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ORIGINAL PAPER

Synthesis of some pyridine, thiopyrimidine, and isoxazoline derivatives based on the pyrrole moiety

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Abstract Condensation of 2-acetylpyrrole with 5-methylfuran-2-carboxyaldehyde and 4-chlorobenzaldehyde in 20% NaOH give the corresponding 2-chalconylpyrroles. Some new 2-alkoxy-3-cyano-4,6-diarylpyridines were synthesized by condensation of chalcones with malononitrile, followed by cyclization in sodium alkoxide. The reactivity of chalcones towards nitrogen nucleophiles such as thiourea and hydroxylamine hydrochloride to provide thiopyrimidines and isoxazolines was investigated.

Keywords Pyrroles · Pyridines · Thiopyrimidine · Isoxazoline

Introduction

Pyrrole ring represent a subunit in a large and varied class of marine natural products possessing interesting and potentially useful pharmacological activities (e.g., lamellarins [1, 2], lukianols [3], ningalins [4], storniamides [5], arcyriarubins [6], and polycitrins [7]) that exhibit remarkable biological properties such as hypolipidemic, [8] antimicrobial, [9] anti-inflammatory [10] and antitumour activity [11]. Other marine natural products possessing a 3,4-substituted pyrrole ring as a common structural subunit such as halitulin was found to be cytotoxic against several tumour cell lines (e.g., P-388, A-549, HT-29 and MEL-28) [12]. Also, a large number of substituted pyridines have been maintained to have several biological activities [13–17]. Moreover, many biologically active compounds include thiopyrimidine [18–22] or isoxazoline [23–25] ring as a structural subunit have been reported. Guided by the above observations, and in continuation of our previous work in the direction of the synthesis of bioactive compounds [26–29], we report here a convenient synthesis of functionalized pyridine, thiopyrimidine and isoxazoline derivatives incorporating pyrrole moiety as a common structural subunit.

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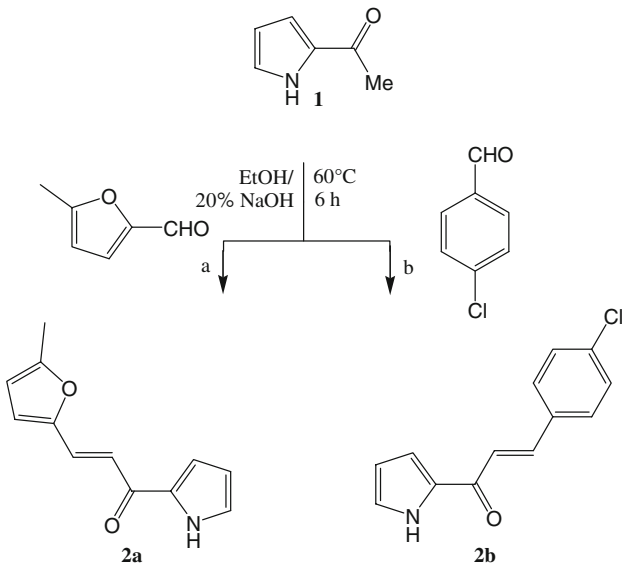
Results and discussion

Chemistry

Chalcones (1,3-diaryl-2-propen-1-ones) are interesting precursors and display interesting biological activities, including cytotoxic and anticancer properties [30–33]. Condensation of the starting compound, 2-acetyl pyrrole (**1**) with 5-methylfuran-2-carboxyaldehyde and 4-chlorobezaldehyde in the presence of 20% NaOH solution at 60 °C for 6 h afforded the corresponding (*E*)-3-(5-methylfuran-2-yl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (**2a**) and (*E*)-3-(4-chlorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (**2b**), in a good yields (82 and 86%). The coupling constant (*J*) in the ^{1}H NMR spectrum of C2-H and C3-H of the isolated (**2a**, **2b**) are in the range of 15.8–16 Hz which are characteristic to (*E*)-isomer of chalcones (Scheme 1).

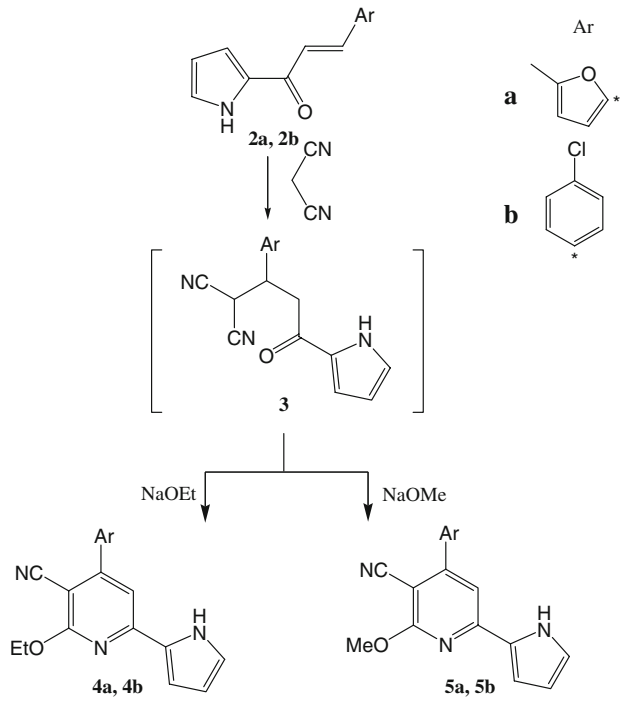
In the present work, new compounds containing 2-alkoxypyridine moieties have been designed for their biological activity, particularly for antitumor properties. It was reported that the reaction of chalcones with malononitrile and ethyl cyanoacetate in the presence of ammonium



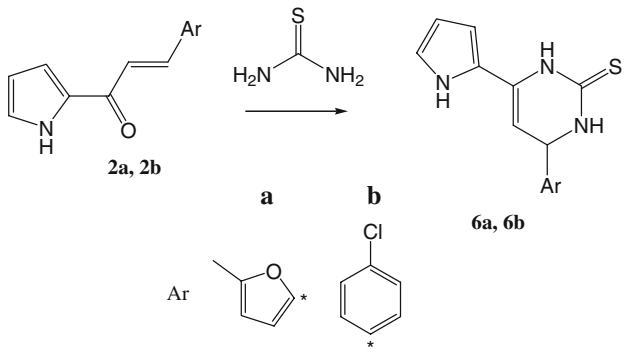
Scheme 1

acetate and absolute ethanol afforded cyanopyridines in low yield [13]. In the same way, the preparation of 2-alkoxy cyanopyridines in good yields was reported via Michael addition of malononitrile to α,β-unsaturated carbonyl system [34]. Here in, 2-chalconylpyrroles (**2a**, **2b**) were condensed with malononitrile in either sodium ethoxide/ethanol or sodium methoxide/methanol to yield the corresponding 2-alkoxycyanopyridines **4a, 4b** or **5a, 5b** in a good yield (78 and 80% or 81 and 83%). The reaction proceeds through Michael addition of α,β-unsaturated ketones to the malononitrile to afford adduct **3** which undergoes a nucleophilic attack by alkoxide anion followed by cyclization and subsequent dehydration of the cyclized product leads to the 2-alkoxycyanopyridines **4a, 4b** or **5a, 5b** (Scheme 2). It was observed that the increase in the carbon number of alkoxyl group caused much prolongation time of the reaction and relatively low yield. The structure of the 2-alkoxycyanopyridine compounds was established on the basis of its elemental analysis and spectral data. For example, the IR spectrum of compound **4a** showed the presence of an absorption peak at 2,255 cm^{-1} due to cyano stretching frequency and its ^1H NMR spectrum revealed a characteristic triplet and quartet signals at $\delta = 1.38$ and 4.59 due to methyl and methylene of the ester group, and singlet at $\delta = 7.76$ ppm due to pyridine proton. In addition, its mass spectrum revealed a peak at $m/z = 293$ corresponding to its molecular ion.

Condensation of **2a**, **2b** with diamine, namely, thiourea in refluxing ethanolic potassium hydroxide afforded 2-thiopyrimidine derivatives **6a, 6b**, in a good yield (77 and 69%) (Scheme 3). The structure of the 2-thiopyrimidine derivatives was established on the basis of its elemental analysis and spectral data. For example, the IR



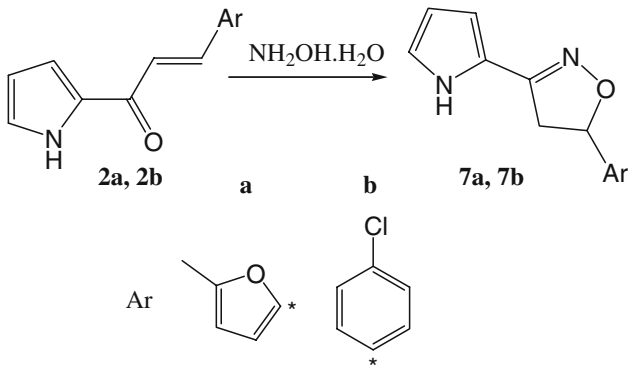
Scheme 2



Scheme 3

spectrum of compound **6a** showed the presence of absorption peaks at 3,250–3,360 cm^{-1} due to amino groups and at 1,215 cm^{-1} due to thione (C=S) group and its ^1H NMR spectrum revealed a characteristic two doublets at $\delta = 5.20$ and 7.41 due to thiopyrimidine (H-4 and H-5) and two singlets at 10.12 and 10.14 ppm due to 2 NH pyrimidine groups. In addition, its mass spectrum revealed a peak at $m/z = 259$ corresponding to its molecular ion.

Also, condensation of **2a**, **2b** with hydroxylamine hydrochloride in the presence of anhydrous sodium acetate in refluxing acetic acid yielded isoxazolines **7a, 7b** in a good yield (69 and 73%) (Scheme 4). The structure of the isoxazoline derivatives was established on the basis of its elemental analysis and spectral data. For example, the ^1H NMR spectrum of compound **7a** revealed a characteristic



Scheme 4

signals at $\delta = 1.65$, 1.80 due to methylene and $\delta = 5.15$ ppm due to methine protons of isoxazoline ring. In addition, its mass spectrum revealed a peak at $m/z = 216$ corresponding to its molecular ion.

Experimental

Chemistry

Melting points were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol EX-270 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as the internal standard. Mass spectra were recorded on a Finnigan SSQ 7000 GC-MS spectrometer. Microanalyses were performed at the Microanalytical Center of Cairo University and results agreed favorably with calculated values.

General procedure for the synthesis of 2-chalconylpyrroles

A mixture of 0.22 g 2-acetylpyrrole (**1**) (2 mmol) and 2 mmol of the appropriate aldehyde (**2a**: 5-methylfuran-2-carboxyaldehyde, **2b**: 4-chlorobenzaldehyde) in 30 cm^3 20% ethanolic NaOH was heated at 60 °C for 6 h. The reaction mixture was left to cool. The obtained solid was filtered off, air-dried, and crystallized from ethanol to give the corresponding chalcones **2a, 2b**.

(E)-3-(5-Methylfuran-2-yl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (**2a,** $C_{12}H_{11}NO_2$)
In 0.33 g (82%) yield; M.p.: 160–162 °C (ethanol); IR (KBr): $\bar{\nu} = 3271$ (NH), 1648 (C=O), 1596 (C=C) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 2.35$ (s, 3H, Me), 6.25 (dd, 1H, H-4, pyrrole, $J = 6.1$, 5.8 Hz), 6.30 (d, 1H, H-4, furan, $J = 6.8$ Hz), 6.85 (d, 1H, H-3, furan, $J = 6.8$ Hz), 7.12 (d, 1H, H-3, pyrrole, $J = 5.8$ Hz), 7.15 (d, 1H, H-5, pyrrole, $J = 6.1$ Hz), 7.20 (d, 1H, H-α, $J = 15.8$ Hz), 7.42 (d, 1H, H-β, $J = 16$ Hz), 11.95 (br s, 1H, NH) ppm; MS (EI, 70 eV): $m/z = 201$ (M^+, 100), 186 (63), 158 (38), 130 (37), 107 (6), 94 (27), 77 (18).

(E)-3-(4-Chlorophenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (***2b***)
In 0.4 g (86%) yield; M.p.: 158–160 °C (ethanol) (Ref. [35] 154–156 °C).

General method for preparation of 2-alkoxy-3-cyano-4, 6-diaryl pyridines

Compound **2a** or **2b** (2 mmol) were added during stirring to a freshly prepared sodium alkoxide solution (2 mmol of sodium in 20 cm^3 of each of absolute methanol or ethanol). Malononitrile (0.2 g, 3 mmol) was then added with continuous stirring at room temperature until the precipitate was separated out. The solid separated was collected by filtration and recrystallized from suitable solvent.

2-Ethoxy-4-(5-methylfuran-2-yl)-6-(1H-pyrrol-2-yl) pyridine-3-carbonitrile (**4a**, $C_{17}H_{15}N_3O_2$)
In 0.46 g (78%) yield; M.p.: 202 °C (DMF); IR (KBr): $\bar{\nu} = 3241$ (NH), 2,255 (CN) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 1.38$ (t, 3H, Me, $J = 6.7$ Hz) 2.37 (s, 3H, Me), 4.59 (q, 2H, CH_2, $J = 6.7$ Hz), 6.23 (dd, 1H, H-4, pyrrole, $J = 5.9$, 5.6 Hz), 6.42 (d, 1H, H-4, furan, $J = 6.8$ Hz), 6.95 (d, 1H, H-3, furan, $J = 6.8$ Hz), 7.10 (d, 1H, H-3, pyrrole, $J = 5.6$ Hz), 7.4 (d, 1H, H-5, pyrrole, $J = 5.9$ Hz), 7.6 (s, 1H, H-5, pyridine), 11.75 (br s, 1H, NH) ppm; MS (EI, 70 eV): $m/z = 293$ (M^+, 100), 278 (16), 265 (51), 236 (11), 194 (7), 179 (3), 132 (4).

4-(4-Chlorophenyl)-2-ethoxy-6-(1H-pyrrol-2-yl)pyridine-3-carbonitrile (**4b**, $C_{18}H_{14}ClN_3O$)
In 0.52 g (80%) yield; M.p.: 197 °C; IR (KBr) (DMF/H_2O): $\bar{\nu} = 3265$ (NH), 2,248 (CN), cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 1.37$ (t, 3H, Me), 4.61 (q, 2H, CH_2), 6.26 (dd, 1H, H-4, pyrrole, $J = 5.7$, 6.1 Hz), 7.11 (d, 1H, H-3, pyrrole, $J = 5.7$ Hz), 7.45 (d, 1H, H-5, pyrrole, $J = 6.1$ Hz), 7.61 (d, 2H, $J = 7.8$ Hz, Ph), 7.72 (d, 2H, $J = 7.8$ Hz, Ph), 7.76 (s, 1H, H-5, pyridine), 11.84 (br s, 1H, NH) ppm; MS (EI, 70 eV): $m/z = 323$ (M^+, 100), 294 (24), 278 (14), 243 (41), 229 (17), 217 (10), 194 (6), 131 (15), 113 (12), 91 (4), 77 (7).

2-Methoxy-4-(5-methylfuran-2-yl)-6-(1H-pyrrol-2-yl) pyridine-3- carbonitrile (**5a**, $C_{16}H_{13}N_3O_2$)
In 0.45 g (81%) yield; M.p.: 212 °C (AcOH); IR (KBr): $\bar{\nu} = 3265$ (NH), 2,242 (CN), cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 2.41$ (s, 3H, Me), 4.05 (s, 3H, OMe), 6.17 (dd, 1H, H-4, pyrrole, $J = 5.6$, 5.8 Hz), 6.32 (d, 1H, H-4, furan, $J = 6.5$ Hz), 6.86 (d, 1H, H-3, furan, $J = 5.5$ Hz), 6.95 (d, 1H, H-3, pyrrole, $J = 5.6$ Hz), 7.48 (d, 1H, H-5, pyrrole,

$J = 5.8$ Hz), 7.51 (s, 1H, H-5, pyridine), 9.43 (br s, 1H, NH) ppm; MS (EI, 70 eV): $m/z = 279$ (M^+, 34), 278 (100), 263 (59), 249 (73), 235 (71), 220 (75), 192 (79), 178 (68), 166 (54), 140 (69), 91 (83), 77 (58).

4-(4-Chlorophenyl)-2-methoxy-6-(1H-pyrrol-2-yl)pyridine-3-carbonitrile (**5b**, $C_{17}H_{12}ClN_3O$)
In 0.51 g (83%) yield; M.p.: 266 °C (AcOH/H_2O); IR (KBr): $\bar{\nu} = 3278$ (NH), 2,240 (CN), cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.1$ (s, 3H, OMe), 6.3 (dd, 1H, H-4, pyrrole, $J = 5.9$, 6.2 Hz), 6.83 (d, 1H, H-3, pyrrole, $J = 5.9$ Hz), 7.1 (d, 1H, H-5, pyrrole, $J = 6.2$ Hz), 7.2 (s, 1H, H-5, pyridine), 7.45 (d, 2H, $J = 7.8$ Hz, Ph), 7.55 (d, 2H, $J = 7.8$ Hz, Ph), 9.5 (br s, 1H, NH) ppm; MS (EI, 70 eV): $m/z = 309$ (M^+, 100), 293 (19), 278 (41), 243 (25), 220 (13), 217 (17), 114 (22), 91 (13), 77 (32).

General procedure for the synthesis 2-thiopyrimidine derivatives

Thiourea (0.076 g, 1 mmol) was added to 1 mmol of **2a, 2b** in 50 cm^3 ethanolic potassium hydroxide (1%). The reaction mixture was refluxed for 4–6 h and then poured gradually with stirring into cold water. The solid formed was filtered off, washed with H_2O, and crystallized from suitable solvent to give **6a, 6b**.

3,4-Dihydro-4-(5-methylfuran-2-yl)-6-(1H-pyrrol-2-yl) pyrimidine-2(1H)-thione (**6a**, $C_{13}H_{13}N_3OS$)
In 0.2 g (77%) yield; M.p.: 272 °C (ethanol/DMF); IR (KBr): $\bar{\nu} = 3,250-3,260$ (3NH), 1215 (C=S) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): $\delta = 2.43$ (s, 3H, Me), 5.20 (d, 1H, H-4, pyrimidine, $J = 5.4$ Hz), 6.11 (dd, 1H, H-4, pyrrole,, $J = 5.7$, 6.1 Hz), 6.21 (d, 1H, H-4, furan, $J = 6.8$ Hz), 6.85 (d, 1H, H-3, furan, $J = 6.8$ Hz), 6.97 (d, 1H, H-3, pyrrole, $J = 5.7$ Hz), 7.35 (d, 1H, H-5, pyrrole, $J = 6.1$ Hz), 7.41 (dd, 1H, H-5, pyrimidine,, $J = 5.4$ Hz), 9.43 (br s, 1H, NH, exchangeable with D_2O), 10.12, 10.14 (br 2s, 2H, 2NH-pyrimidine, exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 259$ (M^+, 11), 239 (31), 211 (19), 187 (9), 109 (29), 98 (58), 83 (53), 71 (93), 56 (100).

4-(4-Chlorophenyl)-3,4-dihydro-6-(1H-pyrrol-2-yl) pyrimidine-2(1H)-thione (**6b**, $C_{14}H_{12}ClN_3S$)
In 0.27 g (69%) yield; M.p.: 251 °C (ethanol/DMF); IR (KBr): $\bar{\nu} = 3249-3356$ (3NH), 1217 (C=S), cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): $\delta = 5.19$ (d, 1H, H-4, pyrimidine, $J = 5.2$ Hz), 6.14 (dd, 1H, H-4, pyrrole, $J = 5.8$, 6.0 Hz), 7.1 (d, 1H, H-3, pyrrole, $J = 5.8$ Hz), 7.27 (d, 1H, H-5, pyrrole, $J = 6.0$ Hz), 7.33 (dd, 1H, H-5, pyrimidine, $J = 5.2$ Hz), 7.35 (d, 2H, $J = 7.8$ Hz, Ph), 7.39 (d, 2H, $J = 7.8$ Hz, Ph), 9.51 (br s, 1H, NH, exchangeable with D_2O), 10.15, 10.21 (br 2s, 2H, 2NH-pyrimidine, exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 389$ (M^+, 17), 357 (13), 345 (31), 310 (24), 280 (16), 217 (37), 114 (27), 91 (15), 77 (38), 56 (100).

General procedure for the synthesis isoxazoline derivatives

A mixture of 1 mmol **2a, 2b**, ~0.1 g hydroxylamine hydrochloride (1 mmol), and 0.082 g anhydrous sodium acetate (1 mmol) in 30 cm^3 glacial acetic acid was heated under reflux for 6 h. The reaction mixture was cooled, poured into ice, the obtained solid was collected by filtration, washed with water, air dried, and crystallized from suitable solvent to give **7a, 7b**.

4,5-Dihydro-5-(5-methylfuran-2-yl)-3-(1H-pyrrol-2-yl) isoxazole (**7a**, $C_{12}H_{12}N_2O_2$)
In 0.15 g (69%) yield; M.p.: 213 °C (AcOH); IR (KBr): $\bar{\nu} = 3332$ (NH), 1586 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): $\delta = 1.65$ and 1.80 (m, CH_2-isoxazole), 2.41 (s, 3H, Me), 5.15 (m, CH-isoxazole), 6.13 (dd, 1H, H-4, pyrrole, $J = 5.7$, 5.9 Hz), 6.24 (d, 1H, H-4, furan, $J = 6.4$ Hz), 6.86 (d, 1H, H-3, furan, $J = 6.4$ Hz), 6.98 (d, 1H, H-3, pyrrole, $J = 5.7$ Hz), 7.3 (d, 1H, H-5, pyrrole, $J = 5.9$ Hz), 9.11 (br s, 1H, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 216$ (M^+, 14), 185 (61), 170 (49), 109 (23), 98 (45), 83 (62), 71 (91), 56 (100).

5-(4-Chlorophenyl)-4,5-dihydro-3-(1H-pyrrol-2-yl) isoxazole (**7b,** $C_{13}H_{11}ClN_2O$)
In 0.18 g (73%) yield; M.p.: 231 °C (AcOH); IR (KBr): $\bar{\nu} = 3311$ (NH), 1582 (C=N), cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): $\delta = 1.6$ and 1.83 (m, CH_2-isoxazole), 4.9 (m, CH-isoxazole), 6.14 (dd, 1H, H-4, pyrrole $J = 5.6$, 5.9 Hz), 7.13 (d, 1H, H-3, pyrrole J = 5.7 Hz), 7.33 (d, 1H, H-5, pyrrole $J = 5.9$ Hz), 7.37 (d, 2H, $J = 7.8$ Hz, Ph), 7.42 (d, 2H, $J = 7.8$ Hz, Ph), 9.51 (br s, 1H, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 246$ (M^+, 32), 244 (69), 216 (9), 181 (12), 151 (36), 139 (13), 111 (27), 94 (100), 78 (30), 66 (41).

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