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Synthesis and Pharmacological Evaluation of Some New Schiff Bases of Succinimide

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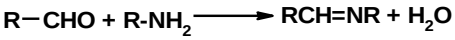
Abstract: A series of Schiff bases were prepared by reaction of equimolar of 4-(N-succinimidyl) phenyl hydrazide**3** and substituted aromatic aldehydes (Benzylaldehyde, Chlorbenzaldehyde, 3-Nitrobenzylaldehyde, 4-Nitrobenzylaldehyde, Salcyladehyde and acetaldehyde) for determining the analgesic and anti-bacterial activities. The structures of the new synthesized compounds were confirmed by physical and spectral analysis. All the synthesized compounds were evaluated *in vivo* for analgesic and *in vitro*for antibacterial activities by using standard experimental models. The results indicated that the new synthesized compounds exhibit good biological activities.

Key words: Schiff bases, Succinimide, Analgesic activity and Anti-bacterial activity

INTRODUCTION

Drugs are chemicals that prevent disease or assist in restoring health to the diseased individuals as such they play an indispensable role in modern. Synthesis of derivatives has beenan importanttool and is aimed at modifying the action of existing drugs, particularlytoreduce the side effects andto potentiatethe action.Succinimide and its N-substituted derivatives are important compounds of many drugs and drug candidates. Cyclic imides and their derivatives contain an imide ring[1-3] and the general structure –CO–N(R)–CO–. A diversity of biological

activities and pharmaceutical uses have been attributed to them, such as succinimide is a part of many active molecules possessing activities such as CNS depressant[4], analgesic[5], antitumor[6], cytostatic[7], anorectic[8], nerve conduction blocking[9], antispasmodic[10], bacteriostatic[11], muscle relaxant[12], hypotensive[13], antibacterial[14], antifungal[15], anti-epileptic[16] and anti-tubercular[17].Compounds containing an azomethazine group (-CH=N-) are known as Schiff bases. They are usually formed by condensation of a primary amine with a carbonyl compound asshown in **scheme1.**



Scheme1: Preparation of Schiffbases

Where R may be an aliphatic or an aromatic group. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic having an effective conjugation system, are more stable[18.] Schiff bases appear to be important intermediates in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most prevalent types of catalytic mechanisms in biochemical processes involves condensation of primary amine in an enzyme, usually that of a lysine residue, with a carbonyl group of the substrate to form an imines or Schiff bases[19.] Schiff's bases containing heterocyclic scaffolds have been known to possess a wide range of biological and pharmacological activities for a long time. In the recent years, they have gained significant interest in the area of drug research and development owing to their broad bioactivities such as antibacterial, antifungal, anti-inflammatory, anticonvulsant, antiviral and anticancer activities.

MATERIALS AND METHODS

All chemicals and solvents, reagents used in the present study were of analytical grade purchased from Sigma**,** Fischer. All the solvents were used after distillation. The melting points were determined by open capillary method and were uncorrected. The purity of compounds was confirmed by thin layer chromatography using Silica coated aluminium sheets (silica gel 60 F254). IR spectra were recorded using KBr on FTIR Shimadzu.

Synthesis:

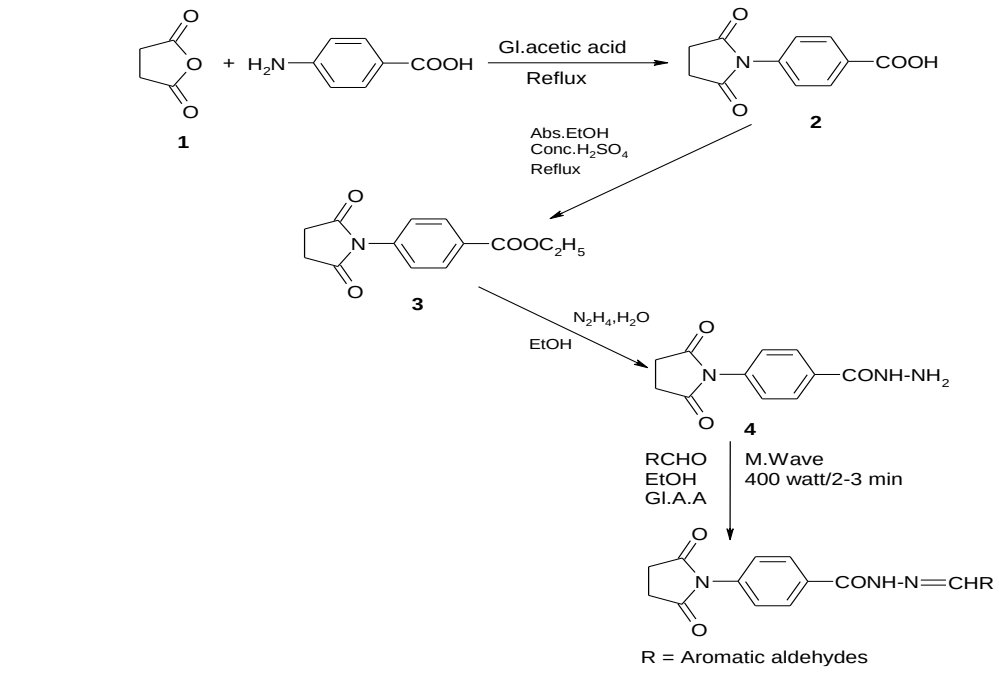
Synthesis of N-(4-carboxy phenyl) Succinimide 2: A mixture of 4-amino benzoic acid (0.01mol,1.37g) and succinic anhydride (0.01mol,1.0 g) in 12mL) of glacial acetic acid was refluxed for 4 hrs with stirring. The resulted mixture was poured in cold water with stirring then the separated solid was filtered, washed twice with distilled water (30mL), dried and finally purified by recrystallization from ethanol.

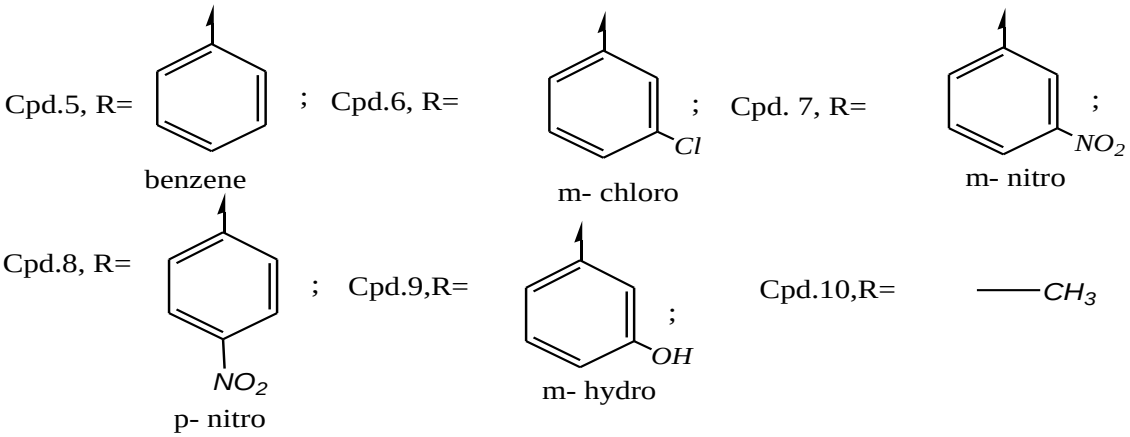
Synthesis of Ethyl-(4-(N-Succinimidyl)) benzoate3: A mixture of compound[1](0.01mol,2.19g) in Absolut ethanol (15mL)and(1.3mL) of conc.H_2SO_4 was refluxed for 6 hrs with stirring then excess alcohol was distilled off and the residue was cooled then poured into cold water. The separated solid was filtered, washed with distilled water, dried then recrystallized from methanol.

Synthesis of 4-(N-succinimidyl) phenyl hydrazide 4: A mixture of compound [2] (0.01mol, 2.47g) and hydrazine hydrate (0.015mol, 0.7mL) was refluxed for 4 hrs then (15mL) of ethanol was added and reflux

was continued for additional 8 hrs with stirring. The formed precipitate was filtered, washed with cold distilled water, dried and recrystallized from n-hexane.

General procedure for the preparation of Schiff bases5-10: The Schiff base was prepared by reaction of equimolar (0.01 M) of 4-(N-succinimidyl) phenyl hydrazide. **3** and substituted aromatic aldehydes. Each reactant was dissolved in a minimum amountof ethanol (5ml)m than mixed together and followed by addition of one drop of glacial acetic acid. This mixture was irradiated to microwave (400 watt) for 2-3 minutes. After the reaction was completed, it allowed to cool, the crude solid product was collected through filtration and washed several times with ethanol then dried. The product was re-dissolved in ethanol for recrystallization as shown in **scheme2.**





Scheme2: Synthesized compounds 2-10

Table 1: Physicochemical properties of new synthesized compounds. 2-10

No.	**Compounds**	**M. F. (M.Wt)**	**Recrys Solvent**	**M.P °C**	**Yield %**	**IR(KBr) cm^{-1}**
2	4-(2,5-dioxopyrrolidin-1-yl)benzoic acid	$C_{11}H_9NO_4$ (219.20)	ETOH	206-208	92	3307 O-H; 3074 C-H aromatic;1693 C=O carboxylic;1666 C=O imide ;1596 C=C Ar; 1377 C-N imide
3	Ethyl-4-(2,5-dioxopyrrolidin-1-yl) benzoate	$C_{11}H_{11}NO_2$ (189.22)	MeOH	88-90	65	1730 C=O ester;1150 C-O ester;3122 C-H aromatic; 1674 C=O imide;1600 C=C Ar; 1369 C-N imide
4	4-(2,5-dioxopyrrolidin-1yl)benzohydrazide	$C_{11}H_{11}NO_2$ (189.22)	n-hexane	102-104	57	3430,3346 NH_2;3240 N-H; 1629 C= O imide; 1367 C-N imide;1602 C=C aromatic; 1683 C=O imide
5	N-benzylidine- 4-(2,5-dioxopyrrolidin-1-yl)benzohydrazide	$C_{18}H_{15}N_3O_3$ (321.34)	EtOH	105-107	85%	2550 C-H aldeh;3900 N-H;1750 C=O imid 1600 C=C Ar ;1500 N=C; 1650 C-O carboxylic
6	N-(3-chlorobenzylidine- 4-(2,5-dioxopyrrolidin-1-yl)benzohydrazide	$C_{18}H_{14}N_3O_3CL$ (355.78)	ETOH	214-216	58%	2350 C-H aldeh;3300 N-H,1750 C=O imid 1600 C=C Ar,1550 N=C,1650 C-O carboxylic 800 C-Cl
7	4-(2,5-dioxopyrrolidin-1-yl)-N-(3-nitrobenzylidine) benzohydrazide	$C_{18}H_{14}N_4O_5$ (366.34)	MeOH	164-166	61%	2300 C-H aldeh;3300 N-H;1700 C=O imid 1600 C=C Ar ;1550 N=C;1650 C-O carboxylic 1350 NO_2
8	4-(2,5-dioxopyrrolidin-1-yl)-N-(4-nitrobenzylidine) benzohydrazide	$C_{18}H_{14}N_4O_5$ (366.34)	MeOH	103-106	50%	2300 C-H aldeh;3350 N-H ;1750 C=O imid 1600 C=C Ar ;1550 N=C;1700 C-O carboxylic 1300 NO_2
9	4-(2,5-dioxopyrrolidin-1-yl)-N-(3-hydroxybenzylidine) benzohydrazide	$C_{18}H_{15}N_3O_4$ (377.34)	ETOH	92-95	50%	3400 O-H;3000 N-H;1750 C=O imid 1600 C=C Ar ;1550 N=C ;1700 C-O carboxylic 1250 C-N
10	4-(2,5-dioxopyrrolidin-1-yl)-N-ethyledinebenzohydrazide	$C_{13}H_{13}N_3O_3$ (259.27)	ETOH	117-120	69%	3300 N-H ; 2900 C-H; 1750 C=O imid 1600 C=C Ar ;1550 N=C ;1650 C-O carboxylic

4. PHARMACOLOGICAL PART:

4.1. Animals:

Male Albino mice were used for different experiments. Animals were bred in the animal house of Tripoli University, each group consisted at least of 4 animals, was housed separately in a cage. Standard food pallet diet and water were available ad lib. The animals were kept at constant room temperature (20-25°C), with 12 hours dark/light cycle. All the experiments in this article were approved by institutional animal ethical committee (IAEC).

4.2. Drug Administration: Test drugs were suspended in 1% w/v carboxymethylcellulose. Control and test animals (n ≥4) were injected intraperitoneally either by test drug or vehicle control in dose 50mg/kg and volume of 1mL/100g. Tests for analgesic activity were performed 30 minutes after drug administration.

4.3. Hot Plate Method:

The animals were placed on hot plate at 55-56°C. End point was recorded when the animal licked its four-limbs or jumped out of the plate. The cut-off time of the experiment was 30 seconds [20, 21].

4.4. Induction of Pain by Acetic Acid:

Albino mice (treated and control groups) were injected intraperitoneally with 1mL/100g of 3% acetic acid, the number of was recorded for a period of 10 minutes ignoring the period of first 10 minutes after injection of acetic acid.

A. Acetic acid induced pain

Control	4	5	6	7	8	9	10
45	11	14	8	10	12	29	8
42	9	22	9	12	13	30	9
31	13	30	8	11	15	10	13
	*	*	*	*	*		*
39.3	**11.0**	**22.0**	**8.3**	**11.0**	**13.3**	**23**	**10.0**
7.4	2.0	8.0	0.6	1.0	1.5	11.3	2.6

Table2 : Analgesic Activity of new Schiff's bases of Succinimide 4-10 by acetic acid method

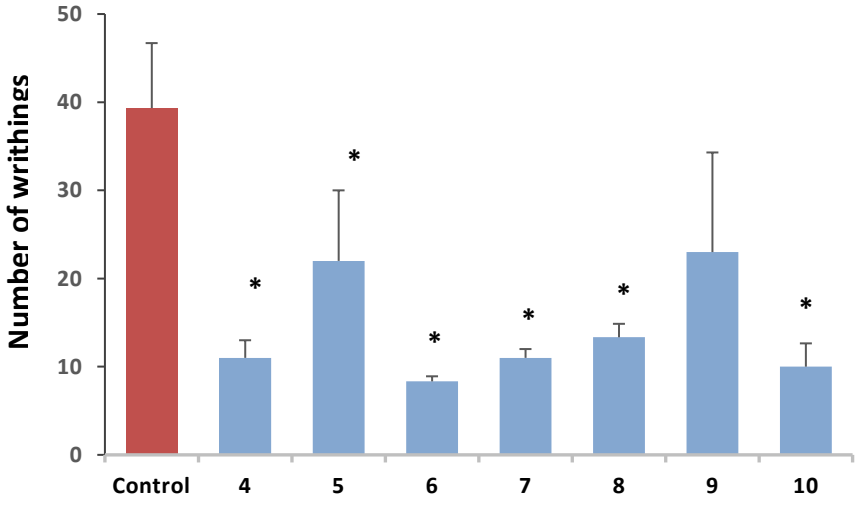


Figure.1. : Analgesic Activity of new Schiff's bases of Succinimide 4-10 by acetic acid method

B. Hot plate thermal pain :

Control	4	5	6	7	8	9	10
7	12	9	9	11	8	14	6
9	11	14	10	8	9	11	11
6	11	12	10	10	11	10	10
	*					*	
7.3	**11.3**	**11.7**	**9.7**	**9.7**	**9.3**	**11.7**	**9.0**
1.5	0.6	2.5	0.6	1.5	1.5	2.1	2.6

Table.3. : Analgesic Activity of new Schiff's bases of Succinimide 4-10 by hot plate method

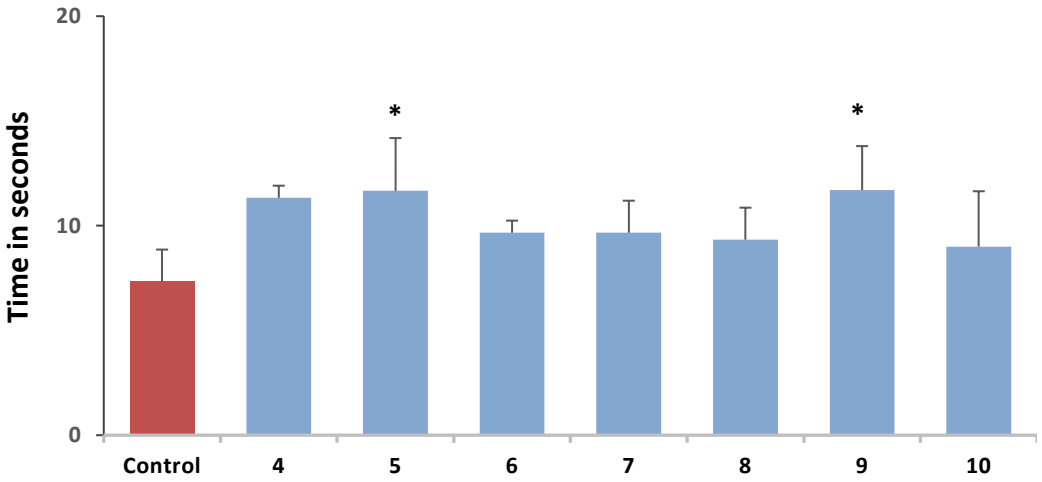


Figure.2: **Analgesic Activity of new Schiff's bases of Succinimide 4-10 by hot plate method**

RESULT & DISCUSION

1. Chemistry: Some Schiff's bases of succinimide were synthesized by reaction of equimolar of 4-(N-succinimidyl) phenyl hydrazide. 3 and substituted aromatic aldehydes with a yield varying from50-85 %. The physicochemical properties of the synthesized compounds are reported in **Table 1**. The purity of these compounds was determined by TLC and their structures were confirmed by IR.

2. Pharmacology: All described, new Schiff's bases of succinimide **4-10**, were evaluated *in vivo* for analgesic activity by using standard experimental models. The evaluation of analgesic activity was done by hot plate (thermally induced pain) and Acetic acid induced pain methods (chemically induced pain), the reaction time was considered as therapeutic endpoint. From the **fig.1 and 2**, all the synthesized compounds **4-10** except compound 9 at dose of 50 mg/kg exhibited significant effect in decreasing the number of writhings reflex produced by acetic acid. In addition compounds 5 and 9 showed significant

increase in hot plate reaction time. Therefore the results suggested that some of these compounds have effect like peripherally and /or centrally acting analgesics, therefore, more experimental work is required to elucidate the mechanism of action of these compounds.

3. MICROBIOLOGY

Biological evaluation: All the prepared compounds in this work were screened for their antibacterial activity against *MRSA: methicillin-resistant staphylococcus aureus,E.Coli:-Escherichia coli, ESBL: Extended spectrum B-lactamase,* ***P.sub****:Pseudomonas,****B.sub****:bacillussubtillis*at 300 µg/discussingNitrofuratoine as the standard antibacterial agent. DMSO (3%) was used as a control. The zone of inhibition was recorded in mm after incubation of plates for 24 hrs (antibacterial). The method employed was cup plate method[22, 23]. The antibacterial activity of the new Schiff bases of succinimide is summarized in **Table4**.

The compounds **5-8** have shown little activity against *staphylococcusaureus*compared to the standard antibacterial drug. The antibacterial data revealed that the compound **6** were more active than other compounds tested against the above microbes. But it was less active than the standard drug. The synthesized compounds have found to be better antimicrobial activity comparing to the control.

Table 4: Antimicrobial activity of synthesized compounds against a narrow spectrum of bacteria.

No.of Comp	Inhibition zone diameter (mm)						
		(-ve) bacteria			(+ve) bacteria		
	Conc. (µg)	*K.P*	*E.Coli*	*P.sub*	*B.sub*	*St.aur*	*MRSA*
5	300	6	6	6	6	11	6
6	300	6	6	6	6	9	6
7	300	10	10	6	6	11	12
8	300	10	10	6	6	11	12
9	300	6	11	6	6	13	6
10	300	6	6	6	6	6	6
DMSO		6	6	6	6	6	6
F(300µg)		18	18	11	11	20	21

Well diameter Zone: 6mm. E.coli: Escherichia coli, MRSA:Metacillin resistant, St.aur: Staphylococcusaureus, k.p:Klebsiella, P.sub:Pseudomonas, B.sub:bacillussubtillis and F:Nitrofuratoil (300 µg)

CONCLUSIONS

It may conclude that the new Schiff's base of succinimide have been successfully synthesized and tested for analgesic and antibacterial activities. The new synthesized compounds either exhibited some analgesic activity in the experimental model test. Nevertheless, some of the compounds were found to possess antibacterial activity against *Staphylococcus aureus* and MERSA when compared with the control.

ACKNOWLEDGMENT

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