Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2011, 3(3): 317-322
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis, characterisation and biological evaluation of some new hydrazide hydrazones

Lakkakula Vinay Kumar, Pujari Jagan Naik, Palthuru Saifulla Khan, Abbavaram Babul Reddy, Talapaneni Chandra Sekhar and Golla Narayana Swamy*

Department of Chemistry, Sri Krishnadevaraya University, Anantapur, A.P. India

---

ABSTRACT

*Methyl acrylate on treatment with 4-chlorobenzenethiol gave 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 hydrazones **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.*

Key words: 3-[(4-chlorophenyl)sulfonyl]propanehydrazide, hydrazide hydrazones, antibacterial activity, antifungal activity.

INTRODUCTION

Schiff bases have a wide variety of applications in many fields, *e.g.*, biological, inorganic and analytical chemistry [1-3]. Schiff bases have also been widely reported to be biologically versatile compounds possessing antifungal, herbicidal and plant growth regulating properties [4]. Hydrazones are a class of Schiff bases which have been found to possess many biological activities, e.g. antibacterial [5, 6], anticonvulsant [7], anti-inflamatory [4], anti-protozoal [9] and antitubercular [10, 11]. In addition, sulfones have gained importance because of their chemotherapeutic properties. Synthesis of the hydrazone 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 hydrazones **4a**–**h** from the aforementioned hydrazide **3.** These hydrazones were also screened for their antibacterial activity, antifungal activity and some of the synthesized compounds showed good antimicrobial activity.

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 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 13.0 g (0.09 mol) of 4-chlorobenzenethiol and 0.10 g of sodium methoxide after drop wise addition of 18 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, dried over anhydrous sodium sulphate. The ether solution was evaporated to get methyl 3-[(4-chlorophenyl)thio]propanoate **1** and it was recrystallised from ethanol.

Yield 16.19 g (78%); mp 38-40^o C; IR (KBr, cm^{-1}): 3086 (Ar-H), 1729 (C=O), 1098 (S-Ar), 1321, 1180 (C-O-C).

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

An Ice cold solution of 16 g (0.069 mol) of methyl 3-[(4-chlorophenyl)thio]propanoate (1) in 20 ml of acetic acid was added 8 ml of 30% hydrogen peroxide and stirred for one day at room temperature. A liquid separated after the removal of acetic acid was extracted with diethyl ether, washed with water, 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 15.22 g (84%); mp 62-65^o 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 15 g (0.057 mol) methyl 3-[(4-chlorophenyl)sulfonyl]propanoate (2) in ethanol, hydrazine hydrate (6 ml) was added and refluxed for 3 h. The reaction mixture was cooled and the solid separated was collected by filtration, dried and recrystallized from ethanol to get pure 3-[(4-chlorophenyl) sulfonyl]propanehydrazide (3).

Yield 11.25 g (75%); mp 134-137^o 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 N'-arylidene-3-(4-chlorophenylsulfonyl) propanehydrazides

A solution of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide (0.0038 mol) and aldehyde (0.0038 mol) was refluxed in alcohol for 4 h in the presence of few drops of glacial acetic acid. Solvent was evaporated and the product was poured onto cold water, filtered and dried. The crude solid was recrystallised from ethanol to give the products.

N'-benzylidene-3-(4-chlorophenylsulfonyl)propanehydrazide (4a)

Yield 1.12 g (84%); mp 156-158^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.94-2.98 (t, 2H, CH_2), 3.62-3.66 (t, 2H, SO_2-CH_2), 7.42-7.955 (m, 9H, Ar-H), 8.09 (N=CH), 11.48 (NH); IR (KBr, cm^{-1}):

3251 (N-H), 3074 (Ar-H), 2943 (Aliphatic C-H), 1671 (Amide C=O), 1605 (C=N), 1086 (S-Ar), 1321, 1143 (SO_2); LC Mass: 351 (M+1).

N'-(2-chlorobenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4b)
Yield 1.19 g (81%); mp 158-161^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.93-2.96 (t, 2H, CH_2), 3.63-3.66 (t, 2H, SO_2-CH_2), 6.29-7.94 (m, 8H, Ar-H), 8.42 (N=CH), 11.41 (NH); IR (KBr, cm^{-1}): 3183 (N-H), 3068 (Ar-H), 2960 (Aliphatic C-H), 1682 (Amide C=O), 1607 (C=N), 1087 (S-Ar), 1319, 1126 (SO_2); LC Mass: 385 (M+1).

N'-(4-chlorobenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4c)
Yield 1.22 g (83%); mp 162-164^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.94-2.98 (t, 2H, CH_2), 3.61-3.65 (t, 2H, SO_2-CH_2), 7.47-8.08 (m, 8H, Ar-H), 8.71 (N=CH), 11.53 (NH); IR (KBr, cm^{-1}): 3219 (N-H), 3072 (Ar-H), 2952 (Aliphatic C-H), 1673 (Amide C=O), 1599 (C=N), 1087 (S-Ar), 1309, 1140 (SO_2); LC Mass: 385 (M+1).

N'-(3-methoxybenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4d)
Yield 1.15 g (79%); mp 164-166^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.91-2.95 (t, 2H, CH_2), 3.61-3.65 (t, 2H, SO_2-CH_2), 3.80 (OCH_3), 6.98-7.94 (m, 8H, Ar-H), 8.02 (N=CH), 11.35 (NH), 1255 (O-CH_3); IR (KBr, cm^{-1}): 3187 (N-H), 3088 (Ar-H), 2985 (Aliphatic C-H), 1670 (Amide C=O), 1610 (C=N), 1087 (S-Ar), 1317, 1147 (SO_2); LC Mass: 381 (M+1).

N'-(4-methoxybenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4e)
Yield 1.19 g (82%); mp 167-170^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.92-2.97 (t, 2H, CH_2), 3.61-3.66 (t, 2H, SO_2-CH_2), 3.80 (OCH_3), 6.98-7.96 (m, 8H, Ar-H), 8.03 (N=CH), 11.35 (NH); IR (KBr, cm^{-1}): 3176 (N-H), 3089 (Ar-H), 2963 (Aliphatic C-H), 1668 (Amide C=O), 1611 (C=N), 1087 (S-Ar), 1320, 1153 (SO_2) 1259 (O-CH_3); LC Mass: 381 (M+1).

N'-(2-hydroxybenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4f)
Yield 1.16 g (83%); mp 188-190^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.93-2.97 (t, 2H, CH_2), 3.63-3.65 (t, 2H, SO_2-CH_2), 6.99-7.94 (m, 8H, Ar-H), 8.06 (N=CH), 9.10 (OH), 11.50 (NH); IR (KBr, cm^{-1}): 3462 (O-H), 3259 (N-H), 3051 (Ar-H), 2982 (Aliphatic C-H), 1688 (Amide C=O), 1617 (C=N), 1086 (S-Ar), 1312, 1134 (SO_2); LC Mass: 367 (M+1).

N'-(4-hydroxy-3-methoxybenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4g)
Yield 1.16 g (77%); mp 160-163^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.90-2.94 (t, 2H, CH_2), 3.61-3.65 (t, 2H, SO_2-CH_2), 6.79-7.93 (m, 7H, Ar-H), 7.96 (N=CH), 9.51 (OH), 11.23 (NH); IR (KBr, cm^{-1}): 3418 (O-H), 3254 (N-H), 3051 (Ar-H), 2943 (Aliphatic C-H), 1673 (Amide C=O), 1602 (C=N), 1085 (S-Ar), 1320, 1147 (SO_2), 1267 (O-CH_3); LC Mass: 397 (M+1).

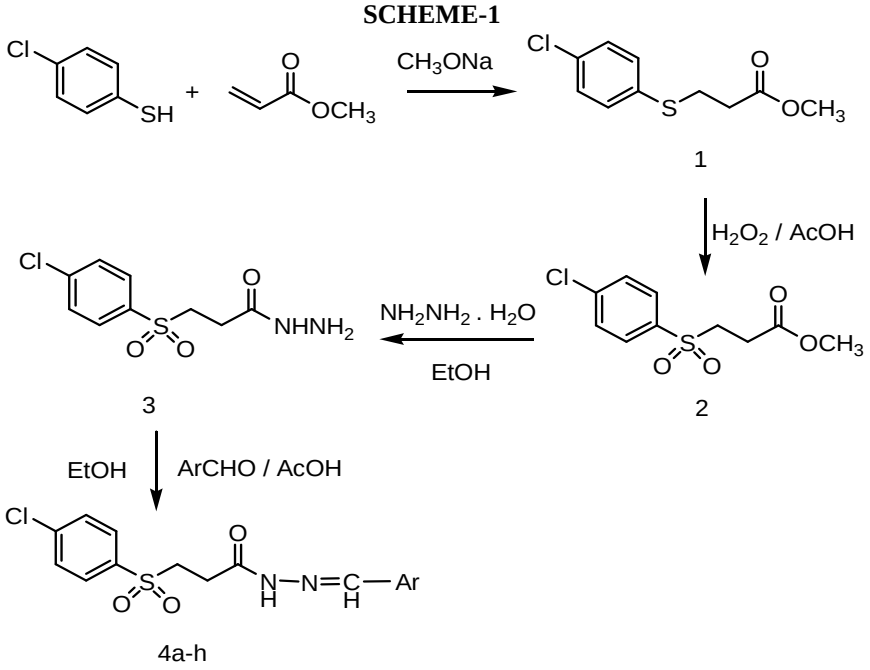
N'-(4-nitrobenzylidene)-3-(4-chlorophenylsulfonyl)propanehydrazide (4h)
Yield 1.24 g (82%); mp 218-221^o C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.99-3.03 (t, 2H, CH_2), 3.62-3.65 (t, 2H, SO_2-CH_2), 7.73-8.42 (m, 8H, Ar-H), 10.15 (N=CH), 11.76 (NH); IR (KBr, cm^{-1}): 3202 (N-H), 3064 (Ar-H), 2940 (Aliphatic C-H), 1671 (Amide C=O), 1600 (C=N), 1090 (S-Ar), 1579,1403 (NO_2), 1305, 1141 (SO_2); LC Mass: 396 (M+1).

RESULTS AND DISCUSSION

The synthetic pathway followed for the synthesis of hydrazones 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. 3-[(4-chlorophenyl)sulfonyl]propanoate **2**. This on treatment with hydrazine hydrate in ethanol under reflux condition resulted in the formation of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide **3**. Benzaldehyde on reaction with 3-[(4-chlorophenyl)sulfonyl]propane hydrazide **3** gave **4a.** The IR spectra of hydrazone **4a** exhibited intense bands at 3251, 1671 and 1605 cm^{-1} confirming the presence of NH, O=C–NH and C=N groups respectively. ^1H NMR showed two triplets corresponding to CH_2-CH_2 grouping. Other characteristic signals were observed at δ 11.48 (1H, NH), 8.09 (1H, N=C-H) confirming the structure of the hydrazone **4a**. Similarly, hydrazones **4b**–**h** were synthesized from hydrazide **3** by reacting with 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, salicylaldehyde, vanillin and 4-nitrobenzaldehyde.

SCHEME-1



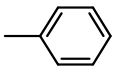
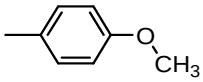
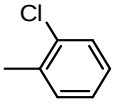
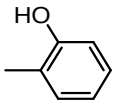
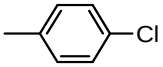
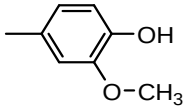
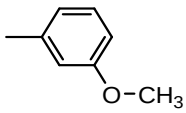
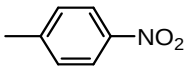
Compound	Ar	Compound	Ar
4a		4e	
4b		4f	
4c		4g	
4d		4h	

Table-I

Compound	Antibacterial activity				Antifungal activity	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhi*	*Candida albicans*	*Aspergillus niger*
4a	17	18	12	13	20	21
4b	11	17	16	10	20	16
4c	17	13	19	19	22	18
4d	19	21	10	10	31	20
4e	18	20	12	18	21	19
4f	17	20	11	14	26	21
4g	19	16	21	19	26	18
4h	16	16	20	16	24	19
Ampicillin sodium	24	22	20	21	-	-
Clotrimazole	-	-	-	-	30	22

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 **4d, 4e** showed prominent activity against gram +ve bacteria. Compounds **4c, 4g** showed significant activity against gram –ve bacteria. These results indicate that the presence of methoxy or chloro group at the phenyl ring increases the antibacterial activity. Moreover, the antibacterial activity was maximum for a compound containing methoxyl and hydroxyl groups.

Antifungal activity

The compounds **4a-h** were also screened for their antifungal activity 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 **4d**, **4f** showed prominent activity against both the fungi. On the other hand, compounds **4a**, **4c**, **4g** and **4h** showed significant activity against aspergillus niger.

CONCLUSION

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

REFERENCES

[1] Z. Cimerman, S. Miljanic, and N, Galic. *Croatica Chemica Acta* 73 (1): 81- 95 (**2000**).
[2] P. Singh, R. L. Goel and B. P. Singh. *J. Ind. Chem. Soc* 52: 958 (**1975**).
[3] B. F. Perry, A. E. Beezer, R. J. Miles, B. W. Smith, J. Miller and M. G. Nascimento. *Microbois* 45: 181 (**1988**).
[4] Dash, B.; Mahapatra, P.K.; Panda, D.; Pattnaik, J.M. *J. Indian Chem. Soc.* **1984**, *61*, 1061–1064.
[5] S. Rollas, N. Gulerman, H. Erdeniz, *Il Farmaco* **2002**, *57*, 171.
[6] M. Cacic, M. Trkovnik, F. Cacic, E. Has-Schon, *Molecules* **2006**, *11*, 134.
[7] S. S. Parmar, A. K. Gupta, T. K. Gupta, V. I. Stenberg, *J. Pharm. Sci.* **1975**, *64*, 154.
[8] R. Kalsi, K. Pande, T. N. Bhalla, J. P. Barthwal, G. P. Gupta, S. S. Parmar, *J. Pharm. Sci.* **1990**, *79*, 317.
[9] A. C. L. Leite, D. R. M. Moreira, M. V. D. Cardoso, M. Z. Hernandes, V. R. A. Pereira, R. O. Silva, A. C. Kiperstok, M. D. Lima, M. B. P. Soares, *Chem Med Chem* **2007**, *2*, 1339.
[10] K. K. Bedia, O. Elcin, U. Seda, K. Fatma, S. Nathaly, R. Sevim, A. Dimoglo, *Eur J Med Chem* **2006**, *41*, 1253.
[11] H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, J. Bernstein, *J. Am. Chem. Soc* **1953**, *75*, 1933.