Research Article *ISSN: 2277-8713*
Sonal Mehta, IJPRBS, 2013; Volume 2(2): 373-385 *IJPRBS*

ISSN: 2277-8713
IJPRBS
A Path for horizing your innovative work
INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

SYNTHESIS AND BIOLOGICAL ACTIVITY OF PYRROLE AND PYRROLIDINE COMPOUNDS FROM 4-BROMO-2-HYDROXYBENZOIC ACID HYDRAZIDE

SONAL MEHTA

Emcure Pharmaceuticals, USA

IJPRBS-QR CODE

PAPER-QR CODE

Accepted Date:
19/04/2013
Publish Date:
27/04/2013

Keywords
4-Bromo-2-Hydroxy Benzoic Acid Hydrazide, Pyrrole, Pyrrolidine, Antibacterial Activity.

Corresponding Author
Ms. Sonal Mehta

Abstract

Condensation of 4-bromo-2-hydroxy benzoic acid hydrazide (1) with aromatic aldehydes to gives the corresponding 4-bromo-2-hydroxy benzoic acid arylidene hydrazides (2a-h). Cyclocondensation of compounds 4-bromo-2-hydroxy benzoic acid arylidene hydrazides (2a-h) with maleic anhydride and succinic anhydride yields respectively 1-(4-bromo-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) and 1-(4-bromo-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (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

4-bromo-2-hydroxy benzoic acid hydrazide is heterocyclised product and the Hydrazides and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the hydrazides, 4-bromo-2-hydroxy benzoic acid hydrazide and their condensed products play a vital role in medicinal chemistry [1-16]. Pyrrole and pyrrolidine compounds give good biological and pharmacological properties [17]. Hence, it was thought of interest to merge both of pyrrole and 4-bromo-2-hydroxy benzoic acid hydrazide, pyrrolidine and 4-bromo-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-bromo-2-hydroxy benzoic acid hydrazide containing pyrrole and pyrrolidine moiety. Hence the present communication comprises the synthesis of 1-(4-bromo-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h) and 1-(4-bromo-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (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-bromo-2-hydroxy benzoic acid arylidene hydrazide (2a-h)

General procedure: – An equimolecular mixture of 4-bromo-2-hydroxy benzoic acid hydrazide (1), (0.01mole) and the aromatic aldehydes (a-h) in ethanol (25mL) was refluxed on a water bath for 2h. 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 1-(4-bromo-2-hydroxybenzamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-h)

General procedure: A mixture 4-bromo-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (0.1 mole) and Maleic anhydride (0.1 mole) were heated at reflux in chloroform (50ml) for about 3.5 hours with TLC monitoring. After the mixture was allowed to stand for 1 days, the solid was filtered. The product thus formed was recrystallized from ethanol to give pure 1-[4-pyridinylcarbonlyamino]-2-oxo-5-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid in (3a-h), which were obtained in 58-61% yield.

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

Preparation of 1-(4-bromo-2-hydroxybenzamido)-5-oxo-2-arylpyrrolidine-3-carboxylic acid (4a-h)

A mixture 4-bromo-2-hydroxy benzoic acid arylidene hydrazide (2a-h) (0.1 mole) and Succinic anhydride (0.1 mole) were heated at reflux in chloroform (50ml) for about 4 hours with TLC monitoring. After the mixture was allowed to stand for 1 day, the solid was filtered. The product thus formed was recrystallized from ethanol to give pure 1-[4-pyridinylcarbonyl amine]-2-oxo-5-aryl-2,5-dihydro-1H-pyrrolidinone-3-carboxylic acid (3a-h) in good 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-bromo-2-hydroxy benzoic acid hydrazide (1), on condensation with aromatic aldehydes, yields 4-bromo-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-bromo-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^{-}

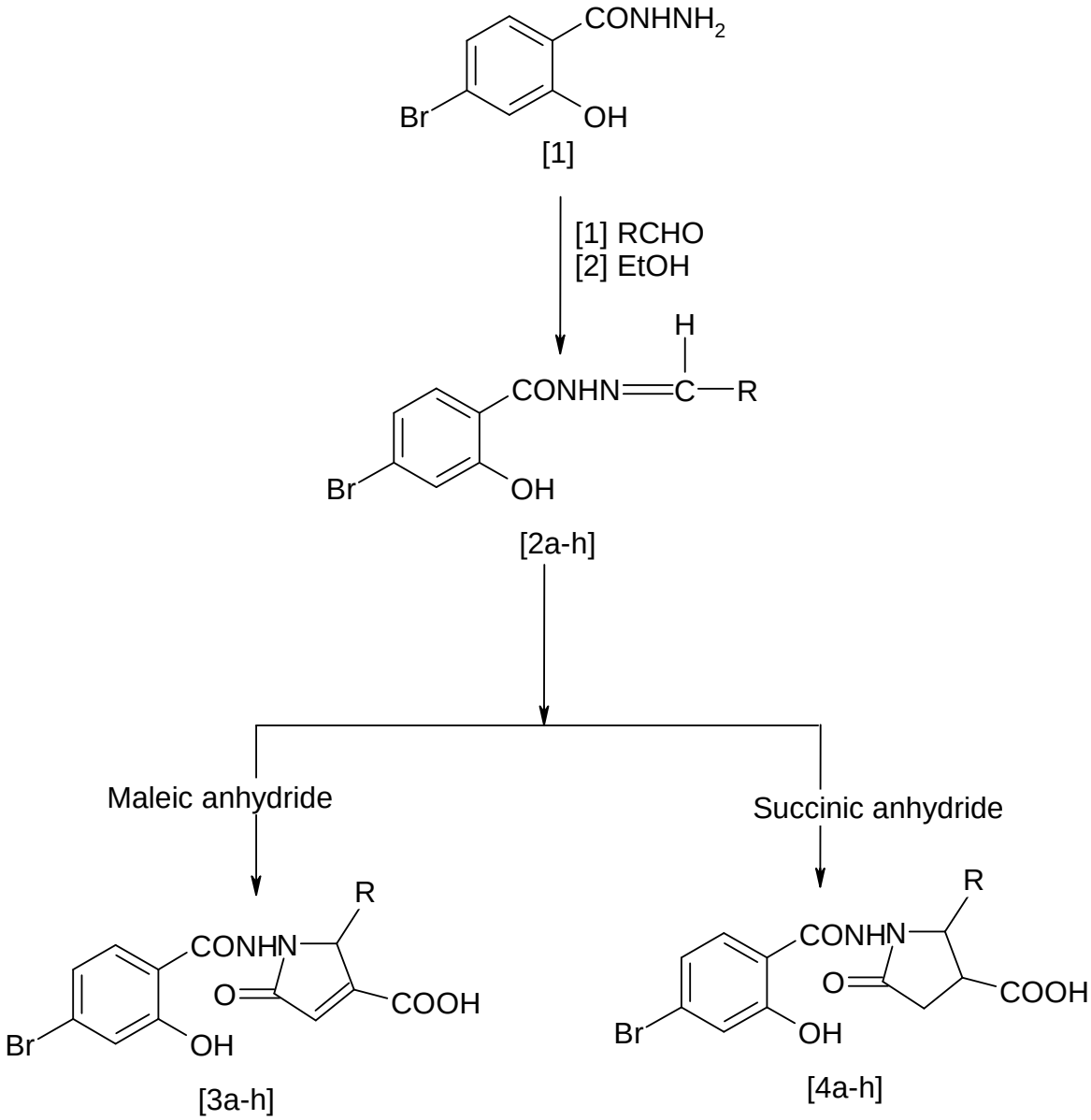
[1] (C-H, of Ar.), 3240-3260 cm^{-1} (-OH). ^{1}H NMR: 6.62-7.82 (8H, m) (Ar-H), 5.50-5.60 (1H, s) (-C_5H of the ring), 7.10-7.15 (1H, s) (-C_3H), 12.90-12.98 (1H, s) (-COOH), 11.70-11.85 (1H, s) (-OH), 3e; 2.36 (3H, s) (-CH_3), 3b,3g; 3.93,3.90 (3H, s) (-OCH_3), 3h; 4.13 (4H q) (CH_2), 1.32 (6H, t) (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-bromo-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). ^{1}H 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), 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 3c and 4f compounds are 443 and 471 respectively.

ACKNOWLEDGEMENT

The authors are thankful to Mr. Nilesh Patel, VP, Emcure Pharmaceuticals, USA for providing laboratory facilities.



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	$C_{14}H_{11}BrN_2O_2$ (319)	75	248	52.55	52.66	3.39	3.44	8.70	**8.77**
2b	$C_{15}H_{13}BrN_2O_3$ (349)	72	251	51.52	51.57	3.69	3.72	7.95	**8.02**
2c	$C_{14}H_{11}BrN_2O_3$ (335)	76	252	50.03	50.14	3.15	3.28	8.29	**8.35**
2d	$C_{14}H_{11}BrN_2O_3$ (335)	77	253	50.05	50.14	3.16	3.28	8.27	**8.35**
2e	$C_{15}H_{13}BrN_2O_2$ (333)	81	249	53.69	53.73	3.82	3.90	8.33	**8.40**
2f	$C_{15}H_{11}BrN_2O_4$ (363)	72	254	49.49	49.59	2.93	3.03	7.60	**7.71**
2g	$C_{15}H_{13}BrN_2O_3$ (365)	71	257	49.21	49.31	3.51	3.56	7.59	**7.67**
2h	**$C_{18}H_{19}BrN_2O_4$ (407)**	**75**	**266**	**52.98**	**53.07**	**4.58**	**4.67**	**6.79**	**6.88**

* 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	$C_{18}H_{13}BrN_2O_5$ (417)	60	235	51.72	51.80	3.09	3.12	6.67	**6.71**
3b	$C_{19}H_{15}BrN_2O_6$ (447)	58	231	50.94	51.01	3.29	3.36	6.21	**6.26**
3c	$C_{18}H_{13}BrN_2O_6$ (433)	62	186	49.82	49.88	2.89	3.00	6.41	**6.47**
3d	$C_{18}H_{13}BrN_2O_6$ (433)	61	188	49.81	49.88	2.89	3.00	6.40	**6.47**
3e	$C_{19}H_{15}BrN_2O_5$ (431)	59	175	52.80	52.90	3.41	3.48	6.43	**6.50**
3f	$C_{19}H_{13}BrN_2O_7$ (461)	63	184	49.39	49.46	2.76	2.82	5.98	**6.07**
3g	$C_{19}H_{15}BrN_2O_7$ (463)	60	181	49.18	49.24	3.19	3.24	5.97	**6.05**
3h	**$C_{22}H_{21}BrN_2O_7$ (505)**	**62**	**228**	**52.18**	**52.28**	**4.09**	**4.16**	**5.49**	**5.54**

* Uncorrected

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	**Calcd.**	**Found**	**Calcd.**	**Found**	Calcd.
4a	$C_{18}H_{15}BrN_2O_5$ (419)	64	239	51.46	51.55	3.51	3.58	6.62	**6.68**
4b	$C_{19}H_{17}BrN_2O_6$ (449)	60	241	50.69	50.78	3.71	3.79	6.22	**6.24**
4c	$C_{18}H_{15}BrN_2O_6$ (435)	58	240	49.59	49.66	3.39	3.45	6.38	**6.44**
4d	$C_{18}H_{15}BrN_2O_6$ (435)	63	237	49.60	49.66	3.37	3.45	6.37	**6.44**
4e	$C_{19}H_{17}BrN_2O_5$ (433)	59	231	52.56	52.66	3.85	3.93	6.41	**6.47**
4f	$C_{19}H_{15}BrN_2O_7$ (463)	60	239	49.18	49.24	3.20	3.24	5.98	**6.05**
4g	$C_{19}H_{17}BrN_2O_7$ (465)	61	241	48.97	49.03	3.56	3.66	5.88	**6.02**
4h	**$C_{22}H_{23}BrN_2O_7$ (507)**	**59**	**239**	**52.01**	**52.07**	**4.45**	**4.54**	**5.43**	**5.52**

* Uncorrected

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

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	**Bacillus subtilis**	**E.coli**	Klebsiella promioe
3a	12	10	14	**13**
3b	11	14	12	**18**
3c	10	12	11	**11**
3d	13	14	14	**13**
3e	16	10	15	**15**
3f	15	17	13	**19**
3g	13	13	19	**17**
3h	18	19	16	**15**
Tetracycline	**22**	**21**	**18**	**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	58	63	64	64	**65**
3b	59	61	65	65	**68**
3c	61	68	68	68	**65**
3d	62	62	60	71	**68**
3e	60	60	63	70	**71**
3f	62	61	67	63	**69**
3g	60	69	69	65	**68**
3h	**63**	**71**	**70**	**72**	**69**

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

Compounds	Gram +Ve		Gram –Ve	
	Staphylococcus aureus	**Bacillus subtilis**	**E.coli**	Klebsiella promioe
4a	13	13	12	**11**
4b	15	15	15	**17**
4c	16	18	13	**13**
4d	13	14	18	**15**
4e	11	15	14	**19**
4f	16	16	14	**18**
4g	18	15	18	**21**
4h	16	16	15	**18**
Tetracycline	**20**	**21**	**20**	**22**

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

Compounds	Zone of Inhibition at 1000 ppm (%)				
	Nigrospora Sp.	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	Fusarium oxyporium
4a	68	69	60	59	**61**
4b	65	65	63	61	**63**
4c	65	68	62	65	**66**
4d	62	61	62	62	**60**
4e	63	63	65	69	**62**
4f	60	59	67	66	**67**
4g	66	61	69	63	**68**
4h	**62**	**63**	**71**	**72**	**70**

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 structure antituberculosis 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 anti mycobacterial 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. Bellina F. and Rossi R. Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions, Tetrahedron 2006, 62, P. 7213-7256.