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Structure–activity studies for a novel series of tricyclic dihydropyridopyrazolones and dihydropyridoisoxazolones as K_{ATP} channel openers☆

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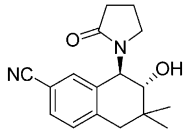
Abstract—In search of a novel chemotype of K_{ATP} channel openers a series of tricyclic dihydropyridopyrazolones and dihydropyridoisoxazolones was synthesized. It was found that cyclopentanone in the left hand portion of the molecule was 4-fold more potent than cyclohexanone. Introduction of gem-dimethyl groups as well as incorporation of oxygen in the cyclohexanone ring in the left hand portion of the molecule increased the potency 10-fold. In the right hand portion of the molecule, the NH-group of the pyrazolone can be effectively substituted by oxygen increasing the activity 5-fold. Incorporation of a methyl group adjacent to the dihydropyridine (DHP) nitrogen not only significantly boosted activity, but also provided an additional benefit of increased metabolic stability. In vitro tests on the tissue from pig bladder strips provided further confirmation of K_{ATP} activity of these compounds.

1. Introduction

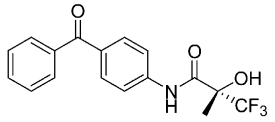
Potassium channels play an important role in regulating cell membrane excitability, action potential generation and epithelial electrolyte transport. K_{ATP} channel openers are amongst the most widely explored channels modulators with regard to their potential for the treatment of various diseases such as bladder overactivity.[1]

K_{ATP} channels exist in the bladder and the ability of potassium channel openers (KCO's) to hyperpolarize cells and relax smooth muscle may provide a method for controlling bladder overactivity. Since a clinical study with cromakalim indicated potential usefulness of KCO's for this application, newer generation of K_{ATP} channel openers such as ZM244085,[1] ZD6169[2–4] and WAY 133536[5,6] are reported to have enhanced bladder selectivity (Chart 1).

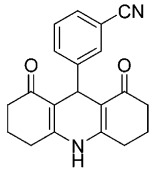
Continued SAR investigation around our previously disclosed series of tricyclic dihydropyridines[7] focused on a new chemotype with pyrazolone and isoxazolone serving as isosteres of a lactam or a lactone ring (Chart 2). SAR studies on this novel series examined the effects of aromatic substitution as well as modifications of the left- and right-hand portions of the molecule.



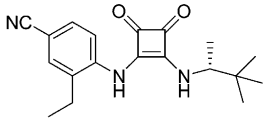
(-)cromakalim



ZD 6169



ZM244085



WAY-133537

Chart 1.

☆Supplementary data associated with this article can be found, in the online version at, 10.1016/j.bmc.2004.01.038

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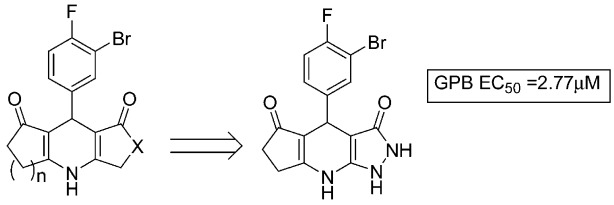


1a X=O, n=1
1b X=NH, n=1
1c X=O, n=2

6a

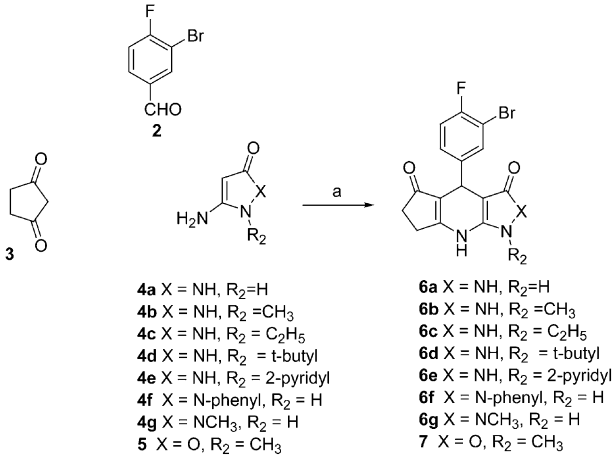
Chart 2.

Compounds were evaluated in cell and tissue-based in-vitro models.

A common property of many dihydropyridine-containing molecules is a susceptibility to CYP3A4 mediated oxidation to the pyridine.[8,9] The tricyclic pyrazolones and isoxazolones described herein offered the potential to increase the metabolic stability by introduction of substituents that sterically hinder access to the dihydropyridine nucleus as well as change the electronic environment of the core. This new series of compounds was tested for its metabolic stability in pooled human liver microsomes and showed superior metabolic stability compared to the reference standards.

2. Chemistry

A series of tricyclic dihydropyridopyrazolones and dihydropyridoisoxazolones was synthesized using the three component Hantzsch reaction as shown on Scheme 1. A mixture of aldehyde **2**, 1,3-cyclopentanedione **3**, and 5-amino-3-pyrazolones **4a–g**[10,11] was heated at reflux in EtOH to yield the desired dihydropyridopyrazolones **6a–g**. Dihydropyridoisoxazolones **7** were obtained by substituting **4** for 3-amino-5-isoxazolone **5**[12] in this reaction. Variations in the aromatic substitution were introduced by replacing of **2** with a variety of aldehydes, either commercially available or synthesized by the methods described in the literature. Variations of the left hand portion of the molecule were accomplished by substituting 1,3-cyclopentanedione **3** in the Hantzsch reaction with the different cyclic diketones, available from commercial sources or synthesized in accordance with the literature methods. Thus, use of 1,3-cyclohexanedione afforded pyrazolone **16** and isoxazolone **24**, and use of 4,4-dimethyl-1,3-cyclohexanedione in the Hantzsch reaction yielded pyrazolone **17** and isoxazolone **25**. Introduction of heteroatoms in the left hand portion of the core was realized by substituting 1,3-cyclopentadione **3** with 2H-pyran-3,5(4*H*,6*H*)-dione[13] to yield **21** and **28** or δ-lactone[14,15] to obtain **20**. Replacement of carbonyl groups with sulfone groups was accomplished by substituting 1,3-cyclopentanedione **3** in the Hantzsch reaction with tetrahydrothiophene-3-oxo-1,1-dioxide[13] to yield **14** and tetrahydrothiopyran-3-one-1,1-dioxide[16] to afford **15**. Lactone derivatives **13** and **23** were synthesized by a two-step sequence outlined in Scheme 2. The Hantzsch reaction was performed with the ester **11**,[17] aldehyde **2** and aminopyrazolone **4b** to yield the bicyclic dihydropyridine **12**, that in turn was cyclized to the desired lactone **13**. A similar sequence was used for the synthesis of lactone isoxazolone **23**.



3

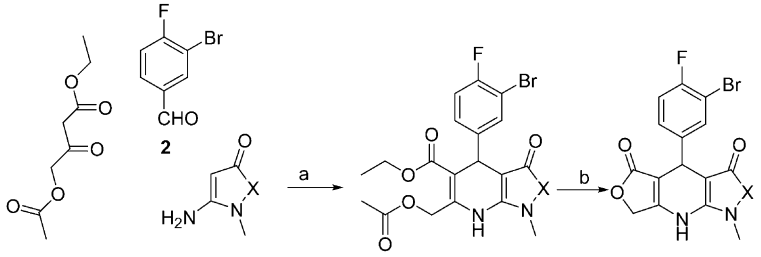
4a X = NH, R_2=H
4b X = NH, R_2 =CH_3
4c X = NH, R_2 = C_2H_5
4d X = NH, R_2 = t-butyl
4e X = NH, R_2 = 2-pyridyl
4f X = N-phenyl, R_2 = H
4g X = NCH_3, R_2 = H
5 X = O, R_2 = CH_3

6a X = NH, R_2=H
6b X = NH, R_2 =CH_3
6c X = NH, R_2 = C_2H_5
6d X = NH, R_2 = t-butyl
6e X = NH, R_2 = 2-pyridyl
6f X = N-phenyl, R_2 = H
6g X = NCH_3, R_2 = H
7 X = O, R_2 = CH_3

Scheme 1. Conditions and reagents: (a) EtOH, reflux.

Resolution of racemic dihydropyridopyrazolones could not be accomplished directly because of the poor solubility and high polarity of these compounds. Boc-derivatives of these compounds also were not amenable to chiral separation. Acetylation of **6b** yielded predominantly *O*-acetyl derivative **8** that was separated on a Chiracel OJ column. The resolved *O*-acetyl intermediates were cleaved under acidic conditions to the desired enantiomers **9** and **10** (Scheme 3). A similar strategy was applied to the separation of racemic pyrazolone **17**. Racemic dihydropyridoisoxazolones **25** and **28**, being more soluble, could be resolved on Chiracel AS column without prior derivatisation.

The absolute stereochemistry of dihydropyridoisoxazolones **26**, **27**, **28**, and **29** was determined by X-ray



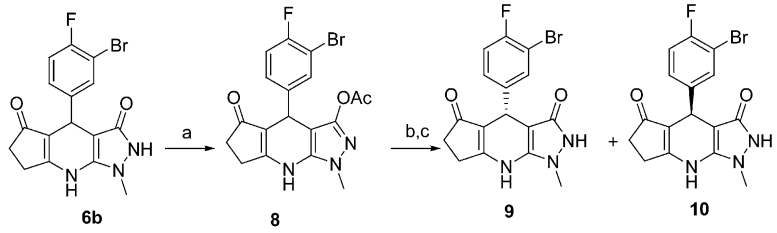
11

4b X = N
5 X = O

12 X=NH
22 X=O

13 X=NH,
23 X =O

Scheme 2. Synthesis of lactone analogues. Conditions and reagents (a) EtOH, reflux, (b) K_2CO_3, MeOH.



Scheme 3. Resolution of enantiomers. Conditions and reagents: (a) acetic anhydride, reflux; (b) Chiracel OJ column hexane:EtOH (3:1); (c) MeOH, 6N HCl.

crystallography. Similar analysis of dihydropyridopyrazolones **9**, **10**, **18**, and **19** was not possible, since we failed to grow crystals large enough to be analyzed.

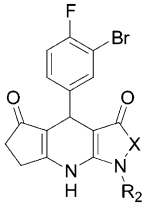
3. Results and discussion

Compounds were assayed for their activity as K_{ATP} openers using primary cultured guinea pig bladder cells. The SAR study reported here was focused on the following issues (i) study of the spatial and electronic limitations of the right hand portion of the molecule, (ii) tolerance to variations of the left hand portion of the molecule, (iii) effects of the substituents on the aromatic ring.

The initial effort was directed at improving the potency of **6a** by modification of the right hand portion of the molecule. As is evident from Table 1, introduction of a methyl group adjacent to the dihydropyridine nitrogen (**6b**) resulted in a very significant increase in activity. Further expansion of the steric bulk around that region revealed limitations of that pocket. Incorporation of an ethyl group as in **6c** was still tolerated, but introduction of *t*-butyl or aromatic and heteroaromatic groups (**6d–f**) in this region resulted in a complete loss of activity. Interestingly, moving the methyl group to the nitrogen adjacent to carbonyl group (**6g**) was detrimental for activity. (In parallel SAR studies X = NMe and R_2 = Me was found to be an allowed substitution pattern on the core with the left hand piece from example **21**). Oxygen in the same position yielded a very potent compound **7**, when $R_2 = CH_3$.

We further focused our efforts on the optimization of the left hand portion of the two promising leads **6b** and **7**. SAR for both classes of compounds (Table 2) is

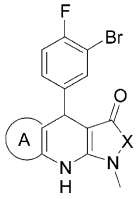
Table 1. SAR of the right-hand side of the tricyclic dihydropyridines



Compd	X	R_2	EC_{50} (μM)[a]
6a	NH	H	2.77[b]
6b	NH	CH_3	0.55
6c	NH	C_2H_5	0.27[b]
6d	NH	*t*-butyl	>10
6e	NH	2-pyridyl	>10
6f	*N*-phenyl	NH	>10[b]
6g	*N*-CH_3	H	>10
7	O	CH_3	0.071

[a] Values are means of three experiments.
[b] Values are means of two experiments.

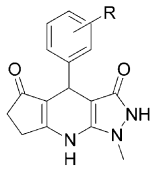
Table 2. SAR of the left hand side of the tricyclic dihydropyridines



A	X = NH	EC_{50} (μM)[a]	X = O	EC_{50} (μM)[a]
	**6b**	0.55	**7**	0.071
	(−)**9**	0.59		
	(+)**10**	>10		
	**13**	0.35	**23**	0.013
	**14**	>10	—	
	**15**	>10	—	
	**16**	1.97[b]	**24**	2.30
	**17**	0.18	**25**	0.13
	(+)**18**	0.18	(*R*)(+)**26**	0.11
	(−)**19**	>10	(*S*)(−)**27**	>10
	**20**	1.14		
	**21**	0.19	**28**	0.13
	—	—	(*S*)(−)**29**	0.25[b]
	—	—	(*R*)(+)**30**	0.025

[a] Values are means of three experiments.
[b] Values are means of two experiments.

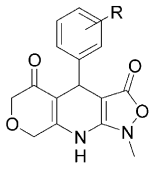
Table 3. SAR of the aromatic substitution of the dihydropyridopyrazolones



Compd	R	EC_{50} (μM)[a]
6b	3-Br, 4-F	0.56
31	4-OCF_3	>10
32	3-Br, 4-CH_3	0.48[b]
33	3-CF_3, 4-F	0.69[b]
34	3-NO_2, 4-Cl	2.3[b]
35	3-I, 4-F	0.32[b]
36	3,4-diCl	0.67[b]
37		>10

[a] Values are means of three experiments.
[b] Values are means of two experiments.

Table 4. SAR of the aromatic substitution of the dihydropyridoisoxazolones



Compd	R	EC_{50} (μM)[a]
28	3-Br, 4-F	0.13
38	3-Br, 4-CH_3	0.21
39	3-CF_3, 4-F	3.24[b]
40	3-NO_2, 4-Cl	0.099
41	3-I, 4-F	0.057
42	3-CN	>10
43		0.023

[a] Values are means of three experiments.
[b] Values are means of two experiments.

almost identical. It was shown that cyclopentanone, as a left hand portion of the molecule (**6b** and **7**), is more potent than cyclohexanone (**16** and **24**). Surprisingly, introduction of gem-dimethyl groups in the cyclohexanone ring (**17** and **25**) restored potency to the level of **6b** and **7**. Incorporation of oxygen in the cyclohexanone ring (**20**, **21** and **28**) also had a favorable effect, that was particularly pronounced with **21** and **28**. Oxygen was also well tolerated in the cyclopentanone rings (**13** and **23**). Replacement of the carbonyl group in the ring A with sulfone (**14** and **15**) resulted in a complete loss of activity. Resolution of enantiomers (**9**, **10**, **18**, **19**, **29**, and **30**) showed that absolute stereochemistry was critical for K_{ATP} activity as activity resided predominantly with one enantiomer.

Further elucidation of structural and electronic limitations of the pharmacophore was accomplished by exploring the effect elicited by changes in aromatic substitution. SAR for the core structure of **6b** is summarized in Table 3. As was previously established for other dihydropyridine KCO's,[7] monosubstitution with OCF_3 group (**31**) results in a loss of activity. 3, 4-Disubstituted compounds, in particular, di-halogen compounds (**6b**, **35**, and **36**) were more potent. The 3-Br group could be replaced with 3-CF_3 as in **33** or I as in **35** with the retention of potency. The 4-F group could be replaced by 4-CH_3, as in **32**, without adverse effect on activity. However, the oxadiazole group in **37** and 3-NO_2, 4-Cl pattern in **34** had unfavorable effect on the potency of compounds.

Similar studies of the aromatic substitution SAR for the core structure **7** are summarized in Table 4. For the most part SAR for core structures **6b** and **7** is parallel. There are a few exceptions, however, for example, 3-Br group could not be replaced with the 3-CF_3 group (**39**) with the retention of potency, and for the core structure **7** both 3-NO_2, 4-Cl (**40**) and oxadiazole (**43**) moieties were well tolerated as a replacement for 3-Br, 4-F-pattern.

The more potent compounds representing both dihydropyridopyrazolones and dihydropyridoisoxazolones were also evaluated in vitro using tissue strips obtained from Landrace pig bladders. The results of this study are presented in Table 5. All of the compounds exhibit activity comparable to cromakalim.

An interesting property of this series of compounds was discovered with the evaluation of their metabolic stability. As is known from the literature, dihydropyridines as a class of compound are subject to rapid metabolism catalyzed by the cytochrome P450(CYP) 3A4 isoform. Shown in Table 6 are metabolism results for a selection of compounds compared with a structural analogue

Table 5. Functional KCO activity in isolated bladder strips

Compd	pEC_{50}[a]
Cromakalim	6.34
6b	6.14
13	6.46
17	6.68
21	6.52
24	6.35
23	6.71

[a] Efficacy(%P1075) ≥ 90%.

Table 6. Metabolic stability in human microsomes

Compd	% Compound remaining
Nifedipine	17
Felodipine	23
1c	20
17	95
21	92
6b	90
35	98
27	92
23	86
13	83
6c	86

from previous work **1c** and the calcium channel antagonist standards: nifedipine and felodipine. As is evident from data introduction of the methylpyrazolone and methyloxazolone in the scaffold not only increased potency, but also imparted greater metabolic stability for these compounds. It is especially evident when comparing the metabolic stability of tricyclic lactone **1c** to compounds **6b** and **17**. This can be explained by a steric and electronic effects of groups adjacent to the dyhydropyridine nitrogen.

In summary, we have identified a new class of potassium channel openers. SAR studies on both dihydropyridooxazolones and dihydropyridopyrazolones helped identify compounds that not only exhibited great potency but were also metabolically stable. We examined the effect of the ring size and substituents in the left hand side portion of the molecule as well as established the optimal aromatic substitution for both classes of compounds. We have also demonstrated novel method for the preparation of enantiomers for these structural classes. The obtained compounds were evaluated for K_{ATP} activity in pig bladder strips and they demonstrated activity comparable to cromakalim.

4. Experimental

4.1. Biology

The series of compounds was evaluated for potassium channel opening activity using primary cultured guinea pig urinary bladder (GPB) cells.[18] Functional activity at potassium channels was measured by evaluating changes in membrane potential using DIBAC dye in a 96-well cell based kinetic assay system, Fluorescent Imaging Plate Reader (FLIPR). Changes in fluorescence were measured and compared to the effect elicited by P1075 — a potent KCO. The effects of all compounds were reversed by glyburide.

In vitro tissue tests were conducted on strips obtained from Landrace pig bladders.[19] Tissues were stimulated by a low frequency current that produced a stable twitch response. P1075 completely eliminated the stimulated twitch response in a dose-dependant fashion. The maximal efficacy of each compound was expressed in comparison to P1075. The amount of agent necessary to cause 50% of the agent's maximal response (EC_{50}) was calculated and agonist potencies were expressed as pEC_{50} (the negative logarithm).

4.2. Human liver microsomal incubations

A standard 0.15 mL incubation mixture contained pooled human liver microsomal protein (0.5 mg/mL) in 50 mM phosphate buffer (pH 7.4) and 25 μM substrate. The microsomes were a mixture of human liver microsomes from eight donors pooled on equal weight basis. Following a 5 min preincubation, reactions were started by the addition of 2 mM NADPH and conducted at 37 °C in a shaking incubator for 30 min. The reaction was stopped by the addition of 100 μL of a mixture of MeOH/acetonitrile (v/v 1:1), containing 15 μM nifedipine, an internal standard, followed by vigorous mixing. After protein precipitation and centrifugation a 100 μL aliquot of the supernatant was taken for HPLC analysis.

The compounds and their metabolites were analyzed by reverse phase HPLC. Separation was achieved at room temperature using a YMC C8 column (4.5°150 mm, pore size 5 μm) with a YMC C8 guard column on a Hewlett-Packard 1050 series HPLC system. Elution was conducted at 1 mL/min using a linear gradient of 80–40–20–0–0–60% of 50 mM ammonium acetate buffer, pH 4.0, water and methanol over 40 min. The methanol was increased from 60% to 80% by 47 min. The gradient was ramped back to 80% buffer and 20% water step wise in next 13 min followed by equilibration of 10 min before the next injection. The parent and metabolites were detected using an Applied Biosystems UV detector at a wavelength of 346 nM.

4.3. Chemistry

Proton NMR spectra were obtained on a General Electric QE 300 or QZ 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as internal standard. Melting points were determined on a Thomas-Hoover Capillary Melting Point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories. Column chromatography was carried out on silica gel 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F_{254} as indicator. Optical rotations were measured with a Perkin–Elmer 541 Polarimeter. X-ray crystal structures were obtained on a Bruker SMART system.

4.4. General procedure

4.4.1. 4-(3-Bromo-4-fluorophenyl)-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6a). 5-Amino-1,2-dihydropyrazol-3-one (0.15 g, 1.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.31 g, 1.5 mmol), and 1,3-cyclopentanedione (0.15 g, 1.5 mmol) in EtOH (3 mL) were heated at 80 °C for 2 days in a sealed tube. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with EtOAc:HCO_2H:H_2O (18:1:1) to provide 0.125 g of **6a** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 2.22 (t, 2H), 2.61 (m, 2H), 4.73 (s, 1H), 7.15 (m, 1H), 7.2 (m, 1H), 7.4 (dd, 1H), 9.75 (s, 1H), 10.21 (s, 1H), 11.3 (bs, 1H); MS (ESI-) *m*/*z* 362 $(M-H)^-$ Anal. ($C_{15}H_{11}N_3BrFO_2 \cdot 0.5H_2O$) C, H, N.

4.4.2. 4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6b). 5-Amino-1-methyl-1,2-dihydropyrazol-3-one (0.23 g, 2 mmol),[10] 3-bromo-4-fluorobenzaldehyde (0.4 g, 2 mmol), and 1,3-cyclopentanedione (0.2 g, 2 mmol) in EtOH (4 mL) were treated as described for **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.6 g (79%) of **6b** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 2.3 (t, 2H), 2.69 (m, 2H), 3.5 (s,

3H), 4.7 (s, 1H), 7.15 (m, 1H), 7.2 (t, 1H), 7.39 (dd, 1H), 9.56 (s, 1H), 10.42(s, 1H); MS (ESI+) m/z 380 $(M+H)^+$. Anal. ($C_{16}H_{13}N_3BrFO_2 \cdot C_2H_6O$) C, H, N.

4.4.3. 4-(3-Bromo-4-fluorophenyl)-1-ethyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6c). 5-Amino-1-ethyl-1,2-dihydropyrazol-3-one (0.13 g, 1 mmol), prepared by the method of Weisberger[11] from ethylhydrazine and ethyl cyanoacetate, 3-bromo-4-fluorobenzaldehyde (0.2 g, 1 mmol), and 1,3-cyclopentanedione (0.1 g, 1 mmol) were processed as in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.23 g (58%) of **6c** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 1.22 (t, 3H), 2.28 (t, 2H), 2.68 (m, 2H), 3.82 (q, 2H), 4.7 (s, 1H), 7.17 (m, 1H), 7.2 (t, 1H), 7.4 (dd, 1H), 9.64 (bs, 1H), 10.4 (s, 1H); MS (ESI-) m/z 392 $(M-H)^-$. Anal. ($C_{17}H_{15}N_3BrFO_2 \cdot 0.5H_2O$) C, H, N.

4.4.4. 4-(3-Bromo-4-fluorophenyl)-1-*tert*-butyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6d). 5-Amino-1-*tert*-butyl-1,2-dihydropyrazol-3-one (0.23 g, 1.5 mmol), prepared by the method of Weisberger[11] from *tert*-butylhydrazine and ethyl cyanoacetate, 3-bromo-4-fluorobenzaldehyde (0.3 g, 1.5 mmol), and 1,3-cyclopentanedione (0.147 g, 1.5 mmol) in EtOH (3 mL) were processed as in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.12 g of **6d** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 1.51 (s, 9H), 2.28 (m, 2H), 2.71 (m, 2H), 4.69 (s, 1H), 7.12 (m, 1H), 7.21 (t, 1H), 7.39 (dd, 1H), 9.43 (bs, 1H), 9.57 (s, 1H); MS (ESI-) m/z 420 $(M-H)^-$. Anal. ($C_{19}H_{19}N_3BrFO_2$) C, H, N.

4.4.5. 4-(3-Bromo-4-fluorophenyl)-1-(2-pyridinyl)-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6e). 5-Amino-1-(2-pyridyl)-1,2-dihydropyrazol-3-one (0.26 g, 1.5 mmol),[11] (3-bromo-4-fluorobenzaldehyde (0.3 g, 1.5 mmol), and 1,3-cyclopentanedione (0.147 g, 1.5 mmol) were processed as in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.2 g of **6e** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 2.32 (m, 2H), 2.8 (m, 2H), 4.82 (s, 1H), 7.22 (m, 3H), 7.48 (dd, 1H), 7.55 (dd, 1H), 7.92 (t, 1H), 8.41 (m, 1H), 10.42 (s, 1H), 10.55 (bs, 1H); MS (ESI-) m/z 439 $(M-H)^-$. Anal. ($C_{20}H_{14}N_4BrFO_2 \cdot 0.25H_2O$) C, H, N.

4.4.6. 4-(3-Bromo-4-fluorophenyl)-2-phenyl-1,2,4,6,7,8-hexahydrocyclopenta [*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6f). 3-Bromo-4-fluorobenzaldehyde (0.3 g, 1.5 mmol), 1,3-cyclopentanedione (0.15 g, 1.5 mmol), and 5-amino-2-phenyl-1,2-dihydropyrazol-3-one (0.26 g, 1.5 mmol) were processed as in **6a**. The reaction mixture was concentrated in vacuo and the obtained residue was chromatographed on silica gel eluting with 10% EtOH/CH_2Cl_2 to provide 0.32 g of **6f**. ^{1}H NMR (DMSO-d_6) δ 2.26 (m, 2H), 2.63 (m, 2H), 4.86 (s, 1H), 7.21 (m, 3H), 7.4 (t, 2H), 7.51 (d, 1H), 7.67 (d, 2H), 10.47 (s, 1H), 11.2 (s, 1H). MS (ESI-) m/z 438 $(M-H)^-$. Anal. ($C_{21}H_{15}N_3FBrO_2$) C, H, N.

4.4.7. 4-(3-Bromo-4-fluorophenyl)-2-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (6g). 3-Bromo-4-fluorobenzaldehyde (0.3 g, 1.5 mmol), 1,3-cyclopentanedione (0.15 g, 1.5 mmol), and 5-amino-2-methyl-1,2-dihydropyrazol-3-one (0.17 g, 1.5 mmol), prepared by the method of words of Taylor[10] were processed as described in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.32 g of **6g**. ^{1}H NMR (DMSO-d_6) δ 2.21 (t, 2H), 2.59 (m, 2H), 3.38 (s, 3H), 4.75 (s, 1H), 7.13 (m, 1H), 7.2 (t, 1H), 7.42 (dd, 1H), 10.16 (s, 1H), 10.51 (bs, 1H). MS (ESI-) m/z 378 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3BrFO_2$) C, H, N.

4.4.8. 4-(3-Bromo-4-fluorophenyl)-1-methyl-4,6,7,8-tetrahydro-1*H*-cyclopenta[*b*]isoxazolo[4,3-*e*]pyridine-3,5-dione (7). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.11 g, 1 mmol), 3-bromo-4-fluorobenzaldehyde (0.2 g, 1 mmol), and 1,3-cyclopentanedione (0.1 g, 1 mmol) in EtOH (2 mL) were processed as in **6a**. The reaction mixture was allowed to cool to room temperature and was evaporated under reduced pressure. The residue was chromatographed eluting with EtOAc:HCO_2H:H_2O (19:0.5:0.5) to provide **7** as a tan solid (0.07 g). ^{1}H NMR (DMSO-d_6) δ 2.35 (t, 2H), 2.72 (m, 2H), 3.29 (s, 3H), 4.6 (s, 1H), 7.23 (d, 2H), 7.5 (d, 1H) 11.0 (s, 1H). MS (ESI) m/z 379 $(M-H)^-$. Anal. ($C_{16}H_{12}N_3FBrO_3$) C, H, N.

4.4.9. 4-(3-Bromo-4-fluorophenyl)-1-methyl-5-oxo-1,4,5,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridin-3-yl acetate (8). Dihydropyridopyrazolone **6b** 1 (0.4 g, 1 mmol) was heated on a steam bath in acetic anhydride (5 mL) for 15 min. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with 5% EtOH/CH_2Cl_2 to provide 0.27 g of **8** as white crystals. ^{1}H NMR (DMSO-d_6) δ 2.35 (t, 2H), 2.36 (s, 3H), 2.74 (m, 2H), 3.35 (s, 3H), 4.59 (s, 1H), 7.25 (d, 2H), 7.55 (d, 1H), 11.0 (s, 1H). MS (ESI-) m/z 423 $(M-H)^-$. Anal. ($C_{18}H_{15}N_3FBrO_3$) C, H, N.

4.4.10. (+) 4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (9). Acetate **8** (0.4 g) was chromatographed on a chiral column (Chiracel OJ 4.6×250 mm using hexane:EtOH (75:25) at 1 mL/min) to provide two enantiomers. The less polar enantiomer had a retention time of 10.9 min (0.174 g). The more polar enantiomer had a retention time of 18.4 min (0.16 g).

The less polar enantiomer (0.17 g) in aqueous MeOH (10 mL) was treated with 6 N HCl (1 mL) and then heated at reflux for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed eluting with 15% EtOH/CH_2Cl_2 to provide 0.09 g of **9**. $[\alpha]_D^{23}$ +168.1° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.3 (t, 2H), 2.7 (m, 2H), 3.5 (s, 3H), 4.7 (s, 1H), 7.18 (m, 1H), 7.2 (t, 1H), 7.39 (dd, 1H), 9.51 (bs, 1H), 10.42(s, 1H). MS (ESI-) m/z 378 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3BrFO_2$) C, H, N.

4.4.11. (−) 4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (10). The more polar enantiomer (0.16 g) in aqueous MeOH (10 mL) was treated with 6 N HCl (1 mL) and then heated at reflux for 1 h. The reaction mixture was evaporated under reduced pressure and the residue

was chromatographed eluting with 15% EtOH/CH_2Cl_2 to provide 0.09 g of **10**. $[\alpha]_D^{23}$ −166.7° (DMSO); ^{1}H NMR (DMSO-d_6) δ 2.3 (t, 2H), 2.7 (m, 2H), 3.5 (s, 3H), 4.7 (s, 1H), 7.18 (m, 1H), 7.2 (t, 1H), 7.39 (dd, 1H), 9.51 (bs, 1H), 10.42 (s, 1H). MS (ESI-) *m*/*z* 378 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3BrFO_2$) C, H, N.

4.4.12. Ethyl 6-[(acetyloxy)methyl]-4-(3-bromo-4-fluorophenyl)-1-methyl-3-oxo-2,3,4,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (12). Ethyl 4-(acetyloxy)-3-oxobutanoate **11** (0.19 g, 1 mmol),[17] 3-bromo-4-fluorobenzaldehyde (0.2 g, 1 mmol) and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.11 g, 1 mmol) in EtOH (3 mL) were heated at 80 °C for 24 h in a sealed tube. The reaction mixture was evaporated under reduced pressure and chromatographed on silica gel eluting with 5% EtOH/CH_2Cl_2 to provide 0.1 g of **12**. ^{1}H NMR (DMSO-d_6) δ 1.03 (t, 3H), 2.1 (s,3H), 3.46 (s, 3H), 3.92 (q, 2H), 4.95 (s, 1H), 5.12 (q, 2H), 7.18 (m, 1H), 7.22 (t, 1H), 7.38 (dd, 1H), 9.43 (s, 1H). MS (ESI-) *m*/*z* 468$(M-H)^-$.

4.4.13. 4-(3-Bromo-4-fluorophenyl)-1-methyl-4,8-dihydro-1*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-3,5(2*H*,7*H*)-dione (13). Diester **12** (0.09 g) and K_2CO_3 (0.03 g) in MeOH (10 mL) were stirred at ambient temperature for 1 h. The solvent was evaporated under reduced pressure and the obtained residue was chromatographed on silica gel eluting with 10% EtOH/CH_2Cl_2 to provide 0.04 g of **13**. ^{1}H NMR (DMSO-d_6) δ 3.49 (s, 3H), 4.76 (s, 1H), 4.9 (q, 2H), 7.23 (m, 2H), 7.42 (dd, 1H), 9.51 (bs, 1H), 9.78 (s, 1H). MS (ESI-) *m*/*z* 378 $(M-H)^-$. Anal. ($C_{15}H_{11}N_3BrFO_3 \cdot 0.5\ C_2H_6O$) C, H, N.

4.4.14. 4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,4,6,7,8-hexahydro-3*H*-pyrazolo[3,4-*b*]thieno[2,3-*e*]pyridin-3-one 5,5-dioxide (14). 5-Amino-1-methyl-1,2-dihydropyrazol-3-one (0.17 g, 1.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.3 g, 1.5 mmol), and tetrahydrothiophene-3-oxo-1,1-dioxide (0.2 g,1.5 mmol) were treated as described for **6a**. The reaction was cooled and the resulting precipitate was filtered off to provide 0.41 g of **14** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 2.88 (m, 1H), 3.03 (m, 1H), 3.4 (m, 2H), 3.48 (s, 3H), 4.92 (s, 1H), 7.21 (m, 1H), 7.24 (t, 1H), 7.4 (d, 1H), 9.55 (s, 1H), 9.89 (s, 1H). MS (ESI-) *m*/*z* 414 $(M-H)^-$. Anal. ($C_{15}H_{13}N_3BrFO_3S$) C, H, N.

4.4.15. 4-(3-Bromo-4-fluorophenyl)-1-methyl-3,4,6,7,8-hexahydro-2*H*-thiopyrano[3,2-*b*]pyrazolo[2,3-*e*]pyridin-3-one, 5,5-dioxide (15). Tetrahydrothiopyran-3-one-1,1-dioxide (0.148 g, 1 mmol), 3-bromo-4-fluoro-benzaldehyde (0.20 g, 1 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.11 g, 1 mmol) were processed as in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.24 g (46%) of **15** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 2.21 (m, 2H), 2.6 (m, 2H), 3.12 (m, 2H), 5.05 (s, 1H), 7.18 (m, 2H), 7.21 (t, 1H), 7.49 (d, 1H), 9.3 (s, 1H), 9.55 (bs, 1H). MS (ESI-) *m*/*z* 428 $(M-H)^-$. Anal. ($C_{16}H_{15}N_3BrFO_3S.\ 0.5\ C_2H_6O$) C, H, N.

4.4.16. 4-(3-Bromo-4-fluorophenyl)-1-methyl-4,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinoline-3,5(2*H*,6*H*)-dione (16). 3-Bromo-4-fluorobenzaldehyde (0.2 g, 1.0 mmol), 1,3-cyclohexanedione (0.11 g, 1.0 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.11 g, 1.0 mmol) were processed as described for **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.27 g of **16**. ^{1}H NMR (DMSO-d_6) δ 1.9 (m, 2H), 2.2 (m, 2H), 2.6 (m, 2H), 3.45 (s, 3H), 4.88 (s, 1H), 7.12 (m, 1H), 7.18 (t, 1H), 7.38 (dd, 1H), 9.53 (s, 1H), 9.72 (s, 1H); MS (ESI-) *m*/*z* 390 $(M-H)^-$. Anal. ($C_{17}H_{15}N_3BrFO_2 \cdot C_2H_6O$) C, H, N.

4.4.17. 4-(3-Bromo-4-fluorophenyl)-1,6,6-trimethyl-4,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinoline-3,5(2*H*,6*H*)-dione (17). 5-Amino-1-methyl-1,2-dihydropyrazol-3-one (0.23 g, 2 mmol), 3-bromo-4-fluorobenzaldehyde (0.4 g, 2 mmol), and 4,4-dimethyl-1,3-cyclohexanedione (0.28 g, 2 mmol) were treated as in **6a** to provide after filtration of the reaction mixture 0.55 g of **17** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 0.92 (s, 3H), 0.98 (s, 3H), 1.78 (t, 2H), 2.63 (m, 2H), 3.43 (s, 3H), 4.83 (s, 1H), 7.11 (m, 1H), 7.17 (t, 1H), 7.33 (dd, 1H), 9.53 (s, 1H), 9.66 (s, 1H). MS (ESI-) *m*/*z* 420 $(M-H)^-$. Anal. ($C_{19}H_{19}N_3BrFO_2$) C, H, N.

4.4.18. (+) 4-(3-Bromo-4-fluorophenyl)-1,6,6-trimethyl-4,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinoline-3,5-(2*H*,6*H*)-dione(18) and (−) 4-(3-bromo-4-fluorophenyl)-1,6,6-trimethyl-4,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]-quinoline-3,5(2*H*,6*H*)-dione (19). Compound **17** (0.6 g) in 5 mL of acetic anhydride was heated for 10 min on a steam bath. The reaction mixture was evaporated under reduced pressure and chromatographed on silica gel to provide 0.36 g of 4-(3-bromo-4-fluorophenyl)-1,6,6-trimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-3-yl acetate as a less polar compound.

The intermediate acetate (0.36 g) was chromatographed on a chiral column (Chiracel OJ column 4.6×250 mm using hexane:EtOH (85:15) at 1 mL/min) to provide two enantiomers. The less polar enantiomer (0.14 g) had a retention time of 7.63 min. The more polar enantiomer (0.14 g) had a retention time of 10.18 min.

The less polar enantiomer (0.14 g), from above, in aqueous MeOH (10 mL) was treated with 6 N HCl (1 mL) and heated at reflux for 2 h. The reaction mixture was evaporated under reduced pressure and chromatographed on silica gel eluting with 10% EtOH/CH_2Cl_2 to provide 0.09 g of **18**. $[\alpha]_D^{23}$ +25.3° (DMSO); ^{1}H NMR (DMSO-d_6) δ 0.92 (s, 3H), 0.98 (s, 3H), 1.78 (t, 2H), 2.63 (m, 2H), 3.44 (s, 3H), 4.83 (s, 1H), 7.12 (m, 1H), 7.16 (t, 1H), 7.33 (dd, 1H), 9.52 (bs, 1H), 9.63 (s, 1H). MS (ESI-) *m*/*z* 420 $(M-H)^-$. Anal. ($C_{19}H_{19}N_3BrFO_2$) C, H, N.

The more polar enantiomer from above (0.16 g) was treated with 6 N HCl (1 mL) and then heated at reflux for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed eluting with 15% EtOH/CH_2Cl_2 to provide 0.08 g of **19**. $[\alpha]_D^{23}$ −23.9° (DMSO). ^{1}H NMR (DMSO-d_6) δ 0.92 (s, 3H), 0.98 (s, 3H), 1.78 (t, 2H), 2.63 (m, 2H), 3.44 (s, 3H), 4.83 (s, 1H), 7.12 (m, 1H), 7.16 (t, 1H), 7.33 (dd, 1H), 9.52 (bs, 1H), 9.63 (s, 1H). MS (ESI-) *m*/*z* 420 $(M-H)^-$. Anal. ($C_{19}H_{19}N_3BrFO_2$): C, H, N.

4.4.19. 4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,4,7,8,9-hexahydropyrano[4,3-*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (20). Dihydro-2*H*-pyran-2,4(3*H*)-dione (0.11 g, 1 mmol), 3-bromo-4-fluoro-benzaldehyde (0.2 g, 1 mmol) and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.12 g, 1 mmol) were processed as described in **6a** to provide 0.27 g of **20** as a tan solid ^{1}H NMR (DMSO-d_6) δ 2.55 (m, 1H), 2.8 (m, 1H), 3.5 (s, 3H), 4.22 (m, 2H), 4.86 (s, 1H), 7.2 (m, 2H), 7.41 (dd, 1H), 9.49 (s, 1H), 9.92 (s, 1H). MS (ESI-) *m*/*z* 392 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3BrFO_3\cdot C_2H_6O$) C, H, N.

4.4.20. 4-(3-Bromo-4-fluorophenyl)-1-methyl-1,2,4,9-tetrahydropyrano[3,4-*b*]pyrazolo[4,3-*e*]pyridine-3,5(6*H*,8*H*)-dione (21). 2*H*-Pyran-3,5(4*H*,6*H*)-dione (0.34 g, 3 mmol), 3-bromo-4-fluoro-benzaldehyde (0.61 g, 3 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.34 g, 3 mmol) in EtOH (6 mL) were processed as in **6a** to provide 0.55 g (46%) of **19** as a tan solid. ^{1}H NMR (DMSO-d_6) δ 3.5 (s, 3H), 4.1 (s, 2H), 4.53 (q, 2H), 4.98 (s, 1H), 7.18 (m, 1H), 7.21 (t, 1H), 7.4 (dd, 1H), 9.65 (bs, 1H), 10.52 (s, 1H). MS (ESI-) *m*/*z* 394,392 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3BrFO_3$) C, H, N.

4.4.21. Ethyl 6-[(acetyloxy)methyl]-4-(3-bromo-4-fluorophenyl)-1-methyl-3-oxo-1,3,4,7-tetrahydroisoxazolo[3,4-*b*]pyridine-5-carboxylate (22). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.17 g, 1.5 mmol), ethyl 4-(acetyloxy)butanoate **11** (0.28 g, 1.5 mmol[17] and 3-bromo-4-fluorobenzaldehyde (0.3 g, 1.5 mmol) in EtOH (4 mL) were heated at 80 °C for 24 h in a sealed tube. The reaction mixture was evaporated under reduced pressure and the residue chromatographed on silica gel eluting with 5% EtOH/CH_2Cl_2 to provide **22** (0.2 g). ^{1}H NMR (DMSO-d_6) δ 1.03 (t, 3H), 2.1 (s, 3H), 3.23 (s, 3H), 3.82 (q, 2H), 4.8 (s, 1H), 5.12 (q, 2H), 7.25 (m, 1H), 7.3 (t, 1H), 7.48 (dd, 1H), 10.2 (s, 1H). MS (ESI-) *m*/*z* 467 $(M-H)^-$.

4.4.22. 4-(3-Bromo-4-fluorophenyl)-1-methyl-4,8-dihydro-1*H*,3*H*-furo[3,4-*b*]isoxazolo[4,3-*e*]pyridine-3,5(7*H*)-dione (23). The intermediate diester **22** (0.16 g) in MeOH (10 mL) was treated with K_2CO_3 (0.05 g) at ambient temperature. After stirring for 1 h, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with 5% EtOH/CH_2Cl_2 to provide **23** (0.04 g). ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H), 4.71 (s, 1H), 4.96 (q, 2H), 7.32 (m, 2H), 7.58 (dd, 1H), 11.18 (bs, 1H). MS (ESI-) *m*/*z* 381 $(M-H)^-$. Anal. ($C_{15}H_{10}BrFN_2O_4$) C, H, N.

4.4.23. 4-(3-Bromo-4-fluorophenyl)-1-methyl-4,7,8,9-tetrahydroisoxazolo[3,4-*b*]quinoline-3,5(1*H*,6*H*)-dione (24). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.086 g, 0.75 mmol), 3-bromo-4-fluorobenzaldehyde (0.15 g, 0.075 mmol), and 1,3-cyclohexanedione (0.084 g, 0.75 mmol) were processed as in **6a** to provide **24** as a tan solid (0.09 g). ^{1}H NMR (DMSO-d_6) δ 1.95 (m, 2H), 2.27 (m, 2H), 2.63 (m, 2H), 3.24 (s, 3H), 4.69 (s, 1H), 7.2 (m, 1H), 7.23 (t, 1H), 7.45 (dd, 1H), 10.2 (s, 1H). S (ESI) *m*/*z* 393 $(M-H)^-$. Anal. ($C_{17}H_{14}N_2BrFO_3$) C, H, N.

4.4.24. 4-(3-Bromo-4-fluorophenyl)-1,6,6-trimethyl-4,7,8,9-tetrahydroisoxazolo[3,4 - *b*]quinoline - 3,5(1*H*,6*H*) - dione (25). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.11 g, 1 mmol), 3-bromo-4-fluoro-benzaldehyde (0.2 g, 1 mmol), and 4,4-dimethyl-1,3-cyclohexanedione (0.11 g, 1 mmol) in EtOH (3 mL) were treated as in **6a**. The reaction mixture was allowed to cool to ambient temperature and evaporated under reduced pressure. The residue was chromatographed eluting with 5%EtOH/CH_2Cl_2 to yield 0.13 g of **25** as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.92 (s, 3H), 1.0 (s, 3H), 1.82 (t, 2H), 2.65 (m, 2H), 3.22 (s, 3H), 4.67 (s, 1H), 7.21 (m, 2HC, 7.43 (dd, 1H), 10.39 (s, 1H). MS (ESI) *m*/*z* 419,421 $(M-H)^-$. Anal. ($C_{19}H_{18}BrFN_2O_3$) C, H, N.

4.4.25. (*R*)(+)-4-(3-Bromo-4-fluorophenyl)-1,6,6-trimethyl-4,7,8,9-tetrahydroisoxazolo[3,4-*b*]quinoline-3,5(1*H*,6*H*)-dione (26) and (*S*)(−)-4-(3-bromo-4-fluorophenyl)-1,6,6-trimethyl - 4,7,8,9 - tetrahydroisoxazolo[3,4 - *b*]quinoline - 3,5(1*H*,6*H*)-dione (27). Dihydropyridoisoxazolone 25 (0.25 g) was separated on chiral column (Chiracel AS 4.6×250 mm using 90:10 hexane:EtOH at 1 mL/min) to provide 0.1 g of enantiomer **26** (retention time of 17 min). $[\alpha]_D^{23}$ +93.33° (DMSO); ^{1}H NMR (DMSO-d_6) δ 0.92 (s, 3H), 1.0 (s, 3H), 1.82 (t, 2H), 2.65 (m, 2H), 3.22 (s, 3H), 4.67 (s, 1H), 7.21 (m, 2HC, 7.43 (dd, 1H), 10.39 (s, 1H). MS (ESI) *m*/*z* 419,421 $(M-H)^-$. Anal. ($C_{19}H_{18}BrFN_2O_3$) C, H, N.

Continued elution of the column provided 0.08 g of **27** (retention time 28.5 min). $[\alpha]_D^{23}$ −96.36° (DMSO); ^{1}H NMR (DMSO-d_6) δ 0.92 (s, 3H), 1.0 (s, 3H), 1.82 (t, 2H), 2.65 (m, 2H), 3.22 (s, 3H), 4.67 (s, 1H), 7.21 (m, 2HC, 7.43 (dd, 1H), 10.39 (s, 1H). MS (ESI) *m*/*z* 419,421 $(M-H)^-$. Anal. ($C_{19}H_{18}BrFN_2O_3$) C, H, N.

4.4.26. 4-(3-Bromo-4-fluorophenyl)-1-methyl-4,9-dihydro-1*H* - isoxazolo[3,4 - *b*]pyrano[4,3 - *e*]pyridine - 3,5(6*H*,8*H*) - dione (28). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.11 g, 1 mmol), 3-bromo-4-fluoro-benzaldehyde (0.2 g, 1 mmol), and 2*H*-pyran-3,5(4*H*,6*H*)-dione (0.11 g, 1 mmol) were treated as in **6a** to provide **28** as a white solid (0.09 g). ^{1}H NMR (DMSO-d_6) δ 3.27 (s, 3H), 4.05 (s, 2H), 4.57 (q, 2H), 4.78 (s, 1H), 7.28 (m, 2H), 7.54 (d, 1H), 10.77 (s, 1H). MS (ESI) *m*/*z* 395 $(M-H)^-$. Anal. ($C_{16}H_{12}BrFN_2O_4$) C, H, N.

4.4.27. (*S*)(−)4-(3-Bromo-4-fluorophenyl)-1-methyl-4,9-dihydro - 1*H* - isoxazolo[3,4 - *b*]pyrano[4,3 - *e*]pyridine - 3,5(6*H*, 8*H*)-dione (29) and (*R*)(+)4-(3-bromo-4-fluorophenyl)-1-methyl - 4,9 - dihydro - 1*H* - isoxazolo[3,4 - *b*]pyrano[4,3 - *e*]pyridine-3,5(6*H*,8*H*)-dione (30). Racemic **27** (0.25 g) was separated on Chiracel AS column eluting with 20% of EtOH/hexane to provide 0.06 g of **29** as the less polar enantiomer. $[\alpha]_D^{23}$ +83.33° (DMSO); ^{1}H NMR (DMSO-d_6) δ 3.27 (s, 3H), 4.05 (s, 2H), 4.57 (q, 2H), 4.78 (s, 1H), 7.28 (m, 2H), 7.54 (d, 1H), 10.77 (s, 1H); MS (ESI) *m*/*z* 395 $(M-H)^-$. Anal. ($C_{16}H_{12}BrFN_2O_4$) C, H, N.

Continued elution of column afforded 0.07 g of **30** as more polar enentiomer $[\alpha]_D^{23}$ −83.07° (DMSO); ^{1}H NMR (DMSO-d_6) δ 3.27 (s, 3H), 4.05 (s, 2H), 4.57 (q, 2H), 4.78

(s, 1H), 7.28 (m, 2H), 7.54 (d, 1H), 10.77 (s, 1H); MS (ESI) m/z 395 $(M-H)^-$. Anal. ($C_{16}H_{12}BrFN_2O_4$) C, H, N.

4.4.28. 1-Methyl-4-[4-(trifluoromethoxy)phenyl]-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (31). 4-Trifluoromethoxybenzaldehyde (0.28 g, 1.5 mmol), 1,3-cyclopentanedione (0.15 g, 1.5 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.17 g, 1.5 mmol) were processed as in **6a** to provide 0.15 g of **31**. ^{1}H NMR (DMSO-d_6) δ 2.3 (t, 2H), 2.68 (m, 2H), 3.49 (s, 3H), 4.72 (s, 1H), 7.18 (d, 2H), 7.23 (d, 2H), 9.5 (bs, 1H) 10.37 (s, 1H); MS (ESI-) m/z 364 $(M-H)^-$. Anal. ($C_{17}H_{14}N_3F_3O_3{\cdot}0.25H_2O$) C, H, N.

4.4.29. 4-(3-Bromo-4-methylphenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (32). 4-Methyl-3-bromobenzaldehyde (0.3 g, 1.5 mmol),[20] 1,3-cyclopentanedione (0.15 g, 1.5 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.17 g, 1.5 mmol) were processed as in **6a** to provide 0.34 g of **32**. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H), 2.29 (t, 2H), 2.67 (m, 2H), 3.5 (s, 3H), 4.63 (s, 1H), 7.04 (dd, 1H), 7.18 (d, 1H), 7.29 (ds, 1H), 9.51 (bs, 1H), 10.37 (s, 1H); MS (ESI-) m/z 361 $(M-H)^-$. Anal. ($C_{17}H_{16}N_3BrO_2$) C, H, N.

4.4.30. 4-[4-Fluoro-3-(trifluoromethyl)phenyl]-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (33). 4-Fluoro-3-trifluoromethylbenzaldehyde (0.28 g, 1.5 mmol), 1,3-cyclopentanedione (0.15 g, 1.5 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.17 g, 1.5 mmol) were processed as in **6a**. The reaction was cooled and the resulting precipitate was filtered off to provide 0.35 g of **33**. ^{1}H NMR (DMSO-d_6) δ 2.21 (m, 2H), 2.7 (m, 2H), 3.51 (s, 3H), 4.8 (s, 1H), 7.35 (t, 1H), 7.45 (m, 1H), 7.55 (d, 1H), 9.6 (bs, 1H), 10.48 (s, 1H); MS (ESI-) m/z 366 $(M-H)^-$. Anal. ($C_{17}H_{13}N_3F_4O_2$) C, H, N.

4.4.31. 4-(4-Chloro-3-nitrophenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (34). 4-Chloro-3-nitrobenzaldehyde (0.27 g, 1.5 mmol), 1,3-cyclopentanedione (0.15 g, 1.5 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.17 g, 1.5 mmol) were treated as in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.3 g of **34**. ^{1}H NMR (DMSO-d_6) δ 2.3 (t, 2H), 2.68 (m, 2H), 3.5 (s, 3H), 4.81 (s, 1H), 7.48 (dd, 1H), 7.6 (d, 1H), 7.78 (d, 1H), 9.61 (bs, 1H), 10.49 (s, 1H); MS (ESI-) m/z 359 $(M-H)^-$. Anal. ($C_{16}H_{13}N_4ClO_4$) C, H, N.

4.4.32. 4-(4-Fluoro-3-iodophenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (35). 4-Fluoro-3-iodobenzaldehyde[21] (0.25 g, 1.0 mmol), 1,3-cyclopentanedione (0.1 g, 1.0 mmol) and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.11 g, 1.0 mmol) were treated as in **6a** to provide 0.27 g of **35**. ^{1}H NMR (DMSO-d_6) δ 2.3 (m, 2H), 2.68 (m, 2H), 3.5 (s, 3H), 4.67 (s, 1H), 7.1 (t, 1H), 7.15 (m, 1H), 7.52 (dd, 1H), 9.52 (s, 1H), 10.4 (s, 1H); MS (ESI-) m/z 424 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3FIO_2$) C, H, N.

4.4.33. 4-(3,4-Dichlorophenyl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (36). 3,4-Dichlorobenzaldehyde (0.17 g, 1.0 mmol), 1,3-cyclopentanedione (0.1 g, 1.0 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.11 g, 1.0 mmol) were processed as described in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.24 g of **36**. ^{1}H NMR DMSO-d_6) δ 2.28 (t, 2H), 2.68 (m, 2H), 3.5 (s, 3H), 4.7 (s, 1H), 7.13 (dd, 1H), 7.33 (d, 1H), 7.49 (d, 1H), 9.58 (s, 1H), 10.45 (s, 1H); MS (ESI-) m/z 348 $(M-H)^-$. Anal. ($C_{16}H_{13}N_3Cl_2O_2$) C, H, N.

4.4.34. 4-(2,1,3-Benzoxadiazol-5-yl)-1-methyl-1,2,4,6,7,8-hexahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-3,5-dione (37). 2,1,3-Benzoxadiazole-5-carboxaldehyde (0.15 g, 1.0 mmol),[21] 1,3-cyclopentanedione (0.1 g, 1.0 mmol), and 5-amino-1-methyl-1,2-dihydropyrazol-3-one (0.11 g, 1.0 mmol) were processed as in **6a**. The reaction was cooled and the resulting precipitate was collected to provide 0.17 g of **37**. ^{1}H NMR (DMSO-d_6) δ 2.32 (m, 2H), 2.71 (m, 2H), 3.51 (s, 3H), 4.87 (s, 1H), 7.5 (dd, 1H), 7.6 (s, 1H), 7.9 (d, 1H), 9.61 (bs, 1H), 10.52 (s, 1H); MS (ESI-) m/z 322 $(M-H)^-$. Anal. ($C_{16}H_{13}N_5O_3$) C, H, N.

4.4.35. 4-(3-Bromo-4-methylphenyl)-1-methyl-4,9-dihydro-1*H*-isoxazolo[3,4-*b*]pyrano[4,3-*e*]pyridine-3,5(6*H*,8*H*)-dione (38). 3-Amino-2-methyl-5(2H)-isoxazolone (0.11 g, 1 mmol), 4-methyl-3-bromobenzaldehyde[20] (0.2 g, 1 mmol), and 2H-pyran-3,5(4H,6H)-dione (0.11 g, 1 mmol) were processed as in **6a**. The reaction mixture was allowed to cool to ambient temperature and was evaporated under reduced pressure. The residue was chromatographed eluting with EtOAc:HCO_2H: H_2O (19:0.5:0.5) to provide **38** (0.07 g). ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H), 3.23 (s, 3H), 4.05 (s, 2H), 4.55 (d, 2H), 4.7 (s, 1H), 7.11 (dd, 1H), 7.23 (d, 1H), 7.47 (d, 1H), 10.8 (s, 1H); MS (ESI) m/z 389 $(M-H)^-$. Anal. ($C_{17}H_{15}N_2BrO_4{\cdot}0.5C_2H_6O$) C, H, N.

4.4.36. 4-[4-Fluoro-3-(trifluoromethyl)phenyl]-1-methyl-4,9-dihydro-1*H*-isoxazolo[3,4-*b*]pyrano[4,3-*e*]pyridine-3,5(6*H*,8*H*)-dione (39). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.11 g, 1 mmol), 4-fluoro-3-trifluromethylbenzaldehyde and 2*H*-pyran-3,5(4*H*,6*H*)-dione (0.11 g, 1 mmol) were processed as in **6a**. The reaction mixture was allowed to cool to ambient temperature and was evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with EtOAc:H-CO_2H:H_2O (19:0.5:0.5) to yield **39** (0.08 g) ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H), 4.07 (s, 2H), 4.58 (q, 2H), 4.87 (s, 1H), 7.42 (t, 1H), 7.59 (m, 2H), 10.8 (s, 1H); MS (ESI) m/z 383 $(M-H)^-$. Anal. ($C_{16}H_{12}N_2F_4O_4$) C, H, N.

4.4.37. 4-(4-Chloro-3-nitrophenyl)-1-methyl-4,9-dihydro-1*H*-isoxazolo[3,4-*b*]pyrano[4,3-*e*]pyridine-3,5(6*H*,8*H*)-dione (40). 3-Amino-2-methyl-5(2H)-isoxazolone (0.085 g, 0.75 mmol), 3-nitro-4-chlorobenzaldehyde (0.14 g, 0.75 mmol) and 2H-pyran-3,5(4H,6H)-dione (0.085 g, 0.75 mmol) were processed as in **6a** to provide **40** (0.09 g). ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H), 4.06 (s, 2H), 4.58 (s, 2H), 4.88 (s, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 7.9 (d, 1H), 10.8 (s, 1H); MS (ESI) m/z 376 $(M-H)^-$. Anal. ($C_{16}H_{12}N_3ClO_6$) C, H, N.

4.4.38. 4-(4-Fluoro-3-iodophenyl)-1-methyl-4,9-dihydro-1H-isoxazolo[3,4 - *b*]pyrano[4,3 - *e*]pyridine - 3,5(6*H*,8*H*) - dione (41). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.086 g, 0.75 mmol), 4-fluoro-3-iodobenzaldehyde[21] (0.19 g, 0.75 mmol) and 2*H*-pyran-3,5(4*H*,6*H*)-dione (0.085 g, 0.75 mmol) were processed as in **6a**. The residue was chromatographed eluting with 5% MeOH/CH_2Cl_2 to provide **41** (0.03 g). ^{1}H NMR (DMSO-d_6) δ 3.23 (s, 3H), 4.06 (s, 2H), 4.58 (q, 2H), 4.72 (s, 1H), 7.18 (t, 1H), 7.25 (m, 1H), 7.63 (dd, 1H), 10.9 (s, 1H); MS (ESI) *m*/*z* 441 $(M-H)^-$. Anal. ($C_{16}H_{12}N_2FIO_4$) C, H, N.

4.4.39. 3-(1-Methyl-3,5-dioxo-3,4,5,6,8,9-hexahydro-1H-isoxazolo[3,4 - *b*]pyrano[4,3 - *e*]pyridin - 4 - yl)benzonitrile (42). 3-Amino-2-methyl-5(2*H*)-isoxazolone (0.085 g, 0.75 mmol), 3-cyanobenzaldehyde (0.14 g, 0.75 mmol) and 2*H*-pyran-3,5(4*H*,6*H*)-dione (0.085 g, 0.75 mmol) were processed as in **6a**. The residue was chromatographed eluting with 5% MeOH/CH_2Cl_2 to provide **42** (0.09 g) as a tan solid. ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H), 4.05 (s, 2H), 4.59 (q, 2H), 4.81 (s, 1H), 7.5 (t, 1H), 7.6 (m, 1H), 7.62 (m, 1H), 7.64 (d, 1H), 10.8 (s, 1H); MS (ESI) *m*/*z* 322 $(M-H)^-$.Anal. ($C_{17}H_{13}N_3O_4 \cdot 0.25H_2O$) C, H, N.

4.4.40. 4-(2,1,3-Benzoxadiazol-5-yl)-1-methyl-4,9-dihydro-1H - isoxazolo[3,4 - *b*]pyrano[4,3 - *e*]pyridine - 3,5(6*H*,8*H*) - dione (43). 3-Amino-2-methyl-5(2H)-isoxazolone (0.11 g, 1 mmol), 2,1,3-benzoxadiazole-5-carboxaldehyde[22] (0.15 g, 1 mmol), and 2*H*-pyran-3,5(4*H*,6*H*)-dione (0.11 g, 1 mmol) were processed as in **6a** to provide **43** (0.09 g). ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H), 4.08 (s, 2H), 4.6 (q, 2H), 4.92 (s, 1H), 7.62 (dd, 1H), 7.76 (s, 1H), 8.0 (dd, 1H), 10.8 (s, 1H); MS (ESI) *m*/*z* 339 $(M-H)^-$. Anal. ($C_{16}H_{12}N_4O_5$) C, H, N.

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