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# Design, synthesis and evaluation of bicyclic benzamides as novel 5-$HT_{1F}$ receptor agonists

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**Abstract**—Several fused bicyclic systems have been investigated to serve as the core structure of potent and selective 5-$HT_{1F}$ receptor agonists. Replacement of the indole nucleus in **2** with indazole and 'inverted' indazole provided more potent and selective 5-$HT_{1F}$ receptor ligands. Indoline and 1,2-benzisoxazole systems also provided potent 5-$HT_{1F}$ receptor agonists, and the 5-$HT_{1A}$ receptor selectivity of the indoline- and 1,2-benzisoxazole-based 5-$HT_{1F}$ receptor agonists could be improved with modification of the benzoyl moiety of the benzamides. Through these studies, we found that the inherent geometries of the templates, not the nature of hybridization of the linking atom, were important for the 5-$HT_{1F}$ receptor recognition.


Serotonin (5-HT) plays an important role in regulating many physiological functions through its interaction with different 5-HT receptors.[1] Currently, there are seven classes of 5-HT receptors identified. Among them, the 5-$HT_1$ receptors are the most complex and consist of the 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1D}$, 5-$HT_{1E}$ and 5-$HT_{1F}$ receptor subtypes.[2,3] Sumatriptan (**1**, Fig. 1) is the first 5-$HT_1$ receptor agonist clinically used for the treatment of migraine. It is a potent 5-$HT_{1B}$, 5-$HT_{1D}$ and 5-$HT_{1F}$ receptor agonist. Its activity at 5-$HT_{1B}$ receptor has been thought to be the cause of its cardiovascular adverse effect observed clinically.[4] Compound **2** (LY334370) is a potent and selective 5-$HT_{1F}$ agonist.[5] It is also effective clinically in treating migraine pain.[6] Since this compound does not show vasoconstriction in the rabbit saphenous vein assay,[7] a model used to predict the adverse cardiovascular effect associated with 'triptans', development of a potent and selective 5-$HT_{1F}$ receptor agonist should provide a safer anti-migraine therapy.

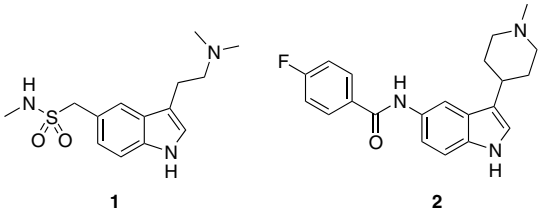


**Figure 1.** Structures of Sumatriptan (**1**) and LY 334370 (**2**).

Both Sumatriptan (**1**) and compound **2** have an indole core structure. As part of our ongoing efforts, we set out to explore new templates to replace the central indole structure and to provide potent and selective 5-$HT_{1F}$ receptor agonists. We have previously reported that pyrrolo[3,2-*b*]pyridine and furo[3,2-*b*]pyridine systems can serve as bioisosteres of the central indole ring and generate potent and selective 5-$HT_{1F}$ receptor agonists.[8] These studies demonstrated that the bicyclic ring system in this family of molecules could be modified in specific ways, which were compatible with effective receptor recognition. In a considerable extension of that work, we systematically studied several bicyclic systems, which contain a five- or six-membered heterocyclic ring fused with a phenyl ring (Fig. 2). These studies include bioisosteric replacement of indole with indazole and 1,2-benzo[*d*]isoxazole, partial saturation of the bicyclic systems, and expansion of five-membered fused systems

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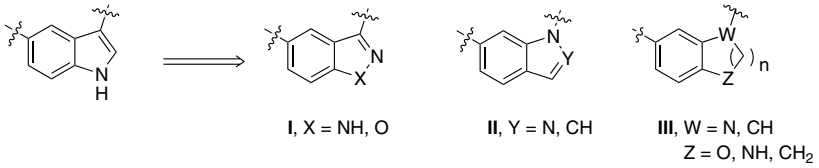



**Figure 2.** Schematic representations of bicyclic systems.

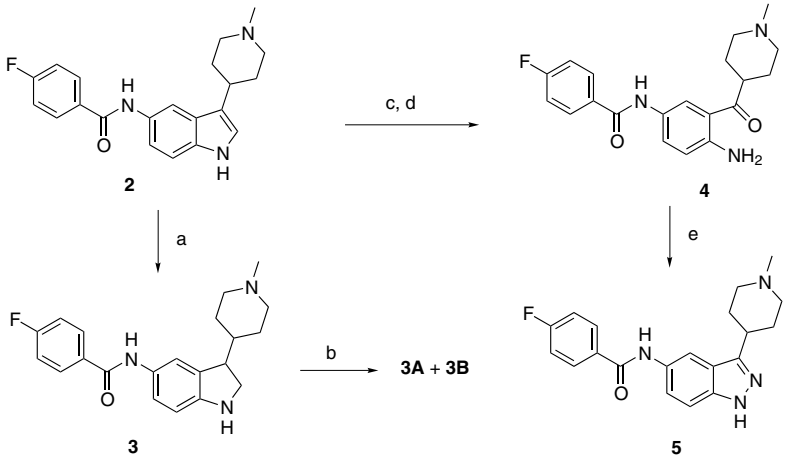
to six-membered fused systems. The present paper describes the design, synthesis and evaluation of these new systems and their effects on 5-$HT_{1F}$ receptor affinity and selectivity over other 5-$HT_1$ receptors.

Indazoles and benzisoxazoles have been used as bioisosteres for indoles,[9,10] and the results are mixed. In the 5-HT area, for example, Fludzinski et al. found that indazole-3-carboxylic acid tropanyl ester had comparable activity to that of indole-3-carboxylic acid tropanyl ester after iv and po administration as a 5-$HT_3$ receptor antagonist.[10a] Whereas Pigini et al. reported that replacement of the indole nucleus of 5-HT with 1,2-benzisoxazole resulted in total loss of affinity for the peripheral 5-HT receptors.[10c] Direct replacement with indazole and benzisoxazole (Fig. 2, Type I, X = NH, O) would generate templates that have similar geometry to the indole system but with different electronic properties (dipole direction, electrostatic interaction with receptors). Matassa et al. reported that replacement of the indole core with an 'inverted' indole template resulted in significant improvement in antagonist properties in their peptidoleukotriene antagonist efforts.[11] We envisioned that 'inverted' indole or indazole (Type II, Y = N, CH) would bring more significant change in molecular properties because of the apparent change in electronic properties compared to the initial indole system. As an extension of Type II structures, we also wanted to explore using $sp^3$ hybridized atoms (Type III, W = N, CH) as linkers between the phenyl moiety and the piperidine ring. This would help us to understand better the geometric effects on 5-$HT_{1F}$ receptor binding affinity and selectivity as we change the ring size from five membered ($n$ = 1) to six membered ($n$ = 2).

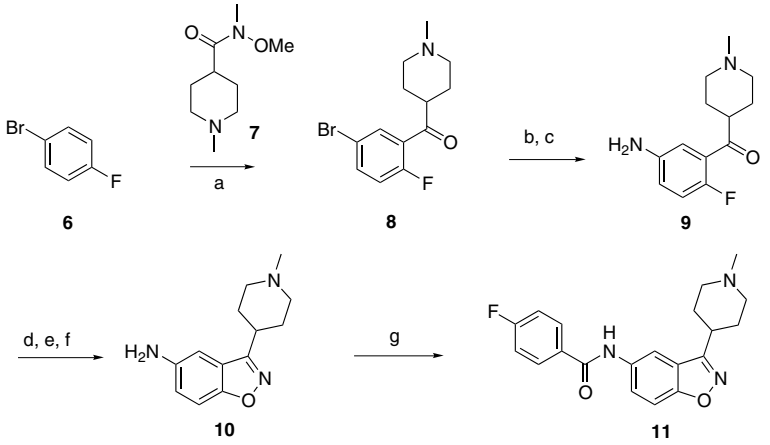
Indoline **3** and indazole **5** were synthesized from compound **2** (Scheme 1). Reduction of **2** with triethylsilane and TFA provided racemic **3**, which can be resolved through chiral chromatography.[12] The synthesis of **5** featured an indole to indazole conversion.[13a] In this case, oxidative cleavage of the indole ring of **2** with $NaIO_4$ followed by hydrolysis provided amino-ketone **4**. Compound **4** was converted to indazole **5** through a modified procedure involving the reduction of the diazo intermediate with $SO_2$.[13b]

To synthesize the 1,2-benzisoxazole derivative **11**, we started with 1-bromo-4-fluorobenzene (Scheme 2). A fluorine-atom directed *ortho*-metallation[14] followed by acylation of Weinreb amide **7** provided bromo-ketone **8**. Then a Pd(0) mediated Buchwald reaction[15] of **8** with benzophenone imine followed by acid hydrolysis converted bromo-ketone **8** to amino-ketone **9**. Upon protection, the resulting ketone was reacted with hydroxylamine hydrochloride to generate an oxime intermediate, which underwent an intramolecular cyclization through a $S_NAr$ nucleophilic displacement reaction to provide **10** with concomitant removal of the protecting group. Acylation of the C-5 amino group provided **11**.

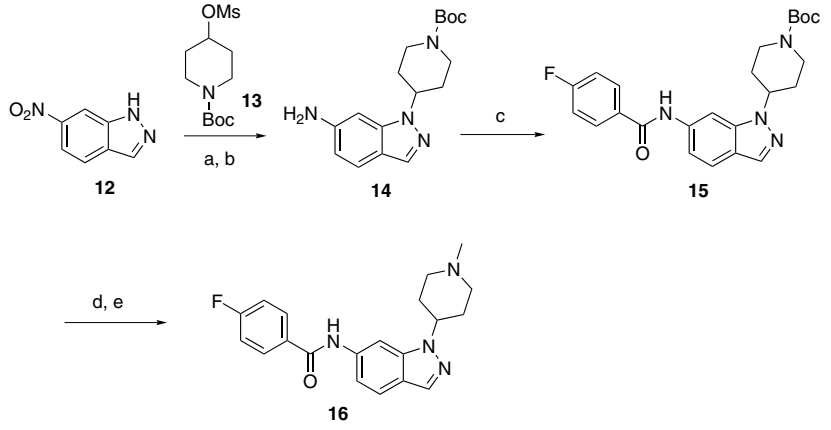
The synthesis of the 'inverted' indazole derivative **16** is shown in Scheme 3. Alkylation of 6-nitro-indazole (**12**) with **13** gave a 1:1 mixture of N-1 and N-2 alkylated products whose structures were confirmed by $^1H$ NMR experiments. The N-1 alkylated product was then reduced to amino-indazole **14** by hydrogenation with Pd/C. Acylation of the C-6 amino group provided **15**. Deprotection followed by reductive alkylation gave **16**.




**Scheme 1.** Reagents and conditions: (a) TFA, $Et_3SiH$, room temp, 99%; (b) chiral resolution; (c) $NaIO_4$, MeOH, room temp, 51%; (d) 5N NaOH, MeOH, 45 °C, 51%; (e) $NaNO_2$, 6N HCl, $SO_2$, 3 °C, 26%.

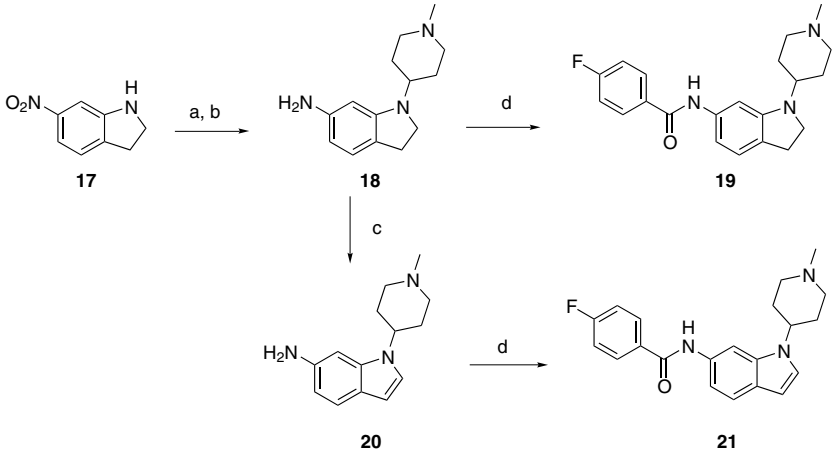


**Scheme 2.** Reagents and conditions: (a) 2,2,6,6,-tetramethylpiperidine, *n*-BuLi, **7**, 55%; (b) benzophenone imine, $Pd_2(dba)_3$, BINAP, $NaOBu^t$, 63%; (c) 1 N HCl, THF, room temp, 83%; (d) 2,4-difluorobenzoyl chloride, 1,4-dioxane, 100%; (e) $NH_2OH{\cdot}HCl$, pyridine, EtOH; (f) NaOH, EtOH, 45% for two steps; (g) 4-fluorobenzoyl chloride, 1,4-dioxane, 50%.

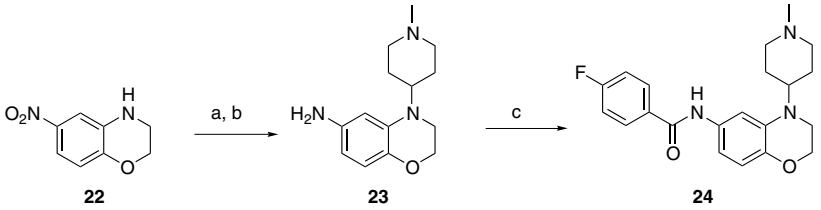


**Scheme 3.** Reagents and conditions: (a) NaH, DMF, **13**, 90 °C; (b) Pd/C, THF, $H_2$ (60 psi), 7 h, room temp, 34% for two steps; (c) 4-fluorobenzoyl chloride, $Et_3N$, THF, room temp, 75%; (d) TFA/$CH_2Cl_2$ (1:1), 97%; (e) HCHO (37% aqueous solution), 1,2-dichloroethane, $NaBH(OAc)_3$, MS 4 Å, room temp, 79%.

The 'inverted' indoline and indole derivatives **19** and **21** were synthesized from 6-nitroindoline (Scheme 4). Reductive alkylation of **17** with 1-methyl-4-piperidone followed by reduction of the nitro group with $SnCl_2$ provided amino-indoline **18**. Compound **18** was converted to the amino-indole **20** through a three-step sequence with DDQ oxidation as the key step. Acylation of **18** and **20** provided compounds **19** and **21**, respectively.



**Scheme 4.** Reagents and conditions: (a) 1-methyl-4-piperidone, $NaBH(OAc)_3$, HOAc, 35%; (b) $SnCl_2{\cdot}2H_2O$, EtOH, 61%; (c) (i) $Boc_2O$, THF, 42%; (ii) DDQ, $CH_2Cl_2$; (iii) TFA, 42% for two steps; (d) 4-fluorobenzoyl chloride, 1,4-dioxane, 95%.



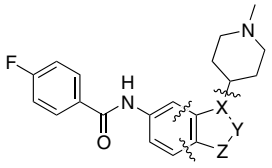

**Scheme 5.** Reagents and conditions: (a) 1-methyl-4-piperidone, $NaBH(OAc)_3$, HOAc, $Na_2SO_4$; (b) 10% Pd/C, EtOH, $H_2$ (1 atm), 12 h, 23% for two steps; (c) 4-fluorobenzoyl chloride, $CH_2Cl_2$, pyridine, 67%.

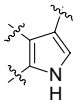
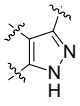
Dihydrobenz-1,4-oxazine **24** was obtained in a similar manner from 6-nitro-2,3-dihydrobenz-1,4-oxazine[16] (**22**) (Scheme 5).

The affinity of these analogues for 5-$HT_{1F}$, 5-$HT_{1A}$, 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors is reported in Table 1. The isosteric replacement of indole with the indazole (**5**) and benzisoxazole (**11**) systems (Type I) resulted in compounds with high affinity at the 5-$HT_{1F}$ receptor. Compound **5** had comparable 5-$HT_{1F}$ affinity to its indole analogue **2** but with a much improved selectivity profile at other 5-$HT_1$ receptors. Compound **11**, on the other hand, did not show improvement in selectivity profile. For the 'inverted' indazole **16**, while its selectivity at 5-$HT_{1A}$ decreased only slightly compared to that of **5**, it still had high affinity at 5-$HT_{1F}$ receptor with excellent selectivity towards the other 5-$HT_1$ receptors. The 'inverted' indole derivative **21** showed no improvement in selectivity over 5-$HT_{1A}$ receptor compared to that of compound **2**. These results indicated that we could optimize the 5-$HT_{1F}$ binding affinity and selectivity profiles by changing the electronic feature of the fused aromatic five-membered ring system. The indazole systems provided the most potent and selective 5-$HT_{1F}$ ligands. 'Inverted' indazole and indole derivatives were still potent 5-$HT_{1F}$ ligands, however, their affinity at 5-$HT_{1A}$ receptor increased compared to their Type I counterpart. These results also suggested that a $sp^2$ carbon–piperidine connectivity is not necessary for the 5-$HT_{1F}$ potency and selectivity.

While the isosteric replacement strategy allowed us to identify templates, which are comprised of a five-membered aromatic ring fused to a phenyl ring, we speculated that a system comprised of a nonaromatic five-membered ring fused to a phenyl ring might also be an effective template for novel 5-$HT_{1F}$ receptor agonists. To test this hypothesis, two indoline derivatives **3** and **19** were synthesized. To our delight, racemic **3** was a potent 5-$HT_{1F}$ receptor ligand and showed improved selectivity at 5-$HT_{1A}$ receptor compared to the indole derivative **2**. Compound **19**, like its 'inverted' indole analogue **21**, was a potent but nonselective 5-$HT_{1F}$ receptor ligand. As an extension of this effort, a 2,3-dihydrobenz-1,4-oxazine derivative **24** (still electron rich) was prepared and this compound only had weak 5-$HT_{1F}$ receptor affinity. These results suggested that the positioning of the basic piperidine nitrogen relative to the phenyl aromatic centre was important for overall effective recognition by the 5-$HT_{1F}$ receptor (Fig. 3). In contrast, change in the nature of atom (X = N or C) hybridization ($sp^2$ to $sp^3$) of the linker to which the piperidine ring was attached was not critical in receptor rec-

**Table 1.** In vitro binding affinity of bicyclic 4-fluorobenzamides[a]



| Compd | | Receptor affinities [$K_i$ (nM)] | | | |
|---|---|---|---|---|---|
| | | 5-$HT_{1F}$ | 5-$HT_{1A}$ | 5-$HT_{1B}$ | 5-$HT_{1D}$ |
| **2** |  | 2.1 | 22 | 240 | 430 |
| **5** |  | 3.9 | 870 | 2300 | 3100 |
| **11** |  | 17 | 160 | ND[b] | ND[b] |
| **16** |  | 4.1 | 310 | 2400 | ND[b] |
| **21** |  | 2.2 | 11 | 260 | 140 |
| **3** |  | 9.0 | 240 | ND[b] | 2300 |
| **19** |  | 4.8 | 12 | 440 | 210 |
| **24** |  | 520 | 860 | ND[b] | 2300 |

[a] Affinities for receptors (expressed as $K_i$, nM) were determined in vitro by radioligand binding assays using cell lines expressing the appropriate human serotonin receptors.[3a,17] Each value is the mean of at least two determinations ($n \geqslant 2$). Standard errors were typically within 10% of the mean value.

[b] ND means the binding affinity at this receptor was not determined and that less than 50% inhibition was obtained at 10 μM concentration.

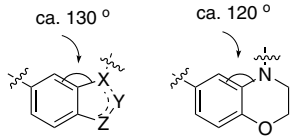



**Figure 3.** A comparison of the geometries of five-membered and six-membered fused templates.

ognition. In fact, the resolved indoline derivatives **3A** (95% ee) and **3B** (75% ee) had very close binding profiles to their racemic mixture (Table 2).

**Table 2.** Comparison of in vitro 5-$HT_1$ binding affinities of racemic and chiral 4-fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-2,3-dihydro-1*H*-indol-5-yl]-benzamides[a]

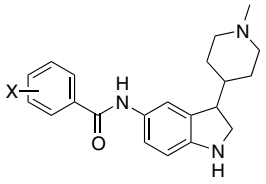
| Compound | Receptor affinities [$K_i$ (nM)] | | | |
|---|---|---|---|---|
| | 5-$HT_{1F}$ | 5-$HT_{1A}$ | 5-$HT_{1B}$ | 5-$HT_{1D}$ |
| **3** | 9.0 | 240 | ND[b] | 2300 |
| **3A** | 8.6 | 250 | ND[b] | ND[b] |
| **3B** | 9.6 | 250 | ND[b] | ND[b] |

[a,b] See corresponding footnote of Table 1 for binding parameters.

In order to improve the 5-$HT_{1A}$ selectivity of the indoline and benzisoxazole based 5-$HT_{1F}$ receptor agonists and to further understand the SAR, we evaluated the 5-arylamido-3-piperidinyl-2,3-dihydro-1*H*-indole series (Table 3) and 5-arylamido-3-piperidinyl-benzo[*d*]isoxazole series (Table 4). Like **3**, compounds **25** and **26** also had high 5-$HT_{1F}$ receptor affinity. Interestingly, their selectivity over 5-$HT_{1A}$ receptor also improved compared to **3**. This series showed good functional activity in the 5-$HT_{1F}$ GTPγS assay and demonstrated full 5-$HT_{1F}$ receptor agonists activity with $EC_{50}$s ranging from 50 to 63 nM and $E_{max}$ > 95%. In the benzisoxazole series, introduction of a chlorine atom into the benzoyl moiety of the benzamide clearly improved the selectivity over the 5-$HT_{1A}$ receptor, and compound **28** had the highest 5-$HT_{1F}$ affinity in this series, yet was very selective over other 5-$HT_1$ receptors. However, this series seems to be 5-$HT_{1F}$ receptor partial agonists with moderate intrinsic efficacy.

In conclusion, we explored several novel bicyclic systems in an effort to identify potent and selective 5-$HT_{1F}$ receptor agonists. We found that the geometries of the bicyclic systems, not the nature of hybridization of the

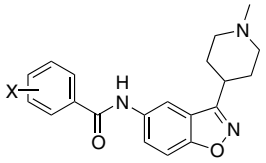
**Table 3.** In vitro 5-$HT_{1F}$ receptor binding affinity, selectivity and efficacy of 5-arylamido-3-piperidinyl-2,3-dihydro-1*H*-indoles




| Compd | X | 5-$HT_{1F}$ $K_i$ (nM)[a] | 5-HT selectivity ratio[b] | | | 5-$HT_{1F}$ GTPγS | |
|---|---|---|---|---|---|---|---|
| | | | 1A/1F | 1B/1F | 1D/1F | $EC_{50}$ (nM)[c] | $E_{max}$ (%5-HT)[d] |
| **3** | 4-F | 9.0 | 30 | ND[b] | 250 | NA[e] | NA[e] |
| **25** | 2,4,6-Tri-F | 17 | 50 | ND[b] | 120 | 50 | 95 |
| **26** | 2-Cl,4-F | 13 | 70 | 80 | 80 | 63 | 98 |

[a] See corresponding footnote of Table 1 for binding parameters.
[b] Ratio of the $K_i$ value (derived from at least two determinations) for 5-$HT_{1A}$, 5-$HT_{1B}$ or 5-$HT_{1D}$ receptor versus the 5-$HT_{1F}$ receptor. ND means not determined, see corresponding footnote of Table 1 for details.
[c] $EC_{50}$ for stimulation of [$^{35}$S]GTPγS binding in mouse LM(tk$^-$) cells expressing the cloned human 5-$HT_{1F}$ receptor.[18] Values are the mean of at least two determinations ($n \geqslant 2$). Standard errors were typically within 10% of mean value.
[d] Maximum stimulation of [$^{35}$S]GTPγS binding expressed relative to the maximum effect of 5-HT.
[e] NA = functional data not available.

**Table 4.** In vitro 5-$HT_{1F}$ receptor binding affinity, selectivity and efficacy of 5-arylamido-3-piperidinyl-benzo[*d*]isoxazoles




| Compd | X | 5-$HT_{1F}$ $K_i$ (nM)[a] | 5-HT selectivity ratio[b] | | | 5-$HT_{1F}$GTPγS | |
|---|---|---|---|---|---|---|---|
| | | | 1A/1F | 1B/1F | 1D/1F | $EC_{50}$ (nM)[c] | $E_{max}$ (%5-HT)[d] |
| **11** | 4-F | 17 | 10 | ND[b] | ND[b] | NA[e] | NA[e] |
| **27** | 2,4-Di-F | 12 | 10 | ND[b] | ND[b] | 470 | 73 |
| **28** | 2-Cl,4-F | 3.6 | 30 | ND[b] | ND[b] | 140 | 71 |

[a–e] See corresponding footnotes in Table 3 for details.

linking atom, were very important for receptor recognition. Through this effort, we discovered that the indole nucleus, embodied in our original lead structure **2**, can be replaced by many bicyclic systems including indazole, indoline and benzisoxazole. These templates can provide structurally diverse, potent and selective 5-$HT_{1F}$ receptor agonists.

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