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GREEN SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF 1-(3-NAPHTHALEN-2-YL)-5-ARYL-4, 5-DIHYDROPYRAZOL- 1-YL)-3-PHENYLPROP-2-EN-1-ONES

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ABSTRACT

A novel new series of 1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one are synthesized from 1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-ethanone derivatives react with Benzaldehyde by using ethanol as a solvent . The whole synthesis processes were monitored by TLC. The structures of new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data's, elemental analysis and biological studies.

KEYWORDS: 2-Acetylnaphthalene, Hydrazine hydrate, Sodium acetate, acetic anhydride, Benzaldehyde.

INTRODUCTION

Pyrazole are important nitrogen containing 5-membered heterocyclic compounds and different methods have been produced for their synthesis, pyrazole constitute interesting group of heterocycles because of their synthetic versatility and effective activities. Pyrazole derivatives with a phenyl group at the 3-position exhibited excellent characteristic of blue photoluminescence and electroluminescence.[1] Pyrazole displayed various biological activities such as antimicrobial[2], antitumor[3], antifungal, antibacterial[4],antiviral, antiparasitic, anti-tubercular and insecticidal agents[5-13], sometimes useful as insecticides[14] and are used in dyeing.[15] Moreover, chalcones have played a crucial part in the development of theory of heterocyclic compounds and also they used extensively in organic synthesis.[16-21] A classical synthesis of these compounds involves the base catalyzed aldol condensation reaction of ketones and aldehydes to give α-β-unsaturated ketones (chalcones). Which undergo a subsequent cyclization reaction with hydrazine's affording pyrazoles. This is followed by treated with aldehydes to obtain a set of phenylpyrazoline derivatives. The structures of the synthesized compounds are assigned on the basis of elemental analysis, IR, ^{1}H, ^{13}C NMR spectral data's, elemental analysis and biological studies.

MATERIALS AND METHODS

The melting points were determined in open capillaries and are uncorrected by using MEL Temp apparatus. IR spectra were recorded on a SHIMADZU.FT-IR Thermo Nicolet spectrometer in KBr pellets. ^{1}H NMR spectra were recorded at 400MHz on BRUKER 400MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard. ^{13}C NMR spectra were recorded at 100MHz on BRUKER 400MHz spectrometer in $CDCl_3$. For recording ^{1}H NMR spectra, solution were prepared by dissolving about 10mg of the compound in 0.5 ml of $CDCl_3$. While for recording ^{13}C NMR spectra, about 50mg of the compound was dissolved in the same volume of the solvent.

General procedure for preparation of 3-(4-aryl)-1-(naphthalene-2-yl) prop-2-en-1-ones (Chalcones)

The purchased 2-acetylnaphthalene is reacts with various substituted benzaldehyde in the presence of ethanol containing NaOH pellets in the 250 ml beaker. The mixture was stirred well for 30 minutes in an ice bath condition then it was poured into the beaker containing crushed ice and kept overnight in the refrigerator. The chalcones were precipitated out as a solid. Then it was filtered, dried and re-crystallized. The purity of the chalcones was checked by TLC by using chloroform as a solvent.

General procedure for synthesis of 1-(3-(naphthalene-2-yl)-5-aryl4, 5-dihydropyrazole-1-yl)-3-phenylprop-2-en-1-ones

A mixture of various substituted naphthalene chalcones (1mmol), hydrazine hydrate (1mmol),25 ml of acetic acid, a pinch amount of sodium acetate, were taken in a dry round bottom flask, the mixture was shaken well and then it was refluxed for 6 hours. The reaction mixtures were monitered by TLC. After the reaction mixture was cooled to room temperature and poured into crushed ice,

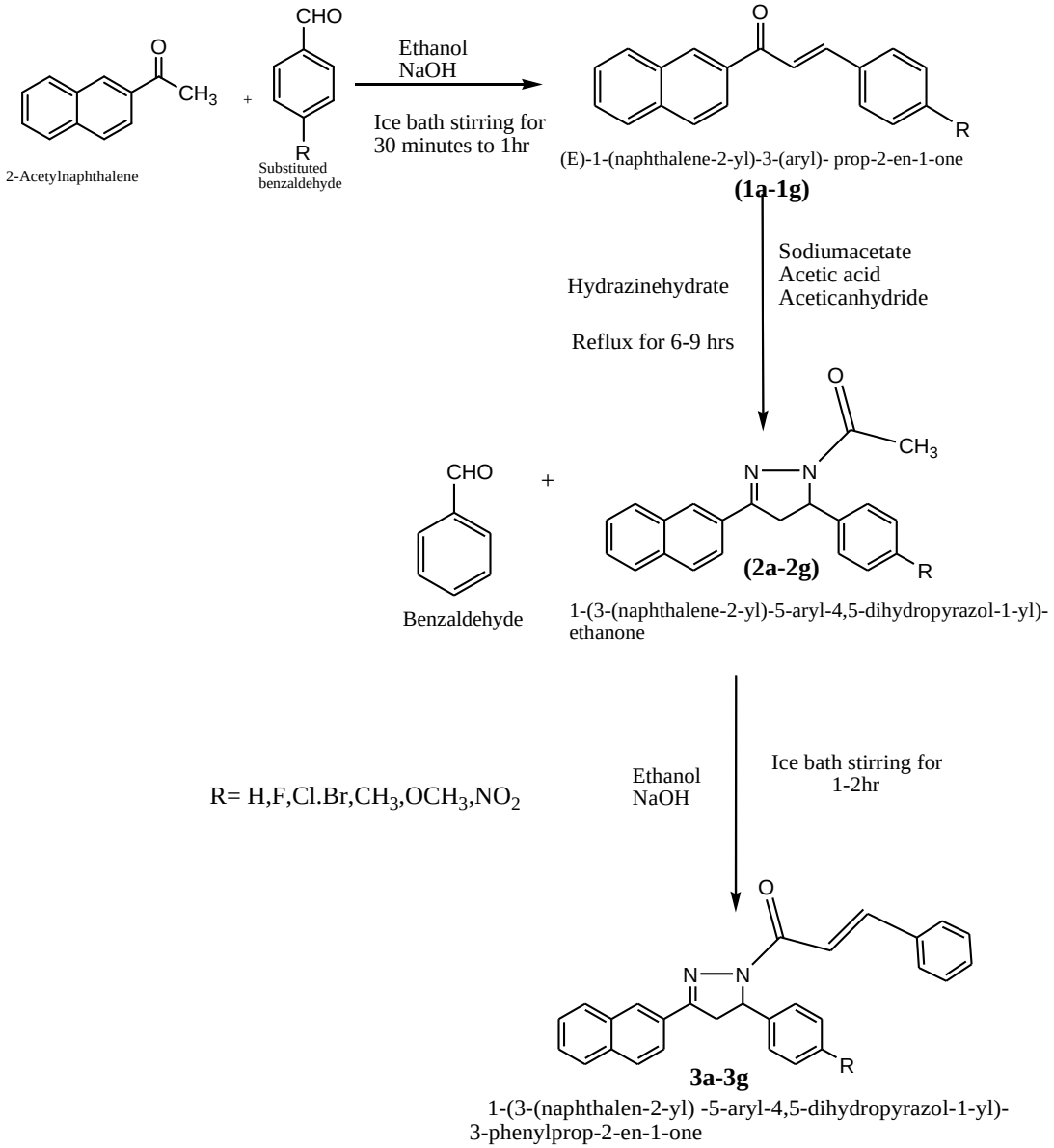
the white precipitate was obtained. After filtration, the precipitate was recrystallized from ethanol.

General procedure for synthesis of 1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one

A mixture of NaOH (2.2 g, 0.055 mol, water (20 ml), ethanol (20 ml),1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-ethanone derivatives (0.043 mol) and benzaldehyde (0.043 mol) was stirred at 0-15ºC for 2-3 hrs and left in the refrigerator overnight. The precipitated solid was then filtered, washed with water, dried, and recrystallized from ethanol. The purity of the compound was checked by TLC by using chloroform as a solvent.

RESULT AND DISCUSSION

A convenient route for the synthesis of α-β-unsaturated ketones (1a-1g) is achieved by base catalyzed condensation of 2-Acetylnaphthalene with the appropriate p-substituted Benzaldehyde in the presence of ethanol in NaOH (Scheme.1a-1g).



Scheme1. Synthesis of compounds 1a-1g, 2a-2g, 3a-3g

In the present communication aromatic aldehydes and 2-Acetylnaphthalene has been chosen to develop pyrazol derivatives. A novel series of substituted 1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one have been synthesized by treating substituted 1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-ethanone derivatives with Benzaldehyde(2a-2g). The synthesized compounds were investigated for antimicrobial activity. The assignment of the structure of the second stage compounds (2a-2g) and final compounds (3a-3g) scheme-1 was based on their correct elemental analyses and spectroscopic data's. The IR spectrum of the compound 3a shows that the characteristic absorption frequency at 1668.43 cm^{-1} is

due to carbonyl stretching frequency of pyrazole chalcone moiety. The absorption band at 1591.27cm^{-1} is due to C=C stretching frequency. The absorption band at 1494.83 cm $^{-1}$ is due to presence of C=N of pyrazole moiety. The absorption frequency around at 3049.46cm $^{-1}$ is assigned to aromatic CH stretching vibration. The absorption bands at 2953.02, 2904.80 cm^{-1} are assigned to aliphatic CH stretching vibration. The bands at 748.38, 715.89, 690.52cm^{-1} are aromatic ring stretching vibration.

ANALYSIS OF ^{1}H NMR SPECTRUM OF COMPOUND (3a)

In the^{1}H NMR spectrum of the methylene protons of H4a & H4e of the pyrazole moiety appeared as two doublets of doublets due to multiple coupling involving both germinal and vicinal protons. The signal (H4-a & H4-e) observed at 3.20 and 3.75 ppm . The doublet of doublet at 3.20 ppm ($J_{4a,5a}$ =18 Hz and $J_{4a,4e}$ = 4 Hz) is assigned to H4-a proton of the pyrazoline moiety. The doublet of doublet 3.75 ppm ($J_{4e,4a}$ =18 Hz & $J_{4e,5a}$ 12 Hz) is assigned to H4e proton of the pyrazoline. Similarly the methine proton (H-5) of the pyrazole moiety is expected to give signal as a doublet of doublet due to vicinal coupling with the magnetically nonequivalent protons of the methylene group (H-4a and H-4e) of the pyrazole moiety and the signal are observed at 5.49 ppm ($J_{5a,4a}$ = 12 Hz and $J_{5a,4e}$ 4 Hz). Also the doublet appeared at 7.56 ppm (J=8Hz) due to the presence of H1 proton of chalcone moiety. The doublet at 8.80 ppm (J=8Hz) due to the presence of H-2 proton of chalcone moiety. H_e aromatic protons appear as a multiplet in the range of 7.24-8.10 ppm. The ^{1}H NMR chemical shift values for remaining compounds are given in the Table-3.

ANALYSIS OF ^{13}C NMR SPECTRUM OF COMPOUND (3a)

In the ^{13}C NMR spectrum of 1-(3-(naphthalene-2-yl)-5-phenyl-4, 5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one (compound 3a)shows that the ^{13}C resonance at 60.13 ppm is assigned to C-5 of pyrazole moiety. The ^{13}C resonance observed at 42.33 ppm is due to C-4 pyrazole moiety. The ^{13}C resonance observed at 42.33ppm is due to C-4 of pyrazole moiety. The ^{13}C resonance observed at 153.96 ppm is assigned tomC-3 of pyrazole moiety. The aromatic carbons are observed in the region of 23.35-129.06 ppm. The ^{13}C resonance at 168.93 ppm is assigned to C=O chalcone moiety. The ^{13}C resonance at 123.35 ppm is due to the presence of C1 carbon of chalcone moiety. The ^{13}C resonance at 14.95 ppm is due to the presence of C-2 carbon of chalcone moiety. The remaining ^{13}C signal at 134.20 and 133.05 are due to ipso carbon. The ^{13}C NMR chemical shift values for remaining compounds are given in the Table-4.

Table 1: Physical data's of the synthesized compounds 1a-1g, 2a-2g, 3a-3g

Entry	Molecular Formula	Molecular weight	Melting Point (° C)	Elemental analysis (%)	
				Found	Calculated
1a	$C_{19}H_{14}O$	258	70	C(88.34),H(5.46),O(6.19)	C(88.2),H(5.41),O(6.19)
1b	$C_{19}H_{13}OF$	276	105	C(82.59),H(4.74),F(6.88),O(5.79)	C(82.50),H(4.70),F(6.87),O(5.79)
1c	$C_{19}H_{13}OCl$	266	128	C(76.55),H(4.16)Cl(13.29),O(6.00)	C(76.55),H(4.40)Cl(13.29),O(6.00)
1d	$C_{19}H_{13}OBr$	295	140	C(69.17),H(3.76),Br(27.07)	C(69.17),H(3.76),Br(26.76)O(5.42)
1e	$C_{20}H_{16}O$	272	85	C(88.20),H(5.92),O(5.87)	C(88.12),H(5.87),O(5.87)
1f	$C_{20}H_{16}O_2$	288	102	C(83.31),H(5.59),O(11.10)	C(83.23),H(5.54),O(11.09)
1g	$C_{19}H_{14}NO_3$	304	110	C(75.24),H(4.32),N(4.62),O(15.82)	C(75.17),H(4.20),N(4.61),O(15.82)
2a	$C_{21}H_{18}N_2O$	314	96	C(80.23),H(5.77),N(8.91),O(5.09)	C(80.15),H(5.72),N(8.90),O(5.08)
2b	$C_{21}H_{17}N_2OF$	332	105	C(75.89),H(5.16),F(5.72),N(8.43),O(4.81)	C(75.81),H(5.11),F(5.71),N(8.42),O(4.81)
2c	$C_{21}H_{17}N_2OCl$	348.4	94	C(72.31),H(4.91),Cl(10.16),N(8.03),O(4.59)	C(72.24),H(4.87),Cl(10.16),N(8.02),O(4.58)
2d	$C_{21}H_{17}N_2OBr$	405	102	C(64.13),H(4.36),Br(20.32),N(7.12),O(4.07)	C(64.07),H(4.32),Br(20.08),N(7.11),O(4.87)
2e	$C_{22}H_{20}N_2O$	328	130	C(80.46),H(6.41),N(8.53),O(4.87)	C(80.38),H(6.08),N(8.52),O(4.87)
2f	$C_{22}H_{20}N_2O_2$	344	92	C(76.72),H(5.85),N(8.13),O(9.29)	C(76.66),H(5.80),N(8.12),O(9.29)
2g	$C_{21}H_{17}N_3O_3$	359	90	C(70.18),H(4.77),N(11.69),O(13.36)	C(70.12),H(4.73),N(11.68),O(13.36)
3a	$C_{28}H_{22}N_2O$	402	138	C(83.56),H(5.51),N(6.96),O(3.98)	C(83.4),H(5.46),N(6.9),O(3.9)
3b	$C_{28}H_{21}N_2OF$	420	120	C(79.98),H(5.03),F(4.52),N(6.66),O(3,81)	C(79.90),H(4.99),F(4.50),N(6.60),O(3,80)

3c	$C_{28}H_{21}N_2OCl$	436	104	C(76.97),H(4.84),Cl(8.11), N(6.41),O(3.66)	C(76.90),H(4.80),Cl(8.11), N(6.40),O(3.66)
3d	$C_{28}H_{21}N_2OBr$	405	108	C(69.86),H(4.40),Br(16.60),N (5.82),O(3.32)	C(69.79),H(4.36),Br(16.41),N (5.81),O(3.32)
3e	$C_{29}H_{24}N_2O$	416	106	C(83.63),H(5.81),N (6.73),O(3.84)	C(83.55),H(5.76),N (6.72),O(3.84)
3f	$C_{29}H_{24}N_2O_2$	432	96	C(80.53),H(5.59),N (6.48),O(7.40)	C(80.46),H(5.54),N (6.47),O(7.39)
3g	$C_{28}H_{21}N_3O_3$	447	98	C(75.15),H(4.73),N (9.39),O(10.73)	C(75.8),H(4.69), N(9.38),O(10.72)

Table-2: IR spectral data of the synthesis compound 1a-1g, 2a-2g, 3a-3g

Entry	C=O stretching	C=C stretching	C=N stretching	Aliphatic CH stretching	Aromatic CH stretching	Aromatic ring stretching
1a	1660.71	1593.20	-	2906.73	3059.10	819.75,752.24
1b	1624.06	1579.70	-	2945.30	3068.75	823.60,752.24
1c	1664.57	1597.06	-	2927.94	3059.10	819.25,756.10,705.95
1d	1651.07	1600.92	-	2961.56	3051.39	815.89,750.31,709.80,680.87
1e	1651.07	1602.85	-	2987.23	3051.39	750.31,706.96,813.36
1f	1654.92	1597.06	-	2991.59,2953.02	3051.39	815.83,759.95,746.45
1g	1660.71	1600.92	-	2924.59	3055.24	813.96,752.24,638.58
2a	1662.71	1425.40	1464.87	2899.01	3026.31	824.56,736.01
2b	1660.71	1425.40	1526.71	2899.01	3026.31	828.56,756.01
2c	1668.75	1426.40	1524.37	3000.01	3026.31	838.56,758.01
2d	1669.71	1425.40	1459.21	2895.01	3026.31	825.56,726.01
2e	1670.71	1425.40	1441.84	2899.01	3026.31	823.56,746.01
2f	1665.71	1425.40	1531.62	2890.01	3026.31	828.56,756.01
2g	1664.71	1425.40	1536.95	2896.01	3026.31	828.56,756.01
3a	1668.43	1591.27	1489.05	2953.02,2904.80	3049.46	748.38,715.59,690.52
3b	1660.71	1591.27	1506.41	2887.44,2833.43	3078.39	744.52,678.94,613.36
3c	1664.57	1595.13	1494.83	2887.44,2833.43	3055.24	748.38,680.87
3d	1670.35	1587.42	1489.05	2999.41,2918.30	3066.82	758.02,684.73
3e	1662.64	1587.42	1496.76	2887.44,2810.28	3043.67	746.45,680.87,613.36
3f	1660.71	1595.43	1504.48	2910.58	3037.39	744.52,709.80,682.80
3g	1660.71	1591.27	1506.41	2887.44,2833.43	3078.39	744.52,678.94,613.36

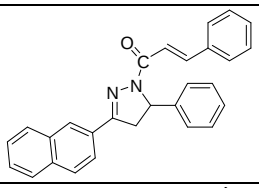
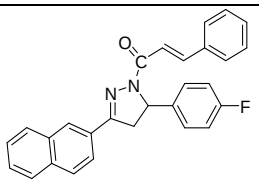
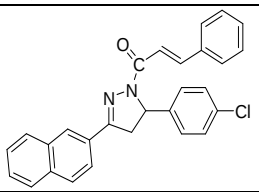
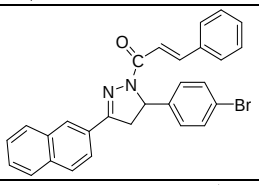
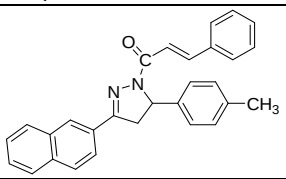
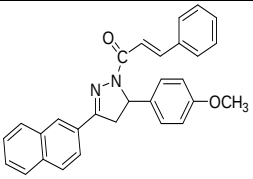
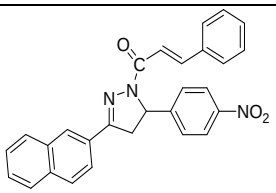
Table-3: ^{1}H NMR spectral data's of the synthesis compound 3a-3g.

Entry	H-4a of pyrazole moiety	H-4e of pyrazole moiety	H-5a of pyrazole moiety	H-1 of chalcone moiety	H-2 of chalcone moiety	Aromatic protons	CH_3 at phenyl ring	OCH_3 at phenyl ring
3a	3.20	3.75	5.49	7.56	8.08	8.02 – 7.12		
3b	3.29	3.88	5.63	7.08	8.05	8.11- 7.02		
3c	3.22	3.82	5.56	7.15	7.93	8.00 – 7.13		
3d	3.28	3.89	5.60	7.16	8.08	8.10 – 7.14		
3e	3.30	3.86	5.62	7.22	8.075	8.08 – 7.16	2.32	
3f	3.34	3.89	5.65	6.89	7.96	7.98 – 6.87		Merged with H4-e proton
3g	3.27	3.92	5.68	7.30	8.08	8.19 – 7.25		

Table 4; ^{13}C NMR spectral data's of the synthesis compound 3a – 3g.

Entry	C-5 of pyrazole moiety	C – 4 of pyrazole moiety	C-3 of pyrazole moiety	C_1 of chalcone moiety	C_2 of chalcone moiety	C=O	Aromatic carbons	Ipso carbons	CH_3 at phenyl ring	OCH_3 at phenyl ring
3a	60.13	42.33	153.96	123.35	141.95	168.93	129.06 – 123.35	134.20,133.05		
3b	59.46	42.27	153.85	115.69	137.77	168.95	128.91 – 115.69	137.74,134.21,133.02		
3c	59.53	42.21	153.83	123.24	140.41	168.98	129.12 - 123.24	140.41,134.22,133.00		
3d	59.59	42.15	153.82	121.60	140.93	168.98	128.82- 121.60	134.23,133.00		
3e	59.92	42.33	153.90	123.35	139.06	168.87	129.62 – 123.35	137.08,134.17,133.05	21.17	
3f	59.58	42.23	153.93	114.25	134.15	168.87	128.53 – 114.25	134.15,133.02		55.29
3g	59.60	42.04	153.83	123.17	135.73	169.12	129.97- 123.17	134.30,133.86,132.97,132.49		

Table 5: Anti microbial activity of the synthesized compounds (3a-3g).

Entry	Structure	Mol.Formula	IUPAC Name	Zone of Inhibition (mm)			
				.25	.5	.75	1.0
3a		$C_{28}H_{22}N_2O$	1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	5	8	12	20
3b		$C_{28}H_{21}N_2OF$	1-(5-(4-flurophenyl)-3-(naphthalene-2-yl)-5-phenyl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	6	9	13	24
3c		$C_{28}H_{21}N_2OCl$	1-(5-(4-chlorophenyl)-3-(naphthalene-2-yl-5-phenyl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	5	8	12	22
3d		$C_{28}H_{21}N_2OBr$	1-(5-(bromophenyl)-3-(naphthalene-2-yl-5-phenyl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	6	7	12	20
3e		$C_{29}H_{24}N_2O$	1-(3-(naphthalene-2-yl)-5-p-tolyl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	4	7	13	19
3f		$C_{29}H_{24}N_2O_2$	1-(5-(4-methoxyphenyl)-3-(naphthalene-2-yl-5-phenyl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	5	9	12	19
3g		$C_{28}H_{21}N_3O_3$	1-(3-(naphthalene-2-yl)-5-(4-nitrophenyl)-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-one	6	9	13	18

Antimicrobial activity

All the synthesised compounds were screened for antibacterial activity against *S.aureus*, *S.epidermis*, *P.aerouginosa* and *E.coli* by agar diffusion method at the concentration of 100µg/ml in DMSO using penicillin G. as standard for antibacterial activity.[5,6] The zone of inhibition was measured in mm and the activity was compared with standard.

RESULT AN D DISCUSSION

The title compounds were synthesized according to the procedures as given in the experimental section. The reactions were monitored by TLC. The physical constants like melting point and solubility were determined for all the intermediate and final products. The compounds were further characterized by IR and H^1 NMR. All the titled compounds were evaluated for their antibacterial activities. Table 5; indicates the anti-microbial activity of the synthesized compounds. The test compounds were screened for anti-microbial activity and the following activity was observed.

***Staphylococcus aureus* (Gram-positive)**

1A, 4A, 5A showed maximum activity of all the compounds tested, were 2A, 6A, 8A, 10A has minimal activity and others 3A, 7A, 9A were moderately active.

***Staphylococcus epidermis* (Gram -positive)**
None of the compounds tested showed maximum activity, all the compounds were having the zone of inhibition at less than 12mm, hence this organism was found to be more resistant to the test compounds.

***Escherichia coli* (Gram-positive)**
1A, and 3A were having maximum inhibition, 10A, 9A, 6A, and 4A showed least activity.

***Pseudomonas aeruginosa* (Gram-negative)**
All the 7 compounds were having almost similar activity with the zone of inhibition between 11-13mm against these bacteria. The flouro substituted compound shows excellent activity against all the microbes.Thus it was found that the chloro substituted phenyl acetylated pyrazole derivatives were more effective against all the organisms tested, than acetylated pyrazole derivatives. The results indicate the presence of a chloro substituted phenyl group attached to pyrazole ring is optimum for antibacterial properties.

CONCLUSION

- The main focus of this research work was to synthesize, purify, characterize and evaluate antimicrobial activities of the newly synthesized pyrazole derivatives.
- A series of titled compounds, i.e., [1a-1g,2a-2g,3a-3g] have been synthesized
- The yield of the synthesized compounds was found to be in range from 65% - 75%.
- Structures of synthesized compounds were confirmed and characterized with the help of analytical data's such as IR and ^{1}H NMR, ^{13}C NMR, elemental analysis and biological studies.
- A single method was used to perform the antimicrobial activities using the agar diffusion method.
- Most of the compounds tested showed good antibacterial activities at the concentration of 100µg/0.1 ml using benzyl penicillin as standard.
- The compounds were tested against four species of bacteria namely, *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Staphylococcus epidermis*. Among the synthesized compounds, derivative 4A, 1A and 5A showed strong antibacterial activity against *Staph.Aureus*, the remaining compounds exhibited mild to moderate activity.
- In case of *E.coli*, 1A and 3A exhibited considerable activity, while the others showed moderate activity.
- All the synthesized compounds had mild antibacterial effect against *Staph. Epidermis* and *P.aeruginosa*.
- Hence, newly synthesized pyrazole derivatives do possess considerable antibacterial activity and further lead optimization should be carried out for the better-expected antibacterial activity
- The synthesis and *invitro* biological activities of a series of 1-(3-(naphthalene-2-yl)-5-aryl-4,5-dihydropyrazol-1-yl)-3-phenylprop-2-en-1-ones (3a-3g) were performed in this study. In general, the compounds having pyrazole groups showed good antibacterial activity.

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