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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW 3-{2-[(4-CHLOROPHENYL)SULFONYL]ETHYL}-5-ARYL-4*H* 1,2,4-TRIAZOLES

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ABSTRACT

Methyl acrylate was treated with 4-chlorobenzenethiol to give methyl 3-[(4-chlorophenyl)thio]propanoate (1). The latter on oxidation with hydrogen peroxide gave methyl-3-[(4-chlorophenyl)sulfonyl]propanoate (2).3-[(4-chlorophenyl)sulfonyl] propane hydrazide (3) was prepared from methyl3-[(4-chlorophenyl)sulfonyl] propanoate (2) by reaction with hydrazine hydrate. A series of new 1,2,4-triazoles (4a-h) were prepared from 3-[(4-chlorophenyl)sulfonyl]propanehydrazide. The structural elucidation of these compounds was based on their IR, ^{1}H NMR and MS spectral data. These compounds were also screened for their antimicrobial activity against four bacteria and two fungi and some of the compounds found to have promising activity.

KEYWORDS : 3-[(4-chlorophenyl)sulfonyl]propanehydrazide, 1,2,4-triazoles, antibacterial activity, antifungal activity.

1.INTRODUCTION

Nitrogen containing heterocycles are very important in the field of medicinal chemistry. 1,2,4-Triazoles and their derivatives represent one of the most biologically active classes of compounds, possessing a wide range of therapeutic properties such as anti-inflammatory (Wade,1982), antifungal (Rollas,1993), antibacterial (Malbec,1984), antiviral (Jones,1965), anticonvulsant (Kane,1988), antidepressant (Kane,1988) and anticancer (Holla,2003) activities. The derivatives of 1,2,4-triazole such as fluconazole (Tsukuda,1998; Narayanan,1993) itraconazole (Krakovsky and Rybak,1990), ravuconazole (Roberts,2000), voriconazole (Sanati,1997; Espinel,1998) and posaconazole (Pfaller,1997) are antifungal drugs. A series of 1,2,4-triazole derivatives have been patented and extensively employed in agriculture (Vamvakides,1990). In addition, organosulfones have gained importance because of their chemotherapeutic properties. Synthesis of the triazole libraries is an effective way for the development of new drugs and it would be a valuable addition to the existing literature. Thus carbonyl group of araldehydes was employed to synthesize the triazoles (4a–h) from the aforementioned hydrazide (3). These triazoles were also screened for their antibacterial activity, antifungal activity and some of the synthesized compounds showed good antimicrobial activity.

2.MATERIALS AND METHODS

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC; silica gel, chloroform: methanol, 19:1). The infrared (IR) spectra were recorded on a Spectrum 100 Fourier transform (FT)–IR spectrometer as KBr pellets, and the wave numbers were given in centimeters. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). All chemical shifts are reported in δ (ppm) using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on shimadzu LC mass spectrometer.

Synthesis of methyl 3-[(4-chlorophenyl)thio]propanoate (1):

A chilled mixture of 14.46g (0.1 mol) of 4-chlorobenzenethiol and 0.10 g of sodium methoxide after drop wise addition of 19 g of methyl acrylate was stirred for sixteen hours at 25 ^{0}C. The contents were filtered to remove base and a small amount of polymerised ester. After the unreacted ester was removed under reduced pressure, the residue was extracted with diethyl ether, washed with water and dried over anhydrous sodium sulphate. The ether solution was evaporated to get methyl 3-[(4-chlorophenyl)thio]propanoate (1). Yield 18.91 g (82%); mp 38-40° C; IR (KBr, cm^{-1}): 3086 (Ar-H), 1729 (C=O), 1098 (S-Ar), 1180 (C-O-C).

Synthesis of methyl 3-[(4-chlorophenyl)sulfonyl]propanoate (2):

To an ice cold solution of 18g (0.078 mol) of 3-[(4-chlorophenyl)thio] propanoate (1) in acetic acid (50 ml), 30% hydrogen peroxide (20 ml) was added and stirred for one day at room temperature. A solid separated after the removal of acetic acid was extracted with diethyl ether, washed with water and dried over anhydrous sodium sulphate. The ether solution was evaporated to get methyl 3-[(4-chlorophenyl)sulfonyl]propanoate (2) and it was recrystallised from ethanol. Yield 17.83 g (87%); mp 62-65° C; IR (KBr, cm^{-1}): 3097 (Ar-H), 1736 (C=O), 1087(S-Ar), 1318, 1155 (SO_2), 1179 (C-O-C).

Synthesis of 3-[(4-chlorophenyl) sulfonyl]propanehydrazide (3): To a solution of 17 g (0.065 mol) of 3-[(4-chlorophenyl)sulfonyl]propanoate (2) in ethanol (6 ml), hydrazine hydrate (11 mmol) was added and refluxed for 3 h.

The reaction mixture was cooled and the solid separated was collected by filtration, dried and recrystallised from ethanol to get pure 3-[(4-chlorophenyl) sulfonyl]propanehydrazide (3).Yield 12.24g (72%); mp 134-137°C; IR (KBr, cm^{-1}): 3362, 3303 (NH_2 and NH), 3091(Ar-H), 1678 (Amide C=O), 1087 (S-Ar), 1306, 1157 (SO_2); HRMS: 285.0077 (M + Na).

General Procedure of Synthesis of 3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-aryl-4*H* 1,2,4-triazole: To a solution of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide (0.0038 mol) in acetic acid a pinch of ammonium acetate was added followed by the addition of aldehyde (0.0038) and the mixture was stirred for 24 hrs at room temperature. The solution was then neutralised with liq. Ammonia and the product obtained was filtered, washed with water and recrystallised from ethanol to give the products.

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-phenyl-4*H* 1,2,4-triazole (4a): Yield 0.87 g (66%); mp 138-140°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.95-3.00 (t, 2H, CH_2), 3.62-3.67 (t, 2H, SO_2-CH_2), 7.42-8.10 (m, 9H, Ar-H), 11.45 (NH); IR (KBr, cm^{-1}): 3252 (N-H), 3074 (Ar-H), 2973 (Aliphatic C-H), 1618 (C=N), 1086 (S-Ar), 1322, 1143 (SO_2); LC Mass: 348 (M+1).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-(2-chlorophenyl)-4*H* 1,2,4-triazole (4b): Yield 0.81 g (56%); mp 144-146° C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.91-2.96 (t, 2H, CH_2), 3.61-3.68 (t, 2H, SO_2-CH_2), 6.29-8.31 (m, 8H, Ar-H), 11.50 (NH); IR (KBr, cm^{-1}): 3184 (N-H), 3069 (Ar-H), 2960 (Aliphatic C-H), 1627 (C=N), 1088 (S-Ar), 1319, 1126 (SO_2); LC Mass: 382 (M+1).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-(4-chlorophenyl)-4*H* 1,2,4-triazole (4c): Yield 0.83 g (57%); mp 148-151° C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.22-3.26 (t, 2H, CH_2), 3.52-3.56 (t, 2H, SO_2-CH_2), 7.26-7.91 (m, 8H, Ar-H), 9.13 (NH); IR (KBr, cm^{-1}): 3213 (N-H), 3070 (Ar-H), 2972 (Aliphatic C-H), 1629 (C=N), 1087 (S-Ar), 1318, 1143 (SO_2); LC Mass: 382 (M+1).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-(3-methoxyphenyl)-4*H*1,2,4-triazole (4d): Yield 0.93 g (65%); mp 140-143° C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.94-2.98 (t, 2H, CH_2), 3.63-3.68 (t, 2H, SO_2-CH_2), 3.79 (OCH_3), 7.15-7.95 (m, 8H, Ar-H), 11.49 (NH); IR (KBr, cm^{-1}): 3187 (N-H), 3089 (Ar-H), 2987 (Aliphatic C-H), 1621 (C=N), 1087 (S-Ar), 1254 (O-CH_3), 1317, 1147 (SO_2); LC Mass: 378 (M+1).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-(4-methoxyphenyl)-4*H* 1,2,4-triazole (4e): Yield 0.89 g (62%); mp 142-145° C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.20-3.24 (t, 2H, CH_2), 3.53-3.56 (t, 2H, SO_2-CH_2), 3.86 (OCH_3), 6.93-7.91 (m, 8H, Ar-H), 8.74 (NH); IR (KBr, cm^{-1}): 3178 (N-H), 3089 (Ar-H), 2964 (Aliphatic C-H), 1619 (C=N), 1089 (S-Ar), 1321, 1152 (SO_2) 1257 (O-CH_3); LC Mass: 379 (M+2).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-(2-hydroxyphenyl)-4*H* 1,2,4-triazole (4f): Yield 0.76 g (55%); mp 194-196° C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.91-2.96 (t, 2H, CH_2), 3.61-3.68 (t, 2H, SO_2-CH_2), 6.87-8.30 (m, 8H, Ar-H), 9.00 (OH), 11.40 (NH); IR (KBr, cm^{-1}): 3436 (O-H), 3260 (N-H), 3051 (Ar-H), 2982 (Aliphatic C-H), 1623 (C=N), 1087 (S-Ar), 1312, 1151 (SO_2); LC Mass: 365 (M+2).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-[4-hydroxy-(3-methoxy)phenyl]-4*H* 1,2,4-triazole (4g): Yield 0.88 g (59%); mp 134-136° C; ^{1}H NMR ($CDCl_3$) δ (ppm): 322-3.26 (t, 2H, CH_2), 3.53-3.57 (t, 2H, SO_2-CH_2), 3.99 (OCH_3), 6.93-7.90 (m, 7H, Ar-H), 5.90 (OH), 8.71 (NH); IR (KBr, cm^{-1}): 3418 (O-H), 3254 (N-H), 3083 (Ar-H), 2943 (Aliphatic C-H), 1621 (C=N), 1085 (S-Ar), 1320, 1147 (SO_2) 1268 (O-CH_3); LC Mass: 394 (M+1).

3-{2-[(4-chlorophenyl)sulfonyl]ethyl}-5-(4-nitrophenyl)-4*H* 1,2,4-triazole (4h): Yield 0.92 g (62%); mp 200-203° C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.27-3.31 (t, 2H, CH2), 3.53-3.56 (t, 2H, SO_2-CH_2), 7.25-7.56 (m, 8H, Ar-H), 8.71 (NH); IR (KBr, cm^{-1}): 3193 (N-H), 3080 (Ar-H), 2940 (Aliphatic C-H), 1632 (C=N), 1090 (S-Ar), 1579,1404 (NO_2), 1305, 1140 (SO_2); LC Mass: 393 (M+1).

3.Results and Discussion

The synthetic pathway followed for the synthesis of triazoles is presented in the Scheme 1. Reaction of methyl acrylate with 4-chlorobenzenethiol afforded methyl 3-[(4-chlorophenyl)thio]propanoate (1). The sulfide (1) on reaction with hydrogen peroxide in acetic acid gave corresponding sulfone *i.e.* methyl3-[(4-chlorophenyl) sulfonyl]propanoate (2). This on treatment with hydrazine hydrate in ethanol under reflux conditions resulted in the formation of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide (3). Reaction of benzaldehyde with 3 in presence of ammonium acetate in acetic acid at room temperature gave 4a. The IR spectra of compound 4a exhibited intense bands at 3251 and 1605 cm^{-1} confirming the presence of NH and C=N groups respectively. ^{1}H NMR showed two triplets corresponding to CH_2-CH_2 grouping. Other characteristic signals were observed at δ 11.48 (s, 1H, NH), confirming the structure of the compound 4a. Similarly, compounds 4b–h were synthesized from hydrazide 3 by reacting with 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, salicylaldehyde, vanillin and 4-nitrobenzaldehyde.

Antibacterial activity: The compounds 4a-h were screened for their antibacterial activity against two gram-positive bacteia viz., Bacillus subtilis and Staphylococcus aureus and two gram-negative bacteia viz., Escherichia coli and Salmonella typhi by using cup plate method. All the experiments were carried out in triplicate. Simultaneously, controls were maintained employing dimethyl formamide to observe the solvent effects. Ampicillin sodium was employed as standard and the results are presented in Table 1.

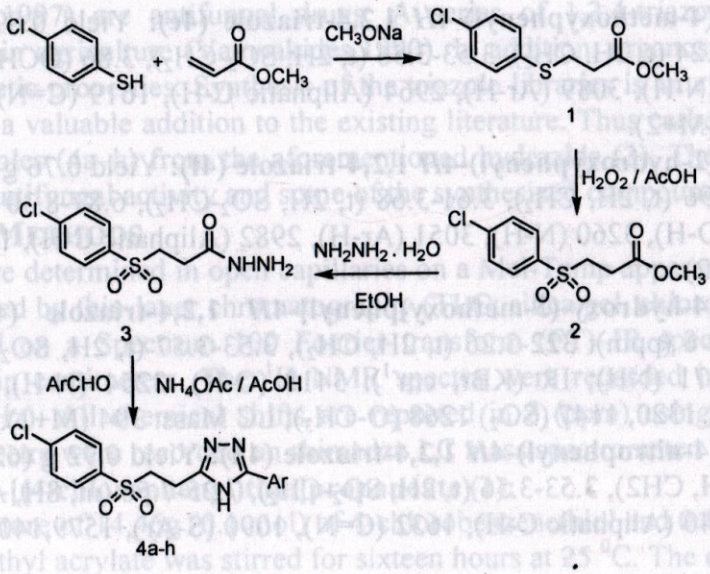
An insight into the data reveals that all the compounds showed moderate to high antibacterial activity. The compounds 4b, 4e, 4f showed prominent activity against gram +ve bacteria. Where as compounds 4d and 4g showed significant activity against gram –ve bacteria. These results express that the presence of methoxyl or chloro or hydroxyl group on benzene ring increases the antibacterial activity. Moreover, the inhibitory activity was maximum for a compound having chloro and hydroxyl groups.

Antifungal activity: The compounds 4a-h were also screened for their antifungal activity (Table-I) against Candida albicans and Aspergillus niger using a standard Clotrimazole in DMF as control. The experiments were performed in triplicate in order to minimize the errors. Compounds 4b, 4c, 4f and 4h showed prominent activity against both the fungi. The remaining compounds showed moderate activity relative to that of standard Clotrimazole.

4.CONCLUSION

This study reports the synthesis of some new disubstituted 1,2,4-triazoles from 3-[(4-chlorophenyl)sulfonyl]propane hydrazide. Structures of new compounds were determined from spectral data. The potential antifungal effects of the synthesized compounds, compared with those of the standard reference Clotrimazole, were investigated using different micro-organisms. The most active compounds were 4b, 4c, 4fand 4h, which exhibited promising and even more activities against *C. albicans and A. niger*. The compounds 4b, 4e, 4f showed prominent activity against gram +ve bacteria, where as compounds 4d and 4g showed significant activity against gram –ve bacteria. Structure-activity relationship studies can provide optimisation of effectiveness of these molecules.

Scheme-1



Compound	Ar	Compound	Ar
4a		4e	
4b		4f	
4c		4g	
4d		4h	

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Table-1

Compound	Antibacterial activity				Antifungal activity	
	B.subtilis	*S.aureus*	*E.coli*	*S.typhi*	*C.albicans*	*A.niger*
4a	20	13	14	17	22	19
4b	25	21	15	21	30	21
4c	21	11	15	13	32	23
4d	18	12	21	19	20	14
4e	19	18	13	13	26	18
4f	21	19	19	13	31	23
4g	16	23	20	17	20	13
4h	20	15	17	18	33	24
Ampicillin sodium	24	22	20	21	-	-
Clotrimazole	-	-	-	-	30	22

REFERENCES

Espinel-Ingroff A, J.Clin.Microbiol., 36, 1998, 198.

Holla B.S, Veerendra B, Shivananda M.K, Poojary B, Eur.J.Med.Chem., 38, 2003, 759.

Jones D.H, Slack R, Squires S, Wooldridge K.R.H, J.Med.Chem., 8, 1965, 676.

Kane J.M, Baron B.M, Dudley M.W, Sorensen S.M, Staeger M.A, Miller F.P, J. Med. Chem., 33, 1990, 2772.

Kane J.M, Dudley M.W, Sorensen S.M, Miller F.P, J.Med.Chem., 3, 1988, 1253.

Krakovsky E.M.D.J, Rybak M, J.Pharmacotherapy, 10, 1990, 146.

Malbec F, Milcent R, Vicart P, Bure A.M, J.Heterocycl.Chem., 21, 1984, 1769.

Narayanan A, Chapman D. R, Upadhyaya S.P, Bauer L, J.Heterocycl.Chem., 30, 1993, 1405.

Pfaller M.A, Messer S, Jones R.N, Antimicrob.Agents Chemother., 41, 1997, 1124.

Roberts J, Schock K, Marino S, Andriole V, T.Antimicrob.Agents Chemother., 44, 2000, 3381.

Rollas S, Kalyoncuoglu N, Sur-Altiner D, Yegenoglu Y, Pharmazie, 48, 1993, 308.

Sanati H, Belanger P, Fratti R, Ghannoum M, Antimicrob.Agents Chemother., 41, 1997, 2492.

Tsukuda Y, Shiratori M, Watanabe H, Ontsuka H, Hattori K, Shirai M, Shimma N, Bioorg.Med.Chem.Lett., 8, 1998, 1819.

Vamvakides A, Pharm.Fr., 48, 1990, 154.

Wade P.C, Vogt B.R, Kissick T.P, Simpkins L.M, Palmer D.M, Millonig R.C, J. Med. Chem., 25, 1982, 331.