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Discovery of a potent series of non-steroidal non α-trifluoromethyl carbinol glucocorticoid receptor agonists with reduced lipophilicity

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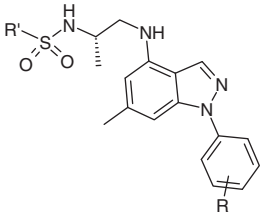
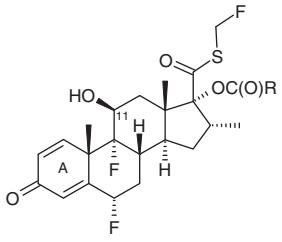
ABSTRACT

A novel series of indazole non-steroidal glucocorticoid receptor agonist has been discovered. This series features a sulfonamide central core and *meta* amides which interact with the extended ligand binding domain. This series has produced some of the most potent and least lipophilic agonists of which we are aware such as **20a** (NFκB pIC_{50} 8.3 (100%), *c* log *P* 1.9). Certain analogues in this series also display evidence for modulated pharmacology.

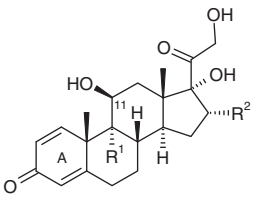


Inflammatory diseases such as asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis have been treated for many years with glucocorticoid agonists.[1] While mild and moderate asthma and allergic rhinitis can be effectively treated with inhaled or intranasally administered glucocorticoids, for example fluticasone propionate **1** and fluticasone furoate **2**, more severe asthma and rheumatoid arthritis are treated with oral glucocorticoids, such as dexamethasone **3** and prednisolone **4** (Fig. 1). However, when oral glucocorticoids are administered over a long period of time, the beneficial effects are overshadowed by side effects such as glucose intolerance, muscle wasting, skin thinning and osteoporosis.[2]

The activity of glucocorticoids is a consequence of binding of the ligand to the glucocorticoid receptor (GR) located within the cytoplasm and subsequent translocation of the receptor-ligand complex to the nucleus. The receptor-ligand complex regulates gene transcription via transcriptional activation (TA) or transcriptional repression (TR). It was suggested that the side effects observed with synthetic glucocorticoids are mainly associated with transactivation and the beneficial anti-inflammatory effects were



1 R = Et
Fluticasone propionate (FP)
2 R = 2-furoyl
Fluticasone furoate (FF)



3 R^1 = F, R^2 = Me
Dexamethasone
4 R^1 = H, R^2 = H
Prednisolone

Figure 1. Steroidal glucocorticoid agonists.

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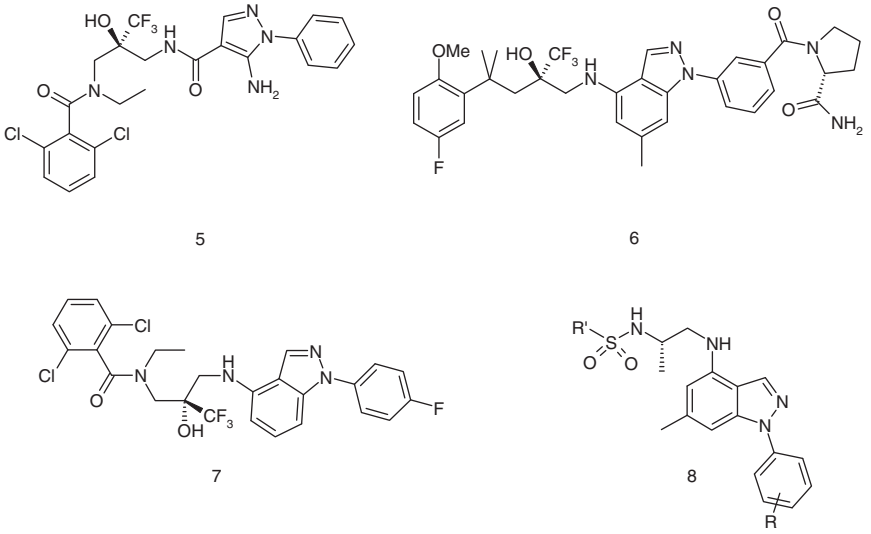
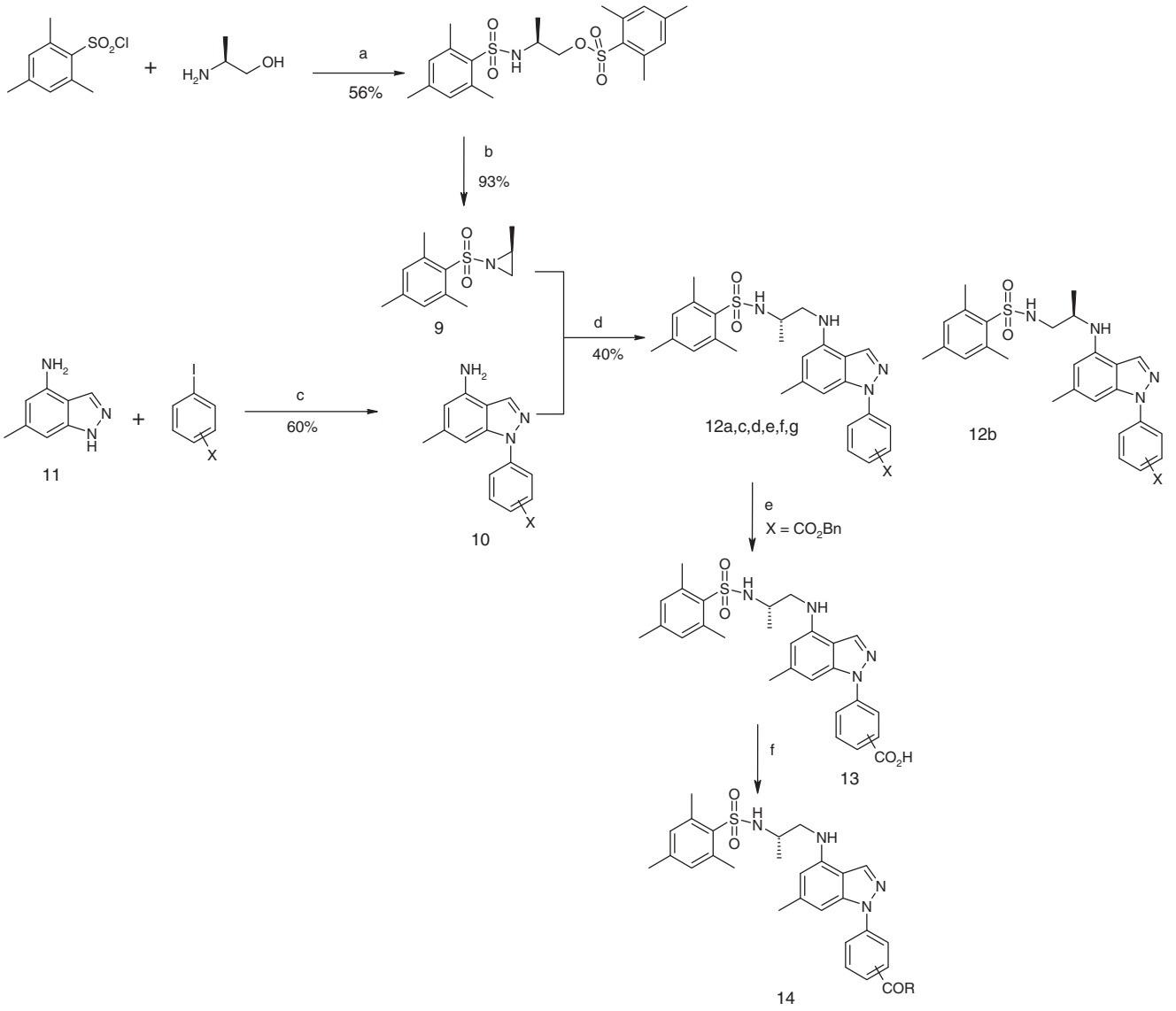


Figure 2. Aryl pyrazole and aryl indazole based GR agonists.



Scheme 1. Reagents and conditions: (a) pyridine; (b) K_2CO_3, DMF; (c) CuI, K_3PO_4, (1*R*,2*R*)-1,2-cyclohexanediamine, dioxane, 110 °C; (d) NMP, 150 °C, microwave; (e) H_2, 10% Pd/C; (f) amine, HATU, DIPEA, DMF.