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Model Studies on a Synthetically Facile Series of *N*-Substituted Phenyl-*N*′-pyridin-3-yl Ureas Leading to 1-(3-Pyridylcarbamoyl) indolines that are Potent and Selective 5-$HT_{2C/2B}$ Receptor Antagonists

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Abstract—A model series of 5-HT_{2C} antagonists have been prepared by rapid parallel synthesis. These *N*-substituted phenyl-*N*′-pyridin-3-yl ureas were found to have a range of 5-HT_{2C} receptor affinities and selectivities over the closely related 5-HT_{2A} receptor. Extrapolation of simple SAR, derived from this set of compounds, to the more active but synthetically more complex 1-(3-pyridylcarbamoyl)indoline series allowed us to target optimal substitution patterns and identify potent and selective 5-$HT_{2C/2B}$ antagonists.

Introduction

The 5-HT_2 receptor family currently consists of 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes, which have been grouped together on the basis of primary structure, secondary messenger system and pharmacological profile.[1,2] Our interest in the 5-HT_{2C} receptor stems principally from the finding that the moderately selective 5-$HT_{2C/2B}$ agonist *meta*-chlorophenylpiperazine (mCPP) causes behavioural indications of anxiety both in animal models and humans, implying that selective 5-$HT_{2C/2B}$ antagonists might be useful anxiolytic agents without causing the side effects associated with less selective therapies.[3–5] Recent evidence also suggests that 5-HT_{2C} receptor ligands may have antidepressant properties and be implicated in the pathophysiology of migraine.[6,7]

Some years ago we reported the indole urea (**1A**, SB-200646) as the first selective 5-$HT_{2C/2B}$ antagonist.[8] This compound had modest 5-HT_{2C} affinity (pK_i 7) with 50-fold selectivity over the closely related 5-HT_{2A} receptor and blocked the hypolocomotion in rats produced by mCPP, thus demonstrating in vivo activity in a 5-HT_{2C} centrally mediated functional model. The introduction of conformational restriction between the indole ring and the urea linker produced the indolinyl urea (**1B**, SB-206553), which had an order of magnitude increased affinity at the 5-HT_{2C} receptor in addition to improved selectivity over 5-HT_{2A} receptors and 4-fold increased potency in vivo.[9,10] Unfortunately, although (**1B**) exhibited significant anxiolytic activity in several different animal models of anxiety, the 1-methylindole moiety was subject to metabolic demethylation to a non selective compound and so was not progressed.[11] One of the strategies we pursued to circumvent this metabolic liability was to investigate the replacement of the tetrahydropyrrolo-*N*-methylindole of (**1B**) with a variety of substituted indolines. However, due to the synthetic complexity of substituted indolines, we decided to initially undertake this work in the more accessible phenyl

Key words: 5-$HT_{2C/2B}$ antagonists; antidepressants; anxiolytics; receptors.

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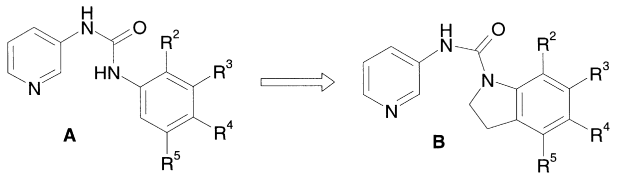


urea series (**A**) using a rapid parallel synthesis approach. Our aim was to identify favourable substituents, so that we could then prepare the equivalently substituted indolines (**B**).

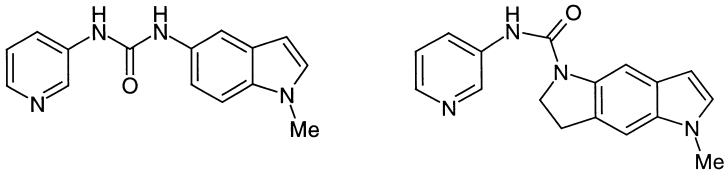
Chemistry

The required biaryl ureas (**1A**–**86A**) were rapidly prepared (Scheme 1) by parallel reaction of a diverse range of anilines with 3-pyridylisocyanate, generated in situ from the corresponding azide.[8] Similarly, the 1-(3-pyridylcarbamoyl) indolines (**B**) were prepared by reacting the appropriate indolines, which were themselves prepared by a variety of routes based on literature methods, with 3-pyridylisocyanate.[15]

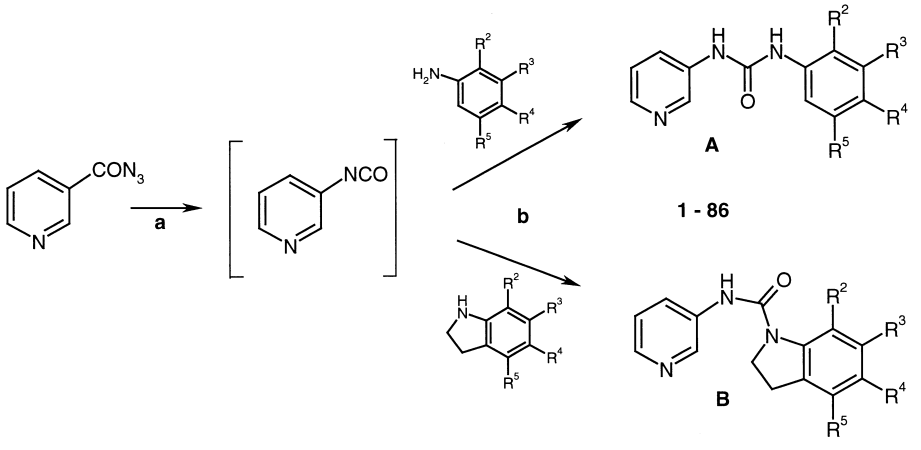
Results and Discussion

The affinities of the compounds were measured by means of radioligand binding studies conducted with cloned 5-HT_{2A} and 5-HT_{2C} receptors expressed in HEK 293 cells using [^{3}H]-ketanserin and [^{3}H]-mesulergine resepectively as radioligands,[10] and results are shown in Tables 1–5.

Considering the biaryl ureas (**1A**–**86A**), encouragingly, some of these compounds demonstrated comparable and even improved 5-HT_{2C} affinity relative to (**1A**) with a range of selectivities over 5-HT_{2A} activity (Tables 1–5). For the mono-substituted compounds (Table 1), whereas introduction of 2-substituents (**3**–**4A**) gave no increase in 5-HT_{2C} affinity relative to the unsubstituted analogue (**2A**), substitution at the 3- or 4-positions (**5**–**26A**) was generally beneficial. Small lipophilic groups were favoured over polar groups and several analogues (**5**, **7**, **11**, **17**, **20A**) were identified with affinities comparable to that of (**1A**). Whereas electron withdrawing lipophilic 3-substituents (**5**, **7A**) were marginally favoured over electron donating lipophilic groups, the reverse was the case for 4-substitution where the thiomethylphenyl urea (**20A**) demonstrated the highest affinity. This compound together with the 4-phenyl analogue (**17A**) also demonstrated encouraging selectivity over 5-HT_{2A} activity. As a consequence of the relatively free rotation about the *N*-aryl bond of the phenyl urea series (**A**) the 3- and 5-positions are equivalent. Thus, the 3-chlorophenyl urea (**5A**) could be considered to correspond to both the 6- and 4-chloro-1-(3-pyridylcarbamoyl) indolines (**5B** and **6B**). However, in all cases where a comparison is available, the 6-substituted indolines had higher 5-HT_{2C} affinity than the corre-

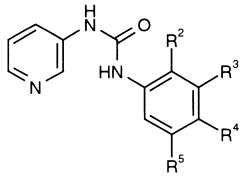


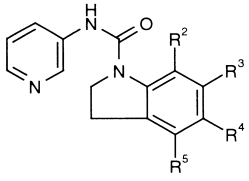
Compound	**1A** (SB-200646)	**1B** (SB-206553)
pKi 5-HT_{2C}	7.0	8.0
sel. *vs* 5-HT_{2A}	50	120
ID_{50} *vs* mCPP	20 mg/kg	5.5 mg/kg



Scheme 1. Reagents: (a) toulene, reflux, 0.5 h; (b) dichloromethane, room temperature, 16 h (50–90%).

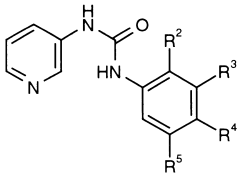
Table 1. The 5-HT_{2C} receptor binding affinities[13,14] and selectivities over 5-HT_{2A} of mono-substituted phenyl (**A**) and indolinyl (**B**) ureas

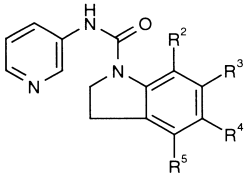




R^2	R^3	R^4	R^5	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$
	N-Me-pyrrolo-			**1A**	7.0	50	**1B**	7.9	160
H	H	H	H	**2A**	< 5.3	—	**2B**	5.9	
Cl	H	H	H	**3A**	< 5.3	—			
OMe	H	H	H	**4A**	IA	—			
H	Cl	H	H	**5A**	7.0	50	**5B**	7.3	13
H	H	H	Cl				**6B**	6.3	9
H	CF_3	H	H	**7A**	6.9	25	**7B**	7.3	12
H	Me	H	H	**8A**	5.7	—			
H	Ph	H	H	**9A**	6.4	6			
H	OMe	H	H	**10A**	5.8	—			
H	SMe	H	H	**11A**	6.7	25			
H	SO_2Me	H	H	**12A**	5.7	—			
H	NO_2	H	H	**13A**	5.9	—			
H	H	Cl	H	**14A**	6.4	—	**14B**	7.1	30
H	H	Me	H	**15A**	6.1	—	**15B**	6.8	30
H	H	^{i}Pr	H	**16A**	6.1	—	**16B**	7.1	25
H	H	Ph	H	**17A**	7.0	60	**17B**	6.9	45
H	H	OMe	H	**18A**	5.6	—			
H	H	OBz	H	**19A**	5.6	—			
H	H	SMe	H	**20A**	7.2	75	**20B**	7.4	110
H	H	NMe_2	H	**21A**	6.5	20	**21B**	6.5	20
H	H	NAcMe	H	**22A**	5.3	—			
H	H	COOEt	H	**23A**	6.5	40			
H	H	COOH	H	**24A**	< 5	—			
H	H	OH	H	**25A**	5.2	—			
H	H	NO_2	H	**26A**	< 6	—	**26B**	6.5	> 20

Table 2. The 5-HT_{2C} receptor binding affinities[13,14] and selectivities over 5-HT_{2A} of disubstituted phenyl (**A**) and indolinyl (**B**) ureas



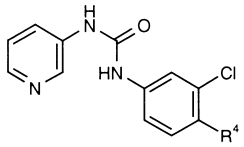


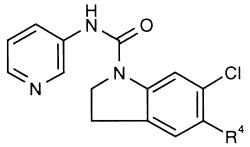
R^2	R^3	R^4	R^5	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$
CN	Cl	H	H	**27A**	< 5	—			
Cl	Cl	H	H	**28A**	< 6.0	—	**28B**	6.1	7
OMe	H	CF_3	H	**29A**	6.6	3			
Me	H	NO_2	H	**30A**	6.5	8			
OMe	H	H	OMe	**31A**	5.9	—			
OMe	H	H	Cl	**32A**	6.3	7			
H	Cl	H	Cl	**33A**	5.7	—			

sponding 4-substituted isomer and apart from (**6B**) only the former have been included in this discussion.

The results of disubstitution are shown in Tables 2–4. In the case of 2,3-, 2,4- and 2,5-disubstitution (Table 2) compounds had low to moderate 5-HT_{2C} affinity confirming the deleterious effect of an *ortho* substituent. This may be due to a steric effect resulting in an unfavourable out of plane conformation of the urea linker relative to the aryl ring. The 3,5-dichlorophenyl urea (**33A**) also had low affinity. In contrast, 3,4-disubstitution (Tables 3 and 4) conveyed an additive effect on 5-HT_{2C} affinity resulting in compounds with improved affinity relative to (**1A**). This substitution pattern corresponds to the position of the fused pyrrolo-functionality of (**1A**) and was favoured over mono-substitution. Having established early on in this work that a 3-halogen substituent was optimal, a series of 3-chloro analogues containing a wide range of 4-substituents was prepared (Table 3) in order to more fully investigate SAR at this position. As

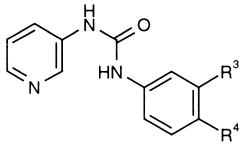
Table 3. The 5-HT_{2C} receptor binding affinities[13,14] and selectivities over 5-HT_{2A} of 3-chloro-4-substituted phenyl (**A**) and 6-chloro-5-substituted indoline (**B**) ureas

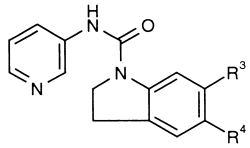




R^4	π of R^4	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$
H	0	**34A**	< 5.3	—	**34B**	5.9	
SO_2Me	−1.63	**35A**	5.0	—			
SOMe	−1.58	**36A**	5.0	—			
SO_2F	0.05	**37A**	7	20			
SO_2NMe_2	—	**38A**	6.5	12			
$CONH_2$	−1.49	**39A**	5.1	—			
CHO	−0.65	**40A**	6.4	12			
CH_2OH	−1.03	**41A**	5.5	—			
COMe	−0.55	**42A**	6.6	25			
COPh	—	**43A**	6.1	3			
COOH	−0.32	**44A**	7.1	80			
COOMe	−0.01	**45A**	7.4	200	**45B**	7.5	190
COOEt	0.51	**46A**	7.1	40			
CN	−0.57	**47A**	5.9	—			
OMe	−0.02	**48A**	6.7	30			
NMe_2	0.18	**49A**	6.4	20			
Me	0.56	**50A**	7.8	40	**50B**	8.2	25
Et	1.02	**51A**	7.4	25	**51B**	8.3	75
^{i}Pr	1.53	**52A**	7.4	75	**52B**	7.7	110
^{n}Pr	1.55	**53A**	7.4	30	**53B**	7.7	60
^{t}Bu	1.98	**54A**	7.2	20	**54B**	7.7	30
Ph	—	**55A**	6.6	10	**55B**	6.9	30
$CH{=}CH_2$	0.82	**56A**	7.3	50	**56B**	8.2	80
SMe	0.61	**57A**	7.5	120	**57B**	8.2	200
SEt	1.07	**58A**	7.8	200	**58B**	8.5	370
S^{i}Pr	—	**59A**	7.3	7.0	**59B**	8.0	510
SCF_3	—	**60A**	7.1	80			
Cl	0.71	**61A**	7.5	50	**61B**	8.1	30

Table 4. The 5-HT_{2C} receptor binding affinities[13,14] and selectivities over 5-HT_{2A} of 3-disubstituted phenyl (**A**) and 5,6-disubstituted indolinyl (**B**) ureas





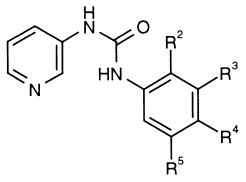
R^3	R^4	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$	Cpd.	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$
F	Me	**62A**	6.7	—	**62B**	7.3	25
Br	Me	**63A**	7.8	70	**63B**	8.4	20
Br	SMe	**64A**	7.9	210	**64B**	8.7	215
Br	SEt	**65A**	8.0	160	**65B**	8.7	1000
I	Me	**66A**	8.4	25	**66B**	8.5	25
CF_3	OEt	**67A**	7.6	250	**67B**	8.2	275
CF_3	Cl	**68A**	7.8	25	**68B**	8.2	25
CF_3	CH_2OEt	**69A**	6.8	40			
CF_3	NO_2	**70A**	6.8	—			
Me	Me	**71A**	6.8	40			
OMe	COOMe	**72A**	5.7	3			
COOEt	CH_2OMe	**73A**	5.7	8			
COMe	SO_2NMe_2	**74A**	5.4	5			
CH_2OMe	Me	**75A**	5.8	7			
OH	CO_2Ph	**76A**	5.6	3			
OH	COMe	**77A**	7.1	70			
OH	COOH	**78A**	5.5	—			
OH	COOMe	**79A**	7.2	90			
CONHEt	CH_2OMe	**80A**	< 5.2	—			

for the 4-mono-substituted ureas small lipophilic substituents (e.g. **50**, **57**, **58**, **61A**) were favoured with polar groups poorly tolerated (e.g. **35**, **36**, **39A**). Considering that the simple aryl ureas have relatively free rotation about the *N*-aryl bond, and hence the measured pK_i is probably a composite of at least two possible binding modes, a good correlation was observed between the lipophilicity (π)[13,14] of small 4-substituents and 5-HT_{2C} binding affinity (Fig. 1). Most of these compounds had improved 5-HT_{2C} affinity relative to (**1A**) and several such as the 3-chloro-4-thioalkylphenyl ureas (**57A** and **58A**) were identified with good 5-HT_{2C} affinities and >100-fold selectivity over 5-HT_{2A} receptor affinity.

Table 4 shows the activity of other 3,4-disubstituted phenyl ureas. As for 3-monosubstitution small lipophilic electron withdrawing groups are favoured with bromo (**63**–**65A**), iodo (**66A**) and trifluoromethyl (**67**–**68A**) giving compounds with good 5-HT_{2C} affinity when in combination with small lipophillic 4-substituents. The 3-bromo-4-thioalkyl (**64A** and **65A**) and the 3-trifluoromethyl-5-ethoxy (**67A**) phenyl ureas demonstrated good 5-HT_{2C} affinity and selectivity. The trisubstituted analogues (Table 5) demonstrated moderate 5-HT_{2C} affinity and low selectivity.

Having rapidly delineated SAR in our model series (**A**), favourable substitution patterns were then incorporated into the indolinyl series (**B**) together with a small number of less favourable combinations in order to confirm a correlation between the two series. As hoped, the indolines generally demonstrated improved 5-HT_{2C} affinity with comparable or improved selectivities over 5-HT_{2A} receptors relative to the model phenyl urea series (**A**) (Tables 1–4). The validity of extrapolating from the less active phenyl urea series was confirmed by a plot of the 5-HT_{2C} affinities of corresponding compounds from the two series (Fig. 2), which revealed an excellent correlation (r = 0.927). In all cases, apart from (**17**) (R^4 = Ph), the indolines were more potent than the corresponding phenyl ureas with an average increase in the 5-HT_{2C} pK_i of 0.5. Several 5,6-disubstituted indolines (**57**–**59B**, **64**–**65B** and **67B**) were identified with affinities and selectivities greater than (**1B**). Especially outstanding was the 6-bromo-5-thioethyl indoline (**65B**) which had a 5-HT_{2C} binding affinity of 2 nM and a selectivity against the 5-HT_{2A} receptor of 1000-fold. We have proposed[15] that the thioalkyl substituent is conferring the desired selectivity by occupying a region of space which is "allowed" for the 5-HT_{2C} receptor but "disallowed" for the 5-HT_{2A} receptor due to steric differences between the structures of the two binding sites. In addition, several compounds (**58B**, **64B** and **65B**) were tested against a range of other monoamine receptors, including serotinergic and dopaminergic subtypes, and found to be greater than 100-fold selective. The synthesis, biological profile, QSAR relationships and molecular modelling of these inolinyl ureas are the subjects of a separate publication.[15]

Table 5. The 5-HT_{2C} receptor binding affinities[13,14] and 5-HT_{2A} selectivities of trisubstituted phenyl ureas (**A**)



Cpd.	R^2	R^3	R^4	R^5	5-HT_{2C} (pK_i)	Selectivity 5-$HT_{2C/2A}$
81A	Cl	Cl	Cl	H	5.5	
82A	Me	H	SMe	Cl	7.7	15
83A	Me	H	NO_2	Me	6.6	10
84A	Me	H	SEt	Cl	7.7	15
85A	H	Cl	Me	Cl	5.5	
86A	H	Cl	OH	Cl	5.6	

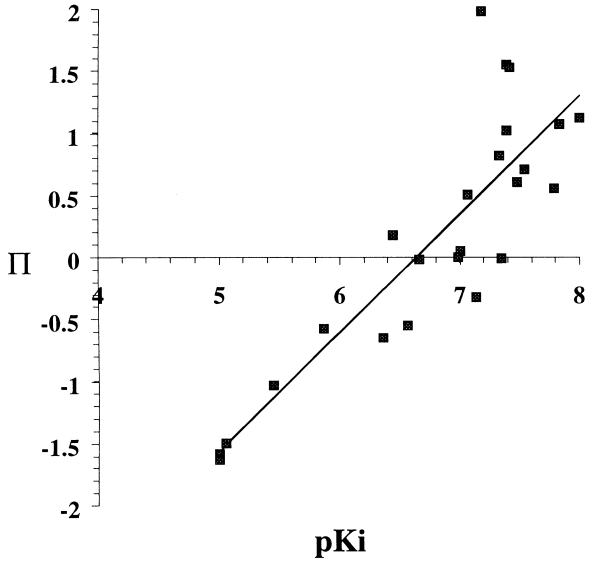


Figure 1. Plot of the 5-HT_{2C} receptor binding affinities of 3-chloro-4-substituted phenyl ureas against the lipophilicity (π) of the 4-substituent (Table 3).

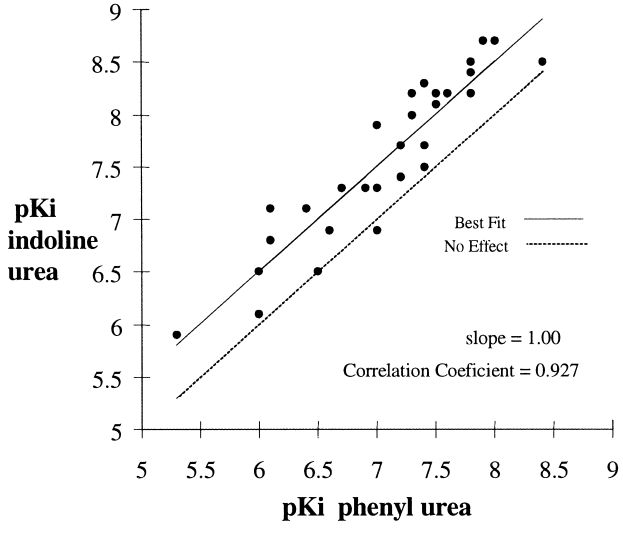


Figure 2. Plot of the corresponding 5-HT_{2C} binding affinities of substituted phenyl (**A**) and indolinyl (**B**) ureas.

Summary

In conclusion we have used a synthetically accessible model series of phenyl ureas (**A**) to generate a large data set of 5-HT_{2C} binding affinities and selectivities and rapidly elucidate SAR. Extrapolation of these results to the more active but synthetically complex 1-(3-pyridylcarbamoyl) indoline series (**B**) allowed us to target optimal substitution patterns and identify potent and selective 5-$HT_{2C/2B}$ antagonists such as (**57**–**59B**, **64**–**65B** and **67B**).

Experimental

Melting points are uncorrected. The elemental analyses were within 0.4% of the theoretical values. HPLC analysis of test compounds was carried out on a Gilson 712 HPLC system, using a model 231 sample injector, 306 pump with 806 manomeric module detector. A Hypersil BDS C18 3 μM (100×3 mm i.d.) column was used with elution under the following conditions: eluant A 0.1% TFA/H_2O v/v, eluant B 0.1% TFA/CH_3CN v/v; flow rate 0.7 mL/min. The elution gradient was 0% B held for 0.5 min, then linearly increased to 75% B over 24.5 min, then held for 5 min. The UV detection wavelength was 218 nm. All final compounds were greater than 95% pure as judged by area under the curve. NMR spectra were recorded on a Bruker AC-200, AC-250 or AM-400 spectrometer using Me_4Si as internal standard. Electron impact mass spectra were determined using a Fisons VG 302 single quadrupole mass spectrometer. Solvents and reagents were of commercial grade and used without purification. Chromatography where required was performed on Merck Art. 7734 silica gel or Fluka silica gel 60 (60739).

The compounds were prepared from commercially available or known anilines and indolines[12] according to the following general procedure. The preparations of (**50A**) and (**26B**) are detailed as representative examples. NMR spectral data and melting points of representative phenyl ureas are illustrated in Table 6.

***N*-(3-Chloro-4-methylphenyl)-*N′*-(3-pyridyl) urea (50A).** Nicotinoyl azide (0.40 g, 2.7 mmol) [**CAUTION!** Heating this material in the absence of solvent can lead to explosive decomposition. Larger-scale (ca. 20 g or above) preparations following this procedure are noticeably exothermic on reaching 70–80°C, and copious volumes of nitrogen are rapidly evolved. Appropriate precautions for the storage and utilisation of this reagent are strongly advised] was stirred at reflux under nitrogen atmosphere in dry toluene (10 mL) for 1 h, with gas evolution. The solution was cooled to ambient temperature, and 3-chloro-4-methylaniline (0.30 mL, 2.4 mmol) was added. The resultant suspension was stirred for 1 h, when the solid was filtered off, washed with 1:1 toluene/dichloromethane, and dried in vacuo at 70°C. This gave the title compound (0.64 g, 85%) as a white solid. The hydrochloride salt

Table 6. ^1H NMR spectral data and melting points of some representative phenyl ureas (**A**)

Cmpd.	^1H NMR (d_6-DMSO δ: ppm J = Hz)	mp (°C)
7A	7.3 (2H, m), 7.55 (2H, m), 7.95 (1H, d, J = 8), 8.0 (1H, s), 8.2 (1H, d, J = 4), 8.6 (1H, d, J = 2), 9.0 (1H, s), 9.2 (1H, s)	180–184
8A (HCl)	2.3 (3H, s), 6.85 (1H, d, J = 7), 7.2 (1H, t, J = 8), 7.3 (2H, m), 7.9 (1H, dd, J = 8.5), 8.3 (1H, m), 8.5 (1H, d, J = 5), 9.1 (1H, d, J = 2), 9.5 (1H, s), 10.35 (1H, s)	182–183
14A	7.3 (3H, m), 7.5 (2H, d, J = 9), 7.95 (1H, m), 8.2 (1H, m), 8.6 (1H, d, J = 2), 8.9 (1H, s), 9.0 (1H, s)	207–209
5A	7.0 (1H, m), 7.3 (3H, m), 7.7 (1H, s), 7.95 (1H, m), 8.2 (1H, m), 8.6 (1H, d, J = 2), 8.95 (1H, s), 9.05 (1H, s)	185–187
61A	7.25–7.42 (2H, m), 7.50 (1H, d, J = 7), 7.83–7.90 (2H, m), 8.23 (1H, d, J = 3), 8.62 (1H, d, J = 1), 8.98 (1H, s), 9.23 (1H, s)	206–210
62A	7.02–7.48 (4H, m), 7.94 (1H, m), 8.19 (1H, m), 8.59 (1H, m), 8.87 (1H, s), 8.92 (1H, s)	190–191
23A	1.32 (3H, t, J = 8), 4.30 (2H, q, J = 8), 7.34 (1H, dd, J = 7.4), 7.60 (2H, m), 7.86–8.02 (3H, m), 8.21 (1H, m), 8.63 (1H, m), 8.96 (1H, s), 9.24 (1H, s)	156–160
45A	3.82 (3H, s), 7.30 (2H, m), 7.78–8.00 (3H, m), 8.25 (1H, m), 8.64 (1H, m), 9.08 (1H, s), 9.39 (1H, s)	170–171
63A	2.28 (3H, s), 7.21–7.39 (3H, m), 7.83–8.00 (2H, m), 8.20 (1H, m), 8.61 (1H, m), 8.89 (2H, m)	168–171
47A	7.28–7.56 (2H, m), 7.80–8.06 (3H, m), 8.26 (1H, m), 8.64 (1H, s), 9.17 (1H, s), 9.54 (1H, s)	262–264
70A	7.37 (1H, dd, J = 7.4), 7.87 (1H, m, J = 7), 7.97 (1H, m, J = 7), 8.14–8.29 (3H, m), 8.67 (1H, m), 9.22 (1H, s), 9.81 (1H, s)	214–216
68A	7.33 (1H, dd, J = 7.4), 7.59–7.71 (2H, m), 7.95 (1H, m), 8.10 (1H, m), 8.22 (1H, m), 8.63 (1H, m), 9.04 (1H, s), 9.32 (1H, s)	196–199
43A	7.41 (2H, m), 7.76–7.88 (2H, m), 7.99 (1H, d, J = 7), 8.25 (1H, br.s), 8.68 (1H, br.s), 9.13 (1H, s), 9.37 (1H, s)	170–175
29A	4.00 (3H, s), 7.16–7.45 (3H, m), 7.98 (1H, m, J = 7 Hz), 8.23 (1H, m), 8.48–874 (3H, m), 9.60 (1H, s)	210
51A	1.16 (3H, t, J = 5), 2.64 (2H, q, J = 5), 7.20–7.40 (3H, m), 7.67 (1H, s), 7.94 (1H, m), 8.20 (1H, d, J = 2), 8.60 (1H, d, J = 1), 8.90 (2H, m)	193–196
53A	0.91 (3H, t, J = 5), 1.56 (2H, q, J = 5), 2.60 (2H, t, J = 5), 7.20–7.35 (3H, m), 7.68 (1H, s), 7.94 (1H, m), 8.19 (1H, d, J = 2), 8.59 (1H, d, J = 1), 8.92 (2H, m)	184–186
54A	1.42 (9H, s), 7.20–7.40 (3H, m), 7.66 (1H, d, J = 2), 7.93 (1H, m), 8.19 (1H, d, J = 5), 8.60 (1H, d, J = 2), 8.90 (2H, m)	190–193

was prepared as a white solid, mp 214.5–216°C. NMR (d_6-DMSO) δ: 2.25 (3H, s), 7.25 (2H, m), 7.68 (1H, s), 7.92 (1H, dd, $J=8$, 5 Hz), 8.33 (1H, d, $J=8$ Hz), 8.49 (1H, d), 9.07 (1H, s), 9.79 (1H, s), 10.37 (1H, s). C,H,N anal. Found: C, 51.4%; H, 4.5%; N, 14.5%. $C_{13}H_{12}ClN_3O{\cdot}HCl{\cdot}0.25H_2O$ requires C, 51.6%; H, 4.5%; N, 13.9%

5-Nitro-1-(3-pyridylcarbamoyl)indoline hydrochloride (26B). A solution of nicotinic acid azide (0.43 g, 2.9 mmol) [**CAUTION!** Heating this material in the absence of solvent can lead to explosive decomposition. Larger-scale (ca. 20 g or above) preparations following this procedure are noticeably exothermic on reaching 70–80°C, and copious volumes of nitrogen are rapidly evolved. Appropriate precautions for the storage and utilisation of this reagent are strongly advised] in toluene (20 mL) was heated at reflux for 0.5 h to form 3-pyridylisocyanate, then cooled to room temperature. A solution of 5-nitroindoline (0.38 g, 2.3 mmol) in dichloromethane (20 mL) was then added and the mixture was stirred overnight at room temperature. The resulting precipitate was treated with excess HCl in ether to give the title compound (**26B**) (0.64 g, 76%) as a light yellow powder, mp 244–247°C (dec.). NMR (d_6-DMSO) δ: 3.32 (2H, t, $J=8$ Hz), 4.35 (2H, t, $J=8$ Hz), 7.8–8.2 (4H, m), 8.5–8.65 (2H, m), 9.14 (1H, d, $J=2$ Hz), 9.78 (1H, s). MS *m/e* 284.0894 (M^+): $C_{14}H_{12}N_4O_3$ requires 284.0909.

References and Notes

1. Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. A. *Pharmacological Reviews* **1994**, *46*, 157.
2. Baxter, G.; Kennett, G. A.; Blaney, F.; Blackburn, T. P. *Trends Pharmacol. Sci.* **1995**, *16*, 105.
3. Kahn, R. S.; Wetzler, S. *Biol. Psychiat.* **1991**, *30*, 1139.
4. Kennett, G. A. *Curr. Opin. Invest. Drugs* **1993**, *2*, 317 and references therein.
5. Kennett, G. A.; Pittaway, K.; Blackburn, T. P. *Psychopharmacology* **1994**, *114*, 90.
6. Moreau, J. L.; Bos, M.; Jenck, F.; Martin, J. R.; Mortas, P.; Wichmann, J. *Eur. Neuropsychopharmacology* **1996**, *6*, 169.
7. Bonhaus, D. W.; Weinhardt, K. K.; Taylor, M.; DeSouza, A.; McNeeley, P. M.; Szczepanski, K.; Fontana, D. J.; Trinh, J.; Rocha, C. L.; Dawson, M. W.; Cao, Z.; Wong, L.; Eglen, R. M. *CNS Drug Reviews* **1997**, *3*, 278.
8. Forbes, I. T.; Kennett, G. A.; Gadre, A.; Ham, P.; Hayward, C. J.; Martin, R. T.; Thompson, M.; Wood, M. D.; Baxter, G. S.; Glen, A.; Murphy, O. E.; Stewart, B. A.; Blackburn, T. P. *J. Med. Chem.* **1993**, *36*, 1104.
9. Forbes, I. T.; Dabbs, S.; Duckworth, D. M.; Ham, P.; Jones, G. E.; King, F. D.; Saunders, D. V.; Blaney, F. E.; Naylor, C. B.; Baxter, G. S.; Blackburn, T. P.; Kennett, G. A.; Wood, M. D. *J. Med. Chem.* **1996**, *39*, 4966.
10. Kennett, G. A.; Wood, M. D.; Bright, F.; Cilia, J.; Piper, D. C.; Gager, T.; Thomas, D.; Baxter, G. S.; Forbes, I. T.; Ham, P.; Blackburn, T. P. *Br. J. Pharmacol.* **1996**, *117*, 427.
11. Unpublished results; Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham.
12. All values represent the mean of at least two determinations, with each determination lying within 0.2 log unit of the mean. 5-HT_{2C} binding affinity: human cloned receptors; HEK 293 cells; [^{3}H]-ketanserin. 5-HT_{2A} binding affinity: human cloned receptors; HEK 293 cells; [^{3}H]-mesulergine.
13. Hansch, C.; Leo, A.J. In *Substituent Constants for Correlation Analysis*; Wiley: New York, 1979.
14. Abraham, M.H. *Chem. Soc. Rev.* **1993**, 73.
15. Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Ham, P.; Jones, G. E.; King, F. D.; Saunders, D. V.; Starr, S.; Thewlis, K. M.; Wyman, P. A.; Blaney, F. E.; Naylor, C. B.; Bailey, F.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **1998**, *41*, 1598.