Parallel Synthesis of 2-Aryl-4-aminobenzimidazoles and Their Evaluation as Gonadotropin Releasing Hormone Antagonists

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2-Trifluoromethyl-4-aminobenzimidazoles were previously identified by screening to be active antagonists of the gonadotropin releasing hormone receptor (GnRH-R). Structure activity relationships and diversity oriented synthesis are shown here in greater detail. 2-Substituted benzimidazoles were synthesized in parallel by the coupling of carboxylic acids with a latent intermediate diamine monomer to yield the desired benzimidazoles in fair yields. A catch and release strategy was employed as a product isolation technique, followed by RP-HPLC to obtain products of desired purity for biological evaluation. Two libraries were prepared and screened to determine the optimal substitution for inhibitory activity against GnRH-R. The initial library focused on substituted phenyl, pyridine, and thiophenes. The follow-up library focused on substitution patterns observed in the initial library members and generated compounds with IC_{50} values lower than 100 nM at the GnRH-R.

Introduction

Gonadotropin releasing hormone (GnRH) or leuteinizing hormone releasing hormone (LHRH) is a decameric peptide synthesized and released in a pulsatile fashion from the hypothalamus.[1] It stimulates the release of the gonadotropins, follicle stimulating hormone (FSH), and leuteinizing hormone (LH), into the general circulation which in turn stimulate sexual hormone production.[2] Inhibition of the GnRH receptor with peptide antagonists and superagonists has resulted in useful therapy for hormone sensitive conditions such as prostate cancer and endometriosis.[3] In recent years there has been interest in developing small molecule GnRH antagonists in the hope of overcoming the limited pharmaceutical properties of peptide based medications.[4] We recently reported the identification of two closely related, small molecule lead GnRH antagonists discovered through a focused screening effort of ligands with affinity for various GPCR's (Scheme 1).[5] Both compounds were shown to have binding affinity to human and rat receptors as well as functional antagonism in both species. Compounds **1** and **2** served as leads for a structure−activity relationship study designed to enhance GnRH-R antagonist activity. Modification of the trifluoromethyl group in the 2-position of the 4-(1-piperazinyl)-benzimidazole template, present in both compounds, into substituted aryl groups was a key element in our investigation into the discovery of derivatives of **1** and **2** with greater potency at the GnRH receptor. A successful strategy would encompass probing additional chemical space at the receptor active site via increased template size and use of the additional pharmacophore space it provided. Of particular interest was the ability to perform the modifications in parallel as a way to enhance program efficiency. The lead structures, however, are relatively complex so a diversity step needed to be considered in the final stages of the preparation to avoid the operational difficulties of carrying several intermediates through multiple synthetic steps simultaneously. We report here, in greater detail from an earlier report,[5] an efficient strategy that accomplished this goal and required only two iterations of library preparation to achieve nanomolar binding potency at the human receptor from lead compounds with micromolar affinity.

Benzimidazoles are characterized as privileged structures[6] in medicinal chemistry because of their ability to interact with a range of different enzymes and receptors. They are well-known as important structural elements in medicinal chemistry that have been used as antihistaminic, antiparasitic, and antiviral agents.[7,8] Efficient preparation of benzimidazole libraries is of considerable interest to medicinal chemists and efforts to develop methods have been the subject of numerous research reports.[9,10] To the best of our knowledge, however, none have described the solution phase parallel synthesis of 4-amino-2-substituted benzimidazoles.[11] We needed to develop a synthetic method that accomplished this task and where formation of the 2-substituted benzimidazole would be the diverse and final step.

Results and Discussion

The majority of literature preparative procedures for benzimidazole libraries involve formation of the heterocycle early in the synthetic process and then elaborate the balance of the structure in the final phases.[9,10] To maximize efficiency, we devised a route utilizing phenylenetriamine

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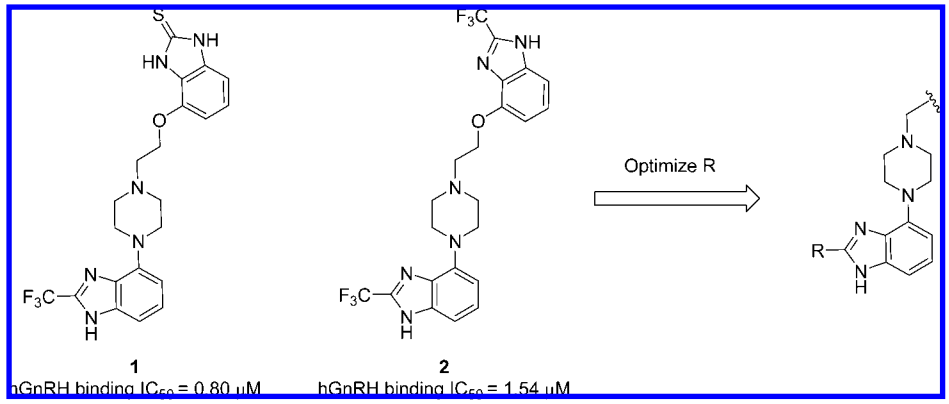
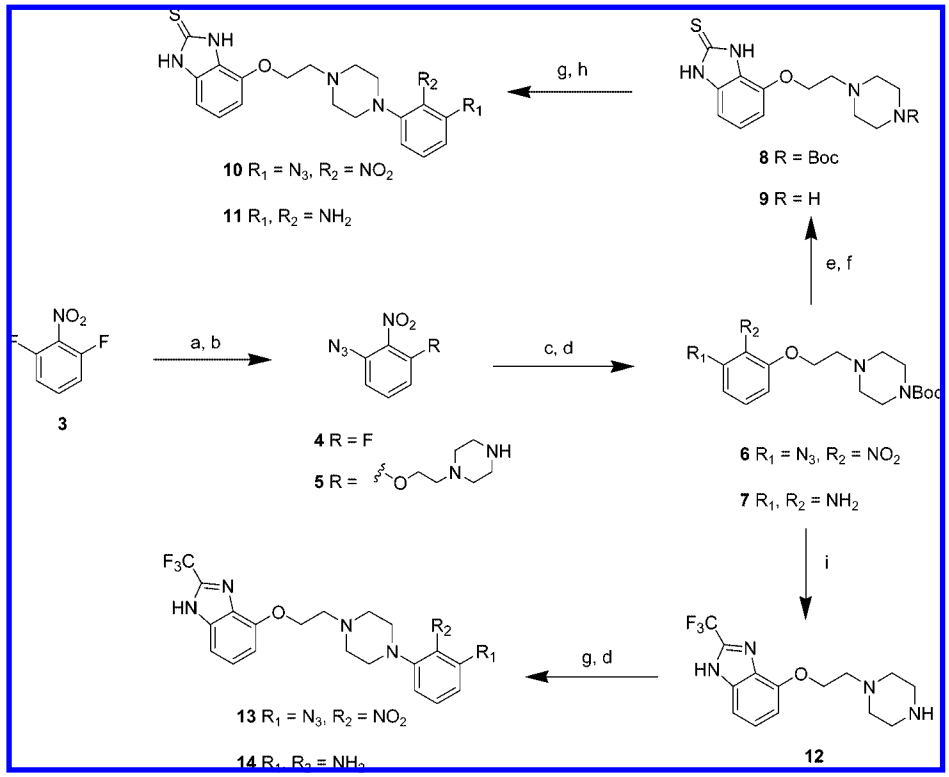
Scheme 1. GnRH Receptor Binding Leads **1** and **2** were Discovered from a GPCR Focused Screen



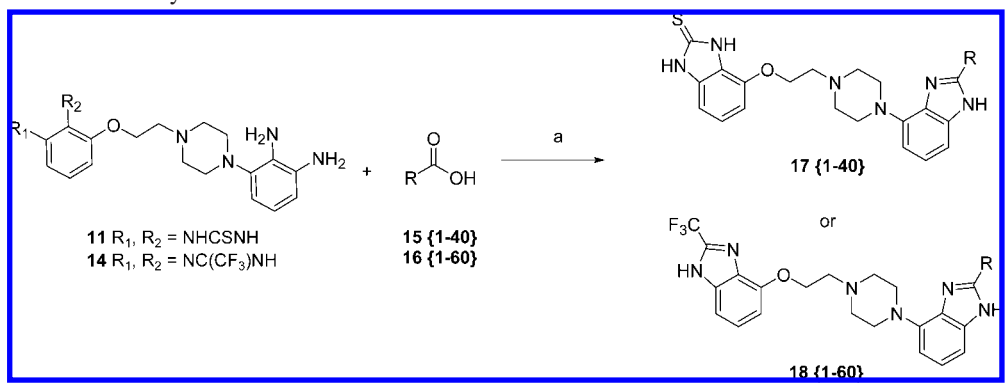
Scheme 2. Preparation of the Phenylenediamine monomers **11** and **14**[a]



[a] Reagents and conditions: (a) NaN_3, DMSO, 100%; (b) 2-(1-piperazinyl)ethanol, NaH, THF, 95%; (c) Boc_2O, PS-NH_2 resin, CH_2Cl_2, 83%; (d) H_2, Pd/C, MeOH, 100%; (e) 1,1′-thiocarbonyldiimidazole, THF, 65 °C, 56%; (f) TFA, PS-dimethylsilane resin, DCM, 69%; (g) **4**, DIPEA, DMSO, 60 °C, 95%; (h) $SnCl_2 \cdot 2H_2O$, NMP, 60 °C, 100%; (i) TFA, 70 °C, 90%.

intermediates, ideal for the diversity step of 2-substituted benzimidazole formation, in the last step of the target synthesis process (Scheme 2). The monomer synthesis proceeded in good overall yield allowing for the preparation of gram quantities of the necessary library intermediates with only a single flash column after formation of the thiobenzimidazole of intermediate **11**. The methods used to obtain the required phenylenetriamines are shown (Scheme 2). Displacement of one fluorine from starting material **3** occurred readily with primary and secondary amines. Displacement of the second fluorine with alkoxides and amines, however, required elevated temperatures that often led to decomposition of the starting aminonitrobenzene. This sluggish performance is most likely because of the increased electron density, hence decreased electrophilicity, on the aromatic ring following the first substitution thus making the second substitution difficult. Alternatively, the first fluorine in this sequence was displaced with azide (1.1 equiv) to provide **4**, followed by substitution of the second fluorine with the sodium salt of 2-(1-piperazinyl)ethanol at reduced temperature to give the ether **5**. Protection of the amine and catalytic hydrogenation of the azide and nitro functions left the phenylenediamine **7**. Treatment of this intermediate with 1,1′-thiocarbonyldiimidazole (thioCDI) followed by deprotection of the Boc group in the presence of a resin bound cation scavenger gave the intermediate **9**. Further treatment of **9** with the monofluoro intermediate **4** gave **10**, which was fully reduced with tin(II) chloride dihydrate to the key intermediate **11**. Phenylenediamine **7** was also treated with hot TFA to provide the deprotected trifluoromethylbenzimidazole intermediate **12**. Key intermediate **14** was obtained

Scheme 3. Preparation of Library Members from Monomers[a]



[a] Reagents and conditions: HATU, NMP then AcOH, 110 °C, MP-SO_3H resin then Et_3N, MeOH.

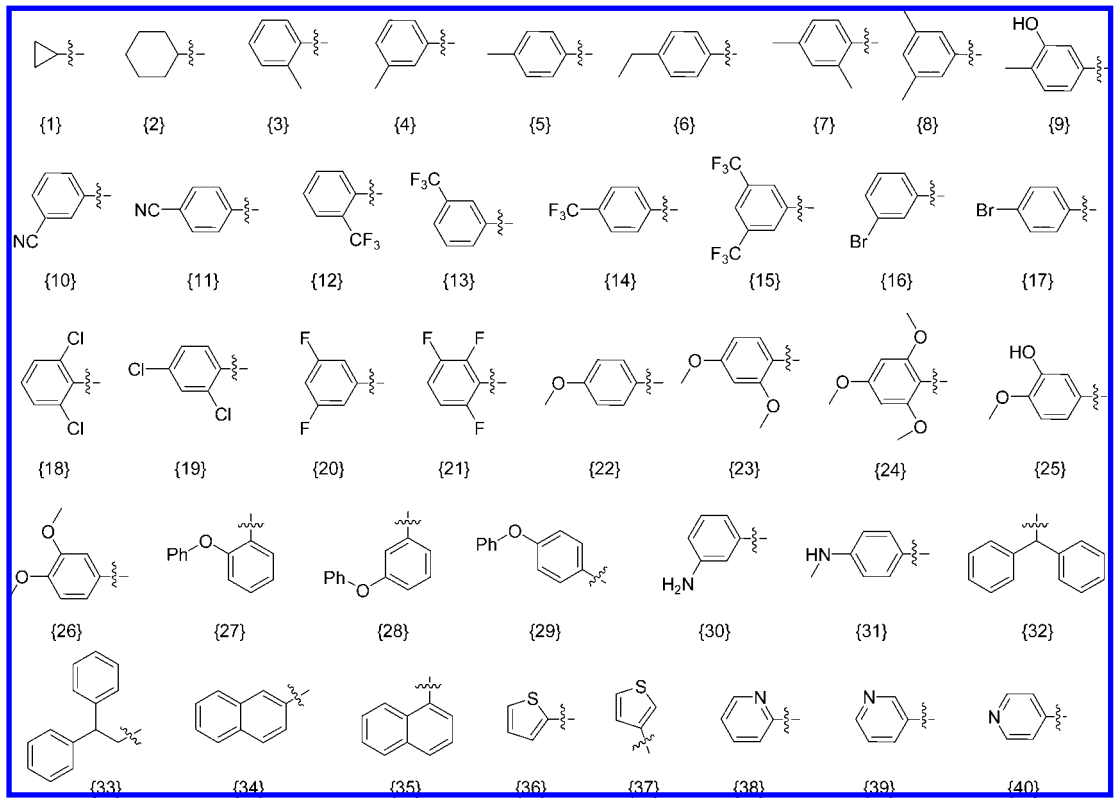


Figure 1. Chemset **15**{*1*−*40*} carboxylic acid monomers.

after treatment of **12** with **4** under conditions described above followed by catalytic reduction of **13**.

The diversity step is shown in Scheme 3. The phenylenediamine **11** was coupled to acids **15**{1−40}, representing a variety of substitution patterns and electronic profiles (Figure 1), via activation with HATU. In situ cyclization occurred after the addition of acetic acid and brief heating. Utilizing a catch and release strategy,[12] we employed polymer-bound sulfonic acid resin to isolate piperazine containing compounds from solution via phase switch methodology. Liberating the product with triethylamine and methanol, followed by concentration, gave the crude product in 37 of 40 cases (**17**{*12*,*18*,*31*} not observed, Table 1). Because of the nature of the binding assays, it was in our interest to ensure high purity at the expense of overall product yield. Hence, compounds were purified by semiprep reversed-phase HPLC, and only the center product fractions were collected and evaporated for compound characterization and biological analysis. Product purity and integrity were determined by HPLC and MS, and selected compounds were analyzed by NMR. Purified yields ranged from 5−25% with an additional five compounds not isolated (**17**{*2*,*3*,*27*,*28*,*36*}). The scale of this library (17 mg) was more than enough to generate sufficient quantities for screening despite sacrificing product yield for purity. These results, as well as binding activity of the initial library are outlined in Table 1. The synthetic results indicate aliphatic, phenyl, and heterocyclic acids can be prepared by this method. Various substitution patterns, as well as diverse electronic properties, are also well tolerated in this sequence; however, ortho-substituted benzoic acids gave the poorest overall yields because of steric factors. This accounted for half of the library failures. Acid substitution patterns were chosen by inspection and represented a cross section of spatial and electronic patterns designed to increase the probability of finding members with suitable binding properties after a single library iteration. A total of 32

Table 1. Characterization and Biological Results of the Initial Library

product	hGnRH activity %Inhib at 10 μm (IC_{50})[a,b]	HPLC purity	% yield	product	hGnRH activity %Inhib at 10 μm (IC_{50})[a,b]	HPLC purity	% yield
17{*1*}	46	>99	11	**17**{*21*}	14	>99	7
17{*2*}	insufficient material	>99	6	**17**{*22*}	94 (0.19 μm)	>99	14
17{*3*}	insufficient material	>99	5	**17**{*23*}	39	>99	9
17{*4*}	47	92	11	**17**{*24*}	69	>99	10
17{*5*}	92 (1.30 μm)	>99	7	**17**{*25*}	92 (0.46 μm)	>99	8
17{*6*}	79 (0.12 μm)	>99	12	**17**{*26*}	64	>99	9
17{*7*}	77 (1.16 μm)	>99	10	**17**{*27*}	insufficient material	>99	5
17{*8*}	0	93.6	24	**17**{*28*}	insufficient material		0
17{*9*}	92 (0.24 μm)	>99	9	**17**{*29*}	84 (0.18 μm)	>99	7
17{*10*}	22	>99	17	**17**{*30*}	89	>99	9
17{*11*}	72 (1.29 μm)	>99	17	**17**{*31*}	n/a		0
17{*12*}	n/a		0	**17**{*32*}	12	>99	7
17{*13*}	15	93.1	11	**17**{*33*}	21	>99	22
17{*14*}	70 (0.54 μm)	92.6	7	**17**{*34*}	75	96.1	11
17{*15*}	6	>99	6	**17**{*35*}	60	>99	7
17{*16*}	27	>99	10	**17**{*36*}	insufficient material	>99	6
17{*17*}	86 (0.24 μm)	95.8	7	**17**{*37*}	97 (0.38 μm)	>99	11
17{*18*}	n/a		0	**17**{*38*}	33	>99	9
17{*19*}	71 (0.51 μm)	93.1	8	**17**{*39*}	44	>99	25
17{*20*}	31	>99	9	**17**{*40*}	47	>99	16

[a] Binding to overexpressed human GnRH receptors in competition with ^{125}I-(D-Trp^6)-GnRH[13]. [b] IC_{50} values are the average of at least two runs performed in triplicate. SD values are within ±15% of the IC_{50} value.

compounds were screened for in vitro binding activity at the GnRH receptor at 10 μM concentration. Selected compounds with greater than 50% inhibition underwent dose response to determine their IC_{50} levels. The results showed that compounds with para phenyl substitution provided the most potent binding agents. Substitution at the para position was superior to meta- or ortho-substitution (see **17**{*4*} vs {*5*} or **17**{*16*} vs {*17*}). Meta-hydroxy substitution on **17**{*5*}, that is, library member **17**{*9*}, increased potency; however, the addition of a second oxygen substituent on the phenyl ring in the series **17**{*22*,*25*,*26*} led to less potent GnRH binding agents. For more highly active para-substituted compounds additional substitution did not lead to increased potency (see **17**{*22*} vs {*23*,*25*} or {*5*} vs {*7*}). In addition, thiophene derivatives showed relatively potent activity (**17**{*37*} IC_{50} = 0.38 μM) compared to pyridines that were only modest binders (**17**{*38*−*40*}).

The most potent compound was **17**{*6*}, the 4-ethylphenyl derivative with a binding IC_{50} of 0.12 μM at the GnRH receptor. For the alkyl derivatives there is a large increase in affinity going from methyl to ethyl. In addition, compounds such as **17**{*29*} suggest a large group can be tolerated in this area. The phenyl ring however needs to be directly attached as both compounds with small alkyl spacer **17**{*32*,*33*} show a significant loss in activity.

On the basis of these results, a follow-up library using 4-substituted aryl groups in the 2 position of the piperazinylbenzimidazole template was proposed. In addition, this library would incorporate the trifluoromethylbenzimidazole functionality of **2** rather than the thiobenzimidazolone for several reasons: The preparation of intermediate **14** was higher yielding than **11** (Scheme 2), so it was more readily available, identical conditions to prepare the first library may be used in the follow-on library (Scheme 3), and the trifluoromethylbenzimidazole group is a bioequivalent of the thiobenzimidazolone in **1** (Scheme 1). Bioequivalence was further demonstrated by including several thiophenes and pyridines in the follow-on library, as well as the required 4-substituted benzoic acids for comparison with the initial library. A collection of sixty acids **16**{*1*−*60*}(Figure 2) was attempted using the same experimental procedure and purification process as the first library (Scheme 3). On the basis of the potency of the para-substituted compounds from the first library this library was screened at both 1 and 10 μM concentrations. Synthetic and biological results at 1 μM of the follow-up library are outlined in Table 2.

The yields obtained for follow-on library members were generally higher than the first library, presumably because of better product isolation due to increased solubility relative to the thiourea based compounds and were sufficient to allow for all sixty compounds to undergo biological testing. In general, binding affinities for members of the follow-up library are more potent than those of the original library members. Six compounds had binding IC_{50} values lower than 100 nM: **18**{*12*,*19*,*37*,*48*,*57*,*59*}.

From these results some structure−activity information was derived. For compounds with alkyl substituents an increase in potency is observed as the branching on the initial carbon is increased. Thus the *t*-butylphenyl derivative, **18**{*37*}, is the most active in this series (hGnRH IC_{50}= 50 nM). In addition, 4-aminophenyl substitutions gave active compounds as well. Dialkyl anilines show similar potency patterns to the aliphatic substituted phenyls (i.e., compare **18**{*18*,*19*}). Aryl ethers at the 4-phenyl position are also tolerated with 4-benzyloxyphenyl and 4-phenoxyphenyl substituents displaying receptor affinity as well. Linear alkyl chain substitution showed a quick drop off in potency from methyl to hexyl. Having additional substitution on the ring showed no increase in potency when compared to simple 4-substituted phenyl derivatives. Thiophene, but not pyridyl, is able to function as a phenyl replacement with **18**{*12*} and **18**{*7*} among the more potent derivatives. Replacement of phenyl groups with thiophenes in a series of uracil GnRH antagonists has been reported to be advantageous for potency.[14] In this series of 2-(thiophenyl)benzimidazoles, potency at the GnRH receptor drops off slightly when compared to the phenyl derivatives (compare **18**{*6* vs *25*}). The data also correlate well with binding data from the first

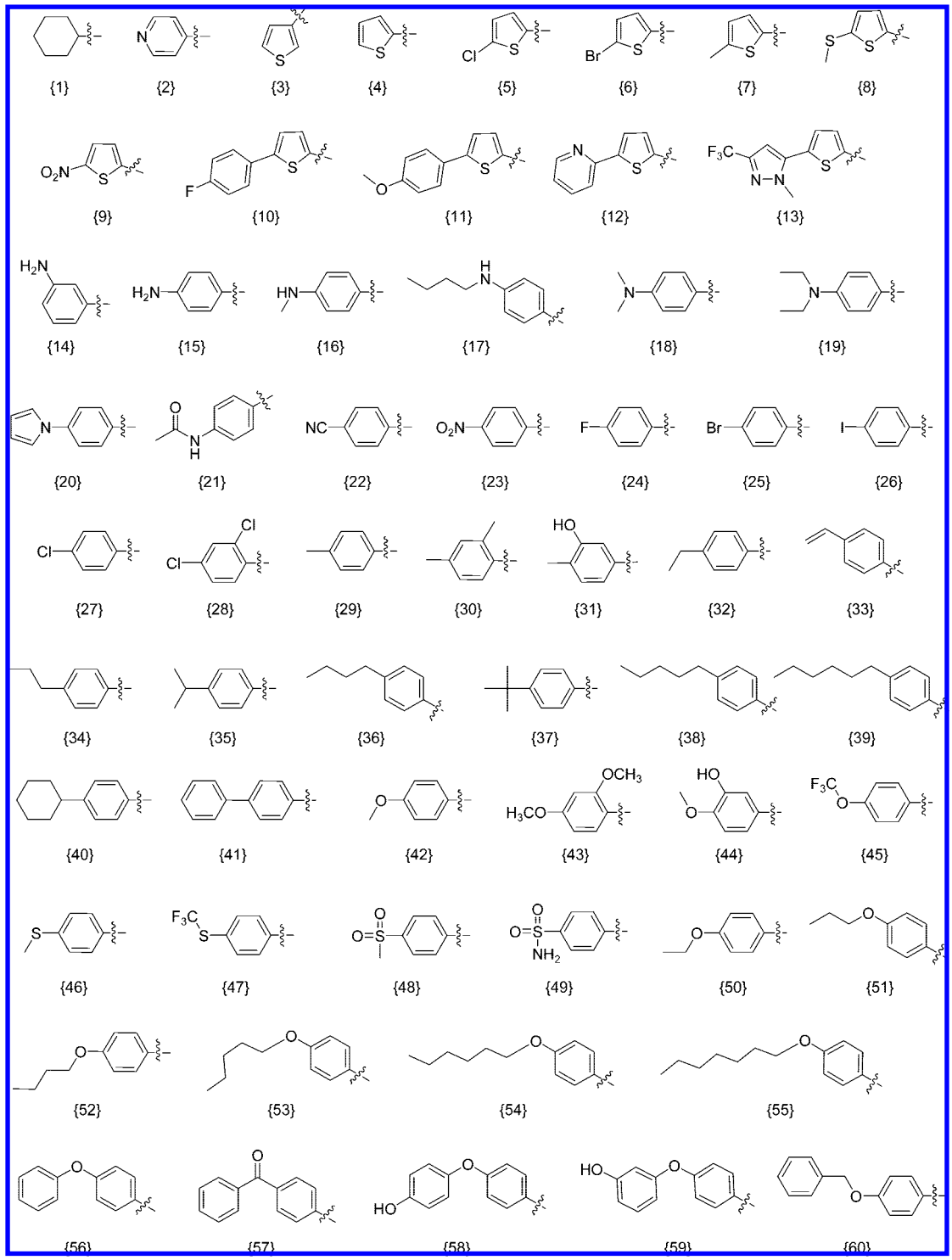


Figure 2. Chemset **16**{*1*−*60*} carboxylic acid monomers.

library. Two matched pairs with IC_{50} values were reported. Similar binding activity for library members (**17**{*6*} IC_{50}=120 nM vs **18**{*32*} IC_{50}=220 nM and **17**{*29*} IC_{50}=180 nM vs **18**{*56*} IC_{50}=150 nM) support the interchangeable nature of the pendant thiobenzimidazolone of lead **1** and the trifluoromethylbenzimidazole of lead **2** although the rank order of compounds may vary slightly.[15] The increase in micromolar binding activity in the lead compounds to nanomolar binding in several library members provided confirmation of our original hypothesis that an aromatic group in this position could serve as an additional template for exploring chemical space as a method for enhancing small molecule-receptor affinity.

Conclusion

A parallel synthetic strategy was employed to generate focused libraries with increased binding potency at the human GnRH receptor starting with lead compounds discovered using a GPCR directed library. Discrete benzimidazoles were prepared from a solution phase method utilizing phenylenediamines in the diversity step. Two focused libraries were prepared with the goal of optimizing substitution at the

Table 2. Characterization and Biological Results of the Follow-up Library

product	hGnRH activity %Inhib @ 1 μm (IC_{50})[a,b]	HPLC purity	% yield	product	hGnRH activity %Inhib @ 1 μm (IC_{50})[a,b]	HPLC purity	% yield
18{*1*}	0	97.8	31	**18**{*31*}	70	>99	27
18{*2*}	19	>99	23	**18**{*32*}	87 (0.22 μm)	>99	7
18{*3*}	44	>99	29	**18**{*33*}	74	>99	24
18{*4*}	29 (1.58 μm)	>99	26	**18**{*34*}	79	>99	26
18{*5*}	29	>99	25	**18**{*35*}	93 (0.12 μm)	>99	27
18{*6*}	27	>99	24	**18**{*36*}	55	>99	19
18{*7*}	31 (0.82 μm)	>99	26	**18**{*37*}	95 (0.050 μm)	>99	24
18{*8*}	78 (0.41 μm)	>99	27	**18**{*38*}	36	>99	24
18{*9*}	7	93.4	13	**18**{*39*}	9	>99	23
18{*10*}	31	>99	22	**18**{*40*}	24	>99	24
18{*11*}	36 (2.34 μm)	>99	16	**18**{*41*}	17	>99	19
18{*12*}	95 (0.083 μm)	>99	19	**18**{*42*}	76	>99	27
18{*13*}	9	>99	21	**18**{*43*}	28	>99	16
18{*14*}	28	>99	6	**18**{*44*}	68	>99	13
18{*15*}	31	97.5	14	**18**{*45*}	76	>99	23
18{*16*}	79	>99	17	**18**{*46*}	86	90.9	25
18{*17*}	46	>99	16	**18**{*47*}	51	>99	14
18{*18*}	88	92.3	19	**18**{*48*}	91 (0.088 μm)	>99	21
18{*19*}	94 (0.068 μm)	>99	18	**18**{*49*}	70	>99	22
18{*20*}	59	>99	21	**18**{*50*}	83	>99	26
18{*21*}	80	>99	25	**18**{*51*}	80	>99	21
18{*22*}	35	>99	25	**18**{*52*}	54	>99	26
18{*23*}	51	>99	21	**18**{*53*}	40 > 99	24	
18{*24*}	3	>99	15	**18**{*54*}	10	>99	24
18{*25*}	59	>99	28	**18**{*55*}	0	>99	22
18{*26*}	84	>99	23	**18**{*56*}	85 (0.15 μm)	>99	16
18{*27*}	40	>99	25	**18**{*57*}	93 (0.053 μm)	>99	23
18{*28*}	52	>99	17	**18**{*58*}	88	>99	19
18{*29*}	52	>99	25	**18**{*59*}	93 (0.096 μm)	96.5	19
18{*30*}	85	>99	18	**18**{*60*}	87 (0.13 μm)	>99	23

[a] Binding to overexpressed human GnRH receptors in competition with ^{125}I-(D-Trp^6)-GnRH[13]. [b] IC_{50} values are the average of at least two runs in triplicate. SD's are within ±15% of the IC_{50} value.

2-position of the piperazinylbenzimidazole template. After two library iterations, six compounds were identified with GnRH receptor binding IC_{50} values less than 100 nM and one as potent as 50 nM. Several of these compounds served as advanced leads for further structural optimization. Some of these results were reported previously. Other results will be reported in due course.

Experimental Section

General. Crude and final product analytical RP-HPLC/ESI-MS was carried out on a Gilson 215 HPLC system coupled to a ThermoFinnigan AQA system with UV detection using the gradient H_2O/CH_3CN (0.1% CF_3CO_2H) 95:5 to 0:100 over 15 min. Preparative RP-HPLC was carried out on a Gilson 215 HPLC with dual wavelength UV detection (220, 254 nM) using the gradient H_2O/CH_3CN (0.1% CF_3CO_2H) 95:5 to 0:100 over 15 min. All products were diluted to 10 mM concentration in DMSO for biological testing. Selected compounds were analyzed by ^{1}H NMR. All samples were acquired in standard DMSO solution using WET solvent suppression technique.[16] Protonated DMSO usually contains significant amount of H_2O clearly visible at around 3.2 ppm in spectra taken without any solvent suppression techniques. Best results can be achieved using carefully optimized WET solvent suppression with selective shaped pulses centered at DMSO and H_2O resonances. The selectivity of solvent suppression can be better than 20 Hz at each suppressed signal without disturbing signals of solute. To suppress intense ^{13}C satellites ^{13}C WALTZ4 low power decoupling was implemented during shaped pulses as described in the work of Smallcombe et al.[16]Approximately 200 μL of sample dissolved in protonated DMSO was placed in 3 mm OD tube. All proton spectra were taken on VARIAN INOVA 500 MHz instrument equipped with a 3 mm indirect detection triple resonance probe with *z* gradient. Proton gradient shimming was used to shim each sample before acquisition. All the spectra were acquired without lock. Residual signal of DMSO at 2.5 ppm was used for referencing. The following abbreviations are used to describe peak splitting when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet. All reagents are of commercial quality unless otherwise indicated.

Measurement of GnRH receptor in Vitro Binding Activity. Assays were conducted using COS cell membranes containing human GnRH receptors incubated with radioactively labeled D-Trp6 GnRH in the presence of test compound. Membrane bound radioactivity was measured after separating the free radioactivity by filtration method, and IC_{50} values were calculated using the SAS system.[13]

General Procedure for the Synthesis of 2-Substituted-4-aminobenzimidazole Chemset 16{*1,40*}. To an 8 mL vial containing a carboxylic acid (**15**{*1*−*40*}, 0.055 mmol) were added stock solutions of the diamine monomer **11** (0.186 mL, 0.25 M) and HATU (0.279 mL, 0.2 M) in NMP. The vials were capped and shaken overnight at room temperature. Glacial acetic acid (0.5 mL) was added to each vial, and they were capped and shaken at 110 °C for 2 h. After the mixture was cooled to room temperature, 4 equiv of Argonaut MP-TsOH resin (0.132 g, 1.4 mmol/g, 0.185 mmol) was added, and the vial shaken overnight. The

samples were filtered and the resin washed with MeOH (3 × 3 mL) and DCM (2 × 3 mL). The resins were treated with 9:1 MeOH/triethylamine (1.5 mL) for five minutes and filtered. The resulting solutions were concentrated to dryness on a Savant Speedvac overnight and purified by preparative RP-HPLC. The center fractions of each product were concentrated in vacuo using a Savant Speedvac. The above procedure was used to prepare library members **17**{*1*−*60*} from phenylenediamine **14** and chemset **16**{*1*−*60*} on the same scale. Characterization of the diamine monomers used, as well as selected compounds from arrays **17** and **18** are listed below.

4-(2-(4-(2,3-Diaminophenyl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione (11): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.40 (bs, 1H), 10.65 (bs, 1H), 7.05 (dd, 1H, J = 8.1 Hz, J = 8.1 Hz), 6.85 (d, 1H, J = 8.0 Hz), 6.81 (dd, 1H, J = 7.9, Hz, J = 1.1 Hz), 6.73 (d, 1H, J = 7.9 Hz), 6.70 (dd, 1H, J = 7.9 Hz, J = 7.9 Hz), 6.55 (dd, 1H, J = 7.9 Hz, J = 1.1 Hz), 4.38 (t, 2H, J = 4.8 Hz), 3.60 (bs, 4H), 3.15 (t, 2H, J = 4.8 Hz), 2.89 (m, 4H).

3-(4-(2-(2-(Trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-yloxy)ethyl)piperazin-1-yl)benzene-1,2-diamine (14): ^{1}H NMR (300 MHz, CD_3OD) δ = 7.20−7.30 (m, 2H), 6.88 (d, 1H, J = 7.0 Hz), 6.46−6.57 (m, 3H), 4.38 (t, 2H, J = 5.5 Hz), 2.98 (t, 2H, J = 5.5 Hz), 2.88 (m, 4H), 2.82 (m, 4H).

4-(2-(4-(2-*m*-Tolyl-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*3*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.72 (br s, 1H), 8.13 (s, 1H), 7.95 (d, 1H, J = 7.8 Hz), 7.70 (d, 1H, J = 7.8 Hz), 7.35 (t, 1H, J = 7.8 Hz), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.89 (m, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.31 (t, 2H, J = 15 Hz), 2.35 (s, 3H).

4-(2-(4-(2-(4-Ethylphenyl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*6*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.11 (d, 2H, J = 8.3 Hz), 7.44 (d, 2H, J = 8.3 Hz), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.89 (m, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.31 (t, 2H, J = 15 Hz), 2.72 (m, 2H), 1.26 (t, 3H, J = 9 Hz).

4-(2-(4-(2-(2,4-Dimethylphenyl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*7*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (bs, 1H), 12.66 (bs, 1H), 9.71 (bs, 1H), 7.95 (d, 1H, J = 8.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.30 (s, 1H), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (bs, 4H), 3.89 (m, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.31 (t, 2H, J = 15 Hz), 2.38 (s, 3H), 2.29 (s, 3H).

4-(2-(4-(2-(3-Cyanophenyl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*10*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.67 (s, 1H), 8.51 (d, 1H, J = 7.8 Hz), 8.00 (d, 1H, J = 7.8 Hz), 7.83 (t, 1H, J = 7.8 Hz), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.89 (m, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.31 (t, 2H, J = 15 Hz).

4-(2-(4-(2-(4-Cyanophenyl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H* benzo[*d*]imidazole-2(3*H*)-thione 17{*11*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.37 (d, 2H, J = 8.3 Hz), 8.08 (d, 2H, J = 8.3 Hz), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.88 (m, 2H), 3.76 (m, 2H), 3.60 (m, 2H), 3.31 (t, 2H, J = 15 Hz).

4-(2-(4-(2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[d]imidazole-2(3*H*)-thione 17{*22*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.14 (d, 2H, J = 8.8 Hz), 7.20−7.10 (m, 5H), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.92 (s, 3H), 3.89 (m, 2H), 3.75 (m, 2H), 3.60 (m, 2H), 3.31 (t, 2H, J = 15 Hz).

4-(2-(4-(2-(Thiophen-3-yl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*37*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.26 (s, 1H), 7.80 (m, 2H), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.89 (m, 2H), 3.75 (m, 2H), 3.53 (br s, 2H), 3.31 (m, 2H).

4-(2-(4-(2-(Pyridin-3-yl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*39*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.72 (m, 2H), 8.61 (m, 1H), 8.53 (m, 1H), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.89 (m, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.31 (m, 2H).

4-(2-(4-(2-(Pyridin-4-yl)-1*H*-benzo[*d*]imidazol-4-yl)piperazin-1-yl)ethoxy)-1*H*-benzo[*d*]imidazole-2(3*H*)-thione 17{*40*}: ^{1}H NMR (500 MHz, DMSO) δ = 12.68 (s, 1H), 12.66 (s, 1H), 9.71 (br s, 1H), 8.85 (m, 2H), 8.26 (d, 1H, J = 6.3 Hz), 8.19 (d, 1H, J = 6.3 Hz), 7.23 (m, 2H), 7.15 (t, 1H, J = 8.3 Hz), 6.89 (m, 2H), 6.73 (m, 1H), 4.59 (br s, 4H), 3.89 (m, 2H), 3.76 (m, 2H), 3.60 (m, 2H), 3.31 (m, 2H).

2-(Thiophen-2-yl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*4*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 7.85 (m, 1H), 7.75 (m, 1H), 7.39 (m, 2H), 7.27 (m, 1H), 7.17 (m, 2H), 7.04 (d, 1H, J = 7.9 Hz), 6.68 (m, 1H), 4.74 (bs, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

2-(5-Methylthiophen-2-yl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*7*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 7.64 (d, 1H, J = 3.4 Hz), 7.39 (m, 2H), 7.14 (m, 2H), 7.04 (d, 1H, J = 7.9 Hz), 6.96 (m, 1H), 6.68 (m, 1H), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H), 3.03 (s, 3H).

2-(5-(Methylthio)thiophen-2-yl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*8*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 7.71 (d, 1H, J = 3.4 Hz), 7.39 (m, 2H), 7.21 (d, 1H, J = 3.9 Hz), 7.15 (m, 2H), 7.04 (d, 1H, J = 7.3 Hz), 6.67 (m, 1H), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H), 2.71 (s, 3H).

2-(5-(4-Methoxyphenyl)thiophen-2-yl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*11*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 7.80 (d, 1H, J = 3.9 Hz), 7.70 (d, 2H, J = 8.8 Hz), 7.53 (d, 1H, J = 3.9 Hz), 7.39 (m, 2H), 7.15 (m, 2H), 7.06 (d, 2H, J = 8.8 Hz), 7.03 (m, 1H), 6.68 (t, 1H, J = 4.4 Hz), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.85 (s, 3H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

2-(5-(Pyridin-2-yl)thiophen-2-yl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*12*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.60 (d, 1H, J = 3.9 Hz), 8.03 (d, 1H, J = 8.3 Hz), 7.93 (m, 2H), 7.85 (d, 1H, J= 3.9 Hz), 7.38 (m, 3H), 7.17 (m, 2H), 7.04 (d, 1H, J = 7.9 Hz), 6.69 (t, 1H, J = 4.4 Hz), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

***N*,*N*-Diethyl-4-(4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-2-yl)aniline 18{*19*}:** ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.03 (d, 2H, J = 8.8 Hz), 7.43−7.31 (m, 4H), 7.04 (d, 1H, J = 7.3 Hz), 6.95 (m, 1H), 6.91 (d, 2H, J = 8.8 Hz), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.53 (m, 4H), 3.25 (bs, 2H), 1.19 (m, 6H).

2-*p*-Tolyl-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-7-yloxy)-ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*29*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.04 (d, 2H, J = 8.1 Hz), 7.42 (d, 2H, J = 8.1 Hz), 7.39 (m, 2H), 7.23 (m, 2H), 7.04 (d, 1H, J = 7.8 Hz), 6.75 (d, 1H, J = 7.8 Hz), 4.75 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (m, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H), 2.34 (s, 3H).

2-(4-Ethylphenyl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-yloxy)ethyl)piperazin-1yl)-1*H*-benzo[*d*]imidazole 18{*32*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.11 (d, 2H, J = 8.3 Hz), 7.45 (d, 2H, J = 8.3 Hz), 7.39 (m, 2H), 7.23 (m, 2H), 7.04 (d, 1H, J = 7.8 Hz), 6.75 (d, 1H, J = 7.8 Hz), 4.75 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (m, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H), 2.73 (q, 2H, J = 9.0 Hz), 1.28 (t, 3H, J = 9.0 Hz).

2-(4-Isopropylphenyl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*35*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.11 (d, 2H, J = 8.3 Hz), 7.48 (d, 2H, J = 8.3 Hz), 7.39 (m, 2H), 7.22 (m, 2H), 7.04 (d, 1H, J = 7.9 Hz), 6.74 (d, 1H, J = 7.9 Hz), 4.74 (bs, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H), 3.04 (m, 1H), 1.30 (d, 6H, J = 10.6 Hz).

2-(4-*tert*-Butylphenyl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*37*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.09 (d, 2H, J = 8.4 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.35 (m, 2H), 7.20 (m, 2H), 7.02 (d, 1H, J = 8.1 Hz), 6.72 (d, 1H, J = 8.1 Hz), 4.71 (br s, 2H), 4.42 (br s, 2H), 3.86 (br s, 2H), 3.79 (br s, 2H), 3.57 (br s, 2H), 3.23 (br s, 2H), 1.35 (s, 9H).

2-(4-(Methylsulfonyl)phenyl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol4yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole 18{*48*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.43 (d, 2H, J = 8.3 Hz), 8.13 (d, 2H, J = 8.8 Hz), 7.39 (m, 2H), 7.22 (m, 2H), 7.04 (d, 1H, J = 7.3 Hz), 6.71(m, 1H), 4.74 (m, 2H), 4.58 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.32 (s, 3H), 3.25 (bs, 2H).

2-(4-Phenoxyphenyl)-4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol4yloxy)ethyl)piperazine-1-yl)-1*H*-benzo[*d*]imidazole 18{*56*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.20 (d, 2H, J = 8.8 Hz), 7.50 (m, 2H), 7.39 (m, 2H), 7.29−7.13 (m, 7H), 7.04 (d, 1H, J = 7.8 Hz), 6.74 (d, 1H, J = 7.8 Hz), 4.74 (m, 2H), 4.51 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

Phenyl(4-(4-(4-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-2-yl)phenyl)methanone 18{*57*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.29 (d, 2H, J = 8.3 Hz), 7.89 (d, 2H, J = 8.3 Hz), 7.77 (d, 2H, J = 7.3 Hz), 7.70 (m, 1H), 7.59 (m, 2H), 7.37 (m, 1H), 7.31 (d, 1H, J = 8.3 Hz), 7.20 (m, 2H), 6.97 (d, 1H, J = 7.8 Hz), 6.69 (m, 1H), 4.63 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

3-(4-(4-(4-(2-(2-(Trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-yloxy)ethyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-2-yl)phenoxy)phenol 18{*59*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.19 (d, 2H, J = 8.8 Hz), 7.39 (m, 2H), 7.25 (m, 1H), 7.20 (m, 4H), 7.04 (d, 1H, J = 7.8 Hz), 6.74 (d, 1H, J = 6.4 Hz), 6.65 (m, 1H), 6.54 (m, 1H), 6.50 (m, 1H), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.90 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

2-(4-(Benzyloxy)phenyl)-4-(4-(2-(2-(trifluoromethyl)-1benzo[*d*]imidazol4yloxy)ethyl)piperazine-1-yl)-1*H*-benzo[*d*]imidazole 18{*60*}: ^{1}H NMR (500 MHz, DMSO) δ = 10.2 (bs, 1H), 8.14 (d, 2H, J = 8.8 Hz), 7.53 (d, 2H, J = 7.3 Hz), 7.46 (m, 2H), 7.39 (m, 3H), 7.26 (d, 2H, J = 8.8 Hz), 7.23 (m, 2H), 7.04 (d, 1H, J = 7.8 Hz), 6.76 (d, 1H, J = 6.8 Hz), 5.26 (s, 2H), 4.74 (m, 2H), 4.48 (bs, 2H), 3.91 (bs, 2H), 3.82 (bs, 2H), 3.60 (bs, 2H), 3.25 (bs, 2H).

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