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An efficient synthesis with antimicrobial screening of N-methyl derivative of 4-(2-bromonaphthalen-6-yl)-6-aryl-6H-1,3-thiazin-2-amines

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ABSTRACT

Biologically active N-Methyl derivative of 4-(2-bromonaphthalen-6-yl)-6-aryl-6H-1,3-thiazin-2-amines have been synthesized by the reaction of N-Methylthiourea with 1-(2-bromonaphthalen-6-yl)-3-arylprop-2-en-1-ones which were obtained from the Claisen-Shimidt reaction of 1-(2-bromonaphthalen-6-yl)ethanone in the presence of base. The structure of the synthesized N-Methyl-1,3-thiazines were determined by using IR and NMR spectral measurements. The antimicrobial activities of the synthesized compounds showed very potent activity against the fungi, Aspergillus nigar and the bacteria, Escherchia coli.

Keywords: Synthesis, bromoacetylnaphthalene, N-Methyl-1,3-thiazin-2-amine, characterization, antimicrobial screening.

INTRODUCTION

The synthesis of heterocyclic compounds containing 1,3-thiazine central core has been the focus of great interest. This is due to the diverse pharmacological activities of 1,3-thiazine with different side chains. Also 1,3-thiazine nucleus is the active core of cephalosporin and cephamycin, which are among the most widely used β-lactum antibiotics [1]. In general heterocycles with more than one hetero atom especially the sulphur and nitrogen with N-C-S linkage are interesting biological agents. The presence of amino group at the second position of 1,3-thiazine moiety are pharmaceutically interesting entities and have used as antifungal [2], antibacterial [3], anti-HIV [4], cannabinoid receptor agonists [5], antioxidant [6], antimycobacterial [7] etc. Bioactive molecules with bromo substitution are very good synthon for biologically active targets [8] and are antimicrobials [9]. Owing to their chemical and biological interest, synthesis of various 2-amino-1,3-thiazine derivatives have been reported in the literature but the N-methyl derivatives of 2-amino-1,3-thiazines with bromo substitution are hitherto unreported and also as part of our continuing study on the synthesis of different 1,3-thiazine derivatives we now report that the title compounds can be conveniently prepared starting from easily available aromatic aldehydes and bromoacetylnaphthalenes. Also assayed their anti microbial activity against some common pathogens viz: *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Aspergillus flavus.*

MATERIALS AND METHODS

All the chemicals were analytical grade and solvents were distilled before use. Melting points of all the synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity

of the compounds were checked by TLC using silica gel G. The IR spectra were recorded on SHIMADZU FT-IR spectrometer using KBr pellet. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker (AMX-400 MHz) using $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ ppm).

Procedure for preparation of 1-(2- bromonaphthalen-6-yl)ethanone (2)
The titled compound was prepared by the acetylation of 2-bromonaphthalene using acetylchloride in nitrobenzene in the presence of anhydrous aluminium chloride [10].

General procedure for preparation of 1-(2-bromonaphthalen-6-yl)-3-aryl prop-2-en-1-ones (3a-g)
Quantitative amounts of substituted aromatic aldehyde (0.02 mol) and 1-(2-bromonaphthalen-6-yl)ethanone (0.02 mol) in ethanol (50 mL),were heated over a water bath while a solution of sodium hydroxide (1.5g in 5mL of water) was added slowly during 15 minutes and the heating was continued for further 15 minutes. The solution was cooled, filtered the product and recrystallised from ethanol.

General procedure for preparation of 4-(2-bromonaphthalen-6-yl)-N-methyl-6-aryl-6H-1,3-thiazin-2-amine (4a-g)
A solution containing 1-(2-bromonaphthalen-6-yl)-3-arylprop-2-en-1-one (0.01mol), N-Methylthiourea (0.01 mol) and KOH (0.02 mol) in ethanol (50 mL) was refluxed for 3-4 hours and the reaction was monitored by TLC. After completion of the reaction, one third of the solvent was removed under reduced pressure, cooled to room temperature, poured to ice cold water and filtered the solid product. The pure N-methylamino-1,3-thiazines were obtained by column chromatographic technique using benzene-ethyl acetate as eluting solvent.

4-(2-bromonaphthalen-6-yl)-N-methyl-6-phenyl-6H-1,3-thiazin-2-amine (4a)
M.F: $C_{21}H_{17}N_2BrS$, Yield: 94%, M.P: 74°C; IR (KBr, cm^{-1}): 3421.53 (NH), 2923.12 (CH_3-Str. in N-CH_3), 1675.33 (C=N), 1523.11 (C=C), 1457.78 (C-NH), 1268.48 (C-S); ^{1}H NMR (δ, ppm): 5.19 (d, 1H, C_5-H, J=4.8 Hz), 5.35 (dd, 1H, C_6-H, $J_{1,2}$=2.0 Hz, $J_{1,3}$=4.4 Hz), 7.84 (NH, merged signal), 3.32 (s, 3H, N-CH_3), 7.31-7.82 [m, 11H (Ar-H)+1H (NH)]; ^{13}C NMR (δ, ppm): 176.09 (C-2), 141.04 (C-4), 101.12 (C-5), 40.46 (C-6), 29.75 (N-CH_3) and 123.89-136.48 (Ar-C).

4-(2-bromonaphthalen-6-yl)-6-(4-bromophenyl)-N-methyl-6H-1,3-thiazin-2-amine (4b)
M.F: $C_{21}H_{16}N_2Br_2S$, Yield: 91%, M.P: 63°C; IR (KBr, cm^{-1}): 3426.48 (NH), 2922.75 (CH_3-Str. in N-CH_3), 1673.37 (C=N), 1531.35 (C=C), 1476.40 (C-NH), 1277.63 (C-S); ^{1}H NMR (δ, ppm): 5.50 (dd, 1H, C_5-H, $J_{1,2}$=2.0 Hz, $J_{1,3}$=4.8 Hz), 5.72 (d, 1H, C_6-H, J=5.2 Hz), 7.88 (s, 1H, NH, D_2O exchangeable), 3.33 (s, 3H, N-CH_3), 7.18-7.98 [m, 10H (Ar-H)+1H (NH)]; ^{13}C NMR (δ, ppm): 176.96 (C-2), 139.68 (C-4), 99.20 (C-5), 40.67 (C-6), 36.64 (N-CH_3) and 123.91-136.52 (Ar-C).

4-(2-bromonaphthalen-6-yl)-6-(2-chlorophenyl)-N-methyl-6H-1,3-thiazin-2-amine (4c)
M.F: $C_{21}H_{16}N_2BrSCl$, Yield: 85%, M.P: 60°C; IR (KBr, cm^{-1}): 3427.24 (NH), 2923.40 (CH_3-Str. in N-CH_3), 1673.68 (C=N), 1530.94 (C=C), 1476.31 (C-NH), 1279.13 (C-S); ^{1}H NMR (δ, ppm): 5.48 (dd, 1H, C_5-H, $J_{1,2}$=2.0 Hz, $J_{1,3}$=4.8 Hz), 5.74 (d, 1H, C_6-H, J=4.8 Hz), 7.84 (NH, merged signal), 3.35 (s, 3H, N-CH_3), 7.48-7.82 [m, 10H (Ar-H)+1H (NH)]; ^{13}C NMR (δ, ppm): 177.01 (C-2), 137.99 (C-4), 99.16 (C-5), 40.66 (C-6), 30.99 (N-CH_3) and 123.90-136.51 (Ar-C).

4-(2-bromonaphthalen-6-yl)-6-(4-chlorophenyl)-N-methyl-6H-1,3-thiazin-2-amine (4d)
M.F: $C_{21}H_{16}N_2BrSCl$, Yield: 92%, M.P: 70°C; IR (KBr, cm^{-1}): 3430.29 (NH), 2921.50 (CH_3-Str. in N-CH_3), 1683.60 (C=N), 1523.55 (C=C), 1475.28 (C-NH), 1277.22 (C-S); ^{1}H NMR (δ, ppm): 5.48 (dd, 1H, C_5-H, $J_{1,2}$=2.0 Hz, $J_{1,3}$=4.8 Hz), 5.74 (d, 1H, C_6-H, J=4.8 Hz), NH-merged with aromatic signal, 3.34 (s, 3H, N-CH_3), 7.34-8.05 [m, 10H (Ar-H)+1H (NH)]; ^{13}C NMR (δ, ppm): 177.02 (C-2), 138.00 (C-4), 99.16 (C-5), 40.67 (C-6), 30.98 (N-CH_3) and 123.90-136.52 (Ar-C).

4-(2-bromonaphthalen-6-yl)-6-(3,4-dimethoxyphenyl)-N-methyl-6H-1,3-thiazin-2-amine (4e)
M.F: $C_{23}H_{21}N_2O_2BrS$, Yield: 82%, M.P: 78°C; IR (KBr, cm^{-1}): 3423.09 (NH), 2926.46 (CH_3-Str. in N-CH_3), 1675.66 (C=N), 1514.80 (C=C), 1461.15 (C-NH), 1259.09 (C-S); ^{1}H NMR (δ, ppm): 5.13 (d, 1H, C_5-H, J=4.8 Hz), 5.34 (dd, 1H, C_6-H, $J_{1,2}$=2.0 Hz, $J_{1,3}$=4.8 Hz), 7.85 (NH, merged signal), 3.33 (s, 3H, N-CH_3), 7.53-8.05 [m, 9H (Ar-H)+1H (NH)], 3.85 (s, 6H, -OCH_3); ^{13}C NMR (δ, ppm): 175.91 (C-2), 136.49 (C-4), 101.28 (C-5), 40.35 (C-6), 30.37 (N-CH_3), 123.85-136.17 (Ar-C), 56.07 and 55.87 (OCH_3).

4-(2-bromonaphthalen-6-yl)-6-(4-methoxyphenyl)-N-methyl-6H-1,3-thiazin-2-amine (4f)
M.F: $C_{22}H_{19}N_2OBrS$, Yield: 78%, M.P: 67°C; IR (KBr, cm^{-1}): 3420.64 (NH), 2925.77 (CH_3-Str. in N-CH_3), 1675.34 (C=N), 1570.55 (C=C), 1459.40 (C-NH), 1247.45 (C-S); ^{1}H NMR (δ, ppm): 5.13 (d, 1H, C_5-H, J=4.8 Hz), 5.32 (dd, 1H, C_6-H, $J_{1,2}$=2.8 Hz, $J_{1,3}$=4.8 Hz), NH-merged with aromatic signal, 3.31 (s, 3H, N-CH_3), 7.54-8.02 [m, 10H (Ar-H)+1H (NH)], 3.75 (s, 3H, -OCH_3); ^{13}C NMR (δ, ppm): 176.00 (C-2), 136.49 (C-4), 101.34 (C-5), 40.30 (C-6), 31.00 (N-CH_3), 55.41 (OCH_3) and 123.85-134.50 (Ar-C).

4-(2-bromonaphthalen-6-yl)-6-(3-nitrophenyl)-N-methyl-6H-1,3-thiazin-2-amine (4g)
M.F: $C_{21}H_{16}N_3O_2BrS$, Yield: 89%, M.P: 76°C; IR (KBr, cm^{-1}): 3440.99 (NH), 2922.12 (CH_3-Str. in N-CH_3), 1619.64 (C=N), 1527.08 (C=C), 1462.02 (C-NH), 1278.63 (C-S); ^{1}H NMR (δ, ppm): 5.07 (d, 1H, C_5-H, J=4.4 Hz), 5.30 (dd, 1H, C_6-H, $J_{1,2}$=1.6 Hz, $J_{1,3}$=4.4 Hz), NH-merged with aromatic signal, 3.31 (s, 3H, N-CH_3), 7.47-8.05 [m, 10H (Ar-H)+1H (NH)]; ^{13}C NMR (δ, ppm): 176.00 (C-2), 136.46 (C-4), 101.29 (C-5), 40.47 (C-6), 30.96 (N-CH_3) and 123.88-134.57 (Ar-C).

Antimicrobial activity
Invitro antimicrobial activity was carried out by using Mueller-Hinton broth method. Antibacterial activities were screened against two gram positive and two gram negative bacterias. Antifungal activities were screened against *Aspergillus flavus* and *Aspergillus niger*. The microorganisms were collected from Microbial type culture collection and gene bank (MTCC), Chandigarh, India. Both antibacterial and antifungal activities were studied by measuring the zone of inhibition on agar plates at concentration 10µg/mL and Gentamicin used as the standard for antibacterial and Fluconazole used as the standard for antifungal activities respectively.

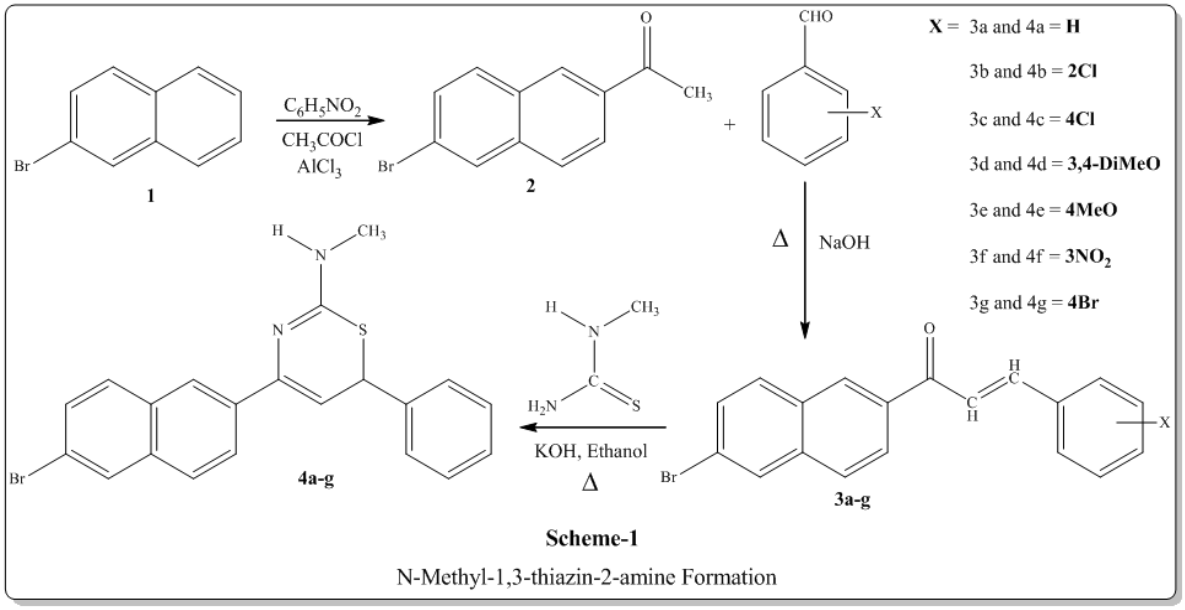
RESULTS AND DISCUSSION

The N-Methyl derivatives of different types of compounds possess diversified biological activities. For instance, the secondary metabolites [11] of N-methylamino acids containing peptide natural products (e.g. vancomycin, cyclosporine and actinomycin D) have found clinical use due in part to the physical properties and chemical stability conferred by the N-methylamino acids present in their structure. Also by the introduction of methyl moiety in to the amino group increase the proteolytic stability and lipophilicity [12-13]. The amino thiazines are also having number of pharmacological properties and based on their findings, in this report, we have synthesized the N-methyl derivatives of 1,3-thiazin-2-amine by using N-methyl thiourea in the following method.

The chalcones (**3a-g**) of 1-(2-bromonaphthalen-6-yl)ethanone (**2**) is prepared by the Claisen-Schmidt condensation of (**2**) with different aromatic aldehydes. The formed chalcones are treated with N-Methylthiourea in the presence of base yields the corresponding substituted N-methyl-1,3-thiazines (**4a-4g**) (**Scheme-1**). The formation of thiazine follows the Michael type addition of N-Methylthiourea to α,β-unsaturated ketone and cyclisation [14].

The structure of the synthesized compounds are characterized by using IR and NMR spectral measurements. The IR spectra of synthesized compounds showed the characteristic absorption bands like 3420-3440 cm^{-1} (NH- Str.), 2920-2926 cm^{-1} (CH_3 Str. in N-CH_3), 1620-1675 cm^{-1} (C=N Str.), 1510-1531 cm^{-1} (C=C Str.), 1450-1475 cm^{-1} (C-NH Str.) and 1247-1279 cm^{-1} (C-S Str.). The IR spectra absorption band at 2920-2926 cm^{-1} is evident from the methyl group at nitrogen atom and without methyl group, the compound 2-amino-1,3-thiazine does not showed any absorption band at this region [15].

The ^{1}H NMR spectra of all the synthesized compounds showed two types of signals for H-5 and H-6 protons in the thiazine moiety. The signal at the chemical shift values from 5.0 to 5.50 ppm is due to H-5 proton and 5.30-5.74 ppm is corresponds to H-6 proton. Both H-5 and H-6 protons showed two types of splitting pattern, one is doublet with coupling constant J=4.8-5.2 Hz and another is doublet of doublet (J=$_{1,2}$=1.6-2.8 Hz, $J_{1,3}$=4.4-4.8 Hz). The doublet of doublet might be the long range coupling of H-5 or H-6 proton with imino proton. The participation of imino proton in long range coupling is derived from the reduced multiplicity of signals for H-5 or H-6 showed doublet insteadof doublet of doublet in the D_2O experiment in NMR. The N-methyl protons signal is appears as a singlet at the chemical shift value 3.3 ppm. The imino proton (-NH) resonates in the aromatic region about 7.8 ppm and is D_2O exchangeable. The aromatic protons showed their characteristic multiplets in the region 7.18-8.0 ppm.



Scheme-1

N-Methyl-1,3-thiazin-2-amine Formation

The ^{13}C NMR spectra of compounds give the characteristic chemical shift values and are (δ, ppm) 30.36 (N-CH_3), 40 (C-6), 99-101 (C-5), 136-141 (C-4), 176-177 (C-NH) and 123-136 (Ar-C) respectively. The ^{13}C NMR spectral data of synthesized compounds also support the structures. In addition with these spectral evidences, the compounds were tested their physical parameters like TLC and melting points are also quite different from starting materials.

Antimicrobial Screening

All the synthesized compounds (**4a-g**) were tested their antibacterial and antifungal activities against representative bacteria-*Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and fungi-*Aspergillus niger* and *Aspergillus flavus* (**Table-1**).

All the compounds are active against gram positive as well as gram negative bacterias especially more active against gram negative bacteria, *Escherichia coli* and fungi- *Aspergillus niger*. Among the synthesized thiazines, the compound without substitution in the phenyl ring (**4a**), phenyl ring containing nitro group (**4g**) and dimethoxy group (**4e**) had the best overall antibacterial profile when compared to standard Gentamicin against *Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli.* The 2-Chloro substituted thiazine (**4c**) is equally active with standared against *Pseudomonas aeruginosa* and other compounds are less active against this bacteria.

Table – 1 ASSAY OF ANTIMICROBIAL ACTIVITY

S. No.	Microbes	Zone of Inhibition (mm in diameter)								
	Bacteria	**Control**	**Standard***	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
1	*Bacillus subtilis*	-	18	18	15	12	19	12	20	14
2	*Staphylococcus aureus*	-	15	17	13	12	17	10	18	11
3	*Escherichia coli*	-	22	23	19	22	25	16	25	16
4	*Pseudomonas aeruginosa*	-	21	15	21	16	18	12	18	18
	Fungi									
5	*Aspergillus niger*	-	11	12	12	14	11	16	13	14
6	*Aspergillus flavus*	-	13	12	06	05	8	12	10	8

**Gentamicin (Bacteria)*
**Fluconazole (Fungi)*

CONCLUSION

A series of N-Methyl derivatives of 4-(2-bromonaphthalen-6-yl)-6-aryl-6H-1,3-thiazin-2-amines were synthesized by the reaction of N-Methylthiourea and 1-(2-bromonaphthalen-6-yl)-3-arylprop-2-en-1-ones in the presence of KOH. The synthesized compounds are characterized by IR and NMR spectra. All the compounds are tested their antimicrobial activity using Gentamicin and Fluconazole as the standard.

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