**Philippine Journal of Science**
144 (1): 91-96, June 2015
ISSN 0031 - 7683

# Synthesis and Biological Evaluation of Fused Pyrans Bearing Coumarin Moiety as Potent Antimicrobial Agents

**Nagamallu Renuka** and **Kariyappa Ajay Kumar**

Post Graduate Department of Chemistry, Yuvaraja's College
University of Mysore, India

**A simple approach for the synthesis of fused pyrans to coumarin moiety is presented. The intramolecular cyclisation of 1-aryl-3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1H-pyrazole-4-carbaldehydes under reflux conditions at 80ºC afforded fused pyrans in a relatively good yield. The synthesized compounds were characterized by spectral studies and elemental analysis. The new compounds were evaluated in vitro for their antifungal and antibacterial activity against different fungi and bacterium species.**

Key Words: antibacterial, coumarins, intramolecular, MIC, pyrazoles

## INTRODUCTION

The growing population of antibiotic resistance of bacteria strains as a result of enzymatic inactivation of the drug, modification of target sites and extrusion by efflux has become one of the major tasks to be addressed in the area of research in drug design and discovery (Spratt 1994). The construction of complex molecular architectures that exhibit greater biological potency in a facile and efficient manner remains an overarching goal for chemists. In the recent years, coumarins have attracted great attention because of their synthetic utility as building blocks for the construction of biologically potent molecules. Coumarin derivatives are known to have a wide range of activities such as antioxidant, antimicrobial, anti-HIV, antibiotic, anticancer, muscle relaxant, anti-inflammatory and anticoagulant properties (Murakami et al. 2000).

Pyrazoles have attracted particular interest over the last few decades due to use of such a ring system as the core nucleus in various drugs. This class of compounds represent a key motif which occupy a prime place in medicinal chemistry due to their competence to exhibit antimicrobial (Gilbert et al. 2006), anticancer (Igor Magedov et al. 2007), anti-inflammatory (Bennamane et al. 2008), anticonvulsant (Ozdemir et al. 2007), antipyretic (Sener et al. 2002), peptide deformylase inhibitor (Cali et al. 2004) activities.

Pyranopyrazoles were first obtained in 1973 by reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene (Junek & Aigner 1973). After this Otto (1974) had proposed the synthesis of the dihydropyrano[2,3-*c*]pyrazoles in 1974 via the base catalyst cycloaddition of 4-aryliden-5-pyrazolone (Otto 1974). Pyran derivatives constitute a useful class of heterocyclic compounds, which are widely distributed in nature (Moriguchi et al. 1997). Pyran and fused pyran derivatives have attracted a great deal of interest due to their association with various kinds of biological properties. Substituted benzo(b)pyran derivatives synthesized were reported to exhibit anticancer activities against three human cell lines even at very low concentrations (Hamman et al. 2005). Pyranochalcones have been reported to exhibit antimutagenic, antimicrobial, antiulcer and antitumor activities (Lee et al. 2007). A regioselective

*Corresponding author: ajaykkchem@gmail.com

palladium-catalyzed allylic alkylation cascade forms furo[3,2-c]pyrans from various cyclic β-dicarbonyl bis-nucleophiles and 3,6-dihydro-2*H*-pyran bis-electrophiles (Bartlett et al. 2013). Pyrano[3,2-*c*]pyran derivatives were synthesized by the reaction of aromatic aldehyde, malononitrile and 4-hydroxy-5-methylpyran-2-one in ethyl alcohol at room temperature catalyzed by $KF/Al_2O_3$ (Wang et al. 2006).

When a biodynamic heterocyclic system is coupled with other heterocyclic systems, such coupled molecules are expected to show enhanced biological activity. With this in view and considering the importance of pyran and pyrazole derivatives, it was thought worthwhile to synthesize new compounds incorporating both these moieties to the coumarin nucleus with the hope of getting molecules of greater biological potency. We herein report the synthesis of a series of new fused pyrans bearing coumarin moiety and *in vitro* evaluation of their antimicrobial activity.

## METHODS

Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a Nujol mull on Shimadzu 8300 spectrometer. The $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Spect 500 MHz and Spect 125 MHz spectrophotometer respectively using DMSO as solvent and TMS as an internal standard. The chemical shifts are expressed in δ ppm. Mass spectra were obtained on Shimadzu LCMS-2010A spectrophotometer (CI). Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyser. Purification of compounds was done by column chromatography on silica gel (70-230 mesh. Merck).

**General procedure for the synthesis of 2-aryl-4-ethoxyl-8-methyl-2*H*-pyrano[2',3':5,6] chromeno[4,3-*c*]pyrazol-10(4*H*)-one 2a-f**

Precursors 1-aryl-3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-1*H*-pyrazole-4-carboxaldehydes **1a-f** (Scheme-1) were obtained by the procedure reported by us earlier (Renuka & Kumar 2013).

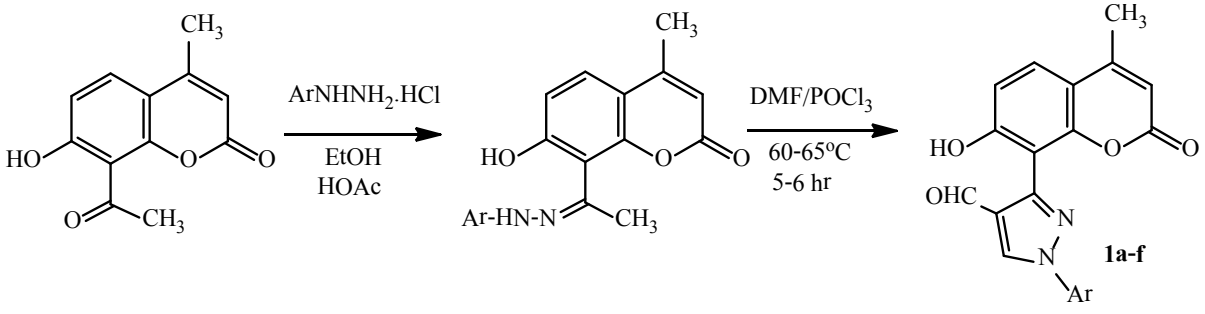
A mixture of 1-aryl-3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-1*H*-pyrazole-4-carboxaldehydes **1a-f** (0.001mol) in ethyl alcohol (10ml) and concentrated sulfuric acid (1mL) was refluxed for 4 hours at 80ºC. The progress of the reaction was monitored by TLC; after completion, the solvent was removed in vacuo. The resulting residue was extracted into ether (30mL), washed successively with NaOH and $NaHCO_3$. The organic phase was dried over anhydrous sodium sulphate. The solvent was evaporated to dryness to get the products **2a-f** (Scheme-2). The products were purified by column chromatography using hexane and ethyl acetate as eluent.

**4-Ethoxy-8-methyl-2-phenyl-2*H*-pyrano[2',3':5,6] chromeno[4,3-*c*]pyrazol-10(4H)-one 2a**

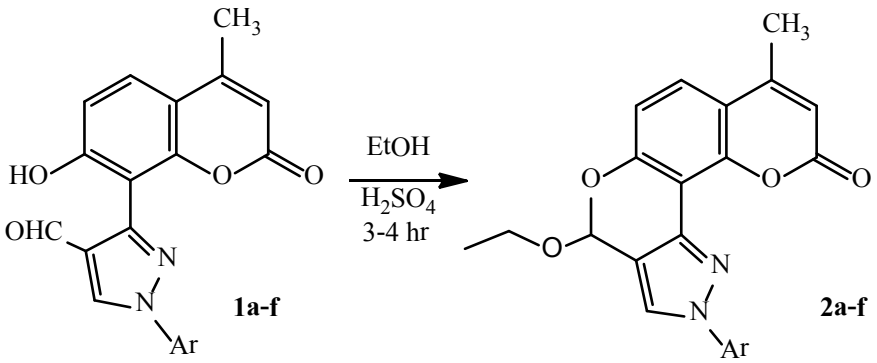
Obtained from 3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1-phenyl-1H-pyrazole-4-carboxaldehyde **1a** as a light yellow solid in 85% yield; purified by column chromatography separations using hexane: ethyl acetate (9:2) as eluent. m.p. 196-198°C. $^1H$ NMR (DMSO-$d_6$): δ 1.10 (t, 3H, $CH_3$), 2.30 (q, 2H, $CH_2$), 3.78 (s, 3H, $CH_3$), 6.3 (s, 1H, $C_9$-H), 6.60 (s, 1H, $C_4$-H), 7.20 (d, 1H, $C_6$-H), 7.43 (d, 1H, $C_7$-H), 7.40-8.20 (m, 5H, Ar-H), 8.80 (s, 1H, $C_3$-H). $^{13}C$ NMR: (DMSO-$d_6$): δ 13.62 (1C, $CH_3$), 18.75 (1C, $CH_3$), 39.49 (1C, $OCH_2$), 80.33 (1C, $C_6$), 115.02 (1C, $C_4$), 115.6 (1C, $C_9$), 116.2 (1C, $C_{7a}$), 117.3 (1C, $C_{11b}$), 118.6 (1C, $C_{3'}$), 119.61 (2C, Ar), 119.76 (1C, $C_3$), 127.39 (1C, $C_7$), 128.11 (1C, Ar), 130.19 (2C, Ar), 134.27 (1C, Ar), 138.23 (1C, $C_{11a}$), 158.5 (1C, $C_{2'}$), 160.46 (1C, $C_8$), 166.04 (1C, $C_{5'}$), 174.15 (1C, $C_{10}$). MS (m/z): 375 [M+1], 359, 345, 329, 283, 270, 238, 177. Anal. Cacld. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48%; Found: C, 70.62; H, 5.01; N, 7.58%.

**4-Ethoxy-2-(2-methoxyphenyl)-8-methyl-2*H*-pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazol-10(4H)-one 2b**

Obtained from 3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1-(2-methoxyphenyl)-1H-pyrazole-4-



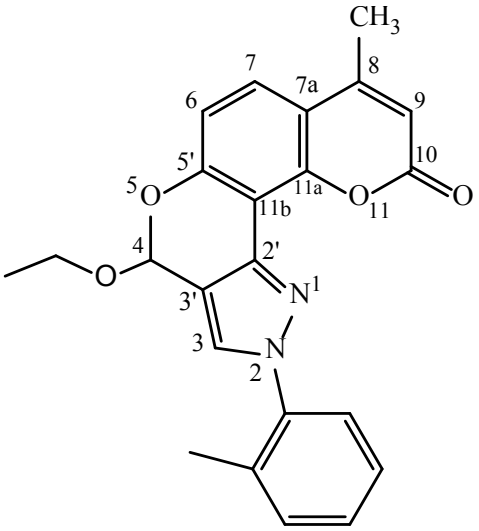

**Scheme 1.** Synthetic pathway for the preparation of formylpyrazoles **1a-f.**




**2** a) Ar = $C_6H_5$; b) Ar = 2-$OCH_3C_6H_4$; c) Ar = 2-$CH_3C_6H_4$;
d) Ar = 2-$ClC_6H_4$; e) Ar = 4-$ClC_6H_4$; f) Ar = 2,4$(NO_2)_2C_6H_3$.

**Scheme 2**. Synthetic pathway for the preparation of fused pyrans **2a-f.**

Additional figure according to accepted numbering system




carboxaldehyde **1b** as a light yellow solid in 82% yield; purified by column chromatography separations using hexane: ethyl acetate (9:1) as eluent. m.p. 122-124°C. $^1$H NMR (DMSO-$d_6$): δ 1.00 (t, 3H, $CH_3$), 2.22 (q, 2H, $CH_2$), 3.66 (s, 3H, $CH_3$), 3.86 (s, 3H, $OCH_3$), 6.32 (s, 1H, $C_9$-H), 6.60 (s, 1H, $C_4$-H), 7.22 (d, 1H, $C_6$-H), 7.40 (d, 1H, $C_7$-H), 7.42 (d, 1H, Ar-H), 7.52 (t, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 8.08 (d, 1H, Ar-H), 8.76 (s, 1H, $C_3$-H). $^{13}$C NMR: (DMSO-$d_6$): δ 13.62 (1C, $CH_3$), 18.75 (1C, $CH_3$), 39.49 (1C, $OCH_2$), 60.2 (1C, $OCH_3$), 80.33 (1C, $C_6$), 115.02 (1C, $C_4$), 115.6 (1C, $C_9$), 116.2 (1C, $C_{7a}$), 117.3 (1C, $C_{11b}$), 118.6 (1C, $C_{3'}$), 118.8 (1C, Ar), 119.2 (1C, Ar), 119.76 (1C, $C_3$), 120.5 (1C, Ar), 121.8 (1C, Ar), 123.4 (1C, Ar), 126.3 (1C, Ar), 127.39 (1C, $C_7$), 138.23 (1C, $C_{11a}$), 158.5 (1C, $C_{2'}$), 160.46 (1C, $C_8$), 166.04 (1C, $C_{5'}$), 174.15 (1C, $C_{10}$). MS (m/z): 405 [M+1], 388 [M+, base peak], 375, 360, 283, 270, 238, 177. Anal. Cacld. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93%; Found: C, 68.11; H, 5.03; N, 7.09%.

**4-Ethoxy-8-methyl-2-(2-methylphenyl)-2*H*-pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazol-10(4H)-one 2c**

Obtained from 3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1-(2-methylphenyl)-1H-pyrazole-4-carboxaldehyde **1c** as a light yellow solid in 92% yield; purified by column chromatography separations using hexane: ethyl acetate (8:2) as eluent.m.p. 156-158°C. $^1$H NMR (DMSO-$d_6$): δ 0.99 (t, 3H, $CH_3$), 2.24 (q, 2H, $CH_2$), 3.01 (s, 3H, $CH_3$), 3.62 (s, 3H, $CH_3$), 6.20 (s, 1H, $C_9$-H), 6.62 (s, 1H, $C_4$-H), 7.14 (d, 1H, $C_6$-H), 7.44 (d, 1H, $C_7$-H), 7.52 (d, 1H, Ar-H), 7.74 (t, 1H, Ar-H), 7.92 (t, 1H, Ar-H), 8.18 (d, 1H, Ar-H), 8.70 (s, 1H, $C_3$-H).$^{13}$C NMR: (DMSO-$d_6$): δ 13.68 (1C, $CH_3$), 16.22 (1C, $CH_3$), 18.90 (1C, $OCH_2$), 39.42 (1C, $CH_3$), 80.24 (1C, $C_6$), 115.12 (1C, $C_4$), 115.6 (1C, $C_9$), 116.2 (1C, $C_{7a}$), 117.3 (1C, $C_{11b}$), 118.6 (1C, $C_{3'}$), 119.2 (1C, Ar), 119.65 (1C, Ar), 119.72 (1C, $C_3$), 127.35 (1C, $C_7$), 128.18 (1C, Ar), 131.5 (1C, Ar), 134.6 (1C, Ar), 136.4 (1C, Ar), 138.32 (1C, $C_{11a}$), 158.08 (1C, $C_{2'}$), 160.26 (1C, $C_8$), 166.12 (1C, $C_{5'}$), 174.00 (1C, $C_{10}$). MS (m/z): 388, 389 [M+1], 373, 359, 344, 283, 270, 238, 177. Anal. Cacld. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21%; Found: C, 71.23; H, 5.28; N, 7.27%.

**2-(2-Chlorophenyl)-4-ethoxy-8-methyl-2*H*-pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazol-10(4H)-one 2d**

Obtained from 1-(2-chlorophenyl)-3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1H-pyrazole-4-carboxaldehyde **1d** as a light yellow solid in 86% yield; purified by column chromatography separations using

hexane: ethyl acetate (8:1) as eluent. m.p. 134-136°C. $^1$H NMR (DMSO-$d_6$): δ 1.02 (t, 3H, $CH_3$), 2.28 (q, 2H, $CH_2$), 3.04 (s, 3H, $CH_3$), 6.24 (s, 1H, $C_9$-H), 6.63 (s, 1H, $C_4$-H), 7.10 (d, 1H, $C_6$-H), 7.42 (d, 1H, $C_7$-H), 7.56 (d, 1H, Ar-H), 7.68 (t, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 8.08 (d, 1H, Ar-H), 8.61 (s, 1H, $C_3$-H). $^{13}$C NMR: (DMSO-$d_6$): δ 13.80 (1C, $CH_3$), 18.88 (1C, $CH_3$), 39.60 (1C, $OCH_2$), 80.30 (1C, $C_6$), 115.12 (1C, $C_4$), 115.6 (1C, $C_9$), 116.2 (1C, $C_{7a}$), 117.3 (1C, $C_{11b}$), 118.68 (1C, $C_{3'}$), 119.40 (1C, Ar), 119.98 (1C, $C_3$), 123.6 (1C, Ar), 127.32 (1C, $C_7$), 128.18 (1C, Ar), 130.3 (1C, Ar), 132.4 (1C, Ar), 135.5 (1C, Ar), 138.44 (1C, $C_{11a}$), 158.40 (1C, $C_{2'}$), 160.40 (1C, $C_8$), 166.16 (1C, $C_{5'}$), 174.02 (1C, $C_{10}$). MS (m/z): 408, 409 [M+1], 393, 379, 364, 283, 270, 238, 177. Anal. Cacld. for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85%; Found: C, 64.53; H, 4.12; N, 7.01%.

**2-(4-Chlorophenyl)-4-ethoxy-8-methyl-2*H*-pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazol-10(4H)-one 2e**

Obtained from 1-(4-chlorophenyl)-3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1H-pyrazole-4-carboxaldehyde **1e** as a pale yellow solid in 74% yield; purified by column chromatography separations using hexane: ethyl acetate (9:2) as eluent. m.p. 113-115°C. $^1$H NMR: (DMSO-$d_6$): δ 1.06 (t, 3H, $CH_3$), 2.24 (q, 2H, $CH_2$), 3.00 (s, 3H, $CH_3$), 6.11 (s, 1H, $C_9$-H), 6.58 (s, 1H, $C_4$-H), 7.13 (d, 1H, $C_6$-H), 7.30 (d, 1H, $C_7$-H), 7.68 (dd, 2H, Ar-H), 8.12 (dd, 2H, Ar-H), 8.58 (s, 1H, $C_3$-H).$^{13}$C NMR: (DMSO-$d_6$): δ 13.86 (1C, $CH_3$), 18.80 (1C, $CH_3$), 39.54 (1C, $OCH_2$), 80.33 (1C, $C_6$), 115.18 (1C, $C_4$), 115.6 (1C, $C_9$), 116.2 (1C, $C_{7a}$), 117.3 (1C, $C_{11b}$), 118.62 (1C, $C_{3'}$), 119.73 (2C, Ar), 119.94 (1C, $C_3$), 127.30 (1C, $C_7$), 130.22 (2C, Ar), 132.4 (1C, Ar), 136.3 (1C, Ar), 138.48 (1C, $C_{11a}$), 158.46 (1C, $C_{2'}$), 160.44 (1C, $C_8$), 166.10 (1C, $C_{5'}$), 174.00 (1C, $C_{10}$). MS (m/z): 408, 409 [M+1], 393, 379, 364, 283, 270, 238, 177Anal. Cacld. for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85%; Found: C, 64.48; H, 4.30; N, 7.01%.

**2-(2,4-Dinitrophenyl)-4-ethoxy-8-methyl-2*H*-pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazol-10(4H)-one 2f**

Obtained from 3-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)-1-(2,4-dinitrophenyl)-1H-pyrazole-4-carboxaldehyde **1f** as a yellow solid in 81% yield; purified by column chromatography separations using hexane: ethyl acetate (9:1) as eluent. m.p. 196-198°C. $^1$H NMR: (DMSO-$d_6$): δ 1.05 (t, 3H, $CH_3$), 2.25 (q, 2H, $CH_2$), 3.02 (s, 3H, $CH_3$), 6.04 (s, 1H, $C_9$-H), 6.55 (s, 1H, $C_4$-H), 7.16 (d, 1H, $C_6$-H), 7.34 (d, 1H, $C_5$-H), 7.58 (d, 1H, Ar-H), 7.98 (d, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 8.68 (s, 1H, $C_3$-H). $^{13}$C NMR: (DMSO-$d_6$): δ 13.86 (1C, $CH_3$), 18.80 (1C-$CH_3$), 39.54 (1C, $OCH_2$), 80.33 (1C, $C_6$), 115.18 (1C, $C_4$), 115.6 (1C, $C_9$), 116.2 (1C, $C_{7a}$), 117.3 (1C, $C_{11b}$), 118.62 (1C, $C_{3'}$), 119.94 (1C, $C_3$), 120.6 (1C, Ar), 123.6 (1C, Ar), 127.30 (1C, $C_7$), 128.4 (1C, Ar), 132.4 (1C, Ar), 138.48 (1C, $C_{11a}$), 140.5 (1C, Ar), 150.4 (1C, Ar), 158.46 (1C, $C_{2'}$), 160.44 (1C, $C_8$), 166.10 (1C, $C_{5'}$), 174.00 (1C, $C_{10}$). MS (m/z): 464, 465 [M+1], 449, 435, 420, 283, 270, 238, 177. Anal. Cacld. for $C_{22}H_{16}N_4O_8$: C, 56.90; H, 3.47; N, 12.06%; Found: C, 56.87; H, 3.52; N, 12.16%.

**Antimicrobial activity**

Minimum inhibitory concentrations (MICs) of the synthesized compounds **2a-f** against different bacterial and fungal strains were determined by a known method (Kumar et al. 2012). Ciprofloxacin and Nystatin were used as standard drugs against bacteria and fungi species. The experiments were performed in triplicate and the results were taken as a mean ± standard deviation (SD). The results of antibacterial and antifungal activity of the synthesized compounds were summarized in Table 1 and Table 2 respectively.

**Table 1**. Minimum Inhibitory Concentrations of the synthesized compounds 2a-f against bacteria species.

| Compound | Minimum inhibitory concentration (MIC's) in µg/mL* | | | | |
|---|---|---|---|---|---|
| | *Staphylococcus aureus* | *Streptococcus pyogenes* | *Salmonella typhimurium* | *Escherichia coli* | *Pseudomonas aeruginosa* |
| 2a | 30$^{a}$±1.05 | 75$^{a}$±1.46 | 40$^{a}$±0.50 | 25$^{a}$±1.00 | 25$^{a}$±0.92 |
| 2b | NA | NA | 75$^{b}$±0.53 | 50$^{b}$±0.43 | NA |
| 2c | 50$^{b}$±0.62 | 100$^{b}$±0.46 | 75$^{b}$±0.53 | 75$^{c}$±0.75 | 100$^{b}$±0.62 |
| 2d | 25$^{c}$±0.46 | 60$^{c}$±0.56 | 60$^{c}$±0.80 | 50$^{b}$±1.00 | 50$^{c}$±0.53 |
| 2e | 20$^{d}$±0.36 | 30$^{d}$±0.62 | 50$^{d}$±0.53 | 40$^{d}$±0.46 | 25$^{a}$±0.65 |
| 2f | 50$^{e}$ ±0.30 | 75$^{e}$±0.26 | NA | NA | NA |
| Ciprofloxacin | 25$^{c}$ ±0.43 | 50$^{f}$±1.28 | 50$^{d}$±0.55 | 25$^{a}$±0.65 | 12.5$^{d}$±0.65 |

The compounds with the different letter in the parenthesis are significantly different at 5% level according to (DMRT) Duncan's Multiple Range Test.

* Values are expressed as mean ± standard deviation (SD).

NA: No activity observed.

**Table 2**. Minimum Inhibitory Concentrations of the synthesized compounds 2a-f against fungi species.

| Compound | Minimum inhibitory concentration (MIC's) in µg/mL* | | | |
|---|---|---|---|---|
| | *Cryptococcus neoformans* | *Aspergillas niger* | *Aspergillas flavus* | *Candida albicans* |
| 2a | $50^{a}$±0.36 | $75^{a}$±0.82 | $75^{a}$±1.05 | $50^{a}$±1.37 |
| 2b | $150^{b}$±0.62 | NA | NA | $150^{b}$±1.34 |
| 2c | $100^{c}$±1.21 | NA | $200^{b}$±1.81 | NA |
| 2d | $30^{d}$±0.70 | $50^{b}$±2.09 | $60^{c}$±0.79 | $30^{c}$±1.25 |
| 2e | $25^{e}$±0.85 | $40^{c}$±1.65 | $40^{d}$±0.70 | $25^{d}$±0.56 |
| 2f | NA | NA | NA | NA |
| Nystatin | $25^{e}$±1.55 | $50^{b}$±0.75 | $50^{e}$±0.43 | $25^{d}$±0.85 |

The compounds with the different letter in the parenthesis are significantly different at 5% level according to (DMRT) Duncan's Multiple Range Test.
* Values are expressed as mean ± standard deviation (SD).
NA: No activity observed.

## RESULTS AND DISCUSSION

In the current study, we intended of introduce the pyran moiety to the coumarin skeleton in order to build a novel family of bioactive molecules. Thus, a series of fused pyran derivatives **2a-f** were synthesized by intramolecular cyclisation of 1-aryl-3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-1*H*-pyrazole-4-carbaxaldehyde **1a-f** in excellent yields.

The structures of the synthesized new compounds were confirmed by spectral and elemental analysis. For instance, in $^{1}$H NMR spectrum, the signals observed in the region δ 10.60-10.80 ppm. due to –CHO group; and in the region δ 9.65-9.90 ppm. due to phenolic –OH group of the compounds **1a-f** (Renuka & Kumar 2013) were found absent in all the synthesized compounds **2a-f**. A consistent pattern signals a singlet in the region δ 6.5-6.6 ppm. due to $-C_4$-H function of pyran ring; triplet in the region δ 0.99-1.10 ppm. due to $-CH_3$ protons, and a quartet in the region δ 2.22-2.30 ppm. due to $-CH_2$ protons, which were absent in $^{1}$H NMR spectra of **1a-f** confirmed the formation of the products. Further, all showed the signals due to aromatic and substituent protons at the expected region.

The $^{13}$C NMR spectra of **2a-f** showed the signals due to aromatic carbons and the substituent carbons at the expected region. The signals observed due to aldehydic carbon of **1a-f** (Renuka & Kumar 2013) in the region δ 165-170 ppm. were absent in **2a-f**. In addition to the signals observed in **1a-f**, compounds **2a-f** showed a consistent pattern of signals due to $C_4$-carbon of the pyran ring which appears in the region δ 115-116 ppm.; $CH_3$-carbon in the region δ 13-14 ppm.; $OCH_2$-carbon in the region δ 39-40 ppm. These additional signals support the formation of products. All the synthesized new molecules showed M+1 ion as a base peak in their mass spectra. Further, satisfactory elemental analysis data confirms the cyclisation of **1a-f** to form the products **2a-f**.

All the new synthesized compounds **2a-f** exerted a wide range of *in vitro* antibacterial activity against the tested organisms. However, compound **2b** failed to inhibit the growth of *Staphylococcus aureus*, *Streptococcus pyogenes,* and *Pseudonomas aeruginosa* even at a higher concentration of 200µg/mL. Similarly, compound **2f** failed to inhibit *Salmonella typhimurium*, *Echerichia coli,* and *Pseudonomas aeruginosa* organisms. Compound **2e** exhibits inhibition to a greater extent in comparison with the standard against the organisms *S. aureus*, *S. pyogenes,* and *S. typhimurium*. Compound **2d** exhibited promising bacterial activity against the organism tested. Compound **2f** displayed lesser or no activity against the organisms tested.

Compounds **2d** and **2e** showed potential antifungal activity against all the organisms tested. However, **2f** showed no activity even at a higher concentration of 200µg/mL. Compound **2a** showed moderate activity against the organisms tested. However, compounds **2b** and **2c** exhibited lesser activity against *Aspergillus niger*, *Aspergillus flavus,* and *Candina albicans,* respectively.

**Statistical analysis**: All values are expressed as mean ± standard deviation did in triplicates of two independent experiments. Statistical analyses of the MIC values were performed by the One-way ANOVA.

Antibacterial activities of compound **2e** against *S. aureus* and *S. pyogenes*, and compound **2a** against *S. typhimurium* are significantly higher than the standard at $p<0.05$. Likewise, compound **2e** exhibited significantly higher antifungal activity against *A. niger* and *A. flavus* compared with the standard at $p<0.05$ confidence level.

## CONCLUSION

The simple easy accessible procedure for the synthesis of fused pyrans and their in vitro antibacterial and antifungal activity results revealed the significance of the study. The synthesized compounds exhibited moderate to good antibacterial and antifungal activity against some of the tested organisms. Compounds, particularly 2d and 2e exhibited greater activity in comparison to the standard drug. The SAR study of the synthesized compounds remains the topic of interest.

## ACKNOWLEDGEMENT

The authors are grateful to the University Grants Commission, New Delhi for financial assistance.

## REFERENCES

BARTLETT MJ, TURNER CA, HARVEY JE. 2013, Pd-catalyzed allylic alkylation cascade with dihydropyransL regioselective synthesis of furo[3,2-*c*] pyrans. Org Lett 15(10): 2430-2433.

BENAAMANE N, NEDJAR-KOLLI B, BENTARZI Y, HAMMAL L, GERONIKAKI A, ELEFTHERIOU P, LAGUNIN A. 2008. Synthesis and in silico biological activity evaluation of new N-substituted pyrazolo-oxazine-2-one systems. Bioorg Med Chem 16: 3059-3066.

CALI P, NAERUM L, MUKHIJA S, HJELMENCRANTZ A. 2004.Isoxazole-3-hydroxamic acid derivatives as peptide deformylase inhibitors and potential antibacterial agents. Bioorg Med Chem Lett 14: 5997-6000.

GILBERT AM, FAILLI A, SHUMSKY J, YANG Y, SEVERIN A, SINGH G, HU W, KEENEY D, PETERSEN PJ, KATZ AH. 2006. Pyrazolidine-3,5-diones and 5-hydroxy-1H-pyrazol-3(2H)-ones, inhibitors of UDP-N-acetylenolpyruvyl glucosamine reductase. J Med Chem 49: 6027-6036.

HAMMAM GAEF, EI-SALAM OIABD, ASHRAF MM, NAGLA HA.2005. Novel fluoro substituted benzo(*b*) pyran with anti-lung cancer activity. Ind J Chem 44B: 1887-1893.

JUNEK H, AIGNER H. 1973, synthesenmitNitrilen, XXXV. Reaktionen von TetracyanathylenmitHeterocyclen. Chem Ber 106: 914-921.

KUMAR K A, RAI KML, VASANTH KUMAR G, MYLARAPPA BN. 2012. A facile route for the synthesis of ethyl *N*-aryl-2,6-dioxo-piperid-3-ene-4-carboxylates and their biological activity. Int J Pharm Pharm Sci 4(Suppl 4): 564-568.

LEE YR, WANG X, XIA L.2007.An efficient and rapid synthetic route to biologically interesting pyranochalcone natural products. Molecules 12:1420-1429.

MAGEDOV IV, MANPADI M, SLAMBROUCK SV, STEELANT WFA, ROZHKOVA E, PRZHEVAL SKII NM, SNEZNA R, ALEXANDER K. 2007. Discovery and investigation of antiproliferative and apoptosis-inducing properties of new heterocyclic podophyllotoxin analogues accessible by a one step multicomponent synthesis. J Med Chem 50: 5183-5192.

MORIGUCHI T, MATSUURA H, ITAKURA Y, KATSUKI H, SAITO H, NISHIYAMA N. 1997. Allixin, a phytoalexin produced by garlic, and its analogues as novel exogenous substances with neurotrophic activity. Life Sci 61: 1413-1420.

MURAKAMI A, GAO G, OMURA M, YANO M, ITO C, FURUKAWA H, TAKAHASHI D, KOSHIMIZU K, OHIGASHI H. 2000. 1,1-Dimethylallylcoumarins potently suppress both lipopolysaccharide- and interferon-gamma-induced nitric oxide generation in mouse macrophage RAW 264.7 cells. Bioorg Med CheM Lett 10: 59-62.

OTTO HH. 1974. Darstellungeiniger 4H-Pyrano[2,3-c] pyrazolderivate. Arch Pharm 307: 444-447.

OZDEMIR Z, KANDILCI HB, GUMUSEL B, CALIS U, BILGIN AA. 2007. Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. Eur J Med Chem 42: 373-379.

RENUKA N, KUMAR KA. 2013. Synthesis and biological evaluation of novel Formyl-Pyrazoles bearing Coumarin moiety as potent antimicrobial and antioxidant agents. Bioorg Med Chem Lett. 23: 6406-6409.

SENER A, SENER MK, BILDMCI I, KASIMOGULLARI R,AKCAMUR Y. 2002.Studies on the reactions of cyclic oxalyl compounds with hyrazines or hydrazones: Synthesis and reactions of 4-benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid. J Heterocycl Chem 39: 869-875.

SPRATT BG. 1994. Resistance to antibiotics mediated by target alterations. Science 264: 388-393.

WANG X-S, ZHOU J-X, ZENG Z-S, LI Y-L, SHI D-Q, TU S-J. 2006. One-pot synthesis of pyrano[3,2-*c*] pyran derivatives catalyzed by $KF/Al_2O_3$. Arkivoc (xi): 107-113.