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Structure–activity studies of a novel series of 5,6-fused heteroaromatic ureas as TRPV1 antagonists

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Abstract—Novel 5,6-fused heteroaromatic ureas were synthesized and evaluated for their activity as TRPV1 antagonists. It was found that 4-aminoindoles and indazoles are the preferential cores for the attachment of ureas. Bulky electron-withdrawing groups in the *para*-position of the aromatic ring of the urea substituents imparted the best in vitro potency at TRPV1. The most potent derivatives were assessed in in vivo inflammatory and neuropathic pain models. Compound **46**, containing the indazole core and a 3,4-dichlorophenyl group appended to it via a urea linker, demonstrated in vivo analgesic activity upon oral administration. This derivative also showed selectivity versus other receptors in the CEREP screen and exhibited acceptable cardiovascular safety at levels exceeding the therapeutic dose.

1. Introduction

The capsaicin-sensitive TRPV1 receptor is a member of the mammalian transient receptor potential (TRP) channel family and is highly expressed on small diameter (C-fiber) nociceptive sensory neurons. It is also expressed at lower levels in other non-neuronal tissues such as skin and bladder.[1] This receptor has been called a polymodal detector of noxious stimuli since it can be activated in several ways. Low pH, heat,[2,3] and vanilloid ligands such as capsaicin and resiniferatoxin[4] activate TRPV1 causing burning pain sensation. Endogenous mediators of inflammation, such as the cannabinoid anandamide[5] and arachidonic acid metabolites[6] can also activate TRPV1.

Interest in the TRPV1 receptor as a therapeutic target has been driven in part by the observation that 'knock-out' mice lacking this receptor exhibited deficits chemically or inflammatory-evoked thermal hyperalgesia.[7,8] Until recently, agonists were the major focus of research, but the therapeutic effect of such agents was compromised by an initial burning effect, possibly due to receptor desensitization.[9] Moreover, attempts to separate analgesic and excitatory effect were not successful.[10] The alternative approach of developing competitive TRPV1 antagonists, which do not cause initial painful sensation, is being extensively pursued,[11] as evidenced by the burgeoning number of publications on the subject.[12–15] A recently published article[16] detailed our efforts in identifying TRPV1 antagonists within a series of 6,6-fused heteroaromatic ureas. Herein we examine the transition to 5,6-fused heteroaromatic rings, such as indole, indazole, and benzimidazole (Chart 1), and discuss the structure–activity relationships associated with this group of novel chemotypes.

2. Chemistry

The synthesis of urea derivatives could be accomplished via Method A (Scheme 1) where the aminoindole **1**, aminoindazoles **2–5**, or benzimidazole **6** was reacted

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Keywords: TRPV1 antagonists; Indole and indazole benzyl ureas.

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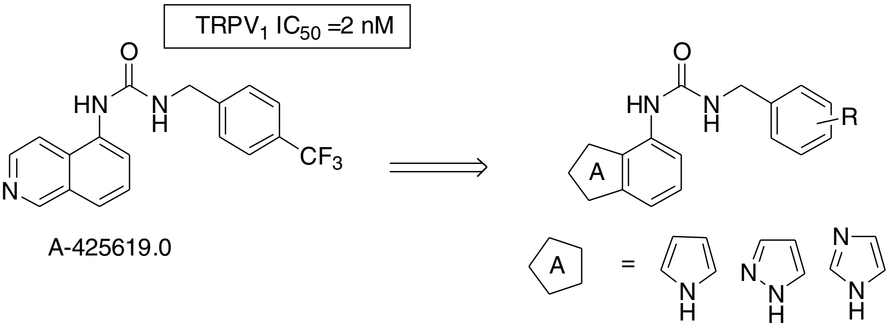
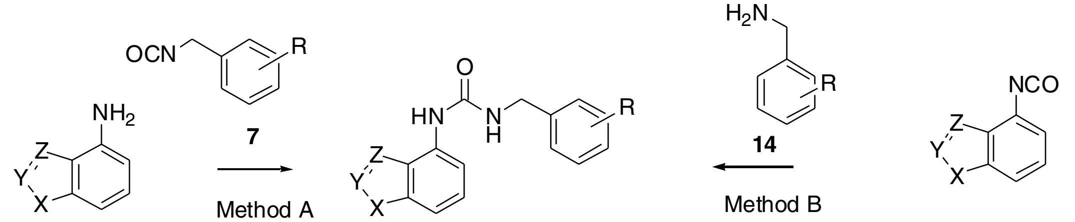


Chart 1.



1 X = NH, Y = CH, Z = CH
2 X = $NCOOCH_3$, Y = N, Z=CH
3 X = NH, Y = N, Z = CH
4 X = NCH_3, Y = N, Z = CH
5 X = N,Y = NCH_3, Z = CH
6 X = $NCOOCH_3$, Y = CH, Z=N

8 X = NH, Y = CH, Z = CH
9 X = $NCOOCH_3$, Y = N, Z = CH
10 X = NH, Y = N, Z = CH
11 X = NCH_3, Y = N, Z = CH
12 X = N,Y = NCH_3, Z = CH
13 X = $NCOOCH_3$,Y = CH, Z=N

15 X = NH, Y= CH, Z = CH
16 X = $NCOOCH_3$, Y = N, Z = CH
17 X = NH, Y = N, Z = CH
18 X = NCH_3, Y = N, Z = CH
19 X = N, Y = NCH_3, Z = CH

Scheme 1.

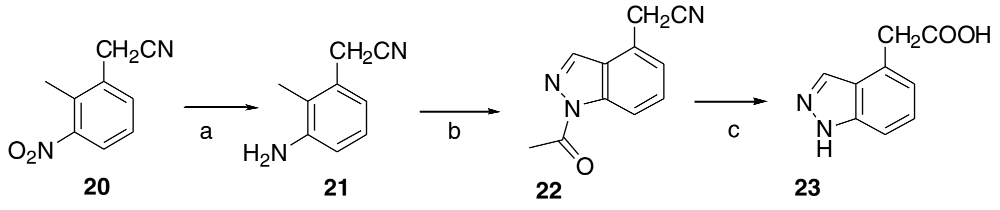
with the various commercially available isocyanates **7**. Reaction of 4-aminoindazoles **3** with isocyanates **7** resulted in the mixture of products generated by the addition of the nitrogen of the ring to the isocyanate. To circumvent this, the urea formation was carried out on the protected indazole **2**.

Method B (Scheme 1) entailed the formation of the isocyanates **15**–**19** by the reaction of the corresponding heterocyclic amines with 20% phosgene solution in toluene. Subsequent reaction with amines **14**, available commercially or synthesized following published procedures, provided ureas **8**–**12**. The formation of isocyanates on the unprotected indazole was not successful, thus **2** was converted to the desired intermediate **16**, prior to reaction with **14**. The deprotection of the intermediate **9** was accomplished with the ethanolic solution of NaOH.

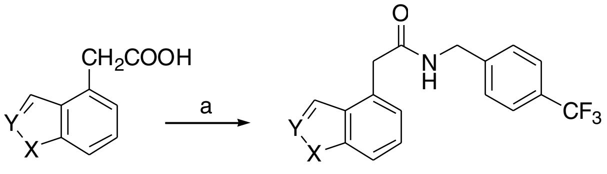
The synthesis of the requisite precursor indazole acid **23** is outlined in Scheme 2. 3-Nitro-2-methyl-phenylacetonitrile[17] **20** was reduced to the corresponding aminoderivative **21** with $NaBH_4$ in the presence of $BiCl_3$.[18] Cyclization to the indazole derivative **22** was accomplished by treatment of **21** with isoamyl nitrite in the presence of acetic anhydride, analogous to the method of Ruchardt and Hassmann[19] Treatment of **22** with base and hydrogen peroxide yielded the desired **23**. Indole acetic acid **24** was synthesized according to literature procedure,[20] and the carbamates **27** were formed by the reaction of indole isocyanate **15** with the corresponding alcohols (Schemes 3 and 4).

3. Results and discussion

In our earlier publication[16] we have described a new series of TRPV1 antagonists bearing various 6,6-bicyclic core structures. The lead compound of that series, A-425619.0, demonstrated in vivo activity in several chronic pain models. Our goal was to expand this series to include 5,6-heterocyclic cores and to study the SAR (Chart 2) that could be broken into three parts: core



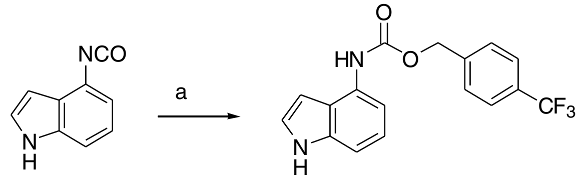
Scheme 2. Reagents and conditions: (a) $NaBH_4$, $BiCl_3$, EtOH, rt; (b) isoamylnitrite, $(CH_3CO)_2O$; (c) H_2O_2/KOH, EtOH, reflux.



23 X = NH, Y = N
24 X = NH, Y = CH

25 X = NH, Y = N
26 X = NH, Y = CH

Scheme 3. Reagents and condition: (a) 4-(trifluromethyl)benzylamine, EDCl, HOAT, THF, rt.



15

27

Scheme 4. Reagents and condition: (a) 4-(trifluoromethyl)benzyl alcohol, THF, reflux.

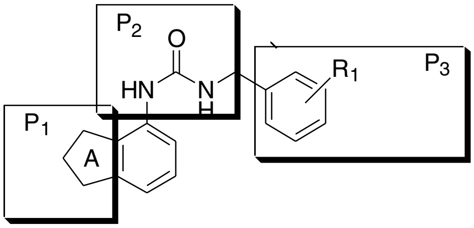
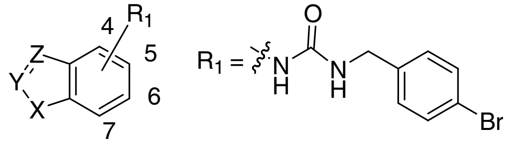


Chart 2.

replacement (P1 region), modification of the linker (P2 region), and benzyl fragment (P3 region). Compounds were evaluated in vitro for their ability to block activation of the recombinant human TRPV1 receptor by capsaicin.

The replacement of isoquinoline ring of the previously identified lead structure with 5,6-heteroaromatic cores resulted in several TRPV1 antagonists that were equipotent to the isoquinoline analogs (Table 1). The site of benzyl attachment to the heteroaromatic fragment is important for the in vitro TRPV1 activity, evidenced by superiority of the 4- and 7-substituted indole ureas **28** and **31** relative to 5- or 6-substituted analogs **29** and **30**. A 10-fold improvement in potency was realized by the introduction of the second nitrogen atom in the ring as in **32**. The position of the second nitrogen atom in relationship to the urea moiety is crucial for the potency at the TRPV1 receptor, since the gains in potency achieved for the indazole **32** were lost in the benzimidazole analog **37**. As demonstrated with the indoles, preferential point of the attachment of the urea is at the 4-position, as illustrated by the comparison of **32** to **33**. Introduction of a methyl group to the indazole core was tolerated only in the 1-position as in **35**. 2-Methylindazole derivative **36** was significantly less potent; addition of the second methyl group as in indole **34** had a similar negative impact.

Table 1. SAR of heterocyclic ureas regioisomers

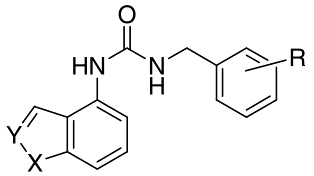


Compound	R$_1$ position	X	Y	Z	IC$_{50}$[a] (μM)
28	4	NH	CH	CH	0.11 ± 0.14
29	5	NH	CH	CH	5.85 ± 1.63
30	6	NH	CH	CH	3.01 ± 0.072[b]
31	7	NH	CH	CH	0.18 ± 0.04
32	4	NH	N	CH	0.013 ± 0.02
33	5	NH	N	CH	3.54 ± 0.12[b]
34	4	NH	C–CH$_3$	C–CH$_3$	1.47 ± 0.14[b]
35	4	N–CH$_3$	N	H	0.076 ± 0.003
36	4	NH	N–CH$_3$	H	1.39 ± 0.072
37	4	NH	CH	N	2.47 ± 0.072

[a] All values are means ± SEM of at least three separate experiments.
[b] Values are means of two experiments.

Having established the preferential position of urea moiety, we focused our attention on the P3 region of the molecule. As shown in Table 2, electron-withdrawing groups (4-CF$_3$ and 4-OCF$_3$) in the *para*-position of benzyl group (e.g., **39** and **40**) increased potency at the TRPV1 receptor. Introduction of the second substituent (e.g., **41** and **42**) was also tolerated. The importance of the size of the substituents is evident by decreased potency of the 4-F-derivative **45**. A similar substitution pattern in the indazole core resulted in the 4- to 6-fold

Table 2. SAR of indole and indazole benzyl ureas



Compound	X	Y	R	IC$_{50}$[a] (μM)
28	NH	CH	4-Br	0.11 ± 0.01
38	NH	CH	3,4-DiCl	0.22 ± 0.04
39	NH	CH	4-CF$_3$	0.06 ± 0.006
40	NH	CH	4-OCF$_3$	0.08 ± 0.01
41	NH	CH	3-F, 4-CF$_3$	0.04 ± 0.006
42	NH	CH	4-Cl, 3-CF$_3$	0.07 ± 0.01[b]
43	NH	CH	4-Cl	0.15 ± 0.011
44	NH	CH	3-F	2.70 ± 0.62[b]
45	NH	CH	4-F	2.71 ± 0.85
46	NH	N	3,4-DiCl	0.021 ± 0.006
32	NH	N	4-Br	0.012 ± 0.002
47	NH	N	4-CF$_3$	0.009 ± 0.001
48	NH	N	4-OCF$_3$	0.011 ± 0.004
49	NH	N	3-CF$_3$	0.044 ± 0.019
50	N–CH$_3$	N	4-OCF$_3$	0.035 ± 0.021
51	N–CH$_3$	N	4-Cl	0.06 ± 0.009
52	N–CH$_3$	N	4-F	0.72 ± 0.10
53	N–CH$_3$	N	3,4-DiCl	0.12 ± 0.019

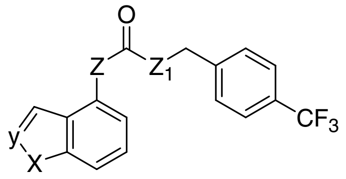
[a] All values are means ± SEM of at least three separate experiments.
[b] Values are means of two experiments.

increase in potency versus indole (**32**, **47**, and **48** vs **28**, **39**, and **40**). Bulky electron-withdrawing groups remain the preferential groups in the 1-methylindazole cores (**50** vs **52**).

As shown in Table 3, we addressed the modification of the P2 region with the intention of improving physicochemical properties of derivatives. Replacement of the urea linker with the amide (e.g., **25** and **26**) improved solubility (typically <1 µg/mL), but decreased the in vitro potency of compounds. This effect was more pronounced in case of indazole **25**. Replacement of urea moiety with the carbamate in **27** also led to lower potency and decreased stability.

Several potent TRPV1 antagonists from the new series were evaluated for their activity in the complete Freund's adjuvant (CFA) model of chronic inflammatory pain[21] (Table 4). Indole and indazole ureas were efficacious in this model with good correlation between in vitro and in vivo profiles. Indazole **46** was profiled more extensively based on its favorable pharmacokinetic properties (Table 5). It was characterized by low plasma clearance ($CL_p = 1.3$ L/h/kg), moderate oral bioavailability ($F = 24\%$), moderate volume of distribution ($V_\beta = 2.5$ L/kg) and, acceptable for this class of compounds, plasma elimination half-life ($t_{1/2} = 1.4$ h, iv administration). In addition to reducing thermal hyperalgesia in the CFA model ($ED_{50} = 30$ µmol/kg, po), **46** was also orally active in several other pain models,[22] such as the acetic acid-induced visceral pain model ($ED_{50} = 32$ µmol/kg) and the Chung model of neuropathic pain ($ED_{50} = 155$ µmol/kg). Assessment of locomotor activity upon oral administration of **46** showed no impairment.

Table 3. SAR of urea replacement



Compound	X	Y	Z	Z_1	IC_{50}[a] (µM)
25	NH	N	CH_2	NH	10.2 ± 4.0[b]
26	NH	CH	CH_2	NH	0.52 ± 0.04
27	NH	CH	NH	O	0.94 ± 0.04

[a] All values are means ± SEM of at least three separate experiments.
[b] Values are means of two experiments.

Table 4. Activity of indole and indazole ureas in CFA model of thermal hyperalgesia and PK properties

Compound	TRPV1 IC_{50}[a] (µM)	CFA ED_{50} (mg/kg), ip[b]	$t_{1/2}$ (h) (iv)[c]
46	0.021 ± 0.006	23	1.4
47	0.009 ± 0.001	22	1.5
39	0.059 ± 0.006	33	—
41	0.038 ± 0.006	25	1.5

[a] All values are means ± SEM of at least three separate experiments.
[b] The data represent means of $n = 6$–12 per dose group.
[c] Pharmacokinetic parameters determined in rats following administration of 10 µmol/kg.

Table 5. Analgesic effects[a] and PK[b] profile of **46**

Human TRPV1 IC_{50} (µM)	0.021 ± 0.006
Spontaneous exploratory behavior 300 µmol/kg po	Nonsignificant
CFA inflammatory pain ED_{50} (µmol/kg) po	30
Chung neuropathic pain ED_{50} (µmol/kg) po	155
Writhing visceral pain ED_{50} (µmol/kg) po	32
V_β (L/kg) (iv)	2.5
Clp (L/h/kg)	1.3
$t_{1/2}$ (h)	1.4
C_{max} (µg/mL) (ip)	0.36
F (%)	30.2
C_{max} (µg/mL) (po)	0.11
F (%)	23.8

[a] The data represent mean of $n = 6$–12 per dose group.
[b] Pharmacokinetic parameters determined in rats following administration of 10 µmol/kg.

With the exception of weak (micromolar) binding to the peripheral BZD receptor, in studies performed by CEREP (70-receptor panel), **46** was found to be highly selective for TRPV1 compared to a diverse set of neurotransmitter receptors, peptide receptors, ion channels, reuptake sites, and enzymes. Importantly, the cardiovascular side-effect profile of **46**, compiled in tests with anesthetized rats, showed no sustained changes in mean arterial pressure and heart rate at doses up to 30× therapeutic dose level.

4. Conclusion

To gain increased understanding of the structural requirements for TRPV1 antagonists, we studied a series of 5,6-fused heteroaromatic benzyl ureas. It was discovered that both indole and indazole ureas have the best potency when urea moiety is attached at the 4-position. Potency of 4-aminoindazole derivatives exceeded the one of comparable indole analogs. Methyl groups were tolerated only in the 1-position of indazole core. Large electron-withdrawing groups, such as CF_3, OCF_3, and 3,4-diCl, in the benzyl portion of the molecule afforded the most potent compounds in vitro. Improved pharmacokinetic properties of **46** led to its activity in several in vivo pain models upon oral administration. Compound **46** was characterized by lack of effect on heart rate and arterial blood pressure at doses exceeding the therapeutic level. Compound **46** did not have a negative effect on the locomotor activity of animals upon oral administration. Overall, these findings provide encouragement for the continuation of research in this field, with the aim of finding more potent TRPV1 antagonists with improved physico-chemical properties.

5. Experimental

5.1. Biology

5.1.1. In vitro assays. The functional activity of compounds at the TRPV1 receptor was determined with a Ca^{2+} influx assay and measurement of intracellular Ca^{2+} levels ($[Ca^{2+}]i$). All compounds were tested over an 11-point half-log concentration range. Compound solutions were prepared in D-PBS (4× final concentration) and diluted serially across 96-well v-bottomed tissue culture plates using a Biomek 2000 robotic automation workstation (Beckman-Coulter, Inc., Fullerton, CA). A 0.2 μM solution of the TRPV1 agonist capsaicin was also prepared in D-PBS. The fluorescent Ca^{2+}-chelating dye fluo-4 was used as an indicator of the relative levels of $[Ca^{2+}]$ in a 96-well format using a Fluorescence Imaging Plate Reader (FLIPR) (Molecular Devices, Sunnyvale, CA). Cells were grown to confluency in 96-well black-walled tissue culture plates. Then, prior to the assay, the cells were loaded with 100 μL per well of fluo-4 AM (2 μM, in D-PBS) for 1–2 h at 23 °C. Washing of the cells was performed to remove extracellular fluo-4 AM (2× 1 mL D-PBS per well), and afterward, the cells were placed in the reading chamber of the FLIPR instrument. Fifty microliters of the compound solutions was added to the cells at the 10 s time mark of the experimental run. Then, after a 3 min time delay, 50 μL of the capsaicin solution was added at the 190 s time mark (0.05 μM final concentration) (final volume = 200 μL) to activate the TRPV1 receptor. Time length of the experimental run was 240 s. Fluorescence readings were made at 1–5 s intervals over the course of the experimental run. The peak increase in relative fluorescence units (minus baseline) was calculated from the 190 s time mark to the end of the experimental run and expressed as a percentage of the 0.05 μM capsaicin (control) response. Curve-fits of the data were solved using a four-parameter logistic Hill equation in GraphPad Prism® (GraphPad Software, Inc., San Diego, CA), and IC_{50} values were calculated.

5.1.2. Complete Freund's adjuvant-induced thermal hyperalgesia. Unilateral inflammation was induced by injecting 150 μL of a 50% solution of complete Freund's adjuvant (CFA) (Sigma Chemical Co., St. Louis, MO) in physiological saline into the plantar surface of the right hind paw of the rat. The hyperalgesia to thermal stimulation was determined 48 h after CFA injections as previously described.[21,22]

5.1.3. Abdominal constriction assay in CD1 mice. Each animal received an intraperitoneal injection of 0.3 mL of 0.6% acetic acid in normal saline to evoke writhing. Abdominal constriction was defined as a mild constriction and elongation passing caudally along the abdominal wall, accompanied by a slight twisting of the trunk and followed by bilateral extension of the hind limbs. The total number of abdominal constrictions was recorded from 5 to 20 min after acetic acid injection. Compound **46** was administered orally 1 h prior to acetic acid injection.

5.1.4. Chung neuropathic pain model. The Chung model consisted in a tight ligation of the L5 and L6 spinal nerves with 3-0 silk threads. Following hemostasis, the wound was sutured and coated with antibiotic ointment. The rats were allowed to recover and then placed in a cage with soft bedding for 14 days before behavioral testing for mechanical allodynia using calibrated von Frey filaments (Stoelting, Wood Dale, Il).

5.1.5. Assessment of locomotor function. Locomotor activity was measured in an open field using photobeam activity monitors (AccuScan Instruments, Columbus, OH). The compound was administered orally 1 h before putting the rats in the locomotor boxes and exploratory behavior was recorded for 30 min.

5.1.6. Assessment of cardiovascular safety. Male, Sprague–Dawley, inactin-anesthetized rats were prepared to measure mean arterial pressure and heart rate. Following a 30-min control period, TRPV1 antagonist or vehicle (PEG400) was administered intravenously over five, 30-min infusions at 1×, 3×, 10×, 30×, 100× of calculated therapeutic dose. A blood sample and hematocrit were collected immediately after the 100× infusion.

5.2. Chemistry

Proton NMR spectra were obtained on a General Electric QE 300 or QZ300 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. Robertson Microlit Laboratories performed elemental analyses. 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. All physical data and yields for final compounds correspond to the indicated salt form unless otherwise noted.

5.2.1. 3-Amino-2-methyl-phenylacetonitrile (21). To a solution of **20**[17] (1 g, 5.7 mmol) in EtOH (50 mL) cooled to 0 °C was added $NaBH_4$ (0.86 g, 22.8 mmol), followed by the addition of $BiCl_3$ (2 g, 6.27 mmol).[18] The reaction mixture was stirred at rt for 1 h and filtered through Celite. The filtrate was concentrated and the residue was partitioned in $NaHCO_3$ soln/EtOAc. The organic layer was dried and concentrated to yield 0.7 g of **21**. ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H), 3.66 (s, 2H), 6.68 (d, 1H, $J = 8.14$ Hz), 6.73 (d, 1H, $J = 7.46$ Hz), 7.02 (t, 1H, $J = 7.8$ Hz). MS (DCI+) *m/z* 147 (M+H).

5.2.2. 1-Acetyl-(1*H*-indazol-4-yl)acetonitrile (22). To a solution of acetonitrile **21** (0.3 g, 2 mmol), potassium acetate (0.2 g, 2.04 mmol), and acetic anhydride (0.6 g, 6 mmol) in toluene, heated at 80 °C for 45 min, isoamylnitrite (0.35 g, 3 mmol) was added dropwise. The reaction mixture was heated at 80 °C for 16 h, upon which it was cooled, diluted with EtOAc, and washed with H_2O. The organic layer was dried over $MgSO_4$ and concentrated. The obtained residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to yield 0.27 g (69%) of **22**. ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H), 4.04 (s, 2H), 7.36 (dd, 1H, $J = 7.29$, 0.85 Hz), 7.56 (dd, 1H, $J = 8.48$, 7.12 Hz), 8.23 (d, 1H, $J = 0.68$ Hz), 8.46 (d, 1H, $J = 8.48$ Hz). MS (DCI+) *m/z* 200 (M+H).

5.2.3. (1*H*-Indazol-4-yl)acetic acid (23). A solution of acetonitrile **22** (0.25 g, 1.3 mmol) in EtOH (5 mL) was heated to reflux for 16 h with 20% KOH (5 mL) and H_2O_2 (1 mL). The solvent was concentrated in vacuo and the residue was partitioned in EtOAc/H_2O, then the aqueous layer was acidified with acetic acid and extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo to yield 0.12 g of acid **23**. ^{1}H NMR (DMSO-d_6): 3.86 (s, 2H), 6.96 (d, 1H, $J = 7.12$ Hz), 7.42 (dd, 1H, $J = 7.12$, 1.35 Hz), 7.42 (d, 1H, $J = 8.48$ Hz), 8.06 (d, 1H, $J = 0.68$ Hz), 12.45 (br s, 1H), 13.03 (br s, 1H). MS (DCI+) m/z 177 (M+H).

5.2.4. 2-(1*H*-Indazol-4-yl)-*N*-(4-trifluoromethylbenzyl)acetamide (25). To a solution of indazole acid **23** (0.15 g, 0.85 mmol) in THF (10 mL) EDCI (0.19 g, 1.0 mmol) and HOAT (0.17 g, 1.2 mmol) were added, followed by the addition of 4-(trifluoromethyl)benzylamine (0.16 g, 0.9 mmol). The reaction mixture was stirred at rt for 16 h, upon which it was concentrated and the obtained residue was chromatographed on silica gel, eluting with 5% EtOH/CH_2Cl_2 to yield 0.07 g of **25** that was converted to HCl salt, mp 190–192 °C. ^{1}H NMR (DMSO-d_6): 3.81 (s, 2H), 4.35 (d, 2H, $J = 6.1$ Hz), 6.9 (d, 1H, $J = 6.78$ Hz), 7.25 (t, 1H, $J = 7.05$ Hz), 7.42 (d, 1H, $J = 8.48$ Hz), 7.46 (d, 2H, $J = 8.14$ Hz), 7.67 (d, 2H, $J = 8.14$ Hz), 8.14 (d, 1H, $J = 1.02$ Hz), 8.74 (t, 1H), 13.0 (br s, 1H). MS (DCI+) m/z 334 (M+H). Anal. ($C_{17}H_{14}F_3N_3O{\cdot}HCl{\cdot}0.4H_2O$) C, H, N.

5.2.5. 2-(1*H*-Indol-4-yl)-*N*-(4-trifluoromethylbenzyl)acetamide (26). To a solution of indole acid **24**[20] (0.25 g, 1.42 mmol) in THF (10 mL) EDCI (0.35 g, 1.85 mmol) and HOAT (0.29 g, 2.13 mmol) were added, followed by the addition of 4-(trifluoromethyl)benzylamine (0.28 g, 1.6 mmol). The reaction mixture was stirred at ambient temperature for 16 h, upon which it was concentrated and partitioned in dil HCl/H_2O. The organic layer was washed with 0.5 M NaOH soln, dried over $MgSO_4$, and concentrated in vacuo. The obtained residue was chromatographed on silica gel, eluting with 30% EtOAc/H_2O to yield 0.3 g of **26**, mp 142–143 °C. ^{1}H NMR (DMSO-d_6): 3.72 (s, 2H), 4.34 (d, 2H, $J = 5.76$ Hz), 6.54 (m, 1H), 6.88 (d, 1H, $J = 6.44$ Hz), 7.02 (t, 1H, $J = 7.12$ Hz), 7.28 (d, 1H, $J = 8.14$ Hz), 7.31 (d, 1H, $J = 2.71$ Hz), 7.45 (d, 2H, $J = 8.14$ Hz), 7.66 (d, 2H, $J = 7.8$ Hz), 8.60 (t, 1H, $J = 5.93$ Hz), 11.06 (s, 1H). MS (DCI+) m/z 333 (M+H). Anal. ($C_{18}H_{15}F_3N_2O$) C, H, N.

5.2.6. (1*H*-Indol-4-yl)-carbamic acid-4-(trifluoromethyl)benzyl ester (27). A mixture of the isocyanate **15** (0.08 g, 0.5 mmol) and 4-(trifluoromethyl)benzyl alcohol (0.09 g, 0.55 mmol) in THF (5 mL) was heated to reflux for 16 h with the catalytic amount of triethylamine. The reaction mixture was concentrated in vacuo and purified by chromatography on silica gel, eluting with 50% hexane/EtOAc to yield 0.09 g of **27** as an oil. ^{1}H NMR (DMSO-d_6): δ 5.32 (s, 2H), 6.73 (s, 1H), 7.0 (t, 1H, $J = 7.8$ Hz), 7.11 (d, 1H, $J = 8.14$ Hz), 7.23 (t, 1H, $J = 2.71$ Hz), 7.38 (d, 1H, $J = 7.46$ Hz), 7.66 (d, 2H, $J = 8.48$ Hz), 7.78 (d, 2H, $J = 8.14$ Hz), 9.52 (s, 1H), 11.08 (s, 1H). Anal. ($C_{17}H_{13}N_2F_3O_2$) C, H, N.

5.3. Method A

Method A is exemplified by the following procedure for **28**.

5.3.1. 1-(4-Bromobenzyl)-3-(1*H*-indol-4-yl)-urea (28). 4-Aminoindole (**1**) (0.13 g, 1 mmol) in THF (3 mL) was treated with 4-bromobenzylisocyanate (0.23 g, 1.1 mmol) for 3 h at ambient temperature. Hexane was added to the reaction mixture to precipitate 0.26 g (75%) of **28** as a tan solid, mp 198 °C. ^{1}H NMR (DMSO-d_6): δ 4.30 (d, 2H, $J = 6.1$ Hz), 6.51 (t, 1H, $J = 2.71$ Hz), 6.89 (t, 1H, $J = 7.12$ Hz), 6.95 (m, 1H), 6.98 (m, 1H), 7.25 (t, 1H, $J = 2.71$ Hz), 7.29 (d, 1H, $J = 8.48$ Hz), 7.55 (d, 2H, $J = 8.48$ Hz), 7.62 (dd, 1H, $J = 7.12$, 1.7 Hz), 8.3 (s, 1H), 11.04 (s, 1H); MS (DCI+) m/z 346 (M+H). Anal. ($C_{16}H_{14}N_3BrO$) C, H, N.

5.3.2. 1-(4-Bromobenzyl)-3-(1*H*-indol-5-yl)-urea (29). 5-Aminoindole (0.1 g, 0.75 mmol) in THF (3 mL) was treated with 4-bromobenzylisocyanate (0.19 g, 0.9 mmol) by Method A to yield 0.21 g (81%) of **29** as a tan solid, mp 215 °C. ^{1}H NMR (DMSO-d_6): δ 4.23 (d, 2H, $J = 4.26$ Hz), 6.3 (m, 1H), 6.48 (t, 1H, $J = 5.93$ Hz), 7.02 (dd, 1H, $J = 8.48$, 2.03 Hz), 7.24 (m, 2H), 7.28 (d, 2H, $J = 8.48$ Hz), 7.52 (d, 2H, $J = 8.14$ Hz), 7.6 (d, 1H, $J = 2.03$ Hz), 8.25 (s, 1H), 10.84 (s, 1H); MS (DCI+) m/z 346 (M+H). Anal. ($C_{16}H_{14}N_3BrO{\cdot}0.75H_2O$) C, H, N.

5.3.3. 1-(4-Bromobenzyl)-3-(1*H*-indol-6-yl)-urea (30). 6-Aminoindole (0.1 g, 0.75 mmol) in THF (3 mL) was treated with 4-bromobenzylisocyanate (0.19 g, 0.9 mmol) by Method A to yield 0.19 g (74%) of **30** as a tan solid, mp 221 °C. ^{1}H NMR (DMSO-d_6): δ 4.27 (d, 2H, $J = 6.2$ Hz), 6.3 (m, 1H), 6.52 (t, 1H, $J = 5.6$ Hz), 6.8 (dd, 1H, $J = 8.48$, 2.03 Hz), 7.16 (dd, 1H, $J = 3.05$, 2.37 Hz), 7.28 (d, 2H, $J = 8.48$ Hz), 7.35 (d, 1H, $J = 8.48$ Hz), 7.52 (ddd, 2H, $J = 8.81$, 2.71, 2.37 Hz), 7.72 (m, 1H), 8.41 (s, 1H), 10.82 (s, 1H); MS (DCI+) m/z 346 (M+H). Anal. ($C_{16}H_{14}N_3BrO$) C, H, N.

5.3.4. 1-(4-Bromobenzyl)-3-(1*H*-indol-7-yl)-urea (31). 7-Aminoindole (0.1 g, 0.75 mmol) in THF (3 mL) was treated with 4-bromobenzylisocyanate (0.19 g, 0.9 mmol) by Method A to yield 0.17 g (71%) of **31** as a tan solid, mp 210 °C. ^{1}H NMR (DMSO-d_6): δ 4.31 (d, 2H, $J = 6.1$ Hz), 6.4 (m, 1H), 6.72 (t, 1H, $J = 6.27$ Hz), 6.88 (t, 1H, $J = 7.8$ Hz), 7.10 (dd, 1H, $J = 7.8$, 1.02 Hz), 7.21 (d, 1H, $J = 7.8$ Hz), 7.29 (m, 1H), 7.32 (d, 2H, $J = 8.48$ Hz), 7.54 (d, 2H, $J = 8.48$ Hz), 8.3 (s, 1H), 11.04 (s, 1H); MS (DCI+) m/z 346 (M+H). Anal. ($C_{16}H_{14}N_3BrO$) C, H, N.

5.3.5. 4-Aminoindazole-1-carboxylic acid methyl ester (2). 4-Nitroindazole (8.0 g, 50 mmol) was added to a solution of diazabicycloundecene (8.0 g, 52 mmol) in DMF (25 mL) at 15 °C under N_2. To the resulting deep red solution methylchloroformate (9.0 g, 100 mmol) was added dropwise while maintaining internal temperature of the mixture below 30 °C. After additional 0.5 h, the mixture was quenched by addition of H_2O (25 mL). The solid was filtered off, washed with H_2O (25 mL), and dried under vacuum to yield 4-nitroindazole-1-carboxylic acid methyl ester (7.7 g, 71%). ^1H NMR ($CDCl_3$): δ 4.19 (s, 3 H), 7.89 (dd, 1H, $J = 8.48$, 7.8 Hz), 8.35 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 8.48$ Hz), 8.85 (d, 1H, $J = 1.02$ Hz).

The intermediate nitroindazole (4.4 g, 20 mmol) was hydrogenated at 40 psi in MeOH (90 mL) in the presence of 5% Pd/C (0.4 g) at 45 °C for 2 h. The catalyst was filtered off and washed with MeOH (20 mL). The filtrate was concentrated in vacuo, the residue was slurried in ethanol (10 mL) and filtered off to give 2.6 g (69%) of **2** as a yellow solid. ^1H NMR (DMSO-d_6): δ 3.99 (s, 3H), 6.13 (s, 2H), 6.41 (dd, 1H, $J = 6.1$, 2.37 Hz), 7.22 (m, 2H), 8.46 (s, 1H).

5.3.6. 1-(4-Bromobenzyl)-3-(1*H*-indazol-4-yl)-urea hydrochloride (32). The aminoindazole **2** (0.19 g, 1 mmol) was treated with 4-bromobenzylisocyanate (0.26 g, 1.2 mmol) by Method A to yield 0.25 g of 4-[3-(4-bromobenzyl)-ureido]-indazole-1-carboxylic acid methyl ester as the intermediate. It was hydrolyzed by stirring in MeOH/THF (1:1) (5 mL) and 0.5 M KOH (1 mL) for 1 h. The reaction mixture was neutralized with acetic acid, diluted with H_2O and 0.16 g of the free base of **32** was filtered off. It was converted to HCl salt by treatment of ethanolic solution with ethereal HCl, mp 126 °C. ^1H NMR (DMSO-d_6): δ 4.32 (d, 2H, $J = 5.43$ Hz), 7.0 (t, 1H, $J = 6.10$ Hz), 7.05 (d, 1H, $J = 8.48$ Hz), 7.18 (t, 1H, $J = 8.14$ Hz), 7.3 (d, 2H, $J = 8.48$ Hz), 7.55 (d, 2H, $J = 8.48$ Hz), 7.61 (d, 1H, $J = 7.46$ Hz), 8.16 (s, 1H), 8.92 (s, 1H), 13.0 (br s, 1H). Anal. ($C_{15}H_{13}N_4BrO{\cdot}HCl$) C, H, N.

5.3.7. 1-(4-Bromobenzyl)-3-(1*H*-indazol-5-yl)-urea, hydrochloride (33). Following the method outlined for **2**, 5-nitroindazole **9** (1.3 g, 8.1 mmol) was converted to 1.3 g of 5-aminoindazole-1-carboxylic acid methyl ester. ^1H NMR (DMSO-d_6): δ 3.99 (s, 3H), 5.21 (s, 2H), 6.85 (m, 1H), 6.93 (d, 1H, $J = 8.81$, 2.37 Hz), 7.80 (d, 1H, $J = 8.81$ Hz), 8.13 (s, 1H). The intermediate 5-aminoindazole-1-carboxylic acid methyl ester (0.11 g. 0.6 mmol) was reacted with 4-bromobenzylisocyanate as in **32** to yield 0.15 g of **33**, mp 258 °C. ^1H NMR (DMSO-d_6) δ 4.28 (d, 2H, $J = 6.1$ Hz), 6.66 (t, 1H, $J = 5.93$ Hz), 7.28 (m, 1H), 7.27 (d, 2H, $J = 8.48$ Hz), 7.39 (d, 1H, $J = 8.80$ Hz), 7.52 (d, 2H, $J = 8.48$ Hz), 7.85 (d, 1H, $J = 1.36$ Hz), 7.93 (s, 1H), 8.57 (s, 1H), 12.84 (br s, 1H). Anal. ($C_{15}H_{13}N_4BrO$) C, H, N.

5.3.8. 1-(4-Bromobenzyl)-3-(1*H*-2,3-dimethylindol-4-yl)-urea (34). 2,3-Dimethyl-1*H*-indol-4-ylamine[23] (0.11 g, 0.7 mmol) was treated by Method A with 4-bromobenzylisocyanate to yield 0.12 g of **34** as a tan solid, mp 190 °C. ^1H NMR (DMSO-d_6): δ 2.25 (s, 3H), 2.27 (s, 3H), 4.24 (d, 2H, $J = 6.1$ Hz), 6.84 (m, 1H), 6.85 (d, 1H, $J = 7.46$ Hz), 6.95 (m, 2H), 7.28 (d, 2H, $J = 8.48$ Hz), 7.52 (d, 2H, $J = 8.48$ Hz), 7.75 (s, 1H), 10.7 (s, 1H). Anal. ($C_{18}H_{18}N_3BrO$) C, H, N.

5.3.9. 1-Methyl-4-nitro-1*H*-indazole and 2-methyl-4-nitro-2*H*-indazole. A solution of 4-nitro-1*H*-indazole (1 g, 10 mmol) in DMF (3 mL) was added to a suspension of NaH (0.3 g, 12.5 mmol) in DMF (7 mL) at 0 °C. The resulting suspension was stirred for 30 min, after which CH_3I (2.05 g, 14.5 mmol) was added dropwise, and the reaction mixture was allowed to stir at rt for 6 h. The resulting mixture was poured into water and the precipitate formed was filtered off. It was chromatographed on silica gel eluting with 2% MeOH/CH_2Cl_2, to yield 0.8 g of 1-methyl-4-nitro-1*H*-indazole as a less polar component. ^1H NMR (DMSO-d_6): δ 4.19 (s, 3H), 7.65 (dd, 1H, $J = 8.31$, 7.63 Hz), 8.19 (d, 1H, $J = 7.46$ Hz), 8.24 (d, 1H, $J = 8.48$ Hz), 8.5 (d, 1H, $J = 1.02$ Hz) and 0.4 g of 2-methyl-4-nitro-2*H*-indazole as a more polar component. ^1H NMR (DMSO-d_6): δ 4.24 (s, 3H), 7.49 (dd, 1H, $J = 8.65$, 7.63 Hz), 8.19 (dd, 2H, $J = 7.97$, 3.9 Hz), 8.88 (d, 1H, $J = 1.02$ Hz).

5.3.10. 1-Methyl-1*H*-indazol-4-ylamine (4). 1-Methyl-4-nitro-1*H*-indazole (6.1 g; 35.4 mmol) in MeOH was hydrogenated in a Parr apparatus at 60 psi with 10% Pd/C (0.5 g) at 50 °C for 1 h. The resulting mixture was filtered through Celite and concentrated in vacuo to afford **4** (4.5 g, 91%). ^1H NMR (DMSO-d_6): δ 3.90 (s, 3H), 5.75 (s, 2H), 6.14 (d, 1H, $J = 7.49$ Hz), 6.62 (d, 1H, $J = 7.81$ Hz), 7.02 (t, 1H, $J = 7.8$ Hz), 8.02 (s, 1H).

5.3.11. 1-(4-Bromobenzyl)-3-(1-methyl-1*H*-indazol-4-yl)-urea (35). The indazole **4** (0.1 g, 0.68 mmol) was reacted by Method A with 4-bromobenzylisocyanate (0.17 g, 0.8 mmol) to yield 0.14 g of **35**, mp 218 °C. ^1H NMR (DMSO-d_6): δ 4.0 (s, 3H), 4.32 (d, 2H, $J = 5.93$ Hz), 6.83 (t, 1H, $J = 5.93$ Hz), 7.12 (d, 1H, $J = 8.42$ Hz), 7.23 (d, 1H, $J = 7.96$ Hz), 7.3 (d, 2H, $J = 8.42$ Hz), 7.52 (d, 2H, $J = 8.42$ Hz), 7.64 (d, 1H, $J = 7.8$ Hz), 8.05 (s, 1H), 8.79 (s, 1H). Anal. ($C_{16}H_{15}N_4BrO$) C, H, N.

5.3.12. 2-Methyl-2*H*-indazol-4-ylamine (5). To a solution of 2-methyl-4-nitro-2*H*-indazole (0.8 g, 4.5 mmol) in EtOH cooled to °C was added $BiCl_3$ (1.71 g, 5.4 mmol), followed by a portionwise addition of $NaBH_4$ (0.68 g, 18 mmol). The reaction mixture was stirred at rt for 1 h, then filtered through Celite and concentrated in vacuo. The obtained residue was partitioned in EtOAc/0.5 M KOH. The organic layer was separated, dried, and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 2% EtOH/CH_2Cl_2 to yield 0.4 g of **5**. ^1H NMR (DMSO-d_6): δ 4.23 (s, 3H), 5.75 (s, 2H), 6.65 (dd, 1H, $J = 6.44$, 1.36 Hz), 7.16 (d, 2H, $J = 7.8$ Hz), 7.85 (s, 1H).

5.3.13. 1-(4-Bromobenzyl)-3-(2-methyl-2*H*-indazol-4-yl)-urea (36). The indazole **5** (0.12 g, 0.8 mmol) was reacted by Method A with 4-bromobenzylisocyanate (0.2 g, 0.9 mmol) to yield 0.15 g of **36**, mp 208–209 °C. ^1H NMR (DMSO-d_6): δ 3.32 (s, 3H), 4.31 (d, 2H, $J = 6.1$ Hz), 6.77 (t, 1H, $J = 6.1$ Hz), 7.10 (m, 2H), 7.3 (d, 2H, $J = 8.48$ Hz), 7.42 (dd, 1H, $J = 6.78$, 1.36 Hz), 7.55 (d, 2H, $J = 8.48$ Hz), 8.11 (s, 1H), 8.65 (s, 1H). Anal. ($C_{16}H_{15}N_4BrO.\ H_2O$) C, H, N.

5.3.14. 4-Aminobenzimidazole-1-carboxylic acid methyl ester (6). To a solution of 1*H*-benzimidazole-4-yl-amine (6 g, 45 mmol) in DMF (30 mL) cooled to 0 °C was added 60% NaH (2 g, 50 mmol). The reaction mixture was allowed to warm to rt and stirred for 1 h, after which methylchloroformate (4.73 g, 50 mmol) was added. The reaction mixture was stirred at rt for 16 h, then poured into water and partitioned in EtOAc/H_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was chromatographed on silica gel eluting with 30% EtOAc/hexane to yield 1.56 g of the title compound. ^1H NMR (DMSO-d_6): δ 4.02 (s, 3H), 5.52 (s, 2H), 6.53 (dd, 1H, 7.29, 1.53), 7.06–7.15 (m, 2H), 8.45 (s, 1H).

5.3.15. 1-(1*H*-Benzimidazole-4-yl)-3-(4-bromobenzyl)-urea hydrochloride (37). The benzimidazole **6** (0.38 g, 2 mmol) in THF (5 mL) was treated with 4-bromobenzyl isocyanate (0.42 g, 2 mmol) by Method A to yield 4-[3-(4-bromobenzyl)-ureido]-benzoimidazole-1-carboxylic acid methyl ester. It was dissolved in a 1:1 mixture of THF and MeOH, and treated with 1 M NaOH (5 mL) overnight at ambient temperature. The resulting solid was filtered to yield 0.59 g of the free base of **37** that was converted to HCl salt. ^1H NMR (DMSO-d_6): δ 4.36 (d, 2H, $J = 5.76$ Hz), 7.17–7.25 (m, 1H), 7.34 (d, 2H, $J = 8.14$ Hz), 7.35–7.42 (m, 2H), 7.49 (t, 1H, $J = 2.37$ Hz), 7.52 (m, 1H), 7.54 (d, 2H, $J = 8.48$ Hz), 9.23 (s, 1H), 9.52 (s, 1H); MS (ESI+) *m/z* 346 (M+H). Anal. ($C_{15}H_{13}N_4BrO{\cdot}HCl{\cdot}0.5H_2O{\cdot}0.5C_2H_5OH$) C, H, N.

5.3.16. 1-(3,4-Dichlorobenzyl)-3-(1*H*-indol-4-yl)-urea (38). The indole **1** (0.13 g, 1 mmol) and 3,4-dichlorobenzylisocyanate (0.22 g, 1.1 mmol) were treated by Method A to yield 0.25 g (75%) of **27** as a tan solid, mp 201 °C. ^1H NMR (DMSO-d_6): δ 4.34 (d, 2H, $J = 5.76$ Hz), 6.52 (t, 1H, $J = 2.71$ Hz), 6.9–7.01 (m, 3 H), 7.25 (m, 1H), 7.33 (dd, 1H, $J = 8.14$, 2.03 Hz), 7.57–7.63 (m, 3H), 8.34 (s, 1H), 11.05 (s, 1H); MS (DCI+) *m/z* 336 (M+H). Anal. ($C_{16}H_{13}N_3Cl_2O$) C, H, N.

5.4. Method B

Method B is exemplified by the following procedure for **39**.

5.4.1. 4-Isocyanato-1*H*-indole (15). 4-Aminoindole **1** (0.5 g, 3.78 mmol) in toluene (50 mL) was heated to reflux for 5 h with triphosgene (0.4 g, 1.35 mmol). The reaction mixture was evaporated in vacuo and the residue was taken up in ether. The precipitate was filtered off and discarded, and the filtrate was concentrated in vacuo to yield 0.4 g of **15** as a yellow oil. ^1H NMR ($CDCl_3$-d_6): δ 6.62 (m, 1H), 6.84 (d, 1H, $J = 8.82$ Hz), 7.1 (t, 1H, $J = 2.71$ Hz), 7.23 (m, 2H), 8.3 (s, 1H).

5.4.2. 1-(4-Trifluoromethylbenzyl)-3-(1*H*-indol-4-yl)-urea (39). The isocyanate **15** (0.16 g, 1 mmol) in THF (3 mL) was treated with 4-(trifluoromethyl)benzylamine (0.19 g, 1.1 mmol) for 3 h at rt. The solvent was evaporated and the residue was chromatographed on silica gel, eluting with 1:1 EtOAc/hexane to yield 0.17 g of **39** as a solid, mp 178 °C. ^1H NMR (DMSO-d_6): δ 4.43 (d, 2H, $J = 5.76$ Hz), 6.52 (t, 1H, $J = 2.71$ Hz), 6.98 (m, 3H), 7.26 (t, 1H, $J = 2.71$ Hz), 7.57 (d, 2H, $J = 8.14$ Hz), 7.62 (dd, 1H, $J = 7.12$, 1.36 Hz), 7.71 (d, 2H, $J = 8.47$ Hz), 8.37 (s, 1H), 11.04 (s, 1H); MS (DCI+) *m/z* 334 (M+H). Anal. ($C_{17}H_{14}N_3F_3O$) C, H, N.

5.4.3. 1-(4-Trifluoromethoxybenzyl)-3-(1*H*-indol-4-yl)-urea (40). The isocyanate **15** (0.16 g, 1 mmol) and 4-(trifluoromethoxy)benzylamine (0.21 g, 1.1 mmol) were treated by Method B to provide 0.23 g (67%) of **40**, mp 177 °C. ^1H NMR (DMSO-d_6): δ 4.36 (d, 2H, $J = 5.76$ Hz), 6.52 (t, 1H, $J = 2.71$ Hz), 6.89–7.01 (m, 3H), 7.24 (t, 1H, $J = 2.71$ Hz), 7.34 (d, 2H, $J = 8.82$ Hz), 7.48 (d, 2H, $J = 8.82$ Hz), 7.63 (dd, 1H, $J = 7.12$, 1.46 Hz), 8.32 (s, 1H), 11.06 (s, 1H); MS (DCI+) *m/z* 349.9 (M+H). Anal. ($C_{17}H_{14}N_3F_3O_2$) C, H, N.

5.4.4. 1-(3-Fluoro-4-trifluoromethylbenzyl)-3-(1*H*-indol-4-yl)-urea (41). The isocyanate **15** (0.16 g, 1 mmol) and 3-fluoro-4-(trifluoromethyl)benzylamine (0.22 g, 1.1 mmol) were treated by Method B to provide 0.24 g (68%) of **41**, mp 198 °C. ^1H NMR (DMSO-d_6): δ 4.43 (d, 2H, $J = 5.76$ Hz), 6.52 (m, 1H), 6.9–7.04 (m, 3H), 7.26 (m, 1H), 7.39 (m, 2H), 7.57 (dd, 1H, $J = 7.46$, 1.36), 7.77 (t, 1H, $J = 7.8$ Hz), 8.40 (s, 1H), 11.05 (s, 1H); MS (DCI+) *m/z* 349.9 (M+H). Anal. ($C_{17}H_{13}N_3F_4O$) C, H, N.

5.4.5. 1-(4-Chloro-3-trifluoromethyl-benzyl)-3-(1*H*-indol-4-yl)-urea (42). The isocyanate **15** (0.16 g, 1 mmol) and 4-chloro-3-(trifluoromethyl)benzylamine (0.27 g, 1.1 mmol) were treated by Method B to provide 0.22 g of **42**, mp 197 °C. ^1H NMR (DMSO-d_6): δ 4.42 (d, 2H, $J = 5.76$ Hz), 6.52 (t, 1H, $J = 2.71$ Hz), 6.91–7.04 (m, 3H), 7.25 (t, 1 H, $J = 2.71$ Hz), 7.56 (dd, 1H, $J = 7.46$, 1.37 Hz), 7.65 (m, 1H), 7.70 (m, 1H), 7.81 (d, 1H, $J = 1.7$ Hz), 8.37 (s, 1H), 11.06 (s, 1H); MS (DCI+) *m/z* 368 (M+H). Anal. ($C_{17}H_{13}N_3ClF_3O$) C, H, N.

5.4.6. 1-(4-Chlorobenzyl)-3-(1*H*-indol-4-yl)-urea (43). The isocyanate **15** (0.2 g, 1.27 mmol) and 4-chlorobenzylamine (0.2 g, 1.4 mmol) were treated by Method B to provide 0.18 g of **43**, mp 205 °C. ^1H NMR (DMSO-d_6): δ 4.32 (d, 2H, $J = 5.76$ Hz), 6.52 (m, 1H), 6.87 (m, 1H), 6.97 (m, 2H), 7.25 (t, 1H, $J = 2.71$ Hz), 7.37 (d, 2H, $J = 8.48$ Hz), 7.40 (d, 2H, $J = 8.48$ Hz), 7.6 (dd, 1H, $J = 7.12$, 1.36 Hz), 8.30 (s, 1H), 11.06 (s, 1H). MS (DCI+) *m/z* 300 (M+H). Anal. ($C_{16}H_{14}N_3ClO$) C, H, N.

5.4.7. 1-(3-Fluorobenzyl)-3-(1*H*-indol-4-yl)-urea (44). The indole **1** (0.13 g, 1 mmol) in THF (3 mL) was treated with 3-fluorobenzylisocyanate (0.23 g, 1.1 mmol) by Method A to yield 0.18 g of **44**, mp 189 °C. ^1H NMR (DMSO-d_6): δ 4.34 (d, 2H, $J = 6.1$ Hz), 6.52 (t, 1H, $J = 2.71$ Hz), 6.88–7.12 (m, 3H), 7.07 (td, 1H, $J = 8.6$, 2.1 Hz), 7.12–7.21 (m, 2H), 7.39 (td, 1H, $J = 7.8$, 6.1 Hz), 7.61 (dd, 1H, $J = 7.8$, 1.70 Hz), 8.32 (s, 1H), 11.06 (s, 1H). MS (DCI+) *m/z* 284 (M+H). Anal. ($C_{16}H_{14}N_3FO$) C, H, N.

5.4.8. 1-(4-Fluorobenzyl)-3-(1*H*-indol-4-yl)-urea (45). The indole **1** (0.13 g, 1 mmol) in THF (3 mL) was treated with 4-fluorobenzylisocyanate (0.23 g, 1.1 mmol) by Method A to yield 0.18 g of **45**, mp 207 °C. ^{1}H NMR (DMSO-d_6): δ 4.32 (d, 2H, $J = 5.76$ Hz), 6.52 (t, 1H, $J = 2.37$ Hz), 6.85 (t, 1H, $J = 6.10$ Hz), 6.95 (m, 2H), 7.18 (t, 2H, $J = 8.99$ Hz), 7.22 (t, 1H, $J = 2.71$ Hz), 7.38 (td, 2H, $J = 6.02$, 2.2 Hz), 7.62 (dd, 1H, $J = 6.95$, 1.53 Hz), 8.28 (s, 1H), 11.06 (s, 1H). MS (DCI+) *m*/*z* 284 (M+H). Anal. ($C_{16}H_{14}N_3FO$) C, H, N.

5.4.9. 1-(3,4-Dichlorobenzyl)-3-(1*H*-indazol-4-yl)-urea hydrochloride (46). The aminoindazole **2** (0.19 g, 1 mmol) in THF (3 mL) was treated as in **32** with 3,4-dichlorobenzylisocyanate (0.22 g, 1.1 mmol) to yield 0.25 g of 4-[3-(3,4-dichloro-benzyl)-ureido]-indazole-1-carboxylic acid methyl ester as a tan solid. Subsequent base hydrolysis of this intermediate as described in **32** yielded 0.1 g of the free base of **46**, that was converted to hydrochloride salt by treatment of ethanolic solution with ethereal HCl, mp 200–202 °C. ^{1}H NMR (free base) (DMSO-d_6): δ 4.35 (d, 2H, $J = 6.1$ Hz), 6.9 (t, 1H, $J = 6.1$ Hz), 7.05 (d, 1H, $J = 8.14$ Hz), 7.19 (t, 1H, $J = 7.8$ Hz), 7.35 (dd, 1H, $J = 8.48$, 2.03 Hz), 7.59 (m, 1H), 7.61 (d, 2H, $J = 8.47$ Hz), 8.09 (s, 1H), 8.83 (s, 1H), 12.99 (s, 1H); MS (DCI+) *m*/*z* 336 (M+H). Anal. ($C_{15}H_{12}N_4Cl_2O{\cdot}HCl$) C, H, N.

5.4.10. 4-Isocyanato-indazole-1-carboxylic acid methyl ester (16). A solution of phosgene in toluene (9.00 mL, approx 20% w/w) was added via syringe to a suspension of **2** (1.72 g, 9.00 mmol) in toluene (300 mL). The reaction was heated to reflux. After 3.5 h, the solution was cooled and concentrated in vacuo. The residue was taken up in Et_2O (325 mL), followed by the addition of Et_3N (10 mL) to remove the excess of HCl. The solution was stirred briefly, filtered, and concentrated to yield **16** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.15 (s, 3H), 7.07 (d, 1H, $J = 7.46$ Hz), 7.5 (dd, 2H, $J = 8.48$, 7.46 Hz), 8.1 (d, 1H, $J = 8.48$ Hz), 8.26 (s, 1H).

5.4.11. 1-(4-Trifluoromethylbenzyl)-3-(1*H*-indazol-4-yl)-urea hydrochloride (47). The isocyanate **16** (0.43 g, 2 mmol) was reacted by Method B with 4-(trifluoromethyl)benzylamine (0.38 g, 2.2 mmol) to yield the intermediate that upon the basic hydrolysis yielded 0.45 g of the free base of **47** that was converted to HCl salt, mp 198–199 °C. ^{1}H NMR (free base) (DMSO-d_6): δ 4.49 (d, 2H, $J = 5.76$ Hz), 6.98 (t, 1H, $J = 5.93$ Hz), 7.06 (d, 1H, $J = 7.45$ Hz), 7.19 (t, 1H, $J = 7.97$ Hz), 7.55 (d, 2H, $J = 8.14$ Hz), 7.6 (d, 1H, $J = 7.8$ Hz), 7.71 (d, 2H, $J = 8.14$ Hz), 8.10 (s, 1H), 8.85 (s, 1H), 13.0 (br s, 1H); MS (DCI+) *m*/*z* 335 (M+H). Anal. ($C_{16}H_{13}F_3N_4O{\cdot}HCl$) C, H, N.

5.4.12. 1-(4-Trifluoromethoxybenzyl)-3-(1*H*-indazol-4-yl)-urea hydrochloride (48). The isocyanate **16** (0.18 g, 0.8 mmol) was reacted by Method B with 4-(trifluoromethoxy)benzylamine (0.19 g, 1 mmol) to yield the intermediate that upon the basic hydrolysis and conversion to HCl salt yielded 0.1 g of **48**, mp 198–199 °C. ^{1}H NMR (DMSO-d_6): δ 4.37 (d, 2H, $J = 5.76$ Hz), 6.96 (t, 1H, $J = 5.43$ Hz), 7.07 (d, 1H, $J = 8.14$ Hz), 7.19 (t, 1H, $J = 8.14$ Hz), 7.36 (d, 2H, $J = 8.14$ Hz), 7.48 (d, 2H, $J = 8.48$ Hz), 7.61 (d, 1H, $J = 7.46$ Hz), 8.13 (s, 1H), 8.88 (s, 1H), 13.0 (br s, 1H); MS (DCI+) *m*/*z* 351 (M+H). Anal. ($C_{16}H_{13}F_3N_4O_2{\cdot}HCl$) C, H, N.

5.4.13. 1-(1*H*-Indazol-4-yl)-3-(3-trifluoromethylbenzyl)-urea hydrochloride (49). The isocyanate **16** (0.18 g, 0.8 mmol) was reacted by Method B with 3-(trifluoromethyl)benzylamine (0.18 g, 1 mmol) to yield the intermediate, that upon the basic hydrolysis and conversion to HCl salt yielded 0.08 g of **49**, mp 188–189 °C. ^{1}H NMR (free base) (DMSO-d_6): δ 4.45 (d, 2H, $J = 6.1$ Hz), 7.06 (d, 1H, $J = 8.14$ Hz), 7.19 (t, 1H, $J = 7.97$ Hz), 7.55–7.72 (m, 6H), 8.09 (s, 1H), 8.83 (s, 1H), 13.00 (s, 1H). MS (ESI$^+$) *m*/*z* 335 (M+H).

5.4.14. 4-Isocyanato-1-methyl-1*H*-indazole (18). The indazole **4** (1.00 g, 6.8 mmol) was suspended in toluene (225 mL), and phosgene (20% in toluene, 7 mL, 13.2 mmol) was added. The reaction mixture was heated to reflux for 3 h, cooled, and concentrated in vacuo. The residue was taken in Et_2O (100 mL) and triethylamine (6 mL) was added. The precipitate formed was filtered off, and the solution was concentrated to yield the intermediate isocyanate **18** as an oil.

5.4.15. (4-Trifluoromethoxybenzyl)-3-(1-methyl-1*H*-indazol-4-yl)-urea (50). The isocyanate **18** (0.29 g, 1.7 mmol) and 4-(trifluoromethoxy)benzylamine (0.32 g, 1.7 mmol) were treated by Method B to yield 0.3 g (48%) of **50**, mp 208–209 °C. ^{1}H NMR (DMSO-d_6): δ 3.99 (s, 3H), 4.38 (d, 2H, $J = 5.76$ Hz), 6.87 (t, 1H, $J = 5.93$ Hz), 7.14 (ddd, 1H, $J = 8.31$, 1.02, 0.85 Hz), 7.25 (t, 1H, $J = 7.97$ Hz), 7.36 (d, 2H, $J = 8.81$ Hz), 7.47 (d, 2H, $J = 8.81$ Hz), 7.63 (dd, 1H, $J = 7.44$, 0.68 Hz), 8.05 (s, 1H), 8.81 (s, 1H). MS (DCI+) *m*/*z* 365 (M+H). Anal. ($C_{17}H_{15}F_3N_4O_2$) C, H, N.

5.4.16. 1-(4-Chlorobenzyl)-3-(1-methyl-1*H*–indazol-4-yl)-urea hydrochloride (51). The isocyanate **18** (0.12 g, 6.8 mmol) and 4-chlorobenzylamine (0.96 g; 6.8 mmol) were treated by Method B to yield 0.09 g of **51** (42%), mp 221–222 °C. ^{1}H NMR (DMSO-d_6): δ 3.99 (s, 3H), 4.34 (br s, 2H,), 7.13 (d, 1H, $J = 6.8$ Hz), 7.21 (br s, 1H), 7.24 (t, 1H, $J = 7.80$ Hz), 7.39 (m, 4H), 7.68 (d, 1H, $J = 7.46$ Hz), 8.25 (s, 1H), 9.25 (s, 1H). MS (ESI$^+$) *m*/*z* 315 (M+H). Anal. ($C_{16}H_{15}ClN_4O{\cdot}HCl$) C, H, N.

5.4.17. 1-(4-Fluorobenzyl)-3-(1-methyl-1*H*-indazol-4-yl)-urea hydrochloride (52). The indazole **4** (0.185 g, 1.26 mmol) and 4-fluorobenzyl isocyanate (0.19 g, 1.26 mmol) were treated by Method A to yield 0.25 g (67%) of **52**, mp 168–170 °C. ^{1}H NMR (free base) (DMSO-d_6): δ 3.99 (s, 3H), 4.33 (d, 2H, $J = 5.76$ Hz), 6.82 (t, 1H, $J = 5.93$ Hz), 7.12–7.18 (m, 3H), 7.21 (d, 1H, $J = 6.44$ Hz), 7.26 (d, 1H, $J = 8.14$ Hz), 7.38 (dd, 2H, $J = 8.82$, 5.43 Hz), 7.65 (d, 1H, $J = 7.46$ Hz), 8.05 (d, 1H), 8.78 (s, 1H); MS (ESI$^+$) *m*/*z* 299 (M+H). Anal. ($C_{16}H_{15}FN_4O{\cdot}HCl$) C, H, N.

5.4.18. 1-(3,4-Dichlorobenzyl)-3-(1-methyl-1*H*–indazol-4-yl)-urea hydrochloride (53). The indazole **4** (0.39 g, 2.65 mmol) and 3,4-dichlorobenzylisocyanate (0.39 mL, 2.65 mmol) were treated by Method A to yield 0.53 g (57%) of **53** as a free base, that was converted to HCl salt, mp 190–192 °C. ^{1}H NMR (free base) (DMSO-d_6): δ 3.99 (s, 3H), 4.35 (d, 2H, $J = 5.76$ Hz), 6.91 (t, 1H, $J = 6.1$ Hz), 7.15 (d, 1H, $J = 8.48$ Hz), 7.25 (t, 1H, $J = 8.48$ Hz), 7.33 (dd, 1H, $J = 8.14, 2.03$ Hz), 7.59 (d, 1H, $J = 2.03$ Hz), 7.60 (d, 1H, $J = 4.07$ Hz), 7.63 (d, 1H, $J = 3.05$ Hz), 8.06 (d, 1H, $J = 1.02$ Hz), 8.86 (s, 1H); MS (ESI$^+$) m/z 349 (M+H). Anal ($C_{16}H_{14}Cl_2N_4O \cdot HCl$) C, H, N.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.03.027.

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