

SYNTHESIS OF 4H-1,4-BENZOTHAZINES SULFONES

Dr. Vibha Shrivastav & Dr. Savita Choudhary

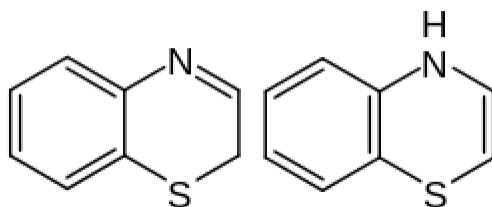
Associate Professor, S.K.Govt College, Sikar, Rajasthan, India

ABSTRACT: The present article describes the synthesis of new 4H-1,4-benzothiazines via condensation and oxidative cyclization of substituted 2-aminobenzenethiols with β -diketones/ β -ketoesters in dimethyl sulfoxide. The oxidation of these synthesized 4H-1,4-benzothiazines with 30% hydrogen peroxide in glacial acetic acid yielded 4H-1,4-benzothiazine sulfones and the reaction of these synthesized benzothiazines with sugar (β -D-ribofuranose-1-acetate-2,3,5-tribenzoate) afforded the new ribofuranosides. These compounds were evaluated for their antioxidant and antimicrobial activities (using broth microdilution method). The structural assignments of the synthesized compounds were made on the basis of elemental analyses and spectroscopic data.

KEYWORDS: 4H-1,4 benzothiazines, sulfones, condensation, cyclization, oxidative, sugar, antimicrobial activities

I. INTRODUCTION

Some novel analogs of 4H-1,4-benzothiazines were synthesized under environmentally benign solvent free conditions by one pot oxidative cyclocondensation of substituted 2-aminobenzenethiols with compounds having active methylene group and then converted in to sulfones.¹ These compounds were examined as antitubercular agents against Mycobacterium tuberculosis H37Rv using REMA plate method. The best results have MICs from 6.4 to 8.8 μ g/mL, comparable to phenothiazines. IR, NMR and mass spectral investigations are included for structural elucidation. Benzothiazine is a heterocyclic compound consisting of a benzene ring attached to the 6-membered heterocycle thiazine. The name is applied to both the 2H- and 4H-isomers of the molecule. 2,1-Benzothiazine, a type of benzothiazines was first reported in the 1960s. Subsequently, their preparation and intensive biological and physiological studies have been reported. In recent years, 2,1-benzothiazines have been of enormous interest to synthetic chemists.² An enantioselective synthesis of such benzothiazines has been developed by Harmata and Hong who have formulated transformations of these compounds designed to target chiral, non-racemic building blocks as well as natural products.³



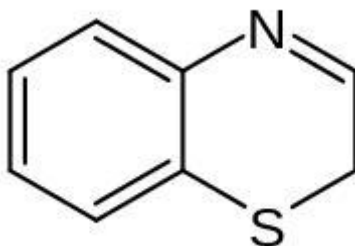
2-H isomer

4-H isomer

International Journal of Innovative Research in Science, Engineering and Technology

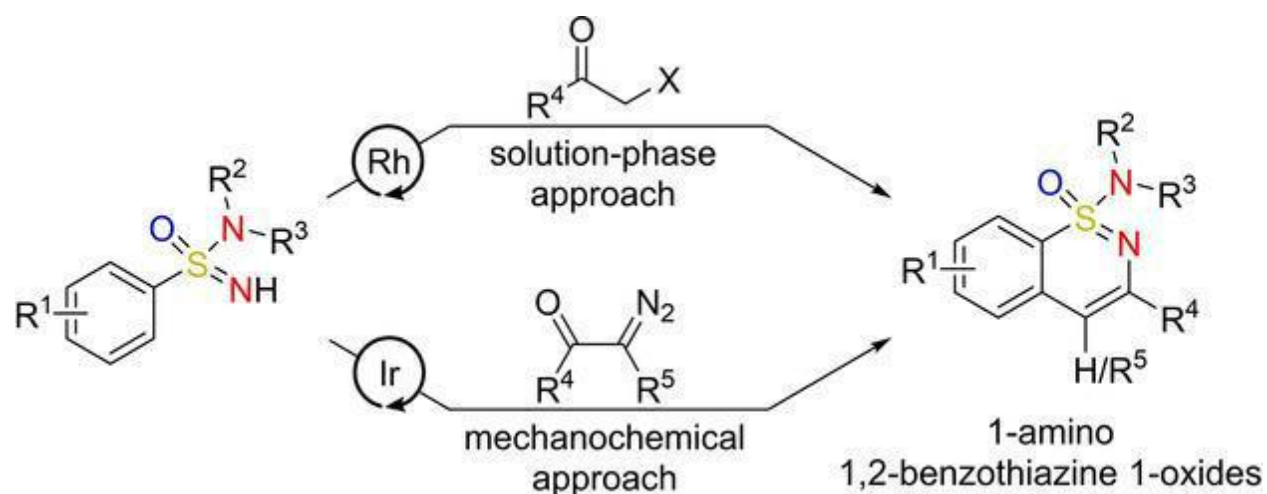
(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015



1,4-benzothiazines

In organic chemistry, a sulfone is a organosulfur compound containing a sulfonyl ($R-S(=O)_2-R'$) functional group attached to two carbon atoms. The central hexavalent sulfur atom is double-bonded to each of two oxygen atoms and has a single bond to each of two carbon atoms, usually in two separate hydrocarbon substituents.



By oxidation of thioethers and sulfoxides

Sulfones are typically prepared by organic oxidation of thioethers, often referred to as sulfides. Sulfoxides are intermediates in this route.^[2] For example, dimethyl sulfide oxidizes to dimethyl sulfoxide and then to dimethyl sulfone.^[1]

Sulfur dioxide is a convenient and widely used source of the sulfonyl functional group. Specifically, Sulfur dioxide participates in cycloaddition reactions with dienes.^[3] The industrially useful solvent sulfolane is prepared by addition of sulfur dioxide to buta-1,3-diene followed by hydrogenation of the resulting sulfolene.^[4]

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

From sulfonyl and sulfonyl halides

Sulfones are prepared under conditions used for Friedel–Crafts reactions using sources of RSO_2^+ derived from sulfonyl halides and sulfonic acid anhydrides. Lewis acid catalysts such as AlCl_3 and FeCl_3 are required.^{[5][6][7]}

Sulfones have been prepared by nucleophilic displacement of halides by sulfinates.^[8]

Reactions⁴

Sulfone is a relatively inert functional group, being weakly basic (compared to sulfoxides). They are non-oxidizing. In the Ramberg–Bäcklund reaction and the Julia olefination, sulfones are converted to alkenes by the elimination of sulfur dioxide.^[9]

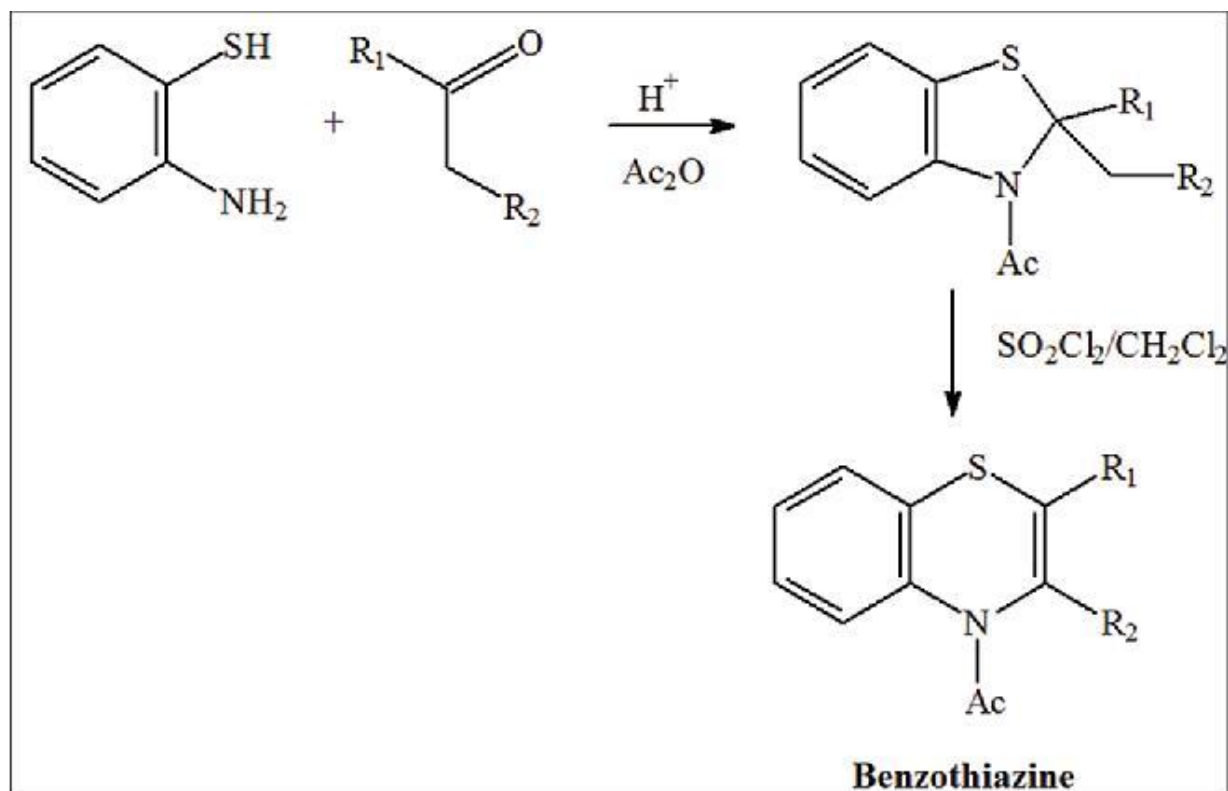


Fig. 1: Synthesis of benzothiazine from ring expansion reaction of benzothiazoline

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

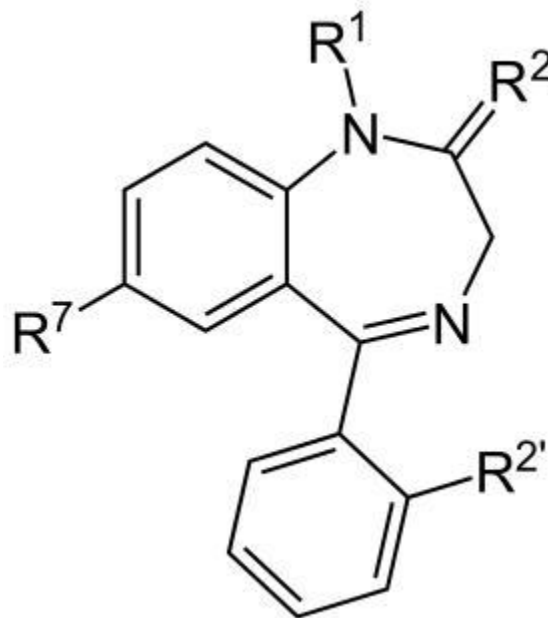
Sulfolane is used to extract valuable aromatic compounds from petroleum.^[4] Polymers

Some polymers containing sulfone groups are useful engineering plastics. They exhibit high strength and resistance to oxidation, corrosion, high temperatures, and creep under stress. For example, some are valuable as replacements for copper in domestic hot water plumbing.^[10] Precursors to such polymers are the sulfones bisphenol S and 4,4'-dichlorodiphenyl sulfone.⁵

Examples of sulfones in pharmacology include dapsone, a drug formerly used as an antibiotic to treat leprosy, dermatitis herpetiformis, tuberculosis, or pneumocystis pneumonia (PCP). Several of its derivatives, such as promin, have similarly been studied or actually been applied in medicine, but in general sulfones are of far less prominence in pharmacology than for example the sulfonamides⁶

II. DISCUSSION

Benzodiazepines (BZD, BDZ, BZs), colloquially called "benzos", are a class of depressant drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. They are prescribed to treat conditions such as anxiety disorders, insomnia, and seizures. The first benzodiazepine, chlordiazepoxide (Librium), was discovered accidentally by Leo Sternbach in 1955 and was made available in 1960 by Hoffmann-La Roche, who soon followed with diazepam (Valium) in 1963.^[1] By 1977, benzodiazepines were the most prescribed medications globally; the introduction of selective serotonin reuptake inhibitors (SSRIs), among other factors, decreased rates of prescription, but they remain frequently used worldwide.^{[2][3]}



Benzodiazepines are depressants that enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA_A receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties. High doses of many shorter-acting benzodiazepines may also cause anterograde

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

amnesia and dissociation.^[4] These properties make benzodiazepines useful in treating anxiety, panic disorder, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures.^[5] Benzodiazepines are categorized as short, intermediate, or long-acting.^[6] Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety.^[6]

Benzodiazepines are generally viewed as safe and effective for short-term use—about two to four weeks^[7]—although cognitive impairment and paradoxical effects such as aggression or behavioral disinhibition can occur. A minority of people have reactions after taking benzodiazepines such as worsened agitation or panic.^[8] Benzodiazepines are associated with an increased risk of suicide due to aggression, impulsivity, and negative withdrawal effects.^[9] Long-term use is controversial because of concerns about decreasing effectiveness, physical⁸ dependence, benzodiazepine withdrawal syndrome, and an increased risk of dementia and cancer.^{[10][11][12][15]} The elderly are at an increased risk of both short- and long-term adverse effects,^{[14][15]} and as a result, all benzodiazepines are listed in the Beers List of inappropriate medications for older adults.^[16] There is controversy concerning the safety of benzodiazepines in pregnancy. While they are not major teratogens, uncertainty remains as to whether they cause cleft palate in a small number of babies and whether neurobehavioural effects occur as a result of prenatal exposure;^[17] they are known to cause withdrawal symptoms in the newborn.⁹

Taken in overdose, benzodiazepines can cause dangerous deep unconsciousness, but they are less toxic than their predecessors, the barbiturates, and death rarely results when a benzodiazepine is the only drug taken. Combined with other central nervous system (CNS) depressants such as alcohol and opioids, the potential for toxicity and fatal overdose increases significantly.^{[18][19]} Benzodiazepines are commonly used recreationally and also often taken in combination with other addictive substances,¹⁰ and are controlled in most countries.^{[20][21][22]}

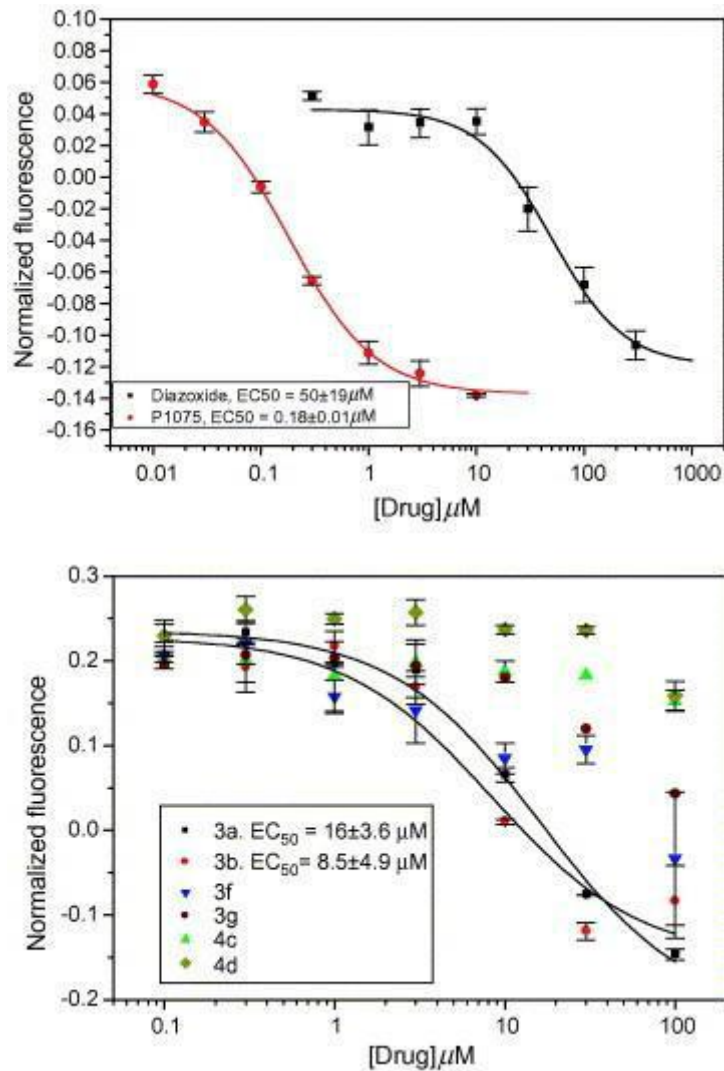
III. RESULTS

Benzodiazepines possess psycholeptic, sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnesic actions,^{[4][5]} which are useful in a variety of indications such as alcohol dependence, seizures, anxiety disorders, panic, agitation, and insomnia. Most are administered orally; however, they can also be given intravenously, intramuscularly, or rectally.^[23]

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015



In general, benzodiazepines are well tolerated and are safe and effective drugs in the short term for a wide range of conditions.^{[24][25]} Tolerance can develop to their effects and there is also a risk of dependence, and upon discontinuation a withdrawal syndrome may occur. These factors, combined with other possible secondary effects after prolonged use such as psychomotor, cognitive, or memory impairments, limit their long-term applicability. The effects of long-term use or misuse include the tendency to cause or worsen cognitive deficits, depression, and anxiety.^{[14][15]} The College of Physicians and Surgeons of British Columbia recommends discontinuing the usage of benzodiazepines in those on opioids and those who have used them long term. Benzodiazepines can have serious adverse health outcomes, and these findings support clinical and regulatory efforts to reduce usage, especially in combination with non-benzodiazepine receptor agonists.¹¹ Because of their effectiveness, tolerability, and rapid onset of anxiolytic action, benzodiazepines are frequently used for the treatment of anxiety associated with panic

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

disorder. However, there is disagreement among expert bodies regarding the long-term use of benzodiazepines for panic disorder. The views range from those holding benzodiazepines are not effective long-term¹ and should be reserved for treatment-resistant cases to those holding they are as effective in the long term as selective serotonin reuptake inhibitors (SSRIs).¹²

The American Psychiatric Association (APA) guidelines^[33] note that, in general, benzodiazepines are well tolerated, and their use for the initial treatment for panic disorder is strongly supported by numerous controlled trials. APA states that there is insufficient evidence to recommend any of the established panic disorder treatments over another.

The choice of treatment between benzodiazepines, SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and psychotherapy should be based on the patient's history, preference, and other individual characteristics.¹³ Selective serotonin reuptake inhibitors are likely to be the best choice of pharmacotherapy for many patients with panic disorder, but benzodiazepines are also often used, and some studies suggest that these medications are still used with greater frequency than the SSRIs. One advantage of benzodiazepines is that they alleviate the anxiety symptoms much faster than antidepressants, and therefore may be preferred in patients for whom rapid symptom control is critical.¹⁴ However, this advantage is offset by the possibility of developing benzodiazepine dependence. APA does not recommend benzodiazepines for persons with depressive symptoms or a recent history of substance use disorder. The APA guidelines state that, in general, pharmacotherapy of panic disorder should be continued for at least a year,¹⁵ and that clinical experience supports continuing benzodiazepine treatment to prevent recurrence. Although major concerns about benzodiazepine tolerance and withdrawal have been raised, there is no evidence for significant dose escalation in patients using benzodiazepines long-term. For many such patients, stable doses of benzodiazepines retain their efficacy over several years.¹⁶

Guidelines issued by the UK-based National Institute for Health and Clinical Excellence (NICE), carried out a systematic review using different methodology and came to a different conclusion. They questioned the accuracy of studies that were not placebo-controlled. And, based on the findings of placebo-controlled studies, they do not recommend use of benzodiazepines beyond two to four weeks, as tolerance and physical dependence develop rapidly, with withdrawal symptoms including rebound anxiety occurring after six weeks or more of use.^{[31][34]} Nevertheless, benzodiazepines are still prescribed for long-term treatment of anxiety disorders, although specific antidepressants and psychological therapies are recommended as the first-line treatment options with the anticonvulsant drug pregabalin indicated as a second- or third-line treatment and suitable for long-term use.¹ NICE stated that long-term use of benzodiazepines for panic disorder with or without agoraphobia is an unlicensed indication, does not have long-term efficacy, and is, therefore, not recommended by clinical guidelines. Psychological therapies such as cognitive behavioural therapy are recommended as a first-line therapy for panic disorder; benzodiazepine use has been found to interfere with therapeutic gains from these therapies.¹⁷

Benzodiazepines are usually administered orally; however, very occasionally lorazepam or diazepam may be given intravenously for the treatment of panic attacks.^[23]

Benzodiazepines have robust efficacy in the short-term management of generalized anxiety disorder (GAD), but were not shown effective in producing long-term improvement overall.^[36] According to National Institute for Health and Clinical Excellence (NICE), benzodiazepines can be used in the immediate management of GAD, if necessary. However, they should not usually be given for longer than 2–4 weeks. The only medications NICE recommends for the longer term management of GAD are antidepressants.

Likewise, Canadian Psychiatric Association (CPA) recommends benzodiazepines alprazolam, bromazepam, lorazepam, and diazepam only as a second-line choice, if the treatment

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

with two different antidepressants was unsuccessful. Although they are second-line agents, benzodiazepines can be used for a limited time to relieve severe anxiety and agitation. CPA guidelines note that after 4–6 weeks the effect of benzodiazepines may decrease to the level of placebo, and that benzodiazepines are less effective than antidepressants in alleviating ruminative worry, the core symptom of GAD. However, in some cases, a prolonged treatment with benzodiazepines as the add-on to an antidepressant may be justified.¹⁸

A 2014 review found a larger effect with medications than talk therapy.^[39] Medications with benefit include serotonin-noradrenaline reuptake inhibitors, benzodiazepines, and selective serotonin reuptake inhibitors.

IV. CONCLUSIONS

Benzodiazepines are sometimes used in the treatment of acute anxiety, as they bring about rapid and marked relief of symptoms in most individuals; however, they are not recommended beyond 2–4 weeks of use due to risks of tolerance and dependence and a lack of long-term effectiveness. As for insomnia, they may also be used on an irregular/"as-needed" basis, such as in cases where said anxiety is at its worst. Compared to other pharmacological treatments, benzodiazepines are twice as likely to lead to a relapse of the underlying condition upon discontinuation.

¹⁹ Psychological therapies and other pharmacological therapies are recommended for the long-term treatment of generalized anxiety disorder. Antidepressants have higher remission rates and are, in general, safe and effective in the short and long term.^[31] Benzodiazepines can be useful for short-term treatment of insomnia. Their use beyond 2 to 4 weeks is not recommended due to the risk of dependence.²⁰ The Committee on Safety of Medicines report recommended that where long-term use of benzodiazepines for insomnia is indicated then treatment should be intermittent wherever possible. It is preferred that benzodiazepines be taken intermittently and at the lowest effective dose. They improve sleep-related problems by shortening the time spent in bed before falling asleep, prolonging the sleep time, and, in general, reducing wakefulness.^{[41][42]} However, they worsen sleep quality by increasing light sleep and decreasing deep sleep. Other drawbacks of hypnotics, including benzodiazepines, are possible tolerance to their effects, rebound insomnia, and reduced slow-wave sleep and a withdrawal period typified by rebound insomnia and a prolonged period of anxiety and agitation.²¹

The list of benzodiazepines approved for the treatment of insomnia is fairly similar among most countries, but which benzodiazepines are officially designated as first-line hypnotics prescribed for the treatment of insomnia varies between countries. Longer-acting benzodiazepines such as nitrazepam and diazepam have residual effects that may persist into the next day and are, in general, not recommended.²²

Since the release of non benzodiazepines in 1992 in response to safety concerns, individuals with insomnia and other sleep disorders have increasingly been prescribed nonbenzodiazepines (2.3% in 1993 to 13.7% of Americans in 2010), less often prescribed benzodiazepines (23.5% in 1993 to 10.8% in 2010).²³ It is not clear as to whether the new non benzodiazepine hypnotics (Z-drugs) are better than the short-acting benzodiazepines. The efficacy of these two groups of medications is similar.²⁴ According to the US Agency for Healthcare Research and Quality, indirect comparison indicates that side-effects from benzodiazepines may be about twice as frequent as from nonbenzodiazepines.²⁵ Some experts suggest using nonbenzodiazepines preferentially as a first-line long-term treatment of insomnia.^[42] However, the UK National Institute for Health and Clinical Excellence did not find any convincing evidence in favor of Z-drugs. NICE review pointed out that short-acting Z-drugs were inappropriately compared in clinical trials with long-acting benzodiazepines. There have been no trials comparing short-acting Z-drugs with appropriate doses of short-acting benzodiazepines. Based on this, NICE recommended choosing the hypnotic based on cost and the patient's preference.²⁶

Older adults should not use benzodiazepines to treat insomnia unless other treatments have failed.^[47] When benzodiazepines are used, patients,²⁷ their caretakers, and their physician should discuss the increased risk of harms,

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

including evidence that shows twice the incidence of traffic collisions among driving patients, and falls and hip fracture for older patients.²⁷

REFERENCES

- 1) Sulfostryl (2,1-benzothiazine 2,2-dioxide). I. Preparation and reactions of 3,4-dihydrosulfostryl. Loev, B.; Kormendy, M.F. J. Org. Chem. 1965, 30, 3163.
- 2) Recent Progress in the Chemistry of 2,1-Benzothiazines. Hong, X.; Harmata, M. Progress in Heterocyclic Chemistry, Chapter 1, G. W. Gribble and J. A. Joule, eds, Pergamon Press, Vol 19, pp 1-43 (2008)
- 3) The Intramolecular, Stereoselective Addition of Sulfoximine Carbanions to α , β -Unsaturated Esters. Harmata, M.; Hong, X. Journal of the American Chemical Society, 2003, 125(19), 5754-5756.
- 4) Benzothiazines in Synthesis. A Total Synthesis of Pseudopteroxazole. Harmata, M.; Hong, X. Organic Letters, 2005, 7(16), 3581-3583.
- 5) Hornback, Joseph (2006). Organic Chemistry. Australia: Thomson Brooks/Cole. ISBN 978-0-534-38951-2.
- 6) ^ Leo A. Paquette, Richard V. C. Carr (1986). "Phenyl Vinyl Sulfone and Sulfoxide". Org. Synth. 64: 157. doi:10.15227/orgsyn.064.0157.
- 7) ^ Robert L. Frank and Raymond P. Seven (1949). "Isoprene Cyclic Sulfone". Org. Synth. 29: 59. doi:10.15227/orgsyn.029.0059.
- 8) ^ Folkins, Hillis O. Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH.
- 9) ^ Truce, W. E.; Vriesen; C. W. (1953). "Friedel—Crafts Reactions of Methanesulfonyl Chloride with Benzene and Certain Substituted Benzenes". J. Am. Chem. Soc. 75 (20): 5032–5036. doi:10.1021/ja01116a043.
- 10) ^ Répichet, S.; Le Roux, C.; Hernandez, P.; Dubac, J.; Desmurs, J. R. (1999). "Bismuth(III) Trifluoromethanesulfonate: An Efficient Catalyst for the Sulfonylation of Arenes". The Journal of Organic Chemistry. 64 (17): 6479–6482. doi:10.1021/jo9902603.
- 11) ^ Truce, W. E.; Millionis, J. P. (1952). "Friedel-Crafts Cyclization of ω -Phenylalkanesulfonyl Chlorides". J. Am. Chem. Soc. 74 (4): 974–977. doi:10.1021/ja01124a031.
- 12) ^ C. W. Ferry, J. S. Buck, R. Baltzly (1942). "4,4'-Diaminodiphenylsulfone". Org. Synth. 22: 31. doi:10.15227/orgsyn.022.0031.
- 13) ^ Carey, Francis A.; Sundberg, Richard J. (2007). Advanced Organic Chemistry. Berlin: Springer. ISBN 978-0-387-68354-6.
- 14) ^ Fink, Johannes (2008). High Performance Polymers. Norwich: William Andrew. ISBN 978-0-8155-1580-7.
- 15) ^ Thomas L. Lemke (2008). Foye's Principles of Medicinal Chemistry. Lippincott Williams & Wilkins. p. 1142. ISBN 9780781768795. Archived from the original on 2014-03-04.
- 16) ^ Craig, Charles R.; Stitzel, Robert E. (2004). Modern Pharmacology with Clinical Applications. Hagerstown: Lippincott Williams & Wilkins. ISBN 978-0-7817-3762-3.
- 17) ^ Drill, Victor Alexander; Di Palma, Joseph R. (1971). Drill's Pharmacology in Medicine. New York: McGraw-Hill. ISBN 978-0-07-017006-3.
- 18) Shorter E (2005). "Benzodiazepines". A Historical Dictionary of Psychiatry. Oxford University Press. pp. 41–42. ISBN 978-0-19-517668-1.
- 19) ^ Balon R, Starcevic V, Silberman E, Cosci F, Dubovsky S, Fava GA, et al. (2013-03-09). "The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed". Revista Brasileira de Psiquiatria. 42 (3): 243–244. doi:10.1590/1516-4446-2013-0773. PMC 7236156. PMID 32159714.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 4, Issue 9, September 2015

- 20) ^ Treating Alcohol and Drug Problems in Psychotherapy Practice Doing What Works. New York: Guilford Publications. 2011. p. 47. ISBN 9781462504381.
- 21) ^ Page C, Michael C, Sutter M, Walker M, Hoffman BB (2002). Integrated Pharmacology (2nd ed.). C.V. Mosby. ISBN 978-0-7234-3221-0.
- 22) ^ Olkkola KT, Ahonen J (2008). "Midazolam and other benzodiazepines". In Schüttler J, Schwilden H (eds.). Modern Anesthetics. Handbook of Experimental Pharmacology. Vol. 182. pp. 335–360. doi:10.1007/978-3-540-74806-9_16. ISBN 978-3-540-72813-9. PMID 18175099.
- 23) ^ Dikeos DG, Theleritis CG, Soldatos CR (2008). "Benzodiazepines: effects on sleep". In Pandi-Perumal SR, Verster JC, Monti JM, Lader M, Langer SZ (eds.). Sleep Disorders: Diagnosis and Therapeutics. Informa Healthcare. pp. 220–222. ISBN 978-0-415-43818-6.
- 24) ^ Ashton H (May 2005). "The diagnosis and management of benzodiazepine dependence". Current Opinion in Psychiatry. 18 (3): 249–255. doi:10.1097/01.yco.0000165594.60434.84. PMID 16639148. S2CID 1709063.
- 25) ^ Saïas T, Gallarda T (September 2008). "[Paradoxical aggressive reactions to benzodiazepine use: a review]". L'Encéphale (in French). 34 (4): 330–336. doi:10.1016/j.encep.2007.05.005. PMID 18922233.
- 26) ^ Dodds TJ (March 2013). "Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature". The Primary Care Companion for CNS Disorders. 19 (2). doi:10.4088/PCC.16r02037. PMID 28257172.
- 27) ^ Lader M (2008). "Effectiveness of benzodiazepines: do they work or not?". Expert Review of Neurotherapeutics (PDF). 8 (8): 1189–1191. doi:10.1586/14737175.8.8.1189. PMID 18671662. S2CID 45155299.