RESEARCH PAPER

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

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ABSTRACT

The present paper is based on the combination of MAOI hydrazide moiety and tricyclic antidepressant moiety. This combination investigates new compounds as 1,3,4-oxadiazinoindole derivatives to find potent and safer antidepressants. Synthesis of 1,3,4-oxadiazinoindole derivatives are started from various animoacids. The sequence of synthesis reactions such as benzoylation reaction, Halo-De-hydroxylation (Nucleophilic substitution reaction), Schotten-Baumann reaction, Nucleophilic addition and finally cyclization reaction (Cyclo-De-Hydroxylation) are involved. Synthesized compounds are characterized via melting point, TLC, FT infrared spectroscopy, 1H-NMR, and mass spectroscopy techniques. All compound's structures are confirmed.

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

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INTRODUCTION

1,3,4-Oxadiazole[1] nucleus is one of those heterocyclic compounds. It exhibits various biological effects such as antiepileptic, antimicrobial, antitumor, anthelminthic, anti-HIV, antialzheimer, antiinflammatory, insecticidal, and pesticidal.[2,3]

The indole ring is an important heterocyclic unit which present in naturally occurring compounds. The indole ring has become an important chemical structural requirement in many APIs, having wonderful structural diversity. Indole, an electron-rich nitrogen heterocycles, have allured chemists because of their fascinating chemistry and diversity in their reactions.[4]

Both biologically active moieties (indole ring and Oxadiazole) are combined for novel 1,3,4-oxadiazinoindole derivatives, which could be more potent and safer drugs for central nervous system (CNS) disorders[5] such as depression, convulsion, etc. On the basis of the above paragraph. So in this paper, 1,3,4-oxadiazinoindole derivatives have been developed and screened for antidepressant activity.[6]

MATERIALS AND METHODS

L-type of amino acids such as glycine, histidine, isoleucine, leucine, phenylalanine, tryptophan, tyrosine (1a-1d, 1f-1h) and Methionine (0e) were used as initial raw materials. Its purity was checked by thin layer chromatography (TLC). Other chemicals were used in laboratory grade reagents such as hydrazine HCl, thionyl chloride, isatin, dimethyl sulfoxide (DMSO), DMF, Silica Gel-G etc. as received. These chemicals were procured from following companies such Loba-Chemie, Qualigens, Merck and CDH.

The synthesis procedure of an 1,3,4-oxadiazinoindole derivatives are shown in Figure 1. Melting/boiling points were measured in open capillary tubes of the Campbel MP equipment Method and are not corrected. TLC plates were prepared using SilicaGel G plates and various mobile phase solvents. It was visualized in an iodine chamber or UV chamber. λ_{max} was recorded using DMSO on a UV-visible spectrophotometer (JASCO V-530) and reported in nm. Fourier transform infrared spectroscopy (FTIR) spectra of the novel compounds were scanned in a potassium bromide disk on an FTIR spectrometer (JASCO V-5300) and reported in a reciprocal wavelength. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken in DMSO-d_6 solution by a "FTNMR Varian-Mercury YH-300" using tetramethyl silane as internal standard and mass spectrum by an MS-ESI (Shinadzu 2010 AT).

Experiment

A general method of synthesis of Compound [(2-(benzamido)-4-(methylthio)butanoic acid] (1e)[7,8]

Dissolved 7.46 g (0.05 mol) of DL-Methionine in 40 mL of 10% sodium hydroxide solution in a conical flask; cooled the

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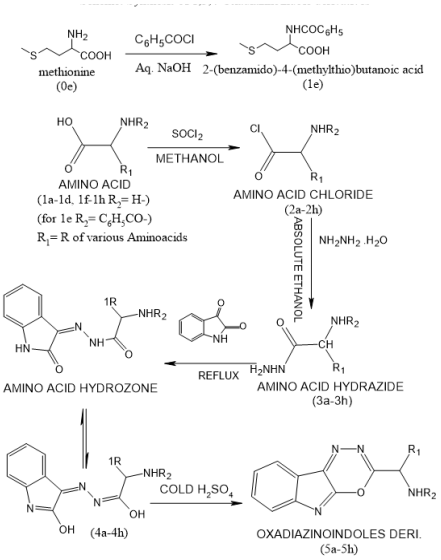


Figure 1: Synthesis of 1,3,4-Oxadiazinoindole derivatives

resulting solution in an ice bath. Added 5.8 mL (0.05 mol) of benzoyl chloride in five portions in the previously cold amino acid solution with regular stirring over a period of 2 hours. Continued stirring for three hours so as to complete the reaction and checked by TLC. The reaction was completed after two hours. The reaction contents were transferred into a beaker and rinsed the conical flask with water. Placed some crushed ice in the solution and acidified the contents by cons. HCl dropwise and carefully with regular stirring to the mixture is become acidic. The resulting crystalline precipitate of benzoyl-methionine was calm on the Buckner funnel, washed with cold water, and drained well with the help of an inverted glass stopper. And benzoic acid was extracted with 55 mL of CCl_4. The resulting content was filtered and washed and the obtained product was on the filter with 20 mL of carbon tetrachloride. The dried product was recrystallized with water.

A general method of synthesis of compounds (Amino acid chlorides)[9-11]

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 over a period of 15 minutes. RBF was set up with a condenser and a calcium chloride guard-tube. The reaction was reflux for 12 hours. Monitoring of the reaction was done by thin layer chromatography. The excess thionyl chloride and solvent were 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 (2a[12] to 2h) were synthesized as per the above procedure.

A general method of synthesis of compounds (Amino acid hydrazides)[13-15]

Amino acid chloride (2a-2h) (0.03 moles) and hydrazinehydrate (0.03 moles, 80%) in dry methanol/ pure ethanol were stirred for one hour. It was refluxed for 10–15 hours on a rotamental. Thin-layer chromatography was used for monitoring the reaction. The contents were cooled. The obtained product was filtered, and washed, with cold ethanol/methanol. Excess of solvent (methanol or ethanol) distilled out. The crude product was dried and purified by the process of recrystallization from methanol.

The compounds (3a to 3h) were synthesized as per the above procedure.

A general method of Synthesis of compounds (Amino acid hydrazones)[16-20]

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

The compounds (4a-4h) were synthesized as per the above procedure.

A general method of synthesis of compounds (1,3,4-oxadiazinoindole derivatives)[13,16,21-24]

Amino acid hydrazone (4a-4h) (0.01 moles) was mixed with a small amount to cold conc. H_2SO_4 (8–12 mL) in 100 mL RBF. Reaction content was kept at RT for over the night on magnetic stirrer. TLC was used for monitoring reaction. After this, reaction content was transferred into cold ice water then neutralized by liquid NH_3 solution to gain solid mass which was filtered, and washed by cold methanol. The residual crude was dried, purified and recrystallized from dimethylformamide-water.

Compounds (5a-5h) were synthesized as per the above procedure

RESULTS

The physiochemical properties of 1,3,4-oxadiazinoindole intermediates (1e, 2a-4h) and 1,3,4-oxadiazinoindole derivatives(5a-5h) show in Table 1.

Spectral characteristics[25-28]

The FTIR spectra of 1,3,4-oxadiazinoindole intermediates (2a-4h) and 1,3,4-oxadiazinoindole derivatives (5a-5h) exhibited many common absorption frequencies (cm^{-1}):

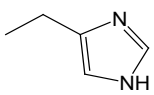
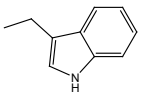
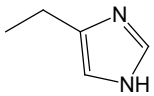
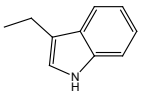
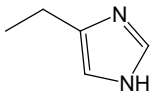
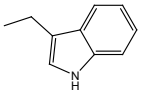
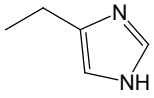
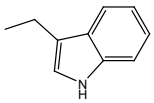
2-(benzamido)-4-(methylthio)butanoic acid(1e)

- IR (KBr) ν(cm^{-1}): 3333 (O-H str), 3210 (NH str), 3100 (Ar. C-H str), 2922 (alip-CH str), 1732 (C=O str), 1631(CONH stretching), 1575-1444 (C=C ar.str), 1219 (C-S-C str).

2-(benzamido)-4-(methylthio)butanoyl chloride(2e)

- IR (KBr)ν(cm^{-1}): 3333 (O-H str), 3100 (C-H ar str), 2922 aliphatic-CH str), 1732 (C=O str), 1631 (CONH str) 1575-1444 (C=C ar str), 1219 (C-S-C str).

Table 1: Physicochemical characteristic of the synthesized derivatives

S. No.	*Compound*	*R_1*	*R_2*	*M.P. (ºC)*	*Yield (%)*	*Rf value*
1	1e	-	-	151	73.3	0.64
2	2a	-H	-H	166	96.3	0.44
3	2b		-H	215	86.4	0.58
4	2c	$-CH(CH_3)C_2H_5$	-H	105	94.3	0.66
5	2d	$-CH_2CH(CH_3)_2$	-H	220	96.4	0.69
6	2e	$-CH_2CH_2SCH_3$	$-COC_6H_5$	243	84.7	0.57
7	2f	$-CH_2-C_6H_5$	-H	92	93.4	0.50
8	2g		-H	181	89.1	0.67
9	2h	$-CH_2-C_6H_4-OH$	-H	204	94.6	0.47
10	3a	-H	-H	171	87.0	0.68
11	3b		-H	191	88.1	0.66
12	3c	$-CH(CH_3)C_2H_5$	-H	186	77.5	0.64
13	3d	$-CH_2CH(CH_3)_2$	-H	251	85.3	0.62
14	3e	$-CH_2CH_2SCH_3$	$-COC_6H_5$	212	84.7	0.46
15	3f	$-CH_2-C_6H_5$	-H	262	88.5	0.65
16	3g		-H	280	74.3	0.74
17	3h	$-CH_2-C_6H_4-OH$	-H	150	71.34	0.63
18	4a	-H	-H	241	47.5	0.75
19	4b		-H	>360	81.3	0.7
20	4c	$-CH(CH_3)C_2H_5$	-H	355	37.7	0.69
21	4d	$-CH_2CH(CH_3)_2$	-H	275	59.3	0.74
22	4e	$-CH_2CH_2SCH_3$	$-COC_6H_5$	>360	66.6	0.59
23	4f	$-CH_2-C_6H_5$	-H	>360	34.0	0.74
24	4g		-H	305	38.3	0.64
25	4h	$-CH_2-C_6H_4-OH$	-H	340	23.8	0.68
26	5a	-H	-H	>350	24.9	0.49
27	5b		-H	>350	74.3	0.58
28	5c	$-CH(CH_3)C_2H_5$	-H	>350	47.7	0.68
29	5d	$-CH_2CH(CH_3)_2$	-H	>350	72.8	0.44
30	5e	$-CH_2CH_2SCH_3$	$-COC_6H_5$	282	48.3	0.64
31	5f	$-CH_2-C_6H_5$	-H	>350	72.4	0.77
32	5g		-H	>350	53.7	0.69
33	5h	$-CH_2-C_6H_4-OH$	-H	>350	44.6	0.61

2-(benzamido)-4-(methylthio)butanehydrazide(3e)

- IR (KBr)ν(cm^{-1}): 3279 (N-H amine str), 3155 (N-H str), 3055 (C-H ar str), 2922 (aliph CH str), 1745(C=O str), 1633 (CONH stretching), 1435-1575 (C=C ar str), 1217 (C-S-C str), 1093 (N-N stretching).

(Z)-2-(benzamido)-4-(methylthio)-N'-(2-oxoindolin-3-ylidene)butanehydrazide(4e)

- IR (KBr)ν(cm^{-1}): 3279 (N- H amine str), 3155 (N- H str), 3055 (C- H ar str), 2922 (aliph C-H stretching), 1730(C=O str), 1618 (C= N str), 1435-1575 (C= C ar str), 1093 (C- S-C str), 1018 (N-N stretching).

([1,3,4]Oxadiazino[6,5-b]indol-3-yl)methanamine(5a)

- IR (KBr)ν(cm^{-1}): 3537 (N- H amine str), 3169 (C- H ar str), 1620 (C=N str), 1481-1550 (C=C ar str), 1336 (C-N str), 1201 (C-O-C stretching).
- UV (DMSO) λ_{max}: 265nm
- ^{1}H NMR (δ ppm, DMSO-d6): 10.2-10.87 (b, 2H, -NH), 7.37-6.8 (m, 4H, ArH), 3.787 (t, 2H, -CH2-), 2.492 and 3.33 (b, DMSO impurity).
- MS (ESI) m/z (rel. abundance): 200.07 (100.0%), 201.07 (10.8%)

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

- IR (KBr)ν(cm^{-1}): 3626 (N- H amine str), 3294 (N- H ar str), 3074 (C- H ar str), 2852 (aliphatic C-H str), 1620(C=N str), 1479(C= C ar str), 1394 (C- N str), 1197 (C- O-C str).
- UV (DMSO) λ_{max}: 266nm
- ^{1}H NMR (δ ppm, DMSO-d_6): 13.993 (b, 1H, secondary amine), 10.89-10.234 (b, 2H, -NH_2), 9.001(s, 1H, C-CH-N of imidazole), 8.649 (b, 1H, N-CH-N), 7.50-6.959 (m, 4H, ArH), 4.16 (s, 1H_a, of methylene), 4.066 (s, 1H_b, of methylene), 2.5 and 3.33 (b, DMSO impurity) and 1.149 (m, 1H, C-CH-C of methane).
- MS (ESI) m/z (rel. abundance): 280.11 (100.0%), 281.11 (15.1%)

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

- IR (KBr)ν(cm^{-1}): 3526 (N- H amine str), 3030 (C- H ar str), 2899 (aliphatic C- H str), 1616 (C= N str), 1417 (C= C ar str), 1340 (C-N str), 1221 (C-O-C str).
- UV (DMSO-d_6) λ_{max}: 266nm
- ^{1}H NMR (δppm, DMSO-d_6): 10.97 (b, 2H, of amine), 6.8-7.7 (m, 4H, ArH), 4.35 (t, 1H, N-CH-C), 2.5 and 3.33

(b, DMSO impurity), 1.9 (m, 1H, CH of methine), 1.14-1.23 (m, 2H, C-CH_2-C of methylene), 1.08 (d, 3H, CH of β_1-methyl), and 0.89 (q, 3H, CH of β_2-methyl).

- MS (ESI) m/z (rel. abundance): 256.13 (100.0%), 257.14 (15.1%).

1-([1,3,4]Oxadiazino[6,5-b]indol-3-yl)-3-methylbutan-1-amine(5d)

- IR (KBr)ν(cm^{-1}): 3389 (N- H amine str), 3130 (C- H ar str), 2861 (aliphatic C- H str), 1616 (C= N str), 1462-1510 (C= C ar str), 1332 (C-N str), 1209 (C- O-C str).
- UV (DMSO) λ_{max}: 265nm.
- ^{1}H NMR (δ ppm, DMSO-d_6): 10.85 (b, 2H, of amine), 7.3- 7.81 (m,4H,ArH), 2.5 and 3.32 (b, DMSO impurity), 2.66 (m, 1H, CH of methine), 1.77(t, 2H, C-CH_2-C of methylene), 1.49 (t, 1H, C-CH-C), and 0.9 (s, 3+3H, CH_3).
- MS (ESI) m/z (rel. abundance): 256.13 (100.0%), 257.14 (15.1%)

N-(1-([1,3,4]Oxadiazino[6,5-b]indol-3-yl)-3-(methylthio) propyl)benzamide(5e)

- IR (KBr)ν(cm^{-1}): 3335 (N- H str), 3063 (C- H ar str), 2852-2920 (aliphatic C- H str), 1732 (C= O str), 1628 (C= N str), 1444-1575 (C=C ar str), 1319 (C- N str), 1217 (C- O-C str), 1028 (C-S-C stretching).
- UV (DMSO) λ_{max}: 262nm
- ^{1}H NMR (δ ppm, DMSO-d_6): 8.91 (b, 1H, of 2ºamine), 7.48-7.86 (m, 5H, ArH phenyl), 7.31-7.81 (m, 4H, ArH of Indole), 3.63 (t, 1H, N-CH-C), 2.5 and 3.33 (b, DMSO impurity), 2.6 (m, 2H, S-CH_2-C), 2.11 (m, 2H, C-CH_2-C), 2.07 (s, 3H, CH_3)
- MS (ESI) m/z (rel. abundance): 378.12 (100.0%), 379.12 (21.6%), 380.11 (4.5%),

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

- IR (KBr)ν(cm^{-1}): 3616(N- H amine stretching), 3325 (N-H str), 3075 (C-H ar str), 2852-2922 aliph C- H str), 1614 (C=N str), 1462-1508 (C=C ar str), 1334 (C-N str), 1207 (C-O-C str).
- UV (DMSO) λ_{max}: 264nm
- ^{1}H NMR (δ ppm, DMSO-d_6): 9.963 (b, 2H, N-H), 7.5-7.4 (m, 4-H, Ar of indole), 6.97-6.89 (m, 5H, ArH), 4.02 (m, 1H, -CH-),2.5 and 3.32 (b, DMSO impurity), 1.14 (d, 2H, -CH_2-).
- MS (ESI) m/z (rel. abundance): 291.12 (18.4%), 292.12 (1.6%), 291.11 (1.5%)

1-([1,3,4]oxadiazino[6,5-b]indol- 3-yl)-2-(1H-indol-2-yl) ethanamine(5g)

- IR (KBr)ν(cm^{-1}): 3566 (N- H amine str), 3244 (N- H str), 3090 (C- H ar str), 2926 (aliphatic C- H str), 1616 (C=N str), 1458-1541 (C= C ar str), 1340 (C- N str), 1213 (C- O-C str).
- UV (DMSO) λ_{max}: 265nm
- ^{1}H NMR (DMSO-d_6): 11.67 (b, 1H, >NH of Indole), 8.6 (b, 2H, NH_2), 7.3-7.81 (m, 4-H, ArH of Benzlidenium), 6.9-7.51 (m, 4H, Ar-H of indole), 6.22 (s, 1H, C-CH-C indole), 3.23 and 2.77 (s, 2H, -CH_2- methylene), 3.14 (m, 1H, C-CH-N of methine).
- MS (ESI) m/z (rel. abundance): 329.13 (100.0%), 330.13 (20.5%), 331.13 (2.0%).

4-(2-([1,3,4]Oxadiazino[6,5- b]indol-3-yl)-2-aminoethyl) phenol(5h)

- IR (KBr)ν(cm^{-1}): 3543 (O- H str), 3242 (N- H amine str), 3084 (C-H ar str), 2814 (aliphatic C- H str), 1614 (C=N str), 1462 (C= C ar str), 1342 (C- N str), 1211 (C- O-C str).
- UV (DMSO) λ_{max}: 264nm
- ^{1}H NMR (δ ppm, DMSO-d_6): 9.973 (b, 2H, -N-H), 7.5-7.4 (m, 4-H, Ar of indole) 6.97-6.89 (m, 4H, ArH), 4.02 (m, 1H, -CH-), 2.49 and 3.33 (b, DMSO impurity), 1.14 (d, 2H, -CH_2-).
- MS (ESI) m/z (rel. abundance): 306.11 (100.0%), 307.12 (18.4%), 308.12 (1.6%),

DISCUSSION

Based on knowledge from literature survey, the monoamine oxidase inhibitors idea does not completely explain pharmacological action of antidepressants nor does it explain depression pathophysiology and cannot justify the less onset of action, because 4–6 weeks are needed to establish therapeutic efficacy. They have more side effects. Thus existing antidepressant drugs including TCA, SSRIs, SNRIs and NSSA are not free from side effects. Although these faults, the monoamine oxidase inhibitor hypothesis has on condition that the rationale for the development of novel antidepressants with a broad range of efficacy and safety in depression treatment.

This research project was aimed to synthesize and characterize for finding less or no side effects of 1,3,4-oxadiazinoindole derivatives (Compounds 5a-5h) as an antidepressant activity.

The synthesis was started via formation of aminoacid chloride from aminoacids. Further, they were converted into amino acid hydrazide, and then aminoacid hydrazones were prepared by reaction with isatin. Finally, cyclization was acted on hydrazone derivatives in the presence of cold H_2SO_4. Like these process, 1,3,4-oxadiazinoindole derivatives (5a–5h) were synthesized.

The synthesized compounds occur as brownish-coloured solids. Yield (5a–5h) was varying from 24.9–74.3%.

All the novel compounds were characterized by sharp MP, chromatographic methods, UV spectroscopy, FTIR, Proton NMR spectroscopy and MS spectroscopy for their structural conformation. The spectrums of synthesized compounds show peaks at the expected wavelength.

CONCLUSION

Our studies suggest that rational methods synthesized all the 1,3,4-oxadiazinoindole derivatives (5a–5h). The synthesized derivatives were exposed to physicochemical characterization. The sharp melting points, TLC, and spectral analysis by FTIR, ^{1}H-NMR, and MS spectra confirmed the homogeneity and purity of all the title derivatives. An attempt has been made to synthesize the compounds that assist antidepressant tricyclic, including hydrazide moiety of MAOI with fewer or no side effects.

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