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A DIVERSITY ORIENTED SYNTHESIS OF 2,10-DIOXO-10*H*-1,2,3,4,4a,5-HEXAHYDROPYRIDAZINO[3,2-*b*]QUINAZOLINES

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Abstract – A parallel method for the synthesis of the title compounds is described. Thus, methyl anthranilates (**5**) are transformed into 2-aminobenzohydrazides (**3**) which were treated with 4-oxo acids (**4**) to afford in high yields and acceptable purity of piridazino[3,2-*b*]quinazolines (**1**). Compounds (**1**) present four diversity centers (R_1, R_2, R_3, and R_4). The range of chemically acceptable substituents at each center has been evaluated. The isolation of a possible intermediate in the formation of **1**, which presents an aminol structure (**10**), has allowed proposing a complete mechanistic rationalization for the formation of structures (**1**).

INTRODUCTION

2,10-Dioxo-10*H*-1,2,3,4,4a,5-hexahydropiridazino[3,2-*b*]quinazolines (**1**) have attracted little attention as scaffolds for library production although they present four possible diversity centers (Figure 1) and have been reported in literature to present broad range of biological activities such as anti-inflammatory and analgesic,[1] anti-insomnia, anticonvulsant, and mental illness.[2,3] The corresponding dehydro derivatives (**2**) have been claimed for the treatment of neurodegenerative diseases of the central nervous system (Alzheimer, Parkinson, and Huntington),[4] for treatment of prostatic hyperplasia[5] and osteoporosis[6] and as very potent herbicides.[7]

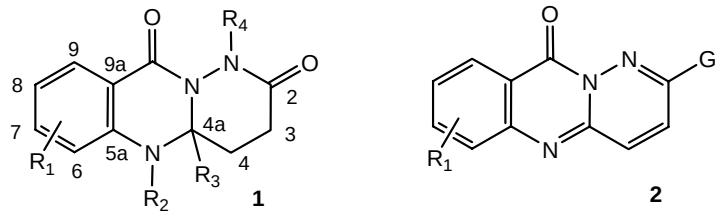
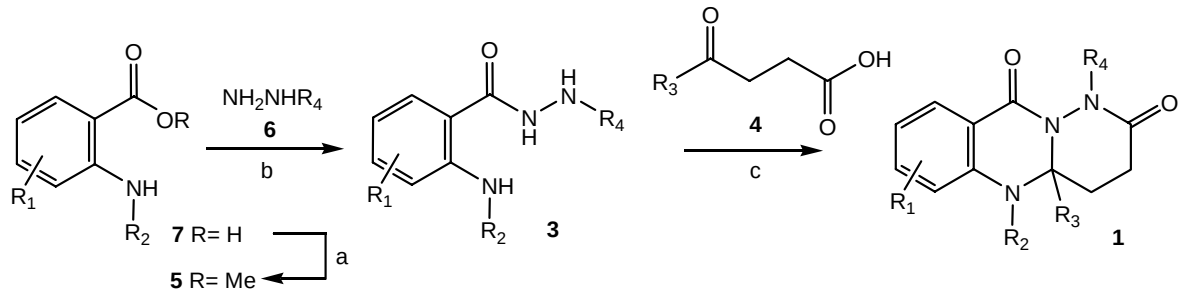


Figure 1

As a part of our work in the area of combinatorial chemistry focused on the preparation of random libraries for agrochemical screening,[8] we decided to prepare small sized libraries of pyrazolo[3,2-*b*]quinazolines (**1**) using a solution-phase parallel synthesis approach. The present paper reports the results of such study.

RESULTS AND DISCUSSION

Compounds (**1**) are usually prepared by condensation of anthranilic hydrazides (**3**) with 4-oxo acids (**4**) (Scheme 1) in moderate to good yields,[1-3,9] a procedure which in most cases is amenable to parallelization. Anthranilic hydrazides (**3**) can also, in principle, be prepared in parallel by treatment of *N*-substituted methyl anthranilates (**5**) with substituted hydrazines (**6**) in refluxing EtOH.[8,10,11] Eleven methyl anthranilates (**5**{*1-11*}) were selected on the basis of price, commercial availability, and diversity (Figure 2), six, esters (**5**{*1-6*}), were purchased and five, esters (**5**{*7-11*}), were prepared from the corresponding acids (**7**{*6-11*}) in almost quantitative yields by treatment with CH_2N_2 in Et_2O. Building blocks (**5**{*1-11*}) are responsible for the diversity in R_1 and R_2.



Reagents and conditions: a) CH_2N_2 in Et_2O; b) EtOH, 60-70ºC; c) benzene, TsOH, reflux

Scheme 1. Chemset numbering of compounds (**1**) is standardized as follows: **1**{building block **5**, building block **6**, building block **4**}. Chemset numbering of intermediates follows the same standardization.

Three hydrazines (**6**{*1-3*}) (Figure 3) were selected to introduce diversity in R_4: hydrazine (**6**{*1*}) (R_4=H), methylhydrazine (**6**{*2*}) (R_4=Me), and phenylhydrazine (**6**{*3*}) (R_4=Ph). Treatment in parallel of methyl anthranilates (**5**{*1-11*}) with 15 equivalents of hydrazine (**6**{*1*}) in EtOH at 60-70ºC for 15-24 h afforded the corresponding hydrazides (**3**{*x,1*}) (x=1-7,9-11) in 43-92% yields. Methyl 2-amino-6-methylbenzoate (**5**{*8*}) did not yield the expected hydrazide (**3**{*8,1*}), possible because of steric

hindrance at the carbonyl group. Compounds (**3**{*x,1*}) (x=1-7,9-11) were isolated by simple filtration from the reaction mixture and used in the step without further purification.

The reaction of methyl anthranilates with phenyl hydrazine (**6**{*3*}) under the same reaction conditions used for **6**{*1*} yielded only the unwanted regioisomer (**8**) (Figure 3). Thus, treatment of methyl *N*-methylanthranilate (**5**{*2*}) with phenylhydrazine (**6**{*3*}) in EtOH at reflux gave only hydrazide (**8**{*2,3*}). The alternative treatment of *N*-methylanthranilic acid (**7**{*2*}) with phenylhydrazine (**6**{3}) using DCC as coupling agent in CH_2Cl_2 at room temperature for 4 h afforded **3**{*2,3*} in 25% yield after separation from the unwanted regioisomer (**8**{*2,3*}) by column chromatography (Figure 3). Using the same reaction conditions anthranilic acid (**7**{*1*}) and *N*-phenylanthranilic acid (**7**{*11*}) yielded 2-amino-*N*'-phenylbenzohydrazide (**3**{*1,3*}) and 2-phenylamino-*N*'-phenylbenzohydrazide (**3**{*11,3*}) in 16% and 25% yields after separation from **8**{*1,3*}and **8**{*11,3*} respectively.

We could not overcome regiochemical problems when methylhydrazine (**6**{*2*}) was used as building block. Treatment of either methyl anthranilate (**5**{*1*}) or the corresponding anthranilic acid (**7**{*1*}) with methylhydrazine (**6**{*2*}) yielded only *N*-methyl derivative (**8**{*1,2*}). Diversity in R_4 will be consequently limited to hydrogen or aryl groups.

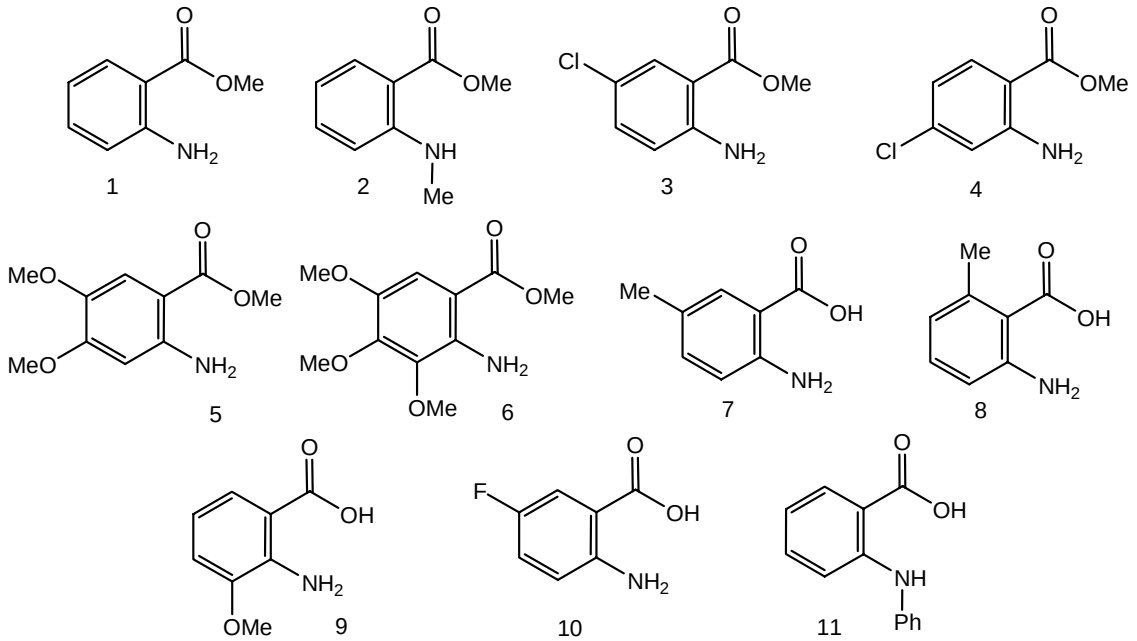


Figure 2: Methyl anthranilates (**5**{*1-6*}) and anthranilic acids (**7**{*7-11*}) used as building blocks

Three commercially available 4-oxo acids (**4**{*1-3*}) (Figure 3) were selected to introduce diversity in R_3. Treatment in parallel of previously prepared hydrazides (**3**) with 1.5 equivalents of 4-oxo acids (**4**{*1-3*}) using TsOH as catalyst in refluxing benzene yielded the expected pyrridazino[3,2-*b*]quinazolines (**1**) in good yields. Isolation was carried out either by filtration, if the product precipitates out of solution, or

the reaction mixture was concentrated *in vacuo* and fractionated in AcOEt/water, to afford pyridazino[3,2-*b*]quinazolines (**1**).

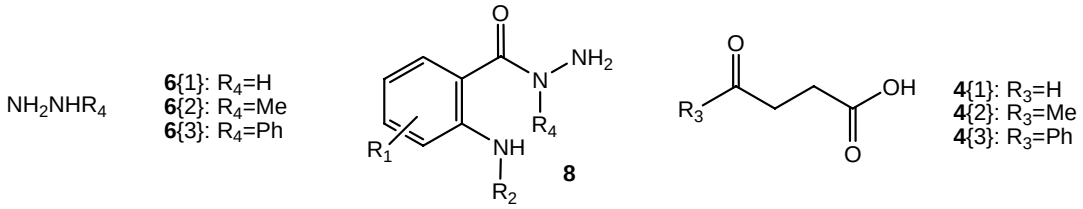


Figure 3: Hydrazines and oxo acids used.

Reactions proceed quite well with 4-oxobutyric acid (**4**{*1*}) and levulinic acid (**4**{*2*}). In general the latter gave better yields. On the contrary, all attempts carried out with 3-benzoylpropionic acid (**4**{*3*}) failed, probably due to the steric hindrance introduced by the phenyl group. Consequently, diversity at R_3 will be limited to hydrogen or alkyl groups. Table 1 summarizes the demonstrative library of pyridazino[3,2-*b*]quinazolines (**1**) prepared. Each compound was characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectral data (Table 2).

Table 1. Compounds (**1**) prepared.

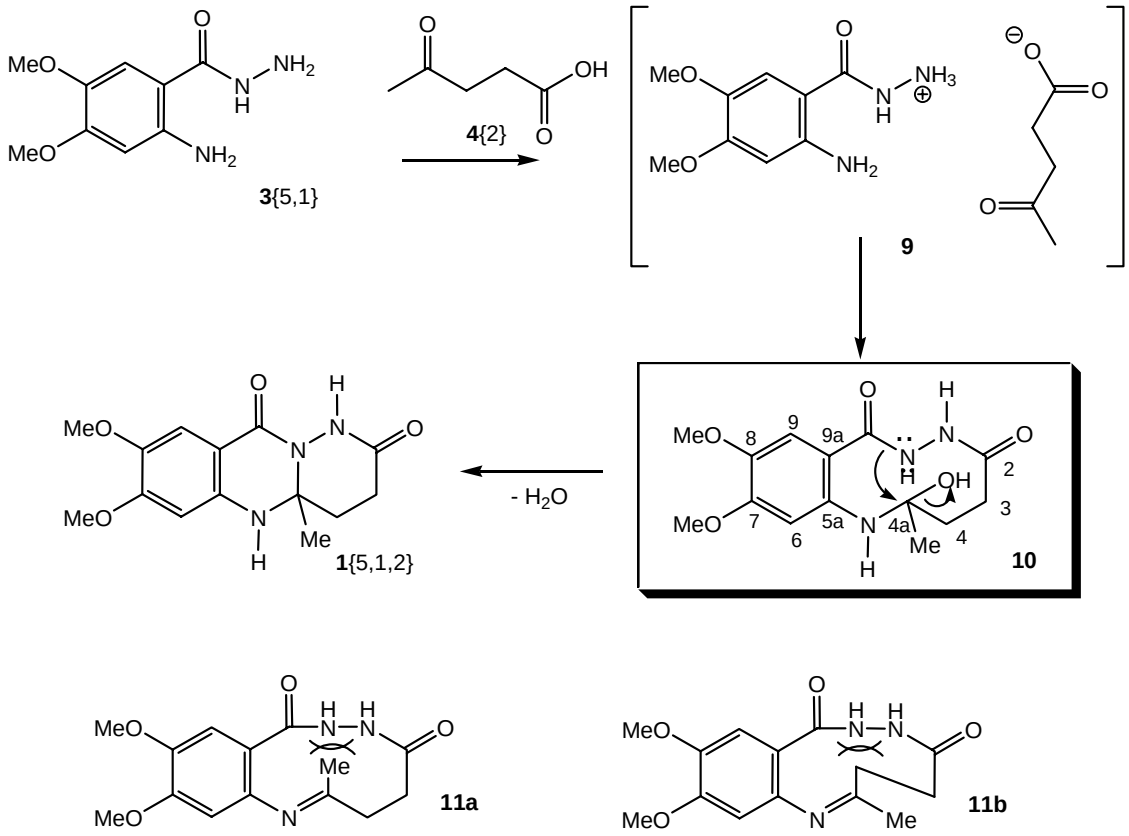
Com-pound	R_1	R_2	R_3	R_4	Yield (%)	mp (ºC)	Elemental Analysis (%): Found (Calculated) C	H	N
1{*1,1,2*}[a]	H	H	Me	H	70	183-185	62.10 (62.33)	5.42 (5.67)	18.00 (18.17)
1{*1,3,2*}[a]	H	H	Me	Ph	22	202-204	70.17 (70.34)	5.63 (5.58)	13.53 (13.67)
1{*2,1,1*}	H	Me	H	H	33	192-195	62.55 (62.33)	5.83 (5.67)	18.03 (18.17)
1{*2,1,2*}	H	Me	Me	H	77	133-135	63.72 (63.66)	6.24 (6.16)	17.42 (17.13)
1{*2,3,2*}	H	Me	Me	Ph	38	166-168	70.89 (71.01)	5.89 (5.96)	13.35 (13.08)
1{*3,1,2*}	8-Cl	H	Me	H	73	183-185	54.12(54.25)	4.76 (4.55)	15.54 (15.82)
1{*4,1,2*}	7-Cl	H	Me	H	77	188-190	53.85 (54.25)	4.81 (4.55)	15.49 (15.82)
1{*5,1,2*}	7,8-OMe	H	Me	H	92	198-200	57.90 (57.72)	5.94 (5.88)	14.15 (14.42)
1{*6,1,2*}	6,7,8-OMe	H	Me	H	38	164-166	56.23 (56.07)	5.81 (5.96)	13.15 (13.08)
1{*7,1.2*}	8-Me	H	Me	H	25	182-185	63.35 (63.66)	6.25 (6.16)	17.06 (17.13)
1{*9,1,2*}	6-OMe	H	Me	H	29	150-155	59.43 (59.76)	5.82 (5.79)	15.96 (16.08)
1{*10,1,2*}	8-F	H	Me	H	53	169-171	57.53 (57.83)	4.62 (4.85)	16.54 (16.86)
1{*11,1,1*}	H	Ph	H	H	17	195-197	69.76 (69.61)	5.35 (5.15)	14.10 (14.33)
1{*11,1,2*}	H	Ph	Me	H	20	187-188	70.49 (70.34)	5.79 (5.58)	13.81 (13.67)
1{*11,3,2*}	H	Ph	Me	Ph	29	208-210	75.21 (75.18)	5.22 (5.52)	10.67 (10.96)

[a]Included in reference 1 but without elemental analysis or spectral data

The formation of compounds (**1**) has been previously reported but the mechanism by which the tricyclic system is formed has not been rationalized. In the preparation of compound (**1**{*5,1,2*}) (Scheme 2) we

isolated a possible reaction intermediate that we assigned to structure (**10**) based on the following spectral data: IR ν (cm^{-1}): 3332, 3274, 3213 (NH, OH), 1703 (C=O); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.84 and 7,50 (s, 1H, H-Ph), 4.23 (br, 4H, NH and OH), 3.97 and 3.94 (s, 3H, OMe), 2.60-2.20 (m, 4H, CH_2CH_2), 1.48 (s, 3H, Me); ^{13}C-NMR ($CDCl_3$) δ (ppm): 171.9 (C=O), 163.5 (C=O), 153.2 (C7), 146.3 (C8), 130.4 (C5a), 111.1 (C9a), 109.5 (C9), 103 (C6), 81.0 (C4a, quaternary carbon), 56.3 (OMe), 56.2 (OMe), 31.7 (CH_2), 30.1 (CH_2), 20.9 (Me). Particularly important to this assignment is the presence in the ^{13}C-NMR spectrum of a quaternary carbon at 81.0 ppm. Aminol (**10**) would be the result of the dehydration of salt **9** followed (or preceded) by condensation without dehydration of the 2-aminophenyl group onto the 4-oxo group. Dehydration of aminol (**10**) to imines (**11a**) or (**11b**) would be disfavored because either the methyl or methylene groups would be necessarily inside the macrocyclic ring with the consequent high steric hindrance (Scheme 2). Aminols (**10**) would lead to the final pyridazino[3,2-*b*]quinazolines (**1**) by nucleophilic displacement of the hydroxyl group by the nitrogen atom bonded to the C10 carbonyl group with subsequent loss of water.

The complete characterization of aminol (**10**) (R_1=7,8-OMe, R_2=H, R_3=Me, R_4=H) by means of MS spectrum was not possible because in the registering conditions (**10**) underwent loss of water to the final pyridazino[3,2-*b*]quinazoline (**1**{5,1,2}).



Scheme 2: Rationalization of compound (**1**{*5,1,2*}) formation

Compounds (**1**) were inactive in assays for herbicidal, fungicidal or insecticidal activities.

EXPERIMENTAL

All melting points were determined with a Büchi 530 capillary apparatus and are uncorrected. IR spectra were recorded in a Nicolet Magna 560 FTIR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined in a Varian Gemini-300 operating in a field strength of 300 and 75.5 MHz, respectively. Chemical shifts are reported in parts per million (δ) and coupling constants (*J*) in Hz, using in the case of ^{1}H-NMR, tetramethylsilane (TMS) or sodium 2,2,3,3-tetradeuteriotrimethylsilylpropionate (TSPNa) as internal standards and setting, in the case of ^{13}C-NMR, the references at the signal of the solvent (77.0 ppm for $CDCl_3$, 39.5 ppm and for DMSO-d_6). . Elemental microanalyses were obtained in a Carlo-Erba CHNS-O/EA 1108 analyzer and gave results for the elements stated with ±0.4% of the theoretical values. Methyl *N*-phenylanthranilate (**5**{*11*}) (R_1=H, R_2=Ph) was obtained according to a reported procedure.[12] Analytical samples of compounds (**5**), (**3**), and (**1**) were obtained by preparative HPLC using a Gilson HPLC provided with a Gilson 215 Liquid Handler and UV detector at 220 and 254 nm. Columns used were a YMC-Pack SIL (150 x 10 mm, 5 μm) for the normal phase and a YMC-Pack ODS-AQ (100 x 10 mm, 5 μm) for the reverse phase.

General procedure for the synthesis of methyl anthranilates (5{*7-10*}). Methyl 5-methylanthranilate (5{*7*}) (R_1=5-Me, R_2=H): A ethereal solution of diazomethane prepared according to the procedure and apparatus of Hudlicky[13] using 2.8 g (13.2 mmol) of Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) in 132 mL of Et_2O, 0.8 g (13.2 mmol) of KOH in 1.3 mL of water, 4.7 mL of Carbitol and 1.3 mL of Et2O, was added dropwise to a suspension of 1.0 g (6.6 mmol) of 5-methylanthranilic acid (**7**{*7*}) in 50 mL of Et_2O. The resulting mixture was stirred for 1 h, concentrated *in* vacuo to afford 1.1 g (99%) of methyl 5-methylanthranilate (**5**{*7*}) as a pale yellow liquid. IR ($CHCl_3$) ν (cm^{-1}): 3477, 3370 (N-H), 1690 (C=O), 1582, 1562, 1502, 1456, 1440; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.66 (d, $^{4}J_{HH}$= 2 Hz, 1H, H6), 7.10 (dd, $^{3}J_{HH}$= 8 Hz, $^{4}J_{HH}$= 2 Hz, 1H, H4), 6.59 (d, $^{3}J_{HH}$= 8 Hz, 1H, H3), 5.55 (br, 2H, NH_2), 3.86 (s, 3H, -$COOCH_3$), 2.23 (s, 3H, C5-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.6 (C=O), 148.2 (C2), 135.2 (C4), 130.8 (C6), 125.4 (C5), 116.8 (C3), 110.7 (C1), 51.5 (-COO<u>C</u>H_3), 20.2 (C5-<u>C</u>H_3); MS, m/z (%):165 (80) [M^+], 133 (100), 104 (25), 84 (31), 69 (61), 49 (38); Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.03; H, 6.93; N, 8.15.

Methyl 6-methylanthranilate (5{*8*}) (R_1=6-Me, R_2=H): As above but using 1.0 g (6.6 mmol) of 6-methylanthranilic acid (**7**{*8*}). Yield: 98%; IR ($CHCl_3$) ν (cm^{-1}): 3483, 3378 (N-H), 1696 (C=O), 1607, 1588, 1465, 1441; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.08 (dd, $^{3}J_{HH}$= 7 Hz, $^{3}J_{HH}$= 7 Hz, 1H, H4), 6.54-6.52 (m, 2H, H5, H3), 5.11 (br, 2H, NH_2), 3.89 (s, 3H, -$COOCH_3$), 2.43 (s, 3H, C6-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 166.1 (C=O), 150.7 (C2), 140.5.8 (C6), 133.8 (C4), 119.2 (C5), 117.5 (C1), 113.0 (C3), 51.5

(-COO<u>C</u>H$_3$), 18.3 (C6-<u>C</u>H$_3$); Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.70; H, 6.80; N, 8.27.

Methyl 3-methoxyanthranilate (5{*9*}) (R_1=3-OMe, R_2=H): As above but using 1.0 g (6.0 mmol) of 3-methoxyanthranilic acid (**7**{*9*}).Yield: 96%; IR ($CHCl_3$) ν (cm^{-1}): 3496, 3377 (N-H), 1693 (C=O), 1615, 1589, 1552, 1478, 1462; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.47 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H6), 6.85 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H4), 6.56 (dd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, 1H, H5), 6.00 (br, 2H, NH_2), 3.87 (s, 6H, -COOCH_3, C3-OCH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.7 (C=O), 147.0 (C3), 141.7 (C2), 122.5 (C6), 114.6, 112.9 (C5, C4), 110.1 (C1), 55.7 (C3-O<u>C</u>H$_3$), 51.5 (-COO<u>C</u>H$_3$); Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.73; H, 6.28; N, 7.45.

Methyl 5-fluoroanthranilate (5{*10*}) (R_1=5-F, R_2=H): As above but using 1.0 g (6.5 mmol) of 5-fluoroyanthranilic acid (**7**{*10*}). Yield: 99%; IR ($CHCl_3$) ν (cm^{-1}): 3483, 3375 (N-H), 1700 (C=O), 1602, 1592, 1567, 1496; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.54 (dd, $^3J_{HF}$= 10 Hz, $^4J_{HH}$ = 3 Hz, 1H, H6), 7.04 (ddd, $^3J_{HF}$= 9 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 3 Hz, 1H, H4), 6.62 (dd, $^3J_{HH}$ = 9 Hz, $^4J_{HH}$= 5 Hz, 1H, H3), 5.58 (br, 2H, NH_2), 3.88 (s, 3H, -COOCH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 167.3 (C=O), 152.80 (C5), 146.2 (C2), 121.2 (C4), 117.5, 115.4 (C3, C6), 111.7 (C1), 51.5 (-COO<u>C</u>H$_3$); Anal. Calcd for $C_8H_8NO_2F$: C, 56.80; H, 4.77; N, 8.28. Found: C, 56.75; H, 4.93; N, 8.12.

General procedure for the synthesis of anthranilic hydrazides (3{*x,1*}). *N*-Methyl anthranilic hydrazide (3{*2,1*}) (R_1=H, R_2=Me, R_4=H): A mixture of 1.0 mL (6.7 mmol) of methyl *N*-methylanthranilate (**5**{*2*}), 3.2 mL (0.10 mol) of hydrazine (**6**{*1*}), and 15 mL of EtOH was heated at reflux for 24 h. The resulting precipitate was filtered, sequentially washed with water and EtOH, and dried over P_2O_5 to afford 0.9 g (85%) of **3**{*2,1*}as a white solid, mp 137-138ºC (mp[10a] 141-142ºC); IR (KBr) ν (cm^{-1}): 3331, 3305 (N-H), 1629 (C=O), 1573, 1532, 1514; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.47 (br, 2H, -CON<u>H</u>NH$_2$, -N<u>H</u>-CH$_3$), 7.36-7.29 (m, 2H, H4, H6), 6.67 (d, $^3J_{HH}$= 8 Hz, 1H, H3), 6.58 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 1 Hz, 1H, H5), 4.80-3.20 (br, 2H, -CONHN<u>H</u>$_2$), 2.86 (s, 3H, -NH-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 170.8 (-<u>C</u>ONHNH$_2$), 150.4 (C2), 133.2 (C4), 127.0 (C6), 114.6 (C5), 113.1 (C1), 111.1 (C3), 29.6 (-NH<u>C</u>H$_3$); MS, m/z (%): 165 (46) [M^+], 134 (100), 77 (35); Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.43. Found: C, 58.49; H, 6.51; N, 25.10.

Anthranilic hydrazide (3{*1,1*}) (R_1=H, R_2=H, R_4=H): As above but using 1.0 g (6.7 mmol) of methyl anthranilate (**5**{*1*}) at 70ºC for 21 h. Yield: 47%, mp 119-121ºC (mp[14] 120-121ºC); IR (KBr) ν (cm^{-1}): 3444, 3326, 3177 (N-H), 1620 (C=O), 1578, 1562, 1506, 1483, 1450; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.30-7.20 (m, 3H, -CON<u>H</u>NH$_2$, H4, H6), 6.80-6.56 (m, 2H, H3, H5), 5.45 (br, 2H, C2-NH$_2$), 4.04 (br, 2H, -CONHN<u>H</u>$_2$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.5 (<u>C</u>ONHNH$_2$), 149.3 (C2), 131.5 (C4), 127.6 (C6),

Table 2. *Spectroscopic Data of Compounds* (1)

Product	IR (KBr) υ (cm^{-1})	^{1}H- NMR ($CDCl_3$/TMS) δ (ppm), *J* (Hz)	^{13}C-NMR (solvent/TMS) δ (ppm)	MS, *m/z* (%)
1{*1,1,2*}	3294, 3213, 3134 (N-H), 1688 (C=O),1654, 1614	9.40-8.20 (br, 1H, NHCO), 7.89 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H9), 7.36 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$ = 2 Hz, 1H, H7), 6.93 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H8), 6.71 (d, $^3J_{HH}$= 8 Hz, H6), 4.80-3.80 (br, 1H, NH), 2.86-2.72 (m, 1H, H3), 2.60-2.46 (m, 1H, H3), 2.42-2.28 (m, 1H, H4), 2.22-2.06 (m, 1H, H4), 1.60 (s, 3H, C4a-CH_3)	169.5 (C2), 157.1 (C10), 144.1 (C5a), 134.2 (C7), 128.4 (C9), 120.1 (C8), 115.3 (C6), 113.9 (C9a), 73.7 (C4a), 36.4 (C3), 28.8 (C4), 23.6 (C4a-$\underline{C}H_3$)	231 (62) [M^+], 216 (100), 202 (36), 119 (69)
1{*1,3,2*}	3274 (N-H), 1717, 1670 (C=O), 1603, 1494, 1486	8.28 (d, $^3J_{HH}$= 8 Hz, 1H, H9), 8.09 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H6), 7.63 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H7), 7.42-7.14 (m, 3H, H8, H3'), 7.06-6.80 (m, 3H, H2', H4'), 6.42 (br, 1H, NH), 2.84-2.42 (m, 2H, H3), 2.36-2.10 (m, 2H, H4), 1.60 (s, 3H, C4a-CH_3)	172.3 (C2), 164.3 (C10), 147.5 (C5a), 135.9 (C1'), 134.2 (C7), 129.4 (C3'), 128.8 (C9), 125.2 (C4'), 122.1 (C8), 120.6 (C6), 118.8 (C9a), 113.9 (C2'), 81.7 (C4a), 30.2 (C3, C4), 22.9 (C4a-$\underline{C}H_3$)	307 (47) [M^+], 200 (100)
1{*2,1,1*}	3317, 3179 (N-H), 1680, 1668 (C=O), 1610, 1572, 1496, 1466	8.77 (br, 1H, NHCO), 7.96 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H9), 7.44 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 2 Hz, 1H, H7), 6.89 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 1 Hz, 1H, H8), 6.71 (d, $^3J_{HH}$ = 8 Hz, 1H, H6), 5.07 (dd, $^3J_{HH}$= 10 Hz, $^3J_{HH}$= 4 Hz, 1H, H4a), 3.00 (s, 3H, NCH_3), 2.80-2.50 (m, 2H, H3), 2.42-2.10 (m, 2H, H4)	167.8 (C2), 160.6 (C10), 146.4 (C5a), 134.8 (C7), 129.0 (C9), 119.0 (C8), 114.0 (C9a), 112.6 (C6), 74.4 (C4a), 34.8 (N-CH_3), 28.6 (C3), 24.7 (C4)	231 (100) [M^+], 202 (43), 160 (63), 146 (48), 105 (72), 104 (45)
1{*2,1,2*}	3333, 3207 (N-H), 1701, 1658 (C=O),1607, 1577, 1489	9.60-8.80 (br, 1H, CONH), 7.96 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H9), 7.46 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 2 Hz, 1H, H7), 6.94 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 1 Hz, 1H, H8), 6.80 (d, $^3J_{HH}$= 8 Hz, H6), 2.95 (s, 3H, N5-CH_3), 2.80-2.68 (m, 1H, H3), 2.68-2.46 (m, 1H, H3), 2.40-2.24 (m, 2H, H4), 1.46 (s, 3H, C4a-CH_3)	166.9 (C2), 156.6 (C10), 146.3 (C5a), 134.6 (C7), 128.4 (C9), 119.3 (C8), 114.2 (C9a), 113.2 (C6), 77.6 (C4a), 33.0 (C3), 31.7 (N-CH_3), 27.9 (C4), 17.7 (C4a-$\underline{C}H_3$)	245 (52) [M^+], 230 (100), 216 (24), 133 (51), 105 (50)
1{*2,3,2*}	1686 (C=O), 1607, 1578, 1491, 1459	7.97 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H9), 7.82-7.66 (m, 2H, H3'), 7.47 (ddd, $^3J_{HH}$= 9 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 2 Hz, 1H, H7), 7.42-7.30 (m, 2H, H2'), 7.18-7.12 (m, 1H, H4'), 6.88 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 1 Hz, 1H, H8), 6.78 (d, $^3J_{HH}$= 9 Hz, 1H, H6), 3.01 (s, 3H, N5-CH_3), 2.80-2.50 (m, 3H, H3, H4), 2.10-1.99 (m, 1H, H4), 1.83 (s, 3H, C4a-CH_3)	169.7 (C2), 163.1 (C10), 146.8 (C5a), 140.7 (C1'), 135.3 (C7), 129.3 (C9), 128.7 (C3'), 125.2 (C4'), 120.1 (C2'), 118.8 (C8), 114.1 (C9a), 113.0 (C6), 81.1 (C4a), 33.1 (N5-CH_3), 32.9 (C3), 31.8 (C4), 26.4 (C4a-$\underline{C}H_3$)	321 (59) [M^+], 175 (100), 133 (42), 105 (29)
1{*3,1,2*}	3308, 3173 (N-H), 1691, 1647 (C=O), 1616, 1584, 1508, 1485	7.87 (d, $^4J_{HH}$= 2 Hz, 1H, H9), 7.31 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$ = 2 Hz, 1H, H7), 6.66 (d, $^3J_{HH}$= 8 Hz, 1H, H6), 4.60-3.00 (br, 1H, -NH-), 2.86-2.70 (m, 1H, H3), 2.60-2.46 (m, 1H, H3), 2.44-2.28 (m, 1H, H4), 2.24-2.06 (m, 1H, H4), 1.60 (s, 3H, C4a-CH_3)	169.3 (C2), 155.9 (C10), 142.5 (C5a), 134.1 (C7), 127.9 (C9), 125.5 (C8), 116.8 (C6), 115.1 (C9a), 73.8 (C4a), 36.3 (C3), 28.8 (C4), 23.7 (C4a-$\underline{C}H_3$)	267 (18) [M^++2], 265 (55) [M^+], 250 (100), 236 (35), 155 (29), 154 (38), 153 (83)
1{*4,1,2*}	3327, 3184 (N-H), 1694, 1655 (C=O), 1609, 1501, 1480	7.82 (d, $^3J_{HH}$= 8 Hz, 1H, H9), 6.89 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H8), 6.71 (d, $^4J_{HH}$= 2 Hz, 1H, H6), 2.86-2.70 (m, 1H, H3), 2.60-2.46 (m, 1H, H3), 2.40-2.24 (m, 1H, H4), 2.24-2.06 (m, 1H, H4), 1.61 (s, 3H, C4a-CH_3)	169.3 (C2), 156.4 (C10), 144.9 (C5a), 140.3 (C7), 129.8 (C9), 120.6 (C8), 115.0 (C6), 112.3 (C9a), 73.8 (C4a), 36.3 (C3), 28.8 (C4), 23.8 (C4a-$\underline{C}H_3$)	267 (18) [M^++2], 265 (56) [M^+], 250 (100), 236 (36), 153 (70)

Table 2. *Spectroscopic Data of Compounds* (**1**) (cont.)

1{*5,1,2*}	3270, 3183 (N-H), 1683, 1638 (C=O), 1617, 1510, 1462	7.35 (s, 1H, H9), 6.24 (s, 1H, H6), 3.89 (s, 3H, C7-OCH_3), 3.87 (s, 3H, C8-OCH_3), 2.82-2.72 (m, 1H, H3), 2.57-2.50 (m, 1H, H3), 2.37-2.28 (m, 1H, H4), 2.16-2.07 (m, 1H, H4), 1.57 (s, 3H, C4a-CH_3)	169.1 (C2), 157.2 (C10), 154.5 (C7), 143.8, 139.4 (C8, C5a), 109.5 (C9), 106.2 (C9a), 99.2 (C6), 73.7 (C4a), 56.3, 56.1 (C7-O$\underline{C}H_3$, C8-O$\underline{C}H_3$), 36.2 (C3), 28.8 (C4), 22.8 (C4a-$\underline{C}H_3$)	291 (73) [M^+], 276 (100), 179 (98)
1{*6,1,2*}	3317, 3194 (N-H), 1695, 1662 (C=O), 1645, 1609, 1507, 1484	8.75 (br, 1H, -NHCO-), 7.18 (s, 1H, H9), 4.51 (br, 1H, -NH-), 3.96 (s, 3H, C6-OCH_3), 3.91 (s, 3H, C7-OCH_3), 3.85 (s, 3H, C8-OCH_3), 2.86-2.72 (m, 1H, H3), 2.58-2.44 (m, 1H, H3), 2.44-2.32 (m, 1H, H4), 2.18-2.06 (m, 1H, H4), 1.56 (s, 3H, C4a-CH_3)	169.8 (C2), 156.9 (C10), 147.0 (C7, C8), 140.1 (C6), 133.3 (C5a), 108.1 (C9a), 105.2 (C9), 74.3 (C4a), 61.0, 60.9, 56.3 (C6-O$\underline{C}H_3$, C7-O$\underline{C}H_3$, C8-O$\underline{C}H_3$), 36.5 (C3), 28.8 (C4), 22.8 (C4a-$\underline{C}H_3$)	321 (82) [M^+], 306 (100), 209 (54), 181 (28)
1{*7,1.2*}	3298, 3194, 3101 (N-H), 1692 (C=O), 1645, 1509	(acetone-d6): 9.60-8.60 (br, 1H, -NHCO-), 7.56 (s, 1H, H9), 7.17 (dd, ^{3}JHH= 8 Hz, ^{4}JHH= 2 Hz, 1H, H7), 6.73 (d, ^{3}JHH= 8 Hz, H6), 6.15 (br, 1H, NH), 2.76-2.00 (m, 4H, H3, H4), 2.25 (s, 3H, C8-CH3), 1.56 (s, 3H, C4a-CH3)	169.5 (C2), 157.2 (C10), 141.8 (C5a), 135.1 (C7), 129.7 (C8), 128.2 (C9), 115.6 (C6), 113.9 (C9a), 73.7 (C4a), 36.3 (C3), 28.8 (C4), 23.3, 20.4 (C4a-CH3, C8-CH3)	245 (52) [M+], 230 (100), 133 (91)
1{*9,1,2*}	3354, 3313, 3217 (N-H), 1679 (C=O), 1653, 1614, 1585, 1509	8.78 (br, 1H, NHCO) 7.51 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H9), 6.93 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H7), 6.85 (dd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, 1H, H8), 4.76 (br, 1H, NH), 3.89 (s, 3H, C6-OCH_3), 2.94-2.74 (m, 1H, H3), 2.62-2.30 (m, 1H, H3), 2.30-2.08 (m, 2H, H4), 1.57 (s, 3H, C4a-CH_3)	169.8 (C2), 157.1 (C10), 146.5 (C6), 134.7 (C5a), 119.6, 118.9 (C9, C8), 113.8 (C7), 113.4 (C9a), 74.0 (C4a), 55.7 (C6-OCH_3), 36.6 (C3), 28.9 (C4), 23.6 (C4a-$\underline{C}H_3$)	261 (69) [M^+], 246 (100), 149 (53), 121 (38)
1{*10,1,2*}	3303, 3171 (N-H), 1690, 1651 (C=O), 1506, 1451	8.72 (br, 1H, NHCO), 7.59 (dd, $^3J_{HF}$= 9 Hz, $^4J_{HH}$= 3 Hz, 1H, H9), 7.11 (ddd, $^3J_{HH}$= 9 Hz, $^3J_{HF}$= 8 Hz, $^4J_{HH}$= 3 Hz, 1H, H7), 6.69 (dd, $^3J_{HH}$= 9 Hz, $^4J_{HF}$= 4 Hz, 1H, H6), 4.20 (br, 1H, -NH-), 2.90-2.68 (m, 1H, H3), 2.62-2.42 (m, 1H, H3), 2.42-2.24 (m, 1H, H4), 2.24-2.04 (m, 1H, H4), 1.59 (s, 3H, C4a-$\underline{C}H_3$)	169.3 (C2), 158.6, 156.1 (C10, C8), 155.5 (C5a), 140.2 (d, $^3J_{CF}$= 7 Hz, C9a), 121.6 (d, $^2J_{CF}$= 93 Hz, C7), 117.2 (d, $^3J_{CF}$= 29 Hz, C6), 114.2 (d, $^2J_{CF}$= 93 Hz, C9), 73.8 (C4a), 36.2 (C3), 28.8 (C4), 23.5 (C4a-CH_3)	249 (59) [M^+], 234 (100), 220 (36), 137 (88), 69 (48)
1{*11,1,1*}	3326, 3203 (N-H), 1682 (C=O), 1607, 1595, 1495, 1485	8.94 (br, 1H, NHCO), 8.02 (dd., $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H9), 7.64-7.46 (m, 2H, H3'), 7.43-7.39 (m, 1H, H4'), 7.30-7.20 (m, 3H, H7, H2'), 6.95 (ddd., $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz ,1H, H8), 6.34 (d, $^3J_{HH}$= 8 Hz, 1H, H6), 5.50 (dd, $^3J_{HH}$= 9 Hz, $^3J_{HH}$= 5 Hz, 1H, H4a), 2.70-2.40 (m, 2H, H3), 2.30-2.07 (m, 2H, H4)	167.5 (C2), 159.2 (C10), 146.8 (C5a), 141.9 (C1'), 134.1 (C7), 130.5 (C3'), 128.6 (C9), 128.2 (C2'), 128.0 (C4'), 120.3 (C8), 116.1 (C6), 114.9 (C9a), 72.9 (C4a), 28.4 (C3), 26.7 (C4)	293 (18) [M^+], 195 (100)
1{*11,1,2*}	3218 (N-H), 1696, 1660 (C=O), 1606, 1593, 1490, 1483	10.20-8.60 (br, 1H, NHCO), 7.98 (d, $^3J_{HH}$= 7 Hz, 1H, H9), 7.66-7.38 (m, 3H, H7, H3'), 7.38-6.94 (m, 3H, H2', H4'), 6.87 (dd, $^3J_{HH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, H8), 6.12 (d, $^3J_{HH}$= 8 Hz, 1H, H6), 2.70-2.35 (m, 2H, H3), 2.35-1.80 (m, 2H, H4), 1.72 (s, 3H, C4a-CH_3)	167.6 (C2), 157.2 (C10), 146.2 (C5a), 139.9 (C1'), 134.0 (C7), 131.7 (C2'), 130.9 (C6'), 130.3 (C3'), 130.1 (C5'), 128.9 (C9), 128.3 (C4'), 119.4 (C8), 115.9 (C6), 114.1 (C9a), 33.3 (C3), 28.2 (C4), 21.7 (C4a-$\underline{C}H_3$)	307 (12) [M^+], 292 (18), 195 (100)
1{*11,3,2*}	1703, 1674 (C=O), 1605, 1492, 1481, 1469	8.04 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H9), 7.84-7.64 (m, 2H, H3'), 7.64-7.42 (m, 3H, H7, H3"), 7.42-7.30 (m, 3H, H2', H4"), 7.26-7.00 (m, 3H, H4', H2"), 6.86 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 1 Hz, 1H, H8), 6.11 (d, $^3J_{HH}$= 8 Hz, 1H, H6), 3.13-3.04 (m, 1H, H3), 2.93-2.81 (m, 1H, H3), 2.69-2.60 (m, 1H, H4), 2.20-2.10 (m, 1H, H4), 1.54 (s, 3H, C4a-CH_3)	168.9 (C2), 164.7 (C10), 146.9 (C5a), 140.9, 140.8 (C1', C1"), 134.8 (C7), 129.3 (C9), 128.7 (C3', C3"), 125.4 (C4', C4"), 120.7 (C2', C2"), 119.0 (C8), 115.9 (C6), 113.8 (C9a), 80.4 (C4a), 33.3 (C3), 31.3 (C4), 26.7 (C4a-$\underline{C}H_3$)	383 (18) [M^+], 237 (31), 195 (100)

116.2 (C5), 114.7 (C3), 113.7 (C1); Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.47; H, 5.85; N, 27.51.

5-Chloroanthranilic hydrazide (3{*3,1*}) (R_1=5-Cl, R_2=H, R_4=H): As above but using 1.0 g (5.4 mmol) of methyl 5-chloroanthranilate (**5**{*3*}) at 60ºC for 21 h. Yield: 58%, mp136-139ºC (mp[14] 129-134ºC); IR (KBr) ν (cm^{-1}): 3452, 3429, 3354, 3327, 3288 (N-H), 1651 (C=O), 1580, 1564, 1515, 1483; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.29-7.25 (m, 2H, H6, -CON<u>H</u>NH_2), 7.18 (dd, $^3J_{HH}$= 9 Hz, $^4J_{HH}$= 2 Hz, 1H, H4), 6.64 (d, $^3J_{HH}$= 9 Hz, 1H, H3), 5.60-3.00 (br, 4H, C2-NH_2, -CONHN<u>H</u>$_2$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 167.2 (<u>C</u>O$NHNH_2$), 148.2 (C2), 131.3 (C4), 127.0 (C6), 117.8 (C5, C3), 114.6 (C1); MS, m/z (%): 187 (9) [M^++2], 185 (25) [M^+], 156 (31), 154 (100), 126 (31); Anal. Calcd for $C_7H_8N_3OCl$: C, 45.30; H, 4.34; N, 22.64. Found: C, 45.12; H, 4.56; N, 22.97.

4-Chloroanthranilic hydrazide (3{*4,1*}) (R_1=4-Cl, R_2=H, R_4=H): As above but using 1.0 g (5.4 mmol) of methyl 4-chloroanthranilate (**5**{*4*}) at 60ºC for 21 h. Yield: 83%, mp 149-151ºC; IR (KBr) ν (cm^{-1}): 3485, 3355, 3315 (N-H), 1656 (C=O), 1577, 1526, 1479; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.21 (d, $^3J_{HH}$= 8 Hz, 1H, H6), 7.20 (br, 1H, -CON<u>H</u>NH_2), 6.69 (d, $^4J_{HH}$= 2 Hz, 1H, H3), 6.62 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H5), 5.58 (br, 2H, C2-NH_2), 4.03 (br, 2H, -CONHN<u>H</u>$_2$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 167.7 (<u>C</u>O$NHNH_2$), 150.7 (C2), 136.0 (C4), 129.4 (C6), 115.0 (C5), 114.3 (C3), 112.4 (C1); MS,: m/z (%): 187 (8) [M^++2], 185 (27) [M^+], 156 (32), 154 (100), 126 (18); Anal. Calcd for $C_7H_8N_3OCl$: C, 45.30; H, 4.34; N, 22.64, Found: C, 45.46; H, 4.04; N, 22.30.

4,5-Dimethoxyanthranilic hydrazide (3{*5,1*}) (R_1=4,5-OMe, R_2=H, R_4=H): As above but using 1.0 g (4.7 mmol) of methyl 4,5-dimethoxyanthranilate (**5**{*5*}) at 60ºC for 21 h. Yield: 77%, mp 178-179ºC; IR (KBr) ν (cm^{-1}): 3415, 3329, 3306, 3273, 3216 (N-H), 1634 (C=O), 1595, 1577, 1511; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.16 (br, 1H, -CON<u>H</u>NH_2), 6.79 (s,1H, H6), 6.21 (s, 1H, H3), 5.40-4.00 (br, 4H, C2-NH_2, -CONHN<u>H</u>$_2$), 3.86 (s, 3H, C4-OCH_3), 3.81 (s, 3H, C5-OCH_3); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.5 (-<u>C</u>O$NHNH_2$), 152.6 (C4), 145.8 (C2), 139.1 (C5), 111.5 (C6), 103.8 (C1), 99.8 (C3), 56.3, 55.1 (C4-O<u>C</u>H_3, C5-O<u>C</u>H_3); MS, m/z (%): 211 (31) [M^+], 180 (100), 152 (12); Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.25; H, 6.18; N, 19.57.

3,4,5-Trimethoxyanthranilic hydrazide (3{*6,1*}) (R_1=3,4,5-OMe, R_2=H, R_4=H): As above but using 1.0 g (4.2 mmol) of methyl 3,4,5-trimethoxyanthranilate (**5**{*6*}) at 60ºC for 21 h. Yield: 43%, mp 105-107ºC; IR (KBr) ν (cm^{-1}): 3475, 3361, 3306, 3330 (N-H), 1625 (C=O), 1578, 1542, 1522, 1487; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.39 (br, 1H, -CON<u>H</u>NH_2), 6.66 (s, 1H, H6), 5.70-4.00 (br, 4H, C2-NH_2, -CONHN<u>H</u>$_2$), 3.93 (s, 3H, C5-OCH_3), 3.87 (s, 3H, C4-OCH_3), 3.79 (s, 3H, C3-OCH_3); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.1 (-<u>C</u>O$NHNH_2$), 145.1, 142.6, 140.2, 138.5 (C5, C4, C3, C2), 108.0 (C1), 106.9

(C6), 60.4, 59.9, 56.3 (C5-O<u>C</u>H$_3$, C4-O<u>C</u>H$_3$, C3-O<u>C</u>H$_3$); MS, m/z (%): 241 (39) [M$^+$], 210 (100); Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.30; H, 6.28; N, 17.74.

5-Methylanthranilic hydrazide (3{*7,1*}) (R_1=5-Me, R_2=H, R_4=H): As above but using 1.2 g (7.0 mmol) of methyl 5-methylanthranilate (**5**{*7*}) at 60ºC for 15 h. Yield: 61%, mp 133-135ºC; IR (KBr) ν (cm^{-1}): 3453, 3366, 3352, 3297, 3182 (N-H), 1624 (C=O), 1582, 1569, 1530, 1497; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.29 (br, 1H, -CON<u>H</u>NH$_2$), 7.09 (s, 1H, H6), 7.06 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H4), 6.63 (d, $^3J_{HH}$= 8 Hz, 1H, H3), 5.24 (br, 2H, C2-NH$_2$), 4.03 (br, 2H, -CONHN<u>H</u>$_2$), 2.23 (s, 3H, C5-CH$_3$); MS, m/z (%): 165 (32) [M$^+$], 134 (100), 106 (30); Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 57.95; H, 6.83; N, 25.20.

3-Methoxyanthranilic hydrazide (3{*9,1*}) (R_1=3-OMe, R_2=H, R_4=H): As above but using 1.1 g (6.1 mmol) of methyl 3-methoxyanthranilate (**5**{*9*}) at 60ºC for 15 h. Yield: 80%, mp 147-149ºC; IR (KBr) ν (cm^{-1}): 3442, 3334, 3316 (N-H), 1638 (C=O), 1610, 1591, 1551, 1518, 1474; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.33 (br, 1H, -CON<u>H</u>NH$_2$), 6.92 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H6), 6.83 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H4), 6.60 (dd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, 1H, H5), 5.74 (br, 2H, C2-NH$_2$), 4.04 (br, 2H, -CONHN<u>H</u>$_2$), 3.87 (s, 3H, C3-OCH$_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.4 (-<u>C</u>ONHNH$_2$), 146.9 (C3), 139.3 (C2), 119.3 (C6), 114.1 (C5), 113.3 (C1), 111.8 (C4), 55.5 (C3-O<u>C</u>H$_3$); MS, m/z (%): 181 (45) [M$^+$], 150 (100); Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03, H, 6.12; N, 23.19). Found: C, 53.06; H, 6.09; N, 22.83.

5-Fluoroanthranilic hydrazide (3{*10,1*}) (R_1=5-F, R_2=H, R_4=H): As above but using 1.1 g (6.7 mmol) of methyl 5-fluoroanthranilate (**5**{*10*}) at 60ºC for 15 h. Yield: 58%, mp 128-130ºC; IR (KBr) ν (cm^{-1}): 3443, 3327, 3191 (N-H), 1647 (C=O), 1592, 1572, 1512, 1486; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.26 (br, 1H, -CON<u>H</u>NH$_2$), 7.05-6.95 (m, 2H, H4, H6), 6.66 (ddd, $^3J_{HH}$= 8 Hz, $^4J_{HF}$= 5 Hz, $^5J_{HH}$= 1 Hz, 1H, H3), 6.00-3.00 (br, 4H, C2-NH$_2$, -CONHN<u>H</u>$_2$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 167.4 (d, $^4J_{CF}$= 2 Hz, <u>C</u>ONHNH$_2$), 152.7 (d, $^1J_{CF}$= 230 Hz, C5), 146.1 (C2), 118.9 (d, $^2J_{CF}$= 22 Hz, C4), 117.4 (d, $^3J_{CF}$= 7 Hz, C3), 113.4 (C1), 113.2 (d, $^2J_{CF}$= 23 Hz, C6); MS, m/z (%): 169 (38) [M$^+$], 138 (100), 110 (37); Anal. Calcd for $C_7H_8N_3OF$: C, 49.70, H, 4.77; N, 24.84. Found: C, 49.63; H, 4.45; N, 24.46.

***N*-Phenylanthranilic hydrazide (3{*11,1*}) (R_1=H, R_2=H, R_4=H):** As above but using 1.0 g (4.5 mmol) of methyl *N*-phenylanthranilate (**5**{*11*}) at 70ºC for 21 h. Yield: 92%, mp 185-187ºC; IR ($CHCl_3$) ν (cm^{-1}): 3320, 3298, 3274 (N-H), 1638 (C=O), 1599, 1574, 1520; ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.06 (br, 1H, -NHPh), 7.53 (br, 1H, -CON<u>H</u>NH$_2$), 7.44-7.10 (m, 7H, H6, H3, H4, H2', H3'), 7.06-6.98 (m, 1H, H4'), 6.76 (ddd, $^3J_{HH}$= 9 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H5), 4.8-2.5 (br, 2H, -CONHN<u>H</u>$_2$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.1 (-<u>C</u>ONHNH$_2$), 143.9 (C2), 141.6 (C1'), 131.7 (C4), 129.4 (C3'), 128.4 (C6), 121.7 (C4'), 119.2 (C2'), 118.2 (C5), 118.03 (C1), 115.0 (C3); MS, m/z (%): 227 (38) [M$^+$], 196 (100), 167 (25); Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.45 H, 5.93; N, 18.50.

General procedure for the synthesis of *N*'-phenylbenzohydrazides (3{*x,3*}). 2-Methylamino-*N*'-phenylbenzohydrazide (3{*2,3*}) (R_1=H, R_2=Me, R_4=Ph): A mixture of 3.0 g (19.8 mmol) of *N*-methylanthranilic acid (**7**{*2*}), 3.0 mL (29.8 mmol) of phenylhydrazine (**6**{*3*}), 4.1 g (19.8 mmol) of DCC in 60 mL of CH_2Cl_2 was stirred for 4 h at rt. The resulting solution was concentrated *in vacuo*, the residue was extracted with CH_2Cl_2, and the extract was washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated *in vacuo* to give a 14:86 mixture of **3**{*2,3*} and the *N*-phenyl derivative (**8**{*2,3*}). The two isomers were separated by column chromatography (AcOEt:hexane, 1:4) to give 0.72 g (16%) of **3**{*2,3*}, mp 127-129ºC; IR ($CHCl_3$) ν (cm^{-1}): 3406, 3296 (N-H), 1640 (C=O), 1602,1579,1519, 1495; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.91 (br, 1H, -N<u>H</u>CH_3), 7.50-7.30 (br, 1H, -CON<u>H</u>NHPh), 7.47 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2Hz, 1H, H6), 7.37 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 2 Hz, 1H, H4), 7.26-7.23 (m, 2H, H3'), 7.78-7.00 (m, 3H, H2', H4'), 6.68 (d, $^3J_{HH}$= 8 Hz, 1H, H3), 6.61 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H5), 6.26 (br, 1H, -CONHN<u>H</u>Ph), 2.81 (s, 3H, -NHC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 170.0 (<u>C</u>ONH), 150.9 (C2), 148.3 (C1'), 133.8 (C4), 129.2 (C3'), 127.1 (C6), 121.3 (C4'), 114.5 (C5), 113.6 (C2'), 112.0 (C6), 111.4 (C3), 29.6 (NH<u>C</u>H_3); MS, m/z (%): 241 (37) [M^+], 134 (100); Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41, Found: C, 69.37; H, 6.57; N 17.22.

2-Amino-*N*'-phenylbenzohydrazide (3{*1,3*}) (R_1=H, R_2=H, R_4=Ph): As above but using 2.9 g (21.4 mmol) of anthranilic acid (**7**{*1*}). Yield: 25%, 169-171ºC (mp[10b] 168-170ºC); IR (KBr) ν (cm^{-1}): 3428, 3334, 3242 (N-H), 1644 (C=O), 1615, 1587, 1571, 1547, 1494, 1444; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.75 (br, 1H, -CON<u>H</u>NHPh), 7.49 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1Hz, 1H, H6), 7.40-7.20 (m, 3H, H4, H3'), 7.04-6.84 (m, 3H, H2', H4'), 6.78-6.60 (m, 2H, H3, H5), 6.27 (br, 1H, -CONHN<u>H</u>Ph), 5.52 (br, 2H, NH_2); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.8 (<u>C</u>ONH), 149.9, 149.8 (C2, C1'), 132.2 (C4), 128.7 (C3'), 128.0 (C6), 118.5 (C4'), 116.4 (C5), 114.7 (C3), 112.8 (C1), 112.3 (C2'); Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.75; H, 5.71; N, 18.06.

2-Phenylamino-*N*'-phenylbenzohydrazide (3{*11,3*}) (R_1=H, R_2=Ph, R_4=Ph): As above but using 2.9 g (13.8 mmol) of *N*-phenylanthranilic acid (**7**{*11*}). Yield: 25%, 118-120ºC; IR ($CHCl_3$) ν (cm^{-1}): 3310 (N-H), 1644 (C=O), 1591, 1577, 1516, 1495; ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.14 (br, 1H, -N<u>H</u>Ph), 8.05 (br, 1H, -CON<u>H</u>NHPh), 7.52 (dd, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1Hz, 1H, H6), 7.44-7.18 (m, 6H, H3, H4, H3', H3"), 7.18-7.08 (m, 2H, H2"), 7.03-6.99 (m, $^3J_{HH}$= 8 Hz, $^4J_{HH}$= 1 Hz, 1H, H4"), 6.96-6.84 (m, 3H, H2', H4'), 6.75 (ddd, $^3J_{HH}$= 8 Hz, $^3J_{HH}$= 7 Hz, $^4J_{HH}$= 2 Hz, 1H, H5), 6.30 (br, 1H, -CONHN<u>H</u>Ph); ^{13}C-NMR ($CDCl_3$): δ (ppm): 169.7 (<u>C</u>ONHNHPh), 148.0 (C1"), 146.2 (C1'), 141.0 (C2), 133.1 (C4), 129.3 (C3", C3'), 127.5 (C6), 123.7 (C1), 122.9 (C4"), 121.5 (C4'), 121.2 (C2"), 117.9 (C5), 115.5 (C3), 113.6 (C2'); MS, m/z (%): 303 (28) [M^+], 196 (100), 167 (19); Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N 13.85. Found: C, 75.48; H, 5.56; N, 13.44.

General procedure for the synthesis of 2,10-dioxo-10*H*-1,2,3,4,4a,5-hexahydro-piridazino[3,2-*b*]quinazolines (1)

A mixture of the corresponding hydrazide (**2**) (1.1 mmol), the 4-oxo acid (**4**) (1.65 mmol), and one crystal of TsOH in 4.0 mL of benzene was heated at reflux for 2 h. In most cases the expected compound precipitates, in which case the reaction mixture was filtered and washed with Et_2O. In remaining cases the reaction mixture was concentrated *in vacuo*, the residue suspended in water and extracted with AcOEt. The combined organic extracts were washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated *in vacuo*. Crude **1** were purified by column chromatography using AcOEt or hexane:AcOEt (1:1) as eluent.

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