



Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF QUINAZOLINE THIONE DERIVATIVES OF 3, 4-DIHYDRO-1(2H)-NAPHTHALENONE

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ABSTRACT

A series of 2-substituted benzylidene-tetralone was prepared from 6-methoxy-tetralone by using an Aldol condensation and then these synthesized benzylidene-tetralone derivatives were further condensed with thiourea to give various substituted quinazoline thione derivatives. All of these compounds have been characterized by IR, NMR and Mass spectral analysis for structure establishment and further evaluated for their antifungal activity against *Aspergillus niger* (MTCC-282) and *Candida albicans* (MTCC-227) by agar diffusion method using fluconazole as standard drug. Among 6-methoxy-benzylidene derivatives; C₁, C₂, C₇ were least active and C₃, C₄, C₅, C₆ were moderately active while among quinazoline thione derivatives; C₈, C₉ were least active and C₁₀, C₁₁, C₁₂, C₁₃ were moderately active. When electron-withdrawing substitutions were made on both ring antifungal activity increased in (NO₂ > F > Cl) order. The maximum zone of inhibition (60.7 % and 69.7 %) was shown by compound C₅ among 6-methoxy-benzylidene derivative and C₁₁ had (72 % and 73 %) activity among quinazoline thione derivative against *Aspergillus niger* and *Candida albicans* respectively.

Keywords: 3, 4-dihydro-1(2H)-naphthalenone, Benzylidene, Quinazoline thione, Antifungal activity.

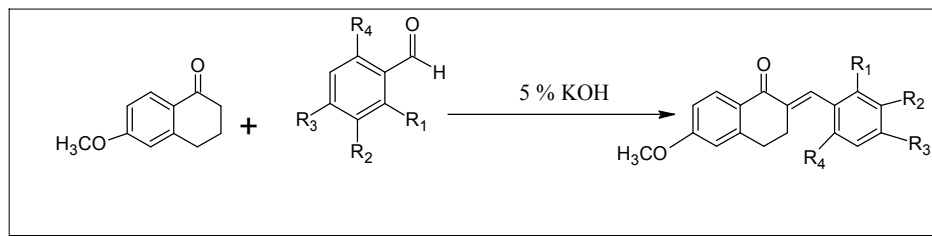
INTRODUCTION

3, 4-dihydro-1(2H)-naphthalenone is chemical name of tetralone, which is a common intermediate in organic synthesis and possess a wide range of biological activities. It is a ketone derivative of tetralin having the molecular formula C₁₀H₁₀O. Tetrahydronaphthyl-heterocycle¹ has useful applications such as anticancer²⁻⁶, antimicrobial⁷⁻⁹, antiviral¹⁰⁻¹¹, moluscidal¹², schistosomicidal¹³⁻¹⁴ and analgesic¹⁵. The present work deals with synthesis of some benzylidene derivatives using 6-methoxy tetralone as a key starting material and these benzylidene derivatives were further condensed with thiourea to give quinazoline thione derivatives which were evaluated for antifungal activity.

MATERIALS AND METHODS

All the chemical and reagent were of synthetic grade and commercially procured from Loba Chemie Pvt. Ltd., Mumbai, India. Melting point range of the synthesized compounds was determined by open capillary method using the melting point apparatus and is uncorrected. Thin layer chromatographic analysis of the synthesized compounds was done on silica gel G coated glass plate and iodine used. IR spectra were recorded on Bruker ATR Spectrometer. The re-crystallized compounds were sent to S.A.I.F, Department of Central Drug Research Institute (CDRI), Lucknow, India for NMR and Mass analysis.

Scheme 1: Synthesis of various benzylidene derivative of 6-methoxy-tetralone



6-methoxy tetralone

Benzaldehyde

Benzylidene tetralone (C₁-C₇)

Procedure for preparation of benzylidene derivatives of 6-methoxy tetralone

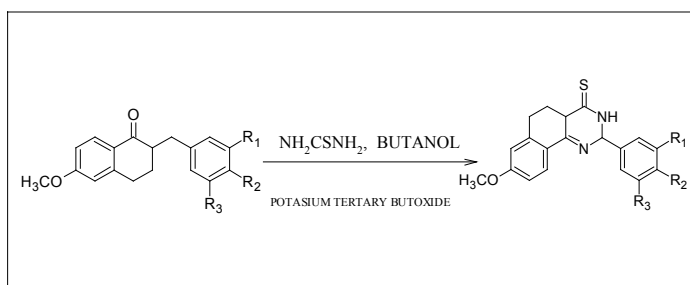
6-methoxy tetralone (10 mmol) and various benzaldehydes (10 mmol) in ethanol (50 ml) were taken in a 100 ml conical flask. Added a solution of 5 % alcoholic KOH to the mixture with stirring on an ice bath at 10⁰C. Completion of reaction

was monitored by TLC. After standing overnight, mixture was poured onto ice cold water. The solid product thus separated was filtered, washed with cold water and re-crystallized from ethanol. Table 1 depicts the physicochemical characters of various benzylidene derivatives of 6-methoxy tetralone.

Table 1: Physicochemical characters of benzylidene derivatives of 6-methoxy tetralone

Code	Structure	M.W	M. F.	M.P range (°C)	%Yield	R _f value
C ₁		264	C ₁₈ H ₁₆ O ₂	84-85	84.6	0.6
C ₂		298	C ₁₈ H ₁₅ Cl ₂	118-119	71.6	0.5
C ₃		282	C ₁₈ H ₁₅ FO ₂	107-108	74.1	0.7
C ₄		347	C ₁₉ H ₁₆ Cl ₂ O ₂	97-98	74.7	0.5
C ₅		347	C ₁₉ H ₁₆ Cl ₂ O ₂	122-124	77	0.6
C ₆		323	C ₂₀ H ₂₁ NO ₂	175-176	72	0.3
C ₇		307	C ₂₀ H ₂₁ O ₂	121-122	45.5	0.6

Scheme 2: Synthesis of quinazoline thione derivatives from benzylidene methoxy tetralone



Benzylidene tetralone-1

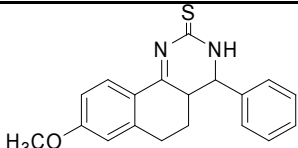
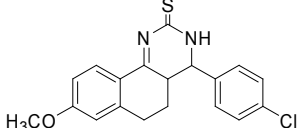
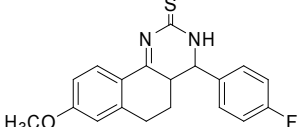
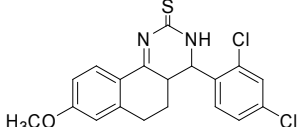
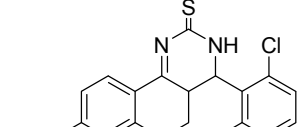
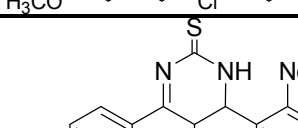
Quinazoline thione (C₈-C₁₃)

Procedure for preparation of various quinazoline thione derivatives of 6-methoxy-benzylidene-tetralone

Potassium tertiary butoxide (11.2 g) in 10 ml of methanol was taken in a 100 ml round bottom flask. Then solution of various substituted benzylidene tetralone (10 mmol) in methanol (7.5 ml) along with a solution of thiourea (0.76 g) in methanol (10 ml) was added. The reaction mixture was

stirred for half an hour and refluxed for 7-8 h on a water bath. Monitoring of reaction was done by TLC. When reaction was completed, the reaction mixture was cooled on an ice bath and solid product thus formed was filtered, washed with cold water and re crystallized with methanol. Table 2 gives the physicochemical character of synthesized quinazoline thione derivatives of 6-methoxy-benzylidene-tetralone.

Table 2: Physicochemical character of various quinazoline thione derivatives of 6-methoxy-benzylidene-tetralone

Code	Structure	M.W	M. F.	M.P. (°C)	%Yield	R _f Value
C ₈		322	C ₁₉ H ₁₈ N ₂ O S	124-126	66.7	0.6
C ₉		356	C ₁₉ H ₁₇ ClN ₂ O OS	132-135	74.6	0.5
C ₁₀		324	C ₁₉ H ₁₇ N ₂ O S	104-105	55.6	0.7
C ₁₁		392	C ₁₉ H ₁₇ N ₂ O S	84-85	65.1	0.5
C ₁₂		392	C ₁₉ H ₁₈ N ₂ O S	86-89	84.6	0.6
C ₁₃		365	C ₁₉ H ₁₇ N ₂ O SNO ₂	87-89	84.6	0.3

Spectral Data

2-benzylidene-6-methoxy-tetralone (C₁): Yield: 1.98 g (94.6 %), M.P range: 118-119 °C, Mass (FAB) [M+H]⁺: 264, ¹H NMR (200 MHz, CDCl₃): δ 3.87(s, 3H, CH₃O), 3.08-3.14 (t, 2H, CH₂), 6.7-8.14 (m, 7H, Ar-H), 7.8 (s, 1H, olefinic proton), 2.88-2.94 (t, 2H, CH₂), IR values :CO = 1603 cm⁻¹ - C=CH, 1651 cm⁻¹.

2-(4-chloro benzylidene)-6-methoxy-tetralone (C₂): Yield: 1.9 g (71.6 %), M.P range: 84-88 °C, Mass (FAB) [M+H]⁺: 299.2, ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H, CH₃O), 2.82-2.98 (t, 2H, CH₂); 3.07-3.17 (t, 2H, CH₂), 6.7-8.13. (m, 6H, Ar-H), 7.76 (s, 1H, olefinic proton) I.R: CO, 1659.2 cm⁻¹, C=C str, 1600.3 cm⁻¹.

2-(4-flouro-benzylidene)-6-methoxy-tetralone (C₃): Yield: 2.4 g (74.71 %), M.P range: 176-178 °C, Mass (FAB) [M+H]⁺: 283, ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H, OCH₃), 3.05-3.10 (t, 2H, CH₂), 6.7-8.13 (m, 7H, Ar-H), 2.90-2.98 (t, 2H, CH₂), 7.78 (s, 1H, olefinic proton) I.R: -C=CH, 1661.0 cm⁻¹; C=O, 1590.cm⁻¹.

2-(2,4-dichloro-benzylidene)-6-methoxy-tetralone (C₄): Yield: 2.3 g (74.71 %), M.P range: 97-98 °C, Mass (FAB) [M+H]⁺: 333, ¹H NMR (200 MHz, CDCl₃): δ 3.88 (s, 3H, OCH₃), 6.7-8.1(m, 7H, Ar-H), 2.62-2.68 (t, 2H, CH₂) 2.9-2.98 (t, 2H, CH₂), 7.78 (s, 1H, olefinic proton), I.R : -C=CH, 1605 cm⁻¹; C=O, 1656 cm⁻¹.

2-(2,6-dichloro-benzylidene)-6-methoxy-tetralone (C₅): Yield: 4.9 g (77 %), M.P range: 105-109 °C, Mass (FAB) [M+H]⁺: 347, ¹H NMR (200 MHz, CDCl₃): δ 3.88 (s, 3H, OCH₃), 6.7-8.1(m, 7H, Ar-H), 2.62-2.68 (t, 2H, CH₂) 2.9-2.98 (t, 2H, CH₂), 7.78 (s, 1H, olefinic proton) I.R : (C=CH str), 1611.4 cm⁻¹; C=O, 1669.9 cm⁻¹.

2-(3-nitro-benzylidene)-6-methoxy-tetralone (C₆): Yield: 4.6. g (72.4 %), M.P range: 154-158 °C, Mass (FAB) [M+H]⁺: 310, ¹H NMR (200 MHz, CDCl₃): δ 3.89 (s, 3H, OCH₃), 6.7-8.1 (m, 8H, Ar-H), 2.62-2.68 (t, 2H, CH₂) 2.9-2.98 (t, 2H, CH₂) 7.78 (s, 1H, olefinic proton), I.R : CO = 1672.2 cm⁻¹; C=CH, 1519 cm⁻¹.

2-(4' dimethyl-amino-phenyl-benzylidene)-6-methoxy-tetralone (C₇): Yield: 1.26 g (45 %), M.P range: 120-122 °C, Mass (FAB) [M+H]⁺: 308, ¹H NMR (200 MHz, CDCl₃): δ 3.8 (s, 3H, OCH₃), 6.7-8.1(m, 7H, Ar-H), 2.62-2.68 (t, 2H, CH₂) 2.9-2.98 (t, 2H, CH₂), 7.76 (s, 1H, olefinic proton), I.R : CO = CO 1671.2 cm⁻¹; C=CH 1598.7cm⁻¹.

Quinazoline thione derivative of 2-benzylidene-6-methoxy-tetralone (C₈): Yield: 2.17 g (66.7 %), M.P range: 124-126 °C, Mass (FAB) [M+H]⁺: 323 (m+1), ¹H NMR (200 MHz, CDCl₃): δ 3.87 (3H, CH₃O), 3.11-3.14. (t, 2H, CH₂), 6.7-8.0 (m, 7H, Ar-H), 2.78-2.94 (s, 1H, olefinic proton), I.R : C = S 1120 cm⁻¹, NH 3300 cm⁻¹.

Quinazoline thione derivative of 2-(4-chloro-benzylidene)-tetralone (C₉): Yield: 1.60 g (74.6 %), M.P range: 132-135 °C, Mass (FAB) [M+H]⁺: 357 (m+1), ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H, CH₃O), 6.57- 7.11 (m, 7H, Ar-H) 2.88-2.94 (s, 1H, olefinic proton), I.R : C = S 1120 cm⁻¹, NH 3300 cm⁻¹.

Quinazoline thione derivative of 2-(4-Fluoro-benzylidene)-tetralone (C₁₀): Yield: 1.28 g (55.6 %), M.P range: 104-105 °C, Mass (FAB) [M+H]⁺: 341 (m+1), ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H, CH₃O), 3.11-3.14 (t, 2H, CH₂), 6.7-7.3 (m, 7H, Ar-H), 2.77-2.94 (s, 1H, olefinic proton), I.R : C = S 1120 cm⁻¹, NH 3300 cm⁻¹.

Quinazoline thione derivative of 2-(2,4-dichloro-benzylidene)-tetralone (C₁₁): Yield: 1.27 g (65.14 %), M.P range: 147-149 °C, Mass (FAB) [M+H]⁺: 393 m+1, ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H CH₃O), 5.5 (d, 1H, CH) 6.7-6.8 (m, 7H, Ar-H), 2.7(d, 2H, CH₂), I.R: C = S 1120 cm⁻¹, NH 3300cm⁻¹.

Quinazoline thione derivative of 2-(2,6-dichloro-benzylidene)-tetralone (C₁₂): Yield: 1.98 g (84.6%), M.P range: 84-85 °C, Mass (FAB) [M+H]⁺: 393 (m+1), ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H, CH₃O), 3.11-3.14 (t, 2H, CH₂); 6.7- 6.8 (m, 7H, Ar-H), 2.88-2.94 (s, 1H, olefinic proton), I.R : C = S 1120 cm⁻¹, NH 3300 cm⁻¹.

Quinazoline thione derivative of 2-(3-nitro-benzylidene)-tetralone (C₁₃): Yield: 1.98 g (84.6 %), M.P range: 84-85 °C, Mass (FAB) [M+H]⁺: 265 (m+1), ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 3H, CH₃O), 3.11-3.14. (t, 2H, CH₂), 6.7-6.8 (m, 7H, Ar-H), 2.88-2.94 (s, 1H, olefinic proton), I.R: C=S 1217 cm⁻¹, C=N 1498 cm⁻¹, NH= 3436 cm⁻¹.

Antifungal activity

All the synthesized compounds were tested *in-vitro* for antifungal activity by using Cup Plate Agar Diffusion Method using fluconazole as standard drug.

Test Microorganisms

Fungal cultures [*Aspergillus niger* (MTCC-282) and *Candida albicans* (MTCC-227)] obtained from Institute of Microbial Technology, Chandigarh, India were used.

Material: Sabouraud - Dextrose Agar, Inoculums, test and standard solution.

Sabouraud-Dextrose Agar

In a 1000 ml volumetric flask taken accurately weighed peptones 10.0 g, dextrose monohydrate 40.0 g, agar 15.0 g and added sufficient water to make final volume to 1000 ml. Dissolved the ingredients with the aid of heat. Filtered the contents and sterilized in an autoclave at 121 °C for 20 minutes and pH was adjusted to 5.5- 6.0 using hydrochloric acid solutions.

Preparation of inoculums

One day prior of these testing, inoculations of the above fungal culture were made in the Sabouraud - Dextrose Agar and incubated the cultures of *Candida albicans* and *Aspergillus niger* at 25 °C for 48 h and 7 days respectively. Using sterile saline solution harvested the *Candida albicans* cultures and diluted with the sterile saline solution to bring the count to about 1 x 10⁸ per ml. Similarly harvested

Aspergillus niger culture with sterile saline solution containing 0.05 per cent w/v of polysorbate 80 and adjusted the spore count to about 1 x 10⁸ per ml with sterile saline solution.

Preparation of test solution

5 mg of each synthesized compound was dissolved in DMSO (5 ml) to give stock solution of concentration 1 mg/ ml. Then stock solution was further diluted to the concentration 100 µg/ml. 0.1 ml of this solution was used for testing.

Preparation of standard solution

Standard drug fluconazole was used. The stock solution was prepared in similar way as mention above to give concentration 100 µg/ ml. 0.1 ml of this solution was used for testing.

Procedure

The agar plates were prepared by pouring 20 ml of the Sabouraud- Dextrose agar medium in to each sterilized petri dish and were allowed to set at room temperature. Then sterile saline solution of *Candida albicans* and *Aspergillus niger* were inoculated over the surface of medium using a sterile cotton swab. The cups were scooped in each plate using a sterile cork borer of 5 mm diameter. The test solution and standard solution (0.1 ml) were added in the cups by using micropipettes and these plates were subsequently incubated at 20-25 °C for 48 h. The zones of inhibition were measured in mm. Table 3 depicts the antifungal activity of benzylidene 6-methoxy-tetralone and its quinazoline thione derivatives.

RESULT

The antifungal activity of the compounds was evaluated against *Aspergillus niger* and *Candida albicans* using fluconazole as standard drug. Among 6-methoxy-benzylidene derivative C₁, C₂, C₇ were least active; the minimum activity i.e., 36 % against *Aspergillus niger* and 38.4 % against *Candida albicans* was shown by unsubstituted benzylidene compound C₁. The zone of inhibition i.e., 40 %, 42.3 % was showed by compound C₂ having *p*-chloro substitution and compound C₇ having *p*-dimethyl group had 36 %, 50 % activity against *Aspergillus niger* and *Candida albicans* respectively. Compounds C₃, C₄, C₅, C₆ were moderately active; the zone of inhibition i.e., 48 %, 57.7 % was showed by compound C₃ having *p*-fluoro group, compound C₄ having 2, 4 dichloro group had 60.7 %, 69.2 % activity, compound C₅ having 2, 6 dichloro group exhibit 56 %, 65.4 % zone of inhibition, compound C₆ having *p*-nitro group had 52 %, 61.5 % activity against *Aspergillus niger* and *Candida albicans* respectively. The maximum zone of inhibition was shown by compound C₅ among 6-methoxy-benzylidene derivative. Similarly among quinazoline thione derivatives compounds C₈, C₉ were least active and compounds C₁₀, C₁₁, C₁₂, and C₁₃ were moderately active. Antifungal activities exhibited by unsubstituted compound C₈ was 39.3 % and 44 % against *Aspergillus niger* and *Candida albicans* respectively. Compound C₉ having *p*-chloro substitution exhibited 48 % and 50 % activity, compound C₁₀ having *p*-fluoro group had 56 % and 61.5 % zone of inhibition, compound C₁₁ having 2, 4 dichloro group exhibited 72 % and 73 % activity, compound C₁₂ having 2, 6 dichloro group exhibited 68 % and 69.2 % zone of inhibition, compound C₁₃ having *p*-nitro group exhibited 64 % and 65.4 % activity against *Aspergillus niger* and *Candida albicans*

respectively. The maximum zone of inhibition was shown by compound C₁₁ among quinazoline thione derivatives.

Table 3: Antifungal activity of benzylidene 6-methoxy tetralone and its quinazoline thione derivatives:

Code	<i>Aspergillus niger</i> (MTCC 282)		<i>Candida albicans</i> (MTCC227)		Inferences Highly active = 75-100 % Moderately active = 51-75 % Least active = 40-50 %
	Zone of Inhibition (mm)	% Zone of Inhibition	Zone of Inhibition (mm)	% Zone of Inhibition	
C ₁	9	36	10	38.4	Least active
C ₂	10	40	11	42.3	Least active
C ₃	12	48	15	57.7	Moderately active
C ₄	15	60	18	69.2	Moderately active
C ₅	14	56	17	65.4	Moderately active
C ₆	13	52	16	61.5	Moderately active
C ₇	9	36	13	50.0	Least active
C ₈	11	44	11	42.3	Least active
C ₉	12	48	13	50	Least active
C ₁₀	14	56	16	61.5	Moderately active
C ₁₁	18	72	19	73.0	Moderately active
C ₁₂	17	68	18	69.2	Moderately active
C ₁₃	16	64	17	65.4	Moderately active
Standard	25	100	26	100	Highly active
Control	4	16	5	19	Inactive

CONCLUSION

In this research work a series of 2-substituted benzylidene-tetralone was prepared from 6-methoxy-tetralone by using an Aldol condensation and then these synthesized benzylidene-tetralone derivatives were further condensed with thiourea to give various substituted quinazoline thione derivatives. All of these compounds have been characterized by IR, NMR and Mass spectral analysis for structure establishment and further evaluated for their antifungal activity against *Aspergillus niger* (MTCC-282) and *Candida albicans* (MTCC-227) by agar diffusion method using fluconazole as standard drug. The results of antifungal activity reveal that unsubstituted benzylidene and quinazoline thione derivatives compound C₁ and C₈ had minimum zone of inhibition. When electron-withdrawing substitutions were made on both ring antifungal activity increased in following order (NO₂ > F > Cl). Condensation of quinazoline ring on benzylidene derivatives increased antifungal activity. Among 6-methoxy-benzylidene derivatives; C₁, C₂, C₇ were least active and C₃, C₄, C₅, C₆ were moderately active while among quinazoline thione derivatives; C₈, C₉ were least active and C₁₀, C₁₁, C₁₂, C₁₃ were moderately active. 2, 4 dichloro substituted compound C₁₁ showed maximum antifungal activity which might be due to presence of two electron-withdrawing chloro groups with less steric hindrance.

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