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Microwave Assisted Synthesis of 2-(3-Methyl-1*H*-Indazol-1-yl) containing 1, 8-Naphthyridine Moiety as possible Antimicrobial Agents

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ABSTRACT: Some new 2-[(3-methyl-1H-indazol-1-yl)-3-substituted phenyl -1, 8-naphthyridine have been synthesized employing microwave techiniques and evaluated for antimicrobial activity. 3-aryl-2-hydrazino-1, 8- naphthyridines **(1)** were reacted with Substituted acetophenones **(2)** in the presence of methanol to furnish 2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3 substituted phenyl -1, 8-naphthyridine **(3a-e)**. These 2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3 substituted phenyl -1, 8-naphthyridine **(3a-e)** were further treated with DMF/KOH to afford 2-[(3-methyl-1H-indazol-1-yl)-3-substituted phenyl -1, 8-naphthyridine **(4a-e)**. The structures of newly synthesized compounds **(3a-e)** and **(4a-e)** have been confirmed by suitable spectroscopial techniques such as IR, ^{1}H NMR and MS. All the compounds were screened for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Escherchia coli* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* and *Asperigillus niger*. The compounds exhibited moderate antibacterial and good antifungal activities. Compound 4b and 4d showed significant antifungal activity against *A. niger* and *C. albicans* respectively.
KEYWORDS: 1H-indazol, naphthyridine, antifungal, antibacterial

INTRODUCTION

Microwave assisted organic synthesis is a fast developing area in synthetic organic chemistry. The basis of this synthetic technique is the empirical observation that some organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. Although different hypotheses have been proposed to account for the effect of microwave on organic reactions the reason for the dramatic acceleration effect is thought to be instantaneous super heating of the reaction medium. Regardless of the exact origin of the microwave effect, it is found to be extremely efficient and applicable to a very broad range of practical synthesis[1-5].1, 8-Naphthyridines[6, 7] and 1*H*-indazol [8-14] because of their great potential biological activity, have attracted a great deal of interest from organic chemists. In view of this and in continuation of our interest on microwave assisted organic reactions[15-19], we report herein the microwave assisted synthesis of some new 2-(3-methyl-1*H*-indazol-1-yl) containing 1, 8-naphthyridine moiety.

The structure of the product [(3a-e) and (4a-e)] has been confirmed by elemental analysis and spectral (IR, ^{1}H NMR and MS) data.

In conclusion, we have demonstrated an efficient, mild and convenient protocol for the synthesis of 2-(3-methyl-1*H*-indazol-1-yl)-1, 8-naphthyridine under microwave irradiation. High yields, short reaction

times and easy work up procedure are other advantages of this methodology.

EXPERIMENTAL

Melting points were determined in open capillary tubes using Syntax apparatus and are uncorrected. IR spectra in KBr were recorded on a JASCO FT/IR-410 spectrometer. ^{1}H NMR spectra was recorded on Bruckner 300 MHz NMR spectrometer (Chemical shift in δ ppm) using TMS as internal standard and mass spectra on a Jeol JMS D-300 spectrometer. Analytical TLC was performed on Merck 60 F-254 silica gel plate's irradiation was carried out in a domestic microwave oven (BPL 2450 MHz, 800G).

GENERAL METHOD:

The title compounds were prepared in the following steps:

General procedure for synthesis of 2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3 substituted phenyl -1, 8-naphthyridine **(3a-e)**

A mixture of 3-aryl-2-hydrazino-1, 8- naphthyridines **1** (0.01 mol), Substituted acetophenones **2** (0.01 mol) and methanol (30 ml) with a few drops of glacial acetic acid was exposed to microwave irradiation at 150 watts for 2 min. After completion of the reaction as indicated by TLC, the reaction mixture was cooled; the solid thus separated was filtered and recrystallized from methanol to give (3a-e).

Synthesis of2-[(3-methyl-1H-indazol-1-yl)-3-substituted phenyl -1, 8-naphthyridine **(4a-e)**

A solution of hydrazone **3** (0.01mol) in DMF (10 ml), KOH (0.05 mol) was irradiated in a microwave oven at 450 watts for 5 min. After complete conversion as indicated by TLC, the reaction mixture was allowed to attain room temp and diluted with cold water. The solid obtained was filtered, washed with water and recrystallized from methanol to afford **(4a-e)**

Physical data of synthesized compounds **(3a-e)** and **(4a-e)** are summarized in Table 1.

2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3-(4-methoxyphenyl)]-1, 8-naphthyridine **3a**

IR (KBr): 3336(NH), 1624 (C=N), 741 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.78-7.37 (m, OH, Ar-H), 7.50 (m, 1H, C_6-H), 7.65 (m, 2H, C_4-H and C_5-H), 8.25 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 10.05 (s, 1H, NH); m/z 468 (m+, 100%), 433 (25.9), 278 (14.1), 251 (11.8), 250 (55.2), 236 (11.6), 235 (9.6), 208 (10.6), 192 (7.7).

2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3-(4-chlorophenyl)]-1,8-naphthyridine **3b**

IR (KBr): 3336(NH), 1624 (C=N), 741 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.50 (m, 1H, C_6-H), 7.65 (m, 2H, C_4-H and C_5-H), 8.25 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 10.05 (s, 1H, NH); m/z 468 (m+, 100%), 433 (25.9), 278 (14.1), 251 (11.8), 250 (55.2), 236 (11.6), 235 (9.6), 208 (10.6), 192 (7.7).

2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3-(3-chlorophenyl)]-1,8-naphthyridine **3c**

IR (KBr): 3336(NH), 1624 (C=N), 741 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.50 (m, 1H, C_6-H), 7.65 (m, 2H, C_4-H and C_5-H), 8.25 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 10.05 (s, 1H, NH); m/z 468 (m+, 100%), 433 (25.9), 278 (14.1), 251 (11.8), 250 (55.2), 236 (11.6), 235 (9.6), 208 (10.6), 192 (7.7).

2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3-(2-chlorophenyl)]-1, 8-naphthyridine **3d**

IR (KBr): 3336(NH), 1624 (C=N), 741 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.50 (m, 1H, C_6-H), 7.65 (m, 2H, C_4-H and C_5-H), 8.25 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 10.05 (s, 1H, NH); m/z 468 (m+, 100%), 433 (25.9), 278 (14.1), 251 (11.8), 250 (55.2), 236 (11.6), 235 (9.6), 208 (10.6), 192 (7.7).

2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3-phenyl-1, 8-naphthyridine **3e**

IR (KBr): 3336(NH), 1624 (C=N), 741 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.50 (m, 1H, C_6-H), 7.65 (m, 2H, C_4-H and C_5-H), 8.25 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 10.05 (s, 1H, NH); m/z 468 (m+, 100%), 433 (25.9), 278 (14.1), 251 (11.8), 250 (55.2), 236 (11.6), 235 (9.6), 208 (10.6), 192 (7.7).

2-[(3-methyl-1H-indazol-1-yl)-3-(4-methoxyphenyl)]-1, 8-naphthyridine **4a**

IR (KBr): 3336(NH), 1615 cm^{-1} (C=N); ^{1}HNMR ($DMSOd_6$ + $CDCl_3$): 2.55 (s, 3H, CH_3), 6.85-7.52 (m, 10H, C_4-H and 9 Ar-H), 7.70 (m, 1H, C_6-H of naphthyridine moiety), 8.30 (m, 1H, naphthyridine moiety); MS : m/z 432 (M^+, 13%), 431(11.6), 341 (16.4), 276 (27.6), 275 (96.1), 250 (31.9), 249 (59), 236 (11.7), 235 (65.7), 171 (100).

2-[(3-methyl-1H-indazol-1-yl)-3-(4-chlorophenyl)]-1, 8-naphthyridine **4b**

IR (KBr): 3336(NH), 1615 cm^{-1} (C=N); ^{1}HNMR ($DMSOd_6$ + $CDCl_3$): 2.55 (s, 3H, CH_3), 6.85-7.52 (m, 10H, C_4-H and 9 Ar-H), 7.70 (m, 1H, C_6-H of naphthyridine moiety), 8.30 (m, 1H, naphthyridine moiety); MS : m/z 432 (M^+, 13%), 431(11.6), 341 (16.4), 276 (27.6), 275 (96.1), 250 (31.9), 249 (59), 236 (11.7), 235 (65.7), 171 (100).

2-[(3-methyl-1H-indazol-1-yl)-3-(3-chlorophenyl)]-1, 8-naphthyridine **4c**

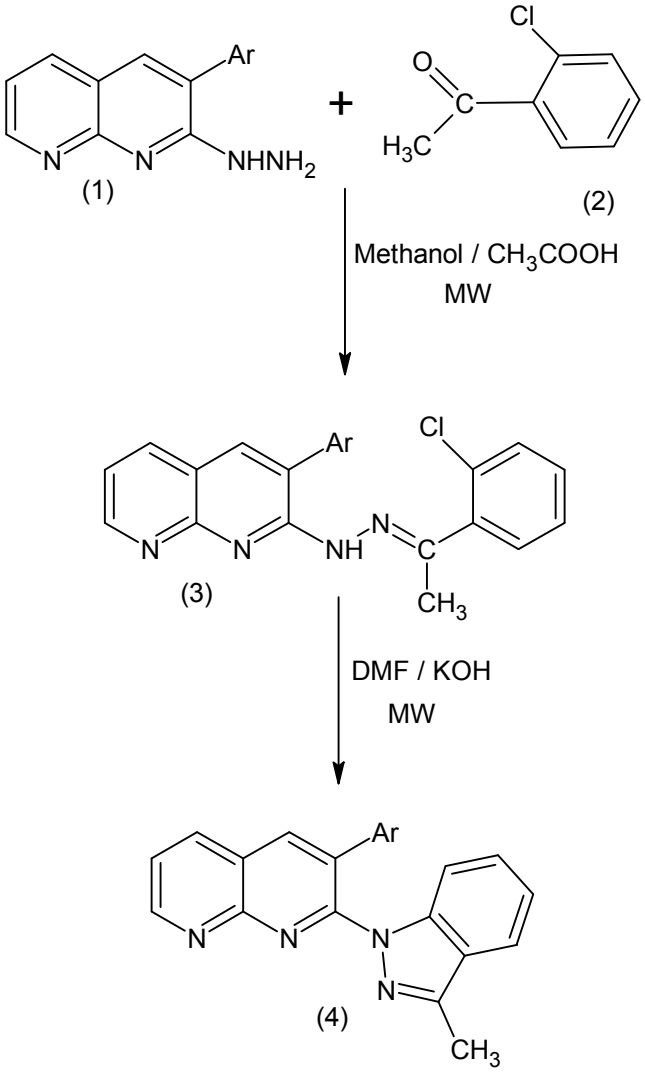
IR (KBr): 3336(NH), 1615 cm^{-1} (C=N); ^{1}HNMR ($DMSOd_6$ + $CDCl_3$): 2.55 (s, 3H, CH_3), 6.85-7.52 (m, 10H, C_4-H and 9 Ar-H), 7.70 (m, 1H, C_6-H of naphthyridine moiety), 8.30 (m, 1H, naphthyridine moiety); MS : m/z 432 (M^+, 13%), 431(11.6), 341 (16.4), 276 (27.6), 275 (96.1), 250 (31.9), 249 (59), 236 (11.7), 235 (65.7), 171 (100).

2-(3-methyl-1H-indazol-1-yl)-3-(2-chlorophenyl)]-1, 8-naphthyridine **4d**

IR (KBr): 3336(NH), 1615 cm^{-1} (C=N); ^{1}HNMR ($DMSOd_6$ + $CDCl_3$): 2.55 (s, 3H, CH_3), 6.85-7.52 (m, 10H, C_4-H and 9 Ar-H), 7.70 (m, 1H, C_6-H of naphthyridine moiety), 8.30 (m, 1H, naphthyridine moiety); MS : m/z 432 (M^+, 13%), 431(11.6), 341 (16.4), 276 (27.6), 275 (96.1), 250 (31.9), 249 (59), 236 (11.7), 235 (65.7), 171 (100).

2-(3-methyl-1H-indazol-1-yl)-3-phenyl-1,8-naphthyridine **4e**

IR (KBr): 3336(NH), 1615 cm^{-1} (C=N); ^{1}HNMR ($DMSOd_6$ + $CDCl_3$): 2.55 (s, 3H, CH_3), 6.85-7.52 (m, 10H, C_4-H and 9 Ar-H), 7.70 (m, 1H, C_6-H of naphthyridine moiety), 8.30 (m, 1H, naphthyridine moiety); MS : m/z 432 (M^+, 13%), 431(11.6), 341 (16.4), 276 (27.6), 275 (96.1), 250 (31.9), 249 (59), 236 (11.7), 235 (65.7), 171 (100).



SCHEME - 1

BIOLOGICAL ACTIVITY:

The antimicrobial activity was determined using disc diffusion[20] method by measuring the inhibition zone in mm. All the newly synthesized compounds i.e. **(3a-e)** and **(4a-e)** were screened *in vitro* for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* and *Bacillus sublitis)* and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa)* at concentration of 500 µg/ml. Antifungal activity was tested against *Candida albicans* and *Aspergillus niger* at concentration of 500 µg/ml. Ciprofloxin (10 µg/disc) was used as a standard drug for antibacterial screening and fluconazole (10 µg/disc) was used as a standard for antifungal screening. All synthesized compounds exhibited moderate antibacterial activities and significant antifungal activities. Each experiment was done in triplicate and the average reading was taken. The results are tabulated in Table 2.

RESULTS:

Synthesis of 3-aryl-2-hydrazino-1, 8- naphthyridines **1** by the reaction of 3-aryl-2-chloro-1, 8- naphthyridines with hydrazine hydrate was reported earlier. Condensation of **1** with Substituted acetophenones **2** in methanol containing a catalytic amount of glacial acetic acid under microwave irradiation afforded the corresponding 2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3 substituted phenyl -1, 8-naphthyridine **(3a-e)** in excellent yields.

The 2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3 substituted phenyl -1, 8-naphthyridine **(3a-e)** on cyclization with DMF/KOH under microwave irradiation furnished 2-[(3-methyl-1H-indazol-1-yl)-3-substituted phenyl -1, 8-naphthyridine (**4a-e)** in good yields. The reaction is very facile, rapid, efficient, mild and is devoid of any by-products. The purity of the products is high. The reaction rate is enhanced tremendously under microwave irradiation as compared to conventional method with improved yields. The structure of the product **[(3a-e)** and **(4a-e)]** has been confirmed by elemental analysis and spectral (IR, ^{1}H NMR and MS) data. The compounds were screened *in vitro* for their antibacterial and antifungal potential by disc diffusion assay against selected pathogenic bacteria and human pathogenic fungi. The results of antibacterial and antifungal activities expressed in terms of zone of inhibition are reported in Table 2.

Table1. Physical and analytical data of the synthesized compounds (3a-e) and (4a-e)

Comp No.	Ar	Reaction time	Mol. Formula	Yield (%)	Mol Wt.	M.p. (^{0}C)	R_f value
3a	p-$CH_3OC_6H_4$	2 min	$C_{23}H_{19}ClN_4$	95	403	220°C	0.7311
3b	P-ClC_6H_4	1.5 min	$C_{22}H_{16}Cl_2N_4$	90	407	220°C	0.7272
3c	m-ClC_6H_4	2 min	$C_{22}H_{16}Cl_2N_4$	85	407	195°C	0.7647
3d	o-ClC_6H_4	2 min	$C_{22}H_{16}Cl_2N_4$	75	407	190°C	0.6860
3e	C_6H_5	1.5 min	$C_{22}H_{17}ClN_4$	80	373	220°C	0.7701
4a	p-$CH_3OC_6H_4$	6 min	$C_{23}H_{18}N_4O$	84	366	245°C	0.7121
4b	P-ClC_6H_4	7 min	$C_{22}H_{15}ClN_4$	95	371	243°C	0.7251
4c	m-ClC_6H_4	7.5 min	$C_{22}H_{15}ClN_4$	90	371	195°C	0.6972
4d	o-ClC_6H_4	8 min	$C_{22}H_{15}ClN_4$	85	371	180°C	0.7211
4e	C_6H_5	7.5 min	$C_{22}H_{16}N_4$	80	336	240°C	0.7011

Tabel 2. Antimicrobial activity-sensitivity testing of compounds (3a-e) and (4a-e)

Compound No.	Zone of inhition in mm					
	Antibacterial activity				Antifungal activity	
	S.aureus	***B.subtilis***	***E.Coli***	***P.aeruginosa***	***C.albicans***	***A.niger***
3a	10	11	8	8	17	17
3b	13	15	9	9	19	19
3c	10	12	8	8	17	17
3d	12	13	9	9	16	16
3e	11	10	9	9	15	15
4a	10	09	8	8	22	24
4b	09	11	9	9	23	26
4c	10	12	8	8	19	22
4d	10	12	9	9	26	22
4e	11	10	8	8	17	20
Ciprofloxacin	26	26	28	25	-	-
Fluconazole	-	-	-	-	26	25

DISCUSSION AND CONCLUSION

Some novel 2-{(2E)-2-[1-(2-chlorophenyl) ethylidene] hydrazino}-3 substituted phenyl -1, 8-naphthyridine derivatives **(3a-e) and** 2-[(3-methyl-1H-indazol-1-yl)-3-substituted phenyl -1, 8-naphthyridine **(4a-e)** have been synthesized and evaluated for antimicrobial activities. The results of antimicrobial studies of newly synthesized compounds reveal that compounds possess antibacterial activities to certain extent and significant antifungal activities. Compound **4b** with chloro substitution found to be the most potent compound of series with antifungal activities more than that of standard drug i.e. fluconazole against *A. niger*. It was followed by compound **4d** which depicted equipotent action as that of standard drug i.e. fluconazole against *C. albicans.* The rest of all compounds have shown moderate activities against tested fungal strains. In general compounds **4a-e** has depicted more potent activities that compounds **3a-e**. Even though, the synthesized compounds did not exhibit appreciable antibacterial activity, the data reported in this article may be helpful guide for the medicinal chemists who are working in this area.

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