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Discovery of 2-(1*H*-indazol-1-yl)-thiazole derivatives as selective EP_1 receptor antagonists for treatment of overactive bladder by core structure replacement

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ABSTRACT

We have designed a series of potent EP_1 receptor antagonists. These antagonists are a series of 2-(1*H*-indazol-1-yl)-thiazoles in which the core structure was replaced with pyrazole-phenyl groups. In preliminary conscious rat cystometry experiments, two representative candidates, **2** and **22**, increased bladder capacity. In particular, the increase using **22** was approximately 2-fold that of the baseline. More detailed profiling of this compound and further optimization of this series promises to provide a novel class of drug for treating overactive bladder (OAB).

Overactive bladder (OAB) is defined by The International Continence Society as a 'symptom syndrome which includes urinary urgency with or without urge incontinence, urinary frequency, and nocturia'.[1] In addition, urinary incontinence is generally defined as an 'involuntary loss of urine that is objectively demonstrable and is a social or hygienic problem', and urinary urgency is generally understood as a 'state at which strong and sudden desire to urinate occurs and the urge cannot be controlled'.[2]

The causes of OAB may include a change in bladder function due to aging, cerebral hemorrhage, cerebral infarction, Parkinson's disease, a neuronal disorder such as spinal injury, lower urinary tract obstruction due to prostatic hypertrophy, and a sensitive bladder due to expression of an irritative voiding symptom caused by a hypersensitive bladder resulting from chronic interstitial cystitis. However, for most cases, the cause remains unknown.[3]

Prostaglandin E_2 (PGE_2) has been suggested as a putative stimulant of afferent nerves of the bladder via the EP_1 receptor. Consequently, EP_1 receptor antagonists are a promising strategy for treating OAB.[4] A number of companies are pursuing EP_1 receptor antagonists, but very limited information on their clinical development is available, except for AstraZeneca's ZD6416,[5] and Ono Pharmaceutical's ONO-8130[6] and ONO-8539.[7] Most recently, KYORIN Pharmaceutical Co., Ltd and Kissei Pharmaceutical Co., Ltd are currently co-evaluating their candidate in Phase I clinical trials.[8]

We previously identified 2-(pyrazolyl-1-yl)-thiazole **1** as showing good EP_1 receptor antagonist activity and selectivity.[9] We further optimized **1** and identified **2** as having high activity and good physicochemical properties.[10] However, we thought it was needed to improve the potency of this series for providing the clinical candidate. To identify new compounds with unique profiles including high potent in vivo activity, we attempted synthetic approaches different from previous strategies applied to **1**. We modified the core structure of **1** because our earlier studies suggested that a smaller structure is more suitable for EP_1 receptor affinity.

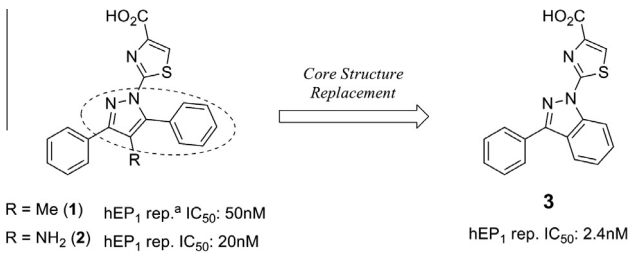

Figure 1. Replacement of core structure of **1**. (a) hEP1 rep.: 'human EP1 reporter assay'.

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0960-894X/

Therefore, we investigated replacing the pyrazole-phenyl with a bicyclic indazole system and generated compound **3**. Compound **3** exhibited significantly increased EP_1 receptor antagonist activity (IC_{50}: 2.4 nM), confirming that we had identified a new structure with high potency (Fig. 1).

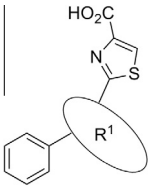
We next investigated the replacement of the pyrazole-phenyl with other bicyclic systems. Indole **4** showed high potency (IC_{50}: 4.0 nM), but was intrinsically unstable (rat CLint: 2396 mL/min/kg). Tetrahydro six-membered derivative **5** retained potency, whereas five, seven and eight membered ring compounds exhibited decreased potency. These data suggested that the six-membered moieties fit into a hydrophobic pocket. Dihydropyran **9** showed decreased potency, together with pyrazolopyridine **10**, **11** and **12**. These data suggested that the pocket accommodating the bicyclic system is unsuitable for polar groups, leading us to identify the indazole ring as the best core structure. We thus further substituted this position (Table 1).

To identify the candidate position for increasing activity, we scanned using fluorine. 4-F (**13**) showed significantly decreased activity (IC_{50}: 500 nM) whereas 5-F (**14**) was tolerated (IC_{50}: 80 nM). Since 6-F (**15**) was found to retain EP_1 receptor antagonist activity (IC_{50}: 2 nM), we focused on the 6-position on the indazole to further optimize the compound. 6-Me (**16**) exhibited increased potency (IC_{50}: 1.0 nM), and the 6-OH substitution (**17**) was tolerated (IC_{50}: 140 nM). These data were similar to that obtained during optimization of the core structure. Conversion of 6-OH (**17**) to 6-OMe (**18**) improved potency (IC_{50}: 1.1 nM) whereas conversion to 6-OEt (**19**) decreased potency (IC_{50}: 100 nM). 6-NH_2 (**20**) retained potency (IC_{50}: 19 nM), whereas there was an increase in the potency of 6-NHMe (**21**) (IC_{50}: 50 nM). Finally, 6-CF_3 (**22**) was identified as exhibiting the best EP1 activity (IC_{50}: 0.6 nM) (Table 2).

We next optimized the 3-position phenyl-group on the indazole ring. Comparison of the activity of 4-F (**23**) and 3-F (**24**) showed that the *para* position was preferred to the *meta* position. 4-Cl (**25**) showed slightly decreased activity whereas 4-MeO (**26**) retained potency. However, 4-CF_3 (**27**) exhibited significantly decreased activity, suggesting that this bulky group could not be accommodated by the ring structure of the compound. Although we speculated that a smaller group will be preferred in this part of the compound, cyclopentenyl (**28**) showed decreased activity (IC_{50}: 80 nM) and cyclohexyl (**29**) showed high potency (IC_{50}: 4 nM). These data suggested that a six-membered ring was a suitable moiety. We also evaluated other heterocyclic systems. 3-Thienyl (**30**) was tolerated, whereas 5-pyrimidyl (**31**) showed significantly decreased activity, indicating that an external position for the hydrophobic structure was preferred. Compounds containing the saturated cyclic system, 1-*N*-piperidyl (**32**) or 4-methyl-1-*N*-piperidyl (**33**), retained potency. However, both these compounds showed positive reactions in the Ames test and so were considered unsuitable due to safety concerns. Consequently, the phenyl group was chosen as the best structure for the 3-position on the indazole ring (Table 3).

Figure 2 compares the profiles of compounds **22** and **2**, which we previously reported as having good profiles.[10] Both compounds show good selectivity for the EP_1 receptor and a good profile, except for low water solubility between pH 1.2 and pH 6.8. The

Table 1
Optimization of core structure R^1



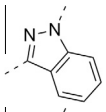
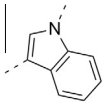
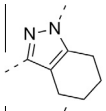
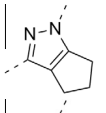
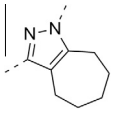
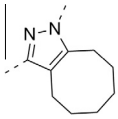
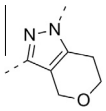
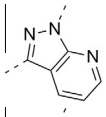
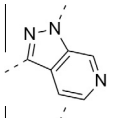
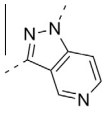
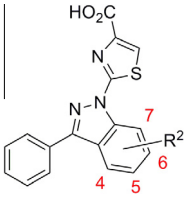
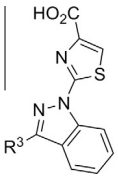
Compd	R^1	hEP_1 rep. 1 μM inhibition	hEP_1 rep. IC_{50} (nM)	rat CLint (mL/kg/min)
3			2.4	194
4			120	2396
5			16	290
6		0%		ND
7			1000	ND
8		6%		ND
9		8%		ND
10			200	65
11			39	69
12		13%		ND

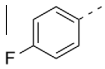
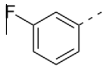
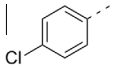
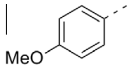
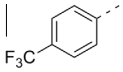
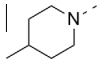
Table 2
Discovery of substituted group R^2



Compd	R^2	hEP_1 rep. IC_{50} (nM)	rat CLint (mL/kg/min)
3	–H	2.4	194
13	4-F	500	280
14	5-F	80	345
15	6-F	2	337
16	6-Me	1	ND
17	6-OH	140	522
18	6-OMe	1.1	196
19	6-OEt	100	ND
20	6-NH_2	19	208
21	6-NHMe	50	ND
22	6-CF_3	0.6	186

Table 3
Discovery of substituted group R^3



Compd	R^3	hEP_1 rep. IC_{50} (nM)	rat CLint (mL/kg/min)
3		2.4	194
23		4.5	278
24		20	385
25		12	753
26		4	618
27		140	809
28		80	196
29		4	490
30		30	190
31		>100	ND
32		16	139
33		32	260

in vitro Activity	**2**	**22**
hEP_1 rep. IC_{50}	20 nM	0.6 nM
Ca assay IC_{50}	60 nM	14 nM
hEP_1 Binding Ki	8 nM	0.45 nM
hEP_2 Binding Ki	>8700 nM	>8700 nM
hEP_3 Binding Ki	>5000 nM	>5000 nM
hEP_4 Binding Ki	>2700 nM	>2700 nM

in vitro ADMET profile	**2**	**22**
hCLint[a]	19 ml/min/kg	192 ml/min/kg
rCLint[b]	29 ml/min/kg	186 ml/min/kg
Protein Bound	99.00%	99.95%
Sol.[c] H_2O	865 μg/ml	37 μg/ml
Sol. pH1.2	867 μg/ml	0 μg/ml
Sol. pH6.8	1012 μg/ml	123 μg/ml
MDCK[d] Papp x 10^{-6}	12.2 cm/s	17.8 cm/s
CYP1A2 IC_{50}	7.10 μM	5.53 μM
CYP2C9 IC_{50}	5.62 μM	7.86 μM
CYP2C19 IC_{50}	6.14 μM	8.26 μM
CYP2D6 IC_{50}	>10 μM	>10 μM
CYP3A4 IC_{50}	>10 μM	>10 μM
Ames test	negative	negative

in vivo Pharmacokinetics	**2**	**22**
species	rat	rat
Dose	10mg/kg p.o.	10mg/kg p.o.
Cmax[e]	6.33 μM	5.34 μM
AUC(0-8)	17.4 μM*hr	9.27 μM*hr
BA[f]	26%	31%

Figure 2. Comparison of the profiles of **2** and **22**. (a) hCLint.: 'human intrinsic clearance'. (b) rCLint.: 'rat intrinsic clearance'. (c) Sol: 'solubility'. (d) MDCK.: 'Madin-Darby canine kidney'. (e) The peak plasma concentration of a drug after administration. (f) BA: 'bioavailability'.

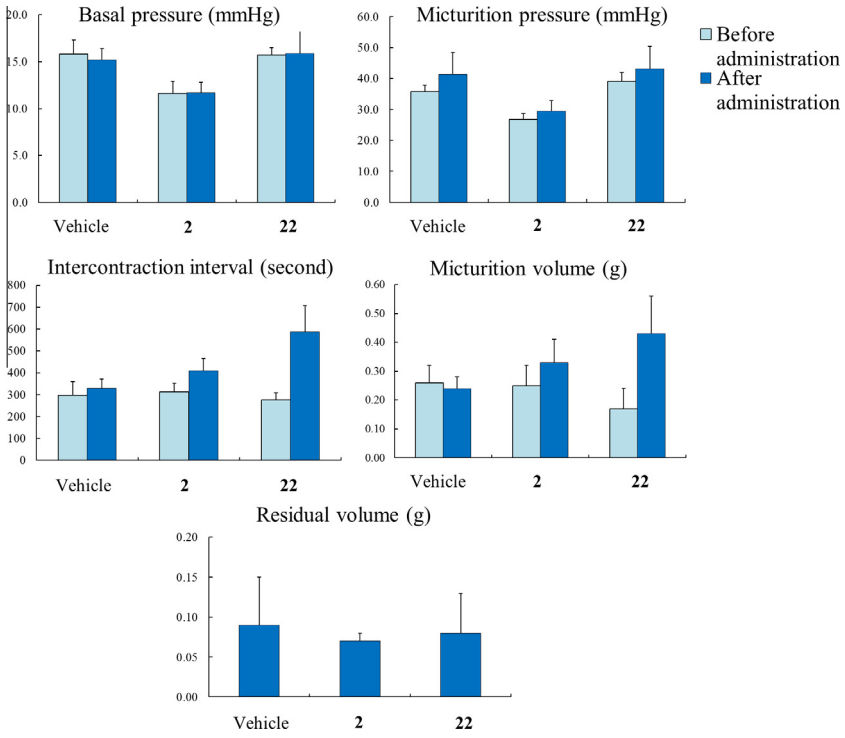
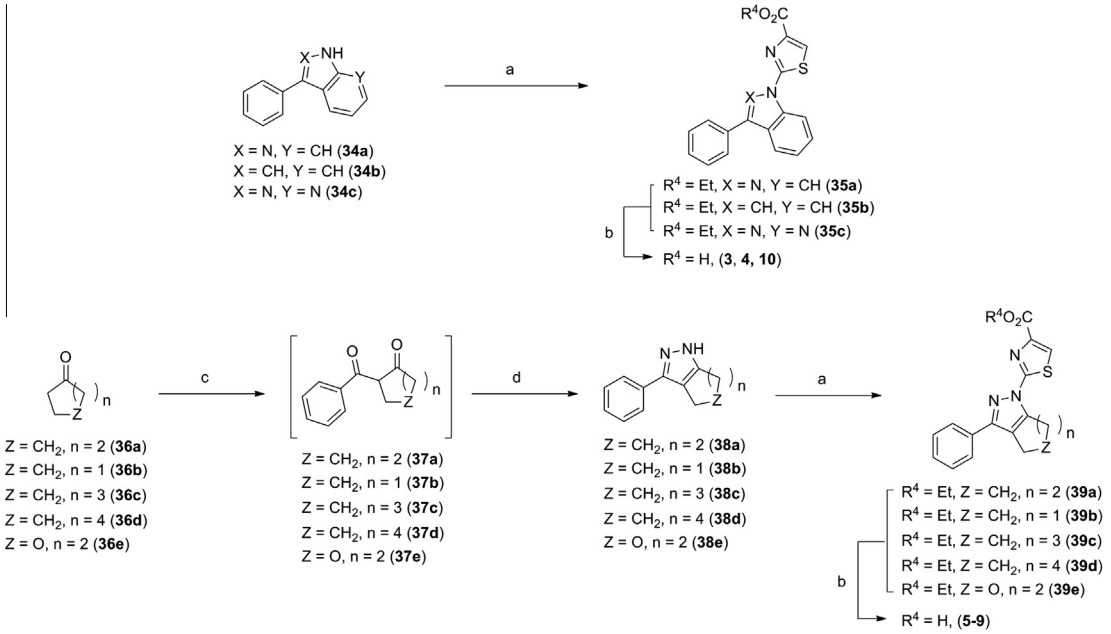


Figure 3. Effect of **2** and **22** on urination reflection parameters in a rat model. Each value represents the mean ± SE of 3 animals. **2** and **22** were intravenously administrated (1 mg/kg).



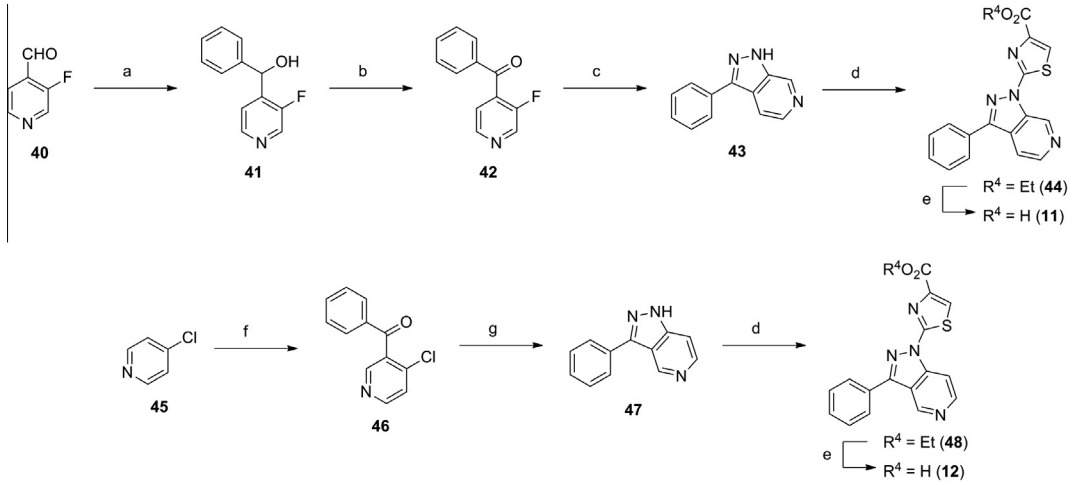
Scheme 1. Reagents and conditions: (a) 2-bromo-thiazolecarboxylate, (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, mesitylene, 185 °C, (**35a**: 45%, **35b**: 47%, **35c**: 48%, **39a**: 16%, **39b**: 5%, **39c**: 6%, **39d**: 15%, **39e**: 19%); (b) 5 M NaOH, EtOH, rt, (**3**: 41%, **4**: 90%, **5**: 89%, **6**: 44%, **7**: 32%, **8**: 36%, **9**: 59%, **10**: 58%); (c) PhCOCl, LHMDS, toluene, 0 °C, 1 h; (d) $(NH_2)_2$–H_2O, AcOH, rt, 3 h (**38a**: 35%, **38b**: 29%, **38c**: 22%, **38d**: 39%, **38e**: 11%).

pharmacokinetic parameters of these compounds in rats are shown. A single oral administration of compound **22** to rats at 10 mg/kg ($n = 3$) provided a C_{max} of 5.34 μM and $AUC_{(0-\infty)}$ of 9.27 μM/L hr. The bioavailability (BA) in rats was calculated to be 26%.

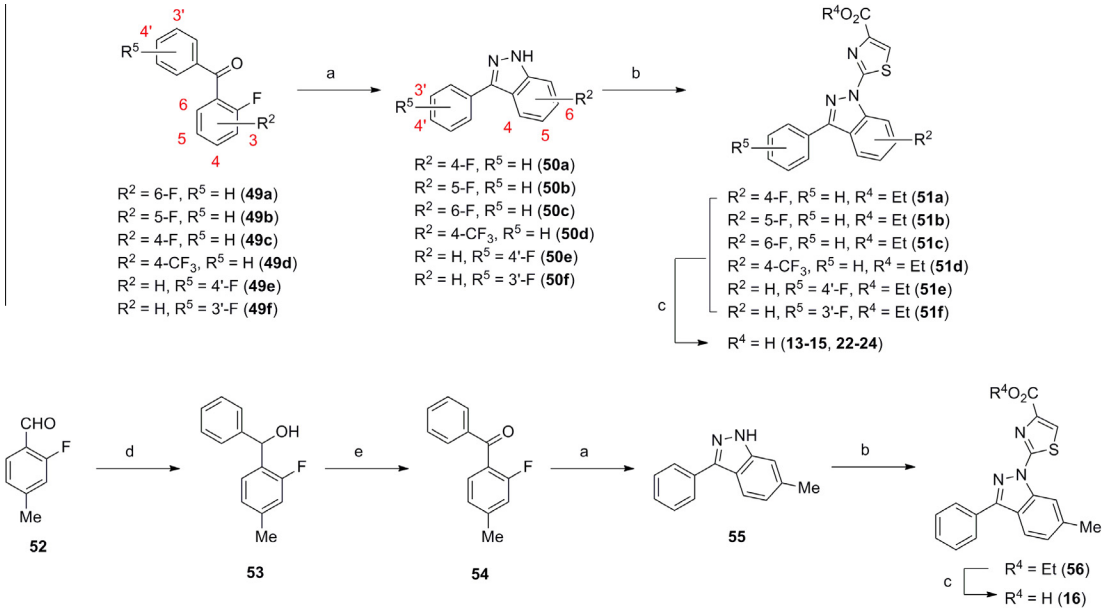
Compound **22** was tested against a battery of 57 receptors and 4 enzymes at a concentration of 10 μM (Cerep, Celle l'Evescault France). No significant activity (<25%) was seen with the exception of the A_1 and A_3 receptors (IC_{50} = >1.0 μM) (data not shown). Thus, compound **22** shows excellent selectivity. These data suggested that the selectivity of compound **22** was improved compared to compound **2**.

In vivo cystometry studies in conscious rats using compounds **2** and **22** were then performed. The effects of compound **2** and **22** (1 mg/kg, iv) on cystometric parameters such as basal pressure, micturition pressure, intercontraction interval, micturition volume and residual volume were evaluated. Both compounds increased micturition volume and the micturition interval, but had no effect on basal pressure, micturition pressure or residual volume (Fig. 3). Both the intercontraction interval and the micturition volume were increased: approximately 1.3 and 2-fold that of the baseline for compounds **2** and **22**, respectively. These data support the hypothesis that the hyperactivity of afferent fiber C of the sensory nerves in the bladder was reduced, indicating that these EP_1 receptor antagonists hold promise for the treatment of OAB.

The synthesis of the 2-(1H-indazol-1-yl)-thiazole derivatives **3**–**10** listed in Table 1 is shown in Scheme 1. Buchwald *N*-arylation[11] of starting material **34a**–**c**[12–14] was used to give the thiazole-ring moiety, followed by hydrolysis to give **3**, **4** and **10**. In the case of compounds **5**–**9**, the synthetic route started from the commercially available ketone **36a**–**e**, which was first α-acylated to the corresponding dione **37a**–**e** with LHMDS and PhCOCl at room temperature and then condensed with $(NH_2)_2$–H_2O to give



Scheme 2. Reagents and conditions: (a) PhMgBr, THF, 0 °C to rt, on, (quant); (b) Dess–Martin periodinane, CH_2Cl_2, rt, on, (97%); (c) $(NH_2)_2$–H_2O, EtOH, reflux, on, (51%); (d) 2-bromo-thiazolecarboxylate, (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, mesitylene, 185 °C, (**44**: 63%, **48**: 19%); (e) 5 M NaOH, EtOH, rt, (**11**: 20%, **12**: 50%); (f) *N*-methoxy-*N*-methyl-benzamide, LDA, THF, −78 °C to rt; (g) $(NH_2)_2$–H_2O, EtOH, rt, 1 h, (2 steps 63%).



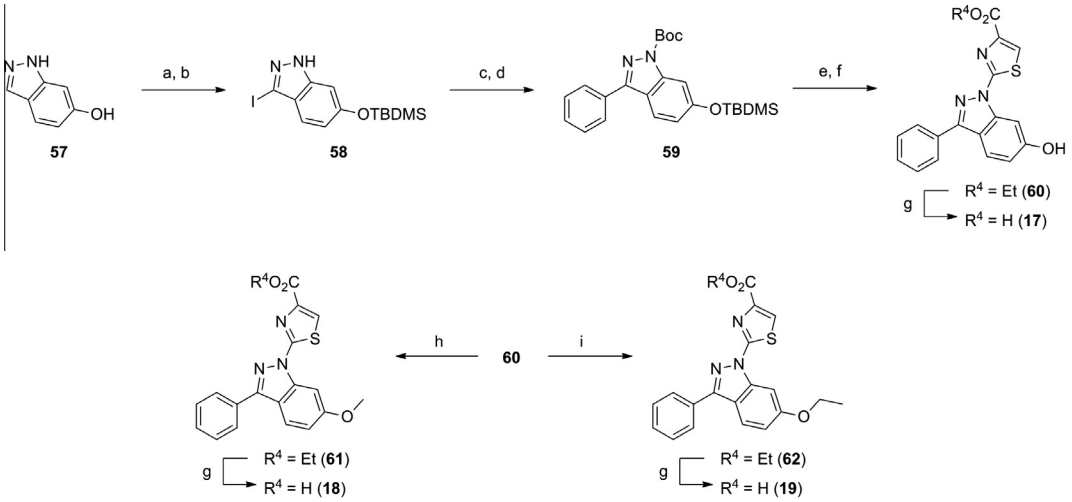
Scheme 3. Reagents and conditions: (a) $(NH_2)_2$–H_2O, CuO, K_2CO_3, xylenes, reflux, on, (**50a**: 16%, **50b**: 21%, **50c**: quant, **50d**: 99%, **50e**: quant, **50f**: 50%, **55**: 24%); (b) 2-bromo-thiazolecarboxylate, (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, mesitylene, 185 °C, (**51a**: 14%, **51b**: 93%, **51c**: 52%, **51d**: 64%, **51e**: 23%, **51f**: 27%, **56**: 62%); (c) 5 M NaOH, EtOH, rt, (**13**: 65%, **14**: 95%, **15**: 67%, **16**: 82%, **22**: 99%, **23**: 39%, **24**: 95%); (d) PhMgBr, THF, 0 °C to rt, on, (73%); (e) Dess–Martin periodinane, CH_2Cl_2, rt, on, (quant).

3,5-diphenyl-4-methyl tetrahydro-indazole derivative **38a**–**e**. The thiazole-ring moiety was synthesized in a similar manner, followed by hydrolysis to give **5**–**9**.

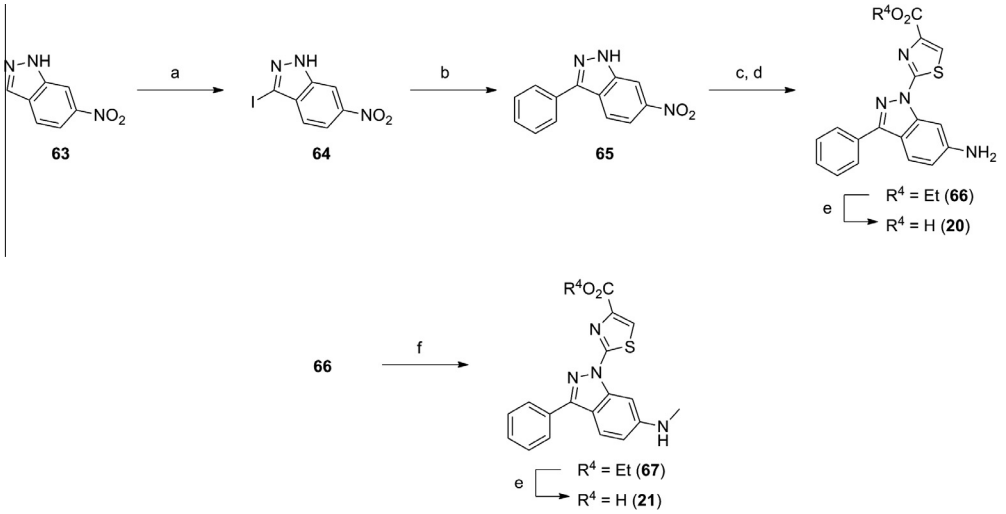
The synthetic route for compounds **11** and **12** is shown in Scheme 2. Commercially available 3-fluoroisonicotinaldehyde (**40**) was first alkylated to alcohol **41** with phenylMgBr and then oxidized with Dess–Martin periodinane to give benzoyl **42**. Benzoyl **42** was condensed with $(NH_2)_2$–H_2O to give 1H-pyrazolo[3,4-c]pyridine **43**, then the thiazole-ring moiety was synthesized and hydrolysis was conducted in a manner similar to **11**. Lithiation of the 3-position of 4-chloropyridine (**45**) and subsequent quenching with Weinreb amide resulted in the formation of benzoyl **46**. In a similar manner, compound (**12**) was synthesized.

Compounds **13**–**16** and **22**–**24** were synthesized according to Scheme 3. Commercially available 1-benzoyl-2-fluorobenzene **49a**–**f** was reacted using the same conditions described by Olmo et al.[15] to give indazole **50a**–**f**. The thiazole-ring moiety was synthesized in a similar manner, followed by hydrolysis to give **13**–**15** and **22**–**24**. For compound **16**, the synthetic route started from 2-fluoro-4-methylbenzaldehyde (**52**), which was alkylated to the corresponding alcohol **53** with PhMgBr, and then oxidized using Dess–Martin periodinane to give benzoyl **54**. Benzoyl **54** was condensed with $(NH_2)_2$–H_2O under copper-mediated conditions[16] to give indazole **55**. A similar procedure was used to synthesize compound **16**.

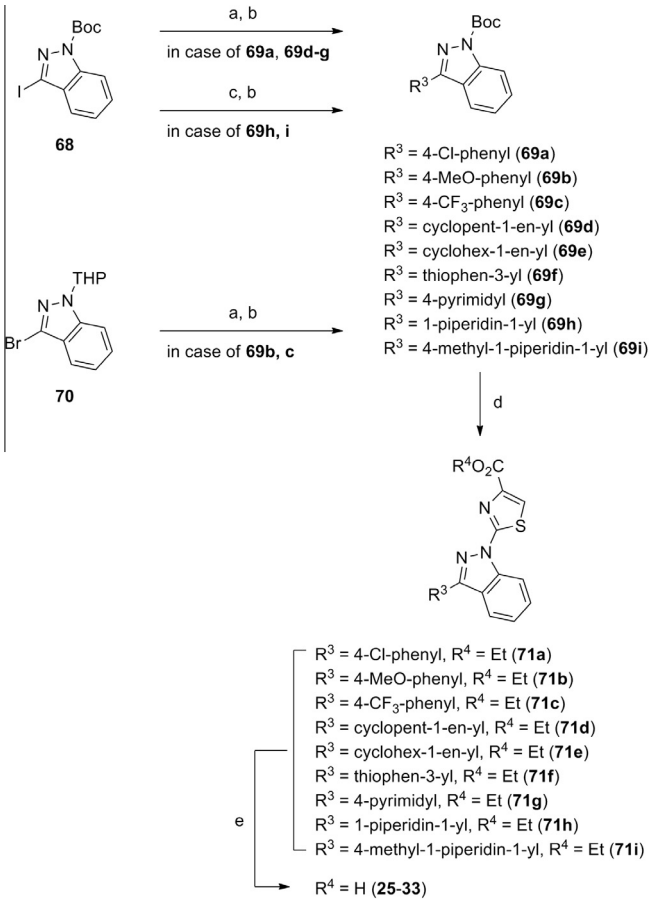
Compounds **17**–**19** listed in Table 2 were synthesized according to Scheme 4. The phenol of **57**[17] was protected with TBDMS-Cl, then regioselective iodation in the presence of potassium *t*-butylate gave intermediate **58**. Protection of the 1-nitrogen on the indazole and Suzuki–Miyaura coupling was used to prepare



Scheme 4. Reagents and conditions: (a) TBDMS-Cl, imidazole, DMF, rt, 3 h, (88%); (b) *t*BuOK, I_2, THF, 0 °C, on, (quant); (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, (quant); (d) $PhB(OH)_2$, Pd_2dba_3, (*o*-tol)$_3$P, K_3PO_4, DMF, 80 °C, on, (31%); (e) TFA, CH_2Cl_2, rt, 3 h, (96%); (f) 2-bromo-thiazolecarboxylate, (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, mesitylene, 185 °C, (54%); (g) 5 M NaOH, EtOH, rt, (**17**: 89%, **18**: 97%, **19**: 90%); (h) MeI, NaH, DMF, rt, 1 h, (18%); (i) EtI, NaH, DMF, rt, 1 h, (30%).



Scheme 5. Reagents and conditions: (a) KOH, I_2, DMF, rt, 1 h, (85%); (b) $PhB(OH)_2$, Pd_2dba_3, (*o*-tol)$_3$P, K_3PO_4, DMF, 80 °C, on, (39%); (c) 2-bromo-thiazolecarboxylate, (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, mesitylene, 185 °C, (48%); (d) H_2 gas, Pd-C, MeOH, rt, on, (55%); (e) 5 M NaOH, EtOH, rt, (**20**: 99%, **21**: 87%); (f) 36% HCHO aq, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt, on, (7%).



Scheme 6. Reagents and conditions: (a) Pd_2dba_3, (*o*-tol)$_3$P, K_3PO_4, DMF, 80 °C, 12 h; (b) cHCl, MeOH, rt, 3 h, (**69a**: 81%, **69b**: 76%, **69c**: 97%, **69d**: 72%, **69e**: 75%, **69f**: 80%, **69g**: 83%); (c) $Pd(OAc)_2$, xantPhos, Cs_2CO_3, dioxane, 90 °C, 12 hours; (d) trifluoroacetic acid, CH_2Cl_2, rt, 3 h, (**69h**: 40%, **69i**: 56%); (e) 2-bromo-thiazolecarboxylate, (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, mesitylene, 185 °C, (**71a**: 52%, **71b**: 48%, **71c**: 53%, **71d**: 45%, **71e**: 55%, **71f**: 41%, **71g**: 45%, **71h**: 48%, **71i**: 25%); (f) 5 M NaOH, EtOH, rt, (**25**: 83%, **26**: 94%, **27**: 87%, **28**: 91%, **29**: 84%, **30**: 88%, **31**: 83%, **32**: 61%, **33**: 24%).

the phenyl moiety after deprotection of the TBDMS and Boc group with TFA. The thiazole-ring moiety was synthesized in a similar manner, followed by hydrolysis to give **17**. Methylation and ethylation of **60** provided **61** and **62**, followed by hydrolysis to give **18** and **19**, respectively.

For compounds **20** and **21**, the synthetic route started from commercially available 6-nitro-indazole **63**, which was iodized with iodine under basic conditions to give **64**. Suzuki–Miyaura coupling of **64** was used to construct the phenyl ring, followed by *N*-arylation and hydrolysis to give **20**. Methylation of **66** using reductive *N*-alkylation provided **67**, followed by hydrolysis to give **21** (Scheme 5).

Compounds **25**–**33** listed in Table 3 were synthesized according to Scheme 6. Suzuki–Miyaura coupling of compound **68**[17] or **70**[18] were used to prepare the aryl moiety, cyclopentyl and cyclohexyl moiety. Buchwald *N*-arylation of compounds **68** was used to prepare the piperidine moiety. After deprotection of Boc or THP with cHCl, the thiazole-ring moiety was synthesized in a similar manner, followed by hydrolysis to give **25**–**33**.

In conclusion, we have designed several EP_1 receptor antagonists from a series of 2-(1H-indazol-1-yl)-thiazoles. In preliminary conscious rat cystometry experiments, two representative candidates, **2** and **22**, increased bladder capacity (intercontraction interval). Compound **22** in particular holds excellent promise. This compound may serve as a candidate for further development of an OAB drug.

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