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Synthesis and antimicrobial activities of novel naphtho[2,1-*b*]pyran, pyrano[2,3-*d*]pyrimidine and pyrano[3,2-*e*][1,2,4]triazolo[2,3-*c*]-pyrimidine derivatives

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Abstract

The synthesis of new naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidines and related heterocycles has been reported. The key intermediate 3-amino-8-bromo-1-(*p*-methoxyphenyl)-1*H*-naphtho[2,1-*b*] pyran-2-carbonitrile (**3c**) was obtained in one pot synthesis by treating α-cyanocinnamonitrile (**1c**) with 6-bromo-2-naphthol (**2**). Antimicrobial activity was shown for some of the synthesized compounds.

Keywords: Naphthopyrans; Pyranopyrimidines; Pyranotriazolopyrimidines; Antimicrobial activities

1. Introduction

Pyrans and fused pyrans are biologically interesting compounds with antibacterial activities [1,2], antifungal activities [3], antitumor activity [4] and hypotensive effect [5]. On the other hand, some pyran derivatives also have various biological properties like antiproliferation effect [6], molluscicidal activities [7], local anesthetic and antiarrhythmic activities [8], antiallergic effect [9,10] and hypolipidemic activity [11]. The present study is part of our program aimed at developing new approaches for the synthesis of fused heterocyclic systems. We reported here the synthesis of naphtho[2,1-*b*]pyran derivatives and their utility as building blocks in the synthesis of novel fused pyrans to evaluate the antimicrobial activity.

2. Chemistry

In continuation of our previous work [12–16] on the synthesis of fused pyrans using enaminonitriles, we report here the synthesis of a variety of new heterocyclic compounds. Thus, condensation of various substituted α-cyanocinnamonitriles (**1a**–**f**) with 6-bromo-2-naphthol (**2**) in ethanolic piperidine afford 1:1 adducts [12,14]. Structure **3** (Scheme 1) was established on the basis of the ^{1}H NMR spectra, which showed 1-*H* at δ 5.27–5.51 ppm (**3a**–**f**). The increased chemical shift for this signal, compared to the expected value (δ 4.0–5.0 ppm) for such protons, can be attributed to the deshielding effect of the diamagnetic current of the naphthyl, aryl and allylic π-electrons [17–19]. The UV spectrum of **3a**–**f** revealed a weak shoulder [14,20], characteristic for 4*H*-pyran, at λ_{max} (CH_3COCH_3) 275 nm (log ε 2.80–2.86) (**3a**–**f**), respectively.

Interaction of 3-amino-8-bromo-1-(*p*-methoxyphenyl)-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (**3c**) with aromatic aldehydes in dioxane–piperidine under reflux gave the corresponding 3-arylmethyleneamino derivatives **4a**–**c** (Scheme 1). When 8-bromo-1-(*p*-methoxyphenyl)-3-phenylmethyleneamino-1*H*-naphtho-[2,1-*b*]pyran-2-carbonitrile (**4a**) was treated with hydrazine hydrate or phenyl hydrazine in ethanol at room temperature or reflux, an addition product formed (**5**), from which elimination of benzaldehyde hydrazone and

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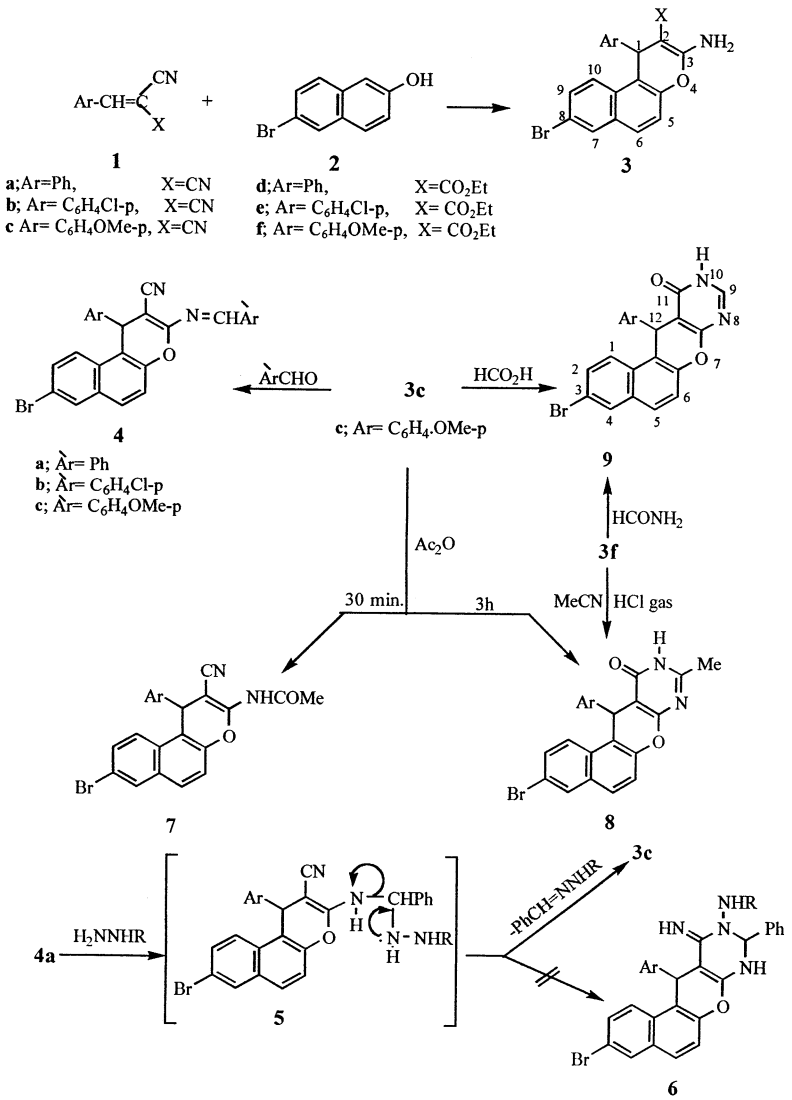
benzaldehyde phenylhydrazone, respectively, gave the enaminonitrile **3c** [14,21] instead of the pyrimidine derivative **6**. Treatment of **3c** with acetic anhydride for 30 min afforded the *N*-acetyl derivative **7**, while heating of **3c** with acetic anhydride under reflux for 3 h afforded the naphthopyranopyrimidin-11-one **8**. Structure **8** is supported by an independent synthesis of the same product from **3f** and acetonitrile in the presence of HCl gas [22] (Scheme 1).

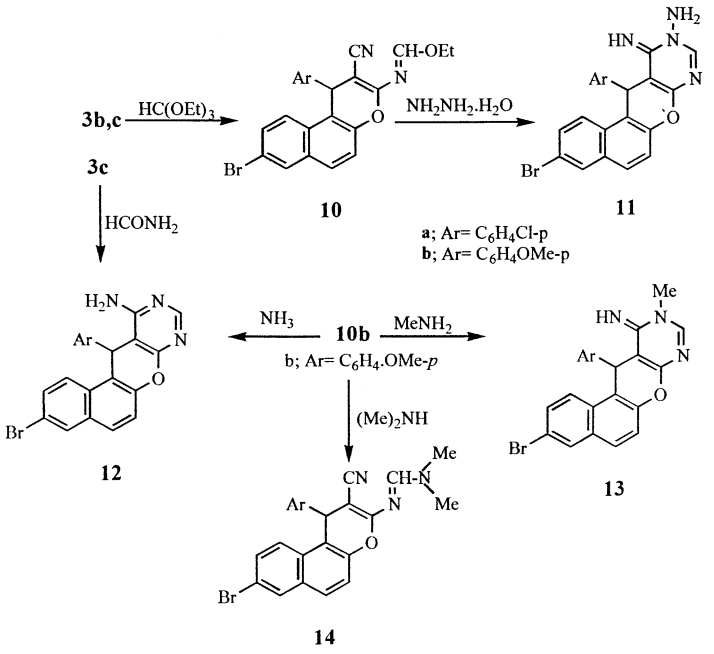
Reaction of **3c** with formic acid gave the naphthopyranopyrimidin-11-one derivative **9**. The structure of **9** was supported by an independent synthesis from **3f** and formamide (Scheme 1). Structures **4**, **7**–**9** were established by spectral data and analogy with our previous work [12,14–16]. Treatment of **3b**,**c** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding ethoxymethyleneamino derivatives **10a**,**b** (Scheme 2). Hydrazinolysis of **10a**,**b** in ethanol at room temperature afforded the imino derivatives **11a**,**b** (Scheme 2). Ammonolysis of **10b** in methanol at room temperature afforded the pyrimidine derivative **12**, the structure of which was supported by its independent synthesis from **3c** and formamide (Scheme 2). Reaction of **10b** with methylamine yielded the pyrimidine derivative **13**, while with dimethylamine the open-chain product **14** was obtained (Scheme 2).

Interaction of **11b** with triethyl orthoformate afforded 11-bromo-14-(*p*-methoxyphenyl)-14*H*-naphtho-[1′,2′:5,6]pyrano[3,2 - *e*][1,2,4]triazolo[2,3 - *c*]pyrimidine (**15a**) (Scheme 3), while with acetyl chloride and ethyl cyanoacetate at reflux the corresponding 2-methyl (**15b**) and 2-acetonitrile (**15c**) derivatives, respectively, were formed. Reaction of **11b** with diethyl oxalate and benzoyl chloride at reflux afforded the corresponding 2-carboxylate (**15d**) and 2-phenyl (**15e**) derivatives, respectively (Scheme 3).

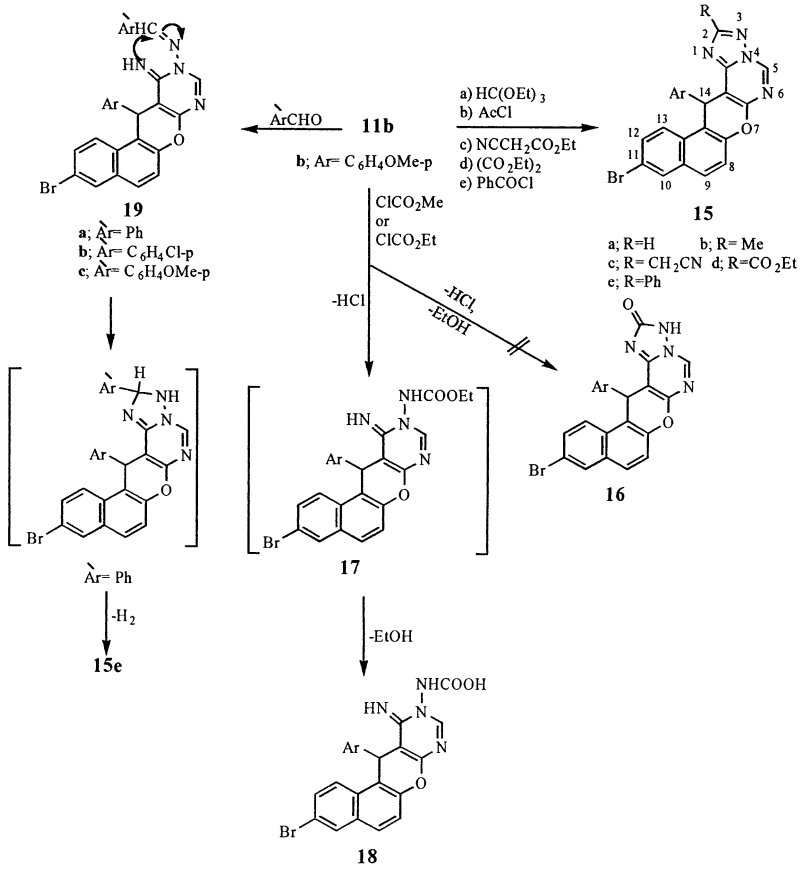
Instead of the anticipated formation of the triazolopyrimidine derivative **16** [13,14], the reaction of **11b**



Scheme 1.



Scheme 2.



Scheme 3.

with methyl or ethyl chloroformate in dry benzene afforded **18**, through nucleophilic displacement followed by spontaneous hydrolysis of the ester intermediate **17** into the corresponding carbamic acid derivative **18**. The formation of ion peak at 448 (13.6%) ($M^+ - CO_2$) for the mass spectrum of 18 (m/z M^+, 0%) supported the proposed structure due to the ready elimination of CO_2 molecule (Scheme 3).

Interaction of **11b** with aromatic aldehydes in dioxane–piperidine for 16 h afforded 10-arylmethyleneamino-3-bromo-11-imino-12-(*p*-methoxyphenyl)-10,11-dihydro-12*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine (**19a**–**c**) (Scheme 3), while heating of **11b** with benzaldehyde in dioxane–piperidine under reflux for 30 h afforded **15e** (m.p. and mixed m.p.). The structure of **19** was supported by spectral data and TLC.

3. Experimental

M.p.s are uncorrected and were determined on a Stuart Scientific Co. Ltd melting point apparatus. IR spectra ν_{max}/cm^{-1} (KBr) were measured on a FT IR/5300 spectrometer. Ultraviolet spectra were recorded on Perkin–Elmer Lambda-3B UV–Visible spectrophotometer; ^1H NMR spectra δ (ppm) on Varian Mercury (300 MHz) spectrometer and mass spectra on a Shimadzu GC-MS-QP 1000 EX spectrometer. Elemental analyses were carried out in the Microanalytical Laboratories of the Faculty of Science, Cairo University, and analytical results for (C, H, N) were within $\pm 0.2\%$ of the calculated values.

*3.1. Reaction of **1a**–**f** with 6-bromo-2-naphthol (**2**)*

3.1.1. General procedure

A solution of **1a**–**f** (0.01 mol) in ethanol (30 ml) was treated with 6-bromo-2-naphthol **2** (2.23 g, 0.01 mol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation (reaction times: 15 min for **1a**–**c**; 120 min for **1d**–**f**). The solid product which formed was collected by filtration and recrystallized from a suitable solvent to give **3a**–**f**.

*3.1.2. 3-Amino-8-bromo-1-phenyl-1H-naphtho[2,1-b]-pyran-2-carbonitrile (**3a**)*

Colorless crystals from benzene, m.p. 240 °C, yield 4.4 g (89%). IR: 3477, 3321 (NH_2), 3064, 2968, 2868 (CH stretching), 2205 (CN). ^1H NMR (DMSO-d_6): 7.15–8.21 (m, 10H, Ar-H), 7.05 (br, 2H, NH_2, cancelled by D_2O), 5.32 (s, 1H, pyran CH). Anal. (C, H, N) for $C_{20}H_{13}BrN_2O$.

*3.1.3. 3-Amino-8-bromo-1-(p-chlorophenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**3b**)*

Yellow crystals from benzene, m.p. 265 °C, yield 3.7 g (90%). IR: 3448, 3319 (NH_2), 2200 (CN). ^1H NMR (DMSO-d_6): 7.19–8.24 (m, 9H, Ar-H), 7.11 (br, 2H, NH_2), 5.37 (s, 1H, pyran CH). Anal. (C, H, N) for $C_{20}H_{12}BrClN_2O$.

*3.1.4. 3-Amino-8-bromo-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**3c**)*

Colorless crystals from benzene, m.p. 235 °C, yield 3.7 g (91%). IR: 3400, 3317 (NH_2), 2966, 2927, 2833 (CH stretching), 2195 (CN). ^1H NMR (DMSO-d_6): 6.81–8.23 (m, 11H, Ar-H + NH_2), 5.27 (s, 1H, pyran CH), 3.68 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{21}H_{15}BrN_2O_2$.

*3.1.5. Ethyl 3-amino-8-bromo-1-phenyl-1H-naphtho[2,1-b]-pyran-2-carboxylate (**3d**)*

Colorless needles from benzene, m.p. 180 °C, yield 3.1 g (74%). IR: 3404, 3300 (NH_2), 3024, 2987, 2901 (CH stretching), 1666 (CO ester). ^1H NMR (DMSO-d_6): 7.07–8.21 (m, 12H, Ar-H + NH_2), 5.49 (s, 1H, pyran CH), 4.11 (q, 2H, CH_2, $J = 6$ Hz) and 1.26 (t, 3H, CH_3, $J = 6$ Hz). Anal. (C, H, N) for $C_{22}H_{18}BrNO_3$.

*3.1.6. Ethyl 3-amino-8-bromo-1-(p-chlorophenyl)-1H-naphtho[2,1-b]pyran-2-carboxylate (**3e**)*

Colorless needles from benzene, m.p. 170°C, yield 3.5 g (77%). IR: 3468, 3302 (NH_2), 2974, 2926, 2901, 2955 (CH stretching), 1682 (CO ester). ^1H NMR (DMSO-d_6): 7.24–8.27 (m, 9H, Ar-H), 7.62 (br, 2H, NH_2, cancelled by D_2O), 5.51 (s, 1H, pyran CH), 4.12 (q, 2H, CH_2, $J = 7.2$ Hz) and 1.28 (t, 3H, CH_3, $J = 7.2$ Hz). Anal. (C, H, N) for $C_{22}H_{17}BrClNO_3$.

*3.1.7. Ethyl 3-amino-8-bromo-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carboxylate (**3f**)*

Colorless needles from benzene, m.p. 200 °C, yield 3.6 g (79%). IR: 3431, 3315 (NH_2), 3045, 2975, 2927 (CH stretching), 1678 (CO ester). ^1H NMR (DMSO-d_6): 6.73–8.21 (m, 11H, Ar-H + NH_2), 5.43 (s, 1H, pyran CH), 4.10 (q, 2H, CH_2, $J = 6.9$ Hz), 3.63 (s, 3H, OCH_3) and 1.27 (t, 3H, CH_3, $J = 6.9$Hz). Anal. (C, H, N) for $C_{23}H_{20}BrNO_4$.

*3.2. 3-Arylmethyleneamino-8-bromo-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**4a**–**c**)*

3.2.1. General procedure

A mixture of **3c** (4.06 g, 0.01 mol), benzaldehyde, *p*-chlorobenzaldehyde and *p*-anisaldehyde (0.01 mol), dioxane (20 ml) and piperidine (0.5 ml) was refluxed for 4 h to give **4a**–**c**.

*3.2.2. 8-Bromo-1-(p-methoxyphenyl)-3-phenylmethyleneamino-1H-naphtho[2,1-b]-pyran-2-carbonitrile (**4a**)*

Yellow crystals from benzene, m.p. 280 °C, yield 4.1 g (82%). IR: 3074, 3013, 2922, 2843 (CH stretching),

2210 (CN), 1641 (C=N). Anal. (C, H, N) for $C_{28}H_{19}BrN_2O_2$.

*3.2.3. 8-Bromo-3-(p-chlorophenylmethyleneamino)-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**4b**)*

Yellow crystals from benzene, m.p. 310 °C, yield 4.1 g (88%). IR: 3078, 2939, 2885 (CH stretching), 2212 (CN), 1641 (C=N). ^{1}H NMR (DMSO-d_6): 9.17 (s, 1H, N=CH), 6.87–8.25 (m, 13H, Ar-H), 5.72 (s, 1H, pyran CH), 3.69 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{28}H_{18}BrClN_2O_2$.

*3.2.4. 8-Bromo-1-(p-methoxyphenyl)-3-(p-methoxyphenylmethyleneamino)-1H-naphtho[2,1-b]-pyran-2-carbonitrile (**4c**)*

Yellow crystals from benzene, m.p. 272 °C, yield 4.7 g (90%). IR: 3050, 3000, 2900, 2805 (CH stretching), 2208 (CN), 1641 (C=N). ^{1}H NMR (DMSO-d_6): 9.06 (s, 1H, N=CH), 6.84–8.22 (m, 13H, Ar-H), 5.65 (s, 1H, pyran CH), 3.86 (s, 3H, OCH_3) and 3.67 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{29}H_{21}BrN_2O_3$.

*3.3. 3-Acetylamino-8-bromo-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**7**)*

A solution of **3c** (4.06 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 ethanol to give colorless needles, m.p. 240 °C, yield 3.6 g (81%). IR: 3200 (NH), 3047, 2916 (CH stretching), 2206 (CN), 1705 (CO acetyl). ^{1}H NMR (DMSO-d_6): 11.15 (br,1H, NH), 6.83–8.22 (m, 9H, Ar-H), 5.55 (s, 1H, pyran CH), 3.66 (s, 3H, OCH_3) and 3.28 (s, 3H, $COCH_3$). Anal. (C, H, N) for $C_{23}H_{17}BrN_2O_3$.

*3.4. 3-Bromo-9-methyl-12-(p-methoxyphenyl)-10,11-dihydro-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]-pyrimidin-11-one (**8**)*

3.4.1. Method (a)

A solution of **3c** (4.06 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 benzene to give colorless needles, m.p. 320 °C, yield 3.9 g (86%). IR: 3260 (NH), 3001, 2850 (CH stretching) and 1651 (CO). Anal. (C, H, N) for $C_{23}H_{17}BrN_2O_3$.

3.4.2. Method (b)

A stream of dry HCl gas was passed through a mixture of **3f** (4.53 g, 0.01 mol) and acetonitrile (30 ml) for 4–6 h. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution to give **8** (m.p. and mixed m.p.) yield 3.1 g (68%).

*3.5. 3-Bromo-12-(p-methoxyphenyl)-10,11-dihydro-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-one (**9**)*

3.5.1. Method (a)

A solution of **3c** (4.06 g, 0.01 mol) in formic acid (20 ml) was heated under reflux for 6 h to give **9** as colorless needles, m.p. 170 °C, yield 2.9 g (67%). IR: 3510 (NH), 3026, 2955, 2924, 2887, 2833 (CH stretching) and 1768 (CO). ^{1}H NMR (DMSO-d_6): 8.30 (s, 1H, pyrimidine CH), 6.90–9.07 (m, 10, Ar-H + NH), 5.54 (s, 1H, pyran CH) and 3.70 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{22}H_{15}BrN_2O_3$.

3.5.2. Method (b)

A solution of **3f** (4.53 g, 0.01 mol) in formamide (20 ml) was heated under reflux for 6 h to give **9** (m.p. and mixed m.p.) yield 3.1 g (73%).

*3.6. 1-Aryl-8-bromo-3-ethoxymethyleneamino-1H-naphtho[2,1-b]pyran-2-carbonitrile (**10a**,**b**)*

3.6.1. General procedure

A mixture of **3b**,**c** (0.01 mol), triethyl orthoformate (0.01 mol) and acetic anhydride (20 ml) was refluxed for 5 h to give **10a**,**b**.

*3.6.2. 8-Bromo-1-(p-chlorophenyl)-3-ethoxy-methyleneamino-1H-naphtho[2,1-b]pyran-2-carbonitrile (**10a**)*

Colorless needles from benzene, m.p. 210 °C, yield 3.5 g (75%). IR: 3036, 2987, 2951, 2827 (CH stretching), 2208 (CN); 1654 (C=N). ^{1}H NMR (DMSO-d_6): 8.74 (s, 1H, N=CH), 7.28–8.25 (m, 9H, Ar-H), 5.68 (s, 1H, pyran CH), 4.34 (q, 2H, CH_2, $J = 6.9$ Hz), 1.32 (t, 3H, CH_3, $J = 6.9$ Hz). Anal. (C, H, N) for $C_{23}H_{16}BrClN_2O_2$.

*3.6.3. 8-Bromo-3-ethoxymethyleneamino-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**10b**)*

Colorless needles from benzene, m.p. 190 °C, yield 3.8 g (82%). IR: 2984, 2937, 2896 (CH stretching), 2212 (CN); 1651 (C=N). ^{1}H NMR (DMSO-d_6) 8.73 (s, 1H, N=CH), 6.85–8.24 (m, 9H, Ar-H), 5.56 (s, 1H, pyran CH), 4.34 (q, 2H, CH_2, $J = 6.9$ Hz), 3.70 (s, 3H, OCH_3) and 1.33 (t, 3H, CH_3, $J = 6.9$ Hz). Anal. (C, H, N) for $C_{24}H_{19}BrN_2O_3$.

*3.7. 10-Amino-12-aryl-3-bromo-11-imino-10,11-dihydro-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine (**11a**,**b**)*

3.7.1. General procedure

A solution of **10a**,**b** (0.01 mol) and hydrazine hydrate (99%, 5 ml) in ethanol (50 ml) was stirred at room temperature (r.t.) for 45 min to give **11a**,**b**.

*3.7.2. 10-Amino-3-bromo-12-(p-chlorophenyl)-11-imino-10,11-dihydro-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidine (**11a**)*

Colorless needles from dioxan, m.p. 290 °C, yield 3.8 g (85%). IR: 3400, 3329 (NH_2), 3200 (NH), 1614 (C=N). Anal. (C, H, N) for $C_{21}H_{14}BrClN_4O$.

*3.7.3. 10-Amino-3-bromo-12-(p-methoxyphenyl)-11-imino-10,11-dihydro-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidine (**11b**)*

Colorless needles from dioxan, m.p. 240 °C, yield 3.9 g (87%). IR: 3341, 3292 (NH_2), 3242 (NH), 3067, 2953, 2907, 2833 (CH stretching), 1649 (C=N). ^{1}H NMR (DMSO-d_6): 8.22 (s, 1H, pyrimidine CH), 8.10 (br, 1H, NH, cancelled by D_2O), 6.75–7.93 (m, 9H, Ar-H), 6.00 (br, 2H, NH_2, cancelled by D_2O), 5.70 (s, 1H, pyran CH) and 3.63 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{22}H_{17}BrN_4O_2$.

*3.8. 11-Amino-3-bromo-12-(p-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine (**12**)*

3.8.1. Method (a)

A stream of NH_3 gas was passed through **10b** (4.62 g, 0.01 mol) in methanol at r.t. for 1 h. The solid product formed in cooling was collected to give **12** as colorless needles (benzene), m.p. 275 °C, yield 4.2 g (88%). IR: 3479, 3350 (NH_2) and 1679 (C=N). ^{1}H NMR (DMSO-d_6): 8.23 (s, 1H, pyrimidine CH), 6.76–8.15 (m, 9H, Ar-H), 7.18 (br, 2H, NH_2, cancelled by D_2O), 5.60 (s, 1H, pyran CH) and 3.63 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{23}H_{19}BrN_4O_3$.

3.8.2. Method (b)

Compound **12** was prepared from **3c** (4.06 g, 0.01 mol) and formamide (0.01 mol) according to the procedure described for **9** (method b) to give **12** (m.p. and mixed m.p.) yield 3.1 g (65%).

*3.9. 3-Bromo-10-methyl-11-imino-12(p-methoxyphenyl)-10,11-dihydro-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidine (**13**)*

Compound **13** was prepared from **10b** (4.62 g, 0.01 mol) and methylamine (0.01 mol) according to the procedure described for **11** to give **13** as colorless crystals (benzene), m.p. 280 °C, yield 3.7 g (83%). IR: 3352 (NH), 3020, 2924, 2837 (CH stretching), 1645 (C=N). ^{1}H NMR (DMSO-d_6): 8.23 (s, 1H, pyrimidine CH), 6.73–8.20 (m, 10H, Ar-H + NH), 5.83 (s, 1H, pyran CH), 3.61 (s, 3H, OCH_3) and 3.28 (s, 3H, N–CH_3). Anal. (C, H, N) for $C_{23}H_{18}BrN_3O_2$.

*3.10. 8-Bromo-3-dimethylaminomethyleneamino-1-(p-methoxyphenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (**14**)*

Compound **14** was prepared from **10b** (4.62 g, 0.01 mol) and dimethylamine (0.01 mol) according to the procedure described for **11** to give **14** as colorless crystals (benzene), m.p. 245 °C, yield 4.0 g (87%). IR: 2920, 2891, 2839 (CH stretching), 2199 (CN), 1647 (C=N). ^{1}H NMR (DMSO-d_6): 8.44 (s, 1H, N=CH), 6.79–8.16 (m, 9H, Ar-H), 5.23 (s, 1H, pyran CH), 3.65 (s, 3H, OCH_3), 3.13 (s, 3H, NCH_3) and 2.98 (s, 3H, NCH_3). Anal. (C, H, N) for $C_{24}H_{20}BrN_3O_2$.

*3.11. 11-Bromo-14-(p-methoxyphenyl)-14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1,2,4]triazolo[2,3-c]-pyrimidine (**15a**)*

A solution of **11b** (4.48 g, 0.01 mol) and triethyl orthoformate (0.01 mol) in dry benzene was refluxed for 6 h to give **15a** as colorless crystals (benzene), m.p. 260 °C, yield 3.6 g (79%). IR: 3032, 3007, 2835 (CH stretching), 1634 (C=N). ^{1}H NMR (DMSO-d_6): 9.63 (s,1H, pyrimidine CH), 8.62 (s, 1H, triazole CH), 6.72–8.23 (m, 9H, Ar-H), 6.26 (s, 1H, pyran CH) and 3.60 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{23}H_{15}BrN_4O_2$.

*3.12. 11-Bromo-2-methyl-14-(p-methoxyphenyl)-14H-naphtho[1′,2′:5,6]pyrano[3,2-e]-[1,2,4]-triazolo[2,3-c]pyrimidine (**15b**)*

Compound **15b** was prepared from **11b** (4.48 g, 0.01 mol) and acetyl chloride (0.01 mol) according to the procedure described for **15a** to give **15b** as colorless crystals (benzene), m.p. 255 °C, yield 4.0 g (84%). IR: 3080, 2980, 2831 (CH stretching), 1667 (C=N). ^{1}H NMR (DMSO-d_6): 8.83 (s, 1H, pyrimidine CH), 6.80–8.26 (m, 9H, Ar-H), 6.64 (s, 1H, pyran CH), 3.63 (s, 3H, OCH_3) and 2.14 (s, 3H, triazole CH_3). Anal.(C, H, N) for $C_{24}H_{17}BrN_4O_2$.

*3.13. 11-Bromo-14-(p-methoxyphenyl)-14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1,2,4]triazolo[2,3-c]-pyrimidin-2-acetonitrile (**15c**)*

A mixture of **11b** (4.48 g, 0.01 mol), ethyl cyanoacetate (0.01 mol) and absolute ethanol (20 ml) was refluxed for 6 h to give **15c** as colorless crystals (ethanol), m.p. 270 °C, yield 3.2 g (65%). IR: 3059, 3030, 2933 (CH stretching) and 2200 (CN), 1636 (C=N). ^{1}H NMR (DMSO-d_6): 9.62 (s, 1H, pyrimidine CH), 6.73–8.24 (m, 9H, Ar-H), 6.25 (s, 1H, pyran CH), 4.47 (s, 2H, CH_2) and 3.59 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{25}H_{16}BrN_5O_2$.

*3.14. Ethyl 11-bromo-14-(p-methoxyphenyl)-14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1,2,4]triazolo[2,3-c]-pyrimidine-2-carboxylate (**15d**)*

Compound **15d** was prepared from **11b** (4.48 g, 0.01 mol) and ethyl oxalate (0.01 mol) according to the procedure described for **15c** to give **15d** as colorless crystals (ethanol), m.p. 213 °C, yield 4.2 g (80%). IR: 3041, 2995, 2961 (CH stretching), 1720 (CO), 1618 (C=N). ^{1}H NMR (DMSO-d_6): 8.66 (s, 1H, pyrimidine CH), 6.78–8.27 (m, 9H, Ar-H), 6.25 (s, 1H, pyran CH), 3.93 (q, 2H, CH_2, $J = 6.9$ Hz), 3.61 (s, 3H, OCH_3), 1.13 (t, 3H, CH_3, $J = 6.9$ Hz). Anal. (C, H, N) for $C_{26}H_{19}BrN_4O_4$.

*3.15. 11-Bromo-2-phenyl-14-(p-methoxyphenyl)-14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1,2,4]triazolo-[2,3-c]pyrimidine (**15e**)*

Compound **15e** was prepared from **11b** (4.48 g, 0.01 mol) and benzoyl chloride (0.01 mol) according to the procedure described for **15a** to give **15e** as colorless crystals (dioxan), m.p. 310 °C, yield 3.3 g (62%). IR: 3005 (CH stretching), 1634 (C=N). ^{1}H NMR (DMSO-d_6): 9.60 (s, 1H, pyrimidine CH), 6.78–8.31 (m, 14H, Ar-H), 6.34 (s, 1H, pyran CH) and 3.61 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{29}H_{19}BrN_4O_2$.

*3.16. N-[3-Bromo-12-(p-methoxyphenyl)-11-imino-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]-pyrimidyl-10]carbamic acid (**18**)*

Compound **18** was prepared from **11b** (4.48 g, 0.01 mol) and methyl chloroformate or ethyl chloroformate (0.01 mol) according to the procedure described for **15a** to give **18** as colorless crystals (benzene), m.p. 275 °C, yield 3.3 g (74%). IR: 3753–2835 centered at 3049 (NH, COOH, CH stretching) and 1649 (CO). ^{1}H NMR (DMSO-d_6): 12.21 (br, 1H, OH), 8.70 (s, 1H, pyrimidine CH), 6.78–8.28 (m, 9H, Ar-H), 6.65 (br, 1H, NH), 6.43 (s, 1H, pyran CH), 3.63 (s, 3H, OCH_3). MS: m/z 450/448 ($M^+ - CO_2$, 16/14%), 434/432 (99/100), 328/326 (90/88), 301/299 (29/30), 220 (13), 193 (16), 164 (15), 63(13). Anal. (C, H, N) for $C_{23}H_{17}BrN_4O_4$.

*3.17. 10-Arylmethyleneamino-3-bromo-11-imino-12-(p-methoxyphenyl)-10,11-dihydro-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidine (**19a–c**)*

3.17.1. General procedure

A mixture of **11b** (4.48 g, 0.01 mol), benzaldehyde, *p*-chlorobenzaldehyde, *p*-anisaldehyde (0.01 mol), dioxane (20 ml) and piperidine (0.5 ml) was refluxed for 16 h to give **19a–c**.

*3.17.2. 3-Bromo-11-imino-12-(p-methoxyphenyl)-10-phenylmethyleneamino-10,11-dihydro-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine (**19a**)*

Pale yellow needles from benzene, m.p. 280 °C, yield 4.3 g (82%). IR: 3184 (NH), 3000, 2926, 2833 (CH stretching), 1628 (C=N). ^{1}H NMR (DMSO-d_6): 11.12 (br, 1H, NH; cancelled by D_2O), 8.35 (s, 1H, pyrimidine CH), 6.73–8.26 (m, 14H, Ar-H), 6.65 (s, 1H, pyran CH), 3.58 (s, 1H, OCH_3). Anal. (C, H, N) for $C_{29}H_{21}BrN_4O_2$.

*3.17.3. 3-Bromo-10-(p-chlorophenylmethyleneamino)-11-imino-12-(p-methoxyphenyl)-10,11-dihydro-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine (**19b**)*

Yellow needles from benzene, m.p. 285 °C, yield 4.8 g (84%). IR: 3198 (NH), 3034, 3003, 2907, 2833 (CH stretching), 1628 (C=N). Anal. (C, H, N) for $C_{29}H_{20}BrClN_4O_2$.

*3.17.4. 3-Bromo-11-imino-10-(p-methoxyphenyl-methyleneamino)-12-(p-methoxyphenyl)-10,11-dihydro-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine (**19c**)*

Yellow needles from benzene, m.p. 260 °C, yield 4.9 g (86%). IR: 3196 (NH), 2959, 2928, 2905, 2833 (CH stretching), 1628 (C=N). ^{1}H NMR (DMSO-d_6): 10.96 (br, 1H, NH; cancelled by D_2O), 8.32 (s, 1H, pyrimidine CH), 6.73–8.25 (m, 13H, Ar-H), 6.63 (s, 1H, pyran CH), 3.82 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3). Anal. (C, H, N) for $C_{30}H_{23}BrN_4O_3$.

*3.18. Preparation of **15e***

A mixture of **11b** (4.48 g, 0.01 mol), benzaldehyde (0.01 mol), dioxan (20 ml) and piperidine (0.5 ml) was refluxed for 30 h to give **15e** (m.p. and mixed m.p.) yield 4.3 g (81%).

4. Biological screening

4.1. Antibacterial activity

Some of the newly synthesized compounds **3b**,**c**,**f**, **4b**,**c**, **7–9**, **10b**, **11b**, **12–14**, **15a–e** and **19b**,**c** 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 [23].

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 nutrient agar (Difco) dishes seeded by test bacteria.The inhibition zone was measured in millimeters at the end of an incubation period of 48 h at 28 °C. DMF showed no inhibition zone. The results are illustrated in Table 1.

4.2. Antifungal activity

Some of the newly synthesized compounds **3b**,**c**,**f**, **4b**,**c**, **7**–**9**, **10b**, **11b**, **12**–**14**, **15a**–**e** and **19b**,**c** 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 [24].

The tested compounds were dissolved in 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 millimeters at the end of an incubation period of 48 h at 28 °C. DMF showed no inhibition zone. The results are illustrated in Table 2.

Table 2
Antifungal activity of some compounds

Comp.	*A. ochraceus* Wilhelm (AUCC-230)	*P. chrysogenum* Thom (AUCC-530)
3b	10	9
3c	13	10
3f	15	15
4b	19	20
4c	18	17
7	18	19
8	22	20
9	17	16
10b	14	13
11b	18	20
12	19	13
13	19	20
14	17	17
15a	20	19
15b	19	20
15c	18	21
15d	20	22
15e	19	18
19b	20	20
19c	20	17
Mycostatine [a] (30 μg)	22	24

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

5. Conclusion

The antibacterial activity of the naphthopyran derivative **3c** was assumed as the base level of activity. The naphthopyran derivatives **3b**,**f** and **4b**,**c** offered an improvement in antibacterial activity over the naphthopyran **3c**. Enhanced activity was obtained with naphthopyranopyrimidine derivatives **8**, **9**, **10b**, **11b**, **12**, **13**, **19c** and naphthopyran derivatives **7** and **14**. The naphthopyranotriazolopyrimidine derivatives **15a**–**e** show more improvement in antibacterial activity over

Table 1
Antibacterial activity of some compounds

Comp.	*S. aureus* (NCTC-7447)	*B. cereus* (ATCC-14579)	*S. marcescens* (IMRU-70)	*P. mirabilis* (NTCC-289)
3b	14	13	15	16
3c	13	14	13	14
3f	15	17	16	18
4b	19	21	20	22
4c	18	19	18	20
7	19	20	19	20
8	22	22	22	22
9	21	20	22	20
10b	18	14	18	15
11b	21	23	21	22
12	19	18	20	18
13	22	21	22	21
14	20	22	20	22
15a	22	21	22	22
15b	23	22	23	23
15c	25	22	25	23
15d	24	23	25	24
15e	21	20	22	22
19b	23	22	23	23
19c	21	20	20	19
Ampicillin [a] (25 μg)	26	25	26	25

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

the naphthopyranopyrimidine and naphthopyran derivatives. In addition, the naphthopyran derivatives **3f**, **4b**, **c**, **7** and **14** offered an improvement in antifungal activity over the naphthopyran **3c**, while on the contrary, the naphthopyran derivative **3b** showed a marked decrease in the activity and the naphthopyranopyrimidine derivative **10b** showed the same activity. The naphthopyrimidine **8**, **9**, **11b**, **12**, **13**, **19c** and naphthopyranotriazolopyrimidine **15a**–**e** derivatives showed a marked increase in antifungal activity over the parent compound **3c**. However, none of the tested compounds showed activity superior to the reference.

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