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A Novel Synthesis of Heterocyclic Compounds Containing Coumarin Moiety of Potential Antimicrobial Activity

M. E. Abd El-Fattah

Chemistry Department, Faculty of Science, Suez Canal University, Ismalillia, Egypt

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The chemical behaviours of 4-methyl-2-oxo-2H-benzopyran-7-yl oxoacetyl hydrazine (**2**) towards some different reagents such as anhydride compounds, aromatic aldehydes, carbon disulphide, and nitrous acid yielded the corresponding pathalazine derivatives (**3**, **4**, **5**), hydrazone derivative (**6**), 1,3,4-oxadiazole derivative (**7**, **8**, **9**) and acid azide (**10**) respectively. Treatment of **10** with absolute alcohols, amines and ethyl amino acid ester gave the corresponding carbamate derivative (**11**), substituted urea derivative (**12**) and ethyl substituted alkyl acetate (**13**) respectively. The biological activity of some synthesized compounds was evaluated.

Key words : Antimicrobial activity, Heterocyclic compounds, Coumarin, Acid azide, 4-Methyl-2-oxo-2H-benzopyran-7-yl oxoacetyl hydrazine

INTRODUCTION

In a previous work (El-Deen *et al.*, 1992; El-Tamany *et al.*, 1995; Soliman *et al.*, 1990) we synthesized some new heterocyclic compounds containing coumarin moiety and we studied its bioligical activities. The aim of the present work was to study the chemical reactions of 4-methyl-2-oxo-2H-benzopyran-7-yl oxo-acetyl hydrazine (**2**) towards some different reagents (such as anhydride compounds, aromatic aldehydes, carbon disulphide and nitrous acid) to produce different new heterocyclic compounds containing coumarin moiety with the expectation of biological activities (Chakraborty *et al.*, 1957; Toda *et al.*, 1958).

RESULTS AND DISCUSSION

The 4-methyl-2-oxo-2H-benzopyran-7-yl oxoacetyl hydrazine (**2**) was prepared from ethyl 4-methyl-2-oxo-2H-benzopyran-7-yl oxoacetate and hydrazine hydrate according to a literature procedure (El-Tamany *et al.*, 1995). 4-Methyl-2-oxo-2H-benzopyran-7-yl oxoacetyl hydrazine (**2**) was fused with anhydride compounds such as (succinic anhydride, maleic anhydride, and phthalic anhydride) at 150~160°C afforded the corresponding phthalazine derivatives (**3**, **4** and **5**, Scheme 1). 7-(5-Aryl-1,3,4-oxodiazol-2-yl methoxy-4-methyl)-2-oxo-2H-1-benzopyran (**7a-b**, Scheme 1) was prepared from the reaction of 4-methyl-2-oxo-2H-1-benzopyran-7-yl oxoacetyl hydrazine (**2**) with aromatic aldehydes (such as benzaldehyde, anisaldehyde and 4-chloro-benzaldehyde) yielded hydrazone derivative (**6**) followed by cyclization via bromination of (**6**) in the presence of sodium acetate with elimination of hydrogen bromide.

7-(5-Mercapto-1,3,4-oxodiazol-2-yl-methoxy)-4-methyl-2-oxo-2H-1-benzopyran (**8**, Scheme 1) was obtained from the action of carbon disulphide on 4-methyl-2-oxo-2H-1-benzopyran-7-yl oxoacetyl hydrazine (**2**) in the presence of alcoholic potassium hydroxide (El-Deen *et al.*, 1994). The structure of 8 was confirmed via the conversion to the corresponding [2-(4-methyl-2-oxo-2H-1-treatment with chloroacetic acid in the presence of potassium carbonate in ethanol.

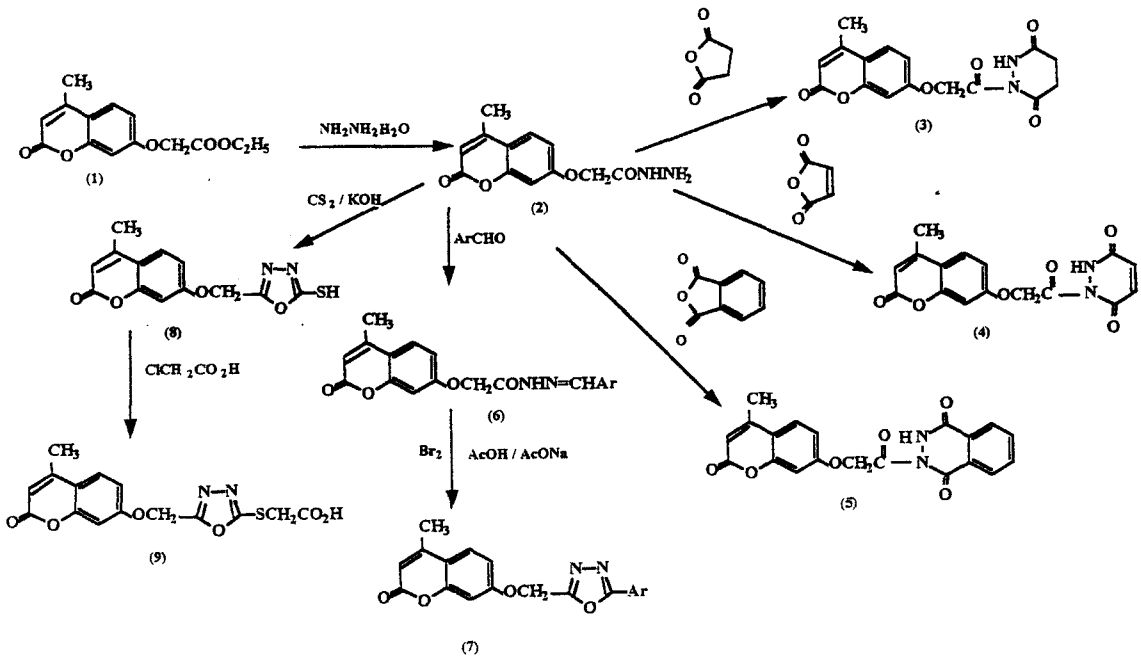
In the present paper, the author studied the reaction of 4-methyl-2-oxo-2H-1-benzo-pyran-7-yl oxoacetyl hydrazine (**2**) with sodium nitrite in the presence of hydrochloric acid to give acid azide derivative (**10**, Scheme 2) according to the literature procedure (El-Kerdawy *et al.*, 1989; Tousif *et al.*, 1986).

The azide (**10**) was allowed to react with certain absolute alcohols (namely, n-propanol and n-butanol) to give alkyl (4-methyl-2-oxo-2H-benzopyran-7-yl oxo methyl amino) ester (**11**, Scheme 2).

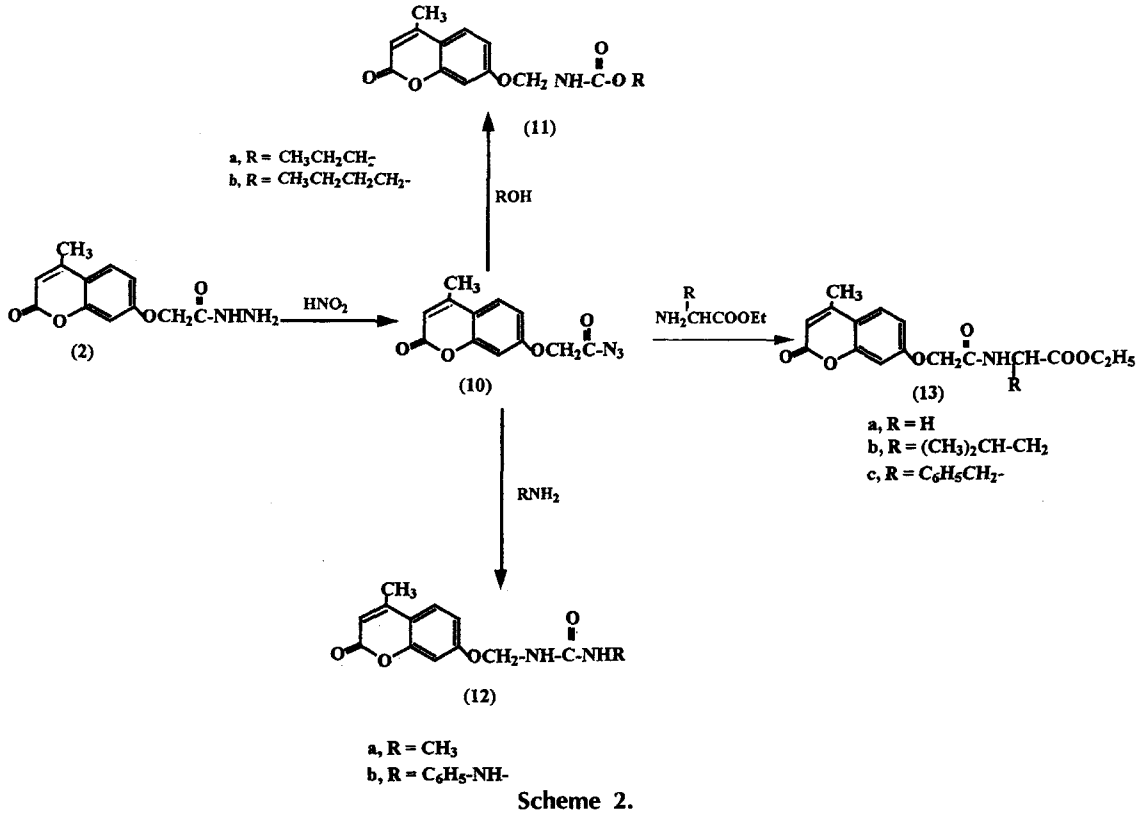
Similarly, treatment of azide (**10**) with amines (such as methyl amine and phenyl hydrazine) afforded the corresponding 1-(4-methyl-2-oxo-2H-benzopyran-7-yl oxomethyl)-3-alkylurea (**12**, Scheme 2).

Subsequently, the reaction of azide (**10**) with amino acid ester (Hofmann *et al.*, 1957, 1960) such as glycine ethyl ester hydrochloride, leucine ethyl ester hydrochloride and phenylalanine ethyl ester hydrochloride to give ethyl (4-methyl-2-oxo-2H-benzopyran-7-yl oxo-methyl carbonyl amino) alkyl-acetate (**13**, Scheme 2).

Correspondence to: M. E. Abd El-Fattah, Chemistry Department, Faculty of Science, Suez Canal University, Ismalillia, Egypt



Scheme 1.



Scheme 2.

Biological activity

Using the Well method (Muria *et al.*, 1982) all the newly compounds were tested biologically with gram negative bacteria (*Escherichia coli, Pseudomonas* sp.) and gram positive bacteria (*Bacillus subtilis, Staphylococcus aureus*) and the results were evaluated in Table I.

Compounds no. **4**, **5** showed very high biological activity with gram negative bacteria (*E. coli*), whereas compounds no. **13b**, **13c** inhibited the growth of gram positive bacteria (*S. aureus*). High biological effects

Table I. Biological activity of some tested compounds

Compound NO	Gram (-) bacteria		Gram (+) bacteria	
	Escherichia coli	*Pseudomonas* sp.	*Bacillius subtilis*	*Staphylococcus aureus*
	Conc. is 100 ppm for all compounds			
3	-	+	+	++
4	++++	++	-	+
5	+++	+	-	+
6a	++	+=	++	+
6b	+	++	+	++
6c	+	+	-	+
7	+++	+	+	+
8	++	+	++	++
9	++	++	-	+
10	++	+++	++	+
11a	-	+	-	-
11b	++	++	-	+++
12a	+++	+++	++	+++
12b	+++	+	++	-
13a	+++	-	++	-
13b	+	+++	++	++++
13c	+++	+++	++	++++

The resulting effects have been tentatively classified as follows
(+) Small clearing zone, slightly active
(++) Medium clearing zone, moderately active.
(+++) Large clearing zone, highly active.
(++++) Very large clearing zone, very high activity.
(-) No learing zone, inactivie.

due to compounds no **12a**, **13b**, **13c** were detected through the test of gram negative bacteria (*Pseudomonas* sp.) while the same tested showed that compounds no. **12a**, **12b**, **13a**, **13c** have high activity against *E. coli*. In the test of Gram positive bacteria, two compounds only (no. **11a**, **12a**) showed high biological activity against (*S. aureus*). In general compounds no. **13b**, **13c** are the most effective compounds followed by no. **4**, **5** due to their strong biological activity (+, +++). A group of compounds including **7**, **12a**, **12b**, **13a** and **13c** showed high biological activity against (*E. coli*). All the tested compounds showed at least medium biological activity against gram positive or gram negaive bacteria. No compounds showed high or strong biological activity against *B. subtilis* as gram positive bacteria. Compound no. **11a** was the lowest biologically active compound throughout the test.

EXPERIMENTAL SECTION

The melting points of these compounds were uncorrected and were determined in glass capillary tube on Mel-Temp melting point apparatus. All compounds were analyzed for their carbon, hydrogen, nitrogen and sulphur contents. Infrared spectra were recorded on a Perkin-Elmer 1430 ratio recording infrared spectrophotometer with CDS data station using KBr. Wafer technique. Nuclear Magnetic Resonance spectra (^{1}H-NMR) were recorded on a Varian-Gemini 200 MHz spectrometer, using TMS as internal standard. Mass spectra were measured with GC-MSQP 100 EX Schimadzu.

Reaction of 2 with anhydride compounds: Formation of phthalazins derivatives (3, 4 and 5)

A mixture of compound **2** and anhydride compounds (such as succinic anhydride, maleic anhydride and phthalic anhydride) was fused in an oil-bath at 150~160°C for 4 hr. The reaction mixture was cooled and washed with 10% sodium carbonate. The residue was washed with water, dried and recrystallized from ethanol to give **3**, **4** and **5**. Compound **3** as white crystals, yield 65%, mp 120°C, Anal. Calcd. for $C_{16}H_{14}N_2O_6$; C, 58.18; H, 4.24; N, 8.48. Found C, 57.92; H, 4.02; N, 8.26.

IR (KBr): ν=3208, 3080, 3040, 2960, 2890, 1725, 1715, 1689, 1605, 1432, 1369, 1250, 1100 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.2 (s, 3H, CH_3), 3.1-3.2 (t, 4H, $2CH_2$-CO), 3.8 (s, 2H, OCH_2) 6.9-8.1 (m, 4H, Ar-H and olefinic proton) and 10.4 (s, 1H, NH) ppm.

Compound **4** as white crystals, 65%, mp 296°C, Anal. Calcd. for $C_{16}H_{12}N_2O_6$; C, 58.53; H, 3.6; N, 8.53. Found C, 58.39; H, 3.50; N, 8.28.

IR (KBr): ν=3205, 3070, 3050, 2980, 1723, 1705, 1685, 1615, 1590, 1435, 1370 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.3 (s, 3H, CH_3), 4.01 (s, 2H, OCH_2), 6.4-8.01 (6H, Ar-H and olefinic proton) and 10.8 (s, 1H, NH) ppm.

Compound **5** as white crystals yield 65%, mp 280 °C, Anal. Calcd. for $C_{20}H_{14}N_2O_6$; C, 63.49; H, 3.70; N,

7.40. Found C, 63.30; H, 3.56; N, 7.28.

IR (KBr): ν=3210, 3050, 3010, 2970, 1735, 1715, 1680, 1610, 1580, 1430, 1365, 1210, 1100 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.3 (s, 3H, CH_3), 4.1 (s, 2H, OCH_2), 6.5-8.3 (m, 8H, Ar-H and pyran ring) and 10.9 (s, 1H, NH) ppm.

MS (m/z): 380 (M^++2), 379 (M^++1), 378 (M^+), 217, 189, 176, 162, 161, 148, 147, 128, 91, 65, 63.

7-Arylidene hydrazinocarbonyl methoxy-4-methyl-2-oxo-2H-benzopyran (6a-c)

A solution of compound **2** (0.01 mol) with aromatic aldehydes (namely, benzaldehyde, anisaldehyde and p-chlorobenzaldehyde) (0.01 mol) in acetic acid (50 ml) was refluxed for 4 hr. The solid separated on cooling was crystallized from acetic acid to give **6**.

Compound **6a** as yellow crystals; yield 85%, mp 250°C, Anal. Calcd. for $C_{19}H_{16}N_2O_4$; C, 68.09; H, 4.76; N, 8.33. Found C, 68.82; H, 4.53; N, 8.02.

IR (KBr): ν=3310-3205, 3096-3052, 1715-1700, 1630-1620, 1615-1605, 1225-1195 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.2 (s, 3H, CH_3), 4.1 (s, 2H, OCH_2), 6.9-8.3 (m, 10H, Ar-H olefinic proton) and 9.6 (s, 1H CONH) ppm.

MS (m/z): 337 (M^++1), 336 (M^+), 305, 266, 217, 184, 176, 161, 130, 77.

Compound **6b** as yellow crystals, yield 76%, mp 233°C, Anal. Calcd. for $C_{20}H_{18}N_2O_5$; C, 65.75; H, 4.91; N, 7.65. Found C, 65.39; H, 4.78; N, 7.46.

IR (KBr): ν=3310-3205, 3096-3052, 1715-1700, 1630-1620, 1615-1605, 1225-1195 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ=2.3 (s, 3H, CH_3), 3.4 (s, 3H, OCH_3), 4.1(s, 2H, OCH_2), 6.8-8.2 (m, 9H, Ar-H and olefinic proton) and 9.8 (s, 1H, CONH) ppm.

Compound **6c** as yellow crystals; yield 80%, mp 260°C, Anal. Calcd for $C_{19}H_{16}N_2O_4Cl$; C, 61.37; H, 4.30; N, 7.53. Found C, 61.06; H, 4.13; N. 7.38.

IR (KBr): ν=3310-3205, 1715-1700, 1630-1620, 1615-1605, 1225-1119 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.3 (s, 3H, CH_3), 4.2 (s, 2H, OCH_2), 6.8-8.1 (m, 9H, Ar-H olefinic proton) and 9.72 (s, 1H, CONH) ppm.

7-(5-Aryl-1,3,4-oxodiazol-2-yl methoxy-4-methyl)-2-oxo-2H-1-benzopyran (7)

A mixture of **6** (0.01 mol), bromine (0.01 mol) and fused sodium acetate (0.02 mol) in acetic acid was heated on water-bath for 2 hr. The reaction mixture was cooled and poured into water. The product obtained was filtered, was heated with hot water and crystallized from ethanol to give compound (7). Compound **7a** as pale yellow crystals; yield 67%, mp 280°C, Anal. Calcd. for $C_{19}H_{14}N_2O_4$; C, 68.26; H, 4.19; N, 8.38. Found C, 68.01; H, 4.03; N, 8.10.

IR (KBr): ν=3080, 2980, 1725-1715, 1623, 1610, 130, 1210, 1050 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.2 (s, 3H, CH_3), 4.1 (s, 2H, OCH_2), 6.8-8.1 (m, 9H, Ar-H and olefinic proton) ppm.

Compound **7b** as white crystals, yeild 68%, mp 290 °C, Anal. Calcd. for $C_{20}H_{16}N_2O_5$; C, 65.93; H, 4.39; N, 7.69. Found C, 65.68; H, 4.11; N, 7.32.

IR (KBr): ν=3080, 2980, 1725-1715, 1623, 1610, 1370, 1210, 1050 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ=2.1 (s, 3H, CH_3), 3.6 (s, 3H, OCH_3), 4.2 (s, 2H, OCH_2), 6.9-8.1 (m, 8H, Ar-H and olefinic proton) ppm.

7-(5-Mercapto-1,3,4-oxodiazol-2-yl methoxy-4-methyl-2-oxo-2H-1-benzopyran (8)

An alcoholic potassium hydroxide solution (0.02 mol) in 5 ml H_2O and 30 ml ethanol was added to a mixture of **2** (0.01 mol) and carbon disulphide (1 mol). The reaction mixture was refluxed for 6 hr and the excess CS_2 was then evaporated. The solid obtained was dissolved in H_2O, filtered off from any insoluble materials and acidified, the white precipitate that formed was filtered off and crystallised from ethanol to give **8** as white crystals, yield 60%, mp 175°C, Anal. Calcd. for $C_{13}H_{10}N_2O_4S$; C, 53.79; H, 3.44; N, 9.65; S, 11.03. Found C, 52.92; H, 3.04; N, 9.25; S, 10.90.

IR (KBr): ν=3220 (NH), 2580 (weak SH), 1720 (CO of pyranone), 1625 (C=N), 1325 cm^{-1} (C=S).

^{1}H-NMR (DMSO-d_6): δ=2.3 (s, 3H, CH_3), 4.2 (s, 2H, OCH_2), 4.9 (br.s, 1H, SH), 6.8-7.9 (m, 4H, Ar-H), 9.8 (br.s, 1H, NHC=S) ppm.

5-(4-Methyl-2-oxo-2H-1-benzopyran-7-yl oxomethyl-1,3,4-oxadiazol thioacetic acid (9)

A mixture of compound **8** (0.01 mol), chloroacetic acid (0.01 mol) and potassium carbonate (0.02 mol) in ethanol (70 ml) was heated under reflux for 4 hr. The reaction mixture was cooled and acidified in 1M HCl. The solid obtained was filtered off, washed with water, dried and recrystallized from ethanol to give compound **9** as white crystals, yield 75%, mp 163°C, Anal. Calcd. for $C_{15}H_{12}N_2O_6S$; C, 51.72; H, 3.44; N, 8.04. Found C, 51.58; H, 3.27; N, 7.86.

IR (KBr): ν=3540-2875 (broad OH), 3080, 2930, 1720, 1705, 1625, 1610, 1595, 1433, 1210, 1100 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ=2.2 (s, 3H, CH_3), 3.2 (s, 2H, SCH_2CO), 4.2 (s, 2H, OCH_2), 6.9-8.1 (m, 4H, Ar-H and olefinic proton), 9.8 (br.s, 1H, OH) ppm.

MS (m/z): 349 (M^++1), 348 (M^+), 331, 321, 320, 305, 273, 189, 176, 159, 149, 120, 91, 63, 51.

4-Methyl-2-oxo-2H-benzopyran-7-yl oxomethyl carbonyl azide (10)

Compound **2** (0.01 mol) was dissolved in concentrated hydrochloric acid (50 ml). A solution of sodium

nitrite (0.02 mol) in water (40 ml) was then added drop wise over a priod of one hour while stirring. The precipitated solid product was filtered, washed with ice cooled-water, dried and crystallized from dry ether to give compound **10** as white crystalls, yield 90%, mp 86°C, Anal. Calcd. for $C_{12}H_9N_3O_4$; C, 55.60; H, 3.47; N, 16.22. Found C, 55.29; H, 3.27; N, 16.01.

IR (KBr): ν=1720, 1715 and 2160 (N_3), 1721, 1715 (C=O), 2163 (N_3) cm.

^{1}-NMR ($CDCl_3$): δ=2.2 (s, 3H, CH_3), 3.9 (s, 2H, OCH_2) and 7.1-8.01 (m, 4H, Ar-H) ppm.

MS (m/z): 259 (M^+), 231, 147, 56.

Alkyl(4-methyl-2-oxo-2H-benzopyran-7-yl oxomethyl amino)esters (11)

A solution of compound **10** (0.01 mol) in dry benzene (25 ml) and the appropriate absolute alcohols (namely, n-propanol and n-butanol) was refluxed for 5 hr. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol to give **11**.

IR (KBr): ν=3290 (NH), 1735 (C=O of ester), 1715 (C=O of pyrone), 1625 (C=N), 1130 (C-O) cm.

Compound **11a** as colourless crystals; yield 67%, mp 130°C, Anal. Calcd. for $C_{15}H_{17}NO_5$; C, 61.80; H, 5.84; N, 9.81. Found C, 61.63; H, 5.51; N, 9.57.

^{1}H-NMR ($CDCl_3$): δ=0.9 (t, J=6.3H, $\underline{CH_3}CH_2$), 1.2 (hexa, J=4, 6, 8, 2H, $CH_3\underline{CH_2}CH_2$), 3.9 (t, J=6.2H, $O\underline{CH_2}CH_2$), 4.2(s, 2H, OCH_2), 7.0-8.01 (m, 4H, Ar-H) and 8.7 (s, 1H, NHCO) ppm.

MS (m/z): 291 (M^+), 289, 276, 248, 217 (100), 176, 148, 116 (100), 89, 74, 56.

Compound **11b** as colourless crystals; yield 80%, mp 167°C, Anal. Calcd. for $C_{16}H_{19}NO_5$; C, 62.95; H, 6.23; N, 4.81. Found C, 62.65; H, 6.03; N, 4.62.

^{1}H-NMR ($CDCl_3$): δ=0.9 (t, J=6.3H, $\underline{CH_3}CH_2$), 1.2-1.35 (m, 4H, CH_2-CH_2), 2.2 (s, 3H, CH_3), 3.8 (t, J=6, 2H, $O\underline{CH_2}$), 4.2 (s, 2H, OCH_2), 7.01-8.01 (m, 4H, Ar-H) and 8.8 (s, 1H, NHCO) ppm.

MS (m/z): 305 (M^+), 299, 290, 245, 234, 189, 176, 148 (100), 120, 91, 69.

1-(4-Methyl-2-oxo-2H-benzopyran-7-yl-oxomethyl)-3-alkyl urea (12)

A solution of compound **10** (0.01 mol) in dry benzene (20 ml) was heated under reflux for 2 hr. The appropriate amount of amines (0.01 mol) (namely, methylamine and phenyl hydrazine) was added and the reflux was continued for an additional 3 hr. After evaporation of the solvent under reduced pressure, the obtained residue was crystallized from ethanol to give (**12**).

IR (KBr): ν=3250-3156(NH), 1720, 1690(C=O), 1610 (C=C) cm^{-1}

Compound **12a** as colourless crystals; yield 90%, mp 233°C, Anal. Calcd. for $C_{13}H_{14}N_2O_4$; C, 59.34; N, 10.69. Found C, 59.01; H, 5.61; N, 10.44.

^{1}H-NMR (DMSO-d_6): δ=2.2 (s, 3H, CH_3), 2.5 (s, 3H, $NHCH_3$), 4.1 (s, 2H, OCH_2), 7.0-8.1 (m, 4H, Ar-H) and 10.1 (s, 2H, NHCONH) ppm.

MS (m/z): 262 (M^+), 232, 204, 189, 176, 148.

Compound **12b** as colourless crystals; yield 90%, mp 205°C, Anal. Calcd. for $C_{18}H_{17}N_3O_4$; C, 53.10; H, 5.02, N, 12.39. Found C, 53.00; H, 4.99; N, 12.09.

^{1}H-NMR (DMSO-d_6): δ=2.2 (s, 3H, CH_3), 4.2 (s, 2H, OCH_2), 6.9-8.1 (m, 9H, Ar-H), 9.3 (s, 1H, NH), 10.2 (s, 2H, NHCONH) ppm.

MS (m/z): 340 (M^++1), 339 (M^+), 324, 313, 299, 233, 217, 176, 148(100), 91, 69.

Ethyl(4-methyl-2-oxo-2H-benzopyran-7-yl oxomethylcarbonylamino) alkylacetate (13)

Azide **10** was taken up in 50 ml of cold ethyl aetate. The ethyl acetate layer was kept cold while washing successively with water, 3% $KHCO_3$, H_2O and briefly dried ever Na_2SO_4. The amino acid ethyl ester (namely, glycine ethyl ester hydrochloride, leucine ethyl ester hydrochloride and phenylalanine ethyl ester hydrochloride) (0.009 mol) was dissolved in 20 ml of dry ethyl acetate and 0.2 ml of triethylamine was added, and the mixture stirred for 20 minutes at 0°C. The cooled dried solution of azide was added to the dry ethylacetate solution of free amino acid ethyl ester and the mixture was kept 24 h at 0°C and then kept 24 hr at room temperature. The mixture was washed with 0.5 N HCl, H_2O 3% $KHCO_3$, H_2O and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residual was recrystallized from ethanol: water (3/1 v/v) to give **13**.

IR (KBr): ν=3220(NH), 1745(CO of ester), 1720 (CO of pyrane), 1690 (CO of amide), 1605 (C=C) cm^{-1}.

Compound **13a** as colourless crystals; yield 70%, mp 164°C, Anal. Calcd. for $C_{16}H_{17}NO_6$; C, 60.18; H, 5.33; N, 4.39. Found C, 59.99; H, 5.03; N, 4.15.

^{1}H-NMR (DMSO-d_6); δ=1.3 (t, J=6, 3H, CH_3), 2.2(s, 3H, CH_3), 2.9 (s, 2H, $NHCH_2CO$), 3.9(q, J=6, 8, 2H, $O\underline{CH_2}CH_3$), 4.2(2H, OCH_2), 7.0~8.1 (m, 4H, Ar-H) and 9.01 (s, 1H, CONH).

Compound **13b** as colourless crystals; yield 80%, mp 76°C, Anal. Calcd. for $C_{20}H_{25}NO_6$; C, 64.00; H, 6.66; N, 3.73. Found C, 63.86; H, 6.56; N, 3.62.

^{1}H-NMR (DMSO-d_6); δ=0.91 (d, J=8, 6H, $(CH_3)_{2CH}$), 1.3(t, J=6, 3H, $\underline{CH_3}CH_2$), 1.68-1.78 [m, 1H, $(CH_3)_{2CH}$-CH_2], 2.01(t, J=6, 2H, $CHCH_2CH$), 2.2(s, 3H, CH_3), 3.1 (t, 1H, $NHCHCH_2$), 3.9 (q, J=6, 8, 2H, $O\underline{CH_2}$), 4.2 (s, 2H, OCH_2-Ar), 7.01-8.01 (m, 4H, Ar-H) and 8.9 (s, 1H, CONH) ppm.

Compound **13c** as colourless crystals, yield 65%,

mp 96°C, Anal. Calcd. for $C_{23}H_{23}NO_6$; C, 67.48; H, 5.62; N, 3.42. Found C, 67.08; H, 5.57; N, 3.15.

^{1}H-NMR (DMSO-d_6); δ=1.3 (t, J=6, 3H, $\underline{CH_3}CH_2$), 2.1 (s, 3H, CH_3), 2.5 (d, J=8, 2H, Ar-$\underline{CH_2}$-CH), 3.1(t, J=6, 1H, $CH_2\underline{CH}N$), 3.9 (q, J=6, 8, 2H, $O\underline{CH_2}$-), 4.2 (s, 2H, OCH_2), 7.0~8.01 (m, 9H, Ar-H) and 9.0 (s, 1H, CONH) ppm.

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