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RESEARCH ARTICLE

Synthesis, Spectral Characterization and Antimicrobial Activities of Ethyl-2-(4-(naphthalene-1-yl)-6-phenyl-pyrimidin-2-yl amino)acetate Derivatives

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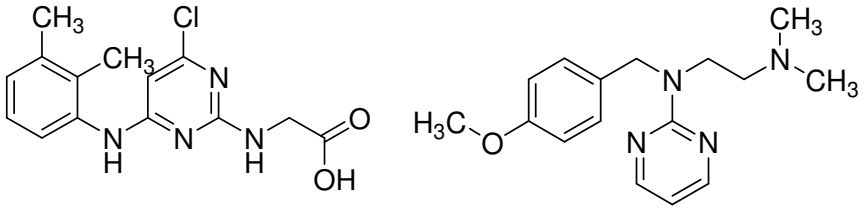
Abstract: The novel series of ethyl-2-(4-naphthalene-1-yl)-6-phenyl pyrimidin-2-yl amino)acetate derivatives were synthesised by the condensation reactions of 4-(naphthalene-1-yl)-6-phenyl pyrimidin-2-amines reacted with chloroethyl acetate and K_2CO_3 as a catalyst. The 4-(naphthalene-1-yl)-6-phenyl pyrimidin-2-amines were occurred by the reaction between naphthalene chalcones and guanidine nitrate in the presence of ethanolic sodium hydroxide solution. The naphthalene chalcones were synthesised from substituted aldehydes treated with 1-acetyl naphthalene. Finally the synthesised compounds were determined by elemental analysis and spectral characterizations such as FT-IR, ^{1}H NMR and ^{13}C NMR. The antimicrobial activities of the new synthesised heterocyclic compound are evaluated against gram positive, gram negative bacterial and fungal strains. The electron withdrawing chloro substituted derivative have an excellent zone of inhibition against bacterial strains.

Keywords: Naphthalene chalcone, Chloroethyl acetate, Guanidine nitrate, K_2CO_3 Antimicrobial activity

Introduction

Sulphur and nitrogen containing heterocyclic compounds are exhibit good biological activities. NMR spectroscopy is a good tool for providing information about structure of the heterocyclic compounds. Chalcone is one of the major classes of natural products. It possess several biological activities such as antibacterial[1-2], anti-fungal[3-4] and anti-tumour activities[5-6]. The pyrimidine derivatives are also known to exhibit diverse pharmacological properties such as effective bactericides and fungicides[7]. The 2-aminopyrimidine structural unit is present in a growing number of both natural products and synthetic compounds with biological properties of particular interest[8]. Pyrimidine compounds are useful drugs which are associated with many biological and therapeutical activities. They can be reported as anti-tumour[9] and used as hypnotic drugs for the nervous system[10]. It exhibits the cardioprotective effects[11]. It is revealed from the literature review the pyrimidine derivatives

found to posses biological activities known as fungicidal[12-13], analgesic[14] and antimicrobial[15]. The substituted amino pyrimidine structures are common in marketed drugs such as aronixil, thonzylamine[16] Figure 1.



Aronixil Thonzylamine

Figure 1. Structure of aronixil and thonzylamine

The substituted amino acetate derivatives show good biological activities. Our synthesized compounds were subjected against three microbial organisms (*Staphylococcus epidermidis, Pseudomonas aeruginosa* and *Candida albicans*), here ciprofloxacin used as a standard drugs. Owing to the documented biological properties of amino acetate derivatives, herein we report the continuation of our work a series of new amino acetate were designed, synthesized by using chloroethyl acetate, potassium carbonate used as a catalyst and their antimicrobial activities were evaluated *in vitro*.

Experimental

The melting points of the compounds were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC on silica gel plate. The FT-IR spectrum (cm^{-1}) of the compounds were recorded using KBr on a Fourier Transform IR spectrometer (model Shimadzu 8400s) in the range of 400-4000 cm^{-1}. ^1H NMR spectra were recorded in Bruker 500 MHz-NMR spectrometer (Astra Zeneca India Ltd) using $CDCl_3$ as a solvent and chemical shifts(δ) values are reported in parts per million.

General procedure for synthesis of chalcones

The one mole of 1-acetonaphthanone and one mole of various substituted aldehydes were taken in a beaker and to this approximately added 30 mL of ethanol containing 2 g of NaOH pellets. This mixture was stirred well for 30 minutes in an ice cold bath then it was poured into the crushed ice and this reaction mixture was kept into overnight at room temperature. The chalcones were precipitated out as solid. Then it was filtered. Dried and recrystallized from ethanol. The purity of the sample was checked by TLC by using chloroform as the solvent.

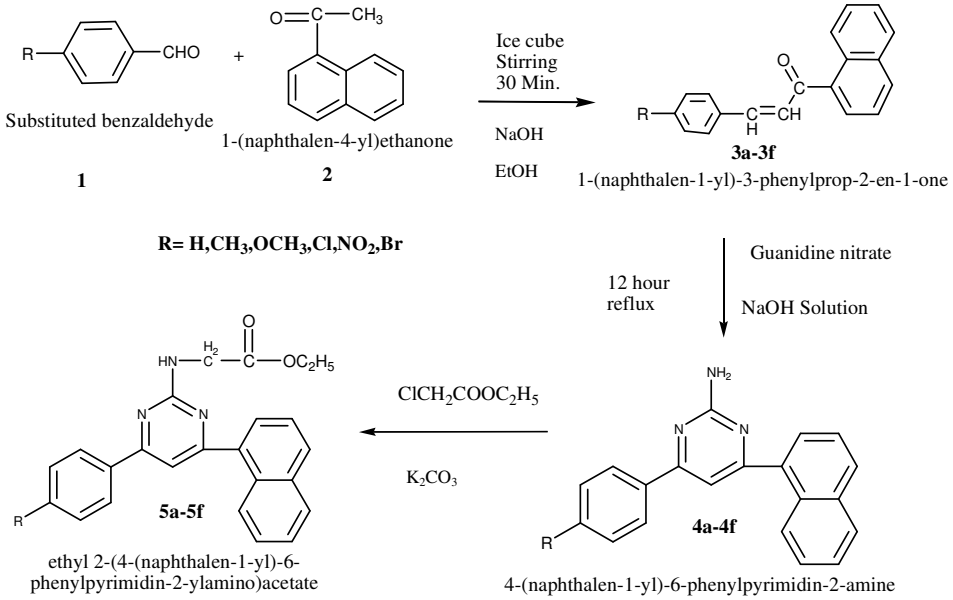
*Synthesis of 4-(naphthalene-3-yl)-6-phenyl-pyrimidin-2-amines (**4a-f**)*

A mixture of various substituted naphthalene chalcones (1 mmol), Guanidine nitrate (1 mmol), 25 mL of ethanol and a 10 mL of 10% solution of sodium hydroxide were added portion wise for 2 hours. Then the reaction mixture was shaken well and it was refluxed for 12-14 hours. The reaction was monitored by TLC. After the reaction mixture was cooled at room temperature and poured into crushed ice, the white precipitate was obtained. Finally the precipitate was filtered, dried and recrystallized from ethanol.

*Ethyl-2-(4-(naphthalene-1-yl)-6-phenylpyrimidin-2-yl amino) acetate (**5a-5f**)*

The 4-(naphthalene-1-yl)-6-aryl-pyrimidin-2-amines (1 mol), chloroethyl acetate, potassium carbonate and toluene (25 mL) is taken in a round bottom flask, the mixture was shaken well

and then it was refluxed for 4-6 h. The completions of the reactions were monitored by TLC. After the reaction mixture was cooled to room temperature and poured into crushed ice, the white precipitate was obtained. After filtration the precipitate was recrystallized from ethanol. The physical and analytical values of the synthesized compounds (3a-5f) are shown in Table 1.

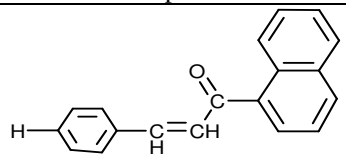
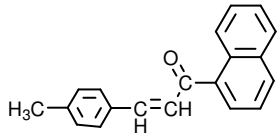
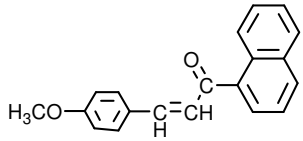


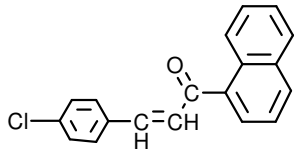
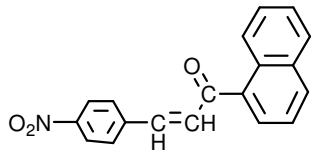
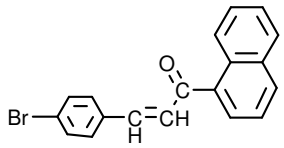
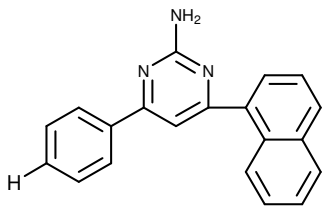
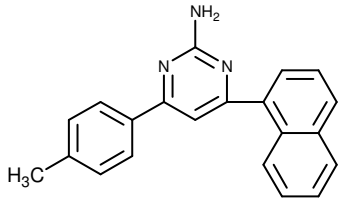
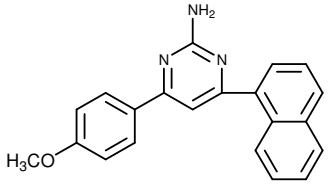
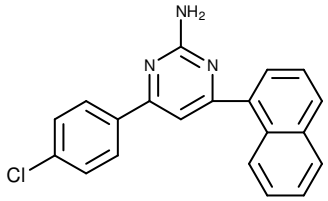
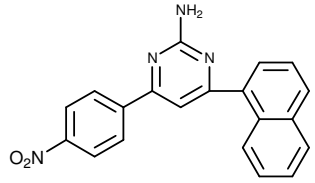
Scheme 1. Synthesis pathway of compounds **5a-5f**

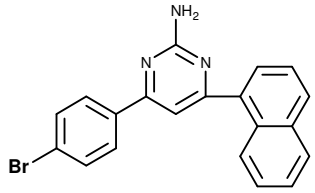
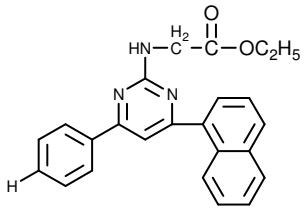
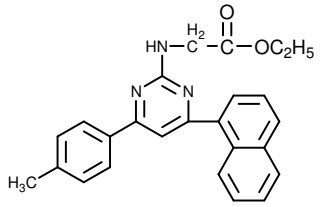
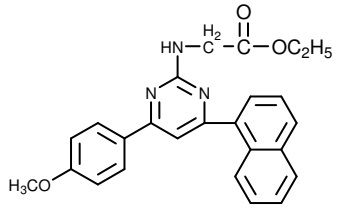
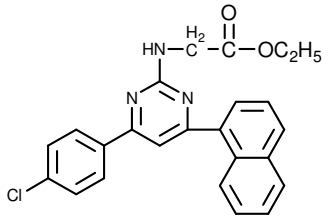
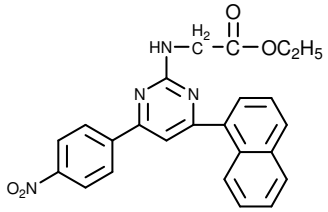
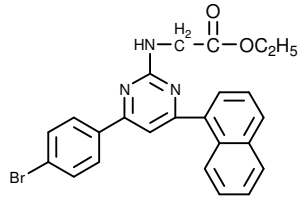
Antimicrobial studies

The synthesized compounds **5a-5f** screened against the anti-bactrial strains such as *Staphylococcus epidermis, Pseudomonas aurgeinosa* and the fungal strain like *Candida albicans.* The antimicrobial studies are carried out by the literature survey method[17].

Table 1. Physical and analytical data of the synthesized compounds **(3a-5f)**

No	Structure of the compound	Molecular formula	Molecular weight	Melting point	% of yield
3a		$C_{19}H_{14}O$	258	102	82
3b		$C_{20}H_{16}O$	272	124	92
3c		$C_{20}H_{16}O_2$	288	88	90

3d		$C_{19}H_{13}OCl$	292	76	85
3e		$C_{19}H_{13}O_3N$	303	130	95
3f		$C_{19}H_{13}O_3Br$	337	80	93
4a		$C_{20}H_{15}N_3$	297	50	75
4b		$C_{21}H_{17}N_3$	311	154	89
4c		$C_{21}H_{17}N_30$	327	118	81
4d		$C_{20}H_{14}N_3Cl$	331	104	80
4e		$C_{20}H_{14}N_4O_2$	342	142	92

4f		$C_{20}H_{14}N_3Br$	376	108	88
5a		$C_{24}H_{21}N_3O_2$	383	76	67
5b		$C_{25}H_{23}N_3O_2$	397	140	83
5c		$C_{25}H_{23}N_3O_3$	413	106	81
ad		$C_{24}H_{20}N_3O_2Cl$	417	89	77
5e		$C_{24}H_{20}N_4O_4$	428	126	84
5f		$C_{24}H_{20}N_3O_2Br$	462	94	78

Results and Discussion

The ethyl-2-(4-naphthalen-1-yl)-6-phenylpyrimidin-2-ylamino)acetate were synthesized from 4-(naphthalene-1-yl)-6-phenylpyrimidin-2-amine react with chloroethyl acetate and potassium carbonate used as a catalyst. The skeleton structure of the synthesized compounds characterized by using IR, ^{1}H NMR and ^{13}C NMR. The 4-(naphthalene-1-yl)-6-phenylpyrimidin-2-amines were synthesized from the naphthalene-1-yl chalcones react with guanidine nitrate in the presence of base solution.

Spectral analysis

FT-IR analysis of the synthesized compounds

The IR spectrum of the compounds (**3a-3f**) shows that the characteristic bands at 1645 to 1655 cm^{-1} due to the presence of C=O stretching frequencies. The absorption bands around 1570 to 1600 cm^{-1} attributed to the presence of C=C stretching frequencies. The aromatic CH stretching frequencies appeared in the range of 3000 to 3100 cm^{-1} and aliphatic CH stretching frequencies appeared in the range of 2900 to 3000 cm^{-1}. The IR spectrum of the **3a-3f** compounds are shown in Table 2. The IR spectrum of the compounds(**4a-4f**) revealed a sharp strong absorption band above 1610 cm^{-1} that can be attributed with the presence of the C=N stretching. The aromatic CH asymmetric and symmetric stretching vibration in the structure of pyrimidine nucleus around 3150 cm^{-1} and for the aliphatic CH group showed a sharp absorption band around 2900 cm^{-1} and another sharp strong absorption band was noticed at around 1560 cm^{-1} for C=C group and the stretching frequency for C-N group obtained 1350 cm^{-1}. The IR spectrum values of the compounds **4a-4f** shown in Table 3.

Table 2. The IR spectrum values of compounds **3a-3f**

Compound	C=C Stretching cm^{-1}	C=O Stretching cm^{-1}	Aromatic CH Stretching cm^{-1}	Aliphatic CH Stretching cm^{-1}	Aromatic ring Stretching cm^{-1}
3a	1602.85	1651.07	3051.39	2953.02	813.36, 750.31, 706.96
3b	1593.20	1660.71	3059.10	2906.73	752.24, 815.83
3c	1597.06	1654.92	3051.39	2991.59, 2953.02	815.83, 759.95, 746.45
3d	1597.06	1664.57	3059.10	2927.94	819.75, 756.10, 705.95
3e	1600.92	1660.71	3055.24	2924.59	813.96, 752.24
3f	1600.92	1651.07	3051.39	-	815.89, 750.31, 709.80, 680.87

The IR spectra of the compounds (**5a-5f**) revealed a sharp strong absorption band at 3300-3400 cm^{-1} that can be assigned with the presence of NH group and aromatic CH asymmetric and symmetric stretching vibration in the structure of ethyl carboxylates around 3100 cm^{-1}. The aliphatic CH group showed a sharp absorption band around at 2900 cm^{-1} and another sharp strong absorption band was noticed at around 1560 cm^{-1} for C=N group and

the stretching frequency for C-N group obtained around 1350 cm^{-1}. The band near 1730 cm^{-1} for ester C=O group. The IR spectrum values of compounds (**5a-5f**) are shown in Table 4.

Table 3. The IR spectrum values of compounds **4a-4f**

Compound	NH Stretching cm^{-1}	C=C Stretching cm^{-1}	C=N Stretching cm^{-1}	Aromatic Stretching cm^{-1}	C-N Stretching cm^{-1}	Aromatic ring Stretching cm^{-1}
4a	3329.14	1637.58	1554.63	3067.17, 3197.96	1357.83	756.10, 684.73
4b	3327.21	1643.35	1562.34	3042.60, 3162.50	1365.60	754.17, 676.24
4c	3319.49	1645.28	1560.41, 1533.41	3041.74, 3172.90	1350.17	796.60, 773.46, 642.80
4d	3302.15	1625.99	1582.34, 1533.41	3061.39, 3182.55	1350.17	773.46, 750.31
4e	3388.93	1620.92	1531.48	3176.76	1348.24	771.53, 678.04
4f	3300.20	1681.93	1534.41	3045.60, 3182.55	1348.24	773.46, 678.94

Table 4. The IR spectrum values of compounds **5a-5f**

Compound	NH cm^{-1}	Ester C=O cm^{-1}	C-H cm^{-1}	C=N cm^{-1}	C-N cm^{-1}	Aliphatic CH cm^{-1}	Aromatic CH cm^{-1}	Aromatic ring stretching cm^{-1}
5a	3334.92	1735.93	1635.64	1556.55	1348.24	2860.43, 2924.09	3047.53,3199.91	827.46, 759.95, 694.37
5b	3327.21	1739.79	1643.35	1564.27	1367.53	2852.72, 2920.23	3056.16,3182.90	754.17, 806.25
5c	3435.22	1734.51	1648.84	1514.12	1342.06	2843.61, 2910.17	3167.82	773.11
5d	3442.94	1735.16	1653.27	1560.41	1384.89	2838.90, 2917.30	3149.71	794.67
5e	3394.72	1734.83	1604.77	1552.40	1396.46	2827.45, 2908.31	3125.49	775.35
5f	3307.92	1732.67	1622.13	1562.34	1354.03	2819.93, 2903.63	3186.40	794.67

*The ^{1}H NMR spectrum of compound **4e***

In the ^{1}H NMR of the compound **4e** (Figure 2) shows that the signal at 5.3 ppm is due to the presence of NH_2 proton of pyrimidine moiety. The signal at 7.0 ppm is attributed to H5 proton of pyrimidine moiety. The aromatic protons appeared in the range of 8.7 to 7.3 ppm.

*The ^{13}C NMR spectrum of compound **4e***

In the ^{13}C NMR of the compound **4e**, (Figure 3) the ^{13}C resonance at 166.34 ppm is due to the presence of C-2 carbon of pyrimidine moiety. The ^{13}C resonance at 163.66 ppm is due to the presence of C-4 carbon of pyrimidine moiety. The ^{13}C resonance at 104.60 ppm is due to the presence of C-5 carbon of pyrimidine moiety. The ^{13}C resonance at 166.10 ppm is attributed to C-6 carbon of pyrimidine moiety. The resonance at 137.78 ppm is assigned to C-4^{1} carbon of

phenyl ring. The aromatic carbons are appeared in the range of 128.95 ppm to 124.12 ppm. The remaining ^{13}C signals at 130.52, 133.25, 134.9 and 134.45 ppm are ipso carbons.

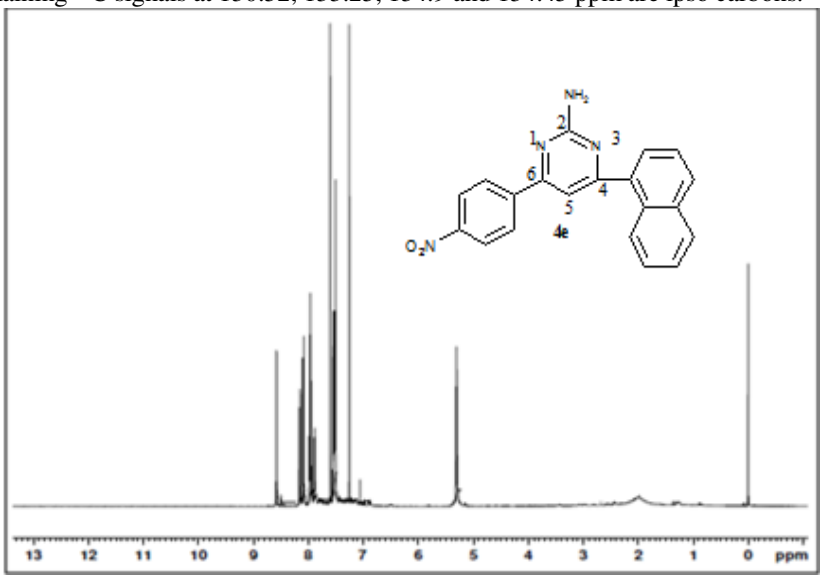


Figure 2. 1H NMR spectrum of compound **4e**

Figure 3. ^{13}C NMR spectrum of compound **4e**

*The ^{1}H NMR spectrum of compound **5e***

^{1}H NMR spectrum of compounds **5e** (Figure 4) shows that the signal at 2.44 ppm is assigned to NH proton of pyridine moiety. The triplet at 1.25 ppm (J=10 Hz) is assigned to the ester methyl protons. The signal at 5.49 ppm is due to the presence of ester methylene protons. The signal at 5.35 ppm is assigned to methylene proton attached with the NH (imine) group. The aromatic naphthalene protons are appeared multiplet in the range of 7.49 to 8.16 ppm.

*The ^{13}C NMR spectrum of compound **5e***

^{13}C NMR spectrum of compound **5e** (Figure 5) shows that the ^{13}C resonance at 166.37 ppm is assigned to C-2 carbon of pyrimidine ring. The ^{13}C resonance at 163.6 ppm is assigned to

C-4 carbon of pyrimidine ring. The ^{13}C resonance at 104.65 ppm is due to the presence of C-5 carbon of pyrimidine ring. The ^{13}C resonance at 166.13 ppm is assigned to C-6 carbon of pyrimidine ring. The ^{13}C resonance at 56.02 ppm is due to the presence of ester methylene carbon. The ^{13}C resonance at 31.93 ppm is assigned to methylene carbon attached with NH group. The ^{13}C resonance at 169.0 ppm is assigned to ester carbonyl carbon. The aromatic carbons appeared in the range of 128.95 to 124.22 ppm. The remaining ^{13}C signals 130.51, 133.26, 134.47, 134.97 ppm are ipso carbons.

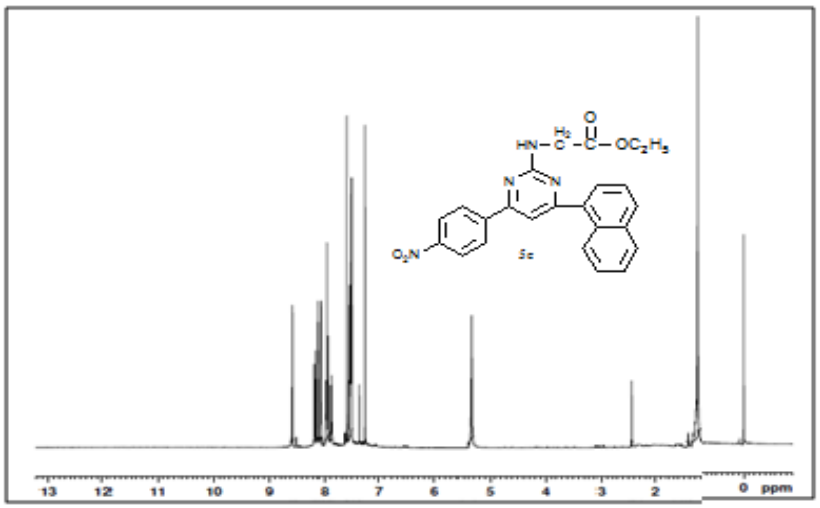


Figure 4. ^{1}H NMR spectrum of compound **5e**

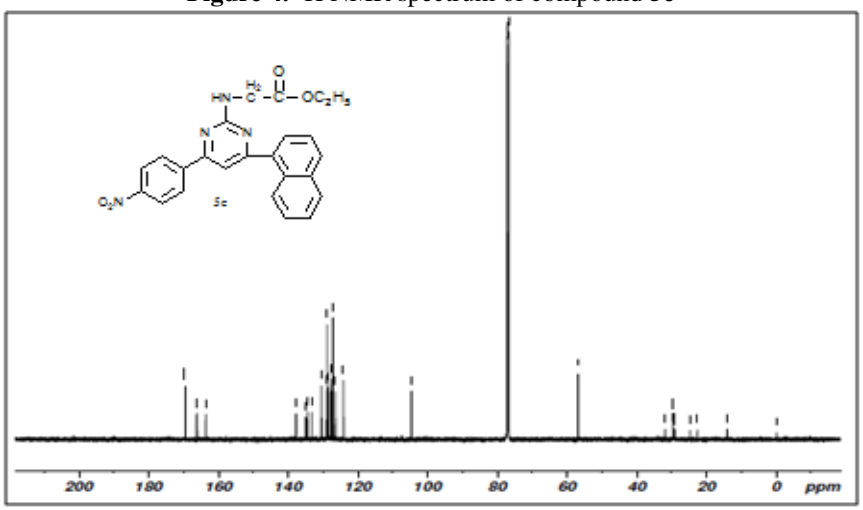


Figure 5. ^{13}C NMR spectrum of compound **5e**

Antimicrobial activity

All of our synthesised compounds (**5a-5f**) were tested for antimicrobial activity against the three test organisms are *Staphylococcus epidermidis* as an example of gram positive, *Pseudomonas aeruginosa* as an example of gram negative and a fungal organism of *Candida albicans*. Here ciprofloxacin used as a standard drugs. The agar disk diffusion method was applied for the

determination of inhibition zone (mm in diameter). From the result of antimicrobial activity of the synthesized compound, the electron donating methoxy substituted phenyl ring shows better zone of inhibition against the bacterial strain *Staphylococcus epidermidis*. The electron withdrawing chloro substituted phenyl ring shows good zone of inhibition against the bacterial strain *Pseudomonas aeruginosa* and the fungal strain *Candida albicans*. The results of antimicrobial activities of other synthesized compounds are shows in the below Table 5.

Table 5. Anti-microbial activity of the synthesized compounds (**5a-5f**)

Sample	Zone of Inhibition (mm in diameter)											
	Anti-bacterial								Anti-fungal			
	Staphylococcus epidermidis				*Pseudomonas aeruginosa*				*Candida albicans*			
	2.5 µL	5.0 µL	7.5 µL	10 µL	2.5 µL	5.0 µL	7.5 µL	10 µL	2.5 µL	5.0 µL	7.5 µL	10 µL
5a (H)	6	9	10	11	7	9	11	13	6	8	9	11
5b (CH_3)	6	10	11	13	8	10	12	13	6	9	11	13
5c (OCH_3)	8	9	11	**14**	5	7	12	15	8	11	13	14
5d (Cl)	-	7	10	12	-	12	13	**19**	-	12	13	**16**
5e (NO_2)	8	10	12	13	10	11	14	16	9	10	11	13
5f (Br)	7	9	10	12	9	11	13	17	7	9	10	12

Conclusion

The titled compounds were synthesized by esterification reactions. The synthesized compounds were characterized by using IR, ^{1}H NMR and ^{13}C NMR spectrum. Spectral and chemical analysis supported to identify the expected structural formula of the compounds. These compounds were subjected to antimicrobial activity. From the results, the electron withdrawing chloro substituted compound have an excellent inhibition against the *Pseudomonas aeruginosa* and *Candida albicans* and the electron donating methoxy substituent have a greater inhibition against the *Staphylococcus epidermidis*.

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