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Synthesis, Characterization And Antimicrobial Screening Of Novel Fused Heterocyclic Compounds

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Abstract

*The 2-(2-bromo-1-(naphthalen-2-yl)ethylidene)malononitrile **(2)** synthesised by the reaction between 1-(naphthalen-2-yl)ethanone **(1)** with malononitrile. The compound **(2)** on reaction with substituted amines **(3a-f)** gives 2-amino-4-(naphthalen-2-yl)-1-aryl-1H-pyrrole-3-carbonitrile **(4a-f)**. A series of 2-methyl-5-(naphthalen-2-yl)-7-aryl-3H-pyrrolo [2,3-d] pyrimidin-4(7H)-one derivatives **(5a-f)**, when 2-amino-4-(naphthalen-2-yl)-1-aryl-1H-pyrrole-3-carbonitrile **(4a-f)** react with Ac_2O in presence of pyridine. Synthesized compounds were characterized by IR, mass (MS) and 1H NMR spectra as well as elemental analysis. They were also screened for their in vitro antibacterial activity against Gram positive bacteria (Bacillus Subtilis Staphylococcus aureus, Gram-negative bacteria (Kllebsiella promioe, E.coil).*

Keywords: *Pyrrole, Pyrimidine, Fused heterocyclic compounds, Spectral studies and Antimicrobial activity.*

INTRODUCTION

Nitrogen containing heterocyclic organic compound are most vital compounds because of their pharmaceutical as well as biological properties.[1-4] Pyrrole is one of the most important heterocyclic compounds for their Non-steroidal anti-inflammatory drugs (NSAIDs), Insecticidal, antibacterial, anti-HIV, antifungal and anticancer activities.[5-9] Pyrimidine moiety is also an important class of N-containing heterocyclics compounds. The fused pyrimidine derivatives reported for their diverse range of biological properties as CNS depressant activity, anti-tumor, anticonvulsant agents, antipyretic, analgesic, antibacterial and antifungal[10-16]. Hence, the present researcher thought to synthesis the pyrimidine and pyrrole fused compounds into one merge molecules. The synthesis approach shown in scheme-1.

RESULTS AND DISCUSSIONS

The 2-amino-4-(naphthalen-2-yl)-1-aryl-1H-pyrrole-3-carbonitrile **(4a-f)** were synthesised by reaction with 2-(2-bromo-1-(naphthalen-2-yl)ethylidene)malononitrile **(2)** with substituted amines **(3a-f)**. Its IR spectrum revealed absorption bands due to NH_2, and C≡N groups near 3360-3310 and 2225 cm^{-1}, respectively. The 1H NMR spectrum revealed (CH_3) protons as a singlet signal around 2.35 ppm, singlet at 5.70 ppm assigned to the NH_2 protons, singlet at 7.82 ppm assigned to the NH_2 and multiplet at 7.50–8.22 ppm assigned to the aromatic protons.

Reaction of 2-amino-4-(naphthalen-2-yl)-1-aryl-1H-pyrrole-3-carbonitrile **(4a-f)** react with Ac_2O in presence of pyridine yielded 2-methyl-5-(naphthalen-2-yl)-7-aryl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one derivatives **(5a-f)**.

The IR spectrum of compound (2) showed two bands in the region of 3245, 3135 cm^{-1} are the stretching modes of NH and 1645 for C=N groups. The 1H NMR showed a singlet at 2.42 ppm for CH_3, 8.10 ppm for NH and 7.30-8.05 for aromatic protons.

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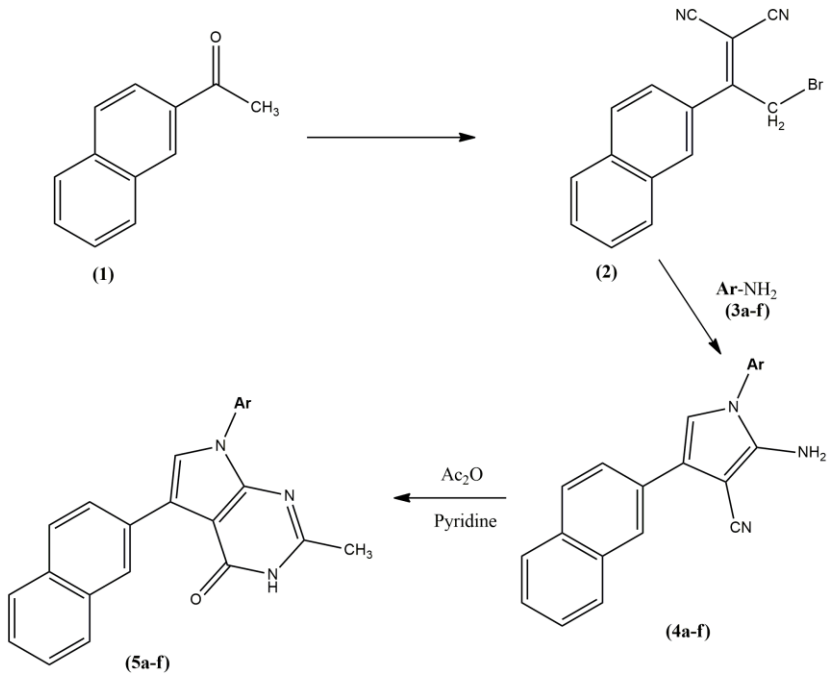


Where **Ar**= C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4,

4-FC_6H_4, 2,4-$Cl_2C_6H_3$, 4-$NO_2C_6H_4$

Scheme-1 synthesis approach

Table 1. Physical and Analytical Data of the Compounds synthesized (4a-f)

Compd.	Molecular formula (Mol. wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%X (X= Cl, Br, F)	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	$C_{21}H_{15}N_3$ (309)	76	275-276	81.53	81.5	4.89	4.8	13.58	13.5	-	-
4b	$C_{21}H_{14}N_3Cl$ (343.5)	73	261-262	73.36	73.3	4.10	4.0	12.22	12.2	10.31	10.3
4c	$C_{21}H_{14}N_3Br$ (388)	70	267-268	64.96	64.9	3.63	3.6	10.82	10.8	20.58	20.5
4d	$C_{21}H_{14}N_3F$ (327)	75	270-271	77.05	77.0	4.31	4.3	12.84	12.8	5.80	5.7
4e	$C_{21}H_{13}N_3Cl_2$ (378)	70	270-272	66.68	66.6	3.46	3.4	11.11	11.1	18.75	18.7
4f	$C_{21}H_{14}N_4O_2$ (354)	73	282-283	71.18	71.1	3.98	3.9	15.81	15.8	-	-

* Uncorrected LC-MS data of 4a-310.5,4c-389.3

Table-2: Analytical Data and Elemental Analysis of Compounds (5a-f)

Compd.	Molecular formula (Mol. wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%X (X= Cl, Br, F)	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	$C_{23}H_{17}N_3O$ (351)	72	237-238	78.61	78.6	4.88	4.8	11.96	11.9	-	-
5b	$C_{23}H_{16}N_3OCl$ (385.5)	69	232-233	71.59	71.5	4.18	4.1	10.89	10.8	9.19	9.1
5c	$C_{23}H_{16}N_3OBr$ (430)	67	229-230	64.20	64.1	3.75	3.7	9.77	9.7	18.57	18.5
5d	$C_{23}H_{16}N_3OF$ (369)	64	245-246	74.78	74.7	4.37	4.3	11.38	11.3	5.14	5.1
5e	$C_{23}H_{15}N_3OCl_2$ (420)	66	218-219	65.73	65.7	3.60	3.5	10.00	10.0	16.87	16.8
5f	$C_{23}H_{16}N_4O_3$ (396)	63	227-228	69.69	69.6	4.07	4.0	14.13	14.1	-	-

* Uncorrected LC-MS data of 5a-352.8,5c-432.1

All the elemental and spectral features suggest that the data are consistent with the predicted structure shown in Scheme-1. The LC-MS of selected compounds shows the peak of M^+ ion which is consistent of their molecular weight. All these facts confirm the structures (4a-f) and (5a-f).

The examination of antibacterial activity data reveals that all compounds toxic against microbes and the compounds **4e** and **5e** found more active against the gram-positive and gram-negative bacteria.

EXPERIMENTAL

1-(naphthalen-2-yl)ethanone was procured from Sigma Aldrich. All other reagents were used laboratory grade.
The IR spectra of all compounds were taken in KBr pellets on a Nicolet 400D spectrometer. Proton NMR spectra were recorded on a Bruker (400 MHz) spectrometer. Deutorated DMSO was used as a solvent. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. All the compounds were checked for their purity by TLC.
The antibacterial activities of both the series of compounds were studied against gram +Ve and –Ve bacteria shown in

Table-1. The activity was measured at a conc, 50µg/ml by agar-cup plate method.[17] Similar conditions using tetracycline as a control was used standard for comparison. The percentage area of inhibition of zone measured. The % age inhibition of growth of bacteria by the compounds is shown in Table-2. [18]

Synthesis of 2-(2-bromo-1-(naphthalen-2-yl)ethylidene)malononitrile (2)
In dry and freshly distilled benzene (50 mL) add 1-(naphthalen-2-yl)ethanone **(1)** (0.02 mol) , NH_4OAc (0.042 mol) and malononitrile (0.02 mol) stir this reaction mixture well. Then this reaction mixture was refluxed for 5 hrs. After it cooled it to room temperature. Removed the solvent and the residue was diluted with water. The organic layer was extracted with ether (4 x 30 mL). The combined solutions were washed with water (3 x 15 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was taken in 20 mL of CCl_4 solution and a solution of bromine (2.5 mmol) was added dropwise in 10 mL of CCl_4 at room temperature over 25 min. The reaction flask was irradiated with a 500-W sunlamp for 2 hrs. After evaporation of the solvent, the residue was filtered over silica gel (10 g) after eluting with hexane/chloroform (9:1). Removal of the solvent and recrystallisation from hexane/chloroform (4:1) gave 2-(2-bromo-1-(naphthalen-2-yl)ethylidene)malononitrile**(2)**[19]. The yield of the product was 82 % and the product melts at 189-190ºC.For $C_{15}H_9N_2Br$ (297) Calcd.: %C, 60.63; %H,3.05; %N,9.43 and % Br, 26.89.Found: %C, 60.6; %H,3.0; %N,9.4 and % Br, 26.8.IR (KBr) (cm^{-1}): IR(KBr)(cm^{-1}): 3056-3040(-C-H of Ar),2925,2850(C-H Ali.), 2225(-C≡N),1590(C=C) and 775(-C-Br). ^{1}H NMR: 7.50-8.20 (7H,m, Ar-H) and 4.05 (2H,s,CH_2).

Synthesis of 2-amino-4-(naphthalen-2-yl)-1-aryl-1H-pyrrole-3-carbonitrile (4a-f) :
Compounds 2-(2-bromo-1-(naphthalen-2-yl)ethylidene)malononitrile (1.0 mmol) **(2)** was dissolved in 15 mL of freshly distilled THF. To the magnetically stirred solution was added substituted amines (3a-f) (2.0 mmol). Then, the reaction mixture was stirred at room temperature for 15-16 hrs. After the solvent was evaporated under reduced pressure, the crude product was filtered through 30 g of neutral alumina, using ethyl acetate/hexane (2:3) mixture. The solid product which precipitated was collected by filtration, washed with solid product with water, dried and crystallized from ether[19]. The yield of the product, melting point and elemental analysis shown in Table-1. IR(KBr)(cm^{-1}): 3360-3310(-NH_2), 3058-3040(-C-H of Ar), 2225(-C≡N),1080,755(-C-Cl), 1525,1321 (-C-NO_2), 560(-C-Br), 1270(-C-F). ^{1}H NMR: 7.50-8.22 (13H,m, Ar-H) and 7.82 (2H,s,NH_2).

Synthesis of 2-methyl-5-(naphthalen-2-yl)-7-aryl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one derivatives (5a-f)
A solution of 2-amino-4-(naphthalen-2-yl)-1-aryl-1H-pyrrole-3-carbonitrile (4a-f) in glacial acetic acid (30 mL) react with Ac_2O in presence of pyridine was heated under reflux for 10–14 hrs. Then the reaction mixture was cooled and poured into ice cold water, and the separated solid was filtered, washed with water, dried, and recrystalized from the mixture of DMF/ethanol (1:5).The solid products were filtered off and air dried and crystallized[20].

The structures assigned to 2-methyl-5-(naphthalen-2-yl)-7-aryl-3H-pyrrolo[2,3-d] pyrimidin-4(7H)-one derivatives (5a-f) were supported by the elemental analysis and IR spectra showing an absorption bands(cm^{-1}) at 3245,3135(-NH), 3058-3040(-C-H of Ar), 2925(-C-H of Ali.), 1645(C=N),1080,755(-C-Cl),1525,1321(-C-NO_2), 560(-C-Br), 1270(-C-F). ^{1}H NMR: 7.30-8.05 (13H,m, Ar-H), 2.42(3H,s,CH_3) and 8.10 (1H,s,NH).

Table-3: Antibacterial Activity of Compounds (4a-f)

Compounds	Gram +Ve		Gram –Ve	
		Staphylococcus aureus	*Klebsiella promioe*	*E.coli*
4a	10	08	09	10
4b	15	13	12	15
4c	11	12	10	12
4d	13	11	11	14
4e	16	14	13	16
4f	15	12	11	14
Tetracycline	20	19	18	22

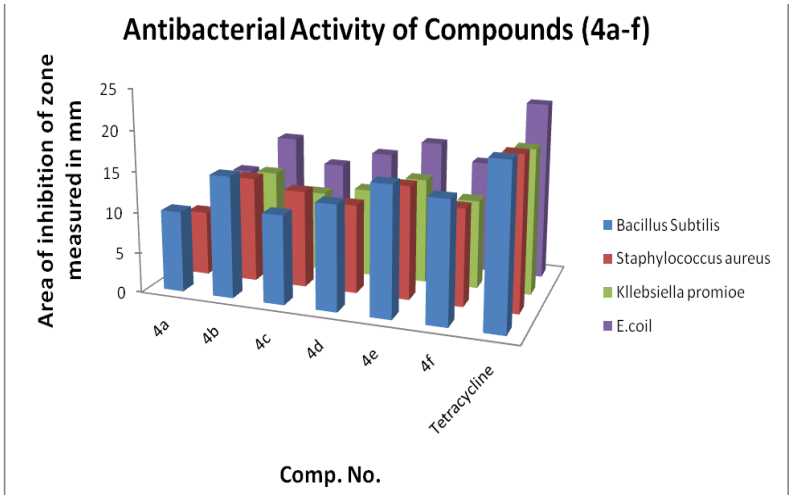
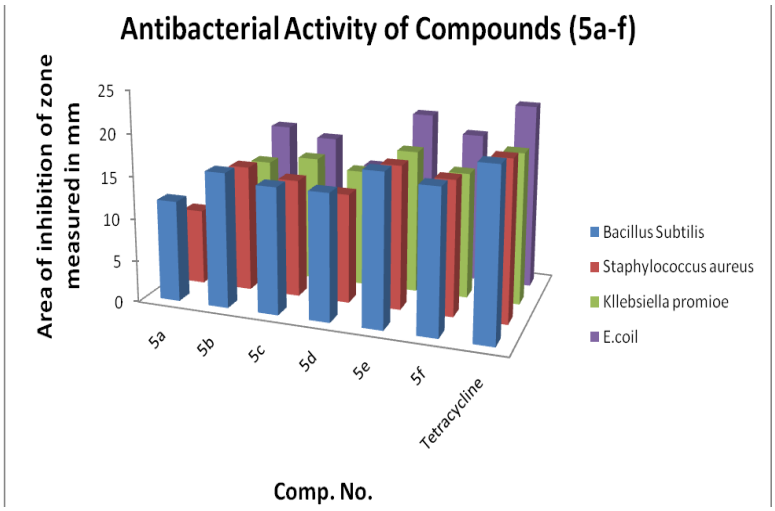


Table-4: Antibacterial Activity of Compounds (5a-f)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
5a	12	09	11	11
5b	16	15	14	17
5c	15	14	15	16
5d	15	13	14	13
5e	18	17	17	20
5f	17	16	15	18
Tetracycline	20	19	18	22



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