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Synthesis, Characterization, and Antimicrobial Activity of some new 3-Substituted Isobenzofuran- 1(3-H) –One Derivatives

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***Abstract*—Prompted by the varied biological and pharmacological properties of isobenzofuranones, an investigation was made on the reaction between o- phthalaldehydic acid (I) and four primary heterocyclic amines. The reaction with amino compounds afforded 3-Substituted Isobenzofuran- 1(3-H) – One Derivatives (B1-B4) in good yield. The structures of the isolated products were confirmed from their spectral and analytical data. The synthesized products were evaluated for their antimicrobial activity. The compounds were tested for their antibacterial and antifungal activities by the ditch-plate technique.**

Keywords: ***Phthalide, Benzolactone, o-phthalaldehydic acid, Antimicrobial Activity.***

Introduction

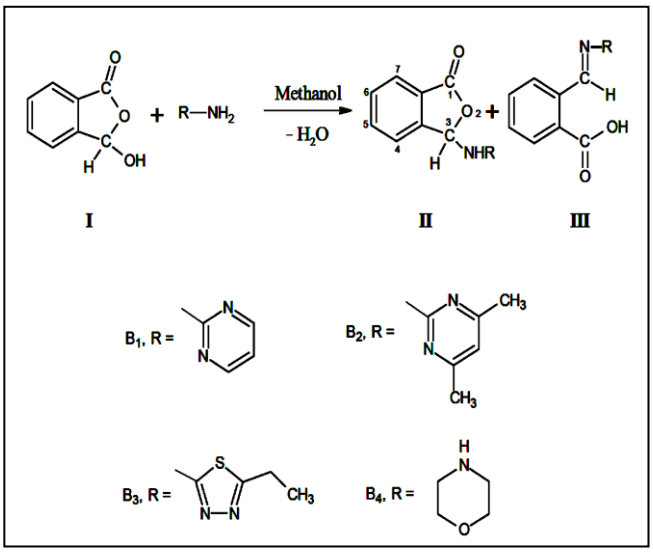
phthalides (Benzolactones) are five-membered cyclic lactones, are found in plants and are known to show diverse biological activities as hormones, pheromones and antibiotics. These compounds possess several important properties1-10, such as germicidal, fungicidal, herbicidal, pesticidal, analgesic, vasorelaxant and hypotensive activities. In addition, phthalide derivatives are useful in the treatment of circulatory and heart related diseases. Many of phthalide derivatives11 have been used as precursors in the synthesis of valuable compounds such as chlorothiadone, anthracyclinone and anthraquinone derivatives, the later compounds possess a wide spectrum of biological activity as antihypertensive and antitumor reagent, The
reaction of o-phthalaldehydic acid with primary and secondary amines have been explained12-14. The reaction mechanism occurs through bimolecular nucleophilic substitution reaction affording 3-Substituted Isobenzofuran- 1(3-H) –One type (II). Other authors15-18 shows that some secondary aromatic and aliphatic amines afforded a Schiff bases of type (III), resulted from the reaction of the amine with formyl group of the acid, as part of our ongoing research on 3-Substituted Isobenzofuran- 1(3-H) – One we decided to study the reaction of o-phthalaldehydic acid (I) with heterocylic aromatic amines having two or more heteroatoms.

Results and Discussion

It was previously reported that the treatment of o-phthalaldehydic acid (I) with substituted anilines gave a N-(3-phthalidyl) amines0 (II). In a similar fashion, 3-aryl amino phthalides (II) were prepared from the condensation of o-phthalaldehydic acid (I) with heterocyclic amines; 2-aminopyrimidine, 2-amino-4-chloro-6-methylpyrimidine, 2- amino-5-ethyl-1,3,4-thiadiazol as an example of heterocyclic primary aromatic amines having more than one hetero atom and morpholine as an example of secondary aliphatic amines in refluxing methanol afforded in each a crystalline solid product. The analytical data of isolated aminophthalides are given in Table-2. TLC of the crude product indicating the presence of one single component. The IR (KBr) of the isolated compounds (Fig. 3, 7, 11, and 13) and (Table-4) shows the presence of two strong absorption bands at 3228- 3295 cm-1 (except in case of morpholine no bands because of secondary amines) and 1743- 1761 cm-1. The former can be attributed to N-H stretching, while the second is due to the presence of a lactonic group. The 1H-NMR spectra in (d6-DMSO) of all products, (Fig. 1, 5, 9, and 12) and (Table-3) shows the presence of one proton either as a singlet or a doublet with J= 9.1- 9.7 Hz exchange with D2O, in the range of 8.2-9.1ppm due to N-H proton and one proton either a singlet in the range 6.51-6.95ppm or a doublet in the range 7.10-7.20 ppm with J= 9.1 Hz due to CH-N proton. On the other hand, 13C- NMR spectra in (d6-DMSO) of compounds [B1-B3] shows number of resolved carbon signals, the carbonyl carbon signal was observed at δ 169.82, 171.34 and 169.41 respectively and the aniline carbon (C-NH) signal was observed at δ 161.78, 169.67 and 166.78 respectively, (**Fig. 2, 6,** and **10**), and the rest of the resolved carbon signals are corresponding to the aromatic carbon atoms of the product.

Furthermore, the mass spectra of most of the isolated products (**Fig. 4 and 8**) show fragments at m/z = 133 due to phthalidyl cation. These results rule out the possibility of Schiff base formation of type III and clearly indicate the formation of N-(3-phthalidyl) amines of type II [B1-B4] scheme-
1. These compounds can only arise if the starting amines react with lactol form of the acid I, through nucleophilic substitution reaction (SN2) on carbon No.3.

Scheme-1



Experimental

All melting points were measured on electrotherrmal melting point and were uncorrected, infrared (IR) spectra were measured using a Shimadzu DR-8001 spectrophotometer as a potassium bromide disc and FTIR. Magnetic resonance spectra (1H-NMR and 13C-NMR spectra) were recorded on a Bruker at 400 MHz and 100 MHz using TMS as the internal standard in DMSO-d6. The chemical shifts values (δ) were recorded in ppm spectrometer. The Mass Spectrum was recorded on VG 7070 E.G.C mass spectrometer. The purity of the compounds was checked by TLC-using Silica gel-G (Merck). Thin layer chromatography was performed using silica gel 60 F254 pre coated aluminium sheets, the progress of the reactions was monitored on silica gel plates using iodine vapours as visualizing agent or by UV light. Reagents and solvents used were purchased from Aldrich Chemicals.

Reaction of 2-formylbenzoic acid with Amines.

A mixture of 2-formylbenzoic acid **1** (1.5g, 0.01mole) and the heterocyclic aromatic and aliphatic amines (0.01mole) in methanol (25ml) was refluxed for about 2-5 hrs, then cooled; in certain cases, a solid start to appear. Evaporating the solvent or filtration afforded the product, which was crystallized from the mentioned solvent

Antimicrobial activity

Materials and Methods

The antibiotics used as positive controls in the disk diffusion assay include: nalidixic acid (30 µg), miconazole (10 µg), and DMSO (10 % v/v) as the constituting solvent and negative control. Test bacteria include Gram-positive (*Staphylococcus aureus* ATCC 11632) and Gram-negative bacteria (*Escherichia coli* ATCC 10536). And tested fungal include (Candida *albicans* P225).

The antimicrobial activities of synthesized compounds N-(3-phthalidyl) Amines **B1- B4** Was screened *in vitro* for their antibacterial activity against *Escherichia coli* (gram negative) and *Staphylococcus aureus* (gram positive), also tested for antifungal activity against *Candida albicans* by the ditch-plate technique19. Using concentrations of 5 mg/ml for each compound. The microorganisms were grown over night in Nutrient broth (NB) at 37 oC and a compared to 0.5 Mackfer land so lut io n before being used. Mueller-Hinton Agar (MHA) was employed as culture media and Dimethyl sulfoxide (DMSO), was used as solvent.As positive controls nalidixic acid as antibacterial drug and miconazole as antifungal drug were used.

Biological Results

The results of antimicrobial activity showed clearly that all tested compound exhibited antifungal activity against yeast-like fungi, the antibacterial activity of the compound showed a good activity against four used strains (**Table-1**).

According to the results, we found that compounds B1-B4 have inhibition power on the three strains E. coli, S. aureus and C. albicans We can deduce that N-(3- phthalidyl) amines (conc.5mg/ml) have more powerful inhibition effect on *S. aureus* compared to *E. coli* and *C. albicans*.

Table – 1: Antibacterial and Antifungal activities of N-(3-phthalidyl) Amines (conc.5mg/ml) for compounds (B1-B4) (Zone on inhibition in mm)

Phthalides (B1- B4)	*E. coli*	*S. aureus*	*C. albicans*
3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1)	26	42	35
3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one (B2)	26	40	32
3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one(B3)	20	48	29
3-Morpholin-4-yl-3H-isobenzofuran-1-one (B4)	22	30	32

Table-2

Analytical data of Phthalides (B1- B4)

Phthalides(B1- B4)	Molecular Formula	Color	Melting Point (°C)	Yield (%)	Solvent for Crystallization
3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1)	$C_{12}H_9N_3O_2$	White	174-175	96	Methanol
3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one (B2)	$C_{13}H_{10}ClN_3O_2$	White	166-167	46	Methanol
3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one(B3)	$C_{12}H_{11}N_3O_2S$	White	154-155	70	Methanol
3-Morpholin-4-yl-3H-isobenzofuran-1-one (B4)	$C_{12}H_{13}NO_3$	White	129-130	84	Methanol

Table-3

Spectral data (^{1}H -NMR and ^{13}C-NMR) of Phthalides (B1-B4)

Phthalides(B1-B4)	^{1}H-NMR (400MHz) d_6-DMSO δ (ppm)	^{13}C-NMR (100MHz) d_6-DMSO δ (ppm)
3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1)	6.51(s, 1H, CH, H-3, J=4.0 Hz) 7.83-7.93(m, 4H, Ar-H), 8.24-8.36 (d,2H, NH_2, H-8, J=4.0 Hz,), 12.60(s,1H, NH, H-9).	85.12(C3), 114.17-146.79(C-aromatic), 159.08(C-9, C-11), 161.78(C=C-N), 169.82(C1).
3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one (B2)	2.30-2.40(s, 3H, CH_3), 7.10-7.20(d,1H, CH, H-3, J=9.1 Hz), 7.36-7.66-7.88(m,4H, Ar-H), 9.10-9.20 (d,1H, NH, H-8, J=9.1 H).	24.18(C-CH_3), 84.57(C3)), 112.44-161.64(C-aromatic), 169.67(C=C-N) 171.34(C1).
3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one(B3)	1.26 (t,3H, CH_3, H-10), 2.90 (q, 2H, CH_2, H-9), 6.95 (s,1H, CH, H-3), 7.70-7.94 (m,4H, Ar-H), 8.79-8.81(s,	14.63(C-10), 23.85(C-9), 86.68(C-3), 124.73-163.46 (C-aromatic), 166.78 (C=C-N), 169.41(C-1).
3-Morpholin-4-yl-3H-isobenzofuran-1-one (B4)	2.70-2.73(d,4H, N-CH_2, CH_2, H-9,10), 3.50-3.59(d,4H, O-CH_2, CH_2, H-11,12), 6.49 (s, 1H, CH, H-3), 7.60-7.87(m,4H, Ar-H).	

Table-4

Spectral data (IR) of Phthalides (B1-B4)

Phthalides(B1-B4)	IR (KBr) ν cm^{-1}
3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (**B1**)	1594(C=N), 1750(C=O) 2849-2918(C-H,aliphatic) ,3000-3039(C-H,aromatic) , 3228(N-H).
3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one (B2)	744(C-Cl), 1615(C=N), 1761(C=O), 2900-2977 (aliphatic), 3000-3200 (aromatic), 3295(NH).
3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one(**B3**)	1578(C=N), 1743(C=O), 2800-2900(aliphatic), 3000-3049(aromatic), 3291(NH).
3-Morpholin-4-yl-3H-isobenzofuran-1-one (**B4**)	745 (C-O-C), 1744(C=O), 2850-2896(aliphatic), 3000-3020(aromatic).
745 (C-O-C), 1744(C=O), 2850-2896(aliphatic), 3000-3020(aromatic).	

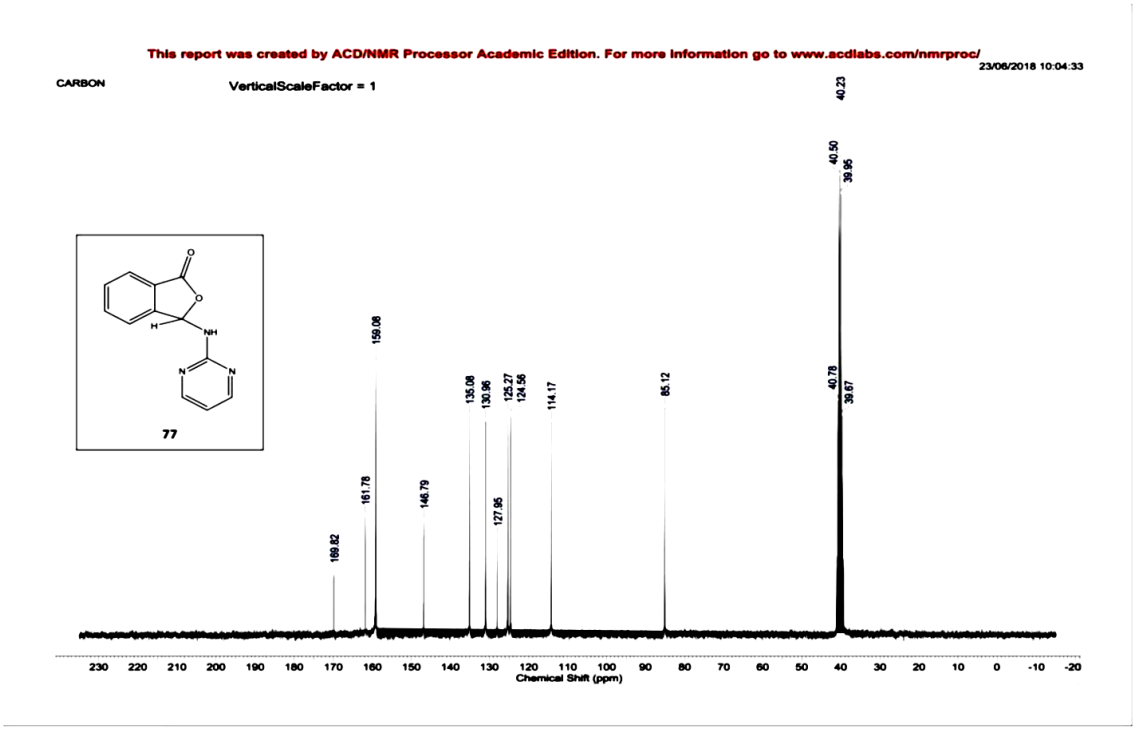


Fig.1. The ^{1}H-NMR spectrum of 3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1) in d^{6}-DMSO.

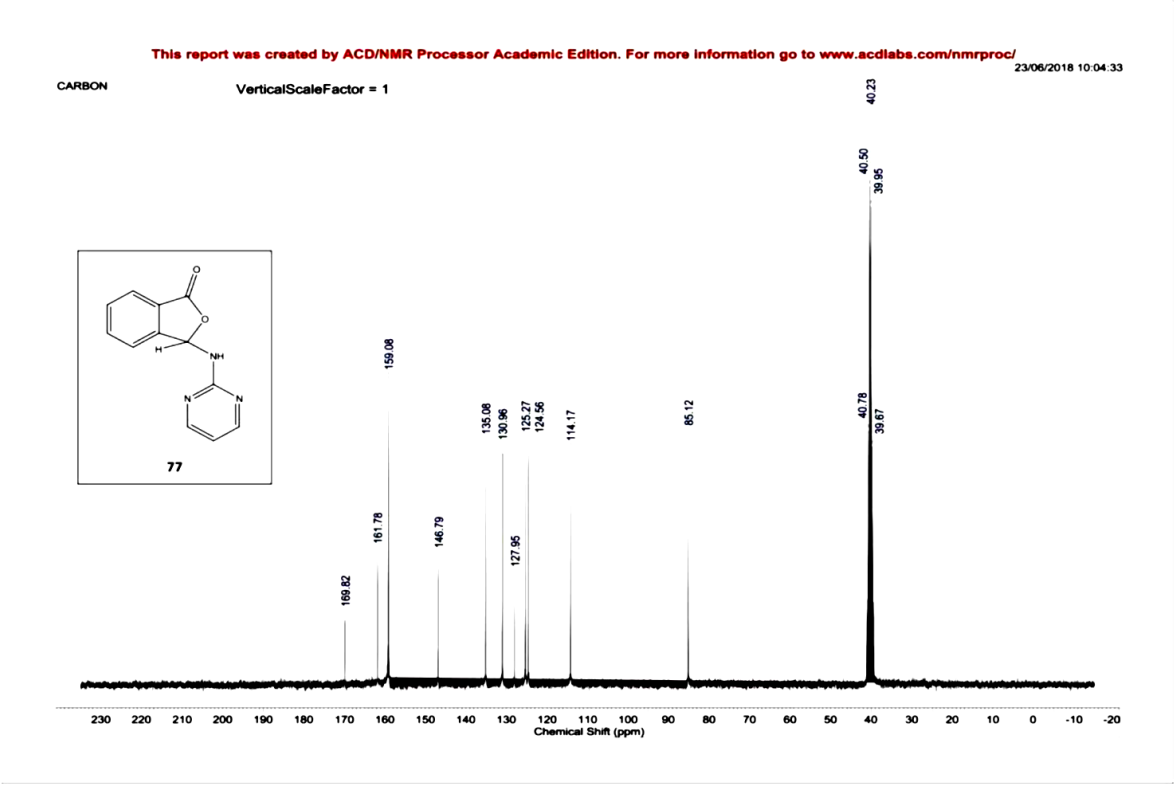


Fig.2. The ^{13}C-NMR spectrum 3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1) in d^6-DMSO.

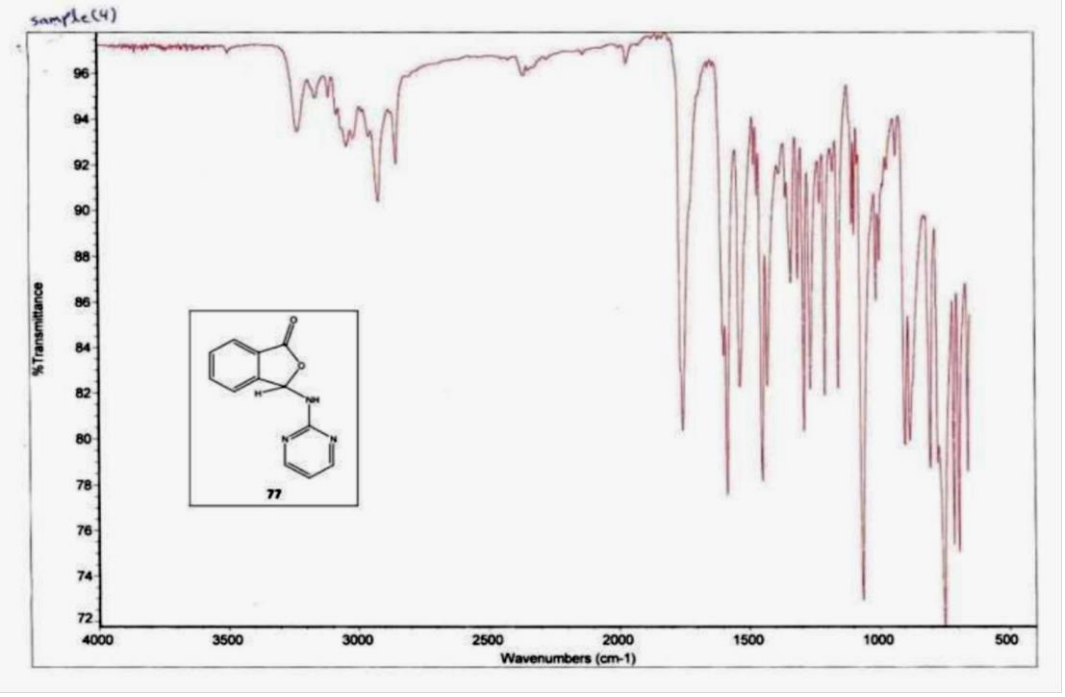


Fig.3. The I.R Spectrum of 3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1).

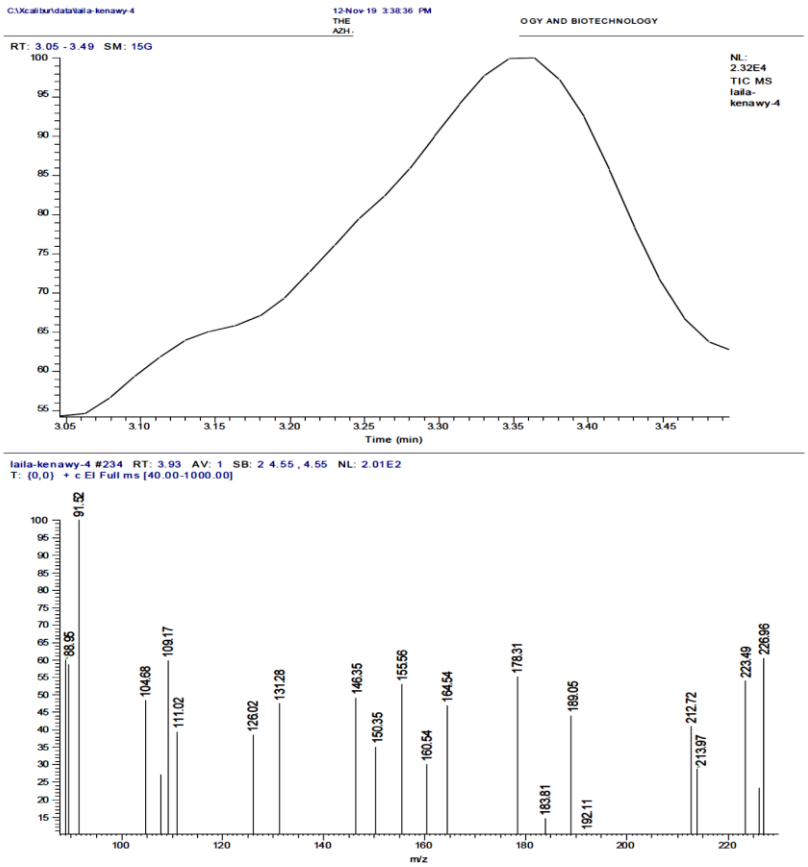


Fig.4. The Mass Spectrum of 3-(pyrimidin-2-ylamino)-2-benzofuran-1(3H)-one (B1).

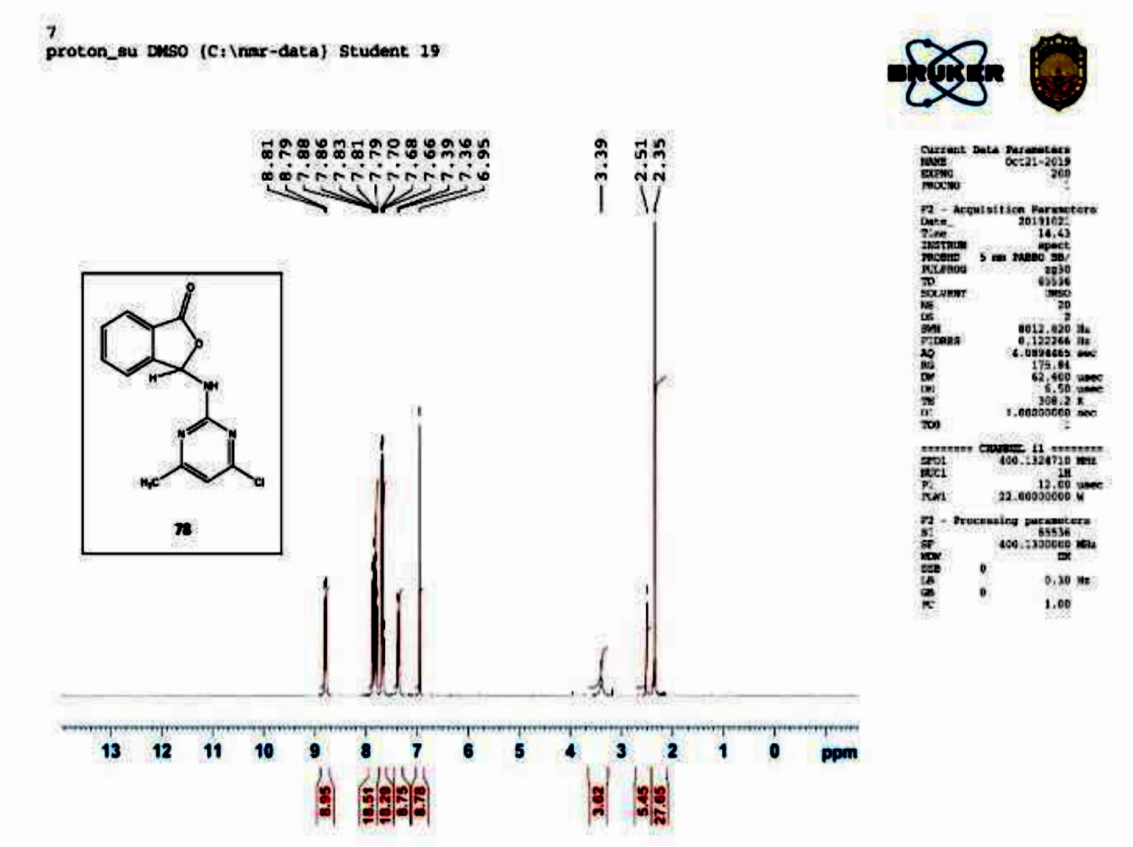


Fig.5. The ^{1}H-NMR spectrum 3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran- 1(3H)-one (B2) in d^{6}-DMSO

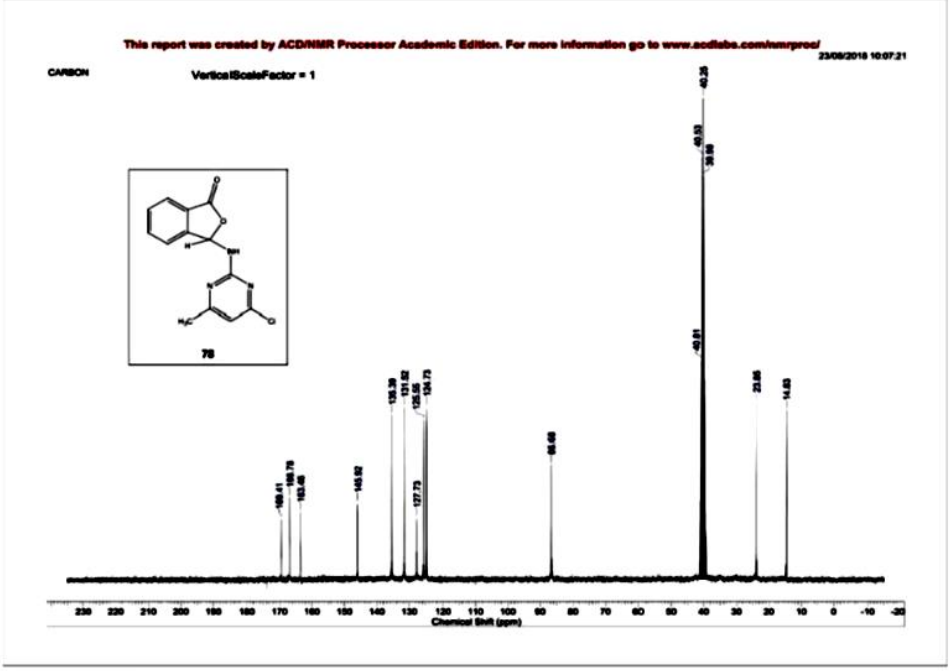


Fig.6. The ^{13}C-NMR spectrum 3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one (B2) in d^6-DMSO.

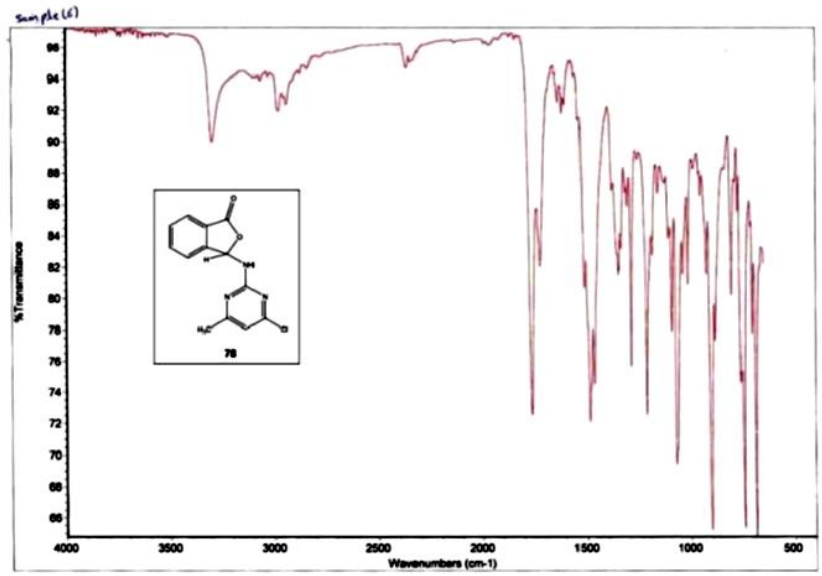


Fig.7. The The I.R spectrum of 3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one(B2) .

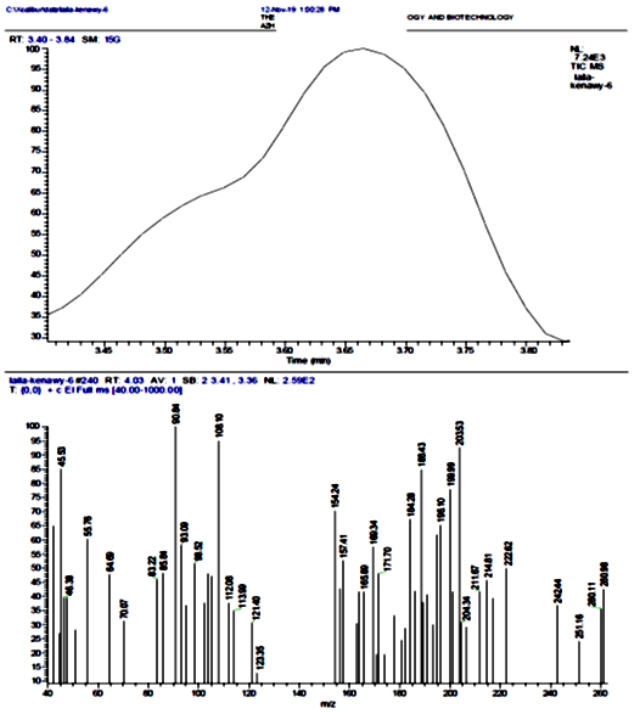


Fig.8. The Mass Spectrum of 3-[(4-chloro-6-methylpyrimidin-2-yl) amino]-2-benzofuran-1(3H)-one (B2).

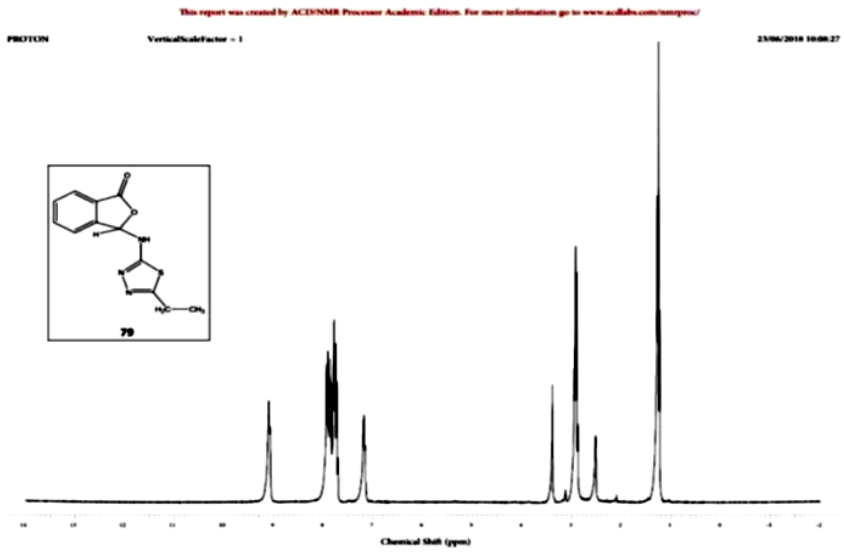


Fig.9. The ^{1}H-NMR spectrum of 3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one (B3). in d^{6}-DMSO.

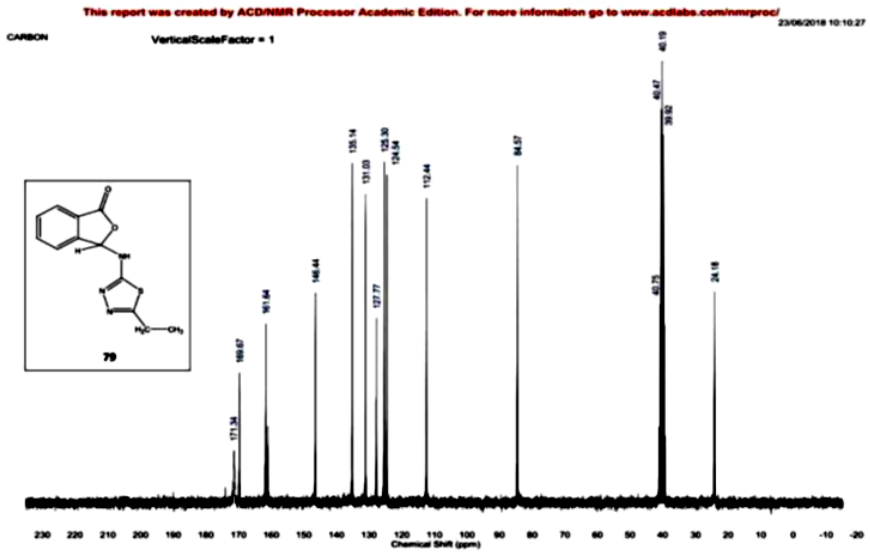


Fig.10. The ^{13}C-NMR spectrum of 3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one(B3) in d^{6}-DMSO.

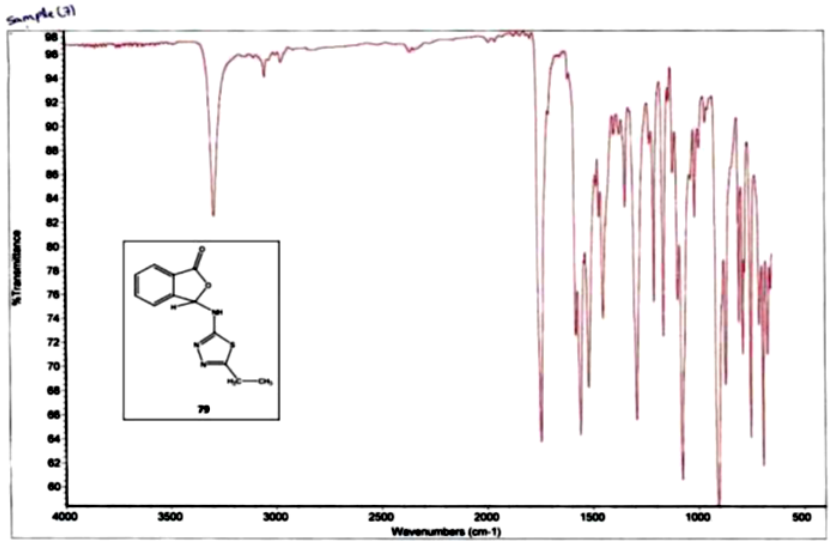


Fig.11. The I.R Spectrum of 3-[(5-ethyl-1,3,4-thiadiazol-2-yl) amino]-2-benzofuran-1(3H)-one(B3)

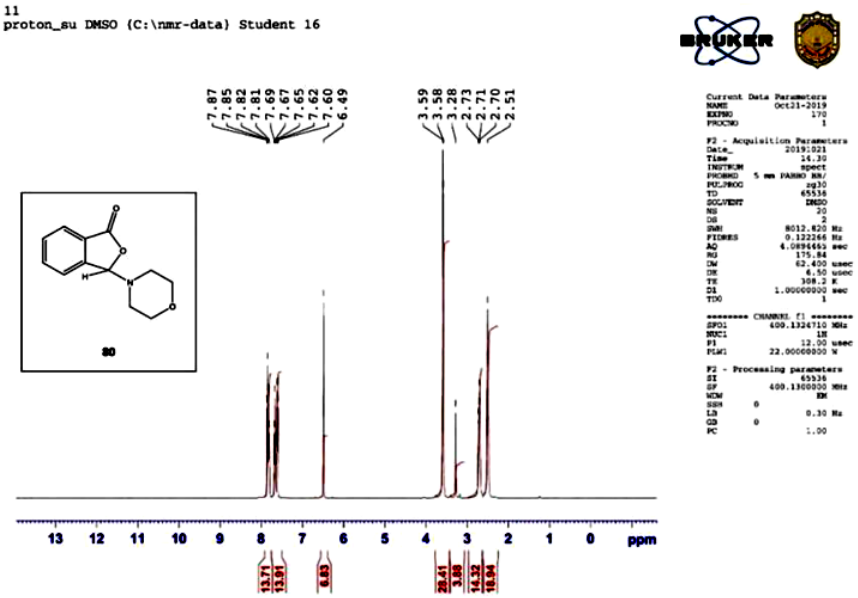


Fig.12. The ^{1}H-NMR spectrum of 3-Morpholin-4-yl-3H-isobenzofuran-1-one (B4) in d^{6}-DMSO.

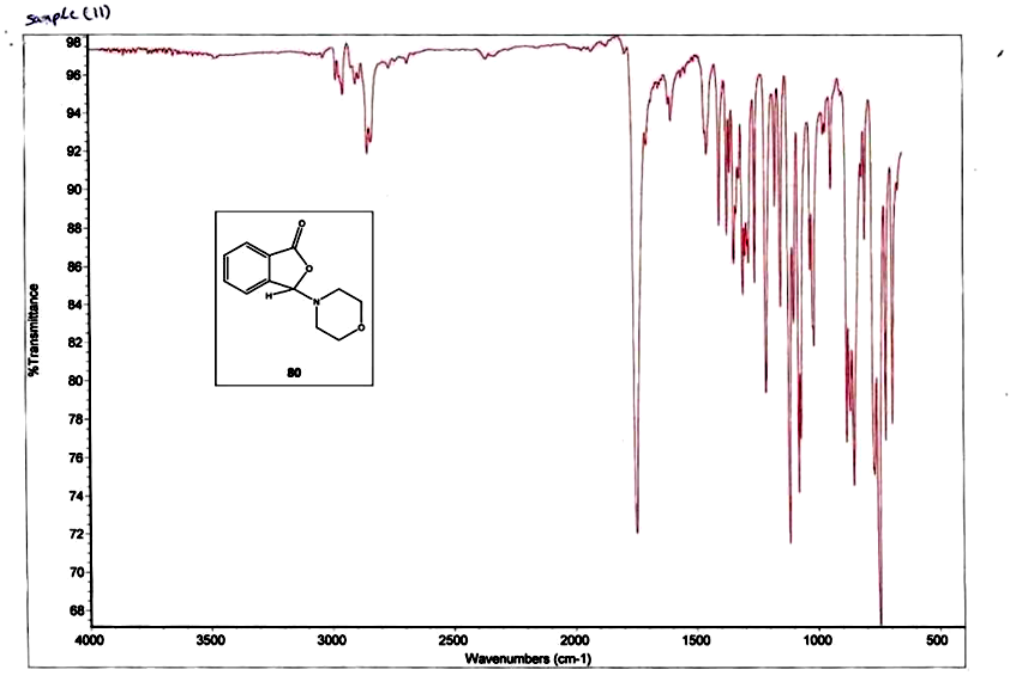


Fig.13. The I.R Spectrum of 3-Morpholin-4-yl-3H-isobenzofuran-1-one (B4).

Acknowledgements
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