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ORIGINAL ARTICLE

Synthesis and biological activities of some fused pyran derivatives

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KEYWORDS

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Aminopyrancarbonitrile;
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Abstract Ethyl benzoylacetate (**1**) reacted with 2-benzylidenemalanonitrile to afford the corresponding pyrane derivative (**2**). The latter compound reacted with 2-benzylidenemalanonitrile, carbon disulfide, formamide and benzylidene cyclohexanone, respectively, to afford the corresponding pyrano derivatives **(3–6)**. Compound **2** reacted with ethyl chloroacetate to give compound **(8)** which cyclized to compound **(9)** in the presence of sodium ethoxide. Treatment of compound **(2)** with acetic acid in the presence of sulfuric acid afforded compound (**7**) which converted to compound **(10)** when reacted with ethylchloroacetate. Compound **(10)** reacted with sodium ethoxide to give compound **(11)**. The structure of the newly synthesized compounds has been established on the basis of their analytical and spectral data.

1. Introduction

The 4*H*-Pyran nucleus is a fertile source of biologically important molecules possessing a wide spectrum of biological and pharmacological activities, such as antimicrobial (Khafagy et al., 2002), antiviral (Smith et al., 1998; Martinez and Marco, 1997), mutagenicity (Hiramoto et al., 1997), antiproliferative (Dell and Smith, 1993), sex pheromone (Bianchi and Tava, 1987), antitumor (Mohr et al., 1975), cancer therapy (Skommer et al., 2006; Anderson et al., 2005; Wang et al., 2000) and central nervous system activity (Eiden and Denk, 1991). Some of these compounds are widely employed as cosmetics and pigments and as potential biodegradable agrochemicals (Hafez et al., 1987). Therefore, the synthesis of such compounds has attracted strong interest. In recent years, 4-functionally substituted 1,3-diarylpyrazole derivatives have received considerable attention due to their wide range of useful biological properties, which include antimicrobial (Damljanovic et al., 2009; Damljanovic et al., 2009; Prakash et al., 2008, 2009; Bekhit et al., 2003, 2008; Bekhit and Abdel-Aziem, 2004; Bekhit and Fahmy, 2000; Chovatia et al., 2007), anti-inflammatory (COX-2 inhibitor and ulcerogenic activity) (Bekhit et al., 2003, 2008; Bekhit and Abdel-Aziem, 2004; Bekhit and Fahmy, 2000), antitubercular (Chovatia et al., 2007), antitumor (Fahmy et al., 2002; Abadi et al., 2003), antiangiogenesis (Abadi et al., 2003), anti-parasitic (Rathelot et al., 2002) and antiviral activity (Hashem et al., 2007; Farghaly and El-Kashef, 2006; Farghaly et al., 2006).

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2. Result and dissection

Benzylidenemalononitrile was reacted with ethyl benzoylacetate **1** in refluxing ethanol catalyzed by piperidine to afford a yellow solid of compound **2** (Elnagdi et al., 1987; Al-Matar et al., 2008) (Scheme 1).

Mass spectrum of this product showed *m/e* 346.38. The IR spectrum showed absorption bands at 3410–3326 (NH_2), 2196 (CN) and 1680 (C=O) cm^{-1}. ^1H NMR spectrum revealed a broad singlet (NH_2) at 7.38. On the basis of these data, the pyran derivative **2** was assigned to this product.

The mechanism for the formation of the pyran derivatives **2** is outlined in Scheme 2. The reaction occurs via an insituinitial formation of the benzylidinemalononitrile, containing C=C double bond which reacts with ethylbenzoylacetate by Michel addition, cycloaddition, isomerization, aromatization to afford6-Amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylic acid ethyl ester **2**.

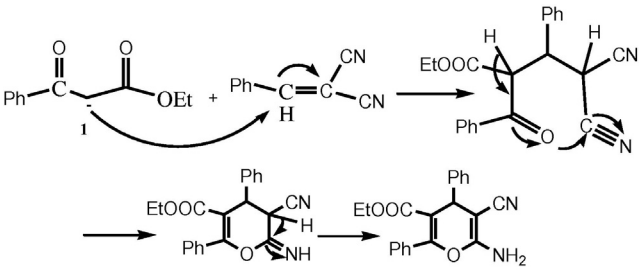
6-Amino-5-cyano-2,4-diphenyl-4H-pyran-3-carboxylic acid ethyl ester **2** underwent nucleophilic addition with benzylidenemalononitrile in refluxing piperidene to afford Ethyl 5-amino-6-cyano-2,4,7-triphenyl-4H-pyrano [2,3-b] pyridine-3-carboxylate **3** in a good yield. The structure of **3** was confirmed on the basis of elemental analysis. The IR spectrum showed absorption bands at 3411 (NH_2) and 2198 cm^{-1} (CN). The formation of **3** is assumed to occur via initial formation of the Michael addition of the amino group in compound **2** to activate the double bond in benzylidenemalononitrile followed by intramolecular cyclization, then it loses hydrogen cyanide to afford compound **3** (Al-Omran et al., 2002; Al-Omran and El-Khair, 2004; El-Khandeel, 1996) (Scheme 3).

Compound **2** was reacted with carbon disulfide in ethanol in the presence of pyridine to give the cyclized compound **4.** This structure was confirmed by IR which revealed absorption bands corresponding to the 2NH and C=S functions and also compound **2** was cyclized to give the corresponding Ethyl 4-amino-5,7-diphenyl-5H-pyrano [2,3-d] pyrimidine-6-carboxylate **5** on treatment with formamide.

Compound **2** was reacted with (*E*)-2-benzylidenecyclohexanone in the presence of piperidine to afford the corresponding Ethyl 5-amino-9-benzylidene-2,4-diphenyl-6,7,8,9-tetrahydro-4H-pyrano [2,3-b] quinoline-3-carboxylate **6**.

Ring transformation of **2** by sulfuric acid in the presence of acetic acid under analogous reaction conditions regioselectively provided Ethyl 5-cyano-6-hydroxy-2,4-diphenyl-1,4-dihydropyridine-3-carboxylate **7** in good yields.

The cyclocondensation of compounds **2** and **7** with ethyl chloroacetate was performed in N,N-dimethylformamide in the presence of catalytic amount of potassium carbonate and to give the corresponding compounds **8** and **10** respectively, which were readily cyclized to the corresponding pyran derivatives **9** and **11** respectively Schemes 4 and 5. Similarly, all these compounds were characterized on the basis of spectral studies. All spectroscopic data have been given in experimental section. All the compounds were screened for their antibacterial and antifungal activities.



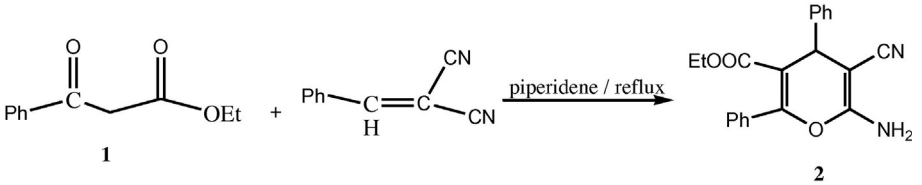
Scheme 2 Plausible mechanistic pathway of the synthesis of pyran derivatives **2**.

3. Antimicrobial activity

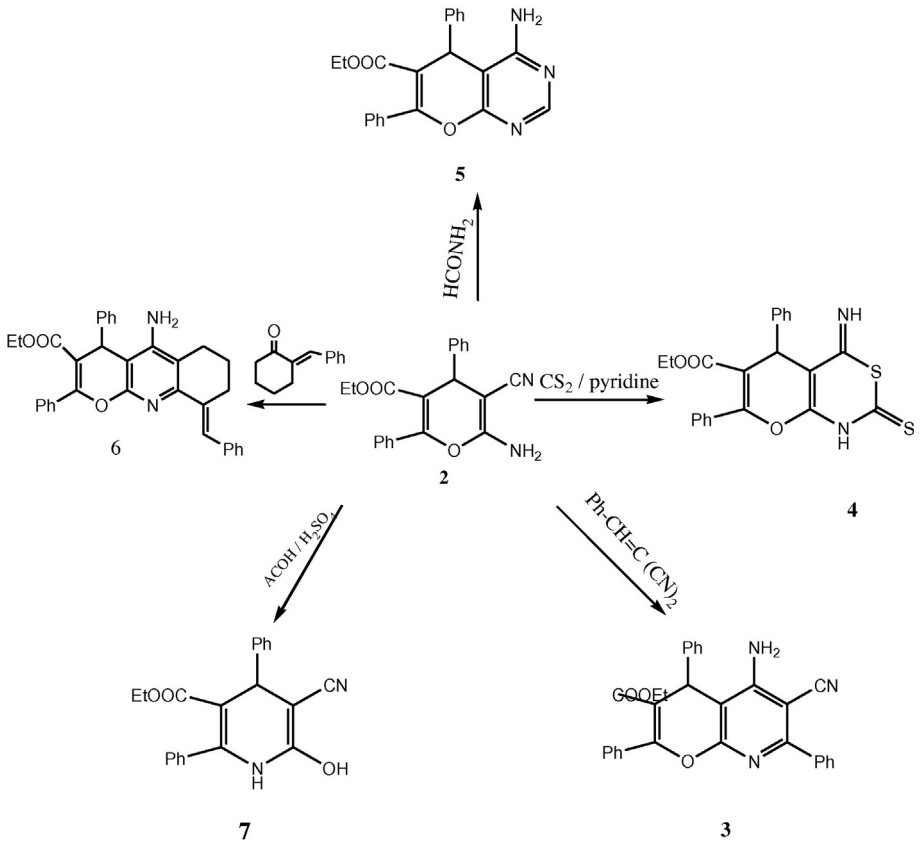
The activity of the synthesized products was tested by the disk diffusion method. The cup-plate technique was used for the determination of these antimicrobial effects. Antibacterial and antifungal assays using a method Whatman No. 4 filter paper discs (0.5 cm diameter) were soaked in the tested sample. The samples of compounds were dissolved in DMSO. 0.24 μg of each sample was dissolved in 0.1 ml DMSO, then 0.1 ml of each sample was used with some gram positive bacteria such as (*Sarcina lutea*, *Staphylococcusaureus* and *Bacillus subtilis)*, gram negative bacteria such as (*Pseudomonas aeuroginosa*, *Escherichia coli*, *Agrobacterium* and *Erwinia* sp.) and fungal (*Aspergillus niger*, *Penicillium funiculosum)* under aseptic conditions. The medium for cultivation of test organisms was nutrient agar, and the petri-dishes were incubated at 30 °C for 24 h. The results were recoded by measuring the inhibition zones caused by various compounds on the microorganisms. Activity of each compound was compared with ciprofloxacin and sulfametoxazol as standards (Davis et al., 1996; Raman et al., 2001). These results are summarized in Table 1. From the results obtained, it is obvious that most of the tested compounds posses slight or no activity at all toward the tested microorganisms. However, some compounds showed considerable activity against the tested bacteria like **7, 9** and **11**. Others exhibit moderate or slight activity against fungi such as **2** and **3**.

4. Experimental section

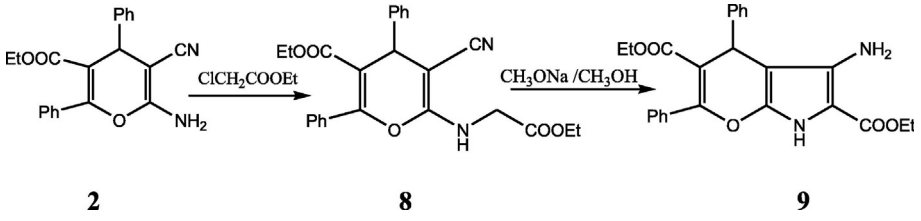
All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr



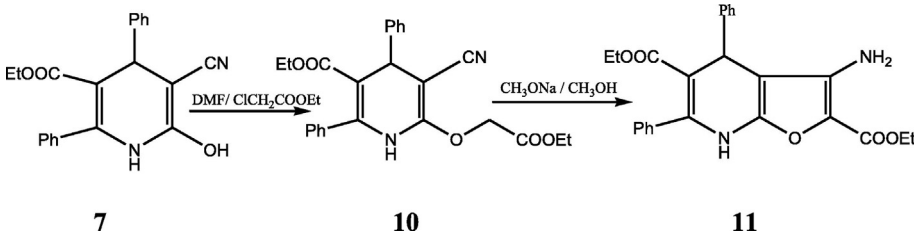
Scheme 1 Synthesis pathway for the preparation of compound **2**.



Scheme 3 Synthetic pathway for the preparation of compounds **3–7**.



Scheme 4 Synthetic pathway for the preparation of compounds **8** and **9**.



Scheme 5 Synthetic pathway for the preparation of compounds **10** and **11**.

discs) on a Shimadzu FT-iR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in DMSO on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in 8 units using TMS as an internal reference, mass spectra were recorded on a GC–MS QPIOOO EX Shimadzu. Elemental analyses were carried out at the Micro analytical Center of the Cairo University.

*4.1. 6-Amino-5-cyano-2,4-diphenyl-4H-pyran-3-ethylcarboxylate (**2**)*

A mixture of benzylidene malononitrile (1.54 g, 0.1 mol) with ethyl benzoylacetate **1** (1.39 g, 0.1 mol) in the presence of piperidine was refluxed for 4 h. The solid product, so formed, was filtered of and recrystallized from ethanol. This compound

Table 1 Antimicrobial activity of the compounds considered.

Compound	Microorganisms**				
	1	2	3	4	5
2	+	+	+	–	–
3	+	+	–	–	–
7	+ + +	–	+	+	+ +
9	–	+ +	+	+	–
11	+ + +	+	+	+	+ +
Sulfametoxazol	+ + +	+	+ +	+ +	+ + +
Ciprofloxacin	+ + +	+ +	+ + +	+	+ + +

The solvent is dimethylsulphoxide (DMSO).
** 1: *Stphylococcus aureus*. 2: *Pseudomonas aeuroginosa*. 3: *Bacillus subtilis*. 4: *Aspergillus niger*. 5: *Penicillium funiculosum*.
+ + +: Highly active. + +: Moderately active. +: Slightly active.
–: Inactive

was obtained as yellow crystals. Yield 78%; m.p. 262–264 °C IR (KBr): 1680 (C═O), 2196 (CN), 3326, 3410 (NH_2) cm^{-1}, ^1H NMR (DMSO-d_6): δ 0.76 (t, 3H, ester CH_3), 3.77 (q, 2H, CH_2), 7.38 (s, 2H, NH_2), 7.25–7.42 (m, 10H, Phenyl). Analysis calculated for ($C_{21}H_{18}N_2O_3$; 346.38) C, 72.82; H, 5.24; N, 8.09. Found; C, 72.63; H, 5.02; N, 7.98.

*4.2. Ethyl 5-amino-6-cyano-2,4,7-triphenyl-4H-pyrano [2,3-b] pyridine-3-carboxylate (**3**)*

A mixture of **2** (3.48 g, 10 mmol) and 2-benzylidenemalononitrile (1.54 g, 10 mmol) in piperidine (20 mL) was refluxed for 4 h. The reaction mixture was then allowed to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from ethanol as pale yellow crystals, 3.11 g (71%), mp. 188–190 °C; IR (KBr): 3411–3290 (NH_2), 2198 (CN), 1679 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.97 (t, 3H, CH_3), 3.56 (q, 2H, CH_2), 7.20–8.14 (m, 15H, Ar-H), 8.20 (brs, 2H, NH_2). Analysis calculated for $C_{30}H_{23}N_3O_3$ (473.52) C, 76.09; H, 4.90; N, 8.87. Found: C, 76.19; H 4.65; N, 8.65.

*4.3. Ethyl 4-imino-5,7-diphenyl-2-thioxo-1,2,4,5-tetrahydropyrano [2,3-d] [1,3] thiazine-6-carboxylate (**4**)*

A mixture of **2** (10 mmol) in dry pyridine (15 ml) and CS_2 (0.76 g, 10 mmol) was refluxed on a water bath for 9 h. The reaction mixture was poured into cooled water and neutralized with dil. HCl. The solid product was collected by filtration, washed with water dried and crystallized from benzene to afford (73% of 4); m.p. 232–236 °C. IR (KBr):3318 (NH), 1578 (C═N), 1280 (C═S), 1722 (C═O) cm^{-1}; ^1H NMR (DMSO-d6): δ 0.983 (t, 3H, ester CH_3), 3.98 (q, 2H, CH_2), 3.37 (s, 1H, 4-H), 6.95 (brs, NH, exchangeable), 7.15–7.32 (m, 10H, Phenyl), 9.08 (brs, NH, exchangeable). Analysis calculated for $C_{22}H_{20}N_2O_3S_2$ (422.52) C, 62.54; H, 4.29; N, 6.63; S, 15.18. Found. C, 62.35; H, 4.73; N, 6.62; S, 15.08.

*4.4. Ethyl 4-amino-5,7-diphenyl-5H-pyrano [2,3-d] pyrimidine-6-carboxylate (**5**)*

A mixture of compound **2** in dry ethanol and formamide (10 ml) was refluxed for 4 h. The precipitate was collected by filtration and recrystallized from ethanol to give **5**. Yield 65%; IR (KBr): 3411–3326 (NH_2), 1610 (C═N), 1678 (C═O) cm^{-1}; ^1H NMR (DMSO-d6): δ: 1.03 (t, 3H, ester CH_3), 3.98 (q, 2H, CH_2), 3.36 (s, 1H, 4-H), 7.05 (s, 2H, NH_2), 7.05–7.32 (m, 10H, Phenyl). Analysis calculated for $C_{22}H_{19}N_3O_3$ (373.4); C, 70.76; H, 5.13; N, 11.25. Found: C, 70.73; H, 5.02; N, 11.03.

*4.5. Ethyl 5-amino-9-benzylidene-2,4-diphenyl-6,7,8,9-tetrahydro-4H-pyrano [2,3-b] quinoline-3-carboxylate (**6**)*

A mixture of (*E*)-2-benzylidenecyclohexanone (1.54 g, 0.1 mol) with compound **2** (0.1 mol) in 50 ml ethanol in the presence of piperidene was refluxed for 3 h. The solid product, so formed, was filtered off and recrystallized from ethanol to give 87% yield; m.p. 234–231 °C. IR (KBr): 3429–3336 (NH_2), 1618 (CN), 1543 (C═C) cm^{-1}; ^1H NMR (DMSO-d6): δ 0.96 (t, 3H, ester CH_3), 1.96 (s, 6H, $3CH_2$), 2.98 (q, 2H, CH_2), 4.35 (s, 1H, 4-H), 6.83 (s, 2H, NH_2), 7.25–7.32 (m, 10H, Phenyl). Analysis calculated for $C_{34}H_{30}N_2O_3$ (514.61); C, 79.35; H, 5.88; N, 5.44. Found: C, 79.39; H, 6.09; N, 5.47.

*4.6. Ethyl 5-cyano-6-hydroxy-2,4-diphenyl-1,4-dihydropyridine-3-carboxylate (**7**)*

To a solution of pyran **2** (0.1 mol) in 30 ml glacial acetic acid was added 1 ml of concentrated sulfuric acid and the mixture was refluxed for 1 h, then left to cool. The precipitated solid was filtered off and recrystallized to afford (85% of 7) m.p. 296–298 °C IR (KBr): 3326–3425 (OH, NH), 2200 (CN), 1705 (C═O) cm^{-1}; ^1H NMR (DMSO-d6): δ 0.93 (t, 3H, ester CH_3), 3.98 (q, 2H, CH_2), 4.39 (s, 1H, 4-H), 6.95 (s, H, NH), 7.15–7.32 (m, 10H, Phenyl), 11.24 (s,1H, OH). Analysis calculated for ($C_{21}H_{18}N_2O_3$ (346.38) C, 72.82; H, 5.24; N, 8.09. Found: C, 72.80; H, 5.11; N, 8.13.

*4.7. Ethyl 5-cyano-6-(2-ethoxy-2-oxoethylamino)-2,4-diphenyl-4H-pyran-3-carboxylate (**8**)*

A solution of **2** (0.1 mol) in 250 ml dry N,N-dimethylformamide was heated at 80–85 °C with ethyl chloroacetate (0.11 mol) in an oil bath in the presence of anhydrous potassium carbonate (0.11 mol). The reaction mixture was cooled and poured onto ice water A pale yellow crystalline solid was separated filtered, washed thoroughly first with cold water and then with cold ethanol, recrystallized from 95% ethanol, yield 70% m.p. 220–222 °C IR (KBr): 3120 (NH), 2197 (CN), 1713 (2 CO) cm^{-1}; ^1H NMR (DMSO-d6): δ1.03 (2t, 6H, ester $2COOCH_3$), 3.98 (2q, 4H, $2CH_2$), 3.30 (s, 1H, 4-H), 2.17 (s, 2H,CH_2), 6.75 (s, 1H, NH), 7.21–7.32 (m, 10H, Phenyl). Analysis calculated for $C_{25}H_{24}N_2O_5$ (432.47) C, 69.43; H, 5.59; N, 6.48. Found: C, 69.49; H, 5.56; N, 6.44.

*4.8. Diethyl 5-amino-2,4-diphenyl-4,7-dihydropyrano [2,3-b] pyrrole-3,6-dicarboxylate (**9**)*

A sample of compound **8** (0.01 mol) in sodium methoxide (0.23 Na/30 mL methanol) was heated under reflux for 2 h, and then allowed to cool. The solid product was collected by filtration, washed with water, and recrystallized to give **9**; yield

67%; m.p. 297–299 °C IR (KBr): 3330 (NH_2). 1706 (C═O); ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 6H, $2CH_3$), 2.28 (s, 1H, H-4), 3.65 (q, 2H, CH_2), 5.78 (s, 1H, NH), 6.86 (brs, 2H, NH_2), 7.14–7.26 (m, 10H, phenyl); Analysis calculated for $C_{26}H_{27}N_2O_5$ (447.5): C, 69.78; H, 6.08; N, 6.26. Found: C, 69.73; H, 6.17; N, 6.01.

*4.9. Ethyl 5-cyano-6-(2-ethoxy-2-oxoethoxy)-2,4-diphenyl-1,4-dihydropyridine-3-carboxylate (**10**)*

This was prepared by the same conditions used for the above prepared compound. The product was crystallized from ethanol to give **10**. IR (KBr): 3326 (NH), 1708 (2 CO) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 0.93 (2 t, 6H, ester $2CH_3$), 3.78 (2 q, 4H, $2CH_2$), 4.21 (s, 1H, 4-H), 6.91 (s, 1H, NH), 7.15–7.32 (m, 10H, Phenyl). Analysis calculated for ($C_{25}H_{24}N_2O_5$: 432.47) C, 69.43; H, 5.59; N, 6.48. Found: C, 69.37; H, 6.09; N, 6.50.

*4.10. Diethyl 3-amino-4,6-diphenyl-4,7-dihydrofuro [2,3-b] pyridine-2,5-dicarboxylate (**11**)*

This was prepared by the same conditions used for the above prepared compound **9**. The product was crystallized from ethanol to give (76% of 11); m.p. 278–280. IR (KBr): 3411–3326 (NH_2), 1718 (CO) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 0.73 (2t, 6H, ester $2CH_3$), 3.88 (2q, 4H, $2CH_2$), 3.64 (s, 1H, 4-H), 5.76 (s, 1H, NH), 6.95 (s, 2H, NH_2), 7.15–7.32 (m, 10H, Phenyl). Analysis calculated for $C_{26}H_{27}N_2O_5$ (447.5) C, 69.78; H, 6.08; N, 6.26. Found: C, 69.76; H, 6.09; N, 6.29.

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