Med Chem Res
DOI 10.1007/s00044-009-9215-7

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A novel approach to the synthesis of 1,2,3-triazoles and their SAR studies

Pratibha Sharma · Ashok Kumar · Siya Upadhyay · Jitendra Singh · Vinita Sahu

Received: 4 February 2009 / Accepted: 15 April 2009

Abstract A series of biologically active 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole derivatives has been synthesized. The compounds were synthesized in excellent yields (80–85%) and the structures were established on the basis of corresponding IR, ^{1}H NMR, and elemental analysis data. The purity has been ascertained on the basis of chromatographic resolution using acetic acid-toluene (4:6 v/v) as binary eluent. All the compounds (**4a**–**l**) have been tested for their antifungal activity against a representative panel of fungal microbes. These synthesized compounds exhibited significant activities against *A. niger, C. albicans, C. azyma,* and *A. flavus.* For all the tests conducted, voriconazole was used as the control drug. The hydrophobic parameter (log P) also has been quantized for correlation of structure with biological activity, and a critical evaluation of structure-activity relationship (SAR) has been performed.

Keywords 4-Acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole · Antifungal activity · SAR · log P

Introduction

1,2,3-triazoles are attractive constructs due to their unique chemical properties and structure, which find many applications in medicinal, pharmacological, and agricultural fields. Members of this family have been widely used due to their profound antibacterial, fungicidal, anti-inflammatory, antiviral, and plant growth regulatory activities (Kupchinsky *et al*., 1998; Moreno-Manas *et al*., 1992; Czollner *et al*., 1990; Orbai and Moneim, 2001; Er-Rhaimini and Mornet, 1992; Silvester, 1994). Also, such

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Published online: 15 May 2009

triazoles derivatives have been found to elicit their role, as peptide nanotubes (Horne *et al*., 2003, 2004; Van Maarseveen *et al*., 2005), protease inhibitors (Whiting *et al*., 2006), cyclopeptide analogues (Roice *et al*., 2004; Punna *et al*., 2005; Angell and Burgess, 2005; Bock *et al*., 2006), and as peptide chain analogues (Angelo and Arora, 2005; Aucagne and Leigh, 2006; Montagnat *et al*., 2006; Paul *et al*., 2006; Zhang and Fan, 2006). However, due to the lack of convenient direct methods for their synthesis, these aromatic heterocycles have not received as much attention as they deserve.

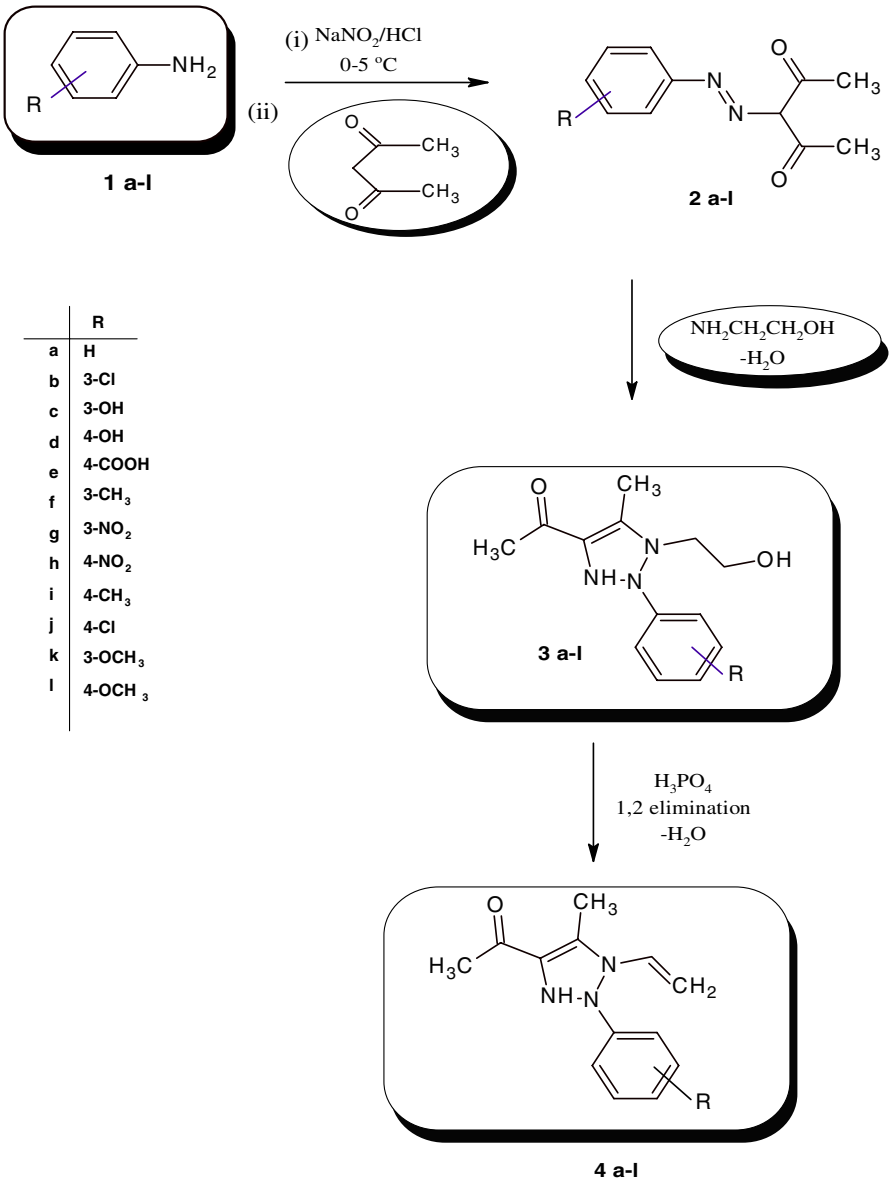
Now, various combinations of several classes of triazole-based antifungal agents (e.g., fluconazole, itraconazole, voriconazole, and posaconazole) are available commercially with their significant drug resistance capability. A systematic perusal of literature revealed that recently a variety of methods have been developed for the synthesis of triazole derivatives, including metal catalyzed synthesis and solvent-free synthesis (Amantini *et al*., 2005; Barral *et al*., 2007; Barluenga *et al*., 2006; Chuprakov *et al*., 2007; Kamijo *et al*., 2003; Lipshutz and Taft, 2006; Rodionov *et al*., 2007).

Buoyed from aforementioned information and in continuation of our previous work on versatile synthesis of biologically active heterocyclic compounds (Sharma *et al*., 2005, 2006a, b, c), this study was designed to compose an elegant synthetic route for a series of 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a–l**) using accessible starting materials. Furthermore, in the present study, we have evaluated the in vitro antifungal activity against a number of fungal microbes: *A. niger, C. albicans, C. azyma, A. flavus.* The resultant SAR screening parameters revealed that the representative compounds possess profound antifungal activities. Furthermore, of a number of various physiochemical parameters, Log P (log of n-octanol water partition coefficient) has been chosen as the most promising parameter, which influences the biological activity to a greater extent.

Chemistry

A series of biologically active 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro 1*H*-1,2,3-triazole derivatives (**4a–l**) were synthesized by initial diazotization of various substituted anilines (**1a–l**) under temperature-controlled conditions (0–5°C). It was followed by treatment with active methylene compound in the presence of mild base to form 3-arylazo-pentane 2,4-dione (**2a–l**). In a subsequent step, 3-arylazo-pentane 2,4-dione (**2a–l**) was refluxed with 2-ethanolamine in presence of potassium acetate to afford 5-membered cyclized product, i.e., 4-acetyl-2-aryl-5-methyl-*N*-hydroxy ethyl-2,3-dihydro-1*H*-1,2,3-triazole (**3a–l**). It was refluxed under acidic condition for 5 h to afford the requisite 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a–l**) in 80–85% yield. The precipitate so obtained were washed with water and recrystallized with ethyl alcohol. The reaction sequence for the title compounds is outlined in Scheme 1.

All synthesized compounds were found in good agreement with the elemental analysis. The structural assignments are in accordance with IR and ^{1}H NMR spectral data. Furthermore, the calculated heat of formations (ΔH) at PM3 semiempirical



Scheme 1 Overview of synthetic pathway of 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a**–**l**)

method using MOPAC 2007 program for the representative compound **4a** was −62.70 kcal/mol, which is in accordance with the stability of 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole derivatives. PM3 optimized geometry of a representative compound (**4a**) is depicted in Fig. 1.

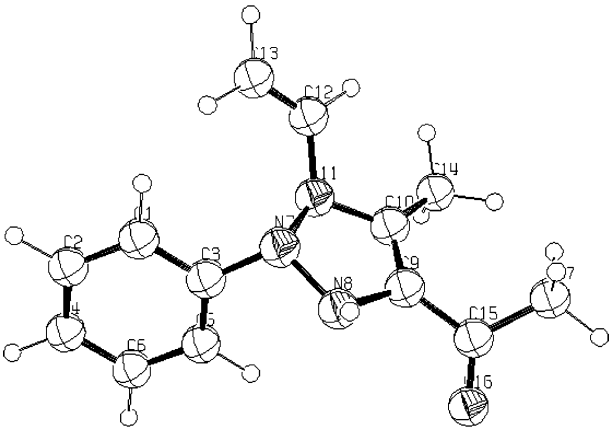


Fig. 1 PM3 optimized ORTEP view of 4-acetyl-2-phenyl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a**)

Results and discussion

All the newly synthesized compounds have been successfully screened in vitro for their antifungal activities against an assortment of fungi, i.e., *Aspergillus niger* 281, *Candida albicans* 227, *Aspergillus flavus* 871, and *Candida azyma*1452 using paper disc method. The saboured dextrose agar media was used for fungal growth. Inocula containing approximately 10^7 colony forming units (CFU) per milliliter of fungi were prepared from broth culture in log phase. The fungi plate was incubated at 30°C for 28 hours. Voriconazole was screened under similar conditions as reference antifungal drug. All of the synthesized compounds delineate significant antimicrobial potency against tested fungal microbes compared with the reference drug, which is further supported by biological investigations shown in Table 1. All tests were conducted in the three replications. The biological activities were reported (Table 1) in terms of percent of inhibition, i.e., % Inhibition $= \{(\alpha - \beta)/\alpha\} \times 100$, where α and β stands for the zone of inhibition of reference drug and synthesized compounds, respectively.

To find out log P (Skagerbeg *et al*., 1989), the calculations were performed at SCF (self consistent field theory) level using PM3 (Hamiltonian Inc.) in MOPAC 6.0 package (Stewart, 1989, 1990). Geometry optimization of all synthesized compound was performed by using Chem 3D software. An overview of the antifungal data shows that the synthesized 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole derivatives (**4a–l**) gave promising results when tested in vitro against various fungi.

It is revealed from the data presented in Table 1 that the compounds bearing chloro, methyl, and methoxy substituent are more active. Hence, alkylation of hydroxyl group tends to enhance the antifungal activity. Also, meta substituted derivatives are more active compared with para substituted. Thus, 4-acetyl-2-(3'-chloro) phenyl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4b**) is highly active. In general, it has been observed that antifungal results follow the pattern:

Table 1 Antifungal screening studies of 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a-l**)

	R	Log P	Percent inhibition ($\alpha - \beta/\alpha \times 100$)			
			C. albicans	*A. niger*	*C. azyma*	*A. flavus*
4a	H	3.33	−31.25	−33.33	−26.67	−13.33
4b	3–Cl	4.04	−93.75	−100.00	−86.67	−73.33
4c	3–OH	2.66	18.75	11.11	26.67	40.00
4d	4–OH	2.66	25.00	16.67	33.33	46.67
4e	4–COOH	3.07	6.25	−11.11	6.67	33.33
4f	3–CH_3	3.82	−62.50	−72.22	−60.00	−46.67
4g	3–NO_2	3.31	−6.25	−33.33	0.00	13.33
4h	4–NO_2	3.31	0.00	−27.78	6.67	20.00
4i	4–CH_3	3.82	−56.25	−66.67	−53.33	−40.00
4j	4–Cl	4.04	−87.50	−94.44	−80.00	−66.67
4k	3–OCH_3	3.36	−43.75	−50.00	−40.00	−26.67
4l	4–OCH_3	3.36	−37.50	−44.44	−33.33	−20.00

Values of α for control drug (voriconazole) are 16, 18, 15, and 15 mm against *C. albicans, A. niger, C. azyma,* and *A. flavus,* respectively

3-Cl > 4-Cl > 3-CH_3 > 4-CH_3 > 3-OCH_3> 4-OCH_3 > H > 3-NO_2 > 4-NO_2 > 4-COOH > 3-OH > 4-OH.

The screening results revealed that the synthesized compounds are highly active against *A. niger* and least against *A. flavus* (Fig. 2). In general activity follows the pattern: *A. niger* > *C. albicans* > *C. azyma*, > *A. flavus*.

Furthermore, hydrophobic properties have been quantized for correlation of structure with biological activity. The data exhibited in Table 1 reveal that the chloro derivative has high value of log P, i.e., 4.04 and the hydroxyl group containing compound has low value of log P, i.e., 2.66. Thus, it is inferred that triazole derivative having chloro group exhibit more antifungal activity than compounds possessing hydroxyl group. A perusal of data reveals a significant correlation ($r^2 = 0.9$–0.97) between biological activity and log P against all microbes. Also, the standard deviation does not exceed ±1.396 (Fig. 3).

Conclusively, we have synthesized a new series of active 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole derivatives (**4a**–**l**) in a highly efficient manner. Furthermore, antifungal studies performed on these compounds revealed that they gave promising results when tested in vitro against various fungi. Hydrophobic properties also justify the correlation of structure with elicited biological activity. The value of log P exhibited a good correlation ($r^2 > 0.9$) with biological activity.

Experimental procedure

All the chemicals used were of AR grade purity. IR spectra were recorded on Perkin Elmer model 377 spectrophotometer in KBr pellets. IR frequencies were measured

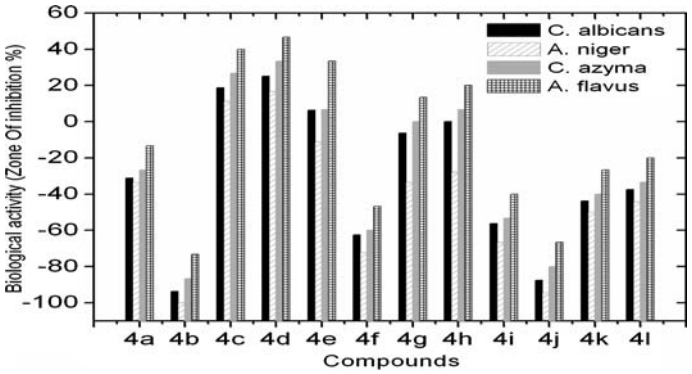


Fig. 2 Graphical representation of biological activity of substituted 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro 1*H*-1,2,3-triazole (**4a–l**)

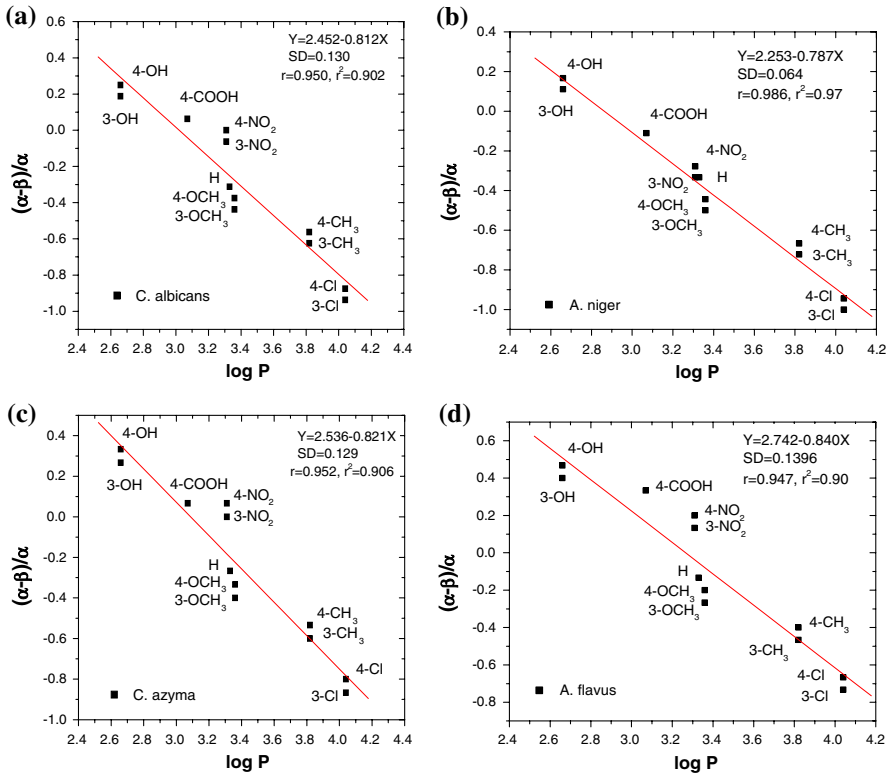


Fig. 3 Plot of biological activity verses log P screened against **a** *C. albicans*, **b** *A. niger*, **c** *C. azyma* **d** *A. flavus*

in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at 25°C on a Bruker DRX-300 instrument (300 MHz FT NMR with low and high temperature facility −90°C to +80°C) with deuterium signal as the lock and TMS

as internal standard. Chemical shifts were measured in δ ppm units. The melting points were determined on an electric melting point apparatus (Biotech Bombay, India) in open capillaries and are uncorrected. The purity of all the synthesized compounds was ascertained by TLC resolution on silica gel-G (E Merck) using acetic acid-toluene (4:6, v/v) as binary eluent. Elemental analyses were performed on Elemental analyzer (Elemental Vario, EL III Carlo Erba 1108) at Central Drug Research Institute, Lucknow, India.

General procedure for the synthesis of 3-arylazo-pentane 2,4-dione (Jain and Pandey, 1987) (**2a–l**)

Pertinent aniline derivatives (**1a–l**) (0.01 M) were dissolved in 4.0 ml of HCl and 4.0 ml of distilled water and kept at freezing temperature in the refrigerator. To this, an aqueous solution of sodium nitrite (2 g, 0.01 M) in 4 ml of distilled water was added drop wise with continuous stirring keeping the temperature in the vicinity of 0–5°C. Meanwhile, in another beaker acetyl acetone (2 g, 0.01 M), sodium acetate (7 g, 0.01 M) and 20 ml of ethyl alcohol were taken and cooled in an ice bath. The diazotized solution was added to this solution drop wise with thorough stirring under temperature-controlled conditions. The reaction mixture was kept for overnight period, filtered through suction, washed with water, and dried in vacuum. Fine, yellow crystals of the 3-arylazo-pentane 2,4-dione (**2a–l**) were obtained, which were recrystallized from a mixture of DMF and ethyl alcohol.

Synthesis of 4-acetyl-2-aryl-5-methyl-*N*-hydroxy ethyl-2, 3-dihydro-1*H*-1,2,3-triazole (**3a–l**)

In a 250-ml, round-bottom flask, 3-phenylazo-pentane 2,4-dione (**2a–l**) (0.15 M) and 2-hydroxy ethanolamine (13.7 g, 2.25 M) in alcoholic solution of potassium acetate (4.6 g, 2.25 M) in 25 ml of ethyl alcohol as a solvent were taken and stirred at room temperature. After stirring for 30 min, precipitate that was generated was filtered and washed with 10 ml of ethyl alcohol. The fine crystals of 4-acetyl-2-aryl-5-methyl-*N*-hydroxy ethyl-2,3-dihydro-1*H*-1,2,3-triazole (**3a–l**) were obtained in good yield.

Synthesis of 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a–l**)

In a 250-ml, round-bottom flask, 4-acetyl-2-aryl-5-methyl-*N*-hydroxy ethyl-2,3-dihydro-1*H*-1,2,3-triazole (**3a–l**) (0.67 M) and 25 ml of 85% ortho-phosphoric acid were taken and refluxed for 30 minutes in the presence of porous porcelain in ethyl alcohol. After cooling to room temperature, precipitate that was obtained was filtered, thoroughly washed with water, and recrystallized from ethyl alcohol. Fine, yellow crystals of 4-acetyl-2-aryl-5-methyl-1-vinyl-2,3-dihydro-1*H*-1,2,3-triazole (**4a–l**) were obtained in 80–85% yield.

*4-Acetyl-2-phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3a**)*

IR (v, cm^{-1}); 3585 (O–H), 3410 (–NH, five membered), 2850, 2940 (C–H, sp^3), 3055 (C–H, sp^2), 2955 (C–H, sp^2), 1711 (C=O), 1610 (C=C), 1475, 1455 (C·····C, ring str.), 1336 (C–N), 1050 (C–O), 948, 892, 825 (sub. phenyl). ^{1}HNMR (δ ppm); 2.34 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 3.72 (s, 1H, OH), 3.91 (t, 2H, CH_2), 4.03 (t, 2H, CH_2), 7.52 (s, 5H, Ar–H), 12.32 (s, 1H, NH); FAB-MS (M^++H) 248; mp (°C) 150–151; Yield (%) 78; Found (calcd) % C, 63.10 (63.14); H, 6.91 (6.93); N, 16.95 (16.99).

*4-Acetyl-2-(3′-chloro)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3b**)*

IR (v, cm^{-1}); 3580 (O–H), 3442 (NH, five membered), 3086 (C–H, sp^2), 2878, 2935 (C–H, sp^3), 1698 (C=O), 1618 (C=C), 1586, 1553, 1405 (C·····C, ring str.), 1343 (C–N), 1052 (C–O), 812, 801 (sub phenyl), 582 (C–Cl). ^{1}HNMR (δ ppm); 2.37 (s, 3H, CH_3), 2.54 (s, 3H, $COCH_3$), 3.75 (s, 1H, OH),3.89 (t, 2H, CH_2), 4.10 (t, 2H, CH_2), 7.31–7.62 (m, 4H, Ar–H), 12.21 (s, 1H, NH); FAB-MS (M^++H) 283; mp (°C) 142–143; Yield (%) 82; Found (calcd) % C, 55.38 (55.42); H, 5.69 (5.72); N, 14.89 (14.91).

*4-Acetyl-2-(3′-hydroxy)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3c**)*

IR (v, cm^{-1}); 3685 (OH, Free), 3425 (NH, five membered), 3091 (C–H, sp^2), 2855, 2942 (C–H, sp^3), 1708 (C=O), 1659 (C=C), 1597, 1553, 1508 (C·····C, ring str.), 1339 (C–N), 1048 (C–O), 903, 812, 752 (sub phenyl). ^{1}HNMR (δ ppm); 2.34 (s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.64 (s, 1H, OH), 3.89 (t, 2H, CH_2), 4.08 (t, 2H, CH_2), 6.81–7.21 (m, 4H, Ar–H), 8.14 (s, 1H, OH), 12.5 (s, 1H, NH); FAB-MS (M^++H) 264; mp (°C) 141–142; Yield (%)75; Found (calcd) % C, 59.25 (59.30); H, 6.48 (6.51); N, 15.90 (15.96).

*4-Acetyl-2-(4′-hydroxy)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3d**)*

IR (v, cm^{-1}); 3665 (OH, Free), 3430 (NH, five membered), 2860, 2952 (C–H, sp^3), 3095 (C–H, sp^2), 1712 (C=O), 1655 (C=C), 1595, 1557, 1505 (C·····C, ring str.), 1341 (C–N), 1049 (C–O), 906, 815, 754 (sub phenyl). ^{1}HNMR (δ ppm); 2.34 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 3.82 (s, 1H, OH), 3.86 (t, 2H, CH_2), 4.13 (t, 2H, CH_2), 6.9–7.3 (m, 4H, Ar–H), 8.36 (s, 1H, OH), 12.42 (s, 1H, NH); FAB-MS (M^++H) 264; mp (°C) 137–138; Yield (%)78; Found (calcd) % C, 59.25 (59.30); H, 6.48 (6.51); N, 15.90 (15.96).

*4-acetyl-2-(4′-carboxy)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3e**)*

IR (v, cm^{-1}); 3300–2617 (OH, br), 3436 (NH, five membered), 2862, 2948 (C–H, sp^3), 3100 (C–H, sp^2), 1705 (C=O), 1652 (C=C), 1593, 1554, 1507 (C·····C, ring

str.), 1340 (C–N), 1053 (C–O), 902, 815, 752 (sub phenyl). ^{1}HNMR (δ ppm); 2.34 (s, 3H, CH_3), 2.57 (s, 3H, $COCH_3$), 3.82 (s, 1H, OH), 3.85 (t, 2H, CH_2), 4.15 (t, 2H, CH_2), 7.62–8.11 (m, 4H, Ar–H) 11.12 (s, H, OH), 12.33 (s, 1H, NH); FAB-MS (M^++H) 292; mp (°C) 147–148; Yield (%)74; Found (calcd) % C, 57.68 (57.72); H, 5.82 (5.88); N, 14.37(14.42).

*4-acetyl-2-(3′-methyl)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3f**)*

IR (v, cm^{-1}); 3658 (OH, Free), 3430 (NH, five membered), 2862, 2956 (C–H, sp^3), 3108 (C–H, sp^2), 1715 (C=O), 1658 (C=C), 1597, 1553, 1512 (C·····C, ring str.), 1333 (C–N), 1052 (C–O), 912, 805, 754 (sub phenyl). ^{1}HNMR (δ ppm); 2.11 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.83 (t, 2H, CH_2), 3.89 (s, 1H, OH), 4.10 (t, 2H, CH_2), 6.91–7.32 (m, 4H, Ar–H), 12.52 (s, 1H, NH); FAB-MS (M^++H) 262; mp (°C) 130–131; Yield (%)70; Found (calcd) % C, 64.31 (64.35); H, 7.31 (7.33); N, 16.04 (16.08).

*4-acetyl-2-(3′-nitro)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3g**)*

IR (v, cm^{-1}); 3651 (OH, Free), 3315 (–NH), 3005 (C–H, sp^2), 2868, 2958 (C–H, sp^3), 3009 (C–H, sp^2), 1715 (C=O), 1621 (C=C), 1471, 1452 (C·····C, ring str.), 1555, 1372 (–NO_2), 1342 (C–N), 1052 (C–O), 946, 894, 822 (sub. phenyl). ^{1}HNMR (δ ppm); 2.29 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 3.82 (t, 2H, CH_2), 3.88 (s, 1H, OH), 4.05 (t, 2H, CH_2), 7.51–8.21 (m, 4H, Ar–H), 12.28 (s, 1H, NH); FAB-MS (M^++H) 293; mp (°C) 135–136; Yield (%) 73; Found (calcd) % C, 53.39 (53.42); H, 5.50 (5.52); N, 19.14 (19.17).

*4-acetyl-2-(4′-nitro)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3h**)*

IR (v, cm^{-1}); 3650 (OH, Free), 3315 (–NH), 3006 (C–H, sp^2), 2862, 2953 (C–H, sp^3), 1712 (C=O), 1627 (C=C), 1471, 1453 (C·····C, ring str.), 1552, 1376 (–NO_2), 1334 (C–N), 1053 (C–O), 952, 895, 820 (sub. phenyl). ^{1}HNMR (δ ppm); 2.32 (s, 3H, CH_3), 2.54 (s, 3H, $COCH_3$), 3.72 (s, 1H, OH), 3.88 (t, 2H, CH_2), 4.15 (t, 2H, CH_2), 7.45–8.33 (m, 4H, Ar–H), 12.5 (s, 1H, NH); FAB-MS (M^++H) 293; mp (°C) 130–131; Yield (%)78; Found (calcd) % C, 53.39 (53.42); H, 5.50 (5.52); N, 19.14 (19.17).

*4-acetyl-2-(4′-methyl)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3i**)*

IR (v, cm^{-1}); 3655 (OH, Free), 3432 (NH, five membered), 2862, 2954 (C–H, sp^3), 3105 (C–H, sp^2), 1714 (C=O), 1658 (C=C), 1597, 1551, 1510 (C·····C, ring str.), 1332 (C–N), 1048 (C–O), 912, 805, 752 (sub phenyl). ^{1}HNMR (δ ppm); 2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.71 (s, 1H, OH), 3.83 (t, 2H, CH_2),

4.10 (t, 2H, CH_2), 7.33 (m, 4H, Ar–H), 12.6 (s, 1H, NH); FAB-MS (M^++H) 262; mp (°C) 132–133; Yield (%)71; Found (calcd) % C, 64.31 (64.35); H, 7.31 (7.33); N, 16.04 (16.08).

*4-acetyl-2-(4′-chloro)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3j**)*

IR (v, cm^{-1}); 3634 (OH, Free), 3445 (NH, five membered), 3063 (C–H, sp^2), 2868, 2958 (C–H, sp^3), 1680 (C=O), 1643 (C=C), 1580, 1551, 1401 (C·····C, ring str.), 1342 (C–N), 1046 (C–O), 811, 807 (sub phenyl), 583 (C–Cl). ^{1}HNMR (δ ppm); 2.34 (s, 3H, CH_3), 2.56 (s, 3H, $COCH_3$), 3.79 (s, 1H, OH), 3.82 (t, 2H, CH_2), 4.05 (t, 2H, CH_2), 7.32–7.66 (m, 4H, Ar–H), 12.1 (s, 1H, NH); FAB-MS (M^++H) 283; mp (°C) 140–141; Yield (%) 78; Found (calcd) % C, 55.38 (55.42); H, 5.69 (5.72); N, 14.88 (14.91).

*4-acetyl-2-(3′-methoxy)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3k**)*

IR (v, cm^{-1}); 3660 (OH, Free), 3442 (NH, five membered), 3046 (C–H, sp^2), 2862, 2949 (C–H, sp^3), 1713 (C=O), 1652 (C=C), 1587, 1551, 1516 (C·····C, ring str.), 1335 (C–N), 1046 (C–O), 913, 814, 756 (sub phenyl). ^{1}HNMR (δ ppm); 2.39 (s, 3H, CH_3), 2.56 (s, 3H, $COCH_3$), 3.71 (s, 3H, OCH_3), 3.82 (t, 2H, CH_2), 3.86 (s, 1H, OH), 4.13 (t, 2H, CH_2), 6.80–7.32 (m, 4H, Ar–H), 12.62 (s, 1H, NH); FAB-MS (M^++H) 278; mp (°C) 130–131; Yield (%)70; Found (calcd) C, 60.60 (60.63); H, 6.88 (6.91); N, 17.28 (17.31).

*4-acetyl-2-(4′-methoxy)phenyl-5-methyl-N-hydroxy ethyl-2,3-dihydro-1H-1,2,3-triazole (**3l**)*

IR (v, cm^{-1}); 3585 (OH, Free), 3442 (NH, five membered), 3056(C–H, sp^2), 2868, 2958 (C–H, sp^3), 1718 (C=O), 1650 (C=C), 1586, 1551, 1515 (C·····C, ring str.), 1332 (C–N), 1048 (C–O), 912, 815, 758 (sub phenyl). ^{1}HNMR (δ ppm); 2.35 (s, 3H, CH_3), 2.52 (s, 3H, $COCH_3$), 3.77 (s, 3H, OCH_3), 3.85 (t, 2H, CH_2), 3.96 (s, 1H, OH), 4.10 (t, 2H, CH_2), 6.71–7.42 (m, 4H, Ar–H), 12.2 (s, 1H, NH); FAB-MS (M^++H) 278; mp (°C) 134–135; Yield (%)73; Found (calcd) C, 60.60 (60.63); H, 6.88 (6.91); N, 17.28 (17.31).

*4-Acetyl-2-phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4a**)*

IR (v, cm^{-1}); 3408 (–NH, five membered), 3030 (C–H, sp^2), 2926 (C–H, sp^2), 1707 (C=O), 1625(C=C), 1473, 1451 (C·····C, ring str.), 1242(C–N), 949, 894, 826 (sub. phenyl). ^{1}HNMR (δ ppm); 2.36 (s, 3H, CH_3), 2.57 (s, 3H, $COCH_3$), 5.10 (d, 2H, CH_2), 5.49 (t, 1H, CH), 7.5 (s, 5H, Ar–H), 12.3 (s, 1H, NH); FAB MS (M^++H) 230; mp (°C) 143–144; Yield (%)79; Found (calcd) % C, 68.01 (68.10); H, 6.51 (6.59); N, 18.24 (18.33).

*4-Acetyl-2-(3′-chloro)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4b**)*

IR (v, cm^{-1}); 3448 (NH, Five membered), 3086 (C–H, sp^2), 2878 (C–H, sp^3), 1698 (C=O), 1643 (C=C), 1641(C=C), 1589, 1552,1403 (C·····C, ring str.), 1441 (C–N), 812, 800 (sub phenyl), 586 (C–Cl). ^{1}HNMR (δ ppm); 2.35 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 5.09 (d, 2H, CH_2), 5.45 (t, 1H, CH), 7.0–7.4 (m, 4H, Ar–H), 12.4 (s, 1H, NH); FAB MS (M^++H) 265; mp (°C) 140–141; Yield (%) 80; Found (calcd) % C, 59.14 (59.21); H, 5.29 (5.35); N, 15.93 (15.86).

*4-Acetyl-2-(3′-hydroxy)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4c**)*

IR (v, cm^{-1}); 3755 (OH, Free), 3436 (NH, five membered), 3091(C–H, sp^2), 2836 (C–H, sp^3), 1708 (C=O), 1659(C=C), 1599, 1555, 1508 (C·····C, ring str.), 1444 (C–N), 905, 815, 753 (sub phenyl). ^{1}HNMR (δ ppm); 2.36 (s, 3H, CH_3), 2.59 (s, 3H, $COCH_3$), 5.0 (s, 3H, OH), 5.12 (d, 2H, CH_2), 5.47 (t, 1H, CH_2), 6.8–7.1 (m, 4H, Ar–H), 12.6 (s, 1H, NH); FAB MS (M^++H) 246; mp (°C) 136–137; Yield (%)72; Found (calcd) % C, 63.59 (63.66); H, 6.08 (6.16); N, 17.06 (17.13).

*4-Acetyl-2-(4′-hydroxy)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4d**)*

IR (v, cm^{-1}); 3758 (OH, Free), 3438 (NH, five membered), 3092 (C–H, sp^2), 2837 (C–H, sp^3), 1710 (C=O), 1660 (C=C), 1600, 1556, 1506 (C·····C, ring str.), 1446 (C–N), 907, 813, 751 (sub phenyl). ^{1}HNMR (δ ppm); 2.37 (s, 3H, CH_3), 2.61 (s, 3H, $COCH_3$), 5.3 (s, 3H, OH), 5.11 (d, 2H, CH_2), 5.49 (t, 1H, CH), 6.9–7.3 (m, 4H, Ar–H), 12.4 (s, 1H, NH); FAB MS (M^++H) 246; mp (°C) 132–133; Yield (%)74; Found (calcd) % C, 63.55 (63.66); H, 6.02 (6.16); N, 17.02 (17.13).

*4-Acetyl-2-(4′-carboxy)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4e**)*

IR (v, cm^{-1}); 3756 (OH, Free), 3434 (NH, five membered), 3100 (C–H, sp^2), 2841 (C–H, sp^3), 1700 (C=O), 1657 (C=C), 1597, 1553, 1509 (C·····C, ring str.), 1442 (C–N), 904, 814, 751 (sub phenyl). ^{1}HNMR (δ ppm); 2.36 (s, 3H, CH_3), 2.59 (s, 3H, $COCH_3$), 5.15 (d, 2H, CH_2), 5.48 (t, 1H, CH), 7.6–8.1 (dd, 4H, Ar–H) 11.1 (s, 3H, OH), 12.3 (s, 1H, NH); FAB MS (M^++H) 274; mp (°C) 137–138; Yield (%)68; Found (calcd) % C, 61.42 (61.53); H, 5.42 (5.53); N, 15.27(15.38).

*4-Acetyl-2-(3′-methyl)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4f**)*

IR (v, cm^{-1}); 3434 (NH, five membered), 3108 (C–H, sp^2), 2892 (C–H, sp^3), 1717 (C=O), 1661 (C=C), 1598, 1555, 1510 (C·····C, ring str.), 1435 (C–N), 910, 806, 753 (sub phenyl). ^{1}HNMR (δ ppm); 2.31 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.52 (s, 3H, $COCH_3$), 5.12 (d, 2H, CH_2), 5.41 (s, 1H, CH), 7.2 (s, 4H, Ar–H), 12.6 (s, 1H, NH); FAB MS (M^++H) 244; mp (°C) 130–131; Yield (%)70; Found (calcd) % C, 69.01 (69.11); H, 6.89 (7.04); N, 17.21 (17.27).

*4-Acetyl-2-(3′-nitro)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4g**)*

IR (v, cm^{-1}); 3309 (–NH), 3005 (C–H, sp^2), 2930 (C–H, sp^2), 1710 (C=O), 1623 (C=C), 1475, 1455 (C·····C, ring str.), 1581, 1376 ($–NO_2$), 1240 (C–N), 949, 893, 821 (sub. phenyl). ^{1}HNMR (δ ppm); 2.30 (s, 3H, CH_3), 2.50 (s, 3H, $COCH_3$), 5.08 (d, 2H, CH_2), 5.46 (s, CH), 7.5–8.2 (m, 4H, Ar–H), 12.3 (s, 1H, NH); FAB MS (M^++H) 275; mp (°C) 143–144; Yield (%) 79; Found (calcd) % C, 56.82 (56.93); H, 5.01 (5.14); N, 20.35 (20.43).

*4-Acetyl-2-(4′-nitro)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4h**)*

IR (v, cm^{-1}); 3308 (–NH), 3006 (C–H, sp^2), 2929 (C–H, sp^2), 1708 (C=O), 1624 (C=C), 1474, 1455 (C·····C, ring str.), 15821, 1378 ($–NO_2$), 1240 (C–N), 951, 894, 821 (sub. phenyl).^{1}HNMR (δ ppm); 2.31(s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 5.09 (d, 2H, CH_2), 5.48 (s, CH), 7.4–8.3 (dd, 4H, Ar–H), 12.5 (s, 1H, NH); FAB MS (M^++H) 275; mp (°C) 140–141; Yield (%)76; Found (calcd) % C, 56.86 (56.93); H, 5.05 (5.14); N, 20.32 (20.43).

*4-Acetyl-2-(4′-methyl)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4i**)*

IR (v, cm^{-1}); 3432 (NH, five membered), 3111(C–H, sp^2), 2896 (C–H, sp^3), 1720 (C=O), 1675 (C=C), 1600, 1557, 1512 (C·····C, ring str.), 1431 (C–N), 911, 808, 751 (sub phenyl). ^{1}HNMR (δ ppm); 2.32 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 5.12 (d, 2H, CH_2), 5.42 (s, 1H, CH), 7.6 (s, 4H, Ar–H), 12.6 (s, 1H, NH); FAB MS (M^++H) 244; mp (°C) 132–133; Yield (%)69; Found (calcd) % C, 69.02 (69.11); H, 6.96 (7.04); N, 17.18 (17.27).

*4-Acetyl-2-(4′-chloro)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4j**)*

IR (v, cm^{-1}); 3450 (NH, five membered), 3083 (C–H, sp^2), 2871 (C–H, sp^3), 1686 (C=O), 1644 (C=C), 1643(C=C), 1587, 1553, 1404 (C·····C, ring str.), 1443 (C–N), 810, 809 (sub phenyl), 584 (C–Cl). ^{1}HNMR (δ ppm); 2.34 (s, 3H, CH_3), 2.56 (s, 3H, $COCH_3$), 5.12 (d, 2H, CH_2), 5.42 (s, CH), 7.2–7.3 (dd, 4H, Ar–H), 12.1 (s, 1H, NH); FAB MS (M^++H) 265; mp (°C) 143–144; Yield (%) 82; Found (calcd) % C, 59.15 (59.21); H, 5.26 (5.35); N, 15.93 (15.86).

*4-Acetyl-2-(3′-methoxy)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4k**)*

IR (v, cm^{-1}); 3433 (NH, five membered), 3053 (C–H, sp^2), 2833 (C–H, sp^3), 1710 (C=O), 1655 (C=C), 1590, 1554, 1510 (C·····C, ring str.), 1429 (C–N), 910, 820, 755 (sub phenyl). ^{1}HNMR (δ ppm); 2.39 (s, 3H, CH_3), 2.57 (s, 3H, $COCH_3$), 3.73 (s, 3H, OCH_3), 5.13 (d, 2H, CH_2), 5.44 (s, 1H, CH), 6.8–7.3 (m, 4H, Ar–H), 12.6 (s, 1H, NH); FAB MS (M^++H) 260; mp (°C) 142–143; Yield (%) 76; Found (calcd) C, 64.72 (64.85); H, 6.50 (6.61); N, 16.12 (16.20).

*4-Acetyl-2-(4′-methoxy)phenyl-5-methyl-1-vinyl-2,3-dihydro-1H-1,2,3-triazole (**4l**)*

IR (v, cm^{-1}); 3434 (NH, five membered), 3056 (C–H, sp^2), 2835 (C–H, sp^3), 1712 (C=O), 1656 (C=C), 1589, 1553, 1512 (C·····C, ring str.), 1433 (C–N), 911, 818, 753 (sub phenyl). ^{1}HNMR (δ ppm); 2.37 (s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.78 (s, 3H, OCH_3), 5.15 (d, 2H, CH_2), 5.46 (s, 1H, CH), 6.7–7.2 (dd, 4H, Ar–H), 12.2 (s, 1H, NH); FAB MS (M^++H) 260; mp (°C) 140–141; Yield (%)75; Found (calcd) C, 64.70 (64.85); H, 6.52 (6.61); N, 16.13 (16.20).

Acknowledgements The authors thank Central Drug Research Institute, Lucknow, India, for providing spectroanalytical facilities and to the Council of Scientific and Industrial Research (CSIR), New Delhi, for providing research fellowship to one of the authors (VS).

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