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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL ISOINDOLINE 1,3-DIONEDERIVATIVES

VIJAY V. DABHOLKAR* and DINESH UDAWANT[#], RAHUL JAISWAR

Organic Research Laboratory, Department of Chemistry,
**K.C. College, Churchgate, Mumbai-400 020*
[#]Guru Nanak College, G.T.B Nagar, Mumbai - 400037, INDIA.
E-mail: vijaydabholkar@gmail.com
dins1323@gmail.com

Abstract:
A new series of 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-substituted-isoindoline-1,3-dione **(5)**have been synthesized by the reaction of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole**(3)**with substituted phthalic anhydride **(4)** under solvent free conditions and the structures of the compounds have been confirmed by IR and NMR. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria, *E coli* and *P.aeruginosa*and gram-positive bacteria, *S aureus*, and *C diphtheriae*using disc diffusion method. Some of these compounds have been found to exhibit excellent antibacterial activity.

Keywords: 1,3,4-Thiadiazole, Isoindoline 1,3-dione, phthalic anhydride

Introduction:

The most important biological activity properties that have been reported for Isoindoline-1,3-dione (phthalimide) derivatives are anti-cancer[1], anti-microbial[2,3], anti-oxidant[4] andanti-inflammatory[5]. According to the World Health Organization (WHO), infectious and parasiticdiseases are still the second cause of death worldwide. This is assumed to be due to resistance to theanti-microbial agents used. There are several studies showing that compounds bearing a Isoindoline-1,3-dione (phthalimide)core may be a scaffold for designing new anti-microbial agents [2]. On the other hand, oxidation resultsin free radicals which damage the cell via causing oxidative stress leading to inflammation[6].
A literature search of suitable nuclei of use as anti-oxidant and anti-inflammatory agents, revealedIsoindoline-1,3-dione (phthalimide) was one of these heterocyclic compounds [1,4,5]. The chemical core of Isoindoline-1,3-dione (phthalimide)(-CO-N(R)-CO-) shows they are hydrophobic and this increases their potential to cross biologicalmembranes in vivo[7]. To increase the biological activity of Isoindoline-1,3-dione derivatives, a molecularhybridization approach was used to introduce different pharmacophore subunits such as 1,3,4-thidiazoles. Isoindoline-1,3-dione (phthalimide) have also been reported to have anti-microbial[8],anti-

oxidant[9] and anti-inflammatory[10–13] activities, apart from other pharmacologicalactions like anti-convulsant[14], CNS depressant[15], anti-tumor[16], anti-proliferative [17] andanti-pyretic [18] effects.

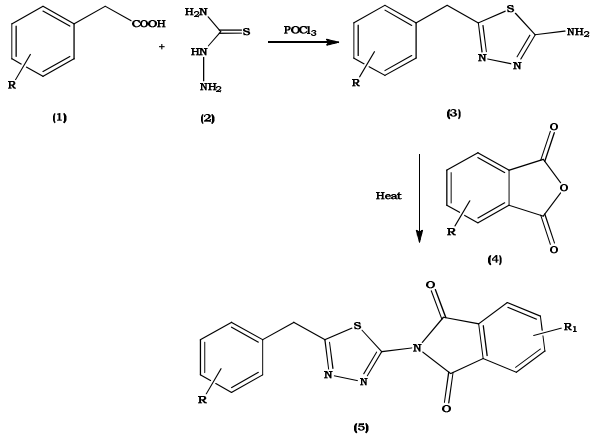
In view of the versatile biological activitiesand the benefits of Isoindoline-1,3-dione (phthalimide) derivatives and as acontinuation of the efforts to synthesis isolated andfused heterocyclic compounds, herein is reporteda facile and convenient route of synthesis of 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-substituted-isoindoline-1,3-dione **(5)**.

Results and discussion

The molecules 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-substituted-isoindoline-1,3-dione**,(3)** were synthesized by the reaction of substituted phenyl acetic acid **(1)** with Thiosemicarbazide**(2)** in presence of phosphorous oxychloride. Further, Compound **(3)** was treated with phthalic anhydride **(4)** to yields, target molecules 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-substituted-isoindoline-1,3-dione**,(5) (Scheme I)**.

The newly synthesized compounds were screened for their antibacterial activity against gram negative as well as gram positive bacteria, which shows promising activity against both.

Scheme I:



The spectral analysis of representative compounds will be as follows:

*2-amino-5-(methoxy)-benzyl-1,3,4-thiadiazole **(3a)***

Yield: 78%; m.p.=191-195°C;

Anal.Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99%.Found: C,54.17; H,4.97,N,18.76%.

IR (cm^{-1}):3205(NH_2), 1496 (C=N)

^{1}H NMR(DMSO-d_6, δ /ppm):3.48(s, 2H, CH_2), 3.86(s, 3H, OCH_3), 6.65 – 6.80 (m, 4H, ArH), 8.4(s, 2H, NH_2).

^{13}C NMR (DMSO-d_6,δ /ppm):41.5 (CH_2), 60.35 (OCH_3), 118.96- 137.89 (C=C &Ar C), 153.43 (C-OCH_3), 172.1 & 173.2 (2 x S-C=N).

*2-amino-5-(2-methyl)-benzyl-1,3,4-thiadiazole **(3b)***

Yield: 71%; m.p.=210-213°C;

Anal.Calcd for $C_{10}H_{11}N_3S$: C,58.51;H,5.40; N,20.47%. Found: C,58.42; H,5.36,N,20.38%.

IR (cm^{-1}):3316(NH_2), 1598 & 1522 (C=N).

^{1}H NMR (DMSO-d_6, δ /ppm):2.65 (s, 3H, CH_3), 3.51(s, 2H, CH_2), 6.69 – 6.96(m, 4H, ArH), 8.32(s, 2H, NH_2).

^{13}C NMR (DMSO-d_6,δ /ppm):23.2 (CH_3), 39.6(CH_2), 124.9- 141.65 (C=C &Ar-C), 169.1 & 170.2 (2 x S-C=N).

2-(5-(4-methoxybenzyl)-1,3,4-thiadiazol-2-yl)-5-methylisoindoline-1,3-dione (5a)
Yield: 81%; m.p.=210-215°C;
Anal.Calcd for $C_{19}H_{15}N_3O_3S$: C,62.45; H,4.14; N,11.50%. Found: C,62.38; H,4.07,N,11.45%.
IR (cm^{-1}): 1722 & 1692 (C=O), 1493 & 1450 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 2.34 (s, 3H, CH_3), 3.65(s, 2H, CH_2), 3.86(s, 3H, OCH_3), 6.81 – 7.32 (m, 7H, ArH),
^{13}C NMR (DMSO-d_6,δ /ppm): 23.91 (CH_3), 41.2(CH_2), 59.5 (OCH_3), 115.16-140.52 (C=C &Ar-C), 165.69 (S-C=N), 169.48(S-C=N),173.53(2xC=O).

2-(5-(2-methylbenzyl)-1,3,4-thiadiazol-2-yl)-5-methylisoindoline-1,3-dione (5b)
Yield: 78%; m.p.=205-209°C;
Anal.Calcd for $C_{19}H_{15}N_3O_2S$: C,65.31; H,4.33; N,12.03%. Found: C,65.24; H,4.23,N,11.89%.
IR (cm^{-1}): 1680 (C=O), 1550 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 2.36 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 6.82 – 7.85 (m, 7H, ArH),
^{13}C NMR (DMSO-d_6,δ /ppm): 24.81 (CH_3), 26.67 (CH_3) 43.21(CH_2), 119.21-135.48 (C=C &Ar-C), 163.67 (S-C=N), 168.91(S-C=N),174.59(2xC=O).

2-(5-(4-Chlorobenzyl)-1,3,4-thiadiazol-2-yl)-5-methylisoindoline-1,3-dione (5c)
Yield: 71%; m.p.=221-25°C;
Anal.Calcd for $C_{18}H_{12}N_3O_2SCl$ C,58.46; H,3.27; N,11.36%. Found: C,58.37; H,3.21,N,11.28%.
IR (cm^{-1}): 1660 (C=O), 1540 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 2.39 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 7.25 – 8.07 (m, 7H, ArH),
^{13}C NMR (DMSO-d_6,δ /ppm): 23.42 (CH_3), 42.14(CH_2), 121.18-138.32 (C=C &Ar-C), 162.13 (S-C=N), 169.34(S-C=N),174.68(2xC=O).

2-(5-(4-methoxybenzyl)-1,3,4-thiadiazol-2-yl)-isoindoline-1,3-dione (5k)
Yield: 78%; m.p. =169-73°C;
Anal.Calcd for $C_{18}H_{13}N_3O_3S$, C,61.53; H,3.73; N,11.96%. Found: C,61.41; H,3.64,N,11.87%.
IR (cm^{-1}): 1780 (C=O), 1540 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 3.54 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 7.61 – 8.62 (m, 8H, ArH),
^{13}C NMR (DMSO-d_6,δ /ppm): 42.14(CH_2), 59.67 (OCH_3), 124.18-138.32 (C=C &Ar-C), 163.13 (S-C=N), 169.34(S-C=N),173.68(2xC=O).

2-(5-(4-Chlorobenzyl)-1,3,4-thiadiazol-2-yl)-5-methylisoindoline-1,3-dione (5l)
Yield: 71%; m.p.=172-176°C;
Anal.Calcd for $C_{18}H_{13}N_3O_2S$ C,64.46; H,3.91; N,12.53%. Found: C,64.38; H,3.84,N,12.47%.
IR (cm^{-1}): 1690 (C=O), 1560 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 2.43 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 7.12 – 8.24 (m, 8H, ArH),

^{13}C NMR (DMSO-d_6,δ /ppm): 24.83 (CH_3), 41.65(CH_2), 118.21-137.67 (C=C &Ar-C), 161.74 (S-C=N), 168.53(S-C=N),172.81 (2xC=O).

2-(5-(4-chlorobenzyl)-1,3,4-thiadiazol-2-yl)-isoindoline-1,3-dione (5m)
Yield: 81%; m.p.=187-191°C;
Anal.Calcd for $C_{17}H_{10}N_30_2SCl$, C,57.39; H,2.83; N,11.81%. Found: C,57.31; H,2.75, N,11.72%.
IR (cm^{-1}): 1736 (C=O), 1566 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 3.44 (s, 2H, CH_2), 6.89 – 7.65 (m, 8H, ArH),
^{13}C NMR (DMSO-d_6,δ /ppm): 40.87(CH_2), 123.43-142.89 (C=C &Ar-C), 160.59 (S-C=N), 164.68(S-C=N),170.41 (2xC=O).

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermalapparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatographyon silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR and ^{13}C NMRspectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba1108 (CHN) Elemental Analyzer.

Synthesis of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3):
General Procedure.
An equimolar mixture of phenyl acetic acid **(1)** (0.01 mol) and Thiosemicarbazide **(2)** (0.01 mol,) in phosphorous oxychloride (10 ml) was refluxed for about 2 hrs. The progress of reaction was monitored on TLC. Upon completion, the reaction mixture was quenched onto crushed ice. The resultant solution was further refluxed for 4hrs and filtered. The filtrate was neutralized with dilute KOH solution, to maintained pH 8-10, thus the product was precipitated out, was filtered, washed with water and purified by recrystallization from ethanolic water to yield **(3)**.
The physical characterization of synthesized compound**(3a-e)** was given in **Table I**.

Table-I
Physical data of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3)

Compounds	R	m.p. (°C)	Yield (%)
3a	4-OCH_3	191-95	78
3b	2-CH_3	210-13	71
3c	4-Cl	220-23	85
3d	2,4-dichloro	245-47	72
3e	H	214-17	69

Synthesis of 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-substituted-isoindoline-1,3-dione, (5)
General Procedure:
An equimolar mixture of compound **(3)** (0.01 mol) and phthalic anhydride **(4)** (0.01 mol) were fused (2 hrs). The progress of reaction was monitored on TLC. Upon completion, the reaction mixture was cooled to room temperature and quenched into cold water. The product

obtained was filtered, washed with water and purified by recrystallization from ethanolic water to yield desired product **(5)**.

The physical characterization of synthesized compound**(5a-o)**was given in **Table II**.

Table-II

Physical data of 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-substituted-isoindoline-1,3-dione (5a-o)

Compounds	R	R1	m.p. (°C)	Yield (%)
5a	4-OCH_3	4-CH_3	210-15	81
5b	2-CH_3	4-CH_3	205-09	78
5c	4-Cl	4-CH_3	221-25	71
5d	2,4-dichloro	4-CH_3	190-98	69
5e	H	4-CH_3	188-92	65
5f	4-OCH_3	3-NO_2	178-81	83
5g	2-CH_3	3-NO_2	194-98	75
5h	4-Cl	3-NO_2	203-06	76
5i	2,4-dichloro	3-NO_2	217-21	71
5j	H	3-NO_2	201-04	63
5k	4-OCH_3	H	169-73	78
5l	2-CH_3	H	172-76	71
5m	4-Cl	H	187-91	81
5n	2,4-dichloro	H	195-98	67
5o	H	H	175-79	72

Antimicrobial and antifungal activities

All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negativebacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using discdiffusion method[19, 20]. The zone of inhibition was measured in mm and the activity was compared withstandard drug. The antimicrobial data was given in **Table III**.

TABLE III:Antibacterial Activity of compound 5

Antibacterial Activity of compound 5				
Compounds	**Zone of inhibition (in mm)**			
	Gram Positive		**Gram negative**	
	S.aureus	**C.diphtheria**	**P.aeruginosa**	**E.coli**
5a	9	10	12	14
5b	8	12	11	16
5c	10	9	10	14
5e	8	13	14	17
5f	11	10	16	12
5g	14	21	23	14
5k	16	24	22	15
5l	17	22	20	18
5m	18	19	21	16
Ampicilintrihydrate	26	28	24	21
DMSO	0	0	0	0

* Diameter of the disc was 6mm;

Concentration of the compounds taken was about 100 µg/mL.

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