# Novel heterocyclic compounds from 2-carboxy-6-methoxybenzofuran-3-acetic acid anhydride

**Jyoti A. Patankar*, Rajiv T. Khombare, Rahul R. Khanwelkar, and Jyoti B. Shet**

*Department of Chemistry, The Institute of Science, 15, Madam Cama Road, Mumbai 400 032, India*

2-Carboxy-6-methoxybenzofuran-3-acetic acid anhydride is utilised for the synthesis of novel polycyclic heteroaromatic compounds in which the benzofuran ring is fused or bound to pyrido[1,4]benzothiazine, thiazole, pyridine, pyrazolo-pyridine, pyrazole, pyrano-pyridine, and pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidines using versatile reaction strategies.

**Keywords:** benzofurans, anhydrides, fused pyrones, pyrazoles, pyridines, pyrimidines, 1,4-benzothiazines, aminothiazoles

Benzofurans[1-4] and 2-pyridones[5-7] are well known for their broad spectrum of biological activities. This has generated much interest in the synthesis of heterocycles bearing the benzofuran and pyridone moieties.

7-Methoxypyrano[3,4-*b*][1]benzofuran-1,3(4*H*)-dione (7-methoxy-2,9-dioxafluorene-1,3(4*H*)-dione, or 2-carboxy-6-methoxybenzofuran-3-acetic acid anhydride) (**1**) has a pyranobenzofuran moiety and an active methylene group at position 4. Its utility is still not much explored in the literature.[8-11] Hence we decided to explore the possibilities of this compound for the synthesis of novel heterocycles, which might be useful for biological applications. Therefore, in continuation of our work on the synthesis of novel heterocyclic compounds,[8,9] we now report the preparation of a number of novel systems originating from the anhydride **1**.

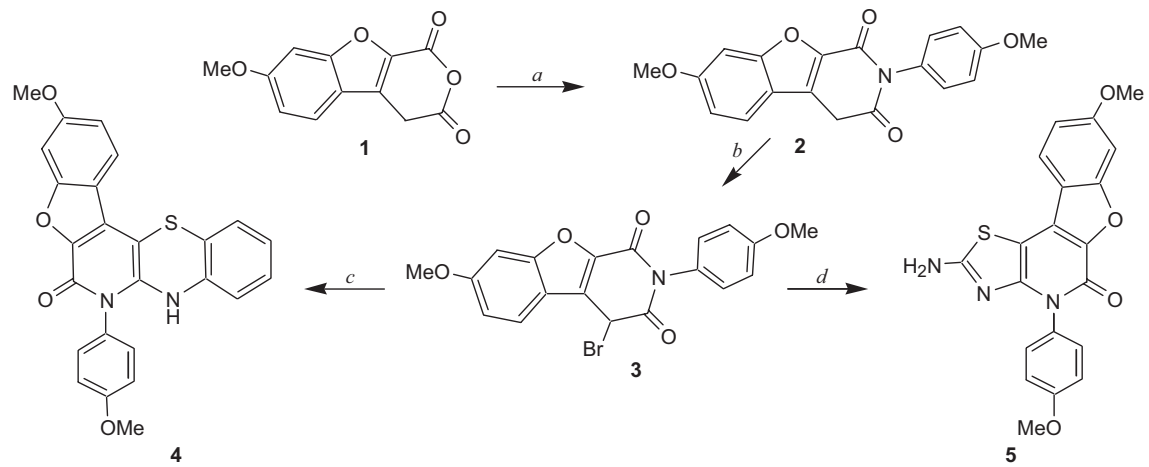
## Results and discussion

Compounds containing the pyridobenzothiazine[12-14] and aminothiazole[15,16] nuclei are well known for their biological activities. Hence, **1** was utilised for the synthesis of the pyridobenzothiazine **4** and the fused aminothiazole **5** (Scheme 1). Compound **1** on fusion with *p*-anisidine gave the N-inserted product **2**, which was brominated to give the monobromo compound **3**, both reactions proceeding in high yield. Compound **3** on heating with *o*-aminothiophenol and thiourea, in the presence of triethylamine in ethanol, gave the expected pyridobenzothiazine derivative **4** and aminothiazole derivative **5**, respectively, in good yields (Scheme 1).

Since pyrazole derivatives are also well known for their biological activities,[17-19] we explored the utility of **1** for the synthesis of pyrazole derivatives of the benzofuran anhydride. Compound **1** reacted with triethyl orthoformate to give the ethoxymethylene derivative **6**. This on reaction with 3-aminopyrazole-4-carbonitrile[20] gave the pyridopyrazole derivative **7** in good yield. The IR spectrum of **7** showed a characteristic peak for the CN functional group at 2228 $cm^{-1}$ and $^{13}C$ NMR spectrum showed a signal at 120.3 ppm for CN carbon. Compound **7** on fusion with *p*-anisidine gave by N-insertion the product **8**. When compound **7** was refluxed in ethanolic NaOH it underwent ring-opening to give the pyridopyrazole derivative **9**. This was confirmed by the $^1H$ NMR spectrum which showed $D_2O$-exchangeable peaks at δ 6.80, 11.95 and 12.11 for the three OH protons, and the disappearance of the CN peak in the IR spectrum. Further support for structure **9** was provided by its esterification in acidic methanol, which formed the methyl diester **10** (Scheme 2).

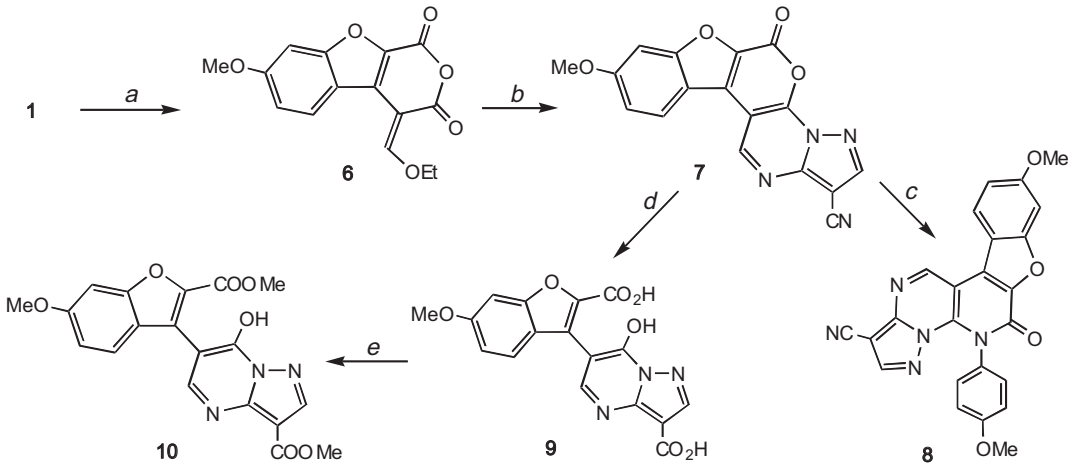
Compound **6** with hydrazine hydrate in ethanol gave the fused pyrazole derivative **11** in good yield. Which was confirmed on the basis of $^1H$ NMR spectrum showing peak at δ 8.11 for NH proton, which was $D_2O$ exchangeable, and absence of peaks for ethyl protons. Compound **11** on fusion with *p*-anisidine gave the N-insertion product **12**. When lactone **11** was heated in ethanolic NaOH it underwent ring-opening; acidification formed the acid **13**, and this on esterification in acidic methanol gave its methyl ester **14** (Scheme 3).

Compound **6** on reaction with piperidine in ethanol and *p*-anisidine in benzene gave condensation products **15** and **16** respectively. Compound **15** on fusion with *p*-anisidine gave the N-insertion product **17**, and compound **16** on treatment with morpholine gave the ring-opening product **18** in good yield. (Scheme 4)

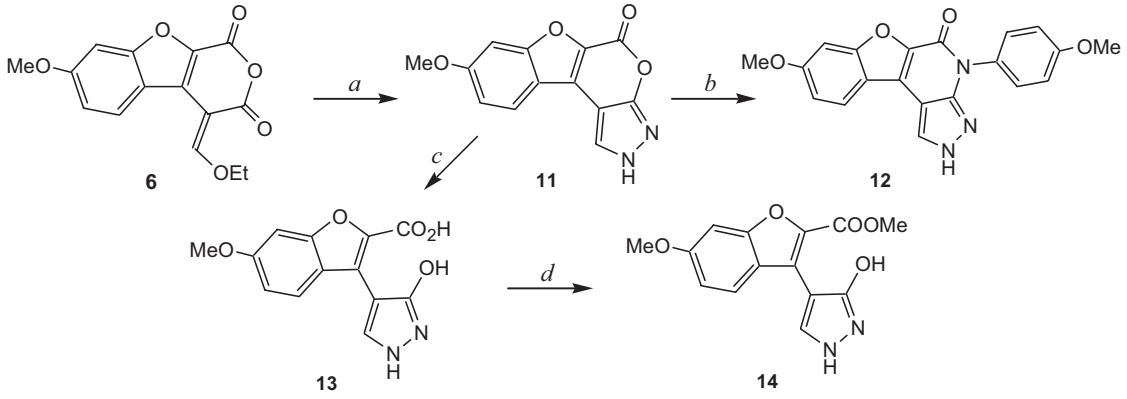



**Scheme 1** *Reagents: a, p*-anisidine, fused at 170-180°C; *b*, $Br_2$/AcOH, 50°C; *c*, 2-aminobenzenethiol, $Et_3N$/EtOH, reflux; *d*, thiourea/$Et_3N$/EtOH, reflux

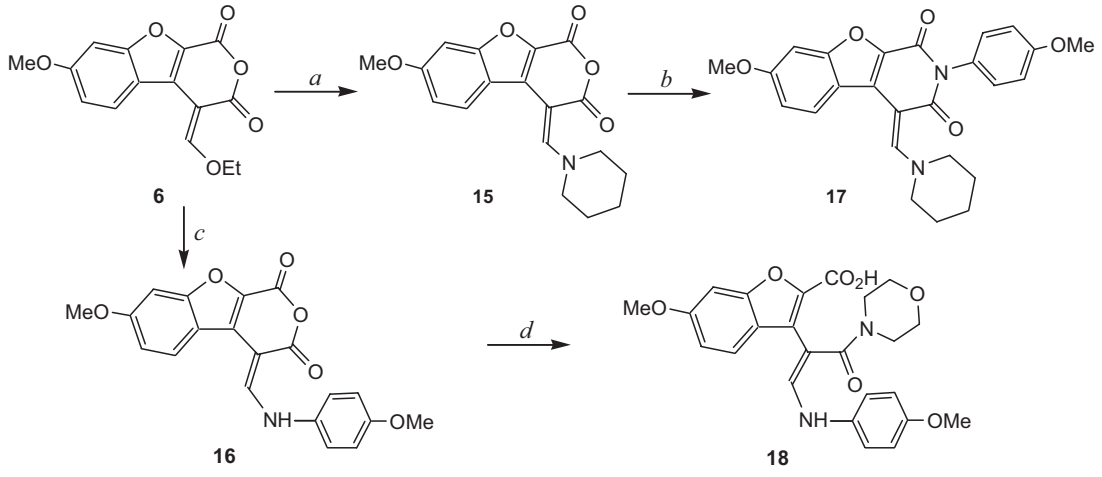
* Correspondent. E-mail: ja_patankar@yahoo.co.in



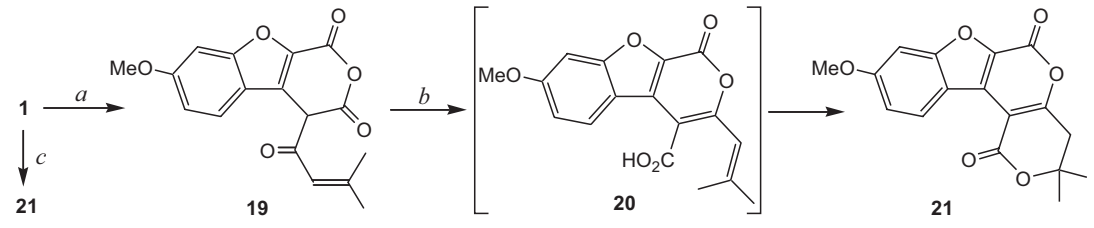
**Scheme 2** *Reagents: a,* $CH(OEt)_3/Ac_2O/C_6H_6$, reflux; *b*, 3-aminopyrazole-4-carbonitrile/EtOH, reflux; *c*, *p*-anisidine, fused at 170-180°C; *d*, NaOH/EtOH, reflux; *e*, MeOH/*p*-TSA, reflux



**Scheme 3** *Reagents: a,* $N_2H_4.H_2O$/EtOH, refl; *b*, *p*-anisidine, fused, 170-180°C; c, NaOH/EtOH, refl; *d*, MeOH/*p*-TSA, refl.



**Scheme 4** *Reagents: a,* piperidine/EtOH, reflux; *b*, *p*-anisidine, fused, 170-180°C; c, *p*-anisidine/$C_6H_6$, reflux; *d*, morpholine/EtOH,



**Scheme 5** *Reagents: a,* β,β–dimethylacryloyl chloride/pyridine, 0-5°C; *b*, pyridine, reflux; *c*, as *a* but heat to reflux

Isocoumarins also possess biological activity.[21-26] The isocoumarin derivative **21** was synthesised as follows. Compound **1** reacted with β,β-dimethylacryloyl choride in pyridine at 0–5°C to give **19**. This on reflux with pyridine gave the isocoumarin analogue **21** in moderate yield via the rearrangement product **20**. Alternatively, **21** was synthesised in good yield by directly refluxing **1** with β,β-dimethylacryloyl choride in pyridine (Scheme 5).

## Conclusion

In this paper we report simple and convenient synthetic routes for the synthesis of novel heterocyclic compounds containing pyridobenzothiazine, aminothiazole, pyrazole, and isocoumarin systems starting from the benzofuran anhydride **1.**

## Experimental

Melting points were taken in open capillaries. IR spectra were recorded on Perkin-Elmer 257-FTIR 1600 series spectrometer, using the KBr disc method for solid materials. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz using a Varian VXR 300 machine at 25°C (chemical shifts in δ ppm). Mass spectra were recorded on Shimadzu QP 2010 GC MS instrument. Elemental analyses were obtained using a Thermoquest Flash1112 series instrument.

*7-Methoxypyrano[3,4-b][1]benzofuran-1,3(4H)-dione* (**1**): The anhydride **1** was synthesised from 3-carboxymethyl-6-methoxy benzofuran-2-carboxylic acid using the reported method.[8]

*7-Methoxy-2-(4-methoxyphenyl)[1]benzofuro[2,3-c]pyridine-1,3(4H)-dione* (**2**): Compound **1** (2.32 g, 0.01 mol) and *p*-anisidine (1.23 g, 0.01 mol) were fused at 170-180°C in an oil bath for one hour. A clear thick solution was obtained, which solidified on cooling. Acetic acid (20 ml) was added and the resulting solution was heated to reflux for 30 minutes. On cooling, the crystalline solid **2** was obtained. It was filtered off, washed with water, and vacuum-dried; yield 85%, m.p. 215°C. IR: $\nu_{max}$ 1694, 1625 cm$^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 7.54–7.51 (d, 2H, H-3',5', $J$ = 8.4 Hz), 7.49–7.46 (d, 1H, H5, $J$ = 7.8 Hz), 7.45–7.42 (d, 2H, H-2',6', $J$ = 8.4 Hz), 7.35–7.34 (d, 1H, H8, $J$ = 2.1 Hz), 6.94–6.91 (dd, 1H, H6, $J$ = 2.1, 8.1 Hz), 4.87 (s, 2H, $CH_2$), 3.85 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$); $\delta_C$ 166.3, 160.3 (2 CO), 158.1, 157.2, 155.7, 145.3, 133.0, 121.1, 120.0, 118.2, 114.7, 113.6, 103.8, 93.5 (14 aromatic C), 56.1, 55.7 (2 $OCH_3$), 20.9 ($CH_2$). Found: C, 67.45; H, 4.27; N, 4.02. $C_{19}H_{15}NO_3$ requires C, 67.45; H, 4.48; N, 4.15%.

*4-Bromo-7-methoxy-2-(4-methoxyphenyl)[1]benzofuro[2,3-c]pyridine-1,3(4H)-dione* (**3**): Compound **2** (3.21 g, 0.01 mol) was dissolved in acetic acid (50 ml) at 50°C, and a solution of bromine (0.51 ml, 0.01 mol) in glacial acetic acid (20 ml) was added dropwise with constant stirring over one hour. After complete addition, reaction mixture was stirred for one hour at the same temperature. The reaction mixture was poured onto crushed ice (100 g) and stirred vigorously to afford the solid product **3 w**hich was filtered off, washed with water, air-dried and recrystallised from chloroform, yield 87%, m.p. 95°C. IR: $\nu_{max}$ 1695, 1628 cm$^{-1}$ (C=O). NMR (DMSO $d_6$): $\delta_H$ 7.55–7.52 (d, 2H, H-3',5', $J$ = 8.4 Hz), 7.50–7.47 (d, 1H, H5, $J$ = 8.1 Hz), 7.44–7.41 (d, 2H, H-2',6', $J$ = 8.4 Hz), 7.34–7.33 (d, 1H, H8, $J$ = 2.1 Hz), 6.94–6.91 (dd, 1H, H6, $J$ = 2.1, 8.1 Hz), 5.81 (s, 1H, CH), 3.84 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$); $\delta_C$ 167.1, 161.2 (2 CO), 157.9, 157.7, 157.2, 145.2, 144.8, 133.1, 123.7, 121.3, 119.7, 113.9, 107.9, 97.7 (14 aromatic carbons), 56.0, 55.7 (2 $OCH_3$), 40.5 (CH) ppm. Found: C, 54.70; H, 3.16; N, 3.17; Br, 19.02. $C_{19}H_{14}BrNO_5$ requires C, 54.83; H, 3.39; N, 3.37; Br, 19.20%.

*10-Methoxy-6-(4-methoxyphenyl)-5H-[1]benzofuro[3',2':3,4]pyrido[3,2-b][1,4]benzothiazin-7(6H)-one* (**4**): The bromo-compound **3** (4.0 g, 0.01 mol) in ethanol (75 ml) was stirred at 50°C, and triethylamine (1.0 g, 0.01 mol) and *o*-aminothiophenol (1.25 g, 0.01 mol) were added. The reaction mixture was refluxed for 5 h. Excess of ethanol was removed under vacuum and the reaction mass was poured onto crushed ice (100 g) and stirred vigorously. The solution was then neutralised with 2N HCl to afford solid product **4**. Which was filtered, washed with water, air-dried and recrystallised using methanol. IR: $\nu_{max}$ 3295 (NH), 1616 (C=O), 1513 cm$^{-1}$ (NH). NMR ($CDCl_3$): $\delta_H$ 7.63–7.60 (d, 2H, H-3',5', $J$ = 8.4 Hz), 7.55–7.52 (d, 1H, H12 $J$ = 8.7 Hz), 7.44–7.43 (d, 1H, H9, $J$ = 2.1 Hz), 7.34–7.31 (d, 2H, H-2',6', $J$ = 8.4 Hz), 6.96–6.93 (dd, 1H, H11, $J$ = 2.1, 8.1 Hz), 6.58–6.52 (m, 4H, aromatic protons), 4.34 (s, 1H, NH, $D_2O$-exchangeable), 3.86 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$); $\delta_C$ 160.3 (CO), 158.8, 158.1, 157.5, 147.3, 146.3, 133.4, 130.5, 130.2, 125.9, 125.4, 122.6, 121.1, 119.6, 118.9, 118.2, 115.3, 114.7, 108.6, 97.8, 91.5 (22 aromatic carbons), 56.0, 55.6 (2 $OCH_3$). MS (EI): $m/z$ 442 ($M^+$). Found; C, 67.70; H, 4.00; N, 6.17; S, 7.02. $C_{25}H_{18}N_2O_4S$ requires C, 67.86; H, 4.10; N, 6.33, S, 7.25%.

*2-Amino-8-methoxy-4-(4-methoxyphenyl)[1]benzofuro[3,2-d]thiazolo[4,5-b]pyridin-5(4H)-one* (**5**): The bromo-compound **3** (4.0 g, 0.01 mol) in ethanol (75 ml) was stirred at 50°C, and triethylamine (1.0 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) were added. The reaction mixture was then heated to reflux for 5 h. Excess of ethanol was removed under vacuum and the reaction mass was poured onto 100 g crushed ice and stirred vigorously. This solution was then neutralised with 2N HCl to afford solid product **5,** which was filtered off, washed with water, air-dried and recrystallised from methanol. Yield 84%, m.p. 145°C. IR: $\nu_{max}$ 3133 (NH), 1618 (C=O), 1511 cm$^{-1}$ (NH). NMR ($CDCl_3$): $\delta_H$ 7.68–7.65 (d, 2H, H-3',5', $J$ = 8.4 Hz), 7.54–7.51 (d, 1H, H10, $J$ = 8.4 Hz), 7.48–7.47 (d, 1H, H7, $J$ = 1 Hz), 7.34–7.31 (d, 2H, H-2',6', $J$ = 8.4 Hz), 7.05–7.02 (dd, 1H, H9, $J$ = 2.1, 8.4 Hz), 4.79 (s, 2H, $NH_2$, $D_2O$-exchangeable), 3.82 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$); $\delta_C$ 170.7 (C–$NH_2$), 159.3 (CO), 158.1, 157.2, 155.7, 145.3, 133.0, 130.8, 123.7, 121.1, 120.0, 118.2, 114.1, 108.7, 107.9, 95.4 (16 aromatic carbons), 56.3, 55.7 (2 $OCH_3$). MS (ESI) $m/z$ 393 ($M^+$). Found; C, 60.88; H, 3.68; N, 10.52; S, 8.02. $C_{20}H_{15}N_3O_4S$ requires C, 61.06; H, 3.84; N, 10.68; S, 8.15%.

*4-Ethoxymethylene-7-methoxy-1H-pyrano[3,4-b][1]benzofuran-1,3(4H)-dione* (**6**): The anhydride **1** (4.0 g, 0.01 mol) was stirred in dry benzene (150 ml) containing triethyl orthoformate (2.22 g, 0.015 mol) and a catalytic amount of acetic anhydride. The reaction mixture was refluxed for two hours. Excess of benzene was removed under vacuum and a light pink solid (**6**) separated from the solution. This was filtered off, washed with cold benzene, and recrystallised from chloroform as white needles (85%, m.p. 144°C). IR $\nu_{max}$ 1755, 1701 cm$^{-1}$ (C=O). NMR ($CDCl_3$): $\delta_H$ 8.09 (s, 1H, CH), 7.66–7.63 (d, 1H, H5, $J$ = 8.1 Hz), 7.35–7.34 (d, 1H, H8, $J$ = 2.1 Hz), 6.96–6.93 (dd, 1H, H6, $J$ = 2.1, 8.1 Hz), 4.53 (q, 2H, $CH_2$), 3.84 (s, 3H, $OCH_3$), 1.80 (t, 3H, $CH_3$); $\delta_C$ 161.3, 151.7 (2 CO), 156.7 (C-O), 160.1, 158.1, 143.2, 130.6, 120.3, 118.0, 108.8, 106.8, 97.4, (9 aromatic carbons), 61.3 ($OCH_2$), 55.5 ($OCH_3$), 11.8 ($CH_3$). Found; C, 62.3; H, 4.02. $C_{15}H_{12}O_6$ requires C, 62.50; H, 4.20%.

*9-Methoxy-6-oxo-6H-[1]benzofuro[2',3':5,4]pyrano[3,2-e]pyrazolo[1,5-a]pyrimidine-1-carbonitrile* (**7**): 3-Aminopyrazole-4-carbonitrile[20] (1.08 g, 0.01 mol) was added to a stirred solution of the enol ether **6** (2.88 g, 0.01 mol) in acetic acid (35 ml). The reaction mixture was refluxed for 6 hours. Excess of acetic acid was removed under vacuum and the solution was poured onto crushed ice (100 g) to afford a solid yellow product (**7**) (91%), m.p. >250°C, which was filtered off, washed with warm water, and dried *in vacuo*. IR: $\nu_{max}$ 2228 (CN), 1692 cm$^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 8.47 (s, 1H), 8.28 (s, 1H), 7.51–7.48 (d, 1H, H11, $J$ = 8.1 Hz), 7.35–7.34 (d, 1H, H8, $J$ = 2.1 Hz), 6.89–6.86 (dd, 1H, H10, $J$ = 2.1, 8.1 Hz), 3.84 (s, 3H, $OCH_3$); $\delta_C$ 165.3 (CO), 161.4, 160.1, 155.2, 154.2, 145.1, 141.7, 137.3, 132.1, 123.0, 121.1, 113.5, 112.6, 102.2, 95.6 (14 aromatic carbons), 120.3 (CN), 55.8 ($OCH_3$). Found; C, 61.25; H, 2.22; N, 16.72. $C_{17}H_8N_4O_4$ requires C, 61.45; H, 2.43; N, 16.86%.

*9-Methoxy-5-(4-methoxyphenyl)-6-oxo-5,6-dihydro[1]benzofuro[2',3':5,4]pyrido[3,2-e]pyrazolo[1,5-a]pyrimidine-1-carbonitrile* (**8**): The lactone **7** (3.32 g, 0.01 mol) and *p*-anisidine (1.23 g, 0.01 mol) were fused in an oil bath at 170–180°C for 45 minutes. A clear thick solution was obtained, which solidified on cooling to room temperature. To this solid, acetic acid (20 ml) was added and the mixture was heated to reflux for 20 minutes. On cooling compound **8** separated as a crystalline solid; it was filtered off, washed with water, and vacuum-dried (yield 88%, m.p. >250°C. IR: $\nu_{max}$ 2227 (CN), 1623 cm$^{-1}$ (C=O). NMR: $\delta_H$ (DMSO-$d_6$) 8.50 (s, 1H, =CH), 8.26 (s, 1H, =CH), 7.62–7.59 (d, 2H, H-3',5', $J$ = 8.4 Hz), 7.53–7.51 (d, 1H, H11, $J$ = 7.8 Hz), 7.47–7.44 (d, 2H, H-2',6', $J$ = 8.4 Hz), 7.33–7.32 (d, 1H, H8, $J$ = 2.1 Hz), 6.94–6.91 (dd, 1H, H10, $J$ = 2.1, 8.1 Hz), 3.85 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$) $\delta_C$ ($CDCl_3$): 166.2 (CO), 163.2, 158.5, 158.3, 158.1, 157.7, 145.3, 133.0, 130.5, 122.6, 119.6, 118.2, 114.3, 110.3, 105.6, 97.5 (20 aromatic carbons), 120.9 (CN), 56.0, 55.8 (2 $OCH_3$). MS (EI): $m/z$ 437 ($M^+$). Found; C, 65.73; H, 3.36; N, 17.07. $C_{24}H_{15}N_5O_4$ requires C, 65.90; H, 3.46; N, 17.19%.

*6-(2'-Carboxy-6'-methoxybenzofuran-3'-yl)-7-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylic acid* (**9**): The lactone **7** (3.32 g, 0.01 mol) was refluxed in 20% ethanolic NaOH solution for 2.5 h. Excess of ethanol was removed under vacuum and the reaction mass was poured onto crushed ice (100 g) and stirred vigorously.

This solution was then neutralised with 2N HCl to precipitate **9**, which was filtered off, washed with water, air-dried and recrystallised from methanol : benzene (1 : 5); yield 78%; m.p. 225°C. IR: $\nu_{max}$ 3432 (OH), 1712, 1698 $cm^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 12.11 (s, 1H, COOH, $D_2O$-exchangeable), 11.95 (s, 1H, COOH, $D_2O$-exchangeable), 8.57 (s, 1H, =CH), 8.38 (s, 1H, =CH), 7.55–7.52 (d, 1H, H4', *J* = Hz), 7.44–7.43 (d, 1H, H7', *J* = 2.1 Hz), 6.96–6.93 (dd, 1H, H5', *J* = 2.1, 8.1 Hz), 6.80 (s, 1H, OH), 3.85 (s, 3H, $OCH_3$); $\delta_C$ 177.3, 172.0 (2 COOH), 170.4, 161.3, 155.2, 154.2, 145.1, 141.7, 137.3, 132.1, 127.1, 121.1, 113.5, 105.6, 102.2, 94.9 (14 aromatic C), 54.7 ($OCH_3$). MS (ESI): *m/z* 369 ($M^+$). Found; C, 55.19; H, 2.887; N, 11.25. $C_{17}H_{11}N_3O_7$ requires C, 55.29; H, 3.00; N, 11.38%.

*Methyl 6-(6'-Methoxy-2'-methoxylcarbonylbenzofuran-3'-yl)-7-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate* (**10**): The diacid **9** (3.69 g, 0.01 mol) was heated to reflux for 3 h in methanol (35 ml) with catalytic *p*-toluenesulfonic acid (60 mg). Excess of methanol was removed under vacuum and the reaction mass was poured onto crushed ice (100 g) and stirred vigorously to afford the solid product **10**. This was filtered off, washed with water, air-dried and recrystallised from methanol : benzene (1 : 5); yield 72%, m.p. 159°C. IR: $\nu_{max}$ 3457 (OH), 1746, 1732 $cm^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 8.55 (s, 1H, =CH), 8.36 (s, 1H, =CH), 7.54–7.51 (d, 1H, H4', *J* = 8.1 Hz), 7.41–7.40 (d, 1H, H7', *J* = 2.1 Hz), 6.99–6.96 (dd, 1H, H5', *J* = 2.1, 8.1 Hz), 6.89 (s, 1H, OH, $D_2O$-exchangeable), 3.84 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$); $\delta_C$ 169.0, 158.3 (2 CO), 168.4, 158.7, 157.2, 155.0, 141.9, 135.3, 132.6, 132.1, 127.6, 122.1, 121.2, 106.4, 102.7, 95.9 (14 aromatic C), 55.5, 51.2, 48.4 (3 $OCH_3$). Found; C, 57.29; H, 3.70; N, 10.43. $C_{19}H_{15}N_3O_7$ requires C, 57.43; H, 3.81; N, 10.58%.

*8-Methoxy[1]benzofuro[3',2':4,5]pyrano[2,3-c]pyrazol-5(2H)-one* (**11**): The enol ether **6** (2.88 g, 0.01 mol) was stirred in ethanol (50 ml), and hydrazine hydrate (80%, 0.75 ml, 0.015 mol) was added dropwise over 10 minutes at room temperature. The reaction mixture was refluxed for 30 min, and on cooling to room temperature a solid product (**11**) separated. This was filtered off, washed with ethanol, air-dried and recrystallised from ethanol; yield 72%, m.p. 149°C. IR: $\nu_{max}$ 3245 (NH), 1684 (C=O), 1570 $cm^{-1}$ (C=N). NMR (DMSO-$d_6$): $\delta_H$ 8.11–8.08 (d, 1H, NH, $D_2O$-exchangeable, *J* = 9 Hz), 7.72–7.69 (d, 1H, CH, *J* = 9 Hz), 7.51–7.48 (d, 1H, H10, *J* = 8.1 Hz), 7.32–7.31 (d, 1H, H7, *J* = 2.1 Hz), 7.00–6.97 (dd, 1H, H9, *J* = 2.1, 8.1 Hz), 3.85 (s, 3H, $OCH_3$); $\delta_C$ 154.3 (CO), 161.4, 158.2, 142.5, 135.3, 132.5, 132.0, 122.4, 121.1, 107.8, 104.7, 96.0 (11 aromatic C), 55.7 ($OCH_3$). Found; C, 60.81; H, 3.05; N, 10.79. $C_{13}H_8N_2O_4$ requires C, 60.94; H, 3.15; N, 10.93%.

*8-Methoxy-4-(4-methoxyphenyl)-2,4-dihydro-5H-[1]benzofuro[3,2-d]pyrazolo[3,4-b]pyridin-5-one* (**12**): Compound **11** (2.56 g, 0.01 mol) and *p*-anisidine (1.23 g, 0.01 mol) were fused in an oil bath at 170–180°C for 45 min. A clear thick solution was obtained, which solidified on cooling. To this solid acetic acid (20 ml) was added and the mixture was refluxed for 20 min, after which cooling gave a crystalline solid **12**, which was filtered off, washed with water, and vacuum dried (yield 87%, m.p. 215°C). IR: $\nu_{max}$ 3210 (NH), 1620 (C=O), 1590 $cm^{-1}$ (C=N). NMR: $\delta_H$ (DMSO-$d_6$) δ 8.12–8.09 (d, 1H, NH, $D_2O$-exchangeable, *J* = 9 Hz), 7.82–7.79 (d, 1H, CH, *J* = 9 Hz), 7.64–7.61 (d, 2H, H-3',5', *J* = 8.4 Hz), 7.51–7.48 (d, 2H, H-2',6', *J* = 8.4 Hz), 7.42–7.39 (d, 1H, H10, *J* = 8.1 Hz), 7.28–7.27 (d, 1H, H7, *J* = 2.1 Hz), 6.96–6.93 (dd, 1H, H9, *J* = 2.1, 8.1 Hz), 3.85 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$); $\delta_C$ ($CDCl_3$): 159.7 (CO), 158.5, 158.1, 157.7, 154.0, 145.5, 132.0, 131.3, 122.5, 121.4, 120.1, 114.7, 108.7, 97.4, 92.0 (17 aromatic C), 56.3, 56.0 (2 $OCH_3$). MS (EI): *m/z* 361 ($M^+$). Found; C, 66.32; H, 4.04; N, 11.51. $C_{20}H_{15}N_3O_4$ requires C, 66.48; H, 4.18; N, 11.63%.

*3-(3-Hydroxy-1H-pyrazol-4-yl)-6-methoxybenzofuran-2-carboxylic acid* (**13**): The lactone **11** (2.56 g, 0.01 mol) was refluxed in 20% ethanolic NaOH for 3 h. Excess of ethanol was removed under vacuum and the reaction mass was poured onto crushed ice (100 g) and stirred vigorously. This solution on neutralisation with 2N HCl afforded the acid **13**, which was filtered off, washed with water, air-dried and recrystallised from methanol : benzene (1 : 5) (yield: 72%, m.p. >250°C). IR: $\nu_{max}$ 3457 (OH), 3265 (NH), 1700 (C=O), 1585 $cm^{-1}$ (C=N). NMR: $\delta_H$ (DMSO-$d_6$) δ12.12 (s, 1H, -COOH, $D_2O$-exchangeable), 8.21–8.18 (d, 1H, NH, $D_2O$-exchangeable, *J* = 9 Hz), 7.66–7.63 (d, 1H, CH, *J* = 9 Hz), 7.54–7.51 (d, 1H, H4, *J* = 8.1 Hz), 7.44–7.43 (d, 1H, H7, *J* = 2.1 Hz), 6.94–6.91 (dd, 1H, H5, *J* = 2.1, 8.1 Hz), 6.44 (s, 1H, OH, $D_2O$-exchangeable), 3.86 (s, 3H, $OCH_3$); $\delta_C$ ($CDCl_3$) 161.7 (CO), 161.5, 157.7, 143.5, 135.1, 132.0, 131.3, 121.8, 120.7, 108.3, 105.1, 97.3 (11 aromatic carbons), 55.8 ($OCH_3$). Found; C, 56.82; H, 3.54; N, 10.09. $C_{131}H_{10}N_2O_5$ requires C, 56.94; H, 3.68; N, 10.22%.

*Methyl 3-(3-hydroxy-1H-pyrazol-4yl)–6-methoxybenzofuran-2-carboxylate* (**14**): Compound **13** (2.74 g, 0.01 mol) was heated to reflux for 3 h in methanol (35 ml) with a catalytic amount of *p*-toluenesulfonic acid (60 mg). Excess of methanol was then removed under vacuum and the reaction mass was poured onto 100 g crushed ice and stirred vigorously to afford a solid product (**14**) which was filtered off, washed with water, air-dried and recrystallised from methanol : benzene (1 : 5); yield 90%, m.p. 171°C. IR: $\nu_{max}$ 3468 (OH), 3272 (NH), 1742 (C=O), 1596 $cm^{-1}$ (C=N). NMR ($CDCl_3$): $\delta_H$ 8.20–8.17 (d, 1H, NH, $D_2O$-exchangeable, *J* = 9 Hz), 7.61–7.58 (d, 1H, CH, *J* = 9 Hz), 7.55–7.52 (d, 1H, H4, *J* = 8.1 Hz), 7.42–7.41 (d, 1H, H7, *J* = 2.1 Hz), 6.94–6.91 (dd, 1H, H5, *J* = 2.1, 8.1 Hz), 6.68 (s, 1H, OH), 3.83 (s, 3H, $OCH_3$), 3.92 (s, 3H, $OCH_3$); $\delta_C$ 159.3 (CO), 158.8, 158.1, 142.3, 134.3, 131.9, 131.3, 122.5, 121.1, 109.0, 105.3, 97.8 (11 aromatic carbons), 56.0, 51.7 (2 $OCH_3$). MS (ESI) (*m/z*): 289 ($M^+$). Found; C, 58.21; H, 4.04; N, 9.53. $C_{14}H_{12}N_2O_5$ requires C, 58.33; H, 4.20; N, 9.72%.

*7-Methoxy-4-(piperidin-1-ylmethylene)-4H-pyrano[3,4-b][1]benzofuran-1,3-dione* (**15**): Piperidine (0.95 g, 0.011 mol) in a little ethanol was added dropwise into a stirred solution of the enol ether **6** (2.82 g, 0.01 mol) in ethanol (50 ml) over 10 min at room temperature. The solution was then heated to reflux for 3 hr. Excess of ethanol was removed *in vacuo* and the residue was poured onto crushed ice (100 g) and acidified with 2N HCl to afford the enamino-anhydride **15**, which was filtered off, washed with water, air-dried and recrystallised from ethanol (yield 87%, m.p. 245°C). IR: $\nu_{max}$ 3300 (NH), 1725, 1670 $cm^{-1}$ (C=O). NMR: $\delta_H$ ($CDCl_3$) 7.65–7.62 (d, 1H, H5, *J* = 8.1 Hz), 7.38–7.35 (d, 1H, H8, *J* = 2.1 Hz), 6.97–6.94 (dd, 1H, H6, *J* = 2.1, 8.1 Hz), 6.91 (s, 1H, CH), 3.74 (m, 4H, $N(CH_2)_2$), 1.90 (m, 4H, $(CH_2)_2$), 1.79 (m, 2H, $CH_2$); $\delta_C$ (DMSO-$d_6$) 161.5, 154.0 (2 CO), 151.6 C=<u>C</u>–N), 160.0, 157.7, 144.7, 130.6, 121.9, 119.8, 107.9, 96.6 (8 aromatic C), 109.3 (<u>C</u>=C–N), 55.7 ($OCH_3$), 50.1, 26.0, 24.7 (5 $CH_2$). Found; C, 65.94; H, 5.11; N, 4.14. $C_{18}H_{17}NO_5$ requires C, 66.05; H, 5.23; N, 4.28%.

*7-Methoxy-4-(4'-methoxyphenylaminomethylene)-4H-pyrano[3,4-b][1]benzofuran-1,3-dione* (**16**): *p*-Anisidine (0.629 g, 5 mmol) in benzene (20 ml) was added dropwise at room temperature into a stirred solution of the enol ether **6** (1.44 g, 5 mmol) in benzene (50 ml). The reaction mixture was then heated to reflux for 3 h. Removal of excess of benzene under vacuum resulted in precipitation of yellow solid **16**, which was filtered off, washed with benzene and 2N HCl to remove unreacted anisidine, and recrystallised from dimethyl formamide (DMF) (yield 87%, m.p. >250°C. IR: $\nu_{max}$ 3300 (NH), 1745, 1680 $cm^{-1}$ (C=O). NMR ($CDCl_3$): $\delta_H$ 11.20 (s, 1H, NH, $D_2O$-exchangeable), 8.22 (s, 1H, =CH), 7.69–7.66 (d, H5, *J* = 8.1 Hz), 7.35–7.34 (d, 1H, H8, *J* = 2.1 Hz), 7.17–7.14 (d, 2H, H-3',5', *J* = 8.4 Hz), 6.96–6.93 (dd, 1H, H6, *J* = 2.1, 8.1 Hz), 6.91–6.88 (d, 2H, H-2',6', *J* = 8.4 Hz), 3.94 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$); $\delta_C$ 160.2, 156.3 (2 CO), 151.7 (C=<u>C</u>–NH), 160.9, 158.0, 144.7, 144.3, 138.7, 130.7, 122.4, 120.7, 115.7, 114.4, 112.3, 97.6 (14 aromatic carbons), 109.1 (<u>C</u>=C–NH), 56.2, 55.7 (2 $OCH_3$). Found; C, 65.59; H, 4.01; N, 3.66. $C_{20}H_{15}NO_6$ requires C, 65.75; H, 4.14; N, 3.83%.

*7-Methoxy-2-(4-methoxyphenyl)-4-(piperidin-1-ylmethylene)-4H-[1]benzofuro[2,3-c]pyridine-1,3-dione* (**17**): *p*-Anisidine (0.629 g, 5 mmol) and the anhydride **15** (1.6 g, 5 mmol) were fused together at 170–180°C and kept at that temperature for 1 h. A clear thick melt was produced, which solidified on cooling. Acetic acid (20 ml) was added and the resulting solution was refluxed for 30 min. Cooling afforded a bright yellow solid (**17**), which was filtered off, washed with water, air-dried and recrystallised from DMF (yield 68%, m.p. >250°C). IR: $\nu_{max}$ 3300 (NH), 1725, 1670 $cm^{-1}$ (C=O). NMR: $\delta_H$ ($CDCl_3$) 7.94 (s, 1H, =CH), 7.53–7.50 (d, 2H, H-3',5', *J* = 8.4 Hz), 7.49–7.46 (d, 1H, H5, *J* = 8.1 Hz), 7.44–7.41 (d, 2H, H-2',6', *J* = 8.4 Hz), 7.33–7.32 (d, 1H, H8, *J* = 2.1 Hz), 6.94–6.91 (dd, 1H, H6, *J* = 2.1, 8.1 Hz), 3.90 (s, 6H, 2 $OCH_3$), 3.76 (m, 4H, $N(CH_2)_2$), 1.93 (m, 4H, 2 $CH_2$), 1.81 (m, 2H, $CH_2$); $\delta_C$ (DMSO-$d_6$) 160.4, 162.0 (2 CO), 155.2 (C=<u>C</u>–N), 154.2, 150.0, 146.1, 141.7, 137.3, 130.1, 127.1, 121.3, 119.1, 113.5, 105.6, 95.1 (14 aromatic carbons), 111.3 (<u>C</u>=C–N), 55.4, 55.2 (2 $OCH_3$), 50.1, 26.1, 24.8 (5 $CH_2$). Found; C, 69.25; H, 5.43; N, 6.32. $C_{25}H_{24}N_2O_5$ requires C, 69.43; H, 5.59; N, 6.48%.

*6-Methoxy-3-[2-(4-methoxyphenylamino)-1-(morpholine-4-carbonyl)vinyl]benzofuran-2-carboxylic acid* (**18**): Morpholine (0.5 g, 6 mmol) was added dropwise over 10 min to a stirred solution of **16** (1.8 g, 5 mmol) in ethanol (50 ml) at room temperature. Stirring was continued for 3 hours at the same temperature. Excess of ethanol was removed under vacuum and the obtained mass was poured onto crushed ice (100 g) and acidified with 2N HCl to afford the yellow solid **18**. This was filtered off, washed with water, air-dried and

recrystallised from ethanol (yield 73%, m.p. 110°C). IR: $\nu_{max}$ 3300 (OH), 1740, 1680 $cm^{-1}$ (C=O). NMR ($CDCl_3$): $\delta_H$ 10.41 (d, 2H, 1 NH, 1 COOH, $D_2O$-exchangeable), 8.23 (s, 1H, =CH), 7.69–7.66 (d, 1H, H4, *J* = 8.1 Hz), 7.35–7.34 (d, 1H, H7, *J* = 2.1 Hz), 7.19–7.16 (d, 2H, H-3',5', *J* = 8.4 Hz), 6.96–6.93 (dd, 1H, H5, *J* = 2.1, 8.1 Hz), 6.94–6.91 (d, 2H, H-2',6', *J* = 8.4 Hz), 3.91 (s, 6H, 2 $OCH_3$), 3.80 (t, 4H, 2 $CH_2$), 3.78 (t, 4H, 2 $CH_2$); $\delta_C$ 164.8, 162.3 (2 CO), 152.6 (C=C–NH), 159.8, 158.1, 144.5, 140.4, 139.0, 130.7, 122.5, 121.1, 116.4, 114.3, 113.2, 97.7 (14 aromatic C), 109.0 (C=C–NH), 71.3 (2 $OCH_2$), 56.1, 56.0 (2 $OCH_3$), 50.6 (2 $NCH_2$). MS (EI): *m/z* 452 ($M^+$). Found; C, 63.58; H, 5.22; N, 6.03. $C_{24}H_{24}N_2O_7$ requires C, 63.71; H, 5.35; N, 6.19%.

*7-Methoxy-4-(3-methyl-1-oxobut-2-enyl)pyrano[3,4-b][1] benzofuran-1,3(4H)-dione* (**19**): β,β-Dimethyacryloyl chloride (1.78 g, 0.015 mol) was added dropwise at 0–5°C to a stirred solution of the anhydride **1** (2.32 g, 0.01 mol) in pyridine (25 ml). The reaction mixture was stirred for 2 h at room temp. It was poured onto crushed ice (100 g) and acidified with 2N HCl to afford the solid **19,** which was filtered off, washed with water, air-dried, and recrystallised from ethyl acetate (yield 80%, m.p. 148°C). IR: $\nu_{max}$ 1748, 1722, 1688 $cm^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 7.55–7.52 (d, 1H, H5, *J* = 8.7 Hz), 7.43–7.42 (d, 1H, H8, *J* = 2.1 Hz), 7.02–6.99 (dd, 1H, H6, *J* = 2.1, 8.1 Hz), 6.89 (s, 1H, =CH), 5.64 (s, 3H, CH), 3.83 (s, 3H, $OCH_3$), 2.07 (s, 3H, $CH_3$), 1.85 (s, 3H, $CH_3$); $\delta_C$ 196.5, 166.3, 160.1 (3 CO), 158.7, 155.3, 145.2, 123.1, 122.6, 117.6, 107.5, 95.7 (8 aromatic C), 147.7 (C$(CH_3)_2$), 123.3 ( =CH), 56.1 ($OCH_3$), 50.2 (CH), 24.9, 19.2 (2 $CH_3$). Found; C, 64.78; H, 4.30. $C_{17}H_{14}O_6$ requires C, 64.97; H, 4.49%.

*9-Methoxy-3,3-dimethyl-3,4-dihydropyrano[4',3':2,3]pyrano[3,4-b] [1]benzofuran-1,6-dione* (**21**): β,β-Dimethylacryloyl chloride (1.78 g, 0.015 mol) was added dropwise to a stirred solution of the anhydride **1** (2.32 g, 0.01 mol) in pyridine (25 ml) at 0–5°C. After complete addition, the reaction mixture was refluxed for 1 h. It was then poured onto crushed ice (100 g) and acidified with 2N HCl, affording the solid lactone **21**, which was filtered off, washed with water, air-dried, and recrystallised using ethyl acetate (yield 67%, m.p. 106°C). IR: $\nu_{max}$ 1689, 1702 $cm^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 7.55–7.52 (d, 1H, H-11, *J* = 8.7 Hz), 7.48–7.47 (d, 1H, H8, *J* = 2.1 Hz), 6.99–6.96 (dd, 1H, H-10, *J* = 2.1 8.1 Hz), 3.84 (s, 3H, $OCH_3$), 3.03 (s, 2H, $CH_2$), 1.98 (s, 6H, 2 $CH_3$); $\delta_C$ 191.3, 168.1 (2 CO), 163.3, 158.5, 156.3, 146.3, 128.5, 121.3, 119.2, 105.7, 97.4, 84.1 (10 aromatic C), 58.2 (C$(CH_3)_2$), 56.1 ($OCH_3$), 44.7 ($CH_2$), 26.5 (2 $CH_3$). MS (EI): *m/z* 314 ($M^+$). Found; C, 64.75; H, 4.32. $C_{17}H_{14}O_6$ requires C, 64.97; H, 4.49%.

The help rendered by TIFR, IIT (Mumbai), and Institute of Science (Mumbai) for IR, NMR, MS measurements and by UDCT Mumbai for elemental analyses of new compounds is gratefully acknowledged. We also thank Prof. K. D. Deodhar, Department of Chemistry, IIT (Mumbai) for their valuable support.

*Received 16 October 2007; accepted 19 March 2008*
*Paper 07/4891 doi: 10.3184/030823408X303231*

## References

1 L.T. Power and M.P. Merters, *J. Med. Chem.,* 1970, **13**, 1102.
2 F. Bohlman, J. Schutz and V. Bohlman, *Tetrahedron Lett.*, 1969**,** 4703.
3 D.R. Rerrin and C.P. Whittle, *Tetrahedron Lett.,* 1971**,** 1673.
4 J. Schmitt, M. Suquet, J. Salle, P. Comoy and J. Le Mear, *Chem. Ther.,* 1966, 305.
5 J.A. Spicer, G.W. Rewcastle, M.D. Kaufman, S.L. Black, M.S. Plummer, W.A. Denny, J. Quin, A.B. Shahripour, S.D. Barrett, C.E. Whitehead, J.B.J. Milbank, J.F. Ohren, R.C. Gowan, C. Omer, H.S. Camp, N. Esmaeil, K. Moore, J.S. Sebolt-Leopold, S. Pryzbranowski, R.L. Merriman, D.F. Ortwine, J.S. Warmus, C.M. Flamme, A.G. Pavlovsky and H. Tecle, *J. Med. Chem.,* 2007, **50**, 5090.
6 J.J. Parlow, R.G. Kurumbail, R.A. Stegeman, A.M. Stevens, W.C. Stallings and M.S. South, *J. Med. Chem.,* 2003, **46**, 4696.
7 I. Collins, C. Moyes, W.B. Davey, M. Rowley, F.A. Bromidge, K. Quirk, J.R. Atack, R.M. McKernan, S.A. Thompson, K. Wafford, G.R. Dawson, A. Pike, B. Sohal, N.N. Tsou, R.G. Ball and J.L. Castro, *J. Med. Chem.,* 2002, **45**, 1887.
8 J.A. Patankar, S.S. Athaiye, R.S. Verma and A.A. Dalvi, *Indian J. Chem.*, 2000, **39B**, 548-550.
9 J.A. Patankar, S.S. Athalye and R.S. Verma, *Indian J. Heterocycl. Chem*., 1996, **5**, 311-314.
10 M. Cushman and E.J. Madaji, *J. Org. Chem.,* 1987, **52**, 907.
11 P. Waykole and R.N. Usgaonkar, *Indian J. Chem.,* 1984, **23B**, 478-479.
12 V. Cecchetti, A. Fravolini, P.G. Pagella, A. Savino and O. Tabarrini, *J. Med. Chem.,* 1993, **36**, 3449-3454.
13 V. Cecchetti, A. Fravolini, R. Friguelli, G. Mascellani, P. Pagella, M. Palmioli, G. Segre and P. Terni, *J. Med. Chem.,* 1987, **30**, 465-473.
14 A. Sharma and E. Tyagi, *Farmazie*, 1991**,** **46**, 746-747.
15 M.D. Chordia, M. Zigler, L.J. Murphree, H. Figler, T.L. Macdonald, R.A. Olsson and J. Linden, *J. Med. Chem.,* 2005, **48**, 5131-5139.
16 Y. Kumar, R. Green, D.S. Wise, LL. Wotring and L.B. Townsend, *J. Med. Chem.,* 1993, **36**, 3849-3852.
17 H. Cheng, M. Kristin, L. DeMello, J. Li, S.M. Sakya, K. Ando, K. Kawamura, T. Kato, R.J. Rafka, B.H. Jaynes, C.B. Ziegler, R. Stevens, L.A. Lund, D.W. Mann, C. Kilroy, M.L. Haven, E.L. Nimz, J. K. Dutra, C. Li, M.L. Minich, N.L. Kolosko, C. Petras, A.M. Silvia and S. B. Seibel, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 2076-2080.
18 B.S. Holla, M. Mahalinga, M.S. Karthikeyan, P.M. Akberali and N.S. Shetty, *Bioorg. Med. Chem.,* 2006, **14**, 2040-2047 and references therein.
19 M.V. Patel, R. Bell, S. Majest, R. Henry and T. Kolasa, *J. Org. Chem.,* 2004, **69**, 7058- 7065 and references therein.
20 R.K. Robins, *J. Am. Chem. Soc.,* 1956, **78**, 784-790.
21 J.E. Kerrigan, J. Oleksyszyn, C.M. Kam, J. Selzler and J.C. Powers, *J. Med. Chem.,* 1995, **38**, 544-552.
22 C.M. Kam, J.E. Kerrigan, R.R. Plaskon, E.J. Duffy, P. Lollar, F.L. Suddah and J.C. Powers, *J. Med. Chem.,* 1994, **37**, 1298-1306.
23 M.A. Hernandez, J.C. Powers, J. Glinski, J. Oleksyszyn, J. Vijayalakshmi and E.F. Mayer, *J. Med. Chem.,* 1992, **35**, 1121-1129.
24 V.H. Belgoankar and R.N. Usgoankar, *Tetrahedron Lett.,* 1975, 3849.
25 U.C. Mashelkar, K.V. Walawalkar and C.N. Arvindakshan, *J. Indian Chem. Soc.*, 1992, **63**, 404.
26 U.C. Mashelkar, K.V. Walawalkar, C.N. Arvindakshan and A. Singh, *J. Indian Chem. Soc.*, 1992, **69**, 404.