Synthesis and Antimicrobial Activity of 1,2,4-Triazoles

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Abstract Several 3-(4'-nitrophenyl)-4-(4"-chloro benzamido)-5-substituted phenyl)-4H-1,2,4-triazole (3a-3e) and 3-(4'-nitrophenyl)-4-(4'-methyl benzenesulphonamido)-5-substituted phenyl)-4H-1,2,4-triazole (4a-4e) have been synthesised. Representative compounds were screened for antibacterial, antifungal activity. Most of them showed significant antibacterial activity.

Key words Synthesis, Antibacterial activity, Antifungal activity, Triazole

Introduction

Nitrogen based heterocyclic compounds are very important in the field of medicinal chemistry. The present triazoles¹ were prepared because of its good biological activities. Compounds including a 1,2,4-triazole nucleus² and 4-N-substituted derivatives³ are known to possess various biological activities. Certain compounds having 1,2,4-triazole nucleus⁴ have been reported as fungicidal,⁵ antimicrobial,⁶ anticonvulsant,⁷ antidepressant,⁸ and antibacterial activities.⁹ Moreover benzamido¹⁰ and sulphonamido¹¹ group are very important to enhance some biological activities like antimalarial, antibacterial, anticancer and antitubercular.¹²

The above mention observation prompted us to synthesis the title compounds with anticipation that the combination of biolabile triazole unit with bioactive sulphonamido compounds may enhance their antimicrobial potency as compared to benzamido derivatives.

Experimental Section

All melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The IR spectra were recorded in KBr on a "Perkin-Elmer RX 1 FT-IR" Spectrophotometer (serial No. 51448) and ¹H NMR spectra were determined with "Perkin Elmer Model-32 NMR spectrometer" at 300MHz using TMS as internal standard and CDCl₃ as solvent.

Preparation of 2-(4'-nitrophenyl)-5-(substituted phenyl)-1,3,4-oxadiazole (2a-e)

A mixture of 4-nitro benzohydrazide (**1**) (0.01mole) and an aromatic acid (**2**) (0.01mole) in POCl₃ (5ml) was refluxed for 5-6 hr. The reaction mixture was cooled to room temperature and then the contents were poured on to crushed ice and neutralised with bicarbonate solution. The resulting solid was dried and crystallized from ethanol: $\nu_{\max}$ 1530 (C=N), 1490 (Asymmetric ArNO₂) and 1347 (symmetric ArNO₂); δ ppm (CDCl₃) 6.96-7.94 (m, 8H, aromatic).

Preparation of 3-(4'-nitrophenyl)-4-(4''-chloro benzamido)-5-substituted phenyl)-4H-1,2,4-triazole (3a-e)

A mixture of 2-(4'-nitrophenyl)-5-(substituted phenyl)-1,3,4-oxadiazole (2a-e) (0.01mole) and 4-chloro benzohydrazide (0.01mole) in dry pyridine (10ml) was refluxed for 6-8 hr. The reaction mixture was cooled to room temperature and then the contents were poured on to crushed ice and neutralised with dilute HCl solution. The resulting solid was dried and crystallized from glacial acetic acid. Physical and characterization data of compound (3a-e) are given in **Table-1**. IR and ¹H NMR spectral data of compound (3a-e) are given in **Table-2**.

Table-1 Physical and characterization data of compound **3a-4e**

Compd	M.P. °C	Yield (%)	M.F. (Mol. Weight)	Found (Calcd.) (%)		
				C	H	N
3-a	210	65	C ₂₁ H ₁₄ ClN ₅ O ₃	60.00	3.34	16.00
			419.820	(60.08)	(3.36)	(16.08)
3-b	230	60	C ₂₁ H ₁₃ Cl ₂ N ₅ O ₃	55.49	2.88	15.39
			454.265	(55.52)	(2.86)	(15.42)
3-c	215	62	C ₂₂ H ₁₆ ClN ₅ O ₅	55.70	3.51	15.58
			449.846	(58.74)	(3.59)	(15.57)
3-d	254	58	C ₂₁ H ₁₃ Cl ₂ N ₅ O ₃	55.49	2.88	15.39
			454.265	(55.52)	(2.86)	(15.42)
3-e	233	60	C ₂₂ H ₁₆ ClN ₅ O ₅	55.70	3.51	15.58
			449.846	(58.74)	(3.59)	(15.57)
4-a	227	66	C ₂₁ H ₁₇ N ₅ O ₄ S	57.89	3.90	16.00
			435.457	(57.92)	(3.93)	(16.08)
4-b	252	60	C ₂₁ H ₁₆ ClN ₅ O ₄ S	53.66	3.40	14.79
			469.902	(53.68)	(3.43)	(14.90)
4-c	237	62	C ₂₂ H ₁₉ N ₅ O ₅ S	56.70	4.09	15.00
			465.483	(56.77)	(4.11)	(15.05)
4-d	280	55	C ₂₁ H ₁₆ ClN ₅ O ₄ S	53.66	3.40	14.79
			469.902	(53.68)	(3.43)	(14.90)
4-e	271	62	C ₂₂ H ₁₉ N ₅ O ₅ S	56.70	4.09	15.00
			465.483	(56.77)	(4.11)	(15.05)

Preparation of 3-(4'-nitrophenyl)-4-(4''-methyl benzenesulphonamido)-5-substituted phenyl)-4H-1,2,4-triazole (4a-e)

A mixture of 2-(4'-nitrophenyl)-5-(substituted phenyl)-1,3,4-oxadiazole (2a-e) (0.01mole) and 4-methyl benzenesulphohydrazide (0.01mole) in dry pyridine (10ml) was refluxed for 6-8 hr. The reaction mixture was cooled to room temperature and then the contents were poured on to crushed ice and neutralised with dilute HCl solution. The resulting solid was dried and crystallized from glacial

acetic acid. Physical and characterization data of compound (**3a-e**) are given in **Table-1**. IR and ^1H NMR spectral data of compound (**3a-e**) are given in **Table-2**.

Result and Discussion

Antibacterial and antifungal activity

All the compounds (3a-3e & 4a-4e) from the series were screened for their antibacterial activity against *B. subtilis*, *S. aureus*, *P. aeruginosa* and *E. coli*. The standard drug used was Furacin and DMF was kept as solvent control. Similarly the antifungal studies were carried out against fungus *C. albicans* and *C. krusei*, using Flucanazol as standard. Compounds **3-e**, **4-c**, **4-d** and **4-e** showed significant antibacterial activity. Compound **3-a** and **4-b** showed significant antifungal activity. Activities of compounds 3a-3e and 4a-4e are given in **Table-3**.

Table-2 IR, ^1H NMR spectral data of compound **3a-4e**

Compd	IR (KBr) (cm^{-1})	NMR (CDCl_3) (δ ppm)
3-a	3318 (NH), 1630 (C=O of amide I) 1525 (C=O of amide II) 810 (C-Cl)	6.95-7.94 (m, 13H, aromatic), 9.79 (s, 1H, NH)
3-b	3325 (NH), 1625 (C=O of amide I) 1525 (C=O of amide II) 810 (C-Cl)	6.95-7.94 (m, 12H, aromatic), 9.79 (s, 1H, NH)
3-c	3318 (NH), 1630 (C=O of amide I) 1515 (C=O of amide II) 810 (C-Cl)	3.73 (s, 3H, OCH_3), 6.94-7.95 (m, 12H, aromatic), 9.79 (s, 1H, NH)
3-d	3330 (NH), 1635 (C=O of amide I) 1525 (C=O of amide II) 810 (C-Cl)	6.95-7.94 (m, 12H, aromatic), 9.79 (s, 1H, NH)
3-e	3318 (NH), 1630 (C=O of amide I) 1510 (C=O of amide II) 810 (C-Cl)	3.73 (s, 3H, OCH_3), 6.94-7.95 (m, 12H, aromatic), 9.79 (s, 1H, NH)
4-a	3320 (NH), 1355(SO_2)	6.90-7.90 (m, 13H, aromatic), 9.67 (s, 1H, NH)
4-b	3318 (NH), 1355(SO_2) 810 (C-Cl)	6.90-7.90 (m, 12H, aromatic), 9.67 (s, 1H, NH)
4-c	3315 (NH), 1355(SO_2)	3.65 (s, 3H, OCH_3), 6.90-7.90 (m, 12H, aromatic), 9.67 (s, 1H, NH)
4-d	3320 (NH), 1355(SO_2) 810 (C-Cl)	6.90-7.90 (m, 12H, aromatic), 9.67 (s, 1H, NH)
4-e	3318 (NH), 1355(SO_2)	3.65 (s, 3H, OCH_3), 6.90-7.90 (m, 12H, aromatic), 9.67 (s, 1H, NH)

REACTION SCHEME

Compound	R	Compound	R
3a	H	4a	H
3b	<i>o</i> -Cl	4b	<i>o</i> -Cl
3c	<i>o</i> -OCH ₃	4c	<i>o</i> -OCH ₃
3d	<i>p</i> -Cl	4d	<i>p</i> -Cl
3e	<i>P</i> -OCH ₃	4e	<i>P</i> -OCH ₃

Table-3. In vitro Antibacterial and Antifungal Activity of compound 3a-4e

Compound	Antibacterial in (µg/ml)				Antifungal in (µg/ml)	
	Gram positive		Gram Negative		C.albicans	C.krusei
	S.a	B.s	E.c	P.a	ATCC 10231	G03
3-a	5	15	10	15	-	20
3-b	-	10	0.4	5	5	0.4
3-c	15	-	15	10	5	15
3-d	10	5	15	-	-	15
3-e	10	25	10	30	10	-
4-a	5	0.4	-	5	10	0.4
4-b	-	0.2	-	0.4	-	25
4-c	30	5	10	15	-	5
4-d	5	20	0.4	25	0.2	5
4-e	10	15	30	10	5	0.4
Zone of inhibition of standard drugs (µg/ml)						
Furacin	40	45	40	50	-	-
Flucanzol	-	-	-	-	40	35
S.a - S. aureus B.s - B.subtilis E.c - E.coli P.a - P.aeruginosa						

Conclusion

From the above result and discussion about the antimicrobial activity it is conclude that the sulphonamido derivatives are more important in the field of medicinal chemistry with compared to benzamido derivatives which was already anticipated in introductory part.

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