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Synthesis and Pharmacological activity of N-substituted Succinimide analogs

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Abstract: A series of *N*-substituted Succinimide were synthesized for the purpose of determining the analgesic and anticonvulsant properties of these compounds. Succinic anhydride and various amines in glacial acetic acid were used for the synthesis of the Succinimide derivatives. All the synthesized compounds were evaluated *in vivo* for analgesic and antiepileptic activities by using standard experimental models. The results indicated that the synthesized Succinimide derivatives exhibit good biological activity.
Keywords: Succinimide, Analgesic activity, anticonvulsant activity.

Introduction

Succinimide (pyrrolidine-2,5-dione) is a cyclic imide in which two carbonyl groups bound to an amine moiety. The Succinimide compounds have the ability to cross biological membranes[1]. Substituted Succinimide is an essential intermediate of organic synthesis and production of pharmacological active derivatives such as CNS depressant[2], analgesic[3], antitumor[4], cytostatic[5], anorectic[6], nerve conduction blocking[7], antispasmodic[8], bacteriostatic[9], muscle relaxant[10], hypotensive[11], antibacterial[12], antifungal[13], anti-convulsant[14] and anti-tubercular[15]. In this work a number of *N*-substituted-Succinimide were synthesized to determining their analgesic and anticonvulsant activities.

Materials and methods:

All chemicals, solvents and reagents are purchased from sigma Aldrich and Fischer company. All solvents were distilled prior to use. The melting points were determined in open capillary method and were uncorrected. The reaction progress was monitored by thin layer chromatography using silica coated aluminum sheets (silica gel 60 F254). IR spectra were recorded using KBr on FTIR Shimadzu.

General Procedure for Synthesis of Compounds 2-8.

Equimolar amounts of succinic anhydride and an appropriate amines in glacial acetic acid (15 ml) were refluxed for 4 h. The hot mixture was poured into cold water, and the formed precipitate was filtered and recrystallized from ethanol or methanol. The yield, melting point and IR-spectra of the prepared succinimide are summarized in Table 1.

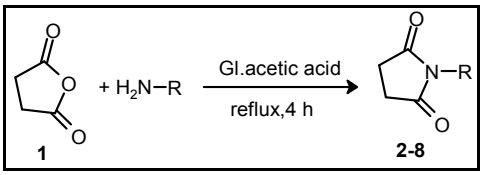
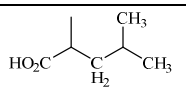
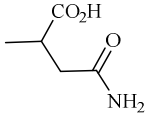
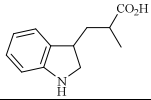
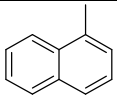
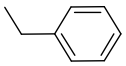


Table 1. Physicochemical properties of N-substituted succinimide.

No.	Systematic name	R	Yield %	mp ºC	IR
2	2-(2,5-dioxopyrrolidin-1-yl)acetic acid	-CH_2O_2H	27.8	160	3065 O-H, 1729 C=O 1682 C=O, 1310 N-C
3	(S)-2-(2,5-dioxopyrrolidin-1-yl)-4-methylpentanoic acid		67.16	180	3100 O-H, 1693 C=O 1415 H-C, 1310 C-N
4	(S)-4-amino-2-(2,5-dioxopyrrolidin-1-yl)-4-oxobutanoic acid		11.28	189	3041 N-H, 3013 O-H 1700 C=O, 1400 H-C 1309 C-N, 1200 C-O
5	(S)-2-(2,5-dioxopyrrolidin-1-yl)-3-(1H-indol-3-yl)propanoic acid		56.04	188	3200 O-H, 1700 C=O 1309 N-C, 1200 H-C
6	1-(thiazol-5-yl)pyrrolidine-2,5-dione		33.30	200	2900 N=C=S, 1715 C=O, 1641 C=N, 1570 C-N
7	1-(naphthalen-1-yl)pyrrolidine-2,5dione		58.8	155	3056 =C-H, 1649 C=O 1375 N-C, 1600 C-C=C
8	1-benzylpyrrolidine-2,5-dione		41.33	100	1700 C=O, 1334 N-C 1455 C-C=C, 1166 C-H 1648 C=C-C

Pharmacology:

Assay for analgesic activity:

Hot plate method:

The experiments were performed on male albino mice (15-18 g). The animals were kept at constant temperature facilities exposed to 12:12 h light: dark cycle. A standard pellet diet and tap water was given *adlibitum*. Each experimental group consists of 4 animals. The succinimide (50 mg/kg) was administered intraperitoneal (IP) 30 min before the test, in a solution of 1% carboxymethyl cellulose (CMC), in constant volume of (0.15-0.18) ml/kg . Control group received the same volume of 1% CMC. The investigated compounds were assessed on the behavioral animal tests.

The animal is placed on a hot plate after 30 minutes of injection of the tested compound or CMC. The temperature was controlled from (55-56 ºC). The time was record when the animal licks its fore limbs or jumps out the plate as a therapeutic end point [16].

Assay for Anticonvulsant Activity:

Intraperitoneal Picrotoxin Induce Seizures:

Male and female albino mice weighing 15-30 g were used for the assay. The animals were allowed free access to food and water except when removed from their cages for experimental procedure. The studied animals were divided into 9 groups, each group has 4 animals. The first one served as a control, the others served for the tested compounds. Each compound was administrated IP (0.2 mL/kg) 30 minutes prior of

picrotoxine (5 mg/kg) administration. The animals were observed for the following parameters: Onset Time of Seizure, Number of Seizures, and Duration of Seizures [17] .

Results and discussion

It has been reported that *N*-substituted succinimdes exhibited good analgesic activity by using hot plate method and taking the reaction time as a therapeutic end point, the results is tabulated in **Table 2**. Compounds **3** and **7** exhibited significant analgesic activity with a longer reaction time compared to the control. Compound **4**, **5** and **8** have been shown good analgesic activity, while compound **2** and **6** have no analgesic activity. In general these succinimides have less analgesic activity compared to the standard drug (morphine) **Table 3**.

Table 2. Analgesic Activity of succinimide derivatives.

No. of mice	Control	**2**	**3**	**4**	**5**	**6**	**7**	8
1	8.14	8.09	12.91	27.02	16.91	9.13	16.05	13.67
2	8.18	12.48	12.01	10.25	10.72	7.34	12.85	11.83
3	8.9	10.17	18	5.51	13.12	5.08	10.71	10.68
4	10.42	9.34	15.09	5.87	8.42	10.31	10.1	8.83
Mean	8.91	10.02	14.5025	12.2925	12.2925	7.965	12.4275	11.2525
STDev	1.1	1.8	2.7	9.6	3.6	2.3	2.7	2.0

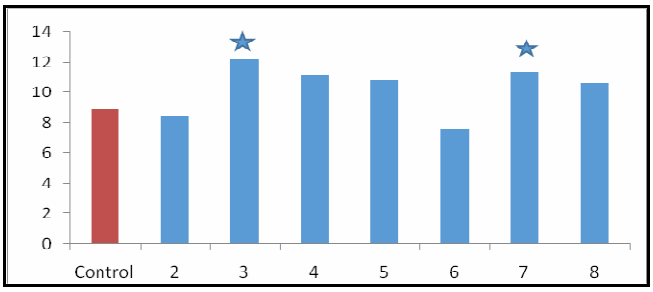


Figure 1. Analgesic Activity of succinimide derivatives.

Table. 3. Analgesic Activity of morphine by hot plate method.

No of mice	**control**	**50mg/kg**	**25mg/kg**	**12.5 mg/kg**	**6.25 mg/kg**
1	8.34	30	25.5	13.18	8.88
2	9	30	30	8.37	27.2
3	8.5	30	30	28.17	20
4	6	30	23	30	
	7.96	30	27.13	19.93	18.7
	1.3	0.0	3.5	10.8	9.2

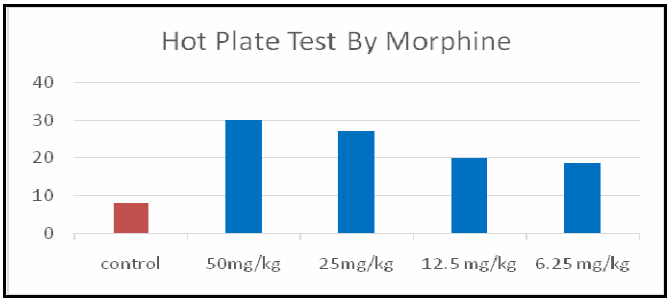


Figure 2. Analgesic Activity of morphine.

The anticonvulsant activity of the synthesized succinimides **2-8** are evaluated in mice using picrotoxin induced convulsions at dose 5 mg/kg. The test compounds are administered IP at a dose of 0.2 ml/kg 30 minutes before administration of picrotoxine. The animals were observed after 15 minutes of picrotoxin administration, and the results are summarized in **Table 4-6, Figures 3, 4.**

Among the newly synthesized compounds significantly indicative of their ability to prevent, decreasing and protection seizure spread. Compounds **2** and **8** have been shown to prolong onset of seizure, where other compounds **4-7** had little effect on the onset time, while compounds **2** and **3** were inactive. Compounds **2**,**3**,**5** and **8** had significantly decreased the number of seizures, whereas all others compounds only decreased the number of seizures. The investigated compounds **3**,**5** and **8** significantly decreased duration of seizures after picrotoxin administration, where compounds **2** , and **4** had little effect on the duration of seizures and while other compounds were inactive. The data obtained from the *in vivo* studies can be further evaluated for the side effects and mechanism of action.

Table 4. Picrotoxin-induced seizures onset time

No of mice	Control	2	3	4	5	6	7	8
1	16.1	19.34	11.9	14.2	21.03	12.29	20.45	20
2	16	19.44	16.95	14.75	14.01	16.57	16.3	19
3	9.05	22.03	17.4	19.23	11.26	18.15	13.51	21
4	13.3	23.3	14.11	17.3	18.01	18.45	12.3	22
		**	*	Not	Not	Not	Not	**
	13.6	21.0	15.1	16.4	16.1	16.4	15.6	20.5
	3.3	2.0	2.6	2.3	4.3	2.8	3.6	1.3

Table 5. Picrotoxin-induced seizures duration of seizures

No of mice	Control	2	3	4	5	6	7	8
1	51	15	11	40	1	60	60	24
2	60	1	19	18	36	*52*	*55*	*37*
3	50	1	6	60	17	20	54	26
4	59	16	25	14	4	57	60	12
		***	***	Not	**	Not	Not	**
	55	8.25	15.25	33	14.5	47.25	57.25	24.75
	5.2	8.4	8.4	21.3	15.9	18.5	3.2	10.2

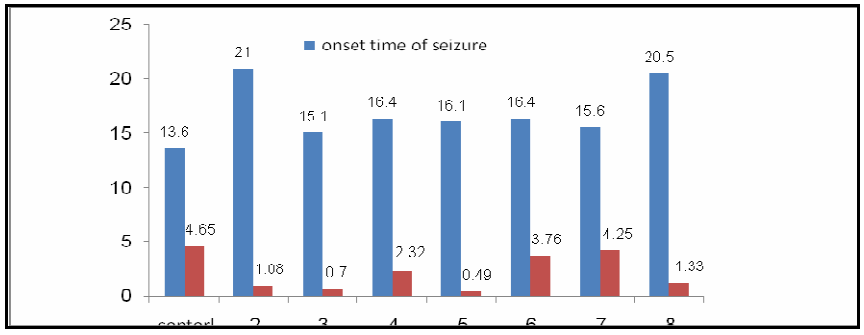


Figure 3. Picrotoxin-induced seizures, onset and duration of seizures.

Table 6. Picrotoxin-induced seizures number of seizures.

No of mice	Control	2	3	4	5	6	7	8
1	4.41	2.2	0.45	1.26	0	*4.8*	*5.2*	*1.5*
2	5.2	0	0.71	1.5	1.13	4.41	3.75	1.13
3	4.2	0	0.34	5.2	0.45	1.56	3.27	1.5
4	4.77	2.1	1.3	1.3	0.37	4.27	4.77	1.2
		**	***	*	***	Not	Not	***
	4.65	1.08	0.70	2.32	0.49	3.76	4.25	1.33
	0.44	1.24	0.43	1.93	0.47	1.48	0.89	0.20

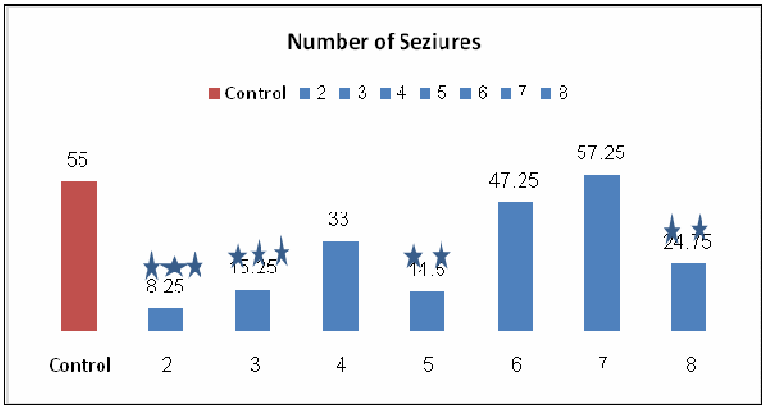


Figure 4. Picrotoxin-induced seizures (Number of seizures).

Conclusion.

The results of the work demonstrated that *N*-substituted succinimides have a good analgesic activity using hot plate method. Also some anticonvulsant activity in picrotoxin screening test is observed with some compounds.

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