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A furan ring expansion approach to the synthesis of novel pyridazino-psoralen derivatives

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Abstract—A convenient preparation of the parent tetrahydrobenzodifuran **2** was developed from resorcinol. The oxidation of one or both furan rings of this key intermediate was accomplished with DDQ and the resulting benzodifuran was subsequently reacted with 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine to afford the expected pyridazino-psoralen derivative in good yield. This simple method allowed the efficient preparation of a pyridazino-psoralen derivative with a formyl group at C-7, which was introduced by directed *ortho*-lithiation in the intermediate **2**. An aminoalkyl side-chain was also introduced to the tetracyclic skeleton through the aldehyde functionality in a reductive amination process, which was accompanied by an unprecedented reduction of the pyridazine ring.

1. Introduction

Psoralens form a group of natural or synthetic compounds that are of great pharmacological interest.[1] One of the most important applications of these compounds is in the field of photochemotherapy, where psoralens are capable of undergoing photoaddition with thymine units present in DNA.[2] However, the utility of the most effective compounds in this class is limited by side-effects that are mainly related to their ability to cross-link the two strands of the DNA helix.[3] One of the most promising strategies to obtain monofunctional psoralens involves incorporating one of the reactive double bonds in a benzene nucleus by forming benzopsoralens (Fig. 1). This approach results in molecules that have a high propensity for intercalation and photoreaction with DNA and also helps to overcome some of the negative phototoxic effects.[4]

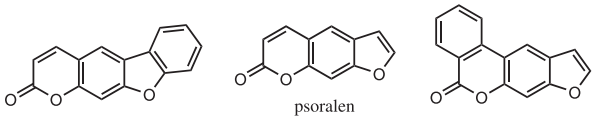

Figure 1.

With this information in mind, we embarked on the preparation of nitrogenated analogues of benzopsoralens reasoning that the inclusion of nitrogen atoms in the polycyclic skeleton may lead to improved interaction with DNA.[5] In particular, we were encouraged by the remarkable antiproliferative activity recently reported for pyrone side tetracyclic psoralen derivatives.[6] Prompted by this result and the widely used Diels–Alder of 1,2,4,5-tetrazines;[7] we focused on the development of a general synthetic route to novel pyridazino psoralens in which the pyridazine ring is attached to the pyrone nucleus of the psoralen skeleton.[8]

In a preliminary attempt to fuse a pyridazine ring to psoralens using 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine, we observed that the cycloaddition was accompanied by opening of the furan ring and concomitant expansion to a pyrone ring upon intramolecular transesterification.[9] We decided to exploit this interesting domino reaction pathway[10] to explore the use of benzodifuran derivatives to prepare these novel pyridazino-psoralens (Scheme 1).

2. Results and discussion

An important intermediate in our synthetic proposal is the tetrahydrobenzodifuran **2** and the synthesis of this compound has been reported from 6-hydroxy-dihydrobenzofuran in three steps.[11] Our initial goal was to develop a more convenient preparation of this intermediate and, in this respect, we envisaged a route based on a magnesium mediated cyclization process, which was reported by Nichols et al. for similar symmetrical benzodifuran derivatives.[12] The synthesis of this compound commenced with dialkylation of resorcinol using excess 1-bromo-2-

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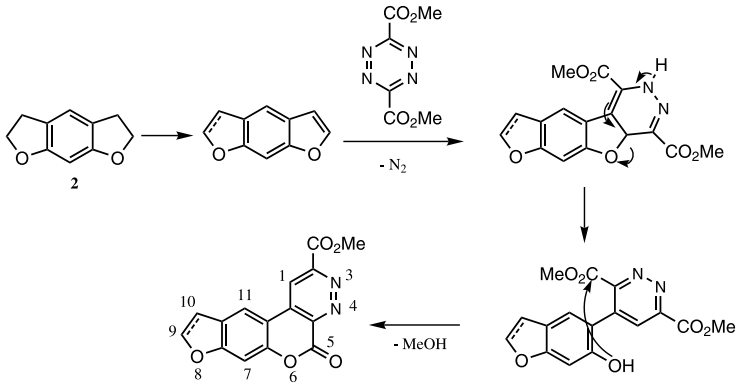
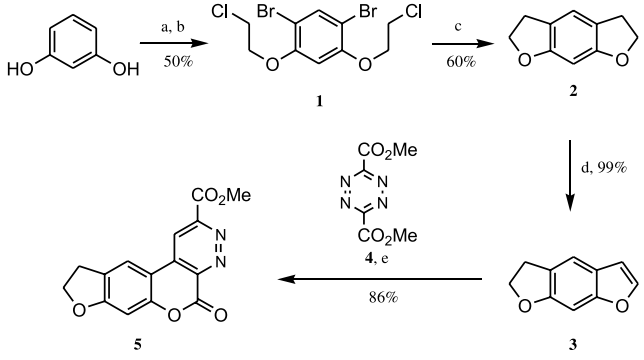


Scheme 1.

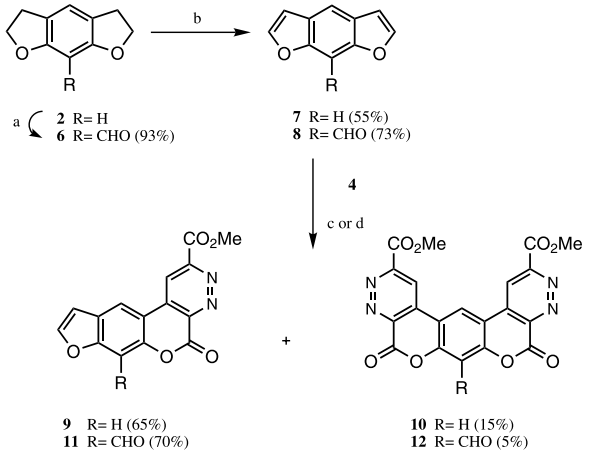
chloroethane and potassium carbonate in acetone reflux. Aromatic dibromination was accomplished using bromine in acetic acid and the product was subjected to Grignard conditions to effect ring closure[13] and afford the desired compound **2** (Scheme 2). This three step procedure only require one chromatographic purification and allowed the preparation of pure compound **2** in useful scale quantities (4.5 g). Starting from other commercially available or easily prepared resorcinol derivatives, this procedure could also be extended to other tetrahydrobenzodifuran derivatives.



Scheme 2. (a) $BrCH_2CH_2Cl$, K_2CO_3, $(CH_3)_2CO$, reflux, 48 h; (b) Br_2, AcOH, rt, 3 h; (c) Mg, EtMgBr (cat) , THF, reflux, 4 h; (d) 1 equiv DDQ, dioxane, rt, 2 h; (e) dioxane, reflux, 6 h.

With an efficient synthesis of **2** established, we attempted the dehydrogenation of only one dihydrofuran ring in order to achieve ring expansion in the Diels–Alder reaction with the tetrazine **4**. It was believed that this approach would avoid competition through reaction of the other ring. Selective oxidation of a dihydrofuran ring of **2** was accomplished using 1 equiv of DDQ in dioxane at room temperature to afford **3** in almost quantitative yield. This result was very satisfactory because this simple conventional oxidation method furnished the unsymmetrical compound **3** in excellent yield; compound **3** could also prove very useful for a variety of different synthetic purposes.[14] The Diels–Alder reaction between tetrazine **4** and compound **3** was performed in refluxing dioxane and gave the expected compound **5**. Under these conditions, analytically pure **5** was obtained in 86% yield by simple filtration of the cold reaction mixture (Scheme 2).

Although the oxidation of the residual dihydrofuran ring in compound **5** seems reasonable, the very low solubility of this compound in common organic solvents is a serious limitation in terms of reactivity. At this point, we examined the selectivity of the Diels–Alder reaction of benzodifurans. Oxidation of both dihydrofuran rings of compound **2** was performed using an excess of DDQ in refluxing dioxane and afforded compound **7** in 55% yield.[15] The Diels–Alder reaction of benzodifuran **7** with tetrazine **4** furnished the expected compound **9** in 65% yield; this compound was isolated pure after filtration of the cold reaction mixture. The filtrate of this reaction was then treated with boiling acetic acid and the symmetrical compound **10** crystallized in 15% yield (Scheme 3).



Scheme 3. (a) (i) *n*-BuLi, Et_2O, −78 °C, then 0 °C, 4 h; (ii) DMF, 0 °C, then rt, 16 h; (b) 3.3 equiv DDQ, dioxane, reflux, 18 h; (c) dioxane, reflux, 2 h; (d) 6:1 dioxane/AcOH, reflux, 8 h.

It was anticipated that analogues of compound **9** bearing an aldehyde group at C-7 would allow the facile preparation of side chain analogues at a later stage in the synthesis of these tetracyclic compounds. With this aim in mind, we planned to examine the reactivity of benzodifuran **8**.

Regioselective *ortho* lithiation of compound **2** followed by quenching the resulting anion with DMF furnished compound **6** in 93% yield. The oxidation of this intermediate with excess of DDQ to give **8** was performed under identical conditions to the oxidation of **2**, but a higher yield (73%) was obtained. Nichols et al. have also noted that the yield of this oxidation is strongly dependent on the nature of the substituents attached to the benzodifuran nucleus.[16] The

first attempt at a Diels–Alder reaction between compound **8** and tetrazine **4** in refluxing dioxane was unsuccessful. We reasoned that the final lactonization would prove difficult due to an intramolecular hydrogen bond with the formyl group that stabilizes the open intermediate (Fig. 2). The stabilizing effect was overcome by performing the reaction in the presence of acetic acid as a protic additive. This modification allowed compounds **11** and **12** to be obtained in 70 and 5% yield, respectively. Once again, the major compound **11** crystallized pure from the reaction mixture and the minor compound was recrystallised from AcOH. As one would anticipate,[13] the introduction of the electron-withdrawing formyl group in the benzodifuran nucleus decreased the reactivity of the dienophile in the inverse-electron demand Diels–Alder reaction; more importantly, such a change increased the monoadduct **11**/diadduct **12** ratio.

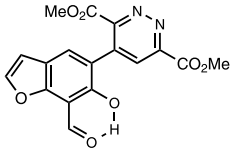


Figure 2.

Finally, we examined the attachment of an aminoalkyl chain to the skeleton of compound **11** through its formyl group on the basis that this kind of side chain usually plays an important role in the biological activity of DNA intercalant agents and other drugs.[17] The reductive amination of compound **11** was performed with *N*,*N*-dimethylethylenediamine in the presence of excess of $NaCNBH_3$.[18] To our surprise, the reduction of the pyridazine ring also occurred under the reaction conditions and compounds **13** and **14** were obtained in 65 and 30% yield, respectively. Unfortunately, assays with 0.5, 1.0 and 1.5 equiv of $NaCNBH_3$ afforded complex mixtures of products. The reaction was also performed with 1.1 equiv of $NaBH(OAc)_3$,[19] but no single major product was detected and further experiments are required to obtain the expected fully aromatised compound. Nevertheless, it was considered appropriate to report this preliminary result because this reduction of the pyridazine ring is unprecedented and could be a valuable synthetic tool in future studies (Scheme 4).[20]

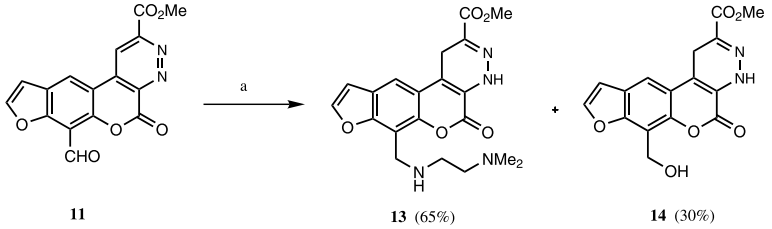
In conclusion, we have described a general procedure for the preparation of novel pyridazino-psoralens, that is both convenient and operationally simple. The synthesis is based on the Diels–Alder reaction between 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine and benzodifuran derivatives. This reaction is followed by a domino furan ring expansion to give a pyrone nucleus. Given the fact that benzofurocoumarins have been shown to possess significant photochemotherapeutic activity, ready access to these new pyridazine analogues provides avenues for investigations.

3. Experimental

3.1. General

All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Solvents were distilled and dried before use-except DMF, which was purchased anhydrous from Aldrich. Reagents were purchased from Aldrich and used without further purification. Chromatographic purification of products was accomplished using forced flow chromatography on silica gel 60 (230–400 mesh). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm). Melting points were determined in capillary tubes using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1640FT spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer at 300 and 75.5 MHz, respectively, using TMS as internal standard (chemical shifts are given as δ values, J in Hz). Mass spectra were obtained using a Hewlet Packard 5988A spectrometer.

3.1.1. 1,5-Dibromo-2,4-bis(2-chloroethoxy)benzene (1). A mixture of resorcinol (10.00 g, 91 mmol), 1-bromo-2-chloroethane (60 mL, 728 mmol), finely powdered K_2CO_3 (38.00 g, 137 mmol) and acetone (60 mL) was stirred and heated at reflux under argon for 72 h. The reaction was cooled to room temperature and filtered through a short pad of Celite 535. The Celite was washed with CH_2Cl_2, and the filtrate and washes were combined and evaporated to dryness by rotatory evaporation. The residue was partitioned between Et_2O and H_2O. The organic phase was extracted with 2 M NaOH (2×100 mL), then H_2O (2×100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated under vacuum. The resulting yellow solid (11.10 g) was suspended in glacial acetic acid (30 mL) and a solution of Br_2 (6 mL) in AcOH (15 mL) was added dropwise at 0–5 °C. The reaction mixture was allowed to reach room temperature and stirred for 3 h. The mixture was poured into ice/water (50 mL) and stirred for 15 min. The precipitate was filtered off and the solid was washed with cold 1:1 AcOH/H_2O (2×50 mL), then with cold H_2O until neutral pH (5×50 mL) and dried under vacuum with P_2O_5 until constant weight (17.73 g, 50%); mp 102–105 °C. ^1H NMR ($CDCl_3$) δ 7.60 (s, 1H, H_6), 6.45 (s, 1H, H_3), 3.80 (t, 4H, J=8.95 Hz, $2CH_2$), 3.07 (t, 4H, J=8.95 Hz, $2CH_2$).



Scheme 4. (a) $NH_2CH_2CH_2NMe_2$, $NaCNBH_3$, DMF–AcOH, rt, 7 h.

EI-MS *m/z* (%) 396 (34), 394 (92), 392 (97), 390 (37), 332 (38), 330 (52), 269 (51), 268 (100), 266 (51).

3.1.2. 2,3,5,6-Tetrahydrobenzo[1,2-*b*;5,4-*b*′]difuran (2). To a suspension of magnesium turnings (3.40 g, 141 mmol) in anhydrous THF (40 mL) was slowly added EtMgBr (3.4 mL, 10 mmol, 3 M solution in Et_2O). An anhydrous THF solution (115 mL) of the dibrominated compound **1** (18.20 g, 46.2 mmol) was then added dropwise under argon atmosphere such that the internal reaction temperature did not exceed 40 °C. Upon completion of the addition, the reaction was heated under reflux for 3 h, after which time TLC (95:5 hexane/EtOAc) indicated completion of the reaction. The reaction was then cooled to room temperature and 1 M HCl (200 mL) was carefully added while cooling with an external ice/water bath. Upon cessation of gas evolution, the solution was extracted with Et_2O (3× 300 mL). The organic layers were combined and washed with aqueous 1 M NaOH (5×75 mL), brine (50 mL), dried (Na_2SO_4), filtered, and evaporated to afford a tan solid (6.16 g). This solid was purified by column chromatography (95:5 hexane/EtOAc) to yield a white solid (4.45 g, 60%); mp 60–63 °C (lit.[11] 75 °C). ^{1}H NMR ($CDCl_3$) δ 6.93 (m, 1H, H_4), 6.26 (s, 1H, H_8), 4.53 (t, 4H, J=8.95 Hz, H_2+H_6), 3.07 (t, 4H, J=8.95 Hz, H_3+H_5). ^{13}C NMR ($CDCl_3$) δ 160.25, 120.31 (CH), 118.16, 92.57 (CH), 72.13 (CH_2), 29.27 (CH_2). EI-MS *m/z* (%) 162 (M^+, 100), 133 (12), 58 (24). HRMS-EI Calcd for $C_{10}H_{10}O_2$: 162.0681. Found: 162.0685.

3.1.3. 2,3-Dihydrobenzo[1,2-*b*;5,4-*b*′]difuran (3). A solution of DDQ (113 mg, 0.5 mmol) in dioxane (8 mL) was added slowly (over 1 h) to a solution of compound **2** (81 mg, 0.5 mmol) in dioxane (2 mL). The reaction mixture was stirred at room temperature for a further 1 h and the precipitate was filtered off and washed thoroughly with CH_2Cl_2. The filtrate and the washes were combined and evaporated to dryness under vacuum. The residue was purified by column chromatography (hexane) to afford a white solid (78 mg, 99%); mp 58–60 °C. ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H, J=2.20 Hz, H_2), 7.30 (s, 1H, H_4), 6.90 (s, 1H, H_8), 6.62 (d, 1H, J=2.20 Hz, H_3), 4.60 (t, 2H, J=8.45 Hz, H_6), 3.24 (t, 2H, J=8.45 Hz, H_5). ^{13}C NMR ($CDCl_3$) δ 158.46, 155.27, 143.80 (CH), 123.24, 120.82, 116.05 (CH), 106.35 (CH), 93.14 (CH), 72.15 (CH_2), 29.42 (CH_2). EI-MS *m/z* (%) 160 (M^+, 100), 131 (60). HRMS-EI Calcd for $C_{10}H_8O_2$: 160.0524. Found: 160.0520.

3.1.4. 9,10-Dihydro-pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (5). A mixture of compound **3** (82 mg, 0.51 mmol) and 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine[21] (83 mg, 0.42 mmol) in dioxane (3 mL) was heated under reflux for 6 h until the red colour of the tetrazine had disappeared. The mixture was allowed to reach room temperature and the precipitate was filtered off and washed with fresh dioxane (1 mL) and diethyl ether (2× 1 mL). A pure yellow solid (TLC 4:1 CH_2Cl_2/EtOAc) was obtained (96 mg, 77%). The filtrate was concentrated under vacuum and purified by column chromatography (9:1 CH_2Cl_2/EtOAc) to afford another crop of pure **5** (12 mg, 9%); mp 279–281 °C (dec). IR (KBr) 1758, 1713, 1580, 1451, 1412, 1265, 1164, 1134 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1H, H_1), 8.51 (s, 1H, H_{11}), 6.95 (s, 1H, H_7), 4.75 (t, 2H, J=8.50 Hz, H_9), 4.05 (s, 3H, OMe), 3.55 (t, 2H, J=8.50 Hz, H_{10}). EI-MS *m/z* (%) 298 (M^+, 100), 240 (72), 185 (38). HRMS-EI Calcd for $C_{15}H_{10}N_2O_5$: 298.0589. Found: 298.0587.

3.1.5. 2,3,5,6-Tetrahydrobenzo[1,2-*b*;5,4-*b*′]difuran-8-carboxaldehyde (6). To a solution of compound **2** (1.62 g, 10 mmol) in anhydrous Et_2O (100 mL) was added *n*-BuLi (10 mL, 1.6 M in hexane) by syringe at −78 °C under argon. The mixture was stirred for 30 min. The external cool bath was replaced by an ice/water bath and the reaction mixture was stirred at 0–5 °C. Upon completion of the reaction (4 h), DMF (2.5 mL, 30 mmol) was added and the mixture was stirred for a further 16 h while the temperature was allowed to increase slowly to room temperature. Then 0.5 M HCl (50 mL) was added at 0 °C to quench the reaction and the mixture was stirred 15 min. The resulting mixture was extracted with Et_2O (4× 100 mL), the organic phases were combined and washed with H_2O (3×50 mL) until neutral pH and finally with brine (50 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under vacuum to afford a tan solid (TLC 7:3 hexane/EtOAc, R_f 0.15), which was used in the next step without further purification (1.76 g, 93%). A sample was purified by column chromatography (7:3 hexane/EtOAc) to yield a yellow crystalline solid; mp 133–134 °C. IR (KBr) 1674, 1610, 1453, 1408, 1234, 1073 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H, CHO), 7.12 (s, 1H, H_4), 4.69 (t, 4H, J=8.60 Hz, H_3+H_5), 3.07 (t, 4H, J=8.60 Hz, H_2+H_6). ^{13}C NMR ($CDCl_3$) δ 186.98 (CH), 160.96, 126.75 (CH), 119.34, 106.76, 73.62 (CH_2), 28.29 (CH_2). EI-MS *m/z* (%) 190 (M^+, 100), 189 (51), 161 (25), 133 (29), 91 (14), 77 (19). HRMS-EI Calcd for $C_{11}H_{10}O_3$: 190.0630. Found: 190.0627.

3.1.6. Benzo[1,2-*b*;5,4-*b*′]difuran (7). A solution of DDQ (3.00 g, 13.2 mmol) in dioxane (70 mL) was added slowly (over 1 h) to a solution of compound **2** (648 mg, 4 mmol) in dioxane (70 mL). Once the addition was complete, the reaction mixture was heated under reflux for 18 h, after which time TLC indicated completion of the reaction. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed well with CH_2Cl_2, and the filtrate and washes were evaporated to dryness under vacuum. The residue was purified by column chromatography (hexane) to give an off-white solid product (347 mg, 55%); mp 57–59 °C (lit.[15] 55–58.5 °C). ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H, H_4), 7.62 (s, 1H, H_8), 7.60 (d, 2H, J=2.20 Hz, H_2), 6.80 (d, 2H, J=2.20 Hz, H_3). ^{13}C NMR ($CDCl_3$) δ 153.36, 145.26 (CH), 124.25, 111.33 (CH), 106.39 (CH), 94.44 (CH). EI-MS *m/z* (%) 158 (M^+, 36), 58 (100). HRMS-EI Calcd for $C_{10}H_6O_2$: 158.0368. Found: 158.0372.

3.1.7. Benzo[1,2-*b*;5,4-*b*′]difuran-8-carboxaldehyde (8). This compound was prepared from **6** (1.76 g, 9.2 mmol) in an analogous manner to **7** from **2**. The crude product was purified by flash chromatography using 9:1 CH_2Cl_2/EtOAc to give a white solid product (1.25 g, 73%); mp 103–104 °C. IR (KBr) 1677, 1592, 1548, 1115, 1016, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 10.84 (s, 1H, CHO), 8.00 (s, 1H, H_4), 7.78 (d, 2H, J=2.20 Hz, H_2), 6.89 (d, 2H, J=2.20 Hz, H_3). ^{13}C NMR ($CDCl_3$) δ 185.77 (CHO), 152.61, 146.51 (CH),

125.33, 119.24 (CH), 106.36 (CH). EI-MS *m/z* (%) 186 (M^+, 100), 185 (87), 157 (26), 129 (22). HRMS-EI Calcd for $C_{11}H_6O_3$: 186.0317. Found: 186.0314.

3.1.8. Pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (9) and 5,9-dioxo-benzo[1,2-*b*;5,6-*b'*]dipyran-bis[3,4-*c*]pyridazine-2,12-di(carboxylic acid, methyl esther) (10). A mixture of compound **7** (128 mg, 0.81 mmol) and 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine (134 mg, 0.68 mmol) in dioxane (3 mL) was heated under reflux for 2 h until the red colour of the tetrazine had disappeared. The mixture was allowed to reach room temperature. The precipitate was filtered off and washed with fresh dioxane (2×1 mL) and diethyl ether (2×1 mL) to give **9** as a pure yellow solid (131 mg, 65%); mp >350 °C (dec 220 °C). IR (KBr) 1760, 1715, 1580, 1455, 1262, 1131 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.12 (s, 1H), 9.00 (s, 1H), 8.16 (d, 1H, J=2.30 Hz, H_9), 7.84 (s, 1H, H_7), 7.10 (d, 1H, J=2.30 Hz, H_{10}), 4.06 (s, 3H, OMe). EI-MS *m/z* (%) 296 (M^+, 76), 238 (100), 210 (44), 183 (32). HRMS-EI Calcd for $C_{15}H_8N_2O_5$: 296.0433. Found: 296.0433.

The filtrate was concentrated under vacuum and glacial AcOH (5 mL) was added to the residue. The mixture was heated under reflux for 30 min and then cooled to room temperature. The off-white precipitate was filtered off and washed with AcOH (1 mL) and diethyl ether (2×1 mL) to give pure **10** (22 mg, 15%); mp >350 °C (dec 250 °C). IR (KBr) 1774 (broad), 1628, 1583, 1282, 1162, 1121, 1050 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.75 (s, 1H, H_{14}), 9.50 (s, 2H, H_1+H_{13}), 7.73 (s, 1H, H_7), 4.11 (s, 6H, 2OMe). ^{13}C NMR (DMSO-d_6) δ 163.92, 156.06, 155.22, 152.40, 143.56, 133.35, 125.01 (CH), 120.96 (CH), 113.04, 106.02 (CH), 53.52 (OCH_3). HRMS-EI Calcd for $C_{20}H_{10}N_4O_8$: 434.0499. Found: 434.0494.

3.2. 7-Formyl-pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (11) and 7-formyl-5,9-dioxo-benzo[1,2-*b*;5,6-*b'*]dipyran-bis[3,4-*c*]pyridazine-2,12-di(carboxylic acid, methyl esther) (12)

These compounds were prepared from **8** (270 mg, 1.45 mmol) in an analogous manner to **9** and **10** from **7**, but using 6:1 Dioxane/AcOH (10 mL) as solvent and heating under reflux for 8 h.

3.2.1. Compound 11. Yield 273 mg (70%); mp >350 °C (dec 225 °C). IR (KBr) 1739 (broad), 1693, 1587, 1341, 1267, 1170, 1141 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.74 (s, 1H, CHO), 9.37 (s, 1H, H_{11}), 9.21 (s, 1H, H_1), 8.33 (d, 1H, J=2.20 Hz, H_9), 7.20 (d, 1H, J=2.20 Hz, H_{10}), 4.08 (s, 3H, OMe). ^{13}C NMR (DMSO-d_6) δ 185.55 (CHO), 163.63, 155.64, 153.95, 152.26, 151.58, 149.60 (CH), 142.72, 133.99, 125.82, 125.12 (CH), 120.64 (CH), 111.56, 109.20, 106.57 (CH), 53.37 (CH_3). EI-MS *m/z* (%) 324 (M^+, 38), 266 (84), 237 (16), 210 (100), 183 (27). HRMS-EI Calcd for $C_{16}H_8N_2O_6$: 324.0390. Found: 324.0385.

3.2.2. Compound 12. Yield 15 mg (5%); mp >350 °C (dec 285 °C). IR (KBr) 1778, 1742, 1719, 1695, 1599, 1279, 1129 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.69 (s, 1H, CHO), 9.95 (s, 1H, H_{14}), 9.57 (s, 2H, H_1+H_{13}), 4.11 (s, 6H, 2OMe). ^{13}C NMR (DMSO-d_6) δ 185.71 (CHO), 163.81, 155.18, 154.69, 152.45, 143.26, 132.96, 130.06, 128.99 (CH), 121.13 (CH), 113.09, 53.49 (CH_3). HRMS-EI Calcd for $C_{21}H_{10}N_4O_9$: 462.0448. Found: 462.0444.

3.3. 7-{[2-(Dimethylamino)ethyl]aminomethyl}-1,4-dihydropyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (13) and 7-hydroxymethyl-1,4-dihydro-pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (14)

To a suspension of compound **11** (65 mg, 0.2 mmol) in DMF (3 mL)/AcOH (0.2 mL) was added *N*,*N*-dimethyl-ethylenediamine (0.055 mL, 0.5 mmol) followed by $NaCNBH_3$ (38 mg, 0.6 mmol). The mixture was stirred at room temperature for 7 h. The reaction was quenched by adding 1 M HCl (1.5 mL) at 0 °C and the reaction mixture was concentrated until dryness under vacuum. Saturated solution of $NaHCO_3$ (5 mL) was added to the residue and diluted with H_2O (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (6×10 mL). The organic phases were combined, washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation of organic solvent, the crude mixture was purified by flash chromatography (9:1 CH_2Cl_2/EtOH, then 9:1:0.1 CH_2Cl_2/EtOH/NH_4OH) to give **13** (52 mg, 65%) and **14** (20 mg, 30%).

3.3.1. Compound 13. Mp >350 °C (dec 180 °C). IR (KBr) 3363, 1726, 1601, 1435, 1387, 1349, 1169, 1101, 1046 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.45 (s, 1H exch., NH), 7.75 (d, 1H, J=2.20 Hz, H_9), 7.55 (s, 1H, H_{11}), 6.85 (d, 1H, J=2.20 Hz, H_{10}), 4.35 (s, 2H, $ArCH_2N$), 3.95 (s, 3H, OCH_3), 3.80 (s, 2H, H_1), 2.75 (t, 2H, J=6.20 Hz), 2.45 (t, 2H, J=6.20 Hz), 2.15 (s, 6H, NMe_2), 2.00 (s, 1H exch., NH). ^{13}C NMR ($CDCl_3$) δ 164.71, 155.08, 154.30, 146.93 (CH), 146.55, 131.23, 124.85, 119.95, 119.53, 114.92, 113.15 (CH), 112.66, 106.68 (CH), 58.91 (CH_2), 52.80 (CH_3), 46.77 (CH_2), 45.38 (CH_3), 41.94 (CH_2), 21.45 (CH_2). EI-MS *m/z* (%) 398 (M^+, 6), 339 (17), 311 (77), 310 (27), 196 (21), 171 (25), 170 (19), 140 (18), 58 (100). HRMS-EI Calcd for $C_{20}H_{22}N_4O_5$: 398.1590. Found: 398.1586.

3.3.2. Compound 14. Mp >350 °C (dec 205 °C). IR (KBr) 3482, 3337, 1705 (broad), 1595, 1444, 1349, 1184, 1109 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.90 (s, 1H exch., NH), 8.12 (d, 1H, J=2.20 Hz, H_9), 7.77 (s, 1H, H_{11}), 7.07 (d, 1H, J=2.20 Hz, H_{10}), 5.31 (t, 1H exch., J=5.40 Hz, OH), 4.90 (d, 2H, J=5.40 Hz, CH_2O), 3.78 (s, 3H, OCH_3), 3.74 (s, 2H, H_1). ^{13}C NMR (DMSO-d_6) δ 164.55, 154.37, 1543.12, 147.56 (CH), 145.63, 129.87, 124.46, 119.88, 119.14, 114.85, 114.18 (CH), 112.61, 106.97 (CH), 51.92 (CH_2), 51.77 (CH_3), 21.07 (CH_2). EI-MS *m/z* (%) 328 (M^+, 29), 310 (26), 268 (53), 240 (49), 222 (100), 196 (74), 140 (44). HRMS-EI Calcd for $C_{16}H_{12}N_2O_6$: 328.0695. Found: 328.0699.

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