RESEARCH ARTICLE

Novel Synthesis, Physicochemical Characterization of 1,3,4-Oxadiazinoindole Derivatives for the Purpose of Antidepressant Activity

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ABSTRACT

The present study synthesized a series of 1,3,4-oxadiazinoindole moiety-containing compounds by combining MAOI's hydrazide moiety and tricyclic moiety having antidepressant activity. The formation of amino acid chloride from amino acids started the synthesis. Further, they were converted into amino acid hydrazide, and then amino acid hydrazones were prepared by reaction of amino acid hydrazide with isatin. Finally, cyclization was acted on hydrazone-containing compounds in the presence of cold H_2SO_4. Synthesized compounds are characterized and confirmed via mass spectroscopy, 1H-nuclear magnetic resonance strategies, fourier transform infrared spectroscopy, thin layer chromatography, and melting point. The compounds were evaluated for antidepressant activity.

Keywords: 1,3,4-oxadiazinoindole moiety, Tricyclic compounds, Hydrazide antidepressant.

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INTRODUCTION

Based on knowledge from the literature review, the monoamine oxidase inhibitors (MAOI) hypothesis does not absolutely explain the therapeutic activity of antidepressants nor does it make clear the pathophysiology of depression.[1,2]

It no longer justifies the gradual onset of motion because 4-6 weeks are required to set up healing efficacy. Moreover, the existing antidepressant drugs, including MAOI, TCA, SSRIs, SNRIs, and NSSA are not free from side effects. Notwithstanding those shortcomings, the MAOI hypothesis has provided the rationale for growing novel antidepressants with an extensive range of efficacy and safety in despair treatment.

The 1,3,4-oxadiazole[3] nucleus is a part of heterocyclic compounds showing various biological effects which include anti-Alzheimer, anti-convulsant, anti-cancer, anti-helminth, anti-HIV, anti-inflammatory, anti-microbial, insecticidal, pesticidal.[4,5] The indole ring moiety is the most critical heterocyclic unit found in obviously occurring compounds. The indole ring moiety has an exquisite structural range and an essential structural requirement in many pharmaceutical agents. Indoles, which are electron-rich nitrogen heterocyclic, have allured chemists because of their fascinating chemistry and diversity in their reactions.[6]

Indole ring and oxadiazole nucleus (both biologically active moieties) are combined to synthesize novel 1,3,4-oxadiazinoindole moiety-containing compounds showing more potent and safer effects for CNS disorders such as depression and convulsion etc. On the basis of the above principle, a series of 1,3,4-oxadizinoindole moiety-containing compounds has been synthesized, characterized, and evaluated for its antidepressant activity.

MATERIAL AND METHODS

L-type amino acids such as valine (1s), β-alanine (1t), serine, threonine, aspartic acid, ornithine, arginine, and alanine (1u-1z) were used as initial raw materials. Their purity was checked by M.P. and TLC. Other chemicals, such as thionyl chloride, hydrazine HCl, isatin, sulphuric acids, sodium hydroxide, acetic acid, ethanol, methanol, DMSO, DMF, Silica Gel-G, ammonia, acetone, benzene, toluene, hexane, chloroform, ethyl acetate, iodine, etc. were of laboratory grade reagents and used as received. These chemicals were procured from Loba-Chemie, Qualigens, Merck, and CDH.

Thin layer chromatography plates were performed with the usage of Silica Gel G and various mobile phase solvents. It was visualized in an Iodine/UV chamber.

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Experiment

Melting/boiling points were decided through open capillary tubes with the usage of Campbel MP Apparatus and had been uncorrected. λmax was recorded using DMSO on a UV-visible spectrophotometer (JASCO V-530) and reported in nm. FTIR spectra of all of the synthesized compounds have been scanned in a KBr disk on an FTIR spectrometer (JASCO V-5300) and reported in cm-1. 1H-NMR spectra were taken in dimethyl sulfoxide-d6 on an NMR Varian-Mercury YH-300 the usage of tetramethyl silane, and mass spectra were taken on MS-ESI (Shinadzu-2010 AT).

The procedure for the Novel compound for each step (Scheme 1) has been described.

A General Method of Synthesis of Compounds (Amino acid chlorides)[7-9]

In 0.05 moles of an amino acid (among 8 amino acids) was dissolved in 60–100 mL methanol. Thionyl chloride 3.63 mL (0.075 moles) was added dropwise to the solution in the round bottom flask for 15 minutes. A reflux condenser and calcium chloride guard tube were fixed on the RBF. The reaction was refluxed for 8–12 hours. Thin-layer chromatography was applied to monitor the reaction. The excess thionyl chloride was removed under a vacuum to afford a dry solid. After that, the crude amino-acid chloride was used directly without any purification for further steps.

The compounds (2s to 2z) were synthesized as per the above procedure.

A General Method of Synthesis of Compounds (Amino acid hydrazides)[0-1]

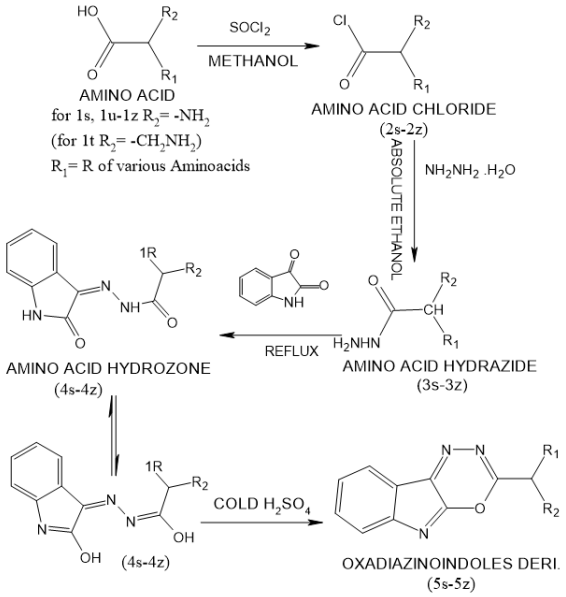
Hydrazine hydrate (0.03 moles, 80%) and amino-acid chloride (2s-2z) (0.03 moles) in dry methanol/ethanol were moved for one hour and refluxed for 10 to 15 hours on a rotamental. A reflux condenser and calcium chloride guard tube were fixed on the RBF. Thin-layer chromatography was used for reaction monitoring. The contents were cooled. The obtained residue was filtered and washed with cold ethanol/methanol. The excess solvent (ethanol/methanol) is distilled out. The residual crude was dried and recrystallized process from methanol.

The compounds (3s to 3z) were synthesized as per the above procedure.

A General Method of Synthesis of Compounds (Amino acid hydrazones)[1-17]

Amino-acid hydrazides 3s-3z (0.02 moles) and isatin 2.94 g (0.02 moles) in 30 to 50 mL dry methanol/absolute ethanol were stirred for 2 hours. A few mL of glacial acetic acid were added to it. The color of the content were changed to red/yellow and continued reflex for 10 to 15 hours on a rotamental. Thin-layer chromatography was used for reaction monitoring. The contents were cooled, and the obtained product was filtered with cold methanol. The excess solvent (ethanol/methanol) is distilled out. The residual crude was dried, and recrystallized from methanol.

The compounds (4s-4z) were synthesized as per the above procedure.



Scheme 1: Synthesis of 1.3.4-Oxadiazinoindole derivatives

A General Method of Synthesis of 1,3,4-oxadiazinoindole Moiety Containing Compounds[13,16,18-21]

Amino acid hydrazone (4s-4z) (0.01 moles) was mixed with a small amount to cold conc. H_2SO_4 (8–12 mL) in 100 mL RBF. The reaction combination was left around RT at night time on a magnetic stirrer. Thin-layer chromatography was applied to monitor the reaction. After this, the reaction combination was transferred into cold ice water and became neutral with NH_3 solution to gain compound, which was washed with cold methanol by filtration. The residual crude compound was dried, followed by the recrystallization process from dimethyl formamide-water.

The compounds (5s-5z) were synthesized as per the above procedure.

RESULT

Spectral Characteristics[22-25]

The FTIR spectra of 1,3,4-oxadiazinoindole intermediates[26] (2s-4z) and 1,3,4-oxadiazinoindole containing compounds (5s-5z) exhibited several commonplace specific absorption frequencies in cm^{-1} and NMR positions of signals in ppm:

2-amino-3-methylbutanoyl chloride (2s)

IR (KBr): 769 (C-Cl stretching), 1743 (C=O stretching), 1457–1587 (C=C ar stretching), 2976 (aliphatic C-H stretching), 3435 (N-H amine stretching).

3-aminopropanoyl chloride (2t)

IR (KBr): 673 (C-Cl stretching), 1716–1749 (C=O stretching), 2847 (aliphatic C-H stretching), 3126 (N-H stretching).

L-asparaginoyl chloride (2w)

IR (KBr): 680–780 (C-Cl stretching), 1640–1670 (C=O stretching), 2860–2960 (aliphatic C-H stretching), 3410 (N-H) Stretching.

Table 1: Physico-chemical characteristics of the synthesized compounds

S. No.	*Compound*	*R_1*	*R_2*	*MP (ºC)*	*Yield (%)*	*Rf value*
1	2s	$-CH(CH_3)_2$	$-NH_2$	204	94.3	0.51
2	2t	-H	$-CH_2NH_2$	159	91.7	0.64
3	2u	$-CH_2OH$	$-NH_2$	59	89.0	0.70
4	2v	$-CH(OH)CH_3$	$-NH_2$	56	90.2	0.49
5	2w	$-CH_2CONH_2$	$-NH_2$	142	92.5	0.55
6	2x	$-(CH_2)_3NH_2$	$-NH_2$	104	95.1	0.63
7	2y	$-(CH_2)_3NHC(NH_2)=NH$	$-NH_2$	>350	88.6	0.59
8	2z	$-CH_3$	$-NH_2$	160	87.8	0.61
9	3s	$-CH(CH_3)_2$	$-NH_2$	175	84.7	0.60
10	3t	-H	$-CH_2NH_2$	183	70.2	0.63
11	3u	$-CH_2OH$	$-NH_2$	228	75.5	0.70
12	3v	$-CH(OH)CH_3$	$-NH_2$	225	80.4	0.58
13	3w	$-CH_2CONH_2$	$-NH_2$	>350	78.6	0.61
14	3x	$-(CH_2)_3NH_2$	$-NH_2$	274	81.1	0..67
15	3y	$-(CH_2)_3NHC(NH_2)=NH$	$-NH_2$	>350	79.8	0.69
16	3z	$-CH_3$	$-NH_2$	168	82.9	0.72
17	4s	$-CH(CH_3)_2$	$-NH_2$	315	38.8	0.80
18	4t	-H	$-CH_2NH_2$	260	56.8	0.73
19	4u	$-CH_2OH$	$-NH_2$	>350	40.7	0.67
20	4v	$-CH(OH)CH_3$	$-NH_2$	>350	45.5	0.71
21	4w	$-CH_2CONH_2$	$-NH_2$	>350	52.0	0.72
22	4x	$-(CH_2)_3NH_2$	$-NH_2$	>350	60.2	0.76
23	4y	$-(CH_2)_3NHC(NH_2)=NH$	$-NH_2$	>350	47.3	0.65
24	4z	$-CH_3$	$-NH_2$	>350	57.3	0.63
25	5s	$-CH(CH_3)_2$	$-NH_2$	>350	40.6	0.67
26	5t	-H	$-CH_2NH_2$	>350	22.4	0.54
27	5u	$-CH_2OH$	$-NH_2$	>350	35.5	0.62
28	5v	$-CH(OH)CH_3$	$-NH_2$	>350	55.6	0.58
29	5w	$-CH_2CONH_2$	$-NH_2$	>350	43.3	0.71
30	5x	$-(CH_2)_3NH_2$	$-NH_2$	>350	51.2	0.66
31	5y	$-(CH_2)_3NHC(NH_2)=NH$	$-NH_2$	>350	63.5	0.63
32	5z	$-CH_3$	$-NH_2$	>350	38.4	0.59

(S)-2,5-diaminopentanoyl chloride (2x)

IR (KBr): Stretching, 620–700 (C-Cl stretching), 1770 (C=O stretching), 2810–2920 (aliphatic C-H stretching), 3470–3330 (N-H)

L-argininoyl chloride (2y)

IR (KBr): 630–740 (C-Cl stretching), 1720 (C=O stretching), 2890–2950 (aliphatic C-H stretching), 3390–3490 (N-H) stretching.

L-alaninoyl chloride (2z)

IR (KBr): 690 (C-Cl stretching), 2910 (aliphatic C-H stretching), 1780 (C=O stretching), 3450 (N-H) stretching.

2-amino-3-methylbutanehydrazide (3s)

IR (KBr): 1138 (N-N stretching), 1473–1614 (C=C ar stretching), 1738 (C=O stretching), 2978 (aliphatic CH stretching), 3125 (N-H stretching), 3503 (N-H amine stretching).

3-aminopropanehydrazide (3t)

IR (KBr): 1103 (N-N stretching), 2814–2961 (aliphatic CH stretching), 1682 (C=O stretching), 3541 (N-H amine stretching), 3275 (N-H stretching).

(S)-3-amino-4-hydrazinyl-4-oxobutanamide (3w)

IR (KBr): 1120 (N-N stretching), 1770 (CONH stretching), 2870 (aliphatic C-H stretching), 3190 (N-H stretching), 3410–3490 (N-H amine stretching).

(S)-2,5-diaminopentanehydrazide (3x)

IR (KBr): 1111 (N-N stretching), 1750 (CONH stretching), 2910 (aliphatic C-H stretching), 3220 (N-H stretching), 3402–3470 (N-H amine stretching).

(S)-1-(4-amino-5-hydrazinyl-5-oxopentyl)guanidine (3y)

IR (KBr): 1140 (N-N stretching), 1710 (CONH stretching), 2930 (aliphatic C-H stretching), 3290 (N-H stretching), 3400–3465 (N-H amine stretching).

(S)-2-aminopropanehydrazide (3z)

IR (KBr): 1122 (N-N stretching), 1670 (C=O stretching), 2820–2960 (aliphatic CH stretching), 3265 (N-H stretching), 3550 (N-H amine stretching).

(Z)-2-amino-3-methyl-N'-(2-oxoindolin-3-ylidene) butanehydrazide(4s)

IR (KBr): 1091 (N-N stretching), 1462–1541 (C=C ar stretching), 1720 (C=O stretching), 1614 (C=N stretching), 3009 (ar C-H stretching), 2890 (aliphatic-CH stretching), 3277 (N-H stretching).

(Z)-3-amino-N'-(2-oxoindolin-3-ylidene) propanehydrazide(4t)

IR (KBr): 1097 (N-N stretching), 1684 (C=O stretching), 1466–1591 (C=C ar stretching), 2924 (aliphatic C-H stretching), 3358 (N-H stretching), 3163 (C-H ar stretching), 3564 (O-H stretching).

(Z)-3-amino-4-oxo-4-(2-(2-oxoindolin-3-ylidene) hydrazinyl)butanamide (4w)

IR (KBr): 1077 (N-N stretching), 1465–1575 (C=C ar stretching), 2884 (aliphatic C-H stretching), 1674 (C=O stretching), 3133 (C-H ar stretching), 3348 (N-H stretching).

(Z)-2,5-diamino-N'-(2-oxoindolin-3-ylidene) pentanehydrazide (4x)

IR (KBr): 1117 (N-N stretching), 1695 (C=O stretching), 1485–1566 (C=C ar stretching), 2879 (aliphatic C-H stretching), 3102 (C-H ar stretching), 3333 (N-H stretching).

(Z)-1-(4-amino-5-oxo-5-(2-(2-oxoindolin-3-ylidene) hydrazinyl)pentyl)guanidine (4y)

IR (KBr): 1094 (N-N stretching), 1690 (C=O stretching), 1470–1515 (C=C ar stretching), 3203 (C-H ar stretching), 2924 (aliphatic C-H stretching), 3408-3370 (N-H stretching).

(Z)-2-amino-N'-(2-oxoindolin-3-ylidene) propanehydrazide (4z)

IR (KBr): 1066 (N-N stretching), 1465–1558 (C=C ar stretching), 1714 (C=O stretching), 3120 (C-H ar stretching), 2866 (aliphatic C-H stretching), 3418 (N-H stretching).

1-([1,3,4]Oxadiazino[6,5-b]indol-3-yl)-2-methylpropan-1-amine(5s)

IR (KBr): 1211 (C-O-C stretching), 1340 (C-N stretching), 1614 (C=N stretching), 1462–1541 (C=C ar stretching), 2828 (aliphatic C-H stretching), 3094 (C-H ar stretching), 3177 (N-H amine stretching).

UV (DMSO) λ_{max}: 263 nm

^{1}H NMR (DMSO-d_6): 8.76 (b, 2H, -NH_2), 7.43-7.51 (m, 4H, ArH), 2.4 and 3.2 (d, DMSO impurity), 2.58 (m, 1H, C-CH-N), 1.76 (m, 1H, C-CH-C), 0.98 (s, 3H-3H, Dimethyl)

MS (ESI) m/z (rel. abundance): 242.12 (100.0%), 243.12 (14.1%)

2-([1,3,4]Oxadiazino [6,5-b]indol-3-yl) ethanamine (5t)

IR (KBr): 1113 (C-O-C stretching), 1456-1614 (C=C ar stretching), 1338 (C-N stretching), 1614 (C=N stretching), 2359 (N-H bending), 3173 (C-H ar stretching), 3564 (N-H amine stretching).

UV (DMSO) λ_{max}: 264 nm

^{1}H NMR (DMSO-d_6): 10.45 (b, 2H, -NH), 7.5-7.0 (m, 4H, ArH), 2.49 and 3.33 (b, DMSO impurity), 1.9 (t, HH, C-CHH-C), 1.14 (m, HH, C-CHH-N).

MS (ESI) m/z (rel. abundance): 214.09 (100.0%), 215.09 (11.9%)

2-([1,3,4]oxadiazino[6,5-b]indol-3-yl)-2-aminoethan-1-ol (5u)

UV (DMSO) λ_{max}: 265 nm

^{1}H-NMR (DMSO-d_6): 8.96 (b, 2H, -NHH), 7.3-7.81 (m, 4H, ArH), 4.94 (t, 1H, -OH), 4.17 (s, 1H, Ha of –CH_2-), 3.92 (s, 1H, Hb of–CH_2-), 2.5 and 3.33 (b, DMSO impurity), 2.76 (m, 1H, C-CH-N).

MS (ESI) m/z (rel. abundance): 230.08 (100.0%), 231.08 (11.9%)

1-([1,3,4]oxadiazino[6,5-b]indol-3-yl)-1-aminopropan-2-ol (5v)

UV (DMSO) λ_{max}: 265 nm

^{1}H NMR (DMSO-d_6): 8.96 (b, HH, -NHH), 7.3-7.81 (m, 4H, Ar-H), 5.37 (d, 1H, -OH), 3.9 (S, 1H, C-CH-O), 2.5 and 3.33 (b, DMSO impurity), 2.66 (m, 1H, C-CH-N), 1.16 (d, 3H, -CH_3).

MS (ESI) m/z (rel. abundance): 244.10 (100.0%), 245.10 (13.0%),

3-([1,3,4]oxadiazino[6,5-b]indol-3-yl)-3-aminopropanamide (5w)

IR (KBr): 1093 (C-O-C stretching), 1456–1615 (C=C ar stretching), 1345 (C-N stretching), 1664 (C=N stretching), 2881 (aliphatic C-H stretching), 2339 (N-H bending), 3183 (C-H ar stretching), 3515–3576 (N-H amine stretching).

UV (DMSO) λ_{max}: 266 nm

^{1}H NMR (DMSO-d_6): 8.76 (b, 2H, -NH_2), 7.3–7.81 (m, 4H, ArH), 7.03 (s, HH, -$CONH_2$), 3.08 (m, 1H, C-CH-N), 2.81 (s, 1H, Ha of–CH_2-), 2.56 (s, 1H, H_b of –CHH),

MS (ESI) m/z (rel. abundance): 257.09 (100.0%), 258.09 (13.0%)

1-([1,3,4]oxadiazino[6,5-b]indol-3-yl)butane-1,4-diamine (5x)

IR (KBr): 1001 (C-O-C stretching), 1459–1584 (C=C ar

stretching), 1298 (C-N stretching), 1616 (C=N stretching), 2911 (aliphatic C-H stretching), 2354 (N-H bending), 3037 (C-H ar stretching), 3567 (N-H amine stretching).
UV (DMSO) λ_{max}: 263 nm
^{1}H NMR (DMSO-d_6): 8.76 (b, HH, -NHH), 7.3-7.81 (m, 4H, Ar-H), 2.66 (m, 1H, C-CH-N), 2.63 (m, HH, C-CHH-N), 1.78 (m, HH, C-CHH-C), 1.51 (m, HH, C-CHH-C), 1.5 (b, 2H, NH_2).
MS (ESI) m/z (rel. abundance): 257.13 (100.0%), 258.13 (14.1%)

1-(4-([1,3,4]oxadiazino[6,5-b]indol-3-yl)-4-aminobutyl) guanidine (5y)

IR (KBr): 1079 (C-O-C stretching), 1495–1549 (C=C ar stretching), 1289 (C-N stretching), 1638 (C=N stretching), 2925 (aliphatic C-H stretching), 2388 (N-H bending), 3007 (C-H ar stretching), 3410–3516 (N-H amine stretching).
UV (DMSO) λ_{max}: 264 nm
^{1}H NMR (DMSO-d_6): 8.76 (b, 2H, -NH_2), 7.84 (s, 1H, =NH), 7.3–7.81 (m, 4H, ArH), 6.63 (s, 2H, -NHH guanidine) 3.34 (m, HH, C-CHH-N), 2.66 (m, 1H, C-CH-N), 2.5 (b, 1H, C-NH-C), 1.78 (m, HH, C-CHH-C), 1.51 (m, HH, C-CHH-C).
MS (ESI) m/z (rel. abundance): 299.15 (100.0%), 300.15 (15.1%)

1-([1,3,4]oxadiazino[6,5-b]indol-3-yl)ethan-1-amine (5z)

IR (KBr): 1120 (C-O-C stretching), 1466–1581 (C=C ar stretching), 1364 (C-N stretching), 1688 (C=N stretching), 3133 (C-H ar stretching), 2347 (N-H bending), 3454 (N-H amine stretching).
UV (DMSO) λ_{max}: 264 nm
^{1}H NMR (DMSO-d_6): 8.76 (b, 2H, -NH_2), 7.3–7.81 (m, 4H, ArH), 2.5 and 3.33 (b, DMSO impurity), 2.86 (m, 1H, C-CH-N), 1.19 (m, 3H, CH_3).
MS (ESI) m/z (rel. abundance): 214.09 (100.0%), 215.09 (11.9%)

DISCUSSION

The synthesis of novel compounds is carried out from various amino acids. A sequence of synthetic reactions such as the Halo-De-Hydroxylation (Nucleophilic Substitution) reaction, Schotten-Baumann reaction, nucleophilic addition reaction, and finally cyclization (Cyclo-De-Hydroxylation) reaction are involved in the process. Accordingly, one by one 1,3,4-oxadiazinoindole moiety-containing compounds (5s-5z) were synthesized.

The synthesized compounds (5s-5z) occurred as brownish-coloured solid. Yield was varying from 22.4 to 63.5%.

All novel compounds were developed and characterized by sharp M.P., chromatographic methods, UV spectroscopy, FTIR spectroscopy, proton-NMR spectroscopy, and mass spectroscopy for the conformation of chemical structural design. The spectrums of synthesized compounds show peaks at the expected wavelength.

CONCLUSION

This study attempts to synthesize novel compounds containing the 1,3,4-oxadiazinoindole moiety (5s-5z) for evaluation as potent antidepressants with fewer or no side effects.

Physicochemical characterization of synthesized novel compounds was confirmed via sharp melting points, TLC, and spectral analysis by FTIR, ^{1}H-NMR, and MS spectral analysis. The purity and homogeneity of novel compounds are confirmed.

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REFERENCE

1. Singh C, Yashwant, Gupta AK, Garg V. Formulation Development and Evaluation of Divalproex Sodium Extended-release Tablets. International Journal of Drug Delivery Technology. 2022; 12(4):1769-1773. DOI: 10.25258/ijddt.12.4.46
2. Jawad MA, Al-Terehi MN, Kadhim AJ. Effect of Antidepressants Medications in Glycemic State of Depression Disorders Patients. International Journal of Pharmaceutical Quality Assurance. 2021; 12(3):217-219. DOI: 10.25258/ijpqa.12.3.10
3. Mosa, IA, Rumez, R.M. and Tomma, JH. Synthesis, Characterization and Screening their Antibactrial Activity of some New Oxazepine and Diazepine Compounds Containing 1,3,4-Oxadiazole Ring Derived from L-Ascorbic Acid. International Journal of Drug Delivery Technology, 2019; 39(3): 321-333. DOI: 10.25258/ijddt.v9i3.1
4. Patil *AS, Shrinivas KM*. An Overview: 1, 3, 4- oxadiazole and its uses. *Asian Journal of Research in Chemistry. 2021; 14(5):389-392.* DOI: *10.52711/0974-4150.2021.00066*
5. *Bala S, Kamboj S, Kumar A*. Heterocyclic 1,3,4-oxadiazole compounds with diverse biological activities. A Comprehensive Review. Journal of Pharmacy Research. 2010; 3(12), 2993- 2997.
6. Banerji A, Saha R, Gupta M, Banerji J, Das M, Subhose V, Prasad PVV, Synthesis of 3,3′- Di-indolylmethanes under mild conditions by Microwave Irradiation Mediated Reactions of Indoles with *C, N*-Diaryl nitrones: *Asian Journal of Research in Chemistry. 2021; 14(4):247-254.* DOI: *10.52711/0974-4150.2021.00042*
7. *Furniss, BS, Hannaford AJ, Smith PW, Tatchell AR.* Vogel's Textbook of Practical Organic Chemistry, Pearson Education Ltd. South Asia, 5th edi. 1989; 1156.
8. *Shi W, Qian X, Song G, Zhang R, Li R.* Syntheses and insecticidal activities of novel 2-fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadiazoles. *Journal of Fluorine Chemistry.* 2000; 106, 173-179. DOI: 10.1016/S0022-1139(00)00323-7
9. *Shah, JB, Patel PM, Patel SK, Patel KC,* Synthesis and physic-chemical properties of aromatic polyesters containing S-triazine rings in the main chain. *Indian Journal of Chemistry.* 2001; 40B, 729-734
10. Desai KG, Raval JP, Desai KR, Neat reaction technology for the synthesis of 4-oxo-thiazolidines derived from 2-SH-benzothiazole and antimicrobial screening of some synthesized 4-thiazolidinones. Journal of the Iranian Chemical Society. 2006; 3(3), 233-24. DOI: 10.1007/BF032472
11. *Singh RP, Singh CR, Tripathi SP. Synthesis and Antifungal activity of new oxadiazoles, Phthalazines and Indolines.* Indian Journal of Heterocyclic Chemistry. 2006, 15(2), 345-348
12. *Bhatt PV, Patel PM,* Synthesis of 5*H*-dibenzo(*b,f*)azepine-5-

carboxylic acid [3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amide from 5*H*-dibenzo(*b,f*) azepine-5-carbonyl chloride. *Indian Journal of Chemistry.* 2005; 44B, 2082-2086

13. *Sarangapani M, Reddy VM.* Synthesis and Screening of Isatin-3-[N2-(alkoxyethyloxy)acetyl]hydrazones. *Indian drugs* 1999; 36 (6) 357-362
14. *Pawar H,* Verma RS, Srivastava VK, Kumar A. Synthesis of some substituted azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-*b*]indoles as prospective antimicrobial agents. *Indian Journal of Chemistry*, 2006; 45B, 2099-2104.
15. *Pandeya SN, Ayyannan SR,* Synthesis of isatin semicarbazones as novel anticonvulsants-role of hydrogen bonding. *J Pharm Pharmaceut Sci*. 2002; 5(3) 266-271
16. *Pandeya SN, Raja AS, Nath G.* Synthesis and antimicrobial evaluation of some 4-or 6-chloroisatin derivatives. *Indian Journal of Chemistry.* 2006; 45B, 494-499
17. *Nizamuddin, Khan MH, Alauddin S, Haque R.* Synthesis and fungicidal activity of some 2- arylamino-1,3,4-thiadiazino[6,5-*b*] indoles and 2-aryl- 1,3,4-oxadiazolo-[2,3-*c*]-1,2,4- triazino [5,6-*b*] indoles. *Indian Journal of Chemistry.* 1999; 38B, 501-504
18. *Tiwari S, Tiwari N, Agarwal T, Khan MH, Nizamuddin.* Synthesis of Some 2-Substituted-1, 3, 4-thiadiazolo (2, 3-c) 1, 2, 4-triazino (5, 6-b) indoles as Fungicides. *Indian Journal of Chemistry.* 1995; 34B, 1010-1012
19. *Mangilalah K, Reddy PR, Rao RB.* Synthesis and antibacterial activity of some novel spiro [3*H*-indole-3,5'-[1 ,3,4] oxadiazolo[3,2-c]thiazole]-2(1*H*)-ones and [1,3,4]oxadiazino -[6,5-b]indoles containing 1, 8 naphthyridine moiety. I*ndian Journal of Chemistry.* 1999; 38B, 1203-1207
20. *Mangilalah K, Babu HR, Rao RB,* Synthesis and antibacterial activity of some new [1,3,4] oxadiazino [6,5-*b*] indoles and acetophenonehydrazones containing 1,8- naphthyridine moiety *Indian Journal of Chemistry.* 2001; 40B, 1270-1274
21. *Mulwad VV, Chaskar AC, Shriodkar* JM. Synthesis and screening of 1, 3, 4-oxadiazinoindolinone and *s*-triazole derivatives of pyranobenzopyran. *Indian Journal of Chemistry.* 2005; 44B, 1465-1469
22. *Silverstein RM, Webster FX.* "Spectrometric Identification of Organic Compounds", 6th edi. 1997, John Wiley & Sons Inc, Hoboken, New Jersey, U.S., 2-216
23. Skoog DA, West DM, Holler FJ, Crouch SR. Fundamentals of Analytical Chemistry, Thomson Brooks/Cole, 8th Edi. Reprint 2004, 707-740
24. Willian K. Organic Spectroscopy, Palgrave, New York, 3rd Edi, reprint 2005, 58-325
25. Shriner RL, Hermann CKF, Morrill TC, Curtin DY, Fuson RC, "The systematic Identification of Organic Compounds" 8th edi. 2004, John Wiley & Sons Inc, Hoboken, New Jersey, U.S., 136-229
26. Patel V, Patel M, Velhal N, Parmar K, Patel J. Analytical Method Development and Validation for the Spectrophotometric Estimation of Hipuuric Acid Prodrug (Methenamine Hippurate). International Journal of Pharmaceutical Quality Assurance. 2023; 14(1):76-80. DOI: 10.25258/ijpqa.14.1.13