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Heteroatom-linked indanylpyrazines are corticotropin releasing factor type-1 receptor antagonists

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Abstract—Low nanomolar corticotropin releasing factor type-1 (CRF_1) receptor antagonists containing unique indanylamines were identified from the heteroatom-linked pyrazine chemotype. The most potent indanylpyrazine had a $K_i = 11 \pm 1$ nM. The oxygen-linked pyrazinyl derivatives were prepared through a copper-catalyzed coupling of a pyridinone to a bromo- or iodopyrazine.
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Corticotropin releasing factor (CRF) was identified as the etiological agent in the dysregulation of the hypothalamic-pituitary-adrenal (HPA) system in depressed patients. For instance, CRF is elevated in cerebrospinal fluid, ACTH, and cortisol responses are exaggerated in the dexamethasone/CRF test and cortisol secretion is increased in depressed patients.[1,2] Furthermore, CRF has been shown to modulate the secretion of the stress hormones ACTH and cortisol.[3] As such, CRF plays an important role in a plethora of stress-related disorders, such as general anxiety disorder, post-traumatic stress disorder, and major depressive disorder. Animal studies indicate that suppression of the CRF type 1 (CRF_1) receptor, by either antisense treatment or in genetic knockout animals, decreased anxiety-related behavior.[4] Furthermore, an open-label clinical trial was completed with the corticotropin releasing factor type-1 (CRF_1) receptor antagonist R121919 where it was found that depressive symptoms improved without impairment of the HPA system.[5]

A research program was initiated owing to the substantial amount of preclinical and clinical evidence supporting the therapeutic benefit of a CRF_1 receptor antagonist. The pyrazine template was subsequently identified as a unique scaffold for analog design.[6] Application of the Buchwald groups methodology utilizing copper(I) iodide mediated amidation of aryl halides in the presence of a diamine in the preparation of 5-(pyridin-2-yl)oxopyrazines is described in this publication.[7] Buchwald's conditions were applied to the coupling of commercially available 4-methylpyridinone to a functionalized bromopyrazine (Fig. 1).[8,9] It was found that pyridinyl ether **5b** (see Table 1 for the structure) was

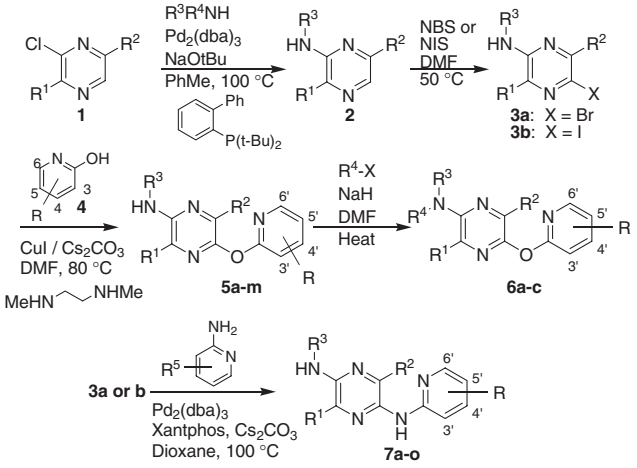

Figure 1. Reaction scheme affording tetra-substituted pyrazines.

Keywords: Corticotropin releasing factor type-1 antagonist; CRF1; Corticotropin releasing hormone type-1; CRH1; Pyrazine; Copper-mediated coupling.
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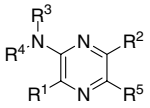
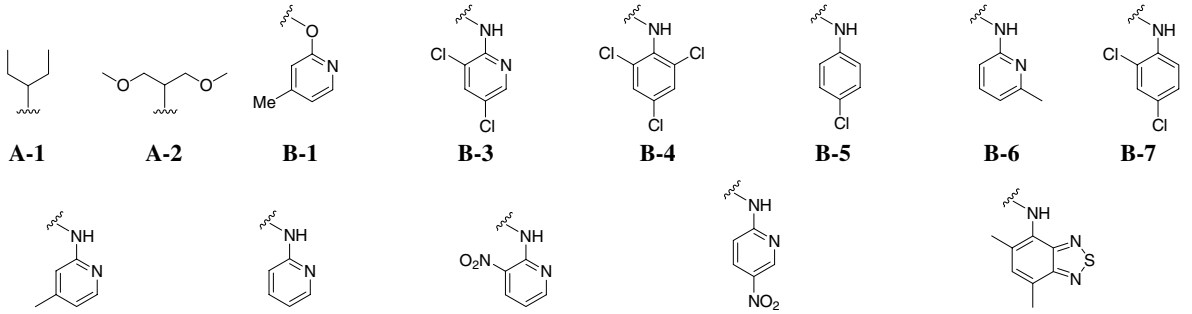
Table 1. Structure and hCRF$_1$ binding affinity of alkyl-containing northern amine compounds prepared via methods shown in Figure 1



Compound	R^1/R^2	R^3	R^4	R^5	hCRF$_1$ K_i (nM)[13]
5a	Me/Me	**A-1**	H	**B-1**	401 ± 119
5b	Et/Et	**A-1**	H	**B-1**	>10,000
5c	Et/Et	**A-2**	H	**B-1**	>10,000
6a	Et/Et	Propyl	Propyl	**B-1**	711 ± 159
6b	Me/Me	Propyl	Propyl	**B-1**	1185 ± 413
6c	Me/Me	Propyl	CH_2-cyclopropyl	**B-1**	1207 ± 384
7a	Et/Et	**A-1**	H	**B-3**	115 ± 52
7b[14]	Et/Et	**A-1**	H	**B-4**	1540 ± 316
7c	Et/Et	**A-1**	H	**B-5**	2703 ± 620
7d	Et/Et	**A-1**	H	**B-6**	3382 ± 656
7e	Me/Me	**A-1**	H	**B-3**	3980 ± 1334
7f	Et/Et	**A-1**	H	**B-7**	>10,000
7g	Et/Et	**A-1**	H	**B-8**	>10,000
7h	Et/Et	**A-2**	H	**B-8**	>10,000
7i	Et/Et	**A-2**	H	**B-3**	>10,000
7j	Et/Et	**A-1**	H	**B-9**	>10,000
7k	Et/Et	**A-1**	H	**B-10**	>10,000
7l	Et/Et	**A-1**	H	**B-11**	>10,000
7m	Et/Et	**A-1**	H	**B-12**	>10,000

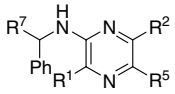


formed upon coupling **4** (R = 4-methyl) to **3a** ($R_1 = R_2$ = Et, R_3 = (3-ethyl)propyl).[10] It was later discovered that pyrazinyl-iodide **3b** afforded higher yields of product **5b** than pyrazinyl-bromide **3a**.[11] Alkylation of **5a**–**c** under standard conditions with heating provided tertiary amine analogs **6a**–**c**. Nitrogen-linked analogs (**7a**–**o**) were prepared from **3a** or **3b** under palladium catalysis using the Xantphos ligand.[12]

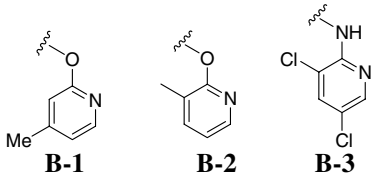
Human CRF$_1$ binding affinities for a series of compounds bearing alkyl groups on the pyrazinylamine are shown in Tables 1 and 2. A striking difference in binding affinity was observed between the dimethyl and diethylpyrazine derivatives **5a** and **5b**, both of which utilize the **B-1** aryl group: dimethylpyrazine analog **5a** was >25-fold more potent than the corresponding diethylpyrazine analog **5b** (K_i = 401 and >10,000 nM, respectively). Surprisingly, the improvement in binding affinity observed with dimethylpyrazine **5a** versus diethylpyrazine **5b** was dependent upon the pendant aryl group. For instance, when the aminopyridine R^5 was **B-3**, diethylpyrazine analog **7a** was ~35-fold more potent than dimethylpyrazine **7e**: (K_i = 115 vs 3980 nM, respectively). The slightly increased potency observed with the aminopyridine aryl group was probed by varying N-linked R^5 groups while keeping the amine side chain constant as **A-1**. Replacing 2-amino-3,5-dichloropyridine (**B-3**) with 2,4-dichloroaniline (**B-7**) resulted in complete loss in binding affinity: **7a** (K_i = 115 nM) versus **7f** (>10,000 nM). A 13- and 24-fold loss in potency versus **7a** was observed when 2,4,6-trichloroaniline (**B-4**) and 4-chloroaniline (**B-5**) were used: see compounds **7b** (K_i = 1540 nM) and **7c** (K_i = 2703 nM). Preparation of the anilino-analog of **5b** afforded analogs **7g** and **7h**, both of which were devoid of activity (K_i > 10,000 nM). Similarly, use of various other nitrogen-linked heterocycles failed to provide compounds with appreciable binding affinity.

In contrast to the results observed with dimethylpyrazine analog **5a**, diethylpyrazine analogs containing the **B-1** aryl group and a phenyl-group in the amine exhibited improved binding affinities: compare diethylpyrazines **5d** and **5g** in Table 2 (K_i = 59 and 530 nM, respectively) with the corresponding dimethyl analogs **5h** and **5i** (K_i = 2123 and 2376 nM, respectively). The location of the methyl group in **B-1** was also found to be important for optimal biological activity. For

Table 2. Structure and hCRF$_1$ binding affinity of phenyl-containing amine compounds prepared via methods shown in Figure 1



Compound	R^1/R^2	R^7	R^5	Selected c Log *P*	hCRF$_1$ K_i (nM)[13]
5d	Et/Et	Et	**B-1**	5.94	59 ± 19
5e	Et/Et	Me	**B-1**		251 ± 17
5f	Et/Et	CH_2OEt	**B-1**	5.30	384 ± 105
5g	Et/Et	*i*-Pr	**B-1**		530 ± 148
5h	Me/Me	Et	**B-1**		2123 ± 371
5i	Me/Me	*i*-Pr	**B-1**		2376 ± 152
5j	Et/Et	Et	**B-2**		2434 ± 534
5k	Et/Et	CH_2OH	**B-1**	4.15	4688 ± 1488
5l	Et/Et	CH_2OPr-*i*	**B-1**	5.27	337 ± 160
5m	Et/Et	CH_2OMe	**B-1**	5.61	>10,000
7n	Et/Et	Et	**B-3**		>10,000
7o	Et/Et	Me	**B-3**		>10,000



B-1 **B-2** **B-3**

instance, 4-methylpyridinyl analog **5d** (R^5 = **B-1**) was >40-fold more potent than 3-methylpyridinyl derivative **5j** (R^5 = **B-2**). Tertiary pyrazinyl-amine groups were found to not be well tolerated. For instance, the binding affinity of **5n**, the *N*-methyl analog of **5d**, prepared via the route delineated in Figure 2, had binding affinity decreased by >170-fold.

Problems associated with high c Log *P* compounds (*i.e.*, poor solubility) prompted an attempt to decrease the c Log *P* of the heteroatom-linked pyrazine CRF$_1$ receptor antagonists. One approach to lowering c Log *P* entailed the preparation of analogs (**5f** and **5k**–**m**) with an oxygen in the amine as shown in Figure 3 (select c Log *P* values are in Table 2). A trend was observed wherein an improvement in CRF$_1$ receptor binding affinity occurred upon increasing the lipophilicity of the alkyl ether. For instance, binding affinity decreased for the ethers in the order *i*-Pr ~ Et ≫ Me (see **5l**, **5f**, and **5m**). Surprisingly, alcohol **5k** exhibited weak binding affinity (K_i = 4.7 μM) while the binding affinity of the methyl ether **5m** was >10 μM. The preparation of additional ethers was de-emphasized since the binding affinity of all of the ether analogs prepared was inferior to **5d** and owing to an inverse trend associating improved binding affinity with increased c Log *P*.

The need to identify compounds having reduced lipophilicity resulted in the extension of this methodology to the use of *cis*-aminoindanol derivatives, as outlined in Figure 4. This work ultimately resulted in the identification of nanomolar affinity CRF$_1$ receptor ligands.

Treating chloropyrazine derivative **1** with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol and $Pd_2(dba)_3$ as shown in Figure 4 provided alcohol **12**. Halogenation of **12**in DMF at 50 °C cleanly provided either bromo- or iodopyrazine **13a** or **13b**, which were treated with a variety of pyridinones, using conditions previously described, to afford alcohol **14**.[15] The (1*R*,2*R*)-stereochemistry was accessed

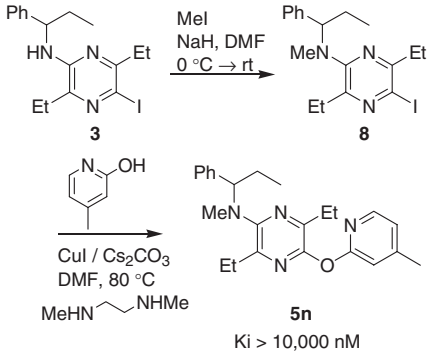


Figure 2. Preparation of *N*-methyl analog of compound **5d**.

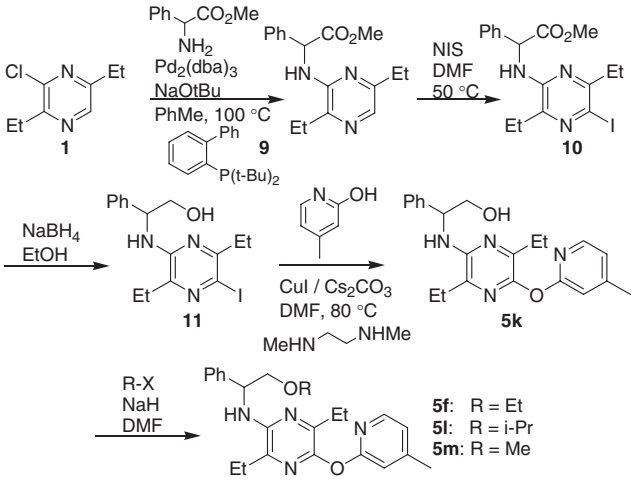


Figure 3. Reaction scheme affording phenylglycinol pyrazines.

via Mitsunobu inversion of alcohol **14** to provide **15**. Derivatization of alcohols **14** or **15** proceeded via alkylation to give products**18**–**20**, **24**–**30** and **32**–**43**. Acylation of **14** (R′ = 4-Me) provided **21**. Employing (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol in the Buchwald amination step enabled access to the enantiomers of compounds shown in Figure 4, in particular **17**, **22** and **23**.

The preparation of bis-N,O-dialkylated materials commenced with alkylation of **13b** to provide **16**, which was then coupled to 2-aminopyridines under palladium catalysis using the Xantphos ligand to provide **44** and **45** (Fig. 5).[16] N-alkylation of **45** under standard conditions afforded **46** and **47**.

The most potent analogs possessed the (1*R*,2*S*)-*cis*-aminoindanol stereochemistry, as evidenced by comparing **18** with the (1*S*,2*R*)-*cis*-analog **22** (K_i = 35 and >10,000 nM, respectively) (Table 3). The ethyl ether *trans*-isomers, **23** and **24**, were significantly less active

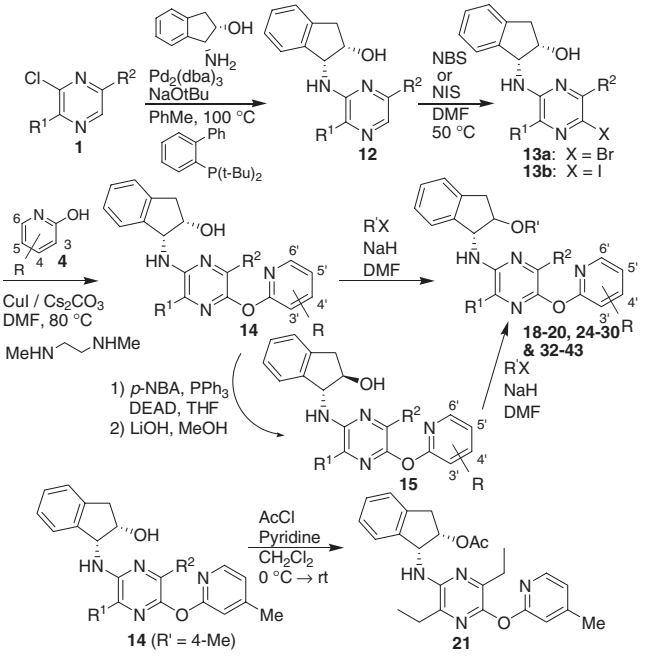


Figure 4. Reaction scheme affording indanyl-substituted pyrazines.

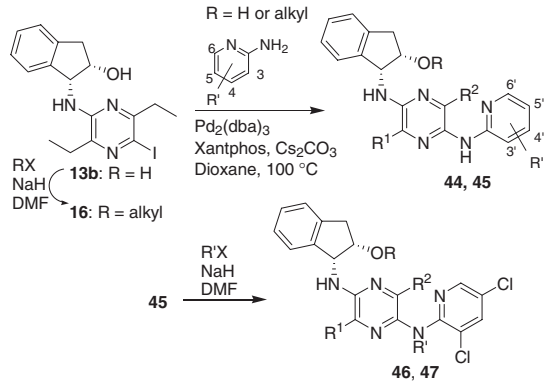


Figure 5. Preparation of 2-aminopyridyl derivatives.

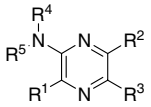
(K_i = 5473 and >10,000 nM, respectively). It was also found that 3,6-diethylpyrazine ($R^1 = R^2$ = Et) was preferred over dimethylpyrazine analogs, as evidenced by comparing **18** and **30** (K_i = 35 and 1217 nM, respectively). The dimethylpyrazinyl ether analog **31** (K_i > 10,000 nM) was obtained as a minor component upon Buchwald coupling (1*R*,2*S*)-*cis*-aminoindanol to 2-chloro-3,6-dimethylpyrazine (compound **1**, $R^1 = R^2$ = Me). The analogous adduct was not detected upon coupling (1*R*,2*S*)-*cis*-aminoindanol to 2-chloro-3,6-diethylpyrazine (compound **1**, $R^1 = R^2$ = Et) implying that the ethyl groups on the pyrazine ring impact the accessibility of the aminoindanol alcohol group. The observed differences in binding affinities between the diethyl- and dimethylpyrazines **18** and **30** may be caused by different pyrazine substitution patterns influencing the orientation of the aminoindanol group.

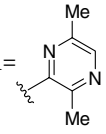
The presence of a hydrophobic group on the indanol was important for activity: alcohol **17** was inactive, acetyl derivative **21** had weak activity while the ethyl ether derivative **18** had nanomolar binding affinity (K_i > 10,000, 2021, and 35 nM, respectively). Decreasing the size of the alkyl chain to a methyl group resulted in a 6-fold loss in binding affinity as seen with analog **28** (K_i = 222 nM). The corresponding propyl and isopropyl ether analogs **26** and **27** were essentially equipotent with ethyl ether **18** (K_i = 30 and 22 nM, respectively). Attesting to the potential influence of the pyrazine substitution on orientation of the indanyl group, compound **32**, a 3,6-dimethylpyrazinyl isopropyl ether analog, was inactive while the 3,6-dimethylpyrazinyl ethyl ether analog **30** had modest binding affinity (K_i > 10,000 and 1217 nM, respectively), but no difference in binding affinity was observed between the ethyl and isopropyl ether-3,6-diethylpyrazine analogs **18** and **27** (K_i = 35 and 22 nM, respectively).

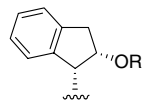
A 3-fold improvement in binding affinity was obtained when a 2-fluoroethyl ether group was used to prepare **19** when compared to the ethyl ether **18** (K_i = 11 and 35 nM, respectively). Cyclopentyl and cyclopropyl analogs **37** and **41** were evaluated as replacements for the ethyl ether in **18**, but 2- and 6-fold losses in binding affinity were observed (K_i = 67 and 214 nM, respectively). Methylation of the indanylamino group had a deleterious effect on binding affinity as evidenced by the 6-fold loss in activity between methyl ethers **28** and **29** (K_i = 222 and 1261 nM, respectively).

The impact on binding affinity upon substituting a nitrogen for the oxygen atom present in analogs **17**–**43** was investigated by preparing compounds **44**–**47**. Compound **44**, the nitrogen analog of **18**, had a K_i > 10,000 nM (>285-fold loss in activity). The majority of historic CRF_1 receptor antagonists incorporate a 2,4-disubstituted aromatic ring into their structure, presumably reinforcing an orthogonal relationship between the aryl ring and the ring system to which it is attached.[2] Assuming nitrogen-linked pyridyl derivatives may adopt an alternate binding mode compared to analogs **17**–**43**, dichloropyridyl derivatives **45**–**47** were prepared as described in Figure 5. Modest binding affinity was

Table 3. Structure and hCRF$_1$ binding affinity of indanylpyrazines prepared via methods shown in Figures 4 and 5



Compound	R^1/R^2	R^3	R^4	R^5	hCRF$_1$ K_i (nM)[13]
17	Et/Et	**B-1**	**A-5**, R = H	H	>10,000
18	Et/Et	**B-1**	**A-3**, R = Ethyl	H	35 ± 2
19	Et/Et	**B-1**	**A-3**, R = CH_2CH_2F	H	11 ± 1
20	Et/Et	**B-13**	**A-3**, R = CH_2CH_2F	H	266 ± 12
21	Et/Et	**B-1**	**A-3**, R = Acetyl	H	2021 ± 195
22	Et/Et	**B-1**	**A-5**, R = Ethyl	H	>10,000
23	Et/Et	**B-1**	**A-6**, R = Ethyl	H	5473 ± 2532
24	Et/Et	**B-1**	**A-4**, R = Ethyl	H	>10,000
25	Et/Et	**B-19**	**A-3**, R = Ethyl	H	436 ± 107
26	Et/Et	**B-1**	**A-3**, R = Propyl	H	30 ± 3.5
27	Et/Et	**B-1**	**A-3**, R = Isopropyl	H	22 ± 9.5
28	Et/Et	**B-1**	**A-3**, R = Methyl	H	222 ± 27
29	Et/Et	**B-1**	**A-3**, R = Methyl	Me	1261 ± 322
30	Me/Me	**B-1**	**A-3**, R = Ethyl	H	1217 ± 160
31	Me/Me	**B-1**	A-3, R= 	H	>10,000
32	Me/Me	**B-1**	**A-3**, R = Isopropyl	H	>10,000
33	Et/Et	**B-18**	**A-3**, R = Ethyl	H	53 ± 9
34	Et/Et	**B-2**	**A-3**, R = Ethyl	H	509 ± 63
35	Et/Et	**B-14**	**A-3**, R = Ethyl	H	456 ± 84
36	Et/Et	**B-15**	**A-3**, R = Ethyl	H	472 ± 74
37	Et/Et	**B-1**	**A-3**, R = Cyclopentyl	H	67 ± 9.5
38	Et/Et	**B-1**	**A-3**, R = THP	H	>10,000
39	Et/Et	**B-1**	**A-3**, R = CH_2 CH_2OH	H	82 ± 6
40	Et/Et	**B-16**	**A-3**, R = Ethyl	H	22 ± 6
41	Et/Et	**B-1**	**A-3**, R = Cyclopropyl	H	214 ± 67
42	Et/Et	**B-16**	**A-3**, R = Propyl	H	58 ± 8
43	Et/Et	**B-17**	**A-3**, R = CH_2CH_2F	H	51 ± 13
44	Et/Et	**B-8**	**A-3**, R = Ethyl	H	>10,000
45	Et/Et	**B-3** R′ = H	**A-3**, R = CH_2CH_2F	H	1733 ± 794
46	Et/Et	**B-3** R′ = Methyl	**A-3**, R = CH_2CH_2F	H	1208 ± 290
47	Et/Et	**B-3** R′ = Ethyl	**A-3**, R = CH_2CH_2F	H	>10,000



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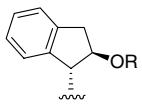

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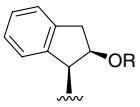

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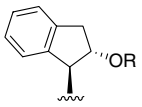

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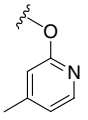

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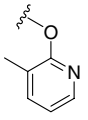

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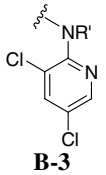

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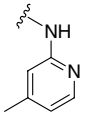

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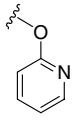

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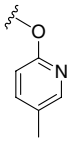
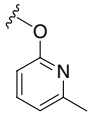
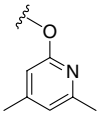


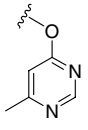
B-14



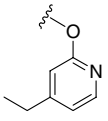
B-15



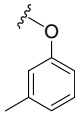
B-16



B-17



B-18



B-19

obtained with analogs **45** and **46** (K_i = 1733 and 1208 nM, respectively) while *N*-ethyl analog **47** was inactive (K_i > 10,000 nM).

Comparing computer models of historic CRF$_1$ receptor antagonists possessing a 2,4-disubstituted aromatic ring with **18** suggested that the methyl group present in **B-1** might occupy the same region of space as the *para*-substituent. Therefore, analog **40** was prepared wherein the 4,6-dimethylpyridinyl derivative was designed to occupy the same region of space as the historic CRF$_1$ receptor antagonists possessing a 2,4-disubstituted aromatic ring. Indeed a slight improvement in binding affinity between **40** and **18** was observed (K_i = 22 and 35 nM). However, the coupling of 4,6-dimethylpyridinone to **13b** ($R^1 = R^2$ = Et) was poor (<20%) and required extended reaction times and the modest difference in binding affinity did not warrant preparation of additional analogs

incorporating this pyridinone. The beneficial impact on binding affinity of the pyridyl ring in **18** was confirmed by preparing 3-methylphenyl derivative **25** (K_i = 35 and 436 nM, respectively). Moving the methyl group around the pyridyl ring, as found in analogs **34**–**36**, resulted in >13-fold losses in binding affinity compared to **18** (K_i = 509, 456 and 472 nM, respectively). 4-Ethylpyridyl analog **33** was approximately 1.5-fold less potent than **18** (K_i = 53 and 35 nM, respectively) and the pyrimidyl analog **43** was >4-fold less potent than **19** (K_i = 51 and 11 nM, respectively).

In conclusion, potent, low nanomolar CRF_1 receptor antagonists were prepared by a multi-step sequence, with the key steps involving a palladium catalyzed coupling of *cis*-1-amino-2-indanols and copper catalyzed coupling of pyridinones to functionalized pyrazines. Different SAR was developed depending upon whether an oxygen or nitrogen atom was the linker between the pyrazine ring and the pendant pyridyl group. Interactions resulting in improved activity for **46** versus **44** are unclear, but nitrogen-linked derivatives may have a different preferred mode of binding than oxygen-linked pyridyl compounds. The most potent analog, **19**, derived from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, had a $K_i = 11 \pm 1$ nM. Compound **19** was not advanced owing to toxicities observed with derivatives in other series' associated with the 2-fluoroethyl ether moiety. Alkyl substitution of the pyridinone ring indicated a preference for 4-methylpyridinone. In an effort to identify CRF_1 receptor antagonists possessing improved drug characteristics, compounds from the indanylpyrazine chemotype are less lypophilic than previously reported heteroatom-linked pyrazines and have improved binding affinities.

References and notes

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8. 2-Chloro-3,6-diethylpyrazine **1** (R^1 = R^2 = ethyl) was prepared following a literature procedure in Sato, Nobuhiro; Matsuura, Tomoyuki *J. Chem Soc., Perkin Trans. 1* **1996**, *19*, 2345.
9. Application of Ullman coupling conditions by heating the bromopyrazine derivative with 2-hydroxy-4-methylpyridine in DMF at 150 °C in the presence of K_2CO_3 and catalytic CuI resulted in complex mixtures containing low yields (<20%) of the desired coupled products. Slightly improved yields were achieved by substituting bromopyrazine **3a** with iodopyrazine **3b**.
10. Catalytic use of *N*,*N*-dimethylethylenediamine was found to provide slightly improved yields of product compared to the use of *trans*-1,2-diaminocyclohexane. Also, cesium carbonate provided improved yields over potassium carbonate.
11. Yields for the coupling reaction ranged from 20% to 70%.
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13. Assay results are reported as duplicates. The following is a description of the preparation of differentiated human neuroblastoma IMR32 cell membranes for use in the standard radioligand binding assay, as well as a description of the binding assay itself. IMR32 cells were maintained in high glucose DMEM supplemented with 10% fetal bovine serum, 1% non-essential amino acids, and 10 U/ml penicillin. In order to increase receptor expression, the cells were differentiated by the addition of 2.5 μM 5-bromo-2′-deoxyuridine to the cell medium. The cells were grown under differentiation conditions for ten days before harvesting for radioligand binding. To prepare the membranes, the differentiated IMR32 cells were grown to confluence and harvested in ice-cold Dulbecco's phosphate-buffered saline. After collection, the cells were pelleted by low speed centrifugation (2500 rpm), and frozen at −80 °C until needed. On the day of the assay, the pellets were thawed and resuspended in 10 ml of 50 mM Hepes, pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 μg/ml aprotinin, 1 μg/ml leupeptin, and 1 μg/ml pepstatin. The cell suspensions were then homogenized, using a Brinkmann polytron (setting 5 for 10 s), and centrifuged for 10 min at 20,000 rpm at 4 °C. Following centrifugation, the pellets were resuspended and assayed for protein concentration. Radioligand binding assays were conducted in disposable polypropylene 96-well plates. The CRF competition assays were initiated by the addition of 150 μl membrane homogenate (30 μg/well) to 150 μl assay buffer (50 mM Hepes, pH 7.0, containing 10 mM $MgCl_2$, 2 nM EGTA, 1 μg/ml aprotinin, 1 μg/ml leupeptin, 1 μg/ml pepstatin, 0.1% ovalbumin, and 0.15 nM bacitracin) containing [^{125}I]Tyr°-CRF (ovine) (140 pM) with or without competing ligand. Radioligand binding was terminated after 2 h at room temperature by filtration through Packard GF/C unifilter plates (presoaked with 0.3% polyethyleneimine) using a Packard cell harvestor. Filters were washed three times with ice-cold phosphate-buffered saline, pH 7.0, containing 0.01% Triton X-100. Filters were then assessed for radioactivity in a Packard TopCount. Apparent dissociation constants (K_i values) from the competition experiments were calculated using an iterative nonlinear regression curve-fitting program (Prism; GraphPAD Software, San Diego, CA).

14. BINAP was used as the ligand for the Buchwald amination providing analog **7b** in 17% yield.
15. Pyridinones **B-4**, **B-6**, and **B-8** were prepared from the appropriate alkyl 2-aminopyridine following the procedure described by Constable, E. C. et al. *Inorg. Chim. Acta* **1996**, *252*, 281.
16. Yin, J.; Zhao, M. M.; Huffman, M.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.