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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1, 3, 5 - OXADIAZINE AND 1, 3, 4 - OXADIAZOLE COMPOUNDS FROM 4-CHLORO-2-HYDROXYBENZOIC ACID HYDRAZIDE

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Abstract

4-chloro-2-hydroxy benzoic acid hydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding 4-chloro-2-hydroxy benzoic acid arylidene hydrazides (2a-h) in good yields. Cyclocondensation of compounds (2a-h) with benzoyl isothiocynate and acetic anhydride yields respectively of 4-chloro-2-Hydroxy – N – (2-Substituted Phenyl)-6-Phenyl-4-Thioxo-2H-1,3,5,-Oxadiazin -3(4H)-Yl) Benzamide (3a-h) and 4-chloro-1-(5-(2-Hydroxyphenyl)-2-(Substituted Phenyl)-1,3,4-Oxadiazole-3) (2H)-yl)ethane (4a-h). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

INTRODUCTION

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [1-13]. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the hydrazides, 4-chloro-2-hydroxy benzoic acid hydrazide and their condensed products play a vital role in medicinal chemistry [14-16]. 1,3,5-oxadiazine and 1,3,4-oxadizole compounds give good biological and pharmacological properties [17-18]. Hence, it was thought of interest to merge both of 1,3,5-oxadiazine and 4-chloro-2-hydroxy benzoic acid hydrazide, 1,3,4-oxadiazole and 4-chloro-2-hydroxy benzoic acid hydrazide moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of 4-chloro-2-hydroxy benzoic acid hydrazide containing 1,3,5-oxadiazine and 1,3,4-oxadiazole moiety. Hence the present communication comprises the synthesis of 4-chloro-2-Hydroxy – N – (2-Substituted Phenyl)-6-Phenyl-4-Thioxo-2H-1,3,5,-Oxadiazin -3(4H)-Yl) Benzamide (3a-h) and 4-chloro-1-(5-(2-Hydroxyphenyl)-2-(Substituted Phenyl)-1,3,4-Oxadiazole-3) (2H)-yl)ethane (4a-h). The synthetic approach is shown in scheme-1.

MATERIAL AND METHOD

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Preparation of 4-chlro-2-hydroxy benzoic acid arylidene hydrazide **(2a-h)**

General procedure: – An equimolecular mixture of 4-chloro-2-hydroxy benzoic acid hydrazide (1), (0.01mole) and the aromatic aldehydes (a-h) in ethanol (15mL) was refluxed on a water bath for 1-2 h. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation of 4-chloro-2-Hydroxy – N – (2-Substituted Phenyl)-6-Phenyl-4-Thioxo-2H-1,3,5,-Oxadiazin -3(4H)-Yl) Benzamide **(3a-h)**

General procedure: A mixture 4-chloro-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (0.01 mole) benzoyl isothiocynate and triethylamine (3 drops) in 1,4-dioxane (30mL) was heated at reflux for about 3h. The reported solid formed upon dilution with water (20mL) was filtered, dried and which were obtained in 57-68% yield.

The yields, melting points and other characterization data of these compounds are given in Table -2.

Preparation of 4-chloro-1-(5-(2-Hydroxyphenyl)-2-(Substituted Phenyl)-1,3,4-Oxadiazole-3) (2H)-yl)ethane **(4a-h)**

A mixture 4-chloro-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (0.003 mole) and acetic anhydride 10mL were heated at reflux for about 4h.after the reaction mixture attained room temp. Excess acetic anhydride was decoposed by water poured in to ice cold water and the solid separated was recrystallized from ethanol to yield. Which were obtained in 55-65% yield.

The yields, melting points and other characterization data of these compounds are given in Table -3.

Biological Screening

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis) and gram-negative bacteria (E.coli, and klebsiella promioe) at a concentration of 50µg/mL by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in cm. Compounds 3f, 3h, 4g, and 4h were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -4 and 5.

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum**,** Fusarium oxyporium. The

antifungal activity of all the compounds (3a-h) & (4a-h) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^{o} C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (3a-h) and (4a-h) is shown in Tables-6 and 7.

RESULTS AND DISCUSSION

It was observed that 4-chloro-2-hydroxy benzoic acid hydrazide (1), on condensation with aromatic aldehydes, yields 4-chloro-2-hydroxy benzoic acid arylidene hydrazides (2a-h). The structures of (2a-h) were confirmed by elemental analysis and IR spectra showing an absorption band at 1620-1640 (C=N), 3030-3080 cm^{-1} (C-H, of Ar.), 3240-3260 cm^{-1} (-OH), 2815, 1250 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR : 6.85-7.84 (8H, m) (Ar - H), 11.70-11.84 (1H, s) (-OH), 11.85-11.98 (1H, s) (-CONH), 8.36-8.80 (1H, s) (-N=CH), 2e; 2.39 (3H, s) (-CH_3), 2b, 2g; 3.89 (3H, s) (-OCH_3), 2h; 4.12 (4H, q) (CH_2), 1.34 (6H, t) (CH_3), 2f; 6.12 (2H, s) (-OCH_2O- cyclic). ^{13}C NMR: 111.8-160.8 (Aromatic), 163.0-164 (-CONH), 146.3-147 (-CH); (2b,2g): 55.7-56.8 (-OCH_3); (2e): 21 (CH_3); (2f): 102.5 (OCH_2O cyclic); (2h): 65.4 (OCH_2), 15.2 (CH_3). The C, H, and N analysis data of all compounds are presented in Table -1.

The structures assigned to 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1667-1690cm^{-1} (C=O of -COOH), 1715-1720 (C=O of pyrrole-2-one), 3030-3080 cm^{-1} (C-H, of Ar.), 3240-3260 cm^{-1} (-OH). ^{1}H NMR: 6.62-7.82 (8H, m) (Ar-H), 5.50-5.60 (1H, s) (-C_5H of the ring), 7.10-7.15 (1H, s) (-C_3H), 5.60-5.68 (1H-s) (CH-oxadiazine), 12.90-12.98 (1H, s) (-COOH), 11.70-11.85

(1H, s) (-OH), 3e; 2.36 (3H, s) (-CH_3), 3b,3g; 3.93,3.90 (3H, s) (-OCH_3), 3h; 4.13 (4H q) (CH_2), 1.32 (6H, t) (CH_3), 3f; 6.11 (2H, s) (-OCH_2O- cyclic). ^{13}C NMR: 110-161 (Aromatic), 55.0-62.5 (-CH), 169.5-171.5 (-COOH), 164.5-165 (-CO of the ring), (3b,3g): 55.4-56.5 (-OCH_3); (3e): 21.5 (CH_3); (3f): 102.8 (OCH_2O cyclic); (3h): 65.3 (OCH_2), 14.6 (CH_3). The C, H, and N analysis data of all compounds are presented in Table-2.

The structures assigned to 1-(4-chloro-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (4a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1667-1690cm^{-1} (C=O of -COOH), 1715-1720 (C=O of pyrrole-2-one), 3030-3080 cm^{-1} (C-H, of Ar.), 3240-3260 cm^{-1} (-OH). ^1H NMR: 6.65-7.85 (8H, m) (Ar-H), 5.52-5.60 (1H, s) (-C_5H), 3.33-3.36 (1H, s) (-C_4H), 2.50-2.54, 2.75-2.80 (2H, s) (-C_3H), 6.44-6.68 (1H-s) (-CH-oxadiazole), 11.70-11.85 (1H, s) (-OH), 12.90-12.95 (1H, s) (-COOH), 4e; 2.38 (3H, s) (-CH_3), 4b, 4g; 3.86 (3H, s) (-OCH_3), 4h; 4.06, (4H, q) (-CH_2), 1.35 (6H, t) (-CH_3), 4f; 6.08 (2H, s) (-OCH_2O cyclic). ^{13}C NMR: 110-161 (Aromatic), 50.0-57.0 (-CH of the ring), 37.0.-37.5 (-CH_2), 172.0-172.5 (-CO), 178.0-179 (-COOH), (4b,4g): 55.5-56.5 (-OCH_3); (4e): 21.6 (CH_3); (4f): 101.5 (OCH_2O); (4h): 65.3 (OCH_2), 15.0 (CH_3). The C, H, and N analysis data of all compounds are presented in Table-3.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS of 3e and 4d compounds are 391 and 340 respectively.

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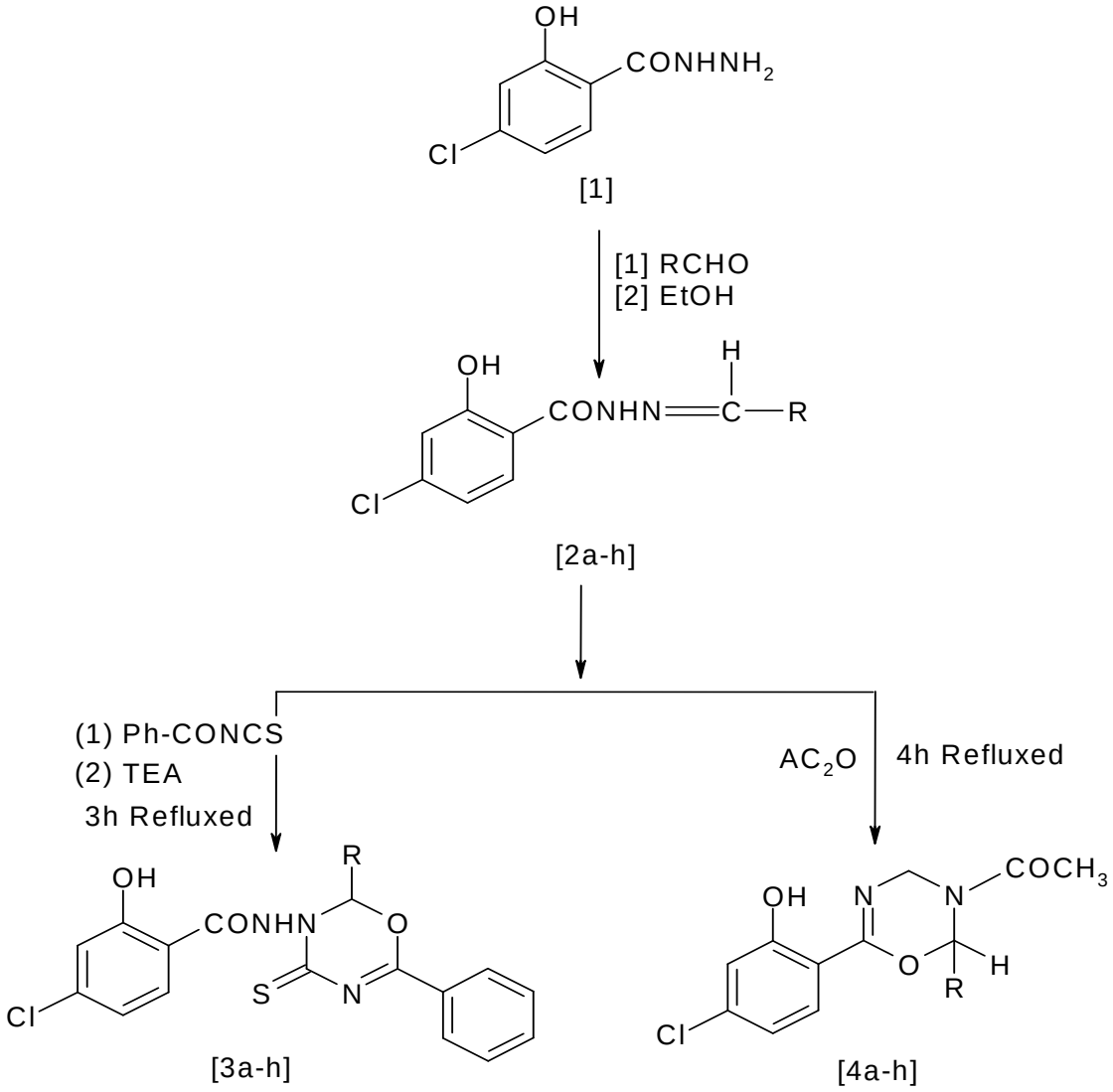

SCHEME – 1

Where, R =

(a) C_6H_5 (b) 4-OCH_3-C_6H_4 (c) 4-OH-C_6H_4 (d) 2-OH-C_6H_4

(e) 4-CH_3-C_6H_4 (f) 3,4-CH_2O_2-C_6H_4 (g) 4-OH-3-OCH_3-C_6H_3 (h) 3,4-C_2H_5-C_6H_4

Table:-1 Analytical Data and Elemental Analysis of Compounds (2a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{14}H_{11}ClN_2O_2$ (274)	85	243	61.18	61.21	3.99	4.04	10.15	**10.20**
2b	$C_{15}H_{13}ClN_2O_3$ (304)	80	246	59.08	59.12	4.25	4.30	9.14	**9.19**
2c	$C_{14}H_{11}ClN_2O_3$ (290)	75	240	57.79	57.84	3.77	3.81	9.58	**9.64**
2d	$C_{14}H_{11}ClN_2O_3$ (290)	81	243	57.78	57.84	3.75	3.81	9.57	**9.64**
2e	$C_{15}H_{13}ClN_2O_2$ (288)	79	244	62.36	62.40	4.51	4.54	9.64	**9.70**
2f	$C_{15}H_{11}ClN_2O_4$ (318)	75	247	56.49	56.53	3.44	3.48	8.73	**8.79**
2g	$C_{15}H_{13}ClN_2O_3$ (320)	77	249	56.14	56.17	3.04	4.09	8.68	**8.73**
2h	**$C_{18}H_{19}ClN_2O_4$ (362)**	**73**	**261**	**59.55**	**59.59**	**5.24**	**5.28**	**7.68**	**7.72**

*** Uncorrected**

Table:-2 Analytical Data and Elemental Analysis of Compounds (3a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		%H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{22}H_{17}ClN_3O_3S$ (372)	64	245	70.90	70.97	4.50	4.57	11.20	11.29
3b	$C_{23}H_{19}ClN_3O_4S$ (402)	65	239	68.61	68.66	4.71	4.73	10.41	10.45
3c	$C_{22}H_{17}ClN_3O_4S$ (388)	61	214	67.97	68.04	4.31	4.38	10.78	10.82
3d	$C_{22}H_{17}ClN_3O_4S$ (388)	63	216	67.97	68.04	4.31	4.38	10.79	10.82
3e	$C_{23}H_{17}ClN_3O_3S$ (386)	60	208	71.47	71.50	4.29	4.40	10.81	10.88

3f	$C_{23}H_{17}ClN_3O_7S$ (416)	58	202	66.29	66.35	4.01	4.09	10.01	10.10
3g	$C_{23}H_{17}ClN_3O_5S$ (418)	55	204	65.96	66.03	4.01	4.07	10.00	10.05
3h	$C_{26}H_{25}ClN_3O_5S$ (460)	59	221	67.79	67.83	5.39	5.43	9.08	9.13

*** Uncorrected**

Table:-3 Analytical Data and Elemental Analysis of Compounds (4a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^0C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{16}H_{14}ClN_2O_3$ (317)	63	215	60.51	60.57	4.39	4.42	8.78	**8.83**
4b	$C_{17}H_{16}ClN_2O_4$ (347)	65	218	58.71	58.78	4.58	4.61	8.01	**8.07**
4c	$C_{16}H_{14}ClN_2O_4$ (333)	68	202	57.61	57.66	4.15	4.20	8.37	**8.41**
4d	$C_{16}H_{14}ClN_2O_4$ (333)	66	205	57.59	57.66	4.17	4.20	8.38	**8.41**
4e	$C_{17}H_{16}ClN_2O_3$ (331)	61	219	61.62	61.63	4.79	4.83	8.38	**8.46**
4f	$C_{17}H_{14}ClN_2O_5$ (361)	59	221	56.49	56.51	3.81	3.87	7.69	**7.75**
4g	$C_{17}H_{16}ClN_2O_5$ (363)	57	216	56.15	56.20	4.38	4.41	7.66	**7.71**
4h	**$C_{20}H_{22}ClN_2O_5$ (405)**	**58**	**224**	**59.21**	**59.26**	**5.36**	**5.43**	**6.85**	**6.91**

*** Uncorrect**

Table:-4 Antibacterial Activity of Compounds (3a-h)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
3a	12	11	14	**13**
3b	16	13	15	**16**
3c	11	12	12	**13**
3d	13	17	13	**18**
3e	16	14	15	**14**
3f	13	20	18	**18**
3g	12	13	11	**15**
3h	18	14	14	**17**
Tetracycline	**22**	**21**	**19**	**21**

Table:-5 Antifungal Activity of Compounds (3a-h)

Zone of Inhibition at 1000 ppm (%)					
Compounds	**Nigrospora Sp.**	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	**Fusarium oxyporium**
3a	63	63	61	61	62
3b	58	60	62	63	64
3c	61	65	65	64	69
3d	66	63	61	65	70
3e	64	62	59	69	69
3f	59	61	61	68	67
3g	57	65	68	61	65
3h	58	69	70	71	66

Table:-6 Antibacterial Activity of Compounds (4a-h)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
4a	11	11	12	**14**
4b	13	12	15	**11**
4c	15	15	16	**12**
4d	13	16	15	**14**
4e	14	14	13	**16**
4f	16	12	11	**14**
4g	18	19	18	**19**
4h	16	15	16	**18**
Tetracycline	**20**	**21**	**20**	**22**

Table:-7 Antifungal Activity of Compounds (4a-h)

Zone of Inhibition at 1000 ppm (%)					
Compounds	**Nigrospora Sp.**	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	**Fusarium oxyporium**
4a	61	65	60	59	61
4b	62	64	61	61	63
4c	60	68	63	63	67
4d	61	61	62	61	63
4e	63	63	61	69	64
4f	62	58	64	62	67
4g	67	61	67	59	65
4h	61	63	71	70	67

REFERENCES

1. Shiradkar M. R., Murahari K. K., Gangadasu H. R., Suresh T., Kalyan C. C., Panchal D., Kaur R., Burange P., Ghogare J., Mokale V., Raut M. Synthesis of new S-derivatives of clubbed triazolyl thiazole as anti-Mycobacterium tuberculosis agents, Bioorg.Med. Chem. 2007, 15, P. 3997-4008.

2. Janin Y. Antituberculosis drugs: Ten years of research, Bioorg. Med. Chem. 2007, 15, P. 2479-2513.

3. Gursoy E., Guzeldemirci-Ulusoy N. Synthesis and primary cytotoxicity evaluation of new imidazo[2,1-b]thiazole derivatives, Eur. J. Med. Chem. 2007, 42, P. 320-326.

4. Kaymakcıoglu K. B., Oruc E. E., Unsalan S., Kandemirli F., Shvets N., Rollas S., Anatholy D. Synthesis and characterization of novel hydrazide-hydrazones and the study of their structureantituberculosis activity, Eur. J. Med. Chem. 2006, 41, P. 1253-1261.

5. Kalsi R., Shrimali M., Bhalla T. N., Barthwal J. P. Synthesis and anti inflammatory activity of indolyl azetidinonesIndian, J. Pharm. Sci. 2006, 41, P. 353-359.

6. Gemma S., Kukreja G., Fattorusso C., Persico M., Romano M., Altarelli M.,Savini L., Campiani G., Fattorusso E., Basilico N. Synthesis of N1-arylidene N2-quinolyl- and

N2-acrydinylhydrazones as potent antimalarial agents active against CQ-resistant P. falciparum strains, Bioorg. Med. Chem. Lett. 2006, 16, P. 5384-5388.

7. Sriram D., Yogeeswari P., Madhu K. Synthesis and in vitro and in vivo antimycobacterial activity of isonicotinoyl hydrazones, Bioorg. Med. Chem. Lett. 2006, 15, P. 4502-4505.

8. Nayyar A., Jain R. Recent advances in new structural classes of anti tuberculosis agents, Curr. Med. Chem. 2006, 12, P. 1873-1886.

9. Walcourt A., Loyevsky M., Lovejoy D. B., Gordeuk V. R., Richardson D. R. Novel aroylhydrazone and thiosemicarbazone iron chelators with anti-malarial activity against chloroquine-resistant and -sensitive parasites, Int.J.Biochem. Cell Biol. 2004, 36, P. 401-407.

10. Mamolo M. G., Falagiani V., Zampieri D., Vio L., Banfi E. , Scialino G. Synthesis and antimycobacterial activity of (3,4-diaryl-3H-thiazole-2-ylidene)hydrazide derivatives, Farmaco 2003, 58, P. 631-637.

11. Terzioglu N., Gursoy A. Synthesis and anticancer evaluation of some new hydrazone derivatives of 2,6-dimethylimidazo[2,1-b]-[1,3,4]thiadiazole 5-carbohydrazide, Eur. J. Med. Chem. 2003, 38, P. 781-786.

12. Kucukguzel S. G., Oruc E. E., Rollas S., Sahin F., Ozbek A. Synthesis, Characterization and biological activity of novel 4-thiazolidinones, 1,3,4-oxadiazoles and some related compounds, Eur. J. Med. Chem. 2002, 37, P. 197-206.

13. Rollas S., Gulerman N., Erdeniz H. Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines, Farmaco 2002, 57, P. 171-174.

14. Al- Mawsawi LQ, Dayam R., Taheri L., Witvrouw M., Debyser Z., Neamati N. Discovery of novel non-cytotoxic salicylhydrazide containing HIV-1 integrase inhibitors, Bioorg. Med. Chem. Lett. 2007, 17(23), P. 6472-6475.

15. Plasencia C., Daym R., Wang Q., Pinski J., Jr. Burke T. R., Quinn D. I., and Neamati N. Discovery and preclinical evaluation of a novel class of small-molecule compounds in hormone-dependent and -independent

cancer cell lines, Mol. Cancer Ther. 2005, 4(7), P. 1105-1113.

16. Zhao H., Neamati N., Sunder S., Hong H., Wang S., Milne G. W., Pommier Y., Jr. Burke T. R. Hydrazide-containing inhibitors of HIV-1 integrase, .J. Med. Chem. 1997, 40(6), P. 937-941.

17. W. Vincent, M. D. James, P. Jose, T. David, V. J. Pierse, B. Derek, H. Tomas and M. D. Robert, EU Pat., 1, 178, 039, Chem. Abstr. 136, 157003f (2002).

18. K. C. Ravindra, H. M. Vagdevi, V. P. Vaidya and B. Padmashali, Ind. J. of Chem. 45B, 2506 (2006).