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Systematic Studies On The Synthesis And Spectroscopic Properties Of Quinazoline Scaffolds

Kumar M[a*], Kumudhavalli M.V[a], Gowramma.B[b], Ponnilavarasan Ilangovan[c]

[a]Department of Pharmaceutical Chemistry, Vinayaka missions College of Pharmacy,*
Vinayaka Mission's Research Foundation, Salem- 636 008, India.
[b]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, Ooty- 643 001, India.
[c]Department of pharmaceutical chemistry, KMCH College of Pharmacy, Coimbatore- 641 035, India.
[*]Address corresponding to this author at Department of Pharmaceutical Chemistry, Vinayaka missions College of Pharmacy,Vinayaka Mission's Research Foundation, Salem- 636 008, India.
E-mail: ponnilavarasan@kmchcop.ac.in

Abstract:
Quinazoline semicarbazone derivatives were synthesized by condensation of quinazoline semicarbazide with different aromatic carbonyl compounds (Isatin, Camphor, Benzophenone, p-dimethyl amino benzaldehyde and Vanillin). The synthesized compounds were characterized by physicochemical determination and their purity was evinced by TLC. Their structures were confirmed by IR, ^{1}H NMR, UV spectroscopy and elemental analysis.

Keywords: Quinazoline semicarbazone, anthranilic acid, spectral analysis.

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1. Introduction:

Synthetic quinazolines and its derivatives of semicarbazones possess interesting biological activities. Most of the biological active quinazolines are having substitutions at C-2 and N-3 positions. Isatin derivatives with 3-amino-2-methyl mercaptoquinazolin-4(3H)-one form Schiff bases and N-Mannich bases of quinazolines [1], quinazolinone derivative was converted into bis [quinazoline-4-thiozo-2-yl] –m-phenylene via different routes [2], synthesis of quinazoline and naphthalenes from 3-methyl-5-phenyl-6-benzylidene-2-cyclohexene-1-one [3], thioglycolic acid and pyrazole derivatives of 4(3H) quinazolinone were synthesized [4]. Anti fungal, antibacterial, anti HIV activity of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4′-chlorophenyl) thiazol-2-yl] thiosemicarbazide [5], fluorinated hydroquinazoline derivatives as antifungal agents [6], antibacterial activity of quinazolines [7], 6-chloro-2-morpholino 4-quinazolyl-5-vitro-2'furyl hydrazone as antibacterial agent [8] were also studied. Apart from antimicrobial activity this quinazoline ring system is present in a number of biologically active compounds which includes antihypertensive activity [9, 10], enzyme inhibition efficiency [11, 12], and as a potent antitumor activity [13]. Some aryl semicarbazone derivatives were reported to be potent antituberculosis [14] and anticonvulsant agents [15]. These results propelled us to synthesize the new derivatives of quinazoline semicarbazone by condensation of quinazoline semicarbazide with different aromatic carbonyl compounds by simple synthesis. Their chemical structures have been confirmed by means of their IR, ^{1}H -NMR, UV data and by elemental analysis. The datas of analytical findings were reported in this paper.

2. Chemistry

The required starting N-benzoyl anthranilic acid (**1**) was synthesized from anthranilic acid and benzoyl chloride in DMF by benzoylation reaction. Addition of acetic anhydride to (**1**) afforded benzoxacin (**2**) in good yields after under reflux. A mixture of (**2**) and hydrazine hydrate in anhydrous pyridine yielded the desired key intermediate of substituted quinazoline (**3**) after treating the cooled, refluxed mixture with sulphuric acid. Aromatic urea of substituted quinazoline (**4**) was obtained by dissolving (**3**) in glacial acetic acid with sodium cyanate. The appropriate (**4**) in water and hydrazine hydrate was made alkaline by adding sodium hydroxide, few ethanol was added to give clear solution then it was refluxed to get quinazoline semicarbazide (**5**). The reaction sequence is outlined in Scheme 1. The awaited quinazoline semicarbazone derivatives were synthesized by condensation reaction of (**5**) individually with Isatin, Vanillin, Camphor, Benzophenone and p-dimethyl amino benzaldehyde dissolved in alcohol with added little quantity of glacial acetic acid is given in Scheme 2. The obtained quinazoline semicarbazone with isatin, Vanillin, Camphor, Benzophenone and p-dimethyl amino benzaldehyde were coded as M^3I, M^3V, M^3C, M^3B and M^3P respectively.

3. Results and Discussion

In this study, a novel series of quinazoline semicarbazones were synthesized. The obvious synthetic pathways for the compounds were represented in Scheme 1 and Scheme 2. The physical parameters of all the compounds were mentioned in section 6. Preliminary examination of the formation of compounds by FT-IR analysis confirmed the absence of NH stretching and the magnitude of imine stretching in the range between 1616 and 1663 cm^{-1} , besides the appearance of additional monosubstituted aromatic amide stretching frequencies in the region 2178 – 3446 cm^{-1} and aromatic stretching at 419 – 809 cm^{-1}. The ^1H NMR spectra of quinazoline semicarbazones displayed additional signals due to aromatic ring derived from carbonyl moiety at aromatic region, while the peak belongs to $–NH_2$ group of hydrazide structure did not appeared. Compound M^3I showed singlet at δ 5.9 – 7.6 ppm for amide, triplet at δ 6.4 – 6.8 ppm for aromatic protons. Compound M^3V showed singlet at δ 6.57 – 6.54 ppm for $-OCH_3$, doublet at δ 7.12 – 7.23 ppm for aromatic protons, and singlet at δ 1.7046 ppm for –OH. The appearance of singlet on the ^1H NMR spectra of compound M^3C at δ 9.2 ppm for imine, at δ 2.0840 ppm for $–CH_3$ and multiplet at δ 8.3 – 8.4 ppm for aromatic protons. For the compound M^3B multiplet aromatic protons resonates at δ 7.2 – 7.9 ppm. ^1H NMR spectra of M^3P is due to triplet at δ 7.62 – 9.6 ppm for aromatic protons, singlet at δ 6.7 – 6.8 ppm for amine and singlet at δ 3.0397 ppm for imine. The NMR spectrums were individually shown in Figure 1. The wavelengths of maximum absorbance (λmax) for all the synthesized compounds were done by UV-Vis spectrophotometer and shown the specific absorptivity and the range falls between 246 and 336 nm.

4. Conclusion

In our study, we have synthesized quinazoline semicarbazones. The semicarbazones was substituted at N-3 position of quinazoline which again proves the novelty of our new quinazoline series as synthetic antibiotics. In future the compounds will be modified further to reduce the molar mass and toxicological barriers. Based on the literature review the compound will be screened for CNS activity like sedatives, hypnotics and psychotics. The importance of the present study provides initial basic spectral confirmation of quinazoline substituted semicarbazones.

5. Experimental protocol

5.1. General

Melting points were determined in open capillary tubes with electro thermal melting point apparatus and are uncorrected. The solubility parameters were reported in Table 1. The purity of the synthesized compounds was confirmed by TLC and it was performed as demonstrated [16]. The dimension of plates: 5 X 20 cm, stationary phase: silica gel-G (E-Merck), Mobile phase: ethyl acetate: n-butanol: water (6:3:1), technique involved is ascending and iodine vapor is used as the detecting agent. Elemental analysis was performed on a Costech Elementel Combution System CHNS-O elemental analyzer. The infrared analysis was carried out by JASCO 4100 FT-IR using KBr pellet disc technique. NMR spectral study for new quinazoline semicarbazone derivatives were done by using DMSO as a solvent in “BRUKER, AV 300 MHz”, transform NMR spectrometer. The maximum absorbance or λmax of synthesized compounds determined in the concentration of 0.01%w/w in DMF by using Shimadzu 1700A UV-Vis spectrophotometer (Pharma Spec).

5.1.2 Synthesis of N-Benzoyl anthranilic acid

Benzoyl chloride was added drop wise to a stirred solution of anthranilic acid in DMF. The reaction mixture was stirred at room temperature for 2 hrs. Water is added to the above solution, and the solid was separated, washed with water, and recrystallized from ethanol.

5.1.3 Synthesis of 2-phenyl-4H-3-benzoxacin-4-one

A mixture of N-benzoyl anthranilic acid (**1**) (0.01 mol) and acetic anhydride (10 ml) was heated under reflux for 3 hrs at 80°C, then cold water is added to form precipitate, excess acetic anhydride was evaporated under reduced pressure and the obtained solid was recrystallized by petroleum ether.

5.1.4 Synthesis of Substituted quinazoline

A mixture of 2-phenyl-4H-3-benzoxacin-4-one (**2**) (0.01 mol) and equimolar quantity of hydrazine hydrate was dissolved in anhydrous pyridine. The mixture was refluxed under water for 2 hrs. The refluxed mixture was cooled and treated with sulphuric acid. The formed precipitate is separated by filteration and washed with water.

5.1.5 Synthesis of aromatic urea of substituted quinazoline

0.1 mol of sample of substituted quinazoline (**3**) was dissolved in 10 ml glacial acetic acid and diluted to 50 ml with distilled water. To this equimolar (0.1 mol) quantity of sodium cyanate in 50 ml of warm water was added with stirring. Allowed to stand for 30 min, cooled in ice, stand for further 30 min, filtered at pump, washed with water and dried. The obtained product was recrystallized by using boiling water.

5.1.6 Synthesis of Quinazoline semicarbazide

To a solution of (0.1 mol) of (**4**) in 20 ml of water, equimolar quantity of hydrazine hydrate was added. The reaction mixture was made alkaline by adding sodium hydroxide. Few ml of ethanol was added to give clear solution. Then it is heated under reflux for 1 ½ hrs in round bottom flask, cooled in ice, filtered and recrystallized from ethanol.

5.1.7 General synthesis of Quinazoline Semicarbazones

To a solution of (0.1 mol) of (**5**) added equimolar quantity of aromatic carbonyl compound dissolved by alcohol. Then a little quantity of glacial acetic acid was added to the above mixture. Solution was refluxed for half an hour, cooled; the separated solid was washed and recrystallized from ethanol.

5.1.7.1 3 - (2 - oxo 1, 2 dihydro indolydene semicarbazone) 2 phenyl - 3H quinazolin 4 - one (M^3I)

Yield: 70%; M.p. 220°C; IR (KBr) cm^{-1} 1415 (N-C=O), 1616 (C=N), 3426 (RHN-C=0), 559.2 (aromatic ring). ^{1}H NMR (300 MHz, δ) 6.42-6.8 (s; aromatic), 6.82-7.4 (m; quinazoline), 5.9-7.6 (s; amide). UV (λmax)/ (DMF)/ (nm); 246. Anal. Calcd. for $C_{23}H_{16}O_3N_6$ (424.41): C, 65.09; H, 3.80; N, 19.80; O,11.31%. Found: C, 65.21; H, 3.78; N, 19.93; O, 11.45%. R_f value: 0.652.

5.1.7.2 3-(4 hydroxy 3-methoxy phenylidene semicarbazone) 2 phenyl 3H quinazolin 4-one (M^3V)

Yield: 71%; M.p. 214°C; IR (KBr) cm^{-1} 1022 (N-C=O), 1663 (C=N), 3447 (RHN-C=0), 634 (aromatic ring). ^{1}H NMR (300 MHz, δ) 7.12-7.23 (d; aromatic), 6.54-6.57 (s; OCH_3), 1.7046 (s; OH). UV (λmax)/(DMF)/(nm); 274. Anal. Calcd. for $C_{23}H_{19}O_4N_5$ (429.43): C, 64.32; H, 4.45; N, 16.30; O,14.90%. Found: C, 64.48; H, 4.56; N, 16.63; O, 14.76%. R_f value: 0.389.

5.1.7.3 3(4-methyl bornane semicarbazone) 2-phenyl 3H quinazolin 4-one (M^3C)

Yield: 69%; M.p. 210°C; IR (KBr) cm^{-1} 1657 (C=N), 3446 (RHN-C=0), 809 (aromatic ring). ^{1}H NMR (300 MHz, δ) 8.3-8.4 (m; aromatic), 2.0840 (s; CH_3), 9.2 (s; C=N). UV (λmax)/(DMF)/(nm); 275. Anal. Calcd. for $C_{25}H_{28}O_2N_5$ (430.52): C, 69.74; H, 6.55; N, 16.26; O,7.43%. Found: C, 69.93; H, 6.29; N, 16.57; O, 7.67%. R_f value: 0.311.

5.1.7.4 3-(diphenylidene semicarbazone) 2-phenyl 3H quinazoline 4-one (M^3B)

Yield: 66%; M.p. 225°C; IR (KBr) cm^{-1} 1647 (C=N), 3415 (RHN-C=0), 700 (aromatic ring). ^{1}H NMR (300 MHz, δ) 7.2-7.9 (m; aromatic), 1.54 (d; R_2NH), 1.10-1.4 (m; $C_4H_8N_2$). UV (λmax)/(DMF)/(nm); 336. Anal. Calcd. for $C_{28}H_{21}O_2N_5$ (459.50): C, 73.19; H, 4.61; N, 15.24; O,6.96%. Found: C, 73.29; H, 4.76; N, 15.35; O, 6.75%. R_f value: 0.605.

5.1.7.5 3-N' (4 dimethyl amino phenylidene semicarbazone) 2 phenyl 3H quinazolin 4-one (M^{3}P)

Yield: 68%; M.p. 242°C; IR (KBr) cm^{-1} 1660 (C=N), 2178.2 (RHN-C=0), 3418.21 (ph-NR$_2$), 419 (aromatic ring). ^{1}H NMR (300 MHz, δ) 7.62-9.6 (t; aromatic), 6.7-6.8 (s; R$_2$N), 3.0397 (s; C=N). UV (λmax)/(DMF)/(nm); 330. Anal. Calcd. for $C_{24}H_{22}O_2N_6$ (426.47): C, 67.59; H, 5.20; N, 19.71; O,7.50%. Found: C, 67.88; H, 5.56; N, 19.99; O, 7.74%. R$_f$ value: 0.401

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7. References

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Figure captions

Scheme 1 Synthesis of Quinazoline semicarbazide
Scheme 2 Synthesis of Quinazoline semicarbazones
Reagents: a) Isatin, b) Vanillin, c) Camphor, d) Benzophenone and e) p-dimethyl amino benzaldehyde

Figure 1 ^{1}H-NMR spectrum for Quinazoline semicarbazone derivatives. (a$_1$ & a$_2$) M^{3}I, (b$_1$ & b$_2$) M^{3}V, (c$_1$, c$_2$ & c$_3$) M^{3}C, (d$_1$ & d$_2$) M^{3}B and (e$_1$ & e$_2$) M^{3}P.

Tables

Table 1 Solubility parameters for quinazoline semicarbazones

Solubility	**M^3 I**	**M^3 V**	**M^3 C**	**M^3B**	**M^3 P**
Water	-	-	-	-	-
Chloroform	+	+	+	+	+
Ethanol	+	+	+	+	+
DMF	++	++	++	++	++
DMSO	+	+	+	+	+
Benzene	+	+	-	+	+
Acetic acid	+	+	-	-	-
Ethyl acetate	++	++	++	++	++
Dilute acids	+	+	-	-	-

(+) Soluble; (++) Sparingly soluble; (-) Insoluble

Figure 1

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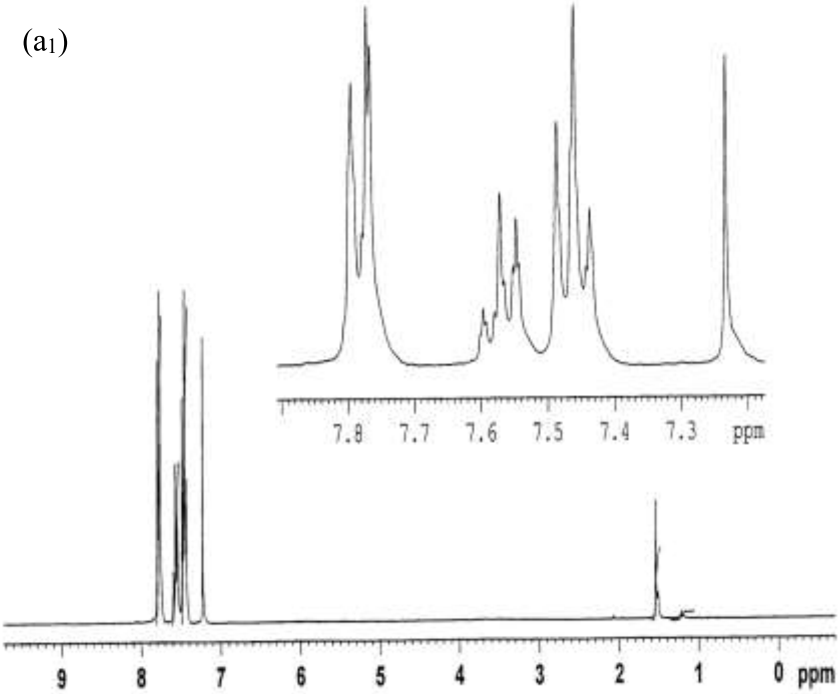

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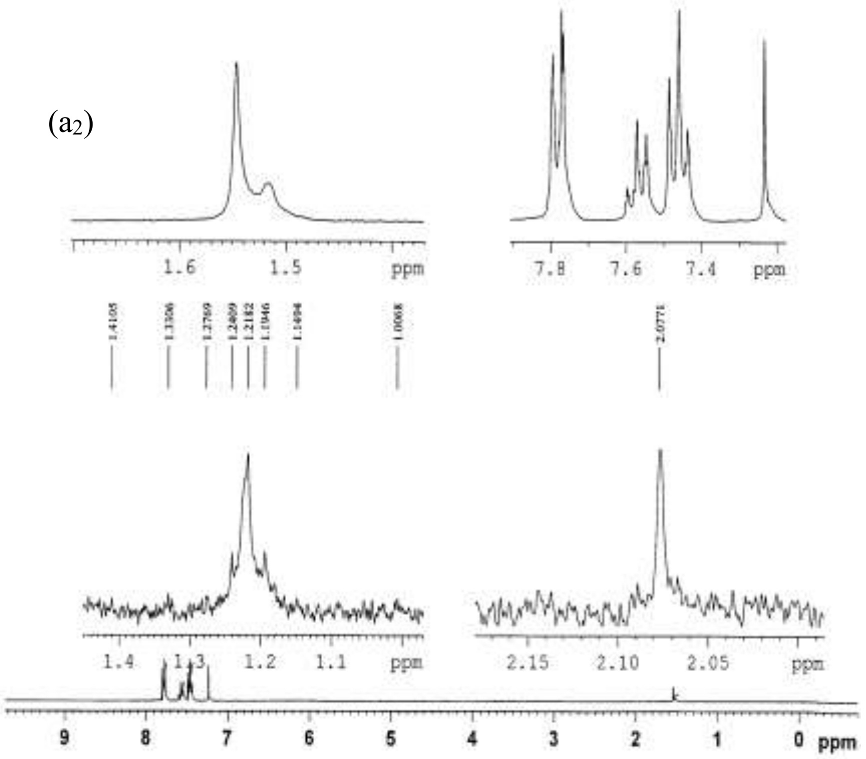
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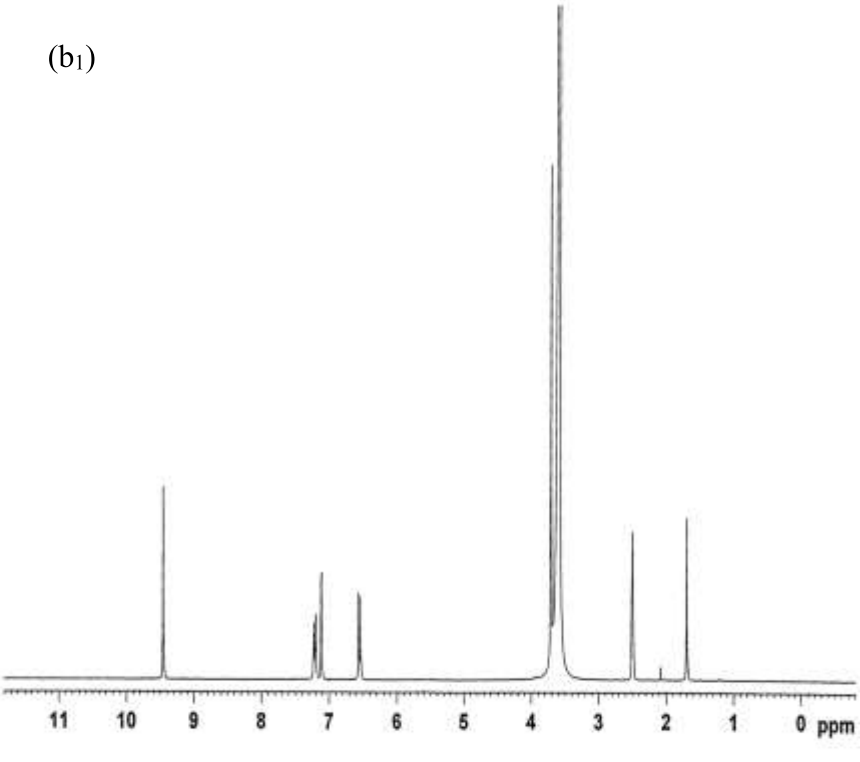
(b$_1$)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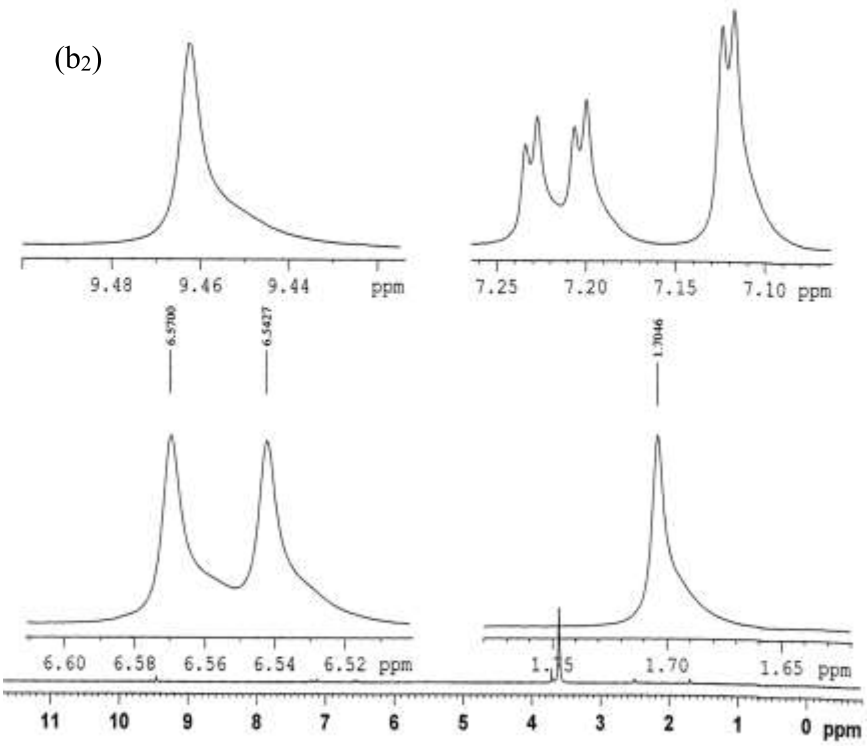
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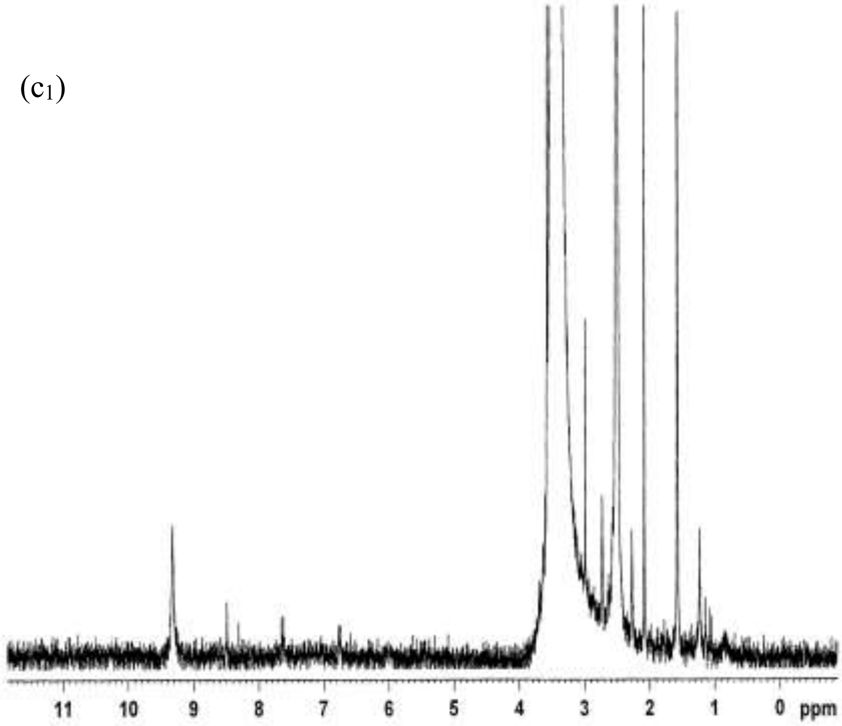
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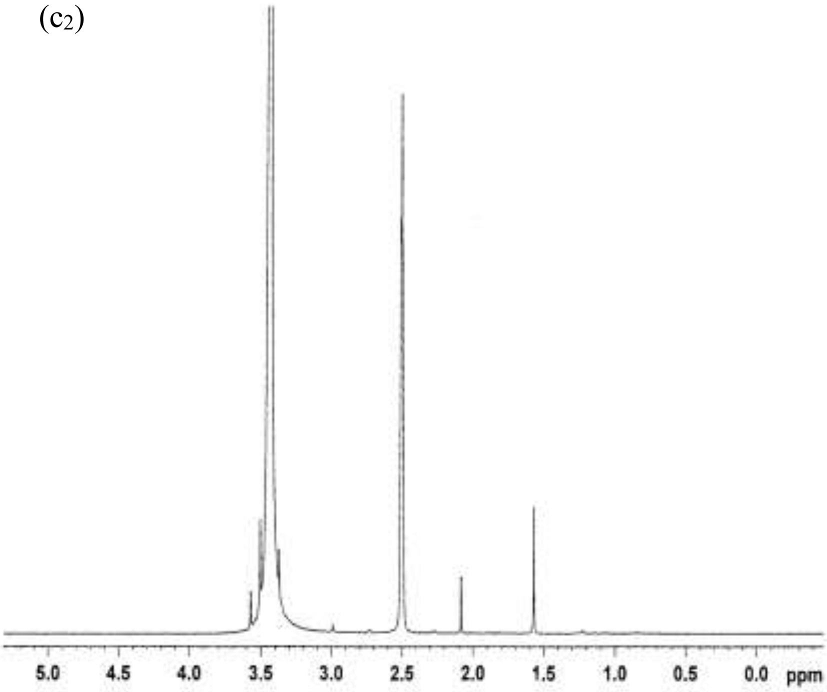
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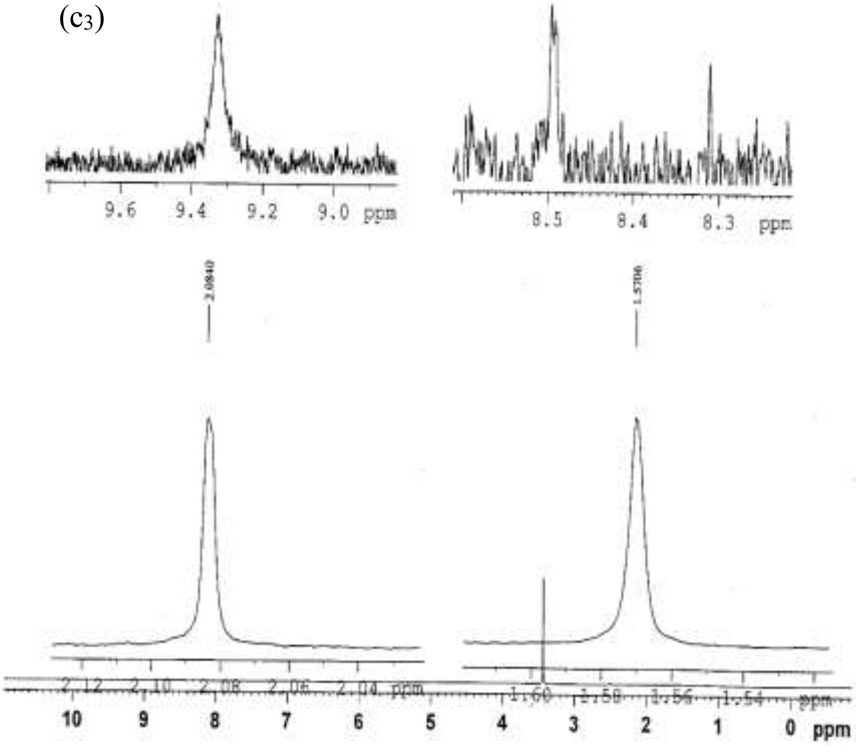
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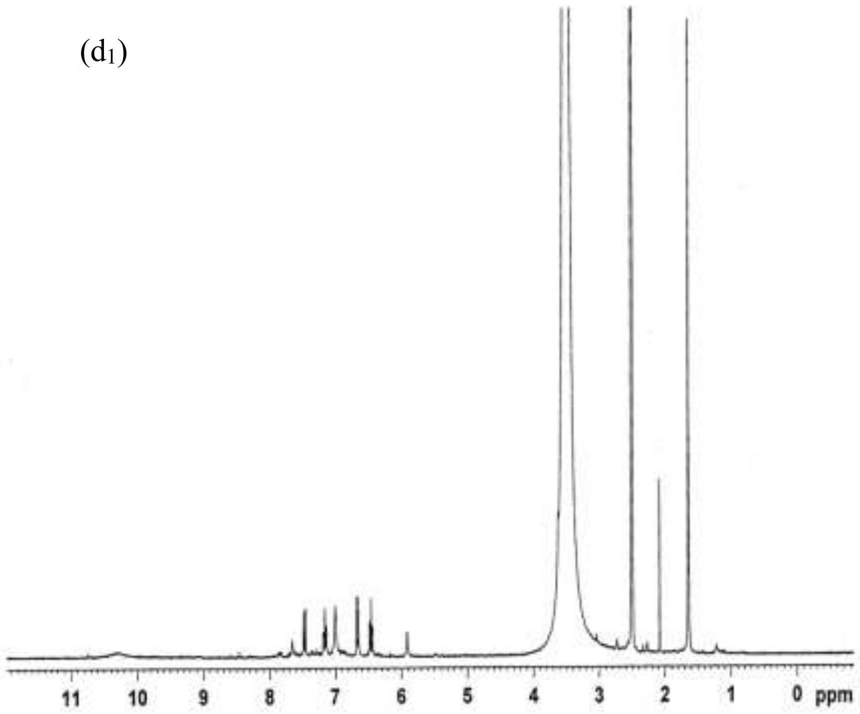
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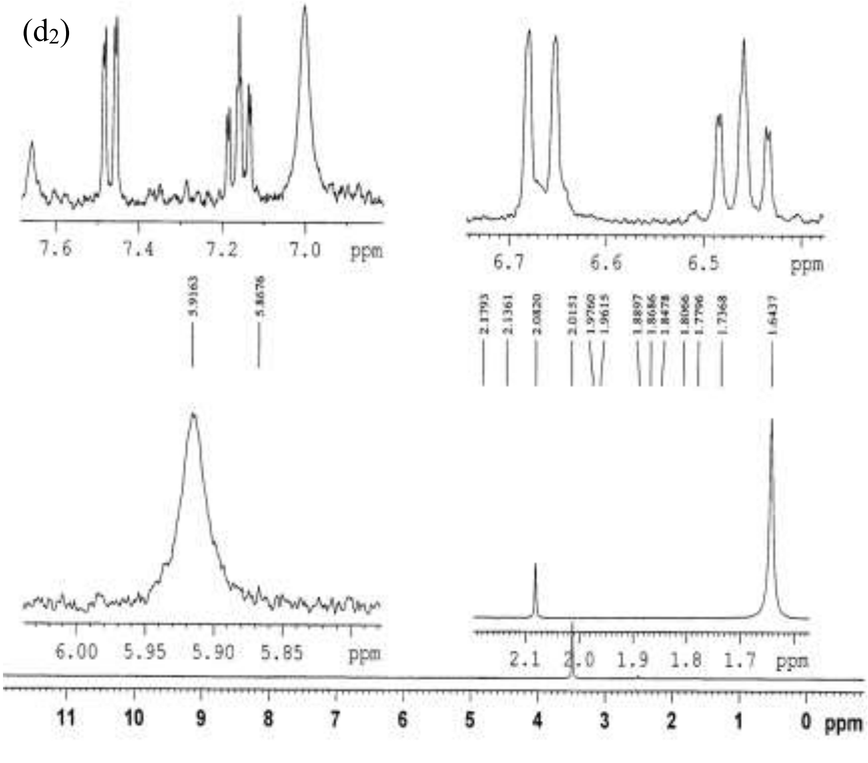
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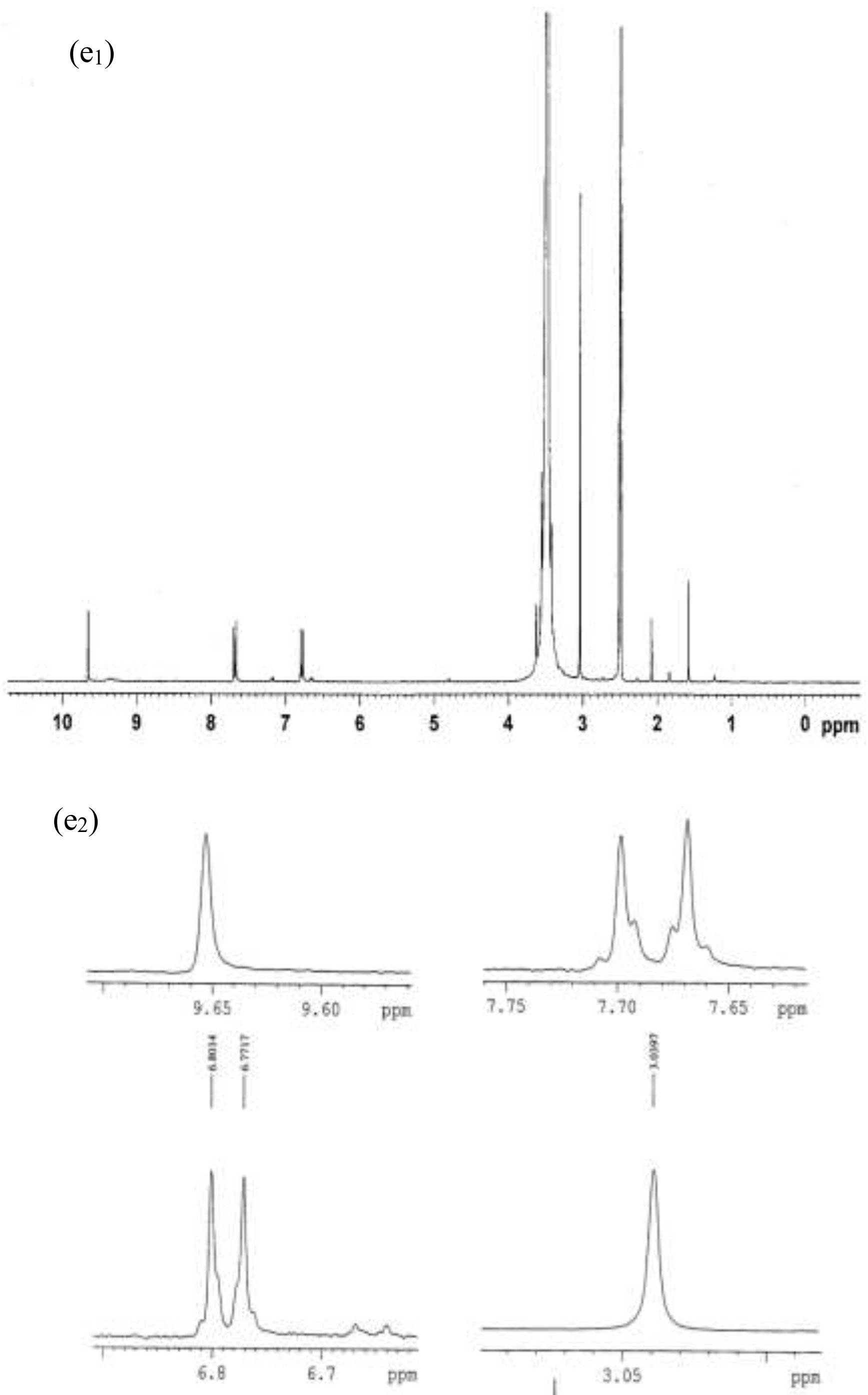
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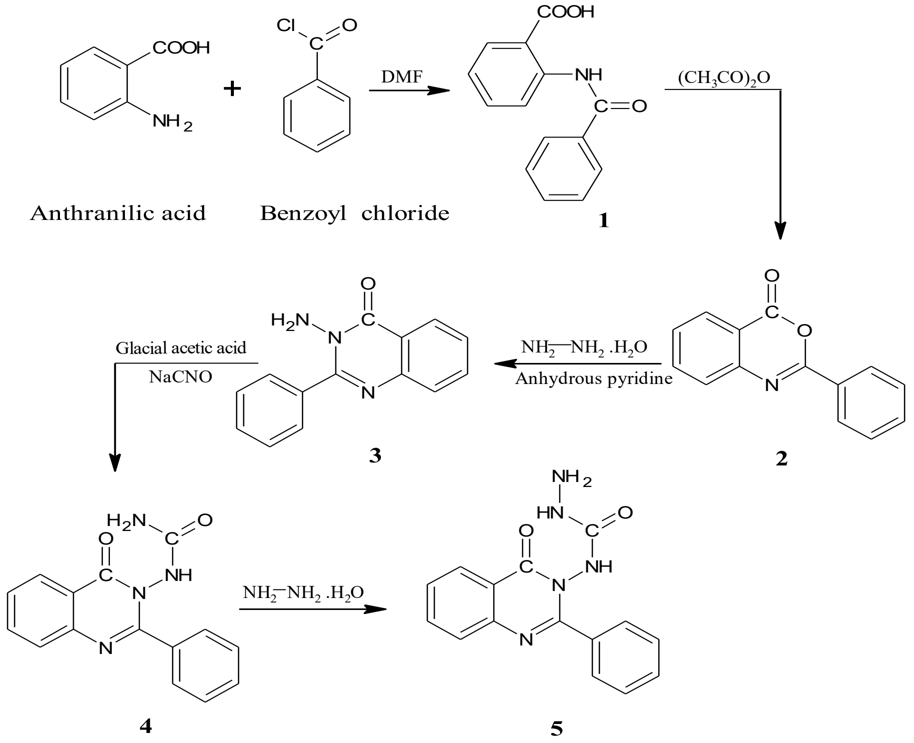
Scheme 1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NH_2—NH_2 .H_2O
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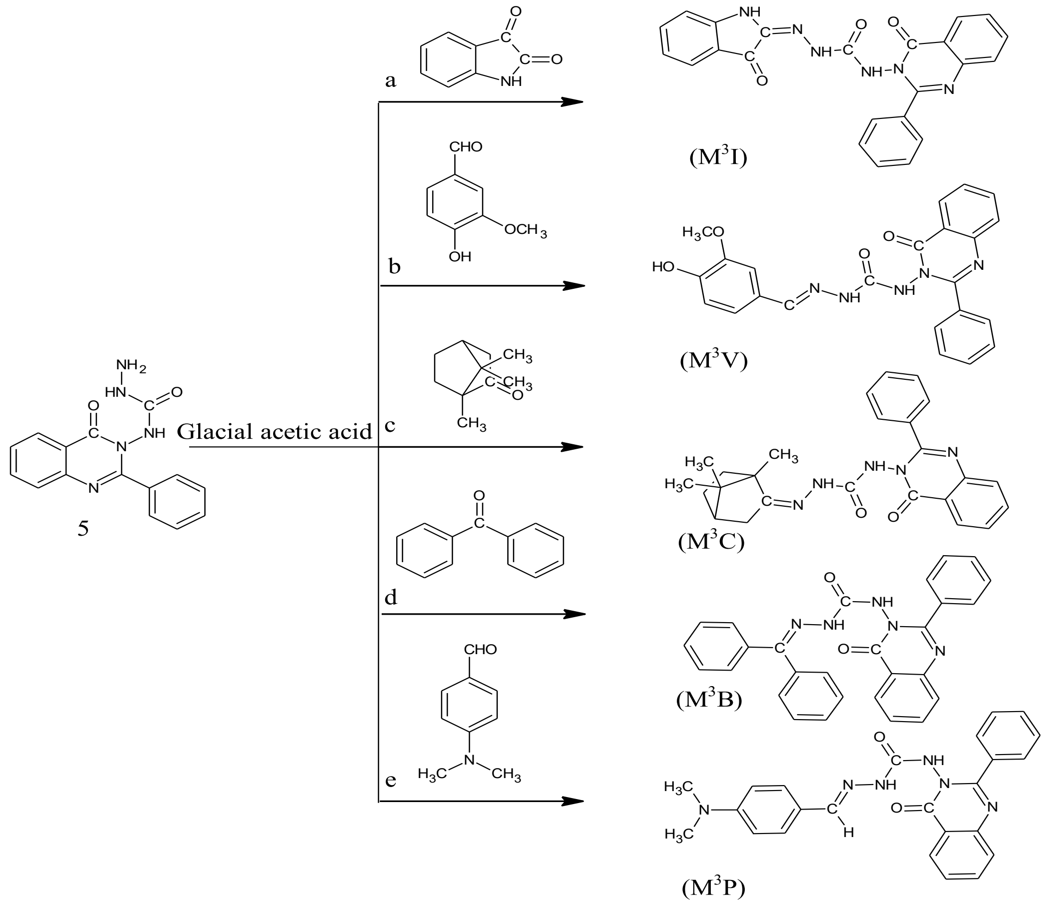
Scheme 2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