Efficient Synthesis and Therapeutic Evaluation of 1, 3-Thiazolidin-4-ones as Potential Antifungal Agents

PRADEEP K. SONI AMIT KANKORIYA AND A.K. HALVE*

School of studies in Chemistry, Jiwaji University,
Gwalior – 474011, India
Phone No. 91-751-2442769
halveanand@yahoo.co.in

Abstract:

Pathogens immune response to existing pharmaceuticals has risen dramatically in the last few decades due to the structural modifications, genomic mutations and biochemical alterations acquired by the microorganisms. Since many drugs available in the market cause side effects or face quickly developed resistance by the pathogens, there is a general consensus that new antifungal compounds are urgently required for conquering these fungi. Our present work highlights the synthesis and fungal sensitivity evaluation of new thiosemicarbazones (3a-i) and 1, 3-thiazolidin-4-ones (4a-i), obtained using appropriate synthetic methodology. The structures of synthesized compounds were assigned on the basis of elemental and spectral data. All the compounds were tested for sensitivity against a panel of fungal organisms using disc diffusion method. It has been observed that chloro and methoxy moiety in target compounds enhance the antifungal activity.

Key words: Thiosemicarbazone, 1,3-thiazolidin-4-one, Disc diffusion method, Antifungal activity.

INTRODUCTION

Thiosemicarbazone and their derivatives are of paramount importance to human race and has been a research subject [1] due to their striking pharmacological characteristics. They possess both, –N–C=S and –CH=N– moieties and are a class of small molecules which have been evaluated over the last 50 years as antiviral[2,3], antitumor[4], antibacterial[5], antifungal[6], antitubercular[7], antimalarial[8], antiamoebic[9]. The azomethine linkage in thiosemicarbazones, is responsible for boosting the antibacterial[10], antifungal[11], tuberculostatic[12] and pesticidal activity[13]. 4-Thiazolidinone derivatives are known to exhibit diverse bioactivities such as antibacterial[14-19] antifungal[20-22], antituberculor[23-25], and anthelmintic activity[26].

Looking for the usefulness of azomethine linkage and 5-membered thiazolidinone nucleus, we have synthesized a new series of 1,3,-thiazolidin-4-ones as potential antifungal agents. The structures of synthesized compounds were assigned on elemental analysis, IR and ^{1}H-NMR spectral data. All these compounds were screened *in vitro* for their antifungal activities against *C. albicans*, *C. tropicalis*, *T. rubrum* and *T. mentagrophytes* using disc diffusion method by measuring the zone of inhibition in mm. Fluconazole has been used as a standard antifungal drug.

MATEREALS AND METHODS

All reagents were AR grade and used after further purification. Melting points were observed in open capillaries and are uncorrected. IR spectra were recorded in potassium bromide discs on a Perkin-Elmer 398 spectrometer. The ^{1}H-NMR spectra were recorded on a Bruker DRX-300 FT-NMR spectrometer. Elemental analysis was performed on a Carlo Erba 1108 analyzer.

1. General procedure for the preparation of thiosemicarbazones (3a-i):

A mixture of, 2-hydroxy-5-[phenyldiazenyl]benzaldehyde(1a-c) and N phenylhydrazine carbothioamide (2a-c) was refluxed in DMF for 8hrs, allowed to cool and finally poured on crushed ice. The solid obtained was filtered, washed with water followed by ethanol. It was recrystallized with diethyl ether. The general structure and synthetic route to the required compounds is outlined in Scheme 1, and physical data of the compounds are highlighted in Table 1. mp:199°C; yield: 70%; IR (KBr) (υcm^{-1}) 3445-3245 (OH & NH), 2950-2860 (CH), 1665 (C=N), 1600 (N=N), 1255 (C=S): ^{1}H NMR (DMSO-d6) (δ,ppm): 6.5 (s, 1H, -OH), 6.95-7.56 (m, 12H, Ar-H), 8.97 (s, 1H, NH-Ar), 9.84 (s, 1H, -CH=N), 10.32 (s, 1H, N-NH); elemental analysis of $C_{20}H_{17}N_5SO$: found (calcd, %) C, 63.88 (63.98): H, 4.50 (4.56): N 18.58 (18.65).

2. General procedure for the preparation of 1, 3-thiazolidin-4-ones (4a-i):

A mixture of 2-{2-hydroxy-5-[phenyldiazenyl]benzylidene}-N-phenylhydrazine carbothioamide (3a-c) and mercaptoacetic acid was refluxed for 10 hrs using DMF in the presence of a pinch of anhydrous $ZnCl_2$ as catalyst. The reaction mixture was then allowed to cool and finally poured into crushed ice. The solid obtained

was filtered, washed with water and recrystallized with aqueous ethanol. mp: 202°C; yield: 55%; IR (KBr) (υcm^{-1}) 3380-3349 (-OH & -NH), 3058 (Ar-H), 2976(C-H), 1704 (-C=O), 1599(-N=N-), 1272(-C=S); ^{1}HNMR (DMSO-d_6) (δ, ppm); 5.8 (2H, s, CH_2), 6.7 (1H, s,-OH), 8.41 (1H, s, N-NH), 6.9-7.5 (13H, m, ArH), 8.80 (1H, s, CH=N), 9.2 (1H, s, Ar-NH); elemental analysis of $C_{22}H_{19}N_5S_2O_2$: found (calcd, %) C, 58.70 (58.78) H, 4.20 (4.26) N, 15.50 (15.58).

Table- 1. Characterization data of the compounds (3a-i) and (4a-i):

Comp. No.	R	R^1	m.p. (°C)	Yield (%)	Mol. Formula	Mol. Weight
3a	H	H	189	70	$C_{20}H_{17}N_5OS$	375
3b	H	Cl	195	65	$C_{20}H_{16}ClN_5OS$	409
3c	H	OCH_3	202	68	$C_{21}H_{19}N_5O_2S$	405
3d	OCH_3	H	185	65	$C_{21}H_{19}N_5O_2S$	405
3e	OCH_3	Cl	188	63	$C_{21}H_{18}ClN_5OS$	439
3f	OCH_3	OCH_3	181	60	$C_{22}H_{21}N_5O_3S$	435
3g	Cl	H	185	67	$C_{20}H_{16}ClN_5OS$	409
3h	Cl	Cl	180	64	$C_{20}H_{15}Cl_2N_5OS$	444
3i	Cl	OCH_3	200	60	$C_{21}H_{18}ClN_5OS$	439
4a	H	H	202	55	$C_{22}H_{19}N_5O_2S_2$	449
4b	H	Cl	192	50	$C_{22}H_{19}ClN_5O_2S_2$	483
4c	H	OCH_3	205	52	$C_{23}H_{21}N_5O_3S_2$	479
4d	OCH_3	H	195	45	$C_{23}H_{21}N_5O_3S_2$	479
4e	OCH_3	Cl	198	54	$C_{23}H_{20}ClN_5O_3S_2$	514
4f	OCH_3	OCH_3	204	52	$C_{24}H_{23}N_5O_4S_2$	590
4g	Cl	H	201	58	$C_{22}H_{19}ClN_5O_2S_2$	483
4h	Cl	Cl	210	50	$C_{22}H_{18}Cl_2N_5O_2S_2$	518
4i	Cl	OCH_3	200	49	$C_{23}H_{20}ClN_5O_3S_2$	514

***In-vitro* Antifungal activity:**

In disc-diffusion assay, few colonies of organisms were inoculated in 2–5 mL Sabourauds broth and allow to grown for 2.5 h. The agar plates were dried and inoculated by spreading the fungal suspension evenly over it. The sterile paper discs (6 mm) impregnated with fixed dose viz., 800 µg/mL of compound were placed on the pre-inoculated surface. The disc-bearing plates were incubated at 37°C and examined at 72 h for zone of inhibition around the disc. An additional negative control disc, impregnated with plane solvent, DMF and a positive control disc, with reference drug, fluconazole were also performed. The results are depicted in Table 2.

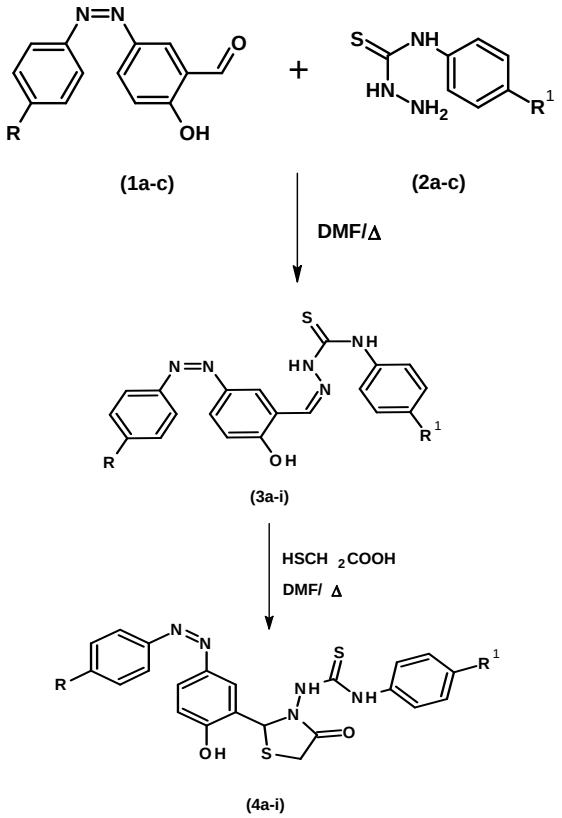
TABLE- 2. *In-vitro* antifungal sensitivity of compounds (3a-i) and (4a-i):

Comp. No.	*Fungal pathogens*			
	C. albicans	*C. tropicalis*	*T. rubrum*	*T. mentagrophytes*
3a	00	08	09	09
3b	09	11	10	10
3c	14	15	18	17
3d	09	12	12	09
3e	13	13	15	18
3f	18	19	20	20
3g	09	09	10	13
3h	12	12	11	10
3i	18	18	20	18
4a	15	17	20	19
4b	10	14	14	09
4c	14	15	17	19
4d	20	22	23	22
4e	10	11	10	13
4f	14	15	13	10
4g	23	21	23	19
4h	22	25	25	22
4i	25	29	28	25
'+' ve	27	31	30	28
'-' ve	--	--	--	--

- ***Antifungal susceptibility of compound was measured in the term of zone of inhibition @ 800 µg/ml.***
- ***'+' ve = Fluconazole and '-'ve = Dimethyl formamide.***

RESULTS AND DISCUSSION

The equimolar quantity of 2-hydroxy-5-[phenyldiazen-1-yl]benzaldehyde(1a-c) & 3-amino-1-phenylthiourea(2a-c) were refluxed in presence of DMF resulted 1[({2-hydroxy-5-[2-phenyl diazen-1-yl] phenyl} methylidene) amino]-3-phenyl thiourea(3a-i). 3-(2-{2-hydroxy-5-[2-phenyl diazen-1-yl] phenyl}-4-oxo-1,3-thiazolidin-3-yl)-1-phenyl thiourea(4a-i) was obtained by incorporation of thiazole ring at azomethine linkage of thiosemicarbazones by refluxing (3a-i) with mercaptoacetic acid in DMF. The structure of compounds was elucidated by spectral data and elemantal analysis.



Scheme- 1. Synthetic protocol of thiosemicarbazones (3a-i) and 1, 3-thiazolidin-4-one (4a-i)

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of a new series of 1, 3-thiazolidin-4-ones. On introducing thiazole ring at the azomethine linkage in thiosemicarbazones, the compounds shows remarkable improvement in antifungal activity. This can be attributed to the presence of N & S atoms in the heterocyclic ring of the target molecule. Further investigation with appropriate structural modification of above compounds may result good antifungal profile.

ACKNOWLEDGEMENTS

Sincere thanks are due to Dean, Birla Institute of Medical Research and College of life sciences, Gwalior, for antimicrobial screening, CDRI Lucknow for spectral analysis and ICMR, New Delhi for financial assistance.

REFERENCES

[1] M.B. Ferrari, F. Bisceglie, G. Pelosi, P. Tarasconi, R. Albertini, P.P. Dall'Aglio, S. Pinelli, A. Bergamo & G. Sava, Synthesis, characterization and biological activity of copper complexes with pyridoxal thiosemicarbazone derivatives. X-ray crystal structure of three dimeric complexes. J. Inorg. Biochem., 2004, 98:301-312.

[2] N. Terzioglu, N. Karali, A. Gursoy, C. Pannecouque, P. Leysen, J. Paeshuyse, J. Neyts & E. De Clercq. Synthesis and primary antiviral activity evaluation of 3-hydrazono-5-nitro-2-indolinone derivatives. Arkivoc, 2006, i:109-118.

[3] A. Kolocouris, K. Dimas, C. Pannecouque, M. Witvrouw, G.B. Foscolos, G. Stamatiou, G. Fytas, G. Zoidis, N. Kolocouris, G. Andrei, R. Snoeck & E. De Clercq. New 2-(1-adamantylcarbonyl)pyridine and 1-acetyladamantane thiosemicarbazones–thiocarbonohydrazones: cell growth inhibitory, antiviral and antimicrobial activity evaluation.. Bioorg. Med. Chem. Lett., 2007, 12:723-727.

[4] V.B. Arion, M.A. Jakupec, M. Galanski, P. Unfried & B.K. Keppler. Synthesis, structure, spectroscopic and in vitro antitumour studies of a novel gallium(III) complex with 2-acetylpyridine 4N-dimethylthiosemicarbazone. J. Inorg. Biochem., 2002, 91:298-305.

[5] S.A. Khan, K. Saleem & Z. Khan, Synthesis, characterization and in vitro antibacterial activity of new steroidal thiazolo quinoxalines. Eur. J. Med. Chem., 2007, 42:103-108.
[6] H. Pervez, M.S. Iqbal, M.Y. Tahir, F.U. Nasim, M.I. Choudhary & K.M. Khan, In vitro cytotoxic, antibacterial, antifungal and urease inhibitory activities of some N4- substituted isatin-3-thiosemicarbazones. J. Enzy. Inhib. Med. Chem., 2008, 23:848-854.
[7] D. Sriram, P. Yogeeswari, R. Thirumurugan & R.K. Pavana. Discovery of new antitubercular oxazolyl thiosemicarbazones. J. Med. Chem., 2006, 49:3448-3450.
[8] S.D. Khanye, G.S. Smith, C. Lategan, P.J. Smith, J. Gut, P.J. Rosenthal & K. Chibale. Synthesis and in vitro evaluation of gold(I) thiosemicarbazone complexes for antimalarial activity. J. Inorg. Biochem., 2010, 104:1079-1083.
[9] S. Singh, F. Athar, M.R. Maurya & A. Azam. Cyclooctadiene Ru(II) complexes of thiophene-2-carboxaldehyde-derived thiosemicarbazones: synthesis, characterization and antiamoebic activity. Eur. J. Med. Chem., 2006, 41:592-598.
[10] A.H. El-masry, H.H. Fahmy & S.H. Ali Abdel Wahed. Synthesis and antimicrobial activity of some new benzimidazole derivatives. Molecules, 2005, 5:1429-1438.
[11] Z.H. Chohan, M. Arif, Z. Shafiq, M. Yaqub & C.T. Supuran. In vitro antibacterial, antifungal & cytotoxic activity of some isonicotinoylhydrazide Schiff's bases and their cobalt(II), copper(II), nickel(II) and zinc(II) complexes. J. Enz. Inhib. Med. Chem., 2006, 21:95-103.
[12] S.N. Pandeya, S. Smitha, M. Jyoti & S.K. Sridhar. Biological activities of isatin and its derivatives. Acta Pharm., 2005, 55:27-46.
[13] A. Dios, R.A. Mitchell, B. Aljabari, J. Lubetsky, K. O'Connor, H. Liao, PD, Senter, K.R. Manogue, E. Lolis, C. Metz, R. Bucala, D.J. Callaway & Y. Al-Abed. Inhibition of MIF bioactivity by rational design of pharmacological inhibitors of MIF tautomerase activity. J. Med. Chem., 2002, 45:2410-2416.
[14] P. Mishra, T. Lukose & S.K. Kashaw. Synthesis and antimicrobial evaluation of some novel 2-imino-3-(4'-carboxamido pyridyl)-5-arylidene-4-thiazolidinones and their brominated derivatives. Indian J. Pharm. Sci., 2007, 69:665-668.
[15] T.M. De Aquino, A.P. Liesen, R.E.A. Silva, V.T. Lima, C.S. Carvalho, A.R. Faria, J.M. Araújo, J.G. Lima, A.J. Alves, E.J.T. Melo & A.J.S. Góes. Synthesis, anti-toxoplasma gondii and antimicrobial activities of benzaldehyde 4-phenyl-3-thiosemicarbazones and 2-[(phenylmethylene) hydrazono]-4-oxo-3-phenyl-5-thiazolidineacetic acids. Bioorg. Med. Chem., 2008, 16:446-456.
[16] S. Bondock, W. Khalifa & A. A. Fadda, Synthesis and antimicrobial evaluation of some new thiazole, thiazolidinone and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde. Eur. J. Med. Chem., 2007, 42:948-954.
[17] T. J. Shah & V.A. Desai. Synthesis of some novel fluorinated 4-thiazolidinones containing amide linkages and their antimicrobial screening. Arkivoc., 2007, xiv:218-228.
[18] P.R. Kumar, M.S. Yadav, M.M.K. Kumar & T.S. Rao, Synthesis and antimicrobial activity of some new substituted aryloxy-4-thiazolidinones. E-J. Chem., 2006, 3;44-48.
[19] S.M. Rida, F.A. Ashour, S.A.M. El-Hawash, M.M. ElSemary, M.H. Badr, & M.A. Shalaby. Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agents. Eur. J. Med. Chem., 2005, 40:949-959.
[20] S. Özkirimli, F. Kazan & Y. Tunali. Synthesis, antibacterial and antifungal activities of 3-(1,2,4-triazol-3-yl)-4-thiazolidinones. J. Enz. Inhib. Med. Chem., 2009, 24:447-452.
[21] Z.A. Kaplancikli, G. Turan-Zitouni, A. Özdemir & G. Revial. Synthesis and anticandidal activity of some imidazopyridine derivatives. J. Enz. Inhib. Med. Chem., 2008, 23:866-870.
[22] I.R. Siddiqui, P.K. Singh & J. Singh. Synthesis and fungicidal activity of novel 4,4‘-Bis(2‘‘-aryl-5‘‘-methyl/unsubstituted-4‘‘-oxo-thiazolidin-3‘‘-yl)b ibenzyl. J. Agric. Food. Chem., 2003, 51:7062-7065.
[23] S.G. Küçükgüzel, E.E. Oruç, S. Rollas, F. Sahin & A. Özbek. Synthesis, characterisation and biological activity of novel 4-thiazolidinones, 1,3,4-oxadiazoles and some related compounds. Eur. J. Med. Chem., 2002, 37:197-206.
[24] G. Küçükgüzel, A. Kocatepe, E. De Clercq, F. Sahin & M. Güllüce, Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. Eur. J. Med. Chem., 2006, 41:353-359.
[25] N. Karali, A. Gürsoy, F. Kandemirli, N. Shvets, F.B. Kaynak, S. Özbey,V. Kovalishyn & Dimoglo A. Synthesis and structure–antituberculosis activity relationship of 1H-indole-2,3-dione derivatives. Bioorg. Med. Chem., 2007, 15;5888-5904.
[26] M.M.J. Vijaykumara, L. Shankarappa, H. Shameer, E. Jayachandran & G.M. Sreenivasa. N-Substituted-3-chloro-2-azetidinones: Synthesis and characterization of novel anthelmintic agents. RJPBCS., 2010, 1:52-58.