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Synthesis and Antimicrobial Activity of Newly Azetidinone Derivatives

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ABSTRACT

4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)aniline [1] undergoes facile condensation with various aromatic aldehydes to gave 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)-N-arylideneaniline [2a-g] in excellent yield. Cyclocondensation of compounds [2a-g] with chloro acetyl chloride yields 1-(4-(1H-naphtho [1,8-de][1,2,3]triazin-1-ylsulfonyl)phenyl)-3-chloro-4-arylazetidin-2-one [3a-g]. The structures of these compounds were established on basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)-N-arylideneaniline, azetidinone, antibacterial activity, spectral studies.

INTRODUCTION

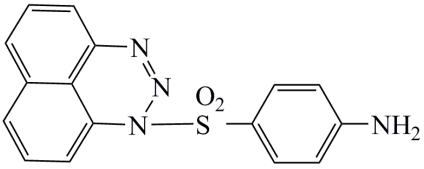
The usage of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side-effects [1]. During the last few decades, considerable attention has been devoted to synthesis of triazole derivatives possessing such comprehensive bioactivities as antibacterial, antifungal [2,3], anti mycobacterial [4], anti-inflammatory [5], analgesic [6], anticancer [7], antihypertensive [8], anticonvulsant [9], antiviral [10], antidepressant [11], anti asthmatic [12], diuretic [13] and hypoglycemic [14] activities. Schiff bases also display biochemical and physiochemical effects.[15-18] Hence, it was thought of interest in merging of both azetidinone and naphthotriazine moieties may enhance the drug activity of compounds up to some extent or might posses some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of naphthotriazine containing an azetidinone moiety. Hence the present communication comprises the synthesis of 1-(4-(1H-naphtho [1,8-de][1,2,3]triazin-1-ylsulfonyl)phenyl)-3-chloro-4-arylazetidin-2-one [3a-g]. The research work is scanned in scheme -1.

MATERIALS AND MATERIALS

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Brucker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Preparation of 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)-N-arylideneaniline [2a-g]

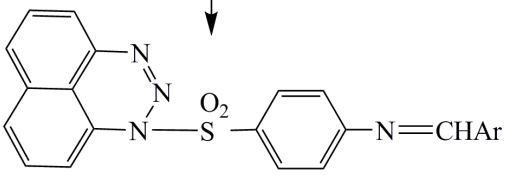
An equimolecular mixture of 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)aniline [1] and aromatic aldehydes (a-h) in ethanol (15ml) was refluxed on a water bath for 2.5 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-1.



4-(1*H*-naphtho[1,8-*de*][1,2,3]triazin-1-ylsulfonyl)aniline

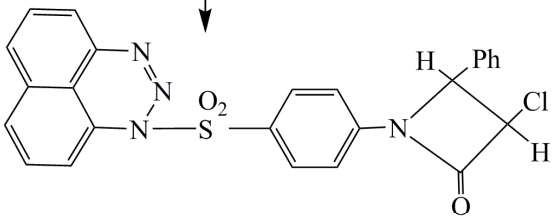
[1]

Ar-CHO**(a-g)**
Ethanol



4-(1*H*-naphtho[1,8-*de*][1,2,3]triazin-1-ylsulfonyl)-*N*-arylideneaniline
[2a-g]

(1) $ClCH_2COCl$
(2) TEA/1,4-Dixane



1-(4-(1*H*-naphtho[1,8-*de*][1,2,3]triazin-1-ylsulfonyl)phenyl)-3-chloro
-4-arylazetidin-2-one**[3a-g]**

Where Ar = (a)-C_6H_5 (b)4-Cl-C_6H_4 (c) 4-Br-C_6H_4
(d) 4-OCH_3-C_6H_4 (e) 2-OH-C_6H_4 (f) 4-OH-C_6H_4
(g) 4-CH_3-C_6H_4

Scheme - 1

Preparation of 1-(4-(1H-naphtho [1,8-de][1,2,3]triazin-1-ylsulfonyl)phenyl)-3-chloro-4-arylazetidin-2-one [3a-g]:

A mixture 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)-N-arylideneaniline[2a-g] (0.002 mole) and triethyl amine (TEA) (0.004 mole) was dissolved in 1,4-dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution chloro acetyl chloride (0.004 mole) was added drop wise within a period of 30 minutes. The reaction mixture was then stirred for an additional 3 hours and left at room temperature for 48 hours. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethyl acetate: 70% benzene as eluent. Recrystallization from ether/n-hexane gave white powered of 1-(4-(1H-naphtho [1,8-de][1,2,3]triazin-1-ylsulfonyl)phenyl)-3-chloro-4-arylazetidin-2-one [3a-g], which was obtained in 60-78% yield. The yields, melting points and other characterization data of these compounds are given in Table-2.

Table: 1 Analytical Data and elemental analysis of compounds [2a-g]

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{23}H_{16}N_4O_2S$ (412)	89	232	66.9	66.97	3.9	3.91	13.5	13.58	7.7	7.77
2b	$C_{23}H_{15}N_4O_2SCl$ (446)	83	237	61.8	61.81	3.3	3.38	12.5	12.54	7.1	7.17
2c	$C_{23}H_{15}N_4O_2SBr$ (491)	79	239	56.2	56.22	3.0	3.08	11.3	11.40	6.5	6.53
2d	$C_{24}H_{18}N_4O_3S$ (442)	82	234	65.1	65.14	4.0	4.10	12.6	12.66	7.2	7.25
2e	$C_{23}H_{16}N_4O_3S$ (428)	82	240	64.4	64.47	3.7	3.76	13.0	13.08	7.4	7.48
2f	$C_{23}H_{16}N_4O_3S$ (428)	83	242	64.4	64.47	3.7	3.76	13.0	13.08	7.4	7.48
2g	$C_{24}H_{18}N_4O_2S$ (426)	81	237	67.5	67.59	4.2	4.25	13.1	13.14	7.5	7.52

Table: 2 Analytical data and elemental analysis of Compounds [3a-g]

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{25}H_{17}N_4O_3SCl$ (488)	89	232	61.3	61.41	3.4	3.50	11.4	11.46	6.5	6.56
3b	$C_{25}H_{16}N_4O_3SCl_2$ (522)	83	237	57.3	57.37	3.0	3.08	10.6	10.70	6.1	6.13
3c	$C_{25}H_{16}N_4O_3SClBr$ (565)	79	239	52.8	52.88	2.8	2.84	9.8	9.87	5.6	5.65
3d	$C_{26}H_{19}N_4O_4SCl$ (518)	82	234	60.1	60.17	3.6	3.69	10.7	10.80	6.1	6.18
3e	$C_{25}H_{17}N_4O_4SCl$ (504)	82	240	59.4	59.47	3.3	3.39	11.0	11.10	6.3	6.35
3f	$C_{25}H_{17}N_4O_4SCl$ (504)	83	242	59.4	59.47	3.3	3.39	11.0	11.10	6.3	6.35
3g	$C_{26}H_{19}N_4O_3SCl$ (502)	81	237	62.0	62.09	3.7	3.81	11.1	11.14	6.3	6.38

BIOLOGICAL SCREENING

Antibacterial activities

Antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ml by agar cup plate method. Methanol system was used as control in this method. Under similar condition using tetracycline as a standard for comparison carried out control experiment. The area of inhibition of zone measured in mm. Compound 3b, 3d and 3f were found more active against the above microbes. Other compounds found to be less or moderate active than tetracycline (Table-3).

Table: 3 Antibacterial Activities of Compounds [3a-g]

Compounds	Gram +Ve		Gram -Ve	
	Bacillus subtilis	*Staphylococcus aureus*	*Klebsiella promioe*	*E.coli*
3a	62	60	57	68
3b	76	65	69	75
3c	67	61	60	61
3d	72	64	71	72
3e	57	60	67	66
3f	76	64	68	72
3g	66	62	64	66
Tetracycline	78	66	85	76

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum, Fusarium oxyporium*. The antifungal activity of all the compounds [3a-g] was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200gm, dextrose 20gm, agar 20gm and water one liter. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^o C for 15 min. at 15atm.pressure. These medium were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\textbf{Percentage of inhibition} = 100(1-Y/X)$$

Where, X = Area of colony in control plate and Y = Area of colony in test plate
The fungicidal activity displayed by various compounds [3a-g] is shown in Table-4.

Table: 4 Antifungal Activities of Compounds [3a-g]

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Aspergillus niger***	***Botrydepladia Thiobromine***	***Fusarium oxyporium***	***Nigrospora Sp.***	***Rhizopus Nigricum***
3a	48	64	65	62	70
3b	65	65	60	67	74
3c	59	62	70	59	61
3d	61	66	68	63	63
3e	57	63	67	60	61
3f	60	72	64	62	63
3g	54	65	60	59	58

RESULTS AND DISCUSSION

It was observed that 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)aniline [1] on condensation with various aromatic aldehydes to yield 4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)-N-arylideneaniline [2a-g].The structures of [2a-g] were confirmed by elemental analysis and IR spectra showing absorption band at 1630-1660cm^{-1}(C=N), 3030-3085 cm^{-1} (C-H of Ar.),2815-2850cm^{-1} (-OCH_3),3400-3580cm^{-1}(-OH). ^{1}H NMR (δ, ppm): 7.30 – 8.20 (m, Ar-H), 8.43-8.80 (s,1H,-N=CH), (2d) 3.90 (s,3H,-OCH_3), (2e),(2f); 4.2(s,1H,-OH), 2g; 2.4 (CH_3). ^{13}C N-MR:156.2-110.6 (Ar-22C), 160.8(-N=CH);(2b):55.5-56.7 (-OCH_3) (2g):21.4 (CH_3). The C, H, N analysis data of all compounds are presented in Table-1.

The cyclo condensation of [2a-g] with chloro acetyl chloride resulted in formation of 1-(4-(1H-naphtho [1,8-de] [1,2,3]triazin-1-ylsulfonyl)phenyl)-3-chloro-4-arylazetidin-2-one [3a-g]. The structures assigned to [3a-g] were supported by the elemental analysis and IR spectra showing absorption bands at 1750-1760 (C=O of monocyclic β-lactam), 3035-3090 cm^{-1} (C-H, of Ar.), 3400-3580 cm^{-1} (-OH), 2820-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR (δ, ppm): 5.0 (d,1H,C_4-H), 5.5(d,1H,C_3-H), 6.9-7.9(m,Ar-H), (3d); 3.9(s,3H), (3e) (3f);11.20(s,1H), (3f);2.4 (s, 3H,CH_3). ^{13}C NMR:143.9-110.1 (Ar-22C), 162.8(-C=O), 68.1, 62.3 (Azitidinone ring),6 (3b):55.5-56.7 (-OCH_3) (3g):21.4 (CH_3). The C, H, N analysis data of all compounds are presented in Table-2.

The examination of data reveals that the elemental contents are consistence with the predicted structure shown in scheme-1.The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS data of selected samples. The LC-MS of samples 3b and 3e give the molecular ion peak (m/z) at 534 and 518 respectively. These values are corresponds to their molecular weight.

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