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Synthesis Characterization and Antimicrobial studies of some Novel Sulphonamides containing Substituted Naphthofuroyl group

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Abstract

Prompted by the varied biological activities of sulphonamides, and Naphthfurans, a series of sulphonamides (5a-f) derived from naphthofurans were prepare by treating sulphonamides (4a-b) with naphofuroic acids (3a-c) employing $POCl_3$ heating for 1hr. at 60-70^{0}C. The structures of these novel compound were comfirmed on the basis of elemental analysis and spectral data. All the title compound were screened for their antimicrobial activites. The screening data indicated that testing compound were found be less active than the standard drug.

Keywords: Naphtho[2,1] furan, sulphonamides, naphthofuroic acids, antifungal and antibacterial activities.

Introduction

Naphthofurans possess a broad range of biological activities that are constituents of important natural products[1-7]. Sulfonamides are drugs commonly used to treat infectious diseases. Their development leads to a medical revelation in drug treatments[8-10]. Sulfonamides exhibit broad range of biological activities[11]. Several sulfonamides are used in therapy such as celecoxib, nimesulide, delavirdine, acetazolamide, methazolamide, furosemide, ethoxzolamide, dichlorphenamide, dorzolamide, brinzolamide, sulpiride, sotalol, tolbutamide, chlorpropamide, tolazamide, acetohexamide, glipizide, gliburide, glymidine, zonisamide, thiothixene and famotidine. So far, modifications of the sulfonamides have proven highly effective and modifications that have been made so far do not exhaust the possible changes that can be made to improve potency and efficacy of these sulfonamides. The present review highlights the recently synthesized sulfonamides possessing important potential biological activities. It would be interesting to see whether new sulphonamide derivatives can be utilized as potent therapeutic agents in future.

Sulfonamides are compounds constituting diverse medicinal applications, widely used as antimicrobial[12-13], anticancer[14], antiinflammatory[15] and antivi-ral agents as well as HIV protease inhibi-tors[16]. Sulfonamide is well recognized as an antimetabolite[17]. It has a similar structure to *p*-aminobenzoic acid (PABA), which is an essential compound for the synthesis of tetrahydrofolate in bacteria[17].

In view of the various biological activities of heterocyclic compounds[18-25], sulphonamides and naphthofurans and it was contemplated to synthesize various novel sulphonamides carrying naphthofuryl ring and to study their antimicrobial activities.

Material and Methods

Ethylnaphtho-[2,1-b]furan-2-carboxylate (2a) was prepared by treating 2-hydroxy-1-naphthaldehyde (1) with ethylchloroacetate in presence of potassium carbonate in dimethylformamide. This compound (2a) was brominated to get compound (2b) and nitrated to get compound (2c). These esters were hydrolyzed in alkaline medium to obtain their respective carboxylic acids (3a, 3b,3c,). The resulting carboxylic acids were then warmed with substituted benzene sulphonamides (4a-b) employing phosphorus oxychloide on a water bath maintained at 40-45 ^{0}C to yield 5-substituted-naphtho[2,1-b] furanoyl-4- substituted sulphonamides (5a-f) . The structures of 5-substituted –naphtho [2,1b] furanoy1-4- substituted sulponamides (5a-f) were confirmed on the basis of elemental analysis and spectral data.

Melting points were determined in open glass capillaries and were found uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin-Elmer Spectrometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz instrument in DMSO-d_6 as solvent and TMS as an internal standard.

Ethyl naphtho-[2,1-b]furan-2-carboxylate 2a: To a solution of 2-hydroxy-1-naphthaldehyde 1 (5.16 g, 0.03 mol) in dry N,N-dimethylformamide (25 ml), ethylchloroacetate (3.66 g, 0.03 mol) and anhydrous potassium carbonate (12.4 g, 0.9 mol) were added and the reaction mixture was refluxed on water bath for 24 h. The reaction mixture was then poured into ice cold water, to obtain the product ethyl naphtho- [2,1- *b*]furan-2-carboxylate 2a as solid, which was collected by filtration, dried and recrystallised from ethanol.

5-Bromo-2-ethylnaphtho-[2,1-b]furan-2-carboxylate 2b: To a solution of 2-ethyl naphthofuran- 2-carboxylate 2a (0.1mol) in glacial acetic acid was added a solution of bromine (0.1mol) in acetic acid (20ml) with stirring during 1h at 10-20^0 C and the stirring was continued for 3h. The reaction mixture was poured into ice-cold water and the solid obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol.

5-Nitro -2-ethyl naphtho- [2,1-b] furan 2-carboxylate 2c: To a solution of 2-ethyl naphthofuran 2-carboxylate 2a (0.1mol) in glacial acetic acid, nitrating mixture was added with stirring during 1h at 10-20^0 C and the stirring was continued for 3h. The reaction mixture was poured into ice-cold water and the solid obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol.

5-Substituted-naphtho[2,1- *b*]furan-2-carboxylic acids (3a-c): 2-Ethyl naphtho[2,1-b]furan 2-carboxylate was dissolved in methanol and mixed with 10% NaOH solution. The mixture was refluxed for 2h. After the completion of the hydrolysis, the reaction mixture was poured into ice cold water and acidified with hydrochloric acid. Solid separated is filtered and recystallised from ethanol. The following naphthofuran-2-carboxylic acids were prepared and mps were recorded.

5-substituted-naphtho[2,1-b]furoyl-4-substituted benzene sulphonamide (5a-f): To an equimolecular mixture of suitable substituted benzene sulphonamide (4 a-b) (10 mmol) and naphthofuroic acid (3a-c) (10mmol), phosphorus oxychloride (2ml, 20 mmol) was added. The resulting solution was refluxed for 1hr. on water bath. The reaction mixture was poured into crushed ice with stirring. The resultant solid was collected, washed with water and dissolved in sodium bicarbonate solution and filtered off. The filtrate was acidified with dilute hydrochloric acid to obtain the solid product (5a-f). These compounds were purified by recrystallisation from ethanol. The characterization data of compounds 5a-f are recorded in table 1.

Results and Discussion

The IR spectra of the title compounds (5a-f) showed characteristic peaks corresponding to both carbonyl and SO_2 stretching frequecies of sulphonamide group. In the IR spectrum of compound (5d), C=O stretching frequency appeared at 1750 cm^{-1} and the symmetric and asymmetric stretching frequencies appeared at 1330 cm^{-1} and 1500 cm-^{1} respectively. The NH stretching frequency of compound (5d) observed at 3300 cm^{-1}.

The ^{1}H NMR (400 M Hz) spectrum of the compound (5d) showed a singlet at δ, 1.74 corresponding to methyl group integrating for three protons and a singlet at δ, 11.63 corresponding to the NH proton of the amide carrying sulphonyl group. The NH proton appeared as downfield signal, since the NH proton is flanked by two strong electron withdrawing groups namely carbonyl and sulphonyl groups. The aromatic protons of the p-tolyl group appeared as two doublets at δ, 8.0 and 8.11 respectively. The remaining six protons of naphthyl group appreared in the region δ, 7.43-7.80.

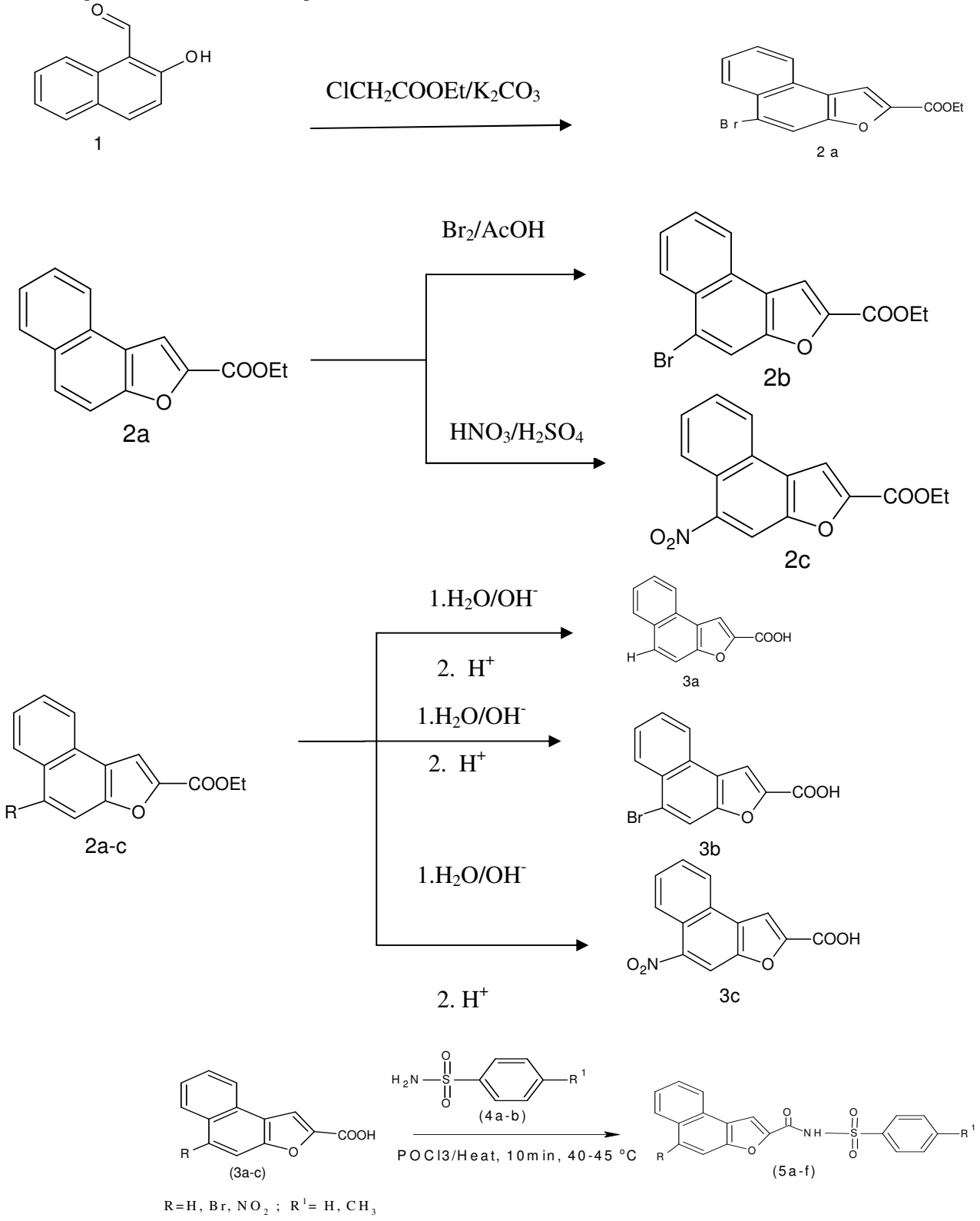
The mass spectrum of compound (5d) showed a molecular ion peak at m/z 444 consistent with its molecular formula $C_{19}H_{12}BrNO_4S$ thus confirming the formation of naphthofuroylsulphonamide.

The physical characterization data of all the compounds has been summarized in table 1

Table-1
Physical characterization data of compounds (3a-c) and (5a-f)

Compd.	R	R^1	Molecular formula	m.p. ^{0}C	Yield (%)	Elemental Analysis(%) Calculated (Found)		
						C	H	N
3a	H	-	$C_{13}H_8O_3$	174	85	73.5(73.2)	3.0(2.98)	-
3b	Br	-	$C_{13}H_7BrO_3$	228	88	53.6(53.22)	2.4(2.33)	-
3c	NO_2	-	$C_{13}H_7NO_5$	>280	75	60.7(60.31)	2.7(2.53)	5.44(5.32)
5a	H	H	$C_{19}H_{13}NO_4S$	223	89	64.95(64.85)	3.7(3.51)	3.98(3.91)
5b	H	CH_3	$C_{20}H_{15}NO_4S$	265	88	65.75(65.68)	4.10(4.04)	3.83(3.74)
5c	Br	H	$C_{19}H_{12}BrNO_4S$	220	86	53.02(52.90)	2.79(2.60)	3.25(3.21)
5d	Br	CH_3	$C_{20}H_{14}BrNO_4S$	231	87	54.05(53.31)	3.15(3.08)	3.15(3.04)
5e	NO_2	H	$C_{19}H_{12}N_2O_6S$	182	83	57.57(57.52)	3.03(2.96)	7.07(6.98)
5f	NO_2	CH_3	$C_{20}H_{14}N_2O_6S$	68	87	58.5(58.32)	3.41(3.23)	6.82(6.79)

The sequence of the reaction is depicted in the scheme



Scheme-1

Antibacterial activity: All the newly synthesized compounds were screened for their *in vitro* antibacterial activities against Gram positive bacteria viz., *Staphyllococcus aureus* and Gram negative bacteria viz., *E.coli* at concentrations of 0.0625 mg, 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg and 2.0 mg. The minimum inhibitory concentrations (MIC values) were determined. Gentamycin was used as the standard drug at concentrations of 25 µg, 50 µg, 100 µg, 200 µg, 400 µg and 800 µg for comparison and the solvent control was kept. The screening data indicated that all the synthesized N-naphthofuroyl sulphonamides showed appreciable antibacterial activity against *E.coli and S.aureus*. The results of antibacterial activity are shown in table 2 and 3.

Antifungal activity: The newly synthesized compounds were also tested for their antifungal activities against *Candida albicans* and *Aspergillus niger* according to tube dilution method at concentrations of 0.0625 mg, 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg and 2.0 mg. Amphotericin was used as the standard drug at concentrations of 25 µg,50 µg, 100 µg, 200 µg, 400 µg and 800 µg for comparison. The minimum inhibitory concentrations (MIC values) were determined. The screening data indicated that all the synthesized N-naphthofuroyl sulphonamides showed appreciable antifungal activity, but it was less than the standard drug. The results of anti microbial activity are shown in table 2 to table 6.

Table-2
Antimicrobial activity screening data at 2 mg concentration of sulphonamides containing substituted napthofuroyl group

	Antibacterial Activity		**Antifungal activity**	
Compound	***Staphyllococcus aureus***	***Escherichia coli***	***A.niger***	***C.albicans***
5a	1.2	1.2	0.5	0.5
5b	1.6	1.3	1.2	0.8
5c	1.2	1.1	0.8	0.9
5d	1.5	1.2	0.9	0.7
5e	1.2	1	0.8	1.3
5f	1.3	1.1	0.8	0

Table-3
Antibacterial activities of the selected samples of sulphonamides containing substituted naphthofuroyl group with zone of inhibition >0.5 cm at different concentrations against *E. Coli*

Samples	**0.0625 mg**	**0.125 mg**	**0.25 mg**	**0.5 mg**	**1.0 mg**	**2.0mg**	**MIC mg**
5a	0	0	0	0.5	1	1.2	0.5
5b	0	0	0	0	0.4	0.9	1
5c	0	0	0	0	0	0.8	2
5d	0.3	0.6	0.7	0.9	1	1.3	0.0625
5e	0	0	0	0	0	0.8	2
5f	0	0	0	0	0	0.9	2
	25 µg	**50 µg**	**100 µg**	**200 µg**	**400 µg**	**800 µg**	**MIC µg**
Gentamycin	1.8	2	2.3	2.6	2.8	3.1	25

Table-4
Antibacterial activities of the selected samples of sulphonamides containing substituted naphthofuroyl group with zone of inhibition >0.5 cm at different concentrations against S. aureus

Samples	**0.0625 mg**	**0.125 mg**	**0.25 mg**	**0.5 mg**	**1.0 mg**	**2.0 mg**	**MIC mg**
5a	0	0	0	0.3	0.9	1	0.5
5b	0.5	0.6	0.7	0.8	1.2	1.4	0.0625
5c	0.2	0.3	0.4	0.5	0.7	1.4	0.0625
5d	0.5	0.7	0.8	0.9	1.1	1.3	0.0625
5e	0	0	0	0	0.2	0.8	1
5f	0	0	0	0	0	0.5	2
	25 µg	**50 µg**	**100 µg**	**200 µg**	**400 µg**	**800 µg**	**MIC µg**
Gentamycin	1.3	1.8	2.1	2.5	2.7	3.4	<25

Table-5
***A*ntifungal activities of the selected samples of sulphonamides containing substituted naphthofuroyl group with zone of inhibition >0.5 cm at different concentrations against A. niger**

Samples	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0mg	MIC mg
5a	0.6	0.7	0.9	1	1.1	1.4	0.0625
5b	0	1	1.1	1.3	1.5	1.6	0.125
5c	0.1	0.6	0.7	0.8	1.4	1.6	0.0625
5d	0.5	0.9	1.2	1.3	1.4	1.8	0.0625
5e	0	0	0	0.7	1	1.7	0.5
	25 µg	**50 µg**	**100 µg**	**200 µg**	**400 µg**	**800 µg**	**MIC µg**
Amphotericin	0	0	0.2	0.3	0.5	0.7	100

Table-6
***A*ntifungal activities of the selected samples of sulphonamides containing substituted naphthofuroyl group with zone of inhibition >0.5 cm at different concentrations against C. albicans**

Samples	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0mg	MIC mg
5a	0.3	0.8	1.1	1.2	1.3	1.4	0.0625
5b	0	0.6	1	1.1	1.2	1.5	0.125
5c	0	0.1	0.2	0.3	1	1.1	0.125
5d	0	0.7	1	0	1.1	1.4	0.125
5e	0	0.6	0.7	0.9	1	2	0.125
5f	0.2	1	1.2	1.3	1.4	1.8	0.0625
	25 µg	**50 µg**	**100 µg**	**200 µg**	**400 µg**	**800 µg**	**MIC µg**
Amphotericin	0	0.2	0.7	0.9	1.3	1.5	50

Conclusion

In the present work we synthesized N-naphthofuroyl sulphonamides **(5a-f)** and evaluated their *in vitro* antibacterial activities against *Staphyllococcus aureus* and *Escherichia coli* and antifungal activities against *Aspergillus niger* and *Candida albicans*. The screening data indicated that all the synthesized N-naphthofuroyl sulphonamides showed appreciable antibacterial and antifungal activities.

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