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ORIGINAL PAPER

Novel benzopyranopyridine derivatives of 2-amino-3-formylchromone

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Enol lactones such as 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic acid lactone, TAL) and 4-hydroxycoumarin when treated with 2-amino-3-formylchromone under basic conditions afforded 3-acetoacetyl benzopyranopyridones and benzopyranopyridines, respectively. A series of pyrazole derivatives was prepared by the reaction of 3-acetoacetyl benzopyranopyridones with different hydrazines. All compounds were characterised on the basis of spectral data and their antibacterial activity evaluated.

Keywords: 2-amino-3-formylchromone, 4-hydroxycoumarin, pyranopyridines, antibacterial

Introduction

Benzopyranopyridine derivatives are of scientific value because they exhibit various biological activities. They have been reported to exhibit potent bronchiodilating activity in the treatment of bronchitis and asthma (Connor et al., 1984). This class of compounds has also shown potential selectivity towards leukaemic cell lines (El-Subbagh et al., 2000). Therefore, synthesis of this condensed heterocyclic system is worthwhile because of its important biological properties such as antiallergic (Nohara et al., 1985), antiangiogenic (Lee et al., 2005), antirheumatic (Evdokimov et al., 2006), antibacterial (Srivastava et al., 2005), anti-inflammatory and analgesic (Hosni & Abdulla, 2008), antagonism towards the antipsychotic dopamine D_4 receptor (Unangst et al., 1997), neurogenic disorders such as Alzheimer's disease, Parkinson's disease, depression, allergic responses, sedation (Borroni et al., 2001), being the properties associated with the structure of these compounds. Ever since establishment of the structure-activity relationship of cromakalim as a potent anti-hypertensive agent, other examples such as EMD52692 and Ro 31-6930 have been reported (Ashwood et al., 1986, 1991; Cecchetti et al., 2006; Bergmann & Gericke, 1990; Paciorek et al., 1990). Some pyridobenzopyranones have also been reported as herbicide safeners (Hagen et al., 1992).

On the other hand, pyrazole skeleton is found in a large number of naturally occurring or synthetic biologically-active heterocyclic compounds (Singh et al., 2006). Pyrazole derivatives have been used as analgesic (Prokopp et al., 2006), anti-inflammatory (Patel et al., 2004), antipyretic (Shchegol'kov et al., 2006), antidepressant (Bailey et al., 1985), antibacterial (Dardari et al., 2006), antimicrobial (Wardakhan & Louca, 2007), and anti-convulsant (Chauhan et al., 1993) agents. They are also applied as herbicides (Vicentini et al., 2005) and fungicides (Vors et al., 2003) used in sunscreen materials (García et al., 1991) and as analytical reagents (Busev et al., 1965).

Motivated by the above findings, and as a part of our continuing study on the functionalisation of pyranopyridines (Siddiqui et al., 2006) and pyranocoumarines (Siddiqui & Asad, 2006), we looked into designing and synthesising new pyranopyridines and their derivatives containing a pyrazole moiety, which might show much better or different biological properties. Hence, the present study describes the synthesis and antibacterial examination of 3-acetoacetyl benzopyranopyridones (*Vb*), pentacyclic benzopyranopyridines (*VIIIa* and *VIIIb*), and pyra-

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Table 1. Characteristics of newly prepared compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.
			C	H	N	S	%	°C
Vb	$C_{17}H_{13}NO_5$	311.29	65.59 65.63	4.20 4.23	4.50 4.52	–	80	196
VIIIa	$C_{19}H_9NO_4$	315.28	72.38 72.41	2.87 2.84	4.44 4.39	–	42	283
VIIIb	$C_{19}H_9NO_4$	315.28	72.38 72.32	2.87 2.82	4.44 4.45	–	19	292
IXa	$C_{16}H_{11}N_3O_3$	293.27	65.53 65.58	3.78 3.82	14.33 14.37	–	71	300d
IXb	$C_{22}H_{15}N_3O_3$	369.37	71.53 71.57	4.09 4.06	11.37 11.40	–	60	280
IXc	$C_{23}H_{14}N_4O_3S$	426.45	64.78 64.82	3.31 3.29	13.14 13.19	7.52 7.55	64	300d
IXd	$C_{17}H_{13}N_3O_3$	307.30	66.44 66.47	4.26 4.23	13.67 13.69	–	65	244
IXe	$C_{23}H_{17}N_3O_3$	383.40	72.05 72.09	4.47 4.42	10.96 10.94	–	71	251
IXf	$C_{24}H_{16}N_4O_3S$	440.41	65.44 65.49	3.66 3.62	12.72 12.75	7.28 7.32	70	260

zolylpyranopyridines (*IXa*–*IXf*) resulting from the reaction of 2-amino-3-formylchromone (*IIIa* and *IIIb*) and enol lactones (triacetic acid lactone *IV* and 4-hydroxycoumarin *VI*).

Experimental

Melting points were measured in a digital melting point apparatus (Macro Scientific Works (Regd.) MSW-401 Delhi, India). IR spectra were recorded on a Perkin–Elmer RXI spectrometer (UK) in KBr and only noteworthy absorptions are listed. ^{1}H NMR spectra were recorded on a Bruker DRX300 spectrometer (Switzerland) using tetramethylsilane (TMS) as internal standard and DMSO-d_6/$CDCl_3$ as solvent. Mass spectra were obtained on a Jeol-SX-102 (FAB) spectrometer (Japan). Elemental analysis was performed on Elementar Vario EL III (Germany) and results agreed favourably with calculated values. *IIIa*, *IIIb*, *IV*, *Va* compounds, and hydrazinobenzothiazole were prepared according to a procedure reported by (Petersen & Heitzer, 1976; Butt & Elvidge, 1963; Siddiqui et al., 2006; Singh et al., 1990). 4-Hydroxycoumarin, hydrazine hydrate, phenylhydrazine, methanol, pyridine, and piperidine were obtained from Otto-kemi Pvt. Ltd. (Mumbai, India). Physicochemical and spectral data of the newly synthesised compounds are given in Tables 1 and 2, respectively.

3-Acetoacetyl-7-methyl-5-oxo-5H-[1]benzopyrano[3,2-e]pyridin-2-one (Vb)

2-Amino-3-formyl-6-methylchromone *IIIb* (4.93 mmol) was dissolved in pyridine (30 mL) containing piperidine (10.5 mmol) and triacetic acid lactone *IV* (7.94 mmol). The reaction mixture was kept at room temperature for 7 days. The product *Vb*, which crystallised from the solution as a canary yellow solid, was filtered, washed with cold water, and dried. The mother liquor was poured into the ice-cold water and acidified with HCl. The solid precipitated, was filtered, washed with water, dried and re-crystallised from chloroform–methanol mixture to yield more *Vb*. The total yield was 1.22 g (3.91 mmol).

4-Oxo-4H-1-benzopyrano[2,3:2,3]pyrido[3,2-b]-4-oxo-4H-1-benzopyran-4-one (VIIIa) and 4-oxo-4H-1-benzopyrano[2,3:2,3]pyrido[2,3-c]-2-oxo-2H-1-benzopyran-2-one (VIIIb)

A mixture of 2-amino-3-formylchromone, *IIIa* (5.29 mmol) and 4-hydroxycoumarin, *VI* (5.29 mmol) in methanol (20 mL) containing a catalytic quantity of pyridine (0.05 mL) was heated under reflux in a water bath for 12 h. After completion of the reaction (checked by TLC), the compound, kept at room temperature, was allowed to precipitate to produce a yellowish-brown solid. The precipitate was filtered, washed thoroughly with methanol and allowed to pass through a column filled with silica gel. The elution of the column with petrol–benzene mixture (φ_{petrol} = 0.6) afforded a yellow compound *VIIIa* (Schurreit, 1987) which was re-crystallised from chloroform as yellow crystals. Further elution of the column with petrol and benzene (φ_r = 0.5) gave a light yellow solid *VIIIb* (Schurreit, 1987). It was re-crystallised from chloroform as light yellow crystals. The yield of *VIIIa* was 0.69 g (2.18 mmol) and *VIIIb* 0.31 g (0.983 mmol).

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data
Vb	IR, $\tilde{\nu}$/cm^{-1}: 3445 (NH), 1668, 1649, 1618 (C═O) ^{1}H NMR ($CDCl_3$), δ: 2.24 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.40 (s, 1H, H^a), 7.59 (m, 2H, H-8, H-9), 8.08 (s, 1H, H-6), 9.04 (s, 1H, H^b), 14.58 (br s, 1H, OH, D_2O exchangeable) MS, m/z (I_r/%): 311 (100) (M^+), 294, 267, 254, 253
VIIIa	IR, $\tilde{\nu}$/cm^{-1}: 1670, 1665 (C═O) ^{1}H NMR ($CDCl_3$), δ: 7.87 (m, 6H, Ar-H), 8.32 (d, 1H, J = 7.8 Hz, H-4), 8.61 (d, 1H, J = 7.5 Hz, H-8), 9.59 (s, 1H, H-6) MS, m/z (I_r/%): 315 (60) (M^+), 259, 195, 167, 120
VIIIb	IR, $\tilde{\nu}$/cm^{-1}: 1751, 1671 (C═O) ^{1}H NMR ($CDCl_3$), δ: 7.86 (m, 7H, Ar-H), 8.37 (d, 1 H, J = 7.8 Hz, H-4), 9.71 (s, 1H, H-6) MS, m/z (I_r/%): 315 (100) (M^+), 287, 271, 259, 243, 195, 166, 120
IXa	IR, $\tilde{\nu}$/cm^{-1}: 3412 (NH), 1664, 1620 (C═O), 1608 (C═C), 1569 (CN) ^{1}H NMR (DMSO-d_6), δ: 2.27 (s, 3H, CH_3), 6.71 (s, 1H, H-4′), 7.87 (m, 4H, Ar-H, H-4), 8.17 (dd, 1H, J = 7.8 Hz, 3Hz, H-6), 8.69 (br s, 2H, NH, D_2O exchangeable) MS, m/z (I_r/%): 293 (50) (M^+), 278, 156, 155, 137, 135, 105
IXb	IR, $\tilde{\nu}$/cm^{-1}: 3428 (NH), 1638 (C═O), 1610 (C═C), 1575 (CN) ^{1}H NMR (DMSO-d_6), δ: 2.25 (s, 3H, CH_3), 6.24 (s, 1H, H-4′), 7.68 (m, 9H, Ar-H, H-4), 7.98 (dd, 1H, J = 7.8 Hz, 1.5 Hz, H-6) MS, m/z (I_r/%): 369 (58) (M^+), 368, 353, 155, 91
IXc	IR, $\tilde{\nu}$/cm^{-1}: 3400 (NH), 1656, 1637 (C═O), 1610 (C═C), 1590 (CN) ^{1}H NMR (DMSO-d_6), δ: 2.11 (s, 3H, CH_3), 7.88 (m, 9H, Ar-H, H-4, H4′), 8.20 (d, J = 8.1 Hz, H-6), 8.64 (br s, 1H, NH, D_2O exchangeable) MS, m/z (I_r/%): 426 (33) (M^+), 425, 155, 135, 106
IXd	IR, $\tilde{\nu}$/cm^{-1}: 3300 (NH), 1646, 1638 (C═O), 1610 (C═C) ^{1}H NMR (DMSO-d_6), δ: 2.30 (s, 6H, $2CH_3$), 6.56 (s, 1H, H-4′), 7.58 (m, 3H, Ar-H, H-4), 7.88 (s, 1H, H-6), 8.36 (br s, 1H, NH, D_2O exchangeable) MS, m/z (I_r/%): 307 (100) (M^+)
IXe	IR, $\tilde{\nu}$/cm^{-1}: 3437 (NH), 1667, 1641 (C═O) ^{1}H NMR (DMSO-d_6), δ: 2.20 (s, 6H, $2CH_3$), 7.52 (s, 1H, H-4′), 7.99 (m, 6H, Ar-H, H-8), 8.48 (s, 1H, H-6), 8.60 (s, 1H, H-4), 8.74–8.76 (d, 1H, J = 6.8 Hz, H-9), 9.12 (br s, 1H, NH, D_2O exchangeable) MS, m/z (I_r/%): 383 (6) (M^+), 307, 279, 251, 226, 170
IXf	IR, $\tilde{\nu}$/cm^{-1}: 3443 (NH), 1646 (C═O) ^{1}H NMR ($CDCl_3$), δ: 2.49 (s, 6H, $2CH_3$), 6.40 (s, 1H, H-4′), 7.61 (m, 5H, Ar-H, H-8), 7.78 (d, 1H, J = 7.3 Hz, H-9), 8.02 (s, 1H, H-6), 8.34 (s, 1H, H-4), 8.81 (br s, 1H, NH, D_2O exchangeable) MS, m/z (I_r/%): 440 (100) (M^+), 425, 424, 423, 307

3-(3-Methylpyrazol-5-yl)-5-oxo-5H-[1]benzopyrano[3,2-e]pyridin-2-one (*IXa*)

Va (3.36 mmol) was dissolved in ethanol (5–10 mL) and hydrazine hydrate (3.36 mmol) was added. The reaction mixture was heated under reflux for 3 h and allowed to cool to room temperature to afford a light yellow solid. It was filtered, washed with ethanol, dried and re-crystallised from a chloroform-methanol mixture. The yield was 0.69 g (2.35 mmol).

3-(3-Methyl-1-phenylpyrazol-5-yl)-5-oxo-5H-[1]benzopyrano[3,2-e]pyridin-2-one (*IXb*)

The equimolar amount of *Va* (3.36 mmol) and phenylhydrazine (3.36 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The reaction mixture was allowed to stand at room temperature as *IXb* crystallised to form yellow crystals. The crystals were filtered, washed with ethanol and dried. The yield was 0.74 g (2.00 mmol).

3-(3-Methyl-1-benzothiazolylpyrazol-5-yl)-5-oxo-5H-[1benzopyrano[3,2-e]pyridin-2-one (*IXc*)

Va (3.36 mmol) was dissolved in ethanol (50 mL) and 2-hydrazinobenzothiazole (3.36 mmol) was added. The reaction mixture was heated under reflux for 5 h. On cooling, a dirty-green solid was obtained, filtered, washed with ethanol, dried and re-crystallised from chloroform. The yield was 0.91 g (2.13 mmol).

7-Methyl-3-(3-methylpyrazol-5-yl)-5-oxo-5H-[1]benzopyrano[3,2-e]pyridin-2-one (*IXd*)

IXd compound was synthesised under similar reaction conditions as *IXa* using *Vb* (3.21 mmol) and hydrazine hydrate (3.21 mmol). The yield was 0.64 g (2.08 mmol).

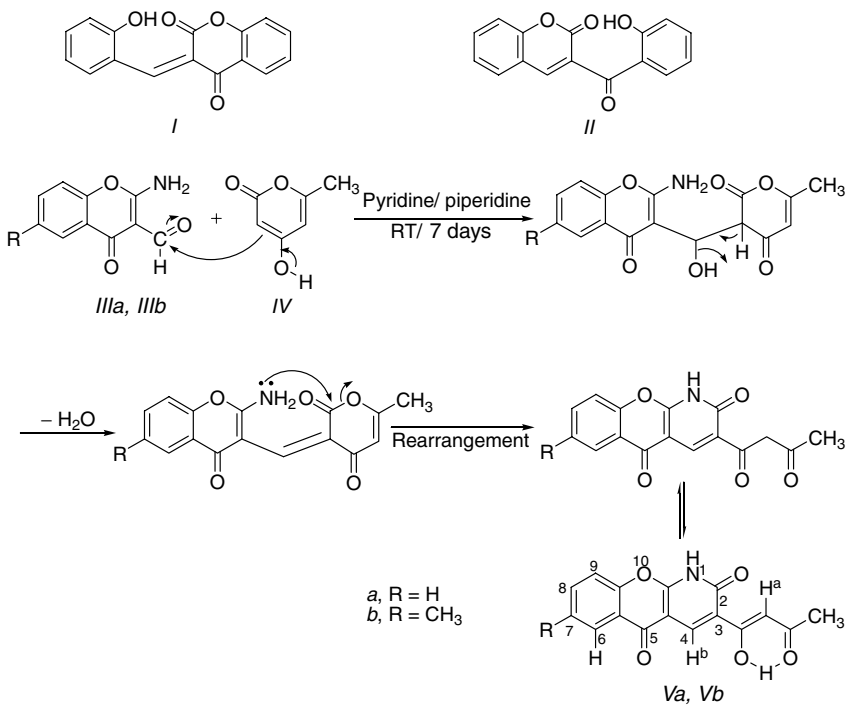

Fig. 1. Formation of 3-acetoacetyl benzopyranopyridones (*Va* and *Vb*).

7-Methyl-3-(3-methyl-1-phenylpyrazol-5-yl)-5-oxo-5H-[1]benzopyrano[3,2-e]pyridin-2-one (*IXe*)

IXe was synthesised under similar reaction conditions as *IXb* using *Vb* (3.21 mmol) and phenyl hydrazine (3.21 mmol). The yield was 0.87 g (2.26 mmol).

7-Methyl-3-(3-methyl-1-benzothiazolylpyrazol-5-yl)-5-oxo-5H-[sl1]benzopyrano[3,2-e]pyridin-2-one (*IXf*)

IXf was synthesised under similar reaction conditions as *IXc* using *Vb* (3.21 mmol) and hydrazinobenzothiazole (3.21 mmol). The yield was 0.98 g.(2.22 mmol).

Antibacterial activity

The microbial cultures were diluted in a nutrient broth to obtain a cell suspension of 10^5 CFU mL^{-1}.

All the newly synthesised compounds were screened for antibacterial activity against gram-positive and gram-negative bacteria by disc diffusion method (Bauer et al., 1966) with a minor modification (Aqil & Ahmad, 2003). Briefly, 0.1 mL of diluted inoculum (10^5 CFU mL^{-1}) of test bacteria was spread on nutrient agar plates. A sterile paper disc was impregnated with 70 μg of compound dissolved in DMSO. A disc without compound was used as a negative control. Plates were incubated at 37 °C for 18 h. The antibacterial activity was evaluated by measuring the zone of inhibition around the disc of the tested compound. Chloramphenicol (30 μg per disc), an antibiotic, was used as a positive control.

Results and discussion

Salicylaldehyde reacts with 4-hydroxycoumarin to give a product to which earlier workers assigned the structure *I* (Sullvian et al., 1943). In a later study, *I* was found to be untenable and it was revised to the structure *II* (de March et al., 1984). Thus, in a series of papers, Spanish researchers showed that structures of type *I* are unstable and they consistently rearrange to the type of structure *II* through intramolecular translactonisation (Cervello et al., 1987) (Fig. 1).

Similarly, when salicylaldehyde was treated with TAL, the rearranged product was obtained. Also, on the basis of the above findings, as the amino group is a stronger nucleophile than the hydroxyl group, an intramolecular translactonisation was anticipated to take place using 2-amino-3-formyl chromone *III*. As —NH_2 and —CHO groups are present in adjacent carbon atoms similar to salicylaldehyde, this reaction will lead to rearranged products.

As predicted, the reaction took place with triacetic acid lactone *IV* and afforded rearranged products *Va* and *Vb* (Fig. 1). *Va* and *Vb* gave a positive ferric chloride test due to the presence of acetoacetyl unit. Thus, these results supported the assumption that the rearrangement proceeded.

The IR spectrum of *Vb* exhibited absorption bands at 1668 cm^{-1}, 1649 cm^{-1}, and 1618 cm^{-1} for chromone, lactam, and chelated carbonyl groups, re-

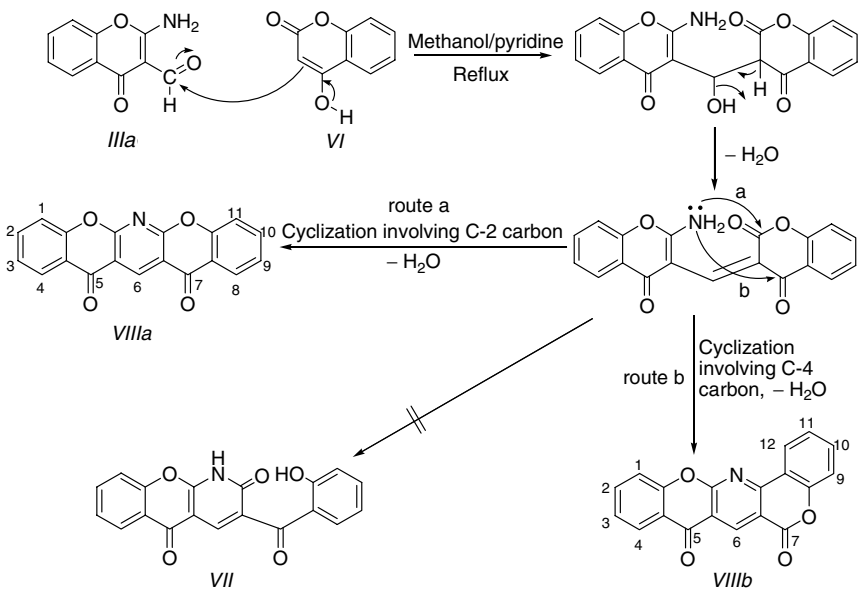

Fig. 2. Pentacyclic benzopyranopyridines (*VIIIa* and *VIIIb*).

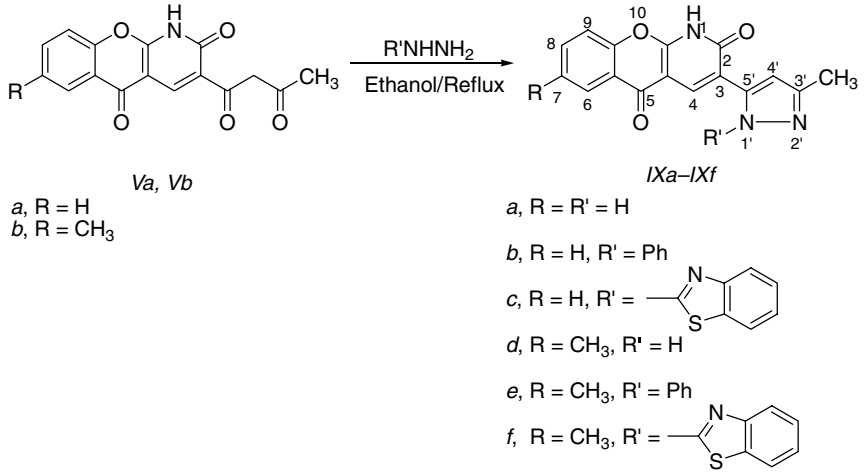

Fig. 3. Synthesis of pyrazoles *IXa–IXf*.

spectively. ^{1}H NMR spectrum of *Vb*, exhibited two upfield singlets at δ 2.24 and 2.49 due to the presence of two methyl groups in the molecule. Three more singlets at δ 6.40, 8.08, and 9.04 were assigned to H^a, H-6, and H^b protons, respectively. The mass spectrum exhibited a M^+ base peak at $m/z = 311$ which further confirmed the structure of the compound to be *Vb*. However, a reaction with 4-hydroxycoumarin *VI*, did not yield the expected rearranged product *VII*. Instead, isomeric compounds *VIIIa* and *VIIIb* were obtained (Fig. 2). The formation of isomeric benzopyranopyridines was similar to the reaction of phenol with β-ketoester to afford a mixture of isomeric coumarin and chromone (Ellis, 1977) through Simonis condensation (Sethna & Shah, 1945). The two isomeric compounds showing M^+ at $m/z = 315$ were identified by means of their IR and ^{1}H NMR spectra. Thus, the IR spectrum of *VIIIa* exhibited the presence of two chromone carbonyl groups at 1670 cm^{-1} and 1665 cm^{-1} whereas the coumarin and chromone carbonyl groups in *VIIIb* appeared at 1751 cm^{-1} and 1671 cm^{-1}, respectively. The ^{1}H NMR of *VIIIa* showed two ortho-coupled doublets (J = 7.8 Hz, 7.5 Hz) for C-4 and C-8 protons of chromone moieties at δ 8.32 and 8.61, respectively. The most deshielded proton H-6 appeared as a singlet at δ 9.59. The ^{1}H NMR of *VIIIb* showed one doublet at δ 8.37 corresponding to the ortho-coupled (H-4) proton, and a singlet at δ 9.71 for H-6 proton.

Pyrazoles are most conveniently synthesised from 1,3-dicarbonyl compounds and hydrazines (Katritzky & Rees, 1984). Due to the presence of an acetoacetyl unit in *Va* and *Vb*, pyrazoles *IXa–IXf* were obtained easily in sufficient quantity on treatment with various substituted hydrazines (Fig. 3). The IR spectra of *IXa* displayed sharp bands at 1664 cm^{-1} and 1620 cm^{-1}

Table 3. Antibacterial activity of new compounds; concentration of 70 μg per disc of the compound tested was used

Test microrganism	Inhibition zone diameter of compounds tested/mm									
	Vb	*VIIIa*	*VIIIb*	*IXa*	*IXb*	*IXc*	*IXd*	*IXe*	*IXf*	Control[a]
S. aureus	8	–	–	–	13	10	–	–	12	22
S. pneumoniae	–	–	–	–	–	–	–	–	–	21
E. coli	–	–	–	–	–	7	–	–	–	23
P. aeuruginosa	–	–	–	–	12	–	–	–	11	–
S. typhi	–	–	–	–	–	12	–	–	–	16
S. dysenteriae	–	–	–	–	8	19	–	–	12	23
K. pneumoniae	–	–	–	–	15	18	–	–	13	23

a) Antibiotic control: chloramphenicol (30 μg per disc).

for chromone and pyridone carbonyl groups. The ^{1}H NMR exhibited singlets at δ 2.27 and 6.71 for methyl and C-4′ protons 9whereas a broad singlet integrating for two protons at δ 8.69 was assigned to two NH protons. The C-6 proton of chromone unit appeared as a split doublet at δ 8.17 (J = 7.8 Hz, 3 Hz). This structure was further confirmed in the mass spectrum, which showed M^+ at m/z = 293.

The compounds exhibited antibacterial activity against both Gram-positive and Gram- negative bacteria except for *VIIIa*, *VIIIb*, *IXa*, *IXd*, and *IXe* which were inactive. Compound *Vb* was active against gram-positive bacteria (*Staphylococcus aureus*) only. The remaining compounds *IXb*, *IXc*, and *IXf* were active against both gram-positive and gram-negative bacteria. Out of the gram-negative bacteria tested, *Klebsiella pneumoniae* and *Shigella dysenteriae* were more sensitive, *Salmonella typhi* showed a medium activity, and *Escherichia coli* exhibited a negligible sensitivity to *IXc*. Of the gram-positive bacteria, only *S. aureus* exhibited minor sensitivity to *IXc*. Compounds *IXb* and *IXf* exhibited medium activity against only one strain of *S. aureus* (gram-positive bacteria) whereas, of the gram-negative bacteria tested, *Pseudomonas aeruginosa* exhibited sensitivity and resistance to chloramphenicol (control). These two compounds exhibited medium activity against *K. pneumoniae*, weak activity against *S. dysenteriae*, whereas *IXf* showed medium activity against both *K. pneumoniae* and *S. dysenteriae* (Table 3).

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References

Aqil, F., & Ahmad, I. (2003). Broad-spectrum antibacterial and antifungal properties of certain traditionally used Indian medicinal plants. *World Journal of Microbiology and Biotechnology*, *19*, 653–657. DOI: 10.1023/A:1025128104056.

Ashwood, V. A., Buckingham, R. E., Cassidy, F., Evans, J. M., Faruk, E. A., Hamilton, T. C., Nash, D. J., Stemp, G., & Willcocks, K. (1986). Synthesis and antihypertensive activity of 4-(cyclic amido)-2*H*-1-benzopyrans. *Journal of Medicinal Chemistry*, *29*, 2194–2201. DOI: 10.1021/jm00161a011.

Ashwood, V. A., Cassidy, F., Evans, J. M., Gagliardi, S., & Stemp, G. (1991). Synthesis and antihypertensive activity of pyran oxygen and amide nitrogen replacement analogs of the potassium channel activator cromakalim. *Journal of Medicinal Chemistry*, *34*, 3261–3267. DOI: 10.1021/jm00115a015.

Bailey, D. M., Hansen, P. E., Hlavac, A. G., Baizman, E. R., Pearl, J., DeFelice, A. F., & Feigenson, M. E. (1985). 3,4-Diphenyl-1*H*-pyrazole-1-propanamine antidepressants. *Journal of Medicinal Chemistry*, *28*, 256–260. DOI: 10.1021/jm00380a020.

Bauer, A. W., Kirby, W. M. M., Sherris, J. C., & Turck, M. (1966). Antibiotic susceptibility testing by a standardized single disk method. *American Journal of Clinical Pathology*, *45*, 493–496.

Bergmann, R., & Gericke, R. (1990). Synthesis and antihypertensive activity of 4-(1,2-dihydro-2-oxo-l-pyridyl)-2*H*-l-benzopyrans and related compounds, new potassium channel activators. *Journal of Medicinal Chemistry*, *33*, 492–504. DOI: 10.1021/jm00164a005.

Borroni, E. M, Huber-Trottmann, G., Kilpatrick, G. J., & Norcross, R. D. (2001). World patent No. 062233. Geneva, Switzerland: World Intellectual Property Organization.

Busev, A. I., Akimov, V. K., & Gusev, S. I. (1965). Pyrazolone derivatives as analytical reagents. *Russian Chemical Reviews*, *34*, 237–249. DOI: 10.1070/Rc1965v034n03ABEH001426.

Butt, M. A., & Elvidge, J. A. (1963). Heterocyclic synthesis with malonyl chloride. Part VIII. Hydroxypyrones from 1,3-diketones. *Journal of Chemical Society*, *1963*, 4483–4489. DOI: 10.1039/JR9630004483.

Cechetti, V., Tabarrini, O., & Sabatini, S. (2006). From cromakalim to different structural classes of KATP channel openers. *Current Topics in Medicinal Chemistry*, *6*, 1049–1068. DOI: 10.2174/156802606777323683.

Cervello, J., Gil, M., de March, P., Marquet, J., Moreno-Mañas, M., Roca, J. L., & Sanchez-Ferrando, F. (1987). Use of selective heteronuclear $^{13}C^1H$ noe measurements. A second note of warning on the assignment of structure to the products formed in the reactions between 4-hydroxy-2*H*-pyran-2-ones and carbonyl compounds. *Tetrahedron*, *43*, 2381–2387. DOI: 10.1016/s0040-4020(01)86824-1.

Chauhan, P. M. S., Singh, S., & Chatterjee, R. K. (1993). Antifungal profile of substituted pyrazoles: A new class of antifilarial agents. *Indian Journal of Chemistry Sect B*, *32*, 858–861.

Connor, D. T., Unangst, P. C., Schwender, C. F., Sorenson, R. J., Carethers, M. E., Puchalski, C., & Brown, R. E. (1984). Synthesis of 1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]

pyridin-5-ones. II. Substitution at the 3-position with 2-aminoethyl and 2-aminopropyl side chains. *Journal of Heterocyclic Chemistry*, *21*, 1561–1564. DOI: 10.1002/jhet.5570210564.

Dardari, Z., Lemrani, M., Sebban, A., Bahloul, A., Hassar, M., Kitane, S., Berrada, M., & Boudouma, M. (2006). Antileishmanial and antibacterial activity of a new pyrazole derivative designated 4-[2-(1-(ethylamino)-2-methyl-propyl)phenyl]-3-(4-methyphenyl)-1-phenylpyrazole. *Archiv der Pharmazie*, *339*, 291–298. DOI: 10.1002/ardp.200500266.

de March, P., Moreno-Mañas, M., & Roca, J. L. (1984). The reactions of 4-hydroxy-2-pyrones with 2-hydroxybenzaldehydes. A note of warning. *Journal of Heterocyclic Chemistry*, *21*, 1371–1372. DOI: 10.1002/jhet.1984.5570210525.

Ellis, G. P. (1977). General methods of preparing chromones. In G. P. Ellis (Ed.), *Chemistry of heterocyclic compounds: Chromenes, chromanones, and chromones,* (Vol. *31*, pp. 526–527). New York, NY, USA: Wiley. DOI: 10.1002/9780470187012.ch9.

El-Subbagh, H. I., Abu-Zaid, S. M., Mahran, M. A., Badaria, F. A., & Al-Obaid, A. M. (2000). Synthesis and biological evaluation of certain α, β-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents. *Journal of Medicinal Chemistry*, *43*, 2915–2921. DOI: 10.1021/jm000038m.

Evdokimov, N. M., Kireev, A. S., Yakovenko, A. A., Antipin, M. Yu., Magedov, I. V., & Kornienko, A. (2006). Convenient one-step synthesis of a medicinally relevant benzopyranopyridine system. *Tetrahedron Letters*, *47*, 9309–9312. DOI: 10.1016/j.tetlet.2006.10.110.

García, H., Iborra, S., Miranda, M. A., Morera, I. M., & Primo, J. (1991). Pyrazoles and isoxazoles derived from 2-hydroxyaryl phenylethynyl ketones: Synthesis and spectrophotometric evaluation of their potential applicability as sunscreens. *Heterocycles*, *32*, 1745–1755. DOI: 10.3987/COM-91-5773.

Hagen, H., Nilz, G., Walter, G., & Landes, A. (1992). German PatentNo. 4,039,272. Munich, Germany: German Patent and Trade Mark Office.

Hosni, H. M., & Abdulla, M. M. (2008). Anti-inflammatory and analgesic activities of some newly synthesized pyridinedicarbonitrile and benzopyranopyridine derivatives. *Acta Pharmaceutica*, *58*, 175–186. DOI: 10.2478/v10007-008-0005-4.

Katritzky, A. R., & Rees, C. W. (1984). *Comprehensive heterocyclic chemistry.* New York, NY, USA: Pergamon press.

Lee, S.-K., Chae, S.-M., Yi, K.-Y., Kim, N.-J., & Oh, C.-H. (2005). 4-[(*N*-Imidazol-2-ylmethyl)anilino]pyranopyridine analogs as novel anti-angiogenic agents. *Bulletin of Korean Chemical Society*, *26*, 619–628. DOI: 10.5012/bkcs.2005.26.4.619.

Nohara, A., Ishiguro, T., Ukawa, K., Sugihara, H., Maki, Y., & Sanno, Y. (1985). Studies on antianaphylactic agents. 7. Synthesis of antiallergic 5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridines. *Journal of Medicinal Chemistry*, *28*, 559–568. DOI: 10.1021/jm50001a005.

Paciorek, P. M., Burden, D. T., Burke, Y. M., Cowlrick, I. S., Perkins, R. S., Taylor, J. C., & Waterfall, J. F. (1990). Preclinical pharmacology of Ro 31-6930, a new potassium channel opener. *Journal of Cardiovascular Pharmacology*, *15*, 188–192.

Patel, M. V., Bell, R., Majest, S., Henry, R., & Kolasa, T. (2004). Synthesis of 4,5-diaryl-1*H*-pyrazole-3-ol derivatives as potential COX-2 inhibitors. *The Journal of Organic Chemistry*, *69*, 7058–7065. DOI: 10.1021/jo049264k.

Petersen, U., & Heitzer, H. (1976). Reaktionen mit 4-oxo-4*H*-chromen-3-carbaldehyd, I herstellung und reaktionen von 2-amino-4-oxo-4*H*-chromen-3-carbaldehyd. *Justus Liebigs Annalen der Chemie*, *9*, 1659–1662. DOI: 10.1002/jlac.197619760913.

Prokopp, C. R., Rubin, M. A., Sauzem, P. D., de Souza, A. H., Berlese, D. B., Lourega, R. V., Muniz, M. N., Bonacorso, H. G., Zanatta, N., Martins, M. A. P., & Mello, C. F. (2006). A pyrazolyl-thiazole derivative causes antinociception in mice. *Brazilian Journal of Medical and Biological Research*, *39*, 795–799. DOI: 10.1590/S0100-879X2006000600013.

Schurreit T. (1987). 4-Hydroxy-2*H*-[1]benzopyran-2-on als Baustein zur Synthese von Bisbenzopyranopyridinen. *Archiv der Pharmazie*, *320*, 500–506. DOI: 10.1002/ardp.19873200605.

Sethna, S. M., & Shah, N. M. (1945). The chemistry of coumarins. *Chemical Reviews*, *36*, 1–62. DOI: 10.1021/cr60113a001.

Shchegolkov, E. V., Khudina, O. G., Anikina, L. V., Burgart, Ya. V., & Saloutin, V. I. (2006). Synthesis, analgesic and antipyretic activity of 2-(antipyrin-4-yl)hydrazones of 1,2,3-triketones and their derivatives. *Pharmaceutical Chemistry Journal*, *40*, 373–376. DOI: 10.1007/s11094-006-0130-7.

Siddiqui, Z. N., & Asad, M. (2006). New heterocyclic derivatives of 3-formyl-4-hydroxycoumarin. *Indian Journal of Chemistry*, *45B*, 2704–2709.

Siddiqui, Z. N., Khuwaja, G., & Asad, M. (2006). One pot synthesis of 3-acetoacetyl-5-oxo-5*H*-[1] benzopyrano [3,2-*e*]pyridin-2-one from triacetic acid lactone. *Indian Journal of Chemistry*, *45B*, 2341–2345.

Singh, P., Paul, K., & Holzer, W. (2006). Synthesis of pyrazole-based hybrid molecules: Search for potent multidrug resistance modulators. *Bioorganic & Medicinal Chemistry*, *14*, 5061–5071. DOI: 10.1016/j.bmc.2006.02.046.

Singh, S. P., Sehgal, S., Tarar, L. S., & Dhawan, S. N. (1990). Synthesis of 2-[3-methyl or trifluromethyl-5-(2-thienyl)-pyrazol-1-yl]thiazol and benzothiazoles. *Indian Journal of Chemistry*, *29B*, 310–314.

Srivastava, S. K., Tripathi, R. P., & Ramachandran, R. J. (2005). NAD^+-dependent DNA ligase (*Rv3014c*) from mycobacterium tuberculosis. Crystal structure of the adenylation domain and identification of novel inhibitors. *The Journal of Biological Chemistry*, *280*, 30273–30281. DOI: 10.1074/jbc.M503780200.

Sullvian, W. R., Huebner, C. F., Stahmann, M. A., & Link, K. P. (1943). Studies on 4-hydroxycoumarins. II. The condensation of aldehydes with 4-hydroxycoumarins. *Journal of the American Chemical Society*, *65*, 2288–2291. DOI: 10.1021/ja01252a008.

Schurreit T. (1987). 4-Hydroxy-2*H*-[1]benzopyran-2-on als Baustein zur Synthese von Bisbenzopyranopyridinen. *Archiv der Pharmazie*, *320*, 500–506. DOI: 10.1002/ardp.19873200605.

Unangst, P. C., Capiris, T., Connor, D. T., Heffner, T. G., MacKenzie, R. G., Miller, S. R., Pugsley, T. A., & Wise, L. D. (1997). Chromeno[3,4-*c*]pyridin-5-ones: Selective human dopamine D_4 receptor antagonists as potential antipsychotic agents. *Journal of Medicinal Chemistry*, *40*, 2688–2693. DOI: 10.1021/jm970170v.

Vicentini, C. B., Guccione, S., Giurato, L., Ciaccio, R., Mares, D., & Forlani, G. J. (2005). Pyrazole derivatives as photosynthetic electron transport inhibitors: New leads and structure-activity relationship. *Journal of Agricultural and Food Chemistry*, *53*, 3848–3855. DOI: 10.1021/jf0500029.

Vors, J.-P., Gerbaud, V., Gabas, N., Canselier, J. P., Jagerovic, N., Jimeno, M. L., & Elguero, J. (2003). The structure of the agrochemical fungicidal 4-chloro-3-(3,5-dichlorophenyl)-1*H*-pyrazole (RPA 406194) and related compounds. *Tetrahedron*, *59*, 555–560. DOI: 10.1016/s0040-4020(02)01487-4.

Wardakhan, W. W., & Louca, N. A. (2007). Synthesis of novel pyrazole, coumarin and pyridazine derivatives evaluated as potential antimicrobial and antifungal agents *Journal of the Chilean Chemical Society*, *52*, 1145–1149. DOI: 10.4067/S0717-97072007000200006.