Synthesis and Spectroscopic, Studies of Some New Piperidin-4-one Derivatives

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Abstract

The homologous series of 2,6-bis(4-Subtituetphenyl)-3-methylpiperidin-4-one compounds were synthesized using Mannich condensation. Then Five series have been synthesized by reaction of different reagents of semicarbazide. With 2,6-bis(4-Subtituetphenyl)-3-methylpiperidin-4-one to sythesize target compounds 2a-2f, 2a-2f, 3a-3f, 4a-4f, 5a-5f and 6a-6f. The chemical structures of the molecules were characterised by FT-IR, 1D NMR and CHN elements analysis.
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Keyword**:** Piperidin-4-one, Spectroscopic, studies, FT-IR, ^{1}H NMR, ^{13}C NMR.

1.Introduction

Piperidones are named by the location of the nitrogen or amine group and the carbonyl group on the ring. It was used in pharmaceutical companies and chemical manufacturers as starting material having anti-microbial activity [1]. Compounds having piperidone are associated with diverse pharmacological properties such as anti-cancer, anti-microbial, anti-convulsant, anti-viral, anti-HlV, anti-fungal and anti-mycobacterial. [2].

The piperidine ring is an ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson et al. asserted that during a recent 10-year period there were thousands of piperidine compounds mentioned in clinical and preclinical studies. [3, 4].

Baliah and his coworker developed an elegant method of synthesis of 2,6-diarylpiperidin-4-onebsased on the earlier work of Petrenko-Kritschenko *et al*. [5-16] The earlier reaction involves the condensation of an ester of acetonedicarboxylic acid with an aromatic al- dehyde and ammonia or a primary amine, leading to the formation of 2,6-diaryl-4-oxopiperidine-3,5-di- carboxylates or their N-substituted derivatives [17-20].

The hetero Diels– Alder (HDA) reaction of imines with Danishefsky' sdiene (1-methoxy-3-trimethylsiloxy-1, 3-butadiene) is an efficient method for construction of functionlized 2,3-dihydro-4-pyridones with control of region-, diastereo- and enantio-selectivity [21-23].

Unlike piperidines, straightforward synthetic routes to substituted piperidin-2,4-diones are limited.[24] Retrosynthesis of piperidin-2,4-diones usually involves 3,4-disconnection or 1,2-disconnection. The synthetic strategies are usually based on δ-amino β-ketoester. Synthetic strategy of synthesize 3,5-bis (benzylidene) piperidin-4-one cyclisation involved by Dieckmann cyclisation, [25-28] or base cyclisation.[30] For piperidin-2-ones a [4+2] cycloaddition is also feasible.

2. Experimental

2. 1 Materials

4-Chlorobenzaldehyd, Butanone, Ammonium acetate, Ethanol, 4-nitrobenzaldyhyde, Thionyichloride, Ethyl-chloroacetate, Tetrahydrofurane, Thio-semecarbazide, Hydrogen chloride, Aceticaci, Aceticanhydride, Benzen, Semicarbazide hydrochloride, Sodium acetate, Acetonitril, Hydroxylamine hydrochloride, Pyridine, Triphenyl phosphine, Iodine, Potassium carbonate, Triethylamine, Chloroform, Calcium chloride, Pipyridine, Ammonium chloride, Potassium cyanide, Sodium hydrogen carbonate, 4-Chloroaniline, Urea, Hydrazine hydrate, Sodium borohydride, 4-Amino benzoicacid, 4-hydroxybenzaldehyde, .2,4-dichloro benzaldehyde.

The chemicals were used directly as received without further purification. Thin-layer chromatography (TLC) was performed on pre-coated silica-gelon aluminum plates using 4:6 ratio of ethyl acetate and petroleum ether as an eluent.

2. 2 Synthesis

Synthetic of intermediates **1**a-1fand title compounds 2a-f, 3a-f, 4a-f, 5a-f and 6a-f are present in Scheme 1. Compound 1a-f was prepared as the method reported in literature [30], Mannich condensation reaction were applied to synthesized Piperidin-4-one in the respective ratio of (2: 1:1) using *p*-chlorobenzaldehyde and butanon with ammonium acetate, respectively in the medium of 95% ethanol heated on a hot plate up to the boiling range and kept overnight. The product piperidine-4-one was separated after 3 days and it was recystallized by slow evaporation.

2. 3. 1 Synthesis of compounds target compounds 2-(2,6-bis(4-substutedphenyl)-3-methylpiperidin-4-ylidene)hydrazinecarbothioamide 2a-f

The title compounds were synthesized according to a method described by Sampath*et;al* [31].All compounds have been prepared in the same methods we will present the synthesis of compound 2a as example:

Mannich condensation reaction were applied to synthesized Piperidin-4-one in the respective ratio of (2:1:1) using ***p***-Chlorobenzaldehyde and butanon with ammonium acetate, respectively in the medium of 95% ethanol heated on a hot plate up to the boiling range and kept overnight [32]. The product piperidine-4-one was separated after 3 days and it was recystallized by slow evaporation.

The analytical, FT-IR, ^{1}H NMR and ^{13}C NMR for compounds **1a** are summarized as follows (for example):

2,6-bis(4-chlorophenyl)-3-methylpiperidin-4-one 1a Yield 65 %. M.p. (218-220)^{o}C. Anal: Calc (%)$C_{18}H_{17}Cl_2NO$ M.W :334.24 C, 64.68; H, 5.13; N, 4.19;Cl,21.21;O,4.79; Found, C, 64.02; H, 5.93; N, 4.83. IR υ_{max} (KBr) (cm^{-1}): 3475.73 (NH), 2974.23 (CH_3), 3035.96 (Ph-CH), 1708.93 (C=O), 1581.63 (C=C aromatic), 682.80 (C-Cl). ^{1}H NMR δ (ppm) (Aceton): 7.21 (d 2H), 7.04 (d 2H), 7.83 (d 2H), 8.05 (d 2H), 2.42 (S NH), 2.72 (d 2H), 2.45 (S 1H). 2.37 (d 1H), 2.27 (d 1H), 1.02 (S CH3). ^{13}C NMR δ (ppm) (Aceton): 168.34 (C=O), 115.10- 149.03 (aromatic), 46.23 (CH_2), 50.13 (CH), 63.20 (CH), 68.34, 15.16 (CH3).

*2. 3. 2 Synthesis of compounds target compounds*Synthesis of compounds (Z)-2-(2,6-bis(4-Subsphenyl)-3-methylpiperidin-4-ylidene)hydrazinecarboxamide 2a-f

A mixtur of 3-methyl-2,6-bis(4-R-phenyl)piperidin-4-one(0.5g,0.0015mml)with thiosemecarbazide (0.1365 gt,0.0015mmol) in (15ml ethanol with (3) drops of hydrogen chloride was refluxed for 2 hrs. After the reaction was completed, the solid product obtained was filtered off, dried and recrystallized from ethanol.

The analytical data for compound **2 b** are presented (for example) as fellow:

(*Z*)-2-(2,6-bis(4-bromophenyl)-3-methylpipridin-4-hydrazinecarbothiomide 2b

Yield 70% Mp(172-174) ^{o}C M.W:370.15 Anal Calc (%) $C_{19}H_{20}Br_2N_4S$ C,45.98; H,4.06; Br, 32.20; N,11.29; S,6.46, Found, C,45.12; H,4.87; N,11.94. IR υ_{max} (KBr) (cm^{-1}): 3165.42-3043.87 (NH_2), 3214.97 (NH), 2825.76 (CH_3), 3024.74 (Ph-CH), 1042.53 (C=S), 1421.86,1415,63 (C=C aromatic), 642.39 (C-Br), 2435.82(S-H), 1589.76(C=N). ^{1}H NMR δ (ppm) (Aceton): 9.08 (S NH_2), 8.12 (d 2H), 8.03(d 2H), 7.67 (d 2H), 7.02 (d 2H), 6.14 (S NH), 3.24 (S NH), 3. 76 (2 H), 2.49 (t 1H), 2.56-2.19 (dd CH), 0.73 (t CH_3). ^{13} NMR δ (ppm) (Aceton): 163.29 (C=S),161.32(C=N), 135.17- 162.07 (aromatic), 70.67 (C=N), 66.94 (C-N), 42.27 (CH_2), 18.37(CH_3).

2.3.3. Synthesis of compounds 1-acyl-2,6-bis(4-substphenyl)-3-methyl pipridine-4-one 2a-f

The title compounds have been prepared according to method described in previous section for synthesis of 3a-f.

The analytical data for compound **3 c** are presented (for example) as fellow:

(*E*)-2-(2,6-bis(4-hydroxyphenyl)-3-methylpiperidin-4-ylidene)hydrazinecarboxamide 3c Yield 78%. M.p.(187-189)^{o}C. $C_{19}H_{22}N_4O_3$. M.W:354.40 Anal: Calc. (%) C,64.39;H,6.26; N,15.81;O,13.54; Found, C, 65.12; H, 5.87; N, 4.90; IR υ_{max} (KBr) (cm^{-1}): 3497.64, 3387.92 (NH_2), 3593.37 (NH), 2986.28 (CH_3), 3055.37 (Ph-CH), 1697.82(C=O), 1593.64, 1587.32

(C=C aromatic), 3264.52 (C-OH).1598.40(C=N), ^{1}H NMR δ (ppm) (Aceton): 9.57 (S NH_2), 8.79 (d 2H), 8.58 (d 2H), 7.95 (d 2H), 7.62 (d 2H) 5.84 (S NH), 5.02 (S NH), 4.81 (2 H), 3.14 (t 1H), 2.96(d1H), 2.57(d1H), 1.32 (t CH3). ^{13} NMR δ (ppm) (Aceton): 171.187 (C=O), 130.33-165.14 (aromatic), 163.12 (C=N) 63.34 (2 C-N), 79.72(C-N), 69.87(C-N), 64.39(CH_2), 18.24(CH_3).

2.3.4. Synthesis of compounds (E)-2,6-bis(4-Substphenyl)-3-methyl-4-oneoxime 4a-f

A mixture of compound [1**a**] (0.501g) and (5 ml) acetic anhydride in (5ml) acetic acide was refluxed for (5hrs).then filtered dried and recrystallized from ethanol and washed with distilled water.

The analytical data for compound 4d are presented as fallow (for example):

1-acyl-2-bis(4-methoxyphenyl)-3-methylpipridine-4-one 4d Yield 74 %. M.p.(176-178)^{o}C. $C_{21}H_{26}N_4O_3$. M.W:382.46 Anal: Calc. (%) C,65.95; H, 6.85; N, 14.65; O, 12.55; Found, C, 65.08; H, 5.85; N, 4.93; IR υ $_{max}$ (KBr) (cm^{-1}): 3326.54, 3187.52 (NH_2), 3514.76 (NH), 2948.83 (CH_3), 3024.93 (Ph-CH), 1664.89 (C=O), 1574.63,1485.82 (C=C aromatic), 1025.36 (C-Cl).1589.24(C=N), ^{1}H NMR δ (ppm) (Aceton): 8.87 (S NH_2), 7.54 (d 2H), 7.21 (d 2H), 6.88 (d 2H), 6.53 (d 2H) 5.22 (S NH), 4.27 (S NH), 4.04 (2 H), 2.41 (t 1H), 2.32(d1H), 2.16(d1H) 0.83 (t CH3). ^{13} NMR δ (ppm) (Aceton): 162.19 (C=O), 113.83-161.24 (aromatic), 160.86 (C=N) 60.24 (2 C-N) 67.81(C-N), 64.23(C-N), 62.86 (CH_2), 13.25(CH_3)

2.3.5. Synthesis of compounds 4-amino-2,6-bis(4-subustphenyl)-3-methylpipridine-4-carbonitrile 5a-f

Amixture of compound [1**a**] (1.5 mmol,0.5g) and (0.5g, 7.3mmol) hydroxylamine hydrochloride dissolved in (5ml) ethanol and (0.5ml)pyridine and refluxed for (1.30 hrs) added (20 g) crushed ice, stirrer, filtered, dried and recystallized from ethanol.

The analytical data for compound 5e are presented as fallow (for example):

(*E*)-3-methyl-2,6-bis(4-nitrophenyl)piperidin-4-one oxime 5e Yild 97% Mp(193-195)^{o}C M.W:370.36 Anal Calc (%) $C_{18}H_{18}N_4O_5$ C,58.37; H, 4.90; N, 15.13; O,21.60, Found, C, 58.90; H, 4.06; N, 15.87; IR υ $_{max}$ (KBr) (cm^{-1}): 3429.14 (OH) 3397.27 (NH), 2974.23 (CH_3), 3085.96 (Ph-CH), 1696.72 (C=N), 1598.65,1582.31 (C=C aromatic), 1091.71 (C-NO). ^{1}H NMR δ (ppm) (Aceton): 9.89 (OH), 8.63 (d 2H), 7.96 (d 2H), 7.72 (d 2H), 7.58 (d 2H), 4.39 (d 2H), 3.26 (t 1H) 6.4. (S NH), 2.94 (2 H),2.62(d2H), 0.98 (t 2 CH3). ^{13} NMR δ (ppm) (Acetone): 129.63-163.15 (aromatic), 69.68 (C=N), 64.08, 32.26 (CH_2), 34.03 (CH), 17.84 (CH_3).

2.3.6. Synthesis of compounds 4-amino-2,6-bis(4-subustphenyl)-3-methylpipridine-4-carbonitrile 6a-f

A mixture of compound [**1a**] (0.86 g) and ammonium chloride (0.207 g) and potassium cyanide (0.205g) then added (10ml) of ammonia stirring for (20hrs) at room temperature, then filtered, dried and recystallized from ethanol.

The analytical data for compound 6f are presented (for example) as fellow:

4-amino-2,6-bis(2,4-dihydroxyphenyl)-3-methylpiperidine-4-carbonitrile 6f Yild 81% Mp (215-217)^{o}C, M.W:355.39 Anal Calc (%) $C_{19}H_{21}N_3O_4$ C, 64.21; H, 5.96; N, 11.82; O, 18.01. Found, C, 64.86; H, 5.11; N, 11.08; IR υ $_{max}$ (KBr) (cm^{-1}): 3198.92, 3172.78(NH2), 3398.87 (NH), 2897.85 (CH_3), 3039.76 (Ph-CH), 3093.82 (C≡N) 1679.79 (C=N), 1593.39 (C=C aromatic), 771.53 (C-OH), 3124.68(C=NH). ^{1}H NMR δ (ppm) (Aceton): (d 2H), 8.73 (d 2H), 7.96 (d 2H), 7.73 (d 2H), 7.68 (S NH2), 3.08 (d 2H), 2.98 (NH), 2.85 (1 H), 2.95 (d 1H), 2.87(S NH), 0.97 (dCH3). ^{13} NMR δ (ppm) (Aceton): 116.15- 147.23 (aromatic), 68.82(CH2), 56.45-53-50 (C-N), 50.76 (CH), 43.25 (C), 15.26 (CH3).

2. 2 Measurements

^{1}H and ^{13}C NMR spectra were recorded in dimethylsulphoxide (Aceton-d_6) and (Ethanol-d_6) at 298 K on a Bruker500 &400 MHz Ultrashied™ FT-NMR spectrometer equipped with a 5 mm BBI inverse gradient probe. Chemicals shift was referenced to internal

tetramethylsilane (TMS). The concentration of solute molecules was 50 mg in 1.0 ml DMSO. Standard Bruker pulse programs [32] were used throughout the entire experiment, at School of Chemical Sciences, Bangalor India. Fourier-Transform Infra-Red (FT-IR) spectra were obtained using KBr pellets and the spectra were recorded in the range of 4000-400 cm^{-1}using a 8400s fourier transitions infrared spectrometer Shimadzu, Japan At the University of Baghdad, College of Science for Women, Chemistry Department.

Elemental (CHN) microanalyses were performed using a Perkin Elmer 2400 LS Series CHNS/O analyzer.

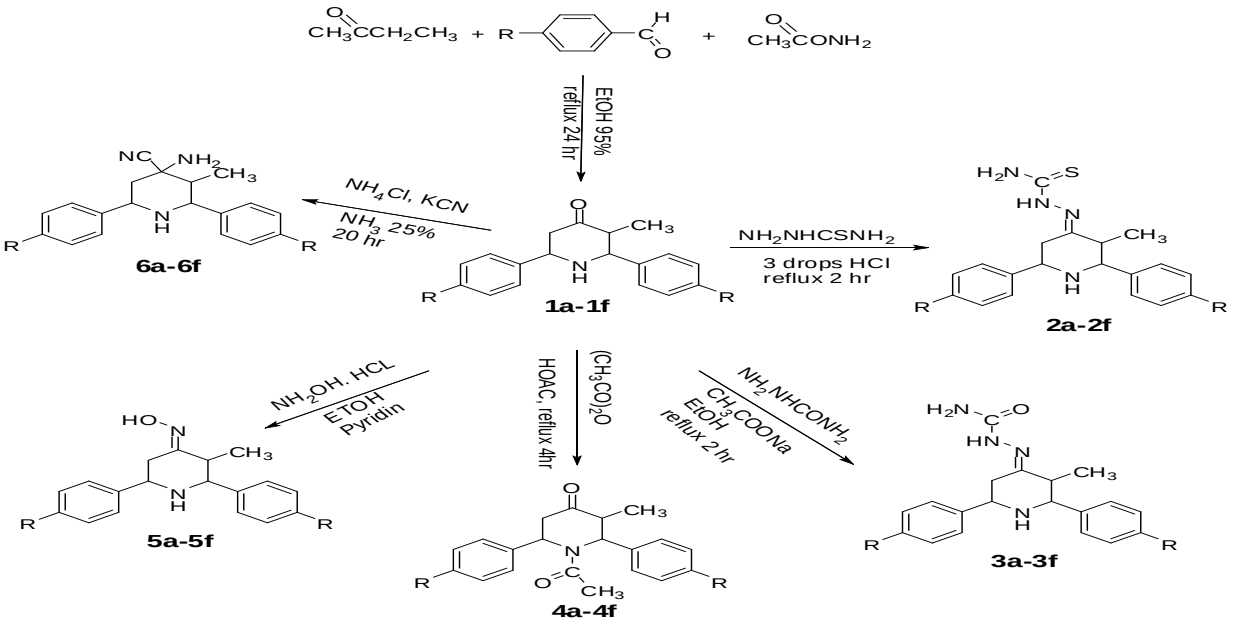
3. Results and Discussion

3. 1 Synthesis and characterization

The symmetric of Piprodin-4-one derivatives were synthesized according to the modified procedures were reported in the literature and synthetic methodology are shown in Scheme.(1). Piprodin-4-onecompounds core compound 1a-1f, were prepared based on Mannich condensation reaction between various substituted benzaldehyde and butanon with ammonium acetate, ratio of (2:1:1) respectively in ethanolic solution (Scheme 3.1). The pure compounds were obtained by recrystallization from absolute ethanol.

Refluxing a mixture of 3-methyl-2,6-bis(4-R-phenyl)piperidine-4-one with thiosemicarbazide in precent of hydrogen hydrochloride in ethanol as solvent give target compounds 2a-2f, Scheme(1). In the same way compounds 3a-3f have been prepared by condensation reaction of by dissolved semicarbazidehydrochloride and sodium acetate anhydrous in distilled water, and 3-methyl-2,6-bis(4-R-phenyl) piperidine-4-one in ethanol as solvent.

Treatments of 3-methyl-2,6-bis(4-R-phenyl) piperidine-4-one and acetic anhydride in present of acetic acid gave titled compounds 1-acyl-2,6-bis(4-substphenyl)-3-methyl pipridine-4-one 4a-4f, after h hours refluxing. Compounds 5a-5f were prepared based on condensation reaction between 3-methyl-2,6-bis(4-R-phenyl) piperidine-4-one and hydroxylamine hydrochloride dissolved in ethanol and pyridine, recrystallized from ethanol. In the same way, compounds 6a-6f also synthesized by condensation reaction of between 3-methyl-2,6-bis(4-R-phenyl) piperidine-4-one and ammonium chloride and potassium cyanide then added ammonia stirring for (20 hrs) at room temperature.



R= 4-Cl, 4-NO_2, 4-Br, 4-OH, 4-OCH_3, 2,4dihydroxy

Scheme (1): The synthetic route toward synthesis target compounds 1, 2, 3, 4, 5 and 6.

3. 2 FT-IR Study

The FT-IR instrument gives characteristics of various functional groups of the target compounds. All the spectra of the titled compounds 1a-1f, 2a-2f, 3a-3f, 4a-4f, 5a-5f, and 6a-6f showed similarities except the different in functional group.

The weak absorption band that appeared at the range of 2987.98-2841.29 cm^{-1} assigned to the (υC_{ph}-C-H) benzylic [35]. Absorption bands can be assigned by symmetric and asymmetric stretching (υCH_3s, υCH_3as) which appeared within the range of 2931-2955 cm^{-1}while weak absorption bands for (υCH_2as, υCH_2s) appeared at the range of 2851-2874 cm^{-1}. In addition to these bands, there is another band observed at the range of 1445-1489 cm^{-1} which can be ascribed to stretching of υC-H [36]. The existence of the aromatic ring in all series compounds is suggested by the following bands: a weak absorption band at 3019-3075 cm^{-1} for aromatic (C_{ph}-H) stretching vibration [33]**.** On the other hand, a strong band at the frequency range of 1597.94, 1584.37 cm^{-1} assigned for the phenyl ring stretching (υC=C) [35].

Carbonyl group C=O in series compounds 1a-1f, 3a-3f, and 4a-4f, can be characterized by the strong band which be observed at the range of 1708.93 cm^{-1}. On the other hand, the C=N gave a band at the frequency 1681.93cm^{-1} with medium intensity in respective series 2a-2f, 3a-3f and 5a-5f.

Likewise, in the fingerprint region the band at 1256 $cm^{-1}$is due to the ether C-O stretching.

In series compounds 2a-2f, 3a-3f, and 6a-6f the broad band, which appeared at the frequency cm^{-1} assign to NH_2 group at the frequency range 3263.56 -3174.83 cm^{-1}. In the same way the broad band at the frequency 3414.00-3456 cm^{-1} assign to OH group in series compounds 5a-5f.

3. 2 ^{1}H-NMR and ^{13}C-NMR Study

^{1}H-NMR data assignment for 1a-1f, 2a-2f, 3a-3f, 4a-4f, 5a-5f, and 6a-6f.^{1}H-NMR spectra in all series compounds showed the two doublet in the most of down field at the chemical shift 8.09 (d 2H), 7.88 (d 2H), 7.56 (d 2H), 7.39 (d 2H), ppm which can be assign to aromatic protons. In the same way in titled compounds in series 2a-2f, 3a-3f, and 6a-6f showed at downfield region the signal corresponding to the proton amine (NH_2) group, which integrates 2H at δ= 8.24 ppm. While the protonts of NH group as singlet at the resonance δ= 6.4. ppm and δ= 8.24 ppm and two doublet at δ= 8.24 ppm and δ= 8.24 ppm in respective series 1a-1f, 2a-2f, 3a-3f, 5a-5f, and 6a-6f. On the other hand the other broad band appeared at the chemical shift range 8.94-9.92 ppm which integrated at one hydrogen corresponding to OH group in respective compounds 5a-5f.

All title compounds showed a doublet at the high field corresponding to (CH_3) group which appeared at the chemical shift 0.86 ppm. The proton of heterocyclic ring in all titled compound appeared at 4.06 (d 2H), 2.92 (t 1H), 2.73 (d 2H), 2.39 (d 2H).

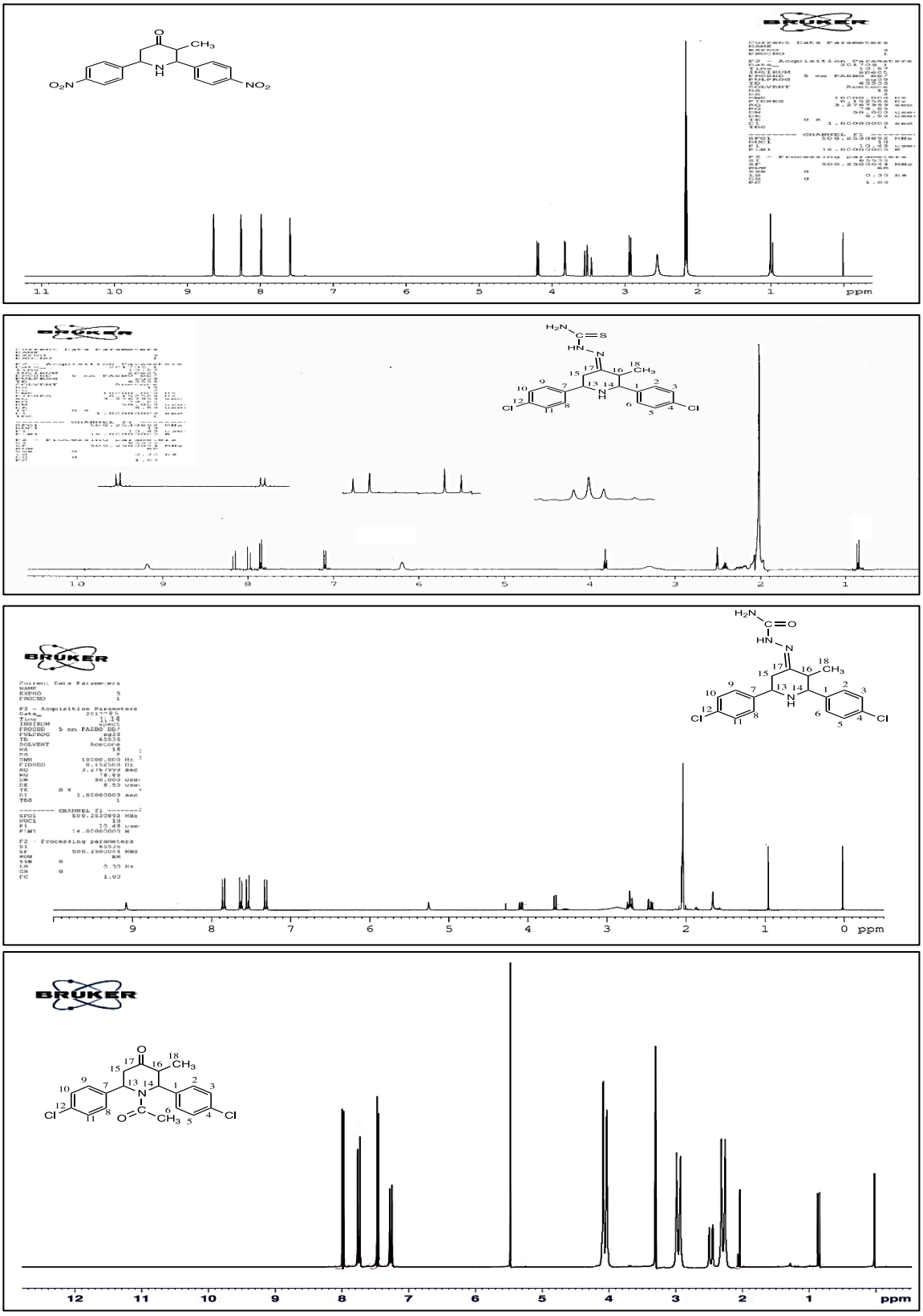


Fig.(1): Showed some ^{1}H NMR spectra of selective compounds.

Analysis of the HMQC for the protonated carbons of the additive rules. The resonances due to the carbonyl group of titled compounds 1a-1f and 4a-4f are located in the downfield region δ = 166.04-166.29, ppm δ = 171.11-174.52 respectively. Moreover, the signal within the range of δ = 67.04 -68.87 ppm can be attributed to the C in the imine (CH=N) group. The resonance appear the frequency ranges δ = 134.11-138.66 ppm,

122.3-123.01 ppm, 132.3-135.56 ppm, 131.0-132,59 ppm, due to the aromatic carbons in aromatic ring. Moreover, the spectra of title compounds confirmed that the signal at the resonance 64.28, 32.49 35.21 assign for carbons of heterocyclic ring. While the methyl group appear at the chemical shift 16.27 ppm.

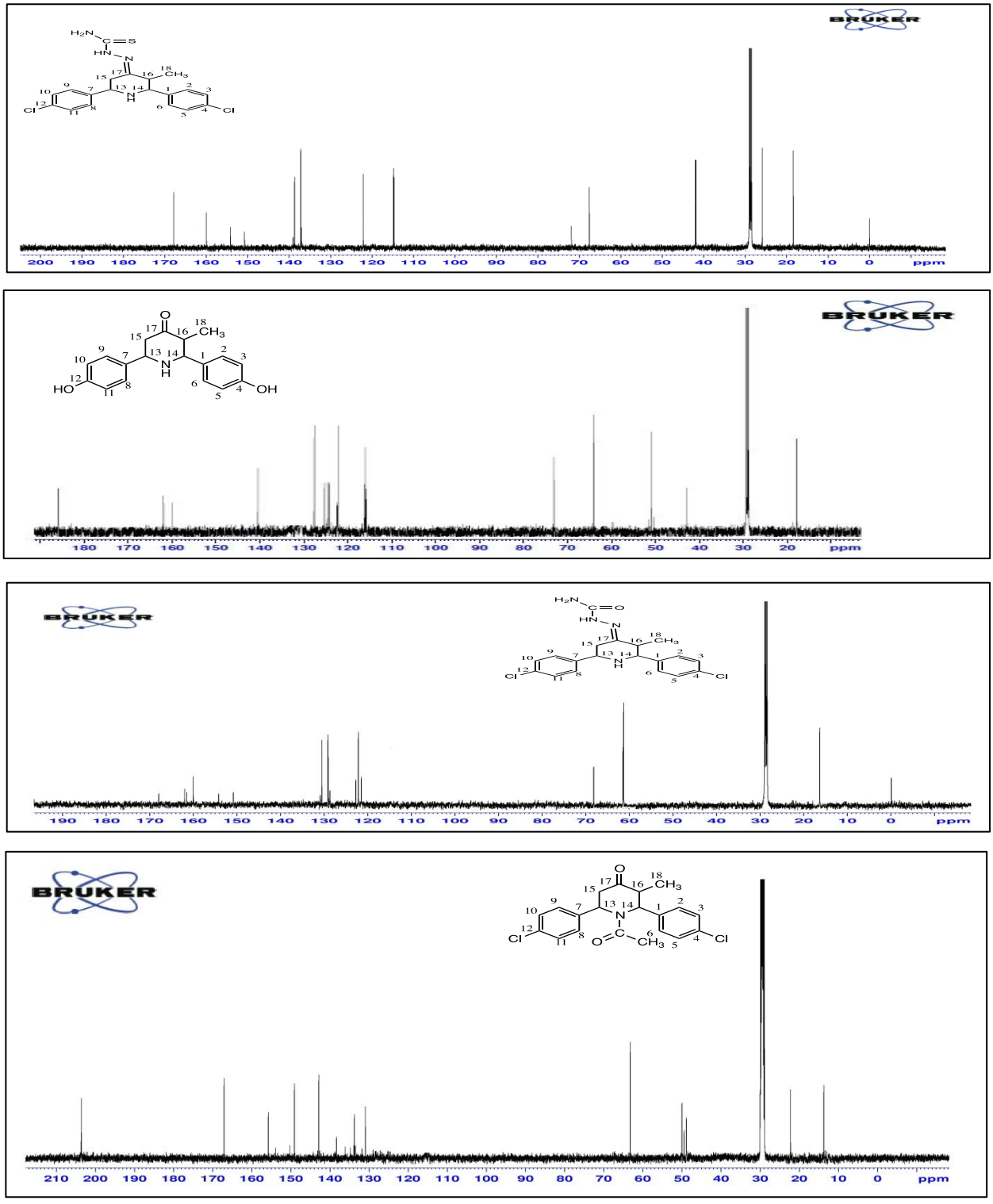


Fig.(2): Show the spectra of selective compounds.

3.3. Conclusion

In this paper the synthesized and characterization of Piperidin-4-one, derivatives as core compound to use in other reaction with different nucleophles such as hydrazinecarbothioamide, hydrazinecarboxamide, acetic anhydride, hydroxylamine hydrochloride and ammonium chloride. These compound have been characterized by CHN analysis, FT-IR and 1D NMR (^{1}H NMR and ^{13}C NMR).

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