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Amino substituted analogs of 1-phenyl-3-phenylimino-2-indolones with potent galanin Gal_3 receptor binding affinity and improved solubility

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Abstract—A series of amino analogs of 1,3-dihydro-1-phenyl-3-[[3-(trifluoromethyl)phenyl]imino]-2*H*-indol-2-one (**1**) were synthesized to improve aqueous solubility, while retaining high affinity for the human galanin Gal_3 receptor. A very potent analog (**9e**, 1,3-dihydro-1-[3-(2-pyrrolidinylethoxy)phenyl]-3-[[3-(trifluoromethyl)phenyl]imino]-2*H*-indol-2-one, K_i = 5 nM) shows good selectivity and solubility of 48 μg/mL at pH 7.4.

In the rat, galanin has been shown to have physiological effects on feeding, insulin release, lactation, gut contractility, and growth, and has effects on central functions such as spinal reflex, learning, memory, and in rodent models of depression.[1] These effects are presumably through galanin's role as a neuropeptide that activates G-protein coupled receptors (GPCRs) to regulate a variety of functions. Three cloned galanin GPCRs have been identified and are designated as Gal_1, Gal_2, and Gal_3.[2] Rat mRNA encoding the galanin Gal_3 receptor has been localized in the hypothalamus, pituitary, spinal cord, pancreas, liver, kidney, stomach, and adrenal gland suggesting possible roles in feeding, digestion, pituitary hormone release, nociception, insulin homeostasis, and glucose homeostasis.[3]

We had previously discovered that 1,3-dihydro-1-phenyl-3-[[3-(trifluoromethyl)phenyl]imino]-2*H*-indol-2-one (compound **1**) is a potent antagonist (K_i = 17 nM, see Table 1) selective for the human galanin Gal_3 receptor.[4] While this is a useful compound in some assays for exploring the role of the galanin Gal_3 receptor, its low aqueous solubility (<1 μg/mL) has limited its utility in some in vitro assays in our hands. In our characterization of compound **1** and related analogs, we discovered that compounds of this series suffer from low aqueous solubility (<1 μg/mL). Herein are described novel analogs of compound **1** that have significantly improved aqueous solubility.

Our strategy for increasing solubility in this series of compounds was to incorporate a basic amino functionality. Since we knew from previous unpublished work in this series that the galanin Gal_3 receptor was least sensitive to substitution on the 1-phenyl group of the 1-phenyl-3-imino-2-indolones, we decided to explore modifications on this ring.

The syntheses of these compounds are illustrated in Schemes 1–3. The reaction conditions have not been optimized in these studies. The hydroxyphenylindolones **7** were synthesized as key intermediates according to the methods in Scheme 1. Isatin (**2**) was condensed with *m*-(trifluoromethyl)aniline, giving imine **3**. Imine **3** was then arylated with substituted phenyl boronic acids under cupric acetate catalysis, giving the intermediates **4** and **6**. Alternatively, isatin (**2**) was arylated with *p*-isopropyloxyphenyl boronic acid under cupric acetate catalysis[5] and the resulting intermediate isatin was condensed with *m*-(trifluoromethyl)aniline, giving the intermediate **5**. A different phenolic protecting group was employed for each of the isomers due to commercial availability of the boronic acids. Each was deprotected

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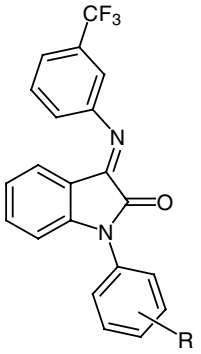
Table 1. Galanin Gal_3 receptor binding affinity for 1-aryl-3-phenylimino-2-indolones[a]



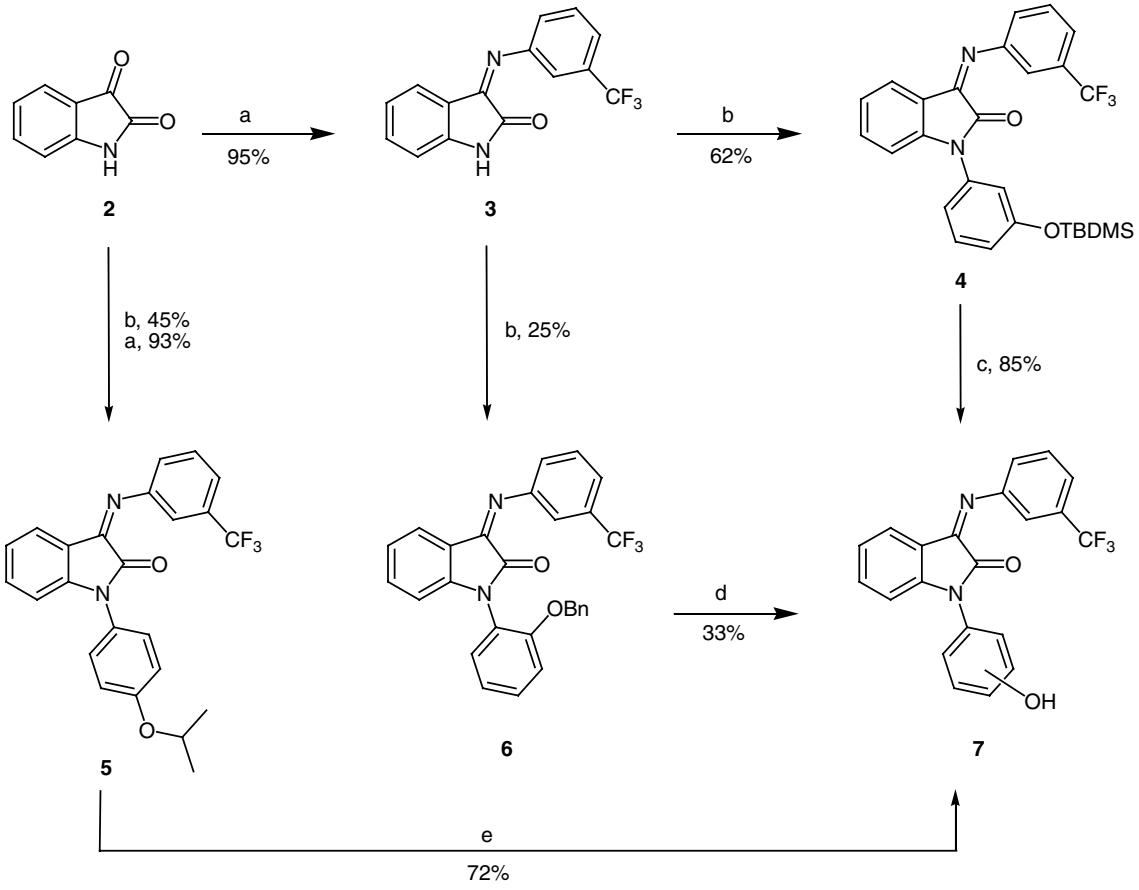
Compound	Substitution	Human Gal_3 K_i (nM)	Solubility pH 7. 4 (μg/mL)
1	R = H	17	<1
ortho-substitution			
9a	$O(CH_2)_2NEt_2$	1000	
9b	$O(CH_2)_2N(CH_2)_4$	790	
meta-substitution			
9c	$O(CH_2)_2NMe_2$	26	
9d	$O(CH_2)_2NEt_2$	87	
9e	$O(CH_2)_2N(CH_2)_4$	5	48
9f	$O(CH_2)_2N(CH_2)_5$	8	7
9g	$O(CH_2)_3NMe_2$	29	
9h	$O(CH_2)_3NEt_2$	21	44
9i	$O(CH_2)_3N(CH_2)_4$	49	
9j	$O(CH_2)_4NEt_2$	45	5
(±)-**11**	$OCH_2CH(OH)CH_2NEt_2$	15	
(*R*)-**11**	$OCH_2CH(OH)CH_2NEt_2$	290	
(*S*)-**11**	$OCH_2CH(OH)CH_2NEt_2$	27	606
14	CH_2NEt_2	38	48
para-substitution			
9k	$O(CH_2)_2NMe_2$	89	
9l	$O(CH_2)_2NEt_2$	78	
9m	$O(CH_2)_3NEt_2$	34	35
9n	$O(CH_2)_4NEt_2$	70	

[a] Binding affinity was determined using a previously described [^{125}I]galanin displacement assay.[6] K_i determinations are an average of two or more independent determinations; the margin of error is within 5% of the mean for all data shown.

with appropriate methods. The imino-2-indolones **9a**–**n** and **11** were synthesized according to methods described in Scheme 2. The hydroxyphenylindolones **7** were treated under basic conditions with dihalogenated linkers to give the intermediates **8** that were then aminated using one of the three methods described in Scheme 3, giving the imino-2-indolones **9a**–**d** and **9f**–**n**. This method failed to give the imino-2-indolone **9e**. For this compound, the hydrochloride salt of 2-(chloroethyl)-1-pyrrolidine was used as the alkylating agent with the *meta*-isomer of phenol **7**, giving the desired product **9e** directly from the phenol. For the synthesis of compound **11**, the *meta*-isomer of phenol **7** was alkylated using epibromohydrin and the resulting epoxide **10** was opened with diethylamine. The enantiomers of compound **11** were synthesized using the appropriate pure enantiomer of epibromohydrin.

Indolone **14** was synthesized according to the method described in Scheme 3. Indolone **3** was arylated with 3-(hydroxymethyl)phenyl boronic acid under cupric acetate catalysis. Alcohol **12** was activated as the mesylate **13** and then treated with diethylamine, giving the desired product.

Among the highest affinity ligands described here are the *meta*-substituted analogs (see Table 1), especially those with an ethoxy linker between the phenyl ring and the amino moiety. These include compounds **9e** and **9f** (K_i = 5 and 8 nM, respectively), both containing a cyclic amine. In comparison, compound **9b**, the *ortho*-analog of compound **9e**, has >150-fold weaker binding affinity (K_i = 790 nM) than compound **9e**. For the *meta*-substituted compounds, the ethoxy linked acyclic amines **9c** and **9d** are slightly weaker in affinity (K_i = 26 and 87 nM, respectively) than the cyclic amines and comparable to the propyloxy analogs **9h** and **9i** (K_i = 21 and 49 nM, respectively) and the butyloxy analog **9j** (K_i = 45). In comparison, compound **9a**, the *ortho*-analog of compound **9d**, has 11-fold weaker binding affinity (K_i = 1000 nM) than compound **9d**, while compound **9l**, the *para*-analog of compound **9d**, has comparable binding affinity (K_i = 78 nM) to compound **9d**.



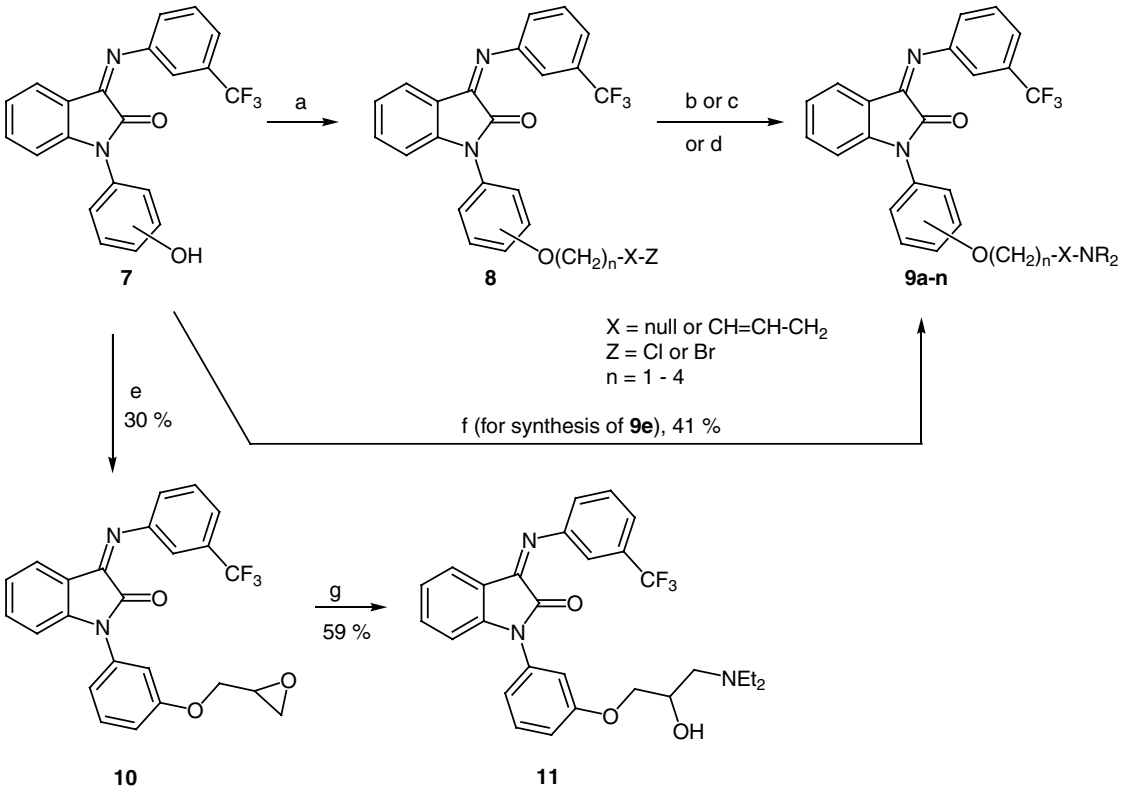
Scheme 1. Reagents and conditions: (a) 3-CF_3-aniline, Δ; (b) $Cu(OAc)_2$, TEA, RO–$PhB(OH)_2$, CH_2Cl_2; (c) TBAF/THF, 2 h, −78 °C; (d) 10% Pd–C, HCO_2NH_4, MeOH, reflux; (e) HBr.

While the dimethylaminomethoxy-containing compound **9c** has ~3-fold stronger binding affinity (K_i = 26 nM) than the diethylamine analog **9d**, the dimethylamine and diethylamine analogs of other compounds with common linkers have comparable binding affinity such as with close analogs **9g** and **9h** (K_i = 29 and 21 nM, respectively) and close analogs **9k** and **9l** (K_i = 89 and 78 nM, respectively). For the *para*-substituted analogs, there appears to be little dependence of binding affinity on linker length when comparing analogs **9l**, **9m**, and **9n**. It is interesting in the *meta*-propyloxy analogs that a hydroxyl in the linker (compound **11**) has no effect on human galanin Gal_3 receptor binding affinity (compared to compound **9h**) if it is of (*S*)-configuration (K_i = 27 nM), but is 10-fold weaker if it is of (*R*)-configuration (K_i = 290 nM). As is evident with compound **14**, the oxygen of the alkoxy linkers is not critical to the binding affinity of these compounds. A general trend that can be concluded from this work is that human galanin Gal_3 receptor binding affinity is strongest in this series for the *meta*-substituted analogs, slightly weaker for the *para*-substituted analogs, and considerably weaker for the *ortho*-substituted analogs.

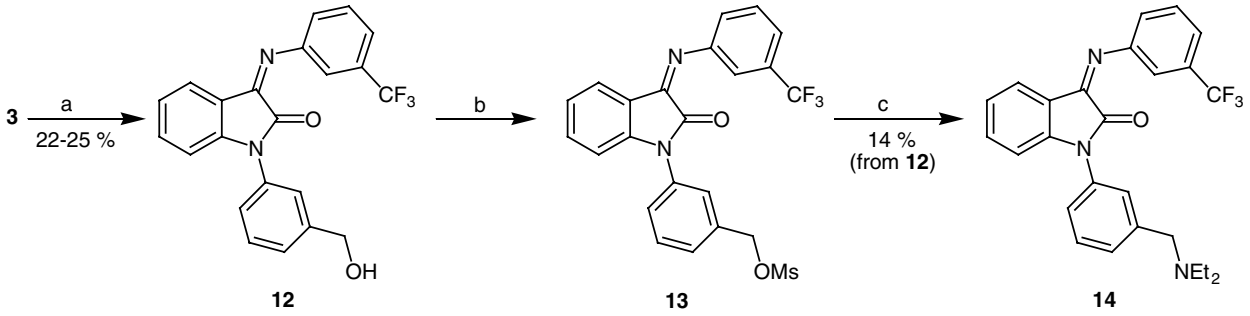
A selection of analogs was tested for aqueous solubility in pH 7.4 buffer. The hydroxyl-containing indolone **11**, with solubility of 606 μg/mL, shows greater than 600-fold improvement over compound **1**. The des-hydroxy analog **9h** has solubility of 44 μg/mL, indicating that the hydroxyl group of indolone **11** provides a major contribution to the solubility of this compound. Other amine-containing indolones tested show solubility of 5–48 μg/mL, all are a significant improvement over compound **1**.

Early in our efforts, compounds **9h** and **9m** were chosen for cross-reactivity profiling. It was found that these amine-containing indolones have binding affinity to mono-aminergic GPCRs, a property not earlier seen in non-amine-containing indolones. For instance, compound **9h** has affinity for the human dopamine D_5 receptor (K_i = 411 nM) that is within 20-fold of its affinity for the galanin Gal_3 receptor (K_i = 21 nM). A selection of the amine-containing indolones was screened against a panel of 16 mono-aminergic GPCRs and transporters. Compound **9e** was found to have a superior profile with the closest cross-reactivities being human adrenergic α_{1a} and dopamine D_5 receptors (K_i = 78 and 939 nM, respectively), greater than 175-fold lower than the affinity for the human Gal_3 receptor affinity (K_i = 5 nM). Compound **9e** was tested at 1 μM against a broad panel of 60 receptors, channels, and enzymes, and not found to have significant activity in any of these assays.

In conclusion, amine-containing indolones have significantly improved solubility compared to non-amine-



Scheme 2. Reagents and conditions: (a) K_2CO_3, KI, 18-crown-6, Br–$(CH_2)_n$–Br or $ClCH_2CH{=}CHCH_2Cl$; (b) HNR_2, acetonitrile, 50 °C; (c) HNR_2, $AgCO_3$, K_2CO_3, DMF, 50 °C; 1 h; (d) HNR_2, $CHCl_3$, microwave 145 °C, 25 min; (e) bromohydrin, K_2CO_3, KI, 18-Crown-6, DMF, 60 °C; (f) K_2CO_3, KI, 18-crown-6, (2-chloroethyl)pyrrolidine·HCl, DMF; (g) HNR_2, EtOH, reflux, 4 h.



Scheme 3. Reagents: (a) 3-hydroxymethylphenylboronic acid, $Cu(OAc)_2$, TEA, CH_2Cl_2; (b) MsCl, Et_3N, CH_2Cl_2; (c) $HNEt_2$, THF.

containing indolones. A very potent compound (**9e**, $K_i = 5$ nM) has been discovered that is selective versus a broad panel of drug cross-reactivity targets and has solubility of 48 μg/mL in pH 7.4 buffer. Compound **9e** should prove to be useful as a new tool to further the understanding of the role of galanin receptors in biological functions and disease states.

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