



Our Heritage(UGC Care Listed)
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A Simple Synthesis Of New 2, 3-Dihydro-1H-1,5-Benzodiazepine Derivatives Using Symmetrical And Unsymmetrical Diamines

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Abstract :


Benzodiazepines are widely used drugs for several indications. This study provides, on the one hand, a global vision of this family starting for their fortuitous discovery, the synthesis of their derivatives, their mechanism of action which is well known nowadays, the actual classification according to the chemical structure and the pharmacokinetic properties and their uses and indications, including the traditional and the new ones. Synthesis of 2,3-dihydro-1H-1,5-benzodiazepine derivatives using symmetrical and unsymmetrical diamines and substituted ketones in presence of zirconium tetrachloride as a catalyst to obtain number of 1,5-benzodiazepine derivatives in very good yields.

Key Words :

Symmetrical and unsymmetrical diamines, zirconium chloride, 1,5-benzodiazepine.

Introduction :

Since their introduction over 30 years ago, benzodiazepines have largely replaced older sedative-hypnotic agents in most countries. Because these drugs are used primarily for their therapeutic effects, abuse and misuse of benzodiazepines are best conceptualized in the context of their appropriate use. Research has of course continued in the effort to develop new anxiolytics with lesser sedative effects or liability for abuse. The most fruitful of these efforts have continued to focus on the benzodiazepine receptor system. In the context of what is known


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about established benzodiazepines, will consider some newer sedative/anxiolytic drugs (i.e., zopiclone, zolpidem, abecarnil, and bretazenil) that act on the benzodiazepine receptor.

Many of the drugs that had represented a great advance in many therapeutic approaches were not the result of a rational design but of a consequence of casual observations, fortuitous discoveries or serendipity. Way back then, a rational design didn't guarantee the exit because the knowledge of the biological systems was not clear or complete. That happened in the beginning of the past century and many of the drugs used nowadays come from this type of discovery, from the curiosity of many investigators that decided to study the reason why they were not achieving their goals.

Discovery starts with chemist Leo Sternbach and his research group, working in the Hoffman-La Roche laboratories in Nutley, New Jersey. They were trying to find new tranquilizers but, due to the limited knowledge of the processes occurring in the brain, they were taking an empirical approach: to search for a new class of drugs purely guided by modifications in the known chemical synthesis.¹ In 1957, they serendipitously identified chlorodiazepoxide, the first benzodiazepine (BZD), while they were studying the activity of quinazoline oxide. They saw that the compound obtained was not a quinazoline-N3 -oxide but a benzodiazepine-N4 - oxide. With a posterior investigation, Sternbach himself managed to explain what happened.²

By 1960, Hoffmann-La Roche introduced the chlorodiazepoxide in clinical treatment under the brand name Librium® and it pursued molecular modifications to improve its activity. By the time of its introduction, it was felt that an explanation of the BZDs mechanism of action might be really helpful to understand the basis of anxiety. Diazepam (Valium®) followed in 1963, which was considered for a long time as the Head of the family. Initially, BZDs appeared to be less toxic and less prone to cause dependence than older drugs used for the same purposes as barbiturates. An important improvement compared to barbiturates was their lack of respiratory depression, an important safety concern.³ Medical professionals accepted benzodiazepines enthusiastically at first, increasing their popularity and patient demand. BZDs were prescribed frequently and often long-term for various conditions. Soon they became the pharmacological family par excellence in the treatment of anxiety disorders and so initiating "the benzodiazepine



saga".⁴ The binding of a BZD to his binding site cause an increment of the GABA affinity for its own binding site. They act as a positive allosteric modulator: the union of the BZD to the receptor does not alter the GABA union, but it increases the total conduction of chloride ions across the neuronal cell membrane. This increment of chloride ions leads to a hyperpolarization of the neuron, and as a result, a decrease of the neuronal activity.⁵

In 1975, BZDs were placed on the Food and Drug Administration (FDA) restricted drug list, reflecting growing concerns about abuse. After years of patients and clinicians reporting tolerance and withdrawal with long-term use, several controlled trials in the 1980s confirmed that BZDs could cause dependence.⁶ With growing data and warnings about BZDs as well as the arrival of safer, more effective anti-anxiety medications like selective serotonin reuptake inhibitors (SSRIs), BZD use slowly declined after the mid-1980s. Despite recommendations against long-term BZD use (more than 2–4 weeks), many providers continued to prescribe them for months or even years, allowing for dependence to occur. Total BZD use actually increased from 1999 to 2014, largely driven by increases in long-term use.⁷

Intentional abusers of BZD usually have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse, used mainly to augment the "high" received from another drug or to offset the adverse effects of other drugs. Few cases of addiction are originated from legitimate use of benzodiazepines. On August 31, 2016, FDA issued a drugsafety communication about serious risks, including death, when opioid pain or cough medicines are combined with benzodiazepines. The safety announcement warned that "health care professionals should limit prescribing opioid pain medicines with benzodiazepines... only to patients for whom alternative treatment options are inadequate".⁸

Pharmacologic dependence is a predictable and natural adaptation of the body when it is long accustomed to the presence of a drug and may occur even in patients taking therapeutic doses of BZD. However, this dependence, which generally manifests itself in withdrawal symptoms upon the abrupt discontinuation of the medication, may be controlled and ended through dose tapering, medication switching, and/or medication augmentation.⁹ Later, cases of Z-drugs reports causing visual hallucinations and amnesia in people with no history of mental disease appeared.



Although the mechanism of action to describe these phenomena is not clear, it is speculated that “GABA receptor ($\alpha 1$ subunit) may be overexpressed or they may be rapid activation after quick absorption in sensitive individuals”.¹⁰

As seen in the reports, this is especially true for those patients with mental disease such bipolar disorder, borderline personality disorders or drug abuse potential, because the sensitization of GABA receptors in some of these patients may predispose to the development of hallucinations.¹¹ Another symptom seen in the reports are bizarre and complex behavioral effects like sleep related complex behaviors¹², proved to be related with z-drugs, particularly zolpidem.¹³ There are also been some reports and posterior studies of suicidal attempts by zolpidem. In 2016 a study demonstrated a significant association between using zolpidem and suicide or suicide attempt in people with or without comorbid psychiatric illnesses.¹⁴ Despite BZDs successful use, tolerance was rapidly discovered and studied. A clinical trial in 1985 performed by the Medical College of Ohio, showed the regional differences in downregulation of brain BZD receptors using a quantitative auto-radiographic method because of the chronic presence of this drug to its receptor locus.¹⁵ Clinical experience showed that benzodiazepines are frequently used for long-term treatment, and there are many explanations for this: prescribing tradition, patient preference, difficulties associated with benzodiazepine withdrawal (even in patients taking low doses) because they have a rapid clinical onset of action, and good efficacy with few initial adverse effects. Long-term intake of a drug can induce tolerance of the secondary effects (because increased amounts are needed to achieve intoxication, or the effects are minimized with continued use) and physical dependence, a risk associated even at therapeutic doses.¹⁶ There is no standard definition of long-term use, but the most common is 6 to 12 months. Tolerance to the sedating effects of benzodiazepines is rapid, but tolerance to the anxiolytic effects develops slowly and to a limited extent.

Experimental Section :

Melting points were determined in open capillary tube with anhydrous substance and were uncorrected. IR spectra of the newly synthesized compound were recorded with potassium bromide pellets technique, ¹H NMR spectra were recorded with the help of AVANCE 300 MHz

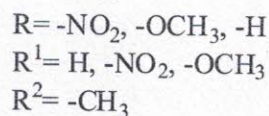
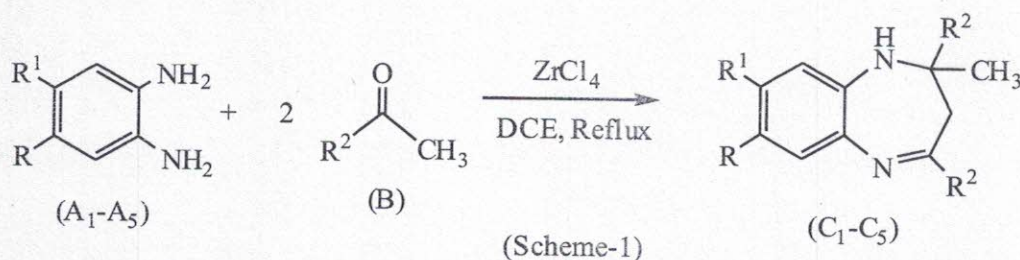


Spectrometer in DMSO using TMS as internal standard. Mass spectra of the compound were recorded on a FT VG-7070H. Mass Spectrometer using EI technique at 70 eV is used. All the reactions of the newly synthesized were monitored by Thin layer chromatography.

Material and Methods :

Synthesis of 2, 3-dihydro-1H-1,5-benzodiazepine derivatives (A₁-A₅) :

Synthesis of 2,3-dihydro-1H-1,5-benzodiazepine derivatives using symmetrical and unsymmetrical diamines and substituted ketones refluxed in the presence of DCE with zirconium tetrachloride as a catalyst to obtain number of 1,5-benzodiazepine derivatives (Scheme-1). This synthesis is novel in the sense that it preserves the simplicity, time consuming and improves the yields.



Results and Discussion :

Concerning the prescriptions, guidelines have failed to reduce the prescriptions: clinicians do not always adhere to recommendations to use BZDs as hypnotics and anxiolytics only for short-term and only after trying psychological therapies. It has been difficult to accept the high risk and low benefits of the long-term in most of the cases. The equivalence of doses between different compounds had presented difficulties, leading to incorrect and excessive dose prescriptions in many situations. Prescriptions of most-potent BZDs (as alprazolam, clonazepam or lorazepam) with excessive dosage are the more problematic, partly of their addictive potential and partly of their dose presentation, that does not allow a gradual dosage reduction.

Conclusion:



The research programme described in this thesis demonstrates the synthesis of new chemical entities adopting various strategies and the compounds are screened for pesticidal activity in order to find a lead molecule for a specified biological activity. The preparation of new phase transfer catalyst and its utilization in various organic reactions is reported for the first time. The preparation of biologically important dihydropyrimidinones and 1,5-benzodiazepines using $ZrCl_4$ in one-pot reaction and the characterization of some of the new regioisomers is significant.

After analyzing the advantages and disadvantages of the Z-drugs, it can be concluded that, even if they are not exactly as BZD, they must be treated with the same precaution due to the amount of adverse effects reports that had appeared over the recent years. Despite the amount of biomedical literature on BZDs and Z-drugs, there is still a need to answer vital questions relevant to their effectiveness and safety in society, for example, the possibility of irreversible effects due to extended treatment, especially those associated to new safety accusations. The constant investigation concerning BZDs is proving that the problems related with these drugs are an actual concern, not only as a medical issue but as a social concern.

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References :

1. Strenbachh, L. The benzodiazepine Story. J. Med. Chem. 1979, 22, 1–7.
2. Rubira, E. R. Medicamentos: Un Viaje a Lo Largo de la Evolución Del Descubrimiento de Famacos; Univ. Santiago de Compostela, 2008.
3. Wick, J. The History of Benzodiazepines. Consult. Pharm. 2013, 28, 538–548.
4. López-Muñoz, F.; Álamo, C.; García-García, P. The Discovery of Chlordiazepoxide and the Clinical Introduction of Benzodiazepines: Half a Century of Anxiolytic Drugs. J. Anxiety Disord. 2011, 25, 554–562.
5. Griffin, C. E.; Kaye, A. M.; Bueno, F. R.; Kaye, A. D. Benzodiazepine Pharmacology and Central Nervous System-Mediated Effects. Ochsner J. 2013, 13, 214–223.



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6. Guina, J.; Merrill, B. Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. *J. Clin. Med.* 2018, 7, 1-22.
7. Kaufmann, C. N.; Spira, A. P.; Depp, C. A.; Mojtabai, R. Long-Term Use of Benzodiazepines and Nonbenzodiazepine Hypnotics, 1999-2014. *Psychiatr Serv.* 2018, 69, 235-238.
8. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning <https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm> (accessed Feb 24, 2018).
9. O'Brien, C. P. Benzodiazepine Use, Abuse, and Dependence. *J. Clin. Psychiatry* 2005, 66, 28-33.
10. Ram, D.; Eiman, N.; Gowdappa, B. Multimodal Hallucination (Audio-Visual, Kinaesthetic and Scenic) Associated with the Use of Zolpidem. *Clin. Psychopharmacol. and Neurosci.* 2015, 13, 215-217.
11. Manfredi, G.; Kotzalidis, G. D.; Lazanio, S.; Savoia, V.; Talamo, A.; Koukopoulos, A. E.; Sani, G.; Trevisi, M.; Tatarelli, R.; Girardi, P. Command Hallucinations with Self-Stabbing Associated with Zolpidem Overdose. *J. Clin. Psychiatry* 2010, 71, 92-93.
12. Park, Y.-M.; Shin, H.-W. Zolpidem Induced Sleep-Related Eating and Complex Behaviors in a Patient with Obstructive Sleep Apnea and Restless Legs Syndrome. *Clin. Psychopharmacol. Neurosci.* 2016, 14, 299-301.
13. Dolder, C. R.; Nelson, M. H. Hypnotic-Induced Complex Behaviours: Incidence, Mechanisms and Management. *CNS Drugs* 2008, 22, 1021-1036.
14. Sun, Y.; Lin, C.-C.; Lu, C.-J.; Hsu, C.-Y.; Kao, C.-H. Association Between Zolpidem and Suicide: A Nationwide Population-Based Case-Control Study. *Mayo Clin. Proc.* 2016, 91, 308-315.
15. Tietz, E.; Rosenbger, H. Autoradiographic localization of benzodiazepine receptor downregulation. *J. Pharmacol. Experiment. Therap.* 1986, 236, 284-292.
16. Busto, U.; Sellers, E. M. Pharmacologic Aspects of Benzodiazepine Tolerance and Dependence. *J. Subst. Abuse Treat.* 1991, 8, 29-33.