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Synthesis, Characterization of Some Novel Substituted Arylated Derivatives

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ABSTRACT

Several substituted arylated N-(2-(2-benzylidine hydrazinyl)-4H-1,2,4-triazol-4-amine and 1-(2-(4H-1,2,4-triazol-4-yl) amino)-3-chloro-4-phenyl azetidin-2-one have been synthesized by the appropriate methods and evaluated for their antibacterial and antifungal activity against Escherichia coli, Shigella dysenteriae, Streptococcus aureus and salmonella typhimurium, antifungal activity against A. niger (An), A. flavus (Af), F. oxisporium (Fo) and T. viride (Tv) and antiinflammatory activity against the carrageenan induced rat paw oedema method in albino rats. In the primary screening some of the products display acceptable biological activity. The structure of the synthesized compound has been established on the basis of their spectral and micro analytical data.

Keywords: synthesis, triazole derivatives, biological activity.

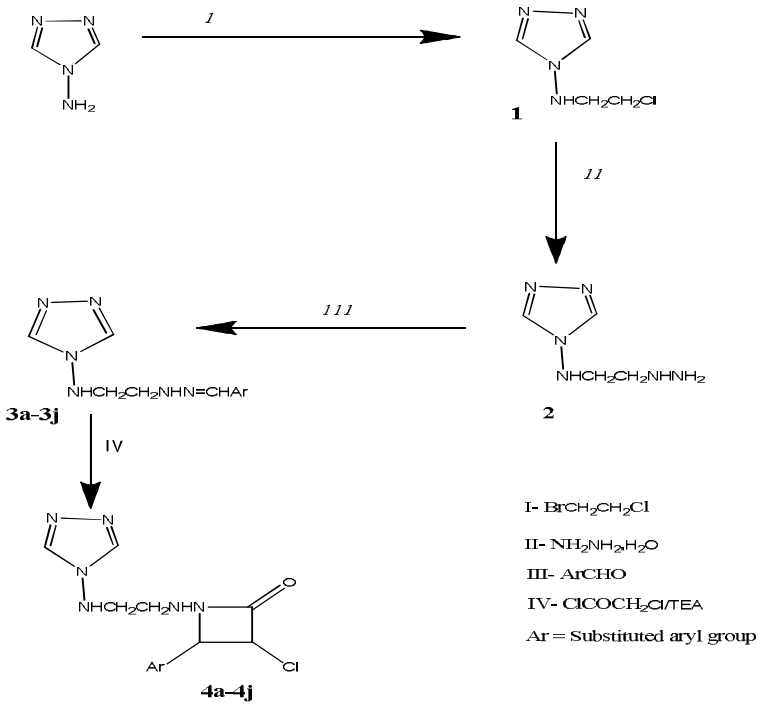
INTRODUCTION

The efficiency of azole derivatives as chemotherapeutic agent is well established and their chemistry has been extensively studied [1,2]. In the past years, the literature is enriched with progressive finding about the synthesis and pharmacological actions of fused heterocycles.[3,4] Literature survey revealed that 1,2,4 triazole derivatives are associated with potent biological activity such as pesticidal potentialities, herbicides, fungicides[6] and bactericidal[7]. 4H-1,2,4-Triazole-4-amine[5] and 2-azetidinones are also associated with pharmacological activity viz. hypnotic, antimicrobial [6], antiviral, anesthetic, anticonvulsant[8,9,10].

MATERIALS AND METHODS

Reaction Scheme: 4H -1, 2, 4-triazole-4-amine on electrophilic substitution with 1-bromo-2-chloro ethane under reflux condition afforded N-(2-chloro ethyl)-4H-1,2,4-triazol-4-amine, **1.** Which on reaction with hydrazine hydrate resulted in the formation of N-(2-hydrazinyl ethyl)-4H-1,2,4-triazole-4-amine **2**. The compound **2** which on condensation with various selected aromatic aldehydes furnished Schiff bases N-(2-(2-benzylidine hydrazinyl)-4H-1,2,4-triazole-4-amine. The β-lactam moiety in the compound was introduced by the cycloaddition of $ClCH_2COCl$ in the presence of Et_3N to give 1-(2-((4H-1,2,4-triazole-4-yl)amino)ethyl)amino)-3-chloro-4-phenyl azetidin-2-one. The purity of the compound was monitored by

TLC and the structure of the product was confirmed by spectral and chemical analysis.Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel G coated TLC plates. IR spectra were recorded on Schimadzu 8201 PC spectrophotometer in KBr. ^{1}H NMR spectra on a Brucker DRX 300 spectrometer in $CDCl_3$ at 300 MHz using TMS as internal standard. ^{13}C NMR spectral data on Brucker advance 400 FT spectrometer in $CDCl_3$. Elemental analyses were perform on Carlo Erba-1108 instrument. The analytical data of all the compounds were highly satisfactory. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallisation before use.



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RESULTS AND DISCUSSION

The structures have been elucidated on the basis of their spectral and micro analytical data.

N-(2-chloroethyl)-4H-1,2,4-triazol-4-amine, 1: The equimolar solution of 4H-1,2,4-triazole-4amine (0.357 mole, 30 g) and 1-bromo-2-chloro ethane (0.357 mole, 51.221g) in methanol (200 mL) was refluxed on water bath for about 2 h, cooled, filtered, washed with ice-cooled water and purified over the column of silica gel using chloroform : acetone (7/3 v/v) mixture as eluent. The elate was concentrated to give a product, which was recrystallized from ethanol to give compound 1. Yield 87% m.p. 78-80 °C. for $C_4H_7N_4Cl$: C 35.97, H 4.21, N 38.11% ; found C 35.92, H 4.31, N 38.01% . IR (ν,cm^{-1}) 1583 (-C=N), 2928 (-CH str.), 1367 (C-C), 3233 (>N-H str.), 766 (C-Cl) ; ^{1}H NMR : 8.24 (s, 1H, J=5.8), 7.80 (s, 1H, C-N-H), 2.90 (t, 3H, N-CH_2 J=5.62).

N-(2-hydrazinyl ethyl)-4H-1,2,4-triazole-4-amine, 2: The compound 1 (0.28 mol) hydrazine hydrate (0.28 mol) in methanol (200 mL) was refluxed on a water bath for about 6 h. It was cooled and filtered to get a product which was purified over the column of silica gel using chloroform: acetone (6:4 v/v) mixture as eluent. The elute was concentrated to obtain a product, recrystallized from chloroform to give compound 2.Yield 2. 81%. m.p. 105-07 °C for $C_4H_{10}N_7$: C 37.22, H 25.82, N 44.21 % ; found : C 36.88, H 25.22, N 43.56. IR (ν,cm^{-1}) 1581 (-C=N), 2925 (-CH str.), 1362 (C-C), 3231 (>N-H str.), 3455, 3411, 3371, 3274 (–$NHNH_2$). ^{1}H NMR : 8.39 (s , 1H, J=5.9), 8.39 (s ,1H,C-N-H), 4.90 (s, IH, -NH), 2.8.0 (t ,3H ,N-CH_2 J=4.62).

N-(2-(2-benzylidenehydrazinyl)-4H-1,2,4-triazol-4-amine, 3 (a-j) : A mixture of compound 2 (1.2 mol) and benzaldehyde (1.2 mol) in methanol (100 mL) with drops of acetic acid was refluxed on a water bath for about 1h. The solvent was distilled off under reduced pressure and solid thus obtained was purified over the column of silica gel using chloroform: methanol (5:5 v/v) mixture as eluent. The elute was concentrated to give a product, which was recrystallized with ethanol to give compound 3a. Yield 84% m.p. 130-32 °C for $C_{11}H_{14}N_6$; C 61.35, H 8.22, N 25.02%; found C 61.29, H 8.21, N 25.01% : IR (ν,cm^{-1}) 1585 (-C=N), 2924 (-CH str.), 1362 (C-C), 3233 (>N-H str.), 2982, 1611, 1583, 733(triazole ring), 3026, 1592, 738 (aromatic ring). ^{1}H-NMR: 8.39 (s, 1H, C-N-H), 4.90 (s, IH, -NH), 2.8.0 (t, 3H ,N-CH_2 J=4.62), 7.29-7.88 (m, 5H, Ar-H), 4.53 (s, 2H, -CH_2).

Likewise other compound 3(b-j) and 4(b-j) were synthesized by treating compound 2 with selected aromatic aldehydes. The characterization data of the compound 3(a-j) and 4(b-j) are given in table 1and2.

Table 1

Compound	Ar	Yield	M.P. (°C)	Molecular Formula	Found % (Calculated %) C	H	N
3b	2-ClC_6H_4	75	135-37	$C_{11}H_{13}N_6Cl$	56.23 (56.29)	6.45 (6.48)	24.01 (24.23)
3c	3-ClC_6H_4	78	140-42	$C_{11}H_{13}N_6Cl$	56.26 (56.29)	6.46 (6.48	24.04 (24.23)
3d	4-ClC_6H_4	76	132-32	$C_{11}H_{13}N_6Cl$	56.24 (56.29)	6.46 (6.48)	24.02 (24.23)
3e	2-BrC_6H_4	81	132-34	$C_{11}H_{13}N_6Br$	48.23 (48.29)	6.20 (6.22)	22.33 (22.36)
3f	3-BrC_6H_4	79	133-35	$C_{11}H_{13}N_6Br$	48.23 (48.29)	6.20 (6.22)	22.33 (22.36)
3g	4-BrC_6H_4	80	134-36	$C_{11}H_{13}N_6Br$	48.25 (48.29)	6.21 (6.22)	22.34 (22.36)
3h	2-$NO_2C_6H_4$	78	155-57	$C_{11}H_{13}N_7NO_2$	54.67 (54.69)	6.72 (6.74)	25.58 (25.60)
3i	3-$NO_2C_6H_4$	76	152-54	$C_{11}H_{13}N_7NO_2$	54.67 (54.69)	6.72 (6.74)	25.58 (25.60)
3j	4-NO_2C6H4	79	150-52	$C_{11}H_{13}N_7NO_2$	54.67 (54.69)	6.72 (6.74)	25.58 (25.60)
4b	2-ClC_6H_4	81	103-05	$C_{13}H_{14}N_6Cl_2$	51.42 (51.45)	6.25 (6.27)	18.91 (18.93)
4c	3-ClC_6H_4	84	112-15	$C_{13}H_{14}N_6Cl_2$	51.44 (51.45)	6.23 (6.27)	18.92 (18.93)
4d	4-ClC_6H_4	79	108-10	$C_{13}H_{14}N_6Cl_2$	51.40 (51.42)	6.21 (6.23)	18.97 (18.99)
4e	2-BrC_6H_4	74	113-15	$C_{13}H_{14}N_6ClBr$	46.28 (46.30)	3.64 (3.68)	17.55 (17.58)
4f	3-BrC_6H_4	75	116-18	$C_{13}H_{14}N_6ClBr$	46.27 (16.30)	3.63 (3.68)	17.56 (17.58)
4g	4-BrC_6H_4	73	120-22	$C_{13}H_{14}N_6ClBr$	46.28 (46.30)	3.65 (3.68)	17.57 (17.58)
4h	2-$NO_2C_6H_4$	68	140-42	$C_{13}H_{14}N_6NO_2$	48.77 (48.77)	3.92 (3.92)	19.27 (19.27)

4i	3-$NO_2C_6H_4$	69	144-46	$C_{13}H_{14}N_6NO_2$	48.75 (48.77)	3.91 (3.92)	19.28 (19.27)
4j	4-$NO_2C_6H_4$	66	138-40	$C_{13}H_{14}N_6NO_2$	48.76 (48.77)	3.92 (3.92)	19.25 (19.27)

Table 2: IR, 1H-NMR spectral data of newly synthesized compound

Compound	Molecular Formula	v/cm^{-1}	δ value
3b	$C_{11}H_{13}N_6Cl$	3366 (-NH), 2986, 1609, 1587, 732 (triazole ring), 1544 (N=CH), 762 (Ar-Cl), 3021, 1589, 1579, 740 (aromatic ring)	4.82 (s, 1H,-NCHAr), 8.36 (s, 1H, -NH), 7.31-7.83 (m, 4H, Ar-H), 4.55 (t, 2H, -CH_2), 4.90 (s, 1H, =NCH)
3e	$C_{11}H_{13}N_6Br$	3362 (-NH), 2987, 1600, 1580, 731 (triazole ring), 1543 (N=CH), 662 (Ar-Br), 3022, 1588, 1579, 741 (aromatic ring)	4.74 (s, 1H,-NCHAr), 8.33 (s, 1H, -NH), 7.31-7.76 (m, 4H, Ar-H), 4.57 (t, 2H, CH_2), 4.81 (s, 1H, =NCH)
3h	$C_{11}H_{13}N_7O_2Cl$	3362 (-NH), 2987, 1600, 1580, 731 (triazole ring), 1543 (N=CH), 3022, 1588, 1579, 741 (aromatic ring), 1522, 1344 ($ArNO_2$).	4.92 (s, 1H,-NCHAr), 8.44 (s, 1H, -NH), 7.81-7.76 (m, 4H, Ar-H), 4.91 (t, 2H, -CH_2), 4.87 (s, 1H, =NCH)
4b	$C_{12}H_{14}N_6OCl$	3362 (-NH), 2987, 1600, 1580, 731 (triazole ring), 1543 (N=CH), 3022, 1588, 1579, 741 (aromatic ring), 1522, 1344 (ArCl), 1772 (>C=O), 772 (Ar-Cl).	4.83 (s, 1H,-NCHAr), 8.37 (s, 1H, -NH), 7.31-7.83 (m, 4H, Ar-H), 4.65 (t, 2H, -CH_2), 4.78 (s, 1H, =NCH), 4.17 (D, J=5.1 Hz, 1H, -NCH-Ar)
4e	$C_{13}H_{14}N_6ClBr$	3372 (NH), 2988, 1601, 1580, 731 (triazole ring), 1543 (N=CH), 3021, 1587, 1579, 740 (aromatic ring), 1522, 1344 (ArCl), 1772 (>C=O), 772 (Ar-Cl).	4.83 (s, 1H,-NCHAr), 8.37 (s, 1H, -NH), 7.31-7.83 (m, 4H, Ar-H), 4.65 (t, 2H, -CH_2), 4.78 (s, 1H, =NCH), 4.17 (D, J=5.1 Hz, 1H, -NCH-Ar)
4h	$C_{13}H_{14}N_6NO_2$	3377 (NH), 3022, 1608, 1580, 731 (triazole ring), 1549 (N=CH), 3100, 1587, 1579, 740 (aromatic ring), 1600, 1452 (ArNO2), 1779 (>C=O).	4.88 (s, 1H,-NCHAr), 8.39 (s, 1H, -NH), 7.33-7.85 (m, 4H, Ar-H), 4.68 (t, 2H, -CH_2), 4.78 (s, 1H, =NCH), 4.27 (D, J=5.1 Hz, 1H, -NCH-Ar).

All the synthesized compounds 1, 2, 3(a-j) and 4(a-j) have been screened *in vitro* for their antifungal activity against A. niger (An), A. flavus (Af), F. oxisporium (Fo) and T. viride (Tv) Af at two concentrations (100 and 500 ppm) by filter paper disc method . Standard fungicide Griseofulvin and antibacterial streptomycin was also screened under the similar conditions for comparison. The antifungal of compound is shown in table 3.

Table 3

Compound	*A. niger*		*A. flavus*		*T. viride*		*F. oxisporium*	
	100 ppm	**500 ppm**	**100 ppm**	**500 ppm**	**100 ppm**	**500 ppm**	**100 ppm**	**500 ppm**
1	+	+	+	+	+	++	+	++
2	-	+	-	+	+	+	-	+
3	+	++	-	+	-	+	+	-
3a	+	+	++	-	+	-	++	+
3b	++	+	+	+	++	+	+	+
3c	+	++	+	++	++	+++	+	++
3d	+	++	++	+++	+	+	++	+

3e	+	+	-	-	+	-	+	+
3f	++	++	+	++	+++	+	-	+
3h	+	++	-	-	+	-	+	+
3i	-	+	+	++	+++	+	-	-
3j	-	-	+	-	-	-	+	+
4a	+	+	+	++	+	++	++	+
4b	++	++	+	+	++	+	++	+++
4c	+++	++	++	++	++	+++	++	+++
4d	++	+	+	++	++	-	++	+
4e	+	++	+	++	+	++	++	+
4f	+	-	+	++	-	+	+	-
4g	++	+++	+	++	+++	+++	++	+
4h	+++	+	++	-	++	+	-	-
4i	+	-	-	+	+	-	+	+
4j	+	++	++	+	++	+	+	++

APPLICATIONS

The synthesized compounds generally possess very good anti-bacterial and anti-fungal agent.

CONCLUSIONS

The above synthesized compounds 1, 2, 3a-3j and 4a-4j have possess anti-fungal and anti-bacterial activity.

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