Synthesis and Invitro bacterial screening of 2-amino- 4-(2-naphthyl)-6-aryl-6H-1,3-thiazines

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Abstract -A new series of biologically important 2-amino-4-(2-naphthyl)-6-aryl-6H-1,3-thiazines were synthesized starting from 1-(2-naphthyl)ethanone with different aromatic aldehydes in basic medium followed by the reaction with thiourea via Michael adduct formation, heterocyclisation and subsequent tautomeric change of adduct. All the synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR spectral studies and Screened their antibacterial activities.

Key words: 2-Amino-6H-1,3-thiazines, naphthylethanones, thiourea.

I. INTRODUCTION

Heterocyclic compounds are widely distributed in nature and are essential for life. They play vital role in the metabolism of all living cells. They are pharmacologically active and in large number such as 1,3-thiazines. Thiazines have drawn much attention because of their use as antimicrobial[1], anti-inflammatory[2], anti-tuberculosis[3], antihypertensive agents[4], inhibitors of platelet aggregation[5] etc. The chalcones are α-β-unsaturated ketones derived from condensation of acetyl compounds with aldehydes and are very versatile substrates for the evolution of various reactions like with thiourea resulting in 1,3-thiazines[6] and physiologically active compounds.

In view of the above mentioned findings and in continuation of our efforts[7]to identify new candidates that may be of value in designing new and potent biological active agents, the present work aims to synthesize some naphthyl substituted-6H-1,3-thiazines and study their invitro antibacterial activities.

II. EXPERIMENTAL

All chemicals were of analytical grade and purchased from E-Merck. The solvents were distilled before use. Melting points of the prepared compounds were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by silica gel coated aluminium plates. The FT-IR spectra were recorded on NICOLET AVATAR-360 FT-IR instruments by using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Brucker AMX-400 spectrometer operating at 400 MHz using DMSO-d_6 as solvent.

Preparation of 1-(2-naphthyl)ethanone (1) .

A mixture of 41.9 g (0.53 M) of acetyl chloride and 100 mL of carbon tetrachloride was taken in a one-liter three necked flask. The flask was equipped with condenser carrying a guard tube and a dropping funnel. About 70 g (0.52 M) of powdered dry $AlCl_3$ was added slowly to the vigorously stirred mixture. The mixture was cooled to 20°C and a solution of naphthalene (32 g, 0.25 M) in 100 mL of CCl_4 was added for 90 minutes from the dropping funnel. After the completion of the addition, the mixture was warmed to 30°C for 30 minutes. The resulting mixture was decomposed with ice and concentrated hydrochloric acid. The product was separated and crystallized from ethanol. Yield: 70%, Melting Point: 54-56ºC

Preparation of 1-(2-naphthyl)-3-arylprop-2-en-1-ones (2a-f).

A mixture of substituted benzaldehyde (0.01 M) and 1-(2-naphthyl)ethanone (0.01 M) in ethanol (95 %, 50 mL) was taken in a 250 mL round-bottomed flask. The reaction mixture was heated over a water bath while a solution of sodium hydroxide (1g in 5 mL of water) was added during 15 minutes and heating was continued for another 15 minutes. The solution was cooled; the product thus obtained was filtered and recrystallized from ethanol. The Yield and melting points are given in Table-1.

Table-1

The melting point yield of compounds (2a-2f)

	Compound Name	Yield %	Melting Point
2a	1-(2-naphthyl)-3-Phenylprop-2-en-1-one	91	101-103
2b	1-(2-naphthyl)-3-(4-bromophenyl)-prop-2-en-1-one	87	104-106
2c	1-(2-naphthyl)-3-(4-methoxyphenyl)-prop-2-en-1-one	90	113-115
2d	1-(2-naphthyl)-3-(3-nitrophenyl)-prop-2-en-1-one	89	112-114
2e	1-(2-naphthyl)-3-(4-chlorophenyl)-prop-2-en-1-one	87	102-104
2f	1-(2-naphthyl)-3-(3,5-dimethoxyphenyl)-prop-2-en-1-one	85	115-117

General procedure for the preparation of 2-amino-4-(2-naphthyl)-6-aryl-6H-

1,3-thiazines (3a-f)

Appropriate chalcones (2a-f) (0.01 M) and thiourea (0.01 M) in ethanol (75 mL) were refluxed in presence of potassium hydroxide (0.05 M in 10 mL of water). The progress of reaction was checked by TLC method and refluxing was continued for further four hours, and confirmed by TLC. The mixture was concentrated under vacuum and was poured in to ice cold water and filtered. The separated product was purified by column chromatography using silica gel as a stationary phase and benzene : ethylacetate (9:1) as mobile phase.

2-Amino-4-(2-naphthyl)-6-phenyl-6H-1,3-thiazine (3a).

Yield: 89% ; m.p: 135°C ; IR (KBr, cm^{-1}): 3408, 1654, 1568, 1238, 1024 ; ^{1}H NMR (δ, ppm): 5.18 (dd, 1H, J=2.8 Hz), 5.57 (broad s, 1H), 9.15 (s,1H), 9.95 (s, 1H) and 7.30-7.98 (m, 12H) ; ^{13}C NMR (δ, ppm): 54.75 (C-6), 101.87 (C-5), 144.03 (C-4), 175.21 (C-NH_2) and 123.71-134.02 (Ar-C).

2-Amino-6-(4-bromophenyl)-4-(2-naphthyl)-6H-1,3-thiazine (3b).

Yield: 85% ; m.p: 126°C ; IR (KBr, cm^{-1}): 3398, 1654, 1558, 1190, 1022, 669 ; ^{1}H NMR (δ, ppm): 5.47 (dd, 1H, J=2.8Hz), 5.55 (dd, 1H, J=2.8Hz), 9.13 (s, 1H), 10.15 (s, 1H), 7.26-7.98 (m, 11H) ; ^{1}H NMR(D_2O): 5.45 (broad d,2H), 9.13 and 10.15 signals disappeared. ^{13}C NMR (δ, ppm): 54.85 (C-6), 99.49 (C-5), 142.53 (C-4), 176.13 (C-NH_2), 120.17-140.94 (Ar-C).

2-Amino-6-(4-methoxyphenyl)-4-(2-naphthyl)-6H-1,3-thiazine (3c).

Yield: 89% ; m.p: 131°C, IR (KBr, cm^{-1}): 3423, 1654, 1564, 1176, 1029 ; ^{1}H NMR (δ, ppm): 5.12 (broad s, 1H), 5.53 (d, 1H, J=4.4Hz), 9.13 (s, 1H), 9.94 (s, 1H), 3.73 (s, 3H), 7.50-8.15 (m, 11H) ; ^{13}C NMR (δ, ppm): 54.21 (C-6), 102.02 (C-5), 158.78 (C-4), 55.10 (OCH_3), 174.88 (C-NH_2), 123.39-136.16 (Ar-C).

2-Amino-4-(2-naphthyl)-6-(3-nitrophenyl)-6H-1,3-thiazine (3d).

Yield: 85% ; m.p: 140°C ; IR (KBr, cm^{-1}): 3398, 1654, 1571, 1182, 1018 ; ^{1}H NMR (δ, ppm): 4.89 (d, 1H), 5.29 (d, 1H), 8.88 (s, 1H), 9.68 (s, 1H), 6.96-8.06 (m, 11H) ; ^{13}C NMR (δ, ppm): 54.55 (C-6), 101.98 (C-5), 141.13 (C-4), 175.08 (C-NH_2), 123.70-136.78 (Ar-C).

2-Amino-6-(4-chlorophenyl)-4-(2-naphthyl)-6H-1,3-thiazine (3e).

Yield: 83% ; m.p: 105°C ; IR (KBr, cm^{-1}): 3404, 1654, 1564, 1236, 1012, 748 ; ^{1}H NMR (δ, ppm): 5.20 (d, 1H), 5.55 (d, 1H), 9.98 (s, 1H), 10.02 (s, 1H), 7.35-8.33 (m, 11H); ^{13}CNMR (δ, ppm): 54.02 (C-6), 101.37 (C-5), 142.90 (C-4), 175.25 (C-NH_2), 123.71-134.33 (Ar-C).

2-Amino-6-(3,5-dimethoxyphenyl)-4-(2-naphthyl)-6H-1,3-thiazine (3f).

Yield: 83% ; m.p: 145°C ; IR (KBr, cm^{-1}): 3433, 1658, 1560, 1261, 1026 ; ^{1}H NMR (δ, ppm): 5.13 (broad s, 1H), 5.57 (broad s, 1H), 9.11 (s, 1H), 9.94 (s, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 6.89-8.15 (m, 11H) ; ^{13}C NMR (δ, ppm): 54.41 (C-6), 101.93 (C-5), 148.81 (C-4), 175.01 (C-NH_2), 123.72-136.46 (Ar-C).

Antibacterial activity

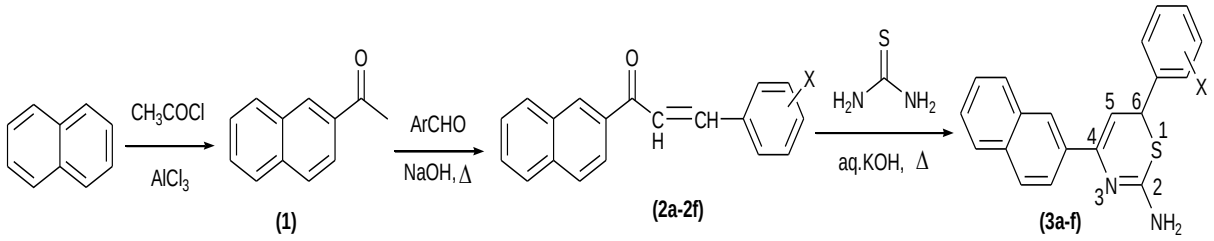
The disk diffusion method was used for the antibacterial evaluation. The MIC was determined by the micro broth dilution technique using Mueller-Hinton broth. Serial two-fold dilutions of the test compounds in DMSO were prepared. The inoculum was prepared in broth, which had been kept at 37 ºC over night. The lowest concentration of the test compounds inhibiting visible growth was taken as the MIC value.

III. RESULTS AND DISCUSSION

The importance of thiazines in the chemistry of biological system has been greatly realized because of their presence as substructure in many natural products of therapeutic importance. Friedel Crafts reaction of naphthalene with acetylchloride in the presence of Lewis acid such as Aluminium chloride afford the 1-(2-naphthyl)ethanone (1) which on condensation with

different substituted aromatic aldehydes in the presence of base yields substituted 1-(2-naphthyl)-3-arylprop-2-en-1-ones (2a-f), in general, said to be naphthylsubstitutedchalcones. The formed chalcones on treatment with thiourea in ethanolic medium containing potassium hydroxide undergoes the formation of Michael adduct and its subsequent heterocyclisation with a tautomeric change[8] afford the target molecule of 2-amino-4-(2-naphthyl)-6-aryl-6H-1,3-thiazines (3a-f) (scheme-1).

The IR spectra of all the synthesized compounds show the characteristic absorption bands in the region of 3390-3450 cm^{-1} for NH stretching, 1650-1660 cm^{-1} for C = N stretching, the absorption bands around 1550 cm^{-1} (C=C str.), 1020 cm^{-1} (C-S-C str.) and around 1240 cm^{-1} (C-N str.). The ^{1}H and ^{13}C NMR spectra of all the synthesized thiazines exhibit the same signals of chemical shifts as references cited[9] like H-6 and H-5 protons are resonate in the region around 5.0 to 6.0 ppm respectively.



3a X=H, **3b** X=4-Br, **3c** X=4-MeO, **3d** X=3-NO_2, **3e** X=4-Cl, **3f** X=3,5-Dimethoxy

Scheme-1: Synthesis of 2-Amino-4-(2-naphthyl)-6-aryl-6H-1,3-thiazines

The aromatic protons show the characteristic multiplets in the region 6.8-8.2 ppm. From the ^{1}H NMR signals of amino protons in the down field region (9-10 ppm), reveals the protons attached to nitrogen atom in amino group oriented in different manner to ring sulphur and nitrogen atom (figure-1).

Nap=Naphthyl

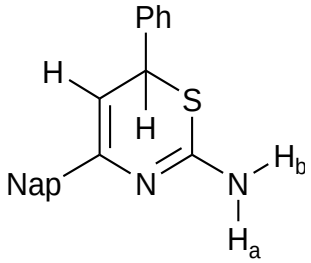


Figure.1. Different orientations of amino protons.

The signals of amino protons are conformed by disappearance of signals using Deuterium oxide to the NMR sample. The multiplicity pattern of H-6 and H-5 protons in their characteristic chemical shifts region exhibits long range coupling with nearest amino protons (J = Less than 3 Hz) for most of the compounds. Some of the compounds not clearly showed their long range coupling. This indiscremency may be of different conformational changes which give the average signal i.e. broadening of signal results. In the ^{1}H NMR spectrum of compound 3b with D_2O having the reduced lines for H-6 and H-5 protons indicates the long range coupling may be due to amino protons.

The compounds 3a-f were evaluated for antibacterial activities against two gram positive and two gram negative bacteria's - Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Klebsiella pneumoniae. Ciprofloxacin was used as a standard drug. The minimum inhibitory concentration (MIC) of the tested compounds used was 10µg/disc and their zone of inhibitions is shown in table-2.

Table – 2
Antibacterial activity

S. No.	Bacteria	Standard Antibiotic Disk*	Zone of inhibition mm in diameter (10µg/disc)						
			C	3a	3b	3c	3d	3e	3f
1	Bacillus subtilis	18	-	09	10	10	10	12	-
2	Staphylococcus aureus	17	-	07	03	08	10	11	-
3	Escherichia coli	18	-	11	10	12	10	13	-
4	Klebsiella pneumoniae	20	-	12	11	07	11	13	-

*Ciprofloxacin

C – Control

All the compounds show moderate activities compared to standard Ciprofloxacin except the compound 3f (No activity). The chloro substituent at para position shows more activity among all other compounds against both gram positive and gram negative bacteria.

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