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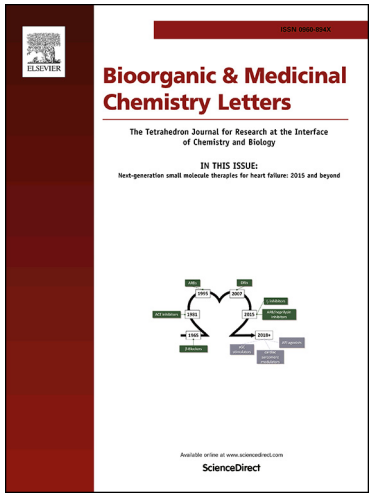

Design and synthesis of functionalized piperazin-1yl-(E)-stilbenes as inhibitors of 17α-hydroxylase-C17,20-lyase (Cyp17)

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Graphical Abstract

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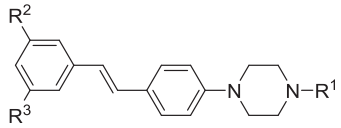

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Design and synthesis of functionalized piperazin-1yl-(E)-stilbenes as inhibitors of 17α-hydroxylase-C17,20-lyase (Cyp17)

Benjamin E Blass[a,*], Pravin Iyer[b], Magid Abou-Gharbia[a], Wayne E Childers[a], John C Gordon[a], Mercy Ramanjulu[a], George Morton[a], Premkumar Arumugam[b], Joshodeep Boruwa[b], John Ellingboe[b], Sayan Mitra[b], Rajashekar Reddy Nimmareddy[b], Shalini Paliwal[b], Jamallamudi Rajasekhar[b], Savithiri Shivakumar[b], Pratima Srivastava[b], Raghuram S. Tangirala[b], Konda Venkataramanaiah[b], Ramreddy Bobbala,[b] Mahesh Yanamandra [b] and L. Krishnakanth Reddy.[b]

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ABSTRACT

The synthesis of steroid hormones is critical to human physiology and improper regulation of either the synthesis of these key molecules or activation of the associated receptors can lead to disease states. This has led to intense interest in developing compounds capable of modulating the synthesis of steroid hormones. Compounds capable of inhibiting Cyp19 (Aromatase), a key enzyme in the synthesis of estrogens, have been successfully employed as breast cancer therapies, while inhibitors of Cyp17 (17α-hydroxylase-17,20-lyase), a key enzyme in the synthesis of glucocorticoids, mineralocorticoids and steroidal sex hormones, are a key component of prostate cancer therapy. Inhibition of CYP17 has also been suggested as a possible target for the treatment of Cushing Syndrome and Metabolic Syndrome. We have identified two novel series of stilbene based CYP17 inhibitors and demonstrated that exemplary compounds in these series have pharmacokinetic properties consistent with orally delivered drugs. These findings suggest that compounds in these classes may be useful for the treatment of diseases and conditions associated with improper regulation of glucocorticoids synthesis and glucocorticoids receptor activation.

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Steroid hormones play critical roles in human physiology. They are primarily synthesized from cholesterol and can be divided into 5 classes, progestogens, glucocorticoids, mineralocorticoids, androgens, and estrogens. Progestogens such as progesterone are required for preparing the uterus for and maintaining pregnancy, while glucocorticoids (e.g. cortisol) stimulate gluconeogenesis, inhibit inflammation, and increase fat and protein catabolism. Androgens (e.g. testosterone) and estrogens (e.g. estradiol) are well known for their role in the development of male and female secondary sex traits. Finally, the mineralonocorticoids (e.g. aldosterone) participate in the regulation of blood volume and pressure via changes in the reabsorption of Na^+ and the excretion of K^+ and H^+ in the distal tubules of the kidneys.

Each of the aforementioned classes of steroid hormones exerts its pharmacological effect through a corresponding receptor (e.g. glucocorticoid receptors, estrogen receptors).[1] Improper regulation of either steroid hormone concentration or receptor activation can have serious, possibly fatal results. Over-production of cortisol, for example, leads to Cushing syndrome, a disease characterized by central obesity, hypertension, dyslipidemia, and insulin resistance that may manifest as impaired glucose tolerance or type 2 Diabetes.[2] Prostate cancer and breast cancer progression have also been linked to aberrant steroid hormone activation of the corresponding receptor.[3] Novel therapies targeting steroid hormone biosynthesis have been effectively employed to slow the progression of breast cancer and prostate cancer. Specifically, Letrozole (Femara®, **1**) and Exemestane (Aromasin®, **2**) are approved for the treatment of breast cancer based on their ability to inhibit Cyp19 (Aromatase), a key enzyme in the synthesis of estradiol. In a similar manner, compounds that inhibit Cyp17 (17α-hydroxylase-17,20-lyase)

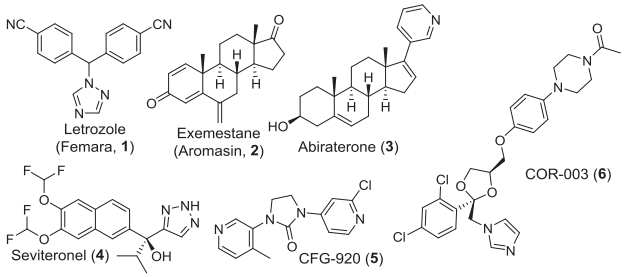

Figure 1: FDA approved CYP17 inhibitors

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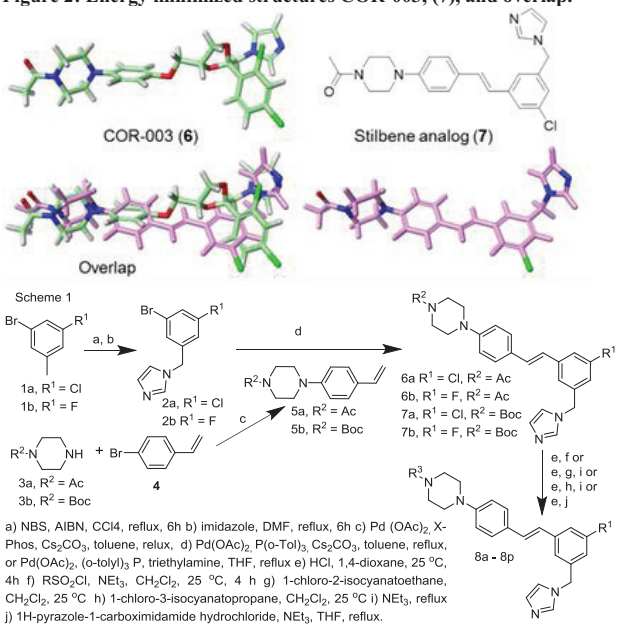
Figure 2: Energy minimized structures COR-003, (7), and overlap



can slow the progression of prostate cancer. The acetate prodrug of Abiraterone (**3**), Zytiga®, was approved by the FDA for this purpose in 2011.[4] Seviteronel (**4**)[5] and CFG-920 (**5**)[6] were identified as Cyp17 inhibitors and are currently undergoing clinical evaluation as novel therapies for the treatment of prostate cancer

The (2S, 4R) isomer of the antifungal agent Ketoconazole, COR-003 (**6**), is also a potent Cyp17 inhibitor (48 nM), but its therapeutic utility in prostate cancer has not been explored. It is, however, currently undergoing clinical evaluation for the treatment of Cushing syndrome (Fig. 1). The clinical manifestations of this condition include central obesity, hypertension, dyslipidemia, and insulin resistance that may manifest as impaired glucose tolerance or type 2 Diabetes.[3] Cushing syndrome is also associated with elevated cortisol levels,[7] a glucocorticoid whose biosynthesis is at least in part regulated by CYP17. Notably, the clinical manifestations of Cushing syndrome are strikingly similar to those of Metabolic Syndrome (MetS), a cluster of abnormalities that occur in concert, including high blood pressure (BP), hyperglycemia, reduced high density lipoprotein cholesterol (HDL-C) levels, elevated triglycerides (TG) and abdominal obesity. As a result of these similarities, it has been hypothesized that CYP17 inhibition may be a viable therapeutic option for the treatment of MetS.[8]

As part of our on-going effort to identify novel Cyp17 inhibitors, we recently reported the preparation and biological properties of a series of sulfonamide analogs of (**6**) (Fig. 2).[9] While we were able to identify highly potent compounds (IC_{50}'s as low as 0.73 nM), our ability to prepare additional analogs in this series was limited by our dependence on a natural product core. In an effort to overcome this limitation, we considered the possibility of replacing the ketoconazole scaffold with a stilbene-derived core. A comparison of the energy minimized structure of COR-003 (**6**) and the corresponding stilbene analog (**7**) suggested that key binding components of the proposed novel scaffold would be similarly positioned (Fig. 2)[10] and a review of the literature indicated that this class of compounds had not been reported. We prepared an initial set of screening samples using the methods described in Scheme 1. Thus, AIBN-mediated bromination of **1a** and **1b** with NBS, followed by nucleophilic displacement of the resulting benzyl bromide with imidazole provided **2a** and **2b**. Separately, Buchwald coupling of 4-

s **5a** and **5b**. Heck coupling with **2a** and **2b** with **5a** provided the corresponding acylated stilbene analogs **6a** and **6b**, while Heck coupling of **2a** and **2b** with **5b** provided the corresponding Boc stilbene analogs **7a** and **7b**. Removal of the Boc group with HCl, followed by condensation of the piperazine with a sulfonyl chloride provided the sulfonamide stilbene analogs (**8a-k**). Alternatively, removal of the Boc group with HCl, followed by condensation of the piperazine with either 1-chloro-2-isocyanatoethane or 1-chloro-3-isocyanatoethane followed by triethyl amine provided the corresponding dihydrooxazole (**8l**, **8m**) and dihydro-4H-1,3-oxazine (**8n**) respectively. Finally, condensation of the aforementioned piperazine with 1H-pyrazole-1-carboximidamide hydrochloride in the presence of provided the guandinyl analogs 8o and 8p.

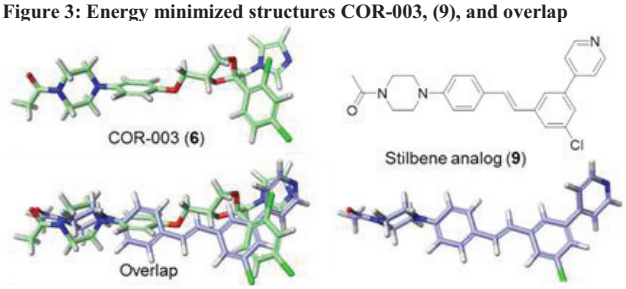
Table 1: Calculated properties and CYP17 inhibition of 1st generation stilbene analogs (6a, 8a to 8o)[11]

Entry	R^1	R^3	MW	TPSA*	cLogP	CYP17 IC_{50} (nM)**
COR-003	NA	NA	531	69	5.2	48
6a	Cl	Ac	421	41	5.57	42
8a	Cl	$MeSO_2$	457	67	4.42	180
8b	Cl	$EtSO_2$	471	67	4.84	24
8c	Cl	cyc-$PrSO_2$	483	67	4.99	21
8d	Cl		509	96	5.08	6.2
8e	Cl		520	80	4.73	17
8f	F	$MeSO_2$	441	67	3.91	58
8g	F	$iPrSO_2$	469	67	4.82	39
8h	F	CF_2HSO_2	477	67	4.61	5
8i	F	cyc-$PrSO_2$	467	67	4.48	34
8j	F	$CNCH_2SO_2$	466	91	3.44	86
8k	Cl		448	46	4.98	100
8l	F		432	46	4.47	117
8m	F		445	46	4.92	42
8n	Cl		421	74	4.65	2500
8o	F		404	74	4.13	1200

*TPSA = topological polar surface area, **n = 3

As indicated in Table 1, our stilbene replacement core is capable of providing compounds with Cyp17 inhibitory potency comparable to that observed with the ketoconazole analog COR-003 (**6**). Specifically, the direct analog (**6a**) had an IC_{50} of 42 nM while the original lead compound (**6**) demonstrated an IC_{50} of 48 nM. We previously reported that the acetamide of (**6**) could be replaced with the corresponding sulfonamide. This strategy was also effective in the stilbene series. Simple alkyl sulfonamides (**8a**, **8b**, and **8c**) all potently inhibited Cyp17 activity (180, 24,

Figure 3: Energy minimized structures COR-003, (9), and overlap



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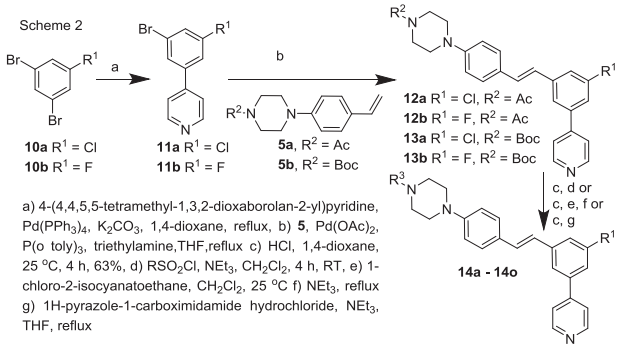
and 21 [illegible] of the imidazole (**8d**, 6.2 nM) and 3-pyridyl (**8e**, 17 nM) were also well tolerated, but the corresponding guanidine derivative (**8n**) demonstrated a significant decrease in Cyp17 potency (IC_{50} = 2500 nM). The corresponding dihydrooxazole (**8k**), on the other hand, retained significant activity at the target (IC_{50} = 100 nM).



These findings suggest the presence of a pocket in this region of the molecule capable of accepting sterically demanding, non-polar substituents.

Replacement of the chlorine atom in the R^1 position with a fluorine atom (e.g., **8f**, **8g**, 8**j**, **8i** and **8h**) provided similarly potent analogs. A comparison of the calculated properties of the fluorine analogs, however, revealed that their cLogP is consistently ~0.5 units lower than the corresponding chlorine analog. This feature provides additional latitude with respect to the choice of substituents in other regions of the molecule that will maintain a cLogP in the drug-like range and could have a beneficial impact on oral bioavailability of potential lead candidates.

Table 2: Calculated properties and CYP17 inhibition of 2nd generation stilbene analogs (12a, 12b, 14a-14o)[10]

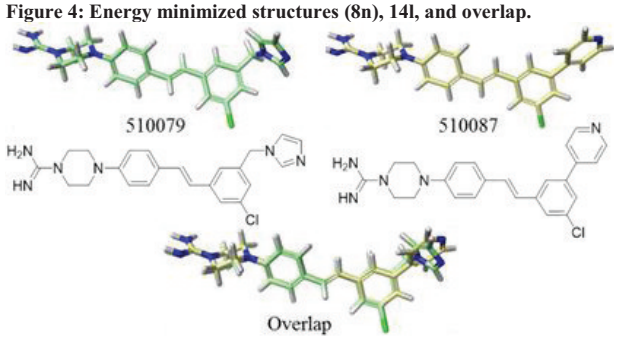
Entry	R^1	R^2	MW	TPSA*	cLogP	CYP17 IC_{50} (nM)**
COR-003	NA	NA	531	69	5.20	48
12a	Cl	Ac	418	36	5.35	5
14a	Cl	$MeSO_2$	454	62	4.20	5
14b	Cl	$iPrSO_2$	482	62	5.12	5
14c	Cl	cyc-$PrSO_2$	480	62	4.77	5
14d	Cl	$CNCH_2SO_2$	479	86	3.74	6
14e	Cl	CF_2HSO_2	490	62	4.90	5
12b	F	Ac	401	36	4.83	4.6
14f	F	$MeSO_2$	438	62	3.68	5
14g	F	$EtSO_2$	452	62	4.10	5
14h	F	$iPrSO_2$	466	62	4.60	1
14i	F	cyc-$PrSO_2$	464	62	4.26	1
14j	F	CF_3SO_2	492	62	5.08	2
14k	F	CF_2HSO_2	474	62	4.39	5
14l	Cl		418	69	4.43	17
14m	F		401	69	3.91	18
14n	Cl		445	41	4.76	5
14o	F		429	41	4.25	5

*TPSA = topological polar surface area, **n = 3

In an effort to expand the utility of our newly discovered stilbene-based Cyp17 inhibitors, we attempted to replace the imidazole of COR-003 (**6**) and (**6a**) with a pyridine ring. A comparison of the energy minimized structure of COR-003 (**6**) [illegible] of the proposed pyridine analog would be similarly positioned (Fig. 3)[12] and a review of the literature once again indicated that this class of compounds had not been reported. Exemplary compounds in this class were prepared using the methods described in Scheme 2. Initial Suzuki coupling of (**10a**) or (**10b**) with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine provided the requisite biaryl species (**11a** or **11b**). Heck coupling with (**5a**) under standard conditions provided the acylated derivative (**12a**) and (**12b**), while Heck coupling with (**5b**) provided the Boc protected analogs (**13a**) and (**13b**). Removal of the Boc group of (**13a**) and (**13b**) under acidic conditions provided the corresponding free piperazines which were readily condensed with sulfonyl chlorides to provide the sulfonamide analogs. Alternatively, removal of the Boc group with HCl, followed by condensation of the piperazine with 1-chloro-2-isocyanatoethane followed by triethyl amine provided the corresponding dihydrooxazole. Finally, condensation of the aforementioned piperazine with 1H-pyrazole-1-carboximidamide hydrochloride in the presence of provided the guandinyl analogs.

As shown in Table 2, our second stilbene core also displayed significant inhibitory potency against Cyp17. Specifically, the chlorinated acyl derivative (**12a**) and the fluorinated acyl derivative (**12b**) were ~8 to 9 times as potent our first generation stilbene derivative (**6a**) and COR-003 (**6**). The increased potency in our second generation stilbene analogs was even more pronounced when the acyl group was replaced with a sulfonamide. Incorporation of a methanesulfonamide into our chlorinated second generation series (**14a**), for example, produced a 36 fold increase in activity when compared to our first generation series (5 nM vs 180 nM). This trend of increased potency in our second generation when compared to our first generation series was sustained across all of the sulfonamides that we examined, as well as the dihydrooxazole bioisosteric analogs. The second generation dihydrooxazoles (**14n**) and (**14o**) were found to be ~20 fold more potent than the corresponding first generation compounds (**8k** and 8l).

Figure 4: Energy minimized structures (8n), 14l, and overlap.



Interestingly, a divergence in the SAR of the first and second generation stilbene series was noted when a guanidine unit was employed in the R^2 position. While first generation compounds (**8n)** and (**8o**) displayed Cvyp17 inhibition in the micromolar range (2500 nM and 1200 nM), the corresponding second generation compounds (**14l**) and (**14m**) were substantially more potent (17 nM and 18 nM, respectively). A comparison and overlay of energy minimized structures of (**8n)** and (**14l**) (Fig. 4)[13] provided a possible explanation. While there is significant degree of overlap between (**8n)** and (**14l**), it is clear that the nitrogen atoms in the heteroaromatic rings do not occupy a similar position in space. It is possible that this change in atomic display provides the pyridine ring of (**14l**) with better opportunities for energetically favorable binding interactions versus the imidazole ring of (**8n)**.

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Table 3 inhibitors COR-003, (12b), (14g), and 14j

Entry	CYP17	CYP19	CYP3A4	CYP3A4/ CYP17	CYP19/ CYP17	GPLM** $t_{1/2}$ (min)
	IC_{50} (nM)*					
COR-003	48	1600	146	3	33	40
12b	5	10000	695	151	2174	60
14g	5	10000	243	49	2000	60
14j	2	1000	9360	1560	167	60

* n = 3, **GPLM = guinea pig liver microsome

In order to identify compounds that might be suitable for advancement into *in vivo* pharmacokinetic and efficacy studies, we expanded our *in vitro* screening studies on key compounds. We were particularly concerned with off-target activity against CYP3A4 and CYP19, as well as guinea pig liver microsome (GPLM) stability Our original lead compound (COR-003) displayed limited selectivity over CYP3A4 (IC_{50} = 146 nM), a key metabolic enzyme known to be linked to drug/drug interactions. We believed that increasing this selectivity window would be advantageous in follow-on compounds advancing towards clinical exploration. Selectivity over Aromatase was also viewed as critical. This enzyme plays an important role in the biosynthesis of estrogen, and interference in this process would be a significant issue. Finally, our *in vivo* efficacy models employ guinea pigs to monitored changes in cortisol synthesis, and as a result GPLM stability could be used as a predictive tool to identify compounds capable of sustained systemic exposure upon dosing. As noted in Table 3, exemplary compounds selected for advancement (**12b**, **14g**, and **14j**) demonstrated improved selectivity over CYP3A4 (49 fold to 1560 fold) and CYP19 (167 to 2174 fold). Excellent GPLM stability was also observed, as all three examples demonstrated $t_{1/2}$ values of 60 minutes.

Given the positive results observed in our second tier *in vitro* assessment, we advanced (**12b**), (**14g**), and (**14l**) into preliminary *in vivo* pharmacokinetic studies using guinea pigs. Compounds were dosed IV (1 mg/kg) and PO (10 mg/kg) and plasma concentrations were assessed via LC/MS/MS over a 24 hour period. As noted in Table 4, all three compounds had moderate half-lives (4.8 to 6 hours) and systemic exposure (IV and PO) was well above the CYP17 IC_{50} values of each compound. Bioavailability was moderate for (**14g**) (22.3%) and (**14j**) (22.1%), but the higher than predicted oral exposure for (**12b**) (AUC = 14890 ng·h/mL, %F = 184.2%) is indicative of non-linear pharmacokinetics. It remains unclear why (**12b**) behaves in this manner, and will likely prevent this compound from progressing into advanced in vivo efficacy studies.

In summary, we have identified two novel series of stilbene derivatives capable of inhibiting CYP17, a key enzyme in the cortisol synthetic pathway and a validated target in prostate cancer therapy. Exemplary compounds examined in this series possess *in vivo* pharmacokinetic properties suitable for *in vivo* efficacy studies to determine their potential for therapeutic utility. The results of these studies are will be reported separately.

Table 4: Guinea pig *in vivo* pharmacokinetic profiles of exemplary stilbene derivatives.

(n = 3)	12b		14g		14j	
Dose(mg/kg)	1	10	1	10	1	10
Delivery*	IV	PO	IV	PO	IV	PO
Cmax(ng/mL)	132	1018	852	540	203	271
Tmax (h)	0.1	3	0.13	3.33	0.2	3.33
$t_{1/2}$ (h)	6	6	5.7	4.8	5	5.25
Vd (L/kg)	14.8	N/A	4.05	N/A	9.1	N/A
Cl (mL/min/kg)	28.5	N/A	8.79	N/A	20.9	N/A
AUC0-inf (ng·h/mL)	586	14890	2000	4190	815	2452
%F	N/A	184.2	N/A	22.3	N/A	22.1

*IV vehicle: 20%DMA, 40%TEG, 40%Water. PO vehicle: 98% HPMC (1% in water), 2% Tween80.

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[10] Energy minimizations were conducted with the Tripos Benchware 3D Explorer software package.
[11] cLogP and TPSA values were calculated using the Dotmatics Browser software suite.
[12] Energy minimizations were conducted with the Tripos Benchware 3D Explorer software package.

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Highlights for article entitled “Design and synthesis of functionalized piperazin-1yl-(E)-stilbenes as inhibitors of 17α-hydroxylase-C17,20-lyase (Cyp17).”

1) Cyp17 (17α-hydroxylase-17,20-lyase) is a validated prostate cancer target.
2) Novel stilbenes disclosed herein are potent, selective inhibitors of Cyp17.
3) *In vivo* PK studies indicate that members of this class are orally bioavailable.

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