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# Tetrahydroquinolin-3-yl carbamate glucocorticoid receptor agonists with reduced PEPCK activation

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ABSTRACT

Continuing studies on tetrahydroquinoline glucocorticoid receptor anti-inflammatory agents lead to the identification of several tetrahydroquinolin-3-yl carbamates that exhibited steroid-like activity in in vitro transrepression assays with reduced transactivation of phosphoenol pyruvate carboxykinase (PEPCK), a key enzyme in the gluconeogenesis pathway.



Synthetic glucocorticoids (GCs), such as prednisolone (**1**) and dexamethasone (**2**, Fig. 1), are widely prescribed to aid in the treatment of numerous inflammatory and autoimmune disorders, such as rheumatoid arthritis, lupus, Crohn's disease, and asthma. However, their desired anti-inflammatory effects must be balanced against such side-effects as osteoporosis, hyperglycemia, muscle wasting, behavioral changes, adrenal suppression, growth retardation, and hypertension.[1] Several of these side-effects often restricts a patient's long term treatment with GCs. Anti-inflammatory activity, as well as many of the side-effects of GCs, are mediated through the glucocorticoid receptor (GR), a ligand-dependent transcription factor which serves to either activate or repress gene transcription.[2] Transcriptional repression (TR) of genes that encode for pro-inflammatory cytokines and metalloproteinases is thought to be responsible for the anti-inflammatory effects of GCs,[2] while transcriptional activation (TA) of certain genes, for example those involved in gluconeogenesis, leads to unwanted side-effects.[3] The discovery of new GR ligands that favor TR over TA may serve to lessen GC-related side-effects while retaining beneficial anti-inflammatory activity. A number of accounts disclosing the development of several chemotypes as dissociated ligands have appeared.[4–11]

We have recently reported a series of GR agonists based on a 6-indole tetrahydroquinoline scaffold (**3** and **4**, Fig. 1).[12] SAR investigation of the tetrahydroquinoline A-ring discovered the importance of a C3-hydroxyl for improving receptor selectivity, while SAR within the B-ring resulted in improved microsomal stability, leading to demonstration of in vivo efficacy for the series. While fully efficacious and receptor selective GR agonists such as **4** were identified, it was our goal to further expand the SAR in an effort to ultimately identify selective glucocorticoid receptor modulators (SGRMs) from the series exhibiting a profile distinct from that of classical steroids in terms of TR/TA activity. Specifically,

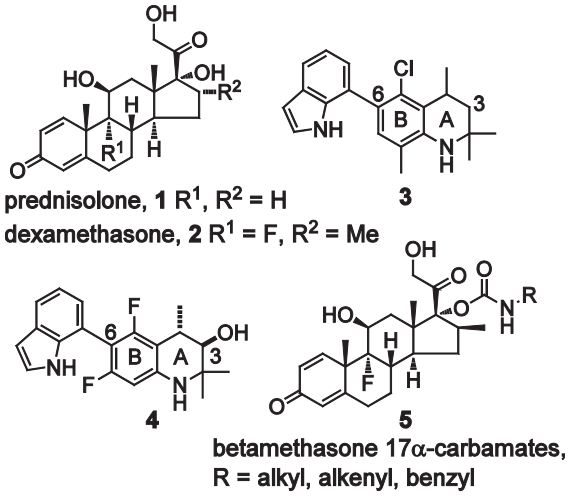


**Figure 1.** Glucocorticoid receptor ligands.

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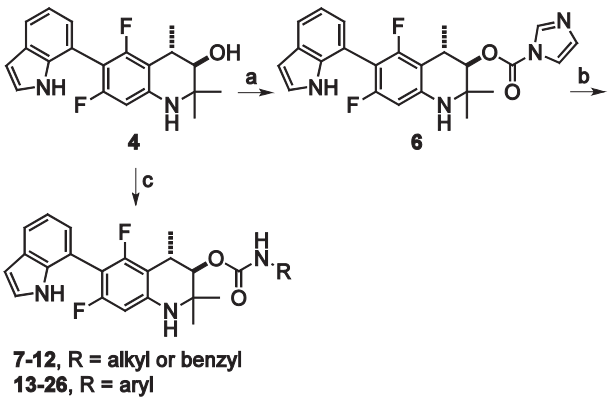
we sought to discover new nonsteroidal anti-inflammatory agents with a reduced impact on glucose elevation.

GR binding was determined using a radiolabeled dexamethasone competitive binding assay with baculovirus-expressed GR.[5] To assess the functional activity of the ligands, GR-mediated TA was measured in co-transfection (CTF) reporter assays in either CV-1 kidney cells, using a mouse mammary tumor virus (MMTV): luciferase reporter containing a glucocorticoid response element (GRE)[13] or in rat H4IIEC3 liver cells using a luceriferase reporter containing the promoter of phosphoenol pyruvate carboxykinase (PEPCK).[14] PEPCK is the rate-limiting step in gluconeogenesis, hence this assay was used to evaluate the potential hyperglycemic effect of the new ligands. Potency ($EC_{50}$) was determined from half-log concentration–response curves and maximal efficacy was determined relative to dexamethasone (**2**). To evaluate TR activity, a CTF assay in HepG2 cells using the promoter of the E-selectin gene was used in order to determine repression of transcriptional activation mediated by NFκB or AP-1[15] while an IL-6 ELISA assay[5] determined inflammatory cytokine repression in primary neonatal human dermal fibroblast (NHDF) cells.

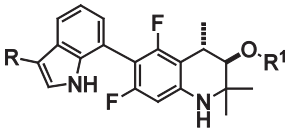


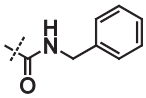
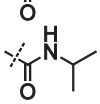
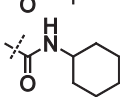
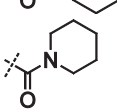

**Scheme 1.** General routes for carbamate synthesis. Reagents and conditions: (a) 1,1′-carbonyldiimidazole, dichloromethane; (b) $RNH_2$, toluene, reflux; (c) RNCO, toluene, 4-(dimethylamino)pyridine, reflux.

Tetrahydroquinolin-3-ol **4** is a fully efficacious GR agonist exhibiting in vitro TR activity similar to **1**. With respect to potential GC-related side-effects, specifically hyperglycemia, **4** exhibited comparable efficacy to **1** in activation of PEPCK. Therefore, in terms of TR (E-selectin and IL-6) versus TA (MMTV agonism and PEPCK), **4** is not selective. In an effort to develop SGRMs from our program, we sought to investigate whether the C3-hydroxyl of **4** could serve as a handle to further expand the tetrahydroquinoline A-ring pharmacophore. A report detailing the development of steroidal GR modulators derived from carbamates of the 17α-hydroxyl group of betamethasone **5** (Fig. 1) has appeared.[8a] We now disclose our findings which demonstrate that carbamates could be successfully incorporated onto the 6-indole tetrahydroquinolin-3-ol core resulting in ligands that show steroid-like binding affinity, MMTV agonism, and TR activity but with reduced TA of PEPCK.

C3-carbamates (**7**–**26**) were constructed as depicted in Scheme 1 using either of two representative routes. For example, **4** was reacted with 1,1′-carbonyldiimidazole in dichloromethane to yield

**Table 1**
In vitro assay results for carbamates **7–12**[a]




| Compd[b] | R | $R^1$ | GR $K_i$ (nM) | GR activation | | E-selectin repression | | IL-6 repression | | PEPCK activation | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Eff. (%) | $EC_{50}$ (nM) | Eff. (%) | $IC_{50}$ (nM) | Eff. (%) | $IC_{50}$ (nM) | Eff. (%) | $EC_{50}$ (nM) |
| **1** | | | 5.3 ± 0.3 | 130 ± 7 | 5.3 ± 3.6 | 100 ± 1.4 | 4.1 ± 0.8 | 97 ± 0.7 | 23 ± 2.6 | 84 ± 4 | 26 ± 7 |
| **4** | H | H | 2.5 ± 0.9 | 138 ± 16 | 0.6 ± 0.2 | 100 ± 2.2 | 1.5 ± 0.7 | 90 ± 3 | 11 ± 5.6 | 75 ± 2 | 98 ± 40 |
| **7** | H |  | 3.0 | 185 ± 30 | 39 ± 20 | 90 ± 1 | 10 ± 1 | — | — | 52 ± 9 | 199 ± 87 |
| **8** | Cl |  | 2.2 | 157 ± 20 | 21 ± 4 | 90 ± 7 | 12 ± 4 | 88 | 52 | 71 ± 7 | 463 ± 240 |
| **9** | Cl |  | 6.8 | 87 ± 8 | 17 ± 4 | 87 ± 2 | 44 ± 25 | 81 ± 5 | 40 ± 20 | 45 ± 4 | 454 ± 30 |
| **10** | Cl |  | 7.8 | 110 ± 18 | 89 ± 20 | 83 ± 3 | 45 ± 12 | 80 ± 4 | 17 ± 5 | 26 ± 4 | 361 ± 20 |
| **11** | Cl |  | 4.3 ± 2.7 | 89 ± 10 | 70 ± 53 | 90 ± 5 | 15 ± 3 | 89 ± 6 | 23 ± 10 | 38 ± 15 | 435 ± 100 |
| **12** | H |  | 132 | — | — | — | — | nt | nt | nt | nt |

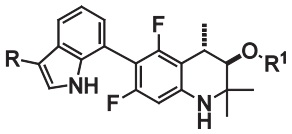
[a] $EC_{50}$ and $IC_{50}$ values determined from half-log concentration response curves. Agonist efficacies represent the percentage maximal response in comparison to dexamethasone (100%). E-selectin repression efficacies represent the percent of maximal inhibition of the response induced by TNFα and IL-1β. IL-6 repression efficacies represent the percent of maximal inhibition of the response induced by IL-1β. Standard errors (SEM) represent the mean value of at least two separate experiments with triplicate determinations. If no SEM is noted, value is from a single determinant. M-dash (—), not active and denotes <20% efficacy or potency >1 μM. nt, denotes not tested.

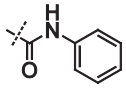
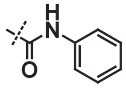
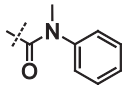
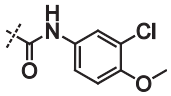
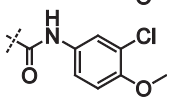
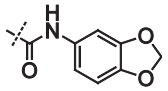
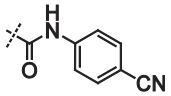
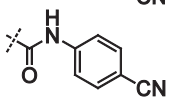
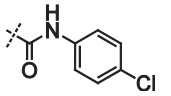
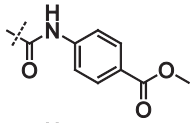
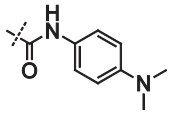
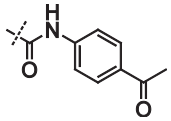
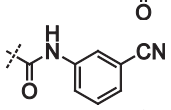
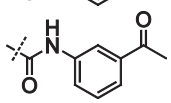
[b] Compounds were tested as racemates.

intermediate acyl imidazole **6**, which upon subsequent treatment with an appropriate amine gave the desired carbamate. Alternatively, **4** and commercially available isocyanates were directly condensed in toluene at reflux.

The glucocorticoid receptor was shown to accommodate derivatization of the C3-hydroxyl group of **4** (Table 1). *N*-Alphatic and *N*-benzyl C3-carbamates **7-11** exhibited GR binding affinity ($K_i$ = 3–8 nM) comparable to **1** and functioned as fully efficacious agonists.

**Table 2**
In vitro assay results for carbamates **13–26**[a]



| Compd | R | R[1] | GR $K_i$ (nM) | GR activation | | E-selectin repression | | IL-6 repression | | PEPCK activation | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Eff. (%) | $EC_{50}$ (nM) | Eff. (%) | $IC_{50}$ (nM) | Eff. (%) | $IC_{50}$ (nM) | Eff. (%) | $EC_{50}$ (nM) |
| **1** | | | 5.3 ± 0.3 | 130 ± 7 | 5.3 ± 3.6 | 100 ± 1.4 | 4.1 ± 0.8 | 97 ± 0.7 | 23 ± 2.6 | 84 ± 4 | 26 ± 7 |
| **4** | H | H | 2.5 ± 0.9 | 138 ± 16 | 0.6 ± 0.2 | 100 ± 2.2 | 1.5 ± 0.7 | 90 ± 2.3 | 11 ± 5.6 | 75 ± 2 | 98 ± 40 |
| **13** | H |  | 6.2 | 194 ± 32 | 105 ± 8 | 73 ± 5 | 40 ± 20 | — | — | nt | nt |
| **14** | Cl |  | 7.6 ± 0.2 | 130 ± 5 | 7.6 ± 2.7 | 98 ± 2 | 9.1 ± 3.4 | 91.4 ± 4.3 | 33.0 ± 18 | 79 ± 4 | 379 ± 142 |
| **15** | H |  | 14.3 | — | — | — | — | — | — | nt | nt |
| **16** | H |  | 11.6 | 119 ± 16 | 11 ± 3 | 90 ± 2 | 7.5 ± 2.5 | 90 ± 7 | 31 ± 13 | 89 ± 20 | 687 ± 48 |
| **17** | Cl |  | 6.7 ± 1.1 | 116 ± 10 | 5.8 ± 1.8 | 97 ± 1 | 5.7 ± 0.9 | 103 ± 2 | 12 ± 3 | 93 ± 2 | 283 ± 10 |
| **18** | H |  | 12.2 | 98 ± 9 | 18 ± 6 | 89 ± 4 | 8.5 ± 2.4 | 86 ± 4 | 50 ± 20 | 74 ± 9 | 874 ± 226 |
| **19** | H |  | 16.1 | 84 ± 10 | 21 ± 5 | 89 ± 4 | 10 ± 2 | 56 ± 2 | 16 ± 1 | nt | nt |
| **20** | Cl |  | 13.7 | 125 ± 30 | 5.1 ± 2.0 | 102 ± 4 | 8.1 ± 5.5 | 102 | 5 | 77 ± 10 | 272 ± 60 |
| **21** | H |  | 70 | 136 ± 13 | 178 ± 40 | 85 ± 4 | 44 ± 15 | 60 | 29 | nt | nt |
| **22** | H |  | 30 | 84 ± 19 | 15 ± 6 | 90 ± 2 | 29 ± 6 | 85 ± 1 | 16 ± 4 | 80 ± 2 | 267 ± 20 |
| **23** | H |  | 5.1 | 112 ± 30 | 3.5 ± 22 | 97 ± 1 | 8.4 ± 1.6 | 86 ± 8 | 39 ± 8 | 63 ± 9 | 361 ± 48 |
| **24** | H |  | 2.9 | 155 ± 13 | 16 ± 10 | 98 ± 3 | 23 ± 15 | 95 ± 5 | 31 ± 12 | 44 ± 1 | 182 ± 70 |
| **25** | H |  | 13.7 | 114 ± 17 | 24 ± 5 | 87 ± 3 | 13 ± 3 | 80 | 38 | 32 ± 3 | 287 ± 40 |
| **26** | H |  | 9.4 | 98 ± 5 | 29 ± 9 | 93 ± 3 | 49 ± 21 | 81 ± 8 | 22 ± 2 | 27 ± 11 | 333 ± 21 |

[a] See Table 1.

The *N*-methyl carbamate **7** showed high TR activity in E-selectin (90% efficacy of dexamethasone) with reduced TA of PEPCK (52% efficacy of dexamethasone) compared to **4**. However, because **7** was inactive in repression of IL-6, its lower PEPCK efficacy does not offer an improved TR/TA profile relative to **4**. Previous SAR studies surrounding the C6-indole ring discovered that in certain analogs a 3-substitutent on the C6-indole ring lead to an increase in TR activity.[12a,16] Thus, **8** showed improved activity in IL-6 with respect to **7**; however this increase in TR activity is accompanied with a resulting increase in PEPCK efficacy, reaching a level comparable to **4**.

Carbamate **12** exhibited weaker binding affinity ($K_i$ = 132 nM) relative to **4** and had no GR functional activity. *N*-Benzyl, *N*-isopropyl or *N*-cyclohexyl carbamates **(9–11)**, possessed a more favorable profile with all showing ⩾80% efficacy in IL-6 repression compared to dexamethasone with reduced efficacy in PEPCK. In the case of *N*-isopropyl carbamate **10** and *N*-cyclohexyl carbamate **11**, the transcriptional activation efficacy of PEPCK was 26% and 38% of dexamethasone, respectively. These values of TA are approximately half of either **1** or **4**. This separation of TR (E-selectin, IL-6) versus TA (PEPCK) efficacy suggests these carbamates offer unique profiles relative to conventional steroids which show high efficacy in both TR (**1** is >97% efficacious in E-selectin and IL-6) and TA (**1** is 84% efficacious in PEPCK) assays.

We next investigated C3-carbamates possessing *N*-phenyl groups (**13–26**, Table 2). With the exception of **15**, regardless of phenyl ring substitution pattern, the analogs maintained high efficacy in the GR agonist assay. Although **15** did serve as a ligand for GR ($K_i$ = 14 nM) it exhibited no functional activity. Comparing **13** with **15** suggests a preference for secondary over tertiary carbamates.

The GR binding assay showed a variety of 3- or 4-substitutents were accepted on the *N*-phenyl ring, with 4-chloro **(21)** and 4-carbomethoxy (**22**) analogs showing the lowest receptor affinity ($K_i$ = 70 and 30 nM) from the series and 4-ketone analog **24** ($K_i$ = 2.9 nM) possessing comparable binding affinity to **4**. For *N*-phenyl carbamates **13, 16**, and **19** an increase in TR activity (E-selectin and IL-6) from the 3-chloro indoles yielded analogs that had prednisolone-like efficacy in PEPCK and therefore diminished TR/TA separation (compare analogs **13** with **14**, **16** with **17** and **19** with **20** from Table 2). Most of the analogs from the *N*-phenyl carbamate series showed transcriptional repression of ⩾80% dexamethasone in both the E-selectin and IL-6 assays. More importantly, we discovered analogs such as **24**, **25** and **26** that also exhibit lower (⩽44%) transcriptional activation in PEPCK, suggesting a preference for TR over TA.

Aware that we have previously shown the C3-hydroxyl group of the tetrahydroquinoline A-ring to be important in controlling receptor selectivity, off-target receptor binding of several key carbamates was monitored (Table 3). In general, mineralocorticoid receptor (MR) binding affinity of the carbamates was not problematic. However, while GR binding affinity within the series was found to be similar to **4**, an increased affinity for progesterone receptor (PR) was observed.

In an effort to develop SGRMs from our GR program, we discovered a new sub-series of nonsteroidal GR ligands derived from tetrahydroquinolin-3-yl carbamates. The carbamates are highly efficacious GR agonists showing good binding affinity. While several analogs exhibited transcriptional repression efficacy similar to **4** in cellular based assays of E-selectin and IL-6, select analogs such as **9–11**, and **24–26** were identified with reduced transcriptional activation of PEPCK compared to steroidal GCs. While the receptor selectivity of the carbamates was diminished, these analogs nonetheless represent important leads in identifying GR agonists with a potentially reduced impact on glucose elevation.

**Table 3**
Cross-reactivity for selected carbamates[a]

| Compd[b] | GR binding $K_i$ (nM) | PR binding $K_i$ (nM) | MR binding $K_i$ (nM) |
|---|---|---|---|
| **4** | 2.5 ± 0.9 | 2095 ± 380 | 1518 ± 390 |
| **9** | 6.8 | 160 | 656 |
| **10** | 7.8 | 213 | 378 |
| **11** | 4.3 ± 2.7 | 93 | 2250 |
| **24** | 3.8 | 231 | 1115 |
| **25** | 13.7 | 662 | 1470 |
| **26** | 9.4 | 680 | 3170 |

[a] Standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations. If no SEM is noted, value is from a single determinant.
[b] Compounds were tested as racemates.

## References and notes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16. Unpublished results from our laboratories. General procedure for the synthesis of 3-chloro indole analogs: **4** (1.0 equiv) was reacted with *N*-chlorosuccinimide (1.05 equiv) in chloroform at 0 °C to provide the resulting 3-chloro indole intermediate which was then subjected to either carbamate synthetic route as depicted in Scheme 1.