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Original Research Article

SYNTHESIS OF NEW INNOVATIVE TRICYCLIC ANTIDEPRESSANTS DRUGS.

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ABSTRACT

INTRODUCTION:

Depression is a chronic, enduring illness that may necessitate lifetime therapy utilising a range of techniques. Premature death is more common in depressed patients as compared to controls. By addressing chemical imbalances of neurotransmitters in the brain. Antidepressants are a class of medications used to treat the signs and symptoms of depressive disorders. The market is flooded with antidepressant medications. Unfortunately, despite the proliferation of new antidepressants that have recently entered clinical use, the effectiveness plateau that the traditional antidepressants displayed has not been reversed.

The search for a more effective antidepressant that is also more tolerable, acts quickly, and has fewer side effects.

MATERIAL &METHOD:

The current research project's objective is to create innovative tricyclic antidepressants as ß-carboline analogues (pyrido(6,5-b) indoles). For this purpose, the chemical study was carried out. The information for the present study was obtained from various internet sources like research articles and paper presentation documents and research book publications. According to the acquired source, the research is based on secondary data gathered from sources.

RESULT & DISCUSSION:

The current compound was created to have the ß-caroline-like activity of a selective MAO-A inhibitor. Due to its potential to increase brain monoamine levels, it was believed that the developed chemical, 2-substituted 1,3,4-oxadiazino[6,5-b] indole, would have an antidepressant effect. According to the study, the molecule's 8 possible derivatives were all created. By esterifying amino acids with methanol while thionyl chloride was present, amino acid esters, the beginning chemical, were created. Esters were next converted to hydrazides, and sulphuric acid was used to cyclize these hydrazones to produce the desired tricylic product. Accordingly, the physicochemical characterization of the 8 synthesized derivatives was carried out by melting point determination, TLC, IR spectra and HNMR spectra.

SYNTHESIS OF TRICYCLIC ANTIDEPRESSANTS DRUGS

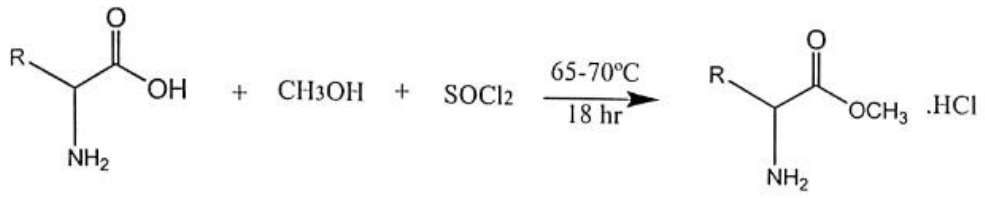
A. Materials:

1. All the chemicals used in the synthesis were procured from Qualigen and Merck. Other laboratory reagents purified prior to use.
2. Melting points were determined on open capillary tube and are uncorrected.
3. The silica gel G used for thin layer chromatography (TLC). 'Silica Gel G' procured from Merck and was coated on laboratory glass slides.
4. TLC plates were visualized using iodine chamber or/ observed under ultraviolet light. IR spectra[i] were recorded using KBr disk on "JASCO V-5300" and are reported in cm^{-1}
5. I H-NMR[ii,iii] spectra were recorded in DMOS-d6 solution on "NMR Varian-Mercury YH-300" operating at field strength of 300 MHz; chemical shifts were reported in parts per million downfield from tetramethylsillane as an internal standard (scale) and peak multiplicities were shown thus:

   br, brod; s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplate.

B. Methods:

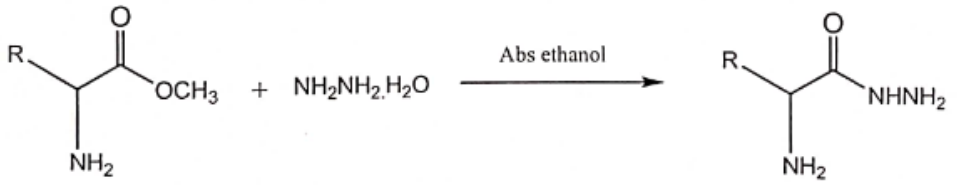
Step 1: Synthesis of Amino acid ester:



Ronald et al. have described the synthesis of methyl ester hydrochloride of most of the amino acids. This esterification method is easy and gives good yields. In this method, methanol is treated with thionyl chloride and then refluxed with amino acid. The solution is concentrated to give crystals of ester hydrochloride. The same method is applied in the present work for the synthesis of methyl esters hydrochlorides of amino acids.

Dymicky et al. described the general, highly efficient method for esterification of amino acids. In this method simultaneous esterification and azeotropic distillation of alcohol, benzene and water azeotrop permits the use of 95% alcohol and hydrochloric acid. This method also provides quantitative yield of highly pure ester hydrochlorides.

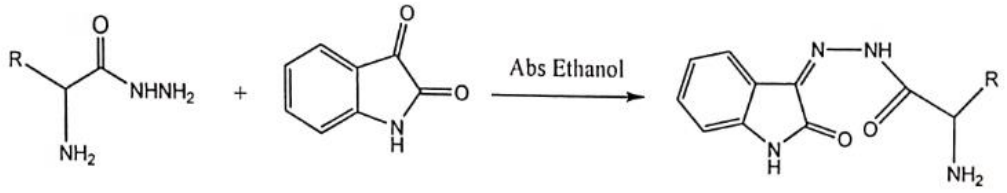
Step 2: Synthesis of Amino acid hydrazide:



The treatment of amino acid ester with hydrazine hydrate or amines is very general reaction for the preparation of hydrazide or amides and subjected to vigorous reflux for a long duration. The reaction is exothermic and must be controlled carefully, usually by cooling or dilution. Primary amines give N-substituted amides, and secondary amines give N, N- disubstituted amides. Aryl amines can be similarly acetylated. In some cases, aqueous alkali is added to combine with the liberated HCI. This is called as Schotten-Baumann procedure. This facilitates removal of chloride ion from acyl chlorides.

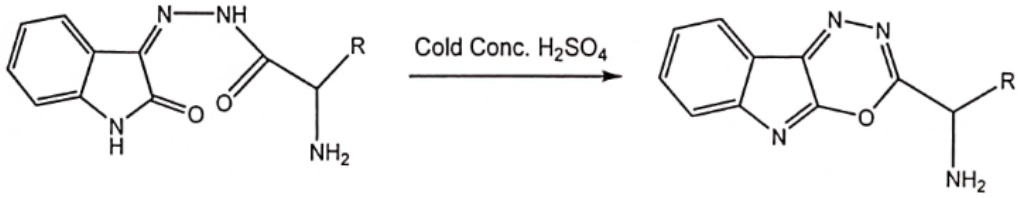
In nucleophilic substitution reactions, the leaving group departs during the rate determining step and so directly affects the rate. The nature of leaving group affects the reactivity in two ways. Firstly, by altering the electron density at the carbonyl carbon and secondly the nature of leaving group affects position of equilibrium. The greater electron withdrawing character of leaving group the greater the partial positive charge on carbon and more rapid the attack by nucleophile, due to this acyl chloride highly reactive.

Step 3: Synthesis of Amino acid hydrazone:



By a nucleophilic substitution, acid hydrazides attack the C-3 of isatin to produce amino acid hydrazones. These derivatives are crystalline, coloured compounds.

Step 4: Synthesis of oxadiazinoindole derivatives:



It is a cyclization reaction in presence of cold concentrated sulphuric acid which results in fusion 6-membered 1,3,4-oxadiazine ring with indole to produce desired oxadiazinoindole derivatives.

Step I: General method of synthesis of compounds 1a – 1h: [iv,v]

Different amino acids (0.05 moles) were taken in 250mL RBF of Combinatorial synthesizer. In another RBF 70 mL methanol was taken, which was kept in ice bath with stirring and to it 3.6 mL (0.05 moles) of thionyl Chloride was added drop wise to the methanol in the round bottom flask over a period of 15min. This resulting mixture was poured in RBF containing amino acid. The reaction was refluxed for 18 hrs. The reaction was monitored by thin layer chromatography (TLC) After completion of reaction the excess thionyl chloride and solvent was removed under vacuum in Kugelrohr type bulb to bulb distillation apparatus. The resulting mass was poured in Petri dish and dried at room temperature till fine crystals of amino acid ester were obtained.

The following compounds were synthesized as per the above method, In parenthesis the name of amino acid from which the ester is synthesised is given,

Sr. No.	**Name**	**Yield**	**M.P.**	**R_f**	**IR (KBr) v (cm^{-1})**

1a	Methyl 2- aminoacetate: (Glycine)	88% (3.95g)	179-181 °C	0.76 (Chloroform: Methanol 2: 1]	3466 (OH and N-H stretching), 2970(Aliphatic —CH stretching), 1739 (C=0 stretching), 1575-1437(Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1103 (C-0 stretching)
1b	Methyl 2-amino-3-phenylpropanoate: (L-phenyl- alanine)	84% (7.6 g)	85-86°C	0.6 [Chloroform: Methanol 2: 1]	3479(N-H stretching), 2947(Aliphatic —CH stretching), 1747 (C=0 stretching), 1583-1448(Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1110 (C-O stretching)
1c	Methyl 2-amino-3-(1 H-imidazol-4-yl) propanoate (L-histidine)	95% (8.1g)	240-242°C	0.57 [Chloroform: Methanol 2: 1]	3214 (N-H stretching), 3105 (Aromatic CH stretching) 2947 (Aliphatic —CH stretching), 1747 (C= stretching), 1600-1431 (Aromatic C=C stretching), 1259 (Aromatic C-N stretching), 1120 (C-O stretching)
1d	Methyl 2-amino-3 (4-hydroxyphenyl) propanoate: (L- tyrosine)	91% (8.95 g)	204-205°C	0.66 [Chloroform: Methanol 2: 1)	3377 (OH and N-H stretching), 3015 (Aromatic CH stretching), 2951(Aliphatic —CH stretching), 1743 (C=O stretching) 1593-1448(Aromatic C=C stretching), 1250 (Aromatic C-N stretching), 1105 (C-O stretching)
1e	Methyl 2-	89%	160-	0.6	3466 (OH and N-H stretching),

	aminopropanoate: (L-alanine)	(4.6g)	162°C	[Chloroform: Methanol 2: 1]	2970(Aliphatic —CH stretching), 1739 (C=O stretching), 1575-1437(Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1103 (C-O stretching)
1f	Methyl Benzoate	-	160-162°C	-	-
1g	Methyl 2- amino- 4-methylpentanoate:11-leucine1	85% (6.2g)	150-152°C	0.57 [Methanol: Water 5: 1]	3373 (OH and N-H stretching), 2939(Aliphatic —CH stretching), 1701 (C=O stretching), 1591-1452 (Aromatic C=C stretching), 1220 (Aromatic C-N stretching), 1134 (C-O stretching)
1h	Methyl 2- amino- 3-methylpentanoate: (L-isoleucine)	88% (6.45g)	157-158°C	0.54 [Methanol: Water 5: 1]	3431 (OH and N-H stretching),2968(Aliphatic —CH stretching), 1741 (C=O stretching), 1520-1458 (Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1140 (C-O stretching)

Step II: General method of synthesis of Hydrazide 2a-2h: [vi,vii,viii]

Hydrazine hydrate [99%] (0.05 moles) was taken in RBF of Combinatorial Synthesizer to it different amino acid esters 1a – 1h (0.05 moles) were added slowly and this reaction mixture was refluxed for 1 hr. After that absolute ethanol 50ml was added to reaction mixture and reaction mixture were refluxed for 4-6 hr. The completion of reaction was checked by thin layer Chromatography (TLC). The contents were cooled and white product obtained was filtered, washed with cold ethanol/methanol. The residual crude product was dried and purified by recrystallization from ethanol to give 2a-2h.

The following compounds were synthesized as per the above method,

Sr. No.	Name	Yield	M.P.	R_f	IR (KBr) v (cm^{-1})
2a	2-aminoacetohydrazide	80% (4.04g)	-	0.45 [Chloroform: Methanol 2:1]	3246 (OH and N-H stretching), 1697 (C=O stretching), 1620-1464 (Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1105 (C-0 stretching)
2b	2-amino- 3-phenylpropanehydrazide	75% (6.71.g)	164-166°C	0.54 [Chloroform: Methanol 2:1]	3421 (OH and N-H stretching), 2945 (Aliphatic —CH stretching), 1712 (C=O stretching), 1520-1458(Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1140 (C-O stretching)
2c	2-amino-3-(1 H- imidazol-4-yl) propanehydrazide	70% (5.91.g)	240-242°C	0.5 [Chloroform: Methanol 2: 1]	3420 (OH and N-H stretching), 3109 (Aromatic CH stretching), 3022(Aliphatic —CH stretching), 1733 (C=O stretching), 1496-1431 (Aromatic C=C stretching), 1242 (Aromatic C-N stretching), 1122 (C-O stretching)

2d	2-amino-3-(4-hydroxyphenyl) propanehydrazide	82% (7.99g)	192-193°C	0.54 [Chloroform: Methanol 2:1]	3481 (OH and N-H stretching),2959 (Aliphatic —CH stretching), 1697 (C=O stretching), 1587-1439 (Aromatic C=C stretching), 1315 (Aromatic C-N stretching), 1132 (C-O stretching)
2e	2- aminopropanehydrazide	74% (3.81g)	-	0.47 [Chloroform: Methanol 2: 1]	Sticky product was obtained.
2f	Benzohydrazide	85% (5.78g)	107-109°C	0.47 [Chloroform. Methanol 5:1]	3298 (N-H stretching), 2959 (Aliphatic —CH stretching), 1660 (C=O stretching), 1566-1446 (Aromatic C=C stretching), 1315 (Aromatic C-N stretching)
2g	2-amino- 4-methylpentanehydrazide	76% (5.51g)	186-188°C	0.66 [Chloroform: Methanol 2:1]	2962 (Aliphatic —CH stretching), 1697 (C=O stretching), 1608-14310 (Aromatic C=C stretching), 1315 (Aromatic C-N stretching)
2h	2-amino-3-methylpentanehydrazide	67% (4.85g)	248-250°C	0.6 [Chloroform: Methanol 2: 1]	3447 (N-H stretching), 2966 (Aliphatic —CH stretching), 1734 (C=O stretching), 1583-1417 (Aromatic C=C

					stretching), 1327 (Aromatic C-N stretching)

Step III: General method of Synthesis of Hydrazone 3a-3h: [ix,x,xi,xii,xiii]

In Combinatorial RBF, hydrazide (0.03 moles) was taken, to it absolute ethanol 60 mL added and refluxed reaction mixture for 30 min. Isatin (0.03 moles) was added to above reaction mixture and reaction was reflux for 18 hr. The completion of reaction was monitored by TLC. After completion the reaction mixture was cooled and filtered. Solid hydrazone was collected. This solid then washed by water. The residual crude coloured product was dried and purified by recrystallization from ethanol to give 3a-3h.

The following compounds were synthesized as per the above method,

Sr. No.	**Name**	**Yield**	**M.P.**	**R_f**	**IR (KBr) v (cm^{-1})**
3a	2-amino-N'- (2-oxoindolin-3-yliidene) acetohydrazide	85% (2.66g)	190-191°C	0.56 [Benzene: Ethyl acetate 2: 1]	3358(-NH stretching),1685 (C=O stretching), 1665 (N-N-C=O stretching), 1589-1467(Aromatic C=C stretching), 1352 (Aromatic C-N stretching)
3b	2-amino-N'- (2-oxoindolin-3-ylidene)-3-phenylpropanehydrazide	88% (4.72g)	205-207°C	0.6 [Benzene: Ethyl acetate 2:1]	3340 (NH stretching), 3159 (Aromatic CH stretching), 1705 (C=O stretching), 1665 (N-N-C=O stretching), 1591-1437 (Aromatic C=C stretching), 1352 (Aromatic C-N stretching)
3c	2-amino-3-(1H-imidazol-4-y1)-N'- (2-oxoindolin-3-ylidene) propanehydrazide	84% (4.25g)	210-212°C	0.66 [Benzene: Ethyl acetate 2: 1]	3159 (Aromatic CH stretching), 1705 (C=O stretching), 1665 (N-N-C=O stretching), 1585-1425 (Aromatic C=C stretching), 1352 (Aromatic C-N

					stretching).
3d	2-amino-3- (4-hydroxyphenyl)-N'- (2-oxoindolin-3-ylidene propanehydrazide	72% (4.21g)	222-225°C	0.7 [Benzene: Ethyl acetate 3: 1]	3358(NH stretching), 3159 (Aromatic CH stretching), 1685 (C=O stretching), 1657 (N-N-C=O stretching), 1589-1467 (Aromatic C=C stretching), 1352 (Aromatic C-N stretching),
3e	2-amino-N'- (2-oxoindolin-3-ylidene) benzohydrazide	90% (2.78g)	212-214°C	0.65 [Benzene: Ethyl acetate 2: 1]	3165 (Aromatic CH stretching), 1715 (C=O stretching), 1665 (N-N-C=O stretching), 1595-1415 (Aromatic C=C stretching), 1352 (Aromatic C-N stretching),
3f	N'- (2-oxoindolin-3- ylidene benzohydrazide	75% (3.06g)	202-204°C	0.6 [Benzene: Ethyl acetate 9: 1]	3194 (Aromatic CH stretching), 2934 (Aliphatic —CH stretching), 1695 (C=O stretching), 1682 (N-N-C=O stretching), 1601-1464 (Aromatic C=C stretching), 1346 (Aromatic C-N stretching)
3g	2-amino-4-methyl-N'-(2-oxoindolin-3-vyidene) pentanehydrazide	60% (2.34g)	225-226°C	0.66 [Benzene: Ethyl acetate 3: 1]	3350 (NH stretching), 3160 (Aromatic CH stretching), 1710 (C=0 stretching), 1645 (N-N-C=O stretching), 1579-1461 (Aromatic C=C stretching), 1352 (Aromatic C-N stretching)
3h	2-amino-3-methyl- N'- (2-	65%	215-	0.66	3418 (NH stretching), 3140

	oxoindolin-3- ylidene pentanehydrazide	(2.53g)	216°C	[Benzene: Ethyl acetate 3: 1]	(Aromatic CH stretching), 1690 (C=O stretching), 1650 (N-N-C=O stretching), 1556-1423 (Aromatic C=C stretching), 1323 (Aromatic C-N stretching)

Step IV: General method for synthesis of Oxadiazinoindole derivatives 4a-4h: [xiv,xv,xvi,xvii]

Different acid hydrazones 4a-4j (0.01 moles) were mixed with small amount to cold conc. H_2S0_4 (8-10 mL) in 100 mL RBF of Combinatorial synthesizer. The reaction mixture was stirred for 4 hr. The completion of reaction was monitored by thin layer chromatography (TLC). After this, reaction mixture was poured into cold ice-water and solid mass obtained Which was filtered, washed with cold water. The residual crude product was dried, purified and recrystallized from dimethyl sulphoxide-acetone to give 4a-4h.

The following compounds were synthesized as per the above method,

Sr. No.	**Name**	**Yield**	**M.P.**	**R_f**	**IR (KBr) v (cm^{-1})**
4a	([1.3.4] oxadiazino [6,5-b] indol-3-yl) methanamine	65% (1.41g)	265-266°C	0.6 [Benzene: Ethyl acetate: methanol: 9:1:1]	3246 (N-H stretching), 2926 (Aliphatic —CH stretching), 1697 (Aromatic C=N stretching), 1620-1464 (Aromatic C=C stretching), 1325 (Aromatic C-N stretching), 1105 (C-O-C stretching)
4b	1-([1,3,4] oxadiazino [6,5-b] indol-3-yl) -2-phenylethanamine	56% (1.72g)	250-251°C	0.61 [Benzene: Ethyl acetate: methanol: 9:1:1]	3200 (N-H stretching), 2926(Aliphatic —CH stretching), 1697 (Aromatic C=N stretching), 1618-1462 (Aromatic C=C stretching)1323 (C-N stretching), 1105 (C-O-C stretching)

4c	1-([1,3,4] oxadiazino [6,5-b] indol-3-yl) -2-(1H- imidazole-4-yl) ethanamine	60% (1.78g)	185-186°C	0.54 [Benzene: Ethyl acetate: methanol: 9:1:1]	3213 (N-H stretching), 2918(Aliphatic —CH stretching), 1685 (Aromatic C=N stretching), 1618-1467 (Aromatic C=C stretching) 1338 (C-N stretching), 1192 (C-O-C stretching)
4d	4-(2-([1,3,4] oxadiazino [6,5-b] indol-3-yl) -2-aminoethyl) phenol	57% (1.84g)	185-186°C	0.66 [Benzene: Ethyl acetate: methanol: 9:1:1]	3234 (N-H/OH overlapping), 2922(Aliphatic —CH stretching), 1695 (Aromatic C=N stretching), 1541-1462 (Aromatic C=C stretching),1325 (C-N stretching), 1105 (0-0-C stretching)
4e	1-([1,3,4] oxadiazino [6,5-b] indol-3-yl) ethanamine	51% (1.18g)	245-246°C	0.45 [Benzene: Ethyl acetate: methanol: 9:1:1]	3234 (N-H stretching), 1699 (Aromatic C=N stretching), 1541-1471 (Aromatic C=C stretching),1321 (C-N stretching), 1105 (C-O-C stretching)
4f	3- phenyl [1,3,4] oxadiazino [6,5-b] indol	48% (1.27g)	260-261 °C	0.45 [Benzene: Ethyl acetate: methanol: 9:1 : 1]	3254 (N-H stretching), 2918(Aliphatic —CH stretching), 1682 (Aromatic C=N stretching), 1606-1458 (Aromatic C=C stretching)1338 (C-N stretching), 1130 (C-O-C stretching) I H NMR (ö ppm, DMSO-d6): 7.89 (d, C2'-H and C6'-H of phenyl ring), 7.62 (m, protons

					of aromatic ring of Oxadiazinoindole (C5-H to C8H),6.98 and 7.4 (m, Protons on C3'-H to C5'-H of phenyl ring),3.35 and 2.5 (DMSO-d6 impurities).
4g	1-([1,3,4] oxadiazino [6,5-b] indol-3-yl) -3-methylbutan -1- amine	50% (1.37g)	235-236 °C	0.4[Benzene: Ethyl acetate: methanol: 9:1 :1]	3391 (N-H stretching), 2959 (Aliphatic -CH stretching), 1699 (Aromatic C=N stretching), 1558-1458 (Aromatic C=C stretching), 1323 (Aromatic C-N stretching), 1105 (C-O-C stretching)
4h	1-([1,3,4] oxadiazino [6,5-b] indol-3-yl) -2-methylbutan -1- amine	45% (1.23g)	255-256 °C	0.54 [Benzene: Ethyl acetate: methanol: 9:1]	3186 (Aromatic C-H stretching), 2962 (Aliphatic — CH stretching), 1697 (Aromatic C=N stretching), 1462 (Aromatic C=C stretching), 1325 (Aromatic C-N

					stretching), 1105 (C-O-C stretching)

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