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RESEARCH ARTICLE

STUDY OF FEW TETRALONE DERIVATIVES

SOURAV DE[1]*, SUBHASIS BANERJEE[2], C.NAVYA KEERTHI[3], B.MOHANA LAKSHMI[3]

[1]Assistant Professor, Seven Hills College of Pharmacy, Venkatramapuram, Tirupati-517561,[2]Assistant Professor, Gupta College of Technological Sciences, Asansol, West Bengal,[3] Seven Hills College of Pharmacy, Tirupati.Email:mpharmsourav@rediffmail.com

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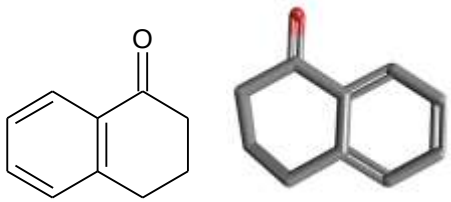
ABSTRACT

Tetralone ring system has drawn an immense attention in the field of drug discovery by virtue of their wide applications as an analgesic, antidepressant, antifungal and antibacterial. The wide range of its therapeutic application paved the way to the researchers to introduce this nucleus frequently in the diversified molecular skeleton to generate novel compounds with high therapeutic value. In this case, we have tried to present various therapeutic applications, which have already been demystified by the researchers. The study may prompt the researcher to generate scaffolds of highest therapeutic efficacy considering the importance of tetralone nucleus. All the synthesized products were characterized by spectral and elemental analysis data.

Keywords: Tetralone, Sertralone, Antidepressant activity, FTIR.

INTRODUCTION

Tetralone is an organic chemical compound with the molecular formula $C_{10}H_{10}O$. It is a common intermediate in organic synthesis. It is a ketone derivative of tetralin.



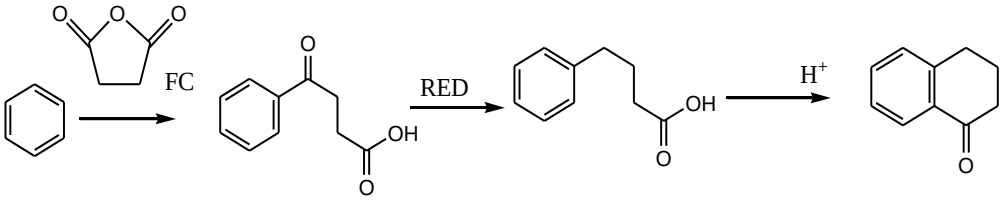
IUPAC NAME**:** 3, 4-dihydronaphthalen-1(2*H*)-one

Antidepressants are drugs which can elevate mood in depressive illness. Practically all depressants affect monoaminergic transmission in the brain. Tricyclic antidepressants (TCAs) are a group of drugs used to treat affective, or 'mood', disorders. Mood disorders are associated with reduced levels of monoamines in the brain. TCA binding to 5-HT and noradrenaline re-uptake transporters prevents the re-uptake of these monoamines from the synaptic cleft and their subsequent degradation. This reuptake blockade leads to the accumulation of 5-HT and noradrenaline in the synaptic cleft and the concentration returns to within the normal range [1-2].

Subsequently characterized analytically, using different spectroscopic techniques in order to ensure the proper formation of the compounds of interest.

In the recent past, tetralone have aroused great interest in the field of drug discovery owing to their wide applications as an analgesic, antidepressant, antifungal and antibacterial. It is a ubiquitous structural feature of many alkaloid natural products and viable drug candidates. The pharmacological effect of potential drugs depends sensitively on the stereochemistry and ring conformation especially in the case of 4 substituted tetralone.

Benzene is reacted with succinic anhydride by a Friedel-Crafts acylation, the intermediate product is reduced and a second Friedel–Crafts acylation takes place upon the addition of acid [3]



Properties

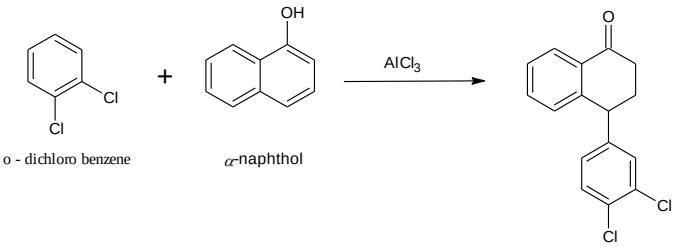
Molecular Formula:	$C_{10}H_{10}O$
Molar mass:	146.1858
Density:	1.101 ± 0.06 g/cm^3
Melting point:	99-103°C

MATERIALS AND METHODS:

Step 1

Preparation of sertralone [4-9]

Mixtures of o-dichlorobenzene (300ml), α-naphthol (100gm) were taken into a four-necked flask and dissolved the mixture by stirring for few minutes. Next, the reaction mixture was cooled to 10 °C temperature in ice-salt bath followed by addition of aluminum chloride in 4 lots (40, 40, 40, 30 grams) at T= 10 – 20 °C. Then the reaction mixture was heated at 60 – 65 °C for 1h. Then the reaction mixture was placed in an ice bath for 30 min with continuous stirring. The white precipitate got separated.



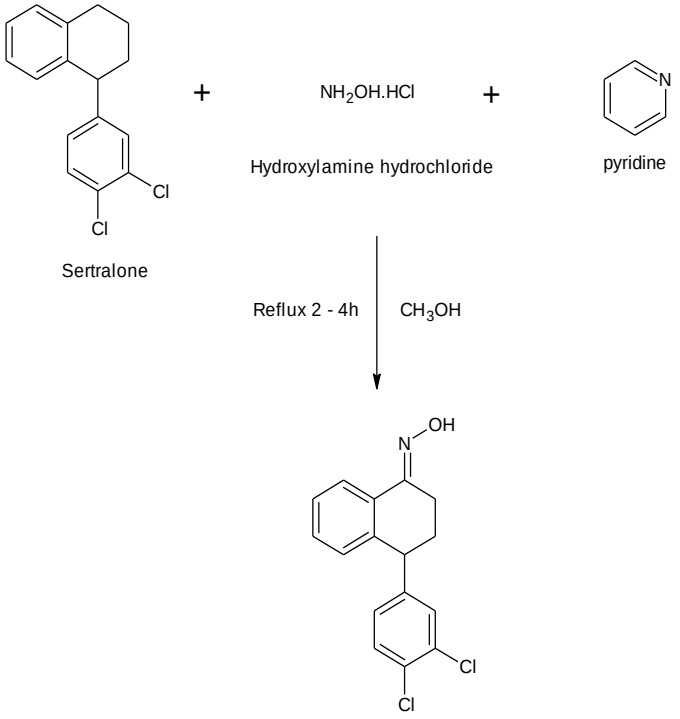
o - dichloro benzene α-naphthol Sertralone

The mixture was kept untouched for an hour. Then the precipitate was filtered out and kept for air drying. After complete drying, the residue was further washed with water for several times. Then methanol was added and cooled for 1.5h at a temperature 0 – 5 °C. Then the precipitate was filtered out and kept for air drying.

Melting point: 99-103°C

Step 2

Preparation of sertralone to oxime:

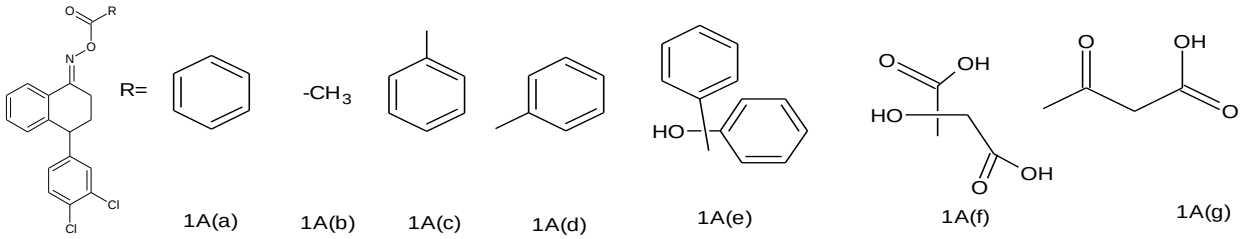


Methanol, sertralone and hydroxylamine hydrochloride were taken into a four-necked flask and dissolve the mixture by using stirring at room temperature for 30 min and no clear solution was observed. Next, the reaction mixture was cooled to 10 °C temperature at salt ice bath followed by addition of dropwise pyridine, and then a slightly exothermic reaction takes place. Then the reaction mixture was reflux for 3hrs. A clear solution got separated. During this process suddenly reaction mass turned into a clear solution after 5 min reaction mass becomes cloudy. Then the solid was filtered, washed with methanol, dried by U/V.

Melting point**:** 98-100 °C

Preparation of tetralone derivatives

According to the literature review, the following 7 compounds were synthesized which involves the introduction of diversified pharmacophoric fragments at position 1 with anchoring the 4th position with the 3,4-Dichlorophenyl group. Derivatives of type 1(a-g) were synthesized followed by the procedure described under experimental section [8-13].



1(A

The mixture of methylene dichloride and oxime was taken into a 100 ml flask at room temperature. The reaction mixture was stirred for 15 min, followed by addition of di cyclohexyl carbodiimide. A clear solution was observed. Benzoic acid was added to the above mixture, the slightly exothermic reaction took place. It was stirred for 17h. In process monitoring of reaction was carried out by doing TLC at a specific time interval. The compound thus formed was filtered and washed with methylene dichloride (MDC). Then the organic layer was washed again with sodium bicarbonate. The organic layer was separated, dried over sodium sulphate [14].

Anti-Depressant Screening Tests [15-17]:

Antidepressant screening tests, not like the models which can be defined as an [organism] or a particular state of an organism that reproduces aspects of human pathology, provide only an end-point behavioral or physiological measure designed to assess the effect of the genetic, pharmacological, or environmental manipulation [20].

Despair Swim Test Apparatus:

Forced swimming test: The forced swimming test (FST) is based on the observation that animals develop an immobile posture in an inescapable cylinder filled with water. In this test, immobility is interpreted as a passive stress-coping strategy or depression-like behavior (behavioral despair). After antidepressant administration, the animals will actively perform escape-directed behaviors with a longer duration than animals with control saline treatment. FST is the most widely used tool in depression research, more specifically as a screen for acute antidepressants [21].

For the determination of antidepressant activity, forced swim test (FST) protocol was employed. During the test, animals were individually placed in a glass cylinder (20 cm in height, 14 cm in diameter) filled with water up to a height of 10cm, at 25 ± 2 °C. All animals were forced to swim for 5 min and the duration of immobility was observed and measured during the 5 min interval of the test. Immobility period was regarded as the time spent by the rats to float in water with no struggle and making only those

movements necessary to keep its head above the water. In order to check the fitness level of each test animal, a pre-test was carried out 24h before the FST by subjecting each test animal to a session of 15 min swimming [22].

RESULT AND DISCUSSION [17-19]

Physico-Chemical properties of synthesized compounds

Table 1:

S.No.	COMPD	Formula	Mol.wt	M.P(^{O}C)	%Yield
1.	1A(a)	$C_{24}H_{17}Cl_2NO_2$	410.29	118-120	65
2.	1A(b)	$C_{18}H_{15}Cl_2NO_2$	348.22	115-118	64
3.	1A(c)	$C_{24}H_{19}Cl_2NO_2$	423.08	110-112	68
4.	1A(d)	$C_{24}H_{21}Cl_2NO_2$	415.62	130-132	68
5.	1A(e)	$C_{30}H_{23}Cl_2NO_3$	516.41	115-117	66
6.	1A(f)	$C_{36}H_{27}Cl_2NO_4$	598.07	140-142	70
7.	1A(g)	$C_{24}H_{19}Cl_2NO_3$	432.52	155-158	67

Compound 1a to 1g were prepared and subsequently characterized analytically, using different spectroscopic techniques in order to ensure the proper formation of the compounds under investigation.

1A (a)

FTIR (KBr) v/cm^{-1}: 2932 (C–H *str*), 2728 (C–H *str* aldehyde), 1733 (C=O *str*), 1249.93 (C–N *str* aliphatic amines), 766 (C–Cl *str*).

1A (b)

FTIR (KBr) v/cm^{-1}: 2940 (ali C–H *str*), 2821 (C–H *str* aldehyde), 1747 (C=O *str*), 1471 (C–C *str* aromatics), 1177 (C–N *str* aliphatic amines), 756 (C–Cl *str*)

1A (c)

FTIR (KBr) v/cm^{-1}: 2943 (ali C–H *str*), 2819 (C–H *str* aldehyde), 1747 (C=O *str*), 1465 (C–H bend alkanes), 1062 (C–N str aliphatic amines), 755 (C–Cl str)

1A(d)

FTIR (KBr) v/cm-1: 2933 (ali C–H *str*), 2825 (C–H *str* aldehyde), 1759 (C=O *str*), 1101 (C–N *str* aliphatic amines), 774 (C–Cl *str*).

1A (e)

FTIR (KBr) v/cm^{-1}: 2931 (ali C–H *str*), 2852 (C–H *str* aldehyde), 1759 (C=O *str*), 1450 (C–H bend alkanes), 1086 (C–N *str* aliphatic amines), 763 (C–Cl *str*)

1A (f)

FTIR (KBr) v/cm^{-1}: 2932 (ali C–H *str*), 2821 (C–H *str* aldehyde), 1762 (C=O *str*), 1470 (C–C *str* aromatics), 1135 (C–N *str* aliphatic amines), 767 (C–Cl *str*)

1A (g)

FTIR (KBr) v/cm^{-1}: 3059 (C=C *str* alkenes), 2933 (C–H *str* aldehyde), 1654 (C=O *str*), 1590 (C–C *str* aromatics), 1482 (C–H bend alkanes), 1062 (C–N *str* aliphatic amines), 757 (C–Cl *str* alkyl halides).

1A(a)

^{1}H-NMR (DMSO-d_6, δ ppm): 8.40-8.37 (m; 3H; dihalogenated ArH), 8.11-8.09 (m; 4H; fused ArH), 7.60-7.58 (m; 5H; Ar-H), 3.67-3.61 (m; 5H; fusedcyclohexyl H)

1A (a)

MS m/z: 410 [M^{+}]; 409 [M-1]; 411 [M+1]

BIOLOGICAL EVALUATION:

Antidepressant activity

Major depressive disorder, also called "clinical depression" or often simply "depression", is a common, long-lasting and diverse psychiatric syndrome that significantly affects a person's thoughts, behavior, feelings and sense of well-being. Symptoms include low mood and aversion to activity. Depressed people may also feel sad, anxious, empty, hopeless, worried, helpless, worthless, guilty, irritable, hurt, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details, or making decisions, and may contemplate or attempt suicide. Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains, or digestive problems that are resistant to treatment may also be present [18-19].

Table 2: Effect of Tetralone Derivative on Despair Swim Test in Rats at Different Time Interval.

Group	Treatment	Duration of immobility (Sec/5min)		% Change in activity	
		30 min	60 min	30 min	60 min
I.	Control (Vehicle)	190.7±1.25	195.4±1.32	-	-
II.	Fluoxetine(10mg/kg)	89.88±1.64***	64.70±1.25***	52.86	66.88
III.	Tetralone Derivative (TRN 5mg/kg)	113.4±1.84***	92.90±0.84***	40.83	52.45

Values were mean ±S.E.M. for (n= 6 rats) expressed as the time (in seconds) of 6 animals in each group. Data analysis was performed using Dunnett's test. ***P < 0.001 vs. control

RESULT

In despair swim test apparatus, the tetralone derivative 5mg/kg p.o. significantly decreased the immobility time. The magnitude of the antidepressant effects of tetralone derivative 5mg/kg p.o. was comparable to that of fluoxetine 10 mg/kg i.p.

CONCLUSION

This study has revealed that tetralone derivatives show novel antidepressant activity. In general, the compounds in series are prepared including their derivatives, considered for analytical study as well as biological evaluation. So many data that are obtained from this process are encouraging which may continue for further studies. The evidence suggests that development of the compounds in series 4 shows antidepressant activities.

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