

SYNTHESIS, CHARACTERIZATION AND QSAR STUDY OF SOME SUBSTITUTED *N'*-[Arylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl) ACETOHYDRAZIDE

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We describe here an easy and efficient method to obtain Schiff bases of 5-phenyl Tetrazole using different aromatic aldehydes. Reaction of 5-phenyl Tetrazole with ethyl chloroacetate to form ethyl (5-phenyl-1*H*-tetrazol-1-yl) acetate (1). Compound 1 react with hydrazine hydrate in ethanol yield 2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide (2). The condensation of (2) with various aldehydes yield the corresponding substituted *N'*-[arylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl)acetohydrazide (3a- j). The compounds obtained were identified by spectral data and were subjected to a prediction of biological activities. A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied and the different derivatives were recommended for the screening of anticonvulsant activity.

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1. Introduction

Tetrazole derivatives possess very interesting pharmacological and biological properties and are reported to exhibit variety of biological activities like antibacterial [1,6], antifungal [2, 3], analgesic [4], anti-inflammatory [5,6], antitubercular activity [7]. Similarly 1,5 substituted tetrazoles have long been known for their pharmaceutical activity as stimulants or depressants on the central nervous system and are reported to show oral antidiabetic and antithrombotic and antimicrobial properties. Compounds containing azomethine group (-CH=N-) is known as schiff bases. Day by day Schiff bases are more frequently applied for the betterment of human welfare. The importance of the Schiff base is due its versatile nature. Literature survey shows that many Schiff bases exhibit biological activities such as antimicrobial, antifungal antibacterial [8,9], antitumor [10], anti-inflammatory [11, 12], and Anticonvulsant [12]. With the discovery of these application of tetrazoles and in continuation of our interest in synthesis of compounds containing both the tetrazole coupling Schiff base systems in the same matrix to serve as a new scaffold for the synthesis of antimicrobial agents. The present work deals with the reaction of of 2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide (2) with different aromatic aldehydes to form schiff's bases (3a-j). The reaction sequence for titled compounds is outlined in Scheme I. Finally, the structures of all the various synthesized compounds were assigned on the basis of IR and ¹H NMR spectral data and these compounds were studied for QSAR. The synthesized compounds were subjected to a prediction of biological activities. A software application (PASS) [15-17] was used for this purpose. The relationship between structure and different biological activities was studied and the different derivatives were recommended for the screening of some specific activities like anticonvulsant activity

2. Experimental

Melting points were determined with open capillary apparatus and were uncorrected. FTIR spectra were recorded on a Shimadzu FT-IR model 8010 spectrophotometer, ¹H NMR spectra

were recorded in DMSO on a Varian mercury FT-NMR model YH- 300 instrument using TMS as internal standard. The purity of compounds were checked by TLC.

General procedure for Synthesis of ethyl (5-phenyl-1H-tetrazol-1-yl) acetate (1)

An equimolar mixture of 5-phenyl tetrazole (0.03 mol, 5 gm), ethyl chloroacetate (0.03mol, 3.67 ml) and anhydrous potassium carbonate (0.03mol, 3.76gm) in methanol (40 ml) was refluxed on a water bath for 4hr, cooled to room temperature, filtered, dried and recrystallized from ethanol. The compound was separated as white amorphous powder.

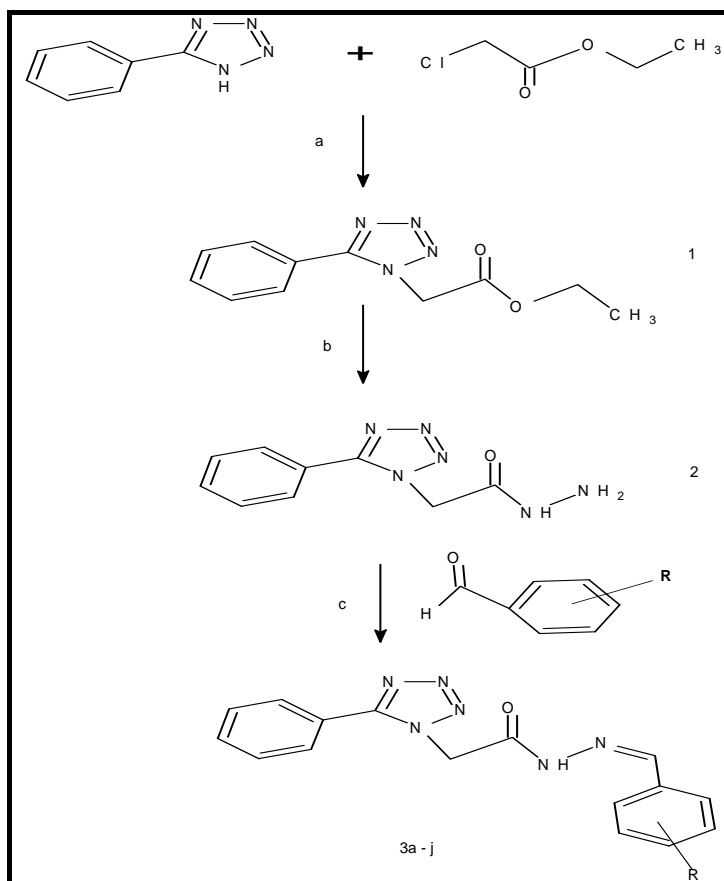
General procedure for synthesis of 2-(5-phenyl-1H-tetrazol-1-yl) acetohydrazide (2)

To a mixture of compound 1, (0.03 mol, 9 gm) in methanol (40 ml), hydrazine hydrate (99% ,0.03 mole, 1.95 ml) was added with continuous stirring to get clear solution. Reflux the reaction mixture on water bath for about 5 hours. The solution was concentrated and allowed to cool overnight. The resulting solid obtained was filtered, washed with cold ethanol, dried and recrystallized from ethanol. The compound was separated as white powder.

General procedure for the synthesis of *N'*-[*arylidene*]-2-(5-phenyl-1H-tetrazol-1-yl)acetohydrazide (3a- j)

Equimolar quantity of the hydrazide compound (2, 0.009 mol) and various aromatic aldehydes (3a-j, 0.009mol) in ethanol and dioxane (50 ml) were heated on a water bath for 8 hrs. The resulting Schiff's bases (3a-j) were cooled and poured into crushed ice. The precipitate thus obtained was filtered washed with cold water and purified by recrystallized from ethanol. The physicochemical and spectral data of the compounds (3a-j) is described in Tables 1 and 2.

Scheme I



Where R: H, , 2-Cl, 4-Cl, 4-Br, 4-CH₃, 3-OCH₃, 4-OCH₃, 2-NO₂, 4-NO₂, 4-N (CH₃)₂.

Scheme: Synthesis, characterization and antimicrobial activity of some substituted *N'*-[arylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide

Reagents and conditions: **a.** Methanol, K₂CO₃ reflux 2 h; **b.** NH₂NH₂, methanol, reflux 5 h; **c.** aryl Aldehydes, abs. EtOH: Dioxane, reflux 8h.

Table 1. Physicochemical Characterization of *N'*-[arylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide

| Sr. No | R | M.P. (°C) | Yield (%) | Mol. Form | M. Wt | C, H, N Calculated | | |
|--------|-------------------------------------|-----------|-----------|---|-------|--------------------|------|-------|
| | | | | | | C % | H % | N % |
| 1 | H | 189° C | 70% | C ₁₆ H ₁₄ N ₆ O | 203 | 62.70 | 4.58 | 27.43 |
| 2 | 2-Cl | 220° C | 34% | C ₁₆ H ₁₃ ClN ₆ O | 200 | 56.37 | 3.84 | 24.64 |
| 3 | 4-Cl | 222° C | 88% | C ₁₆ H ₁₃ ClN ₆ O | 202 | 56.37 | 3.84 | 24.64 |
| 4 | 4-Br | 245° C | 64% | C ₁₆ H ₁₃ BrFN ₆ O | 206 | 49.87 | 3.39 | 21.81 |
| 5 | 4-CH ₃ | 256° C | 69% | C ₁₇ H ₁₆ N ₆ O | 211 | 63.70 | 5.01 | 26.20 |
| 6 | 3-OCH ₃ | 258° C | 78% | C ₁₇ H ₁₆ N ₆ O ₂ | 222 | 60.68 | 4.75 | 24.92 |
| 7 | 4-OCH ₃ | 260° C | 74% | C ₁₇ H ₁₆ N ₆ O ₂ | 225 | 60.68 | 4.75 | 24.92 |
| 8 | 2-NO ₂ | 198° C | 64% | C ₁₆ H ₁₃ N ₇ O ₃ | 188 | 54.65 | 3.70 | 27.87 |
| 9 | 4-NO ₂ | 199° C | 83% | C ₁₆ H ₁₃ N ₇ O ₃ | 189 | 54.65 | 3.70 | 27.87 |
| 10 | (CH ₃) ₂ -N- | 206° C | 78% | C ₁₈ H ₉ N ₇ O | 231 | 61.84 | 5.44 | 28.02 |

Table 2. Spectral Characterization of *N'*-[arylidene]-2-(5-phenyl-1H-tetrazol-1-yl) acetohydrazide

| Sl No. | R | IR (KBr) cm-1 | ¹ H NMR (DMSO D ₆) δ ppm |
|--------|------------------------------------|--|---|
| 3a | H | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-), | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 10H, Ar), 5.56 (s, 2H, -CH ₂) |
| 3b | 2-Cl | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-),785(C-Cl) | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂). |
| 3c | 4-Cl | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-),785(C-Cl) | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂). |
| 3d | 4-Br | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-),697(C-Br). | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂). |
| 3e | 4-CH ₃ | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-). | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂),2.88(s,3H,CH ₃). |
| 3f | 3-OCH ₃ | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-),1165(-OCH ₃). | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂),4.02(s,3H,-OCH ₃) |
| 3g | 4-OCH ₃ | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-), 1165(-OCH ₃). | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂),4.02(s,3H,-OCH ₃) |
| 3h | 2-NO ₂ | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-),1564 (-NO ₂). | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂). |
| 3i | 4-NO ₂ | 3430(-NH), 3054(Ar-CH), 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-),1564 (-NO ₂). | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂). |
| 3j | (CH ₃) ₂ -N | 3430(-NH),3054(Ar-CH), 3155(-N(CH ₃) ₂). 2376,2247(-NCH ₂), 1656 (-CO), 1625(-N=CH-), | 9.27 (s, 1H, NH), , 7.95 (s, 1H, N=CH).7.91- 6.80 (m, 9H, Ar), 5.56 (s, 2H, -CH ₂),2.44 (s,6H,-N(CH ₃) ₂) |

Table 3. QSAR Analysis of Anticonvulsant Activity with $Pa > 30\%$ 3 Possible activities at $Pa > 30\%$

| Sr. No | R | Pa | Pi | Substructure descriptors |
|--------|-------------------------------------|-------|-------|--------------------------|
| 1 | H | 0.613 | 0.020 | 28 |
| 2 | 2-Cl | 0.642 | 0.017 | 33 |
| 3 | 4-Cl | 0.724 | 0.010 | 33 |
| 4 | 4-Br | 0.663 | 0.015 | 33 |
| 5 | 4-CH ₃ | 0.578 | 0.025 | 33 |
| 6 | 3-OCH ₃ | 0.448 | 0.045 | 36 |
| 7 | 4-OCH ₃ | 0.445 | 0.052 | 36 |
| 8 | 2-NO ₂ | 0.574 | 0.022 | 35 |
| 9 | 4-NO ₂ | 0.602 | 0.021 | 35 |
| 10 | (CH ₃) ₂ -N- | 0.548 | 0.030 | 36 |

Pa = probable activity, Pi = probable inactivity

3. Result and discussion

Keeping in view the biological activity and medicinal importance of Tetrazoles and schiff bases, we synthesized some schiff bases of 5-phenyl tetrazole by reaction of hydrazides with different aromatic aldehydes. The compounds of the type substituted *N*-[Arylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide (3 a-j) were studied for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities such that the $Pa > 30\%$. A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied. It was found that the *N*-[4-chlorophenylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide are expected to exhibit spectacular anticonvulsant activity, whereas the It was found that the *N*-[4-methoxyphenylidene]-2-(5-phenyl-1*H*-tetrazol-1-yl) acetohydrazide are expected to exhibit little anticonvulsant activity. Other derivatives of Tetrazole containing 2-chloro, 4-bromo and 4-nitro benzaldehyde are also expected to exhibit good anticonvulsant activity and the compound containing dimethylamino banzaldehyde moiety shows moderate activity.

Hence these compounds are recommended for the screening of anticonvulsant activity.

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