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Synthesis And Biological Evaluation Of Novel 5-Methyl-1, 4-Disubstituted 1h-1, 2, 3-Triazole Derivatives

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Abstract: *Six triazole derivatives have been synthesized using p- toludine and p- anisidine as starting materials. Diazotization in presence of NaN_3 and followed by cyclisation esterification with absolute methanol and followed by reduction with $NaBH_4$ and oxidation with NaOCl and NaBr in presence of 2, 2, 6, 6-tetramethyl-1-piperinyloxy free radical (TEMPO) gave 5-methyl-1-(4-methyl phenyl)-1H-1, 2, 3-triazole-4-carbaldehyde and 5-methyl-1-(4-methoxy phenyl)-1H-1, 2, 3-triazole-4-carbaldehyde (5a & 5b). Finally, compounds 5a and 5b on condensation with primary amines like cyclohexyl amine, (+) phenyl ethyl amine, (-) phenyl ethyl amine using sodium triacetoxy borohydride gave 5-methyl- 1, 4- disubstituted-1H-1, 2, 3-triazole derivatives (6a – f).*

All the compounds were characterized by physical (melting point and TLC) and spectral data (IR, Mass, ^{1}HNMR). The synthesized compounds were screened for antibacterial and anti-inflammatory activities. Some of the compounds were found to possess mild antibacterial activity at the tested concentrations. In anti-inflammatory study, compounds (6a, 6b, 6d, and 6e) showed good activity when compared with that of standard drug ibuprofen. Therefore these compounds can be further exploited to get the lead compound.

Key Words: *Triazole, sodium triacetoxy borohydride, carbaldehydes, amines, antibacterial, anti-inflammatory.*

I. Introduction

Triazoles are an important class of bioactive molecules having a wide spectrum of biological activities. A large number of 1, 2, 3-triazole derivatives have been reported to be synthetic intermediates and pharmaceuticals[2-3]. Several therapeutically interesting 1, 2, 3-traizoles have been reported, including anti-HIV agents[4-7], antimicrobial compounds[8], selective adrenergic receptor agonists[9], kinase inhibitors[10-11], and other enzyme inhibitors[12-13].These observations prompted us to synthesize the title compounds with presumption that incorporation of amines and triazole nuclei would produce new compounds with significant antibacterial and anti-inflammatory activity.

Anti microbial activity:

The synthesized compounds were tested for their antibacterial activity by cup plate method by measuring the zone of inhibition on agar plates in mm against gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis) and two gram negative bacteria (Escherichia coli and Pseudomonas aureginosa) at a concentration of 50 µl using Ciprofloxacin and Ampicillin as standard drugs and DMSO as a control. The screening results of the compounds indicated that all the compounds exhibited mild to moderate activity. Antifungal activity of the synthesized compounds was performed by turbidimetric method against two fungi (Candida albicans, and Saccharomyces cerevisiae) using Ketoconazole as a standard drug and DMSO as control where the compounds showed very least activity.

Anti inflammatory activity:

All the synthesized compounds were screened for anti-inflammatory activity by carrageen an induced rat paw edema method of winter et al[14].Ibuprofen was used as a standard. From the data obtained, the mean edema volume and percentage reduction in edema was calculated. Looking at the anti-inflammatory activity, compounds 6a, 6b, 6d, 6e have significant anti-inflammatory activity and the results are comparable to that of standard ibuprofen

II. Materials And Methods:

Melting points were determined using open capillary tubes on ANALAB melting point apparatus and are uncorrected. Completion of the reactions were monitored from time to time by analytical TLC using E-Merck silica gel $F_{254,}$ 0.25mm precoated aluminium plates and visualized under UV light (254nm).The purity of the compounds was checked by single spot in TLC and the solvent system for the TLC was determined by trial and error basis. All the IR spectra were recorded on SHIMADZU FT-IR spectrophotometer by using 1% KBr

discs. All the ^1H NMR spectra have been recorded in $CDCl_3$ solvent unless otherwise mentioned. ^1H NMR Chemical shifts are reported on Brucker 400 MHz relative to tetra methyl silane as internal standard in delta scale. Mass spectra of the compounds were recorded on mass spectrophotometer (Aligent 1100series; EI/ES-MS).

III. Results And Discussion:

General procedure:

Synthesis of 5-methyl-1-(4-methyl phenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (5a)from 5-methyl-1-(4-methyl phenyl)-1*H*-1,2,3-triazole-4-yl) methanol

1.5 g (0.007 moles) of 5-methyl-1-(4-methyl phenyl)-1H-1,2,3-triazole-4-yl) methanol, 0.810 g (0.0078 moles) of sodium bromide,1.88 g (0.022 moles) of sodium bicarbonate, 0.001 g (0.0000765 moles) of TEMPO, 15 ml methylene chloride and 7.5 ml water were taken into a round bottom flask. Reaction mass cooled to 10 ^0C. To this 0.71 g (0.00084 moles) of sodium hypochlorite was added and reaction mass was maintained below 10 ^0C. after reaction completion isolate the product, filtered and washed with heptane and dried at 40 ^0C under vacuum to yield a crystalline solid.

Synthesis of 5-methyl-1-(4-methoxy phenyl)-1*H*-1, 2, 3-triazole-4-carbaldehyde (5b) from 5-methyl-1-(4-methoxy phenyl)-1*H*-1, 2, 3-triazole-4-yl) methanol

By following the above procedure, 5-methyl-1-(4-methoxy phenyl)-1H-1,2,3-triazole-4-carbaldehyde (5b) has also been prepared using (0.0066 moles)of 5-methyl-1-(4-methoxy phenyl)-1H-1,2,3-triazole-4-yl) methanol, (0.0067 moles)of sodium bromide, (0.0193 moles)of sodium bicarbonate, (0.000066 moles) of TEMPO, 15 ml methylene chloride and 7.5 ml water and (0.0072 moles) of sodium hypochlorite.

Note: TEMPO is 2, 2, 6, 6-tetramethyl-1-piperrinoyloxy free radical on silica gel. It is a recyclable catalyst in oxidation of alcohols

Synthesis of 5-methyl-1,4- disubstituted-1H-1, 2, 3-triazole derivatives with primary amines:

0.5 g (0.00213 moles) of primary amine dissolved in 6 ml of methylene chloride was taken in a round bottom flask. To this 0.65 g (0.00307 moles) of sodium triacetoxy borohydride and 0.33 g (0.00549 moles) glacial acetic acid were added and stirred for 10 min. To the above mixture 0.5 g (0.00223 moles) 5-methyl-1-(4-methyl phenyl)-1H-1,2,3-triazole-4-carbaldehyde dissolved in methylene chloride was added dropwise and maintained for 4 h at room temperature. The progress of the reaction was monitored by TLC. At the end of the reaction, the mixture was basified with 10% aqueous potassium carbonate solution and extracted with methylene chloride. The extract was washed with brine solution, concentrated and purified by column chromatography.

Following the above procedure, 5-methyl-1-(4-methoxy phenyl)-1H-1,2,3-triazole derivatives (6d),(6e) and (6f) has also been prepared using 0.00223 moles of 5-methyl-1-(4-methoxy phenyl)-1H-1,2,3-triazole-4-carbaldehyde.

Analytical data of the above compounds:

N-{[5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazole-4yl]methyl}methyl cyclohexanamine (6a): *This compound was obtained as white solid. **mp** 190 -192^0C; **IR**: 1592 cm^{-1} (N=N=NH stretch), 3445.4 cm^{-1} (NH stretch), 1655.2 cm^{-1} (N-H bend), 1349.9 cm^{-1}, (C-N stretch); **Mass (m/z):** 285 (M+1); **^1H NMR** ($CDCl_3$, 400Mhz): 1.1-1.197 (m, 2H); 1.226-1.334 (m, 2H,); 1.62-1.65 (m, 1H); 1.70 (bs, 2H); 1.74-1.77 (m, 2H); 1.94-1.97 (m, 2H); 2.29 (s, 3H), 2.44 (s, 3H); 2.53-2.58 (m, 1H); 3.89 (s, 2H), 7.32 (s, 4H).*

N-{[5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazole-4yl]methyl}methyl}-1-(+)phenyl ethanamine (6b): *This compound was obtained as pale yellow solid. **mp** 195-198^0C; **IR** :1592 cm^{-1} (N=N=NH stretch), 3315.6 cm^{-1} (NH stretch), 1653 cm^{-1} (NH bend); **Mass (m/z):** 307 (M+1); **^1H NMR** ($CDCl_3$, 400Mhz): 7.24-7.45 (m, 12H, Ar-H), 3.85-3.91(m, 1H), 3.66-3.75 (m, 2H), 2.44 (s, 3H), 2.41(s, NH), 2.15 (s, 3H)*

N-{[5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazole-4yl]methyl}methyl}-1(-)phenyl ethanamine(6c): *This compound was obtained as pale yellow solids.**mp:196-198^0C; IR:**3297.3 cm^{-1} (NH stre)1654 cm^{-1}(NH bend); mass(m/z):307(M+1).*

N-{[5-methyl-1-(4-methoxyphenyl)-1H-1,2,3-triazole-4yl]methyl}methyl cyclohexanamine (6d): *This compound was obtained as pale yellow solids.**mp:201-203^0C; IR**: 1591 cm^{-1} (N=N=NH*

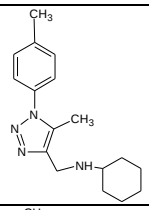
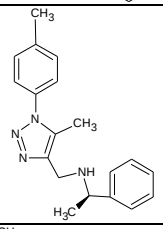
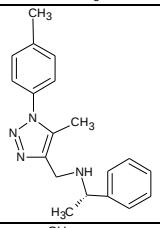
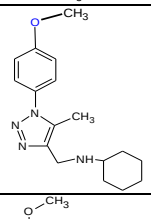
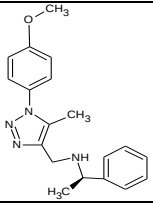
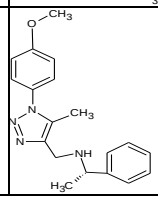
stretch), 3394 cm^{-1} (NH stretch), 1654 cm^{-1} (N-H bend), 1349.9 cm^{-1} (C-N stretch); ***Mass (m/z):*** *301(M+1);*

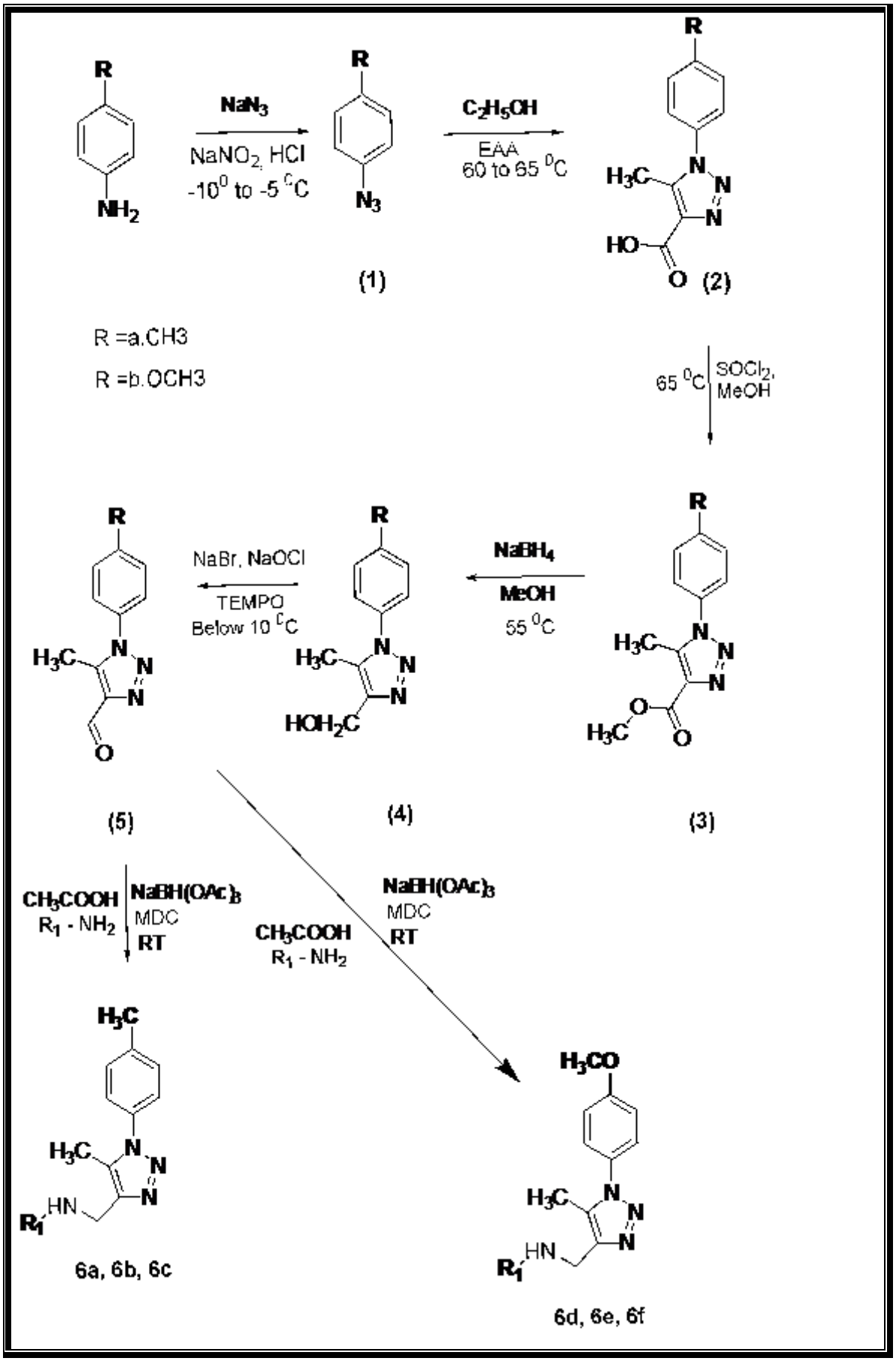
(1*R*)-N-{[5-methyl-1-(4-methoxyphenyl)-1H-1,2,3-triazole-4yl]methyl}methyl}-1-phenyl ethanamine (6e) :*This compound was obtained as white solid.**mp:**210°c; **IR:** 3445.5 cm^{-1} (NH stretch), 1654 cm^{-1} (NH bend); **Mass(m/z):**323 (M+1); **^{1}H NMR**($CDCl_3$, 400Mhz): 1.88-1.89 (d, 3H, CH_3), 2.36(s, 3H, Ar-H), 3.87 (s, 3H, OCH_3), 3.99-4.167 (s, 2H, CH_2), 7.00-7.22 (s, 2H, Ar-H), 7.33-7.48 (m, 3H, Ar-H), 7.82-7.84 (d, 2H, Ar-H),10.17 (s, 1H, Ar-H), 10.38 (s, 1H, Ar-H)*

(1*S*)-N-{[5-methyl-1-(4-methoxyphenyl)-1H-1, 2, 3-triazole-4yl]methyl}methyl}-1-phenyl ethanamine (6f): *This compound was obtained as white solid. **IR** : 1591.3 cm^{-1} (N=N=NH stretch), 3298.4cm^{-1} (NH stretch), 1654.2 cm^{-1} (NH bend) ; **Mass (m/z):** 323(M+1); **^{1}H NMR**($CDCl_3$, 400Mhz)**:** 7.00-7.031 (2H, m, Ar-H), 7.278 (2H, d, Ar-H), 7.31-7.429 (5H, m, Ar-H), 1.40-1.44 (3H, m, CH_3), 0.93 (s, 1H, CH), 3.87-3.92 (t, 3H, CH_3), 2.26 (s, 3H, OCH_3), 1.40-1.44 (t, 3H, CH_3)*

TABLE 1

Physical data of 5-methyl-1, 4-disubstituted- 1*H*-1,2,3-triazoles

S.NO	*Compd*	*STRUCTURE*	*M. P (^{0}C)*	*Yield (%)*
1	*6a*		*192*	*72*
2	*6b*		*198*	*69*
3	*6c*		*197*	*70*
4	*6d*		*203*	*68*
5	*6e*		*210*	*65*
6	*6f*		*208*	*72*


R
NaN3
NaNO2, HCl
-10^0 to -5 ^0C
C2H5OH
EAA
60 to 65 ^0C
NH2
N3
(1)
H3C
HO
O
(2)
R =a.CH3
R =b.OCH3
65 ^0C
SOCl2,
MeOH
NaBH4
MeOH
55 ^0C
NaBr, NaOCl
TEMPO
Below 10 ^0C
HOH2C
H3C
O
(5)
(4)
(3)
CH3COOH
R1 - NH2
NaBH(OAc)3
MDC
RT
HN
R1
6a, 6b, 6c
H3CO
6d, 6e, 6f

SCHEME

TABLE 2: Anti-bacterial activity of 5-methyl-1,4-disubstituted 1H-1,2,3-triazole derivatives

compound	*R*	*Zone of inhibition*			
		Bacillus subtilis(+ve) mm	*Staphylococcus aureas(+ve) mm*	*Escheresia coli(-ve) mm*	*Pseudomonas aeruginosa mm*
6a	*CH3*	*16*	*12*	*NA*	*NA*
6b	*CH3*	*18*	*20*	*NA*	*NA*
6d	*OCH3*	*NA*	*12*	*NA*	*10*
6e	*OCH3*	*10*	*12*	*NA*	*11*
Ciprofloxacin (10µg/50µl)	---	*38*		*29*	

TABLE 3: Anti-inflammatory activity of 5-methyl-1, 4-disubstituted 1H-1, 2, 3-triazole derivatives mean paw edema volume (ml)

Treatment	Dose (mg/kg)	30 min	1h	2h	3h	4h
Control	100	0.28±0.014	0.39±0.025	0.60±0.047	0.82±0.013	0.82±0.029
Standard (Ibuprofen)	100	0.18±0.045	0.20±0.059	0.22±0.06	0.17±0.038	0.25±0.043
6a	100	0.22±0.057	0.24±0.038	0.28±0.014	0.33±0.029	0.31±0.029
6b	100	0.20±0.043	0.22±0.047	0.26±0.050	0.29±0.015	0.30±0.030
6c	100	0.21±0.013	0.23±0.056	0.33±0.048	0.42±0.018	0.50±0.038
6d	100	0.21±0.027	0.23±0.053	0.27±0.035	0.34±0.026	0.31±0.058
6e	100	0.20±0.048	0.21±0.025	0.25±0.053	0.24±0.052	0.29±0.052
6f	100	0.22±0.031	0.24±0.022	0.34±0.034	0.43±0.022	0.49±0.026

Edema volume=mean±SEM

TABLE 4: Percentage protection against edema formation:

Treatment	*Dose (mg/kg)*	*R*	*30 min*	*1h*	*2h*	*3h*	*4h*
Standard (Ibuprofen)	*100*	*----*	*35.71%*	*48.71%*	*63.33%*	*79.26%*	*69.51%*
6a	*100*	*CH3*	*21.42%*	*38.46%*	*53.33%*	*59.75%*	*59.75%*
6b	*100*	*CH3*	*28.57%*	*43.58%*	*56.66%*	*64.63%*	*63.41%*
6c	*100*	*CH3*	*25.00%*	*41.02%*	*45.06%*	*48.78%*	*39.90%*
6d	*100*	*OCH3*	*25.00%*	*41.02%*	*55.00%*	*58.53%*	*62.19%*
6e	*100*	*OCH3*	*28.57%*	*46.15%*	*58.33%*	*70.73%*	*64.63%*
6f	*100*	*OCH3*	*21.42%*	*38.46%*	*43.33%*	*47.54%*	*38.82%*

IV. Conclusion:

Among the compounds tested (6a) and (6b) exhibited mild activity against Bacillus subtillis , Staphylococcus aureus and compounds (6d) , (6e) exhibited mild activity against Staphylococcus aureus and Pseudomonas aeruginosa at a concentration of 1000 µg/50µl compared with the standard drug ciprofloxacin (10µg/50µl).None of the compounds have shown any activity against fungal strains Candida albicans and Saccharomyces cerevisiae at a concentration of 1000µg/50µl.In anti-inflammatory screening the compounds (6a),(6b),(6d),(6e) have shown good anti-inflammatory activity at a concentration of 100 mg/kg compared with the standard drug ibuprofen(100mg/kg).Therefore, these compounds can be further exploited to get lead compounds.

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