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Research Article

SYNTHESIS AND CHARACTERIZATION OF *N*-SUBSTITUTED-5-METHYL-1-(4-METHYLPHENYL)-1*H*-1, 2, 3-TRIAZOLE-4-CARBOXAMIDE DERIVATIVES

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ABSTRACT

A series of *N*-substituted-5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide derivatives were synthesized by treating 5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid with thionyl chloride followed by reaction with various amines. IR, ^1H NMR spectra and mass spectral data are confirming the synthesis of *N*-substituted-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide derivatives.

Keywords: *N*-substituted-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid, 1-azido-4-methylbenzene, 1-azido-4-methylbenzene.

INTRODUCTION

Triazoles, like many other five membered heterocyclic compounds are used very often in the pharmacological and medicinal applications. 1, 2, 3–triazole and its derivatives enhanced considerable attention for the past few decades due to their chemotherapeutical value. Many 1,2,3–triazoles are found to be more potent anti-microbial [9], anti-inflammatory [12], analgesic [1], local anesthetic [2], antiallergic, anti-convulsant [8], antineoplastic [11], anti malarial [7], anti-HIV [3] and anti cancer activities [4]. Some of the 1, 2, 3-triazoles are used as deoxyribose nucleic acid (DNA) cleaving agents [13] and potassium channel activators [6, 11]. These moieties have been widely used in the synthetic intermediates and industrial applications, such as dyes, anti corrosive agents, photo stabilizers, photographic materials and agrochemicals [5].

1, 2, 3-Triazoles are useful building blocks in chemistry and are stable to moisture, oxygen, light and also metabolism in the body. Moreover, these moieties can be turned to form powerful pharmacophores and also plays an important role in bio-conjugation. 1, 2, 3-Triazole moieties are attractive connecting units, since they are stable to metabolic degradation and capable of hydrogen bonding which can be favorable in binding of biomolecular targets. In view of pharmacological significance of triazole derivatives, we were planned to synthesize some new triazole (*N*-Substituted-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide derivatives) derivatives.

MATERIALS AND METHODS

Reagents used in the present work includes 4-Methylaniline, Sodium nitrite, sodium azide, sodium ethoxide, Thionyl chloride, Benzylamine, N,N-diethylethylenediamine, dilute HCl, anhydrous sodium sulfate, ethyl acetate, ethylacetoacetate, chloroform, methylene dichloride, sodium hydroxide were obtained from the NATCO research centre, Sanathnagar, Hyderabad. All these reagents were of Analytical grade. Both ^1H-NMR and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker NMR spectrophotometer in $CDCl_3$ or CD_3OD and chemical shifts (δH) are expressed in parts per million (δ) relative to tetramethylsilane (TMS). Mass spectra were obtained with a Varian 1200L (-70eV) instrument with straight penetration by an electronic impact, and IR spectra were recorded on Perkin Elmer spectrophotometer by using KBr pellets. Melting points were taken in open capillary tubes and are uncorrected. Reactions were monitored by thin layer chromatographic (TLC) technique using silica gel plates.

Preparation of 1-azido-4-methylbenzene (III)

P- Toluidine (I) (25.0 g) was dissolved in 250 ml of dilute HCl (1:1) in a Round Bottomed (RB) flask. Reaction mass was cooled to -10°C to -5°C. Sodium nitrite (16.12 g) was added in small portions (4 portions) to the reaction mass by maintaining the temperature at -10°C to 0°C and maintained the reaction for 2 hr. A solution of sodium azide (30.37 g in 123 ml DM H_2O) was added in a drop wise manner to the reaction mixture at 0°C. After addition maintained the reaction at 0°C for 1hr, sodium acetate solution (383.17 g in 927 ml of distilled H_2O) was added from addition funnel to the reaction mass. Reaction mixture was stirred for 1hr at 0°C. The progress of the reaction was monitored by TLC. The product was extracted by using ethyl acetate followed by washing with water up to neutral pH. Organic layer was dried with anhydrous sodium sulfate and then concentrated by distillation at room temperature.

Preparation of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV)

Sodium ethoxide and ethylacetoacetate (2.5:1.0) were taken into a RB flask. Reaction must be carried out under N_2 atmosphere. 1-azido-4-methylbenzene (31 g) (III) was added drop wise to the reaction mass. Raise the temperature of the reaction mass up to refluxion. Reaction was monitored by TLC. If TLC shows positive, reaction mass was quenched in to ice water. pH of the reaction mixture was adjusted to acidic by using 10 N HCl leads to solid formation. Filtered the reaction mass and the solid was dried.

R = CH_3 (M.P: 180-185°C), R = OCH_3 (M.P: 187-190°C).

Preparation of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carbonyl chloride (V)

4.0 g of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV) was dissolved in 70 ml of $CHCl_3$ in a RB flask with stirring under N_2- atmosphere. Thionyl chloride (4.03 ml) was added to the reaction mass at room temperature in drop wise manner. Reflux the reaction mass for 3 hr. Cool the reaction mixture and distilled off the excess thionyl chloride.

Preparation of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide derivatives (VI)

Benzylamine (1.56 ml) and methylene dichloride (15 ml) were taken in to a RB flask. Cool the reaction mass to 0-5°C. A solution of 5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carbonyl chloride (V) (7.04 g in 5 ml of methylene dichloride) was added drop wise to the reaction mass between 0°C and 5°C. After addition, raised the temperature of the reaction mass to room temperature, and maintained at this temperature for 2 hr. Reaction was monitored by TLC. Two layers were separated. Collected the organic layer and the aqueous layer are extracted with methylene dichloride. Collected the entire organic layer and was washed with 2 N sodium hydroxide solutions. Again H_2O washing was given to the organic layer. Organic layer was dried over anhydrous sodium sulfate and distilled off the solvent completely.

Similar procedure was followed for the preparation of *N*-[2-(diethylamino) ethyl]-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide by using N, N-diethylethylenediamine instead of benzylamine.

RESULTS AND DISCUSSION

4-Methyl aniline (I) when treated with sodium nitrite forms sodium salt which is converted to 4-methyl-1-azidobenzene (III) by reacting

with sodium azide and sodium acetate. 4-Methyl-1-azidobenzene (III) was cyclized to 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV) in presence of sodium ethoxide and ethylacetoacetate.

5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (IV) was confirmed by the characteristic peak for C=O group at 1684 cm^{-1}, N=N group at 1515.7 cm^{-1} and OH *star* is at 2650.8 cm^{-1} in IR spectra shown in Figure 1. The compound (IV) was also confirmed by ^1H NMR spectra (Figure 2) and M+1 peak at 218.2 m/z of mass spectra (Figure 3). Melting point of the compound (IV) was ranging from 182-185°C. Physicochemical properties of the compound (IV) were given in Table 1.

Scheme

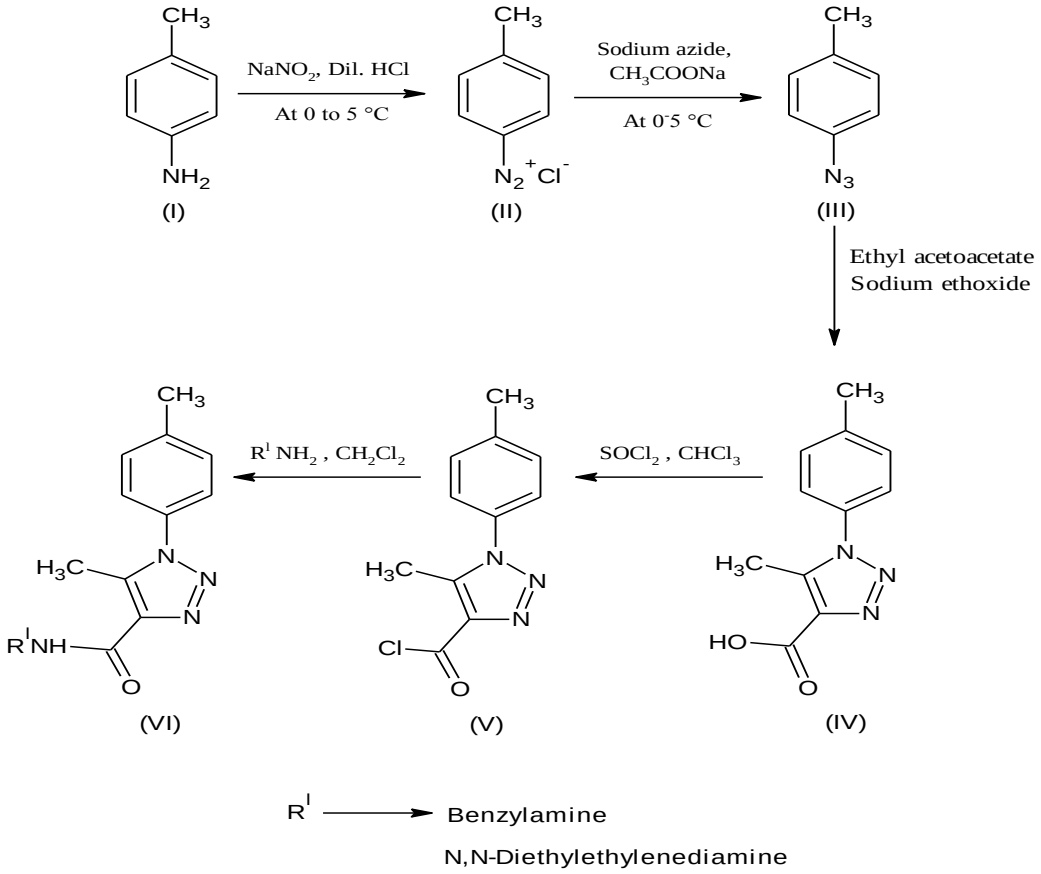

Table 1: Physicochemical properties of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV).

PHYSICOCHEMICAL PROPERTIES	DATA
Molecular formula	$C_{11}H_{11}N_3O_2$
Molecular weight	217
Melting point	182-185°C
Solubility	Chloroform
R_f	1.2 (Chloroform: Methanol = 7:3)
IR (KBr) cm^{-1}	1684.4 (acid C=O *str*), 1591.4 (Ar C=C *str*), 2650.8 (OH *str*), 3082.0 (Ar C-H *str*), 2963.8 (C-H), 1515.7 (N=N)
^1H NMR (400MHz)	2.466(s,3H, methyl), 2.543(s, 3H, methyl), 7.405-7.459 (m, 4H, phenyl)
Mass Spectra	(M+1) peak at m/z 218.2

5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV) on reaction with thionyl chloride 5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carbonyl chloride (V) was formed.

N-benzyl-5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide (VIa) was prepared by the reaction of 5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carbonyl chloride (V) with benzylamine. *N*-benzyl-5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide (VIa) was confirmed by the characteristic peak for amide C=O group at 1665.7 cm^{-1} and amide N-H *str* at 3314.0 cm^{-1} in IR spectra shown in Figure 4. The compound (VIa) was also confirmed by ^1H NMR spectra (Figure 5) and M+1 peak at 307.27 m/z of mass spectra (Figure 6). Melting point of the compound (VIa) was ranging from 133-136°C and the percentage yield was 80%. Physicochemical properties of the compound (VIa) were given in Table 2.

Table 2: Physicochemical parameters of *N*-benzyl-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIa).

PHYSICOCHEMICAL PROPERTIES	DATA
Molecular formula	$C_{18}H_{18}N_4O$
Molecular weight	306
Melting point	133-136°C
R_f	1.0 (n-Hexane : Ethylacetate = 5 : 5)
Solubility	Methanol
IR (KBr) cm^{-1}	1665.7 (amide C=O *str*), 1593.3(Ar C=C *str*), 3075.9 (Ar C-H *str*), 3314.0 (amide N-H *str*), 2963.8 (C-H), 1515.7 (N=N)
^1H NMR (400MHz)	2.464 (s, 3H, methyl), 2.630 (s, 3H, methyl), 4.657-4.672 (m, 2H, methylene), 7.405-7.459 (m, 6H, phenyl), 7.630 (t, 1H, amide)
Mass Spectra	(M+1) peak at m/z 307.27

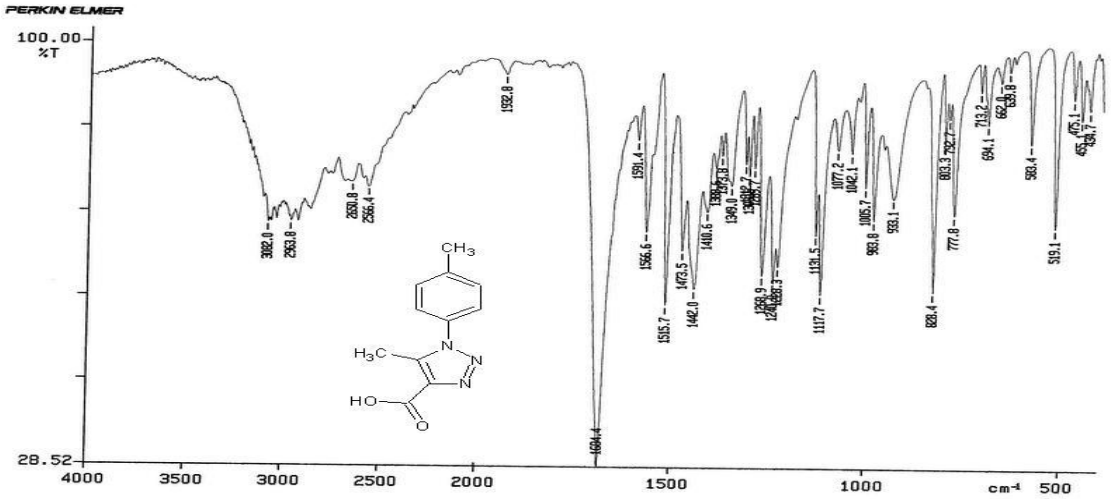

Fig 1: IR spectrum of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV)

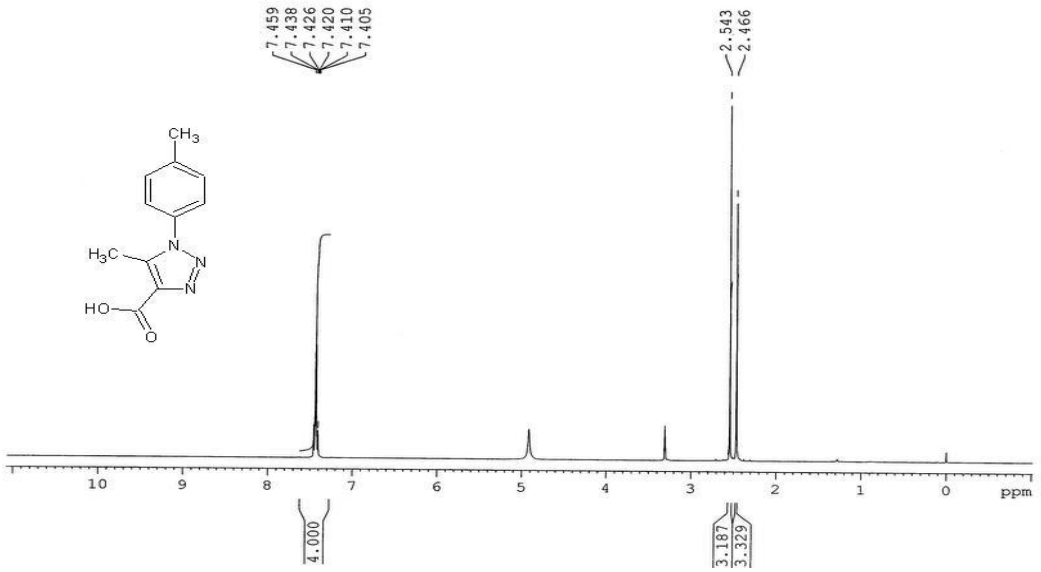

Fig 2: NMR spectrum of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV)

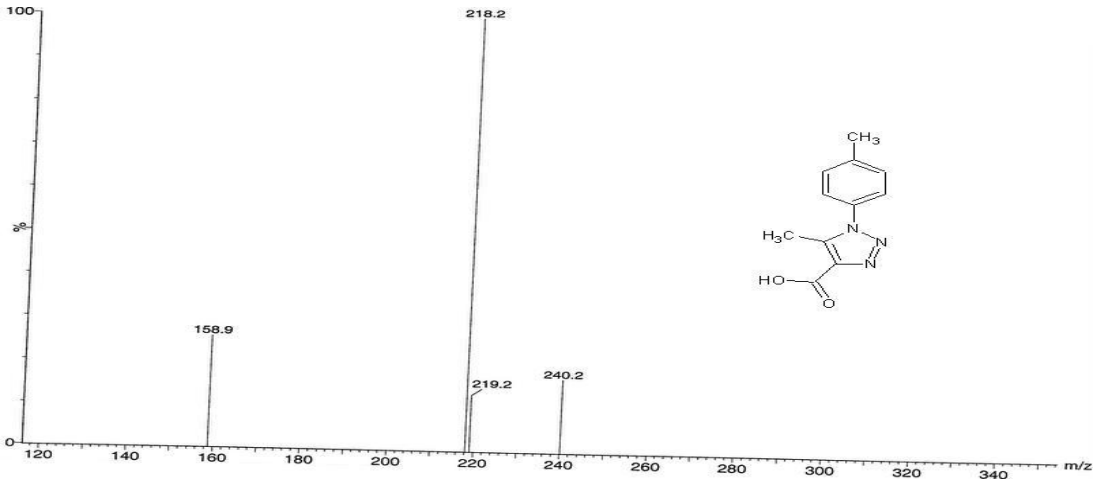

Fig 3: Mass spectrum of 5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxylic acid (IV)

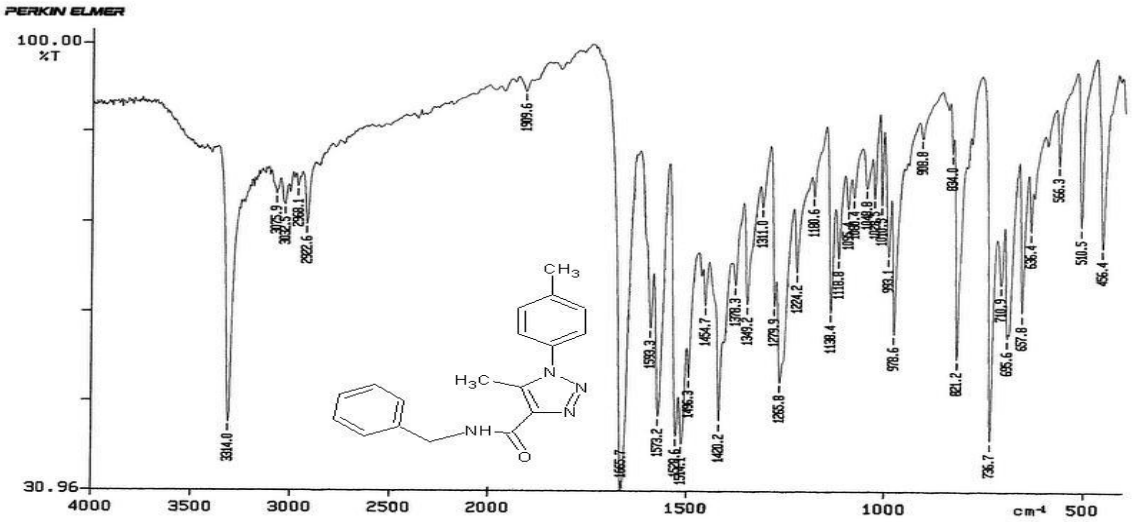

Fig 4: IR spectrum of N-benzyl-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIa)

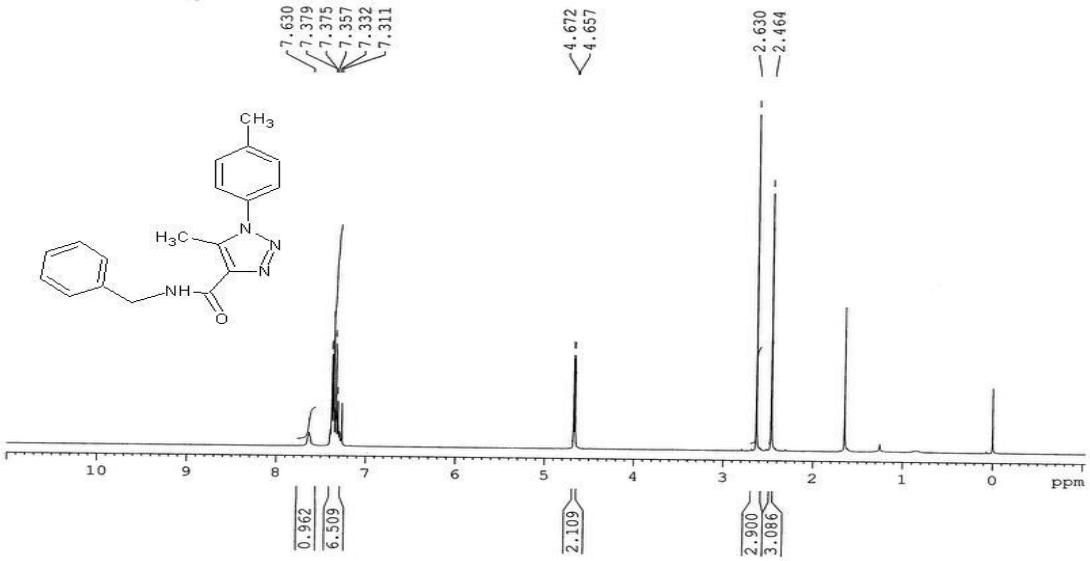

Fig 5: NMR spectrum of N-benzyl-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIa)

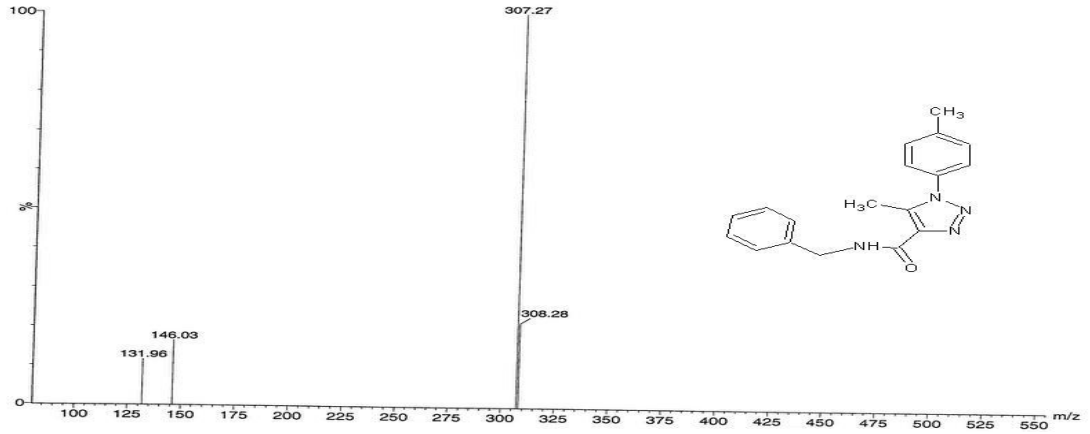

Fig 6: Mass spectrum of N-benzyl-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIa).

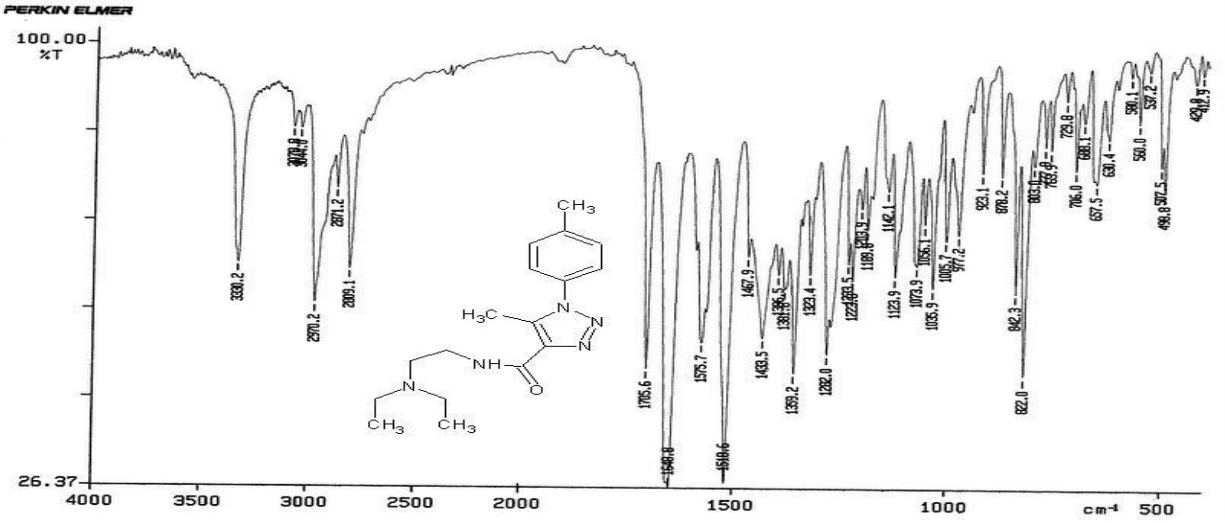

Fig 7: IR spectrum of *N*-[2-(diethylamino) ethyl]-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIb)

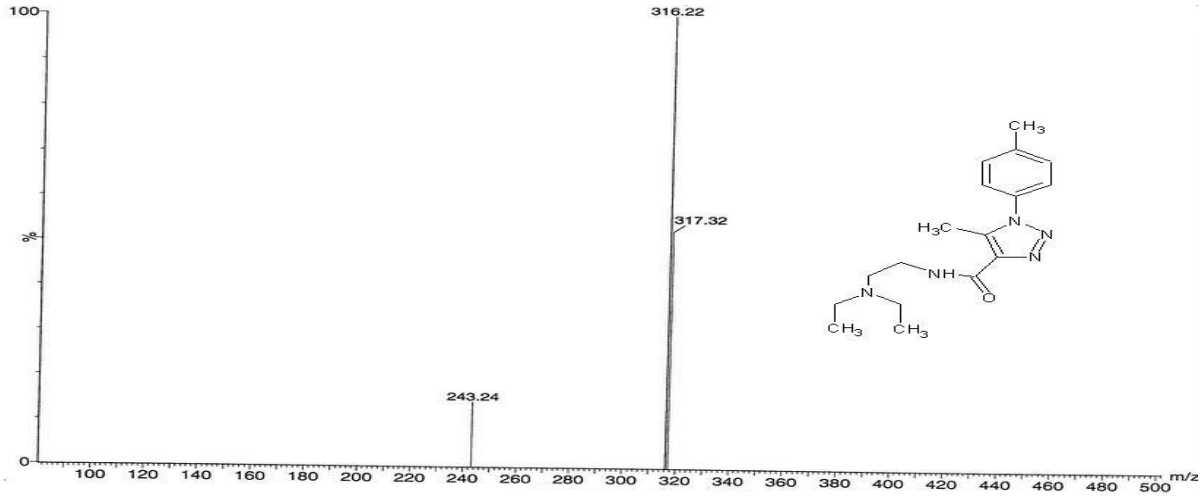

Fig 8: Mass spectrum of *N*-[2-(diethylamino) ethyl]-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIb)

N-[2-(diethylamino) ethyl]-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIb) was prepared by the reaction of 5-methyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carbonyl chloride (V) with N,N-diethylethylenediamine. The resulting compound (VIb) was confirmed by the characteristic peak for amide C=O *str* group at 1648.8 cm^{-1} and amide N-H *str* at 3333.0 cm^{-1} in IR spectra shown in figure7. The compound (VIb) was also confirmed by M+1 peak at 314.22 m/z of mass spectra (Figure 8). Melting point of the compound (VIb) was ranging from 76-78°C and the percentage yield was 70%. Physicochemical properties of the compound (VIb) were given in Table 3.

Table 3: Physicochemical parameters of *N*-[2-(diethylamino) ethyl]-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide (VIb)

PHYSICOCHEMICAL PROPERTIES	DATA
Molecular formula	$C_{17}H_{23}N_5O$
Molecular weight	313
Melting point	76-78°C
R_f	1.3 (Chloroform: Methanol = 9:1)
Solubility	Methanol
IR (KBr) cm^{-1}	1648.8 (amide C=O *str*), 1575.7(Ar C=C *str*), 3078.2 (Ar C-H *str*), 3333.0 (amide N-H *str*), 2970.2 (C-H), 1510.6 (N=N)
Mass Spectra	(M+1) peak at m/z 314.22

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CONCLUSION

In conclusion, we have prepared and characterized some new triazole derivatives (*N*-substituted-5-methyl-1-(4-methylphenyl)-1*H*-1, 2, 3-triazole-4-carboxamide derivatives).

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