Synthesis and Cytotoxic Activities of Pyrrole[2,3-*d*]pyridazin-4-one Derivatives

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1-Methyl-2-phenyl (1) and 1,3-dimethyl-2-phenyl (2) -substituted pyrrole[2,3-*d*]pyridazinones, as well as their tetracyclic analogues 3—6, were synthesized and evaluated *in vitro* by the National Cancer Institute against 60 human tumor cell lines derived from nine cancer cell types. Biological results showed that the antitumor activities of these compounds were related to the planarity of their ring systems with potency increasing in the order 2<4≃5<6<3. Among them, the most potent compound 3 showed significant cell line cytotoxicity, particularly against the renal cancer subpanel [GI_{50} (μM) 5.07] and displayed significant potency [GI_{50} (μM) 3.04—4.32] against MOLT-4, SR (leukemia), NCI-H460 (non-small cell lung), HCT-116 (colon), and SF-295 (CNS) cancer cells, respectively.

Key words pyrrole[2,3-*d*]pyridazin-4-one derivative; cytotoxic activity; structure–activity relationship

The pyrrole[2,3-*d*]pyridazine (I) system is rarely reported on the literature. Although the synthesis of I derivatives was first described by Fisher more than 70 years ago,[1—3] to our knowledge only two reports have appeared since then dealing with pyrrole[2,3-*d*]pyridazin-4-ones (II) as inhibitors of human cancer cell proliferation[4] and with pyrrole[2,3-*d*]-pyridazin-7-ones (III) as carbohydrate-modified nucleosides active as antiviral and antiproliferative agents.[5]

Our continuing interest in the chemistry and pharmacology of pyridazines and polycyclic congeners[6] led us to incorporate II into tetracyclic derivatives **3**—**6** provided with an almost planar structure potentially intercalating[7] with DNA, and to test them as inhibitors of human cancer cell proliferation. In addition, 1-methyl-2-phenylpyrrole[2,3-*d*]pyridazin-4-one (**1**) and substituted 1,3-dimethyl-2-phenylpyrrole[2,3-*d*]pyridazin-4-one (**2**) derived from **3** by removal or cleavage of the carbon bridge between the phenyl and pyrrole moieties were synthesized to compare the variation in biological effects due to the loss of planarity of the ring system.

A survey of the literature revealed that not only the tetracyclic compounds **3**—**6** but also the pyrrolepyridazinones **1** and **2** were unknown.

Chemistry

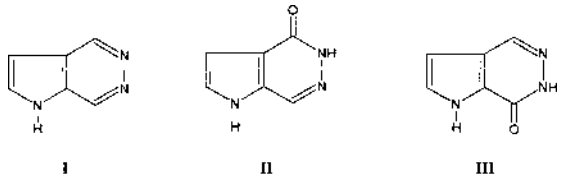
The synthesis of **1** and **2** as well as of **3**—**6** was performed following a common strategy. That is, formylation of the appropriate esters **7a**—**f** with Vilsmeier's reagent in acetonitrile afforded the corresponding 2-formyl derivatives **8a**—**f** which were finally condensed with hydrazine to give the desired compounds **1**—**6** (Chart 3).

The starting esters **7** were obtained by the following procedures. The synthesis of **7a**, **c**, **d** was performed by condensing the appropriate bromoketone **9a**, **c**, **d** with ethyl cyanoacetate to give the cyanoketoesters **10**, which after reaction with gaseous HCl in Et_2O cyclized to the pyrrole derivatives **11**. *N*-Methylation of **11** with Me_2SO_4 and KOH in EtOH, followed by dehalogenation of **12** with $HCOONH_4$ and 10% Pd–C, gave **7a**, **c**, **d** (Chart 4). The 3-methyl derivative **7b** was in turn obtained by *N*-deacetylation of the known ethyl 1-acetyl-2-phenyl-3-methylpyrrole-4-carboxylate **13**,[8] followed by *N*-methylation with Me_2SO_4 and KOH in EtOH (Chart 5).

The synthesis of the benzocycloheptapyrrole ester **7e** was carried out by a sigmatropic rearrangement[9,10] of the adduct (**16**) of benzosuberone oxime **15** with methyl propiolate to give **17**, which was finally *N*-methylated as reported above to **7e** (Chart 6). Finally, the benzo[*g*]indole derivative **7f** was obtained by dehydrogenation of **7d** with DDQ in CH_2Cl_2 (Chart 7).

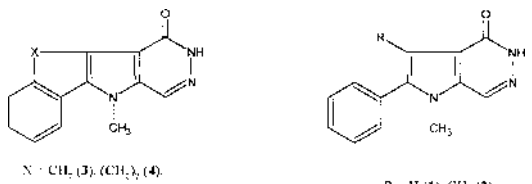
Results and Discussion

The tetracyclic compounds **3**—**6** as well as their frameworks **1** and **2** have been submitted to a preliminary screening by the National Cancer Institute (NCI) for evaluation in an *in vitro* preclinical antitumor screening program[11—13] against 60 human tumor cell lines derived from leukemia, non-small cell lung cancer, colon cancer, central nervous system (CNS) cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. The dose-response curves for each cell line were measured in all compounds with five different drug concentrations (10^{-4}—10^{-8} M) and the concen-



I II III

Chart 1



X = CH_2 (3), $(CH_2)_2$ (4), $(CH_2)_3$ (5), CH=CH (6)

R = H (1), CH_3 (2)

Chart 2

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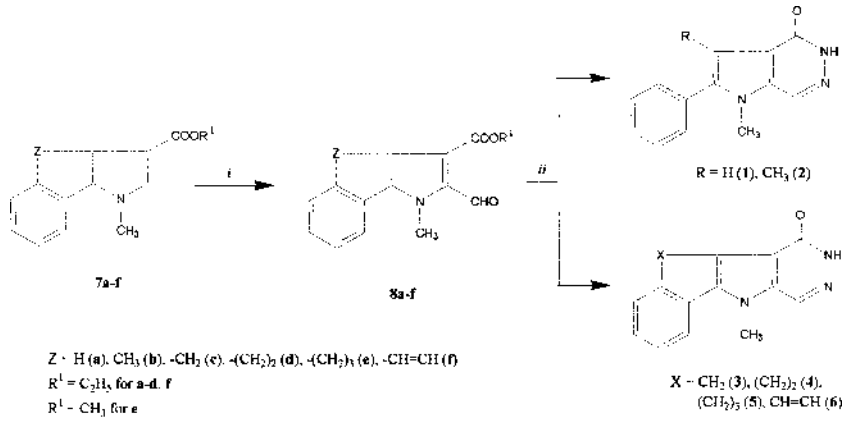
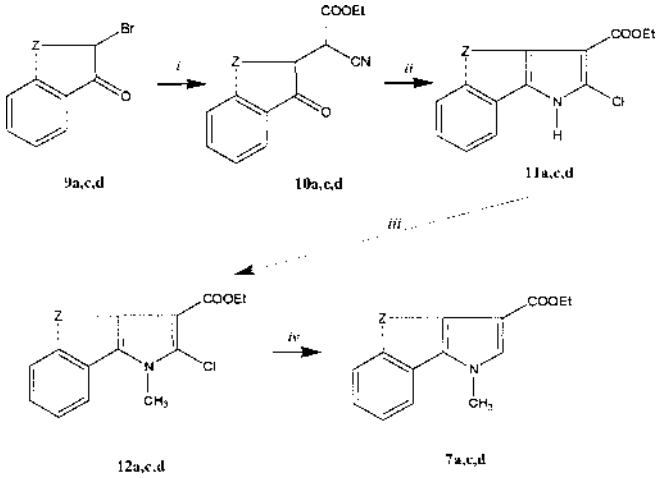


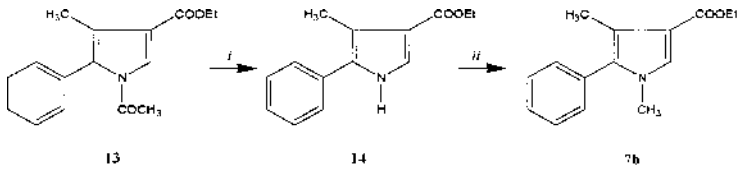
Reagents: i) $(CH_3)_2N^+=CHCl\ Cl^-$, CH_3CN; ii) $H_2NNH_2 \cdot H_2O$ 98%.

Chart 3



Reagents: i) $NCCH_2COOEt$, K_2CO_3, Me_2CO; ii) gaseous HCl, Et_2O; iii) KOH, EtOH, Me_2SO_4, Me_2CO; iv) $HCOONH_4$, 10% Pd–C, MeOH.

Chart 4



Reagents: i) 2.5 M NaOH; ii) KOH, EtOH, Me_2SO_4, Me_2CO.

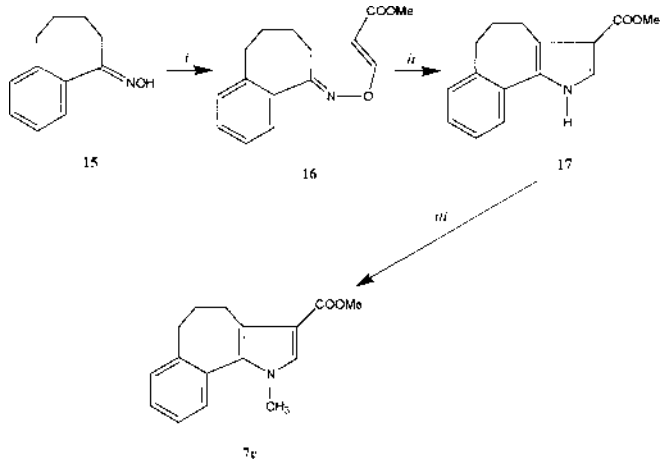
Chart 5

tration causing 50% cell growth inhibition (GI_{50}) as compared to the control was calculated (Table 1). Among the tetracyclic structures **3**—**6**, a significant activity was found for the indenopyrrole[2,3-*d*]pyridazinone **3** (X=CH_2) (GI_{50}= 11.7 μM) and for the benzo[*g*]pyridazin[4,5-*b*]indol-7-one **6** (X=CH=CH) (GI_{50}=15.5 μM). In particular, compound **3** exhibited significant cell line-selective cytotoxicity against the renal cancer subpanel (GI_{50}=3.46 μM) and against MOLT-4, SR (leukemia), NCI-H460 (non-small cell lung), HCT-116 (colon) and SF-295 (CNS) cancer cells, respectively (Fig. 1). Interestingly, the inhibition properties in this series seem to be related to the planarity of the ring system, with compounds **4** (X=CH_2CH_2) and **5** (X=$CH_2CH_2CH_2$) being less active (GI_{50} of 26.9 and 24.5 μM, respectively).

However, this hypothesis is not consistent with the results for 1-methyl-2-phenylpyrrole[2,3-*d*]pyridazinone **1**, which was inactive, and 1,3-dimethyl-2-phenylpyrrole[2,3-*d*]pyridazinone **2**, which possessed only weak activity (GI_{50}=36.3 μM), thus revealing that planarity does not greatly influence anticellular activity.

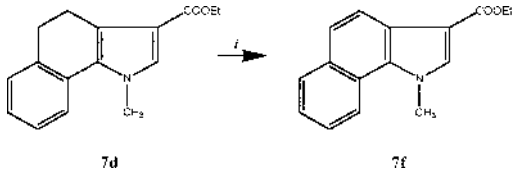
In conclusion, the synthesis and preliminary evaluation of the tetracyclic structures **3**—**6** derived from indenopyridazi-

none suggest that the observed cytotoxic activity could derived from intercalation of the planar structures with DNA. On the basis of this hypothesis compounds **3** and **6** will be selected as lead compounds for a structure–activity study involving the replacement of the amidic 4-carbonyl with aminic side chains to increase interaction with nucleic acids. Further research on this is in progress.



Reagents: i) Methylpropiolate, DMSO, TEA: ii) Δ; iii) KOH, EtOH, Me_2SO_4, Me_2CO.

Chart 6



Reagents: i) DDQ, CH_2Cl_2.

Chart 7

Experimental

Chemistry, General Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Flash chromatography was performed using Merck Silica Gel 60 (230—400 mesh ASTM). Thin-layer chromatography (TLC) was performed with Polygram® SIL N-HR-/HV_{254} precoated plastic sheets (0.2 mm). ^{1}H-NMR spectra were measured in $CDCl_3$ with superconducting FT-NMR using a XL-200 Varian apparatus at 200 MHz.

Chemical shifts are expressed in δ (ppm) downfield from internal tetramethylsilane (TMS) and coupling constants in Hz. Significant ^{1}H-NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hz. IR spectra were recorded as thin films or Nujol mulls on NaCl plates with a Perkin-Elmer 781 IR spectrophotometer and are expressed in ν (cm^{-1}). UV–VIS spectra were recorded as ethanolic solutions with Perkin-Elmer Lambda 5 and Hitachi U-2001 spectrophotometers and the absorption wavelengths are expressed in nm followed by ($\log \varepsilon$). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Starting benzosuberone oxime and α-bromotetral-1-ones were prepared as described in the literature,[14,15] α-bromoacetophenone, α-bromoindan-1-one were commercially available (Aldrich Chemical Co.).

The physico-chemical data of the compounds **1**—**17** are reported in Tables 2 and 3.

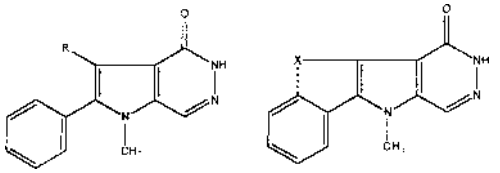
General Alkylation Procedure for Compounds 10a, c, d A solution of the bromo-derivative (5 mmol) in acetone (11 ml) was added dropwise to a suspension of $NCCH_2CO_2Et$ (40 mmol) and K_2CO_3 (10 mmol) at 40—45 °C. The reaction mixture was stirred at 40—45 °C for 1 h and then cooled at room temperature. After the addition of AcOEt (10 ml) and water (10 ml) under stirring, the organic layer was separated, washed with a solution of 10% KH_2PO_4 (7.5 ml) and brine (5 ml), dried (Na_2SO_4), concentrated under reduced pressure to give a crude oil. The oil was distilled (150 °C/1 mmHg) to remove excess $NCCH_2CO_2Et$ and the residue was purified by flash chromatography (Petroleum ether/AcOEt, 8/2) to give the desired products **10a**, **c**, **d**.

Ethyl 2-Cyano-4-oxo-4-phenylbutanoate (**10a**): mp: 51—52 °C [lit[16]: 53—55 °C].

Ethyl 2-Cyano-2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)acetate (**10c**): IR: 1715 (C=O), 1745 (C=O), 2250 (CN); UV: 247.0 (4.14), 289.5 (3.56), 294.5 (3.57); ^{1}H-NMR [$CDCl_3$]: 1.21 (t, 3H, CH_3), 2.58—2.59 (dd, 2H, CH_2), 2.93—3.03 (dd, 2H, CH), 3.40—3.52 (dd, 1H, CH), 4.11 (q, 2H, CH_2), 7.38 (t, 1H, CH), 7.46 (d, 1H, CH), 7.60 (t, 1H, CH), 7.77 (d, 1H, CH). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.38; N, 5.75; Found: C, 68.96; H, 5.36; N, 5.71.

Ethyl 2-Cyano-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (**10d**):

Table 1. Inhibition of *in Vitro* Cancer Cell Lines by Pyrrolpyridazinone Derivatives **1**—**6** (GI_{50}[a])



R=H (**1**), CH_3 (**2**) X=–CH_2 (**3**), –$(CH_2)_2$ (**4**), –$(CH_2)_3$ (**5**), –CH=CH (**6**)

Cell line	**1** GI_{50} (μM)	**2** GI_{50} (μM)	**3** GI_{50} (μM)	**4** GI_{50} (μM)	**5** GI_{50} (μM)	**6** GI_{50} (μM)
Leukemia	N.A.[b]	36.3	9.1	23.9	21.5	14.6
Non-small cell lung cancer	N.A.	46.7	13.8	30.9	28.5	14.0
Colon cancer	N.A.	31.6	8.9	26.9	24.5	13.6
CNS cancer	N.A.	40.7	12.5	34.6	32.2	15.5
Melanoma	N.A.	31.6	14.7	21.8	19.4	14.9
Ovarian cancer	N.A.	38.0	12.8	39.8	37.4	17.1
Renal cancer	N.A.	38.0	7.7	23.4	21.0	19.0
Prostate cancer	N.A.	36.3	15.1	31.6	29.2	17.3
Breast cancer	N.A.	30.2	16.2	22.9	20.5	15.8
Mean	N.A.	36.3	11.7	26.9	24.5	15.5

a) GI_{50} These values are the concentrations [μM] needed to achieve 50% growth inhibition of the given human cancer cell line subpanels. Data obtained from NCI *in vitro* disease-oriented tumor cells screening. *b*) N.A.=Not active compound in primary anticancer assays on a three cell line panel consisting of MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS).

Table 2. Physicochemical Data of the Compounds **1**—**6**

	mp (°C)[a]	Yield (%)
1	321—322	52.9
2	286—287	27.3
3	287—288	45.5
4	254—256	33.3
5	210—212	37.0
6	300—301	35.5

a) All compounds were crystallized from EtOH.

Table 3. Physicochemical Data of the Compounds **7**—**17**

	mp (°C or bp/mmHg)	Yield (%)
7b	59—60/0.5	85.6
7c	94—96	81.9
7d	59—60/0.5	70.6
7e	79—80/0.5	95.6
7f	116—118	87.9
8a	60/0.5	51.6
8b	40/0.5	95.5
8c	118—120	70.0
8d	74—76	66.7
8e	43	67.6
8f	52	77.5
10c	58—60	72.3
10d	54—56	96.5
11c	206—208	69.8
11d	185—186	43.0
12a	59—60	95.6
12c	102—104	95.2
12d	53—55	95.3
14	108—110	60.0
16	Colorless oil	95.0
17	124	25.0

IR: 1680 (C=O), 1740 (C=O), 2250 (CN); UV: 208.7 (3.80), 238.7 (3.96); ^{1}H-NMR [$CDCl_3$]: 1.37 (t, 3H, CH_3), 2.36 (q, 2H, CH_2), 3.12 (t, 2H, CH_2), 4.33 (q, 2H, CH_2), 4.36 (q, 1H, CH), 4.45 (d, 1H, CH), 7.30 (d, 1H, CH), 7.34 (t, 1H, CH), 7.54 (t, 1H, CH), 8.06 (d, 1H, CH). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44; Found: C, 70.20; H, 5.89; N, 5.47.

General Procedure for Compounds 11a, c, d A solution of the cyanoketo esters (**10a**, **c**, **d**) (6.7 mmol) in Et_2O (30 ml for **10a**, **d**, 15 ml for **10c**), cooled at a 0—5 °C in an ice-water bath, was bubbled with gaseous HCl (1.86 g, 5.1 mmol). The solution was stirred at room temperature for 24 h. Then excess HCl and Et_2O were removed by flashing with N_2. The solid residue was triturated in MeOH to give **11a**, **c**, **d** as cream-colored crystals.

Ethyl 2-Chloro-5-phenyl-1*H*-pyrrole-3-carboxylate (**11a**): mp: 119 °C [lit[16]: 118—120 °C].

Ethyl 2-Chloro-1*H*-indeno[1,2-*b*]pyrrole-3-carboxylate (**11c**): IR: 1670 (C=O), 3240 (NH); UV: 226.5 (4.34), 232.0 (4.31), 285.5 (4.51), 294.5 (4.43); ^{1}H-NMR [$CDCl_3$]: 1.40 (t, 3H, CH_3), 3.66 (s, 2H, CH_2), 4.35 (q, 2H, CH_2), 7.11 (t, 1H, CH), 7.25 (t, 1H, CH), 7.42 (d, 1H, CH), 7.47 (d, 1H, CH), 11.58 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.54; N, 5.35; Found: C, 64.08; H, 4.60; Cl, 13.40; N, 5.32.

Ethyl 2-Chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (**11d**): IR: 1660 (C=O), 3210 (NH); UV: 222.5 (4.55), 233.5 (4.36), 291.5 (4.45), 296.0 (4.47), 309.0 (4.36); ^{1}H-NMR [$CDCl_3$]: 1.38 (t, 3H, CH_3), 2.88—3.05 (m, 4H, CH_2×2), 4.35 (q, 2H, CH_2), 7.10—7.26 (m, 4H, Ph), 8.78 (br s 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.11; Cl, 12.85; N, 5.07; Found: C, 65.51; H, 5.14; Cl, 12.90; N, 5.09.

General Procedure for Compounds 12a, c, d and 7b, e KOH 0.28 g (4.99 mmol) was dissolved in a solution of chloroesters **11a**, **c**, **d** or esters **14** and **17** (4.14 mmol) in EtOH (23 ml). The solvent was then removed under reduced pressure and to the residue dissolved in acetone (18.6 ml) and Me_2SO_4 0.78 ml (8.28 mmol) was added. The mixture was stirred at room temperature (30 min for **11c**, 1 h for **11a** and **14**, 3 h for **17**, 4.5 h for **11d**).

Panel / Cell Line	GI_{50}
Leukemia	
CCRF-CEM	9.09E-06
HL-60 (TB)	1.47E-05
K-562	1.82E-05
MOLT-4	3.45E-06
RPMI-8226	1.59E-05
SR	3.79E-06
Non-Small Cell Lung Cancer	
A549/ATCC	6.56E-06
EKVX	2.27E-05
HOP-62	2.25E-05
HOP-92	2.52E-05
NCI-H226	1.38E-05
NCI-H23	2.43E-05
NCI-H322M	1.09E-05
NCI-H460	3.04E-06
NCI-H522	1.78E-05
Colon Cancer	
COLO 205	1.09E-05
HCT-116	3.64E-06
HCT-15	1.11E-05
HT29	9.63E-06
KM12	1.63E-05
SW-620	7.24E-06
CNS Cancer	
SF-268	1.20E-05
SF-295	4.32E-06
SF-539	1.92E-05
SNB-19	1.81E-05
SNB-75	1.61E-05
U251	1.35E-05
Melanoma	
LOX IMVI	6.65E-06
MALME-3M	1.63E-05
M14	1.56E-05
SK-MEL-2	2.13E-05
SK-MEL-28	2.44E-05
SK-MEL-5	1.22E-05
UACC-257	1.08E-05
Ovarian Cancer	
IGROV1	6.79E-06
OVCAR-3	1.27E-05
OVCAR-4	2.14E-05
OVCAR-5	3.12E-05
OVCAR-8	1.17E-05
SK-OV-3	6.49E-06
Renal Cancer	
786-0	6.37E-06
A498	6.62E-06
ACHN	5.07E-06
CAKI-1	1.33E-05
RXF 393	1.55E-05
SN12C	7.62E-06
TK-10	5.81E-06
UO-31	5.53E-06
Prostate Cancer	
PC-3	2.15E-05
DU-145	1.06E-05
Breast Cancer	
MCF7	1.15E-05
NCI/ADR-RES	1.60E-05
MDA-MB-231 ATCC	1.40E-05
HS 578T	2.65E-05
MDA-MB-435	1.43E-05
MDA-N	1.29E-05
BT-549	1.83E-05
T-47D	2.56E-05

Fig. 1. *In Vitro* Cytotoxic Activities of **3**

The numerical values listed are GI_{50} values, which are the molar concentrations causing 50% growth inhibition.

The solid precipitate was filtered off and the solution concentrated under reduced pressure to give an oil that solidified on standing.

Ethyl 1-Methyl-2-chloro-5-phenyl-1*H*-pyrrole-3-carboxylate (**12a**): IR: 1700 (C=O): UV: 225.0 (4.36), 270.8 (4.32); ^{1}H-NMR [$CDCl_3$]: 1.36 (t, 3H, CH_3), 3.58 (s, 3H, CH_3), 4.33 (q, 2H, CH_2), 6.63 (s, 1H, CH), 7.40 (m, 5H, CH×5). *Anal.* Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; Cl, 13.44; N, 5.31; Found: C, 63.56; H, 5.31; Cl, 13.41; N, 5.28.

Ethyl 1-Methyl-2-chloro-1,4-dihydro-indeno[1,2-*b*]pyrrole-3-carboxylate (**12c**): IR: 1700 (C=O); UV: 238.0 (3.45), 277.0 (3.84); ^{1}H-NMR [$CDCl_3$]: 1.39 (t, 3H, CH_3), 3.65 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 4.35 (q, 2H, CH_2), 7.15 (t, 1H, CH), 7.29 (t, 1H, CH), 7.44 (t, 1H, CH), 7.50 (d, 1H, CH). *Anal.* Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.11; Cl, 12.87; N, 5.08; Found: C, 65.52; H, 5.12; Cl, 12.91; N, 5.10.

Ethyl 1-Methyl-2-chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (**12d**): IR: 1700 (C=O); UV: 223.5 (4.48), 234.0 (4.35), 296.5 (4.38), 308.0

(4.29); ^{1}H-NMR [$CDCl_3$]: 1.38 (t, 3H, CH_3), 2.82—2.98 (m, 4H, CH_2×2), 3.88 (s, 3H, CH_3), 4.34 (q, 2H, CH_2), 7.13—7.41 (m, 4H, CH×4). *Anal.* Calcd for $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.56; Cl, 12.23; N, 4.83; Found: C, 66.05; H, 5.52; Cl, 12.10; N, 4.80.

Ethyl 1,4-Dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**7b**): IR: 1705 (C=O); UV: 235.0 (4.39), 271.0 (4.36); ^{1}H-NMR [$CDCl_3$]: 1.34 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 4.30 (q, 2H, CH_2), 7.29—7.31 (m, 3H, CH×3), 7.36—7.50 (m, 3H, CH×3). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.75; Found: C, 73.85; H, 7.01; N, 5.72.

Methyl 1-Methyl-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*b*]pyrrole-3-carboxylate (**7e**): IR: 1695 (C=O); UV: 240.0 (3.77), 245.0 (3.75), 306.5 (4.55); ^{1}H-NMR [$CDCl_3$]: 1.37 (t, 3H, CH_3), 2.13 (q, 2H, CH_2), 2.35 (t, 2H, CH_2), 2.54 (t, 2H, CH_2), 3.96 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 6.90 (s, 1H, CH), 7.25—7.35 (m, 4H, CH×4). *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.25; H, 6.71; N, 5.48; Found: C, 75.10; H, 6.65; N, 5.45.

General Procedure for Compounds 7a, c, d To a solution of chloroesters **12a**, **c**, **d** (2.72 mmol) and $HCOONH_4$ 0.86 g (13.6 mmol) in MeOH (22 ml) 0.18 g of 10% Pd–C was added. The mixture was stirred under nitrogen (2 h for **12a**, **d** and 4 h for **12c**) and then filtered on Celite and the solution concentrated. The oily residue was taken up with water and extracted with ethyl ether. The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure to give an oil (**7a**, **d**) or a solid (**7c**).

Ethyl 1-Methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**7a**): bp: 145 °C/0.5 mmHg [lit[17]: 148 °C/0.5 mmHg].

Ethyl 1-Methyl-1,4-dihydro-indeno[1,2-*b*]pyrrole-3-carboxylate (**7c**): IR: 1695 (C=O); UV: 234.5 (4.27), 282.5 (4.39); ^{1}H-NMR [$CDCl_3$]: 1.37 (t, 3H, CH_3), 3.66 (s, 2H, CH_2), 3.93 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 7.16 (d, 1H, CH), 7.27 (s, 1H, CH), 7.30 (t, 1H, CH), 7.44 (d, 1H, CH), 7.50 (d, 1H, CH). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.80; Found: C, 74.80; H, 6.29; N, 5.82.

Ethyl 1-Methyl-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (**7d**): IR: 1700 (C=O); UV: 226.0 (4.78), 234.0 (4.65), 253.0 (4.24), 294.0 (4.61), 307.0 (4.47); ^{1}H-NMR [$CDCl_3$]: 1.35 (t, 3H, CH_3), 2.86 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 3.93 (s, 3H, CH_3), 4.34 (q, 2H, CH_2), 7.10—7.30 (m, 4H, CH×4), 7.43 (d, 1H, CH). *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.25; H, 6.71; N, 5.48; Found: C, 75.07; H, 6.68; N, 5.46.

Ethyl 4-Methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (14) A suspension of *N*-acetyl-pyrrolester **13**[8] (1.10 mmol) in 2.5 M NaOH (3 ml) was refluxed for 30 min. The solution was cooled at room temperature and the precipitate was filtered off, washed with water, dried to give the ester **14**. IR: 1675 (C=O), 3270 (NH); UV: 235.0 (4.39), 271.0 (4.36); ^{1}H-NMR [$CDCl_3$]: 1.36 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 7.41—7.47 (m, 6H, CH×6), 8.42 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.10; Found: C, 73.07; H, 6.57; N, 6.08.

Ethyl 1-Methyl-1*H*-benzo[*g*]indole-3-carboxylate (7f) To a solution of the *N*-methyl-ester **7d** (2.66 mmol) in CH_2Cl_2 (10 ml) 1.81 g (7.98 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was added and the mixture was stirred at room temperature for 5 min. The solvent was evaporated and the residue was purified by flash chromatography on Al_2O_3 (EtPet/AcOEt 8/2) to give **7f** as a solid, mp 116—118 °C. IR: 1690 (C=O); UV: 226.3 (4.75), 236.0 (4.70), 255.0 (4.47); ^{1}H-NMR [$CDCl_3$]: 1.43 (t, 3H, CH_3), 4.24 (s, 3H, CH_3), 4.41 (q, 2H, CH_2), 7.45—7.54 (m, 2H, CH×2), 7.64 (d, 1H, CH, J_{AB}=8.2 Hz), 7.70 (s, 1H, CH), 7.96 (d, 1H, CH), 8.30 (d, 1H, CH, J_{AB}=8.2 Hz), 8.40 (d, 1H, CH). *Anal.* Calcd for $C_{16}H_{16}NO_2$: C, 75.86; H, 6.36; N, 5.53; Found: C, 76.01; H, 6.39; N, 5.55.

General Procedure for Compounds 8a—f To a solution of pyrrole ester **7a**—**f** (4.71 mmol) in CH_3CN (11.5 ml), *N*-*N*′-dimethylchloromethylene ammonium chloride (Vilsmeier's reagent) (6.11 mmol) was added and the suspension was stirred at room temperature (1.5 h for **7b**, **c**, **d**, 2 h for **7a**, 3 h for **7e**, **f**). The solvent was concentrated under reduced pressure and the oily residue was taken up with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with AcOEt, the organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated under reduced pressure to yield alternatively an oil (**8a**, **b**) purified by bulb-to-bulb distillation under a vacuum, or a solid (**8c**—**f**) purified by flash chromatography.

Ethyl 1-Methyl-2-formyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**8a**): IR: 1660 (C=O), 1715 (C=O); UV: 247.3 (4.28), 269.1 (4.14), 247.2 (4.11), 325.1 (4.38), 340.5 (4.28); ^{1}H-NMR [$CDCl_3$]: 1.38 (t, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.38 (q, 2H, CH_2), 6.74 (s, 1H, CH), 7.37—7.51 (m, 5H, CH×5), 10.47 (s, 1H, CH). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44; Found: C, 70.22; H, 5.89; N, 5.48.

Ethyl 1,4-Dimethyl-2-formyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**8b**): IR: 1665 (C=O), 1700 (C=O); UV: 249.0 (4.08), 278.0 (3.95), 331.0 (4.35); ^{1}H-NMR [$CDCl_3$]: 1.40 (t, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.40 (q, 2H, CH_2), 7.25—7.30 (m, 2H, CH×2), 7.45—7.52 (m, 3H, CH×3), 10.37 (s, 1H, CH). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16; Found: C, 70.48; H, 6.30; N, 5.14.

Ethyl 1-Methyl-2-formyl-1,4-dihydro-indeno[1,2-*b*]pyrrole-3-carboxylate (**8c**): IR: 1640 (C=O), 1700 (C=O); UV: 268.0 (4.08), 281.0 (3.99), 291.0 (3.87), 355.5 (4.35); ^{1}H-NMR [$CDCl_3$]: 1.43 (t, 3H, CH_3), 3.76 (s, 2H, CH_2), 4.33 (s, 3H, CH_3), 4.41 (q, 2H, CH_2), 7.30—7.40 (m, 2H, CH×2), 7.54 (d, 1H, CH), 7.64 (d, 1H, CH), 10.41 (s, 1H, CH). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20; Found: C, 71.18; H, 5.59; N, 5.18.

Ethyl 1-Methyl-2-formyl-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (**8d**): IR: 1655 (C=O), 1700 (C=O), UV: 226.0 (4.78), 234.0 (4.65), 253.0 (4.24), 294.0 (4.61), 307.0 (4.47); ^{1}H-NMR [$CDCl_3$]: 1.40 (t, 3H, CH_3), 2.87—3.00 (m, 4H, CH_2×2), 4.25 (s, 3H, CH_3), 7.25—7.35 (m, 3H, CH×3), 7.60 (d, 1H, CH), 10.38 (s, 1H, CH). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.04; N, 4.94; Found: C, 72.35; H, 6.07; N, 4.96.

Methyl 1-Methyl-2-formyl-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*b*]pyrrole-3-carboxylate (**8e**): IR: 1650 (C=O), 1700 (C=O); UV: 226.0 (4.74), 230.0 (4.45), 251.5 (4.29), 297.0 (4.50); ^{1}H-NMR [$CDCl_3$]: 1.35 (t, 3H, CH_3), 2.15 (q, 2H, CH_2), 2.37 (t, 2H, CH_2), 2.58 (t, 2H, CH_2), 3.97 (s, 3H, CH_3), 4.33 (q, 2H, CH_2), 7.26—7.34 (m, 4H, CH×4), 10.30 (s, 1H, CH). *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71; Found: C, 72.63; H, 6.42; N, 4.70.

Ethyl 1-Methyl-2-formyl-1*H*-benzo[*g*]indole-3-carboxylate (**8f**): IR: 1660 (C=O), 1700 (C=O); UV: 226.0 (4.70), 243.0 (4.65), 253.0 (4.24), 292.5 (4.7), 307.3 (4.46); ^{1}H-NMR [$CDCl_3$]: 1.43 (t, 3H, CH_3), 2.88—2.98 (m, 4H, CH_2×2), 4.24 (s, 3H, CH_3), 7.45—7.54 (m, 2H, CH×2), 7.64 (d, 1H, CH, J_{AB}=8.2 Hz), 7.96 (d, 1H, CH), 8.30 (d, 1H, CH, J_{AB}=8.2 Hz), 8.40 (d, 1H, CH), 10.35 (s, 1H, CH). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; Found: C, 72.62; H, 5.38; N, 5.00.

Methyl (*E*,*E*)/(*Z*,*E*)-3-[(6,7,8,9-Tetrahydro-5*H*-benzo-[*a*]cyclohepten-5-ylidenamido)oxy]-2-propenoate (16) To a solution of the benzosuberone oxime **15**[14] (6.2 mmol) and a few drops of triethylamine in anhydrous dimethyl sulfoxide (DMSO) (6 ml), a solution of methylpropiolate (12.4 mmol) in anhydrous DMSO (2.5 ml) was added dropwise at room temperature and in the presence of drops of triethylamine. The reaction mixture was heated to 65—70 °C for 24 h. The cooled reaction solution was poured into crushed ice and the aqueous layer was extracted with CH_2Cl_2. The organic phase was collected, washed with water, dried (Na_2SO_4) and concentrated to yield a brown residue. Purification by flash chromatography (petroleum ether/AcOEt, 8/2) afforded the desired *O*-vinyl oxime ether **16** as a mixture of (*E*,*E*) and (*Z*,*E*) isomers.

IR: 1740 (C=O), 1644 (C=N), 1602 (C=C); UV: 257.8 (4.50), 206.4 (4.38); ^{1}H-NMR [$CDCl_3$]: 1.57—1.87 (m, 4H, CH_2×2), 2.68—2.84 (m, 4H, CH_2×2), 3.72 and 3.74 (s×2, 3H, CH_3, of (*Z*,*E*) and (*E*,*E*) isomers), 6.23 and 6.90 (q AB×2, 2H, J_{AB}=7.4, 12.80 Hz, C_2H and C_3H of (*Z*,*E*) and (*E*,*E*) isomers), 7.14—7.44 (m, 4H, CH×4). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.60; N, 5.40; Found: C, 69.32; H, 6.58; N, 5.38.

Methyl 1,4,5,6-Tetrahydrobenzo[6,7]cyclohepta[*b*]pyrrole-3-carboxylate (17) A neat mixture of the (*E*,*E*) and (*Z*,*E*) isomers **16** (3.6 mmol) was heated to 130 °C for 15 h to give a brown residue. Purification by flash chromatography (petroleum ether/AcOEt 8/2) afforded the desired product **17**.

IR: 3300 (NH), 1680 (C=O), 1600 (C=C); UV: 309.8 (4.15), 235.2 (3.81), 231.0 (3.79), 204.8 (4.01); ^{1}H-NMR [$CDCl_3$]: 1.97—2.15 (m, 2H, CH_2), 2.76—2.86 (m, 4H, CH_2×2), 3.86 (s, 3H, CH_3), 6.81 (d, 1H, *J*=2.2 Hz, C_2H), 7.16—7.50 (m, 4H, CH×4), 9.11 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.80; Found: C, 74.80; H, 6.43; N, 5.40.

General Ring Closure Procedure with Hydrazine Hydrate for Compounds 1—6 A mixture of formyl ester **8a**—**f** (1.85 mmol) in $H_2NNH_2 \cdot H_2O$ (98%, 1.80 ml, 37.1 mmol) was refluxed for 0.25—4 h (0.25 h for **8c**, 1 h for **8a**, **b**, **d**, 4 h for **8e**, **f**) and then poured onto ice. The solid precipitate was filtered and washed with H_2O to give a crude product that was purified by trituration with ethyl ether to yield the expected products **1**—**6**.

1-Methyl-2-phenyl-1*H*-pyrrol[2,3-*d*]pyridazin-4(5*H*)-one (**1**): IR: 1630 (C=N), 1660 (C=O), 3210 (NH); UV: 232.3 (4.336), 304.1 (4.295); ^{1}H-NMR [$CDCl_3$]: 3.84 (s, 3H, CH_3), 6.81 (s, 1H, CH), 7.47—7.58 (m, 5H, CH×5), 8.20 (s, 1H, CH), 12.08 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.37; H, 4.91; N, 18.65; Found: C, 69.20; H, 4.89; N, 18.50.

1,3-Dimethyl-2-phenyl-1*H*-pyrrol[2,3-*d*]pyridazin-4(5*H*)-one (**2**): IR: 1640 (C=O), 3280 (NH); UV: 278.0 (4.043), 310.0 (4.398); ^{1}H-NMR [$CDCl_3$]: 2.42 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 7.33—7.54 (m, 5H, CH×5), 8.07 (s, 1H, CH), 10.25 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for

$C_{14}H_{13}N_3O$: C, 70.27; H, 5.47; N, 17.56; Found: C, 70.57; H, 5.50; N, 17.59.

5-Methyl-5,10-dihydroindenopyrrol[2,3-*d*]pyridazin-1(2*H*)-one (**3**): IR: 1650 (C=O); UV: 235.5 (4.631), 243.5 (4.085), 313.0 (4.329), 327.0 (4.653), 340.0 (4.779); ^{1}H-NMR [$CDCl_3$]: 2.80 (s, 2H, CH_2), 4.15 (s, 3H, CH_3), 7.29 (t, 1H, CH), 7.39 (t, 1H, CH), 7.58 (d, 2H, CH×2), 8.23 (s, 1H, CH), 12.10 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; Found: C, 71.10; H, 4.71; N, 17.73.

11-Methyl-5,6-dihydrobenzo[*g*]pyridazin[4,5-*b*]indol-7(8*H*)-one (**4**): IR: 1650 (C=O), 3170 (NH); UV: 240.5 (4.600), 276.5 (5.084), 318.0 (4.609), 331.0 (4.705); ^{1}H-NMR [$CDCl_3$]: 2.94 (t, 2H, CH_2), 3.16 (t, 2H, CH_2), 4.09 (s, 3H, CH_3), 7.26—7.39 (m, 3H, CH×3), 7.62 (d, 1H, CH), 8.09 (s, 1H, CH), 12.27 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72; Found: C, 71.98; H, 5.23; N, 16.73.

12-Methyl-5,6,7,12-tetrahydrobenzo[3′,4′]cyclohepta[1′,2′-4,5]pyrrol-[2,3-*d*]pyridazin-8(9*H*)-one (**5**): IR: 1645 (C=O), 3160 (NH); UV: 227.5 (4.950), 236.5 (4.924), 301.0 (4.609), 331.0 (5.005); ^{1}H-NMR [$CDCl_3$]: 2.18 (q, 2H, CH_2), 2.39 (t, 2H, CH_2), 2.58 (t, 2H, CH_2), 4.02 (s, 3H, CH_3), 7.28—7.38 (m, 5H, CH×5), 8.60 (s, 1H, CH), 12.20 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.69; N, 15.83; Found: C, 72.10; H, 5.67; N, 15.80.

11-Methylbenzo[*g*]pyridazin[4,5-*b*]indol-7(8*H*)-one (**6**): IR: 1645 (C=O), 3160 (NH); UV: 257.5 (4.658), 275.5 (5.084), 318.0 (4.589), 331.0 (4.705); ^{1}H-NMR [$CDCl_3$]: 4.28 (s, 3H, CH_3), 7.47—7.56 (m, 2H, CH×2), 7.66 (d, 1H, CH, J_{AB}=8.2 Hz), 7.97 (d, 2H, CH×2), 8.31 (d, 1H, CH, J_{AB}=8.2 Hz), 8.35 (d, 1H, CH), 8.40 (s, 1H, CH), 12.30 (br s, 1H, NH exchanged with D_2O). *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.85; Found: C, 71.97; H, 4.41; N, 16.83.

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