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SYNTHESES AND BIOLOGICAL ACTIVITY OF SOME 3, 5-DRIARYL-4H-1, 2, 4-TRIAZOLE DERIVATIVES

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ABSTRACT

The syntheses of a series of novel 3, 5-diaryl-4-4H-1, 2, 4-triazole derivatives are described. A total of eight new compounds were synthesized and characterized by spectral and elemental analyses. Some compounds were screened for antibacterial activity against *S. aureus, E. coli, B. subtilis* and *P. aeruginosa*. Compounds containing aryl substituents at position six and the 1, 2, 4- triazole moiety at position one or two showed reasonable antibacterial activity.

KEYWORDS

1, 2, 4-triazole, ethylbenzoatebenzoylhydrazone, hydrazine hydrate, $NaBH_4$, antibacterial activity.

INTRODUCTION

The chemistry of heterocyclic compounds continues to be an active field in the organic chemistry. Triazole- derivatives have occupied a unique position in heterocyclic chemistry due to their antimicrobial activities. [1-2] 1, 2, 4-Triazoles as antibacterial agents can be grouped according to the mode of action, i.e. the ability to inhibit the synthesis of the cell wall, cell membrane, proteins and nucleic acids of bacteria. The syntheses of 1, 2, 4-triazoles has also attracted wide spread attention due to the diverse agricultural, industrial and biological activities, including anti-inflammatory, analgesic, antitumoral, anticonvulsant and tranquilizing activities shown by these compounds. In view of these observations and in continuation of our earlier work[3-23] on the syntheses of some 1, 2, 4- and 1, 2, 3- triazole derivatives, we now report the syntheses of more novel triazole derivatives derived from 4-amino-3, 5-diphenyl-4H-1, 2, 4-triazole.

MATERIAL AND METHODS

Melting and boiling points were determined on a Gallen Kamp apparatus in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on a Jasco FT-IR 5300 spectrophotometer and proton magnetic resonance (PMR) spectra (DMSO-d6) on a Varian EM-390 spectrometer using TMS as an internal standard (chemical shift in δ ppm). Mass spectra were recorded on a Jeol JMS-D 300Mass spectrometer operating at 70eV.The purity of the compounds was confirmed by TLC using silica gel G and purified by column chromatography. For TLC, Merck silica gel 60G plate was used. For column chromatography, Merck silica gel 60 (0.063-0.200mm) was used. The necessary chemicals were obtained from Merck and Fluka. All compounds showed satisfactory elemental analyses.

(i) 4-Amino-3, 5-diphenyl-4H-1,2, 4-triazole (1):

Ethylbenzoatebenzoylhydrazone (0.01 mol) was reacted with hydrazine hydrate (0.01 mol) in the presence of 1-propanol (50 mL), the reaction mixture

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was refluxed for a period of 30 hours. After cooling, the precipitate was filtered and dried. The dried product was washed with 30 mL of benzene. The insoluble part in benzene was recrystallized from 1-propanol to afford the compound 4-amino-3, 5-diphenyl-4H-1, 2, 4-triazole **(1)** and was used directly for the next step without further purification (yield 88%).

(ii) General procedure for compounds (2a-d):

A suspension of compound **1** (0.01 mol), corresponding aldehydes (0.01 mol) and glacial acetic acid (30mL) was heated under reflux for 5 hours. After cooling, the mixture was poured in to a beaker containing 100mL of ice-water and the precipitate was filtered and dried. The dried product was recrystallized from an appropriate solvent to give the desired compounds (yield 85-92%).

3, 5-Diphenyl-4-(4-methylbenzylidenamino)-4H-1, 2, 4-triazole (2a):

Recrystallized from ethanol, (yield 92%) m.p. 245 ^{0}C. Anal.Calc. for $C_{22}H_{18}N_4$, C, 62.22; H, 2.33; N, 26.09 %; Found C, 61.69; H,3.22; N, 25.98% ; IR (KBr) : 1605,1570 (C=N) and 761 cm^{-1} (monosubstituted benzene); PMR: δ 3.72 (2H,d, CH_2), 7.32 (1H, t, NH), 6.72 (2H, d, Ar-H), 7.13 (2H, d, Ar-H), 7.43-7.65 (6H, m, Ar-H) and 7.80-8.03 ppm (4H, m, Ar-H); MS: m/z 296 (M^+) other peaks observed at 175, 161, 141, 97, 77, 68, 53 and 41.

3, 5-Diphenyl-4-(4-nitrobenzylidenamino)-4H-1, 2, 4-triazole (2b):

Recrystallized from ethanol, (yield 85%) m.p. 236 ^{0}C. Anal.Calc. for $C_{21}H_{15}N_5O_2$, C, 59.32; H, 2.43; N, 25.19 %; Found C, 60.09; H, 2.88; N, 24.68% ; IR (KBr) : 1615,1596 (C=N) and 762 cm^{-1} (monosubstituted benzene); PMR: δ 3.76 (2H,d, CH_2), 7.31 (1H, t, NH), 6.78 (2H, d, Ar-H), 7.15 (2H, d, Ar-H), 7.40-7.63 (6H, m, Ar-H) and 7.80-8.03 ppm (4H, m, Ar-H); MS: m/z 296 (M^+) other peaks observed at 159, 125, 120, 114, 99, 78, 68, 58 and 49.

3, 5-Diphenyl-4-(4-chlorobenzylidenamino)-4H-1, 2, 4-triazole (2c):

Recrystallized from ethanol, (yield 85%) m.p. 232 ^{0}C. Anal.Calc. for $C_{21}H_{15}N_4Cl$, C, 60.12; H, 2.63; N, 25.29 %; Found C, 59.99; H, 2.61; N, 25.48% ; IR (KBr) : 1599,1562 (C=N) and cm^{-1} (monosubstituted benzene); PMR: δ 3.77 (2H,d, CH_2), 7.30 (1H, t, NH), 6.77 (2H, d, Ar-H), 7.15 (2H, d, Ar-H), 7.41-7.62 (6H, m, Ar-H) and 7.81-8.01 ppm (4H, m, Ar-H); MS: m/z 296 (M^+) other peaks observed at 137, 133, 123, 103, 83, 76, 66, 56 and 46.

3,5-Diphenyl-4-(4-ethoxybenzylidenamino)-4H-1, 2, 4-triazole (2d):

Recrystallized from ethanol, (yield 90%) m.p. 185 ^{0}C. Anal.Calc. for $C_{22}H_{18}N_4O$, C, 60.36; H, 2.45; N, 24.89 %; Found C, 60.19; H, 2.96; N, 24.49% ; IR (KBr) : 1595,1567 (C=N), 755 cm^{-1} (monosubstituted benzene); PMR: δ 3.78 (2H,d, CH_2), 7.31 (1H, t, NH), 6.78 (2H, d, Ar-H), 7.16(2H, d, Ar-H), 7.40-7.64 (6H, m, Ar-H) and 7.80-8.02 ppm (4H, m, Ar-H); MS: m/z 296 (M^+) other peaks observed at 139, 127, 122, 94, 89, 72, 61, and 49.

(iii) General procedure for compounds (3a-d):

A suspension of compound **2a-d** (0.01 mol), methanol (50 mL) and $NaBH_4$ (0.01 mol) was heated under reflux for 30 minutes and then allowed to cool. After concentration at 25 ^{0}C under reduced pressure, the crude solid was washed with water, filtered and dried. The dried product was recrystallized from an appropriate solvent to give the desired compounds (yield 85-95%).

3, 5-Diphenyl-4-(4-methylbenzylamino)-4H-1, 2, 4-triazole (3a):

Recrystallized from ethyl acetate, (yield 95%) m.p. 193^{0}C. Anal.Calc. for $C_{22}H_{20}N_4$, C, 60.22; H, 2.23; N, 25.09 %; Found C, 60.19; H, 2.60; N, 24.48%; IR (KBr) : 3295 (NH), 1575 (C=N) and 760 cm^{-1} (monosubstituted benzene); PMR: δ 2.25 (3H,s, CH_3), 3.72 (2H, d, CH_2), 5.42 (1H, t, NH), 6.71(2H, d, Ar-H), 6.92(2H, d, Ar-H), 7.52(6H, m, Ar-H) and

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7.92 ppm (2H, m, Ar-H); MS: m/z 299 (M^+) other peaks observed at 177, 136, 118, 114, 99, 75, 65, 56 and 46.

3, 5-Diphenyl-4-(4-nitrobenzylamino)-4H-1, 2, 4-triazole (3b):

Recrystallized from ethanol, (yield 85%) m.p. 225^{0}C. Anal.Calc. for $C_{21}H_{17}N_5O_2$, C, 60.42; H, 2.83; N, 25.39 %; Found C, 59.89; H,2.70; N, 24.54% ; IR (KBr) : 3242 (NH), 1605 (C=N) and 762 cm^{-1} (monosubstituted benzene); PMR: δ 3.82 (2H,d, CH_2), 7.21 (1H, t, NH), 6.95(2H, d, Ar-H), 7.49(6H, m, Ar-H), 7.82(2H, d, Ar-H) and 7.95 ppm (2H, m, Ar-H); MS: m/z 299 (M^+) other peaks observed at 138, 129, 119, 109, 88, 77, 74, 54 and 48.

3, 5-Diphenyl-4-(4-chlorobenzylamino)-4H-1, 2, 4-triazole (3c):

Recrystallized from ethyl acetate, (yield 93%) m.p. 212^{0}C. Anal.Calc. for $C_{21}H_{17}N_4Cl$, C, 60.13; H, 2.33; N, 25.99 %; Found C, 60.11; H, 2.55; N, 24.99% ; IR (KBr) : 3292 (NH), 1600 (C=N) and 761 cm^{-1} (monosubstituted benzene); PMR: δ 3.75(2H,d, CH_2), 7.30 (1H, t, NH), 6.77 (2H, d, Ar-H), 7.15(2H, d, Ar-H), 7.41-7.62 (6H, m, Ar-H) and 7.81-8.01 ppm (4H, m, Ar-H); MS: m/z 299(M^+) other peaks observed at 169, 149, 131, 114, 99, 87, 63, 55 and 46.

3, 5-Diphenyl-4-(4-methoxybenzylamino)-4H-1, 2, 4-triazole (3d):

Recrystallized from ethyl acetate, (yield 85%) m.p. 176^{0}C. Anal.Calc. for $C_{22}H_{20}N_4O$, C, 60.02; H, 2.92; N, 24.72 %; Found C, 59.96; H, 2.82; N, 24.82% ; IR (KBr) : 3298 (NH), 1615 (C=N) and 762 cm^{-1} (monosubstituted benzene); PMR: δ 3.62 (3H, s, OCH_3), 3.71 (2H, d, CH_2), 7.11 (1H, t, NH), 6.75 (2H, d, Ar-H), 6.79 (2H, d, Ar-H), 7.49-7.72 (6H, m, Ar-H) and 7.91-8.09 ppm (4H, m, Ar-H); MS: m/z 299 (M^+) other peaks observed at 179, 149, 133, 108, 79, 73, 52 and 43.

(iv) Biological activity:

The antibacterial activity of eight compounds **(2a-d & 3a-d)**, was investigated by employing the filter paper disc method.[24-26] Representative organisms selected for evaluation of antibacterial activity were *S. aureus, E. coli, B. subtilis* and *P. aeruginosa*. The antibacterial activity of each of the compounds was evaluated in triplicate at 100 µg mL^{-1}and 10 µg mL^{-1} concentrations. The compounds were tested as a solution or suspension in DMF (99.80 % anhydrous). An important and useful control drug Ampicillin was also tested under similar conditions, with view to compare the results. The result indicates that all of the synthesized compounds showed moderate to strong activity against these bacterial strains. See Table 1. All compounds showed good activity against *S. aureus, E. coli, B. subtilis and P. aeruginosa*. From the above observation it is clear that the triazole derivatives of 3, 5-driaryl-4H-1, 2, 4-triazole derivatives are more active and also the substituents phenyl, 4-methoxyphenyl and 4-nitrophenyl in 3, 5-driaryl-4H-1, 2, 4-triazole derivatives plays a prominent role in the antimicrobial activity. Thus ampicillin is more effective in its antibacterial activity compared to all of the synthesized compounds.

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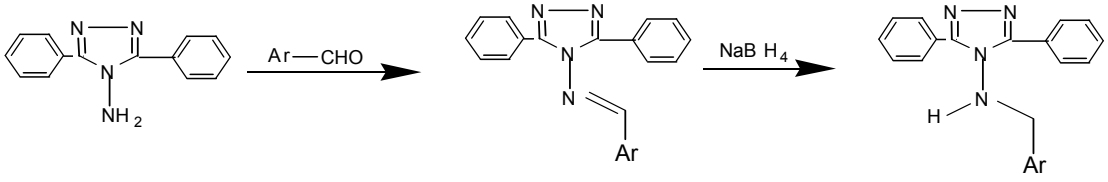
Table 1.
Evaluation of antibacterial activity of the compounds (2a-d) & (3a-d)

Compd.	Average zone of Inhibition/mm							
	S. aureus		*E. coli*		*B. subtilis*		*P.aeruginosa*	
	100 µg mL^{-1}	10 µg mL^{-1}	100 µg mL^{-1}	10 µg mL^{-1}	100 µg mL^{-1}	10 µg mL^{-1}	100 µg mL^{-1}	10 µg mL^{-1}
2a	18	15	16	14	17	15	18	16
2b	17	16	16	15	16	14	21	18
2c	16	15	16	14	15	14	16	15
2d	14	14	15	14	15	13	17	15
3a	19	16	17	15	16	14	16	15
3b	18	16	15	13	16	14	16	13
3c	17	15	21	18	16	14	17	15
3d	19	17	19	17	15	15	16	14
Standard (Ampicillin)	28	22	26	20	24	20	24	20
Control	00	00	00	00	00	00	00	00

RESULTS

4-amino-3, 5-diphenyl-4H-1, 2, 4-triazole **1** which is required as starting material were obtained in an one-pot reaction by heating ethylbenzoatebenzoylhydrazone, hydrazine hydrate and 1-propanol, under reflux conditions for 30 hours. The reaction mixture is cooled, washed with benzene, insoluble part in benzene was crystallized from 1-propanol to afford the compound **1** (88%). Compounds **2a-d** were prepared by the condensation of compound **1** with various aldehydes in acetic acid. During the reduction of compounds **2a-d**, the formation of multiple products was possible due to the possibility of the reduction of hetero ring. However, the reduction was performed on the imino group of **3a-d** without affecting the hetero ring by using $NaBH_4$ as selective reducing agents. See Scheme 1.

Scheme 1



(1) (2) (3)

Compound Ar

2,3a 4-Methylphenyl
b 4- Nitrophenyl
c 4- Chlorophenyl
d 4-Methoxyphenyl

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DISCUSSION

The IR spectrum of the compound **2a-d** showed C=N characteristic absorption bands between 1562-620 region. The PMR spectrum of **2a-c** exhibits a singlet characteristic signals at δ 1.83-1.95 (3H, s, CH_3) and mass spectra of **2a-d** showed molecular ion peaks at m/z 296 (M^+) in confirmity with the assigned molecular formulae. The IR spectrum of the compound **3a-d** showed NH characteristic absorption bands between 3298-310 region. The PMR spectrum of **3a-d** exhibits triplet characteristic signals at δ 5.42-7.30 (1H, t, NH) and a doublet at 3.71-4.10 (2H, d, CH_2) and mass spectra of **3a-d** showed molecular ion peaks at m/z 299(M^+) in confirmity with the assigned molecular formulae. These compounds were tested against various bacterial strains and the details are provided in the experimental section. These compounds were tested against various bacterial strains and the details are provided in the experimental section. All synthesized compounds showed reasonable activity against *S. aureus*, *E. coli*, *B. subtilis* and *P. aeruginosa* but the control of ampicillin is more active than all of the synthesized compounds.

CONCLUSION

In conclusion, a group of triazole derivatives incorporating 1, 2, 4-triazole rings were synthesized and characterized. These compounds seem to have potential as precursors for the synthesis of triazole structures with diverse antibacterial activities.

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