International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-3, 2012

Study of Novel Pyrrole Derivatives

Prasad A[1*], Nimavat KS[2], Vyas KB[3]

[1]*Research Scholar, JJT University, Jhunjhunu, Rajasthan, India.*

[2]*Government Science College, Gandhinagar, Gujarat, India.*

[3]*Sheth L. H. Science College, Mansa, Gujarat, India.*

Manuscript No: IJPRS/V1/I3/00125, Received On: 03/07/2012, Accepted On: 06/07/2012

ABSTRACT

Substituted benzaldehydes on simplistic condensation with 2-(5-((naphthalen-1-yloxy) methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide(1) was give the consequent N'-arylidene-2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) aceto hydrazide (2a-e) in fine yield. Cyclo condensation of compounds (2a-e) with maleic anhydride yields 2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamido)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e). 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.

KEYWORDS

2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide, pyrrole, antibacterial and antifungal activities.

INTRODUCTION

The heterocyclic systems find wide use in medicine, agriculture and industry. One of the other compounds says, oxadiazoles and their condensed products play a vital role in medicinal chemistry[1-3]. Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties[4-13]. Another heterocyclic moiety says, pyrrole and its substituted derivatives furnish good pharmacological properties[14-20]. Hence, it was thought of interest to merge both of pyrrole and oxadiazole 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 oxadiazole containing pyrrole moiety. Hence the current communication covers the study of 1-(2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid. The synthetic approach is shown in scheme-1.

***Address for Correspondence:**
Ashok Prasad
Research Scholar,
JJT University, Jhunjhunu,
Rajasthan, India.
E-Mail Id: prasadashok@indiatimes.com

EXPERIMENTAL

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 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.

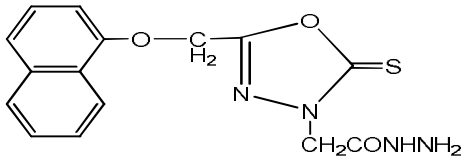
Preparation of N'-arylidene-2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (2a-e):

A mixture of 2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-

yl)acetohydrazide (1) (0.01mole) and substituted benzaldehydes (0.01mole) (a-e) in ethanol (15ml) was refluxed on a water bath for 2-3.5 hrs. 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-(2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e):

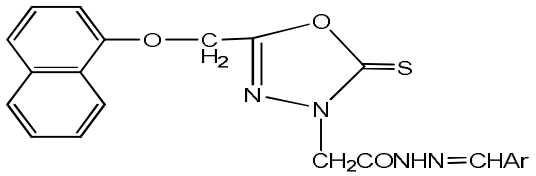
A mixture of Maleic anhydride (0.01mole) and N'-arylidene-2-(5-((naphthalen-1-yloxy) methyl) -2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (2a-e) (0.01 mole) in chloroform (50ml) was refluxed for 4-5.5 hrs. The reaction mixture was allowed to stand for 36hrs, the solid was filtered. The product thus formed was recrystallized from ethanol to give 2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamido)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e), which were obtained in 64-81% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.



2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetohydrazide

(1)

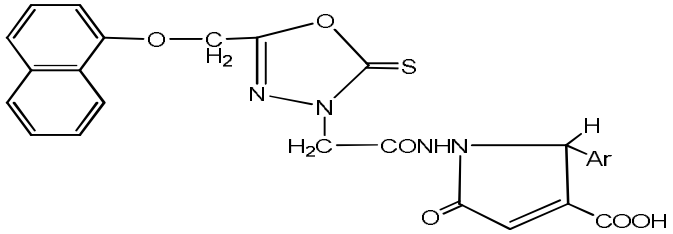
Ar-CHO/Ethanol



N'-arylidene-2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetohydrazide

(2a-e)

maleic anhydride



1-(2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetamido) -5-oxo-2-aryl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid

(3a-e)

Where Ar = (a) C_6H_5, (b) 4-CH_3-C_6H_4, (c) 2-OH-C_6H_4, (d) 4-OH-C_6H_4, (e) 4-OCH_3-C_6H_4

SCHEME : 1

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

Compd.	Molecular formula (Mol. Wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		% H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{22}H_{18}N_4O_3S$ (418)	435	93	242-244	63.1	63.14	4.3	4.34	13.3	13.39
2b	$C_{23}H_{20}N_4O_3S$ (432)	456	88	232-234	63.8	63.87	4.6	4.66	12.9	12.95
2c	$C_{22}H_{18}N_4O_4S$ (434)	452	86	226-228	60.7	60.82	4.1	4.18	12.8	12.90
2d	$C_{22}H_{18}N_4O_4S$ (434)	453	84	241-243	60.8	60.82	4.1	4.18	12.8	12.90
2e	$C_{23}H_{20}N_4O_4S$ (448)	462	81	234-235	61.5	61.59	4.4	4.49	12.4	12.49

***** Uncorrected

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

Compd.	Molecular formula (Mol. wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		% H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{25}H_{19}N_4O_6S$ (503)	521	65	220-222	59.6	59.64	3.7	3.80	11.1	11.13	6.3	6.37
3b	$C_{26}H_{21}N_4O_6S$ (517)	533	63	223-224	60.3	60.34	4.0	4.09	10.8	10.83	6.1	6.20
3c	$C_{25}H_{19}N_4O_7S$ (519)	538	67	217-218	57.8	57.80	3.6	3.69	10.7	10.78	6.1	6.17
3d	$C_{25}H_{19}N_4O_7S$ (519)	537	64	224-226	57.7	57.80	3.6	3.69	10.7	10.78	6.1	6.17
3e	$C_{26}H_{21}N_4O_7S$ (533)	548	65	225-226	58.5	58.53	3.9	3.97	10.4	10.50	6.0	6.01

* Uncorrected

RESULTS AND DISCUSSION

It was observed that 2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (1), on condensation with aromatic aldehydes, yields N'-aryl-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (2a-e). The structures of (2a-e) 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.), 2815-2850 cm^{-1} (-OCH_2). ^1H NMR : 6.95 – 7.91 (7H, m) (Ar - H), 11.80-11.81 (1H, s) (-CONH), 8.43-8.80 (1H, s)(-N=CH), 2b; 2.41 (3H, s) (-CH_3), 2c,2d; 4.09 (2H,s) (OH),2e; 3.90 (3H, s) (-OCH_3).^{13}C NMR:117.9-118.1, 121.8-122.0, 128.9-129.1, 129.5-130.0, 131.2-131.5, 133.9-134.3, 159.6-160.0 (Ar-10C), 163.5-163.8(-CONH), 146.9-150.4 (-CH); 2b: 22.5 (CH_3) ; 2e: 55.5 -56.7 (-OCH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 1-(2-(5-((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamido)-5-oxo-2-aryl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1720 cm^{-1} (C=O of pyrrole ring), 3040-3058 cm^{-1}(C-H, of Ar.),3450-3550 cm^{-1}(-OH),1660-1670 cm^{-1} (-CO of -COOH), 1628-1645 cm^{-1} (C=N), 2815-2850 cm^{-1} (-OCH_3), 1185 (C=S),1620(C=N ring), 765(C-O-C ring). ^1H NMR: 6.9–8.1(m, 12H, Ar-H), 11.80 (s,1H, CONH), 4.72(1H,s, C_2H of the ring), 5.19(1H,s,C_4H),12.96(1H,s)(-COOH), 4.1(s,1H,CH_2), 2.62 (s,1H,CH_2), 3b; 2.1 (3H, s, CH_3), 3c;11.20 (s,1H, OH), 3d;11.20(s,1H,OH), 3e; 3.90 (3H, s,OCH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

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 data of Samples 3b and 3e gives the molecular ion peak (m/z) at 533 and 548 respectively. These values are corresponds to their molecular weight.

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 3c and 3d were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -3.

Table: 3 Antibacterial Activity of Compounds (3a-e)

Compounds	Gram +Ve		Gram -Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
3a	55	51	67	61
3b	56	52	69	62
3c	67	58	75	77
3d	66	57	72	75
3e	58	53	58	69
Tetracycline	68	60	77	80

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 activities of all the compounds (3a-e) were measured on each of these plant pathogenic strains on a potato

Table 4: Antifungal Activity of Compounds (3a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Rhizopus Nigricum***	***Nigrospora Sp.***	***Fusarium oxyporium***	***Botrydepladia Thiobromine***	***Aspergillus Niger***
3a	57	59	63	59	59
3b	56	62	64	57	58
3c	69	68	69	72	65
3d	65	69	68	74	63
3e	61	59	66	59	57

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-e) is shown in Tables-4.

ACKNOWLEDGEMENT

The authors are thankful to M/S Shree Tirupati Industries, Palanpur, Gujarat, India for providing chemicals and laboratory facilities for carrying out the research work.

REFERENCES

1. Küçükgüzel ŞG, Kocatepe A, De Clercq E, Şahin F, Güllüce M, “Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide”, Eur. J. Med. Chem., 2006, 41, 353-359.
2. Kaymakçıoğlu KB, Oruç EE, 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, 1253-1261.
3. Ragavendran JV, Sriram D, Patel SK, Reddy IV, Bharathwajan N, Stables J, Yogeeswari P, “Design and synthesis of anticonvulsants from a combined phthalimide-GARA- anilide and hydrazone pharmacophore”, Eur J Med Chem., 2007, 42, 146–151.
4. Gürsoy E, Güzeldemirci-Ulusoy N, “Synthesis and primary cytotoxicity evaluation of new imidazo[2,1-b]thiazole derivatives”, Eur. J. Med. Chem., 2007, 42, 320-326.
5. Kalsi R, Shrimali M, Bhalla TN, Barthwal JP, “Synthesis and anti-inflammatory activity of indolyl azetidinones”, Indian J. Pharm. Sci., 2006, 41, 353-359.

6. Janin Y, "Antituberculosis drugs: ten years of research", Bioorg. Med. Chem., 2007, 15, 2479-2513.

7. Karegoudar P, Parasa DJ, Ashok M, Mahalinga M, Poojary B, Holla BS. "Synthesis, antimicrobial and ant-inflammatory activities of some 1,2,4-triazolo[3,4-b][1,3,4]thiazoles and 1,2,4-triazolo[3,4-b]thiadiazines bearing trichlorophenyl moiety", Eur J Med Chem., 2008, 43, 208–815.

8. Padmavathi V, Reddy GS, Padmaia A, Kondaiah P, Shazia A., "Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4- triazoles., Eur J Med Chem., 2008, 44, 206–212.

9. Ragavendran JV, Sriram D, Patel SK, Reddy IV, Bharathwajan N, Stables J, Yogeeswari P., "Design and synthesis of anticonvulsants from a combined phthalimide-GARA - anilide and hydrazone pharmacophore", Eur J Med Chem., 2007, 42, 146–151.

10. Zora M, Gormen M. "Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene", J Organomet Chem., 2007, 692, 5026–5032.

11. Acharya BN, Saraswat D, Kaushik MP. "Pharmacophore based discovery of potential antimalarial agent targeting haem detoxification pathway", Eur J Med Chem., 2008, 43, 2840–2852.

12. Xia Yong, Fan CD, Zhao BX, Zhao J, Shin DS, Miao JY., "Synthesis and structure relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide hydrazone derivatives as potential agents against A549 lung cancer cells", Eur J Med Chem., 2008, 43, 2347– 2353.

13. Bedia KB, Elcin O, Deda U, Fatma K, Nathaly S, Sevim R, Dimoglo A, "Synthesis and characterization of novel hydrazide-hydrazones and the study of their structure anti - tuberculosis", Eur J Med Chem., 2008, 41, 1253–1261.

14. Solankee AN, Patel KP, Patel RB, "A facile synthesis and studies of some new 4 - thiazolidinones and 5-arylidenes" Advances in Applied Science Research, 2012, 3(1), 117-122.

15. Che C, Mao SF, Mu CW, Xu YJ, Qin ZH, "Studies on pyridine derivatives (VII): synthesis and insecticidal activities of pyridine derivatives with an 1,3,4-thiadiazole moiety" Chin. J. Pestic. Sci., 2002, 4(3), 75–78.

16. Zou XJ, Lai LH, Jin GY, Zhang ZX, "Synthesis, fungicidal activity and 3D QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles", J. Agric. Food Chem. 2002, 50, 3757–3760.

17. Turgut Z, Yolacan C, Aydogan F, Ocal N, "Synthesis of New Pyrazolo thiazole Derivatives from 4-Thiazolidinones" Molecules, 2007, 12(9), 2151-2159.

18. Suman SP and Bahel SC., "Synthesis of 2-arylamino-5-aryl/aryloxymethyl-1,3,4-thiadiazoles, N1-aryl/aryloxyacetyl-3-methyl-5-pyrazolones as possible fungicides", J. Indian Chem. Soc., 1979, 56, 374–376.

19. Tozkoparan B, Gokhan N, Aktay G, Yesilada E and Ertan M., "6-Benzylidene thiazolo [3,2-b]-1,2,4-triazole-5(6H)-ones substituted with ibuprofen: Synthesis, characterization and evaluation of anti-inflammatory activity", Eur. J. Med. Chem., 2000, 35, 743–750.

20. Turgut Z, Yolacan C, Aydogan F, Ocal N, "Synthesis of New Pyrazolothiazole Derivatives from 4-Thiazolidinones", Molecules, 2007, 12, 2151-2159.

