Full Paper

Synthesis and Histamine H_3 and H_4 Receptor Activity of Conformationally Restricted Cyanoguanidines Related to UR-PI376*

Roland Geyer and Armin Buschauer

Department of Pharmaceutical/Medicinal Chemistry II, Faculty of Chemistry and Pharmacy, University of Regensburg, Regensburg, Germany

Recently, we identified highly potent agonists of the human histamine H_4 receptor (hH_4R) among a series of imidazolylbutylcyanoguanidines. Aiming at improved selectivity for the hH_4R relative to the H_3 receptor (hH_3R), the flexible tetramethylene linker connecting imidazole ring and cyanoguanidine group was replaced by conformationally restricted carbocycles. Introduction of a *para*- or a *meta*-phenylene spacer yielded only very weakly active compounds at both hH_3R and hH_4R (investigated in [^{35}S]GTPγS binding assays using Sf9 insect cell membranes expressing hH_xR subtypes). By contrast, the incorporation of a more flexible cyclohexane-1,4-diyl linker resulted in EC_{50} or K_B values $\geq$110 nM at hH_4R and hH_3R. Quality of action, potency and receptor subtype selectivity of the investigated compounds depend on the stereochemistry: *Cis*-configured diastereomers prefer the hH_4R and are partial agonists, whereas *trans*-isomers are antagonists at the hH_4R. At the hH_3R the *trans*-diastereomers are superior to the *cis*-isomers by a factor of 10. The results on imidazolylcycloalkylcyanoguanidines suggest that variation of ring size and optimization of the stereochemistry may be useful to increase the potency and selectivity of hH_4R agonists relative to the hH_3R.

Keywords: Conformational restriction / Cyanoguanidines / Histamine / H_4 receptor / UR-PI376

Received: April 14, 2011; Revised: May 9, 2011; Accepted: May 13, 2011

DOI 10.1002/ardp.201100144

Introduction

The biological effects of the biogenic amine histamine are mediated by four histamine receptor (HR) subtypes, all belonging to class A of G-protein coupled receptors [1, 2]. The most recently identified fourth HR subtype, the H_4R, was discovered based on its high sequence homology to the H_3R in the years 2000 and 2001, independently by several research groups [3–9]. The H_4R is mainly localized in various cells of the immune system like eosinophils, T-lymphocytes, dendritic cells, mast cells, and basophils [3, 6, 7, 10–14]. Furthermore, results of *in-vitro* and *in-vivo* studies suggest that the H_4R plays a crucial role in immunological and inflammatory processes [15–17]. Hence, the H_4R is considered a promising drug target for the treatment of inflammatory and immunological diseases like allergic rhinitis, rheumatoid arthritis, bronchial asthma and pruritus [18–20]. Nevertheless, recent reports on β-arrestin-mediated signaling [21] and partial agonistic effects of the standard H_4R antagonist JNJ7777120 [22] at certain H_4R species orthologs suggest that the interpretation of ligand effects *in vivo* in terms of agonism or antagonism should be interpreted with caution [23, 24]. Therefore, both selective antagonists and agonists are required as pharmacological tools to further explore the role of the H_4R [25].

Previously, we identified hH_4R agonists among N^G-acylated imidazolylpropylguanidines which were initially designed

Correspondence: Prof. Armin Buschauer, Institut für Pharmazie, Universität Regensburg, Universitätsstr. 31, D-93053 Regensburg, Germany
E-mail: armin.buschauer@chemie.uni-regensburg.de
Fax: +49-941 9434820

*In memoriam Prof. Dr. Dr. Dr. h. c. Walter Schunack

as H_2 receptor agonists [26, 27]. Structural optimization resulted in highly potent agonists with selectivity for the hH_4R over the hH_1R and the hH_2R but lack of selectivity compared to the hH_3R [28–30]. Replacement of the basic acylguanidine group with a cyanoguanidine moiety, which is uncharged at physiological pH, turned out to be key in terms of H_4R agonism and selectivity. Highest potency resided in imidazolylalkylcyanoguanidines with a tetramethylene linker, connecting the imidazole and the cyanoguanidine moiety. 2-Cyano-1-[4-(1*H*-imidazol-4-yl)butyl]-3-[(2-phenylthio)ethyl]guanidine (UR-PI376, **1**) (Fig. 1) was the most potent and selective agonist with an EC_{50} of 34 nM (intrinsic activity (α) 0.93) displaying a more than 25-fold selectivity over the hH_3R and negligible activities at the hH_1R and hH_2R (investigated in [^{32}P]GTPase assays on hH_xR expressing Sf9 cell membranes) [28]. Unlike other selective hH_4R agonists, such as 5-methylhistamine [31], VUF8430 [32] or OUP-16 [33], UR-PI376 is devoid of agonistic activities at hHR subtypes other than the hH_4R [28].

Discrimination between the closely related H_3 and H_4 receptors turned out to be a critical issue in the development of selective H_4R agonists. As demonstrated by Hashimoto et al. [33] and Kitbunnadaj et al. [34], the stereochemical requirements of selective hH_3R and hH_4R ligands should be considered. Aiming at elucidating the structure-activity and structure-selectivity relationships of cyanoguanidines derived from UR-PI376 we explored the replacement of the flexible tetramethylene chain by conformationally constrained spacers (Fig. 1). Based on a previously suggested model of UR-PI376 binding to the hH_4R four small series of cyanoguanidines were constructed by introducing a phenyl ring or a cyclohexyl ring, respectively, as in the imidazolylphenylamine VUF5801 (**2**) which was reported to have some hH_4R affinity (pK_i 5.8) [34], and the imidazolylcyclohexylamines VUF5803 (**3**) and VUF5804 (**4**), which were described as non-selective H_3R and H_4R agonists ((**3**) H_4R: pK_i 7.7, α 1.3; H_3R: pK_i 7.0; (**4**) H_4R: pK_i 6.5, α 1.1; H_3R: pK_i 7.4) [34].

Results and discussion

Chemistry

The imidazolylphenylcyanoguanidines **30–44** were synthesized in five steps (Schemes 1 and 2). According to ten Have et al. [35] the cycloaddition of tosylmethyl isocyanide (TosMIC, **5**) [36] to aldimines (**10–12**), which are readily prepared from the corresponding benzaldehydes **6–8** and *N*-tosylamide (**9**) [37], was used. Reduction of the nitro- or the cyano group in **13–15** gave the amines **2**, **16** and **18** which were transformed to the cyanoguanidines by analogy with a previously described synthetic route [38]. Aminolysis of diphenyl cyanocarbonimidate (**19**) [39, 40] with primary amines **20–24** at ambient temperature gave the isourea intermediates **25–29** which crystallized from diethyl ether [28]. Conversion of the isoureas to the cyanoguanidines **30–34** was performed by heating in a microwave oven with **18** in acetonitrile (Scheme 1). In case of the synthesis of **35–44** the order of the coupling steps was reverted due to the low nucleophilicity of aniline derivatives, i.e. **19** was treated first with building block **2** or **16** to yield **45** or **46**, respectively, and afterwards with an aliphatic amine (**20–24**) (Scheme 2).

The 1,4-disubstituted cyclohexanes **53–56** were synthesized as outlined in Scheme 3. 4-Aminocyclohexanecarboxylic acid (**47**) was Boc-protected [41] and the carboxylic acid **48** was reduced with borane to yield the alcohol (**49**) [42]. Swern oxidation [43] gave the corresponding aldehyde **50**, which was successively treated with TosMIC (**5**) and ammonia in

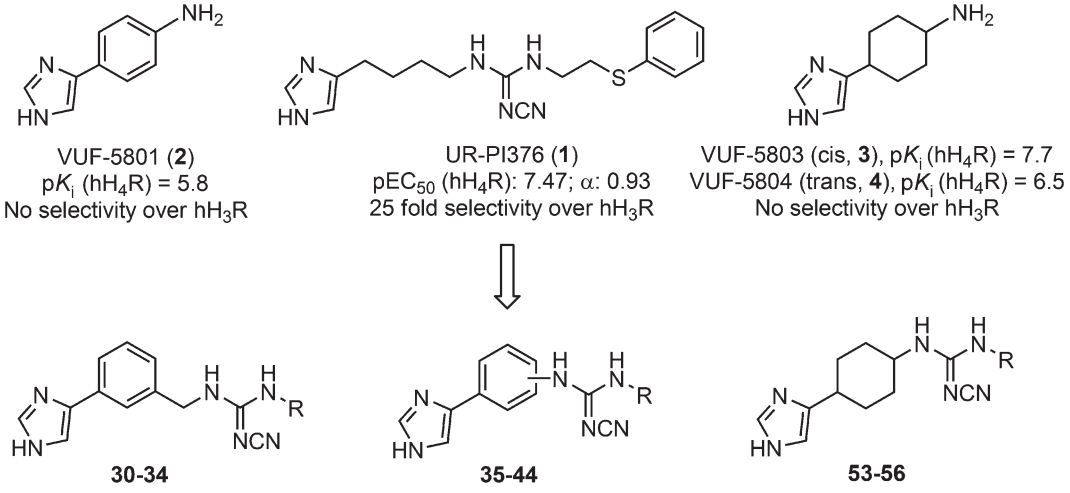
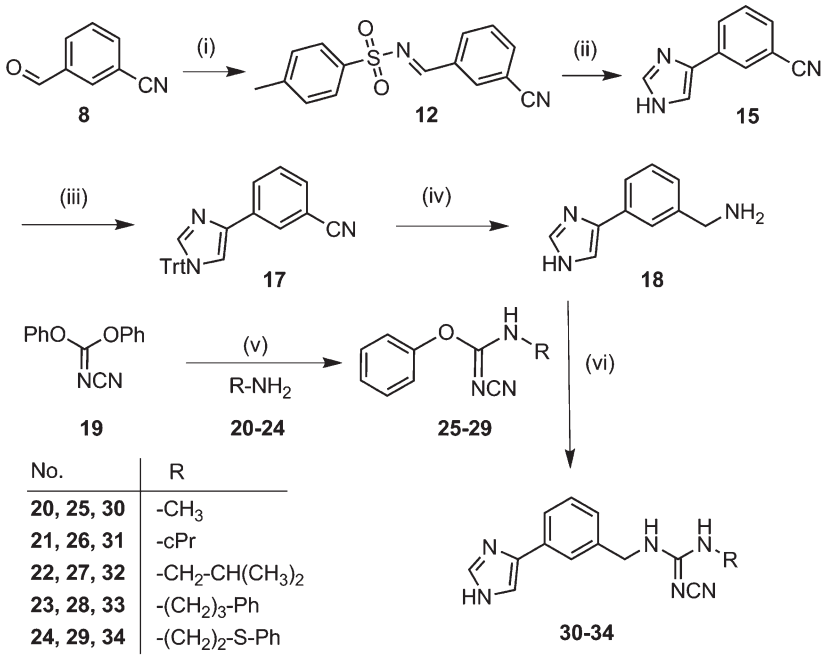


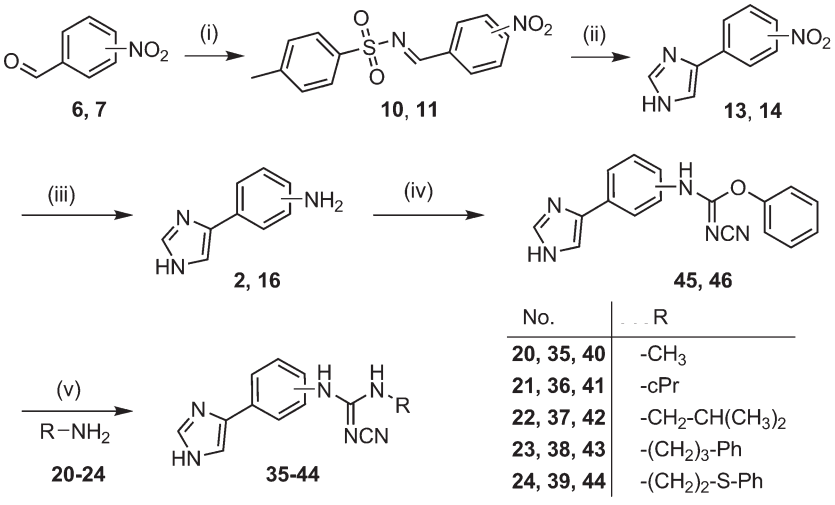
Figure 1. Replacement of the flexible tetramethylene chain in UR-PI376 with conformationally restricted substructures.



No.	R
20, 25, 30	-CH_3
21, 26, 31	-cPr
22, 27, 32	-CH_2-$CH(CH_3)_2$
23, 28, 33	-$(CH_2)_3$-Ph
24, 29, 34	-$(CH_2)_2$-S-Ph

[a] **Reagents and conditions:** (i) 4-Methylbenzenesulfonamide (**9**), toluene, 24 h, reflux, 80% (ii) TosMIC (**5**), K_2CO_3,EtOH/DME 2:1, reflux, 2 h, 45% (iii) TrtCl NEt_3, DMF/DCM, 24 h, rt, 96% (iv) a) $LiAlH_4$, THF/diethyl ether, 0 °C - reflux, 3 h, 89% b) HCl, ion exchanger, 81% (v) 2-propanol, rt, 1 h, 66% - 84% (vi) MeCN, microwave 140 °C, 15 min, 70-87%.

Scheme 1. Synthesis of the cyanoguanidines **30–34**[a].

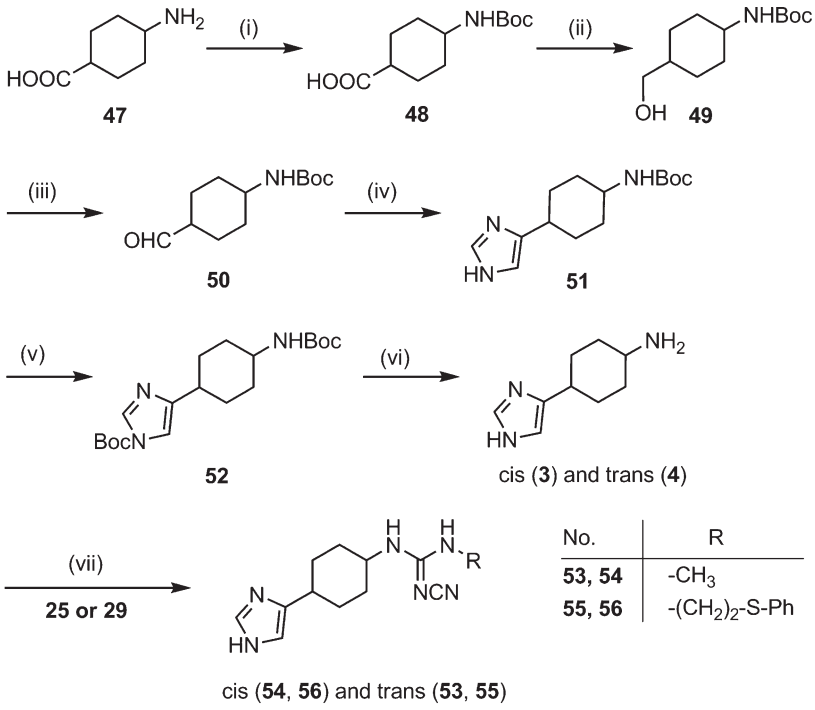


No.	R
20, 35, 40	-CH_3
21, 36, 41	-cPr
22, 37, 42	-CH_2-$CH(CH_3)_2$
23, 38, 43	-$(CH_2)_3$-Ph
24, 39, 44	-$(CH_2)_2$-S-Ph

[a] **Reagents and conditions:** (i) 4-Methylbenzenesulfonamide (**9**), toluene, 24 h, reflux, 90% (ii) TosMIC (**5**), K_2CO_3,EtOH/DME 2:1, reflux, 2h, 56% (iii) H_2 5 bar, Pd/C 10%, MeOH, 24 h, rt, 93% (iv) diphenyl cyanocarbonimidate (**19**), 2-propanol, rt, 36 h, 76% (v) MeCN, microwave 140 °C, 15 min, 55-94%.

Scheme 2. Synthesis of the cyanoguanidines **35–44**[a].

methanol to introduce the imidazole ring [36]. After Boc-protection of the imidazole nitrogen in **51**, the mixture of *cis*- and *trans*-**52** was separated by flash chromatography [34]. Deprotection under acidic conditions and liberation of the amines as free bases with the help of a basic ion exchanger gave the *cis*- and *trans*-imidazolylcyclohexylamines **3** and **4** [28, 34]. The cyanoguanidines **53–56** were synthesized by analogy with the above described procedure.



[a]**Reagents and conditions:** (i) Boc_2O, NaOH, 88% (ii) $BH_3 \cdot THF$, 99% (iii) DMSO, NEt_3, $(COCl)_2$, 69% (vi) a) TosMIC (**5**), NaCN, b) 7 M NH_3 in MeOH, 70% (v) Boc_2O, NaOH, 92% (vi) a) separation of diastereomeres, b) HCl, ion exchanger, 93% (vii) MeCN, microwave 140 °C, 15 min, 68-93%.

Scheme 3. Synthesis of the cyanoguanidines **53–56**[a].

Pharmacology

The synthesized cyanoguanidines were investigated for agonism and antagonism at hH_4R and hH_3R subtypes in [^{35}S]GTPγS binding assays using membrane preparations of Sf9 insect cells co-expressing the hH_4R plus $G\alpha_{i2}$ plus $G\beta_1\gamma_2$ or co-expressing the hH_3R plus $G\alpha_{i2}$ plus $G\beta_1\gamma_2$. Additionally, for reasons of comparison the amine precursors (**2–4**, **16**, **18**) and UR-PI376 (**1**) were characterized.

In the following agonistic potencies are expressed as EC_{50} values. Intrinsic activities (α) refer to the maximal response induced by the standard agonist histamine. Compounds identified to be inactive as agonists (α <0.1 or negative values, respectively, determined in the agonist mode; cf. Tables 1 and 2) were investigated in the antagonist mode. The corresponding K_B values of neutral antagonists and inverse agonists (Tables 1, 2) were determined from the concentration-dependent inhibition of the histamine-induced increase in [^{35}S]GTPγS binding.

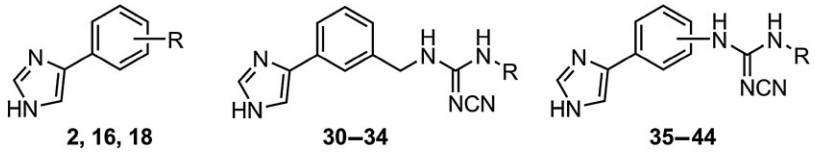
Imidazolylphenylcyanoguanidines 30–44 (Table 1)

Free rotation about single bonds in a flexible linker might result in various conformations, with the single conformers having different affinities for the common target. The synthesis of conformationally restricted analogues of a lead compound often results in increased specific binding to the biological target, and is a useful approach to explore the bioactive conformation of flexible molecules and to refine models of ligand-receptor interactions [44–46]. Therefore, we evaluated if the replacement of the flexible tetramethylene chain in **1** with a phenyl ring is tolerated by the hH_4R. The substituents at the cyanoguanidine (''eastern part'' of the molecule) were selected with respect to comparison of the structure-activity relationships with those of recently published flexible compounds [28].

The amines **2**, **16** and **18** were devoid of agonistic activity in the [^{35}S]GTPγS assay on hH_3R and hH_4R. VUF5801 (**2**) showed inverse agonism at both, the hH_4R (K_B 2500 nM, α −0.64) and the hH_3R (K_B 1260 nM, α −0.57); the K_B values correspond to published binding data of **2** [34]. The *meta*-isomer **16** is a weak antagonist at the hH_4R and the hH_3R (K_B >10 000 nM), whereas the homologue **18** turned out to prefer the hH_3R: Compound **18** is a weak antagonist at the hH_4R (K_B >10 000 nM) and an inverse agonist at the hH_3R (K_B 430 nM, α −1.3).

Similar to the results for the building blocks **2**, **16** and **18**, none of the synthesized cyanoguanidines showed agonistic activity, neither at the hH_4R nor at the hH_3R. The determined K_B values for antagonistic/inverse agonistic activity were above 10 μM except for several compounds bearing bulkier alkyl or phenyl(thio)alkyl substituents at the cyanoguanidine

Table 1. Potencies and efficacies of the synthesized cyanoguanidines **30–44** and the amines **2**, **16** and **18** at the hH_3R and hH_4R in the [^{35}S]GTPγS assay.[a]



Compound no.	Phenyl substitution	R	hH_3R			hH_4R		
			(EC_{50}) or K_B (nM)	α	N	(EC_{50}) or K_B (nM)	α	N
Histamine			(13 ± 2)	1	3	(11 ± 3)	1	5
UR-PI376 (**1**)			720 ± 38	−0.52	2	(37 ± 3)	0.88	3
VUF5801[b] (**2**)	*para*	-NH_2	1260 ± 50	−0.57	2	2500 ± 126	−0.64	2
16	*meta*	-NH_2	>10 000	−0.09	2	>10 000	−0.06	2
18	*meta*	-CH_2NH_2	430 ± 10	−1.3	2	>10 000	0.09	2
30		-CH_3	>10 000	−0.06	4	>10 000	−0.16	4
31		-cPr	>10 000	−0.01	4	>10 000	−0.18	4
32		-$CH_2CH(CH_3)_2$	>10 000	−0.05	4	>10 000	−0.21	4
33		-$(CH_2)_3$-Ph	>10 000	−0.23	4	>10 000	−0.28	4
34		-$(CH_2)_2$-S-Ph	>10 000	−0.15	3	5200 ± 150	−0.19	2
35	*para*	-CH_3	>10 000	0.02	3	>10 000	−0.03	2
36	*para*	-cPr	>10 000	−0.11	3	>10 000	−0.11	2
37	*para*	-$CH_2CH(CH_3)_2$	>10 000	−0.05	3	1970 ± 470	−0.1	3
38	*para*	-$(CH_2)_3$-Ph	4100 ± 200	−0.06	3	2400 ± 100	−0.19	2
39	*para*	-$(CH_2)_2$-S-Ph	4585 ± 850	−0.06	3	935 ± 13	−0.21	2
40	*meta*	-CH_3	>10 000	0.05	3	>10 000	0.08	2
41	*meta*	-cPr	>10 000	−0.01	3	>10 000	−0.1	2
42	*meta*	-$CH_2CH(CH_3)_2$	6700 ± 200	−0.09	3	>10 000	−0.13	2
43	*meta*	-$(CH_2)_3$-Ph	>10 000	0.01	2	>10 000	−0.23	2
44	*meta*	-$(CH_2)_2$-S-Ph	1100 ± 200	−0.13	3	>10 000	−0.31	2

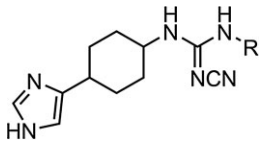
[a]Functional [^{35}S]GTPγS binding assay with membrane preparations of Sf9 cells expressing the $hH_3R + G\alpha_{i2} + G\beta_1\gamma_2$ or the $hH_4R + G\alpha_{i2} + G\beta_1\gamma_2$ was performed as described in the Section Pharmacology. N gives the number of independent experiments performed in duplicate each. The intrinsic activity (α) of histamine was set to 1.00 and α values of other compounds were referred to this value. The α values of neutral antagonists and inverse agonists were determined at a concentration of 10 μM. The K_B values of neutral antagonists and inverse agonists were determined in the antagonist mode versus histamine (100 nM) as the agonist. [b]Published pK_i values measured by [^{3}H]-histamine (H_4R) or [^{3}H]-N^α-methylhistamine (H_3R) binding to membranes of SK-N-MC cells expressing the human H_4 or H_3 receptor in presence of the ligand: pK_i (hH_4R) 5.8, pK_i (hH_3R) 6.0 [34].

moiety (K_B values in the range of 1–5 μM). The activities of the compounds at the hH_4R and hH_3R were not significantly affected by the substitution pattern. Obviously, the phenylene linker is too rigid to enable optimal orientation of the ligand in the binding pocket. Additionally, the change in electronic properties due to the additional π-system might contribute to the dramatic decrease in affinity for hH_3R and hH_4R compared to compound **1**.

Imidazolylcyclohexylcyanoguanidines 53–56 (Table 2)

The compounds with a cyclohexylene instead of a phenylene spacer retain some conformational flexibility. The *cis*- and *trans*-configured amines VUF5803 (**3**) and VUF5804 (**4**), which were used as building blocks, proved to be partial agonists (α: 0.7–0.9) in the [^{35}S]GTPγS assay at both histamine receptor subtypes. The *cis*-isomer prefers the hH_4R (EC_{50} values: hH_4R 15 nM, hH_3R: 115 nM) while higher potency at the hH_3R resides in the *trans*-isomer (EC_{50} values: hH_4R 300 nM, hH_3R 46 nM). The potencies in the [^{35}S]GTPγS assay correspond to published binding data for **3** and **4** [34]. The compounds **53–56** were synthesized as prototypical cyanoguanidines reminiscent of characteristic structural features of OUP-16 [33] and UR-PI376 (**1**), respectively. The investigation in the [^{35}S]GTPγS assay revealed that the phenylthioethyl substituted cyanoguanidines **55** and **56** were superior to the methyl substituted analogues. This is in agreement with structure-activity relationships of flexible cyanoguanidines [28], corroborating that arylalkyl residues are suitable to increase the affinity for both receptors compared to the methyl substitution. Similar to **3** and **4** the

Table 2. Potencies and efficacies of the synthesized cyanoguanidines **53–56** and the amines **3**, **4** at the hH_3R and hH_4R in the [^{35}S]GTPγS assay.[a]



Compound	Config.	R	hH_3R			hH_4R		
			(EC_{50}) or K_B (nM)	α	N	(EC_{50}) or K_B (nM)	α	N
Histamine			(13 ± 2)	1	3	(11 ± 3)	1	5
VUF5803[b] (**3**)	*cis*		(115 ± 11)	0.87	2	(15 ± 1)	0.88	2
VUF5804[b] (**4**)	*trans*		(46 ± 7)	0.71	2	(300 ± 20)	0.92	2
53	*trans*	-CH_3	>10 000	−0.38	2	>10 000	−0.01	2
54	*cis*	-CH_3	(>10 000)	0.41	3	(1840 ± 40)	0.55	2
55	*trans*	-$(CH_2)_2$-S-Ph	180 ± 16	−0.62	2	188 ± 5	−0.02	2
56	*cis*	-$(CH_2)_2$-S-Ph	1900 ± 300	−0.86	2	(110 ± 7)	0.32	3

[a]Functional [^{35}S]GTPγS binding assay with membrane preparations of Sf9 cells expressing the $hH_3R + G\alpha_{i2} + G\beta_1\gamma_2$ or the $hH_4R + G\alpha_{i2} + G\beta_1\gamma_2$ was performed as described in the Section Pharmacology. N gives the number of independent experiments performed in duplicate each. The intrinsic activity (α) of histamine was set to 1.00 and α values of other compounds were referred to this value. α values of neutral antagonists and inverse agonists were determined at 10 μM. The K_B values of neutral antagonists and inverse agonists were determined in the antagonist mode versus histamine (100 nM) as the agonist. [b]Published pK_i values measured by [^{3}H]-histamine (H_4) or [^{3}H]-N^{α}-methylhistamine (H_3) binding to membranes of SK-N-MC cells expressing the human H_4 or H_3 receptor in presence of the ligand: VUF5803: pK_i (hH_4R) 7.7, pK_i (hH_3R) 7.0; VUF5804: pK_i (hH_4R) 6.5, pK_i (hH_3R) 7.4 [34].

preference for hH_3R and hH_4R depends on the stereochemistry with higher activities at the hH_4R residing in the *cis*-isomers. However the cyanoguanidines are less potent partial agonists than the corresponding amines and show some efficacy-selectivity depending on the configuration. At the hH_4R both *cis*-configured compounds (**54**, **56**) are hH_4R partial agonists (α: 0.55 and 0.32) while the *trans*-isomers (**53**, **55**) are neutral antagonists. At the hH_3R only the methyl substituted *cis*-configured compound **54** is a weak partial agonist, whereas the other three cyanoguanidines act as inverse agonists with intrinsic activities from −0.38 to −0.86. The *trans*-isomer **55** is by a factor of 10 more potent than the corresponding *cis*-diastereomer **56** at the hH_3R.

Conformational constraints are, in principle, tolerated in cyanoguanidine-type hH_3R and hH_4R ligands. The planar geometry of a phenylene spacer proved to be inappropriate. By contrast, conformationally constrained analogues of cyanoguanidine-type hH_4R agonists like UR-PI376 (**1**), in which the flexible tetramethylene chain was replaced by a *cis*-configured 1,4-cyclohexylene spacer, turned out to be moderately potent and selective hH_4R agonists. The same holds for the building block, *cis*-4-(1*H*-imidazol-4-yl)cyclohexylamine. The situation is less clear in case of the *trans*-configured analogues, but there is a tendency toward preference for the hH_3R.

In conclusion, the results suggest the optimization of imidazolylcycloalkylcyanoguanidines with regard to ring size, balance between rigidification and flexibility, regioisomers and stereochemical properties to explore the three-dimensional requirements of high hH_4R affinity and selectivity.

Experimental

Chemistry

Commercial reagents and chemicals were purchased from Acros Organics (Geel, Belgium), IRIS Biotech GmbH (Marktredwitz, Germany), Alfa Aesar GmbH & Co. KG (Karlsruhe, Germany), Merck KGaA (Darmstadt, Germany), Sigma-Aldrich Chemie GmbH (Munich, Germany), TCI Europe (Zwijndrecht, Belgium) and used without further purification. Deuterated solvents for NMR spectroscopy were from Deutero GmbH (Kastellaun, Germany). All solvents were of analytical grade or distilled prior to use. If moisture-free conditions were required, reactions were performed in dried glassware under inert atmosphere (argon or nitrogen). Anhydrous DMF was purchased from Sigma-Aldrich Chemie GmbH. Flash chromatography was performed on silica gel (Merck silica gel 60, 40–63 μM). Reactions were monitored by TLC (DCM/MeOH 90:10 v/v) on aluminum plates coated with silica gel (Merck silica gel 60 F_{254}, thickness 0.2 mm). The compounds were detected by UV light (254 nm), a 0.3% solution of ninhydrine in *n*-butanol (amines) or a 1.0% solution of Fast Blue B salt (imidazole containing compounds) in EtOH/H_2O 30:70 (v/v). All melting points are uncorrected and were measured on a Büchi 530 (Büchi GmbH, Essen, Germany) apparatus. Microwave assisted reactions were performed on an Initiator 2.0 synthesizer (Biotage, Uppsala, Sweden).

Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded with Bruker Avance 300 (^{1}H: 300.1 MHz, ^{13}C: 75.5 MHz) NMR spectrometers (Bruker BioSpin GmbH,

Rheinstetten, Germany). Chemical shifts are given in δ (ppm) relative to external standards. The multiplicity of carbon atoms (^{13}C-NMR) was determined by DEPT 135 (distortionless enhancement by polarization transfer). Mass spectra (MS) were recorded on a Finnigan MAT 95 (EI-MS 70 eV, HR-MS), Finnigan SSQ 710A (CI-MS (NH_3)) and on a Finnigan ThermoQuest TSQ 7000 (ES-MS) spectrometer. The peak-intensity in % relative to the strongest signal is indicated in parenthesis. Elemental analyses (C, H, N, Heraeus Elementar Vario EL III) were performed by the Analytical Department of the University Regensburg and are within ±0.4% unless otherwise noted.

Purity of tested compounds was >95% as determined by high-performance liquid chromatography.

*General procedure for the synthesis of compounds **35–44** [38, 47]*

The respective isourea **45** or **46** (1 eq) and the pertinent primary amine **20–24** (1 eq) in MeCN were heated by microwave irradiation at 140°C for 15 min. After removal of the solvent *in vacuo*, the crude product was purified by flash chromatography (DCM/MeOH 98:2 to 80:20 v/v).

*2-Cyano-1-[4-(1H-imidazol-4-yl)phenyl]-3-methylguanidine **35***

Compound **35** was prepared from **45** (0.09 g, 0.3 mmol) and a 33% solution of methylamine in ethanol (0.037 mL, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.06 g, 83%); mp 138°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 2.84 (s, 3H, C*H*$_3$), 7.28 (d, 2H, ^3J = 8.5 Hz, Ph-*H*), 7.44 (s, 1H, Im-*H*-5), 7.72 (d, 2H, ^3J = 8.6 Hz, Ph-*H*), 7.76 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 29.00 (+, *C*H$_3$), 116.42 (+, Im-*C*-5), 119.36 (C_{quat}, *C*≡N), 126.45 (+, 2 Ph-*C*), 126.78 (+, 2 Ph-*C*), 132.61 (C_{quat}, Ph-*C*), 136.77 (C_{quat}, Im-*C*-4), 137.27 (+, Im-*C*-2), 139.30 (C_{quat}, Ph-*C*), 161.01 (C_{quat}, *C*=N). HRMS (EI-MS) calcd. for $C_{12}H_{12}N_6$ [$M^{+\cdot}$] 240.1123; found 240.1120. Anal. ($C_{12}H_{12}N_6 \cdot 0.4\ CH_3OH \cdot 0.6\ H_2O$) C, H, N. $C_{12}H_{12}N_6$ (240.26).

*2-Cyano-3-cyclopropyl-1-[4-(1H-imidazol-4-yl)-phenyl]guanidine **36***

Compound **36** was prepared from **45** (0.09 g, 0.3 mmol) and cyclopropylamine (0.021 mL, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.05 g, 62%); mp 215°C (dec.); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 0.70 (m, 2H, C*H*$_2$), 0.87 (m, 2H, C*H*$_2$), 2.67 (m, 1H, C*H*), 7.36 (d, 2H, ^3J = 8.6 Hz, Ph-*H*), 7.42 (s, 1H, Im-*H*-5), 7.69 (d, 2H, ^3J = 8.6 Hz, Ph-*H*), 7.73 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 8.33 (−, 2 *C*H$_2$), 24.47 (+, *C*H), 116.45 (+, Im-*C*-5), 118.94 (C_{quat}, *C*≡N), 125.56 (+, 2 Ph-*C*), 126.30 (+, 2 Ph-*C*), 131.84 (C_{quat}, Ph-*C*), 137.17 (C_{quat}, Im-*C*-4), 137.27 (+, Im-*C*-2), 139.25 (C_{quat}, Ph-*C*), 161.43 (C_{quat}, *C*=N). HRMS (EI-MS) calcd. for $C_{14}H_{14}N_6$ [$M^{+\cdot}$] 266.1280; found 266.1280. Anal. ($C_{14}H_{14}N_6 \cdot 0.6\ CH_3OH$) C, H, N. $C_{14}H_{14}N_6$ (266.30).

*2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-isobutylguanidine **37***

Compound **37** was prepared from **45** (0.09 g, 0.3 mmol) and isobutylamine (0.03 mL, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.08 g, 94%); mp 103°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 0.91 (d, 6H, ^3J = 6.7 Hz, 2 C*H*$_3$), 1.88 (m, 1H, C*H*), 3.08 (d, 2H, ^3J = 7.1 Hz, C*H*$_2$CH), 7.27 (d, 2H, ^3J = 8.6 Hz, Ph-*H*), 7.45 (s, 1H, Im-*H*-5), 7.74 (d, 2H, ^3J = 8.6 Hz, Ph-*H*), 7.74 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 20.38 (+, 2 *C*H$_3$), 29.66 (+, *C*H), 50.23 (−, *C*H$_2$), 116.37 (+, Im-*C*-5), 119.37 (C_{quat}, *C*≡N), 126.48 (+, 2 Ph-*C*), 126.89 (+, 2 Ph-*C*), 132.79 (C_{quat}, Ph-*C*), 136.74 (C_{quat}, Im-*C*-4), 137.29 (+, Im-*C*-2), 139.37 (C_{quat}, Ph-*C*), 160.46 (C_{quat}, *C*=N). HRMS (EI-MS) calcd. for $C_{15}H_{18}N_6$ [$M^{+\cdot}$] 282.1593; found 282.1592. Anal. ($C_{15}H_{18}N_6 \cdot 0.4\ CH_3OH$) C, H, N. $C_{15}H_{18}N_6$ (282.34).

*2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-(3-phenylpropyl)guanidine **38***

Compound **38** was prepared from **45** (0.076 g, 0.25 mmol) and 3-phenylpropan-1-amine (0.036 mL, 0.25 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.07 g, 81%); mp 88°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.86 (m, 2H, C*H*$_2$CH$_2$Ph), 2.63 (t, 2H, ^3J = 7.5 Hz, C*H*$_2$Ph), 3.28 (t, 2H, ^3J = 7.2 Hz, NC*H*$_2$), 7.11–7.29 (m, 7H, Ph-*H*), 7.44 (s, 1H, Im-*H*-5), 7.73 (d, 2H, ^3J = 8.6 Hz, Ph-*H*), 7.73 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 32.29 (−, *C*H$_2$), 34.12 (−, *C*H$_2$), 42.67 (−, *C*H$_2$), 116.39 (+, Im-*C*-5), 120.18 (C_{quat}, *C*≡N), 126.43 (+, 2 Ph-*C*), 126.89 (+, 2 Ph-*C*), 127.01 (+, Ph-*C*), 129.45 (+, 2 Ph-*C*), 129.50 (+, 2 Ph-*C*), 132.80 (C_{quat}, Ph-*C*), 136.69 (C_{quat}, Im-*C*-4), 137.29 (+, Im-*C*-2), 140.41 (C_{quat}, Ph-*C*), 142.90 (C_{quat}, Ph-*C*), 160.32 (C_{quat}, *C*=N). HRMS (EI-MS) calcd. for $C_{20}H_{20}N_6$ [$M^{+\cdot}$] 344.1749; found 344.1745. Anal. ($C_{20}H_{20}N_6 \cdot 0.5\ H_2O$) C, H, N. $C_{20}H_{20}N_6$ (344.41).

*2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-[2-(phenylthio)ethyl]guanidine **39***

Compound **39** was prepared from **45** (0.076 g, 0.25 mmol) and 2-(phenylthio)ethanamine (0.038 g, 0.25 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.08 g, 88%); mp 140°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 3.10 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$), 3.44 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$), 7.20 (m, 3H, Ph-*H*), 7.29 (m, 2H, Ph-*H*), 7.38 (m, 2H, Ph-*H*), 7.45 (s, 1H, Im-*H*-5), 7.74 (d, 2H, ^3J = 8.5 Hz, Ph-*H*), 7.74 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 33.32 (−, SC*H*$_2$), 42.29 (−, *C*H$_2$), 116.45 (+, Im-*C*-5), 120.31 (C_{quat}, *C*≡N), 126.77 (+, 2 Ph-*C*), 126.98 (+, 2 Ph-*C*), 127.29 (+, Ph-*C*), 130.16 (+, 2 Ph-*C*), 130.31 (+, 2 Ph-*C*), 133.13 (C_{quat}, Ph-*C*), 136.30 (C_{quat}, Im-*C*-4), 136.95 (C_{quat}, Ph-*C*), 137.33 (+, Im-*C*-2), 139.89 (C_{quat}, Ph-*C*), 160.32 (C_{quat}, *C*=N). HRMS (EI-MS) calcd. for $C_{19}H_{18}N_6S$ [$M^{+\cdot}$] 362.1314; found 362.1306. Anal. ($C_{19}H_{18}N_6S \cdot 0.1\ CH_3OH$) C, H, N. $C_{19}H_{18}N_6S$ (362.45).

*2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-methylguanidine **40***

Compound **40** was prepared from **46** (0.09 g, 0.3 mmol) and a 33% solution of methylamine in ethanol (0.037 mL, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.015 g, 21%); mp 97°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 2.84 (s, 3H, C*H*$_3$), 7.15 (d, 1H, ^3J = 8.5 Hz, Ph-*H*), 7.40 (t, 1H, ^3J = 8.1 Hz, Ph-*H*), 7.48 (s, 1H, Im-*H*-5), 7.58–7.61 (m, 2H, Ph-*H*), 7.74 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.97 (+, *C*H$_3$), 116.46 (+, Im-*C*-5), 119.32 (C_{quat}, *C*≡N), 122.53 (+, Ph-*C*), 123.89 (+, Ph-*C*), 124.56 (+, Ph-*C*), 124.11 (C_{quat}, Ph-*C*), 130.85 (+, Ph-*C*), 135.81 (C_{quat}, Im-*C*-4), 137.35 (+, Im-*C*-2), 138.64 (C_{quat}, Ph-*C*), 161.03 (C_{quat}, *C*=N). HRMS (EI-MS) calcd. for $C_{12}H_{12}N_6$ [$M^{+\cdot}$] 240.1123; found 240.1120. Anal. ($C_{12}H_{12}N_6 \cdot 0.5\ CH_3OH \cdot 0.3\ H_2O$) C, H, N. $C_{12}H_{12}N_6$ (240.26).

2-Cyano-3-cyclopropyl-1-[3-(1H-imidazol-4-yl)-phenyl]guanidine ***41***

Compound **41** was prepared from **46** (0.09 g, 0.3 mmol) and cyclopropylamine (0.021 mL, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.05 g, 63%); mp 137°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 0.71 (m, 2H, C*H*$_2$), 0.87 (m, 2H, C*H*$_2$), 2.68 (m, 1H, C*H*), 7.23 (d, 1H, ^3J = 8.0 Hz, Ph-*H*), 7.35 (t, 1H, ^3J = 8.0 Hz, Ph-*H*), 7.44 (s, 1H, Im-*H*-5), 7.54 (d, 1H, ^3J = 7.8 Hz, Ph-*H*), 7.66 (s, 1H, Ph-*H*), 7.73 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 8.31 (−, 2 *C*H$_2$), 24.50 (+, *C*H), 116.41 (+, Im-*C*-5), 118.94 (C$_{quat}$, *C*≡N), 121.83 (+, Ph-*C*), 123.24 (+, Ph-*C*), 123.94 (+, Ph-*C*), 130.33 (+, Ph-*C*), 133.80 (C$_{quat}$, Ph-*C*), 137.07 (C$_{quat}$, Im-*C*-4), 137.29 (+, Im-*C*-2), 139.03 (C$_{quat}$, Ph-*C*), 161.58 (C$_{quat}$, *C*=N). HRMS (LSI-MS) calcd. for $C_{14}H_{15}N_6$ [MH$^+$] 267.1358; found 267.1357. Anal. ($C_{14}H_{14}N_6 \cdot 0.9\ CH_3OH$) C, H, N. $C_{14}H_{14}N_6$ (266.30).

2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-isobutylguanidine ***42***

Compound **42** was prepared from **46** (0.09 g, 0.3 mmol) and isobutylamine (0.03 mL, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.06 g, 71%); mp 95°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 0.91 (d, 6H, ^3J = 6.7 Hz, C*H*$_3$), 1.88 (m, 1H, C*H*), 3.08 (d, 2H, ^3J = 7.1 Hz, C*H*$_2$CH), 7.14 (d, 1H, ^3J = 7.8 Hz, Ph-*H*), 7.40 (t, 1H, ^3J = 7.7 Hz, Ph-*H*), 7.47 (s, 1H, Im-*H*-5), 7.60 (m, 2H, Ph-*H*), 7.74 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 20.39 (+, 2 *C*H$_3$), 29.64 (+, *C*H), 50.24 (−, *C*H$_2$), 116.58 (+, Im-*C*-5), 119.38 (C$_{quat}$, *C*≡N), 122.53 (+, Ph-*C*), 123.91 (+, Ph-*C*), 124.50 (+, Ph-*C*), 130.94 (+, Ph-*C*), 130.28 (C$_{quat}$, Ph-*C*), 136.22 (C$_{quat}$, Im-*C*-4), 137.37 (+, Im-*C*-2), 138.68 (C$_{quat}$, Ph-*C*), 160.47 (C$_{quat}$, *C*=N). HRMS (LSI-MS) calcd. for $C_{15}H_{19}N_6$ [MH$^+$] 283.1671; found 283.1674. Anal. ($C_{15}H_{18}N_6 \cdot 0.75\ CH_3OH$) C, H, N. $C_{15}H_{18}N_6$ (282.34).

2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-(3-phenylpropyl)guanidine ***43***

Compound **43** was prepared from **46** (0.076 g, 0.25 mmol) and 3-phenylpropan-1-amine (0.036 mL, 0.25 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.07 g, 81%); mp 78°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.86 (m, 2H, C*H*$_2$CH$_2$Ph), 2.63 (t, 2H, ^3J = 7.9 Hz, C*H*$_2$Ph), 3.29 (t, 2H, ^3J = 7.2 Hz, NC*H*$_2$), 7.09–7.26 (m, 6H, Ph-*H*), 7.40 (t, 1H, ^3J = 8.2 Hz, Ph-*H*), 7.46 (s, 1H, Im-*H*-5), 7.59 (m, 2H, Ph-*H*), 7.74 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 32.27 (−, *C*H$_2$), 34.11 (−, *C*H$_2$), 42.68 (−, *C*H$_2$), 116.43 (+, Im-*C*-5), 119.39 (C$_{quat}$, *C*≡N), 122.51 (+, Ph-*C*), 123.92 (+, Ph-*C*), 124.49 (+, Ph-*C*), 126.99 (+, Ph-*C*), 129.44 (+, 2 Ph-*C*), 129.47 (+, 2 Ph-*C*), 130.96 (+, Ph-*C*), 134.78 (C$_{quat}$, Im-*C*-4), 136.20 (C$_{quat}$, Ph-*C*), 137.37 (+, Im-*C*-2), 138.64 (C$_{quat}$, Ph-*C*), 142.90 (C$_{quat}$, Ph-*C*), 160.25 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{20}H_{20}N_6$ [M$^{+\cdot}$] 344.1749; found 344.1740. Anal. ($C_{20}H_{20}N_6 \cdot 0.6\ CH_3OH$) C, H, N. $C_{20}H_{20}N_6$ (344.41).

2-Cyano-1-[3-(1H-imidazol-4-yl)phenyl]-3-[2-(phenylthio)ethyl]guanidine ***44***

Compound **44** was prepared from **46** (0.076 g, 0.25 mmol) and 2-(phenylthio)ethanamine (0.038 g, 0.25 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.05 g, 55%); mp 51°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 3.11 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$), 3.44 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$), 7.08–7.19 (m, 2H, Ph-*H*), 7.27 (m, 2H, Ph-*H*), 7.39 (m, 3H, Ph-*H*), 7.48 (s, 1H, Im-*H*-5), 7.61 (m, 2H, Ph-*H*), 7.75 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 33.26 (−, S*C*H$_2$), 42.21 (−, *C*H$_2$), 116.75 (+, Im-*C*-5), 120.21 (C$_{quat}$, *C*≡N), 122.76 (+, Ph-*C*), 124.18 (+, Ph-*C*), 124.71 (+, Ph-*C*), 127.26 (+, Ph-*C*), 130.14 (+, 2 Ph-*C*), 130.28 (+, 2 Ph-*C*), 131.08 (+, Ph-*C*), 133.43 (C$_{quat}$, Ph-*C*), 136.91 (C$_{quat}$, Ph-*C*), 137.04 (C$_{quat}$, Im-*C*-4), 137.40 (+, Im-*C*-2), 138.31 (C$_{quat}$, Ph-*C*), 160.30 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{19}H_{18}N_6S$ [M$^{+\cdot}$] 362.1314; found 362.1309. $C_{19}H_{18}N_6S$ (362.45).

General procedure for the synthesis of compounds ***30–34*** *and* ***53–56*** *[38, 47]*

Hydrochlorides of **3**, **4** and **18** were converted into the bases by passing a basic ion exchanger (Merck, ion exchanger III, mobile phase: MeOH). The respective isourea (1 eq) and the pertinent amine (1 eq) in MeCN were heated by microwave irradiation at 140°C for 15 min. After removal of the solvent *in vacuo*, the crude product was purified by flash chromatography (DCM/MeOH 98:2 to 80:20 v/v).

2-Cyano-1-[3-(1H-imidazol-4-yl)benzyl]-3-methylguanidine ***30***

Compound **30** was prepared from **18** (0.05 g, 0.3 mmol) and **25** (0.051 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.06 g, 82%); mp 77°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 2.82 (s, 3H, C*H*$_3$), 4.44 (s, 2H, C*H*$_2$), 7.18 (d, 1H, ^3J = 7.6 Hz, Ph-*H*), 7.34 (t, 1H, ^3J = 7.7 Hz, Ph-*H*), 7.43 (s, 1H, Im-*H*-5), 7.60 (d, 1H, ^3J = 7.8 Hz, Ph-*H*), 7.64 (s, 1H, Ph-*H*), 7.75 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.82 (+, *C*H$_3$), 46.04 (−, *C*H$_2$), 116.45 (+, Im-*C*-5), 121.02 (C$_{quat}$, *C*≡N), 124.76 (+, Ph-*C*), 124.94 (+, Ph-*C*), 126.79 (+, Ph-*C*), 127.33 (C$_{quat}$, Ph-*C*), 130.03 (+, Ph-*C*), 133.42 (C$_{quat}$, Im-*C*-4), 134.75 (+, Im-*C*-2), 140.29 (C$_{quat}$, Ph-*C*), 162.13 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{13}H_{14}N_6$ [M$^{+\cdot}$] 254.1280; found 254.1281. Anal. ($C_{13}H_{14}N_6 \cdot 0.75\ CH_3OH$) C, H, N. $C_{13}H_{14}N_6$ (254.29).

2-Cyano-3-cyclopropyl-1-[3-(1H-imidazol-4-yl)benzyl]guanidine ***31***

Compound **31** was prepared from **18** (0.05 g, 0.3 mmol) and **26** (0.058 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.07 g, 87%); mp 62°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 0.63 (m, 2H, C*H*$_2$), 0.82 (m, 2H, C*H*$_2$), 2.52 (m, 1H, C*H*), 4.49 (s, 2H, C*H*$_2$), 7.19 (d, 1H, ^3J = 7.6 Hz, Ph-*H*), 7.34 (t, 1H, ^3J = 7.6 Hz, Ph-*H*), 7.44 (s, 1H, Im-*H*-5), 7.59 (d, 1H, ^3J = 7.7 Hz, Ph-*H*), 7.64 (s, 1H, Ph-*H*), 7.76 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 8.16 (−, 2 *C*H$_2$), 23.87 (+, *C*H), 46.01 (−, *C*H$_2$), 116.77 (+, Im-*C*-5), 120.61 (C$_{quat}$, *C*≡N), 124.84 (+, 2 Ph-*C*), 126.88 (+, Ph-*C*), 126.99 (C$_{quat}$, Ph-*C*), 129.99 (+, Ph-*C*), 134.56 (C$_{quat}$, Im-*C*-4), 134.62 (+, Im-*C*-2), 140.67 (C$_{quat}$, Ph-*C*), 162.64 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{15}H_{16}N_6$ [M$^{+\cdot}$] 280.1436; found 280.1435. Anal. ($C_{15}H_{16}N_6 \cdot 1.5\ CH_3OH$) C, H, N. $C_{15}H_{16}N_6$ (280.33).

2-Cyano-1-[3-(1H-imidazol-4-yl)benzyl]-3-isobutylguanidine ***32***

Compound **32** was prepared from **18** (0.05 g, 0.3 mmol) and **27** (0.063 g, 0.3 mmol) in MeCN (4.5 mL) according to the general

procedure. Flash chromatography yielded a yellow solid (0.07 g, 82%); mp 75°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 0.84 (d, 6H, ^3J = 6.7 Hz, C*H*$_3$), 1.80 (m, 1H, C*H*), 3.02 (d, 2H, ^3J = 7.1 Hz, C*H*$_2$CH), 4.46 (s, 2H, PhC*H*$_2$), 7.19 (d, 1H, ^3J = 7.6 Hz, Ph-*H*), 7.35 (t, 1H, ^3J = 7.6 Hz, Ph-*H*), 7.42 (s, 1H, Im-*H*-5), 7.61 (d, 1H, ^3J = 7.9 Hz, Ph-*H*), 7.64 (s, 1H, Ph-*H*), 7.74 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 20.22 (+, 2 *C*H$_3$), 29.56 (+, *C*H), 46.04 (−, *C*H$_2$), 50.11 (−, *C*H$_2$), 115.39 (+, Im-*C*-5), 120.70 (C$_{quat}$, *C*≡N), 124.74 (+, Ph-*C*), 124.98 (+, Ph-*C*), 126.67 (+, Ph-*C*), 127.99 (C$_{quat}$, Ph-*C*), 130.09 (+, Ph-*C*), 134.86 (+, Im-*C*-2), 135.24 (C$_{quat}$, Im-*C*-4), 140.08 (C$_{quat}$, Ph-*C*), 161.42 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{16}H_{20}N_6$ [$M^{+\cdot}$] 296.1749; found 296.1749. Anal. ($C_{16}H_{20}N_6$) C, H, N. $C_{16}H_{20}N_6$ (296.37).

2-Cyano-1-[3-(1H-imidazol-4-yl)benzyl]-3-(3-phenylpropyl)guanidine ***33***

Compound **33** was prepared from **18** (0.04 g, 0.23 mmol) and **28** (0.065 g, 0.23 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.065 g, 79%); mp 59°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.80 (m, 2H, C*H*$_2$CH$_2$Ph), 2.52 (t, 2H, ^3J = 7.5 Hz, C*H*$_2$Ph), 3.22 (t, 2H, ^3J = 7.0 Hz, NC*H*$_2$), 4.44 (s, 2H, PhC*H*$_2$N), 7.08 (m, 3H, Ph-*H*), 7.19 (m, 3H, Ph-*H*), 7.35 (t, 1H, ^3J = 7.7 Hz, Ph-*H*), 7.42 (s, 1H, Im-*H*-5), 7.61 (d, 1H, ^3J = 7.7 Hz, Ph-*H*), 7.66 (s, 1H, Ph-*H*), 7.73 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 32.23 (−, *C*H$_2$), 33.81 (−, *C*H$_2$), 42.35 (−, *C*H$_2$), 46.03 (−, *C*H$_2$), 115.44 (+, Im-*C*-5), 120.10 (C$_{quat}$, *C*≡N), 124.71 (+, Ph-*C*), 125.02 (+, Ph-*C*), 126.70 (+, Ph-*C*), 126.94 (+, Ph-*C*), 127.44 (C$_{quat}$, Ph-*C*), 129.43 (+, 4 Ph-*C*), 130.13 (+, Ph-*C*), 134.90 (+, Im-*C*-2), 136.12 (C$_{quat}$, Im-*C*-4), 140.06 (C$_{quat}$, Ph-*C*), 142.78 (C$_{quat}$, Ph-*C*), 161.35 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{21}H_{22}N_6$ [$M^{+\cdot}$] 358.1906; found 358.1901. Anal. ($C_{21}H_{22}N_6 \cdot 0.3\ CH_3OH$) C, H, N. $C_{21}H_{22}N_6$ (358.44).

2-Cyano-1-[3-(1H-imidazol-4-yl)benzyl]-3-[2-(phenylthio)ethyl]guanidine ***34***

Compound **34** was prepared from **18** (0.04 g, 0.23 mmol) and **29** (0.069 g, 0.23 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.06 g, 70%); mp 64°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 3.05 (t, 2H, ^3J = 7.2 Hz, C*H*$_2$), 3.40 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$), 4.40 (s, 2H, PhC*H*$_2$N), 7.12–7.18 (m, 2H, Ph-*H*), 7.24 (m, 2H, Ph-*H*), 7.31–7.37 (m, 3H, Ph-*H*), 7.43 (s, 1H, Im-*H*-5), 7.62 (m, 2H, Ph-*H*), 7.73 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 33.63 (−, S*C*H$_2$), 42.16 (−, *C*H$_2$), 46.17 (−, *C*H$_2$), 118.36 (+, Im-*C*-5), 121.36 (C$_{quat}$, *C*≡N), 124.73 (+, Ph-*C*), 125.08 (+, Ph-*C*), 126.68 (+, Ph-*C*), 127.39 (+, Ph-*C*), 127.39 (C$_{quat}$, Ph-*C*), 130.14 (+, 3 Ph-*C*), 130.60 (+, 2 Ph-*C*), 136.74 (C$_{quat}$, Ph-*C*), 137.21 (+, Im-*C*-2), 137.26 (C$_{quat}$, Im-*C*-4), 139.65 (C$_{quat}$, Ph-*C*), 161.29 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{20}H_{20}N_6S$ [$M^{+\cdot}$] 376.1470; found 376.1467. Anal. ($C_{20}H_{20}N_6S \cdot 0.5\ CH_3OH \cdot 0.8\ H_2O$) C, H, N. $C_{20}H_{20}N_6S$ (376.48).

2-Cyano-1-[trans-4-(1H-imidazol-4-yl)cyclohexyl]-3-methylguanidine ***53***

Compound **53** was prepared from **4** (0.08 g, 0.48 mmol) and **25** (0.085 g, 0.48 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.11 g, 93%); mp 120–121°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.47 (m, 4H, C*H*$_2$), 2.05 (m, 4H, C*H*$_2$), 2.55 (m, 1H, C*H*-Im), 2.80 (s, 3H, C*H*$_3$-N), 3.59 (m, 1H, C*H*-N), 6.76 (s, 1H, Im-*H*-5), 7.55 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.78 (+, *C*H$_3$), 32.84 (−, 2 *C*H$_2$), 33.63 (−, 2 *C*H$_2$), 36.68 (+, *C*H-Im), 52.08 (+, *C*H-N), 115.93 (+, Im-*C*-5), 120.31 (C$_{quat}$, *C*≡N), 135.68 (+, Im-*C*-2), 143.15 (C$_{quat}$, Im-*C*-4), 161.23 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{12}H_{18}N_6$ [$M^{+\cdot}$] 246.1593; found 246.1592. Anal. ($C_{12}H_{18}N_6 \cdot 0.65\ H_2O$) C, H, N. $C_{12}H_{18}N_6$ (246.31).

2-Cyano-1-[cis-4-(1H-imidazol-4-yl)cyclohexyl]-3-methylguanidine ***54***

Compound **54** was prepared from **3** (0.08 g, 0.48 mmol) and **25** (0.085 g, 0.48 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.09 g, 76%); mp 125–127°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.71 (m, 4H, C*H*$_2$), 1.85 (m, 2H, C*H*$_2$), 1.95 (m, 2H, C*H*$_2$), 2.79 (s, 3H, C*H*$_3$-N), 2.84 (s, 1H, C*H*-Im), 3.76 (m, 1H, C*H*-N), 6.86 (s, 1H, Im-*H*-5), 7.59 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.79 (+, *C*H$_3$), 28.84 (−, 2 *C*H$_2$), 29.96 (−, 2 *C*H$_2$), 34.05 (+, *C*H-Im), 50.31 (+, *C*H-N), 117.56 (+, Im-*C*-5), 120.31 (C$_{quat}$, *C*≡N), 135.75 (+, Im-*C*-2), 141.54 (C$_{quat}$, Im-*C*-4), 161.20 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{12}H_{18}N_6$ [$M^{+\cdot}$] 246.1593; found 246.1593. Anal. ($C_{12}H_{18}N_6 \cdot 0.55\ H_2O$) C, H, N. $C_{12}H_{18}N_6$ (246.31).

2-Cyano-1-[trans-4-(1H-imidazol-4-yl)cyclohexyl]-3-[2-(phenylthio)ethyl]guanidine ***55***

Compound **55** was prepared from **4** (0.08 g, 0.48 mmol) and **29** (0.144 g, 0.48 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.12 g, 68%); mp 95–96°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.45 (m, 4H, C*H*$_2$), 2.03 (m, 4H, C*H*$_2$), 2.54 (m, 1H, C*H*-N), 3.11 (t, 2H, ^3J = 6.9 Hz, C*H*$_2$-N), 3.42 (t, 2H, ^3J = 6.9 Hz, C*H*$_2$-S), 3.45 (m, 1H, C*H*-Im), 6.75 (s, 1H, Im-*H*-5), 7.19 (m, 1H, Ph-*H*-4), 7.30 (m, 2H, Ph-*H*), 7.40 (m, 2H, Ph-*H*), 7.55 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 32.68 (−, 2 *C*H$_2$), 33.58 (−, 2 *C*H$_2$ + *C*H$_2$-S), 36.59 (+, *C*H-Im), 42.31 (−, *C*H$_2$-N), 52.12 (+, *C*H-N), 115.13 (+, Im-*C*-5), 119.97 (C$_{quat}$, *C*≡N), 127.34 (+, Ph-*C*-4), 130.18 (+, 2 Ph-*C*), 130.44 (+, 2 Ph-*C*), 135.35 (C$_{quat}$, Im-*C*-4), 135.70 (+, Im-*C*-2), 137.01 (C$_{quat}$, Ph-*C*-1), 160.28 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{19}H_{24}N_6S$ [$M^{+\cdot}$] 368.1783; found 368.1781. Anal. ($C_{14}H_{24}N_6S \cdot 0.25\ H_2O$) C, H, N. $C_{14}H_{24}N_6S$ (368.50).

2-Cyano-1-[cis-4-(1H-imidazol-4-yl)cyclohexyl]-3-[2-(phenylthio)ethyl]guanidine ***56***

Compound **56** was prepared from **3** (0.08 g, 0.48 mmol) and **29** (0.144 g, 0.48 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.13 g, 73%); mp 88–90°C; ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.70 (m, 4H, C*H*$_2$), 1.85 (m, 4H, C*H*$_2$), 2.80 (m, 1H, C*H*-N), 3.10 (t, 2H, ^3J = 6.8 Hz, C*H*$_2$-N), 3.43 (t, 2H, ^3J = 6.8 Hz, C*H*$_2$-S), 3.69 (s, 1H, C*H*-Im), 6.84 (s, 1H, Im-*H*-5), 7.17 (m, 1H, Ph-*H*-4), 7.28 (m, 2H, Ph-*H*), 7.39 (m, 2H, Ph-*H*), 7.58 (s, 1H, Im-*H*-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.64 (−, 2 *C*H$_2$), 30.03 (−, 2 *C*H$_2$), 33.70 (−, *C*H$_2$-S), 34.37 (+, *C*H-Im), 42.33 (−, *C*H$_2$-N), 49.91 (+, *C*H–N), 117.19 (+, Im-*C*-5), 120.04 (C$_{quat}$, *C*≡N), 127.35 (+, Ph-*C*-4), 130.17 (+, 2 Ph-*C*), 130.42 (+, 2 Ph-*C*), 135.77 (+, Im-*C*-2), 136.97 (C$_{quat}$, Ph-*C*-1), 141.92 (C$_{quat}$, Im-*C*-4), 160.32 (C$_{quat}$, *C*=N). HRMS (EI-MS) calcd. for $C_{19}H_{24}N_6S$ [$M^{+\cdot}$] 368.1783; found 368.1777. Anal. ($C_{14}H_{24}N_6S \cdot 0.25\ H_2O$) C, H, N. $C_{14}H_{24}N_6S$ (368.50).

Pharmacology

Histamine dihydrochloride was purchased from Alfa Aesar GmbH & Co. KG (Karlsruhe, Germany). Thioperamide hydrochlo-

ride was synthesized according to a previously described method [48]. Guanosine diphosphate (GDP) was from Sigma-Aldrich Chemie GmbH (Munich, Germany), unlabeled GTPγS was from Roche (Mannheim, Germany). [^{35}S]GTPγS was from PerkinElmer Life Sciences (Boston, MA). GF/C filters were from Whatman (Maidstone, UK).

[^{35}S]GTPγS binding assays were performed as previously described for the H_3R [49, 50] and H_4R [51]. H_3R assays: Sf9 insect cell membranes coexpressing the hH_3R, mammalian $G\alpha_{i2}$ and $G\beta_1\gamma_2$ were employed, H_4R assays: Sf9 insect cell membranes coexpressing the hH_4R, mammalian $G\alpha_{i2}$ and $G\beta_1\gamma_2$ were employed.

The respective membranes were thawed, sedimented by a 10-min centrifugation at 4°C and 13 000 × *g*. Membranes were resuspended in binding buffer (12.5 mM $MgCl_2$, 1 mM EDTA, and 75 mM Tris/HCl, pH 7.4). Each assay tube contained Sf9 membranes expressing the respective HR subtype (15–30 μg protein/tube), 1 μM GDP, 0.05% (w/v) bovine serum albumin, 0.2 nM [^{35}S]GTPγS and the investigated ligands (dissolved in a mixture (v/v) of 80% millipore water and 20% DMSO) at concentrations of 10 nM to 100 μM in binding buffer (total volume 250 μL). All H_4R assays additionally contained 100 mM NaCl.

For the determination of K_B values at hH_3R and hH_4R (antagonist mode of the [^{35}S]GTPγS binding assay) histamine was added to the reaction mixtures (final concentration: 100 nM). IC_{50} values were converted to K_B values using the Cheng-Prussoff equation [52]. Incubations were conducted for 90 min at 25°C and shaking at 250 rpm. Bound [^{35}S]GTPγS was separated from free [^{35}S]GTPγS by filtration through GF/C filters, followed by three washes with 2 mL of binding buffer (4°C) using a Brandel Harvester. Filter-bound radioactivity was determined after an equilibration phase of at least 12 h by liquid scintillation counting. The experimental conditions chosen ensured that no more than 10% of the total amount of [^{35}S]GTPγS added was bound to filters. Non-specific binding was determined in the presence of 10 μM unlabeled GTPγS.

The authors are grateful to Mrs. Maria Beer-Krön, Mrs. Gertraud Wilberg and Mrs. Sabine Dirrigl for expert technical assistance. This work was supported by the Graduate Training Program (Graduiertenkolleg) GRK 760, "Medicinal Chemistry: Molecular Recognition - Ligand-Receptor Interactions", of the Deutsche Forschungsgemeinschaft and by ESF COST Action BM0806, 'Recent advances in histamine receptor H_4R research'.

The authors have declared no conflict of interest.

References

[1] S. J. Hill, C. R. Ganellin, H. Timmerman, J.-C. Schwartz, N. P. Shankley, J. M. Young, W. Schunack, R. Levi, H. L. Haas, *Pharmacol. Rev.* **1997**, *49*, 253–278.

[2] L. B. Hough, *Mol. Pharmacol.* **2001**, *59*, 415–419.

[3] T. Oda, N. Morikawa, Y. Saito, Y. Masuho, S. Matsumoto, *J. Biol. Chem.* **2000**, *275*, 36781–36786.

[4] T. Nakamura, H. Itadani, Y. Hidaka, M. Ohta, K. Tanaka, *Biochem. Biophys. Res. Commun.* **2000**, *279*, 615–620.

[5] T. Nguyen, D. A. Shapiro, S. R. George, V. Setola, D. K. Lee, R. Cheng, L. Rauser, S. P. Lee, K. R. Lynch, B. L. Roth, B. F. O'Dowd, *Mol. Pharmacol.* **2001**, *59*, 427–433.

[6] Y. Zhu, D. Michalovich, H.-L. Wu, K. B. Tan, G. M. Dytko, I. J. Mannan, R. Boyce, J. Alston, L. A. Tierney, X. Li, N. C. Herrity, L. Vawter, H. M. Sarau, R. S. Ames, C. M. Davenport, J. P. Hieble, S. Wilson, D. J. Bergsma, L. R. Fitzgerald, *Mol. Pharmacol.* **2001**, *59*, 434–441.

[7] K. L. Morse, J. Behan, T. M. Laz, R. E. West, Jr, S. A. Greenfeder, J. C. Anthes, S. Umland, Y. Wan, R. W. Hipkin, W. Gonsiorek, N. Shin, E. L. Gustafson, X. Qiao, S. Wang, J. A. Hedrick, J. Greene, M. Bayne, F. .J Monsma, Jr, *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1058–1066.

[8] C. Liu, X.-J. Ma, X. Jiang, S. J. Wilson, C. L. Hofstra, J. Blevitt, J. Pyati, X. Li, W. Chai, N. Carruthers, T. W. Lovenberg, *Mol. Pharmacol.* **2001**, *59*, 420–426.

[9] F. Coge, S.-P. Guenin, H. Rique, J. A. Boutin, J.-P. Galizzi, *Biochem. Biophys. Res. Commun.* **2001**, *284*, 301–309.

[10] M. Gschwandtner, K. Rossbach, D. Dijkstra, W. Baumer, M. Kietzmann, H. Stark, T. Werfel, R. Gutzmer, *Allergy* **2010**, *65*, 840–849.

[11] E. Zampeli, E. Tiligada, *Br. J. Pharmacol.* **2009**, *157*, 24–33.

[12] F. Gantner, K. Sakai, M. W. Tusche, W. W. Cruikshank, D. M. Center, K. B. Bacon, *J. Pharmacol. Exp. Ther.* **2002**, *303*, 300–307.

[13] W. Bäumer, S. Wendorff, R. Gutzmer, T. Werfel, D. Dijkstra, P. Chazot, H. Stark, M. Kietzmann, *Allergy* **2008**, *63*, 1387–1394.

[14] R. Gutzmer, S. Mommert, M. Gschwandtner, K. Zwingmann, H. Stark, T. Werfel, *J. Allergy Clin. Immunol.* **2009**, *123*, 619–625.

[15] H. Engelhardt, R. A. Smits, R. Leurs, E. Haaksma, I. J. de Esch, *Curr. Opin. Drug Discov. Dev.* **2009**, *12*, 628–643.

[16] E. Tiligada, E. Zampeli, K. Sander, H. Stark, *Expert Opin. Investig. Drugs* **2009**, *18*, 1519–1531.

[17] R. Kiss, G. M. Keseru, *Expert Opin. Ther. Pat.* **2009**, *19*, 119–135.

[18] R. A. Smits, R. Leurs, I. J. P. de Esch, *Drug Discov. Today* **2009**, *14*, 745–753.

[19] J. M. Cowden, M. Zhang, P. J. Dunford, R. L. Thurmond, *J. Invest. Dermatol.* **2010**, *130*, 1023–1033.

[20] J. M. Cowden, J. P. Riley, J. Y. Ma, R. L. Thurmond, P. J. Dunford, *Respir. Res.* **2010**, *11*, 86.

[21] E. M. Rosethorne, S. J. Charlton, *Mol. Pharmacol.* **2010**, *79*, 749–757.

[22] J. A. Jablonowski, C. A. Grice, W. Chai, C. A. Dvorak, J. D. Venable, A. K. Kwok, K. S. Ly, J. Wei, S. M. Baker, P. J. Desai, W. Jiang, S. J. Wilson, R. L. Thurmond, L. Karlsson, J. P. Edwards, T. W. Lovenberg, N. I. Carruthers, *J. Med. Chem.* **2003**, *46*, 3957–3960.

[23] D. Neumann, S. Beermann, R. Seifert, *Pharmacology* **2010**, *85*, 217–223.

[24] R. Seifert, E. H. Schneider, S. Dove, I. Brunskole, D. Neumann, A. Strasser, A. Buschauer, *Mol. Pharmacol.* **2011**, *79*, 631–638.

[25] P. Igel, S. Dove, A. Buschauer, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7191–7199.

[26] P. Ghorai, A. Kraus, T. Birnkammer, R. Geyer, G. Bernhardt, S. Dove, R. Seifert, S. Elz, A. Buschauer, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3173–3176.

[27] P. Ghorai, A. Kraus, M. Keller, C. Götte, P. Igel, E. Schneider, D. Schnell, G. Bernhardt, S. Dove, M. Zabel, S. Elz, R. Seifert, A. Buschauer, *J. Med. Chem.* **2008**, *51*, 7193–7204.

[28] P. Igel, R. Geyer, A. Strasser, S. Dove, R. Seifert, A. Buschauer, *J. Med. Chem.* **2009**, *52*, 6297–6313.

[29] P. Igel, E. Schneider, D. Schnell, S. Elz, R. Seifert, A. Buschauer, *J. Med. Chem.* **2009**, *52*, 2623–2627.

[30] P. Igel, D. Schnell, G. Bernhardt, R. Seifert, A. Buschauer, *ChemMedChem.* **2009**, *4*, 225–231.

[31] H. D. Lim, R. M. van Rijn, P. Ling, R. A. Bakker, R. L. Thurmond, R. Leurs, *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1310–1321.

[32] H. D. Lim, R. A. Smits, R. A. Bakker, C. M. E. vanDam, I. J. P. deEsch, R. Leurs, *J. Med. Chem.* **2006**, *49*, 6650–6651.

[33] T. Hashimoto, S. Harusawa, L. Araki, O. P. Zuiderveld, M. J. Smit, T. Imazu, S. Takashima, Y. Yamamoto, Y. Sakamoto, T. Kurihara, R. Leurs, R. A. Bakker, A. Yamatodani, *J. Med. Chem.* **2003**, *46*, 3162–3165.

[34] R. Kitbunnadaj, M. Hoffmann, S. A. Fratantoni, G. Bongers, R. A. Bakker, K. Wieland, A. el Jilali, I. J. de Esch, W. M. Menge, H. Timmerman, R. Leurs, *Bioorg. Med. Chem.* **2005**, *13*, 6309–6323.

[35] R. ten Have, M. Huisman, A. Meetsma, A. M. van Leusen, *Tetrahedron Lett.* **1997**, *53*, 11355–11368.

[36] D. A. Horne, K. Yakushijin, G. Buechi, *Heterocycles* **1994**, *39*, 139–153.

[37] M. Huisman, R. t. Have, A. M. van Leusen, *Synth. Commun.* **1997**, *27*, 945–952.

[38] A. Buschauer, *Arzneim.-Forsch.* **1987**, *37*, 1008–1012.

[39] R. L. Webb, C. S. Labaw, *J. Heterocycl. Chem.* **1982**, *19*, 1205–1206.

[40] R. L. Webb, D. S. Eggleston, C. S. Labaw, J. J. Lewis, K. Wert, *J. Heterocycl. Chem.* **1987**, *24*, 275–278.

[41] L. Salmon-Chemin, E. Buisine, V. Yardley, S. Kohler, M.-A. Debreu, V. Landry, C. Sergheraert, S. L. Croft, R. L. Krauth-Siegel, E. Davioud-Charvet, *J. Med. Chem.* **2001**, *44*, 548–565.

[42] N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnam, T. P. Stocky, *J. Org. Chem.* **1973**, *38*, 2786–2792.

[43] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651–1660.

[44] R. B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, San Diego **2004**.

[45] A. Kozikowski (Ed.), *Drug Design for Neuroscience*, Raven Press, New York **1993**.

[46] C. G. Wermuth (Ed.), *The Practice of Medicinal Chemistry*, Academic Press, San Diego **1996**.

[47] R. Geyer, *Diploma Thesis*, Department of Pharmaceutical and Medicinal Chemistry II, University of Regensburg, Regensburg, Germany **2008**.

[48] J. H. M. Lange, H. C. Wals, Av. den Hoogenband, Av. de Kuilen, J. A. J. den Hartog, *Tetrahedron* **1995**, *51*, 13447–13454.

[49] A. Rouleau, X. Ligneau, J. Tardivel-Lacombe, S. Morisset, F. Gbahou, J. C. Schwartz, J. M. Arrang, *Br. J. Pharmacol.* **2002**, *135*, 383–392.

[50] D. Schnell, K. Burleigh, J. Trick, R. Seifert, *J. Pharmacol. Exp. Ther.* **2010**, *332*, 996–1005.

[51] E. H. Schneider, D. Schnell, D. Papa, R. Seifert, *Biochemistry* **2009**, *48*, 1424–1438.

[52] Y.-C. Cheng, W. H. Prusoff, *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

