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Design, Synthesis and Characterization of Novel Arylamides Containing 1,2,4-triazole Nuclei for Possible Antimicrobial Activity

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Abstract Diphenyl aceto hydrazide on reaction with carbon disulfide and potassium hydroxide gave potassium α,α -diphenyl acetamido dithiocarbamate, which on cyclisation with hydrazine hydrate yielded key intermediate 3-mercapto-4,N-amino-5-benzhydryl-1,2,4-triazoles. The key intermediate on condensation with different acid chloride afforded our titled compounds. The synthesised compounds have been confirmed elemental analyses and further supported by spectral data. All the synthesised compounds have been evaluated for their *in vitro* antimicrobial activity.

Key words 1,2,4-triazoles, arylamides and antimicrobial activity

Introduction

Arylamides have widely used as pharmacologically useful entities. Arylamides are known to be useful as anticancer¹, antimicrobial², anticonvulsant³ and antiviral⁴ agents. These valid observations prompted us to synthesise some novel arylamides bearing 1,2,4-triazole nuclei.

Diphenyl acetic acid on esterification gave ethyl diphenyl acetate, which on condensation with hydrazine hydrate gave starting compound diphenyl aceto hydrazide (**I**). The reaction of (**I**) with CS₂ and alcoholic KOH gave potassium α,α -diphenylacetamido dithiocarbamate (**II**), which on cyclisation with hydrazine hydrate yielded 3-mercapto-4,N-amino-5-benzhydryl-1,2,4-triazoles (**III**). The condensation of different acid chloride with 1,2,4-triazole nuclei (**III**) furnished our target molecules (**IVa-l**).

The constitutions of all the synthesised products were established on the basis of elemental analyses, IR, ¹HNMR and mass spectral study.

Antimicrobial activity

Antimicrobial screening was conducted using cup-plate agar diffusion method⁵ at a concentration of 40 μ g/ml. All the products were assessed for their *in vitro* antimicrobial activity against different strains of bacteria such as *B. megaterium*, *S. aureus*, *P. vulgaris*, *E. coli* and fungi like *A. niger*.

REACTION SCHEME

Table-I Antimicrobial data of the compounds IVa-l

Compd No	Antibacterial activity			Antifungal activity	
	E. coli	P.vulgaris	B. mega	S.aureus	A.niger
4a	16	10	18	12	14
4b	18	12	15	14	18
4c	14	13	14	16	12
4d	20	16	16	18	14
4e	14	15	18	13	19
4f	13	12	20	11	16
4g	15	11	19	15	20
4h	17	10	13	10	16
4i	14	15	18	15	17
4j	18	12	21	17	13
4k	20	13	18	14	21
4l	16	11	17	11	17
Ampicillin	23	15	23	22	-
Amoxicillin	21	18	22	23	-
Norfloxacin	23	17	24	17	-
Penicillin	25	24	19	20	-
Greseofulvin	-	-	-	-	25

Experimental

All the melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography was used for monitoring the reaction and to check purity. IR spectra recorded on Shimadzu FTIR – 8400 on KBr disc. ¹H NMR spectra were recorded on 300 MHz spectrometer using TMS as an internal standard, FAB mass spectra were recorded on JEOL SX 102/DA 6000 spectrophotometer. All the compounds gave satisfactory elemental analysis.

Potassium *a,a*-diphenylacetamido dithiocarbamate (II)

A mixture of potassium hydroxide (0.84g, 0.015M) in 25ml of absolute alcohol, diphenyl aceto hydrazide (I) (2.26g, 0.01M) and CS₂ (1.14ml, 0.015M) was stirred for 12 hrs. and then diluted with 200ml of dry ether. Resulting solid was filtered and washed with dry ether. Yield 3.02g, 89%.

3-Mercapto-4,*N*-amino-5-benzhydryl-1,2,4-triazole (III)

A suspension of potassium salt (II) (3.4g, 0.01M), hydrazine hydrate (1ml, 0.02M) and water (2ml) was refluxed for 2 hrs. Dilute the reaction mixture with 100ml of ice-cold water and acidify with glacial acetic acid. The resulted white solid precipitate was filtered, washed with cold water and crystallized by the mixture of DMF and ethanol. Yield 1.74g, 62%, m.p. 207°C.

3-Mercapto-4,*N*-aroylamino-5-benzhydryl-1,2,4-triazoles (IVa-l)

3-Mercapto-4,*N*-amino-5-benzhydryl-1,2,4-triazole (III) (2.82g, 0.01M) and different acid chlorides (0.01M) in dry pyridine (20ml) was refluxed for 9 hrs. The content was poured on to crushed ice and neutralized with dilute HCl. The isolated product was filtered, washed with cold water and crystallized from ethanol. When R= *N,N*-di-methyl, Yield 2.54g, 72%, m.p. 134°C. Anal. Calcd for C₁₈H₁₉N₃OS; C, 61.17; H, 5.42; N, 19.81; found: C, 61.14; H, 5.38; N, 19.78%; IR (KBr) cm⁻¹: 3219 (N-H), 2424.4 (S-H), 1693.4 (C=O), 1606.6 (C=N), 1510.2 (C=C); ¹H NMR (CDCl₃+DMSO-d₆) ppm: 2.09 (s, 1H, -SH), 2.95 (s, 3H, -N-CH₃), 3.12 (s, 3H, -N-CH₃), 5.72 (s, 1H, -CH), 7.25-7.35 (m, 10H, Ar-H). In mass spectra molecular weight=353, m/z=354(m+1).

Similarly other arylamides were synthesised, Yield 55-84%. The m.p. of the products, when R= phenyl, 232°C; R= 4-chlorophenyl, 189°C; R= 2-chlorophenyl, 198°C; R= 2-fluorophenyl, 149°C; R= methyl, 117°C; R= *N,N*-di methyl, 134°C; R= *N,N*-di ethyl, 153°C; R= 4-nitrophenyl, 213°C; R= 3,4-di nitro phenyl, 234°C; R= 4-methylphenyl, 177°C; R= 2-methylphenyl, 164°C; R= 3-pyridyl, 147°C.

Conclusion

It was concluded from Table-I that most of the compounds showed moderate activity against the above microbes. Compound of type (IVa-l) showed significant activity when R= methyl (zone of inhibition 18-21 mm), R= 4-methylphenyl (zone of inhibition 13-21 mm), R= 2-methylphenyl (zone of inhibition 12-21 mm), R= 3-pyridyl (zone of inhibition 16-21 mm) towards all the types of bacteria and fungi tested.

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