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Synthesis and QSAR of Quinazoline Sulfonamides As Highly Potent Human Histamine H_4 Receptor Inverse Agonists

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Hit optimization of the class of quinazoline containing histamine H_4 receptor (H_4R) ligands resulted in a sulfonamide substituted analogue with high affinity for the H_4R. This moiety leads to improved physicochemical properties and is believed to probe a distinct H_4R binding pocket that was previously identified using pharmacophore modeling. By introducing a variety of sulfonamide substituents, the H_4R affinity was optimized. The interaction of the new ligands, in combination with a set of previously published quinazoline compounds, was described by a QSAR equation. Pharmacological studies revealed that the sulfonamide analogues have excellent H_4R affinity and behave as inverse agonists at the human H_4R. In vivo evaluation of the potent 2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (**54**) ($pK_i = 8.31 \pm 0.10$) revealed it to have anti-inflammatory activity in an animal model of acute inflammation.

Introduction

The histamine H_4R[a] receptor (H_4R) is a G-protein coupled receptor (GPCR) that belongs to the histamine receptor family which is composed of the H_1R, H_2R, H_3R, and H_4R receptors.[1] After its discovery in 2000, the H_4R has attracted much attention because it plays a role as a mediator of allergic and inflammatory processes.[2,3] This receptor is mostly found in peripheral tissues, but its RNA (ribonucleic acid) has also been found in the brain.[4] The H_4R is expressed on cells of the immune system and blood forming organs.[5−7] A considerable amount of work has been done to clarify the role of the H_4R in (patho)physiological processes and H_4R ligands have been shown to be efficacious in a variety of animal models of inflammatory disease.[3,8,9] Although the H_4R is considered a potential drug target for the treatment of asthma, allergic rhinitis (hay fever), and pruritis (itch), it has not yet been validated for these clinical applications.[2] Most compounds that have been used for the elucidation of the role of the H_4R have unfavorable kinetics such as low half-life or lack of selectivity (thioperamide, clobenpropit).[10,11] To firmly establish the clinical potential of H_4R ligands, there remains a need for good pharmacological tools that do not suffer from the above-mentioned problems.

Recently, we described a pharmacophore model for the H_4R that was subsequently used in a rational fragment based drug discovery approach for the development of potent quinoxaline H_4R ligands.[12] Subsequent scaffold hopping from the quinoxaline to the quinazoline heterocycle led to the identification of thiophene and furan substituted quinazolines **1** (VUF10497) and **2** (VUF10499) (Figure 1).[13] Although the H_4R affinity of quinazolines **1** and **2** is high, an effort was made to replace the thiophene and furan moieties.[13] Both these compounds are quite lipophilic, and the introduction of polar replacements for the thiophene and furan moieties was considered to be beneficial for solubility. Therefore, several amines were coupled to the quinazoline scaffold, leading to the identification of a sulfonamide substituted quinazoline with high affinity for the H_4R (compound **3**, Figure 1). The identification of compound **3** was followed-up with a SAR study to explore the tolerance to substitution and alteration of the newly discovered *N*-ethyl sulfonamide compound. Several analogues were synthesized and evaluated for H_4R affinity to study the effects of various substituents on the sulfonamide nitrogen, chain length, or the replacement of the sulfonamide moiety with several bioisosteres.

Substituents on the 4-position of both the initial series of quinazoline compounds and the new sulfonamide-containing quinazolines are believed to occupy the same pocket in the H_4R binding site. This pocket was discovered after the construction of a pharmacophore model based on reference H_4R antagonist (5-chloro-1*H*-indol-2-yl)(4-methylpiperazin-1-yl)-methanone (JNJ7777120) and H_4R agonist clozapine.[3,12−14] In an effort to more quantitatively describe the binding of the compounds in the H_4R pocket, a QSAR model was constructed using the H_4R affinity data of a significant

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[a] Abbreviations: GPCRs, G protein-coupled receptors; H_1R, histamine H_1 receptor; H_2R, histamine H_2 receptor; H_3R, histamine H_3 receptor; H_4R, histamine H_4 receptor; SAR, structure−activity relationship; QSAR, quantitative structure−activity relationship; DIPEA, diisopropylethylamine; CMC, carboxymethylcellulose; LOO−CV, leave-one-out cross-validation; rms, root-mean-square; HEK, human embryonic kidney.

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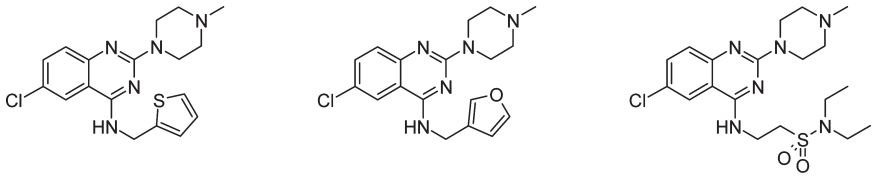
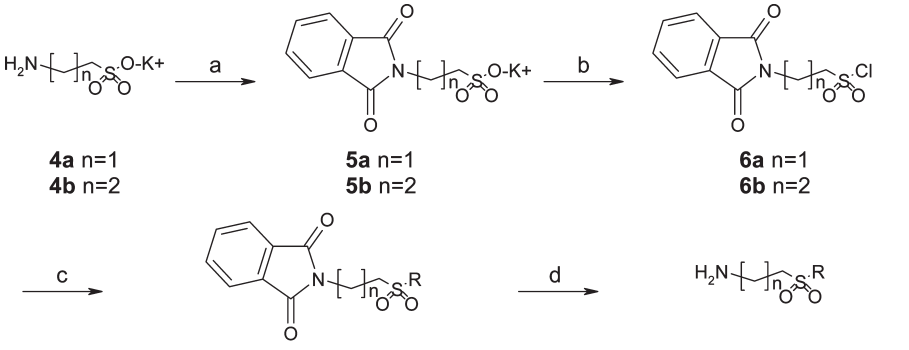


1, pK_i= 8.12 **2**, pK_i= 7.66 **3**, pK_i= 8.25

Figure 1. H_4R inverse agonists **1** and **2** and newly discovered sulfonamide substituted quinazoline **3** with high affinity for the histamine H_4 receptor.

Scheme 1[a]



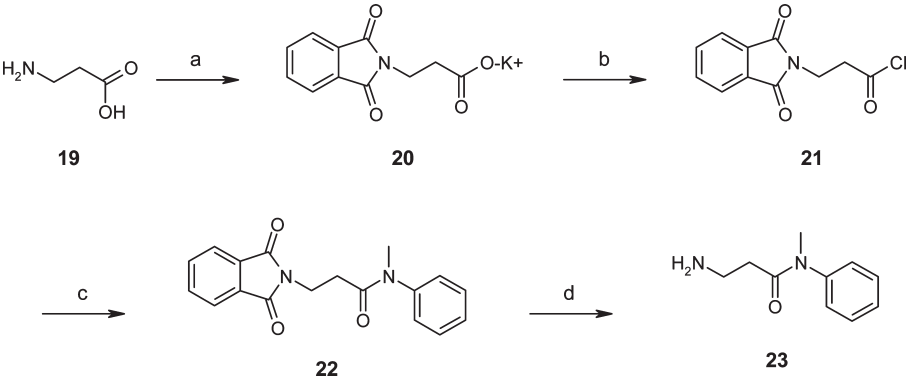
4a n=1, **4b** n=2; **5a** n=1, **5b** n=2; **6a** n=1, **6b** n=2

7a R= $NHCH_3$, n=1; **7b** R= $NHCH_3$, n=2; **8** R= $N(CH_3)_2$, n=1; **9** R= NHPh, n=1; **10** R= NH_2, n=1; **11** R= NH(4-I-Ph), n=1; **12** R= 4-morpholino, n=1

13a R= $NHCH_3$, n=1; **13b** R= $NHCH_3$, n=2; **14** R= $N(CH_3)_2$, n=1; **15** R= NHPh, n=1; **16** R= NH_2, n=1; **17** R= NH(4-I-Ph), n=1; **18** R= 4-morpholino, n=1

[a] Reagents and conditions: (a) phthalic anhydride, KOAc, AcOH; (b) PCl_3, toluene; (c) R_1R_2NH, rt; (d) H_2NNH_2, EtOH.

Scheme 2[a]



19 **20** **21** **22** **23**

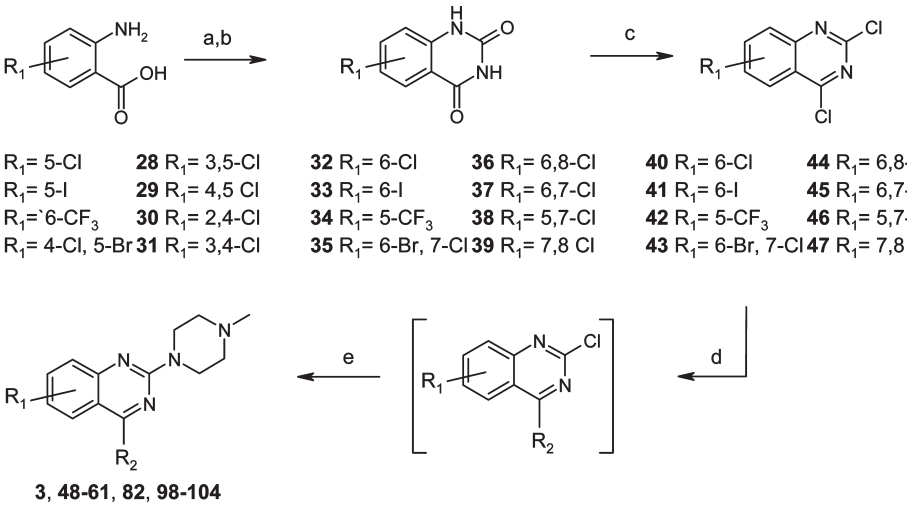
[a] Reagents and conditions: (a) AcOH, KOAc, phthalic anhydride, reflux; (b) $SOCl_2$, DMF, DCM, reflux; (c) *N*-methylaniline, DCM, rt; (C) H_2NNH_2, EtOH, reflux.

number of previously reported quinazoline compounds in combination with the new sulfonamide compounds described in this publication.[13]

Chemistry

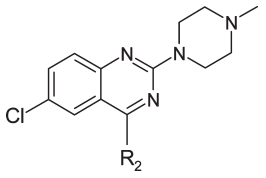
The quinazoline sulfonamides were synthesized by a converging synthesis route that requires the preparation of both the sulfonamide- and 2,4-dichloroquinazoline precursors that can subsequently be coupled together. Treatment of the combined intermediate quinazoline with *N*-methylpiperazine then gives the desired compounds. Starting from taurine (**4a**), sulfonic acid **5a** was synthesized according to a procedure described in literature (Scheme 1).[15] Subsequent treatment of **5a** with PCl_5 then gave sulfonylchloride **6a**.[15] The same synthetic sequence was used for the preparation of **6b** from its precursors **4b** and **5b**. The conversion of **6** to various sulfonamide analogues **7a**, **7b**, and **8**−**12** was carried out successfully in a number of solvents such as dioxane and chloroform with an excess of the corresponding amines. Deprotection of the terminal amine functionality of the sulfonamide precursors gave primary amines **13a**, **13b**, and **14**−**18**. Efficient deprotection was achieved using hydrazine in ethanol, following a procedure described in literature for the synthesis of 2-aminoethanesulfonamide hydrochloride (**10**).[16]

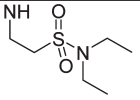
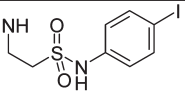
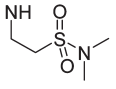
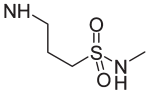
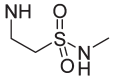
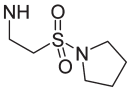
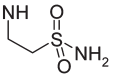
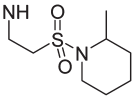
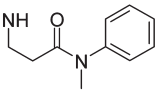
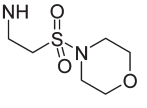
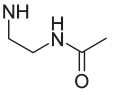
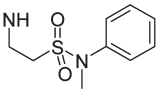
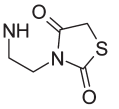
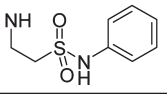
Scheme 3[a]



[a] Reagents and conditions: (a) urea, 160 °C; (b) 0.5 M NaOH; (c) *N*,*N*-diethylaniline, $POCl_3$, reflux; (d) NH_2R, DIPEA, EtOAc, rt; (e) *N*-methylpiperazine, microwave, 120 °C, 10 min.

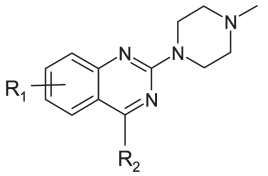
Table 1. SAR Study of the Sulphonamide Side Chain of Quinazoline H_4R Ligands



No	R_2	pK_i±SEM[a]	No	R_2	pK_i±SEM[a]
3		8.12 ± 0.05	**55**		7.15 ± 0.18
48		7.90 ± 0.09	**56**		7.48 ± 0.29
49		8.37 ± 0.17	**57**		7.57 ± 0.18
50		7.75 ± 0.13	**58**		8.35 ± 0.08
51		8.00 ± 0.11	**59**		6.65±0.11
52		8.03 ± 0.16	**60**		6.31±0.09
53		8.27± 0.01	**61**		6.75±0.11
54		8.31 ± 0.10			

[a] Measured by displacement of [^{3}H]histamine binding using membranes of HEK cells transiently expressing the human H_4R. pK_i's are calculated from at least three independent measurements as the mean ± SEM.

Table 2. H_4R Affinity of Quinazoline Derivatives Used As the Training and Test Set



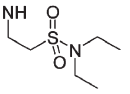
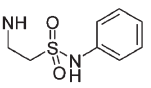
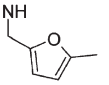
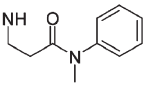
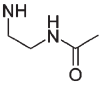
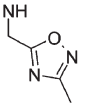
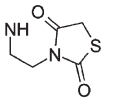
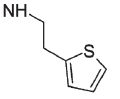
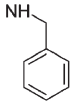
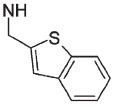
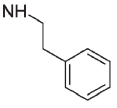
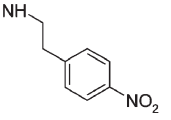
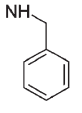
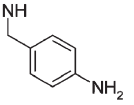
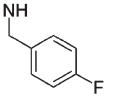
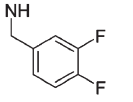
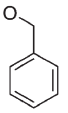
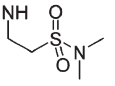
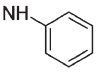
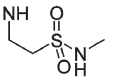
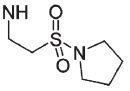
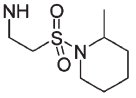
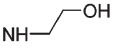
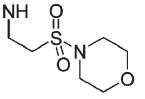
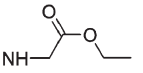
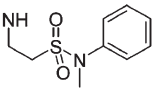
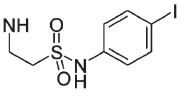
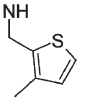
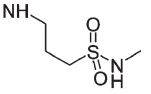
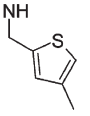
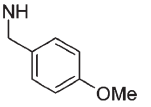
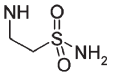
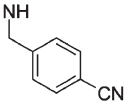
No	R_1	R_2	pK_i±SEM[a]	No	R_1	R_2	pK_i±SEM[a]
		Training set				Training set	
1	6-Cl		8.12±0.02	**72**	6-Cl, 8-CH_3		6.73±0.02
3	6-Cl		8.12±0.02	**73**	6-F		6.65±0.03
54	6-Cl		8.31±0.10	**74**	6-Cl		6.87±0.02
59	6-Cl		6.65±0.11	**75**	6-Cl		7.57±0.05
60	6-Cl		6.31±0.09	**76**	6-Cl		6.43±0.01
61	6-Cl		6.75±0.11	**77**	6-Cl		7.22±0.03
62	H		5.12±0.06	**78**	6-Cl		7.45±0.02
63	H		5.55±0.03	**79**	6-Cl		6.98±0.02
64	H	NH_2	5.76±0.05	**80**	6-Cl		6.97±0.10
65	H		5.97±0.07	**81**	6-Cl		6.25±0.04
66	H		5.83±0.11	**82**	6-Cl		7.30±0.03
67	6-Cl		6.59±0.03	**83**	6-Cl		6.25±0.03
68	6-Cl		7.10±0.01	**84**	6-Cl		6.98±0.02
69	6-Cl		6.21±0.02	**85**	6-Cl		6.73±0.09
70	7-Cl		6.02±0.03[b]	**86**	6-Cl		6.23±0.03
71	5-CH_3		6.20±0.06[b]				

Table 2. Continued

No	R_1	R_2	pK_i±SEM[a]	No	R_1	R_2	pK_i±SEM[a]
		Test set				Test set	
2	6-Cl		7.05±0.04	**87**	H		5.39±0.03
48	6-Cl		7.90 ± 0.09	**88**	H		5.07±0.05
49	6-Cl		8.37 ± 0.17	**89**	6-Cl		6.12±0.01[b]
50	6-Cl		7.75 ± 0.13	**90**	6-Cl		6.81±0.07
51	6-Cl		8.00 ± 0.11	**91**	6-Cl		6.36±0.07[b]
52	6-Cl		8.03 ± 0.16	**92**	6-Cl		6.05±0.06[b]
53	6-Cl		8.27±0.01	**93**	H		6.22±0.01[b]
55	6-Cl		7.15 ± 0.18	**94**	6-Cl		7.47±0.04
56	6-Cl		7.48 ± 0.29	**95**	6-Cl		7.41±0.04
57	6-Cl		7.57 ± 0.18	**96**	6-Cl		6.44±0.01
58	6-Cl		8.35 ± 0.08	**97**	6-Cl		6.89±0.13

[a] Measured by displacement of [^{3}H]histamine binding using membranes of HEK cells transiently expressing the human H_4R. pK_i's are calculated from at least three independent measurements as the mean ± SEM. [c] $n = 2$.

β-Alanine (**19**) was treated with phthalic anhydride in the presence of potassium acetate and acetic acid (Scheme 2). The intermediate salt (**20**) was converted to its corresponding acid chloride (**21**) with thionylchloride. This freshly prepared acid chloride was used immediately to react with *N*-methylaniline to form carboxamide **22**. The nitrogen in the phtalimide group was deprotected with hydrazine in ethanol to give primary amine **23**.

Anthranilic acids **24**−**31** with various aromatic substituents were treated with molten urea to give quinazoline-2,4(1*H*,3*H*)-diones **32**−**39** in excellent yields (Scheme 3).[17] As has been described earlier for 2,4,6-trichloroquinazoline, these intermediates were then chlorinated with phosphorus oxychloride in the presence of diisopropyl ethylamine to give key 2,4-dichloroquinazoline intermediates **40**−**47**.[13]

Primary amines **13a**, **13b**, and **14**−**18** and several commercially available primary amines were then coupled selectively to the 4-position of the different 2,4-dichloroquinazolines at room temperature in the presence of diisopropylethylamine (DIPEA). Conversions were typically very high, and upon completion, excess *N*-methylpiperazine was added and coupled to the 2-position using microwave assisted heating. Using this previously described one-pot procedure, no work-up of the 4-substituted quinazoline intermediate was required and target compounds **3**, **48**−**61**, **82**, and **98**−**104** were obtained in good to excellent yields.[12] The experimental procedures for the synthesis of these compounds and their corresponding intermediates are described in the Experimental Section and Supporting Information of this manuscript. Experimental details for the synthesis of the previously

Table 3. Definition of the Molecular Descriptors Found for the H_4R QSAR Model, Generated with the QuaSAR Descriptor Module in MOE 2006.08

descriptor	definition
a_ICM	entropy of the element distribution in the molecule
PEOE_VSA+5	sum of the van der Waals surface area of atoms, whose PEOE[a] partial charge is between 0.25 and 0.30
PEOE_VSA-3	sum of the van der Waals surface area of atoms, whose PEOE partial charge is between −0.20 and −0.15
PEOE_VSA_FPOS	sum of the van der Waals surface area of atoms, whose PEOE partial charge is positive, divided by the total surface area
SMR_VSA1	subdivided surface area descriptor based on the sum of the approximate accessible van der Waal's surface area, calculated for each atom with contribution to molar refractivity in the range of 0.11 to 0.26
GCUT_PEOE_1	descriptor calculated from the eigenvalues of a modified graph adjacency matrix. The diagonal of the matrix takes the value of the PEOE partial charges.

[a] PEOE is a partial charge descriptor calculated using the partial equalization of orbital electronegativities.

synthesized compounds used in the QSAR model are described in literature.[13]

Results and Discussion

In an attempt to improve the solubility of **1** and **2** (Figure 1), we replaced the aromatic heterocycles of these compounds by a variety of polar moieties. Using parallel synthesis, our library of primary amines was coupled to intermediate **40** to give a series of quinazoline-containing compounds, including diethyl sulfonamide **3**. H_4R affinity screening of this compound revealed high affinity ($pK_i = 8.12$), and it was therefore chosen as a starting point for further optimization and exploration of the SAR of this series.

When the diethyl sulfonamide of **3** is replaced with a dimethylsulfonamide (**48**, Table 1), a comparable affinity is found. Removal of one of the methyl groups from **48** leads to a 3-fold increase in potency (compare **48** and **49**). When the diethyl groups of **3** are constrained in a cyclic pyrrolidine system (compound **50**), some affinity is lost although other fused rings are well tolerated as illustrated by 2-methylpiperidine and morpholine analogues **51** and **52**. The replacement of one of the methyl substituents of **48** with a phenyl group, leading to compound **53**, increases the affinity slightly but no further increase was observed when the *N*-methyl group was removed (compare **53** and **54**). Substitution of the sulfonamide phenyl ring of **54** with a 4-iodo substituent gives a 14-fold decrease in H_4R affinity (**55**). Although the exact reason of this decrease is unknown, it can be speculated that the 4-iodophenyl group is simply too large to be accommodated by the H_4R. When the ethylene spacer between the nitrogen atom on the 4-position of the quinazoline and the sulfonamide group was extended, a drop in affinity was observed (compare **49** and **56**), which suggests an optimal spacer length of two methylene units between the sulfonamide moiety and the quinazoline heterocycle. Replacement of the $-NH_2$ group of the sulfonamide moiety with a methyl group gave sulfone **57** that has decreased H_4R affinity compared to most sulfonamides in Table 1 and indicates the importance of the basic nitrogen group for H_4R binding. In fact, when the sulfonamide moiety remains unsubstituted as in compound **58**, one of the highest affinities ($pK_i = 8.35$) is observed. The importance of the sulfonamide group for H_4R binding is emphasized by the failure to replace the sulfonamide group with a suitable bioisostere. Indeed, carboxamide (compound **59**), reversed carboxamide (compound **60**), or thiazolidinedione (compound **61**) all failed to give compounds with good H_4R affinity.

This SAR study demonstrates that substitution of the quinazoline heterocycle with various *N*-ethylaminosulfonamides leads to highly potent H_4R ligands. Most importantly, the amino group in the sulfonamide moiety of these quinazolines is quite tolerant to substitution with a variety of aromatic and aliphatic groups, leading to many compounds with affinities in the single-digit nanomolar range.

In parallel with the preparation of several new sulfonamide analogues, a QSAR study was performed on a large number of quinazolines that was previously prepared during our H_4R drug discovery program.[13] The H_4R affinities (pK_i values) of all compounds used in the QSAR study have all been generated in the same H_4R radioligand displacement assay.[13] A total of 44 compounds were selected and divided into two sets: 31 compounds were put in the training set and 22 compounds were put in the test set (Table 2). All computational chemistry work was performed on an AMD Athlon 3500+ 2.2 GHz, with 2 GB RAM using Molecular Operating Environment (version 2006.08, Chemical Computing Group Inc., Canada).[18] All structures were drawn with the builder module. Conformational analysis using the stochastic conformation search algorithm was then performed using the conformational import module provided by the software with no filters and no constraints applied. The conformational analysis and energy minimization were performed using stochastic conformation search with a rms gradient of 0.001 Å and iteration limit of 10000 using the MMFF94 force field.[19−21] All nonquantum chemical descriptors provided by the software were then calculated for the lowest energy conformations. The relationship between the H_4R pK_i and the descriptors of the training set was identified by stepwise regression analysis using SPSS 14.0 for Windows. The following statistical measures were used: N = number of samples, F-test for quality of fit, r = coefficient of correlation, R^2 = coefficient of determination, and S = standard error of estimation. Equation 1 resulting from the stepwise regression analysis is considered the "best" QSAR model of quinazoline derivatives as ligands of the H_4R. The descriptors selected by stepwise regression analysis are shown in Table 3 and were found to be nondependent on each other (the cross correlation between descriptors was <0.7 as determined by the Pearson correlation method). In case the selected descriptors for the "best model" were not independent, the relationship was re-examined without the descriptor that had the lowest correlation with the affinity. The observed, calculated, and predicted (leave-one-out) affinity values of the training set are presented in Table 4.

$$\begin{aligned} pK_i hH_4R &= 3.632(\pm 2.253) + 5.891(\pm 0.656)[\mathbf{aICM}] \\ &\quad -0.054(\pm 0.012)[\mathbf{PEOE\_VSA+5}] \\ &\quad -0.027(\pm 0.008)[\mathbf{SMR\_VSA1}] + 0.086(\pm 0.038) \\ &\quad [\mathbf{PEOE\_VSA-3}] + 11.174(\pm 4.976)[\mathbf{GCUT\_PEOE\_1}] \\ &\quad -1.616(\pm 0.792)[\mathbf{PEOE\_VSA\_FPOS}] \qquad (1) \\ N &= 31, r = 0.918, R^2 = 0.842, S = 0.333, F_{6,24} \\ &= 21.302, F_{5\%,6,24} = 2.508, q^2 = 0.789. \end{aligned}$$

Leave-one-out cross-validation (LOO−CV) was employed to determine the cross-validated coefficient (q^2) as an internal validation of the models. The best model was then applied to predict the pK_i H_4R of the test set as an external validation. The R^2, $R_0{}^2$, and k values were determined accordingly.[22]

The correlation between observed, calculated, and predicted (leave-one-out) affinity values of the training set is shown in Figure 2. The leave-one-out method resulted in a cross-validated q^2 of 0.789, which is considered to be good according to the standard set by Erikssons et al.[23] As the external validation, we initially used equation 1 to predict the test set. The values of the descriptors and the cross correlation between them can be found in the Supporting Information.

Table 4. Observed, Calculated and Predicted Affinity Values of the Training and Test Set

	observed	calculated	predicted		observed	calculated	predicted
no.	pK_i[a]	pK_i[b]	pK_i[c]	no.	pK_i[a]	pK_i[b]	pK_i[c]
		Training Set		**83**	6.25	6.62	6.65
1	8.12	7.41	7.35	**84**	6.98	6.67	6.62
3	8.12	8.19	8.22	**85**	6.73	6.68	6.65
54	8.31	8.21	8.18	**86**	6.23	6.24	6.25
59	6.65	6.72	6.73			Test Set	
60	6.31	6.41	6.43	**2**	7.05	7.02	
61	6.75	6.77	6.86	**48**	7.90	8.29	
62	5.12	5.28	5.36	**49**	8.37	8.33	
63	5.55	5.72	5.76	**50**	7.75	8.11	
64	5.76	5.61	5.54	**51**	8.00	7.93	
65	5.97	5.77	5.71	**52**	8.03	8.45	
66	5.83	5.67	5.60	**53**	8.27	8.01	
67	6.59	6.60	6.61	**55**	7.15	8.83	
68	7.10	6.85	6.83	**56**	7.48	8.12	
69	6.21	6.19	6.19	**57**	7.57	8.27	
70	6.02	6.73	6.79	**58**	8.35	8.62	
71	6.20	5.96	5.87	**87**	5.39	5.94	
72	6.73	6.90	6.93	**88**	5.07	5.03	
73	6.65	6.43	6.34	**89**	6.12	6.59	
74	6.87	6.86	6.86	**90**	6.81	6.62	
75	7.57	7.30	7.25	**91**	6.36	6.54	
76	6.43	6.42	6.41	**92**	6.05	6.70	
77	7.22	7.20	7.20	**93**	6.22	6.16	
78	7.45	7.26	7.24	**94**	7.47	7.26	
79	6.98	7.24	7.29	**95**	7.41	7.45	
80	6.97	7.17	7.21	**96**	6.44	6.57	
81	6.25	7.11	7.25	**97**	6.89	7.32	
82	7.30	6.98	6.92				

[a] pK_i values taken from Table 2. [b] Calculated from equation 1. [c] Determined by leave-one-out method.

The model has good predictive ability according to the criteria of Golbraikh and Tropsha:[22] (i) The q^2 of the training set is larger than 0.5 ($q^2 = 0.789$), (ii) the R^2 of the test set is larger than 0.6 ($R^2 = 0.816$), (iii) subtraction of the R^2 of the test set by the $R_0{}^2$, divided by the R^2 of the test set, is smaller than 0.1 ($(R^2 - R_0{}^2)/R^2$ is 0.006), (iv) the slope of the regression through the origin (the k value) is between the required value of 0.85 and 1.15 ($k = 1.037$). Nevertheless, one compound (compound **55**) in the test set has a residual value of 1.68, higher than 3*S*, indicating that the model failed to predict this particular compound. Compound **55** has an iodine atom, which no compound in the training set has. This feature increases the **a_ICM** descriptor of compound **55**. Notably, the **a_ICM** value of compound **55** is the highest among the compounds in the training and test sets. This shows the limitation of such QSAR model to accurately predict the affinity of compound outside its domain of applicability.

The QSAR model (equation 1) shows a positive correlation with **a_ICM**, **PEOE_VSA−3**, and **GCUT_PEOE_1**, and a negative correlation with **PEOE_VSA+5**, **SMR_VSA1**, and **PEOE_VSA_FPOS**. It means that new ligands with high **a_ICM**, **PEOE_VSA−3**, and **GCUT_PEOE_1** and low **PEOE_VSA+5**, **SMR_VSA1**, and **PEOE_VSA_FPOS** value should have higher affinity for the hH_4R.[18,24−26]

The results describe the importance of various physicochemical descriptors on the H_4R binding. The ratio of the object in the training set and the number of descriptors is about 5:1. Although this ratio is the case in many QSAR,[22,27,28] we are aware that the use of such a number of descriptors can lead to an overfitting model.[28] The homogeneity criterion indicated by Erikssons et al.[23] can be violated because our aim was to generate a model that can explain the whole data set, as diverse as possible. The main point of diversity in this series of compounds is at the quinazoline 4-position. Substituents at this position were postulated to interact at a particular H_4R binding pocket that was identified by pharmacophore modeling studies.[14] In addition, the QSAR equation could accurately predict the affinity of several new quinazoline sulfonamides

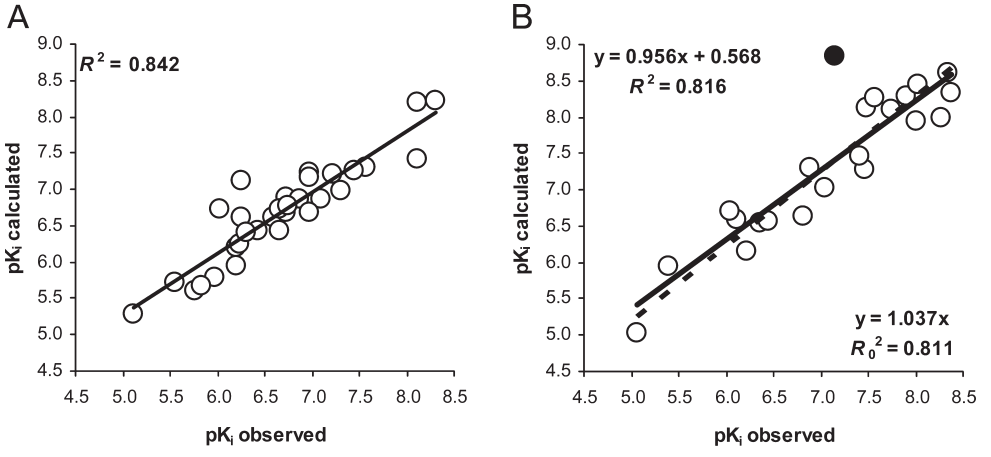
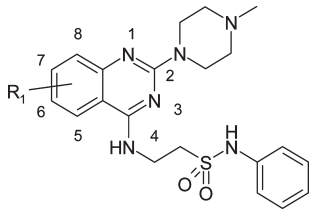


Figure 2. Graph between observed and calculated affinity of the training set (A). The straight line presents the graph between observed and calculated affinity of the test set (B). The equation and R^2 value are presented in the top left of figure B. The dotted line represents the regression through the origin (the intercept is 0). The equation and $R_0{}^2$ value are presented in the bottom right of (B). Compound **55**, which has residual more than 3*S*, is indicated as a black-filled point.

that were synthesized for the SAR study described in this work (Figure 2B). The QSAR study will be used in our ongoing efforts to more accurately describe ligand−receptor interaction.

During the optimization of the quinazoline 4-position for H_4R affinity, very little attention was paid to substitution of the all-carbon aromatic ring of the quinazoline heterocycle (positions 5−8 of the quinazoline heterocycle, Table 5).[13] Substitution at this position has been explored thoroughly in other classes of H_4R compounds, e.g., series of thienopyrrole, quinoxaline, indole, and benzimidazole based ligands.[10,12,29,30] In the case of the new quinazoline scaffold, we explored the introduction of various halogen atoms on the aromatic ring. The observed pK_i's of the compounds in Table 5 show that a chlorine on the 6-position (compound **54**) is, as expected when considering previously published SAR data, crucial for high H_4R affinity. The SAR described by the compounds in Table 5 is similar to the aforementioned classes of H_4R compounds. Interestingly, an iodine atom on the 6-position gives a comparable affinity to that of the chlorine substituted analogue (compare **54** and **98**). A chlorine atom on the 7-position does not enhance H_4R binding, and the lowest potencies are therefore found with compounds **99** and **100** that both lack a halogen atom at the 6-position but occupy the 7-position with a chlorine atom. When the 6-position is occupied with a chlorine or bromine atom and the 7-position is simultaneously substituted with a chlorine atom, the affinity is restored and quite good affinities are found for compounds **101** ($pK_i = 7.72 \pm 0.16$) and **102** ($pK_i = 7.81 \pm 0.02$). The 6,8-dichloro substitution pattern (compound **103**) and the introduction of a 5-CF_3 group (compound **104**) also give ligands with affinities comparable to that of **54**. This SAR study shows that in the phenyl sulfonamide series a 6-chlorine atom remains the optimal substituent for high H_4R affinity, although several other substitution patterns such as 5-CF_3, 6,8-Cl, and 6-I are also well tolerated and give compounds with excellent H_4R affinity.

Table 5. Phenyl Sulfonamide Substituted Quinazolines with Various Small Lipophilic Substituents



no.	R_1	pK_i[a]
54	6-Cl	8.31 ± 0.10
98	6-I	8.24 ± 0.06
99	5,7-Cl	6.82 ± 0.03
100	7,8-Cl	6.51 ± 0.04
101	6,7-Cl	7.72 ± 0.16
102	6-Br, 7-Cl	7.81 ± 0.02
103	6,8-Cl	7.95 ± 0.12
104	5-CF_3	8.09 ± 0.07

[a] Measured by displacement of [^{3}H]histamine binding using membranes of HEK cells transiently expressing the human H_4R. pK_i's are calculated from at least three independent measurements as the mean ± SEM.

The most potent examples from this quinazoline sulfonamide series are compounds **54** and **58** that both have higher affinity for the H_4R than histamine ($pK_i = 7.92 \pm 0.07$) and thioperamide ($pK_i = 7.20 \pm 0.06$) (Figure 3A). Both compounds were also evaluated in an H_4R driven CRE-ss-galactosidase reporter gene assay (Figure 3B). In this assay, histamine shows full agonistic behavior ($\alpha = 1$) while thioperamide shows inverse agonistic behavior ($\alpha = -1$). Both **54** and **58** were found to act as inverse agonists with respective pIC_{50} values of 7.48 ± 0.14 and 8.00 ± 0.15. The inverse agonism displayed by **54** ($\alpha = -0.28$) was less pronounced than thioperamide, whereas the inverse agonism of **58** ($\alpha = -1.64$) was much more pronounced than thioperamide. In vivo anti-inflammatory properties of compound **54** were investigated using a carrageenan-induced paw edema model in rats.[31] It has been shown previously that in this model compounds with affinity for the H_4R can inhibit the swelling of the paw after chemically induced inflammation. The affinity for the rat H_4R of **54** and **58** was found to be 8.81 ± 0.02 ($n = 2$) and 7.00 ± 0.10 ($n = 2$), respectively, with observed inverse agonistic behavior for both **54** and **58**. In this in vivo model, subcutaneous administration at 30 mg/kg of sulfonamide **54** revealed considerable anti-inflammatory activity (Figure 4).

The observed reduction of edema was significant after both 2 and 4 h. These encouraging results show that the novel sulfonamide compounds described in this publication are interesting candidates for further in vivo characterization.

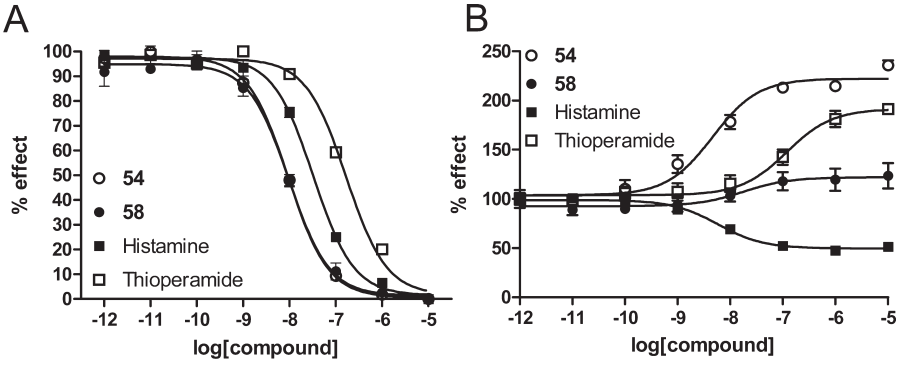


Figure 3. Compounds **54** and **58** bind to the hH_4R with high affinity as determined by [^{3}H]histamine displacement. (A) Quinazolines **54** ($\alpha = -0.28$) and **58** ($\alpha = -1.64$) show inverse agonistic behavior in a functional assay performed in parallel with H_4R agonist histamine and H_4R inverse agonist thioperamide (B). The α values for histamine and thioperamide have been arbitrarily set at 1 and −1, respectively. Corresponding pIC_{50}'s values for **54** and **58** are 7.48 ± 0.14 and 8.00 ± 0.15, respectively ($n = 3$).

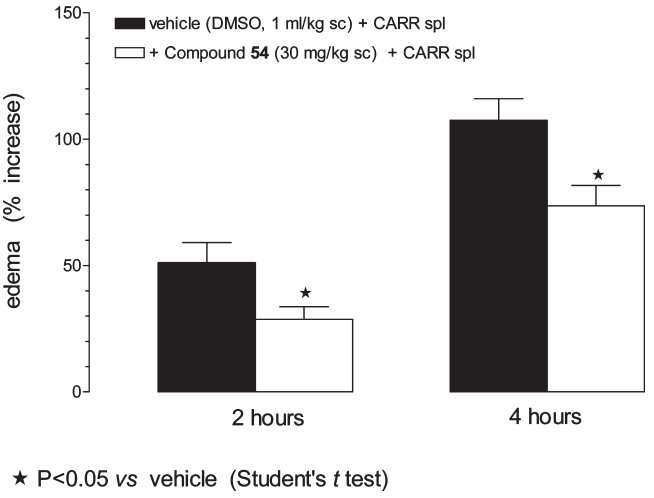


Figure 4. Anti-inflammatory effects of compound **54** on paw edema induced by subplantar injection of carrageenan (1% in CMC) in rats. Data are expressed as mean ± SEM, $n = 6$ rats per group. Comparisons between control (vehicle) and treated (compound **54**) groups were made by the unpaired Student's t test. $^*P < 0.05$ vs vehicle.

Conclusion

During the optimization of the quinazoline heterocycle that was discovered as a good scaffold for high H_4R affinity compounds, two alkyl- and aryl sulfonamide analogues were synthesized from proprietary building blocks. The quinazoline sulfonamides were found to tightly bind to the H_4R, and a subsequent SAR study of these compounds indicated that the sulfonamide moiety is crucial for high H_4R affinity. Moreover, the sulfonamide moiety appears to be very tolerant to substitution with a variety of aromatic, aliphatic, or fused ring systems. Subsequently, a QSAR model for the affinity of this new series of H_4R ligands was developed with good predictive ability for the affinity of quinazolines with variations in the sulfonamide moiety. In the course of these studies, several compounds were discovered with excellent affinity for the H_4R in the low nanomolar range. Additional pharmacological evaluation of two selected analogues revealed that the two analogues displayed inverse agonism at the human H_4R. Compound **54**, administered in rat, significantly reduced the inflammation caused by the injection of carrageenan in the paw, thereby demonstrating the in vivo anti-inflammatory property of this promising class of quinazoline H_4R inverse agonists.

Experimental Section

General Remarks. Chemicals and reagents were obtained from commercial suppliers and were used without further purification. Yields given are isolated yields unless mentioned otherwise. Flash column chromatography was typically carried out on an Argonaut Flashmaster II flash chromatography system using prepacked Isolute Flash Si II columns with the UV detector operating at 254 nm. All melting points are uncorrected and were measured on an Optimelt automated melting point system from Stanford research systems. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AC200. ^{1}H NMR spectra of compounds **98**−**104** were measured on a Bruker Avance 400 at 75 °C.

Microwave assisted chemistry was performed with a Biotage Initiator typically using 2 or 5 mL vials obtained from Biotage.

Analytical HPLC-MS analyses were conducted using a Shimadzu LC-8A preparative liquid chromatograph pump system with a Shimadzu SPD-10AV UV−vis detector with the MS detection performed with a Shimadzu LCMS-2010 liquid chromatograph mass spectrometer. The buffer used for The LCMS analyses is a 0.4% (w/v) NH_4CO_3 solution in water, adjusted to pH 8.0 with NH_4OH. The analyses were performed using the following condition: An Xbridge (C18) 5 μ column (100 mm × 4.6 mm) with the following two solvents; solvent A, 90% MeCN−10% buffer; solvent B, 90% water−10% buffer; flow rate = 2.0 mL/min; start 95% B, linear gradient to 90% A in 10 min, then 10 min at 90% A, then 10 min at 95% B. Total run time 30 min. Compound purities were calculated as the percentage peak area of the analyzed compound by UV detection and are ≥95%.

HRMS analyses were perfomed with a Bruker micrOTOF-Q using electrospay ionization.

In Vitro Pharmacology. The pK_i's at the human H_4R were determined according to a procedure described in literature.[12] Functional behavior at the H_4R determined in the CRE-ss-galactosidase reporter gene assay was performed as previously reported.[13]

In Vivo Pharmacology—Carrageenan-Induced Edema Model. Determination of the anti-inflammatory activity of compound **54** at 30 mg/kg in the carrageenan induced paw edema model for inflammation was performed acoording to a method described in literature.[31]

Synthetic Methods. Potassium 3-Phthalimidopropane-1-sulfonate (5b). Starting from 3-amino-1-propanesulfonic acid (3.0 g, 9.74 mmol), this compound was prepared according to the procedure described for **5a**.[14] Yield: 6.09 g (100%). ^{1}H NMR (D_2O) δ (ppm) 7.74 (s, 4H), 3.71 (t, $J = 6.9$ Hz, 2H), 2.97−2.89 (m, 2H), 2.12−1.98 (m, 2H).

3-Phthalimidopropanesulfonylchloride (6b). Potassium-3-phthalimidopropane-1-sulfonate (6.0 g, 20.9 mmol) was suspended in dry toluene (25 mL) under a nitrogen atmosphere and heated to reflux. Then 4.11 g (19.7 mmol) of PCl_5 was added in portions and the mixture was heated at reflux for 60 min. A second portion of 4.11 g (19.7 mmol) of PCl_5 was added, and heating was continued for 90 min. The reaction mixture was evaporated to dryness, and crushed ice was added to the residual solid. When the ice had just melted, the solid was filtered off and dried in vacuo to yield 5.64 g (94%) of a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88−7.81 (m, 2H), 7.78−7.71 (m, 2H), 3.87 (t, $J = 6.5$ Hz, 2H), 3.77−3.69 (m, 2H), 2.48−2.34 (m, 2H).

2-Phthalimidoethane-*N*-methylsulfonamide (7a). 2-Phthalimidoethanesulfonylchloride (2.0 g, 7.3 mmol) was added portionwise to a solution of 2.0 M methylamine in THF (15 mL), and the solution obtained this way was stirred at room temperature. After 48 h, the reaction mixture was poured in water (50 mL), causing the title compound to precipitate. The product was collected by filtration and recrystallized from EtOH:water, 50:1 to yield 1.04 g (50%) of the desired product as a white solid; mp 145.3−147.6 °C (lit. 142−144 °C).[32]

2-Phthalimidoethanesulfonamide (16). 2-Phthalimidoethanesulfonylchloride (2.0 g, 7.3 mmol) was added portionwise to a solution of 0.5 M of ammonia in dioxane (15 mL), and the solution obtained this way was stirred at room temperature. After 48 h, the reaction mixture was poured in water (50 mL), causing the title compound to precipitate. The product was collected by filtration. Yield: 1.52 g (78%) of a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm) 7.92−713 (m, 4H), 7.06 (s, 2H), 6.88−3.93 (m, 2H), 3.37−3.30 (m, 2H).

Potassium-1-phthalimidpropane-2-carboxylate (20). To a solution of β-alanine (25.0 g, 0.28 mol) in acetic acid (100 mL) was added potassium acetate (29.5 g, 0.30 mol), and the resulting mixture was heated at reflux for 10 min, during which a clear solution was obtained. Then phthalic anhydride (44.5 g, 0.30 mol) was added and reflux was continued for 2.5 h causing a precipitate to form. The mixture was then cooled in an ice bath and the product was filtered off. Washing with acetic acid and a small amount of EtOH abs. furnished the product as 28.0 g

(39%) of a white salt. ^{1}H NMR (DMSO-d_6) δ (ppm) 7.88−7.79 (m, 4H), 3.76 (t, J = 7.5 Hz, 2H), 2.53 (t, J = 7.6 Hz, 2H).

3-Phthalimido-*N*-methyl-*N*-phenyl-propionamide (22). To a suspension of **20** (3.0 g, 11.7 mmol) in DCM (15 mL) and DMF (2 drops) was added thionylchloride (0.94 mL, 12.9 mmol), and the resulting mixture was heated at reflux. After 2 h, the solvent was removed and the remaining solid was carefully added to a solution of *N*-methylaniline (3.1 g, 29.3 mmol) in chloroform (15 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred for 48 h. After completion, the organic phase was washed with 1 M HCl and dried over Na_2SO_4. Removal of the solvent yielded a solid that was recrystallized from EtOH abs. to yield 3.38 g (94%) of a white solid. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.79−7.73 (m, 2H), 7.69−7.62 (m, 2H), 7.41−7.14 (m, 5H), 3.92 (t, J = 7.6 Hz, 2H), 3.22 (s, 3H), 2.44 (t, J = 7.5 Hz, 2H).

3-Amino-*N*-methyl-*N*-phenyl-propionamide (23). A suspension of **22** (3.0 g, 9.73 mmol) was heated at reflux in EtOH (50 mL), after which hydrazine (0.34 mL, 10.7 mmol) (64% in water) was added. After 3 h, a white precipitate formed that was removed by filtration. The filtrate was evaporated to dryness to yield g (100%) of the title compound that was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.41−7.30 (m, 3H), 7.15 (d, J = 6.8 Hz, 2H), 3.23 (s, 3H), 2.88 (t, J = 6.1 Hz, 2H), 2.18 (t, J = 6.1 Hz, 2H).

3-(6-Chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-methylpropanesulfonamide (57). 2,4,6-Trichloroquinazoline (200 mg, 0.86 mmol) was added to a solution of DIPEA (0.46 mL) and 3-aminopropane-*N*-methylsulfonamide hydrochloride (162 mg) in THF (3.0 mL), and the mixture was stirred overnight at room temperature. The solution was diluted with EtOAc and washed with water and brine. Drying over Na_2SO_4 and removal of the solvent gave a solid that was purified over SiO_2 (EtOAc: Hex, 1:1) to yield the 3-(2,6-dichloro-quinazoline-4-amino)-*N*-methylpropanesulfonamide intermediate. This intermediate was added to a microwave tube containing *N*-methylpiperazine (1.0 mL) and THF (3.0 mL), and this solution was heated at 130 °C. After 15 min, the obtained mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and evaporated to give the crude product as a yellow solid. Purification over SiO_2 (EtOAc: MeOH:Et_3N, 90:5:5) gave the title compound as a white solid. Yield: 104 mg (30%); mp 213.6−214.5 °C. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.48−7.32 (m, 3H), 5.91 (m, 1H), 5.91 (m, 1H), 3.88 (t, J = 5.0 Hz, 4H), 3.78 (q, J = 6.2 Hz, 2H), 3.12 (t, J = 7.2 Hz, 2H), 2.78 (s, 3H), 2.45 (t, J = 5.1 Hz, 4H), 2.32 (s, 3H), 2.22 (p, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm); 158.9, 158.4, 150.3, 132.3, 126.8, 123.8, 121.8, 111.0, 54.4, 47.1, 45.6, 43.01, 28.3, 22.6. MS (ESI) m/z 413 $(M + H)^+$.

General method A: synthesis of phtalimido sulfonamides from their corresponding sulfonyl chloride precursors. The following procedure is representative for the synthesis of intermediates **11** and **12.**

2-Phthalimidoethane-*N*-phenylsulfonamide (9). 2-Phthalimidoethanesulfonylchloride (2.0 g, 7.3 mmol) was added to a solution of aniline (2.3 g, 24.6 mmol) in chloroform (15 mL) in portions, and the resulting mixture was stirred at room temperature for 16 h. The organic phase was then washed with water and 1 M HCl. Removal of the solvent gave the crude product as a solid that was recrystallized from EtOH to yield 1.76 g (73%) of the title compound as white crystals. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.87−7.83 (m, 2H), 7.77−7.70 (m, 2H), 7.32−7.10 (m, 5H), 4.09−4.03 (m, 2H), 3.47−3.41 (m, 2H).

General method B: deprotection of phtalimido sulfonamides to their corresponding primary amines. The following procedure is representative for the synthesis of intermediates **13a**, **13b**, **14**, **15**, **17**, and **18**.

2-Aminoethanesulfonamide Hydrochloride (16). A suspension of 2-phthalimidoethanesulfonamide (1.52 g, 6.78 mmol) was heated at reflux in EtOH (30 mL), after which hydrazine (0.36 mL, 7.41 mmol) (64% in water) was added. After 3 h, a white precipitate formed that was removed by filtration. The filtrate was evaporated to dryness and added to water (150 mL). The aqueous suspension was acidified with conc HCl, and residual insoluble material was filtered off. The clear filtrate was evaporated to dryness, and the crude sulfonamide was recrystallized from EtOH/water (9:1) to yield the final product as 764 mg (64%) of white crystals; mp 134.0−135.0 °C. ^{1}H NMR (D_2O) δ (ppm) 3.62−3.55 (m, 2H), 3.51−3.44 (m, 2H).

General method C: synthesis of quinazoline-diones from their corresponding anthranilic acid precursors. The following procedure is representative for the synthesis of intermediates **33**−**36** and **38**−**39**.

6,7-Dichloroquinazolin-2,4(1*H*,3*H*)-dione (37). 2-Amino-4,5-dichloro benzoic acid (920 mg, 4.58 mmol) and urea (2.75 g, 45.8 mmol) were stirred at 160 °C. After 6 h, the mixture was cooled to 100 °C and an equivalent volume of water was added while stirring was continued for 5 min. The formed precipitate was filtered off and washed with water to yield a solid cake that was suspended in a solution of 0.5 N NaOH in water. The suspension was heated to boil for 5 min and then cooled to rt. The pH was adjusted to 2 with conc HCl, and the quinazoline-dione was filtered off. After washing with water:methanol (1:1), the product was dried in vacuo to yield 994 mg (94%) of a light-brown powder. ^{1}H NMR (DMSO-d_6) δ (ppm) 7.89 (s,1H), 7.33 (s,1H).

General method D: synthesis of 2,4-dichloroquinazolines from their corresponding quinazoline-dione precursors. The following procedure is representative for the synthesis of intermediates **41**−**44**, **46**, and **47**.

2,4,6,7-Tetrachloroquinazoline (45). 6,7-Dichloroquinazolin-2,4(1*H*,3*H*)-dione (800 mg, 3.46 mmol), DIPEA (1.23 mL, 7.27 mmol), and $POCl_3$ (4.0 mL) were heated at reflux. After 3 h, the reaction mixture was cautiously poured over crushed ice and stirred vigorously. This aqueous mixture was extracted with CH_2Cl_2 DCM, and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline solid that was redissolved in CH_2Cl_2, after which it was filtered over a pad of silica using CH_2Cl_2 as eluent. Removal of the organic phase gave the product as 657 mg (71%) of a beige solid. ^{1}H NMR ($CDCl_3$) δ (ppm) 8.34 (s,1H), 8.31 (s,1H). ^{13}C NMR ($CDCl_3$) δ (ppm) 162.7, 156.2, 150.6, 141.8, 134.2, 129.0, 126.6, 121.3.

General method E: synthesis of 2,4-disubstituted quinazolines from their corresponding 2,4-dichloroquinazoline precursors. The following procedure is representative for the synthesis of compounds **3**, **49**−**56**, **58**−**61**, **82**, and **98**−**104**.

2-(6-Chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*,*N*-dimethylethanesulfonamide (48). 2,4,6-Trichloroquinazoline (200 mg, 0.86 mmol) was added to a microwave tube containing EtOAc (3.0 mL) and DIPEA (0.32 mL, 1.81 mmol). 2-Aminoethane-*N*,*N*-dimethylsulfonamide hydrochloride (162 mg, 0.86 mmol) was then added, and the resulting mixture was stirred at rt until TLC indicated complete conversion of the starting material to the 4-subsituted quinazoline intermediate. *N*-Methylpiperazine (1.0 mL) was added, and the reaction mixture was heated at 120 °C for 10 min under microwave irradiation. The obtained suspension was then diluted with EtOAc (~50 mL) and washed with water and brine. Drying of the organic phase with Na_2SO_4 and evaporation of the solvent gave the crude product that was purified over SiO_2 (90% EtOAc, 5% Et_3N, 5% MeOH) to yield 117 mg (33%, calculated over the two steps) of the title compound as an off-white solid; mp 172.4−173.6 °C. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.45−7.32 (m, 3H), 6.34 (m, 1H), 4.09 (q, J = 5.8 Hz, 2H), 3.89 (t, J = 5.0 Hz, 4H), 3.25 (t, J = 6.0 Hz, 2H), 2.89 (s, 6H), 2.46 (t, J = 5.0 Hz, 4H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm) 158.5, 150.7, 133.2, 127.3, 125.9, 120.2, 110.7, 55.0, 46.4, 46.1, 43.6, 37.3, 35.2. MS (ESI) m/z 413 $(M + H)^+$.

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Supporting Information Available: Experimental details for compounds **3**, **7b**, **8**, **11**, **12**, **13a**, **13b**, **14**, **15**, **17**, **18**, **33**−**36**, **38**, **39**, **41**−**44**, **46**, **47**−**61**, **82**, **89**−**104**. LCMS purity data for compounds **3**, **48**−**61**, **82**, and **98**−**104** as determined by LCMS. Values and correlation matrix of the most influential descriptors from eq 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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