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In-vivo Central Nervous System - Locomotor Activity of Some Synthesized 2-[(1-((phenyl amino) methyl) Substituted 1-benzoimidazol-2-yl) alkyl] Isoindoline-1, 3-diones

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Some new two series of 1, 2-disubstituted benzimidazolyl isoindoline derivatives (6a-n) were synthesized by mannich reaction of 2- substituted benzimidazolyl isoindolines (4a-b) with various aromatic primary amines (5a-g) with formaldehyde in acid as a condensing agent. The 2-(1,3-dioxoisoindolin-2-yl) carboxylic acids (3a-b) cyclised with 1,2 diamino benzene yield (4a-b). The pthalic anhydride (1) and amino acids (2a-b) fused at 180°C-185°C to give (3a-b). The compounds (4a-b) and (6a-n) were screened for their in-vivo central nervous system locomotor activities. Among these tested isoindolines 4a, 4b, 6a, 6b, 6e, 6f were only shows elevated central nervous system depressant potency and remaining isoindolines were depicted bad central nervous system depressant activity.

Key words: Benzimidazoles, benzimidazolyl isoindolines, isoindolines, central nervous system stimulant, central nervous system depressant.

Heterocyclic's analogues have depicted a central position in the field of novel synthetic drug developments owing to their high reactivity in the biological receptors/membranes, pharmacological properties and are widely implicated in various biochemical metabolic processes. Many five membered, six membered, fused five or six membered heterocyclic's compounds have shown diversified biological activities ranging from antibacterial, antifungal, antiprotozoal, anti-tubercular, antiviral, hypnotics, anti epileptic, anti-ulcer, diuretics, anticancer, antihypertensive, anthelminitics , antimalarial, analgesic, anti-inflammatory, CNS stimulant, CNS depressant[1] etc. Among this nitrogen containing fused heterocyclic's derivatives such as benzodiazepine, benzimidazole, phenothiazine, indole, purine, quinoline, pteridine analogues are highly focused due to its fascinating biological activities. Out of the above mentioned heterocyclics, we decided to choose the synthesis of indole and benzimidazole nucleus because both are integral part of a some of biologically active natural products such as indole found in psilocin as hallucinogens, ergotamine for migraine, vinca alkaloids as anti cancer, reserpine as antihypertensive and benzimidazole present in vitamin B_{12} cyanocobalamine. They also comprise the ring system in a number of drugs to name a few indomethazine, indoprofen, omeprazole, albendazole, etc.

The literature survey of the research articles are reported that benzimidazole derivatives possess a antimicrobial[2], antiviral[3], antifeedant, acaricidal[4], antiproliferative agent[5], antitubercular[6], antiulcer[7], antioxidant , analgesic, anti-inflammatory[8],

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anthelminitic[9], central nervous system depressant[10], HIV-RT inhibitor[11], anti-allergic[12], anticancer[13], DNA topoisomerase inhibitors[14], histamine H_4-receptor antagonist[15] activities.. The earlier research reports indicated that the indoline derivatives also displayed wide range of biological activities such as antibacterial[16], analgesic ,anti-inflammatory [17], cyclooxygenase inhibitor[18], antihistamine[19], antioxidant[20], antiproliferative[21], acetylcholinesterase inhibitors[22], inhibitor of human neuronal nitric oxide synthase[23], anticonvulsant[24], antidepressant[25] and neuroprotective[26]. Hence novel synthesis of heterocyclic's fused derivatives is being continuously reported with specifying wide variety of biological activities. Indoline analogs are most extensively studied nucleus, which can be used as the starting material or intermediate/ subunit for new leads in a drug discovery by synthesis of fused heterocyclic analogues[27].

We after following this reports, it was thought of interest to fuse both indoline and benzimidazole moieties attempted by synthesise using isoindoline as a starting material which hope to give some variations in the biological activity. So our research work involves the synthesis of some new benzimidazole fused isoindoline heterocyclics followed by in-vivo central nervous system locomotor activity screening evaluation of the derivatives.

EXPERIMENTAL

Synthesis of 2-(1, 3-dioxo isoindolin-2-yl) alkylacids (3a&3b)

An equimolecular quantity of pthalic anhydride (1) and glycine (2a, series 1) and alanine (2b, series 2) in a glass beaker were kept in a previously heated sand bath at 180-185°C. The beaker heated for five minutes with continuous stirring, melted mixtures were kept aside for few minutes allow to cool, the liquid mass solidified. The swhite solids (3a-b) obtained were then recrystallised from ethyl alcohol.

Synthesis of 2-(1-(1-benzimidazol-2-yl) alkyl) isoindoline-1, 3-dione (4a&4b)

An equimolecular quantity of 3a (series 1) / 3b (series 2) and 1,2 diaminobenzene were taken in a round bottomed flask, refluxed in 30 ml of 4N hydrochloric acid (for 0.1 molar) for two hours. The reaction mixtures were cooling gave a products 2-((1-benzoimidazol-2-yl) methyl) isoindoline-1,3-dione (4a) and 2-(1-(1-benzoimidazol-2-yl) ethyl) isoindoline-1,3-dione (4b).which were filtered with ice cold water, dried and then recrystallised from ethyl alcohol.

Synthesis of 2-[(1-((phenyl amino) methyl) substituted 1-benzoimidazol-2-yl) alkyl] isoindoline-1, 3-diones (6a-n)

The 0.1 molar quantity of 4a (series 1)/ 4b (series 2) were taken in a round bottomed flask, with 0.2 molar 35% formaldehyde mixed in acetic acid and to this 0.2 molar quantity of following primary aromatic amines (5a-g) was added separately namely aniline (5a), para-aminobenzoicacid (5b), anthranillic acid (5c),sulphanilic acid (5d), sulphonamide (5e), ortho-aminophenol (5f) and para-aminophenol (5g), and the mixtures were refluxed for 4 hours. The round bottomed flask mixtures were cooled and poured in to a beaker containing ice cold water with stirring to settle the products (6a-n). These were filtered with ice cold water separately, kept over night in a freezer, dried and recrystallised from ethyl alcohol.

The products are chemically named as 2-((1-((phenylamino) methyl)-1-benzo imidazol-2-yl) methyl) isoindoline-1,3-dione (6a), 2-(1-(1-((phenylamino) methyl)-1-benzoimidazol-2-yl) ethyl) isoindoline-1,3-dione (6b), 4-((2-((1,3-dioxoisoindolin-2-yl) methyl)-1-benzoimidazol-1-yl) methyl amino) benzoicacid (6c), 4-((2-(1-(1,3-dioxoiso indolin -2-yl) ethyl)-1-benzoimidazol-1-yl) methylamino) benzoic acid (6d), 2-((2-((1,3-dioxoiso indolin-2-yl) methyl)-1-benzoimidazol-1-yl) methylamino) benzoic acid (6e), 2-((2-(1-(1,3-dioxoiso indolin-2-yl) ethyl)-1-benzoimidazol-1-yl) methyl amino) benzoicacid (6f), 4-((2-((1,3-dioxo isoindolin-2-yl) methyl)-1-benzo imidazol-1-yl) methylamino) benzene sulfonic acid (6g), 4-((2-(1-(1,3-dioxoisoindolin-2-yl)ethyl)-1-benzo imidazol-1-yl) methyl amino) benzene sulfonicacid (6h), 4-((2-((1,3-dioxoisoindolin-2-yl) methyl)-1-benzoimidazol -1-yl) methyl amino) benzene sulfonamide (6i), 4-((2-(1-(1,3-dioxo isoindolin-2-yl)ethyl)-1-benzo imidazol -1-yl) methylamino) benzene sulfonamide (6j), 2-((1-((2-hydroxy phenyl amino) methyl)-1-benzoimidazol-2-yl) methyl) isoindoline-1,3-dione (6k), 2-(1-(1-((2-hydroxy phenyl amino) methyl)-1-benzoimidazol-2-yl) ethyl) isoindoline-1,3-dione (6l), 2-((1-((4-hydroxy phenyl amino) methyl)-

1-benzoimidazol-2-yl) methyl) isoindoline-1,3-dione (6m), 2-(1-(1- ((4- hydroxyphenylamino) methyl)-1-benzoimidazol-2-yl) ethyl) isoindoline -1,3-dione (6n) The purity of the two series (series 1- 4a,6a, 6c,6e,6g,6i,6k,6m) and (series 2- 4b, 6b, 6d, 6f, 6h ,6j, 6l, 6n) synthesized benzimidazolyl isoindolines were identified by melting point determination. Qualitatively identified by thin layer chromatography using coated silica gel-60 F_{254} aluminium sheets using chloroform: ethanol (8:2) as a solvent eluent followed by visualized in a ultra violet chamber (Table-1).

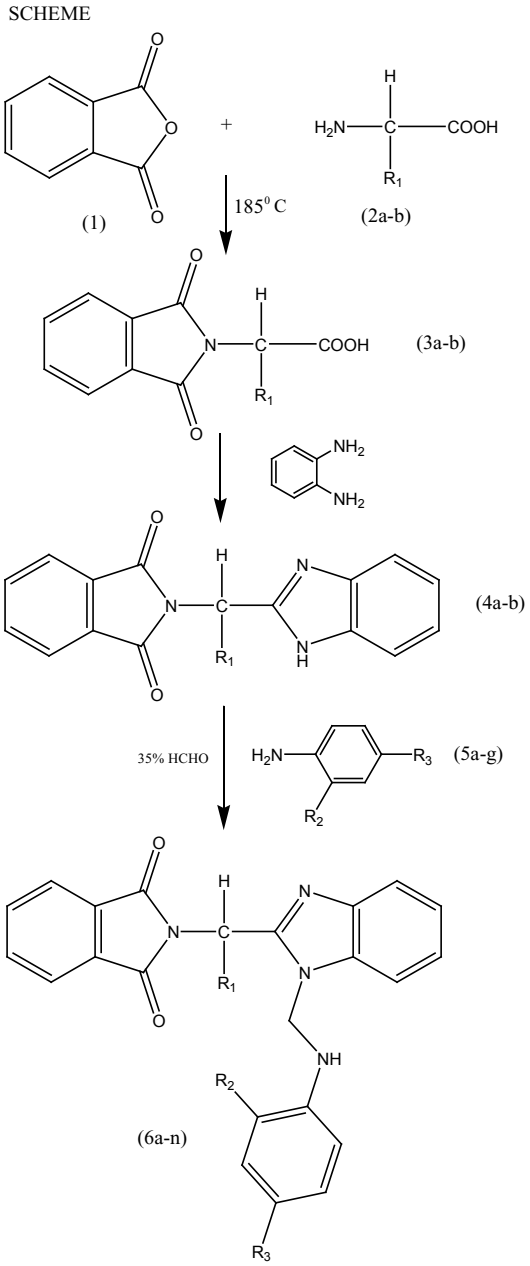
Pharmacological study

Animals

The selected Albino mice of wistar strain either sex were procured from the animal house. The animals were maintained in polypropylene cages in standard environmental conditions at 25^0c-30^0c in a 12 hours light/dark cycle and acclimatized for one week under laboratory conditions. The animals were fed with standard rodent laboratory pellet diet and water libitum. The experiments carried out according the protocols with guidelines duly approved by the Institutional Animal Ethical Committee (Registration no- 661/02/C) of CPCSEA (Committee for Purpose of Control and Supervision of Experiments on Animals).

Evaluation for Central nervous system-Locomotor activity

The central nervous system stimulant or depressant locomotor activity of isoindolines was evaluated by using digital actophotometer[28]. Adult albino mice of either sex weighing 20-28 g were divided into control, standards and test isoindoline groups of five animals in to each group and numbered. The 0.25ml of 1% CMC suspension vehicle were administered for five days once daily before starting the experiment. The animals were fasted for six hours before experiment and they were allowed to adapt to the activity cage environment for at least five minutes. The activity cage was calibrated prior to experimentation. The mouse was placed individually in the digital activity cage and the basal activity counts of each mouse were noted for15 minutes 2 days before to start experiment. A count is recorded when the beam of light falling on the photoelectric cell of actophotometer which connected in circuit with a counter, is cut off by mice. This test involves placing a mouse separately in an activity cage which enables movement of the mice across a light beam to be recorded as a locomotion count. The tested isoindoline compounds were administered orally by intragastric (stomach) tube at a doses of 10 mg/kg, 20 mg/kg & 30 mg/kg body weight in the form of suspension in 0.25ml of 1% CMC while two other groups received diazepam at a dose of 5mg/kg and caffeine at a dose of 10mg/kg body weight as a standard drugs, also given in the form



Scheme 1:

of suspension in 0.25ml of 1% CMC.The control group mice received with 0.25ml suspension of 1% CMC in water. The locomotor behaviour was monitored after 60 minutes of administration of drugs, the actophotometer counts were measured for a period of 15 minutes. The difference in the number of counts for each groups was recorded. The mean score for standard and test isoindoline groups were compared the results with control group.The percentage increase or decrease in locomotor activity was then calculated.

Locomoton average number of movements in percentage for the synthesized benzimidazolyl isoindolines at 30mg/kg concentration compared with standard CNS stimulant caffeine at 10mg/kg and standard CNS depressant diazepam 5mg/kg.

RESULTS AND DISCUSSION

In this study, two series of some substituted benzimidazolyl isoindoline derivatives were prepared and physical analytical studies was carried out by for conforming the purity. They were evaluated for their central nervous system locomotor activity by using actophotometer and the results are shown in Table 2. The data noticed that most of the isoindolines were shows varying degrees of reducing locomotor activities against control group was observed at 20mg/kg and 30mg/kg concentrations. The most of the isoindolines produce significant depressant activity at the all tested 10mg/kg , 20mg/kg, 30mg/kg concentrations but only 6k, 6m not produced significant decrease of locomotor activity were observed at all the tested concentrations . In this context , the isoindolines 6b,6e,6f were only expressed higher depressant activity and isoindolines 6a,4a,4b also gave considerably good depressant activity when compared to standard CNS depressant drug diazepam. The bar diagram shows that both series of isoindolines exerts almost same degree of percentage locomotion movements. Among this isoindolines 6c, 6d, 6g, 6h, 6j were displayed comparably lower depressant activity. However, isoindolines 6i, 6k,6l,6m,6n exhibited bad central nervous system depressant properties than the compared other isoindolines. All the synthesized isoindolines were fails to show central nervous system stimulant activity when compared to standard CNS stimulant drug caffeine.

When Structure activity relationship studies are concerned, 1-ortho phenyl carboxylic acid substituted (6e, 6f) and 1- phenyl substituted benzimidazolyl isoindolines (6a,6b) were only displays good depressant activity. The unsubstituted benzimidazolyl isoindolines (4a, 4b) also displays

Table 1. Physical analysis of synthesised benzimidazolyl isoindolines

S. No	Indolines	Molecular formula	R_1	R_2	R_3	Melting Point^oC	$R_f$value	Yield %
1	4a	$C_{16}H_{11}N_3O_2$	H	-	-	186-187	0.76	78
2	4b	$C_{17}H_{13}N_3O_2$	CH_3	-	-	192-193	0.72	75
3	6a	$C_{23}H_{18}N_4O_2$	H	H	H	197-198	0.45	63
4	6b	$C_{24}H_{20}N_4O_2$	CH_3	H	H	201-202	0.42	61
5	6c	$C_{24}H_{18}N_4O_4$	H	H	COOH	253-254	0.78	67
6	6d	$C_{25}H_{20}N_4O_4$	CH_3	H	COOH	257-258	0.73	64
7	6e	$C_{24}H_{18}N_4O_4$	H	COOH	H	208-209	0.75	52
8	6f	$C_{25}H_{20}N_4O_4$	CH_3	COOH	H	213-214	0.70	48
9	6g	$C_{23}H_{18}N_4O_5S$	H	H	SO_3H	277-278	0.59	65
10	6h	$C_{24}H_{20}N_4O_5S$	CH_3	H	SO_3H	282-283	0.56	62
11	6i	$C_{23}H_{19}N_5O_4S$	H	H	SO_2NH_2	225-226	0.51	69
12	6j	$C_{24}H_{21}N_5O_4S$	CH_3	H	SO_2NH_2	233-234	0.48	66
13	6k	$C_{23}H_{18}N_4O_3$	H	OH	H	237-238	0.85	44
14	6l	$C_{24}H_{20}N_4O_3$	CH_3	OH	H	242-243	0.79	40
15	6m	$C_{23}H_{18}N_4O_3$	H	H	OH	246-247	0.87	57
16	6n	$C_{24}H_{20}N_4O_3$	CH_3	H	OH	251-252	0.81	54

Solvent system (TLC): chloroform: 90% ethanol (8:2)

Table 2. In vivo Central nervous system- locomotor activity of synthesized benzimidazolyl isoindolines (4a-b & 6a-n) by using actophotometer method

Groups	Average number of movements in 15 minutes					
	10 mg/kg	Percentage	20 mg/kg	Percentage	30 mg/kg	Percentage
4a	134.4±1.03***	87.7	109.6±1.60***	71.5	105.0±2.28***	68.5
4b	133.6±1.12***	87.2	103.0±1.41***	67.2	100.8±2.31***	65.7
6a	129.0±1.09***	84.2	101.0±1.58***	65.9	100.2±2.17***	65.4
6b	126.2±0.96***	82.3	96.02±1.88***	62.7	93.6±2.20***	61.0
6c	146.0±1.04**	95.3	126.4±1.28***	82.5	120.0±2.58***	78.3
6d	143.0±1.14***	93.3	117.0±1.78***	76.3	111.8±2.72***	72.9
6e	128.0±1.18***	83.5	99.2±2.08***	64.7	94.6±3.10***	61.7
6f	121.6±1.03***	79.3	92.6±1.56***	60.4	89.6±3.02***	58.4
6g	143.6±1.12***	93.7	117.6±1.93***	76.7	115.2±2.99***	75.1
6h	140.4±1.07***	91.6	112.4±1.32***	73.3	108.2±2.59***	70.6
6i	145.0±1.09***	94.6	131.0±1.78***	85.5	128.4±2.24***	83.8
6j	144.4±0.81***	94.2	126.0±1.70***	82.2	120.8±2.78***	78.8
6k	152.2±0.86	99.3	146.6±2.20	95.6	144.8±3.33	94.5
6l	150.0±0.94	97.9	143.2±1.93*	93.4	134.0±2.82***	84.4
6m	152.8±1.06	99.7	148.2±2.05	96.7	147.2±3.15	96.0
6n	150.4± 1.16	98.1	141.8± 1.65**	92.5	139.0± 2.91*	90.7
CE	208.4±1.63***	136.0	Not tested	–	Not tested	–
DM	073.2±1.39*** (5 mg/kg)	47.7	Not tested	–	Not tested	–
CL	153.2±1.02		Nil			

Each value represents the mean ± SEM (n=5). Significance levels *P<0.5, **P<0.01 and ***P<0.001 as compared with the respective control.
C–Caffeine D–Diazepam CL–control

considerable depressant properties than other tested isoindolines . A close examination of bar diagrams shows that the 2-ethyl substituted benzimidazolyl isoindolines (series 2) were marked more depressant activity than 2-methyl substituted benzimidazolyl isoindolines (series 1).The 1-para phenyl sulfonic acid substituted (6g,6h) and 1-para phenyl acid substituted benzimidazolyl isoindolines (6c,6d) were depicted more appreciable depressant activity than 1- para phenyl sulfonamide substituted benzimidazolyl isoindolines (6i,6j). Any way, the 1-para phenyl sulfonic acid substituted (6g,6h) analogues were more potent than 1-para phenyl carboxylic acid substituted (6c,6d) analogues. The

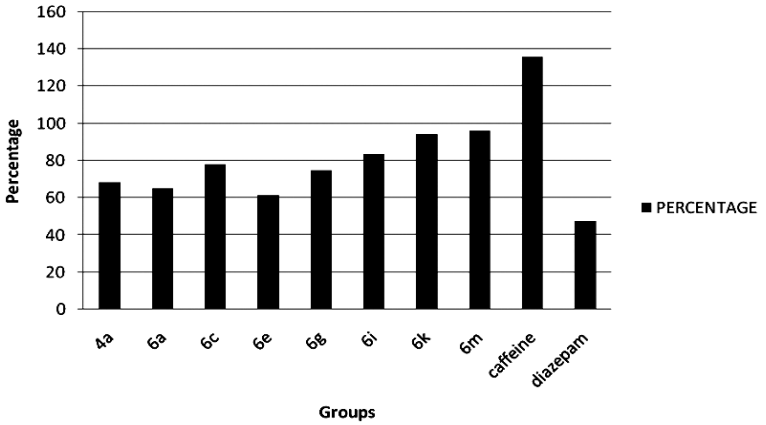


Fig. 1.

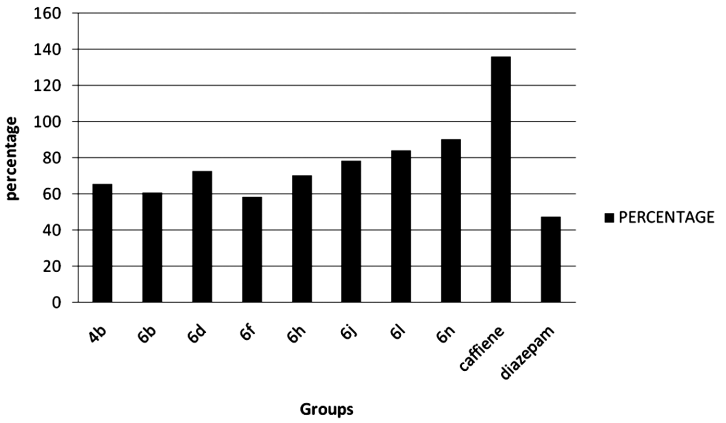


Fig. 2.

1- phenyl hydroxy group substituted (6k, 6m, 6n) analogues were exerting very weak depressant activity.

CONCLUSION

The results proves that 1-phenyl substituted (6a,6b) and that 1-phenyl carboxylic acid substituted (6f,6e) benzimidazolyl isoindolines were produced good central nervous system depressant activity but the 1-phenyl hydroxyl substituted (6k, 6l, 6m and 6n) analogues were fails to give considerable central nervous system depressant activity. Moreover, the 1-phenyl ortho substituted and 2-ethyl substituted benzimidazolyl isoindolines were depicted more central nervous system depressant activity then the corresponding 1-phenyl para substituted and 2-methyl substituted analogues. All the tested benzimidazolyl isoindolines were fails to exert central nervous system stimulant activity.

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