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ORIGINAL RESEARCH ARTICLE

Synthesis, Characterization and Biologial Evaluation of 2-amino-3-(n-cyclohexyl carboxamido)- 4,5,6,7-tetrahydrobenzo (b) Thiophine Derivatives.

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ABSTRACT

Derivatives of 2- amino- 3- (N- cyclohexyl carboxamido)- 4,5,6,7- tetrahydrobenzo (b) thiophine were prepared and evaluated as antimicrobial. Despite finding that 2- amino- 3- (N- cyclohexyl carboxamido)- 4,5,6,7- tetrahydrobenzo (b) thiophine possess the activity on allosteric receptor as antimicrobial agents.

Key words: Thiophine Derivatives, 2-amino-3-(n-cyclohexyl carboxamido)- 4,5,6,7-tetrahydrobenzo

INTRODUTION

The first allosteric enhancers (AEs) acting at the adenosine A1 receptor (A1AR) were reported by Bruns *et al*. in 1990. These compounds were primarily 2-amino-3- benzoylthiophenes and 2-amino-3-benzoyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridines and were found to decrease the rate of dissociation of agonist, but not antagonist radioligand from the orthosteric binding site. In addition to allosteric activity, some of these compounds also have weak activity as competitive antagonists of the A1AR. PD81, 723 were one of the more potent and effective of the initial series of enhancers and have subsequently been commonly used for benchmarking new AEs. Since this initial discovery, other researchers have directed significant effort to refining the structure–activity relationships of the 3-, 4- and 5-positions of the 2-aminothiophene cores. Replacement of the thiophene by benzene resulted in a marked reduction of activity. Substitution at the 4-position increased activity by a factor of 3 (phenyl > methyl > H), while substitution at the 5-position had little effect on activity. Bulky (or hydrophobic) substituents at the meta- and para-positions of the 3-benzoyl group and also 3-naphthoyl groups greatly enhanced enhancer activity. Thus, the A1AR is thought to contain an allosteric binding site able to accommodate 3-aroyl substituents that are bulky and/or hydrophobic but not necessarily planar. A second region in the allosteric binding site interacts constructively with alkyl substituents at thiophene C-4 and/or C-5 and the 2-amino and 3-keto groups were found to be crucial for activity.

There is various types of the compound which have thiophine ring such as ticarcillin, cefoxitin, cephalohtin & Cephalorodine have shown good antibacterial activity.

Antifungal agents like *sertaconazole* and *ticonazole* also contain the thiophene nucleus. Anticonvulsant activity like *Tigabine (Gabitril)* also contain thiophine nucleus which block GABA reuptake.

So far various new thiophenes have been synthesized and screened for activity. The encouraging results provided us the impetus to continue the investigation.

Hence, we have attempted the syntheses of some new compounds containing cyclohexane and thiophene as a fused nucleus. The synthetic route employed is by adapting of the well-known and versatile Gewald reaction.

The main object of the study is, firstly synthesized the starting compound 2-amino-3-(N-cyclohexyl carboxamido)-4,5,6,7-tetrahydro benzo (b) thiophine and second is that, derivatize the new compound from the starting compound which have some biological activity

In our present study, we have derivatized the starting compound to various 2-substituted amino-3-(N-cyclohexylamido)-4,5,6,7-tetrahydro benzo (b) thiophenes. A series of compounds have been synthesized.

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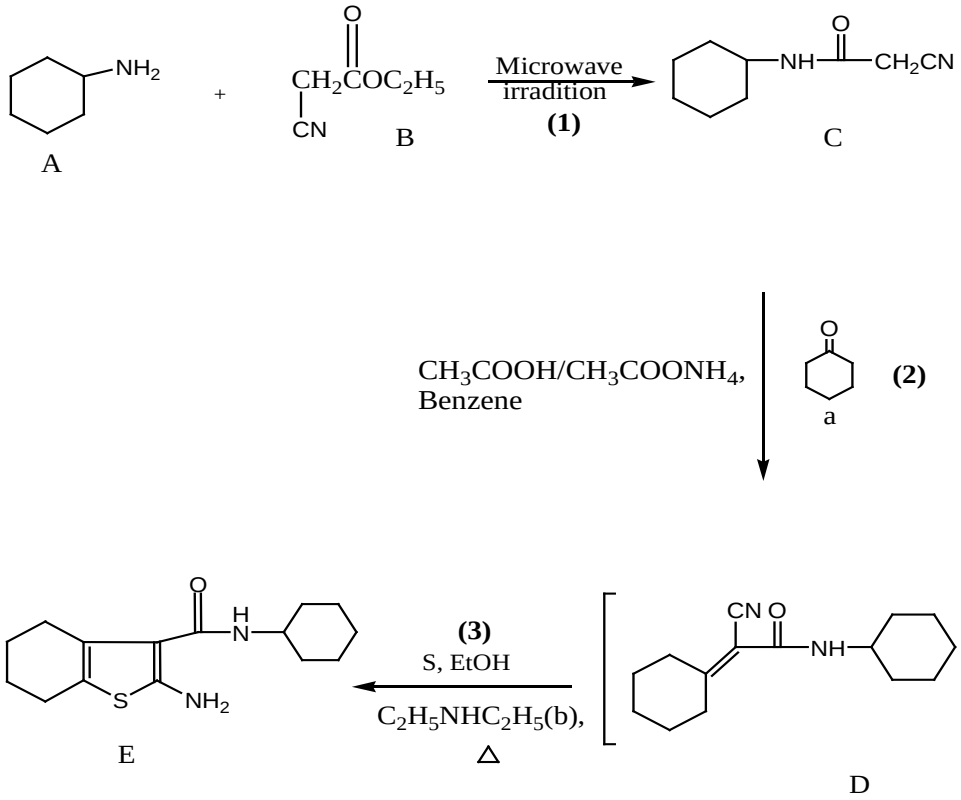
EXPERIMENTAL

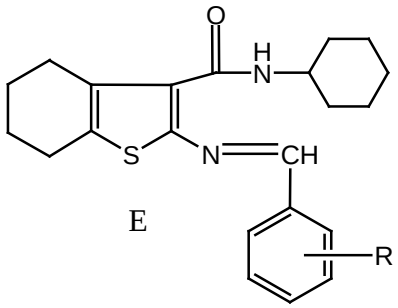
SCHEME FOR THE SYNTHESIS OF THE STARTING COMPOUND:



Synthesis of 2-amino-3-(N-cyclohexyl carboxamido)-4,5,6,7-tetrahydrobenzo(b)thiophine

SYNTHESIZED DERIVATIVES:

- Structure of common compound;



- **Number of Compound Synthesize:**

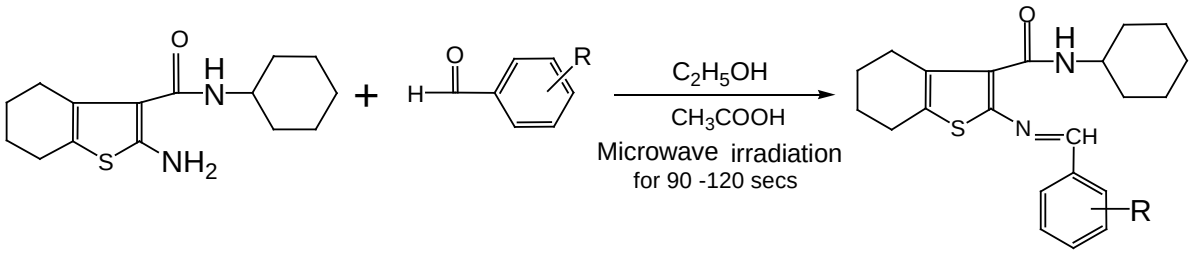
R =

(1) 4'-chloro

(2) p-dimethyl amino

General method for the synthesis of 2-[(substituted benzylidene)imino]- 3-(N-cyclohexylamido)-4,5,6,7-tetrahydro benzo (b)thiophenes (Schiff bases).

Reaction:



2-amino-3-(N-cyclohexylamido)
-4,5,6,7-tetrahydro benzo (b) thiophene

R =

1. 4'-chloro
2. p-dimethylamino

Procedure

A mixture of the starting compound and the required aryl aldehydes in propan-2-ol and catalytic amount of glacial acetic acid (2-5 drops) was taken in a conical flask and was irradiated for 90 to 120 secs. The mixture was cooled to room temperature. The solid separated was filtered, washed with propan-2-ol and recrystallized.

Procedure for synthesis of 2-amino-3-(N-cyclohexyl carboxamido)-4,5,6,7 tetrahydro benzo (b) thiophene (starting compound):

A mixture of cyclohexylamine (57.19 ml; 0.5 M) and ethyl cyano acetate (53 ml; 0.5 M) was taken in a conical flask and irradiated at 900 watt for 70 secs. The reaction mixture was left at room temperature overnight. The solid obtained was collected, washed with methanol and dried. Recrystallized from ethanol: water mixture (5:1). A mixture of cyclohexyl cyanoacetamide (1.66 g; 0.01 M), Cyclohexanone (1.03 ml; 0.01 M), ammonium acetate (2 g) and glacial acetic acid (2 ml) in benzene (100 ml) was refluxed for 8 hours with an arrangement for continuous separation of water using dean stark apparatus. After 8 hours the reaction mixture was cooled, diluted with 10 ml benzene and washed with sodium carbonate solution (10% w/v in water) and water successively thrice and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the intermediate crude product obtained was immediately processed for next step. To a mixture of 2-cyano-2-(cyclohex-1-ylidene)-cyclohexyl carboxamide in alcohol (30 ml) was added sulphur (1.28 g; 0.04 M) in portions followed by the addition of, diethyl amine (4.0 ml) drop wise with stirring. The reaction mixture was stirred for 15-20 min. at 40-45^{0}C and chilled over night. The solid obtained was filtered, washed with ethanol and crystallized from ethanol: water mixture (9:1) (60.60% yield).

[(4'-chloro benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-I) :

A mixture of the starting compound(0.005 M) and small amount of 4-chloro benzaldehyde (0.005 M) in propan-2-ol (30 ml) and catalytic amount of glacial acetic acid (2-5 drops) was taken in conical flask and was irradiated at 900W for 90-120 sec.

Substituted benzaldehydes Compound No.

ARC - I

ARC - II

The mixture was cooled at room temperature. The solid separated was filtered, washed with propan-2-ol an recrystallized from DMF: Water mixture (5:1) (50.53 % yield).

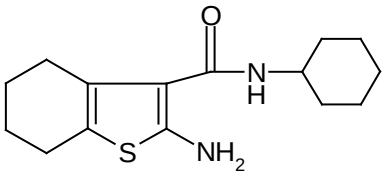
[(4'-dimethyl amino benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-II) :

A mixture of the starting compound(0.005 M) and small amount of 4-dimethyl amino benzaldehyde (0.005 M) in propan-2-ol (30 ml) and catalytic amount of glacial acetic acid (2-5 drops) was taken in conical flask and was irradiated at 900W for 90-120 sec. The mixture was cooled at room temperature. The solid separated was filtered, washed with propan-2-ol an recrystallized from DMF: Water mixture (5:1) (yield 50.33%)

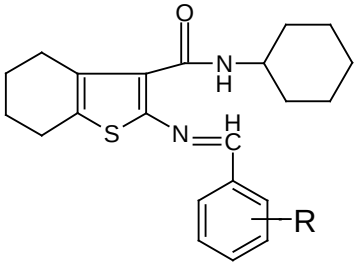
Meltiing Points were determined with an Eletrothermal melting point apparatus. All the observation were carried out perfectly.

RESULTS AND DISCUTION:

We have synthesized the above 2-Amino-3-(N-cyclohexylcarboxamido)-4,5,6,7-tetrahydro benzothiophene.



We have synthesized the above 2-Amino-3-(N-cyclohexylcarboxamido)-4,5,6,7-tetrahydro benzothiophene.



R= Cl, N-(CH_3),

The newly synthesized compounds were characterized by spectral data and were screened for their antimicrobial activity.

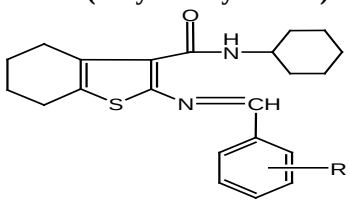
Synthesis is carried out to screen some new 2-substituted amino-3-(N-cyclohexyl carboxamido)-4,5,6,7-tetrahydro benzo (b) thiophenes for antimicrobial activity.

- **Characterization for 2-amino-3-(N-cyclohexyl carboxamido)-4,5,6,7 tetrahydro benzo (b) thiophene (starting compound):**
  M.P.: 129 ºC,IR Spectrum (KBr, cm^{-1}):3459 (-NH_2); 3293 (-NH-); 2992 (Ali-CH); 2927 (Ali-CH); 1652 (C=O); 815 (C-N); 695 (S-C).
- **Characterization for 2-[(4'-chloro benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-I) :**
  M.P.:180 `C,IR Spectrum (KBr, cm^{-1}): 3449 (-NH_2); 29279 (Ali-CH); 1658 (C=O); 1549(C=N); 760 (C-Cl)
- **Characterization for 2-[(4'-dimethyl amino benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-II) :**
  M.P. 108 `C, IR Spectrum (KBr, cm^{-1}): 3413 (-NH); 3172 (Ali-CH); 2972 (Ali-CH); 1669 (C=0); 1546 (C=N); 826 (C-N).

Their specific IR peaks confirm the formation of these new Schiff bases. Apart from this, the IR spectrum of the compound shows a distinct primary amino group peak at 3459 cm^{-1} and where as in ARC (I-II)**.** There is absence of primary amino group peak and appearance of imine group peak at 1546 cm^{-1} itself is sufficient to explain the formation of the new derivatives.

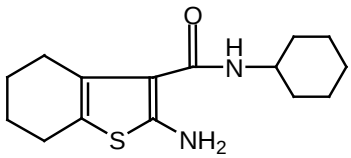
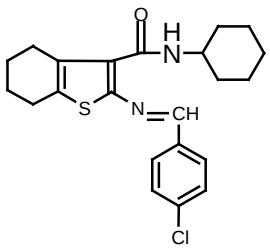
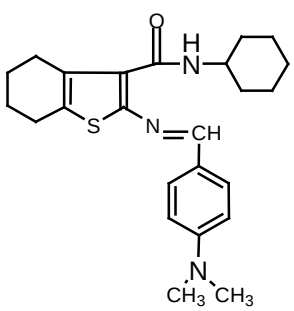
On the other hand, the structures of newly synthesized compounds were also been ascertained based on the NMR spectrum of the representative compounds.

Table 1:Structural derivatives of 2-imino-3-(N-cyclohexyl amido)- 4,5,6,7- tetrahydro benzo (b) thiophenes.



No.	R
ARC- I	p-chloro
ARC- II	p-dimethyl amino

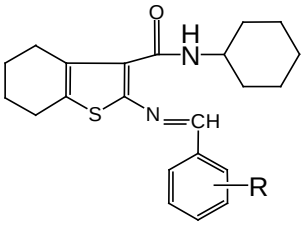
Table 2:SPECTRAL DATA FOR THE COMPOUND

Comp.No.	Structure	λ_{max} (nm)	IR (KBr) cm^{-1}	^{1}H NMR
1.		301	3459 (-NH_2); 3293 (-NH-); 2992 (Ali-CH); 2927 (Ali-CH); 1652 (C=O); 815 (C-N); 695 (S-C).	δ = 1.2-1.6 (m,10 H, cyclohexane);1.9 (4, H, m, cyclohexane); 3.5 (t, 4H, cyclohexane);3.9 (t, 1H, cyclohexane);4.2(d, 2H, NH_2) 8.3 (s,1H, NH).
2. ARC-I		362	3449 (-NH_2); 29279 (Ali-CH); 1658 (C=O); 1549 (C=N); 760 (C-Cl)	δ =7.45 (d, 2H, Aro CH); 7.75 (d, 2H, Aro CH); 1.1-1.9 (m, 14 H, cyclohexane); 2.1(d, 4H, cyclohexane); 3.5 (d, 1H, cyclohexane); 8.3-(s,1H, NH); 8.5 (d,1H, CH).
3. ARC- II		374	3413 (-NH); 3172 (Ali-CH); 2972 (Ali-CH); 1669 (C=O); 1546 (C=N); 826 (C-N)	**δ =** 1.2-1.9 (m, 14H, cyclohexane); 2.6 (t, 4H, cyclohexane); 2.9 (s, 6H, CH_3); 3.6-(d, 2H, cyclohexane); 6.8-(d, 2H, Aro CH); 7.8(d, 2H, Aro CH); 8.1 (s, 1H, NH); 8.2 (d, 1H, CH).

ANTIMICROBIAL ACTIVITY:

Antimicrobial activity of these compounds are also determined. The values are as follows.

Common compound:



(ARC I - II)

Table 3:Antimicrobial activity of the new 2-[(substituted benzylidene) imino]-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo (b) thiophenes (Schiff bases):

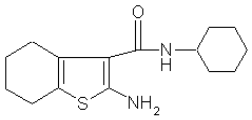
Compound No.	R	Zone of Inhibition (mm.)			
		Klebsiella pneumoniae **Gram (-ve)**	***E. coli*** **Gram (-ve)**	***S. aureus*** **Gram(+ve)**	***B.subtilis*** **Gram (+ve)**
ARC - I	4'-Cl	16	14	13	20
ARC – II	4'-N-$(CH_3)_2$	NA	NA	13	14

Dose concentration: 50 µg / 0.1 ml
NA : No activity
Control : DMF (Dimethyl formamide)

Table 4:Antifungal activity of the new 2-[(substituted benzylidene) imino]-3-(N-cyclohexylamido)-4,5,6,7-tetrahydro benzo (b) thiophenes (Schiff bases):

Compound No.	R	Zone of Inhibition (mm.)	
		Aspergillus niger	***Candida albicans***
ARC – VII	4'-Cl	14	11
ARC – X	4'-N-$(CH_3)_2$	NA	NA

NA : No activity
Control : DMF (Dimethyl formamide)



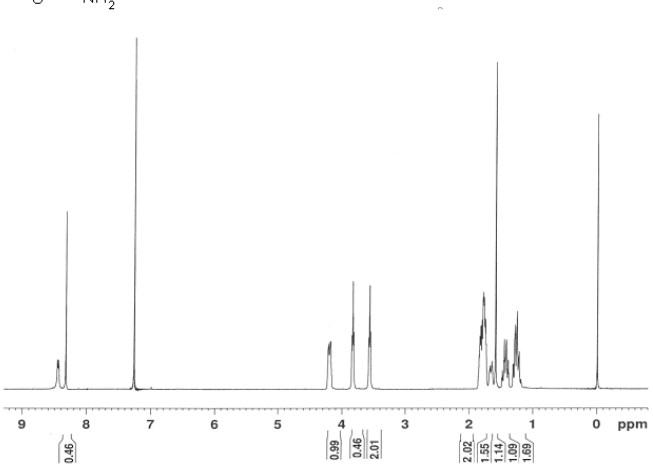


Figure. 1: NMR Spectra of 2-amino-3-(N-cyclohexyl carboxamido)-4,5,6,7 tetrahydro benzo (b) thiophene (starting compound).

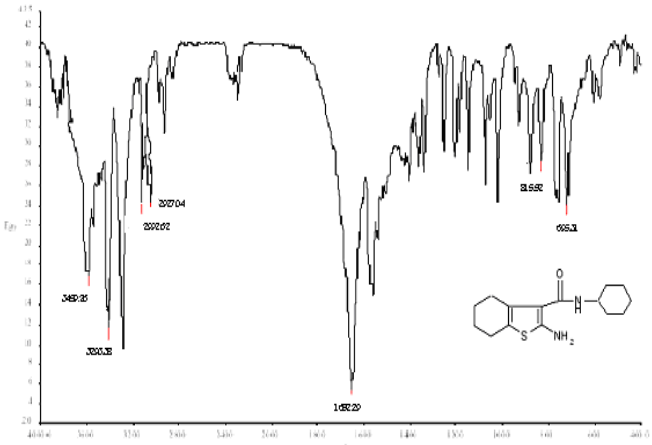


Figure. 2: IR Spectra of 2-amino-3-(N-cyclohexyl carboxamido)-4,5,6,7 tetrahydro benzo (b) thiophene (starting compound):

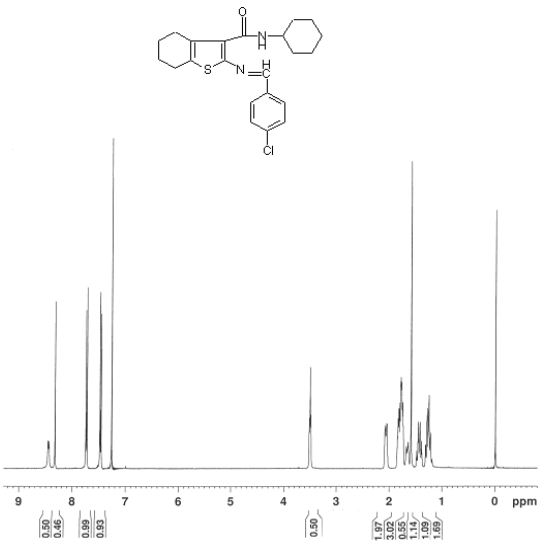


Figure. 3. NMR Spectra of 2-[(4'-chloro benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-I)

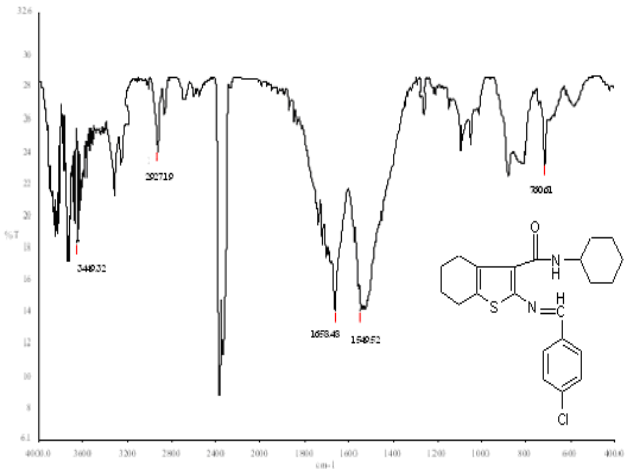


Figure. 4. IR Spectra of 2-[(4'-chloro benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-I)

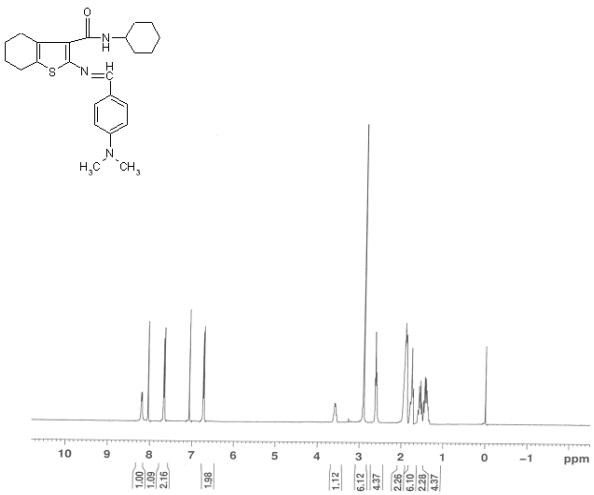


Figure. 5. NMR Spectra of 2-[(4'-dimethyl amino benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-II)

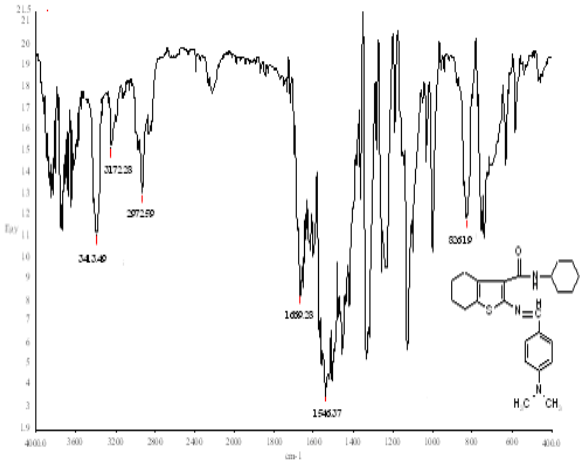


Figure. 6. IR Spectra of 2-[(4'-dimethyl amino benzylidine) imino-3-(N-cyclohexyl amido)-4,5,6,7-tetrahydro benzo(b) thiophine (ARC-II)

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