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Synthesis and Pharmacological activities of 2-Substituted-3-Hydro/Aryl-3, 4-Dihydro-4-Oxo-Naphtho[2,1-B] Furo [3,2-D] Pyrimidines.

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Abstract

The desired pyrimidines were prepared by using ethyl 3-amiononaphtho [2,1-b] furan-2-carboxylatye **1**. It was treated with various acid chlorides/anhydrides to obtain corresponding acyl derivatives **2a-f**, which were then hydrolyzed to get respective acids **3a-f**. The 2-substituted-4H-naphtho[2,1-b] furo-m-oxazin-4-ones **4a-f,** were synthesized by cyclode hydration of acids **3a-f** by using acetic anhydride. The compounds **4 a-f** on nucleophilic substitution reaction with aliphatic and aromatic amines afforded 2-substituted-3-hydro/aryl-3,4-dihyro-4-oxo-naphtho[2,1-b] furo[3,2-d] pyrimidines **5a-f** and **6a-f** respectively. The structures of newly synthesized compounds were established by analytical and spectral studies. Evaluation of antibacterial and antifungal activity of the synthesized compounds was carried out by agar well diffusion method, antioxidant activity by DPPH method. Encouraging results were obtained.

Keywords
Naphtho furans, naphtho furo pyrimidines, antibacterial activity, antifungal activity, antioxidant activity.

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INTRODUCTION:

Pyrimidine is an important ring system present in the basic nucleus in DNA and RNA (1) antibiotics, antimalarials, anticancer and anti-inflammatory drugs and is associated with diverse biodynamic properties (2-4). Several derivatives of naphtho[2,1-b] furan have been synthesized in our laboratory and are found to possess significant biological and pharmacological activities (5-7). Pyrimidine derivatives show very good antimicrobial and antioxidant activity (8-9). The novel pyrido[2,3-d] pyrimidine derivatives exhibit antiviral and cytotoxic properties (10). Many of the naphofuran derivatives, synthesized in our laboratory have been shown to exhibit diverse biological and pharmacological properties (11-16). Hence, it was contemplated to synthesize pyrimidine derivatives encompassing naphthofuran moiety and evaluate them for antimicrobial and antioxidant activities.

MATERIALS AND METHODS:

Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded in KBr on Perkin Elmer and Nicolet spectrometers. NMR spectra were recorded on AMX and Brucker 400 MHz using DMSO or $CDCl_3$ as solvent and TMS as an internal standard [chemical shifts are given in δ in (ppm) values] and mass spectrum on Brucker apex-11 mass spectrophotometer at 70 eV. The compounds were checked for their purity by TLC silica gel G plates using ethyl acetate-petroleum ether (v/v) by varying polarity and the spots located by iodine vapor.

Synthesis of ethyl 3-acetamidonaphtho[2,1-b] furan-2-carboxylates (2 a-c)

Ethyl 3-aminonaphtho[2,1-b] furan-2-carboxylate **1** (2.55 g, 0.01 mol) was treated with acetic anhydride (4 ml) and then warmed on water bath for 30 min. The reaction mixture on decomposition with ice water gave **2a** as colorless solid. It was recrystallized from ethanol. The dry material (53.44% yield) melted at 93°C.

Similarly compounds **2 b-c** were synthesized using propionic anhydride and succinic anhydride.

Synthesis of ethyl 3-benzamidonaphtho[2,1-b] furan – 2-carboxylates (2 d-f).

Ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate **1** (2.55 g, 0.01 mol) was suspended in 2N aq. sodium hydroxide (25 ml) and then treated with benzoyl chloride (7.5 ml) in portions while shaking vigorously. After shaking for 30 minutes, the reaction mixture was poured to ice cold water. The product **2d** thus obtained was filtered, washed with water and recrystallized from ethanol.

Similarly compounds **2 e-f** were synthesized using appropriately substituted acid chlorides.

Synthesis of 3- substituted aminonaphtho[2,1-b] furan -2-carboxylic acids (3 a-f).

The compound **2a** (2.97g, 0.01mol) was dissolved in ethanol (10ml) by warming and then treated with a solution of ethanolic potash (1.25 g, in 12 ml ethanol) and the reaction mixture was just boiled for 2 min. It was diluted with cold water which on acidification with dilute hydrochloric acid liberated the carboxylic acid 3**a** as colorless solid. This was filtered, washed with water and recrystallized from ethanol. The dry material (72.22% yield) melted at 116°C.

Similarly the compounds **3 b-f** were synthesized from the compounds **2 b-f**.

Synthesis of 2-substituted -4-H-naphtho[2,1-b] furo-m-oxazin-4-ones (4 a-f).

The compound **3a** (2.69g 0.01 mol) was heated under reflux in acetic anhydride (8 ml) for about an hour. Excess of acetic anhydride was distilled off under reduced pressure. The residual product was treated with petroleum ether and crystalline solid of **4a** thus obtained was collected and recrystallized from ethanol. The dry material (38.12% yield) melted at 102°C.

Similarly the compounds **4 b-f** were synthesized from the compounds **3 b-f**.

Synthesis of 2-substituted-3-hydro-3,4-dihydro-4-oxo-naphtho[2,1-b]furo[3,2-d] pyrimidines(5 a-f).

The compound **4a** (2.51g, 0.01 mol) was suspended in liquor ammonia (10 ml) and heated on water bath for about one hour. An aqueous solution of sodium hydroxide (10%, 5 ml) was then added refluxed for further 10 minutes. The reaction product was filtered and the clear filtrate when acidified with acetic acid gave the pyrimidine **5a** as colourless solid.

Similarly the compounds **5 b-f** were synthesized from **4 b-f.**

Synthesis of 2-substituted-3-aryl-3,4-dihydro-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidines (6a-f).

The compound **4a** (2.51g, 0.01 mol) was suspended in aniline (10 ml) and heated on water bath for about one hour. A solution of 10% aqueous sodium hydroxide (5 ml) was then added and heated further for 10 minutes. The reaction product was filtered and the clear filtrate when acidified with acetic acid gave the pyrimidine **6a** as colourless solid.

Similarly the compounds **6 b-f** were synthesized from **4 b-f**

The sequence of the reactions is depicted in the scheme (Figure 1).

The physical and analytical data of the synthesized compounds is presented in table 1.

Antimicrobial activity:

In vitro Antibacterial activity was determined by agar well diffusion method. Against 24 hr old cultures of *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* using 0.01 g/ml and 0.005 g/ml of Streptomycin as standard. The compounds were tested at the concentration of 0.01 g/ml and 0.005 g/ml in dimethyl sulfoxide for all the organisms. The zone of inhibition was compared with the standard drugs after 24 hr incubation at 37°C. The results of antibacterial activity are presented in table 2.

Similarly antifungal activity was carried out by agar well diffusion method against *Aspergillus Niger, Aspergillus flavus* using 0.01 g/ml of Fluconazole as standard. The compounds were tested at the concentration of 0.005 g/ml in dimethyl sulfoxide for all the organisms. The zone of inhibition was compared with the standard drugs after 48 hr incubation at 25 °C. The results of antifungal activity are presented in table 3.

Antioxidant activity.

DPPH radical scavenging activity

Free radical scavenging activity of the test compounds were determined by DPPH assay method and compared with standard drug ascorbic acid.

Drug stock solutions (0.4 mg/ml) were diluted to final concentration of 50,100,200,400 µg/ml in methanol.2.5 ml of 0.1 mM (3.94 mg in 100 ml) DPPH methanol solution was added to 1 ml of drug solution of different concentration and allowed to react at room temperature. After 30 minutes the absorbance values were measured at 517 nm and converted to percentage antioxidant activity (AA %)

The capability to scavenge the DPPH· radical was calculated using the following equation:

DPPH· Scavenging effect (%) = $[(A_{Control} - A_{Sample} / A_{Control}) \times 100]$

Where in $A_{Control}$ is the initial concentration of the stable DPPH radical without the test compound and A_{Sample} is absorbance of the remaining concentration of DPPH in the presence of samples.

The readings were recorded in table 4. The graphs (Fig 2 & fig 3) were obtained by plotting the % inhibition against concentration in µg/ml. The activity has been expressed in IC_{50} which was calculated from the graphs.

RESULTS AND DISCUSSION:

Ethyl 3-aminonaphtho[2,1-b] furan-2-carboxylate **1** was synthesized by well-established procedure in our laboratory[11-12]. It involved the conversion of 2-naphthol into 2-hydroxy-1-naphthaldehyde through Reimer-Tiemann reaction employing chloroform and sodium hydroxide in presence of ethanol. The aldehyde on treatment with hydroxylamine hydrochloride in ethanol produced oxime, which on subsequent dehydration using acetic anhydride yielded 2-hydroxy-1-naphthnitrile in good yield. The compound on reaction with ethyl chloroacetate under basic condition underwent condensation and Thorpe-Zeigler cyclization in one step resulting in the formation of ethyl 3- aminonaphtho[2,1-b] furan-2-carboxylate **1**.

The amino ester **1** was converted into ethyl-3-acylaminonaphtho[2,1-b] furan-2-carboxylates **(2 a-c)** by treating it with acetic anhydride, propionic anhydride and succinic anhydride respectively. The structure of **2a** i.e. ethyl 3-acetamidonaphtho[2,1-b] furan-2-carboxylate was established by its spectral data. It exhibited strong absorption band at 1705b cm^{-1} and 1685 cm^{-1} due to ester carbonyl group and amide carbonyl groups. ^{1}H NMR spectrum showed a quartet and triplet at δ 3.3 and at δ 2.5 due to $–CH_2$ and $–CH_3$ protons , a singlet at δ 2.4 due to $–CH_3$ protons, a multiplet at δ 7.2-8.1 due to aromatic protons and D_2O exchangeable singlet at δ 12.1 due to –NH proton.

Similarly ethyl 3-benzamidonaphtho[2,1-b] furan-2-carboxylates **(2d-f**) were synthesized by Schotten-Baumann reaction between amino ester **1** and appropriately substituted benzoyl chlorides in presence of aqueous sodium hydroxide. The structure of **2d** i.e. ethyl 3-benzamidonaphtho[2,1-b] furan-2-carboxylate was established by its spectral data. It exhibited strong absorption band at 1737cm^{-1} and 1681 cm^{-1} due to ester carbonyl group and amide carbonyl groups in its IR spectrum. ^{1}H NMR spectrum showed a quartet and triplet at δ 2.8 and at δ 1.2 due to $–CH_2$ and $–CH_3$ protons, a multiplet at δ 7.6-8.4 due to aromatic protons and D_2O exchangeable singlet at δ 12.1 due to –NH proton.

The 3-substituted esters **(2a-f)** were subjected to hydrolysis with ethanolic potassium hydroxide to obtain corresponding acids i.e. 3-substituted naphtho[2,1-b] furan-2-carboxylic acids **(3 a-f).** The IR spectrum of **3a** exhibited two absorption bands at 1676 cm^{-1} and 1625 cm^{-1} corresponding to acid and amide carbonyl groups respectively. Broad absorption bands at 3045 cm^{-1} and 3726 cm^{-1} due to OH and NH stretching frequencies respectively. The ^{1}H NMR spectrum was conspicuous by the absence of quartet and triplet due to ester $–CH_2$-CH_3 protons confirming the hydrolysis. Instead, peaks at δ 11.6 for OH proton and at δ 12.93 for NH proton which were D_2O exchangeable were observed. The aromatic protons as expected appeared as multiplet at δ 7.2-8.1.

The conversion of acids **(3 a-f)** into 2-substituted-4-H-naphtho[2,1-b] furo-m-oxazin-4-ones **(4 a-f)** was accomplished by treating the acids **(3 a-f)** with acetic anhydride where in cyclodehydration occurred very smoothly. The IR spectra of these compounds were conspicuous by the absence of two carbonyl absorption bands showing the absence of carboxylic carbonyl group and amide carbonyl group. Instead they exhibited characteristic absorption band at 1686 cm^{-1} and 1685 cm^{-1} due to carbonyl group of oxazinones of compounds **4d** and **4e** respectively. To obtain an additional evidence for the structures assigned to compounds **4 a- f,** ^{1}H NMR spectrum of **4d** and **4f** were recorded. ^{1}H NMR spectrum of **4d** exhibited multiplet at δ 7.4 – 8.4 and **4f** showed a multiplet at δ 7.2 – 8.3 due to aromatic protons. To confirm the structure ^{13}C NMR spectrum of compound **4d** was recorded.

The conversion of oxazinones **(4 a-f)** into 2-substituted-3-hydro-3,4-dihydro-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidines **(5 a-f)** was accomplished by treating the oxazinones **(4 a-f)** with liquor ammonia. The formation of **5d** and **5e** were supported by its IR

spectrum which showed the Stretching N-H band at 3408.12 and 3394.85 cm^{-1} and carbonyl absorption band at 1740.71 and 1678.83 cm^{-1} respectively. And also in **5e** the aromatic nitro asymmetric band at 1552.72 cm^{-1}. In ^{1} H NMR spectrum of **5d** and **5f** showed aromatic protons appeared as mutiplet at δ 7.28-8.1and δ 7.12-8.12 respectively. Whereas NH proton appeared as gave D_2O exchangeable singlet at δ 11.6 for both **5d** and **5f**. The mass spectrum of **2f** was recorded to obtain further evidence to support the assigned structures. It exhibited molecular ion peak at 348 corresponding to its molecular weight and as expected isotopic peak due to chlorine atom appeared at 349. The ratio of these isotopic peaks was observed as 3:1.

The conversion of oxazinones **(4 a-f)** into 2-substituted-3-aryl-3,4-dihydro-4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimidines (**6 a-f)** was accomplished by treating the oxazinones (4 a-f) with aniline. The formation of **6e** was supported by its IR spectrum which showed the N-H band at 3385.85cm^{-1}, carbonyl absorption band at 1740.71cm^{-1} and the aromatic nitro asymmetric band at 1523.97cm^{-1}. The ^{1}H NMR spectrum of **6d** showed only one signal as the multiplet at δ 7.15-8.15. Similarly ^{1}H NMR spectrum of **6e** showed only a multiplet at δ 7.18-8.37. The downfield shift of aromatic protons was due to the presence of nitro group in the molecule. The ^{1}H NMR spectrum of **6f** exhibited multiplet due to aromatic protons between δ 7.15-8.15. To obtain further support for assigned structures, mass spectrum of **6d** was recorded as a representative example. It showed molecular ion peak at m/z 389 corresponding to its molecular weight. To confirm the structure ^{13} C NMR spectrum of compound **6d** was recorded.

In vitro antibacterial activity of the compounds was carried out by agar well diffusion method using 24 hour old culture of gram positive bacterium *Staphylococcus aureus* and gram negative bacteria *Escherichia coli and Pseudomonas aeruginosa* by agar well diffusion method using Streptomycin as a standard. The compounds **6e** and **6f** exhibited zone of inhibition of **13** and **14** mm at the concentration of 0.01g/ml as compared with standard Streptomycin with zone of inhibition of 16 cm of against *Escherichia coli*. The compounds 6**b** and **6e** exhibited zone of inhibition of 17 and 14 mm at the concentration of 0.01g/ml as compared with standard Streptomycin with zone of inhibition of 20 mm of against *Pseudomonas aeruginosa.* The compounds 5**d, 6b** and **6f** exhibited zone of inhibition of 13, 14 and 14 mm at the concentration of 0.01g/ml as compared with standard Streptomycin with zone of inhibition of 15 mm of against *Staphylococcus aureus.*

In vitro antifungal activity of the compounds was carried out by agar well diffusion method against *Aspergillus Niger, Aspergillus flavus* using Fluconazole as a standard. The compounds **5f, 6a** and **6f** were found to be active against *Aspergillus* Niger and the compounds **5b** and **6f** were found to be active against *Aspergillus flavus.*

The results indicate that presence of halogen in aromatic ring enhanced activity to considerable extent.

All the derivatives of newly synthesized compounds were screened for invitro antioxidant activity by DPPH assay method, and compared with standard drug (ascorbic acid). All the pyrimidine derivatives **5 a-f** exhibited less antioxidant activity. The substituation of hydrogen by phenyl group at the position 3 of pyrimidine ring **6 a-f** enhanced the antioxidant activity to certain extent. However, all the compounds were having more IC_{50} value than the standard drug.

In the series of synthesized compounds, **5f** showed good free radical scavenging activity, **5c, 5e, 5d** and **6c** showed moderate activity, whereas **5a** showed minimum antioxidant activity.

Table 1: Physical characterization data of synthesized compounds

Compound	R	Molecular formula	m.p. ^{0}C	Yield %	Found % (calculated)		
					C	H	N
5a	CH_3	$C_{15}H_{10}O_2N_2$	123	44.13	71.99 (71.92)	4.03 (3.99)	11.19 (11.18)
5b	C_2H_5	$C_{16}H_{12}O_2N_2$	135	45.62	72.72 (72.72)	4.58 (4.5)	10.60 (10.60)
5c	CH_2CH_2COOH	$C_{17}H_{12}O_4N_2$	137	49.12	66.23 (66.23)	3.92 (3.8)	9.09 (9.09)
5d	C_6H_5	$C_{20}H_{12}O_2N_2$	171	59.73	76.91 (76.92)	3.87 (3.8)	8.97 (9.09)
5e	4-$NO_2C_6H_4$	$C_{20}H_{11}O_4N_3$	219	65.21	67.49 (67.22)	3.00 (3.08)	11.91 (11.76)
5f	4-Cl C_6H_4	$C_{20}H_{11}O_2N_2Cl$	232	69.13	70.49	3.01	8.96

					(69.26)	(3.17)	(8.08)
6a	CH_3	$C_{21}H_{14}O_2N_2$	142	46.12	77.29 (77.30)	4.32 (4.29)	8.58 (9.81)
6b	C_2H_5	$C_{22}H_{16}O_2N_2$	157	46.18	77.63 (77.64)	4.74 (4.70)	8.23 (8.23)
6c	CH_2CH_2COOH	$C_{23}H_{16}O_4N_2$	172	48.13	71.86 (71.87)	4.20 (4.16)	7.28 (7.29)
6d	C_6H_5	$C_{26}H_{16}O_2N_2$	245	57.12	80.40 (80.41)	4015 (4.12)	7021 (7.21)
6e	4-$NO_2C_6H_4$	$C_{26}H_{15}O_4N_3$	256	68.29	71.85 (72.05)	3.29 (3.46)	9.41 (9.69)
6f	4-Cl C_6H_4	$C_{26}H_{15}O_2N_2Cl$	258	72.12	73.59 (73.84)	3.61 (3.55)	6.52 (6.6)

Table 2: Antibacterial activity of the synthesized compounds.

Compound	Zone of Inhibition in mm					
	E.C		P.A		S.A	
	a=0.01 g/ml	b=0.005 g/ml	a=0.01 g/ml	b=0.005 g/ml	a=0.01 g/ml	b=0.005 g/ml
Standard	16	10	20	12	15	11
Distilled water	Nil	Nil	Nil	Nil	Nil	Nil
DMSO	Nil	Nil	Nil	Nil	Nil	Nil
5a	6	5	5	4	5	6
5b	7	6	8	6	8	7
5c	11	10	7	5	8	7
5d	10	10	9	7	13	10
5e	6	4	8	7	8	7
5f	6	5	8	8	11	10
6a	7	6	7	6	11	9
6b	12	11	17	16	14	12
6c	5	6	7	6	10	8
6d	9	7	8	7	12	10
6e	13	11	14	12	11	10
6f	14	13	8	7	14	13

E.C: *Escherichia coli*, P.A: *Pseudomonas aeruginosa*, S.A: *Staphylococcus aureus.*

Table 3: Antifungal activity of the synthesized compounds.

Compound	Zone of Inhibition in mm			
	A.N		A.F	
	a=0.01 g/ml	b=0.005 g/ml	a=0.01 g/ml	b=0.005 g/ml
Standard	13	11		
Distilled water	Nil	Nil	Nil	Nil
DMSO	Nil	Nil	Nil	Nil
5a	10	8	7	6
5b	8	8	12	11
5c	6	5	8	7
5d	10	9	6	5
5e	6	5	6	5
5f	11	10	7	6
6a	12	11	6	5
6b	6	5	9	7
6c	6	6	7	6
6d	7	6	8	6
6e	7	6	9	6
6f	12	10	13	11

A.N: *Aspergillus Niger*, A.F: *Aspergillus flavus*

Table 4: Quantitative screening of antioxidant activity DPPH assay method.

Compound	Percentage of scavenging activity				IC_{50}
	50µg/ml	100µg/ml	200µg/ml	400µg/ml	µg/ml
Standard	48.37	60.21	76.28	97.74.	57.35
5a	19.20	30.75	41.16	50.16	395.1
5b	35.65	48.70	57.68	68.74	113.7
5c	46.44	58.85	66.15	75.86	68.02
5d	40.17	51.29	64.15	71.14	93.66
5e	43.93	54.89	66.60	70.68	77.56
5f	44.96	58.31	69.56	73.23	64.53
6a	22.18	35.94	48.00	54.25	267.1
6b	33.06	39.11	49.22	59.11	215.4
6c	40.32	52.19	59.89	69.32	92.23
6d	33.64	45.26	52.07	57.01	172.5
6e	32.16	41.98	49.63	54.72	230.1
6f	32.42	42.75	50.32	53.55	214.12

Reaction Scheme

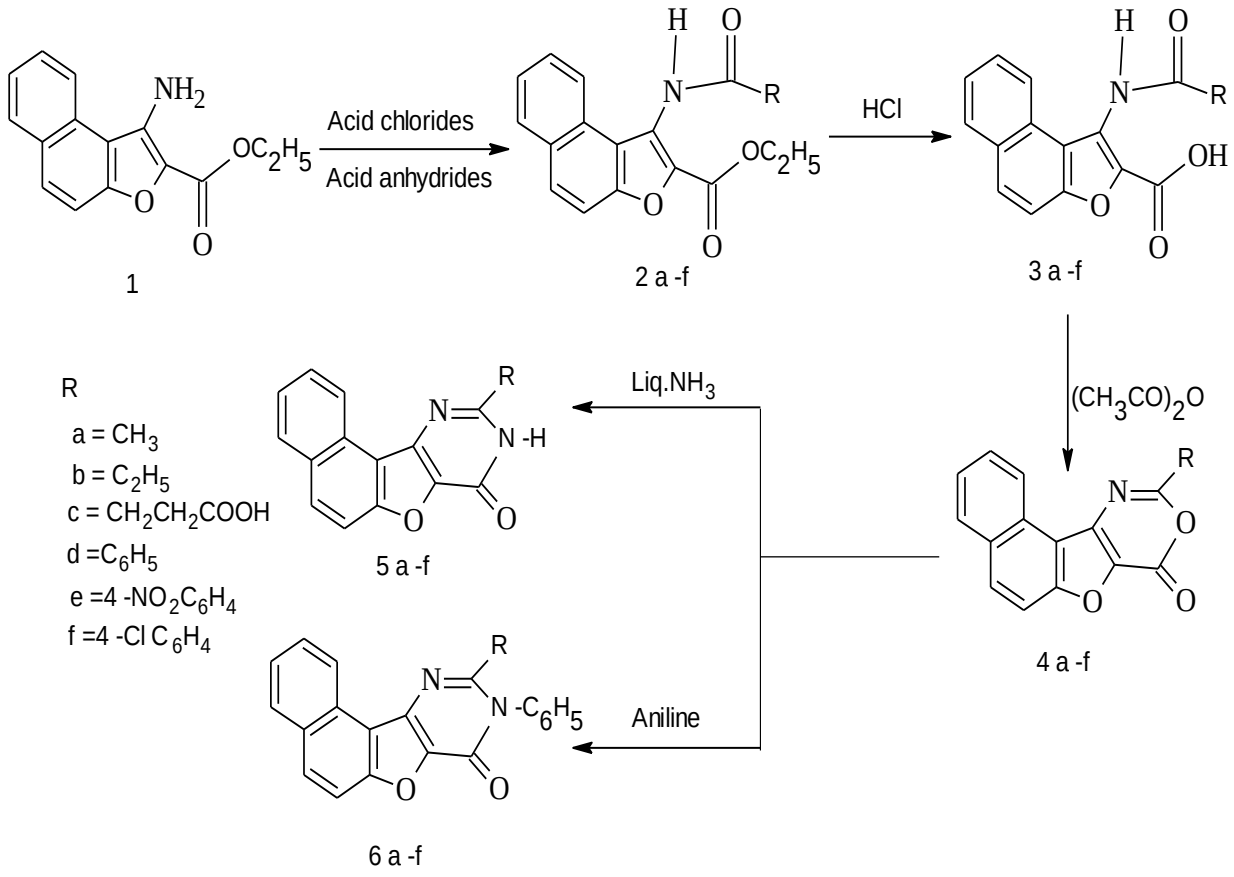

Figure 1: Quantitative screening of Antioxidant activity by DPPH method.

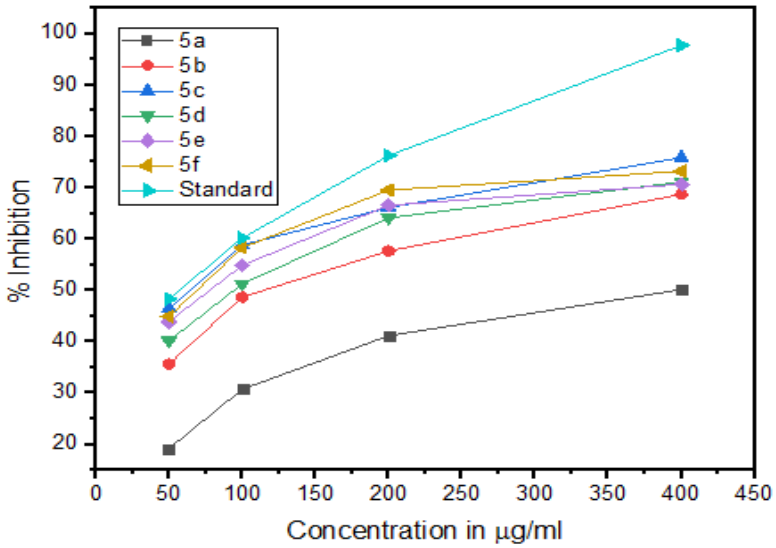

Figure 2

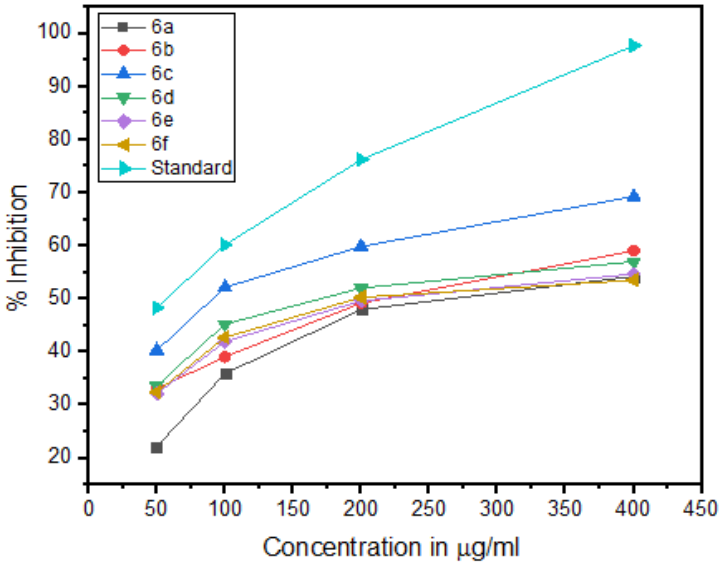

Figure 3

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