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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-benzylidiene derivatives; C_1, C_2, C_7 were least active and C_3, C_4, C_5, C_6 were moderately active while among quinazoline thione derivatives; C_8, C_9 were least active and C_{10}, C_{11}, C_{12}, C_{13} were moderately active. When electron-withdrawing substitutions were made on both ring antifungal activity increased in (NO_2 > F> Cl) order. The maximum zone of inhibition (60.7 % and 69.7 %) was shown by compound C_5 among 6-methoxy-benzylidiene derivative and C_{11} had (72 % and 73 %) activity among quinazoline thione derivative against *Aspergillus niger* and *Candida albicans* respectively.
Keywords: 3, 4-dihydro-1(2H)-naphthalenone, Benzylidiene, Quinazoline thione, Antifungal activity.

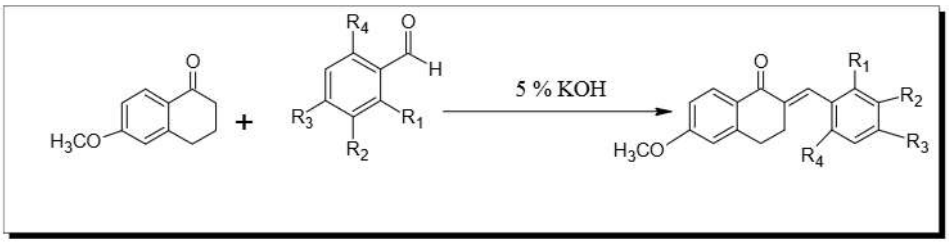
INTRODUCTION

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 $C_{10}H_{10}O$. Tetrahydronaphthyl-heterocycle[1] has useful applications such as anticancer[2-6], antimicrobial[7-9], antiviral[10-11], moluscidal[12], schistosomicidal[13-14] and analgesic[15]. The present work deals with synthesis of some benzylidiene derivatives using 6-methoxy tetralone as a key starting material and these benzylidiene 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 benzylidiene derivative of 6-methoxy-tetralone

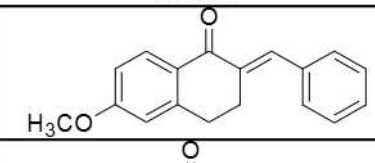
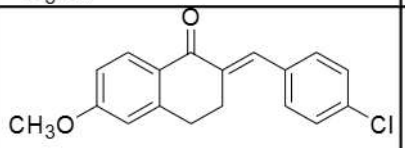
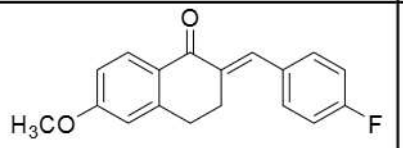
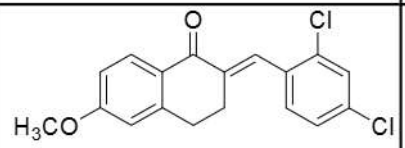
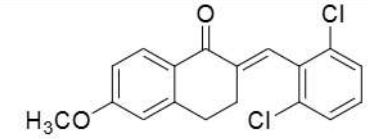
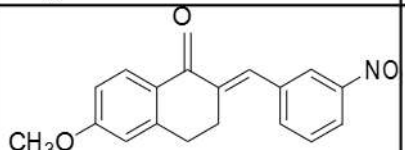
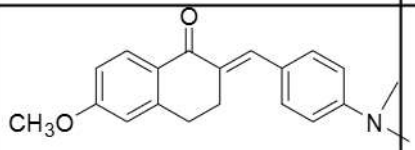


6-methoxy tetralone **Benzaldehyde** **Benzylidiene tetralone (C_1-C_7)**

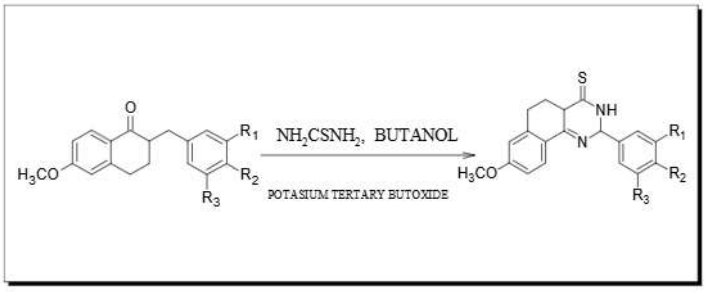
Procedure for preparation of benzylidiene derivatives of 6-methoxy tetralone

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 10^0C. 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 benzylidiene derivatives of 6-methoxy tetralone.

Table 1: Physicochemical characters of benzylidiene 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	$C_{19}H_{16}Cl_2O_2$	97-98	74.7	0.5
C_5		347	$C_{19}H_{16}Cl_2O_2$	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 benzylidiene methoxy tetralone

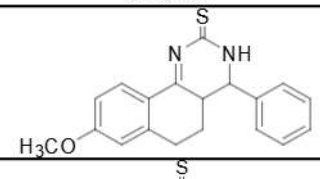
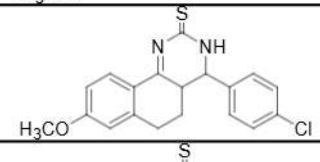
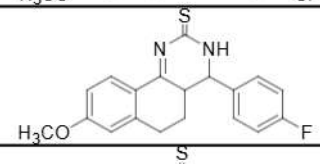
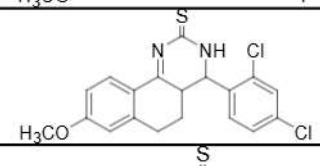
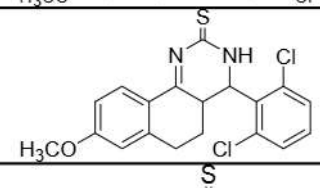
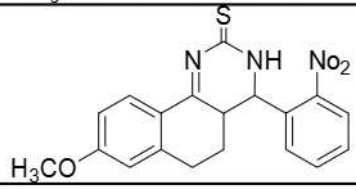


Benzylidiene tetralone-1 **Quinazoline thione (C_8-C_{13})**

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

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

Code	Structure	M.W	M. F.	M.P. (°C)	%Yield	R_f Value
C_8		322	$C_{19}H_{18}N_2OS$	124-126	66.7	0.6
C_9		356	$C_{19}H_{17}ClN_2OS$	132-135	74.6	0.5
C_{10}		324	$C_{19}H_{17}N_2OS$	104-105	55.6	0.7
C_{11}		392	$C_{19}H_{17}N_2OS$	84-85	65.1	0.5
C_{12}		392	$C_{19}H_{18}N_2OS$	86-89	84.6	0.6
C_{13}		365	$C_{19}H_{17}N_2OSNO_2$	87-89	84.6	0.3

Spectral Data

2-benzylidene-6-methoxy-tetralone (C_1): Yield: 1.98 g (94.6 %), M.P range: 118-119 ^{0}C, Mass (FAB) [M+H] : 264, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87(s, 3H, CH_3O), 3.08-3.14 (t, 2H, CH_2), 6.7-8.14 (m, 7H, Ar-H), 7.8 (s, 1H, olefinic proton), 2.88-2.94 (t, 2H, CH_2), IR values :CO = 1603 cm^{-1} - C=CH, 1651 cm^{-1}.

2-(4-chloro benzylidene)-6-methoxy-tetralone (C_2): Yield: 1.9 g (71.6 %), M.P range: 84-88 ^{0}C, Mass (FAB) $[M+H]^+$: 299.2,^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H, CH_3O), 2.82-2.98 (t, 2H, CH_2); 3.07-3.17 (t, 2H, CH_2), 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 (C_3): Yield: 2.4 g (74.71 %), M.P range: 176-178 ^{0}C , Mass (FAB) $[M+H]^+$: 283, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s ,3H, OCH_3), 3.05-3.10 (t, 2H, CH_2), 6.7-8.13 (m,7H, Ar-H), 2.90-2.98 (t, 2H, CH_2), 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 (C_4): Yield: 2.3 g (74.71 %), M.P range: 97-98 ^{0}C, Mass (FAB) $[M+H]^+$: 333, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.88 (s, 3H, OCH_3), 6.7-8.1(m, 7H, Ar-H , 2.62-2.68 (t, 2H, CH_2) 2.9-2.98 (t, 2H, CH_2), 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 (C_5): Yield: 4.9 g (77 %), M.P range: 105-109 ^{0}C, Mass (FAB) $[M+H]^+$: 347, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.88 (s, 3H, OCH_3), 6.7-8.1(m,7H, Ar-H, 2.62-2.68 (t, 2H, CH_2) 2.9-2.98 (t, 2H, CH_2), 7.78 (s, 1H, olefinic proton) I.R : (C=CH str), 1611.4 cm^{-1}; C=O, 1669.9 cm^{-1}.

2-(3-nitro-benzylidiene)-6--methoxy-tetralone (C_6): Yield: 4.6. g (72.4 %), M.P range: 154-158 ^{0}C, Mass (FAB) $[M+H]^+$: 310, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.89 (s-,3H, OCH_3), 6.7-8.1 (m, 8H, Ar-H), 2.62-2.68 (t, 2H, CH_2) 2.9 -2.98 (t, 2H, CH_2) 7.78 (s,1H, olefinic proton), I.R : CO = 1672.2 cm^{-1}; C=CH, 1519 cm^{-1}.

2-(4`4`dimethyl-amino-phenyl-benzylidiene)-6-methoxy-tetralone (C_7): Yield: 1.26 g (45 %), M.P range: 120-122 ^{0}C, Mass (FAB) $[M+H]^+$: 308, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.8 (s, 3H, OCH_3), 6.7-8.1(m, 7H, Ar-H , 2.62-2.68 (t, 2H, CH_2) 2.9 -2.98 (t, 2H, CH_2), 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 (C_8): Yield; 2.17 g (66.7 %), M.P range; 124-126 ^{0}C, Mass (FAB) $[M+H]^+$: 323 (m+1), ^{1}H NMR (200 mHz, $CDCl_3$): δ 3.87 (3H, CH_3O), 3.11-3.14. (t, 2H, CH_2), 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 (C_9): Yield; 1.60 g (74.6 %), M.P range; 132-135 ^{0}C, Mass (FAB) $[M+H]^{+}$ 357 (m+1), ^{1}H NMR (200 mHz,$CDCl_3$): δ 3.87 (s, 3H, CH_3O), 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 (C_{10}): Yield: 1.28 g (55.6 %), M.P range: 104-105 ^{0} C, Mass (FAB) $[M+H]^{+}$ 341 (m+1), ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H, CH_3O), 3.11-3.14 (t, 2H, CH_2), 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 (C_{11}): Yield: 1.27 g (65.14 %), M.P range: 147-149 ^{0}C, Mass (FAB) $[M+H]^{+}$ 393 m+1, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H CH_3O), 5.5 (d, 1H, CH) 6.7-6.8 (m,7H, Ar-H), 2.7(d, 2H, CH_2) , I.R: C = S 1120 cm^{-1}, NH 3300cm^{-1}.

Quinazoline thione derivative of 2-(2,6-dichloro-benzylidene)-tetralone (C_{12}): Yield: 1.98 g (84.6%), M.P range: 84-85 ^{0}C, Mass (FAB) $[M+H]^{+}$ 393 (m+1), ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H, CH_3O), 3.11-3.14 (t, 2H, CH_2) ; 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 (C_{13}): Yield: 1.98 g (84.6 %), M.P range: 84-85 ^{0}C, Mass (FAB) $[M+H]^{+}$ 265 (m+1), ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H, CH_3O), 3.11-3.14. (t, 2H, CH_2), 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 ^{0}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 10^8 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 10^8 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 *Aspergilus 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 ^{0}C for 48 h. The zones of inhibition were measured in mm. Table 3 depicts the antifungal activity of benzylidiene 6-methoxy-tetralone and its quinazoline thione derivatives.

RESULT

The antifungal activity of the compounds was evaluated against *Aspergilus niger* and *Candida albicans* using fluconazole as standard drug. Among 6-methoxy-benzylidiene derivative C_1, C_2, C_7 were least active; the minimum activity i.e., 36 % against *Aspergilus niger* and 38.4 % against *Candida albicans* was shown by unsubstituted benzylidiene compound C_1. The zone of inhibition i.e., 40 %, 42.3 % was showed by compound C_2 having *p*-chloro substitution and compound C_7 having *p*-dimethyl group had 36 %, 50 % activity against *Aspergilus niger* and *Candida albicans* respectively. Compounds C_3, C_4, C_5, C_6 were moderately active; the zone of inhibition i.e., 48 %, 57.7 % was showed by compound C_3 having *p*-fluoro group, compound C_4 having 2, 4 dichloro group had 60.7 %, 69.2 % activity, compound C_5 having 2, 6 dichloro group exhibit 56 %, 65.4 % zone of inhibition, compound C_6 having *p*-nitro group had 52 %, 61.5 % activity against *Aspergilus niger* and *Candida albicans* respectively. The maximum zone of inhibition was shown by compound C_5 among 6-methoxy-benzylidiene derivative. Similarly among quinazoline thione derivatives compounds C_8, C_9 were least active and compounds C_{10}, C_{11}, C_{12}, and C_{13} were moderately active. Antifungal activities exhibited by unsubstituted compound C_8 was 39.3 % and 44 % against *Aspergilus niger* and *Candida albicans* respectively. Compound C_9 having *p*-chloro substitution exhibited 48 % and 50 % activity, compound C_{10} having *p*-fluoro group had 56 % and 61.5 % zone of inhibition, compound C_{11} having 2, 4 dichloro group exhibited 72 % and 73 % activity compound C_{12} having 2, 6 dichloro group exhibited 68 % and 69.2 % zone of inhibition, compound C_{13} having *p*-nitro group exhibited 64 % and 65.4 % activity against *Aspergilus niger* and *Candida albicans*

respectively. The maximum zone of inhibition was shown by compound C_{11} among quinazoline thione derivatives.

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

Code	*Aspergilus niger* (MTCC 282)		*Candida albicans* (MTCC227)		Inferences
	Zone of Inhibition (mm)	% Zone of Inhibition	Zone of Inhibition (mm)	% Zone of Inhibition	Highly active = 75-100 % Moderately active = 51-75 % Least active = 40-50 %
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 benzylidiene and quinazoline thione derivatives compound C_1 and C_8 had minimum zone of inhibition. When electron-withdrawing substitutions were made on both ring antifungal activity increased in following order (NO_2 > F> Cl). Condensation of quinazoline ring on benzylidiene derivatives increased antifungal activity. Among 6-methoxy-benzylidiene derivatives; C_1, C_2, C_7 were least active and C_3, C_4, C_5, C_6 were moderately active while among quinazoline thione derivatives; C_8, C_9 were least active and C_{10}, C_{11}, C_{12}, C_{13} were moderately active. 2, 4 dichloro substituted compound C_{11} showed maximum antifungal activity which might be due to presence of two electron-withdrawing chloro groups with less steric hindrance.

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