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ORIGINAL PAPER

Novel syntheses of some new 3,4-dihydrospiro{benzimidazo [1,2-*a*]pyridine-3,3′-indolin}-2′-one derivatives

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Abstract 2-Methylbenzimidazole **1** reacted with 3-dicyanomethylidine-1-ethyl-2-oxoindoline **2** in ethyl acetate to afford 1-amino-2-cyano-3,4-dihydro-1′-ethylspiro{benzimidazo[1,2-*a*]pyridine-3,3′-indolin}-2′-one **6**, which was used as a key intermediate in the synthesis of fused spiropolyheterocyclic derivatives of benzimidazopyridopyrimidine and/or benzimidazonaphthyridine nucleus incorporating an indoline moiety.

Keywords Synthesis · Spiro · Spiroheterocycles · Spiro{benzimidazo[1,2-*a*] pyridine-3,3′-indolin}

Introduction

Imidazole derivatives show diverse biological activities; for example, they are used as factor Xa inhibitors [1], alpha-2-adrenoceptor agonists [2], and antithrombotics [3].

Several annulated pyridines isolated from natural sources possess broad-spectrum therapeutic activity. Members of this class were found to be protectors against gastric erosion [4], coronary vasodilators, and blood-pressure-heightening agents [5]. They have also been shown to be tuberculostatic, antiviral, fungicidal, insecticidal, and pesticidal [6, 7], and pyrimidine derivatives have been used as adenosine kinase inhibitors [8].

In this context, and as a continuation of our previous work [9–16], we report herein on the synthesis of some new spiroheterocycles of benzimidazopyridines and benzimidazopyridopyrimidine and/or benzimidazonaphthyridine containing an indoline moiety.

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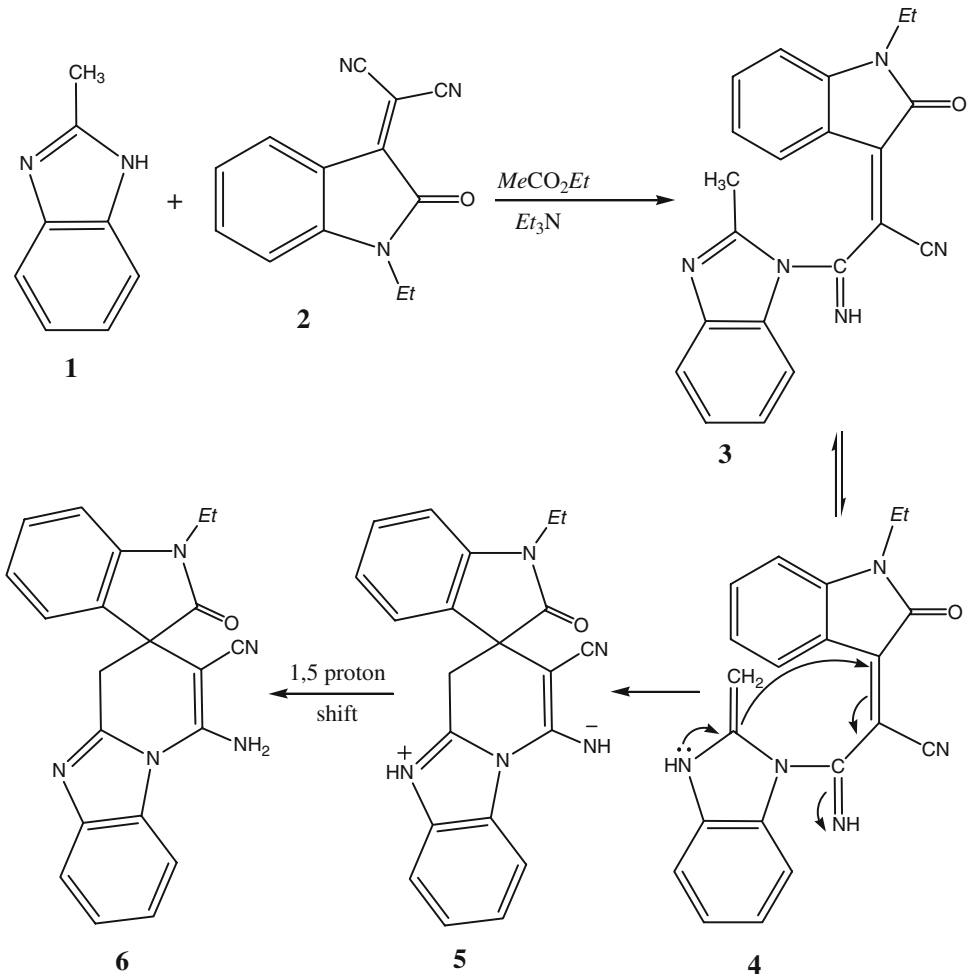
Results and discussion

Our syntheses started with the reaction of 2-methylbenzimidazole **1** with 3-dicyanomethylidine-1-ethyl-2-oxoindoline **2** in ethyl acetate in the presence of a catalytic amount of triethyl amine to afford 1-amino-2-cyano-3,4-dihydro-1′-ethylspiro{benzimidazo[1,2-*a*]pyridine-3,3′-indolin}-2′-one **6**. The formation of compound **6** can be rationalized as follows: initial nucleophilic attack by the *NH* of compound **1** on one nitrile carbon of **2** gives rise to intermediate **3**, which is in equilibrium with the tautomer **4** [17]. The latter exhibits nucleophilic character at the terminal methylene carbon atom, which attacks *C3* of **2** giving **5**, which is ultimately isolated as formula **6** (Scheme 1). The structure of the prepared compound **6** was established from these elemental analyses and spectral data. Its IR spectrum showed absorption bands at υ 3,300, 3,150 cm^{-1} for the (NH_2) group, a strong absorption band at 2,200 cm^{-1} corresponding to the (CN) group, and an absorption band at 1,705 cm^{-1} for the (C=O) group. Its ^{1}H-NMR spectrum in DMSO-d_6 showed signals at δ 6.35 (s, 2H, exchangeable with D_2O) for the NH_2 protons, 3.42 (q, 2H), 1.15 (t, 3H) for the ethyl protons, and a signal at 1.96 (s, 2H) for the methylene protons in the pyridine ring. Also, the ^{13}C-NMR spectra confirmed the structure of **6**, where the key signals were at δ 33.2 for the methylene carbon in the pyridine ring, 54.3 (quaternary sp^3 carbon), 117.5 (CN), and 170.9 (C=O).

Compound **6** was subjected to further reactions to give fused spiroheterocyclic systems incorporating a pyrimidine and/or a pyridine nucleus in addition to benzimidazole and indoline moieties.

Scheme 1



Reaction of **6** with formamide gave 4-amino-5,6-dihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6]pyrido[2,3-*d*]pyrimidine-5,3′-indolin}-2′-one **7**, while the reaction with formic acid afforded 3,5,6-trihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6] pyrido[2,3-*d*]pyrimidine-5,3′-indoline}-2′,4-dione **8**. Interaction of **6** with ethyl cyanoacetate in acetic acid gave 4-amino-3-cyano-1,5,6-trihydro-1′-ethylspiro{benzimidazo [1,2-*a*][1,8]naphthyridine-5,3′-indolin}-2,2′-dione **9**, while the reaction with *o*-phenylenediamine in absolute ethanol containing a few drops of pyridine yielded 1-amino-2-(1*H*-benzimidazol-2-yl)-3,4-dihydro-1′-ethylspiro{benzimidazo [1,2-*a*]pyridine-3,3′-indolin}-2′-one **10** (Scheme 2).

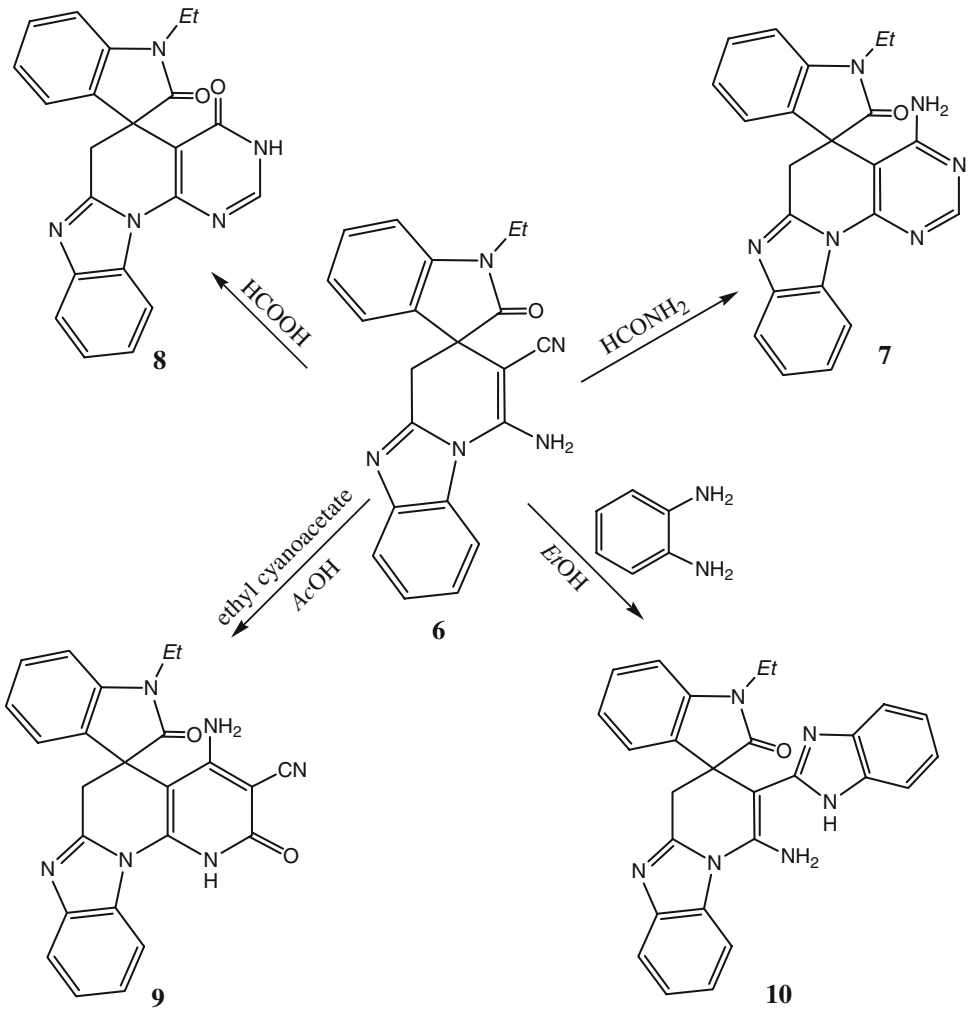
The chemical structures of the compounds (**7–10**) were identified from elemental analyses and spectral data. For example, the IR spectrum of compound **7** showed strong absorption bands at$\acute{\upsilon}$ 3,250, 3,100 cm^{-1} for the (NH_2) group, with an absence of the band corresponding to a cyano group.

The ^{1}H-NMR spectrum of compound **9** revealed signals at δ 10.05 (s, 1H, exchangeable with D_2O) for the NH proton, 7.98–6.46 (m, 8H) for the aromatic protons, and 6.09 (s, 2H, exchangeable with D_2O) for the NH_2 protons. The IR spectrum of compound **10** revealed an absence of a cyano group and the presence of absorption bands at $\acute{\upsilon}$ 3,350 cm^{-1} for the (NH) group, and 3,300, 3,200 cm^{-1} for the (NH_2) group.

Compound **8** was converted to its 4-chloro derivative **11** by refluxing with phosphorus oxychloride. The latter compound was reacted with hydrazine hydrate to give 5,6-dihydro-1′-ethyl-4-hydrazinospiro{benzimidazo[1′,2′:1,6] pyrido[2,3-*d*]pyrimidine-5,3′-indolin}-2′-one **12**. The latter compound was reacted with triethyl orthoformate to afford the corresponding 13,14-dihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6]pyrido[2,3-*d*] [1,2,4]triazolo[5″,1″-*f*]pyrimidine-14,3′-indolin}-2′-one **13**, while the reaction with acetic anhydride afforded the corresponding 13,14-dihydro-1′-ethyl-2-methylspiro{benzimidazo[1′,2′:1,6]pyrido-[2,3-*d*][1,2,4]triazolo[5″,1″-*f*]pyrimidine-14,3′-indolin}-2′ -one **14** [18–20] (Scheme 3).

The IR spectrum of compound **11** showed an absence of an absorption band corresponding to the (NH) group, while the IR spectrum of compound **12** revealed strong absorption bands at $\acute{\upsilon}$ 3,400, 3,300 cm^{-1} for the NH_2 group and

Scheme 2



3,200 cm^{-1} for the (NH) group. The IR spectra of compounds **13** and **14** showed the disappearance of bands corresponding to the (NH_2) and (NH) groups; the ^{1}H-NMR spectrum of **14** revealed an additive singlet signal at δ 2.99 for the methyl protons, and an absence of signals corresponding to NH and NH_2 protons.

Compound **9** converted to its 2-chloro derivative **15** by refluxing with phosphorus oxychloride. The latter compound was readily reacted with hydrazine hydrate in pyridine to give 3,4-diamino-5,6-dihydro-1′-ethylspiro{benzimidazo[1,2-*a*]pyrazolo[4′,3′-*g*][1,8]naphthyridine-5,3′-indolin}-2′-one **16** (Scheme 4).

The chemical structures of compounds **15** and **16** were deduced from elemental analyses and spectral data. For example, ^{1}H-NMR of compound **16** in DMSO-d_6 showed three singlet signals exchanged with D_2O at δ 6.42 for the NH proton, and 5.86 and 4.99 for the two NH_2 protons (Table 1).

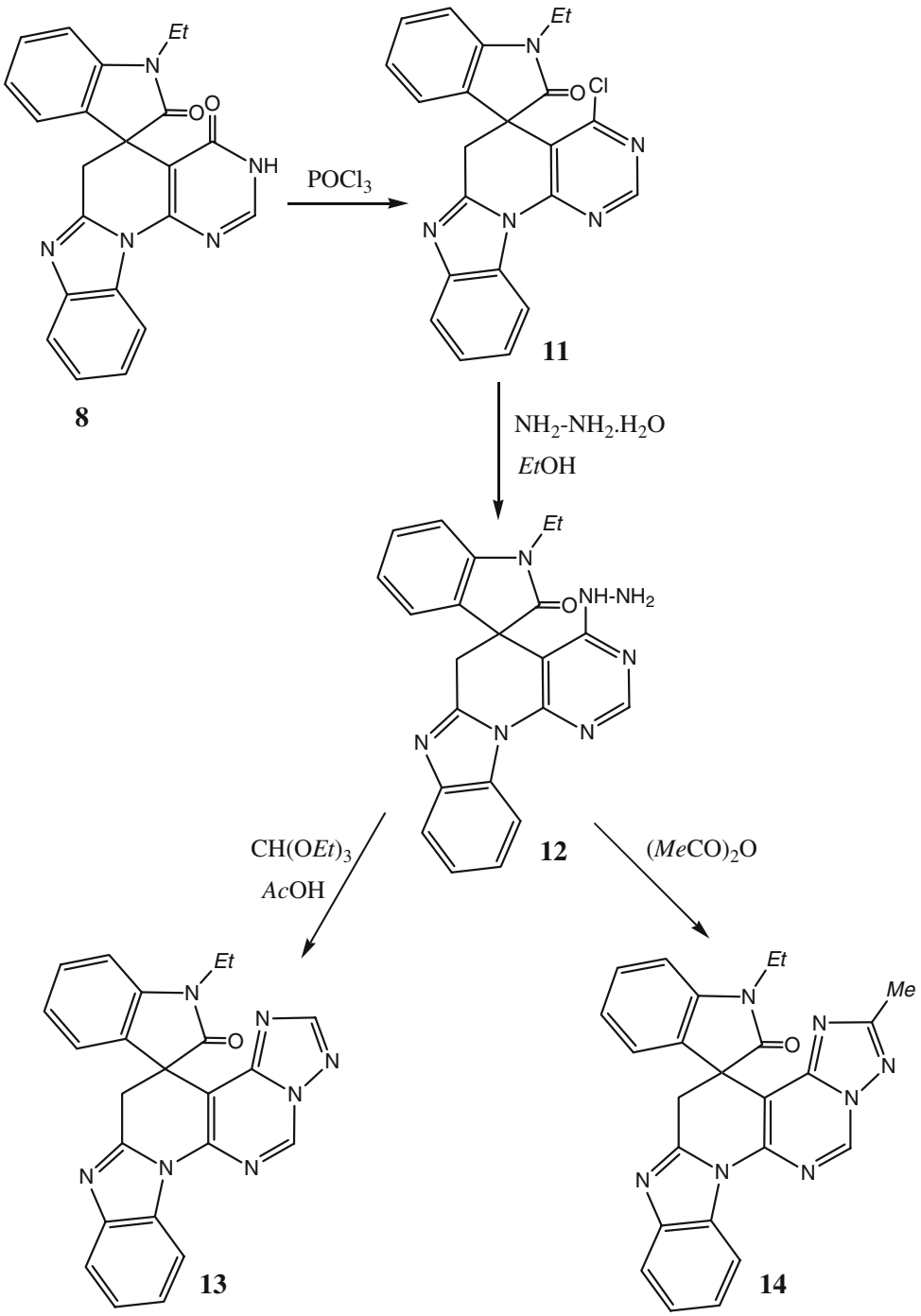
6,7-Dihydro-1′-Ethylspiro{benzimidazo[1′,2′:1,6]pyrido [2,3-*d*]benz-imidazo[2″,1″-*f*]pyrimidine-6,3′-indolin}-2′-one **17** was obtained through the cyclization reaction of compound **10** by refluxing with triethyl orthoformate, while 6,7,14-trihydro-1′-ethyl-2′-oxospiro{benzimidazo [1′,2′:1,6]pyrido[2,3-*d*]benzimidazo[2″,1″-*f*]pyrimidine-6,3′-indolin}-15-thione **18** was obtained by the reaction of **10** with carbon disulfide in pyridine (Scheme 5).

The IR spectrum of compound **18** revealed absorption bands at υ 3,200 and 1,440 cm^{-1} for the (NH) and (C=S) groups, respectively. Its ^{1}H-NMR spectrum in DMSO-d_6 showed a singlet signal at δ 11.71 upon exchange with D_2O, indicating an NH proton.

Experimental

The time required to complete each reaction was monitored by TLC. All melting points are uncorrected and were measured on a Gallenkamp (Loughborough, UK) apparatus. The IR spectra were recorded on a Shimadzu (Kyoto, Japan) 470 IR spectrometer (KBr) υ cm^{-1}. The ^{1}H and

Scheme 3

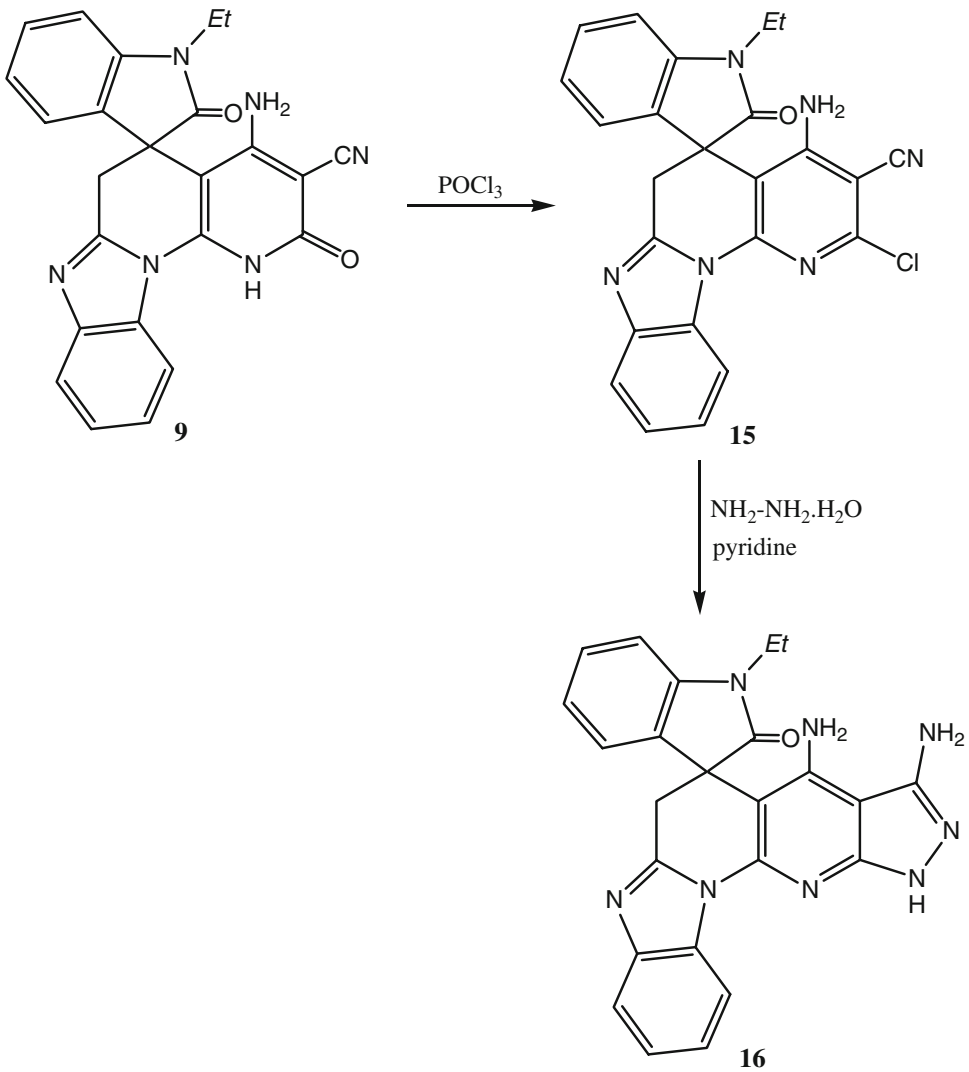


^{13}C-NMR spectra were measured on a Varian (Palo Alto, CA, USA) EM-200 MHz spectrometer with TMS used as internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Mass spectra were determined on a JEOL (Tokyo, Japan) 600 spectrometer. Column chromatography was performed with silica gel (230–400 mesh). Elemental analyses (C, H, N, and S) were performed on an Elementar Analysensysteme GmbH (Hanau, Germany) VarioEL $V_{2.3}$; the results were found to be in good agreement with the calculated values.

3-Dicyanomethylidine-1-ethyl-2-oxoindoline ***(2)***
Preparation was accomplished as described in [21–23] from 1*H*-indolin-2,3-dione (isatin).

1-Amino-2-cyano-3,4-dihydro-1′-ethylspiro{benzimidazo[1,2-a]pyridine-3,3′-indolin}-2′-one (**6**, $C_{21}H_{17}N_5O$)
A solution of 2-methylbenzimidazole **1** (1.32 g, 10 mmol) and 3-dicyanomethylidine-1-ethyl-2-oxoindoline **2** (2.23 g, 10 mmol) in 20 cm^3 of ethyl acetate and 1 cm^3 of triethyl amine was heated under reflux for 4 h. After cooling, the solvent was evaporated under vacuum. The residue was

Scheme 4



purified by silica-gel column chromatography using ethyl acetate-toluene (2:1) as eluent (R_f= 0.75). The product was collected and recrystallized from ethanol to afford brown crystals, yield 2.48 g (70%), mp 220–222 °C; IR (KBr): υ = 3,300–3,150 (NH_2), 2,200 (CN), 1,705 (C=O), 1,625 (C=N) cm^{-1}; EI-MS: *m/z* (%) = 355 (M^+, 1), 169 (92), 142 (54), 114 (100); ^{1}H-NMR (DMSO-d_6): δ = 7.85–6.59 (m, 8H, arom. protons), 6.35 (s, 2H, NH_2, D_2O exchangeable), 3.42 (q, 2H, CH_2-*Me*), 1.96 (s, 2H, CH_2), 1.15 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): δ = 12.3 (CH_3), 33.2 (CH_2), 43.5 (CH_2), 54.3 (quaternary C), 70.1 (C), 115.4 (2CH), 117.5 (CN), 122.2 (CH), 123.1 (2CH), 124.7 (CH), 127.5 (C), 128.1 (CH), 129.8 (CH), 130.6 (C), 138.9 (C), 141.5 (C=N), 144.7 (C), 156.9 (C), 170.9 (C=O) ppm.

4-Amino-5,6-dihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6] pyrido[2,3-d] pyrimidine-5,3′-indolin}-2′-one
(**7**, $C_{22}H_{18}N_6O$)

A mixture of compound **6** (0.355 g, 1 mmol) and 5 cm^3 of formamide was heated under reflux for 5 h. The reaction mixture was allowed to cool, and the product formed was filtered off, washed with water, dried, and recrystallized from ethanol: acetic acid (2:1) to give brown crystals, yield 0.23 g (60%), mp 230–232 °C; IR (KBr): υ = 3,250–3,100 (NH_2), 1,705 (C=O), 1,645 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 8.63 (s, 2H, NH_2, D_2O- exchangeable), 8.00 (s, 1H, CH), 7.86–6.64 (m, 8H, arom. protons), 3.32 (q, 2H, CH_2-*Me*), 1.95 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

3,5,6-Trihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6]pyrido [2,3-d] pyrimidine-5,3′-indoline}-2′,4-dione
(**8**, $C_{22}H_{17}N_5O_2$)

A mixture of compound **6** (0.355 g, 1 mmol) and 10 cm^3 of formic acid was heated under reflux for 4 h; the reaction mixture was cooled, the formed solid product was filtered off, dried and recrystallized from acetic acid to give dense yellow crystals, yield 0.25 g (67%), mp 241–243 °C; IR (KBr): υ = 3,200 (NH), 1,705 (C=O), 1,640 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 10.54 (s, 1H, NH, D_2O-exchangeable), 8.22 (s, 1H, CH), 7.96–6.48 (m, 8H, arom.

Table 1 The results from elemental analyses of the new synthesized compounds (**6**–**18**)

Comp. No.	Elemental analyses (C, H, N, S, and halogen) (%)	
6	Calcd.	**C**; 70.97 **H**; 4.82 **N**; 19.71
	Found	**C**; 70.86 **H**; 4.73 **N**; 19.64
7	Calcd.	**C**; 69.10 **H**; 4.74 **N**; 21.98
	Found	**C**; 69.09 **H**; 4.70 **N**; 21.91
8	Calcd.	**C**; 68.92 **H**; 4.47 **N**; 18.27
	Found	**C**; 68.79 **H**; 4.23 **N**; 18.19
9	Calcd.	**C**; 68.24 **H**; 4.29 **N**; 19.89
	Found	**C**; 68.17 **H**; 4.20 **N**; 19.82
10	Calcd.	**C**; 72.63 **H**; 4.97 **N**; 18.82
	Found	**C**; 72.51 **H**; 4.86 **N**; 18.78
11	Calcd.	**C**; 65.76 **H**; 4.01 **N**; 17.43 **Cl**; 8.82
	Found	**C**; 65.58 **H**; 3.90 **N**; 17.35 **Cl**; 8.77
12	Calcd.	**C**; 66.49 **H**; 4.82 **N**; 24.67
	Found	**C**; 66.42 **H**; 4.74 **N**; 24.57
13	Calcd.	**C**; 67.80 **H**; 4.21 **N**; 24.06
	Found	**C**; 67.73 **H**; 4.09 **N**; 23.98
14	Calcd.	**C**; 68.40 **H**; 4.54 **N**; 23.26
	Found	**C**; 68.32 **H**; 4.45 **N**; 23.19
15	Calcd.	**C**; 65.38 **H**; 3.89 **N**; 19.06 **Cl**; 8.04
	Found	**C**; 65.28 **H**; 3.80 **N**; 18.96 **Cl**; 7.95
16	Calcd.	**C**; 66.04 **H**; 4.62 **N**; 25.67
	Found	**C**; 65.97 **H**; 4.54 **N**; 24.59
17	Calcd.	**C**; 73.67 **H**; 4.42 **N**; 18.41
	Found	**C**; 73.56 **H**; 4.35 **N**; 18.34
18	Calcd.	**C**; 68.83 **H**; 4.13 **N**; 17.20 **S**; 6.56
	Found	**C**; 68.74 **H**; 4.00 **N**; 17.00 **S**; 6.47

protons), 3.34 (q, 2H, CH_2-*Me*), 1.96 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): $\delta = 12.4$ (CH_3), 33.6 (CH_2), 43.4 (CH_2), 54.7 (quaternary C), 113.3 (C), 115.3 (2CH), 122.1 (CH), 123.0 (2CH), 124.8 (CH), 127.5 (C), 127.9 (CH), 129.7 (CH), 130.6 (C), 138.8 (C), 141.5 (C=N), 141.9 (C), 144.9 (C), 150.1 (CH=N), 162.7 (C=O), 170.9 (C=O) ppm.

4-Amino-3-cyano-1,5,6-trihydro-1′-ethylspiro{benzimidazo[1,2-a][1,8]naphthyridine-5,3′-indoline}-2,2′-dione (**9**, $C_{24}H_{18}N_6O_2$)

A mixture of compound **6** (1.77 g, 5 mmol), and ethyl cyanoacetate (0.57 g, 2 mmol) in 20 cm^3 of acetic acid was heated under reflux for 6 h. The solid product formed during reflux was collected by filtration, washed well with ethanol, dried, and recrystallized from acetic acid to give brown crystals, yield 1.27 g (60%), mp 255–257 °C; IR (KBr): $\upsilon = 3{,}300$–$3{,}200$ (NH_2), 3,100 (NH), 2,200 (CN), 1,700 (C=O), 1,620 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): $\delta = 10.05$ (s, 1H, NH, D_2O-exchangeable), 7.98–6.46 (m, 8H, arom. protons), 6.09 (s, 2H, NH_2, D_2O-exchangeable), 3.35 (q, 2H, CH_2-*Me*), 1.90 (s, 2H, CH_2), 1.13 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): $\delta = 12.4$ (CH_3), 34.5 (CH_2), 43.7 (CH_2), 53.3 (quaternary C), 69.7 (C), 102.8 (C), 115.2 (2CH), 115.9 (CN), 122.1 (CH), 122.4 (C), 123.0 (2CH), 124.9 (CH), 127.4 (C), 127.9 (CH), 129.8 (CH), 130.6 (C), 138.8 (C), 141.5 (C=N), 144.9 (C), 161.8 (C=O), 170.9 (C=O), 177.2 (C) ppm.

1-Amino-2-(1H-benzimidazol-2-yl)-3,4-dihydro-1′-ethylspiro{benzimidazo[1,2-a]pyridine-3,3′-indolin}-2′-one (**10**, $C_{27}H_{22}N_6O$)

A mixture of compound **6** (3.55 g, 10 mmol), *o*-phenylenediamine (1.08 g, 10 mmol) in 20 cm^3 of absolute ethanol containing a few drops of pyridine was heated under reflux for 12 h. The solid product obtained after cooling was purified by column chromatography using silica gel as stationary phase and ethyl acetate-benzene (5:2) as eluent ($R_f = 0.50$). The product was collected and recrystallized from acetic acid to give red crystals, yield 1.78 g (40%), mp 260–262 °C; IR (KBr): $\upsilon = 3{,}350$ (NH), 3,300–3,200 (NH_2), 1,705 (C=O), 1,620 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): $\delta = 12.00$ (s, 1H, NH, D_2O- exchangeable), 8.00–6.31 (m, 12H, arom. protons), 5.76 (s, 2H, NH_2, D_2O-exchangeable), 3.34 (q, 2H, CH_2-*Me*), 2.00 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): $\delta = 12.4$ (CH_3), 34.2 (CH_2), 43.7 (CH_2), 60.5 (quaternary C), 99.3 (C), 115.3 (4CH), 122.1 (CH), 123.1 (4CH), 124.9 (CH), 127.6 (C), 127.9 (CH), 129.7 (CH), 130.7 (C), 137.4 (C), 138.9 (3C), 141.5 (2C=N), 144.9 (C), 170.9 (C=O) ppm.

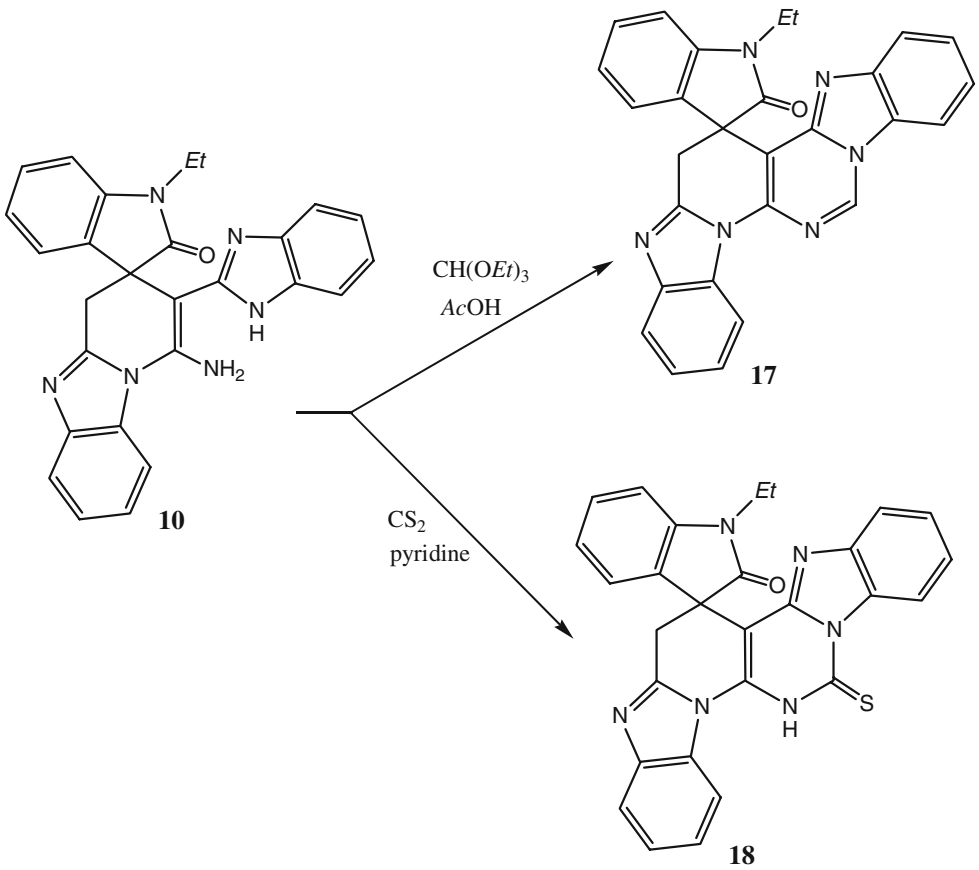
4-Chloro-5,6-dihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6]pyrido[2,3-d] pyrimidine-5,3′-indolin}-2′-one (**11**, $C_{22}H_{16}ClN_5O$)

Compound **8** (1.92 g, 5 mmol) was refluxed in 15 cm^3 phosphorus oxychloride for 4 h, cooled, and then poured into ice/water (containing a few drops of pyridine) to give a precipitate, which was collected by filtration. This was dried and recrystallized from ethanol to give orange crystals, yield 1.16 g (58%), mp 199–201 °C; IR (KBr): $\upsilon = 1{,}700$ (C = O), 1,625 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): $\delta = 8.35$ (s, 1H, CH), 8.00–6.54 (m, 8H, arom. protons), 3.36 (q, 2H, CH_2-*Me*), 2.01 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

5,6-Dihydro-1′-ethyl-4-hydrazinospiro{benzimidazo[1′,2′:1,6]pyrido[2,3-d] pyrimidine-5,3′-indolin}-2′-one (**12**, $C_{22}H_{19}N_7O$)

A mixture of compound **11** (0.40 g, 1 mmol) and 10 cm^3 hydrazine hydrate was heated under reflux for 1 h, then 20 cm^3 of ethanol was added and the reaction mixture was further heated under reflux for 4 h. After cooling, the solid product formed was collected by filtration. It was then dried and recrystallized from ethanol to give dense yellow crystals, yield 0.24 g (60%), mp 242–244 °C; IR (KBr): $\upsilon = 3{,}400$–$3{,}300$ (NH_2), 3,200 (NH), 1,705 (C=O), 1,645

Scheme 5



(C=N) cm^{-1}; ^{1}H-NMR (*CDCl₃*): $\delta = 8.25$ (s, 1H, CH), 7.97–6.41 (m, 8H, arom. protons), 5.80 (s, 1H, NH, D_2O-exchangeable), 4.60 (s, 2H, NH_2, D_2O-exchangeable), 3.32 (q, 2H, CH_2-*Me*), 1.92 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

13,14-Dihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6]pyrido [2,3-d][1,2,4]triazolo[5″,1‴-f]pyrimidine-14,3′-indolin}-2′-one (**13**, $C_{23}H_{17}N_7O$)

A few drops of acetic acid were added to a suspension of compound **12** (0.40 g, 1 mmol) in 10 cm^3 triethyl orthoformate, and the reaction mixture was heated under reflux for 6 h. The solvent was concentrated and the residue was subjected to silica-gel column chromatography using toluene-ethyl acetate (3:2) as eluent ($R_f = 0.27$). The product was collected and recrystallized from acetic acid to give orange crystals, yield 0.20 g (50%), mp 251–253 °C; IR (KBr): $\upsilon = 1{,}705$ (C=O), 1,625 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): $\delta = 7.97$–6.41 (m, 10H, arom. protons), 3.33 (q, 2H, CH_2-*Me*), 1.94 (s, 2H, CH_2), 1.11 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): $\delta = 12.4$ (CH_3), 38.9 (CH_2), 43.6 (CH_2), 58.5 (quaternary C), 115.2 (2CH), 122.1 (CH), 123.0 (2CH), 124.9 (CH), 127.9 (CH), 129.3 (C), 129.8 (CH), 135.1 (C), 138.2 (C), 138.9 (C), 139.6 (CH=N), 141.4 (C=N), 144.7 (C), 148.6 (C=N), 150.7 (CH=N), 164.1 (C), 170.9 (C=O) ppm.

13,14-Dihydro-1′-ethyl-2-methylspiro{benzimidazo [1′,2′:1,6]pyrido[2,3-d] [1,2,4]triazolo[5″,1‴-f]pyrimidine-14,3′-indolin}-2′-one (**14**, $C_{24}H_{19}N_7O$)

Compound **12** (0.40 g, 1 mmol) in 10 cm^3 acetic anhydride was heated under reflux for 5 h. The reaction mixture was allowed to cool and then poured into ice/water mixture. The formed solid product was collected by filtration, washed with water several times, dried and recrystallized from acetic acid to give orange crystals, yield 0.22 g (52%) mp 258–260 °C; IR (KBr): $\upsilon = 1{,}705$ (C=O), 1,625 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): $\delta = 8.31$ (s, 1H, CH), 7.95–6.64 (m, 8H, arom. protons), 3.34 (q, 2H, CH_2-*Me*), 2.99 (s, 3H, CH_3), 1.92 (s, 2H, CH_2), 1.13 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): $\delta = 12.4$ (CH_3), 18.7 (CH_3), 39.1 (CH_2), 43.6 (CH_2), 58.6 (quaternary C), 115.2 (2CH), 122.1 (CH), 123.0 (2CH), 124.9 (CH), 127.9 (CH), 129.5 (C), 129.8 (CH), 135.1 (C), 138.1 (C), 138.9 (C), 139.4 (CH=N), 141.4 (C=N), 144.8 (C), 148.6 (C=N), 158.0 (C=N), 164.0 (C), 170.9 (C=O) ppm.

4-Amino-2-chloro-3-cyano-5,6-dihydro-1′-ethyl-spiro{benzimidazo[1,2-a] [1,8]naphthyridine-5,3′-indolin}-2′-one (**15**, $C_{24}H_{17}ClN_6O$)

Compound **9** (0.84 g, 2 mmol) was refluxed in 10 cm^3 phosphorus oxychloride for 5 h, cooled, poured into

ammonia-ice/water mixture to give a precipitate, which was collected by filtration, dried and recrystallized from acetic acid to give red crystals, yield 0.56 g (63%), mp 203–205 °C; IR (KBr): $\acute{\upsilon}$ = 3,250–3,100 (NH_2), 2,200 (CN), 1,705 (C=O), 1,645 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 7.97–6.31 (m, 8H, arom. protons), 6.05 (s, 2H, NH_2, D_2O-exchangeable), 3.34 (q, 2H, CH_2-*Me*), 1.96 (s, 2H, CH_2), 1.14 (t, 3H, CH_3) ppm.

3,4-Diamino-5,6-dihydro-1′-ethylspiro{benzimidazo[1,2-a] pyrazolo[4′,3′-g][1,8]naphthyridine-5,3′-indolin}-2′-one (**16**, $C_{24}H_{20}N_8O$)

A mixture of compound **15** (0.44 g, 1 mmol) and 5 cm^3 hydrazine hydrate was heated under reflux in 10 cm^3 of pyridine for 7 h. The solid product, which separated from the cold solution, was purified by silica-gel column chromatography using ethyl acetate as eluent (R_f = 0.30), and recrystallized from acetic acid to give scarlet red crystals, yield 0.19 g (45%), mp 267–269 °C; IR (KBr): $\acute{\upsilon}$ = 3,400–3,300 (NH_2), 3,220–3,140 (NH_2), 3,100 (NH), 1,705 (C=O), 1,645 (C=N), 1,625 (C=N) cm^{-1}; EI-MS: *m/z* (%) = 436 (M^+, 50), 391 (53), 257 (60), 197 (90), 41 (100); ^{1}H-NMR (DMSO-d_6): δ = 7.99–6.59 (m, 8H, arom. protons), 6.42 (s, 1H, D_2O-exchangeable), 5.86 (s, 2H, NH_2, D_2O-exchangeable), 4.99 (s, 2H, D_2O-exchangeable), 3.33 (q, 2H, CH_2-*Me*), 1.91 (s, 2H, CH_2), 1.11 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): δ = 12.4 (CH_3), 39.0 (CH_2), 43.6 (CH_2), 58.6 (quaternary C), 90.5 (C), 115.2 (2CH), 117.5 (C), 122.1 (CH), 123.0 (2CH), 124.9 (CH), 127.9 (CH), 129.8 (CH), 135.1 (C), 138.1 (C), 138.8 (C), 141.5 (C=N), 144.8 (C), 151.8 (2C=N), 155.7 (C), 158.4 (C), 170.9 (C=O) ppm.

6,7-Dihydro-1′-ethylspiro{benzimidazo[1′,2′:1,6]pyrido [2,3-d]benzimidazo[2″,1‴-f]pyrimidine-6,3′-indolin}-2′-one (**17**, $C_{28}H_{20}N_6O$)

A few drops of acetic acid were added to a suspension of compound **10** (0.44 g, 1 mmol) in 10 cm^3 triethyl orthoformate, and then the reaction mixture was heated under reflux for 8 h. The solid product, which separated from the cold solution, was filtered off and recrystallized from acetic acid to give dense yellow crystals, yield 0.20 g (45%), mp 280–282 °C; IR (KBr): $\acute{\upsilon}$ = 1,705 (C=O), 1,640 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 8.31 (s, 1H, CH), 7.95–6.41 (m, 12H, arom. protons), 3.34 (q, 2H, CH_2-*Me*), 1.93 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

6,7,14-Trihydro-1′-ethyl-2′-oxospiro{benzimidazo [1′,2′:1,6]pyrido[2,3-d]benzimidazo[2″,1‴-f]pyrimidine-6,3′-indolin}-15-thione (**18**, $C_{28}H_{20}N_6OS$)

A mixture of compound **10** (0.44 g, 1 mmol) and 5 cm^3 of carbon disulfide in 10 cm^3 of pyridine was heated under reflux for 20 h. The solid product thus formed on hot was collected by filtration, washed several times with water, dried, and recrystallized from methanol to give brown crystals, yield 0.18 g (38%), mp > 300 °C; IR (KBr): $\acute{\upsilon}$ = 3,200 (NH), 1,705 (C=O), 1,645 (C=N), 1,440 (C=S) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 11.71 (s, 1H, NH, D_2O-exchangeable), 7.95–6.40 (m, 12H, arom. protons), 3.34 (q, 2H, CH_2-*Me*), 1.98 (s, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm; ^{13}C-NMR (DMSO-d_6): δ = 12.4 (CH_3), 34.3 (CH_2), 43.7 (CH_2), 60.7 (quaternary C), 99.5 (C), 115.2 (4CH), 122.1 (CH), 123.1 (4CH), 124.8 (CH), 127.8 (C), 127.9 (CH), 129.8 (CH), 130.7 (2C), 137.4 (C), 138.9 (2C), 141.5 (2C=N), 144.9 (C), 170.9 (C=O), 182.0 (C=S) ppm.

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