Tetrazoles as Antidiabetic Agents

Subjects: Biochemistry & Molecular Biology

Contributor: Rostislav E. Trifonov

Tetrazole heterocycle is a promising scaffold in drug design, and it is incorporated into active pharmaceutical ingredients of medications of various actions: hypotensives, diuretics, antihistamines, antibiotics, analgesics, and others. This heterocyclic system is metabolically stable and easily participates in various intermolecular interactions with different biological targets through hydrogen bonding, conjugation, or van der Waals forces.

tetrazoles antidiabetic agents type 2 diabetes mellitus peroxisome proliferator-activated receptors (PPARs) agonists

1. Introduction

Diabetes mellitus is an incurable disease defined by a metabolic disorder with hyperglycemia, contributing to a number of dangerous diseases: hypertension, thrombosis, neurodegenerative disorders, and so on. Hyperglycemia may be due to poor cellular susceptibility to insulin (insulin resistance) or type 2 diabetes mellitus (T2DM), as well as insufficient secretion of insulin by the pancreas (type 1 diabetes mellitus). Currently, the number of T2DM cases is constantly increasing, and the disease is now considered to be one of the non-transmittable chronic disease epidemics. The problem affects different populations, genders, and ages. Overall, T2DM accounts for about 90% of all cases of diabetes mellitus. To date, there are hundreds of millions of known documented cases of T2DM in the world. Note that not all cases of diabetes are reliably documented. According to International Diabetes Federation (IDF) data, the total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045 [1][2]. Type 1 diabetes mellitus can be controlled with the external administration of insulin. In contrast, a direct injection of insulin in the case of T2DM will not significantly reduce blood glucose. Here, drug therapy is required to target the various biological mechanisms responsible for metabolic processes. A great deal of studies have been dedicated to the development of such drugs, and these studies are being intensively developed [3].

A large number of natural compounds with antihyperglycemic effects are known [4][5], but it is the synthetic drugs that are most widely used in the treatment of diabetes. Dozens of the biological targets of low-molecular antidiabetic agents are well recognized: the incretin hormones Glucagon-like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) themselves; their regulators such as Dipeptidyl Peptidase-4 (DPP-4); G protein-Coupled Receptors (GPCRs) such as GPR40, GPR120, and GPR119; Glucose Metabolism Pathway-Based Targets, such as Glucose Kinase (GK), Protein Kinase B (AKT/PKB); Insulin-Based Targets like Protein Tyrosine Phosphatase 1B (PTP1B); and other types of targets like Sodium-Glucose Cotransporter Protein-2 (SGLT-2), Peroxisome Proliferator-Activated Receptors (PPARs), etc. [6]. Antidiabetic drugs can have

fundamentally different chemical structures, and they can hardly be assigned to a certain type. As can be seen, for example, from **Figure 1**, the following chemical compounds of different classes can be used as hypoglycemic agents: biguanides, sulfonylureas, thiazolidinediones, pyrimidines, purines, sugars, oligonucleotides, peptides, and many others [7][8]. In addition, other multiple medications are commonly used in combination with antidiabetic drugs to suppress secondary effects associated with T2DM and high blood sugar levels: cardiovascular and neurological agents, immunomodulators, and many others. Thus, medical treatments for T2DM are complex processes, and drug therapy, in combination with proper diet and lifestyle, can significantly improve the patient's condition and reduce the dangerous consequences of hyperglycemia. Nevertheless, to date, there are no universal and highly effective drugs, either of natural or synthetic origin, to cure T2DM. The known drugs have a number of side effects, which has even led to a ban on the use of some of them [7]. Therefore, the development of more effective medications for the treatment of T2DM remains very important.

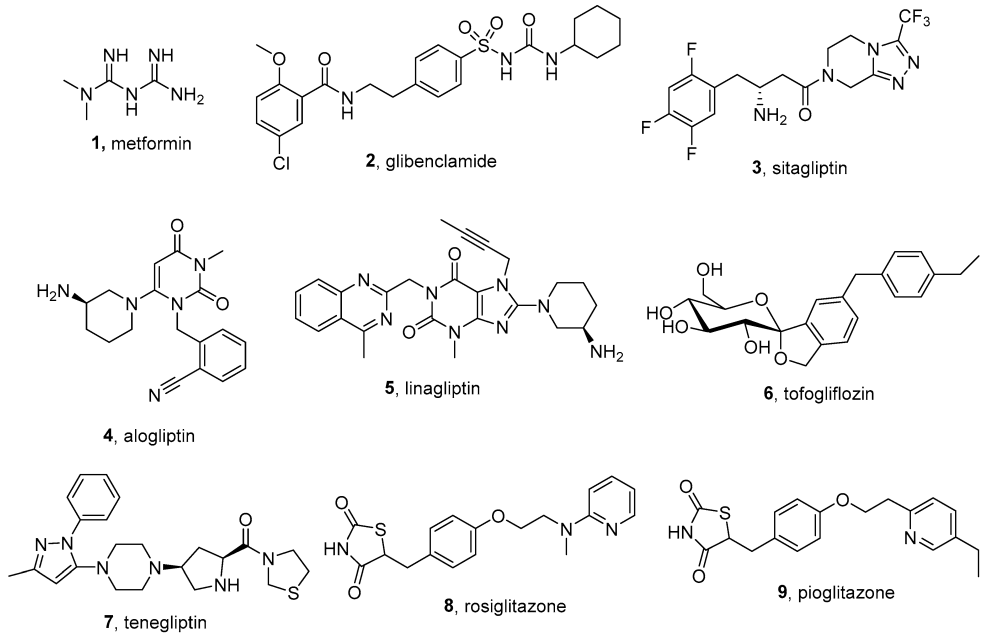


Figure 1. Some low-molecular oral antidiabetic medications: **1**—metformin (known since 1922, decreases glucose production in the liver, increases the insulin sensitivity of body tissues), **2**—glibenclamide (known since 1960s, stimulates insulin secretion by pancreatic β-cells, increases insulin release), **3**—sitagliptin (DPP-4 inhibitor, Merck), **4**—alogliptin (DPP-4 inhibitor, Takeda Pharmaceutical Company), **5**—linagliptin (DPP-4 inhibitor, Boehringer Ingelheim), **6**—tofogliflozin (SGLT-2 inhibitor, Chugai Pharma), **7**—teneligliptin (DPP-4 inhibitor, Mitsubishi Tanabe Pharma), **8**—rosiglitazone (PPAR agonist, GlaxoSmithKline), **9**—pioglitazone (PPAR agonist).

2. Tetrazoles for Biomedicine

It can be seen from **Figure 1** and the cited literature sources that most of the known antidiabetic drugs in use include nitrogen heterocyclic moieties: azoles, azines, annelated azoloazines, oxazoles, thiazoles, and some others. The development of novel antidiabetic agents often involves the use of polynitrogen heterocyclic systems with more than two endocyclic heteroatoms (triazoles, tetrazoles, oxadiazoles, or their fused derivatives) as key

scaffolds [8][9][10]. These moieties are very promising in drug design because they are often metabolically stable, easily participate in various intermolecular interactions through hydrogen bonding, conjugation, or van der Waals bonding with biological targets, and many of them are bioisosters of functional groups of endogenous molecules [11].

Among other heterocyclic systems, the tetrazole cycle has a unique structure and unique properties. Despite the fact that the tetrazole cycle contains only one endogenous carbon atom and four nitrogen atoms, it is a very thermally and metabolically stable system. Previously, the synthesis and properties of tetrazoles have been discussed in detail in numerous reviews and monographs, including by the authors of this research [12][13][14][15][16].

Tetrazolyl moiety is present in the top 10 most frequent nitrogen heterocycles in US FDA-approved drugs and in a total of 16 pharmaceuticals [11]. This heterocycle is incorporated into active pharmaceutical ingredients of medications of various actions: hypotensives **10**–**12**, diuretic **13**, antihistamines **14**–**15**, antibiotics, analgesics, and some others (**Figure 2**) [17].

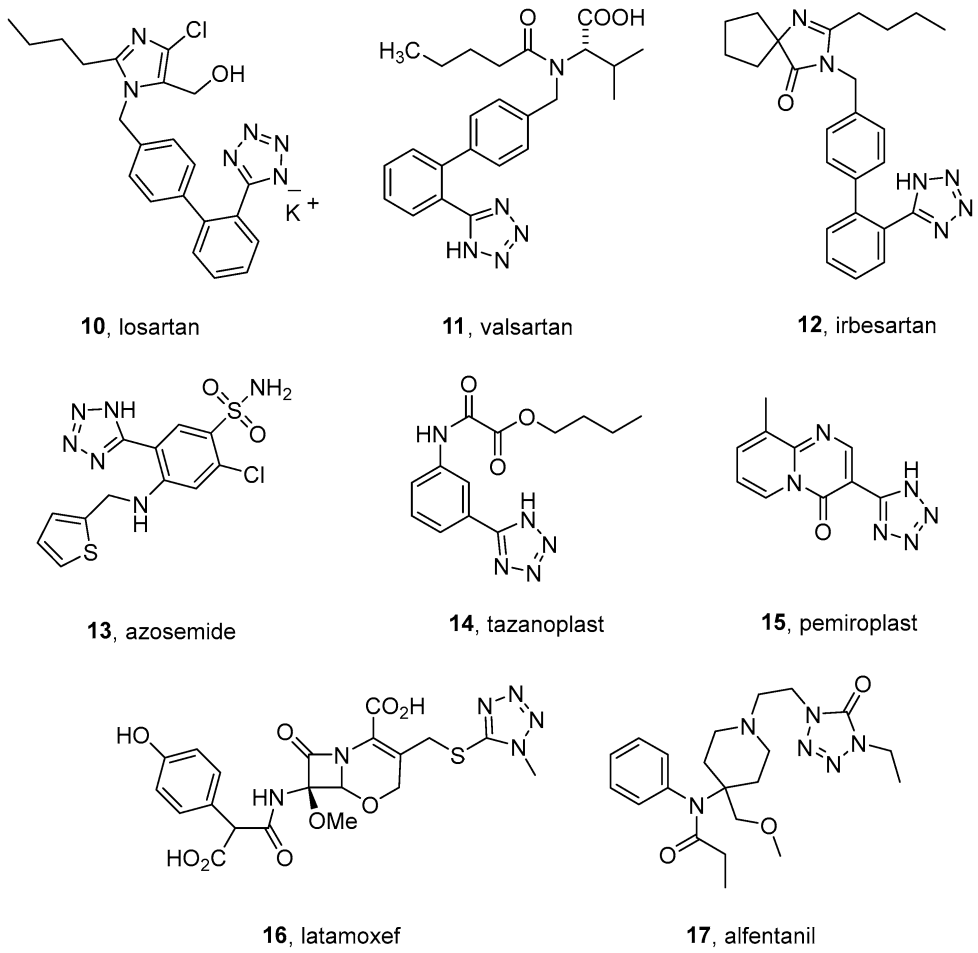


Figure 2. Some examples of tetrazole-containing medications.

Quite a lot of research has been devoted to the medicinal chemistry of tetrazoles, the results of which are summarized in a number of reviews on this topic [16][17][18][19][20][21]. Significant achievements have been made in

the field of drug development for hypotensive, anticancer drugs, semi-synthetic antibiotics, and agents acting on the central nervous system [17][19]. However, there are few data points, and there is no systematic analysis of the antidiabetic activity of tetrazole derivatives.

Tetrazoles vary greatly in properties depending on their prototropic form and substituent isomerism (**Figure 3**).

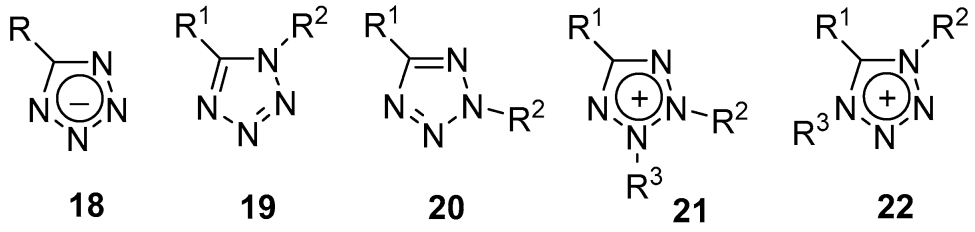
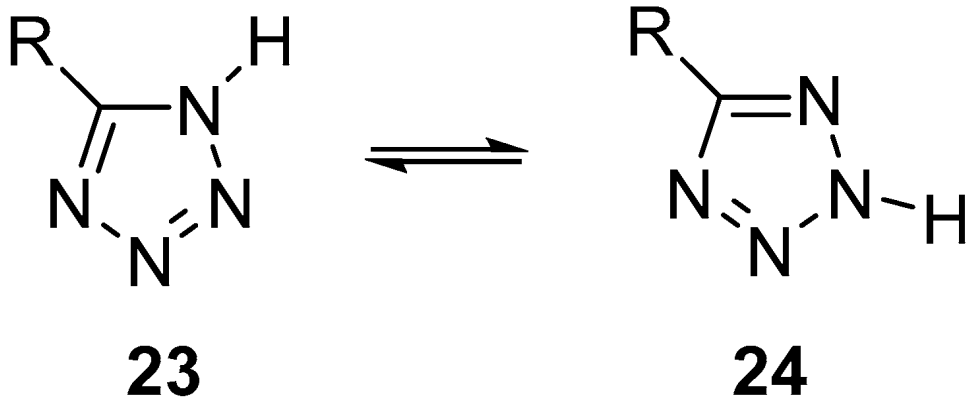


Figure 3. Main isomeric forms of tetrazoles.

Tetrazolate anions (tetrazolides) **18** are highly nucleophilic particles that are very soluble in water and other polar solvents and easily coordinate with transition metal ions [22]. Neutral 1*H*-tetrazoles **19** are usually more polar and thermally stable than 2*H*-tetrazoles **20**. Isomeric tetrazolium ions **21**, **22** are also very different in their properties. For example, cycle **21** can easily open under radiolysis, while ion **22** is still stable under these conditions [23]. The high stability of tetrazole forms can be partially explained with the sufficiently high aromaticity of the heterocycle. All the forms are planar and highly conjugated systems. Thus, the structural criteria of aromaticity for 2*H*-tetrazoles **20**, especially tetrazolides **18**, are close to those for benzene [24].

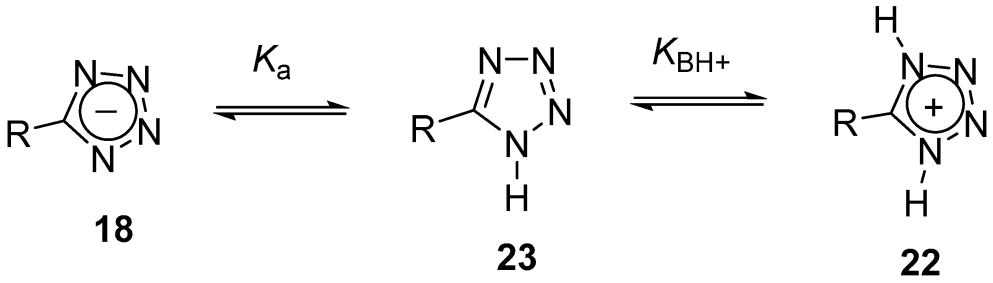
N*H*-Unsubstituted tetrazoles may exist as 1*H*- and 2*H*-tautomers **23** and **25** (Scheme 1). The most polar form **23** (where R is an electron-donor substituent or hydrogen) is preferred in condensed media (solutions or crystals), whereas the less polar 2*H*-form **24** with the same substituents prevails in the gas phase and non-polar solvents [25].



Scheme 1. Tautomerism of NH-unsubstituted tetrazoles.

Tetrazoles are relatively strong N*H*-acids and weak bases (Scheme 2). The acidity of N*H*-tetrazoles **23** is comparable to that of aliphatic carboxylic acids. The acidity of parent tetrazole is pK_a 4.9, and depending on the

nature of the C^5-substituent, it can vary from 6 (for 5-aminotetrazole) to −1 (for 5-nitrotetrazole). Tetrazoles are also weak bases that ionize in strong mineral acids (for parent tetrazole, pK_{BH+} −2.7), and their basicity can vary in the range pK_{BH+} −1 ÷ −9 [25].



Scheme 2. Ionizations of tetrazoles.

A special mention should be made of the unique ability of the tetrazole cycle to form stable hydrogen bonds simultaneously with several proton donors and acceptors (**Figure 4**). Such interactions are often predominant in the binding of active molecules to their biological targets. Based on theoretical and experimental pK_{HB} values, tetrazoles are sufficiently strong bases for the formation of hydrogen bonding, and the substituent at position *5* of the cycle has a noticeable effect on the basicity [26].

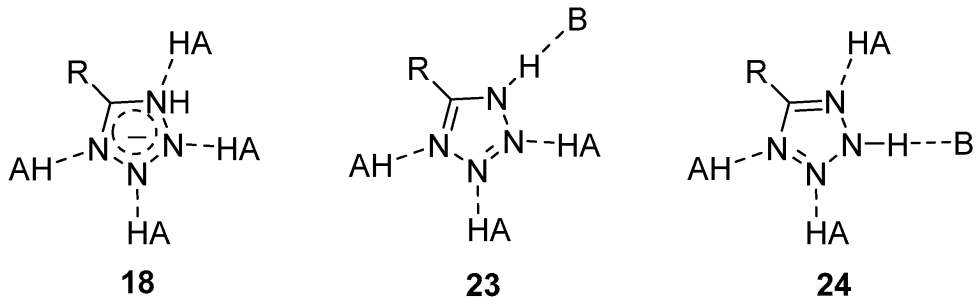


Figure 4. Possible ways of hydrogen bonding for different prototropic forms of 5-R-tetrazoles.

It is now generally accepted that neutral 1*H*-tetrazole forms **19**, **23** are metabolically stable bioisosteric analogs of *cis*-amide and carboxyl groups, and tetrazolide **18** is an analog of carboxylate anion. However, in recent years, this concept of bioisosterism has been refined. As shown by Allen and co-authors, based on the analysis of crystallographic data and the results of theoretical calculations, the nature of hydrogen bond formation in pairs—1*H*-tetrazole-COOH and tetrazolide-carboxylate—is somewhat different [27]. The authors of the cited work also indicated that the functional groups of biomolecules linked by hydrogen bonds to 1*H*-tetrazole or tetrazolate anion are located at a distance greater by approximately 1.2 Å compared to the isosteric fragments of -COOH and -COO^-. The recent quantitative studies of the hydrogen bonding basicity of tetrazoles also support the fact that their ability to form hydrogen bonds is unique and significantly different from the carboxylic group [26].

References

1. IDF Diabetes Atlas. International Diabetes Federation Diabetes Atlas, 10th ed.; International Diabetes Federation: Brussels, Belgium, 2021.
2. Chatterjee, S.; Khunti, K.; Davies, M.J. Type 2 diabetes. Lancet 2017, 389, 2239–2251.
3. Salmen, T.; Serbanoiu, L.-I.; Bica, I.-C.; Serafinceanu, C.; Muzurovic, E.; Janez, A.; Busnatu, S.; Banach, M.; Rizvi, A.A.; Rizzo, M.; et al. Review on critical view over newest antidiabetic molecules in light of efficacy. Int. J. Mol. Sci. 2023, 24, 9760.
4. Shi, Y.; Si, D.; Chen, D.; Zhang, X.; Han, Z.; Yu, Q.; Liu, J.; Si, J. Bioactive compounds from Polygonatum genus as anti-diabetic agents with future perspectives. Food Chem. 2023, 408, 135183.
5. Xu, B.; Li, Z.; Zeng, T.; Zhan, J.; Wang, S.; Ho, C.-T.; Li, S. Bioactives of Momordica charantia as Potential Anti-Diabetic/Hypoglycemic Agents. Molecules 2022, 27, 2175.
6. Su, J.; Luo, Y.; Hu, S.; Tang, L.; Ouyang, S. Advances in Research on Type 2 Diabetes Mellitus Targets and Therapeutic Agents. Int. J. Mol. Sci. 2023, 24, 13381.
7. Mahgoub, M.O.; Ali, I.I.; Adeghate, J.O.; Tekes, K.; Kalasz, H.; Adeghate, E.A. An Update on the Molecular and Cellular Basis of Pharmacotherapy in Type 2 Diabetes Mellitus. Int. J. Mol. Sci. 2023, 24, 9328.
8. Kerru, N.; Singh-Pillay, A.; Awolade, P.; Singh, P. Current anti-diabetic agents and their molecular targets: A review. Eur. J. Med. Chem. 2018, 152, 436–488.
9. Rusinov, V.L.; Sapozhnikova, I.M.; Spasov, A.A.; Chupakhin, O.N. Fused azoloazines with antidiabetic activity. Russ. Chem. Bull. 2022, 71, 2561–2594.
10. Mohammad, B.D.; Baig, M.S.; Bhandari, N.; Siddiqui, F.A.; Khan, S.L.; Ahmad, Z.; Khan, F.S.; Tagde, P.; Jeandet, P. Heterocyclic Compounds as Dipeptidyl Peptidase-IV Inhibitors with Special Emphasis on Oxadiazoles as Potent Anti-Diabetic Agents. Molecules 2022, 27, 6001.
11. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J. Med. Chem. 2014, 57, 10257–10274.
12. Butler, R.N. Tetrazoles. In Comprehensive Heterocyclic Chemistry II; Katritzky, A.R., Rees, C.W., Scriven, E.F.V., Eds.; Pergamon: Oxford, UK; New York, NY, USA, 1996; Volume 4, pp. 621–678.
13. Ostrovskii, V.A.; Koldobskii, G.I.; Trifonov, R.E. Tetrazoles. In Comprehensive Heterocyclic Chemistry III; Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., Taylor, R.J.K., Zhdankin, V.V., Eds.; Elsevier: Oxford, UK, 2008; Volume 6, pp. 259–423.

14. Ostrovskii, V.A.; Popova, E.A.; Trifonov, R.E. Tetrazoles. In Comprehensive Heterocyclic Chemistry IV; Black, D., Cossy, J., Stevens, C., Eds.; Elsevier: Oxford, UK, 2022; Volume 6, pp. 182–232.
15. Ostrovskii, V.A.; Popova, E.A.; Trifonov, R.E. Developments in tetrazole chemistry (2009–16). Adv. Heterocycl. Chem. 2017, 123, 1–62.
16. Popova, E.A.; Trifonov, R.E. Synthesis and biological properties of amino acids and peptides containing a tetrazolyl moiety. Russ. Chem. Rev. 2015, 84, 891–916.
17. Popova, E.A.; Trifonov, R.E.; Ostrovskii, V.A. Tetrazoles for biomedicine. Russ. Chem. Rev. 2019, 88, 644–676.
18. Ostrovskii, V.A.; Trifonov, R.E.; Popova, E.A. Medicinal chemistry of tetrazoles. Russ. Chem. Bull. 2012, 61, 768–780.
19. Popova, E.A.; Protas, A.V.; Trifonov, R.E. Tetrazole Derivatives as Promising Anticancer Agents. Anti-Cancer Agents Med. Chem. 2017, 17, 1856–1868.
20. Kaushik, N.; Kumar, N.; Kumar, A.; Singh, U.K. Tetrazoles: Synthesis and Biological Activity. Immunol. Endocr. Metab. Agents Med. Chem. 2018, 18, 3–21.
21. Myznikov, L.V.; Hrabalek, A.; Koldobskii, G.I. Drugs in the tetrazole series. Chem. Heterocycl. Compd. 2007, 43, 1–9.
22. Popova, E.A.; Trifonov, R.E.; Ostrovskii, V.A. Advances in the synthesis of tetrazoles coordinated to metal ions. ARKIVOC 2012, 45–65.
23. Pikaev, A.K.; Kriminskaya, Z.K. Radiolysis of tetrazolium salt solutions. Russ. Chem. Rev. 1998, 67, 745–754.
24. Trifonov, R.E.; Alkorta, I.; Ostrovskii, V.A.; Elguero, J. A theoretical study of the tautomerism and ionization of 5-substituted NH-tetrazoles. J. Mol. Struct. THEOCHEM 2004, 668, 123–132.
25. Trifonov, R.E.; Ostrovskii, V.A. Protolytic equilibria in tetrazoles. Russ. J. Org. Chem. 2006, 42, 1585–1605.
26. Kaplanskiy, M.V.; Faizullina, O.E.; Trifonov, R.E. Experimental and Theoretical Quantitative Studies of the Hydrogen Bonding Basicity of 2,5-Disubstituted Tetrazoles and Some Related Heterocycles. J. Phys. Chem. A 2023, 127, 5572–5579.
27. Allen, F.H.; Groom, C.R.; Liebeschuetz, J.W.; Bardwell, D.A.; Olsson, T.S.G.; Wood, P.A. The Hydrogen Bond Environments of 1 H -Tetrazole and Tetrazolate Rings: The Structural Basis for Tetrazole–Carboxylic Acid Bioisosterism. J. Chem. Inf. Model. 2012, 52, 857–866.