

Kinetics Study of the Formation of Pyrimidine Thione from the Reaction of 2,6-Dibenzylidene-cyclohexanone and its Derivatives with Thiourea

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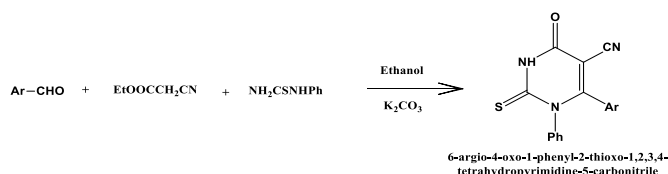
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Abstract—Kinetics of the addition of thiourea to 2,6-dibenzylidene-cyclohexanone and its derivatives have been studied. The reaction is found as a pseudo-first order process which includes a nucleophilic attack by thiourea at the carbonyl group of the ketone system to produce the heterocyclic pyrimidine thione "thiopyrimidine" (Claisen route mechanism). The effect of the substituents at the para position of the 2,6-dibenzylidene-cyclohexanone and its derivatives on the rate of reaction, at different temperatures, is studied. Arrhenius parameters, entropies, enthalpies and free energies of activations are estimated. A suitable mechanism, which is correspondent with the results and with Claisen routes mechanism, is suggested for this reaction.

Index Terms—2,6-dibenzylidene-cyclohexanone and its derivatives, mechanism route, kinetics study, thiourea, thiopyrimidine.

I. INTRODUCTION

Thiopyrimidine derivatives are widely used as anticancer agents. They can be synthesized from the reaction of the phenyl thiourea and ethylcyanoacetate with aromatic aldehydes in ethanol to give a thiopyrimidine carbonitrile, as in the following reaction:



Thiopyrimidine carbonitrile, in turn, converts to a new derivative of thiopyrimidine which can also be used as anticancer precursor (El-Ansary, et al., 2015).

A considerable attention has been paid concerning the reactivity of carbonyl compound towards the addition of nucleophiles. Several factors influence the overall rate of reaction under various conditions. Among the crucial factors are structural features of the carbonyl compound, and the nature of the nucleophile, (Brown, Wheeler and Ichikawa, 1957; Clayden, et al., 2001). Another kinetic study was performed on condensation reaction of thiourea with substituted aldehyde to give Schiff-base compounds/complexes. The rate constants of the reaction of Schiff-bases with Maleic acid, Succinic acid and Phthalic anhydride were studied and showed that the reaction was of first-order (Al-Hadithi, Al-Rawi and Al-Hity, 2007).

The present study is concerned with the kinetics of the formation of pyrimidine thione and its derivatives and to find out the electronic effect of substituents on the reaction rates and on the stability of the presumed activated complexes. The attained information was of great assistance in postulation of the mechanism which occurs under mild experimental conditions.

II. EXPERIMENTAL PART

The kinetic studies were monitored by uv-visible spectrophotometric method at fixed wavelengths. Agilent Cary-100 uv-visible was used to monitor the disappearance of the 2,6-dibenzylidene-cyclohexanone and its derivatives under study at constant temperature with $\pm 0.01\%$ °C, using a temperature controller in conjunction with uv-visible

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spectrophotometer. The kinetic runs were carried out using multicell holder at fixed $\lambda_{max} = (339.00 - 364.00 \text{ nm})$. Quickfit quartz cuvettes type (Q) were used. A working solution containing 0.1 M of thiourea and 2×10^{-4} M of 2,6-dibenzylidenecyclohexanone and its derivatives in dimethyl sulfoxide (DMSO) and absolute ethanol as solvent in strong basic medium ($pH \geq 12$) was used. A blank cell containing the same reaction medium except 2,6-dibenzylidenecyclohexanone and its derivatives was also used. All kinetic data were processed on computer programs using Microsoft Excel 2010 and Sigma Plot 11.0.

III. RESULTS AND DISCUSSION

The kinetics of the reaction between thiourea and 2,6-dibenzylidenecyclohexanone and its derivatives in DMSO as a solvent and in basic medium of sodium ethoxide to form the thiopyrimidine have been studied. The reaction was found to be relatively slow, when monitored at a temperature range between (308.15-328.15)K; second order, presumably first order with respect to each of reactants (thiourea and 2,6-dibenzylidenecyclohexanone and its derivatives) when using 1:1 mixing mole ratio of reactants. The study also showed a pseudo first order decrease of the concentration of the 2,6-dibenzylidenecyclohexanone as shown in the Fig. 1., at 318.15 K, using a mole ratio of 1:500 (2,6-dibenzylidenecyclohexanone: thiourea). The decrease in concentration of 2,6-dibenzylidenecyclohexanone was monitored at different intervals and at fixed $\lambda_{max} = (352.00 \text{ nm})$.

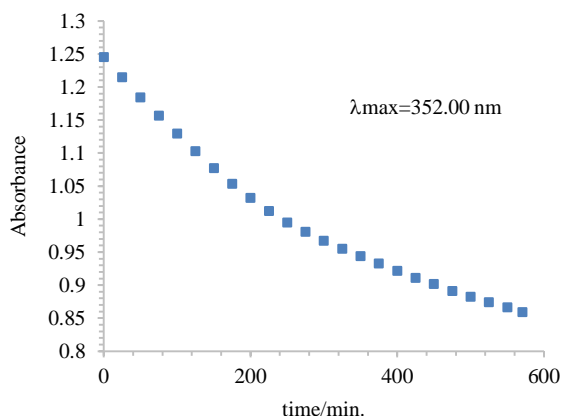


Fig. 1. Decrease of the concentration of 2,6-dibenzylidenecyclohexanone at different time at 318.15K.

At this wave length the monitored parent reactant neither interfered with thiourea $\lambda_{max} = (264.00 \text{ nm})$, nor with any of thiopyrimidine (product), $\lambda_{max} = (263.00 \text{ nm})$, and sodium ethoxide in ethanol, $\lambda_{max} = (203.00 \text{ nm})$ as shown in Fig. 2.

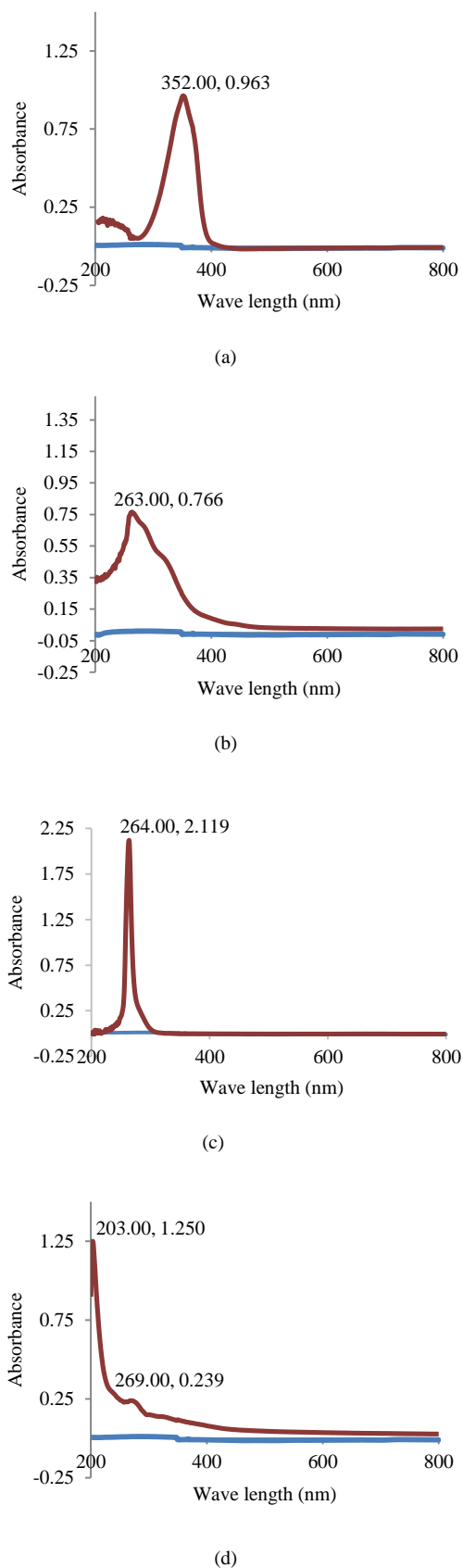
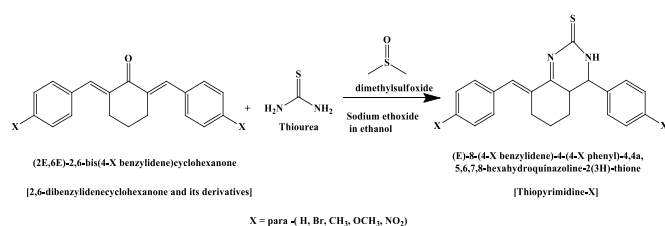


Fig. 2. Full spectra of individual reactants, product and used solvent; (a) λ_{max} 2,6-dibenzylidenecyclohexanone in DMSO, (b) λ_{max} thiopyrimidine-H product in DMSO, (c) λ_{max} thiourea in DMSO and (d) λ_{max} sodium ethoxide in ethanol.

The reaction was also monitored using a full scan uv-visible spectrum. No other products or side reactions were noticed and A_{∞} of the 2,6-dibenzylidenecyclohexanone and its derivatives was always approached to zero showing that no equilibrium process did ever exist. The products structure was confirmed by IR (Jihad, 2011) and (H^1 , C^{13})-NMR (Appendix A). These observations suggest that the addition reaction proceeds clearly according to the simple stoichiometry of the reaction below:



Typical runs found that the parent reactant or any of its derivatives follows the pseudo first order equation in terms of absorption functions at different temperatures [$\ln(A_{\infty} - A_0)/(A_{\infty} - A_t)$ vs. time]. The plots were found as linear for at least 90% of reactions.

$$\ln(A_{\infty} - A_0) / (A_{\infty} - A_t) = kobs.t \quad (1)$$

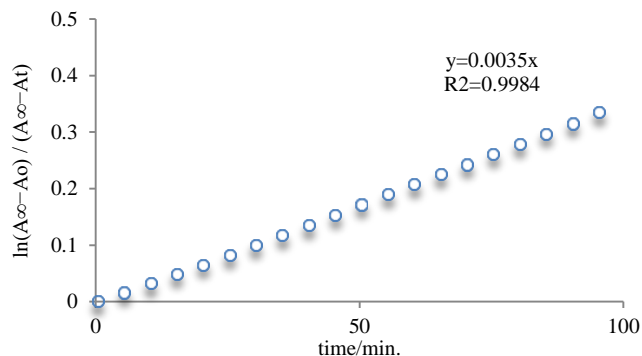


Fig. 3. Pseudo first order plot for the decrease in concentration 2,6-dibenzylidenecyclohexanone at 318.15K.

The results are shown in Table I.

TABLE I
OBSERVED RATE CONSTANTS FOR THE REACTION OF DIFFERENT 2,6-DIBENZYLIDENECYCLOHEXANONE AND ITS DERIVATIVES WITH THIOUREA AT DIFFERENT TEMPERATURES

Temp./ °K	10^3 kobs. / s ⁻¹				
	p-H	p-Br	p-CH ₃	p-OCH ₃	p-NO ₂
308.15	3.30±0.03	7.70±0.02	10.00±0.07	13.00±0.83	39.50±1.53
313.15	4.70±0.18	9.00±0.35	13.30±0.27	20.20±1.02	42.80±1.78
318.15	5.80±0.19	11.50±0.09	16.70±0.61	29.50±0.88	47.50±1.43
323.15	8.30±0.25	15.00±0.31	23.30±1.42	38.30±0.96	51.70±1.09
328.15	10.0±0.16	17.50±0.37	33.30±2.32	-----	55.00±1.04

Arrhenius plots (Dabbagh, 2010) were performed for all reactions; energies of activation, A-factors and entropies of activation at (318.15) K, were estimated as a listed in Table II:

TABLE II
ARRHENIUS PARAMETERS AND ENTROPIES OF THE ACTIVATION FOR THE REACTIONS OF DIFFERENT 2,6-DIBENZYLIDENECYCLOHEXANONE AND ITS DERIVATIVES WITH THIOUREA.

Compounds	E_a / kJ .mol ⁻¹	A / s ⁻¹	ΔS^\ddagger / J.K ⁻¹ .mol ⁻¹	ΔG^\ddagger / kJ.mol ⁻¹	R ²
diarylidene- H	46.6864	2.809×10^3	-187.7566	106.4212	0.9927
diarylidene-Br	36.2989	1.070×10^2	-214.9250	104.6773	0.9912
diarylidene-CH ₃	49.7743	2.677×10^4	-169.0118	103.5454	0.9900
diarylidene-OCH ₃	60.0404	2.051×10^6	-132.9374	102.3344	0.9908
diarylidene- NO ₂	14.2826	1.045×10^1	-272.5510	100.9947	0.9956

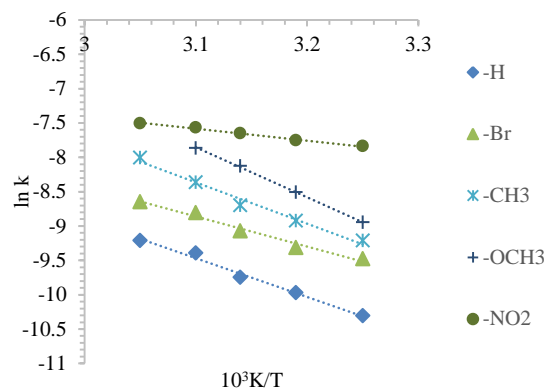
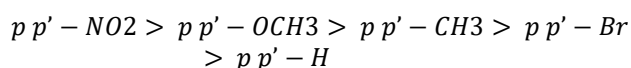


Fig. 4. Arrhenius plot for the reaction of different 2,6-dibenzylidenecyclohexanone and its derivatives with thiourea at different temperatures.

The electronic effects of all substituents at both sides of the 2,6-dibenzylidenecyclohexanone and its derivatives molecule play an important role on affecting the rate of reaction, since they either enrich or pauperize the reaction center at the α , β unsaturated system with electrons. The differences in rates were found to be in the following order at all reaction.

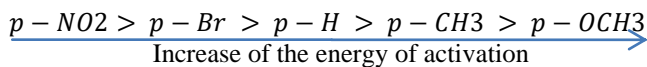


This sequence of arrangements indicates that electronic effects play important role in enhancing or reducing the rate of reaction in comparison with the parent 2,6-dibenzylidenecyclohexanone. The p-OCH₃ and p-CH₃ groups which are electron donating groups (Dabbagh, et al., 2012), enrich the reaction center with electron density and increase the repulsive forces with thiourea nucleophile. As a result, the rate of reaction is reduced (Table I). On the other hand, electron withdrawing group such as p-NO₂ reduce the electron density at the reaction center resulting in partial positive reaction center, thus providing a better chance for thiourea nucleophile to attack, resulting a relative acceleration of reaction rate (Dabbagh and Al-Gwari, 2013).

It is concluded, from these observations, that the condensation process of the various 2,6-dibenzylidenecyclohexanone and its derivatives with thiourea proceeds via a nucleophilic addition reaction mechanism.

The values of the activation parameters are also important to discern the mechanism under all studied circumstances. The

activation energies for all reactants in the range between (14-60) kJ/mole. The variation in values may be attributed to the electron donating or withdrawing capabilities of the attacking group. These values come in the line with as discussed above, i.e. fast reaction requires low activation energy and vice versa, as in the following sequence:



This observation is also explicable with the attack of the nucleophile to the partially positive reaction center. It is noticed that the values of E_a for the p-Br substituent and the parent 2,6-dibenzylidenecyclohexanone are very close to each other, this is unsurprising since the bromo group carries dual donating and withdrawing character at the same time (Haji, 2013).

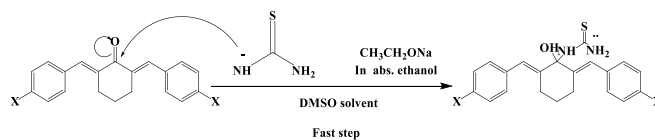
The entropies of activation ΔS^\ddagger , which are related to A-factor (Table II), are all largely negative values, indicating the formation of a restricted high polar transition state which suffers from lack of certain degrees of freedom as compared to the reactants (Dabbagh, Al-hamdany and Al-Sabawi, 2012). The decrease in the values of A-factor and correspondingly to ΔS^\ddagger provides an important indication about the stability of the transition state and hence gives good support for explaining the reason of the differences in the values of rate constants. Again, it can be clearly discerned the effect of electronic properties of the different substituents on the transition state by noting the differences in ΔS^\ddagger value for the p-NO₂ which is much lower than others due to the decrease of electron density at the reaction center leading to the formation of a highly oriented stable transition state. In contrast, the highest ΔS^\ddagger value for the p-OCH₃ may be attributed to destabilized transition state since it enriches the reaction center with electron density. The -ve values of ΔS^\ddagger thus suggested the formation of a restricted transition state which may occur via a cyclization process.

The values of the free energies of activation in Table II show a relative constancy for all reacting 2,6-dibenzylidenecyclohexanone and its derivatives. These results indicated that all the corresponding reactants were operative in similar mechanistic routes (Rajalakshmi and Ramachandramoorthy, 2013).

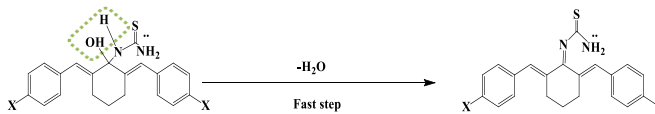
From these investigations it can be concluded that electronic effect plays an important role in the stabilization of the formed transition state. Also the reaction of the 2,6-dibenzylidenecyclohexanone and its derivatives with the thiourea nucleophile proceeds via the formation of a relatively slow step with adequate activation energies (Al-Hamdany, Dabbagh and Shareef, 2012).

The values of rate constants, Arrhenius parameters, ΔG^\ddagger and also the -ve values of ΔS^\ddagger are all in quite agreement with the following mechanistic Claisen-routes steps:

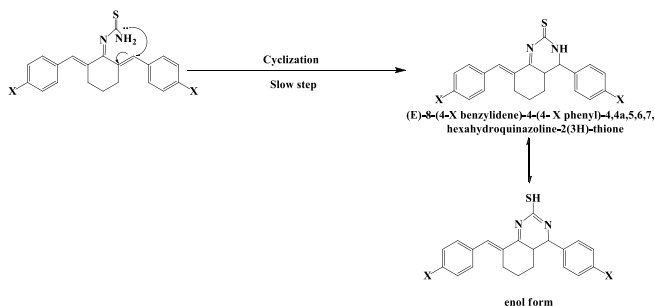
First step: A fast nucleophilic attack by thiourea to the carbonyl group of the α, β unsaturated carbonyl system followed by proton transfer from nitrogen to form OH group as at the followings:



Second step: A fast step corresponding to a loss of water molecule to form a double bond:

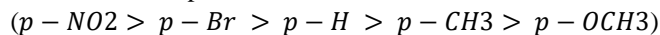


Final slow step: corresponds to a unimolecular cyclization process resulted by the intramolecular nucleophilic attack by the primary amine group of the thiourea side molecule to form the thiopyrimidine (keto-enol) product.



IV. CONCLUSION

In this paper we have studied the kinetics and the detailed mechanism of the reaction of para substituted 2,6-dibenzylidenecyclohexanone and its derivatives with thiourea in order to produce the corresponding thiopyrimidine. The reaction is a first order with both reactants. The low values of A-factor and correspondingly the negative values of ΔS^\ddagger provided a support to the restricted activated complex which lacked some degrees of freedom in the slow step. The order of reactivities with para substituents is;



and this supported the availability of electron density at the reaction center. The relative constancy of ΔG^\ddagger values indicated that the reaction of all the substituted 2,6-dibenzylidenecyclohexanone and its derivatives is operative in the same mechanism.

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APPENDIX A

IR, UV and (H^1 , C^{13})-NMR of fused pyrimidine thiones:

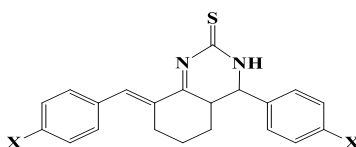


TABLE A-I
IR, AND UV-VISIBLE SPECTROPHOTOMETER FOR THE PRODUCTS OF FUSED PYRIMIDINE THIONE

Compounds Name	I.R. (KBr), ν (cm^{-1})										UV (DMSO solvent) λ_{max} (nm)
	C=C	C-H	C=N	C=C	N-H	C-O-C	C-Br	C-NO ₂	C-C	C=S	
8-benzylidene-4-phenyl-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	1539	1028	1623	1601	3199	-----	-----	-----	-----	1188	263
8-(4-bromobenzylidene)-4-(4-bromophenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	1528	1071	1678	1589	3393	-----	625	-----	-----	1011	264
8-(4-methylbenzylidene)-4-(p-tolyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	1539	1114	1647	1611	3188	-----	-----	-----	951	1018	269
8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	1539	1113	1636	1607	3208	2835	-----	-----	-----	1028	284
8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	1516	1107	1644	1593	3321	-----	-----	1344	-----	1017	272

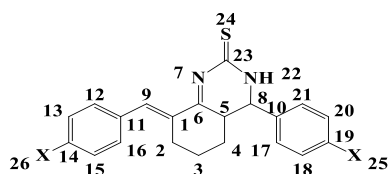


TABLE A-II
H¹-NMR FOR PRODUCTS OF PYRIMIDINE THIONE

Compounds Name	H ¹ -NMR (DMSO), ppm						
	H2, H22	H3, H4	H5	H8	H9	Ar-H	Others
8-benzylidene-4-phenyl-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	2.800	1.629	2.267	3.562	6.476	7.519	-----
8-(4-bromobenzylidene)-4-(4-bromophenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	2.759	1.448	2.160	3.294	6.318	7.606	-----
8-(4-methylbenzylidene)-4-(p-tolyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	2.800	1.529	2.267	3.362	6.476	7.519	Ar-CH ₃
8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	2.753	1.201	2.256	3.334	6.617	7.885	Ar-OCH ₃
8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	3.003	1.454	2.264	4.026	6.585	7.965	-----
4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	3H, m	4H, m	1H, q	1H, d	1H, s	5H, m	(2.350)6H,s
4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	3H, m	4H, m	1H, q	1H, d	1H, s	5H, m	(3.778)6H,s
4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	3H, m	4H, m	1H, q	1H, d	1H, s	5H, m	-----

TABLE A-III
C¹³-NMR FOR PRODUCTS OF PYRIMIDINE THIONE

Compounds Name	C ¹³ -NMR (DMSO), ppm									
	C1	C2	C3, C4	C5	C6	C8	C9	C23	Ar-C	Ar-C-X
8-benzylidene-4-phenyl-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	128.160	27.325	25.011	39.115	167.373	58.287	129.271	183.970	137.362	---
8-(4-bromobenzylidene)-4-(4-bromophenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	124.362	26.854	24.012	39.154	165.013	54.227	127.490	181.033	132.590	---
8-(4-methylbenzylidene)-4-(p-tolyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	126.737	27.085	22.386	39.098	161.023	57.127	129.252	183.614	133.644	-CH ₃ 21.367
8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	127.572	28.131	23.083	39.089	160.341	59.264	129.846	188.929	132.392	-OCH ₃ 54.905
8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-4,4a,5,6,7,8-hexahydroquinazoline-2(3H)-thione	126.726	27.789	22.397	39.298	161.712	58.033	129.409	183.013	133.852	---