An efficient one pot synthesis of some new 1, 4-dihydropyridine derivatives using multicomponent reaction

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ABSTRACT. Synthesize target molecules, multicomponent reaction of 4-(4-aminophenyl)morpholin-3-one with various pyrazole aldehydes and ethylacetoacetate or methylacetoacetate afforded various 1,4-dihydropyridines derivatives. The newly synthesized compounds were characterized by IR, Mass, ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis.

1. INTRODUCTION

The biological importance of 1,4-dihydropyridines is well documented. Various substituted derivatives of these heterocycles have shown utility against a range of biological targets. A large number of DHP and related compounds have been reported for their anti-inflammatory activity[1-4]. Some new work is also reported so far on the anti-inflammatory activity of 1,4-dihydropyridines possessing analgesic,[5] hypotensive,[6] anti-tumor,[7] and coronary dialating activities[8].

Various methodologies have been described for the synthesis of 1,4-dihydropyridines. During the course of our ongoing interest on synthesis of various heterocyclic compounds using active methylene group containing compounds, we observed that all these compounds are versatile intermediate for the synthesis of dihydropyridines.

2. EXPERIMENTAL SECTION

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^1H (400 MHz), ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl_3 and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

2.1 General synthesis of (E)-1-phenyl-2-(1-phenylethylidene) hydrazine(1) :-

Appropriately substituted Acetophenone (0.1 mole) was dissolved in 50 ml of ethanol into 250 ml beaker. Phenyl hydrazine (0.1 mole) was added to above flask along with 3-4 drops of glacial acetic acid. The reaction mixture was stirred for 1 hour at room temperature. The progress and the completion of reaction were checked by thin layer chromatography using ethyl acetate : hexane (6 :4) as a mobile phase. After the completion of the reaction, the reaction mixture was kept to room temperature for 1 hours and the crystalline product was separated by filtration. The product was washed with ethanol and dried to give substituted acetone phenyl hydrazone in good yield which was pure enough to use as such for the next step.

2.2 General synthesis of 1-(1,3-diphenyl-1*H*-pyrazol-4-yl)ethanone(2) :-

Dimethylformamide (0.32 mole) was transferred into 25 ml flat bottom flask. Phosphorous oxychloride (0.032 mole) was added drop wise to above flask under stirring at 0-5°C. After completion of the addition, the mixture was stirred at this temperature for 10-15 min. freshly prepared acetophenonehydrazone 0.03 mole was added to above mixture and the content was heated on water bath for 5-6 hours. The progress and the completion of reaction were checked by thin layer chromatography. After the reaction to be completed, the reaction mixture was cooled to room temperature and the content of the flask was poured on crushed ice to isolate the product. The separated product was filtered off and it was washed with cold water to remove acidity. It was dried at 65°C and recrystallized from the mixture of DMF-Methanol to give crystalline pyrazole aldehyde in good yield.

2.3 General synthesis of various substituted 1,4-dihydropyridines (3A-3T) :-

A mixture of pyrazole aldehyde (0.01 mol), ethylacetoacetate or methylacetoacetate (0.02 mol) in ethanol with few drops of piperidine as base was stirred for 1 hrs at 65-70 °C in a stoppered flask. After formation of arylidine compound (checked by TLC) , 4-(4-aminophenyl)morpholin-3-one was added to the reaction mixture. The reaction mixture was refluxed for 18-20hours. During the reaction the progress and the completion of reaction were checked by thin layer chromatography. After the reaction to be completed, the reaction mixture was kept to room temperature for 1 hours and the reaction mixture was poured into crushed ice. The solid product was separated by filtration. The solid crude product was washed with ethanol, crystallized from methanol.

Scheme-1

Scheme-2

Scheme 1. (a) glacial acetic acid, ethanol, reflux for 5-6 hours; (b) DMF-POCl₃, 70-80°C, 5-6 hours;

Scheme 2. (c) 1-2 drops conc.HCl, ethanol, reflux.

Table 1. Physical constant of 1,4-dihydropyridines derivatives (3A-3T)

Sr.no	Comp.	R	R ₁	Time hr.	Yield %	Melting Range ^o C
1	3A	-C ₂ H ₅	H	20	84	238-241
2	3B	-C ₂ H ₅	4-CH ₃	18	86	250-252
3	3C	-C ₂ H ₅	4-F	22	80	264-266
4	3D	-C ₂ H ₅	4-Cl	21	78	236-238
5	3E	-C ₂ H ₅	4-Br	23	80	238-240
6	3F	-C ₂ H ₅	3-Br	23	82	236-240
7	3G	-C ₂ H ₅	2-OCH ₃	24	75	220-225
8	3H	-C ₂ H ₅	4-OCH ₃	24	78	226-230
9	3I	-C ₂ H ₅	3-NO ₂	26	69	250-252
10	3J	-C ₂ H ₅	4-NO ₂	25	71	250-255
11	3K	-CH ₃	H	18	86	252-255
12	3L	-CH ₃	4-CH ₃	20	87	236-238
14	3M	-CH ₃	4-F	23	76	242-245
15	3N	-CH ₃	4-Cl	24	73	255-258
16	3O	-CH ₃	4-Br	24	71	263-266
17	3P	-CH ₃	3-Br	23	75	250-254
18	3Q	-CH ₃	2-OCH ₃	22	80	266-268
19	3R	-CH ₃	4-OCH ₃	21	82	260-265
20	3S	-CH ₃	3-NO ₂	24	70	244-246
21	3T	-CH ₃	4-NO ₂	25	73	234-238

4. SPECTRAL DATA

Diethyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3A): Brown solid; melting range 238-241°C; IR (KBr): 3742, 3377, 3095, 2974, 2324, 2130, 1919, 1735, 1550, 1236, 1192, 1001, 923, 833, 783, 725, 636, 588, 505, 443 cm⁻¹; ¹H NMR: δ 1.100-1.140 (t, 6H, J=6.9Hz), 2.239-2.241 (s, 6H), 3.466-3.490 (t, 2H), 3.510-3.534 (t, 2H), 3.936-4.064 (q, 2H), 4.310 (s, 2H), 4.486-4.637 (q, 2H), 5.447-5.457 (s, 1H), 6.783-7.333 (d, 4H, J=6.8 Hz), 7.394-7.419 (t, 2H), 7.420-7.467 (t, 1H), 7.468-7.488 (t, 1H), 7.490-7.531 (t, 2H), 7.664-7.692 (d, 2H, J=6.5Hz), 7.697-7.733 (d, 2H), 8.607 (s, 1H); ¹³C NMR: 14.17, 16.30, 27.17, 41.79, 60.06, 64.31, 66.67, 104.30, 118.45, 122.49, 123.00, 127.55, 128.47, 129.39, 129.59, 130.66, 137.81, 140.05, 141.19, 158.44, 165.55, 167.72; MS (m/z): 647 (M⁺); Anal. Calcd for C₃₈H₃₈N₄O₆: C, 70.57; H, 5.92; N, 8.66; Found: C, 70.60; H, 5.90; N, 8.76.

Diethyl 2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate(3B): Brown solid; melting range 250-252°C; IR (KBr): 3738, 3383, 2324, 1919, 1730, 1550, 1236, 1170, 1072, 999, 922, 895, 792, 767, 684, 646, 559, 455 cm⁻¹; ¹H NMR: δ 1.100-1.145 (t, 6H, J=6.7Hz), 2.240-2.242 (s, 6H), 2.328-2.333 (s, 3H), 3.466-3.490 (t, 2H), 3.513-3.536 (t, 2H), 4.230-4.299 (q, 2H), 4.315 (s, 2H), 4.334-4.470 (q, 2H), 5.449-5.460 (s, 1H), 6.774-6.804 (d, 2H, J=6.5Hz), 7.187-7.217 (d, 2H), 7.269-7.299 (d, 2H), 7.395-7.414 (d, 2H), 7.419-7.445 (t, 2H), 7.498-7.546 (t, 1H), 7.664-7.702 (d, 2H), 8.612 (s,

1H); ^{13}C NMR: 13.90, 16.35, 27.20, 41.81, 60.09, 64.35, 66.70, 104.35, 118.48, 122.48, 123.12, 127.58, 128.50, 129.38, 129.60, 130.68, 137.88, 140.15, 141.20, 158.44, 165.57, 167.77, 167.88; MS (m/z): 661 (M^+); Anal. Calcd for $\text{C}_{39}\text{H}_{40}\text{N}_4\text{O}_6$: C, 70.89; H, 6.10; N, 8.48; Found: C, 70.85; H, 6.15; N, 8.50.

Diethyl-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3C): Brownsolid; melting range 264-266°C; IR (KBr): 3740, 3601, 3393, 3052, 2936, 2868, 1921, 1734, 1691, 1559, 1525, 1450, 1290, 1180, 1075, 998, 890, 798, 645, 560 cm^{-1} ; MS (m/z): 665 (M^+); Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{FN}_4\text{O}_6$: C, 68.66; H, 5.61; N, 8.43; Found: C, 68.70; H, 5.55; N, 8.40.

Diethyl-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3D): White solid; melting range 236-238°C; IR (KBr): 3635, 3258, 3110, 3055, 2966, 2870, 2750, 2550, 1790, 1650, 1582, 1533, 1478, 1250, 1190, 1090, 998, 846, 768, 660, 559 cm^{-1} ; MS (m/z): 680 (M^+); Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{ClN}_4\text{O}_6$: C, 67.00; H, 5.47; N, 8.23; Found: C, 67.10; H, 5.50; N, 8.20.

Diethyl-4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3E): Brownsolid; melting range 238-240°C; IR (KBr): 3740, 3645, 3239, 3098, 2965, 2840, 1779, 1678, 1583, 1548, 1475, 1285, 1186, 1048, 1037, 837, 719, 689, 550 cm^{-1} ; MS (m/z): 725 (M^+); Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{BrN}_4\text{O}_6$: C, 62.90; H, 5.14; N, 7.72; Found: C, 62.95; H, 5.10; N, 7.68.

Diethyl-4-(3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3F): Brownish solid; melting range 236-240°C; IR (KBr): 3389, 3289, 3089, 2979, 2880, 2755, 2550, 1658, 1620, 1587, 1418, 1349, 1242, 1190, 1077, 998, 885, 788, 684, 655, 588, 515 cm^{-1} ; MS (m/z): 725 (M^+); Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{BrN}_4\text{O}_6$: C, 62.90; H, 5.14; N, 7.72; Found: C, 62.87; H, 5.12; N, 7.65.

Diethyl-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3G): Brown solid; melting range 220-225°C; IR(KBr): 3640, 3232, 3070, 2969, 2871, 1794, 1659, 1590, 1531, 1415, 1260, 1130, 1028, 878, 734, 660, 555 cm^{-1} ; MS (m/z): 677 (M^+); Anal. Calcd for $\text{C}_{39}\text{H}_{40}\text{N}_4\text{O}_7$: C, 69.21; H, 5.96; N, 8.28; Found: C, 69.25; H, 5.99; N, 8.32.

Diethyl-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3H): Brown solid; melting range 226-230°C; IR (KBr): 3620, 3240, 3114, 3058, 2933, 2870, 1750, 1624, 1590, 1331, 1261, 1205, 1170, 1038, 828, 794, 655, 560 cm^{-1} ; MS (m/z): 677 (M^+); Anal. Calcd for $\text{C}_{39}\text{H}_{40}\text{N}_4\text{O}_7$: C, 69.21; H, 5.96; N, 8.28; Found: C, 69.18; H, 5.94; N, 8.30.

Diethyl-2,6-dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3I): Brown solid; melting range 250-252°C; IR (KBr): 3650, 3537, 3238, 3098, 2968, 2878, 1770, 1665, 1588, 1530, 1483, 1366, 1327, 1243, 1199, 1071, 1025, 998, 844, 730, 688, 548 cm^{-1} ; MS (m/z): 692 (M^+); Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{N}_5\text{O}_8$: C, 65.98; H, 5.39; N, 10.12; Found: C, 66.10; H, 5.42; N, 10.10.

Diethyl-2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3J): Brown solid; melting range 250-255°C; IR (KBr): 3660, 3238, 3090, 2943, 2881, 1760, 1640, 1580, 1545, 1480, 1266, 1170, 1072, 1035, 800, 880, 738, 667, 589 cm^{-1} ; MS (m/z): 692 (M^+); Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{N}_5\text{O}_8$: C, 65.98; H, 5.39; N, 10.12; Found: C, 65.94; H, 5.40; N, 10.14.

Dimethyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3K): Brownsolid; melting range 252-255°C; IR (KBr): 3240, 3113, 2968, 1649, 1591, 1521, 1411, 1346, 1261, 1201, 1128, 1028, 904, 835, 790, 732, 659, 555, 453, 426 cm^{-1} ; ^1H NMR: δ 2.239-2.241 (s, 6H), 3.440 (s, 6H), 3.466-3.490 (t, 2H), 3.512-3.535 (t, 2H), 4.312 (s, 2H), 5.432-5.442 (s, 1H), 6.784-7.298 (d, 4H, $J=7.0\text{Hz}$), 7.395-7.449 (t, 2H), 7.461-7.482 (t, 1H), 7.502-7.521 (t, 1H), 7.522-7.556 (t, 2H), 7.664-7.693 (d, 2H, $J=6.5\text{Hz}$), 7.704-7.740

(d, 2H), 8.610 (s, 1H); ^{13}C NMR: 14.20, 16.40, 28.18, 42.03, 60.10, 64.34, 66.70, 105.30, 119.45, 124.49, 126.50, 127.55, 128.48, 129.59, 130.61, 137.85, 140.05, 143.19, 160.44, 165.60, 167.70; MS (m/z): 619 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{34}\text{N}_4\text{O}_6$: C, 69.89; H, 5.54; N, 9.06; Found: C, 69.92; H, 5.58; N, 9.10.

Dimethyl-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate(3L): Brown solid; melting range 236-238°C; R_f 0.44 (3:7 hexane-EtOAc); IR (KBr): 3233, 3188, 3064, 2918, 2864, 1741, 1680, 1624, 1542, 1449, 1390, 1280, 1213, 1136, 1035, 966, 835, 768, 670, 595 cm^{-1} ; MS (m/z): 633 (M^+); Anal. Calcd for $\text{C}_{37}\text{H}_{36}\text{N}_4\text{O}_6$: C, 70.24; H, 5.74; N, 8.86; Found: C, 70.28; H, 5.78; N, 8.83.

Dimethyl-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3M): Off brown solid; melting range 242-245°C; IR (KBr): 3280, 3145, 2836, 2755, 2350, 1740, 1638, 1556, 1522, 1475, 1377, 1285, 1195, 998, 817, 769, 668, 520 cm^{-1} ; MS (m/z): 637 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{33}\text{FN}_4\text{O}_6$: C, 67.91; H, 5.22; N, 8.80; Found: C, 67.94; H, 5.20; N, 8.85.

Dimethyl-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3N): Brown solid; melting range 255-258°C; IR (KBr): 3244, 3188, 3063, 2938, 2866, 1755, 1665, 1632, 1438, 1390, 1280, 1228, 1145, 1055, 955, 845, 780, 688, 592 cm^{-1} ; MS (m/z): 653 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{33}\text{ClN}_4\text{O}_6$: C, 66.20; H, 5.09; N, 8.58; Found: C, 66.18; H, 5.15; N, 8.60.

Dimethyl-4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3O): Brown solid; melting range 26-266°C; IR (KBr): 3270, 3150, 3059, 2950, 2854, 1650, 1598, 1488, 1337, 1298, 1230, 1185, 1036, 979, 837, 757, 665, 558 cm^{-1} ; MS (m/z): 698 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{33}\text{BrN}_4\text{O}_6$: C, 61.98; H, 4.77; N, 8.03; Found: C, 62.01; H, 4.80; N, 8.10.

Dimethyl-4-(3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3P): Off brown solid; melting range 250-254°C; IR (KBr): 3330, 3220, 3165, 3073, 2929, 2880, 1670, 1560, 1442, 1360, 1271, 1188, 1078, 969, 830, 750, 678, 523 cm^{-1} ; MS (m/z): 698 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{33}\text{BrN}_4\text{O}_6$: C, 61.98; H, 4.77; N, 8.03; Found: C, 61.92; H, 4.75; N, 8.00.

Dimethyl-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3Q): Brown solid; melting range 266-268°C; IR (KBr): 3350, 3260, 3180, 3078, 2950, 2870, 1698, 1599, 1490, 1430, 1270, 1180, 1075, 1040, 875, 784, 682, 598 cm^{-1} ; MS (m/z): 649 (M^+); Anal. Calcd for $\text{C}_{37}\text{H}_{36}\text{N}_4\text{O}_7$: C, 68.51; H, 5.59; N, 8.64; Found: C, 68.53; H, 5.61; N, 8.60.

Dimethyl-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3R): Off brown solid; melting range 260-265°C; IR (KBr): 3230, 3188, 3078, 2939, 2899, 1744, 1668, 1540, 1480, 1340, 1310, 1298, 1167, 1073, 880, 770, 677, 594 cm^{-1} ; MS (m/z): 649 (M^+); Anal. Calcd for $\text{C}_{37}\text{H}_{36}\text{N}_4\text{O}_7$: C, 68.51; H, 5.59; N, 8.64; Found: C, 68.53; H, 5.61; N, 8.68.

Dimethyl-2,6-dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3S): Brown solid; melting range 244-246°C; IR (KBr): 3255, 3180, 3076, 2959, 2870, 1750, 1668, 1533, 1475, 1333, 1310, 1290, 1182, 1078, 884, 775, 677, 597 cm^{-1} ; MS (m/z): 664 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{33}\text{N}_5\text{O}_8$: C, 65.15; H, 5.01; N, 10.55; Found: C, 65.25; H, 5.10; N, 10.60.

Dimethyl-2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(3-oxomorpholino)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3T): Brown solid; melting range 234-238°C; IR (KBr): 3180, 3077, 2945, 2875, 1715, 1667, 1593, 1559, 1477, 1286, 1159, 1098, 1060, 886, 790, 687, 590 cm^{-1} ; MS (m/z): 664 (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{33}\text{N}_5\text{O}_8$: C, 65.15; H, 5.01; N, 10.55; Found: C, 65.13; H, 5.03; N, 10.53.

5. Conclusion

In summary, we have described the synthesis of substituted 1,4-dihydropyridine derivatives in moderate yield. The reaction of various pyrazole aldehydes (PALs) with ethylacetoacetate or methylacetoacetate (active methylene group containing compounds) and 4-(4-aminophenyl)morpholin-3-one was afforded the 1,4-dihydropyridine derivatives in good yield. All synthesized compounds were characterized by IR, NMR and Mass spectrometry analysis and are incorporated with the structure of compounds **3A-3T**. In vitro affectivity of antimicrobial agents can be demonstrated by observing their capacity to inhibit bacterial growth on suitable media. The production of a zone depends on two factors namely bacterial growth and concentration of antimicrobial agent. The hole/well punch method was first used by Bennett. This diffusion method has proved more effective than many other methods. According to Lt. General Raghunath the well technique is 5-6 times more sensitive than using disk method.

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