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NOTE

Conventional and microwave irradiation technique for the synthesis of some pyrimidine and pyrazoline derivative from 1-{4′-[(4″-methylpiperazinyl)-diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one and studies of their antimicrobial activity

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Abstract : A series of compounds namely 6-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-4-(substitutedphenyl)pyrimidine-2-yl-amide (3a-j), 3-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-5-(substitutedphenyl)pyrazole (4a-j) and 3-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-5-(substitutedphenyl)pyrazolecarboxamide (5a-j) have been prepared by the reaction of chalcone derivative 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (2a-j) with guanidinium nitrate, hydrazine hydrate and semicarbazide hydrochloride respectively. The reactions have been carried out by both microwave and conventional methods. The microwave-assisted reactions are carried out in a "Q-Pro-M-Modified Microwave System". The compounds have been screened for their antimicrobial activities against different microorganisms. The structures of novel synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H NMR and Mass spectral data.

Keywords : Synthesis, pyrimidine, pyrazoline, antimicrobial activity, microwave.

Introduction

Recently, an ever-growing interest in the application of microwave irradiation in organic synthesis has led to the development of a variety of extremely useful synthetic transformations[1,2]. The microwave assisted[3] organic reactions occur more rapidly, safely and with higher chemical yields[4] render the microwave method superior to conventional method. Microwave assisted reactions were carried out in "Q-Pro-M-Modified Microwave System".

Nitrogen containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. The increasing importance of pyrimidine and its derivatives as intermediates for the synthesis of biologically active compounds has led to continuing development of new simple procedures for their synthesis. Pyrimidine and condensed pyrimidine derivatives possessing anti-inflammatory and analgesic activities are well documented in literature. The pyrimidine derivatives have been reported to possess a variety of biological activities[5-8], notable among which are the antibacterial[9], anticancer[10], anti-inflammatory[11] and analgesic[12] activities.

Pyrazoline as a class of heterocyclic compounds have been studied extensively for the past several years because of their broad spectrum of biological activity and variety of medicinal applications. A number of biological activities[13,14] are associated with pyrazoline. Numerous reports have appeared in literature describing antibacterial, analgesic[15], anticancer[16], anti-inflammatory and cardiovascular properties of heterocyclic ring such as pyrazoline.

Results and discussion

A mixture of *p*-aminoacetophenone and con. HCl was warmed on water bath to make clear solution. Then this mixture was cooled to 0-5 °C and $NaNO_2$ solution was added to it, until the starch iodide paper becomes blue black. The mixture was stirred for one hour. After diazotization, *N*-methylpiperazine solution in NaOH was added to the above solution with constant stirring. The pH of the reaction mixture was maintained at 7-8 by the simultaneous addition of solid sodium bicarbonate in portions to yield 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-ethan-1-one[17] (1). To a solution of (1) in KOH, various

substituted aldehyde were added portion-wise with constant stirring to furnish the compound 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (**2a-j**).

Compound, (**2a-j**) upon cyclization with guanidinium nitrate, hydrazine hydrate and semicarbazide hydrochloride by microwave irradiation technique yields the title compounds (**3a-j**), (**4a-j**) and (**5a-j**) in good yield. The above-mentioned compounds were also synthesized by the conventional method. It is noteworthy that the reaction which required 6–8 h in conventional method, was completed within 3–5 min by microwave irradiation technique and yield have been remarkably improved from 62–77% to 83–91%.

In IR spectrum of (**3c**), significant bands appeared at 3226 (-NH_2) and 1592 (-N=N-) cm^{-1}. In the ^1H NMR spectrum of (**3c**), structure was evidenced by the appearance of signals at δ 5.16 and 6.52 due to -NH_2 and -CH respectively. In the IR spectrum of (**4e**), compound revealed significant bands at 3221 (-NH) and 1598 (-N=N-) cm^{-1}. In the ^1H NMR spectrum of (**4e**), signals were observed at δ 8.35 and 6.03 due to -NH and -CH respectively, which confirming the formation of pyrazole ring. In IR spectrum of (**5c**), significant bands appeared at 3210 (-NH_2), 1668 (-C=O) and 1595 (-N=N-) cm^{-1}. In the ^1H NMR spectrum of (**5c**), structure was evidenced by the appearance of signals at δ 4.16, 4.96–5.08 and 5.40 due to -CH, -CH_2 and -$CONH_2$ of pyrazoline ring respectively, which confirming the formation of pyrazoline ring.

In mass spectra of (**3c**) and (**5c**), the molecular ion peak appeared at 373 (M^+) and 391 (M^+). In the mass spectrum of (**4e**), the molecular ion peak appeared at 380 (M^+) and 382 (M+2) due to the presence of chlorine atom in the structure. In the formation of compounds (**3c**) and (**4e**), aromatization takes place in the presence of base while in the formation compound (**5c**) cyclisation was carried out using semicarbazide and we have not added base, so final elimination of proton is not take place and aromatization becomes not possible.

Antibacterial activity : All the compounds were tested for *in vitro* screening against gram-positive *Staphylococcus aureus* and gram-negative *E. coli* and *P. aeruginosa*. The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[18] at three-test concentrations 128, 256 and 512 μg/mL. Inoculums of standard suspension (0.1 mL of the test organism strain which contains 10^6 bacilli/mL) were added. The tubes were incubated at 37 °C for 48 h and then examined for the presence or absence of growth of the organism. The lowest concentration, which showed no visible growth, was taken as an end point minimum inhibitory concentration (MIC). The MIC level of compounds against these organisms are given in Table 2.

Antifungal activity : The antifungal activity of compounds has been assayed *in vitro* at a concentration of 128, 256 and 512 μg/mL against *Candida albicans*, which were maintained on nutrient agar slants, which were stored at 4 °C. None of the compounds was found to possess better activity than Dithane-M 45 (Table 2).

Experimental

The melting points were determined in open capillaries and are uncorrected. The homogeneity of compounds was checked by TLC on silica gel 'G' coated glass plates. IR spectra were recorded in KBr on Shimadzu FT-IR 8300 spectrometer and ^1H NMR spectra were recorded in Bruker Avance II and Varian instruments at 400 MHz in DMSO by using TMS as internal standard. Mass spectra of the synthesized compounds have been recorded on a Jeol SX 102/DA-600 spectrometer. Microwave assisted reactions were carried out in "Q-Pro-M Modified Microwave System". The elemental analysis (%N) was carried out by total Kjeldahl method at Atul Limited, Valsad.

1-{4′-[(4″-Methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (**2a-j**) :

Conventional method : To a solution of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}ethan-1-one (**1**) (0.01 mol) in ethanol, 40% KOH (2 ml) and various substituted aldehyde (0.01 mol) were added portion-wise with constant stirring. The mixture was stirred for 2 h and then it was refluxed for 4–6 h. The reaction mixture was then cooled at room temperature and the contents were poured into crushed ice and dil. HCl was added. The separated product was filtered and recrystallized from ethyl acetate. Yield 65–77%.

Table 1. Characterization data of the compounds

Compd.	Functional group	M.p. (°C)	Mol. formula	Conventional Time (h)	Conventional Yield (%)	Microwave Time (min)	Microwave Yield (%)	N(%) Calcd.	N(%) Found
3a	2-OCH_3	189	$C_{22}H_{25}ON_7$	7–8	70	4–5	85	24.30	24.38
3b	4-OCH_3	179	$C_{22}H_{25}ON_7$	7–8	72	4–5	88	24.30	24.37
3c	-H	201	$C_{21}H_{23}N_7$	7–8	74	4–5	90	26.25	26.33
3d	3-Br	241	$C_{21}H_{22}N_7Br$	7–8	70	4–5	86	21.67	21.75
3e	2-Cl	208	$C_{21}H_{22}N_7Cl$	7–8	71	4–5	89	24.03	24.11
3f	-$N(CH_3)_2$	186	$C_{23}H_{28}N_8$	7–8	69	4–5	85	26.90	26.98
3g	3-NO_2	209	$C_{21}H_{22}O_2N_8$	7–8	74	4–5	88	26.77	26.85
3h	2-OH	215	$C_{21}H_{23}ON_7$	7–8	72	4–5	90	25.17	25.25
3i	3-OCH_3 4-OH	195	$C_{22}H_{25}O_2N_7$	7–8	71	4–5	84	23.37	23.45
3j	3-OCH_3 4-OCH_3	191	$C_{23}H_{27}O_2N_7$	7–8	74	4–5	89	22.61	22.69
4a	2-OCH_3	158	$C_{21}H_{24}ON_6$	6–7	69	4–5	85	22.20	22.32
4b	4-OCH_3	175	$C_{21}H_{24}ON_6$	6–7	65	4–5	89	22.20	22.29
4c	-H	>300	$C_{20}H_{22}N_6$	6–7	70	4–5	90	24.11	24.22
4d	3-Br	>300	$C_{20}H_{21}N_6Br$	6–7	74	4–5	91	19.66	19.76
4e	2-Cl	146	$C_{20}H_{21}N_6Cl$	6–7	77	4–5	89	21.94	22.01
4f	-$N(CH_3)_2$	>300	$C_{22}H_{27}N_7$	6–7	63	4–5	88	25.04	25.15
4g	3-NO_2	203	$C_{20}H_{21}O_2N_7$	6–7	67	4–5	86	24.92	25.03
4h	2-OH	221	$C_{20}H_{22}ON_6$	6–7	70	4–5	88	23.05	23.15
4i	3-OCH_3 4-OH	167	$C_{21}H_{24}O_2N_6$	6–7	67	4–5	89	21.30	21.41
4j	3-OCH_3 4-OCH_3	>300	$C_{22}H_{26}O_2N_6$	6–7	69	4–5	85	20.57	20.69
5a	2-OCH_3	225	$C_{22}H_{27}O_2N_7$	7–8	62	4–5	83	23.26	23.35
5b	4-OCH_3	237	$C_{22}H_{27}O_2N_7$	7–8	65	3–4	85	23.26	23.37
5c	-H	189	$C_{21}H_{25}ON_7$	7–8	66	3–4	87	25.04	25.15
5d	3-Br	>300	$C_{21}H_{24}ON_7Br$	7–8	65	3–4	86	20.84	20.91
5e	2-Cl	203	$C_{21}H_{24}ON_7Cl$	7–8	71	3–4	89	23.02	23.11
5f	-$N(CH_3)_2$	206	$C_{23}H_{30}ON_8$	7–8	66	3–4	85	25.78	25.87
5g	3-NO_2	210	$C_{21}H_{24}O_3N_8$	7–8	69	3–4	88	25.67	25.77
5h	2-OH	191	$C_{21}H_{25}O_2N_7$	7–8	70	3–4	90	24.06	24.18
5i	3-OCH_3 4-OH	>300	$C_{22}H_{27}O_3N_7$	7–8	71	3–4	89	22.41	22.52
5j	3-OCH_3 4-OCH_3	198	$C_{23}H_{29}O_3N_7$	7–8	67	3–4	87	21.71	21.80

Table 2. Antimicrobial activity of the compounds

Compd.	*E. coli* 128 µg/mL	*E. coli* 256 µg/mL	*E. coli* 512 µg/mL	*P. aeruginosa* 128 µg/mL	*P. aeruginosa* 256 µg/mL	*P. aeruginosa* 512 µg/mL	*S. aureus* 128 µg/mL	*S. aureus* 256 µg/mL	*S. aureus* 512 µg/mL	*C. albicans* 128 µg/mL	*C. albicans* 256 µg/mL	*C. albicans* 512 µg/mL
3a	-	-	+	-	-	+	-	+	+	-	-	-
3b	-	-	+	-	-	+	-	-	+	-	-	-
3c	-	+	+	-	+	+	-	+	+	-	-	-

Table-2 (contd)

3d	-	+	++	-	+	++	-	+	++	-	-	+
3e	-	+	++	-	-	++	-	+	++	-	-	-
3f	-	+	+	-	+	+	-	-	+	-	-	-
3g	-	-	+	-	-	+	-	-	+	-	-	-
3h	-	+	+	-	+	+	-	+	+	-	-	-
3i	-	-	+	-	+	+	-	-	+	-	-	-
3j	-	-	+	-	-	+	-	-	+	-	-	-
4a	-	+	++	-	-	+	-	+	++	-	-	-
4b	-	+	++	-	+	++	-	+	++	-	-	-
4c	-	-	++	-	+	++	-	+	++	-	-	-
4d	-	+	++	-	+	++	-	+	++	-	-	+
4e	-	+	++	-	+	+	-	-	++	-	-	-
4f	-	-	+	-	-	+	-	-	+	-	-	+
4g	-	-	+	-	-	++	-	-	+	-	-	+
4h	-	-	+	-	+	+	-	-	+	-	-	+
4i	-	-	+	-	-	+	-	-	+	-	-	-
4j	-	-	++	-	+	++	-	+	++	-	-	-
5a	-	+	++	-	-	+	-	-	+	-	-	-
5b	-	+	++	-	+	+	-	+	+	-	-	-
5c	-	-	+	-	-	++	-	+	++	-	-	-
5d	-	+	++	-	+	++	-	+	++	-	-	+
5e	-	+	++	-	+	++	-	-	++	-	-	+
5f	-	-	+	-	-	+	-	-	+	-	-	+
5g	-	-	+	-	-	++	-	+	+	-	-	+
5h	-	-	++	-	+	+	-	-	+	-	-	+
5i	-	-	+	-	-	+	-	-	+	-	-	-
5j	-	+	++	-	+	++	-	+	++	-	-	-
Streptomycin	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	-	-
Dithane-M 45	-	-	-	-	-	-	-	-	-	-	++++	++++

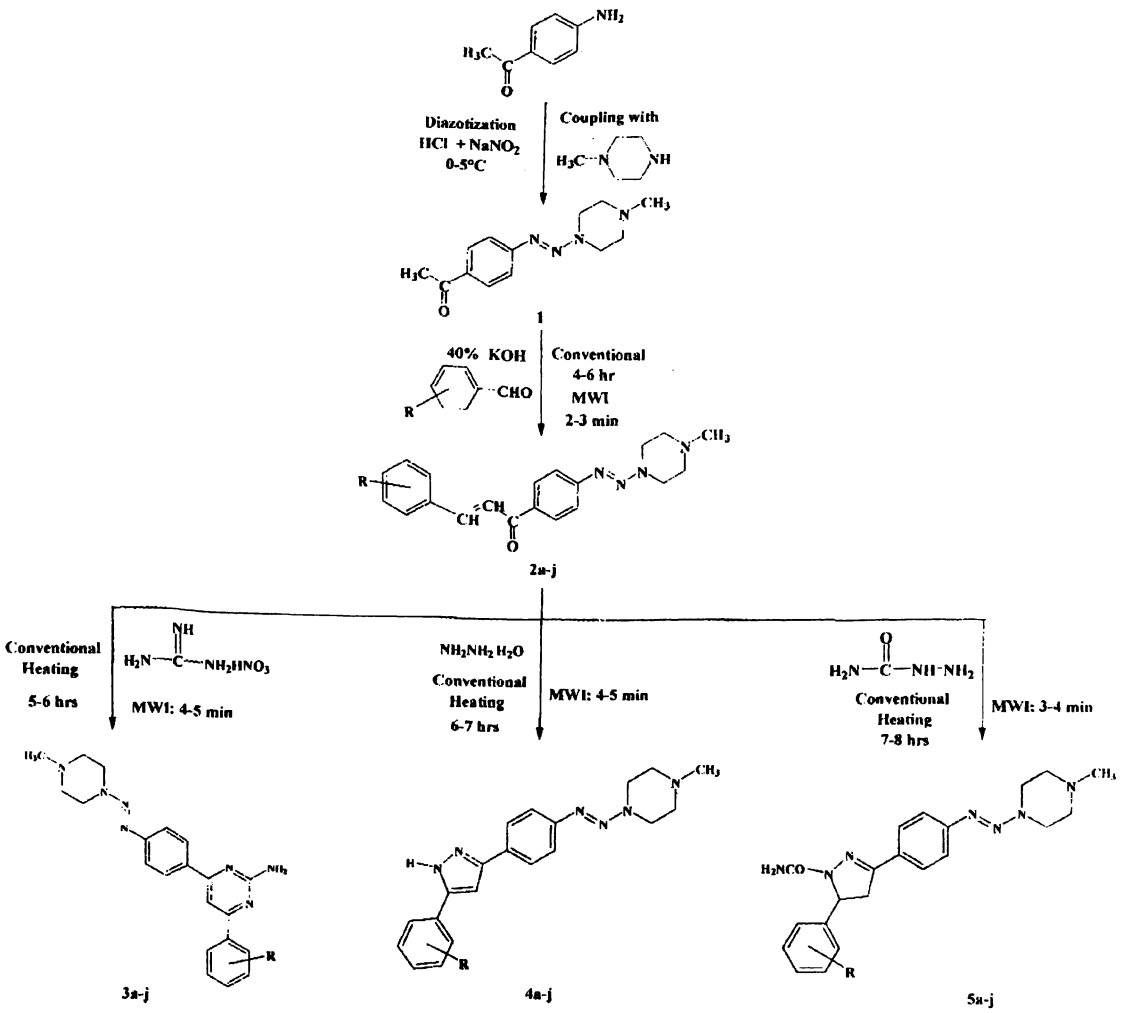
(-)< 6 mm, (+) = 7-10 mm, (++) = 11-15 mm, (+++) = 16-21 mm, (++++) = 22-28 mm.

Microwave method : A mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}ethan-1-one (**1**) (0.01 mole) in ethanol, 40% KOH (2 ml) and various substituted aldehyde (0.01 mol) were added portion-wise with constant stirring. The mixture was stirred for 2 h, and subsequently subjected to microwave irradiation for specified time of 2-3 min at power level 500 W. The reaction mixture was then cooled, poured into crushed ice and dil. HCl was added. The separated product was filtered and recrystallized from ethyl acetate. Yield 78-91%.

6-{4′-[(4″-Methylpiperazinyl)diazenyl]phenyl}-4-(substitutedphenyl)pyrimidine-2-yl-amine (**3a-j**) :

Conventional method : A mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)-prop-2-en-1-one (**2a-j**) (0.01 mol), guanidinium nitrate (0.01 mol) and NaOH (0.02 mol) in DMF (30 ml) was heated at reflux temperature for 5-6 h. The reaction mixture was then cooled, poured into crushed ice. The product thus obtained was filtered, washed with water and recrystallized from acetone.

Microwave method : In a 250 ml R.B.F., a mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (**2a-j**) (0.01 mol), guanidinium nitrate (0.01 mol), and NaOH (0.02 mol) was dissolved in DMF (30 ml) by slow warming and shaking. The reaction mixture was stirred for some time at room temperature and subsequently subjected to microwave irradiation for specified time of 4-5 min at power level 500 W. The reaction solution was then cooled, poured

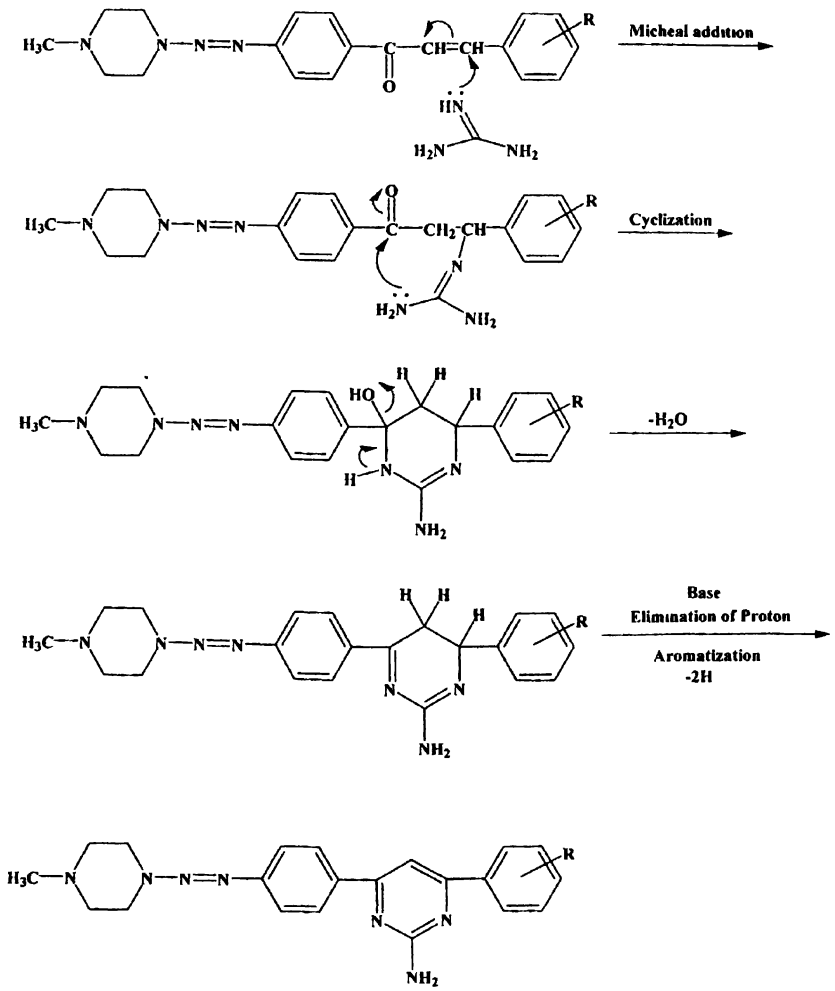


	R		R
a	2-OCH_3	f	4-$N(CH_3)_2$
b	4-OCH_3	g	3-NO_2
c	-H	h	2-OH
d	3-Br	i	3-OH, 4-OCH_3
e	2-Cl	j	3,4-di-OCH_3

Scheme 1

into crushed ice. The product thus obtained was filtered, washed with water and recrystallized from acetone.

(**3c**) : IR (KBr) : 3226 (-NH_2), 1641 (-C=N), 1592 (-N=N-) cm^{-1}; ^1H NMR : δ 8.27-6.56 (9H, m, Ar-H), 6.52 (1H, s, -CH (pyrimidine ring)), 5.16 (2H, s, -NH_2), 2.93-2.61 (8H, m, $(-CH_2)_2$ (piperazine ring)), 2.21 (3H, s, N-CH_3); MS (*m/z*) : 373 (M^+), 359, 346, 275, 247, 218.



Reaction mechanism of **3a-j**

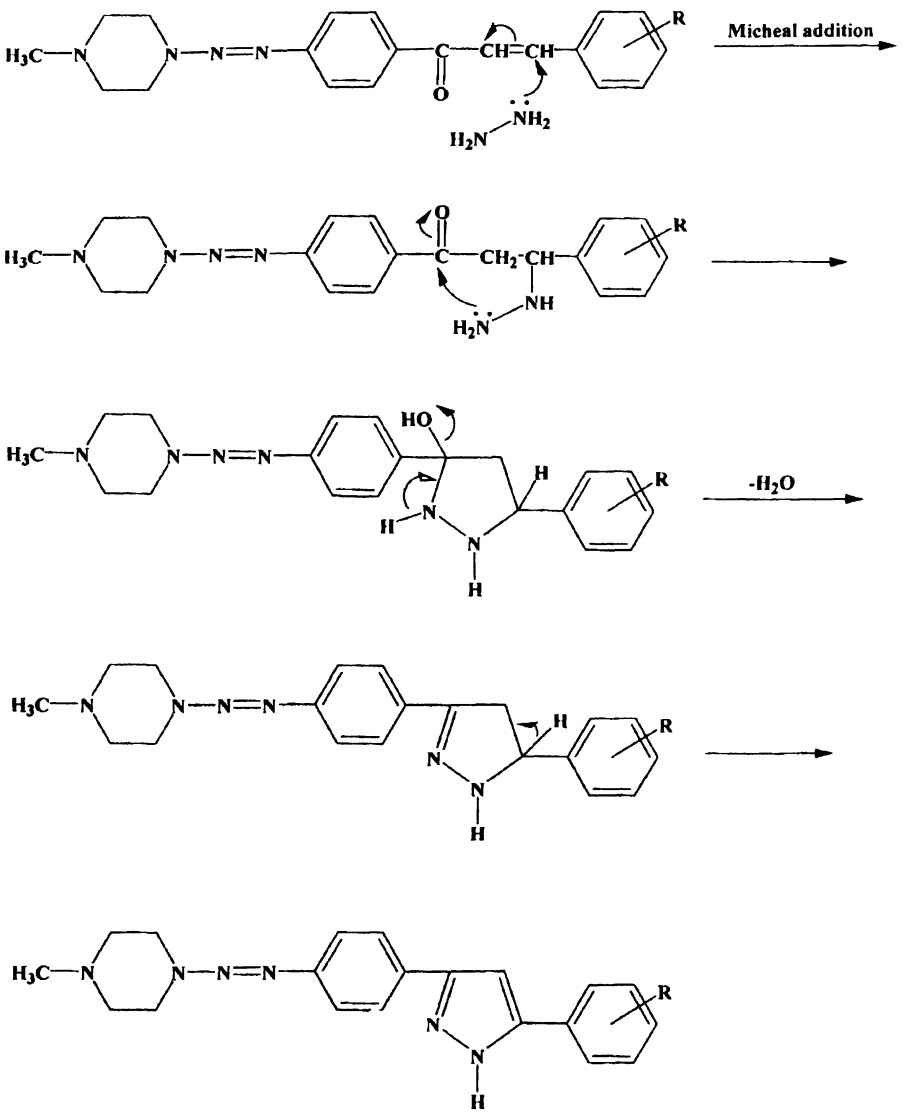
3-(4′-[(4″-Methylpiperazinyl)diazenyl]phenyl}-5-(substitutedphenyl)pyrazole (**4a-j**) :

Conventional method : A mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)-prop-2-en-1-one (**2a-j**) (0.01 mol) and hydrazine hydrate (0.015 mol) in DMF (30 ml) was refluxed gently on sand bath for 6–7 h. The resulting mixture was then treated with crushed ice. The product obtained was filtered, washed with water and recrystallized from acetone.

Microwave method : In a 250 ml R.B.F., a mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (**2a-j**) (0.01 mol) and hydrazine hydrate (0.015 mol) in DMF (30 ml) was taken. The reaction mixture was stirred for some time at room temperature and subsequently subjected to microwave irradiation for specified time of 4–5 min at power level 500 W. The reaction solution was then cooled, poured into crushed ice. The product thus obtained was filtered, washed with water and recrystallized from acetone.

(**4e**) : IR (KBr) : 3223 (-NH), 2982 ($-CH_3$), 1598 (-N=N-), 750 (C-Cl) cm^{-1}; ^1H NMR : δ 8.35 (1H, s, -NH (pyrazole ring)), 8.16–6.68 (8H, m, Ar-H), 6.03 (1H, s, -CH (pyrazole ring)), 2.95–2.72 (8H, m, $(-CH_2)_2$ (piperazine ring)), 2.64 (3H, s, $N-CH_3$); MS (*m/z*) : 380 (M^+), 382 (M + 2), 282, 284, 254, 256, 191, 106.

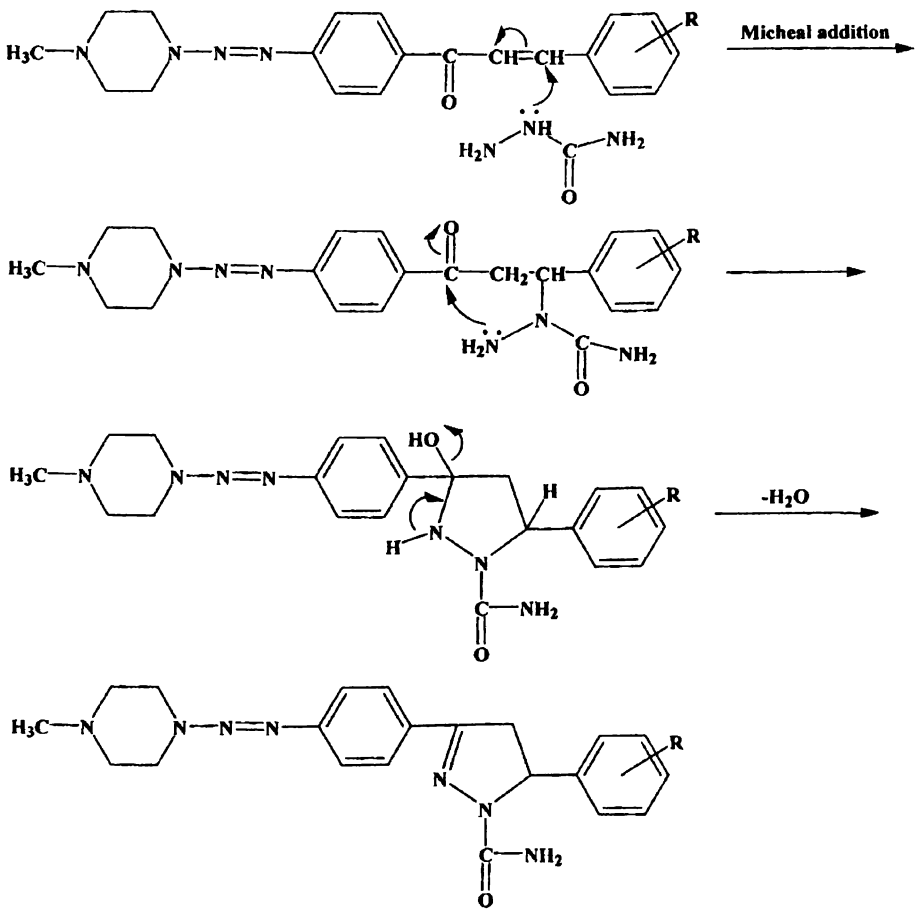
3-{4′-[(4″-Methylpiperazinyl)diazenyl]phenyl}-5-(substitutedphenyl)pyrazolecarboxamide (**5a-j**) :



Reaction mechanism of **4a-j**

Conventional method : A mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)-prop-2-en-1-one (**2a-j**) (0.01 mol) and semicarbazide hydrochloride (0.02 mol) in DMF (30 ml) was refluxed gently on sand bath for 7-8 h. The resulting mixture was then treated with crushed ice and the product thus obtained was filtered, washed with water and recrystallized from acetone.

Microwave method : In a 250 ml R.B.F., a mixture of 1-{4′-[(4″-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (**2a-j**) (0.01 mol) and semicarbazide hydrochloride (0.02 mol) was dissolved in DMF (30 ml) by slow warming and shaking. The reaction mixture was stirred for some time at room temperature and subsequently subjected to microwave irradiation for specified time of 3-4 min at power level 500 W. The



Reaction mechanism of **5a-j**

resulting mixture was then treated with crushed ice and the product thus obtained was filtered, washed with water and recrystallized from acetone.

(**5c**) : IR (KBr) : 3210 (-NH_2), 2924 (-CH_3), 1668 (-C=O), 1595 (-N=N-) cm^{-1}; ^1H NMR : δ 8.04-6.73 (9H, m, Ar-H), 5.40 (2H, s, -NH_2), 5.08-4.96 (2H, dd, -CH_2 (pyrazoline ring)), 4.16 (1H, dd, *J* 10.21 Hz, -CH (pyrazoline ring)), 3.95-3.68 (4H, m, (-CH_2)$_2$ (piperazine ring)), 2.68 (3H, s, N-CH_3), 2.51-2.35 (4H, m, (-CH_2)$_2$ (piperazine ring)); MS (*m/z*) : 391 (M^+), 389 (M-2H), 375, 247, 106.

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