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Research Article

Synthesis of Some Piperidine, Pyrmidine and Diazipine Compounds Containing Furyl Derivatives

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Abstract

It was known that nearly 65% of anti-cancer drugs granted market approved by FDA between 210-1015 are heterocyclic compounds and about 95% of heterocyclic compounds are drugs. Heterocyclic compounds containing nitrogen atoms in their structures (nitrogen based)were also proved by FDA during the above period that they form two third of cancer drugs. There are many corresponding reviews associated with the impact and usage of different heterocyclic compounds as anti- platelet, anti-hypertensions and a lot of biological and medicinal applications. So according to the importance of heterocyclic compounds in therapeutic and a variety of pharmaceutical, medicinal applications which attracts attentions of many researchers on synthesizing new compounds of this class. We are here synthesizing some new nitrogen containing heterocyclic compounds, Piperidine compounds(E_{4-8}), 1,4-Dihydropyridine derivatives(E_{9-20}) And finally diazepine compounds(E_{31-37})The synthesized compounds were studied using IR and1H NMR Spectral methods and were discussed.

Keywords: Piperidine; Pyrmidine; Azipine; Furfural

Introduction

Furfural is known as important intermediate for a variety of chemical compounds for example semi carbazides and semi carbazones [1], 2-(2-Furyl) [1,3] dioxolane [2]. It was also found that furfural is also used for medicinal and industrial applications [3] S Lewkowski in (2001) has synthesized 2,5-furan dicarboxylic acid by multistep synthesis starting from furfural [4].It was known that mucochloric acid had remarkable activity. against malaria disease . This compound was used as a precursor for the synthesis of 4-amino-5-hydrony-2-(5H) furan [4] Dichalcon compound was prepared from furfural on treatment with ketones [5]. Mucobromic acid is a derivative of furfural [6]. 6-(2-furyl)1,4,5,6-tetralydro tetrazine 3(2H)thione was also prepared by treatment of furfural with thiocarbohydrizide [5]. Mandalika in 2012 has synthesized furil from furfural which was the first compound used as insect sized [3] while in 2013 furfural diethyl acetel was prepared by treatment of furfural with ethanol in presence of some selective catalysis [7-9]. This derivative was used for many synthetic routes. N-(E)-furan-2-methyleden-2-(1,3-beuzothiuzol-2-yl-sulfonyl) aceto hydrazide was prepared from the reaction of furfural with 2-methyl benzothiezole by conventional and microwave methods [10] in (2011) M Baummann et al. have publish a review for the most selling 5-membered ring heterocyclic, pharmaceuticals which indicate the importance of furfural as a moiety for drug synthesis [11]. Furthermore, flavon compound contains furfural ring, furfur aldehyde exhibited IC so values of 75.9, 51.0 and 59.3 mM for HT29, MCF7 and A498 respectively as anti-cancer cell lines [10]. it was also used for the synthesis of 2,3-diamino quinoline [12]. Mucobromic acid was also used for the synthesis of 2-hydroxy-3-(2-indolyl)-4-bromo furan-5-one by Suzuki reaction13.Many heterocyclic compounds containing furfural moiety have proved to have many pharmaceutical applications [13,14]. In our present study we started synthesizing nitrogen based heterocycles from furfural as precursor for these compounds which are peridines, pyrimidines and azipene these nitrogen containing compounds have proved their activities against nervous system diseases including depression, psychological disorder and schizophrenia [15-17] so they are used as a pharmaceutical compounds for many applications [18-20]. Benzodiazepines are effective for treating a range of psychological and neurological disorders, due to its effects on the neurons that

trigger stress and anxiety reactions Carbamazepine, or CBZ, is an anticonvulsant medication and a mood-stabilizing agent. It acts by decreasing the amount of excitement in the brain and is used for epilepsy and the treatment of bipolar disorders. Carbamazepine is effective in controlling seizures by blocking specific brain impulses [21]. It is also used to treat ADD (Attention Deficit Disorder), ADHD (Attention Deficit Hyperactive Disorder), and schizophrenia (a psychiatric condition). According to the above importance of both furfural as a furyl heterocyclic moiety and of these new nitrogen compounds and in continuing of our previous work [22] we have investigating these new series of compounds which are promising nitrogen base heterocyclic compounds in which they need further study to prove their biological actions.

Experimental

All melting points were un corrected using Electro thermal melting point apparatus. The chemical compounds were supplied by Aldrich, Fluka and BDH chemical companies.IR spectra were performed using Infrared spectrophotometer Tenson Bruker Co.Germany.1H NMR were recorded using Bruker 400MHz/ Gazisosmanpasa, University (Turkey)in DMSO D6 as solvent. 4,5-Dibromo furfural(1) was prepared using the same published procedure [Dsim] reagent(2) was prepared according to the published procedure. Cellulose sulfuric acid(3) was also prepared following the published procedure.

Synthesis of 2-(furan-2-yl)-6-aryl Piperidine-4-one(E_{4-8})

A mixture of 0.01mol. of ammonium acetate in 30ml. ethanol was mixed with 0.05mol. of benzaldehyde, 0.05mol. of furfural and 0.025mol. of 2-butanon.The mixture was refluxed for 2h, cooled and left for 24 h. at room temperature after that 15ml. of conc. HCl was then added, 20ml. of acetone. The suspended solution was treated ammonia solution then with water. The sold product filtered off and crystallized from ethanol physical and IR spectral data are presented in (Tables 1).

Table 1: Physical properties of compounds E_{4-8}.

Comp. No.	R	m.p. ^{o}C)	Molecular Formula	Yield (%)	Color
E4	-H	212-214	$C_{15}H_{15}NO_2$	70	Red
E5	-OCH_3	167-169	$C_{16}H_{17}NO_3$	65	Brown
E6	-C1	184-486	$C_{15}H_{14}ClNO_2$	60	Brown
E7	-NO_2	160-162	$C_{15}H_{14}N_2O_2$	73	Red
E8	-$N(CH_3)_2$	200-202	$C_{17}H_{20}N_2O_2$	53	Red

Synthesis of some 1,4-dihydro Pyridine Derivatives ($E_{9,10}$)

A mixture of (0.96g, 0.01mol.) furfural, 0.02mol. of (methyl aceto acetate or acetyl), 0.013mol. of ammonium acetate and 25 ml. of water. The reaction mixture was stirred at 70^{o}C for 90 min. After that ethanol was added. The precipitated compound was filtered off, dried and crystallized from ethanol, physics and IR spectral data were as follows: compound 6, mp. 188-190^{o}C , yield 74% as white crystals, compound 10 has mp. 177-179^{o}C, yield 62% as yellow crystals . The IR spectra of those two compounds showed the following main absorption bands: 3346-3448cm^{-1},1705,1697,1653 and 1192, 1099,1219,1122.

Synthesis of some 1,4-dihydro Pyrimidine Derivatives (E_{11-14})

A mixture of furfural (2.4g, 0.025mol.), Urea or thiourea (0.033mol.) and acetyl acetone or methyl acetoacetate (0.12 g., 0.004mol.) of compound (2) was refluxed on 90^{o}C for 20 min. using oil bath, cooled, water was added to precipitate the product which was filtered off and crystallized from ethanol , physical and IR spectral data were shown in (Table 2).

Table 2: Physical properties of compounds E_{11-14}.

Comp. No.	R	X	m.p. ^{o}C	Molecular Formula	Yield (%)	Color
E11	-CH_3	O	215-217	$C_{11}H_{12}N_2O_3$	57	D-yellow
E12	-CH_I	S	240-242	$C_{11}H_{12}N_2O_2S$	55	Yellow
E13	-OCH_3	O	272-274	$C_{11}H_{12}N_2O_4$	55	D-yellow
E14	-OCH3	S	257-259	$C_{11}H_{I2}N_2O_3S$	53	Brown

Synthesis of 2-Methyl-4-(furan -2yl)-6-substituted phenyl-1,4- dihydro-3-pyridine carboxylate (E_{15-20})

Ethyl acetoacetate (0.001mol. and compounds E_{25-31}) each 0.01mol. and 0.01mol. Ammonium acetate were mixed with compounds (3), (0.05g.) in 5ml. of H_2O. The final mixture was refluxed with stirring for the indicated time (Table 5), cooled, 25mol. of dichloromethane was then added , filtered. The filtrate was evaporated under reduced pressure. The solid product was recrystallized from ethanol, physical and IR spectral data were shown in (Tables 3).

Table 3: Physical properties of compounds E_{15-20}.

Comp.No.	R	Time (min)	m_p_ CC)	Molecular Formula	Yield (%)	color
E15	-H	90	122-124	$C_{19}H_{19}NO_3$	6 5	Brown
E16	-CH_3	90	130-132	$C_{20}H_{21}NO_3$	65	1- brown
E17	-OCH_3	90	120-122	$C_{20}H_{21}NO_4$	16	Brown
E18	-F	60	135-137	$C_{19}H_{18}FNO_3$	57	1- brown
E19	-Cl	60	100-102	$C_{19}H_{18}ClNO_3$	55	Brown
E20	-NO2	60	165-167	$C_{19}H_{18}N_2O_5$	54	d- yellow

Synthesis of 1-(4-substituted phenyl)-3-(4,5-dibrono furan-2-yl or furan-2yl)-2-propene-1-one(E_{21-30})

Furfural or 4,5-dibromo furfural (0.034mol.) and (0.034mol.) of acetophenone or its substitutes were mixed together and stirred at 5-15°C for 10 min., sodium hydroxide 10% was then added drop wise. After complete addition, the mixture was stirred for further 3-4 hours. The reaction mixture was left for 24 hours. The solid ppt. was washed with cold water, physical and IR spectral data are presented in (Tables 4).

Table 4: Physical properties of compounds E_{21-30}.

Comp. No.	R	x	m.p_ (°C)	Molecular Formula	Yield (%)	Color	Crystal Sol v.
E21	-H	-H	31-33	$C_{13}H_{10}O_2$	66	d-yellow	Ether
E22	$-CH_3$	-H	50-52	$C_{14}H_{12}O_2$	50	Yellow	Ether
E23	$-OCH_3$	-H	59-61	$C_{14}H_{12}O_3$	52	Orange	Ether
E24	-F	-H	62-64	$C13H_9FO_2$	58	Yellow	benzene
E25	-Cl	-H	70-72	$C_{13}H_9ClO_2$	70	yellow	chloroform
E26	-Br	-H	75-77	$C_{13}H_9BrO_2$	50	Yellow	pt.ether
E27	$-NO_2$	-H	142-144	$C13H_9NO_4$	90	Orange	benzene
E28	-F	-Br	1191-193	$C_{13}H_7Br_2FO_2$	42	Lead	benzene
E29	-Cl	-Br	89-91	$C_{13}H_7Br_2ClO_2$	50	Lead	chloroform
E30	$-NO_2$	-Br	182-184	$C_{13}H_7Br_2N0_4$	55	yellow-green	benzene

Synthesis of 2-(Furan-2-yl)-4-phenyl -2,3-dihydro -1H-benzo[b] ,[1,4]-diazepines(E_{31-37})

Compounds (E13-23), 0.01mol., ortho phenylene diamine (0.01mol.) were mixed together, cellulose- sulfonic acid (0.01 mol.) was then added . The reaction mixture was refluxed at 80°C for a given time Tables (10) the reaction was monitored by TLC after completion it was cooled and extracted with 3x10 of ether. The combined ether was dried, and the solvent was evaporated under reduced pressure. The solid product was crystallized from ether-ethyl acetate, Physical and spectral data are presented in (Table 5).

Table 5: physical properties of compounds E_{31-37}.

Comp- No	R R	X	Time (min)	m.p. (°c)	Molecular Formula	Yield (%)	Color
E31	- H	-H	90	114-116	$C_{19}F1_{16}N_20$	50	Brown
E32	$-CH_3$	-H	90	109-111	$C2_0H_{18}N20$	50	Brown
E33	$-0CH_3$	-H	95	95-97	$C_{20}H18N_20_2$	48	Yellow
E34	-Cl	-H	100	66-68	$C_{19}H_{1s}C1N_20$	55	Yellow
E35	$-NO_2$	-H	120	62-64	$C_{19}H_{13}N_30_3$	60	1-yellow
E36	-F	-Br	90	140-142	$C_{19}H_{13}Br_2N_3O_3$	50	d-brown
E37	$-NO_2$	- Br	120	90-92	$C_{19}H_{13}Br_2FN_20$	57	1-brown

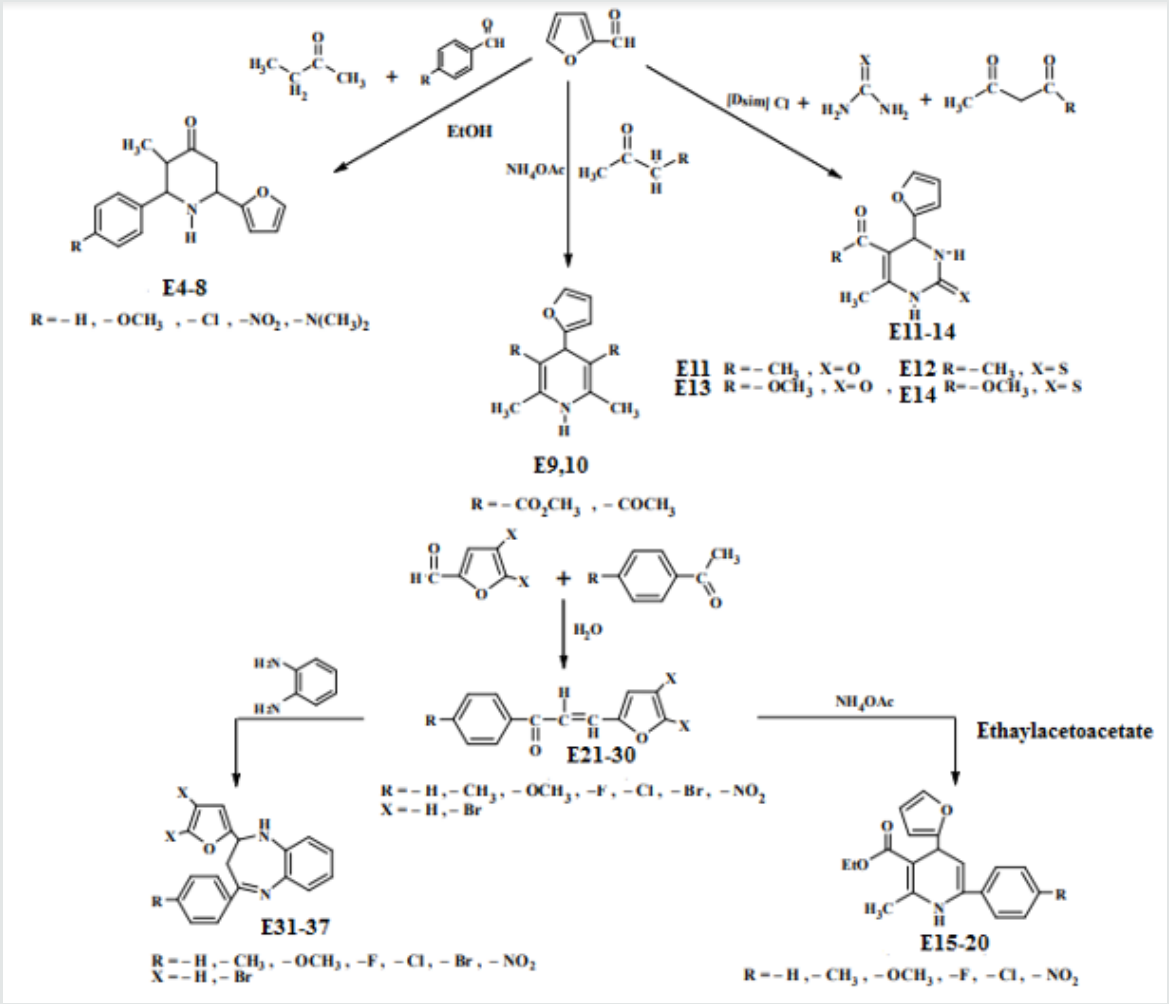
Results and Discussion

Compounds (E_{4-8}) were prepared from the reaction of furfural with benzaldehyde or its derivatives in presence of 2-butanone and ammonium acetate in ethanol as a solvent (scheme 1) .These compounds were characterized by IR cm^{-1}: 3155-3428 belong to NH,1705-1735 for C=O while the aromatic appeared at 1632-1662, C-O sym and assym . absorbed at 1009 and 1176 respectively . Proton magnetic resonance of compound E5 showed the following resonating signals ∫ppm : 8.64(s) for NH, (m) signal at 7.04-7.06 for benzene and furan ring (7H) , singlet signal at 3.82 belongs to $-OCH_3$ of the phenyl substituted (3H), doubled signal at 3.39 and 3.44 for the CH proton Piperidine ring (2H) while the CH_2 of Piperidine ring appeared at 2.50ppm. The 1HNMR spectrum of compound E10 was characterized by the following resonating signals ∫ ppm.: 9.01(s) for NH proton, 7.40 (d) for 5H of furan ring, 6.24 for 4H of the furan ring, 5.83 (d) for proton 3 of furan ring , 5.04 (s) for the Piperidine ring proton, 3.60 for OCH_3 protons and 2.25 (s) for CH_3 (6H) (Table 6).

Table 6: IR spectral data of compounds E_{4-8}.

Comp.No.	R	IR V (cm^{-1}),Br				
		NH	C=0	C=C, C_C	C-$O_{Assym, sym}$	Others
E4	- H	3428	1735	1602-1470	1176 , 1029	—
E5	$-OCH_3$	3373	1723	1618-1462	1250 , 1026	—
E6	- CI	3385	1720	1632-1485	1161 , 1024	735 (C-C1)

E7	- NO_2	3381	1714	1598-1403	1174 , 1014	1338sY(NO_2) 1519asy (NO_2)
E8	-$N(CH_3)_2$	3155	1705	1631-1403	1120 , 1009	1180 (C-N)



Scheme 1.

Compound (E_{11-14})

This series of compounds were prepared by condensation of compounds (E_{4-8}) with Urea, thiourea , acetyl acetone or methyl aceto acetate using [Dsim] as catalyst(scheme1). The synthesized compound was characterized by IR (Table 7).

Table 7: IR spectral data of compounds E_{4-8}.

Comp. No.	R	X	IR V (cm^{-1}), KBr				
			NH	C=0	C=X	C=C	C-N
E11	- CH_3	O	3336	1693	1620	1498	234
E12	- CH_3	S	3338	1705	1103	1661	1235
E 13	- OCH_3	0	3288	1700	1635	1500	1199
E14	- OCH_3	S	3313	1676	1116	1571	1191

The first two compounds of this series (E_{11-12}) were characterized by 1HNMR as follows: For E11 compound (s) signal at 9.30ppm. Belongs to NH proton, (d) at 7.50ppm. For proton at position 5 of furan ring, (t) signal at 6.35ppm. fpr proton of position 4 of furan ring, (d) signal at 6.10ppm. For proton of position 3 of furan ring, (d) at 5.3ppm. For the Piperidine proton, (5) of 3.37ppm. belongs to C=OCH_3 protons and (d) at 2.23ppm. for CH_3 protons. While compound E12 characterized by the following resonating signals ∫ppm.: 10.31, 9.7 (s) belong to NH proton, (s) at 7.58 for position (5) proton of furan ring, (t) at 6.38 for position (4) proton,

(d) at 6.17 for position (3) proton of furan ring, (d) at 5.36 for the Piperidine proton, (s) at 3.30 assigned to $COCH_3$ and (s) at 2.20 to CH_3 equivalent to 3H.

Compounds (E_{15-20})

This series of compounds were prepared from the condensation of the corresponding chalcones with ethyl aceto acetate, ammonium acetate using cellulose sulfonic acid as catalyst. These compounds were characterized by the following IR absorption bands; see (Table 8). This Table revealed the presence of NH absorbed at 3284-3420cm^{-1} for NH, 1703-1739cm^{-1} for C=C while C-O sym and assym appeared at 1026-1261cm^{-1}, see Table 8. 1HNMR spectrum of compound E16 gave the following resonating signals ∫ppm.: multiplet(m) signal at 7.42,7.59,7.65,7.77,7.82 and 8.07 related to 5 position protons of furan and the aromatic ring protons, NH proton respectively. Triplet signal at 6.40 belongs to proton of furan ring, (d) at 6.33 for position 3 proton of furan ring, (d) at 5.00 for proton 5 of furan ring, (d) at 4.63 for Piperidine proton of position 4, (q) at 4.18 for CH_2 of ester moiety, (s) at 3.88 for CH_3 of the substituted at 2 position of Piperidine, (s) at 2.50 for CH_3 of ester, 1.94 as double belongs to CH_3 of ester see.

Table 8: IR spectral data of compounds E_{15-20}.

Comp. No.	R	IR V, (cm^{-1}), KBr				
		NH	C=O	C=C, C-C	C-O Asy, sym	Others
E15	- H	3341	1735	1597-1448	1235, 1116	-
E16	- CH_3	3420	1703	1615-1453	1243-1112	_
E 17	- OCH_3	3411	1705	1620-1441	1261 , 1026	_
E18	- F	3412	1739	1600-1411	1242 , 1157	1012(C-F)
E19	- C1	3284	1736	1592-1478	1227-1105	774 (C-CI)
E20	- NO_2	3389	1721	1604-1447	1249-1145	1320sy(NO_2) 1519asy(NO_2)

Compounds (E_{21-30})

This series of chalcone compounds were prepared from the condensation of 4,5-di bromo furfural with some acetophenones (Scheme 1). The synthesized compounds were characterized by IR, Table. This Table revealed the presence of C=O stretching vibration at 1660-1697cm^{-1}, C=C Aliphatic appeared at 1578-1664cm^{-1}, while the aromatic C=C absorbed at 1416-1576cm^{-1} together with C-O sym and assym as indicated in (Table 9). These chalcone compounds were used as starting materials for the preparation of diazipine compounds by the condensation with ortho phenylene diamine using sulfamic acid to increase the positive character of the carbonyl chalcones. The final(diazipin) compounds were characterized by the following IR bands cm^{-1}: 3188-3346 for NH, 1631-1661 for C=N, 1452-1611 for Aromatic C=C stretching, C-O sym and assym. of 1009-1253, see (Table 10). As a representative sample of this series compound E36 was studied by 1HNMR . The spectrum showed the following resonating signals: (m) signal at 6.96,7.36 and 7.81 for furan ring protons in which aryl and phenyl ring protons appeared within the same range, (s) signal at 6.26 for proton of position 2 of azipine ring, (s) signal at 3.33 for NH, singlet (s) signal at 2.50 for CH_3 which is consider with DMSO signal, (d) at 2.24 belongs CH_2 of a zipine ring protons.

Table 9: IR spectral data of compounds E_{21-30}.

Comp. No.	R	X	IR .0 (cm^{-1}), KBr				
			C=0	C=C	C=C, C-C	C-O Asym, sym	Others
E21	- H	- H	1662	1601	1576 1454	1194 , 1014	—
E22	-CH3	- H	1667	1609	1551 1416	1212 , 1027	—
E 23	-CH3	-H	1665	1604	1551 1442	1212 , 1151	—
E24	- F	- H	1666	1599	1555 1454	1223-1112	1014(C-F)
E25	- Cl	- H	1693	1612	1509 1440	1215 , 1123	755 (C-CI)
E 26	- Br	- H	1678	1605	1552 1475	1217-1146	808(C-Br)
E27	-NO_2	- H	1697	1608	1548 1470	1223-1019	1323sy(NO_2) 1547asy(NO_2)
E28	-F	- Br	1678	1596	1507 1424	1267-1082	1020(C-F) 830(C-Br)
E 29	-Cl	- Br	1660	1578	1541 1464	1195-1120	712(C-C1) 790(C-Br)
E 30	-NO_2	- Br	1686	1664	1520 1478	1202-1026	1318sy(NO_2) 1547asy(NO_2) 888(C-Br)

Table 10: IR spectral data of compounds E_{31-37}.

Comp. No.	R	X	IR V (cm^{-1}), KBr				
			NH	C=N	C=C, C- C	C-$O_{Asy, sy}$	Others
E31	-H II	-H	3286	1631	1591-1458	I 1247,1116	—
E32	$-CH_3$	- H	3.367	1658	1608-1456	11273,1016	—
E33	-OCH3	- H	3386	1657	1600-1475	11227,1009	—
E34	-Cl	- H	3386	1656	1605-1478	11278,1012	755 (C-Cl)
E35	$-NO_2$	-H	3381	1656	1611-1452	11223,1019	$1346_{sy}(NO_2)$ $1548_{asy}(NO_2)$
E36	-F	- Br	3386	1661	1599-1457	I 1212,1151	1030(C-F)809(C-Br)
E37	-NO2	-Br	3346	1653	1597-1470	1221,1068	$13935_{sy}(NO_2)$ $1559_{asy}(NO_2)$ 818(C-Br)

Conclusion

As it was stated in the introduction part of this work on the importance of heterocyclic compounds as drugs or co- drug and especially for those when furyl moiety and nitrogen residue were part of the whole compound structure .In this investigation we are focusing on those two important categories, So according to the resulted data given in the experimental part together with discussed results we have succeeded in getting these type of heterocyclic compounds with nitrogen base and at the same time having furyl moiety from furfural precursors which means more activities for both type of compounds that becomes two in one final compound structures, pyridines, pyrimidines and azipines.

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