INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF INDAZOLINE TETRALONE

Sandeep Arora*, Anil Pareek, Navneet Agrawal and BP. Nagori

Lachoo Memorial College of Science and Technology, Pharmacy Wing, Jodhpur, 389, First C Road Sardarpura Jodhpur-342 003, Rajasthan, India.

ABSTRACT

A series of 2-substituted benzylidene -tetralones were synthesize by using synthetic scheme aldol condensation and further condense with phenyl hydrazine and synthesize substituted indazoline derivatives. All these compounds have been analyzed by IR, NMR and Mass spectroscopy for structure assignment and were further evaluated for their antimicrobial activity. The Antibacterial activities of these compounds were studied using agar difusion method. Among these compound Di chloro & fluro indazoline indazoline derivatives are highly potent and against antimicrobial activity.

Keywords: Tetralone, Benzylidiene, Indazoline, Antimicrobial activity.

INTRODUCTION

1, 2, 3, 4-Tetrahydronaphthyl-heterocycles bearing compounds constitute a class of continued interest to the pharmaceutical, chemical and agrochemical communities. Many of these compounds have useful applications such as anticancer[1-5], antibacterial[6,7], Antiviral[8], and analgesic activities[11,12]. Literature survey indicated that this type of compounds could be enzymatically oxidized within the living cells to give products related to Naphthaquinones which are known to possess various potent biological activities The present work deals with synthesis of some benzylideine derivative of tetralone using 1-tetralone as a key starting material and form indazoline derivatives which were further investigate for antimicrobial activity.

2. MATERIALS AND METHODS

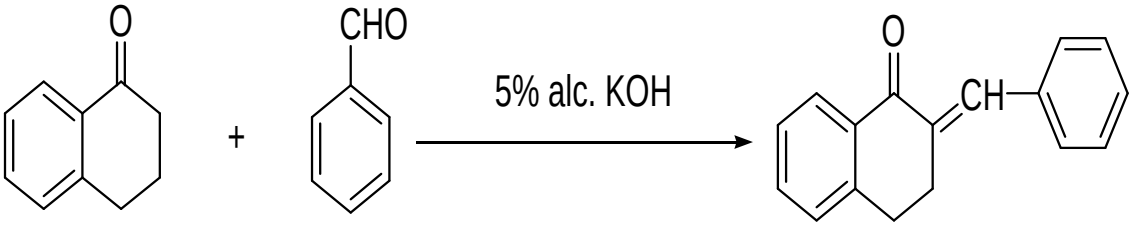
Melting point range of the synthesized compounds was determined by open capillary method using the melting point apparatus. Thin layer chromatographic analysis of the synthesized compounds was done on silica gel G coated glass plate. An IR spectrum of the intermediates and final compounds synthesized, the can be recorded by a modified reflectance technique which depends on the total internal reflectance of light in Bruker ATR spectrophotometer.

3. Experimental Section

Scheme: 1 Synthesis of 2-benzylidene tetralone-1

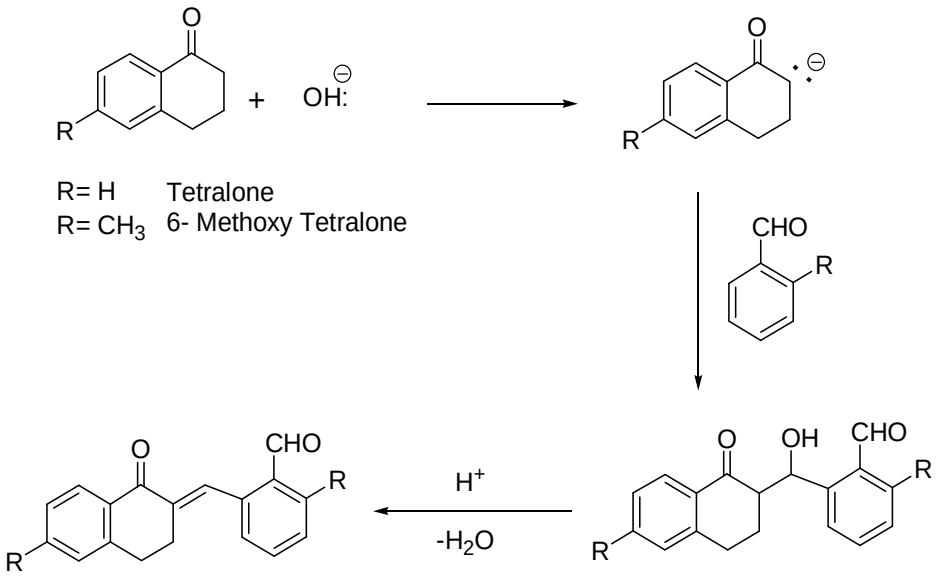
A mixture of α-tetralone (10 m.mole. 1.32 ml) & p-chlorobenzaldehyde (10 m.mole. 1.4 g) in ethanol (50ml) was stirred, cooled to 10 ^{0}C and then treated with a solution of 5% alc. KOH (0.56g) in ethanol (11.2ml). The cooling bath was removed & the solution allowed to warm at room temperature, a crystalline product started separating at 22^{0}C. After standing overnight at room temperature, the mixture was poured onto 200 ml of ice-water (200 ml). This product was filtered, washed with cold water allowed to dry over night. The product was crystallized with methanol.

Scheme 1:



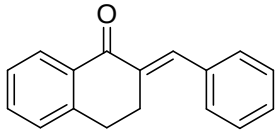
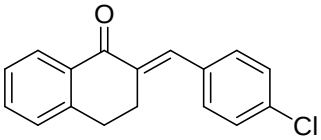
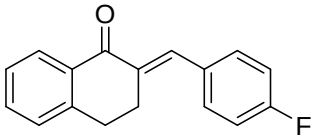
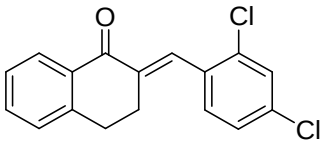
Proposed Mechanism

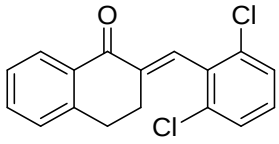
MECHANISM OF BENZYLIDINE FROM TETRALONE AND 6 METHOXY TETRALONE



R= H Tetralone
R= CH_3 6- Methoxy Tetralone

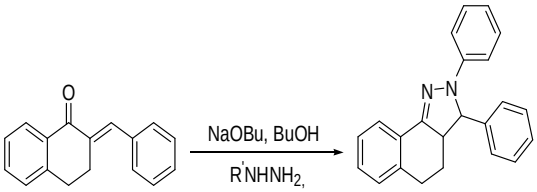
Physical data of benzylidiene derivatives (1-5)

S NO	STRUCTURE	M.W	M. F.	M.P.	%Yield
1		234	$C_{17}H_{14}O$	103-105^0 C	84.6
2		268	$C_{17}H_{13}ClO$	120-122^0 C	66.26
3		252	$C_{17}H_{13}FO$	105-108^0 C	76.2
4		303	$C_{17}H_{12}C_{l2}0$	156-158^{0}C	91.88

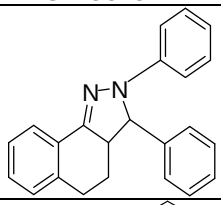
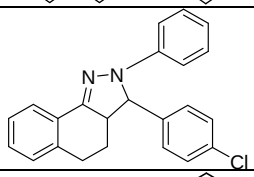
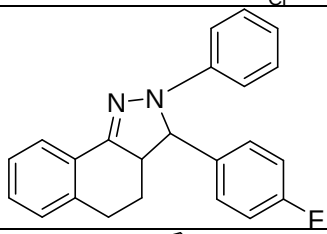
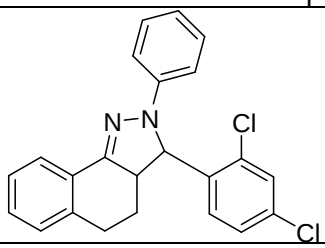
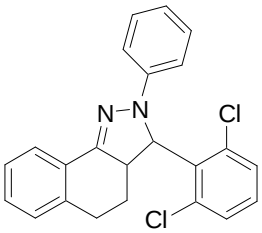
5		303	$C_{17}H_{12}Cl_20$	119-121^0 C	76.2

Scheme: 2: **Synthesis of Indazoline derivative of 2-benzylidene tetralone**

A mixture of 2-benzylidene tetralone-1 (2.34 gm,10mmol) and phenyl hydrazine (6ml 0.04 mol) and sodium metal (0.5 g) were taken in ethanol (20ml) stirred it for 5 minutes then reflux for 10 hours. Monitoring of reaction was done by TLC every one hour .Then removed solvent under reduced pressure and remaining residue was purified by crystallization and column chromatography.



Physical data of indazoline derivatives (6-10)

SNO	STRUCTURE	M.W	M F	M.P.	%Yield
6		324	$C_{23}H_{20}N_2$	122-126°C	45.23
7		359	$C_{23}H_{19}N_2Cl$	131-132°C	35.2
8		342	$C_{23}H_{19}N_2F$	149-150°C	36.2
9		392	$C_{23}H_{19}N_2Cl_2$	135-137°C	42.2
10		392	$C_{23}H_{19}N_2Cl_2$	139-141°C	39.2

3. RESULTS AND DISCUSSION

3.1 Spectral investigation

1. Synthesis of 2-benzylidene tetralone- (1)

Yield: 3.79 gm (80.98 %) M.P :98-100 ^{0} C . Mass (FAB) [M+H] 235.2 ,^{1}H NMR(200 MHz, $CDCl_3$): δ 7.16- 7.25 (m,8H, Ar-H); 7.62 (s, 1H, olefinic proton); 2.85-2.98 (t, 2H,CH_2); 3.07-3.11(t, 1H, CH2) ,I.R: CO, 1659.4cm^{-1}; C=CH, 1594.3 cm^{-1}

2. Synthesis of 2-(4-Chloro benzylidene) tetralone (2)

Yield: 1.92g (76.2%), M.P:105-108^0 C , Mass (FAB)[M+H]$^+$:251,^{1}H NMR(200 MHz, $CDCl_3$):δ 7.36-7.50 (m,8H, Ar-H);7.82 (s,1H , olefinic proton); 2.95-2.98 (t, 2H, CH_2);3.07-3.11(t,1H, CH_2), I.R: C=O, 1661.0 cm^{-1}; CH, 1591.7.cm^{-1}3)

3. Synthesis of 2-(4-fluoro benzylidene) tetralone(3)

Yield:1.92g (76.2%),M.P:105-108^0 C, Mass (FAB)[M+H]:251,^{1}H NMR(200 MHz, $CDCl_3$):δ 7.36-7.50 (m,8H, Ar-H);7.82 (s,1H , olefinic proton); 2.95-2.98 (t, 2H, CH_2);3.07-3.11(t,1H, CH_2),I.R : C=O, 1661.0 cm^{-1}; CH, 1591.7.cm^{-1}

4.Synthesis of 2-(2, 4-dichloro-benzylidene) tetralone(4)

Yield: 2.78 g (91.88%), M.P 156-158^0 C Mass (FAB)[M+H]$^+$: 303 ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.34-8.14(m,8H, Ar-H);8.141(δ,1H olefinicproton); 2.95-2.98 (t, 2H, CH_2); 3.07 - 3.11(t, 1H, CH_2),I.R : CH, 160.9.6 cm^{-1}; C=O, 1669.6cm^{-1}

5. Synthesis of 2-(2, 6-dichloro-benzylidene) tetralone(5)

Yield: 2.65 (87.45%, M.P :157 162 ^{0} C, Mass (FAB) [M+H] $^+$: 303 ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.34-8.14 (m, 8H, Ar-H), 8.1413 (δ,1H, olefinic proton), 2.95-2.98 (t, 2H, CH_2),3.07-3.11 (t,1H, CH_2) I.R:(C=C str), 1669.9 cm^{-1}; C=O, 1611.4 cm^{-1}

6. Synthesis of Indazoline derivative of 2-benzylidene tetralone

Yield: 1.46g (45.23.%) M.P: 122-126^0 C, Mass (FAB) [M+H]$^+$: 324,^{1}H NMR(200 MHz, $CDCl_3$);δ 2.56-.2.70 (q,1H, CH_2), 2.88 -2.91 (t,1H, CH_2),2.17 -2.34 (q, 2H, CH), 3.25 (d,1H, CH) ,7.09-8.07 (m, 14H, Ar-H),I.R: C=N 1492 cm^{-1} NH= 3440 cm^{-1}

7. Synthesis of Indazoline derivative of 2-(4-Chloro benzylidene) tetralone

Yield: 1.0g (35.6%), M.P:128-132 ^{0} C, Mass (FAB) [M+H]$^+$: 359,^{1}H NMR(200 MHz, $CDCl_3$:δ 2.65-2.67 (t, 2H, CH_2) 2.04- 2.08 (q,1H, CH_2), 2.1 -2.5 (q,1H, CH), 3.9 (d,1H, CH), 6.42-7.99 (m, 13H, Ar-H I.R: C=N 1494 cm^{-1} ,NH= 3443 cm^{-1})

8. Synthesis of Indazoline derivative of2-(4-fluoro benzylidene) tetralone

Yield: 1.23g (36.29%),M.P: 145-150 ^{0} C, Mass (FAB)[M+H]$^+$: 342,^{1}H NMR(200 MHz, $CDCl_3$) : δ 2.56-2.70 (q,1H, CH_2) 2.88 - 2.91 (t,1H, CH_2),2.17 -2.34 (q, 2H, CH), 3.25 (d, 1H, CH) ,7.09- 8.07 (m,14H, Ar-H),I.R: C=N 1494 cm^{-1} NH= 3443 cm^{-1}

9.Synthesis of Indazoline derivative of 2-(2, 4-dichloro-benzylidene) tetralone

Yield : 1.65g (42.2. %),M.P:135-138^0 C, Mass (FAB)[M+H]$^+$: 392,^{1}H NMR(200 MHz, $CDCl_3$: δ 2.37(t,1H, CH_2) 2.86 -2.91 (t,1H, CH_2),2.26 (q,1H , CH) 3.63 (d,1H, CH) , 7.096 -7.26 (m, 13H, Ar-H), I.R: C=N 1494 cm^{-1} NH= 3443 cm^{-1}

10 Synthesis of Indazoline derivative of2-(2, 6-dichloro-benzylidene) tetralone

Yield 1.92 gm (71.6%),M.P :145-148^0 C,Mass (FAB) [M+H]$^+$: 269,^{1}H NMR(200 MHz, $CDCl_3$: δ 2.65 - 2.67 (t, 2H, CH_2) 2.04 -2.08 (q,1H , CH_2),2.1 -2.5 (q, 1H, CH), 3.9 (d,1H, CH) , 6.42-7.99 (m,13H, Ar-H I.R: C=N 1494 cm^{-1} NH= 3443 cm^{-1}

3.2 Antimicrobial Assay (Agar Diffusion Technique)

All the synthesized compounds were tested for *in vitro* antibacterial and antifungal activities against *E.coli, P.aeruginosa,* and *C.albicans* strains with respect to Ciprofloxacin and Fluconazole as the positive control drugs. Zone of inhibition (in mm) values for analogs and positive control drugs were determined by disc plate method13. All the compounds were dissolved in DMSO; the plates were incubated at 26 ^{o} C for 24 hrs and the resulting zone of inhibition (in mm) was measured. Antimicrobial screening for analogs and positive control drugs were performed at a concentration of 100 and 200 µg/mL and the results are illustrated in Table-3. From the antimicrobial screening results it was observed that, the compound.The antimicrobial screening results reveals that condensation of heterocyclic ring on benzylidiene derivatives show marked antibacterial activity against *Escherichia* coli and pseudomaonas bacterial strain and introduction of chloro and fluro group possess potent anti microbial activity like IZT 7, 8 due to electron withdrawing nature and IZT10 show maximum antibacterial and antifungal activity.

Table 6.1: Antibacterial and antifungal study of different synthesized compounds

S. No.	Compound	Zone of Inhibition (mm)		
		E.coli (MTCC443)	P.aeruginosa (MTCC424)	C.albicans (MTCC227)
1.	IZT - 1	18	13	15
2.	IZT - 2	26	30	34
3.	IZT - 3	19	20	22
4.	IZT - 4	12	13	20
5.	IZT - 5	23	21	19
6.	IZT - 6	24	22	21
7.	IZT - 7	18	19	22
8.	IZT - 8	26	24	28
9.	IZT - 9	34	38	36
10.	IZT - 10	36	39	37
13.	Ciprofloxacin	33	38	-
14.	Fluconazole	-	-	36

4. CONCLUSION

In this paper we have discuss synthesis of Indazolines from 2-arylidene-1-tetralone All the synthesized compounds were evaluated for their antimicrobial activity. The antimicrobial screening results reveals that by condensation of heterocyclic ring on benzylidiene derivatives show marked antibacterial activity against *Escherichia coli* bacterial strain and introduction of chloro and fluro group possess potent anti microbial activity like IZT 7, 8 due to electron withdrawing nature and IZT10 show maximum antibacterial and antifungal activity.

5. REFERENCES

1. Al-Mutairi MS, Al-Abdullah ES, Haiba ME, Khedr MA and Zaghary WA. Synthesis, Molecular Docking and Preliminary in-Vitro Cytotoxic Evaluation of Some Substituted Tetrahydro- naphthalene (2',3',4',6'-Tetra-O-Acetyl-β-D-Gluco/-Galactopyranosyl) Derivatives. Molecules. 2012;17(4):4717-32.
2. Zaghary WA, Haiba ME and Anwar MM. Synthesis and In-Vitro Anticancer Evaluation of Some New (Tetrahydronaphthalen-2-yl) Nitrogen Heterocycles. Egypt Pharm J. 2005;4(1):145-56.
3. WahYee S and Simons C. Synthesis and CYP24 inhibitory activity of 2-substituted-3,4- dihydro-2H-naphthalen-1-one (tetralone) derivatives. Bioorg. Med Chem Lett. 2004;14(22):5651-54.
4. Woo LW, Howarth NM, Purohit A, Hejaz HA and Reed MJ. Potter Steroidal and nonsteroidal sulfamates as potent inhibitors of steroid sulfatase. J Med Chem. 1998; 41(7):1068 83.
5. Van Landeghem AAJ, Poortman J, Nabuurs M and Thijssen JHH. Endogenous Concentration and Subcellular Distribution of Estrogens in Normal and Malignant Human Breast Tissue. Cancer Res. 1985;45:2900-06.
6. Tomás-Gallardo L, Santero E, Camafeita E, Calvo E, Schlömann M and Floriano B. Molecular and biochemical characterization of the tetralin degradation pathway in Rhodococcus sp. strain TFB. Microbial Biotechnology. 2009;2:262-73.
7. Ferrante AA, Augliera J, Lewis K and Klbianov AM. Cloning of an organic solvent resistance gene in Escherichia coli:The unexpected role of alkylhydroperoxide reductase. Proc Natl Acad Sci. USA. 1995;92:7617-21.
8. Stigliani J, Boustie J, Amoros M, Montanha J and Girre M. Molecular Modelling and Antipoliovirus Activity of Some Isoquinoline. Pharm Pharmaco-Commun. 1998;4(1):65–68. American Chemical Science Journal. 3(3):203-220, 2013 219
9. Kamel MM and Michael JM. Synthesis and moulscicidal activity of some salicylamido tetralins. Egypt J Bilharziasis. 1988;10:121-25.
10. Nabih AA, Zayed J, Metri M, Kamel M and Motawie MS. Synthesis of some tetrahydronaphthyl-1,2,4-triazines of possible schistosomicidal activity. Pharmazie. 1984;39:862-3.
11. Fathalla OAM, Anwar MM, Haiba ME and Nofal S. Synthesis of Novel Tetrahydronaphthalen- 2-yl-Heterocycles For Analgesic, Anti-inflammatory an Antipyretic Evaluation. Acta Pol Pharm. 2009;66:259-270.
12. Ebeid MY, Fathalla OA, EL-zahar MI, Kamel MM, Abdou WAM and Anwar

MM. Newtetralyl thiazoles – The Anti-HIV And Anticancer Screening of 3-[4-[6-(1,2,3,4- Tetrahydronaphthyl)-Thiazol-2- yl-2-(p- Chlorophenyl)-Thiazolidin-4- One. Bull Fac Pharm Cairo Univ. 1996;34(2):125- 35.
13. Booth J and Boyland E. Metabolism of polycyclic compounds. 5. Formation of 1:2- dihydroxy- 1:2-dihydronaphthalenes. Biochem J. 1949;44(3):361–5.
14. Bueding E and Peters L. Effect of naphthoquinones on Schistosoma mansoni in vitro and in vivo. J Pharmacol Exp Ther. 1951;101(2):210-29.
15. El-Sayed A, Soliman Magdy IEl, zahar, Afaf El-Masry, Mohsen Kamel and Rasha S Gohar. Synthesis and anticancer evaluation of novel tetrahydronaphthalen-6-ylthiazole heterocycles against human HePG2 and MCF7 cell lines. Derpharma Chemica. 2010;2(5):507.
16. Zelle RE, Hancock AA, Buckner SA, Basha FZ, Tietje K, DeBernardis JF and Meyer MD. Synthesis and pharmacological characterization of ABT-200: a putative novel antidepressant combining potent α-2 antagonism with moderate NE uptake inhibition. Bioorg. Med. Chem. Lett. 1944;4(11):1319-22.
17. Shekhawat KS, Jhankal KK and Sharma DK. Synthesis of 4-(5',6',7', 8' tetrahydronaphthalene)- 1-tetralone.Der Pharmacia Sinica. 2013;4(1):17-20
18. Obrecht D, Spiegler C, Schoenholez P, Muller K, Heimgartner H and Stierli F. A New General Approach to Enantiomerically Pure Cyclic and Open-Chain (R)- and (S)-α,α-Disubstituted α- Amino Acids Helv. Chim. Acta. 1992;75:1666-96.
19. Jetter MC, Youngman MA, McNally JJ and McDonnell ME. Zhang S, Dubin AE, et al. Heteroaryl β-tetralin ureas as novel antagonists of human TRPV1. Bioorg. Med. Chem. Lett. 2007;17(22):6160–63
20. Vaidya NA, Panos CH, Kite A, Iturrian WB and Blanton CD. Jr. Synthesis of 3,4-dihydro-4-oxoquinazoline derivatives as potential anticonvulsants. J Med Chem. 1983;26(10):1422-5.