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Research Article

ENVIRONMENTALLY BENIGN SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1-[3-(2-NAPHTHYL)[1,8]NAPHTHYRIDIN-2-YL]-3-(2-OXO-2*H*-3-CHROMENYL)-1*H*-4-PYRAZOLECARBALDEHYDES

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ABSTRACT

An efficient and convenient protocol for the transformation of 3-[2-(3-(2-naphthyl)][1,8]naphthyridin-2-yl)ethanhydrazonyl]-2*H*-2-chromoenones(hydrazones) **4** to 1-[3-(2-naphthyl)][1,8]naphthyridin-2yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazole carbalde- hydes **5** is achieved under microwave irradiation utilizing POCl₃-DMF over silica gel with high yields. The purity of the products is high. The process is environmentally benign and experimental procedure is very simple. The structural assignments to compounds **4** and **5** are based on their elemental analyses and spectral (IR, ¹H NMR and MS) data. The compounds **5** have been screened for their antibacterial activity.

Keywords: Pyrazolecarbaldehydes, 1,8-naphthyridine and 2*H*-2-chromenones.

1. INTRODUCTION

Napthyridines are novel 1.8class of heterocyclic compounds possessing a wide variety of biological activities¹⁻³ pyrazole derivatives have been reported to exhibit versatile biological action⁴⁻⁶ The 2-H-2chromenones occupy a prominent position in the realm of heterocyclic compounds7-9. Therefore, the synthesis of new representatives in these classes of heterocyclic compounds remained urgent. Microwave-assisted organic synthesis has emerged as a new lead in organic synthesis¹⁰⁻¹² The application of microwave (MW) heating under solvent-free reaction conditions¹¹ and on inorganic solid support¹³ is a promising alternative to polluting reactions and has been a current field of interest. In view of this and in continuation of the interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives,¹⁴⁻¹⁶ we report herein an efficient and convenient method for synthesis the of 1-[3-(2naphthyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2H-3-chromenyl)-1H-4-pyrazolecarbaldehydes in solvent-free conditions under microwave irradiation using silica gel as solid support.

2. MATERIAL AND METHODS

Melting points were determined on a Cintex melting point apparatus and are uncorrected.

Homogeneity of the compounds was checked by precoated TLC plates (Merck, 60F-254). IR spectra were recorded in KBr on a brukar spectrophotometer, ¹H NMR spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard and mass spectra on a Shimadzu Lab Solutions . Microwave irradiation was carried out in a domestic microwave oven(LG MG 556P, 2450 MHz).

3. RESULTS AND DISCUSSIONS

1-[3(2-Naphthyl)[1,8]naphthyridin-2-yl]

hydrazine **2** obtained by the hydrazinolysis of 2chloro-3-(2-naphthyl)[1,8]naphthyridine **1** with hydrazine hydrate, on condensation with different 3-acetylcoumarins (3-acetyl-2H-2chromenones) **3** in the presence of catalytic amount of DMF under MW irradiation afforded corresponding 3-[2-(3-(2-naphthyl) the [1,8]naphthyridin-2-yl)ethan-hydrazonyl]-2*H*-2chromenones (hydrazones) 4 in excellent yields. The hydrazones 4 when subjected to the Vilsmeier-Haack reaction with POCl₃-DMF/SiO₂ under MW irradiation furnished the respective 1-[3-(2-naphthyl)[1,8]naphthyridn-2-yl]-3-(2oxo-2*H*-chromenyl)-1*H*-4pyrazole

carbaldehydes **5.** Reactions are not time consuming and the yields of the products are very good. The purity of the product is high.

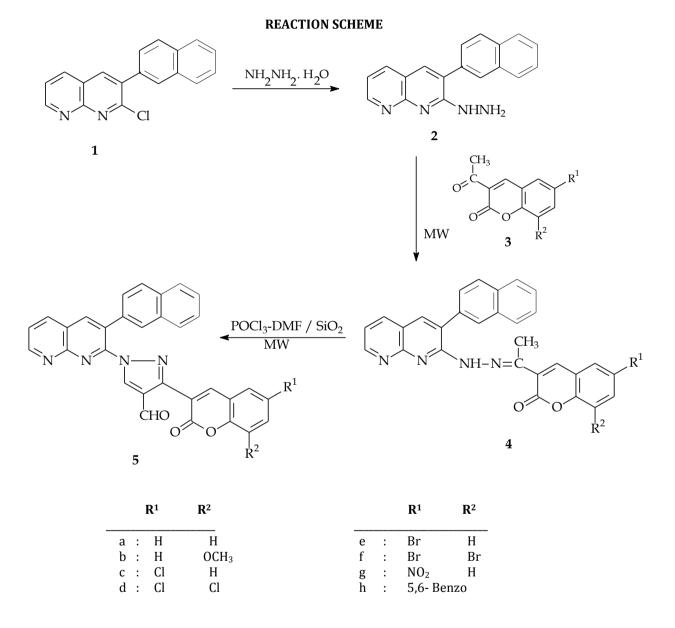
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The experimental procedure is very simple. The process is environmentally benign. The reaction proceeds to only 6-8% in 2.5 -4.0 min, when conducted under conventional

conditions in an oil- bath preheated to 120 °C (measured immediately after MW irradiation)thus demonstrating the advantage of the MW heating method.

The structures of compounds **4** and **5** were determined by spectral (IR, ¹H NMR and MS) and analytical data.

The experimental simplicity, short reaction times, high yields and excellent purity and absence of solvent are the advantages of this method.



4. Experimental Section

4.1. General procedure for the synthesis of 3-[2-(3-(2-naphthyl)[1,8]naphthyridin-2yl)ethanhydrazonyl]-2*H*-2-chromenones (hydrazones), 4

A mixture of **1-[3-(2-naphthyl[1,8]napthyridine-2-yl]hydrazine 2** (0.01 mol), 3acetylcoumarin **3** (0.01 mol) and DMF (5 drops) was exposed to microwave at 200 W intermittently at 10 sec intervals for the specified time (Table I). After completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford **4** (Table I).

4.1.1. Spectral data of the synthesized compounds (4a-h) 4a

IR (KBr): 3343 (NH), 1722 (lactone, C=O), 1614 (C=N), 1521 cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.70 (s, 3H, CH₃), 7.88 (m, 2 H C₅-H, C₆-H), 8.05 (s, 1H, C₄-H,), 8.38 (m, 1H, C₇-H), 8.43 (s, 1H, C₄-H of coumarin), 7.03-7.82(m, 11H, Ar-H), 10.20 (s, 1H, NH); MS(ESI): *m/z* 457.35 [M+H]⁺

4b

IR (KBr): 3347 (NH), 1723 (lactone, C=O), 1607 (C=N), 1524cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.72 (s, 3H, CH₃), 3.98 (s, 3H, OCH₃), 7.90 (m, 2H, C₅ –H C₆-H), 8.10 (s, 1H, C₄-H,), 8.32 (m, 1H, C₇-H), 8.40 (s, 1H, C₄-H of coumarin), 7.00-7.75 (m, 10H, Ar-H), 10.18 (s, 1H, NH); MS(ESI): m/z 487.35 [M+H]⁺

4c

IR (KBr): 3346 (NH), 1730 (lactone, C=O), 1618 (C=N), 1522 cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.74 (s, 3H, CH3), 7.92(m, 2H, C₅-H C₆-H), 8.04 (s 1H, C₄-H,), 8.37 (m, 1H, C₇-H), 8.42 (s, 1H, C₄-H of coumarin), 7.20-7.64 (m, 10H, Ar-H), 10.20 (s, 1H, NH)); MS(ESI): *m/z* 491.35[M+H]⁺

4d

IR (KBr): 3344 (NH), 1726 (lactone, C=O), , 1615 (C=N), 1530 cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.75 (s, 3H, CH₃), 7.90 (m, 2H, C₅-H C₆-H), 8.07 (s, 1H, C₄-H,), 8.40 (m, 1H, C₇-H), 8.45 (s, 1H, C₄-H of coumarin), 7.18-7.66 (m, 9H, Ar-H), 10.22 (s, 1H, NH)); MS(ESI): *m/z* 525.30 [M+H]⁺

4e

IR (KBr): 3353 (NH), 1728 (lactone, C=O),1621 (C=N), 1594 cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.70 (s, 3H, CH₃), 7.86 (m, 2H, C₅-H C₆-H), 8.03 (s, 1H, C₄-H,), 8.38 (m, 1H, C₇-H), 8.40 (s, 1H, C₄-H of coumarin), 7.04-7.80 (m, 10H, Ar-H), 10.22 (s, 1H, NH); MS(ESI): *m/z* 535.25 [M+H]⁺

4f

IR (KBr): 3345 (NH), 1723 (lactone, C=O), 1623 (C=N), 1598cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.76 (s, 3H, CH₃), 7.90(m, 2H, C₅-H C₆-H), 8.08 (s, 1H, C₄-H,), 8.40 (m, 1H, C₇-H), 8.58 (s, 1H, C₄-H of coumarin), 7.22-7.78 (m, 9H, Ar-H), 10.17 (s, 1H, NH); MS(ESI): *m/z* 613.20 [M+H]⁺

4g

IR (KBr): 3340 (NH), 1725 (lactone, C=O), 1620 (C=N), 1592 cm-1 (C=C); 1H NMR (CDCl₃ + DMSO-*d*₆) : δ 2.73 (s, 3H, CH₃), 7.98 (m, 2H, C₅-H C₆-H), 8.10 (s, 1H, C₄-H,), 8.45 (m, 1H, C₁₀-H),

8.48 (s, 1H, C₄-H of coumarin), 7.20-7.75 (m, 10H, Ar-H), 10.20 (s, 1H, NH); MS(ESI): *m/z* 502.30 [M+H]⁺

4h

IR (KBr): 3343 (NH), 1724 (lactone, C=O), 1619 (C=N), 1589 cm-1 (C=C); 1H NMR (CDCl₃ + DMSO- d_6) : δ 2.75 (s, 3H, CH₃), 7.94 (m, 2H, C₅-H C₆-H), 8.09 (s, 1H, C₄-H,), 8.42 (m, 1H, C₁₃-H), 8.48 (s, 1H, C₄-H of coumarin), 7.15-7.82 (m, 13H, Ar-H), 10.22 (s, 1H, NH); MS(ESI): m/z 507.35 [M+H]⁺

4.2. General procedure for the synthesis of 1-[3-(2-naphthyl][1,8]naphthyridin-2-yl)-3-(2oxo-2*H*-3-chromenyl)-1*H*-4pyrazolecarbaldehydes, 5

To the Vilsmeier-Haack reagent (0.03 mol) at 0-5°C, compound 4 (0.01 mol) was added portion wise. After the addition was complete, the reaction flask was kept at RT for 5 min and silica gel (3 g) was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder is then irradiated in microwave oven at 400 W intermittently at 30 sec intervals for the specified time (Table 1). on completion of reaction as indicated by TLC the reaction mixture was cooled, treated with chilled water and filtered. The solid obtained by the neutralization of the filtrate with NaHCO3 was filtered, washed with water and purified by recrystallization from methanol to furnish 5 (Table 1).

4.2.1. Spectral data of the synthesized compounds (5a-h): 5a

IR (KBr): 1726 (lactone, C=O),1680 (aldehyde C=O) 1612 (C=N), 1567 cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 7.95 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.38 (m, 1H, C₇-H of naphthyridine), 8.48 (s, 1H, C₄-H of coumarin), 7.10-7.65 (m, 12H, CH of pyrazole, 11 Ar-H), 9.70 (s, 1H, CHO); MS(ESI): m/z 495.30 [M+H]⁺

5b

IR (KBr): 1722 (lactone, C=O),1669 (aldehyde C=O) 1612 (C=N), 1580cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 3.92 (s, 3H, OCH3), 7.90 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.35 (m, 1H, C₇-H of naphthyridine), 8.50 (s, 1H, C₄-H of coumarin), 7.00-7.68 (m, 11H, CH of pyrazole, 10Ar-H), 9.72 (s, 1H, CHO); MS(ESI): *m/z* 525.35 [M+H]⁺

5c

IR (KBr): 1731 (lactone, C=O), 1673(aldehyde C=O) 1610 (C=N), 1566 cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 7.93 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.36 (m, 1H, C₇-H of

naphthyridine), 8.40 (s, 1H, C₄-H of coumarin), 7.12-7.60 (m, 11H, CH of pyrazole, 10 Ar-H), 9.70 (s, 1H, CHO); MS(ESI): *m/z* 529.35[M+H]⁺

5d

IR (KBr): 1730 (lactone, C=O), 1675 (aldehyde, C=O), 1607 (C=N), 1572cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 7.92 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.40 (m, 1H, C₇-H of naphthyridine), 8.43 (s, 1H, C₄-H of coumarin), 7.15-7.64 (m, 10H, CH of pyrazole, 9 Ar-H), 9.75 (s, 1H, CHO); MS(ESI): *m*/*z* 563.35 [M+H]⁺

5e

IR (KBr): 1731 (lactone, C=O) 1672 (aldehyde C=O),1606 (C=N), 1567 cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 7.95 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.38 (m, 1H, C₇-H of naphthyridine), 8.44 (s, 1H, C₄-H of coumarin), 7.10 – 7.78 (m, 11H, CH of pyrazole, 10 Ar-H), 9.73 (s, 1H, CHO); MS(ESI): *m/z* 573.20 [M+H]⁺

5f

IR (KBr): 1732 (lactone, C=O), 1670 (aldehyde C=O) 1605 (C=N), 1559 cm⁻¹ (C=C); ¹H NMR

 $(CDCl_3 + DMSO-d_6) : \delta$ 7.93 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.40 (m, 1H, C₇-H of naphthyridine), 8.42 (s, 1H, C₄-H of coumarin), 7.12-7.76 (m, 10 H, CH of pyrazole, 9Ar-H), 9.76 (s, 1H, CHO); MS(ESI): *m/z* 651.25 [M+H]⁺

5g

IR (KBr): 1730 (lactone, C=O), 1682 (aldehyde C=O) 1610 (C=N), 1562 cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 7.98 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.45 (m, 1H, C₇-H of naphthyridine), 8.48 (s, 1H, C₄-H of coumarin), 7.10-7.66 (m, 11H, CH of pyrazole, 10 Ar-H), 9.74 (s, 1H, CHO); MS(ESI): m/z 540.30 [M+H]⁺

5h

IR (KBr): 1723 (lactone, C=O), 1669 (aldehyde C=O) 1617 (C=N), 1560 cm⁻¹ (C=C); ¹H NMR (CDCl₃ + DMSO- d_6) : δ 8.00 (m, 3H, C₄-H, C₅-H C₆-H of naphthyridine), 8.43 (m, 1H, C₇-H of naphthyridine), 8.45 (s, 1H, C₄-H of coumarin), 7.20-7.70 (m, 14H, CH of pyrazole, 13 Ar-H), 9.78 (s, 1H, CHO); MS(ESI): m/z 545.35 [M+H]⁺.

Reaction (min) m. p. (rc) Yield (rg) Mol. formula Found (rg) (rc) (rc) (rc) 4a 0.25 195 96 $C_{29H_20N_4O_2}$ (rd) (rd) (rd) (rd) (rd) (rd) (rd) (rd)	Table 1: Characterization of compounds 4 and 5								
Compd (min) Imme (min) (°Ć) (%) Mol. formula (23)H20N402 C H N 4a 0.25 195 96 $C_{29}H_{20}N_40_2$ (76.30) 76.42 (76.30) 4.44 12.31 (74.17) 4.42 (12.27) 4b 0.5 179 98 $C_{30}H_{20}N_40_2$ (74.06) 74.17 (74.06) 4.55 11.57 (11.57) 4c 0.25 208 97 $C_{29}H_{19}CIN_40_2$ (70.95 3.90 (66.30) 3.45 10.70 (66.30) 4.47 10.70 (65.06) 4d 0.5 215 96 $C_{29}H_{19}BrN_40_2$ (65.17) 3.60 (10.50 (55.60) 10.50 (56.70) 2.95 915 (9.12) 4e 0.5 187 95 $C_{29}H_{19}BrN_40_2$ (55.67) 2.95 915 (9.12) 4g 0.5 198 96 $C_{29}H_{19}N_50_4$ (69.45) 69.57 (8.83 3.82 (11.06) 4h 0.5 221 96 $C_{31}H_{19}N_40_3$ (78.25) 4.38 (11.06) 11.06 (78.25) 4.38 11.06 (75.29) 3.67 (11.33) 5b 3.0 170 <th></th> <th rowspan="2">pd Time M.p. Yield Mol. formu</th> <th>mn</th> <th>Viold</th> <th></th> <th colspan="3">Found (%) (Cacld)</th>		pd Time M.p. Yield Mol. formu	mn	Viold		Found (%) (Cacld)			
4a 0.25 195 96 C ₂₉ H ₂ 0N402 (76.30) 4.42 (12.27) 4b 0.5 179 98 C ₃₀ H ₂₂ N403 74.17 4.57 11.57 4c 0.25 208 97 C ₂₉ H ₁₉ ClN402 71.08 3.92 11.44 4d 0.5 215 96 C ₂₉ H ₁₉ ClN402 66.42 3.47 10.70 4d 0.5 215 96 C ₂₉ H ₁₈ Cl2N402 66.42 3.47 10.70 4d 0.5 192 96 C ₂₉ H ₁₈ Br2N402 66.42 3.47 10.70 4f 0.5 187 95 C ₂₉ H ₁₈ Br2N402 65.17 3.60 10.50 4g 0.5 198 96 C ₂₉ H ₁₉ Br2N402 56.83 2.96 9.15 4h 0.5 221 96 C ₂₉ H ₁₉ N ₅₀₄ 69.57 3.83 14.01 5a 2.5 152 86 C ₃₁ H ₁₈ N403 75.40 3.68 11.36	Compd		Mol. formula	С	Н	Ν			
4b 0.5 179 98 C ₃₀ H ₂₂ N ₄ O ₃ 74.17 (74.06) 4.42 4.56 (12.27) 4c 0.25 208 97 C ₂₉ H ₁₉ ClN ₄ O ₂ 71.08 (70.95) 3.90 (11.41) 4d 0.5 215 96 C ₂₉ H ₁₉ ClN ₄ O ₂ 66.42 (66.30) 3.45 (10.66) 4e 0.25 192 96 C ₂₉ H ₁₉ BrN ₄ O ₂ 65.17 (55.06) 3.58 (10.46) 4f 0.5 187 95 C ₂₉ H ₁₉ BrN ₄ O ₂ 66.83 3.45 (10.66) 4g 0.5 187 95 C ₂₉ H ₁₉ BrN ₄ O ₂ 66.83 2.96 9.15 4g 0.5 187 95 C ₂₉ H ₁₉ BrN ₄ O ₂ 66.83 2.96 9.15 4g 0.5 198 96 C ₂₉ H ₁₉ N ₅ O ₄ 69.57 3.83 14.01 69.57 3.83 14.01 (10.9) 75.40 3.68 (13.46) 5a 2.5 152 86 C ₃₁ H ₁₈ N _{4O3} 70.51 3.26	40	0.25	105	06	Coold on N. O.	76.42	4.44	12.31	
4b 0.5 179 98 C ₃₀ H ₂₂ N ₄ O ₃ (74.06) 4.56 (11.52) 4c 0.25 208 97 C ₂₉ H ₁₉ ClN ₄ O ₂ (70.95) 3.90 (11.41) 4d 0.5 215 96 C ₂₉ H ₁₉ ClN ₄ O ₂ 66.42 3.47 10.70 4e 0.25 192 96 C ₂₉ H ₁₉ BrN ₄ O ₂ 65.17 3.60 10.50 4f 0.5 187 95 C ₂₉ H ₁₉ BrN ₄ O ₂ 56.83 2.96 9.15 4g 0.5 187 95 C ₂₉ H ₁₉ BrN ₄ O ₂ 56.83 2.96 9.15 4g 0.5 198 96 C ₂₉ H ₁₉ BrN ₄ O ₂ 69.57 3.83 14.01 5a 2.5 198 96 C _{29H19} N ₅₀₄ 69.57 3.83 14.01 5b 3.0 170 87 C ₂₃ H ₂₂ N ₄₀₂ 78.38 4.40 11.09 5b 3.0 170 87 C ₃₂ H ₂₀ N ₄₀₄ 75.40 3.68 10.	44	0.23	195	90	C2911201N4O2	(76.30)	4.42	(12.27)	
4c0.2520897 $C_{29}H_{19}CIN_{4}O_{2}$ 71.083.9211.444d0.521596 $C_{29}H_{19}CIN_{4}O_{2}$ 71.083.9211.444d0.521596 $C_{29}H_{18}Cl_2N_{4}O_{2}$ 66.423.4710.704e0.2519296 $C_{29}H_{19}BrN_{4}O_{2}$ 65.173.6010.504f0.518795 $C_{29}H_{19}BrN_{4}O_{2}$ 65.173.8010.4664g0.519896 $C_{29}H_{19}N_{5}O_{4}$ 69.573.8314.014h0.522196 $C_{33}H_{22}N_{4}O_{2}$ 78.384.4011.095a2.515286 $C_{31}H_{18}N_{4}O_{3}$ 75.403.6811.365b3.017087 $C_{32}H_{20}N_{4}O_{4}$ 73.393.8510.725d4.013485 $C_{31}H_{17}CIN_{4}O_{3}$ 70.513.2610.635c3.511086 $C_{31}H_{17}BrN_{4}O_{3}$ 65.053.919.815b3.511086 $C_{31}H_{17}BrN_{4}O_{3}$ 65.053.919.815b3.511086 $C_{31}H_{17}BrN_{4}O_{3}$ 65.053.919.8164.932.99(9.77)3.5414884 $C_{27}H_{13}Br_2N_{4}O_{3}$ 57.202.498.625b3.511086 $C_{31}H_{17}BrN_{4}O_{3}$ 65.053.919.8165.953.5148	4h	0.5	179	98	CaeHaaN4Oa				
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5b 3.5 104 86 CarHasNiQa 77.32 3.72 10.33	5g	3.5	148	84	$C_{31}H_{17}N_5O_5$				
						<u>`</u>			
	5h	3.5	104	86	$C_{35}H_{20}N_4O_3$				
					1	(77.20)	5.70	[10.29]	

 Table 1: Characterization of compounds 4 and 5

5. Antibacterial activity

All the title compounds **5** were evaluated for their antibacterial activity against the Gramnegative Escherichia coli and Gram-positive *Bacillus subtilis* using filter paper disc method of Vincent and Vincent method¹⁷ at 250 and 500 μ g/disc concentrations. Gentamycin was used as standard for comparison. The results are given in Table 2. Compounds 5b, 5c and 5d showed promising antibacterial activity.

Table 2	: Antibacte	rial activity resu	ults of the com	pounds 5

	Inhibition zone (in mm)					
Compd	Е. со	oli at	B. subtilis at			
compu	250	500	250	500		
	µg/disc	µg/disc	µg/disc	µg/disc		
5a	8.0	10.5	5.5	9.0		
5b	10.0	12.5	6.5	9.0		
5c	11.0	18.5	7.0	12.0		
5d	10.0	13.5	6.0	10.5		
5e	8.5	10.5	5.5	8.5		
5f	8.0	9.5	5.0	7.5		
5g	6.0	8.0	4.5	6.5		
5h	7.0	9.0	6.0	10.0		
Gentamycin	12.0	22.0	8.0	15.0		

6. CONCLUSION

In summary, we have developed an efficient strategy for the synthesis of -[3-(2-naphthyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazole carbaldehydes. This method provides the desired products under operationally simple and convenient conditions with good yields. This approach involves a simple experimental procedure with broad substrate scope and is sustainable to wide range of functionalities. All the desired products showed very promising antibacterial activity against the standards.

7. ACKNOWLEDGMENTS

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