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Discovery of substituted phenyl urea derivatives as novel long-acting β_2-adrenoreceptor agonists

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ABSTRACT

The synthesis of diverse functionalized ureas in a semi-parallel fashion is described, as well as their β_1/β_2-adrenergic activities and the corresponding structure–activity relationship (SAR). We have focused on lipophilicity and duration of action, and we have discovered a strong correlation in this series of molecules. A quantitative structure–activity relationship (QSAR) analysis will be presented that quantifies this relationship.

The search for new ultra long-acting β_2-adrenoreceptor agonists (LABA's), for the treatment of asthma and COPD, has become a very active area of drug discovery in recent years. Once-a-day compounds are entering the market (indacaterol[1], **3**) or in advanced clinical phase (vilanterol[2], **4**) and will potentially become the therapy of choice over salmeterol **1** or formoterol **2**, the two currently marketed (twice-daily) long acting β_2-adrenoreceptor agonists (Fig. 1). Duration of action is one of the most challenging issues in the field, and there are many publications[3–6] related to this topic. Two distinct hypotheses have been put forward to explain this issue: the exo-site hypothesis[7] and the diffusion microkinetic hypothesis.[8]

The exosite theory requires the presence of a specific binding site for the drug, apart from the orthosteric site, which contributes to retain the agonist for receptor activation. Such a mechanism would result in longer receptor residence time.

On the other hand the microkinetic theory is based on the partition of the drug into the membrane. Thus, in theory, lipophilic compounds will remain longer in the cellular membrane resulting in drugs with extended duration of action. The more soluble a molecule is in aqueous media, the more prone to be diffused away from the tissue.

We focused our attention on the microkinetic theory, and the effect of lipophilicity on duration of action was investigated in a series of compounds developed in our LABA research program.

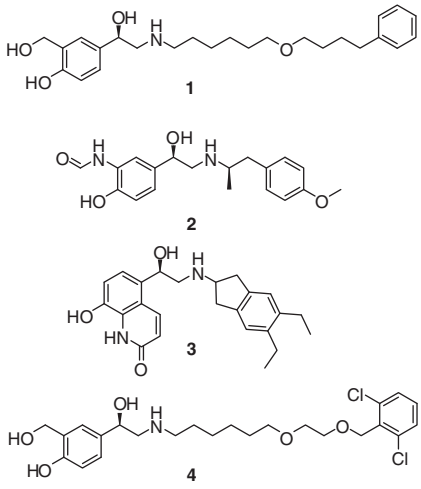

Figure 1. Structures of salmeterol **1**, formoterol **2**, indacaterol **3**, and vilanterol **4**.

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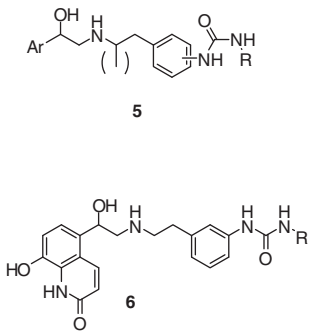


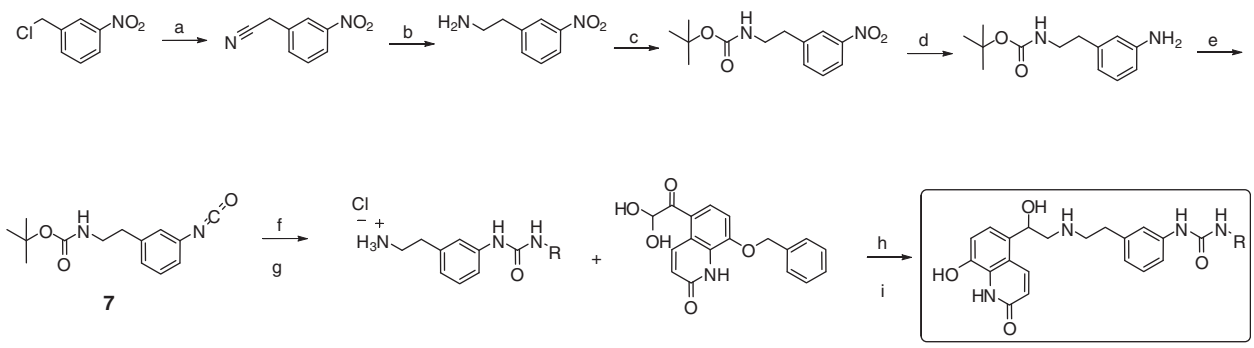
Figure 2. Structures of general scaffold **5** and refined scaffold **6**.

Our aim was to find potent, selective and long-acting β_2 agonists suitable for inhaled dry powder formulation. The starting points were β_2-adrenoreceptor agonists with the general formula **5** where Ar = saligenin or 8-hydroxycarbostyril moieties (Fig. 2).

As was the case for other compounds in the literature, the carbostyril moiety provided higher potency compared to saligenin and additionally *meta* substitution of phenyl urea showed improved potency over *para* substitution.

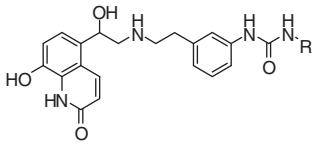
In general, the presence of an α-methyl adjacent to amine afforded less selective compounds versus the β1 receptor and this feature was removed early from our strategy.

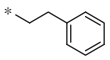
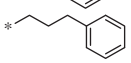
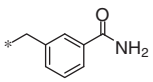
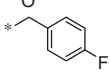
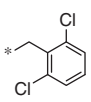
Thus **6** became our refined scaffold for further modifications (Fig. 2).



Scheme 1. Reagents and conditions: (a) KCN, MeOH/H_2O, 95 °C, 4 h, 62%; (b) $BH_3{\cdot}SMe_2$, THF, rt, 24 h, 43%; (c) $(BOC)_2O$, THF, rt, 2 h, 85%; (d) Pd/C 10%, H_2(30 psi), rt, 3 h, MeOH, 44%; (e) triphosgene, Et_3N, CH_2Cl_2, rt, 2.5 h, no isolation; (f) isocyanate split into aliquots, NH_2-R (1.1 equiv), rt, on; (g) HCl concd, dioxane, rt, 2 h, 51–82% (yields over three last steps); (h) Et_3N, $NaBH_4$, DMSO/MeOH, rt, 6 h, 43–77%; (i) Pd/C 10%, H_2, MeOH, rt, 4 h, 25–87%.

Table 1
Biological data and calculated log *P* values for urea analogues



Compound number	R	*c* log *P*[a]	In vitro duration of action (% of trachea tone recovery in 1 h)[b]	β_2 potency in G-P trachea (EC_{50}; nM)[c]	β_1 potency in rat left atria (EC_{50}; nM)[d]	In vivo potency[e] (μg/ml)	
						(IC_{50} at 4 h)	(IC_{50} at 24 h)
8		2.28	12	0.07	>10,000	0.2	3
9		2.31	15	0.2	900	0.3	>100
10		2.72	9	0.09	>10,000	2	>>10
11		3.15	2	0.05	>10,000	1	3
12		0.83	52	0.13	—	—	—
13		2.22	23	0.2	550	—	—
14		2.36	16	0.2	6300	—	—
15		3.51	4	0.2	1600	~4	>>100