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One Pot three component organocatalyzed synthesis of octahydroquinazolinones

Bhupal Singh Karki, Shivani Verma, Akansha Agrwal and Virendra Kasana

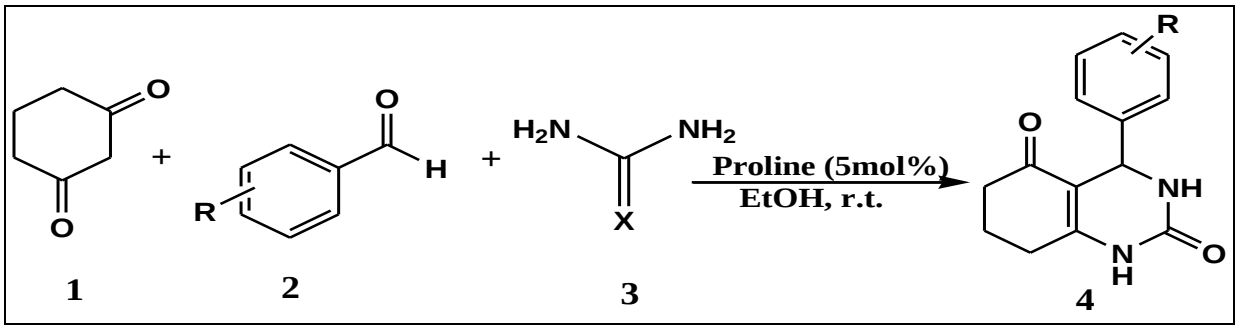
Abstract
Efficient one pot three component synthesis of octahydroquinazolinone derivatives by reacting substituted aromatic aldehyde, 1,3-dicyclohexanedione, urea/thiourea at room temperature catalyzed by L-proline as an ecofriendly catalyst with excellent yield (70-95%) and short reaction time is reported. The structures of synthesized derivatives were characterized and confirmed by FT-IR and ^{1}HNMR data.

Keywords: Octahydroquinazolinone, L-proline and organocatalysis

1. Introduction
The starting of Biginelli reaction by the cyclocondensation reaction of an aldehyde, ethylacetoacetate and urea for the synthesis of dihydropyrimidones was first reported by Italian Chemist Pietro Biginelli [1, 2]. Octahydroquinazolinone may be synthesized by the same reaction using aldehyde, 1,3-dicyclohexanedione and urea/thiourea. These cyclocondensation give the moderate yield (20-50%) and were time-consuming. Octahydroquinazolinone have vast applicability as calcium antagonist [3], antibacterial [4], antimicrobial activity [5] and Insecticidal activity [6].
Various catalytic systems have been reported for the synthesis of octahydroquinozolinone such as sulfuric acid in water [7], trimethylsilyl chloride (TMSCl) [8], p-toluene sulfonic acid[9], acidic ionic liquid [tbmim]Cl_2/$AlCl_3$ [10], ammonium metavanadate [11], thiamine hydrochloride [12], lanthanum oxide [13], Lemon juice [14], ZnO nanoparticle [15], vanadium n-propylamino phosphate[16], zirconium oxychloride octahydrate [17], sodium p-toluene sulfonate in MW[18], tungstate sulfuric acid [19], molybdenum oxide nanoparticle [20], aluminate sulfonic acid nanoparticle[21], polyvinylpolypyrrolidone-supported cholorosulfonic acid[22] and (Me (Im)^{12}) $H_4CuPW_{11}O_{39}$[23]. Most of the methods reported in the literature use hazardous catalysts or solvents and critical conditions, so the protocol using environmentally benign catalysts and without the use of hazardous solvents is desirable.

2. Material and Methods
2.1 Materials
All the reagents, chemicals were purchased from hi-media and were used without further purification. 1H NMR spectra were recorded on 400 MHz JEOL JNM ECS400 instrument using DMSO. The purity of products and reaction progress was checked by TLC on silica gel plates using hexane: ethylacetate (80:20) solvent system and visualized using iodine vapors and UV detection.

2.2 Methods
In round bottom flask urea/thiourea (5 mmol), 1,3-dicyclohexandione (5 mmol), substituted benzaldehyde (5 mmol) and proline (10 mol%) as a catalyst were taken with 5ml ethanol as solvent media (Scheme 1). Soon after addition of solvent, a pale color solution was obtained. The reaction mixture was then stirred at room temperature, after some time of stirring precipitate formed. Ice cold water was added and the reaction mixture was further stirred for 5min. The solid product obtained was filtered and washed with cold water. The obtained crude product was dried and recrystallized from ethanol.



Scheme1: Synthesis of octahydroquinazolinone (X=O/S)

3. Result and Discussion

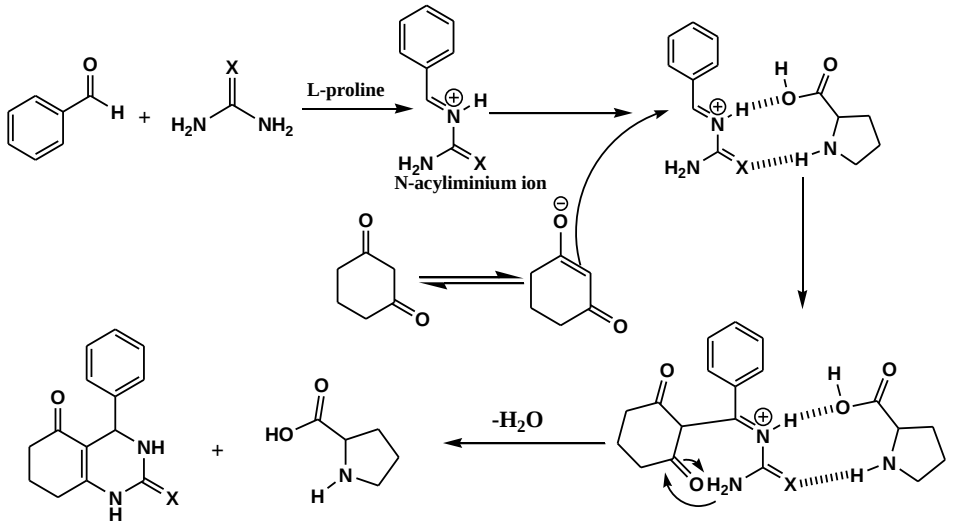
The reaction conditions were standardized by the representative reaction taking benzaldehyde (5 m mol), 1,3-cyclohexanedione (5 m mol) and urea (5 m mol) as starting material and proline (10 mol%) as catalyst under neat condition (Table 1). After 10 min precipitate was appeared. Workup of the reaction gave the product in 80% yield as confirmed by TLC. The same reaction was repeated also by taking less amount (5 mol%) of the catalyst under same conditions. The time for completion of reaction now increased to 1 hr and yield reduced to 60%. By further reducing the amount of catalyst (2 mol%), it was observed that reaction time increased to 2.5 hr. To examine the efficacy and requirement of catalyst, the same reaction was carried out in absence of catalyst. It was observed that reaction took 4 hr to complete the reaction with 40% yield. From the experiment, it was found that 10 mol% was the optimum amount of catalyst.

Table 1: Standardization of catalyst amount at room temperature

S. No.	Catalyst amount (mol%)	Time	Yield%
1	20	9 min	81
2	10	10 min	80
3	5	1 hr	60
4	2	2.5 hr	40
5	0	4 hr	40

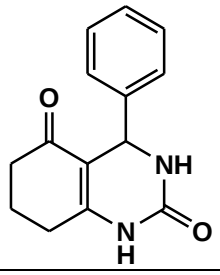
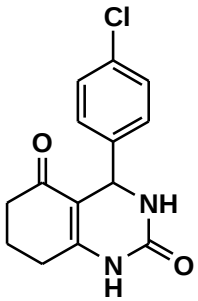
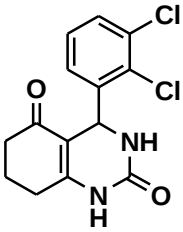
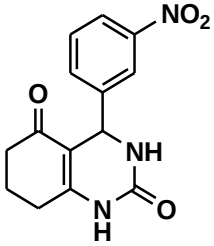
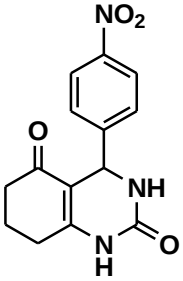
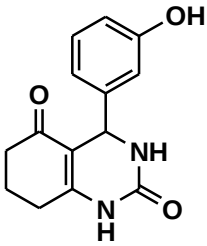
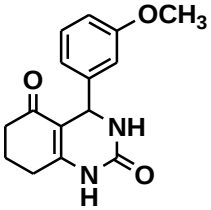
The percent yield, melting point, color and time took for completion of reaction are given in table 2. The perusal of table 2 reveals that the time taken for completion of reaction for most of the compounds (4a-4f, 4i, 4j) was 10-30 min. For compound 4g the time is 95 min while for the compound 4h is 24 hr, exceptionally longer. The exceptionally longer time for the preparation of compound 4h is attributed to the presence of $-N(CH_3)_2$ group on the benzene ring of aldehyde, since $-N(CH_3)_2$ decreases the electrophilicity of carbonyl carbon. The yield of compound 4h is very low due to same reasons. All other compounds were obtained in good to excellent yield. The compound (4k-4t) were synthesized by the reaction of substituted benzaldehyde, 1,3cyclohexanedione and thiourea in the presence of L-proline as a catalyst according to scheme 1.

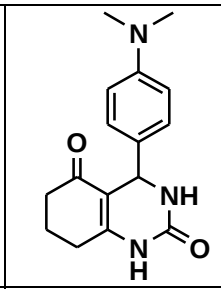
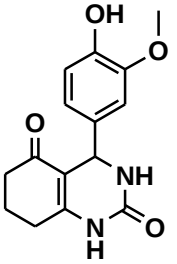
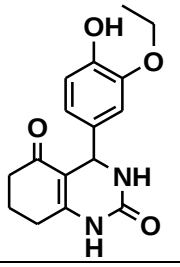
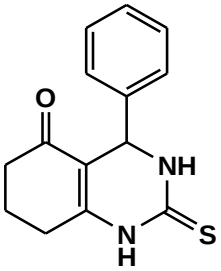
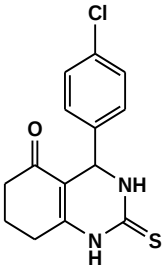
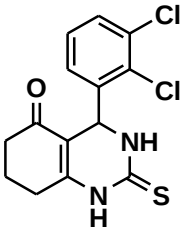
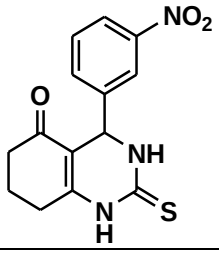
The plausible mechanism for the formation of octahydroquinazolinone based on earlier reports [24] is suggested in scheme 2. It involves initial formation of N-acyliminium ion intermediate from an aldehyde and urea/thiourea in presence of catalyst. The N-acyliminium ion intermediate undergoes complex formation with L-proline via hydrogen bonding to produce N-acyliminium ion-L-proline complex. Formation of complex clearly shows that complexation of L-proline with N-acyliminium ion via hydrogen bonding increases the electrophilicity of carbon atom attached to benzene ring and nucleophilicity of N-atom in NH_2 group. N-acyliminium ion-L-proline complex reacts with 1,3-cyclohexanedione enolate anion to form C-C bond and charges on nitrogen is also neutralized to form a complex by the nucleophile attack of 1,3-cyclohexanedione enolate on carbon attached to benzene ring. The intermediate undergoes cyclization leading to the transition state. Thus the formation of carbon-carbon and carbon-nitrogen bond occurs via cyclization. This clearly indicates the importance of L-proline as a catalyst for the formation of both C-C and C-N bond. Elimination of water from transition state and removal of L-proline gives product.

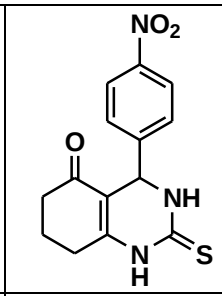
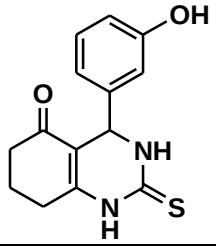
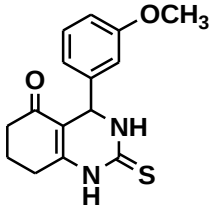
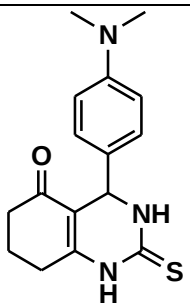
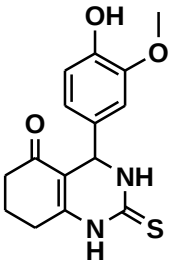
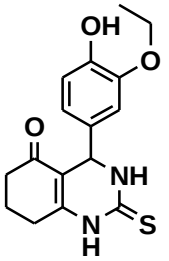


Scheme 2: Plausible mechanism for the formation of octahydroquinazolinone

Table 1: L-proline catalyzed synthesis of octahydroquinazolinone derivatives

Compound Code	Product	Percent yield (%)	Color	M.P.^{0}C	Time of reaction (min)
4a		80	White	220-223	10
4b		85	White	196-198	5
4c		90	White	198-202	20
4d		60	White	168-172	25
4e		95	White	180-183	15
4f		70	Yellow	160-163	30
4g		80	Brown-yellow	160-163	95

4h		20	Orange	163-165	24 hr
4i		90	White	180-183	27
4j		83	White	160	20
4k		80	White	96-98	20
4l		85	White	176-179	10
4m		90	White	176-179	20
4n		92	White	186-188	10

4o		95	White	172-174	10
4p		70	White	175-178	10
4q		75	White	157-159	120
4r		10	Orange	150-153	24 hr
4s		60	White	188-190	37
4t		75	White	160-163	140

3.1 Spectral analysis

4-phenyl-4,6,7,8-tetrahydro-1H,3H-quinazoline-2,5-dione: IR (cm^{-1}): 3467, 3318, 3054, 2961, 1720, 1603, 1HNMR (DMSO) 2.11(2H,m, CH_2), 2.38(2H, m, CH_2), 2.45 (2H, m, CH_2), 5.33(1H, s, CH), 6.9-7.1(5H,m, Ar), 9.8(1H, s, NH), 11(1H,s, NH)

4-(2,3-dichlorophenyl)-4,6,7,8-tetrahydro-1H,3H-quinazoline-2,5-dione: IR (cm^{-1}): 3125, 2963, 2869, 1717, 1613, 1HNMR (DMSO) 2.11((2H,m, CH_2), 2.41(2H,m, CH_2), 2.50(2H,m, CH_2), 5.70(1H, s, CH), 7-7.3(3H, m, Ar), 10.3(1H,s, NH), 11(1H, s, NH)

4-(3-ethoxy-4-hydroxyphenyl)-4,6,7,8-tetrahydro-1H,3H-quinazoline-2,5-dione: IR (cm^{-1}): 3316, 3181, 2961, 2874, 1704, 1605, 1HNMR (DMSO) 1.30(2H,t, CH_3), 2.12 (2H, m,CH_2), 2.41(2H, m,CH_2), 2.50(2H, m,CH_2), 3.89-3.91(2H, q, CH_2), 5.60(1H, s,CH),6.53-6.80(3H, m, Ar), 8.88(1H, s,NH), 9.75(1H, s, NH), 10.20(1H, s, OH)

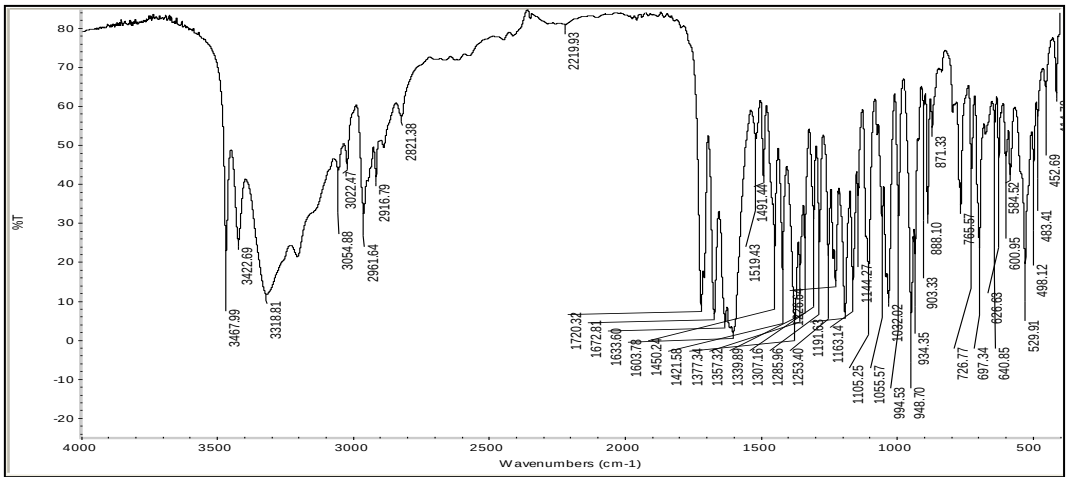
4-(p-chlorophenyl)-2-thioxo-4,6,7,8-tetrahydro-1H,3H-quinazoline-5-one: IR (cm^{-1}): 3072, 2944, 2874, 1908, 1629, 1HNMR (DMSO) 2.14(2H, m, CH_2), 2.49(2H, m, CH_2), 2.50(2H, m, CH_2), 5.82(1H,s,CH), 6.88-7.19(4H, m, Ar), 8.8(1H, s, NH), 10(1H, s,NH)

4-(3-nitrophenyl)-2-thioxo-4,6,7,8-tetrahydro-1H,3H-quinazoline-5-one: IR (cm^{-1}): 3372, 3164, 2951, 1723, 1632, 1HNMR (DMSO) 2.18(2H, m, CH_2), 2.49(2H, m, CH_2), 2.50(2H, m, CH_2),6.01(1H, s, CH), 7-7.06(4H, m, Ar), 7.9(1H, s, NH), 8(1H, s, NH)

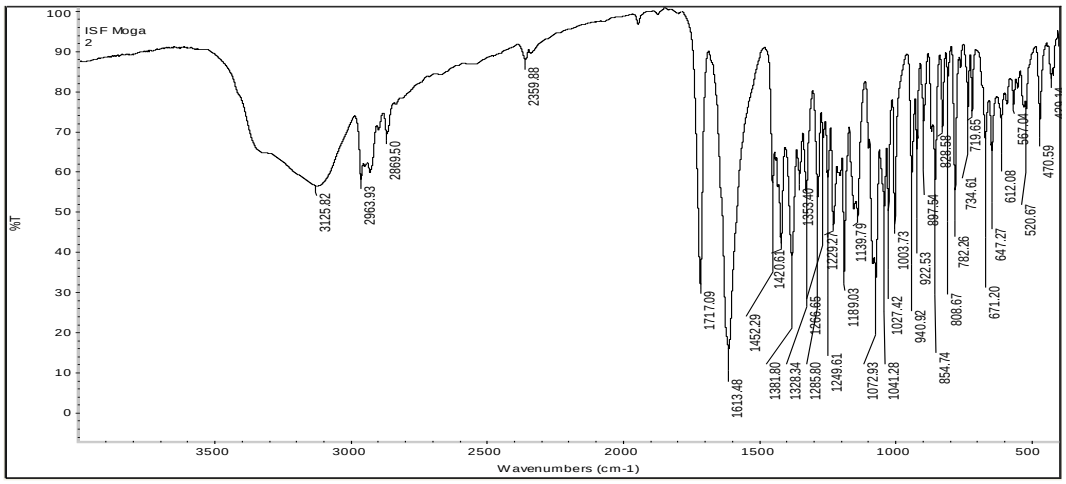
4-(3-methoxyphenyl)-2-thioxo-4,6,7,8-tetrahydro-1H,3H-quinazoline-5-one: IR (cm^{-1}): 3375, 2937, 2837, 1719, 1647, 1HNMR (DMSO) 2.10 (2H, m, CH_2), 2.40(2H, m, CH_2), 2.50(2H, m, CH_2), 5.77 (1H, s, CH), 6.62-6.80(4H, m, Ar), 6.87(1H, s, NH), 8.68(1H, s, NH)

4-(4-hydroxy-3-methoxyphenyl)-2-thioxo-4,6,7,8-tetrahydro-1H,3H-quinazoline-5-one: IR (cm^{-1}): 3427, 3138, 2949, 2837, 1720, 1598, 1HNMR (DMSO) 2.10 (2H, m, CH_2), 2.49(2H, m, CH_2), 2.50(2H, m, CH_2), 5.18(1H, s, CH), 5.6(3H, s,CH_3), 6.5-6.9(3H, m, Ar), 8.64(1H, s, NH), 9.76(1H, s, NH), 10.2(1H, s, OH)

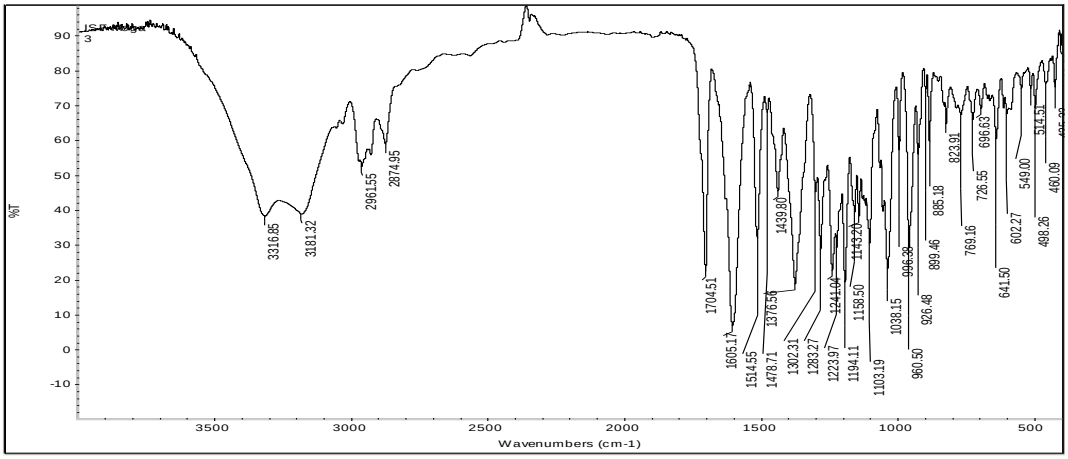
Supplementary File



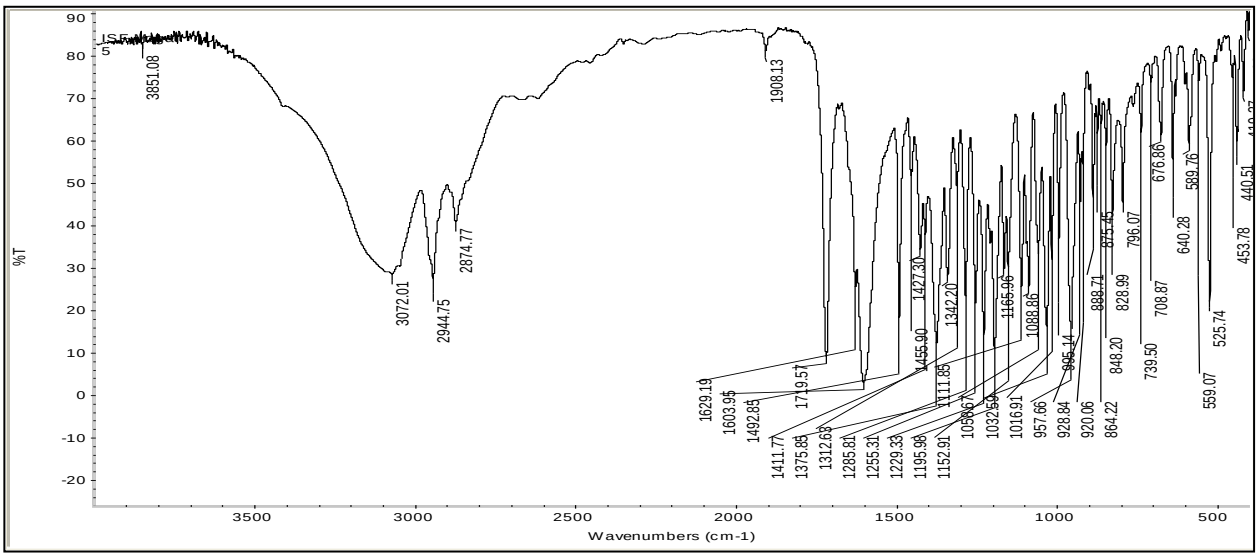
IR Spectra of 4-phenyl-4, 6, 7, 8-tetrahydro-1H, 3H-quinazoline-2, 5-dione



IR Spectra of 4-(2, 3-dichlorophenyl)-4, 6, 7, 8-tetrahydro-1H, 3H-quinazoline-2, 5-dione



IR Spectra of 4-(3-ethoxy-4-hydroxy-phenyl)-4, 6, 7, 8-tetrahydro-1H, 3H-quinazoline-2, 5-dione



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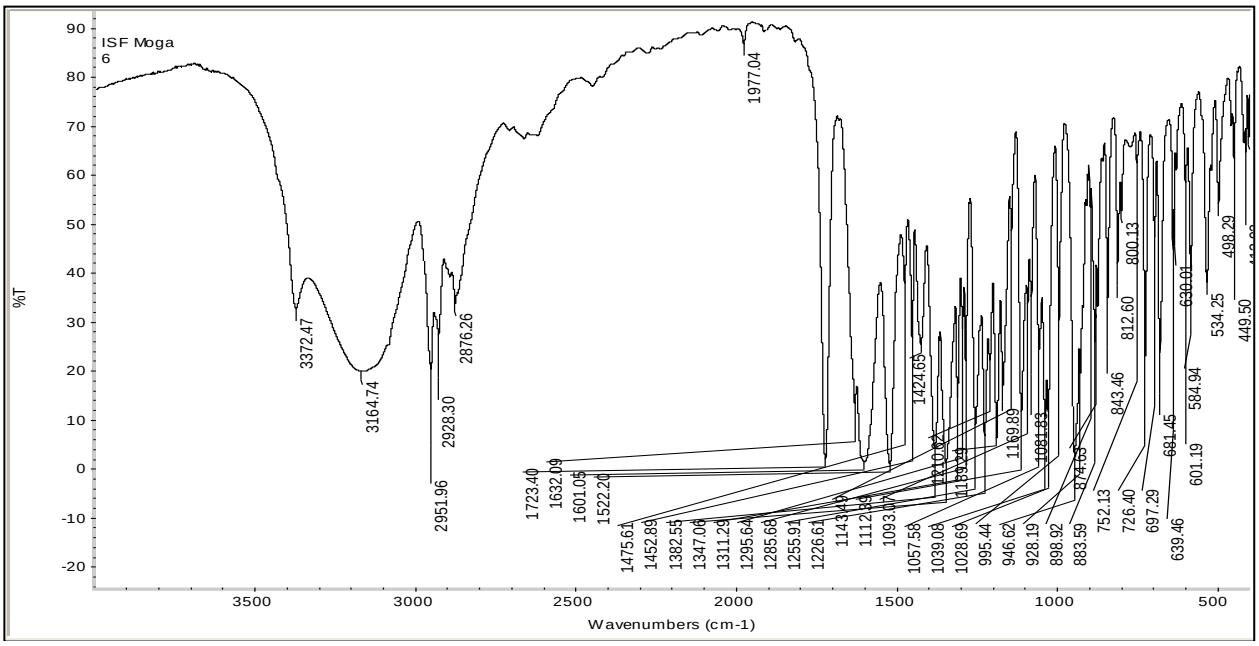
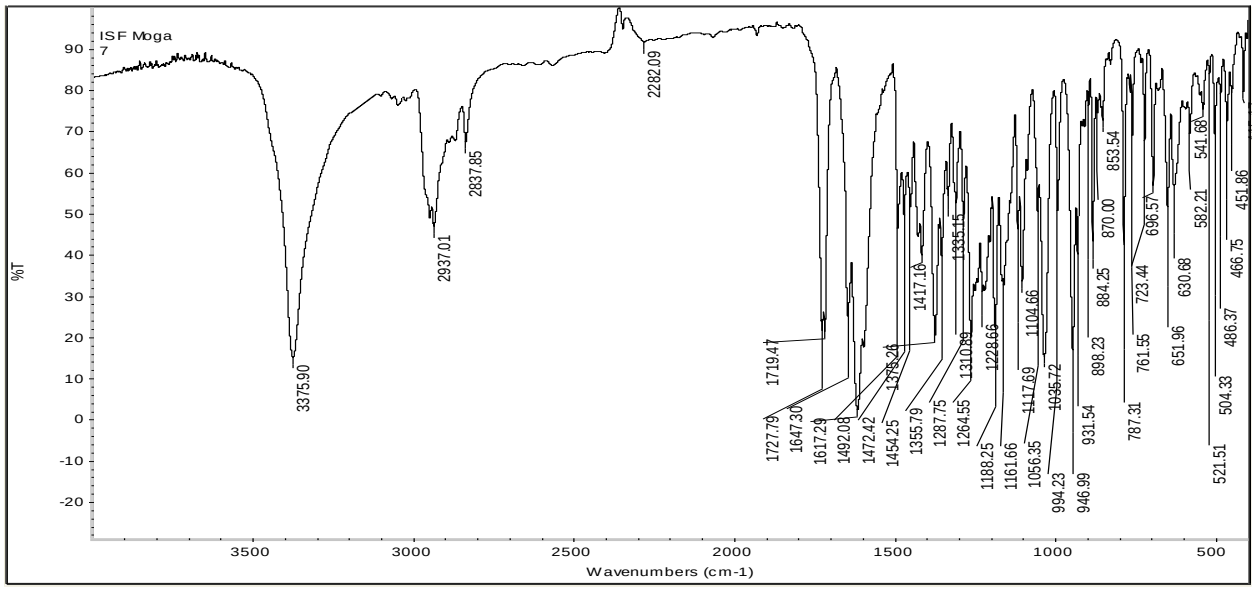
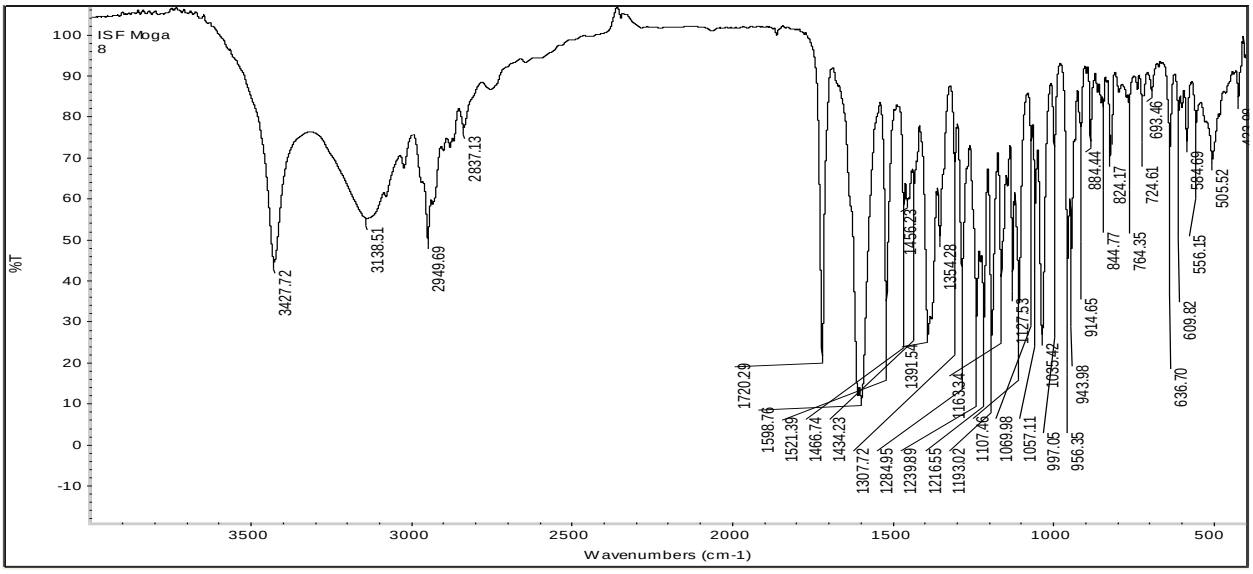


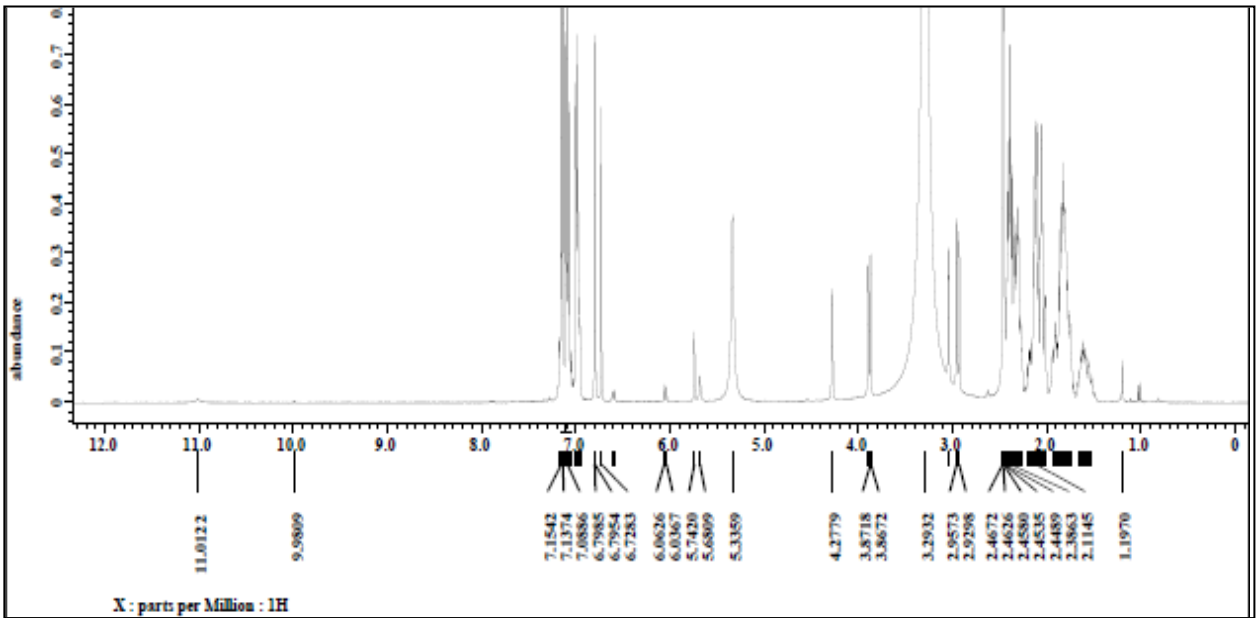
IR Spectra of 4-(3-nitrophenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one



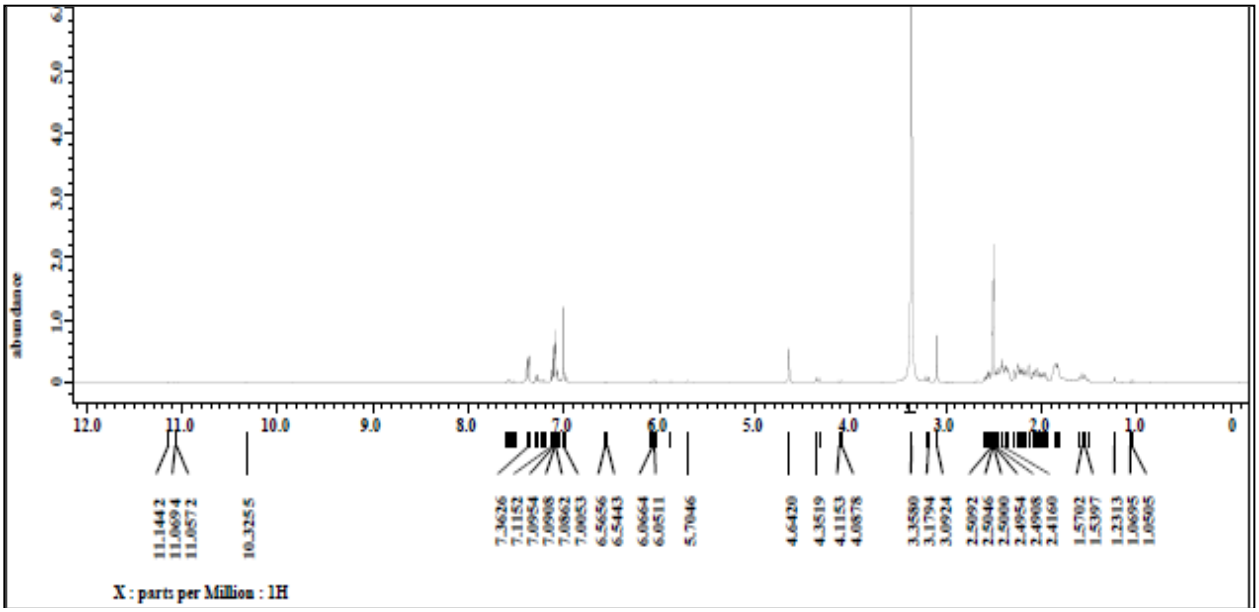
IR Spectra of 4-(3-methoxyphenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one



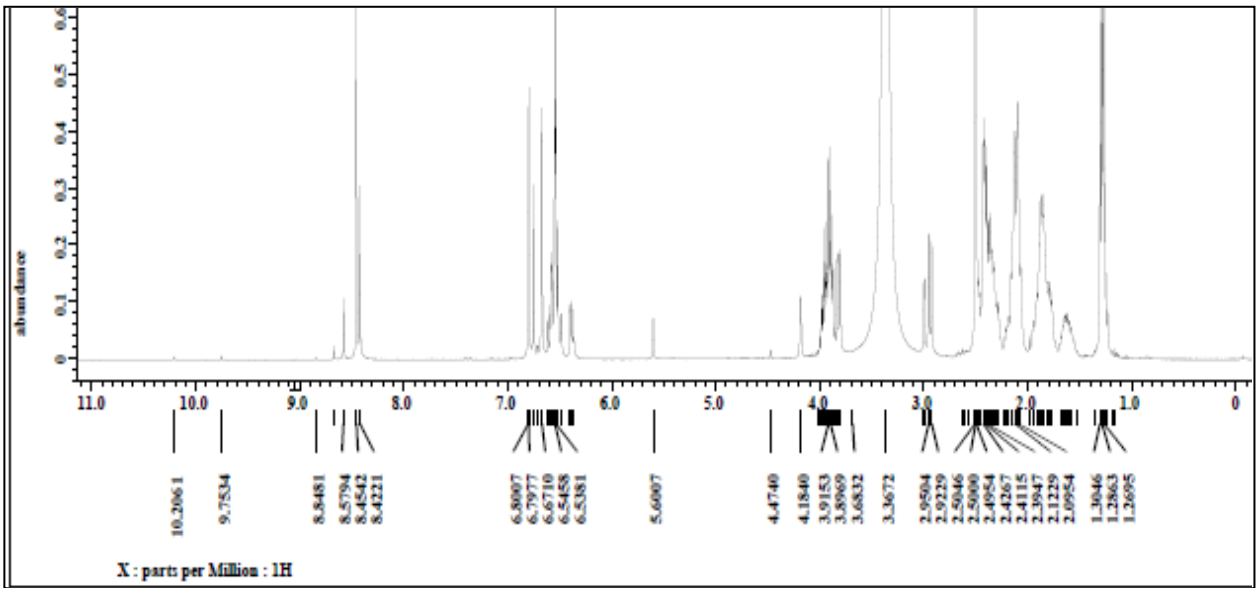
IR Spectra of 4-(4-hydroxy-3-methoxyphenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one



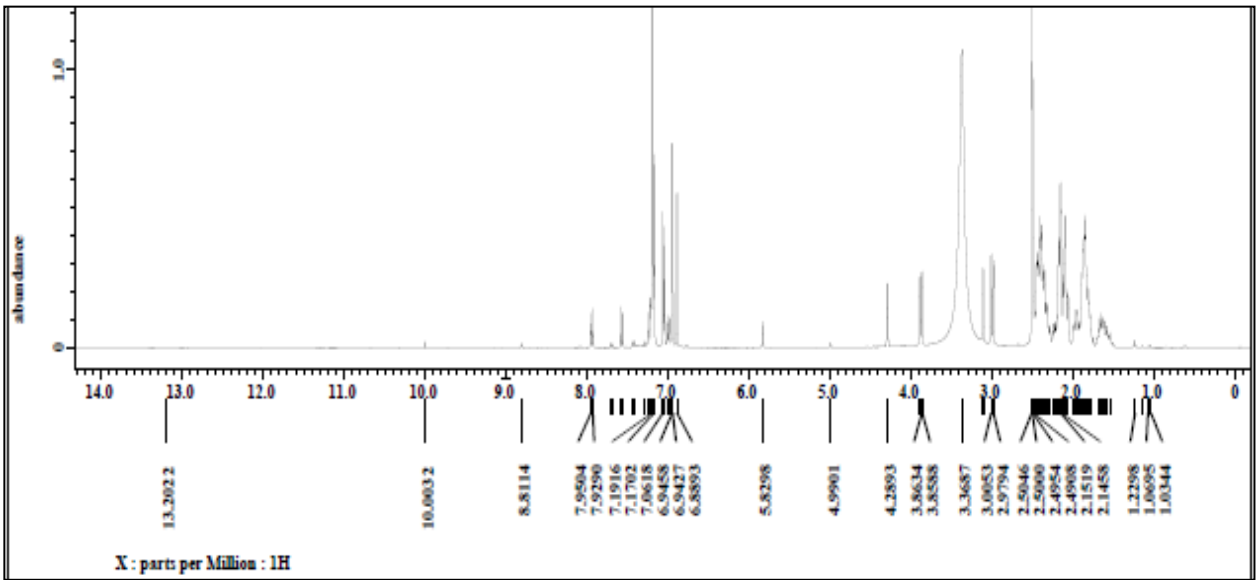
NMR spectra of 4-phenyl-4, 6, 7, 8-tetrahydro-1H, 3H-quinazoline-2, 5-dione



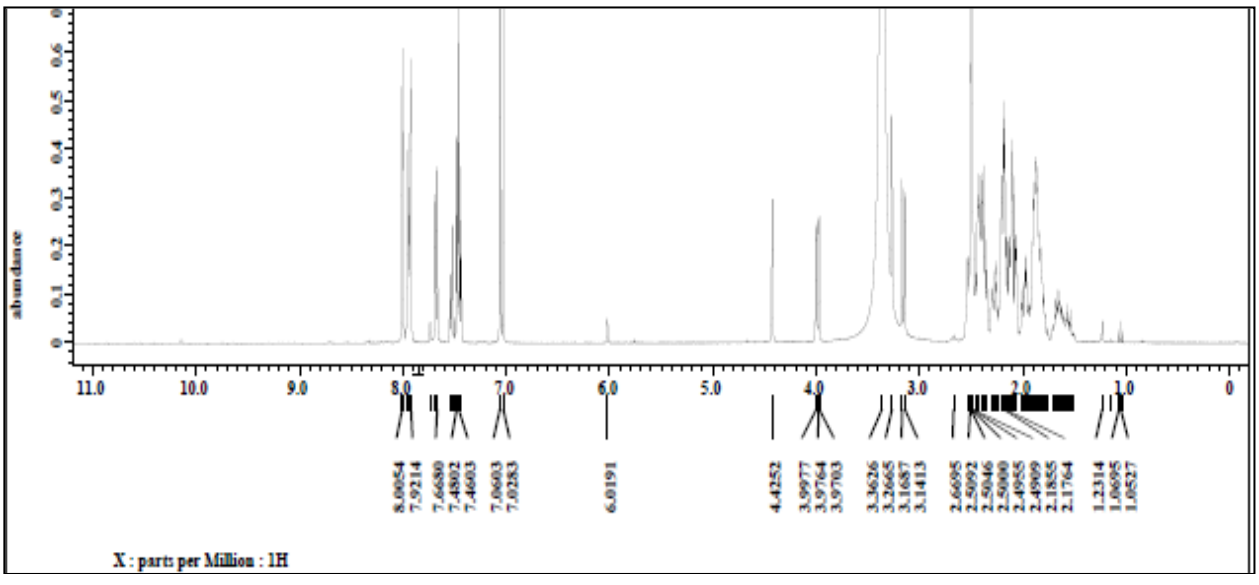
NMR spectra of 4-(2, 3-dichlorophenyl)-4, 6, 7, 8-tetrahydro-1H, 3H-quinazoline-2, 5-dione



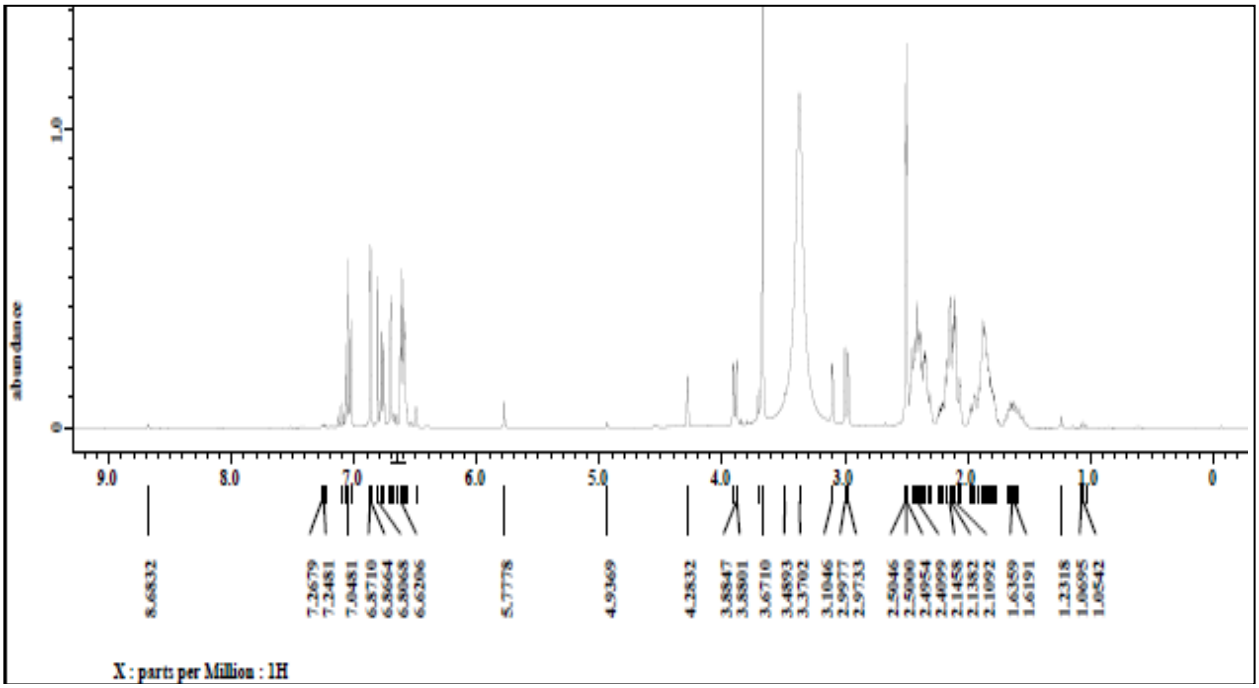
NMR spectra of 4-(3-ethoxy-4-hydroxy-phenyl)-4, 6, 7, 8-tetrahydro-1H, 3H-quinazoline-2, 5-dione



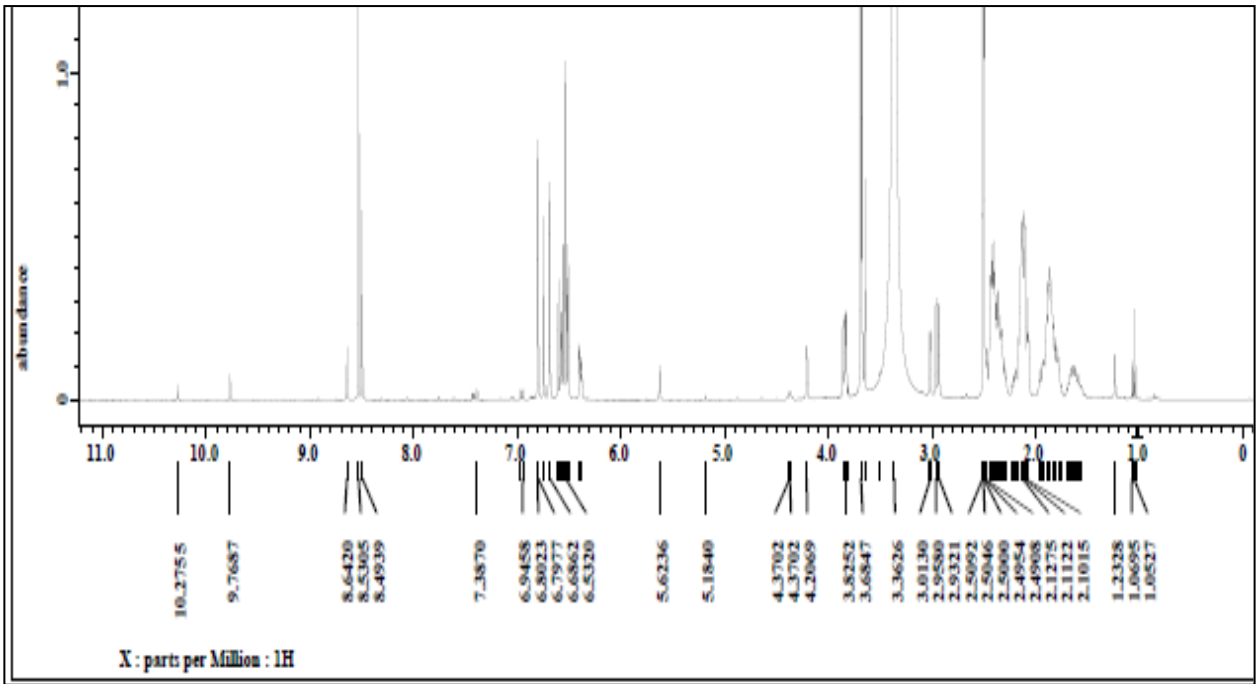
NMR spectra of 4-(4-chlorophenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one



NMR spectra of 4-(3-nitrophenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one



NMR spectra of 4-(3-methoxyphenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one



NMR spectra of 4-(4-hydroxy-3-methoxyphenyl)-2-thioxo-4, 6, 7, 8-tetrahydro-1H, 3H-quinazolin-5-one

4. Conclusion

In conclusion, we have developed highly efficient, ecofriendly method for the synthesis of octahydroquinazolinone derivatives in the presence of L-proline as catalyst at room temperature with less reaction time and high yield.

5. Acknowledgement

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