Bioorganic & Medicinal Chemistry Letters 21 (2011) 6343–6347

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Steroidal C-21 mercapto derivatives as dissociated steroids: Discovery of an inhaled dissociated steroid

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ARTICLE INFO

Article history:
Received 20 July 2011
Revised 19 August 2011
Accepted 25 August 2011
Available online 31 August 2011

Keywords:
Inhaled asthma
Hydrocortisone
C-21 mercapto derivatives
Dissociated Steroid
Transactivation and transrepression

ABSTRACT

A series of C-21 mercapto derivatives of hydrocortisone have been synthesized and evaluated in cell based transrepression and transactivation assays. The benzothiazole derivative, compound **6** not only showed a dissociated profile in vitro functional assays but also a pharmacological profile in a Brown-Norway rat therapeutic index model of asthma that dissociated side effects (thymolysis) while maintaining efficacy against pulmonary inflammation and lung function.

Glucocorticoids (anti-inflammatory steroids) have been on the market for more than 60 years and represent the most effective therapy for both acute and chronic inflammatory conditions[1] including allergic and non allergic diseases such as asthma, COPD, rheumatoid arthritis and many more. The discovery of cortisone in 1948 and the endogenous glucocorticoid hydrocortisone **1** in 1951 and its use for the treatment of rheumatoid arthritis generated enormous interest in the use of glucocorticoids for the treatment of various inflammatory diseases that triggered an explosive development in the discovery of synthetic glucocorticoids. The earlier research in this area generated compounds with improved glucocorticoid receptor affinity and selectivity to other nuclear receptors such as progestrone and mineralocorticoid. The most commonly used synthetic glucocorticoids are prednisolone, dexamethasone, budesonide, mometasone furoate **2** and fluticasone propionate **3**. Although currently marketed glucocorticoids are very effective for the treatment of inflammatory conditions, their long term use is limited by a number of serious side effects[2] such as skin thinning, decreased bone density, HPA axis suppression and glucose intolerance. The therapeutic index of classical steroids has been further improved[3] by both route of administration and by adjusting the pharmacokinetic profile of the compound. The development of topical steroids such as mometasone furoate[4] **2** significantly helped allergy and asthma patients to manage exacerbations and provided higher quality of life.

Mechanistically, glucocorticoids are involved in two major gene transcription pathways,[5] transrepression and transactivation. Broadly speaking, transrepression is the interaction of the glucocorticoid receptor-steroid monomer complex with the transcription factors such as AP-1 and NFκ-B, which is believed to be the major contributor of the antiinflammatory activity of glucocorticoids. However, most of the systemic side effects are due to the interaction of glucocorticoid receptor-steroid dimer complex with DNA, which brings increased transcription called transactivation. The transactivation of genes by GR is suggested to be key in determining the metabolic side effects of glucocorticoids. The transactivation mechanism involves glucocorticoid receptor dimerization and DNA binding to DNA palindromes, referred to as glucocorticoid response elements (GRE), and subsequent recruitment of coactivators to transcriptionally activate (transactivate) target genes, such as tyrosine amino transferase (TAT). The major side effects such as decreased bone density skin thinning, HPA axis suppression and diabetes are hypothesized to be due to the genomic events as a result of the interaction of glucocorticoid receptor-steroid dimer complex with DNA. Hence, a glucocorticoid that can separate transactivation from transrepression may display an improved safety profile and is called a dissociated steroid[6] or selective glucocorticoid receptor modulator. A number of pharmaceutical companies are actively pursuing research towards the discovery and development of both steroidal[7]

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doi:10.1016/j.bmcl.2011.08.108

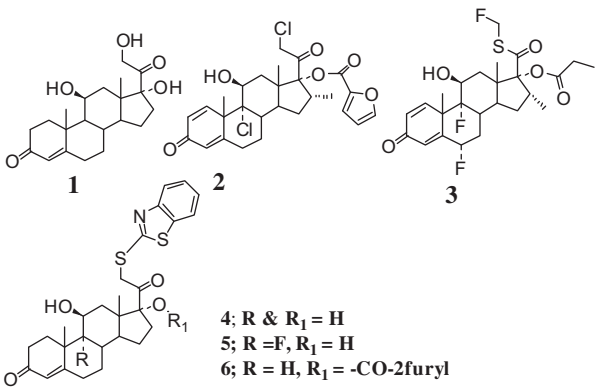


Figure 1. C-21 mercapto derivatives as dissociated steroids.

and non steroidal[8] dissociated glucocorticoids for the treatment of various inflammatory diseases. Herein, we report our efforts towards the discovery of compound **6**, a C-21 mercapto-benzothiazole readily prepared from hydrocortisone, that demonstrated a dissociated profile both in vitro and in vivo.

Initial screening of an internal compound library identified various C-21 mercapto hydrocortisone derivatives as initial hits. These compounds were evaluated in transrepression and transactivation in vitro cell based assays. Transrepression was measured in a TNF stimulated IL-6 cytokine synthesis assay in human bronchial epithelial cells (H292 cells). Functional transactivation was measured by the induction of tyrosine amino transferase (TAT), an enzyme with well characterized endogenous glucocorticoid response elements that catalyzes the degradation of tyrosine to *p*-hydroxy phenyl pyruvate. Human HepG2 liver cells and rat H4II-E cell lines have been used for TAT functional assays. A recombinant human Hela-GRE-luciferase assay has been used for measuring transactivation in addition to TAT assays.[9]

One of the initial lead compounds, a hydrocortisone C-21 mercaptobenzothiazole **4** (Fig. 1) showed moderate inhibitory activity towards IL-6 cytokine synthesis (EC_{50} = 36 nM) and a weak induction of tyrosine amino transferase in both human HEPG2 liver cells (E_{max} = 5%) and rat H4II-E cells (E_{max} = 0%) (Table 1). Compound **4** was further evaluated in a number of in vivo assays. In an allergen challenge model using Brown-Norway rats (Table 2), compound **4** delivered by intratracheal insufflation showed significant inhibition of inflammatory cell influx (ED_{50} = 0.42 mg/kg) comparable to the standard fluticasone propionate **3** (ED_{50} = 0.14 mg/kg), which is a full agonist for transactivation. Compound **4** further demonstrated safer profile in rats compared to the standard **3** with less of a decreased in body weight, adrenal weight and thymus weight (Table 3) in an intraperitoneal dosing study. Since compound **4** showed significant antiinflammatory activity and a better safety profile, it was further evaluated[10,11] by dosing via nose-only dry powder inhalation in the allergen challenged Brown-Norway rat model. In this critical inhalation model, compound **4** demonstrated only moderate efficacy of 27% inhibition of total BAL cells with a lung concentration of 85 μg/kg. It therefore warranted additional SAR optimization of transrepression potency and physicochemical properties for an inhaled candidate.

Generally inhaled steroids achieve their anti-inflammatory and improved safety profile through a combination[12] of high affinity for the glucocorticoid receptor, antiinflammatory potency, long lung retention and an extensive hepatic first pass metabolism of systemically absorbed fraction of the drug. The long lung retention is often the result of optimum lipophilicity and high receptor affinity of the drug molecule. Compound **4** is derived from the endogenous glucocorticoid hydrocortisone, which is not only a weaker steroid but also displays poor selectivity to other nuclear receptors. In recent years, a number of very potent synthetic steroids have been developed, particularly with improved selectivity and antiinflammatory efficacy. Table 4 summarizes various steroidal core modifications with C-21 mercaptobenzothiazole motif. Although introduction of a 9-fluoro analog **5** (Fig. 1) showed a slight improvement in IL-6 inhibition, the compound demonstrated moderate activity in the transactivation assay. On the other hand, the prednisolone analog **7** showed a significant dissociated profile with

Table 1
Transactivation and transrepression in cell based assays

Compd	IL-6 inhibition IC_{50}[a] (nM) E_{max} (%)	Rat TAT EC_{50}[a] (nM) E_{max} (%)	hTAT EC_{50}[a] (nM) E_{max} (%)
4	36 (97)	(0)	(5)
Fluticasone propionate **3**	0.075 (99)	0.76 (110)	0.7 (113)

Note: The top concentration for the E_{max} when there are no EC_{50} available is 1 μM.
[a] Values are means of two experiments.

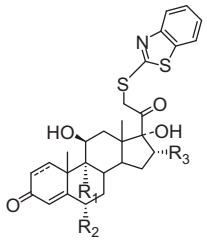
Table 2
Antiinflammatory efficacy: allergic Brown-Norway rat model (intratracheal dosing study)

Compd	Inhibition of inflammatory cell influx (single dose, i.t, ED_{50} (mg/kg)
Fluticasone propionate **3**	0.14
4	0.42

Table 3
Three day intraperitoneal dose: effect on body, adrenal and thymus wt

Compd	Body wt change ED_{50} (mg/kg)	Adrenal wt change ED_{50} (mg/kg)	Thymus wt change ED_{50} (mg/kg)
Fluticasone propionate **3**	0.34	0.52	0.14
4	>100	>100	>100

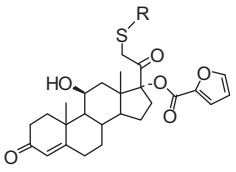
Table 4
Effect of C-21 mercaptobenzothiazole modification on various steroid cores

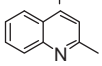
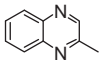
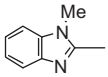
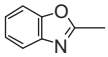
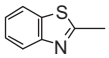
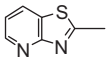


Compd	R_1	R_2	R_3	hGR IC_{50} (nM[a])	IL-6 inhibition IC_{50} (nM)[a] (E_{max}%)	hGRE EC_{50} (nM)[a] (E_{max}%)	rTAT EC_{50}, nM[a] (E_{max}%)
4				4.8	36 (97)	(30)	(0)
5				4.6	18.8 (95)	535 (63)	(21)
7	H	H	H	3.8	35 (78)	(29)	(19)
8	F	H	Me	18	4.4 (98)	45.5 (68)	(33)
9	F	F	Me	13	1.9 (100)	17 (66)	27 (79)
10	Cl	H	Me	17	4.95 (88)	50 (60)	(29)
11	H	Me	H	18	39.1 (95)	295 (55)	(34)

Note: Compounds **4** and **5** is derived from hydrocortisone with one double bond and compounds from **7**-**11** has two double bonds. The top concentration for the E_{max} when there are no EC_{50} available is 1 μM.
[a] Values are means of two experiments.

Table 5
Transactivation and transrepression data for C-17 furoates



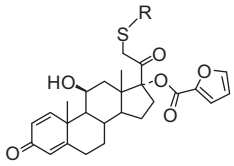
	Compd	IL-6 inhibition IC_{50} (nM)[a] (E_{max}%)	Rat TAT EC_{50} (nM)[a] (E_{max}%)	hu.TAT EC_{50} (nM)[a] (E_{max}%)
12		15.9 (86)	(4)	(33)
13		2.85 (96)	(11)	(22)
14		1.4 (98)	(9)	(41)
15		3.7 (98)	(17)	(39)
16		2.2 (97)	(9)	55.6 (53)
17		2 (100)	(2)	(5)
18		14.3 (94)	(2)	(15)
19		9.7 (94)	(7)	(35)
20		0.9 (100)	(12)	22.4 (57)

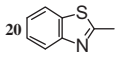
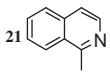
Note: The top concentration for the E_{max} when there are no EC_{50} available is 1 μM.
[a] Values are means of two experiments.

a transrepression potency similar to the hydrocortisone analog **4**. The dexamethasone and fluticasone analogs **8** and **9** demonstrated remarkable improvement in the IL-6 inhibitory activity. The mometasone analog **10** with a 9-chloro substitution also demonstrated excellent antiinflammatory activity. Interestingly, most of the 9-halo derivatives (**5**, **8**, **9** and **10**) showed slightly higher transactivation to the corresponding deshalogenated analogs.

The promising dissociated profile of the hydrocortisone and prednisolone series of compounds **4** and **7** encouraged us to further optimize SAR, particularly to improve transrepression potency and

Table 6
Prednisolone C-17 furoate series: transactivation and transrepression in cell based assays



	Compd	IL-6 inhibition IC_{50} (nM)[a] (E_{max}%)	hGRE EC_{50} (nM)[a] (E_{max}%)	rTAT EC_{50} (nM)[a] (E_{max}%)	rTAT EC_{50} (nM)[a] (E_{max}%)
20		0.75 (99)	14.1 (93)	18.7 (62)	50.8 (43)
21		2.1 (96)	17.3 (73)	(32)	(24)
22		2.1 (98)	13.3 (97)	(24)	(43)

Note: The top concentration for the E_{max} when there are no EC_{50} available is 1 μM.
[a] Values are means of two experiments.

lipophilicity. We have shown in the past with the discovery of mometasone furoate[11] that C-17 esters, especially furoates are known to improve receptor affinity and transrepression potency. We therefore prepared a series of C-17 furyl esters of different C-21 mercapto compounds in the hydrocortisone (Table 5) and prednisolone series (Table 6). As we expected, most of the compounds demonstrated single digit nanomolar potency towards IL-6 inhibition, a several fold improvement from the corresponding desfuroate compound. For example compound **6** showed an IL-6 inhibition IC_{50} of 2 nM compared to the desfuroate compound **4** (IC_{50} = 36 nM). Most of the compounds listed in Table 5 demonstrated an excellent dissociated profile except compounds **16** and **19** which incorporate a benzoxazole and 3,4-dimethylthiazole motifs respectively. Each showed moderate activity in the human TAT transactivation assay.

Table 6 summarizes a list of C-17 furoates prepared from the parent steroid prednisolone. Most of the compounds listed in Table 6 showed higher transactivation in the recombinant human GRE luciferase assay. However, this series of compounds demonstrated excellent transrepression potency, for example, compound **20** showed an IC_{50} of 0.75 nM with full efficacy (E_{max} = 99%) towards IL-6 inhibition.

After identifying hydrocortisone based C-17 furoates with an excellent dissociated profile and potent anti-inflammatory activity in cell based assays, selective analogs were evaluated in a dry powder nose only inhalation model. The benzothiazole compound **6** demonstrated full antiinflammatory efficacy and an improved safety profile compared to the standard fluticasone propionate **3** (Fig. 2). Studies were performed in ovalbumin-challenged[10,11] rats that were sensitized to ovalbumin by intraperitoneal injection of ovalbumin and aluminum hydroxide, then challenged with aerosolized ovalbumin (1% for 30 min). Twenty four hours after the ovalbumin challenge, a bronchoalveolar lavage sample was obtained and inflammatory cell numbers were enumerated. Additionally, the rats were surgically prepared for the measurement of lung functions and changes in the forced vital capacity (FVC) were measured. The safety profile of compound **6** was assessed from changes in thymus weight[13], which is a sensitive measure of steroid side effect liability. The nose-only inhalation system was used to conduct dose/response experiments and calculate a therapeutic index (TI). The TI was calculated from the dose at which there was a 20% reduction in thymus weight (ED_{20}[thymolysis]) and a 70% reversal of the ovalbumin induced reduction in lung function as measured by forced vital capacity (ED_{70}[FVC]) and expressed in as the ratio (TI = ED_{20}(thymolysis)/ED_{70}(FVC)).

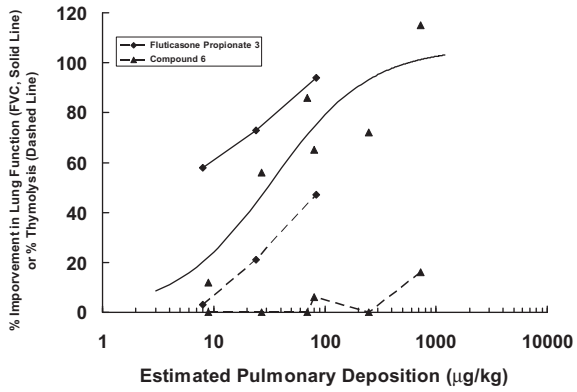
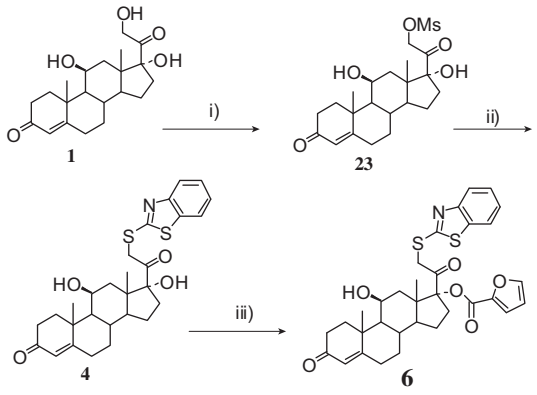


Figure 2. Therapeutics index model: compound **6** versus Fluticasone propionate **3** towards lung function and thymolysis.

In the nose-only inhalation experiment, micronized compound **6** at concentrations of 10% drug admixed with micronized lactose and 100% drug delivered by nose only inhalation once a day for 3 days. The results with inhaled compound **6** demonstrated dose-dependent improvement in lung function with an ED_{70} of 47 μg/kg daily estimated pulmonary deposition. Importantly, compound **6** failed to induce thymolysis ⩾20% at any dose tested up to 730 μg/kg. The TI of compound **6** was greater than 15 compared to the positive control fluticasone propionate. This further demonstrated that compound **6** has exceeded our primary goal of achieving a TI 10 fold greater than that of fluticasone propionate which has a TI of 1.1 (ED_{70}(FVC) = 21 μg/kg and ED_{20}(thymolysis) = 23 μg/kg). Data in the Brown-Norway rat model with other clinically effective inhaled corticosteroids such as beclomethasone dipropionate and budesonide also showed a non-dissociated profile similar to fluticasone propionate with a TI ~1. Moreover, compound **6** showed negligible plasma exposure (AUC = 7h ng/ml; 10 mpk dose) in a rapid rat oral pharmacokinetic study. The development of compound **6**, a glucocorticoid with reduced side effects, will allow safer treatments for patients who require long-term suppression of inflammation.

A general procedure for the preparation of the above mentioned compounds is outlined in the Scheme 1. The commercially available hydrocortisone **1**, was converted to the mesylate **23** by using the standard procedure. Treatment of the mesylate **23** with



Scheme 1. Reagents and conditions: (i) CH_3SO_2Cl, Hunig's Base, CH_2Cl_2, 0 °C to rt, 92%; (ii) 2-mercaptobenzothiazole, K_2CO_3, acetone, reflux, 85%; (iii) furoyl chloride, DMAP, CH_2Cl_2, 0 °C to rt, 81%.

2-mercaptobenzothiazole in acetone afforded compound **4**, which was treated with furoyl chloride to afford the final compound **6**.

In summary, compound **6** represents a novel inhaled steroid with a pharmacological profile in the Brown-Norway rat therapeutic index model of asthma that 'dissociates' the side-effect (thymolysis) while maintaining efficacy against pulmonary inflammation and lung function. Thus C-21 mercapto derivatives of hydrocortisone offers a new class of steroids with an improved safety profile.

Acknowledgments

We thank Dr. John C. Hunter, Dr. Malcom Maccoss, Dr. John Piwinski and Dr. William Greenlee from the Merck Research Laboratory.

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