from the Lewis acid catalyzed aza-Michael addition of an enantiomerically pure hydrazine to alkenylsulfonic esters, followed by cleavage of the chiral auxiliaries and protection of the amine to give the N-protected 1,2-aminosulfonate esters (Scheme 1). Deportation and ring closure gave the β-sultams.



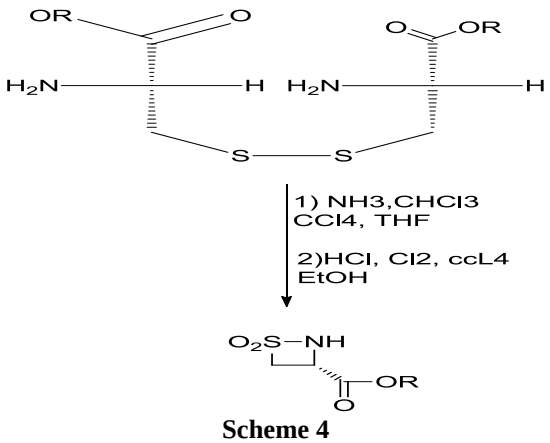
Scheme 2

With compounds in hand, the formation of the β-sultams ring was undertaken (Scheme 2). N-Protected 1, 2-amino thiol was obtained by cleavage of the Sbenzyl group of compounds with lithium in ammonia without epimerization. Subsequent oxidation of the thiol moiety with H2O2 in methanol with an excess of ammonium heptamolybdate, followed by direct conversion of the corresponding amino sulfonic acids to their sodium salts, and chlorination using a phosgene solution in toluene afforded the Nprotected 1,2-aminosulfonyl chlorides Finally, the ring closure was performed by cleavage of the Mock-protecting group with HBr-AcOH and in situ cyclisation with an excess of triethylamine, yielding the β-sultams with excellent diastereomeric and enantiomeric excesses.



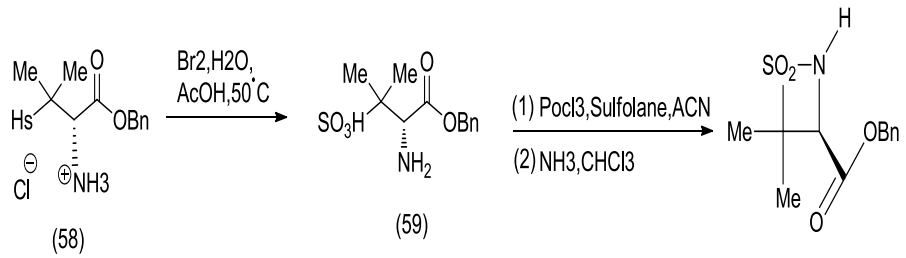
Scheme 3

The group also reported the synthesis of β-sultams from L-cystine dialkyl ester hydrochlorides, obtained from L-cystine, by oxidative chlorination (Scheme3).



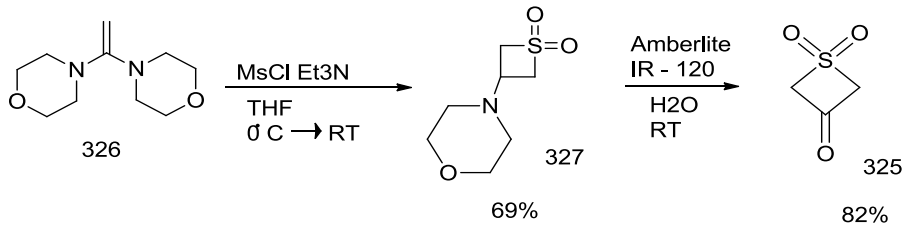
Scheme 4

Also synthesized the 4, 4-dimethyl-1, 2-thiazetidin-3-carboxylate 1, 1-dioxide from D-penicillamine benzyl ester hydrochloride (Scheme 4). Oxidation of compound with bromine in dilute acetic acid yielded the taurine derivative which, after chlorination with phosphorus oxychloride in acetonitrile and sulfolane, and subsequent cyclisation with triethylamine gave the enantiomerically pure β-sultams.



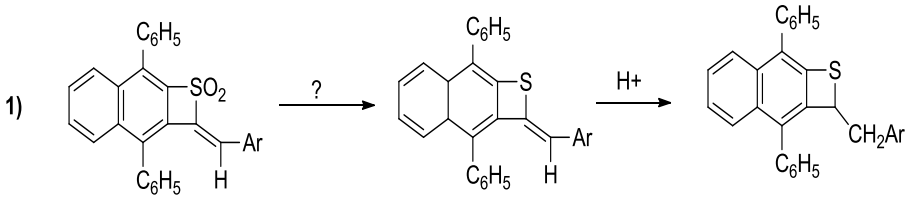
Scheme 5

Since the Thietanes and the corresponding sulfones were found to have intriguing properties in the drug discovery setting, we sought to further explore their chemistry. Oxetan-3-one was generally the preferred building block for the introduction of oxetane subunits onto molecular frameworks. Likewise, dioxothietan-3-one was believed to serve as an equally potent building block for the introduction of the thietan-S, S-dioxide unit. Its preparation was carried out according to a literature procedure (Scheme 5) 1, 1-Bis (morpholino) ethylene was treated with methanesulfonyl chloride and triethylamine (insitu formation of sulfide) to afford 3-morpholino-thiete-S, S-dioxide in 69% yield. Subsequent hydrolysis of the enamine was affected using acidic amberlite IR-120 in water; the desired dioxothietan-3-one was ob-tainted after filtering and lyophilizing the reaction mixture. The isolated compound was purified by bulb-to-bulb sublimation to afford pure product in 82% yield.



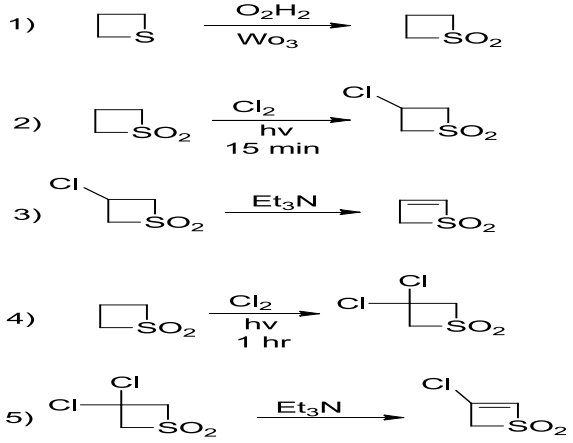
Scheme 6

This investigation into the condensation reaction of aromatic Aldehyde and Cyclic Foue-membered ring Sulfones was undertaken to prepare derivatives of Thietane Sulfones with unsaturation exocyclic to the ring. The reduction of the double bond or ring opening which occurs with thiete sulfones. Only 2,2-dimethyl-3,8-diphenyl-2H-naphtho [3,2-b] Thiete 1,1-dioxide and 2,2-dimethyl-3,10 diphenyl-2H-anthra- [3,2-b] Thiete 1,1-dioxide are reduced cleanly to the sulphides and these Thiete sulfones have no active methylene group.



Scheme 7

Preparation of Thiete 1, 1-dioxide and 3-Chlorothiete 1, 1-dioxide Thiete 1, 1-dioxide and 3-Chlorothiete 1, 1-dioxide could be produced through the following synthetic routes.



1) Thietane 1, 1-dioxide. The pH of a solution of tungstic acid in 280 mL of distilled water is adjusted to 11.5 by addition of 10% aqueous sodium hydroxide; the white suspension of the tungstate catalyst is added to a 1-L, round-bottomed flask fitted with a mechanical stirrer and a pressure-equalizing addition funnel. The tungstic acid–water mixture is cooled to 0–10°C by means of an ice–salt bath; glacial acetic acid (50 mL) and trim ethylene sulfide (Thietanes) are added. The chilled mixture is stirred, and 30% hydrogen peroxide (189 mL) is added carefully by means of the addition funnel over a period of 2 hr. The mixture is stirred at 0–10°C for an additional hour, transferred to an evaporating dish, and heated to near dryness on a steam bath. The chloroform solutions are combined and dried over anhydrous magnesium sulfate and the solvent is removed via a rotary evaporator to give a white solid.

2) 3-Chlorothietane 1, 1-dioxide. Thietane 1, 1-dioxide is placed in a three-necked, 500-mL, round-bottomed flask fitted with a magnetic stirrer, reflux condenser and a chlorine bubbler Carbon tetrachloride (300 mL) is added to the flask and the suspension is irradiated by a 250-W sunlamp positioned as close as possible to the reaction flask without touching it while chlorine is bubbled through the solution for 15 min at a moderate rate. A copious white precipitate forms and irradiation and addition of chlorine must be stopped at this point (or 10 min after the first appearance of a precipitate) to avoid dichlorination. The reaction mixture is cooled to room temperature

3) Thiete 1, 1-dioxide. A sample of 3-chlorothietane 1, 1-dioxide is dissolved in dry Toluene in a 500-mL, two-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, heating mantle (or silicone oil bath), and thermometer. The reaction is heated to 60°C and triethylamine (28.7 g, 0.28 mol, and 39.5 mL) is added through the condenser. The reaction mixture is stirred for 4 hr and triethylamine hydrochloride is removed by filtration and washed with toluene.

4) 3, 3-Dichlorothietane 1, 1-dioxide. Thietane 1, 1-dioxide is placed in a 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and chlorine gas bubble. Carbon tetrachloride (350 mL) is added and the solution is irradiated with a 250-W sunlamp while chlorine is bubbled through the stirred mixture for 1 hr.

5) 3-Chlorothiete 1, 1-dioxide. A solution of 3, 3-dichlorothietane 1, 1-dioxide (4.0 g, 0.023 mol) in toluene (150 mL) is placed in a 250-mL, round-bottomed, two-necked flask equipped with a heating mantle (or silicone oil bath), magnetic stirrer, reflux condenser, and thermometer. The solution is heated to 60°C and triethylamine is added drop wise through the condenser over a 10-min period. The solution is stirred for 2 hr at 60°C and cooled to room temperature.

BIOLOGICAL ACTIVITIES OF THIETES

Role of bacterial cell walls

A cell membrane, which is usually surrounded by a cell wall and sometimes by an additional outer layer. An internal cytoplasm with ribosome's, a nuclear region, and in some cases granules and/or vesicles. A variety of external structures, such as capsules, flagella, and pili. The rigid cell wall lies outside the cell membrane in nearly all bacteria. It performs two Important functions. First, it helps to maintain the characteristic shape of the cell. The cell.

Membrane is the osmotic barrier that allows the retention of nutrients and the exclusion of other Compounds. Second, it prevents the cell from bursting by allowing it to withstand a range of Harsh conditions such as various temperatures, pH and osmotic pressure. For example, Gram-positive and Gram-negative bacteria have internal osmotic pressures which are 10 to 30 times and 3 to 5 times the external osmotic pressure, respectively. The robust structure of the bacterial wall of both Gram-positive and Gram-negative species is due to the cross linking of linear polysaccharide chains by short segments of peptides called peptidoglycan.

MODE OF ACTION OF B-LACTAMS ANTIBIOTICS

Thiete is a valence isomer of the unknown compound thioacrolein =S) Thiete is a heterocyclic compound containing an unsaturated four-membered ring with three carbon atoms This project is concerned with the synthesis of β-lactams and β-sultams and the development of new routes for the synthesis of bi cyclic versions of these molecules as potential anti-bacterial agents. To understand how β-lac tams kill bacteria requires a little knowledge of how a bacterial cell wall is formed and why bacteria need cell walls. the Biological activity describes the beneficial or adverse effects of a drug on pertaining to living matter. When a one or more drug compound is a complex chemical mixtures this activity is exerted by the substance's active molecules ingredient or pharmacophore but can be modified by the other constituents. A primeval the difference various properties of chemical a union of one or more part pharmacological activity plays a important role since it suggests uses of the compounds in the medical applications the chemical compounds make visible some adverse and toxic effectively which may prevent their use in medical practice. Activity is generally dosage-dependent. it is common to have effects ranging from beneficial to adverse for one substance when going from low to high doses. That is an effective atoms and group of molecule a compound not only must be active against a target to the reference point but also possess the appropriate Absorption distribution metabolism and eliminated properties to make it is suitable for use as an a adapted for occasion drug molecules first the synthesis of 3-thioxo-β-sultams via the [2+2] cycloaddition of sullenness with isothiocyanates can be further investigated, e.g. the generation of sulfide at lowers

temperatures. The [2+2] cycloaddition of thioketenes with N-sulfonamides has not been explored and could Inoute to pyrrolizialkylation of 3-oxo-βsulfonyl group in the four-membered ring changed dramatically the reactivity of the double bond, thus impeding the access to bi cyclic β-sultams through a new route. The presence of the sulfonyl group also affected the reactivity of the carbonyl in 3-oxo-β-sultams since the thionation of those molecules remained unsuccessful whereas that of 1-azetines was smoothly perform chloride, to undergo a ring enlargement yielding a 1,2,3-oxathiazolin-2-oxide. A series of isothiazol-1, 1-dioxides was synthesized. Their olefinic double bond reacted di astereospecifically.

PHARMACOLOGICAL ACTIVITY OF THIETES:

The beneficial or adverse effects of a drug on living matter. When a drug is a complex chemical mixture the atomic process that occurs during a chemical reaction this activity is exerted by the substance's active ingredient or pharmacopoeia but can be modified by the other constituents the act of making something different Among the various properties of produce by molecule changes chemical compounds pharmacological and the biological activity plays of extreme mostly important to the resolution a crucial role since it suggests uses of the compounds in the medical applications. the chemical compounds or atoms may be adverse effect and which something is poisonous or harmful effects which may prevent their use in medical practice. Activity is generally dosage-dependent. Further, it is common to have effects ranging from beneficial to adverse for one substance when going from low to high doses. Activity depends a serious examination of critically on a completed to the perfection fulfillment of the absorption distribution metabolism and elimination or excretion (ADME) criteria. To be an capable or producing a intended result effective drug a compound not only must be active against a target, but also possess the appropriate ADME (Absorption, Distribution, Metabolism, and Excretion) properties necessary to the make it has suitable for use as a drug. Whereas a material is considered bio active if it has interaction with the effect on any cell tissue specialized cell in the human body similar and smaller Eukaryotic cell pharmacological activity is usually taken to describe beneficial effects i.e. the effects of drug candidates as well as a substance's toxicity damage an organism. the study of mineral molecules of the solid inorganic molecule and biological activity is often meant as the formation of a white element calcium phosphate deposits on the surface of objects placed in simulated body fluid, the pH adjustable solution with eclectically positive or negative charge ratio ion content similar to the body fluid like blood.

ANTIMICROBIAL ACTIVITIES OF THIETES

In recent years, the microbial resistance to traditional antibiotics has resulted in the emergence of many antibiotic-resistant strains of bacteria, prompting an urgent requirement for new classes of antibiotics. Alpha-helical and beta-sheet cat-ionic antimicrobial peptides have been proposed as potent candidates, having characteristics which includes the strong ability to kill target cells, a wide spectrum of activity against both gram- negative and gram-positive bacteria, activity Against pathogens resistant to traditional antibiotics, and a relative difficulty in selecting resistant mutants in vitro Although the how something is done the exact mode of action of antimicrobial peptides combining the amino group of one amino acid with the carboxylic group has not been established, all cat-ionic amphipathic related to amphitheater peptides interact with membranes and it has been proposed that the cytoplasmic membrane that is the relating the cytoplasm is the main target a practice range for target practice of some peptides, whereby the act of gathering peptide accumulation in the membrane causes increased permeability and a loss of barrier function Recently, factors believed to be important for antimicrobial activity have been identified, including peptide hydrophobicity the property of being water repellent the presence of positively charged residues, an amphipathic nature that segregates basic and hydrophobic residues.

CONCLUSION

The mono cyclic Thietanes and Thiete rings. One of them describes syntheses from a cyclic compounds of a substance formed by the chemical of two or more element or groups in definitely classified by number of ring atoms contributed by each component, the second the ring synthesis by transformation of other ring systems. Some 1-azetines have been synthesized and reacted successfully with di phenylcyclopropenone and nitrile oxides to afford the corresponding bi cyclic compounds. The thermolysis of the strained cycloadducts (or their reaction with dimethylacetylene dicarboxylate where appropriate) released the strain of the four member ed ring to afford five- and six-membered heterocyclic such as 1, 2, 4-oxadiazoles, a pyridine, and a pyrimidine. the same fashion, one example of 3,4-dihydro-2H-pyrrole was synthesized and reacted with diphenylcyclopropenone to open a new r dines, a five-fused heterocyclic present in a wide range of alkaloids. 1, 2-Thiazetin-1, 1-dioxides, the sulfonyl analogues of 1-azetines, were also synthesized via the -sultams and via the ring contraction of an isothiazol-1, 1-dioxide. Unfortunately marked by or in resulting in bad luck, they failed to react with DPP, nitrile oxides any of a class of organic compound containing the cyano radical (CNO) or dienes. The introduction of the Sued However, 3-di ethyl amino-1,2-thiazetin-1,1-dioxide reacted with a Lewis acid, zinc ch with nitrile oxides, a nitrile i mine and an a chemical compound containing the azido group combined with an element or radical that is azide to give the corresponding bicycles, thus forming two new stereogenic centers. Two isothiazolin-1, 1-dioxides lacking the olefinic double bond failed to react with DPP and 1, 3-dipoles, thus confirming the lack of Reactivity of the sulfonamides moiety observed with 1, 2-thiazetin-1, 1-dioxides. unsubstantiated and N-acylated β- and γ-

sultams were synthesized and assessed as taurine prodrugs in laboratory Alzheimer and alcohol detoxification models.

ACKNOWLEDGEMENT

The author's grateful wish to express their gratitude to Emcure Pharmaceutical Pvt. Ltd., Pune. and the authors are also wish to my friends and my Brothers. For the samples of pure Compound. The authors are also thankful to the Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Maharashtra. For the providing all the facilities to carry out the research work successfully.

REFERENCES

1. Lesniak S, Lewkowski J, Kudelska W, Zając A, "Thietanes and Thietes: Monocyclic". Comprehensive Heterocyclic Chemistry-III, 2008; 2: 389–428.
2. Dittmer DC, Patwardhan BH, Bartholomew JT, "Thietes and Derivatives". Sci. Synth., 2007; 33: 187–202.
3. Sedergran TC, Yokoyama M, Dittmer DC, Block E, DeWang M, "Thietanes and Thietes: Monocyclic". Comprehensive Heterocyclic Chemistry II, 1996; 1(24): 773–802.
4. Dittmer DC, Davis FA, Young DJ, "Evidence for a Thiete (Thiacyclobutene)". J. Chem., 1965; 87(9): 2064–2065.
5. Butkevich AN, Sokolov VV, Tomashevskii AA, Potekhin AA, Chem. of Heterocyclic Comp., 2007; 43(3): 544-568.
6. Takahashi K, Dittmer DC, Davis FA, Thiets, Thiacyclobutane, 1967; 8(41): 4061-4063.
7. Gotthardt H, Nieberl S, Thiones with Photochemical and Thermal Reaction. Swptember, 1976; 17(39): 3563-3566.
8. Donald M, Dittmer C, Peter LF, Franklin C, Davis a, Derivatives of Thiacyclobutene, Thiete, Journal of Org. Chem., 2002; 37(8): 10.21-10.27.
9. Franklin C, Davis A, Awad SB, Robert H, Jenkins Jr, Robert L, Billmers, Linda A, Jenkins Synthesis of Thiete sulfoxides J. Org. Chem., 1983; 48(18): 3071–3074.
10. Chen Y, Guarneri MT, Vasil AI, Vasil ML, Mant CT, Hodges RS, Role of peptide hydrophobicity in the mechanism of action of alpha-helical antimicrobial peptides. Antimicrobial agents and chemotherapy, 2007; 51(1): 398-406.
11. Chen Y, Mant CT, Farmer SW, Hancock RE, Vasil ML, Hodges RS, Rational design of alpha-helical antimicrobial peptides with enhanced activities and specificity/therapeutic index. The Journal of biological chemistry, 2005; 280(123): 16-29.