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4-Hydroxycoumarin in heterocyclic synthesis Part III. Synthesis of some new pyrano[2,3-*d*]pyrimidine, 2-substituted[1,2,4]triazolo[1,5-*c*]pyrimidine and pyrimido[1,6-*b*][1,2,4]triazine derivatives

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Abstract

The synthesis of new [1]benzopyrano[3′,4′:5,6]pyrano[2,3-*d*]pyrimidines and related heterocycles has been reported. The key intermediate 2-amino-3-cyano-4-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (**3**) was obtained in one pot synthesis from the reaction of 4-hydroxycoumarin and acetaldehyde–malononitrile (**2**). The antimicrobial screening was performed for some of the synthesized compounds.

Keywords: Pyrano[3,2-*c*]benzopyrans; Pyrano[2,3-*d*]pyrimidines; [1,2,4]Triazolo[1,5-*c*]-pyrimidines; Pyrimido[1,6-*b*][1,2,4]triazine; Antimicrobial activity

1. Introduction

Several derivatives of the pyran or of fused pyran ring systems are endowed with different types of biological activities. It has been reported that pyran derivatives exhibit antimicrobial activity [1], growth stimulating effects [2], antifungal and plant growth regulation effects [3], antitumor activity [4], central nervous system (CNS) activity [5] and hypotensive effect [6]. Moreover pyran derivatives are well known for antihistaminic activity [7], platelet antiaggregating activity and local anaesthetic activity [8–10], antiallergenic effect [11], antidepressant effect [12] and as antiproliferation agents [13,14]. With this in mind and in continuation of our previous work [15–19] on the synthesis of new fused 4*H*-pyran using enaminonitriles as starting material, we report here the synthesis of a variety of new [1]benzopyrano[3′,4′:5,6]pyrano[2,3-*d*]-pyrimidines along with their antimicrobial activity.

2. Chemistry

This synthesis involves Michael cycloaddition reaction of the readily available 4-hydroxycoumarin (**1**) with α-cyanocrotononitrile (**2**) in ethanolic piperidine to afforded 2-amino-3-cyano-4-methyl-4*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-5-one (**3**) [19]. Treatment of **3** with acetic anhydride for 0.5 and/or 3 h under reflux afforded *N*-acetyl and [1]benzopyrano[3′,4′:5,6]-pyrano[2,3-*d*]pyrimidine-6,8-dione derivatives (**4**) and (**5a**), respectively. Also, interaction of **3** with benzoyl chloride or formic acid gave the corresponding pyrimidine derivatives (**5b**,**c**), while its treatment with formamide afforded the aminopyrimidine derivative (**6**). On the basis of spectral data, structure **5B** was excluded [16–19]. Structure **5A** was established on the basis of IR spectrum which showed an absorption band at 1665 (**5a**), 1659 (**5b**), 1790 cm^{-1} (**5c**) characteristic to (CO) and ^1H NMR spectrum which revealed a broad single at δ 7.47 (**5a**) and at δ 7.33 ppm (**5c**) characteristic for NH proton. Structures **3**–**6** were established by spectral data and analogy with our pervious work [16–19] (Scheme 1).

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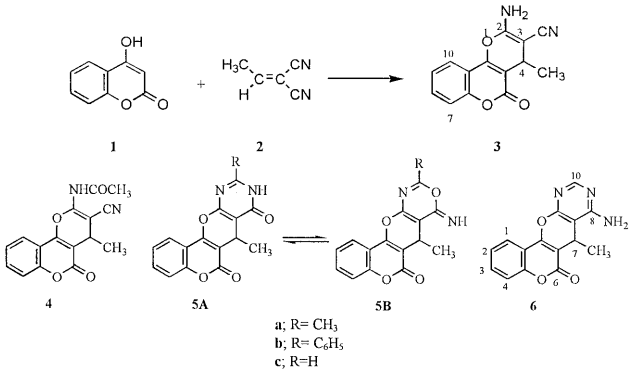


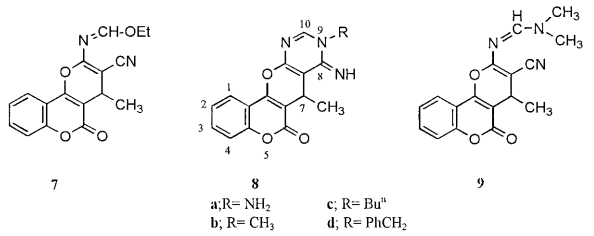
Scheme 1.

The enaminonitrile (**3**) proved to be a useful key intermediate in the synthesis of a variety of new pyranopyrimidine, pyranotriazolopyrimidine and pyranopyrimidotriazine derivatives. Thus, treatment of **3** with triethylorthoformate–Ac_2O gave the corresponding ethoxymethyleneamino derivative (**7**). Hydrazinolysis of **7** in ethanol at room temperature yielded 9-amino-8,9-dihydro-8-imino-7-methyl-6*H*,7*H*-[1]benzopyrano-[3′,4′:5,6]pyrano-[3,2-*d*]pyrimidine-6-one (**8a**). Aminolysis of **7** with aliphatic primary amines gave the corresponding pyranopyrimidine-6-one derivatives (**8b**–**d**), while with dimethylamine gave the dimethylamino-methyleneamino derivative (**9**). Ammonolysis of **7** in methanol gave 8-amino-7-methyl-6*H*,7*H*-[1]benzo-pyrano[3′,4′:5,6]pyrano[2,3-*d*]pyrimidine-6-one (**6**) (melting point and mixed melting point) (Scheme 2).

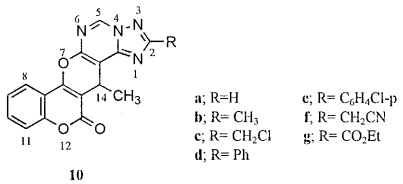
Treatment of **8a** with some carboxylic acid chlorides gave the corresponding 14-methyl-2-substituted-13*H*,14*H*-[1]benzopyrano[3′,4′:5,6]pyrano[3,2-*e*][1,2,4]-triazolo-[1,5-*c*]pyrimidine-13-one (**10b**–**e**), while cyclo-condensation of **8a** with ethyl cyanoacetate and diethyl oxalate gave the corresponding 2-cyanomethyl and 2-ethoxycarbonyl derivatives (**10f**,**g**), respectively. Also, **8a** was reacted with triethyl orthoformate to afforded the corresponding [1,2,4]triazolo[1,5-*c*]pyrimidine-13-one derivative (**10a**). Structures **7**–**10** were established by spectral data and analogy with our previous work [16–19] (Scheme 3).

Instead of the anticipated formation of the triazolopyrimidine derivative **13** [17,18], the reaction of **8a** with ethyl chloroformate, through nucleophilic displacement followed by spontaneous hydrolysis of the ester intermediate **11**, led to the corresponding carbamic acid derivative **12**. The formation of ion peak at 296 (38%) ($M^+ - CO_2$) for the mass spectrum of **12** (m/z M^+, 0%) supported the proposed structure due to the ready elimination of CO_2 molecule (Scheme 4).

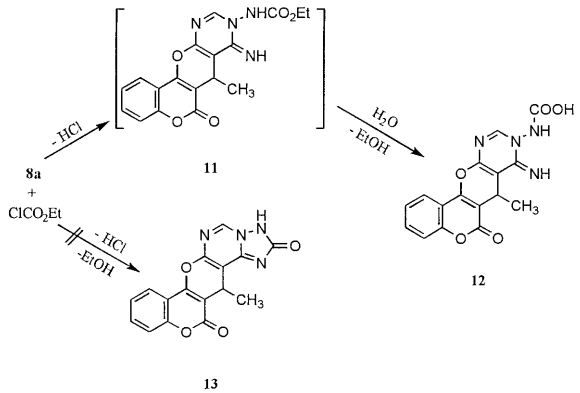
Interaction of **8a** with ethylchloroacetate in methanolic sodium methoxide leads to cyclocondensation with elimination of EtOH and HCl to afforded the triazin-3,14-dione derivative (**14**), while **8a** was reacted with alcoholic CS_2–KOH to give 14-methyl-2,3-dihydro-13-



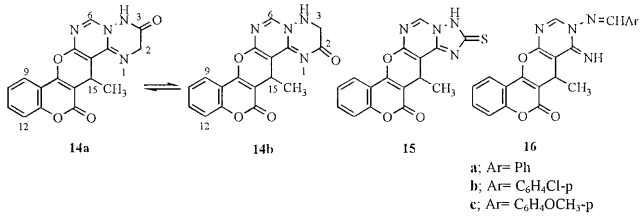
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

oxo-2*H*,13*H*,14*H*-[1]benzopyrano[3′,4′:5,6]pyrano[3,2-*e*]-[1,2,4]triazolo[1,5-*c*]-pyrimidine-2-thione (**15**) (Scheme 5). On the basis of reaction conditions and spectral data [20] structure **14b** was excluded. Structure **14a** was established on the basis of the reaction conditions (sodium methoxide) by first formation of sodium salt on the less basic imino nitrogen atom, which cyclizes into **14a**, with elimination of NaCl and EtOH. The IR spectrum of **14a** showed an absorption band at 1665 cm^{-1} characteristic to (CO), if we had structure

14b, an absorption band for the carbonyl band at higher frequency than that observed for **14a** would be expected [20].

Finally, the treatment of **8a** with aromatic aldehydes gave the pyrimidine derivatives (**16a–c**) instead of the expected triazolopyrimidine derivatives such as (**10d,e**) [20] (Scheme 5).

3. Experimental

All melting points are uncorrected and were determined on a Stuart Scientific Co. Ltd. melting points apparatus. IR spectra were recorded on a FTIR/5300 spectrometer in KBr. ^{1}H NMR spectra were measured on a Varian Gemini (200 MHz), Varian Mercury (300 MHz) spectrometers in the suitable deutereted solvent using tetramethylsilane (TMS) as the internal standard. Mass spectra on a Shimadzu GC–MS QP 1000 EX spectrometer. Elemental analyses were determined on a Perkin–Elmer 240 C microanalyser and the results for the indicated elements were within $\pm 0.3\%$ of the calculated values.

*3.1. 2-Amino-3-cyano-4-methyl-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**3**)*

This compound was prepared according to the literature [19].

*3.2. 2-Acetylamino-3-cyano-4-methyl-4H,5H-pyrano[3,2-c][1]benzopyran-5-one (**4**)*

A solution of **3** (2.54 g, 0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 30 min. The solid product formed was filtered, washed with cold ethanol, dried and recrystallized from benzene to give pale yellow needles, m.p. 198°C, yield 2.52 g (85%). IR: ν (cm^{-1}) 3425 (NH), 1720 (CO δ-lacton), 1674 (CO acetyl). *Anal.* (C,H,N) for $C_{16}H_{12}N_2O_4$.

*3.3. 7,10-Dimethyl-8,9-dihydro-6H,7H,8H-[1]-benzopyrano[3′,4′:5,6]pyrano[2,3-d]-pyrimidin-6,8-dione (**5a**)*

A solution of **3** (2.54 g, 0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 3 h. The solid product formed was filtered, washed with cold ethanol, dried and recrystallized from DMF to give colorless crystals, m.p. 350°C, yield 2.37 g (80%). IR: ν (cm^{-1}) 3283 (NH), 1711 (CO δ-lacton), 1665 (CO). ^{1}H NMR (DMSO-d_6): δ 1.33 (d, 3H, CH_3, $J = 6.6$ Hz), 2.34 (s, 3H, CH_3), 3.78 (q, 1H, pyran CH, $J = 6.6$ Hz), 7.47 (br, 1H, NH cancelled by D_2O), 7.48–7.88 (m, 4H, Ar–H). *Anal.* (C,H,N) for $C_{16}H_{12}N_2O_4$.

*3.4. 7-Methyl-10-phenyl-8,9-dihydro-6H,7H,8H-[1]-benzopyrano[3′,4′:5,6]pyrano-[2,3-d]pyrimidin-6,8-dione (**5b**)*

A solution of **3** (2.54 g, 0.01 mol) in benzoyl chloride (20 ml) was heated under reflux for 6 h. The excess benzoyl chloride was evaporated under reduced pressure and the solid residue was recrystallized from DMF to give colorless crystals, m.p. > 360°C, yield 2.51 (75%). IR: ν (cm^{-1}) 3270 (NH), 1713 (CO δ-lacton), 1659 (CO). MS: m/z 358 (M^+, 1.11%), 343 (100%), 267 (46.38), 240 (12.34), 198 (0.97), 144 (0.87), 116 (3.38), 100 (1.60), 76 (3.32). *Anal.* (C,H,N) for $C_{21}H_{14}N_2O_4$.

*3.5. 7-Methyl-8,9-dihydro-6H,7H,8H-[1]-benzopyrano[3′,4′:5,6]pyrano[2,3-d]-pyrimidin-6,8-dione (**5c**)*

Compound **5c** was prepared from **3** (2.54 g, 0.01 mol) and formic acid (20 ml) according to the procedure described for **5b** to give **5c** as colorless needles, m.p. 192°C, yield 2.12 g (75%). IR: ν (cm^{-1}) 3210 (NH), 1790 (CO), 1719 (CO δ-lacton). ^{1}H NMR (DMSO-d_6): δ 1.31 (d, 3H,CH_3, $J = 6.4$ Hz), 4.00 (q, 1H, pyran CH, $J = 6.4$ Hz), 7.33 (br, 1H, NH cancelled by D_2O), 7.43–7.91 (m, 4H, Ar–H), 8.16 (s, 1H, pyrimidine CH). *Anal.* (C,H,N) for $C_{15}H_{10}N_2O_4$.

*3.6. 8-Amino-7-methyl-6H,7H-[1]benzopyrano-[3′,4′:5,6]pyrano[2,3-d]pyrimidine-6-one (**6**)*

3.6.1. Method (a)

A solution of **3** (2.54 g, 0.01 mol) in formamide (20 ml) was heated under reflux for 6 h. The cold reaction mixture was then poured into ice-cold water with stirring. The solid product formed was filtered, washed with water, dried and recrystallized from benzene to give colorless crystals, m.p. 330°C, yield 1.97 g (70%). IR: ν (cm^{-1}) 3396, 3339 (NH_2), 1705 (CO δ-lacton). MS: m/z 281 (M^+, 2.70%), 266 (100%), 239 (24.97), 224 (1.29), 185 (0.31), 140 (1.98), 121 (1.01), 92 (1.65), 63 (1.57). *Anal.* (C,H,N) for $C_{15}H_{11}N_3O_3$.

3.6.2. Method (b)

A stream of NH_3 gas was passed through **7** (3.1 g, 0.01 mol) in methanol at room temperature (r.t.) for 1 h. The solid product formed on cooling was collected to give **6** (m.p. and mixed m.p.) yield 2.53 g (90%).

*3.7. 2-Ethoxymethyleneamino-3-cyano-4-methyl-4H,5H-pyrano[3,2-c][1]benzo-pyran-5-one (**7**)*

This compound was prepared according to the literature [19].

3.8. Preparation of **8a–d** and **9**

3.8.1. General procedure

A solution of **7** (3.1 g, 0.01 mol), hydrazine hydrate (5 ml, 99%), appropriate primary amine (methylamine, *n*-butylamine and benzylamine) (5 ml) and dimethylamine (5 ml) in ethanol (50 ml) was stirred at r.t. for 1 h. The white solid product formed was filtered washed with cold ethanol, dried and recrystallized from the appropriate solvent.

3.8.2. 9-Amino-8,9-dihydro-8-imino-7-methyl-6H,7H-[1]benzopyrano[3′,4′:5,6]-pyrano[2,3-d]-pyrimidine-6-one (**8a**)

Colourless crystals from dioxane, m.p. 238°C, yield 2.58 g (87%). IR: ν (cm^{-1}) 3400, 3302 (NH_2), 3192 (NH), 1705 (CO δ-lacton). ^{1}H NMR (DMSO-d_6): δ 1.36 (d, 3H, CH_3, $J = 6.4$ Hz), 4.2 (q, 1H, pyran CH, $J = 6.4$ Hz), 6.79 (br, 2H, NH_2), 7.38–7.94 (m, 5H, Ar–H + NH), 8.81 (s, 1H, pyrimidine CH). *Anal.* (C,H,N) for $C_{15}H_{12}N_4O_2$.

3.8.3. 7,9-Dimethyl-8,9-dihydro-8-imino-6H,7H-[1]-benzopyrano[3′,4′:5,6]pyrano-[2,3-d]pyrimidine-6-one (**8b**)

Colourless crystals from benzene, m.p. 250°C, yield 2.57 g (87%). IR: ν (cm^{-1}) 3346 (NH), 1724 (CO δ-lacton). ^{1}H NMR (DMSO-d_6): δ 1.29 (d, 3H, CH_3, $J = 6.6$ Hz), 3.35 (s, 3H, N–CH_3), 3.88 (q, 1H, pyran CH, $J = 6.6$ Hz), 7.30 (br, 1H, NH), 7.46–7.71 (m, 4H, Ar–H), 8.15 (s, 1H, pyrimidine CH). *Anal.* (C,H,N) for $C_{16}H_{13}N_3O_3$.

3.8.4. 9-(n-Butyl)-8,9-dihydro-7-methyl-8-imino-6H,7H-[1]benzopyrano[3′,4′:5,6]-pyrano[2,3-d]-pyrimidine-6-one (**8c**)

Colourless needles from benzene, m.p. 240°C, yield 2.86 g (85%). IR: ν (cm^{-1}) 3210 (NH), 1720 (CO δ-lacton). *Anal.* (C,H,N) for $C_{19}H_{19}N_3O_3$.

3.8.5. 9-Benzyl-8,9-dihydro-7-methyl-8-imino-6H,7H-[1]benzopyrano[3′,4′:5,6]pyrano-[2,3-d]-pyrimidine-6-one (**8d**)

Colourless crystals from benzene, m.p. 255°C, yield 3.04 g (82%). IR: ν (cm^{-1}) 3373 (NH), 1701 (CO δ-lacton). *Anal.* (C,H,N) for $C_{16}H_{13}N_3O_3$.

3.8.6. 3-Cyano-2-dimethylaminomethyleneamino-4-methyl-4H,5H-pyrano[3,2-c][1]-benzopyran-5-one (**9**)

Colourless crystals from benzene, m.p. 250°C, yield 2.47 g (80%). IR: ν (cm^{-1}) 2197 (CN), 1722 (CO δ-lacton). ^{1}H NMR (DMSO-d_6): δ 1.4 (d, 3H, CH_3, $J = 6.6$ Hz), 3.06 (s, 3H, N–CH_3), 3.24 (s, 3H, N–CH_3), 3.48 (q, 1H, pyran CH, $J = 6.6$ Hz), 7.42–8.14 (m, 4H, Ar–H), 8.48 (s, 1H, N=CH). *Anal.* (C,H,N) for $C_{17}H_{15}N_3O_3$.

3.9. Synthesis of triazolopyrimidine derivatives (**10a–g**)

3.9.1. General procedure

A mixture of **8a** (2.96 g, 0.01 mol), triethyl orthoformate (0.01 mol), acetyl chloride (0.01 mol), chloroacetyl chloride (0.01 mol), benzoyl chloride (0.01 mol) and *p*-chlorobenzoyl chloride (0.01 mol) in dry benzene (20 ml) was refluxed for 3 h to give **10a–e**, while a mixture of **8a** (2.96 g, 0.01 mol), ethyl cyanoacetate (0.01 mol) and diethyl oxalate (0.01 mol) in absolute ethanol (20 ml) was refluxed for 3 h to give **10f**,**g**, respectively.

3.9.2. 14-Methyl-13,14H-[1]benzopyrano[3′,4′:5,6]-pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine-13-one (**10a**)

Colourless crystals from DMF, m.p. 278°C, yield 2.66 g (87%). IR: ν (cm^{-1}) 1717 (CO δ-lacton). MS: m/z 306 (M^+, 4.02%), 291 (100%), 264 (5.47), 224 (0.71), 182 (91.73), 145 (2,37), 121 (2.95), 92 (1.16), 69 (0.36). *Anal.* (C,H,N) for $C_{16}H_{10}N_4O_3$.

3.9.3. 2,14-Dimethyl-13H,14H-[1]benzopyrano-[3′,4′:5,6]pyrano[3,2-e][1,2,4]triazolo-[1,5-c]-pyrimidine-13-one (**10b**)

Colourless crystals from DMF, m.p. 305°C, yield 2.50 g (78%). IR: ν (cm^{-1}) 1725 (CO δ-lacton). MS: m/z 320 (M^+, 14.58%), 266 (60), 239 (100%), 185 (24.79), 121 (90.42), 92 (14.58). *Anal.* (C,H,N) for $C_{17}H_{12}N_4O_3$.

3.9.4. 2-Chloromethyl-14-methyl-13H,14H-[1]-benzopyrano[3′,4′:5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine-13-one (**10c**)

Colourless crystals from dioxane, m.p. 276°C, yield 2.37 g (67%). IR: ν (cm^{-1}) 1724 (CO δ-lacton). MS: m/z 354 (M^+, 0.85%), 339 (6.24), 281 (100%), 239 (78.28), 213 (4.6), 187 (9.53), 129 (12.64), 121 (69.99), 92 (15.94), 55 (38). *Anal.* (C,H,N,Cl) for $C_{17}H_{11}ClN_4O_3$.

3.9.5. 14-Methyl-2-phenyl-13H,14H-[1]benzopyrano-[3′,4′:5,6]pyrano[3,2-e][1,2,4]-triazolo[1,5-c]-pyrimidine-13-one (**10d**)

Colourless crystals from dioxane, m.p. 300°C, yield 2.87 g (75%). IR: ν (cm^{-1}) 1719 (CO δ-lacton). ^{1}H NMR (DMSO-d_6): δ 1.37 (d, 3H, CH_3, $J = 6.6$ Hz), 4.22 (q, 1H, pyran CH, $J = 6.6$ Hz), 7.53–7.95 (m, 9H, Ar–H), 8.82 (s, 1H, pyrimidine CH). MS: m/z 382 (M^+, 0.68%), 281 (100%), 239 (71.07), 187 (7.47), 121 (59.67), 92 (14.70). *Anal.* (C,H,N) for $C_{22}H_{14}N_4O_3$.

3.9.6. 2-(p-Chlorophenyl-14-methyl-13H,14H-[1]-benzopyrano[3′,4′:5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine-13-one (**10e**)

Colourless crystals from dioxane, m.p. > 360°C, yield 3.50 g (75%). IR: ν (cm^{-1}) 1723 (CO δ-lacton). *Anal.* (C,H,N) for $C_{22}H_{13}ClN_4O_4$.

3.9.7. 2-Cyanomethyl-14-methyl-13H,14H-[1]-benzopyrano[3′,4′:5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine-15-one ***(10f)***

Colourless crystals from benzene, m.p. 286°C, yield 2.45 g (71%). IR: ν (cm^{-1}) 2262 (CN), 1724 (CO δ-lacton). MS: m/z 345 (M^+, 3.4%), 330 (100%), 290 (1.85), 264 (2.95), 236 (3.27), 185 (3.63), 129 (7.35), 92 (1.90). *Anal.* (C,H,N) for $C_{18}H_{11}N_5O_3$.

3.9.8. 2-Ethoxycarbonyl-14-methyl-13H,14H-[1]-benzopyrano[3′,4′:5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine-13-one ***(10g)***

Colourless crystals from dioxane, m.p. 265°C, yield 2.87 g (76%). IR: ν (cm^{-1}) 1740 (CO ester), 1720 (CO δ-lacton). *Anal.* (C,H,N) for $C_{19}H_{14}N_4O_5$.

3.10. N-[7-Methyl-8-imino-6-oxo-6H,7H-[1]-benzopyrano[3′,4′:5,6]pyrano[2,3-d]-pyrimidyl-9]-carbamic acid ***(12)***

A solution of **8a** (2.96 g, 0.01 mol) and ethyl chloroformate (0.01 mol) in dry benzene (30 ml) was refluxed for 3 h. The solid precipitate was filtered and recrystallized from DMF–ethanol to give colorless crystals, m.p. 295°C, yield 2.38 g (70%). IR: ν (cm^{-1}) 3710–2610 centered at 3092 (NH, COOH, CH stretching), 1663 (CO), 1720 (CO δ-lacton). MS: m/z 340 (M^+, 0%), 296 ($M^+ - CO_2$, 38%), 281 (100%), 267 (44.6), 252 (17.6), 239 (62.4), 121 (53.3), 92 (17.0), 64 (17.9). *Anal.* (C,H,N) for $C_{16}H_{12}N_4O_5$.

3.11. 15-Methyl-3,4-dihydro-2H,14H,15H-[1]-benzopyrano[3′,4′:5,6]pyrano[3,2-d]-pyrimido[1,6-b]-[1,2,4] triazine-3,14-dione ***(14)***

A mixture of **8a** (2.96 g, 0.01 mol), ethyl chloroacetate (0.01 mol), methanol (20 ml) and sodium metal (0.23 g, 0.01 mol) was refluxed for 6 h. The reaction mixture was cooled and poured into cold water. The colorless solid product formed was filtered, washed with cold ethanol, dried and recrystallized from dioxane, m.p. 282°C, yield 2.28 g (68%). IR:ν (cm^{-1}) 3375 (NH), 1665 (amide CO), 1717 (CO δ-lacton). *Anal.* (C,H,N) for $C_{17}H_{12}N_4O_4$.

3.12. 14-Methyl-2,3-dihydro-13-oxo-2H,13H,14H-[1]-benzopyrano[3′,4′:5,6]pyrano-[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine-2-thione ***(15)***

A mixture of **8a** (2.96 g, 0.01 mol), ethanol (30 ml), KOH (0.3 g, 0.01 mol) and carbon disulfide (3 ml) was refluxed for 15 h. After removal of the ethanol, water was added and the alkaline solution was acidified with acetic acid to give pale yellow crystals, recrystallized from dioxane, m.p. 320°C, yield 1.59 g (47%). IR: ν (cm^{-1}) 3390 (NH), 1710 (CO δ-lacton), 1040 (C=S). MS: m/z 338 (M^+, 0%), 266 (60.65), 239 (12.83), 212 (0.88), 185 (12.60), 121 (22.57), 92 (15.14), 55 (100%). *Anal.* (C,H,N) for $C_{16}H_{10}N_4O_3S$.

3.13. Synthesis of 9-arylmethylideneamino-8,9-dihydro-8-imino-7-methyl-6H,7H-[1]benzopyrano[3′,4′:5,6]-pyrano[2,3-d]pyrimidine-6-one ***(16a–c)***

3.13.1. General procedure

A mixture of **8a** (2.96 g, 0.01 mol), benzaldehyde, *p*-chlorobenzaldehyde or *p*-anisaldehyde (0.01 mol), piperidine (0.05 ml) and dioxane (30 ml) was refluxed for 6 h. The solid precipitate was filtered and recrystallized from the appropriate solvent.

3.13.2. 8-Imino-7-methyl-9-phenylmethylideneamino-8,9-dihydro-6H,7H-[1]benzo-pyrano[3′,4′:5,6]-pyrano[2,3-d]pyrimidine-6-one ***(16a)***

Colourless crystals from dioxane, m.p. 245°C, yield 3.10 g (81%). IR: ν (cm^{-1}) 3298 (NH), 1701 (CO δ-lacton). ^{1}H NMR (DMSO-d_6): δ 1.37 (d, 3H, CH_3, $J = 6.4$ Hz), 4.63 (q, 1H, pyran CH, $J = 6.4$ Hz), 7.46–7.92 (m, 9H, Ar–H), 8.33 (s, 1H, N=CH), 8.41 (s, 1H, pyrimidine CH), 11.42 (br, 1H, C=NH). *Anal.* (C,H,N) for $C_{27}H_{16}N_4O_3$.

3.13.3. 9-p-Chlorophenylmethylideneamino-8-imino-7-methyl-8,9-dihydro-6H,7H-[1]-benzopyrano[3′,4′:5,6]-pyrano[2,3-d]pyrimidine-6-one ***(16b)***

Colourless crystals from dioxane, m.p. 280°C, yield 3.47 g (83%). IR: ν (cm^{-1}) 3290 (NH), 1699 (CO δ-lacton). *Anal.* (C,H,N) for $C_{22}H_{15}ClN_4O_3$.

3.13.4. 9-p-Methoxyphenylmethylidenamino-8-imino-7-methyl-8,9-dihydro-6H,7H-[1]benzopyrano[3′,4′:5,6]-pyrano[2,3-d]pyrimidine-6-one ***(16c)***

Colourless crystals from dioxane, m.p. 276°C, yield 3.52 g (85%). IR: ν (cm^{-1}) 3211 (NH), 1715 (CO δ-lacton). *Anal.* (C,H,N) for $C_{23}H_{18}N_4O_4$.

4. Biological screening

4.1. Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against four species of bacteria, Gram positive bacteria namely *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579) and gram negative bacteria *Serratia marcescens* (IMRU-70) and *Proteus mirabilis* (NTCC-289) using Ampicillin (25 μg) as reference compound [21].

The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1% concentration. Filter paper discs (Whatman No. 3 filter paper, 5 mm diameter) were saturated with former

Table 1
Antibacterial activity of some compounds

Comp.	*Staphylococcus aureus* (NCTC-7447)	*Bacillus cereus* (ATCC-14579)	*Serratia marcescens* (IMRU-70)	*Proteus mirabilis* (NTCC-289)
3	18	19	18	20
5a	20	21	23	20
6	21	22	20	19
7	19	15	14	16
8b	18	17	19	19
9	19	18	20	19
10c	20	22	21	20
10d	20	22	20	19
12	22	18	23	20
14	20	22	21	22
15	22	23	23	25
16b	19	20	24	22
16c	22	24	23	22
Ampicillin [a] (25 μg)	26	25	26	27

[a] Paper discs manufactured by Bristol–Myers Squibb, Giza, Egypt.

solution. The saturated filter paper discs were placed on the nutrient agar (Difco) dishes seeded by test bacteria. The inhibition zone was measured in mm at the end of an incubation period of 48 h at 28°C. *N*,*N*-Dimethylformamide (DMF) showed no inhibition zone. The results are illustrated in Table 1.

4.2. Antifungal activity

The newly synthesized compounds were screened for their antifungal activity against two species of fungi, *Aspergillus ochraceus Wilhelm* (AUCC-230) and *Penicillium chrysogenum Thom* (AUCC-530) using the Mycostatine (30 μg) as reference compound [22].

Table 2
Antifungal activity of some compounds

Comp.	*Aspergillus ochraceus Wilhelm* (AUCC-230)	*Penicillium chrysogenum Thom* (AUCC-530)
3	16	18
5a	13	13
6	14	12
7	13	12
8b	19	15
9	19	17
10c	18	19
10d	19	17
12	19	17
14	20	19
15	18	16
16b	16	16
16c	17	18
Mycostatine [a] (30 μg)	22	24

[a] Paper discs manufactured by Bristol–Myers Squibb, Giza, Egypt.

The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1% concentration. Filter paper discs (Whatman No. 3 filter paper, 5 mm diameter) were saturated with former solution. The saturated filter paper discs were placed on the Glucose–Czapek's agar medium (Difco) dishes seeded by test fungi. The inhibition zone was measured in mm of the end of an incubation period of 48 h at 28°C. *N*,*N*-Dimethylformamide (DMF) showed no inhibition zone. The results are illustrated in Table 2.

5. Conclusions

From the biological assay it was found that compounds containing pyrimidine moiety (**5a**,**6**,**8b**,**12**,**16**) and compounds containing both pyrimidine and triazole or triazine moieties (**10c**,**d**,**14**,**15**) were found to be the most active compounds against *S. aureus*, *B. cereus*, *S. marcescens* and *P. mirabilis* compared to Ampicillin, while compounds containing the pyran moiety (**3**,**7**,**9**) were found to be active against *S. aureus*, *P. mirabilis* and showed moderate active against the others species of bacteria. In addition compound (**8b**,**9**,**10c**,**d**,**12**,**14**) were to be the most active compound against *A. ochraceus Wilhelm* and *P. chrysogenum Thom* compared to Mycostatine, while the other compounds showed moderate activity against *A. ochraceus Wilhelm* and *P. chrysogenum Thom*.

References

[1] M.P. Georgiadis, E.A. Cauladouros, A.K. Delitheos, Synthesis and antimicrobial properties of 2*H*-pyran-3(6*H*)-one derivatives and related compounds, J. Pharm. Sci. 81 (1992) 1126–1131.

. [2] (a) J. Zamocka, E. Misikova, J. Durinda, Study of the preparation, properties and effect of (5-hydroxy)- or (5-methoxy-4-oxo-4*H*-pyran-2-yl)methyl-2-alkoxycarbanilates, Cesk-Farm (Ceska a Slovenska Farmacie) 41 (1992) 170–172. (b) J. Zamocka, E. Misikova, J. Durinda, Study of the preparation, properties and effect of (5-hydroxy)- or (5-methoxy-4-oxo-4*H*-pyran-2-yl)methyl-2-alkoxycarbanilates, Chem. Abstr. 116 (1992) 106031q.

[3] (a) T. Ohira, M. Yatagai, Extractives of *Abies mariesii* Masters II. The efficient extraction of maltol using supercritical fluid and its antifungal and plant growth regulation effects, J. Jpn. Wood Res. Soc. 39 (1993) 237–242. (b) T. Ohira, M. Yatagai, Extractives of *Abies mariesii* Masters II. The efficient extraction of maltol using supercritical fluid and its antifungal and plant growth regulation effects, Chem. Abstr. 119 (1993) 19585d.

[4] S.J. Mohr, M.A. Chirigos, F.S. Fuhrman, J.W. Pryor, Pyran copolymer as an effective adjuvant to chemotherapy against a murine leukemia and solid tumor, Cancer Res. 35 (1975) 3750–3754.

[5] F. Eiden, F. Denk, Synthesis and CNS activity of pyran derivatives: 6,8-dioxabicyclo(3,2,1)octanes, Arch Pharm. Weinheim Ger. (Arch. Pharm.) 324 (1991) 353–354.

[6] V.K. Tandon, M. Vaish, S. Jain, D.S. Bhakuni, R.C. Srimal, Synthesis, ^{13}C NMR and hypotensive action of 2,3-dihydro-2,2-dimethyl-4*H*-naphtho[1,2-*b*]pyran-4-one, Indian J. Pharm. Sci. 53 (1991) 22–23.

[7] K. Gorlitzer, A. Dehre, 1,3-Dicarbonyl compounds. Part 22: 3-Acyl-4*H*[1]benzofuro[3,2-*b*]pyran-4-ones, Arch Pharm. Weinheim Ger. (Arch. Pharm.) 317 (1984) 526–530.

[8] A. Bargagna, M. Longobardi, E. Mariani, P. Schenone, E. Marmo, 2*H*,5*H*-[1]Benzothiopyrano[4,3-*b*]pyran derivatives with platelet antiaggregating activity, Farmaco 45 (1990) 405–413.

[9] A. Bargagna, M. Longobardi, E. Mariani, P. Schenone, E. Marmo, Benzo[6,7]cyclohepta[1,2-*b*]pyran derivatives with platelet antiaggregating and other activities, Farmaco 46 (1991) 461–475.

[10] A. Bargagna, M. Longobardi, E. Mariani, P. Schenone, C. Falzarano, Cyclohepta(*b*)pyran derivatives with platelet antiaggregating and other activities, Farmaco 47 (1992) 345–355.

[11] K. Gorlitzer, A. Dehre, E. Engler, 2-(1*H*-Tetrazol-5-yl)-4,5-dihydroindeno-[1,2-*b*]pyran-4-one, Arch Pharm. Weinheim Ger. (Arch. Pharm.) 316 (1983) 264–270.

[12] A. Ermili, G. Roma, M. Buonamici, A. Cuttica, M. Galante, Psychopharmacological study with K-8409, a 1*H*-naphtho[2,1-*b*]pyran 3-dialkylamino substituted derivative, Farmaco Ed. Sci. 34 (1979) 535–544.

[13] (a) C.P. Dell, C.W. Smith, Antiproliferative derivatives of 4*H*-naphtho[1,2-*b*]pyran and process for their preparation, European Patent Appl. EP 537949. (b) C.P. Dell, C.W. Smith, Antiproliferative derivatives of 4*H*-naphtho[1,2-*b*]pyran and process for their preparation, Chem. Abstr. 119 (1993) 139102d.

[14] (a) M. Brunavs, C.P. Dell, P.T. Gallagher, W.M. Owton, C.W. Smith, 4*H*-Naphtho[1,2-*b*]pyran cell Antiproliferation agents, European Patent Appl. EP 557075. (b) M. Brunavs, C.P. Dell, P.T. Gallagher, W.M. Owton, C.W. Smith, 4*H*-Naphtho[1,2-*b*]pyran cell antiproliferation agents, Chem. Abstr. 120 (1994) 106768t.

[15] A.M. El-Agrody, Activated nitriles in heterocyclic synthesis: synthesis of several new naphtho[2,1-*b*]pyran-3-one derivatives, J. Chem. Res. (S) (1994) 50–51.

[16] A.M. El-Agrody, Condensation reactions of α-cyanocinnamonitriles with naphthols: synthesis of naphthopyranopyrimidines and a naphthopyranone, J. Chem. Res. (S) (1994) 280–281.

[17] A.M. El-Agrody, S.M. Hassan, Activated nitriles in heterocyclic synthesis: synthesis of several new 2-substituted pyrano-1,2,4-triazolopyrimidine derivatives, J. Chem. Res. (S) (1995) 100–101.

[18] (a) A.M. El-Agrody, H.A. Emam, M.H. El-Hakim, M.S. Abd El-Latif, A.H. Fakery, Activated nitriles in heterocyclic synthesis: synthesis of several new 2-substituted of pyrano[2,3-*d*]pyrimidine and pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives, J. Chem. Res. (S) (1997) 320–321. (b) A.M. El-Agrody, H.A. Emam, M.H. El-Hakim, M.S. Abd El-Latif, A.H. Fakery, Activated nitriles in heterocyclic synthesis: synthesis of several new 2-substituted of pyrano[2,3-*d*]pyrimidine and pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives, J. Chem. Res. (M) (1997) 2039–2048.

[19] A.M. El-Agrody, M.S. Abd El-Latif, A.H. Fakery, A.H. Bedair, Heteroaromatization with 4-hydroxycoumarin. Part I: Synthesis of some new pyranocoumarins and coumarinopyranopyrimidines, J. Chem. Res. (S) (2000) 26–27

[20] A.S. Aly, N.M. Fathy, S.A. Swelam, F.M.E. Adel-Megeid, Synthesis of furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and furo[3,2-*e*]pyrimido[4,3-*f*]-[1,2,4]triazin-3-one: a new ring system, J. Pharm. Sci. 36 (1995) 1577–1586.

[21] W. Hewitt, S. Vincent, Theory and Application of Microbiological Assay, Academic, New York, 1989.

[22] A. Cremer, Antibiotic Sensitivity and Assay Tests, fourth ed., Butterworth, London, 1980, p. 521.