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Novel two step synthesis of bis/Mono 1-aryl-1H-tetrazole-5-carboxylic acid

Sambandam Chandrakumari, Dhanavel Sivakumar, Haridoss Manikandan, and Mannuthusamy Gopalakrishnan

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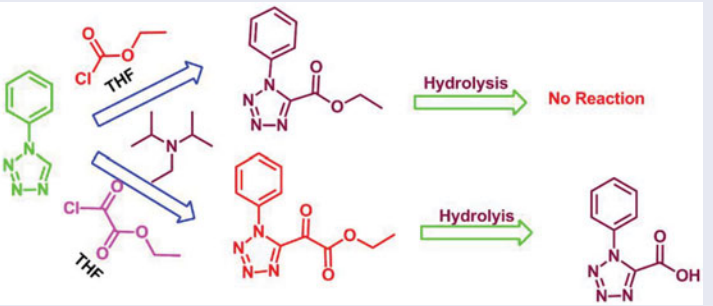
ABSTRACT

Some novel compounds of bis/mono 1-aryl-1H-tetrazole-5-carboxylic acid are synthesized by the hydrolysis of two different synthesized esters, they are ethyl-1-aryl-1H-tetrazole-5-carboxylate and ethyloxo (1-aryl-1H-tetrazol-5-yl)acetate. The ethyl-1-aryl-1H-tetrazole-5-carboxylate is resistant to get hydrolyzed, whereas the ethyloxo(1-aryl-1H-tetrazol-5-yl) acetate undergoes hydrolysis process and converts the ester to title compound. All the synthesized compounds are characterized by IR, ^{1}H and ^{13}C NMR, mass and elemental analysis.The ethyl-1-aryl-1H-tetrazole-5-carboxylateis optimized by DFT B3LYP method and the HOMO and LUMO energy is 5.14 eV and also there is a formation of a weak bond between O_{18} and C_8 as observed from the AIM analysis result.

GRAPHICAL ABSTRACT



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AIM; 1-aryl-1H-tetrazole-5-carboxylic acid; DFT; ethyl-1-aryl-1H-tetrazole-5-carboxylate; ethyloxo(1-aryl-1H-tetrazol-5-yl) acetate

Introduction

Carboxylic acids are small organic acid molecules found as amino acids, triglycerides, and prostanoids, in many endogenous substances and play a vital role as pharmacophore in therapeutic agents.[1] Tetrazoles (CN_4H) are the aromatic heterocyclic compounds. In recent days, researchers have shown their considerable attention on tetrazoles and tetrazole derivatives because they have numerous multi-varieties of biological applications such as antibacterial,[2] antifungal,[3] antiviral,[4–6] analgesic,[7]

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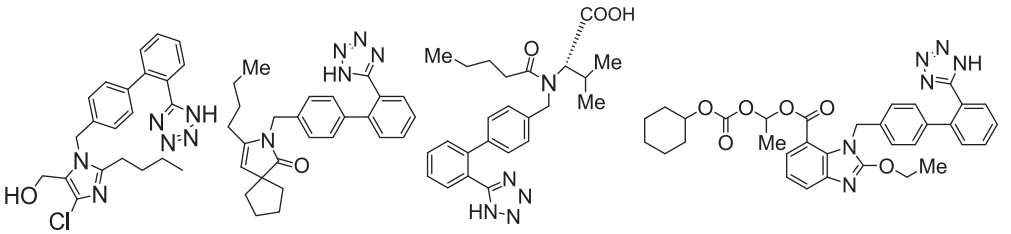
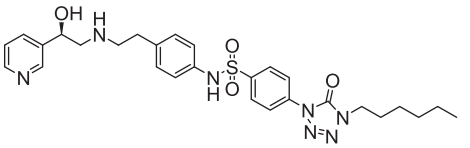
anti-inflammatory,[8–10] and antihypertensive activities[11]. A wide variety of tetrazole moiety and its derivatives are important in medicinal chemistry research. Tetrazoles draw more attention because of its potential biological activity and industrial applications.[12] Losartan, Valsartan, Irbesartan, and Candesartan are medicinally important AII receptor antagonist hypotensive tetrazole containing drugs play an important role in the regulation of blood pressure and homeostasis. Angiotensin II is an octapeptide formed from Angiotensin I within the renin-angiotensin system (RAS) from the reaction catalyzed by an angiotensin-converting enzyme and it is a powerful vasoconstrictor. Losartan, Valsartan, and candesartan have (1 H-tetrazol-5-yl) biphenyl moiety as their common structural fragment and have garnered attention from drug manufacturers for almost 15 years in the pharmaceutical market.[13,14] The biphenyl moiety and its position in the compound have efficient molecular docking energy.[15] The β-aderno blockers containing tetrazolone moiety in the molecular structure and is used in the treatment of arterial hypertonia and concomitant diseases.[16,17] The structure of Losartan, Irbesartan, Valsartan, Candesartan and β-adernoblockers are given below.





(*R*)-4-(4-hexyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)-*N*-(4-(2-((2-hydroxy-2-(pyridin-3-yl)ethyl)amino)ethyl)phenyl)benzenesulfonamide

The DFT B3LYP is a computational method which calculates the geometries and energies of the molecules. An organic synthetic chemist uses computational chemistry to describe the optimized geometry structure and electronic behaviors of molecules. DFT is very useful to predict the electronic structure (ground state) for atoms, molecules and condensed phase which is used by physics and chemistry fellow due to its low cost. By using this DFT theory, we are able to describe the properties of electron density of an atom or molecules. DFT B3LYP is a very reliable method of calculating the geometries and energies of heterocyclic molecules.[18,19] Bader's QTAIM theory helps us to define the structure of molecules.[20,21] The QTAIM theory is applicable to unravel the atom–atom interaction in covalent and non-covalent interactions such as weak Vander Waal's, π–π, X–H–π, conventional hydrogen bonding, cation-π interactions, halogen bonds, etc. and also other applications in chemistry.[22] The concept of assumption in

atoms and bonds are useful in interpretation, classification, prediction, molecular structure and communication chemistry. This theory is about the molecular structure, atoms, bonds and distribution function of electron density dealing with the probability of electronic charge in the real space and attraction between the charge and the nuclei. The hypothesis concepts of molecular structure in QTAIM helps to define the bonds linked to the atoms will result in impart the structure. QTAIM defines the structure, chemical bonding based on the topology of density of electrons. Bader's QTAIM theory help to define the structure of molecules,[23–28] It exploits the electron or charge density of molecules. Distribution of electron density in molecules, mainly affects the interaction between the two nuclei (chemical bonding). The results from both experimental[29] and theoretical[30] density of electrons are used to know the nature of the chemical bonding

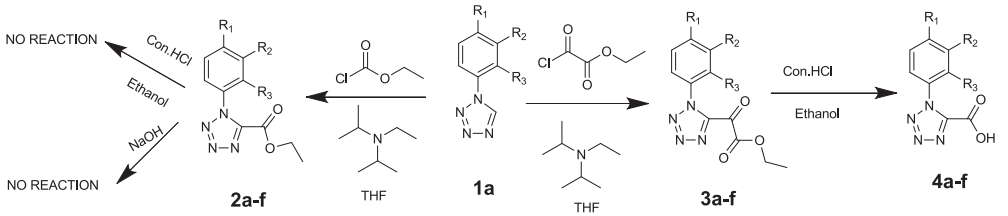
The structure of the synthesized compounds **4a–4f.**

Results and discussion

A very well-known standard method to synthesize the acid molecule is the hydrolysis process of an ester. Ester compounds are the best precursor to produce the acid compound. Our objective here is to synthesize new types of aryl tetrazole acids through two sets of reactions; one is aryl tetrazole with ethyl chloroformate and other is the aryl tetrazole with ethyl-2-chloro-2-oxoacetate in THF solvent medium and DIPEA used as a catalyst. Two different esters are formed, they are ethyl-1-aryl-1H-tetrazole-5-carboxylate **2a** and ethyloxo(1-aryl-1H-tetrazol-5-yl) acetate **3a** which is formed by dehydrohalogenation route (Scheme 1) (Alkyl tetrazole esters and alkyl tetrazole acids failed to synthesize due to the poor yield of alkyl tetrazole). The compound ethyl-1-phenyl-1H-tetrazole-5-carboxylate **2a** was taken as a precursor to synthesize compound **4a**. The **2a** was prepared by treating 1-phenyl-1H-tetrazole with ethyl chloroformate and diisopropylethylamine in THF. The reaction mixture was refluxed at 80 °C for 16 h. The synthetic pathway is shown in Scheme 1. The ester was formed by the removal of HCl. The dehydrohalogenation route was employed. Then, **2a** (0.5 g) was treated with both concentrated HCl in ethanol and 20% of an aqueous solution of NaOH separately. However, the expected product of 1-phenyl-1H-tetrazole-5-carboxylic acid did not form.

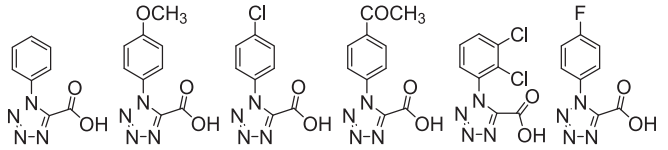
The tetrazole ester **2a** was resistant to hydrolyzation and to know the reasons; the molecule was subjected to theoretical studies such as DFT B3LYP method, (631 G d, p) as the basis set and AIM analysis. The molecule **2a** was optimized with two different conformers **A** and **B**. In conformer **A** (Fig. 1) the carbonyl bearing oxygen and phenyl carbon are **syn** to each other and found vice–versa, in an anti position to each other in conformer **B** (Fig. 2). The major conformer **A** has less enthalpy of reaction, whereas the minor conformer **B** has more enthalpy of reaction.

The HOMO and LUMO energy of conformer **A** is 5.17 eV, which is relatively high energy and energy gap. According to Pearson and Parr concept,[31,32] "Hardness measures the resistance to change in the electron distribution in a molecule".[33] The energy gap is found to be more between the HOMO and LUMO orbitals (Fig. 3), hence, there is a rapid increase in the hardness of the molecule. Hardness and reactivity of the molecule are inversely proportional to each other. Therefore, more the hardness in the molecule lesser will be the reactivity in reaction. We found this as the main reason for



Compds.	R_1	R_2	R_3
4a	H	H	H
4b	-OCH_3	H	H
4c	Cl	H	H
4d	-$COCH_3$	H	H
4e	H	Cl	Cl
4f	F	H	H

The structure of the synthesized compounds 4a-4f



4a **4b** **4c** **4d** **4e** **4f**

Scheme 1. Synthesis of bis/mono 1-aryl-1H-tetrazole-5-carboxylic acid. Reactions conditions (i) **3a**–**h** : Reflux at 80 °C for 16 h , (ii) **4a**–**h**: 80 °C for 6 h.

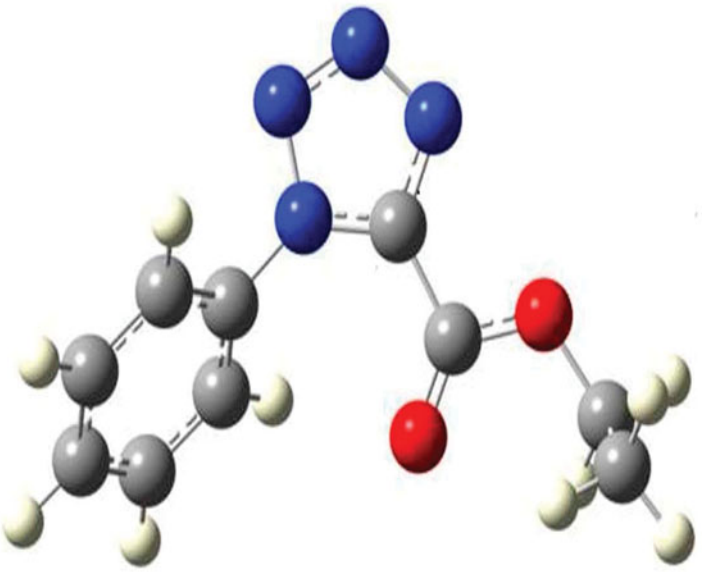


Figure 1. Major conformer A.

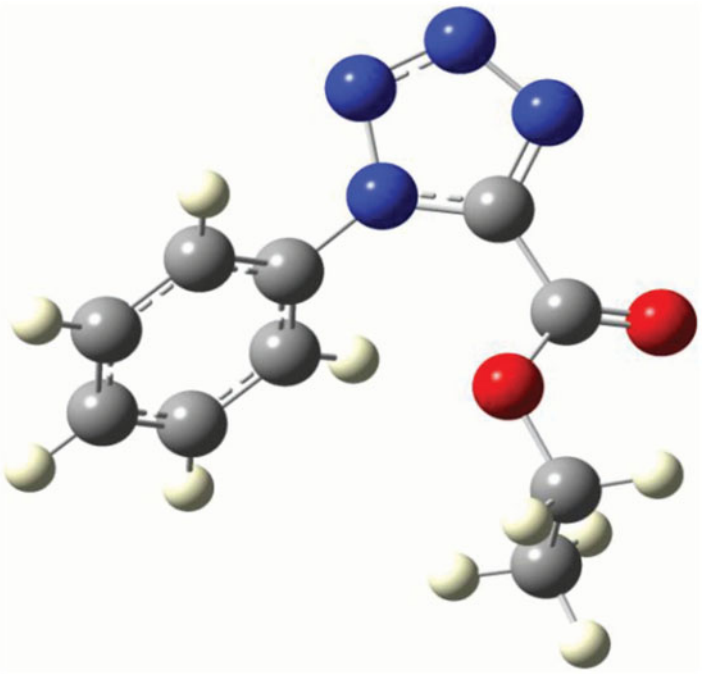


Figure 2. Minor conformer B.

ethyl-1-phenyl-1H-tetrazole-carboxylate **2a** which did not undergo hydrolysis reaction under both acidic and basic condition.

Additionally, to strengthen the reason, the AIM analysis[34] was also performed for the compound **2a**. The results show a weak bond formation between the carbonyl oxygen and the phenyl carbon (Fig. 4). This will decrease the reactivity of the oxygen group. The lone pair of electrons on the oxygen atom was used for the formation of a weak bond. Hence, it will block the reactivity of the molecule.

The contour map of Laplacian of electron density (ρBCP) for conformer **A** (Fig. 5) indicates that the weak bond of (3, −1) topology between C_8 and O_{18} is found in the positive (green) regions of Laplacian of electron density ρBCP. The bond between C_8 and H_{12} is strong and it lies in negative Laplacian of electron density (red). Thus, the AIM analysis predicts the non-bonded electrons in the oxygen atom of the carbonyl group used up for the weak bond formation between C_8 and O_{18}. This may be the reason for the unreactivity of the carbonyl group in molecule **A**.

Hence, we synthesized the title compounds **4a**–**h** using the precursors **3a**–**h**. (Schemes 1–3) All the newly synthesized compounds are confirmed by spectral data. The 1-phenyl-1H-tetrazole **1a** (1.46 g, 10 mmol) is treated with ethyl-2-chloro-2-oxoacetate (1.36 g, 10 mmol) and diisopropylamine (1 mL) in THF (100 mL). It was refluxed at 80 °C for 16 h. The IR spectrum of compound **3a** exhibited the tetrazole ring characteristic frequency at 957 cm^{-1}, N=N absorption band at 1543 cm^{-1} and C=N frequency signal at 1644 cm^{-1}. The absorption bands at 1704 and 1741 cm^{-1} confirmed the presence of the ester group and the keto group. The frequency at 2918–2954 cm^{-1} revealed the presence of ethyl group. The absorption signal at 3057 cm^{-1} indicated the aromatic

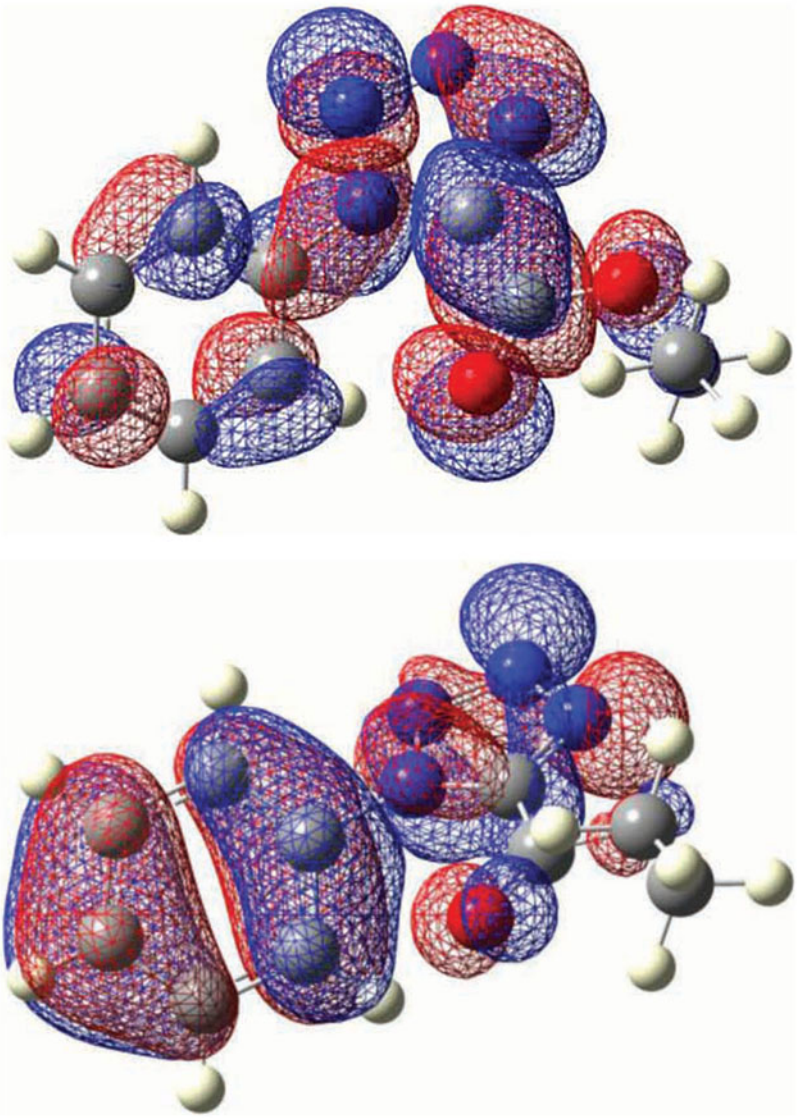


Figure 3. HOMO and LUMO images of Conformer A.

C–H. In ^{1}H NMR spectrum, the triplet signal at 1.71 ppm and the quartet signal at 4.13 ppm indicated the presence of methyl and methylene protons. The aromatic protons resonated multiplet signal from 7.50 to 7.80 ppm. In ^{13}C NMR spectrum, the peak at 13.95 and 60.56 ppm indicated the presence of methyl and methylene carbon. The aromatic carbons appeared from 128.53 to 137.58 ppm. The tetrazole carbon appeared at 157.43 ppm. The carbon signal at 169.82 ppm and 173.35 ppm confirmed the presence of ester and keto carbon. The mass spectrum was obtained as [M+] peak. The calculated elemental analysis value was C, 52.17; H, 4.38; N, 20.28 and the experimental elemental analysis value was C, 52.86; H, 4.26; N, 20.68.

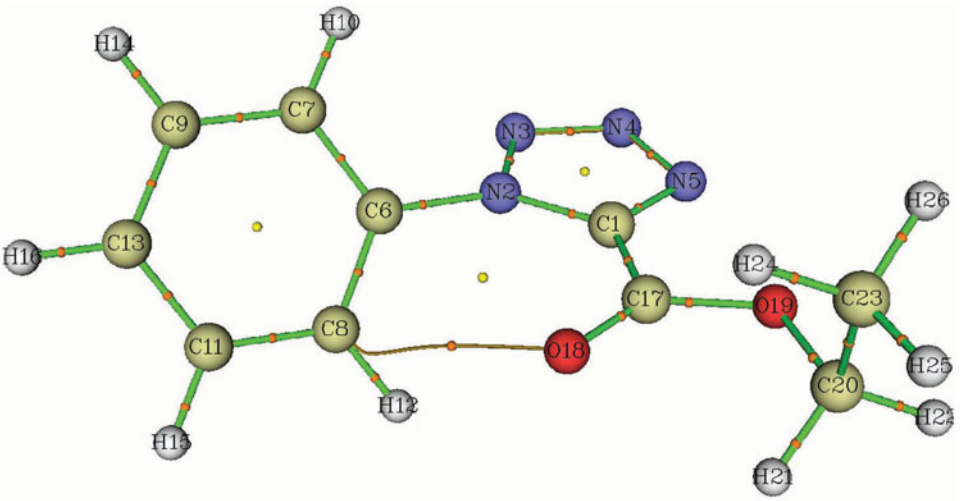


Figure 4. AIM analysis result – visualized using Multi wave function analyzer. Weak bond between O_{18} and C_8.

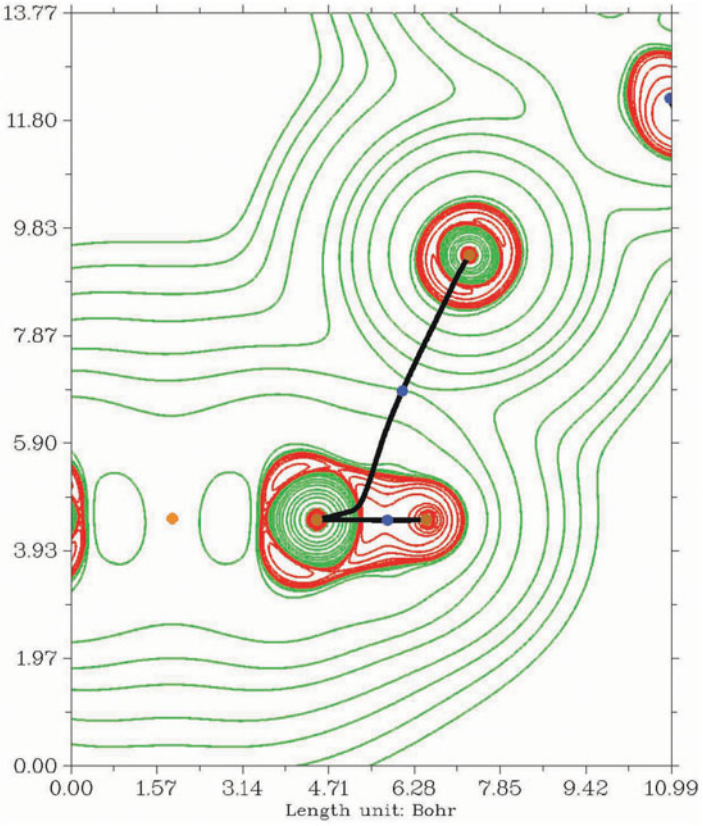
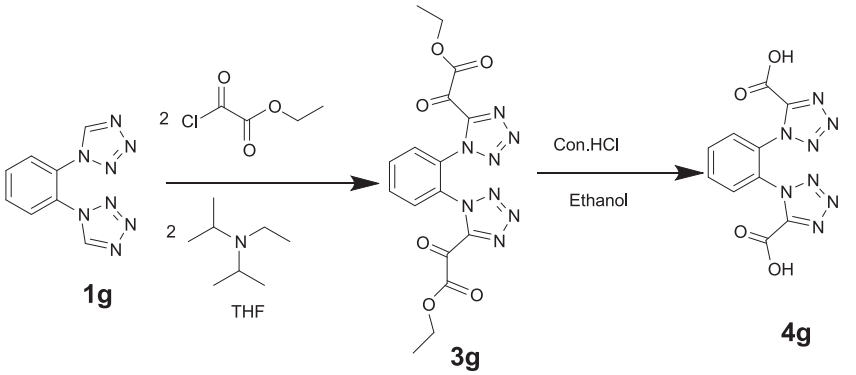
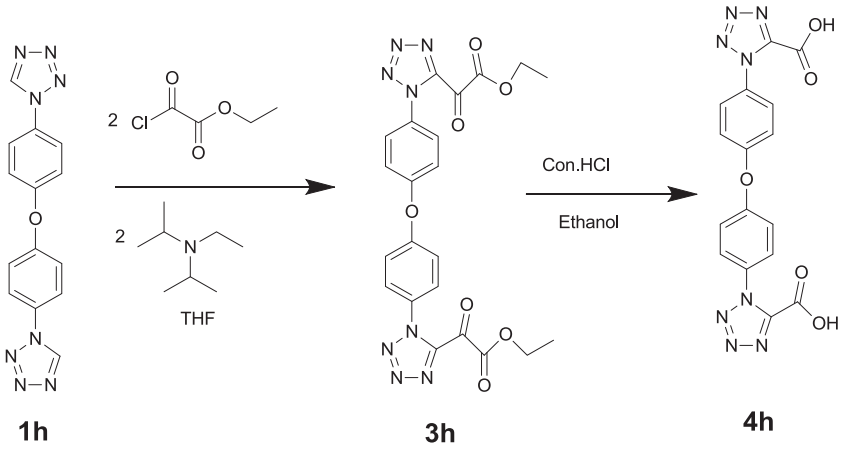


Figure 5. Contour diagram to identify the red and green region.



Scheme 2. Synthesis of 1, 1′-(1, 2-phenylene) bis (1 H-tetrazole-5-carboxylic acid) Reactions conditions (i) **3g**: Reflux at 80 °C for 16 h, (ii) **4g**: 80°Cfor 6 h.



Scheme 3. Synthesis of 1, 1′-(oxy bis (4, 1-phenylene) bis (1 H-tetrazole-5-carboxylic acid) Reactions conditions (i) **3h** : Reflux at 80 °C for 16 h , (ii) **4h**: 80 °C for 6 h.

After confirming the structure of compounds, the hydrolysis process was preceded. The synthesized ethyloxo(1-aryl-1H-tetrazol-5-yl) acetate (0.5 g) was treated with 1 mL concentrated HCl and 10 mL of ethanol. The reaction mixture was refluxed for 6 h. The solid product was filtered off and dried. The compound 1-aryl-1H-tetrazole-5-carboxylic acid **4a**–**4f** was characterized by IR, NMR, mass technique and elemental analysis. The tetrazole ring characteristic peak appeared at 961 cm^{-1}, N=N band at 1523 cm^{-1}, and C=N frequency peak appeared at 1601 cm^{-1}. The stretching frequencies appeared at 1716, 3079, and 3337 cm^{-1} attributed to the presence of acid carbonyl group, aromatic C–H and the hydroxyl group **4a**. In proton NMR the aromatic protons resonated multiplet signals from 7.60 to 7.93 ppm. The aliphatic protons signals have vanished and the OH proton appeared as a sharp singlet in 10.13 ppm. In carbon NMR, the aromatic carbons were in the range of 128.43 to 134.03 ppm. The tetrazole carbon appeared at 142.63 ppm. The aliphatic carbon signals had vanished and the carbonyl carbon appeared in 161.90 ppm. The mass spectrum obtained as [M + H] peak at 191.1.

The calculated elemental analysis value was C, 50.53; H, 3.18; N, 29.46 and the experimental elemental analysis value was C, 50.86; H, 3.14; N, 29.53. The data for the compound 3a-h, 4a-h are given in supplementary data.

Experimental procedure

Materials and methods

The melting points (°C, uncorrected) of the synthesized compounds were checked by using the digital auto melting point apparatus (Labtronics 110, India) in open capillary tube. All the reagents and solvents were purchased in Sigma–Aldrich and Merck, India. All the reactions were carried out at an appropriate temperature and the products were checked by TLC silica gel 60 F 254 using the eluents pet ether and ethyl acetate in the ratio 7:3. All the compounds were characterized by the FT-IR spectrometer (Agilent Cary 650) using KBr pellets; ^{1}H NMR spectroscopy in DMSO (400 MHz, Brucker), ^{13}C NMR spectroscopy in DMSO (100 MHz, Bruckner) using tetramethylsilane (TMS) as an internal standard. GC- Mass spectra were measured by Saturn 2200 (Varian (CP-3800)). Optimization using DFT, B3LYP method was performed in Gaussian 03 software package and the AIM analysis was performed in AIMALL software package.

General procedure for synthesis of Mono ethyloxo(1-aryl-1H-tetrazol-5-yl) acetate (3a–f) and 1-aryl-1H-tetrazole-5-carboxylic acid 4a–f

The mono1-aryl-1H-tetrazoles **1a–f** were synthesized by the literature method.[35,36] The 1-substituted-aryl-amine (10 mmol) was treated with sodium azide (10 mmol), triethyl orthoformate (10 mmol) in 100 mL of acetic acid. It was refluxed for 24 h at 80 °C. The reaction progress was checked by TLC. Once the reaction was completed, the reaction mixture was transferred into a beaker containing ice. The solid product was separated on cooling, filtered and dried. The equimolar mixture of 1-substituted-aryl-tetrazole (5 mmol) **1a–f** is treated with ethyl-2-chloro-2-oxoacetate (5 mmol) in the presence of a catalytic amount of DIPEA in THF (100 mL) (Scheme 1). It was refluxed for 16 h. The process of the reaction was checked by TLC. After the formation of a product, the reaction mixture was poured into ice. The solid product was separated, filtered and dried. The compound was purified by column chromatography using the pet ether and benzene in the ratio 7:3. The yield of the product was 88–95%. Then, the title compound (0.5 g) was synthesized by hydrolysis of compounds **3a–f** in the presence of Concentrated HCl (1 mL) and 10 mL of ethanol (Scheme 1). The reaction was refluxed for 6 h. The formation of the product was confirmed with the help of TLC and the reaction was quenched by pouring the mixture into ice. The solid product was filtered off and dried. The products **4a–f** were obtained in good yield of 90%.

General procedure for the synthesis for the synthesis of bis phenyl-1-aryl-1H-tetrazole-5-carboxylic acid 4 g–h

The bis-1-aryl-1H-tetrazoles **1 g–h** were synthesized by the literature method.[24,25] O-Phenylene diamines/4,4-oxydianiline (10 mmol) was treated with sodium azide

(20 mmol), triethyl orthoformate (20 mmol) in acetic acid (100 mL) (Schemes 2 and 3) The reaction mixture was refluxed for 24 h at 80 °C. The reaction progress was checked by TLC. Once the reaction was completed, the reaction mixture was transferred into a beaker containing ice. The solid product separated on cooling was filtered and dried. Then, the 1,2-di(1H-tetrazol-yl) benzene/1,1-(oxybis (4,1-phenylene) bis (1 H-tetrazole) (5 mmol) was treated with ethyl-2-chloro-2-oxoacetate (10 mmol) in THF(100 mL) in the presence of DIPEA. It was refluxed for 16 h. Again, the reaction progress was checked by TLC. Once the reaction was completed, the reaction mixture was poured into ice. The solid product separated on cooling was filtered and dried. The compound was purified by column chromatography using 7:3 of pet ether and benzene. The yield of the products **3g** and **3h** was 82–85%. Then, the title compound (0.5 g) was synthesized by hydrolysis of compounds **3g** and **3h** in the presence of Concentrated HCl (2 mL) and 20 mL of ethanol. It was refluxed for 6 h. The formation of the product was confirmed with the help of TLC and the reaction was quenched by pouring the mixture into ice. The solid product was filtered off and dried. The products **4g–h** are obtained in good yield of 90%.

Diethyl-1,1'-(oxybis(1,2-phenylene)bis(1H-tetrazole-5,1-diyl)bis(oxoacetate)),(3g)

1,2-di(1H-tetrazol-yl) benzene (2.14 g, 10 mmol) was treated with ethyl-2-chloro-2-oxoacetate (2.73 mL, 20 mmol) in the presence of diisopropyl ethylamine (2 mL) as a catalyst in THF(100 ml). Brown color solid; mp 102 °C; IR (KBr, $\nu_{max,}$ cm^{-1})942 (Characteristic tetrazole ring),1520 (N=N),1599 (C=N), 1690 (ester group),1735 (keto group), 2926–2983 (aliphatic C–H), 3069 (aromatic C–H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72 [6H, t], 4.20 [4H, q], 7.22–7.53 ppm [4H, m]; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.95,60.56, 125.43, 125.53, 125.53, 125.65, 126.15, 129.67, 156.88, 169.82, 173.16, ppm.MS, *m/z* (%): 415.1 $[M+H]^{+}$; anal. Calcd. for. $C_{16}H_{14}N_8O_{6:}$ C, 46.38; H, 3.41; N, 27.04. Found: C, 46.51; H, 3.54; N, 27.16.

1, 1'-(1, 2-phenylene) bis (1 H-tetrazole-5-carboxylic acid),(4g)

Diethyl-2,2'-(1,1'-(oxybis(1,2-phenylene)bis(1H-tetrazole-5,1-diyl)bis(2-oxoacetate) (0.5 g) was treated with Concentrated HCl (2 mL) and 20 mL of ethanol. It was refluxed for 6 h. Pale brown crystalline solid; mp 136–140 °C; IR (KBr, $\nu_{max,}$ cm^{-1}) 943(Characteristic tetrazole ring),1499 (N=N),1608 (C=N), 1663(C=O group), 3045 cm^{-1} (aromatic C–H), 3409 (OH group); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.91–7.54 [4H, m],11.92 ppm [2OH, s]; ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.61, 123.51, 126.02,142.16, 161.55 ppm.MS, *m/z* (%): 298.5 $[M+H]^{+}$; anal. Calcd. for. $C_{10}H_6N_8O_{4:}$ C, 39.74; H, 2.00; N, 37.08. Found: C, 39.81; H, 2.14; N, 37.13.

Conclusion

In conclusion two different types of esters are synthesized and used as a precursor to synthesize bis/mono 1-aryl-1H-tetrazole-5-carboxylic acid (**4a–h**), they are Ethyl-1-phenyl-1H-tetrazole-5-carboxylate (**2a**) and ethyloxo(1-aryl-1H-tetrazol-5-yl) acetate (**3a–h**).

The ester **2a** is resistant to hydrolyzation because of the formation of a weak bond between the O_{18} and C_8 whereas the esters (**3a–h)** undergo hydrolyzation process to produce mono and bis 1-aryl-1H-tetrazole-5-carboxylic acid. All the synthesized 16 compounds are characterized by IR, NMR and mass spectra. Future studies may stress on the biological activities of the synthesized compounds.

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References

[1] Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. Privileged Molecules for Protein Binding Identified from NMR-Based Screening. *J. Med. Chem.* **2000**, *43*, 3443–3447. DOI: 10.1021/jm000164q.

[2] Bekhit, A. A.; El-Sayed, O. A.; Aboulmagd, E.; Park, J. Y. Tetrazolo[1,5-a]Quinoline as a Potential Promising New Scaffold for the Synthesis of Novel anti-Inflammatory and Antibacterial Agents. *Eur. J. Med. Chem.* **2004**, *39*, 249–255. DOI: 10.1016/j.ejmech.2003.12.005.

[3] Murali Krishna, S.; Padmalatha, Y.; Ravindranath, L. K. Tetrazoles as a Core Unit Biological Evaluation Agent. *Int. J. Med. Pharm. Res.* **2015**, *3*, 1004–1010.

[4] Sidwell, R. W.; Huffman, J. H.; Khare, G. P.; Allen, L. B.; Witkowski, J. T.; Robins, R. K. Broad-Spectrum anti-Viral Activity of Virazole: 1-beta-D-Ribofuranosyl-1,2,4-Triazole-3-Carboxamide. *Science* **1972**, *177*, 705–706. DOI: 10.1126/science.177.4050.705.

[5] Mohite, P. B.; Bhaskar, V. H. Potential Pharmacological Activities of Tetrazoles in the New Millennium. *Int. J. Pharmtech. Res.* **2011**, *3*, 1557–1566.

[6] Hutchinson, D. W.; Naylor, M. The Antiviral Activity of Tetrazole Phosphonic Acids and Their Analogues. *Nucl. Acids Res.* **1985**, *13*, 8519–8530. DOI: 10.1093/nar/13.23.8519.

[7] Maxwell, J. R.; Wasdahl, D. A.; Wolfson, A. C.; Stenberg, V. I. Synthesis of 5-Aryl-2H-Tetrazoles, 5-Aryl-2H-Tetrazole-2-Acetic Acids, and [(4-Phenyl-5-Aryl-4H-1,2,4-Triazol-3-yl)Thio]Acetic Acids as Possible Superoxide Scavengers and Antiinflammatory Agents. *J. Med. Chem.* **1984**, *27*, 1565–1570. DOI: 10.1021/jm00378a007.

[8] Bhaskar, V. H.; Mohite, P. B. Design, Synthesis, Characterization and Biological Evaluation of Some Novel 1,5-Disubstituted Tetrazole as Potential anti-Inflammator Agents. *J.Optoelectron. Biomed. Mater.* **2010**, *2*, 231–237.

[9] Rajasekaran, A.; Thampi, P. P. Synthesis and Analgesic Evaluation of Some 5-[beta-(10-phenothiazinyl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles. *Eur. J. Med. Chem.* **2004**, *39*, 273–279. DOI: 10.1016/j.ejmech.2003.11.016.

[10] Maria Dorathi Anu, M.; Jayanthi, M.; Damodar Kumar, S.; Raja, S.; Thirunavukkarasu, S. V. Synthesis, Characterization, Antibacterial & anti- Inflammatory Effects of Substituted Tetrazole Derivatives Based on Different Types of Carbazone and Benzaldehyde. *Int. J. Chemtech. Res.* **2013**, *5*, 1982–1990.

[11] Hayao, S.; Havera, H. J.; Strycker, W. G.; Leipzig, T. J.; Rodriguez, R. New Antihypertensive Aminoalkyltetrazoles. *J. Med. Chem.* **1967**, *10*, 400–402. DOI: 10.1021/jm00315a025.

[12] Abe, T.; Goto, T.; Hattori, Y.; Ito, S.; Kido, K.; Kurahashi, Y.; Maurer, F.; Otsu, Y.; Sawada, H.; Shibuya, K.; et.al. 1-Phenyl-5-Anilinotetrazoles Derivatives, Their Preparation and Their Use as Microbiocides, Insecticides and/or Herbicides. U.S. Patent 5,981,438. **1998**.

[13] Le Bourdonnec, B.; Cauvin, C.; Meulon, E.; Yous, S.; Goossens, J. F.; Durant, F.; Houssin, R.; Henichart, J. P. Comparison of 3D Structures and at(1) Binding Properities of

Pyrazolidine- 3,5-Diones and Tetrahydropyridazine-3,6-Diones with Parent Antihypertensive Drug Irbesartan. *J. Med. Chem.* **2002**, *45*, 4794–4798. DOI: 10.1021/jm010457z.

[14] Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. Medicinal Chemistry of Tetrazoles. *Russ. Chem. Bull.* **2012**, *61*, 768–780. DOI: 10.1007/s11172-012-0108-4.

[15] Hansch, C.; Kurup, A.; Garg, R.; Gao, H. Chem-Bioinformatics and QSAR: A Review of QSAR Lacking Positive Hydrophobic Terms. *Chem. Rev.* **2001**, *101*, 619–672. DOI: 10.1021/cr0000067.

[16] Mathvink, R. J.; Samuel Tolman, J.; Chitty, D.; Candelore, R. M.; Cascieri, M. A.; Colwell, L. F. Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; et al. Potent Selective 3-Pyridylethanolamine β_3 Adrenergic Receptor Agonists Possessing a Thiazolebenzenesulfonamide Pharmacophore. *Bioorganic Med. Chem. Lett.* **2000**, *10*, 1971–1973. DOI: 10.1016/S0960-894X(00)00390-5.

[17] Chung, J. Y. L.; Ho, G. J.; Chartrain, M.; Roberge, C.; Zhao, D. L.; Leazer, J.; Farr, R.; Robbins, M.; Emerson, K.; Mathre, D. J.; et al. The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids. *Tetrahedron Lett.* **1999**, *40*, 6739. DOI: 10.1016/S0040-4039(99)01353-2.

[18] Nathaniel, R.; Mineva, T.; Nikolova, R.; Bojilova, A. Density Functional Study of the Interaction of 3-(ω-Bromoacetyl) Coumarin with Phosphites. *Int. J. Quantum Chem.* **2006**, *106*, 1357–1366. DOI: 10.1002/qua.20893.

[19] Jursic, B. S.; Zdravkovski, Z. Theoretical Study of Benzofusedthieno [3,2-b] Furans in the Reaction with Electrophiles. *Int. J. Quantum Chem.* **1995**, *54*, 161. DOI: 10.1002/qua.560540304.

[20] Bohórquez, H. J.; Boyd, R. J.; Matta, C. F. Molecular Model with Quantum Mechanical Bonding Information. *J. Phys. Chem. A.* **2011**, *115*, 12991. DOI: 10.1021/jp204100z.

[21] Bader, R. F. W. *In Atoms in Molecules: A Quantum Theory*; Clarendon Press: Oxford, UK, **1990**.

[22] Grabowski, S. J. What Is the Covalency of Hydrogen Bonding. *Chem. Rev.* **2011**, *111*, 2597–2625. DOI: 10.1021/cr800346f.

[23] Bader, R. F. W. A Quantum Theory of Molecular Structure and Its Application. *Chem. Rev.* **1991**, *91*, 893–928. DOI: 10.1021/cr00005a013.

[24] Bader, R. F. W. The Quantum Mechanical Basis of Conceptual Chemistry. *Monatshefte Für Chemie* **2005**, *136*, 819–854. DOI: 10.1007/s00706-005-0307-x.

[25] Bader, R. F. W. Atoms in Molecules. *Acc. Chem. Res.* **1985**, *18*, 9–15. DOI: 10.1021/ar00109a003.

[26] Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University press: Oxford, UK, **1990**.

[27] Grabowski, S. J.; Sokalski, W. A.; Leszczynski, J. Nature of X-H^{+5}-$^{-5}$H-Y Dihydrogen Bonds and X-H-σ Interactions. *J. Phys. Chem. A.* **2004**, *108*, 5823–5830. DOI: 10.1021/jp049874o.

[28] Popelier, P. L. A. Charactreization of a Dihydrogen Bond on the Basis of the Electron Density. *J. Phys. Chem. A.* **1998**, *102*, 1873–1878. DOI: 10.1021/jp9805048.

[29] Arputharaj, D. S.; Hathwar, V. R.; Row, T. N. G.; Kumaradhas, P. Topological Electron Density Analysis and Electrostatic Properties of Aspirin; An Experimental and Theoretical Study. *Cryst. Growth Des.* **2012**, *12*, 4357–4366. DOI: 10.1021/cg300269n.

[30] Parthasarathi, R.; Subramanian, V.; Sathyamurthy, N. Hydrogen Bonding without Borders: An Atoms-In-Molecules Perspective. *J. Phys. Chem. A.* **2006**, *110*, 3349–3351. DOI: 10.1021/jp060571z.

[31] Pearson, R. G. Absolute Electronegativity and Absolute Hardness of Lewis Acid and Bases. *J. Am. Chem. Soc.* **1985**, *107*, 6801–6806. DOI: 10.1021/ja00310a009.

[32] Parr, R. G.; Pearson, R. G. Absolute Hardness: Companion Parameters to Absolute Electronegativity. *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516. DOI: 10.1021/ja00364a005.

[33] Pearson, R. G. Chemical Hardness and Density Functional Theory. *J. Chem. Sci.* **2005**, *117*, 369–377. DOI: 10.1007/BF02708340.
[34] Filarowski, A.; Majerz, I. Aim Analysis of Intramolecular Hydrogen Bonding in O-hydroxy aryl Schiff bases. *J. Phys. Chem. A.* **2008**, *112*, 3119–3126. DOI: 10.1021/jp076253x.
[35] Shanmugam, G.; Bhakiaraj, D.; Elavarasan, S.; Elavarasan, T.; Gopalakrishnan, M. Benign by Design Synthesis of Novel 1H-Tetrazoles: Spectral Characterization and Antibacterial Activities. *Chem. Sci. Trans.* **2013**, *2*, 1304–1311.
[36] Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. Drugs in Tetrazole Series. *Chem. Heterocycl. Compd.* **2007**, *43*, 1–9. DOI: 10.1007/s10593-007-0001-5.