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Synthesis and antibacterial studies of some new pyrazoline and isoxazoline derivatives

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ABSTRACT

*Some new 1-hydro-3(1-napthyl amino)-5-aryl-2-pyrazolines **2(a-h)** and 3-(1-napthyl amino)-5-aryl-2-isoxazolines **3(a-h)** were synthesized by reacting 1-(napthyl amino)-3-aryl-2-propene-1-ones **1(a-h)** with hydrazine hydrate and hydroxyl amine hydrochloride in ethanol under reflux condition, respectively. Structures of the synthesized compounds were confirmed by the spectral analysis. Antibacterial activity of these compounds is also reported.*

Keywords:1,3-diaryl-2-propen-1ones, pyrazolines, isoxazolines, antibacterial activity;

INTRODUCTION

Pyrazoline derivatives constitute an interesting class of organic compounds with diverse chemical [1] and pharmacological applications. Several pyrazoline derivatives possess important pharmacological activities and therefore they are useful materials in drug research. Pyrazolines are used as antibacterial [2], antifungal [3] antitumour [4] immunosuppressive [5] and anti-tubercular agents [6]. Some of the pyrazoline derivatives are reported to possess anti-inflammatory [7], anticancer [8], antidiabetic [9] and antidepressant properties [10]. On the other hand, isoxazolines have been reported to possess a variety of significant and diverse pharmacological properties such as antibacterial [11], antifungal [12,13], anti-inflammatory [14] and anti-HIV [15] activity. Keeping these biological observations of pyrazolines and isoxazolines in mind and in continuation of our research work on the synthesis of biologically active heterocyclic compounds [16-18], it was planned to synthesize some new series of pyrazolines and isoxazolines containing napthyl moiety.

EXPERIMENTAL SECTION

Melting points were determined by an open capillary method and are uncorrected. The chemicals and solvents used are of laboratory grade and were purified. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO-d6) on Avance-300 MHz spectrometer using TMS as an internal standard. The mass were recorded on EI-shimadzu GC-MS spectrometer.

General procedure for the synthesis of 1-hydro-3(1-naphyl amino)-5-aryl-2-pyrazolines 2(a-h)

An equimolar mixture of 1-(1-napthyl amino)-3-aryl-2-propen-1-one **1** (1 Mmol), and hydrazine hydrate (1 Mmol) were taken in ethanol and refluxed for 5 hr. The progress of the reaction was monitored by thin layer chromatography (TLC) by time to time. After completion of the reaction, the contents were kept at room temperature and poured into cold water. The solid obtained was filtered, washed with cold water. Then crude product was crystallized from ethanol to give the corresponding product **2**.

Spectroscopic data of selected compounds

1-Hydro-3-(1-napthyl amino)-5-(2-hydroxy-5-chloro phenyl)-2-pyrazoline ***(2b)***

IR (KBr, cm^{-1}): 1595, 3348; ^{1}H NMR (DMSO-d_6, δ ppm): δ 3.45 (dd, 1H, H_A), 3.68 (dd, 1H, H_B), 5.11 (dd, 1H, H_X), 7.18-7.98 (m, 10H, Ar-H), 8.21 (s, 1H, -NH), 8.36 (s, 1H, -NH), 11.96 (s, 1H, -OH); EIMS (*m/z*): 338 (M^+).

1-Hydro-3-(1-napthyl amino)-5-(4-hydroxy phenyl)-2-pyrazoline ***(2e)***

IR (KBr, cm^{-1}): 1602, 3356; ^{1}H NMR (DMSO-d_6, δ ppm): δ 3.48 (dd, 1H, H_A), 3.73 (dd, 1H, H_B), 5.23 (dd, 1H, H_X), 5.66 (s, 1H, -OH), 7.11-8.05 (m, 11H, Ar-H), 8.25 (s, 1H, -NH), 8.41 (s, 1H, -NH); EIMS (*m/z*): 303 (M^+).

1-Hydro-3-(1-napthyl amino)-5-(4-chloro phenyl)-2-pyrazoline ***(2f)***

IR (KBr, cm^{-1}): 1599, 3342; ^{1}H NMR (DMSO-d_6, δ ppm): δ 3.32 (dd, 1H, H_A), 3.58 (dd, 1H, H_B), 5.15 (dd, 1H, H_X), 7.18-8.11 (m, 11H, Ar-H), 8.22 (s, 1H, -NH), 8.42 (s, 1H, -NH); EIMS (*m/z*): 321 (M^+).

General procedure for the synthesis of 3-(1-naphtyl amino)-5-aryl-isoxazolines 3(a-h)

An equimolar mixture of 1-(1-napthyl amino)-3-aryl-2-propen-1-one **1** (1 Mmol), and hydroxyl amine hydrochloride (1.5 Mmol) were taken in ethanol and refluxed for 6 hr. The progress of the reaction was checked by thin layer chromatography (TLC) by time to time. After completion of the reaction, the contents were kept at room temperature and poured into cold water. The solid obtained was filtered, washed with cold water. Then crude product was crystallized from ethanol to give the corresponding product **3.**

Spectroscopic data of selected compounds

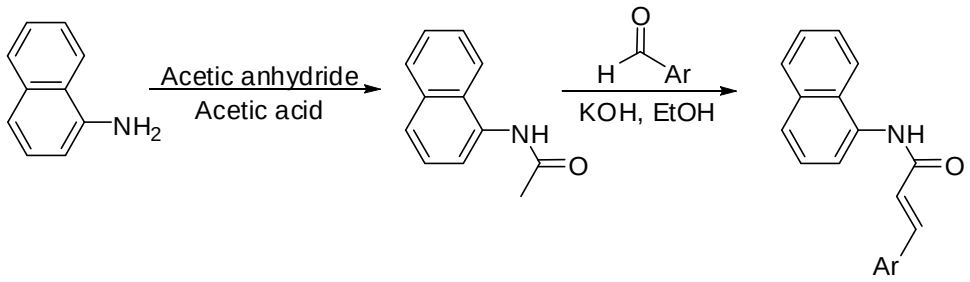
3-(1-napthyl amino)-5-(2-hydroxy phenyl)-isoxazoline ***(3a)***

IR (KBr, cm^{-1}): 1606, 3332; ^{1}H NMR (DMSO-d_6, δ ppm): δ 3.38 (dd, 1H, H_A), 3.55 (dd, 1H, H_B), 4.95 (dd, 1H, H_X), 7.11-8.19 (m, 11H, Ar-H), 8.34 (s, 1H, -NH), 11.74 (s, 1H, -OH); EIMS (*m/z*): 304 (M^+).

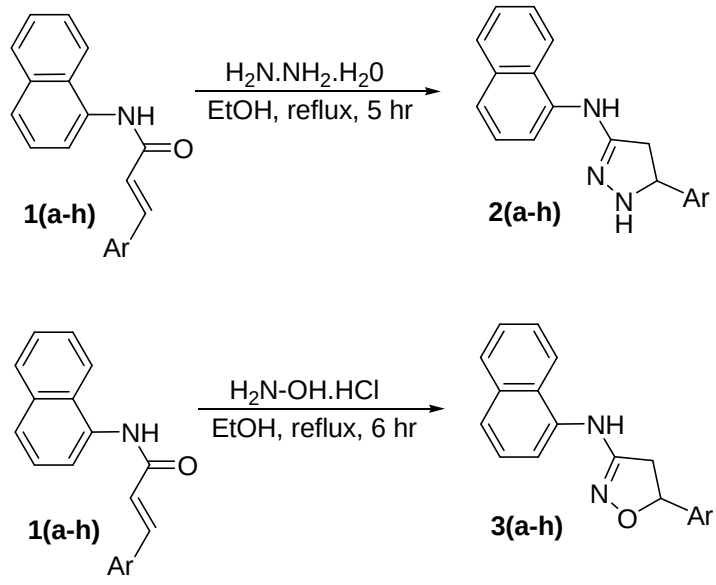
3-(1-napthyl amino)-5-(4-chloro phenyl)-isoxazoline ***(3f)***
IR (KBr, cm^{-1}): 1602, 3346; ^1H NMR (DMSO-d_6, δ ppm): δ 3.41 (dd, 1H, H_A), 3.64 (dd, 1H, H_B), 5.16 (dd, 1H, H_X), 7.18-8.22 (m, 11H, Ar-H), 8.38 (s, 1H, -NH); EIMS (*m/z*): 323 (M^+).

3-(1-napthyl amino)-5-(4-chloro phenyl)-isoxazoline ***(3g)***
IR (KBr, cm^{-1}): 1611, 3335; ^1H NMR (DMSO-d_6, δ ppm): δ 3.31 (dd, 1H, H_A), δ 3.46 (s, 3H, OCH_3), 3.71 (dd, 1H, H_B), 5.28 (dd, 1H, H_X), 7.08-8.18 (m, 11H, Ar-H), 8.32 (s, 1H, -NH); EIMS (*m/z*): 318 (M^+).

Antibacterial activity
All the synthesized products **2(a-h)** and **3(a-h)** were evaluated for their antibacterial activity by agar well diffusion method [20] against gram-positive *Bacillus subtilis*, *Staphylococcus aureus* and gram-negative *Escherichia coli* and *Salmonella typhi* bacteria species. The antibiotic *Penicillin* (25 µg/mL) was used as reference antibacterial substance for comparison. Dimethyl sulphoxide (1%, DMSO) was used a control. The culture strains of bacteria were maintained on nutrient agar slant at 37±0.5 °C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10^5 CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 25 µg/mL separately for each bacterial strain. All the plates were incubated at 37±0.5 °C for 24 h. Zone of inhibition of compounds in mm were noted.



Scheme-1: Synthesis of 1-(napthyl amino)-3-aryl-2-propene-1-ones



Scheme-2: Synthesis of 2-pyrazolines and isoxazolines

RESULTS AND DISCUSSION

In this present communication, synthesis and antibacterial activity of some new 2-pyrazolines and isoxazolines derivatives containing napthyl moiety is reported from corresponding 1,3-diaryl-2-propen-1-ones. Initially, 1-(napthyl amino)-3-aryl-2-propene-1-ones **1(a-h)** were prepared by our earlier reported method (Scheme-1) [19]. These 1-(napthyl amino)-3-aryl-2-propene-1-ones **1(a-h)** were treated with hydrazine hydrate and hydroxyl amine hydrochloride in ethanol under reflux condition for 5-6 hr to gave the corresponding 2-pyrazoline **2(a-h)** and isoxazolines **3(a-h)**, respectively (Scheme-2, Table-1).

Table-1: Physico-chemical data of 2- pyrazolines 2(a-h) and isoxazolines 3(a-h)

Entry	Product	Ar	Yield (%)	M. P. (°C)
1	2a	2-OH-C_6H_4	66	132
2	2b	2-OH-5-Cl-C_6H_3	65	158
3	2c	2-OH-3-Br-5-Cl-C_6H_2	68	115
4	2d	2-OH-3,5-dibromo-C_6H_2	62	128
5	2e	4-OH-C_6H_4	70	215
6	2f	4-Cl-C_6H_4	72	151
7	2g	4-OCH_3-C_6H_4	66	145
8	2h	3-OCH_3-4-OH-C_6H_3	62	169
9	3a	2-OH-C_6H_4	68	128
10	3b	2-OH-5-Cl-C_6H_3	65	150
11	3c	2-OH-3-Br-5-Cl-C_6H_2	68	135
12	3d	2-OH-3,5-dibromo-C_6H_2	66	126
13	3e	4-OH-C_6H_4	68	145
14	3f	4-Cl-C_6H_4	70	138
15	3g	4-OCH_3-C_6H_4	68	152
16	3h	3-OCH_3-4-OH-C_6H_3	65	164

Table-2: Antibacterial activity of 2-pyrazolines derivatives 2(a-h) and 3(a-h)

Compound	BS	SA	EC	ST
2a	12	11	14	15
2b	13	12	12	12
2c	10	13	12	16
2d	13	10	14	15
2e	16	12	18	14
2f	15	11	13	12
2g	13	12	15	14
2h	16	11	11	10
3a	11	14	13	16
3b	13	10	13	13
3c	10	12	15	15
3d	14	14	14	16
3e	16	13	12	14
3f	16	16	15	16
3g	15	16	14	14
3h	16	18	18	15
Penicillin	18	20	22	18

Zone of inhibition measured in mm;
BS-Bacillus subtilis; SA-Staphylococcus aureus; EC-Escherichia coli; ST-Salmonella typhi;

The newly synthesized compounds **2(a-h)** and **3(a-h)** were established on the basis of IR, ^{1}H NMR and MASS spectroscopy method. The IR spectra of the compounds showed the absence of unsaturated carbonyl group, indicating the formation of product. In ^{1}H NMR spectra, the ABX spin pattern observed in both pyrazolines and isoxazolines which proved the structures of the products. Phenolic proton appeared as a singlet near δ 11.0-12.0 ppm due to the hydrogen bonding, while other aromatic and aliphatic protons were observed at excepted regions. The mass spectra of the 2-pyrazoline derivatives were showed molecular ion peak corresponding to their molecular formula.

The results of the antibacterial activity data are given in Table-2. The investigation of antimicrobial screening data revealed that the tested compounds were showed moderate to good activity. In comparison with standard penicillin, compounds **2e**, **2f**, **2h**, **3e**, **3f**, **3g** and **3h** were showed good activity against *B. subtillis*. Only the compound **3f**, **3g** and **3h** were found to be active against *S. aureus*. Compounds **2e** and **3h** were found to be active against *E. coli*. Compounds **2c**, **3a**, **3d** and **3f** were displayed good activity against *S. typhi*. Remaining all the compounds were displayed moderate activity.

CONCLUSION

In summary, we have synthesized a new series of 2-pyrazoline and isoxazoline derivatives containing napthyl amino moiety by the treatment of 1-(napthyl amino)-3-aryl-2-propene-1-ones with hydrazine hydrate and hydroxyl amine hydrochloride respectively, in ethanol under reflux condition. Further these compounds were evaluated for their antibacterial activity. Some of the compounds showed good activity against gram positive and gram negative bacterial strains.

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