Research Article
ISSN: 0974-6943

*Popat B. Mohite et al. / Journal of Pharmacy Research 2010, 3(1),43-46*

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# Synthesis and Anti-Inflammatory Activity of Some 5-Phenyl-1-(Acyl)-1, 2, 3, 4-Tetrazole.

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**Received on: 20-09-2009; Revised on: 09-10-2009; Accepted on:12-12-2009**

## ABSTRACT

A series of novel 5-phenyl,1-acyl 1,2,3,4-tetrazoles (**3–10**) have been synthesized via condensation of 5-phenyl-1,2,3,4-tetrazoles (**2**) with various acylating reagents. 5-phenyl- 1,2,3,4-tetrazoles was synthesized by the cycloaddition of Benzonitrile(**1**) with sodium azide and ammonium chloride in presence of Dimethylformamide as solvent. All synthesized compounds which were characterized to be new substituted Tetrazoles. Their structures were determined by 1H NMR,FT-IR, mass spectra and elemental analyses. The compounds synthesized were screened for anti-inflammatory activity. Compounds 4, 7 and 9 possess potent anti-inflammatory activity.

***Keywords:*** Tetrazoles, Dimethylformamide, Benzonitrile. Anti-inflammatory activity

## INTRODUCTION

The most common serious drawback of all analgesic and anti-inflammatory drugs is that they cause serious acidity problems which limits their use in many cases. As a result most of the patients were unable to continue these drugs for their ailment from diseases. To circumvent the acidity or gastrointestinal effects of anti inflammatory drugs several newer templates or leads were selected which include indole nucleus, arylalkyl acid nucleus, pyrazolone, indan etc. and attempt has been taken to discover novel anti-inflammatory agent without or less gastrointestinal effects (Winter C.A. *et al*, 1963 and Remington, 1990). These nuclei were undergone some structural or molecular modifications either by introducing functional groups or ring fusion. Both the modifications resulted many promising anti-inflammatory agents. It was already established that tetrazole, an aromatic azapyrrole group, is metabolically stable (Fidgor *et al, 1967)* and has acidic characteristics closely similar to that of the carboxylic group (Herbst, 1956). At the same time it has been reported that anti-inflammatory and related biological activities have been improved or abolished by the substitution of a 5-tetrazole group in place of carboxyl function (Ganellin, 1967). In this context a number of indanyltetrazoles have been synthesized and encouraging anti-inflammatory activity has been noted (Roy *et al.,* 1983, Ray *et al.*, 1990, and Roy *et al.*, 1985. The remarkable achievements were 5- (6'-methoxyindan-1'-yl)tetrazole and 5-(5',6'-dimethoxyindan- 1'-yl)tetrazole. According to the Burger, 1970, many medicinal chemists look on halogen substitution, especially chlorination, as a reasonable means of stepping up the activity. Based on these findings, some new novel 5-phenyl,1-(acyl)-1,2,3,4-tetrazoles were synthesized and their anti-inflammatory activity was determined.

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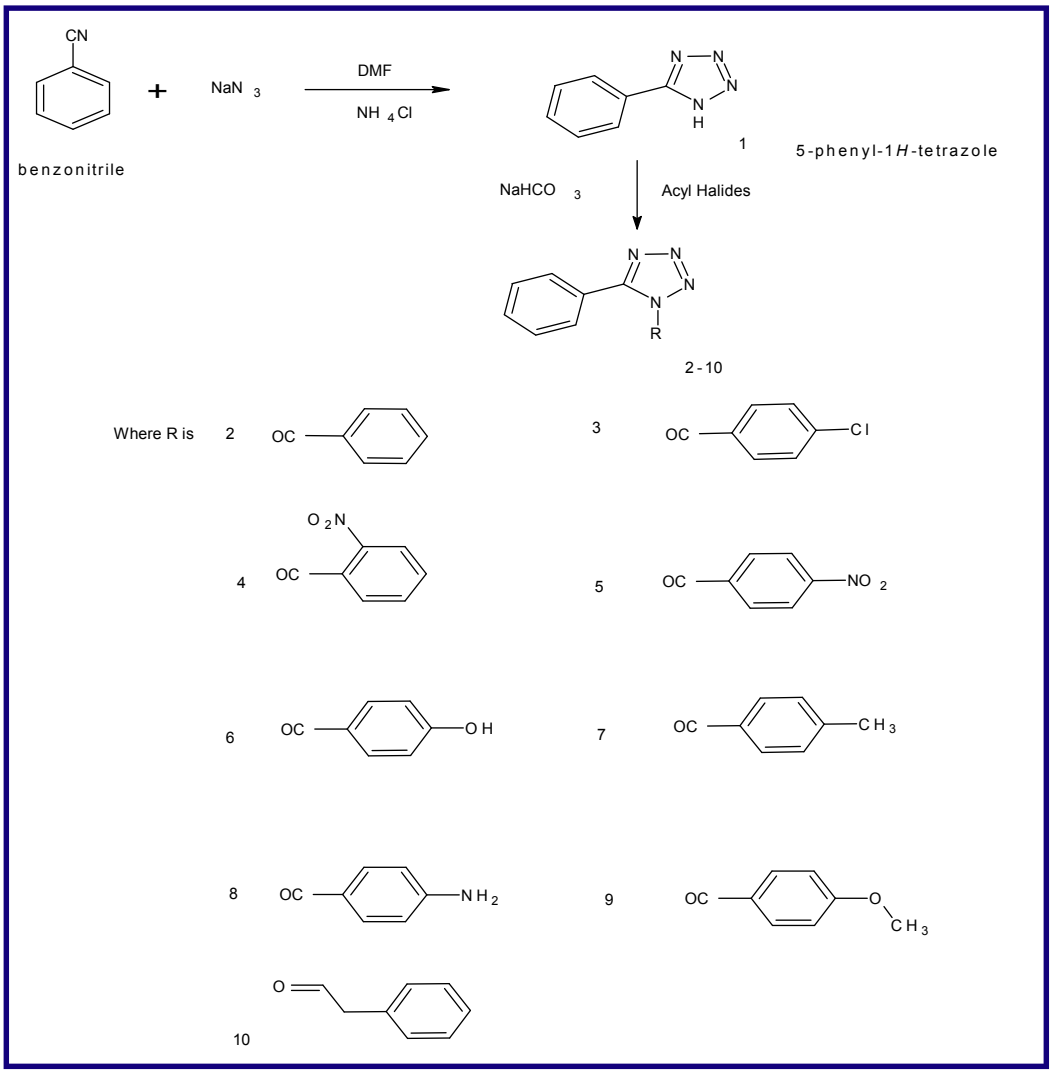
### Chemistry

Compounds were prepared as shown in Fig. 1. The 1,5-disubstituted tetrazoles can be synthesized by number of methods, viz.reaction of hydrazoic acid or its salts with imidoyl chloride or imino ethers or diazo coupling of heterocyclic hydrazines or hydrocyanic acid. Most of these methods have limited use in preparative organic chemistry because the use of hydrazoic acid presents considerable experimental difficulties due its toxicity and tendency to explode. However, the simple route reported by Finnegan et al. was adopted for the preparation of 5-phenyl-1-(acyl)- 1,2,3,4- tetrazoles. This route replaces the toxic hydrazoic acid by inorganic azide to afford the titled compounds in good yield (59–88%). Compound **1** was cyclized using sodium azide and ammonium chloride to yield compound **2**. The substituted tetrazoles were synthesized from **2** by acylation reaction **(Figure 1)**

### Experimental

Melting points were determined by Veego melting point apparatus and are not corrected. Infrared spectra were obtained on a Shimadzu FT-IR spectrophotometer using potassium bromide discs. Nuclear magnetic resonance spectra were recorded on Brucker 400

**Figure 1 Synthesis of Tetrazole Derivatives**




MHz spectrophotemeter. Chemical shifts are reported in parts per million (*d*) units relative to internal standard tetramethylsilane. Elemental analysis were performed and the analyses indicted by the symbols of the elements were within ±0.4% of theoretical values.

**Synthesis of 5-phenyl -1,2,3,4-tetrazole (1)**

The method described by Finnegan et al. was followed to synthesize the tetrazole. A mixture of compound **1** (3.3 g, 10 mmol), sodium azide (0.65 g, 10 mmol) dimethylformamide (10 ml) and ammonium chloride (5.3 g, 10 mmol) was heated in a oil bath for 7 h at 125 °C. The solvent was removed under reduced pressure.The residue was dissolved in 100 ml of water and carefully acidified with concentrated hydrochlori acid to pH 2. The solution was cooled to 5 °C in ice bath. Compound **2** recrystallized from aqueous methanol .m.p.215$^{O}$C.

**5-phenyl-1-(benzoyl)-1,2,3,4-tetrazole (2)**

Compound **1** was treated with an equimolar amount of Benzoyl chloride in 10 ml of 10% w/v sodium bicarbonate solution.The mixture was shaken vigorously in astoppered test tube. When the odour of benzoyl chloride has disappeared, the contents were acidified with dilute hydrochloric acid to congo red. cooled in ice cold water and filtered. The dried compound **2** was recrystallized from aqueous ethanol, and was obtained in 55% yield as a white solid; m.p. 107–108 °C. IR: 1455 (C–H), 1735 (C=O),, 1285 (N–N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3)d 6.8–8.1 (10H, m, Ar–H). Anal. Calcd. for C14H10N4O: C, 67.19; H, 4.09; N, 22.39;O,6.39.. Found:C, 67.14; H, 3.98; N,22.33,O;6.30.

**5-phenyl -1-(p-chlorobenzoyl)-1,2,3,4-tetrazole (3)**

Compound **3** was prepared using the same procedure as for **2**, and was obtained in 68% yield as a light yellow solid: m.p. 160–162 °C. IR: 1455 (C–H), 1735 (C=O), 1285 (N–N=N–),1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) 6.8–8.1 (9H, m, Ar–H). Anal. Calcd. for C14H9CLN4O: C, 59.06; H,3.19; N, 19.68; Found:C, 59.01; H, 3.11; N, 19.54.

**Table No.1 Anti-Inflammatory Activity of Synthesized Compounds against Carrageenan Induced Paw Edema Method**

| Sr. No. | Name of the compounds | Paw volume (Mean ± SEM) | Decrease in paw volume (in %) |
|---|---|---|---|
| 1 | Control | 0.049 ± 0.001 | 00.0 |
| 2 | Diclofenac sodium | 0.062 ± 0.001 | 60.50 |
| 3 | 1 | 0.053 ± 0.003 | 2 |
| 4 | 2 | 0.052 ± 0.002 | 6 |
| 5 | 3 | 0.068 ± 0.002 | 39 |
| 6 | 4 | 0.061 ± 0.003 | 24 |
| 7 | 5 | 0.062 ± 0.002 | 27 |
| 8 | 6 | 0.070 ± 0.002 | 43 |
| 9 | 7 | 0.060 ± 0.001 | 22 |
| 10 | 8 | 0.054 ± 0.001 | 10 |
| 11 | 9 | 0.075 ± 0.002 | 53 |
| 12 | 10 | 0.050 ± 0.001 | 20 |

All the compounds tested at 0.2 mM concentration.

Values are Mean ± SEM, N=6, when compared with standard drug followed by student't' test.

**5-phenyl -1-(o-nitrobenzoyl)-1,2,3,4-tetrazole (4)**

Compound **4** was prepared using the same procedure as for **2**, and was obtained in 75% yield as a white solid: m.p.109–110 °C. IR: 3084 (C–H), 1735 (C=O), 1596 and 1570 ,1541 (N=O), 1455 (C–H), 1348 and 1208 (N=O), 1285 (N–N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) *d* 6.7–9 (9H, m, Ar–H). Anal. Calcd. for C14H9N5O3: C, 56.95; H, 3.07; N, 23.72; Found:C, 56.82; H, 3.01; N, 23.33.

**5-phenyl -1-(p-nitrobenzoyl)-1,2,3,4-tetrazole (5)**

Compound **5** was prepared using the same procedure as for **2**, and was obtained in 65% yield as a white solid: m.p.171–172 °C. IR: 1458 (C–H), 1735 (C=O), 1348 and 1127 (N=O), 1283 (N–N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1HNMR (DMSO-d6) 6.9–8.3 (9H, m, Ar–H). Anal. Calcd. For C14H9N5O3: C, 56.95; H,3.07; N, 23.72; Found:C, 56.82; H, 3.01; N, 23.33.

**5-phenyl-1-(p-hydroxybenzoyl)-1,2,3,4-tetrazole (6)**

Compound **6** was prepared using the same procedure as for **2**, and was obtained in 62% yield as a light brown solid: m.p. 208-210 °C. IR: 1458 (C–H), 1735 (C=O), 1283 (N–N=N–), 1108 and 1138 (tetrazole ring), 885 (O–H) cm–1. 1H-NMR (CDCl3) 5.12 (1H, s, OH), 6.85–7.37 (9H, m,Ar–H). Anal. Calcd. for C14H10N4O2: C, 63.15; H,3.79; N, 21.01; Found:C, 63.02; H, 3.66; N, 22.93.

**5-phenyl-1-(p-aminobenzoyl)-1,2,3,4-tetrazole (7)**

Compound **7** was prepared using the same procedure as for **2**, and was obtained in 61% yield as a dark brown solid: m.p. >210 °C. IR: 1458 (C–H), 1735 (C=O), 1320 (C–N), 1285 (N–N=N) 1108 and 1138 (tetrazole ring) ,3342 (NH2) cm–1. 1H-NMR (DMSO-d6), ) 3.63 (2H, s, NH2), 6.8–7.9 (9H, m, Ar–H). Anal.Calcd. for C15H10N4O: C, 68.17; H,4.58; N, 21.20; Found:C, 68.10; H, 4.51; N, 21.18.

**5-phenyl-1-(p-methylbenzoyl)-1,2,3,4-tetrazole (8)**

Compound **8** was prepared using the same procedure as for **2**, and was obtained in 64% yield as a light grey solid: m.p. 121–122 °C. IR: 1457 (C–H), 1735 (C=O), 1283 (N–N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (DMSO- *d* 2.5 (3H, s, CH3),d 6.6–7.8 (9H, m, Ar–H). Anal. Calcd. for C14H11N5O: C, 63.39; H,4.18; N, 26.40; Found:C, 63.30; H, 4.11; N, 26.28.

**5-phenyl-1-(p-methoxybenzoyl)-1,2,3,4-tetrazole (9)**

Compound **9** was prepared using the same procedure as for **2**, and was obtained in 68% yield as a light brown solid: m.p.160-162 °C. IR: 2985 (C–H), 1735 (C=O), 1604 (C=C),1596 and 1570 (tetrazole ring), 1457 (C–H), 1283 (N– N=N–), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) *d* 2.4 (3H, s, -OCH3) 6.4–8.1 (9H, m, Ar–H). Anal. Calcd. for C15H12N4O2: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.25; H, 4.24; N, 19.91.

**5-phenyl-1-(phenyl acetyl)-1,2,3,4-tetrazole (10)**

Compound **10** was prepared using the same procedure as for **2**, and was obtained in 59% yield as a light brown solid: m.p. 127–128 °C. IR: 1583 (C=C), 1735 (C=O), 1457 (C–H), 1283 (N–N=N), 1108 and 1138 (tetrazole ring) cm–1. 1H-NMR (CDCl3) 6.8–7.3 (10H, m, Ar–H). Anal.Calcd. for C15H12N4O: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.12; H, 4.51; N,21.12.

**Anti-inflammatory activity:**

The anti-inflammatory activity was evaluated by carrageenan induced rat paw edema method. Albino rats of wistar strain weighing 150-200 gm of either sex were divided in to 15 groups each with six animals .Tween 80 suspension (10% v/v) of the test compounds were administered intraperitonialy in a dose of 20 mg/kg.The control group was given only 10% v/v tween 80 suspension. One group was administered with Diclofenac sodium as standard intraperitonialy in a dose of 2 mg/kg.After 30 min.of the administration of test compounds paw edema was induced in albino rats by injecting 0.1 ml carageenin (1% v/v suspension in normal saline) in to subplanter region of the left hind paw , after 3 hours the increase in rat paw volume was recorded .The anti-inflammatory activity was measured in terms of % inhibition of edema of each group was calculated against the control group using the following formula.

$$\% \text{ INHIBITION} = \frac{C - T}{C} \times 100$$

Where C and T represent the average percentage increase in paw volume of the control and test groups respectively. The results were analyzed statistically by student't' test and recorded in **Table 1.**

**Table No.1 Anti-Inflammatory Activity of Synthesized Compounds against Carrageenan Induced Paw Edema Method**

| Sr. No. | Name of the compounds | Paw volume (Mean ± SEM) | Decrease in paw volume (in %) |
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| 12 | 10 | 0.050 ± 0.001 | 20 |

- All the compounds tested at 0.2 mM concentration.

Values are Mean ± SEM, N=6, when compared with standard drug followed by student't' test.

## RESULTS AND DISCUSSION

Benzonitrile was readily converted to 5-phenyl-1, 2, 3, 4-tetrazole by treating them with sodium azide and ammonium chloride in dimethylformamide. The secondary amino group of tetrazole at position 1 of tetrazole is free and hence 8 different derivatives are synthesized using various acyl chlorides. Infra red spectrum of compound **1** showed a sharp absorption and at 3421 cm–1 which is attributed to secondary amino group group. The synthesized compounds (**2–10**) showed absorption bands at 1048, 1120, 1208, 1296 and 1598 cm–1 which is attributed to tetrazole ring. Characteristic absorption bands were observed for carbonyl group, nitro group, hydroxyl group, amino group, methyl group, methoxyl group and aromatic region of the synthesized compounds. 1H-NMR spectra of the synthesized compounds showed two triplets at *d* 2.8 and *d* 4.2. A triplet at *d* 2.8 is due to two protons which are attached to the carbon atom of the nitrile function. The triplet at *d* 4.2 is due to the two protons attached to the carbon atom of nitrile function. 1-H (NH) proton of the tetrazole is undetectable in NMR spectra. Aromatic protons showed multiplets in the range of *d* 6.8–7.3. The expected signals with appropriate multiplicities for different types of protons were observed for the derivatives.

It is apparent from table 2 that the compounds 2, 4, 5, 7, 8 afforded 6-27%protection against carageenin induced edema, whereas the standard drug Diclofenac sodium under similar condition exhibited 60.50 inhibitions. Among the compounds 3, 6, 9 were found to be more potent compounds as they exhibited 39%, 43% and 53%inhibition respectively.

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## ACKNOWLEDGMENTS

We are highly thankful to Principal M.E.S. College Pharmacy,Sonai and Prashant Patil Gadakh , Secreatary ,Mula Education Society for providing excellent research facilities**.**

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**Source of support: Nil, Conflict of interest: None Declared**