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Discovery of (3*S*,3a*R*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (PF-3882845), an Orally Efficacious Mineralocorticoid Receptor (MR) Antagonist for Hypertension and Nephropathy

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We have discovered a novel class of nonsteroidal pyrazoline antagonists of the mineralocorticoid receptor (MR) that show excellent potency and selectivity against other nuclear receptors. Early analogues were poorly soluble and had a propensity to inhibit the hERG channel. Remarkably, both of these challenges were overcome by incorporation of a single carboxylate moiety. Structural modification of carboxylate-containing lead ***R*-4g** with a wide range of substituents at each position of the pyrazoline ring resulted in ***R*-12o**, which shows excellent activity against MR and reasonable pharmacokinetic profile. Introduction of conformational restriction led to a novel series characterized by exquisite potency and favorable steroid receptor selectivity and pharmacokinetic profile. Oral dosing of **3*S*,3a*R*-27d** (PF-3882845) in the Dahl salt sensitive preclinical model of salt-induced hypertension and nephropathy showed blood pressure attenuation significantly greater than that with eplerenone, reduction in urinary albumin, and renal protection. As a result of these findings, **3*S*,3a*R*-27d** was advanced to clinical studies.

Introduction

Almost one in three adults in the U.S. has high blood pressure (BP[a]), putting them at a markedly increased risk of major cardiovascular and renal diseases and shortened life expectancy.[1] Several classes of antihypertensive drugs have been developed. These include diuretics, calcium channel blockers (CCB), and drugs that target the renin−angiotensin−aldosterone system (RAAS), known as renin inhibitors, angiotensin converting enzyme inhibitors (ACE), and angiotensin receptor blockers (ARBs).[2]

Aldosterone is a steroid hormone that mediates sodium reabsorption by binding to the mineralocorticoid receptor (MR), a member of the nuclear receptor (NR) superfamily of ligand-dependent transcription factors. Abnormal activation of the MR by elevated levels of aldosterone in the presence of salt imbalance causes hypertension and other detrimental effects to the cardiovascular system such as glomerular and tubular sclerosis.[3] Although upstream inhibitors of RAAS have demonstrated clinically successful drug therapy in treating congestive heart failure (CHF), the utility of ACE inhibitors is limited because of "aldosterone breakthrough", a phenomenon where aldosterone levels elevate overtime. Direct blockade of aldosterone activation of the MR may provide an improved or add-on therapy to existing standard of care.

There are two approaches to treat this abnormal level of aldosterone activation of the MR. One approach involves lowering elevated aldosterone levels using aldosterone synthase inhibitors.[4] Alternatively, MR antagonists, such as spironolactone and more recently eplerenone, selectively block MR activation by aldosterone, resulting in a lowering of blood pressure in hypertensive patients and improved cardiac function, reduced hospitalizations, and reduced mortality in heart failure patients.[5] Furthermore, human clinical trials have demonstrated that administration of MR antagonists spironolactone and eplerenone resulted in a greater reduction in albuminuria compared to ACE inhibitors with similar hypotensive effects in hypertensive patients, demonstrating the therapeutic potential of MR antagonists for diabetic nephropathy.[6]

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[a] Abbreviations: MR, mineralocorticoid receptor; BP, blood pressure; CCB, calcium channel blocker; RAAS, renin−angiotensin−aldosterone system; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; NR, nuclear receptor; CHF, congestive heart failure; HTS, high-throughput screening; SFC, supercritical fluid chromatography; DMF, *N*,*N*-dimethylformamide; NBS, *N*-bromosuccinimide; THF, tetrahydrofuran; TEA, triethylamine; DME, dimethoxyethane; LDA, lithium diisopropylamide; THP, tetrahydropyran; NOE, nuclear Overhauser effect; LiHMDS, lithium hexamethyldisilazide; SAR, structure−activity relationship; PR, progesterone receptor; AR, androgen receptor; GR, glucocorticoid receptor; ER, estrogen receptor; PK, pharmacokinetic; iv, intravenous; po, oral dosing; CL, clearance; V_{dss}, volume of distribution at steady state; *F*, oral bioavailability; SS, salt sensitive; SBP, systolic blood pressure; b.i.d., twice a day; UACR, urinary albumin to creatinine ratio.

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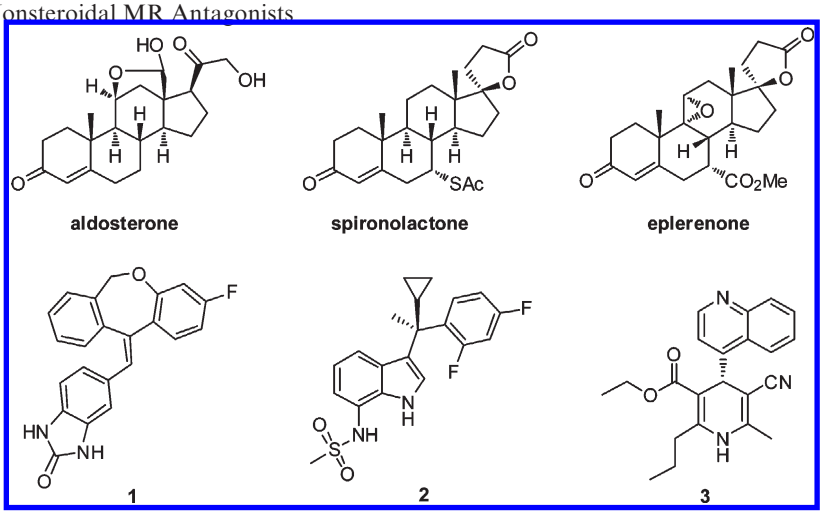
Chart 1. Steroidal and Nonsteroidal MR Antagonists



In general, steroidal MR antagonists present issues of complex chemical synthesis, undesirable physical properties, and poor selectivity versus other steroid hormone receptors. For example, spironolactone therapy has been limited because of poor selectivity versus other NRs and undesirable side effects (gynecomastia, hyperkalemia, menstrual irregularities).[5c,7] Thus, there has been an effort to discover novel classes of selective, potent, nonsteroidal MR antagonists in recent years (e.g., **1**, **2**, Chart 1).[8] As part of our research program directed toward the discovery of new nonsteroidal MR antagonists, we and others have recently reported that dihydropyridines (e.g, **3**) also possess excellent MR antagonist activity.[9]

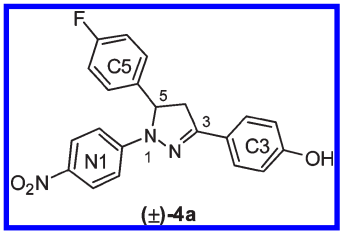
In an effort to discover a nonsteroidal MR antagonist with superior druglike properties and improved nuclear hormone receptor selectivity profile, we identified pyrazoline compound **4a**, a racemate, during a high-throughput screening (HTS) campaign. Pyrazoline derivatives and related nonsteroidal scaffolds have also been described by others as ligands for the estrogen, progesterone, and androgen receptors.[10] Described herein is the modification of this novel class of nonsteroidal MR antagonists, which has led to the identification of potent and selective conformationally restricted pyrazoline MR antagonists. On the basis of its favorable potency, selectivity, pharmacokinetic profile, and in vivo efficacy in the Dahl salt-sensitive model of hypertension,[11] pyrazoline **3*S*,3a*R*-27d** (PF-3882845) was selected as a clinical candidate.

Results and Discussion

Pyrazoline **4a** (Chart 2) was identified as having MR antagonist activity on aldosterone-induced activation of a luciferase reporter driven by MR ligand binding domain in HUH7 cells (IC_{50} = 460 nM).[12] Although having an acceptable activity as a starting point, **4a** had many undesirable features that needed to be amended in order to develop a bona fide lead, namely, the presence of a nitro and a phenol group and a triaryl scaffold that rendered it very insoluble and lipophilic. We modified each position in the pyrazoline ring (termed as N1, C3, and C5) and then incorporated the preferred groups in a final array of analogues.

Chemistry. The synthesis of pyrazolines **4a**−**k** is shown in Scheme 1.[13] The first step is the formation of chalcone intermediate **6** by base- or acid-catalyzed Claisen−Schmidt condensation of an aryl or alkyl aldehyde with an aryl methyl ketone. Treatment of **6** with commercially available phenylhydrazines **7** under acidic conditions afforded the racemic pyrazoline in reasonable overall yields. Ester containing pyrazolines were hydrolyzed under basic conditions to give the corresponding carboxylic acids (e.g., **4f**,**i**). Select examples were then resolved by chiral supercritical fluid chromatography (SFC) to yield the individual enantiomers.

Chart 2. Pyrazoline HTS Hit

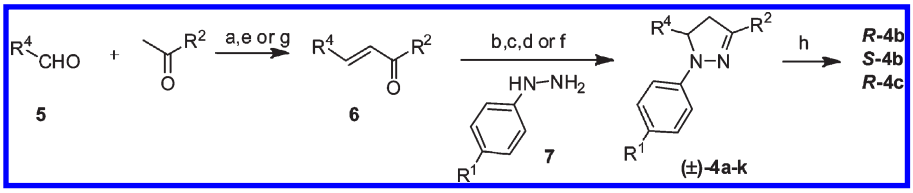


Carboxylic acid containing pyrazolines **12a**−**p** were synthesized as shown in Scheme 2. Condensation of chalcones **10** with the appropriate arylhydrazine **9** gave carboxylates **12a**−**p** directly or via subsequent basic hydrolysis of the corresponding esters **11**. Those arylhydrazines (**9**) that were not commercially available were prepared by fluoride displacement of the corresponding cyanofluorobenzene **8** with hydrazine in ethanol. Select examples were resolved by chiral SFC to give the *R*-enantiomers (vide infra).

Pyrazolines **15a**−**g** were prepared via a cycloaddition route[14] (Scheme 3). Condensation of arylhydrazines **9** with methyl 4-formylbenzoate under basic conditions gave arylhydrazones **13** in good yield. Arylhydrazones **13** were treated with *N*-bromosuccinimide (NBS) to generate bromoimidates **14**, which in turn were treated with triethylamine to effect the 1,3-dipolar cycloaddition with alkyl and aryl olefins. After hydrolysis of the methyl ester, pyrazolines **15a**−**g** were obtained as racemates in good yield.

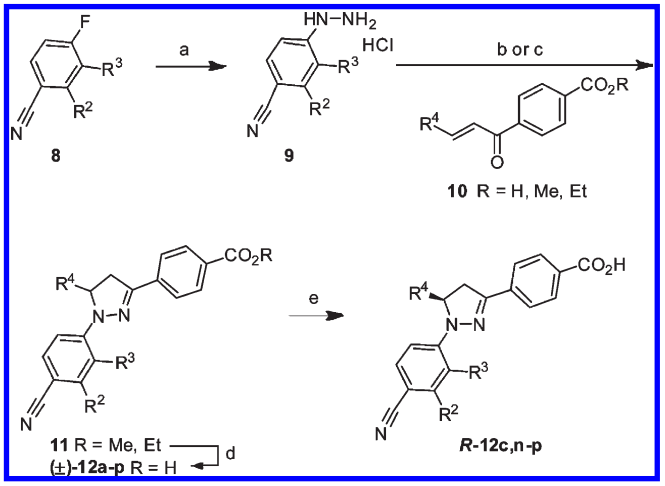
To enable the efficient synthesis of optically pure pyrazoline analogues with preferred N1 and C5 groups and various C3 carboxylate substitution paterns, advanced intermediate ***R*-17** was synthesized via 1,3-dipolar cycloaddition of an in situ generated bromonitrilimine and an alkene[14a,15] (Scheme 4). Hydrazone **16** was prepared from 4-cyanophenylhydrazine by reaction with glyoxylic acid in acqueous hydrochloric acid. Treatment of **16** with a solution of NBS in DMF at 0 °C followed by addition of the alkene compound in the presence of triethylamine (TEA) at room temperature gave intermediate

Scheme 1. Synthesis of Trisubstituted Pyrazolines **4a**−**k**[a]



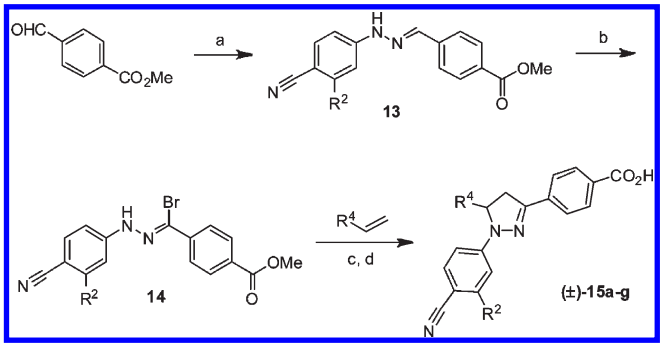
[a] Reagents and conditions: (a) NaOH, EtOH; (b) **7**·HCl, EtOH, 80 °C; (c) **7**, H_2SO_4 or HCl, EtOH, reflux; (d) (i) **7**, HCl, *n*-BuOH, reflux; (ii) KOH or NaOH; (e) HCl, EtOH, reflux; (f) **7**, AcOH, 80 °C; (g) $Si(OEt)_4$, KF, DMF, 50 °C; (h) chiral SFC.

Scheme 2. Synthesis of Benzoic Acid Substituted Pyrazolines **12a**−**p**[a]



[a] Reagents and conditions: (a) (i) hydrazine monohydrate, EtOH; (ii) HCl; (b) EtOH, 80 °C; (c) NaOH, EtOH, 80 °C; (d) NaOH; (e) chiral SFC.

Scheme 3. Synthesis of Benzoic Acid Substituted Pyrazolines **15a**−**g**[a]



[a] Reagents and conditions: (a) **9**·HCl, Et_3N, DMF; (b) NBS, Me_2S, $ClCH_2CH_2Cl$, 0 °C to room temp; (c) Et_3N, THF; (d) NaOH.

17 in racemic form and acceptable yields. Preparative chiral SFC afforded chiral intermediate ***R*-17**.

To positively establish the configuration at C5 for the MR active pyrazoline, each enantiomer of **17** was reacted with *p*-benzoic boronic acid, and both resulting pyrazoline **4g** enantiomers were tested for MR activity. The X-ray crystal structure of ***R*-17** enantiomer yielding MR active enantiomer ***R*-4g** was obtained, and the configuration at C5 was determined to be *R* (Figure 1).

The desired C5 cyclopentyl intermediate ***R*-20** was also prepared via the 1,3-dipolar cycloaddition route shown in Scheme 4. However, this route suffered from poor yields, scalability, and reproducibility (data not shown). An alternative approach[16] is detailed in Scheme 5. Cyclopentanecarboxaldehyde was condensed with ethyl 2-(diethoxyphosphoryl)acetate to give unsaturated ester **18** in good yield. Condensation of **18** with arylhydrazine **9a** under basic conditions gave pyrazolinone **19** in good yield. Racemic chloropyrazoline **20** was obtained upon treatment of **19** with phosphorus oxychloride in 60% yield over three synthetic steps. Chiral resolution of (±)-**20** by SFC gave ***R*-20**. Desired C5-cyclopentyl pyrazolines ***R*-21a**−**e** were prepared by efficient Suzuki coupling of intermediates ***R*-20** with substituted methyl benzoateboronic acids or pinacol esters followed by basic hydrolysis.

Pyrazoline ***R*-12o** was further derivitized as shown in Scheme 6. Deprotection of the methyl ether with boron tribromide followed by alkylation with 2-(3-bromopropoxyl)-tetrahydro-2*H*-pyran, ester hydrolysis, and tetrahydropyran deprotection with acid resulted in propyloxy ether analogue ***R*-22**. Additionally, ***R*-12o** was deprotonated at the C4 position with lithium diisopropylamide (LDA) and then alkylated with iodomethane. Hydrolysis of the methyl ester gave a single stereoisomer **4*S*,5*S*-23**.

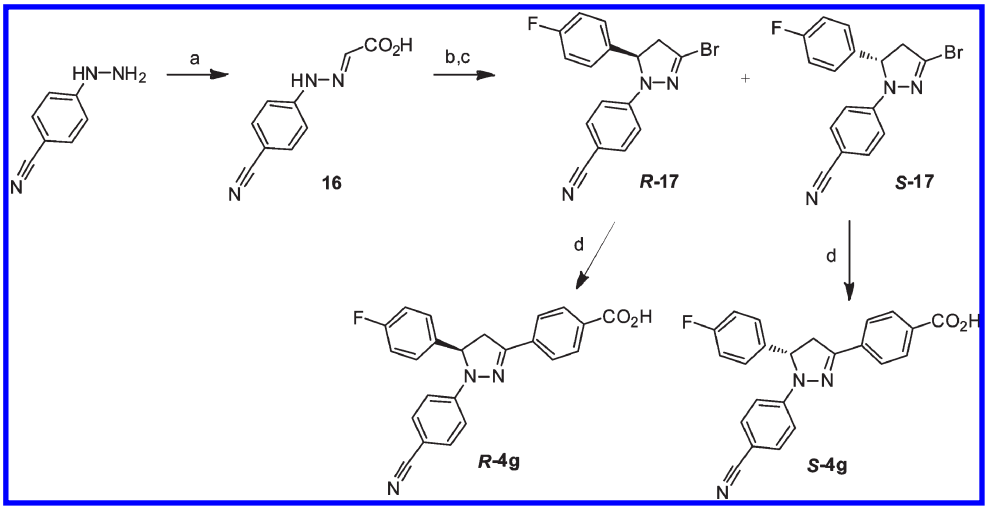
In an effort to enhance potency, we prepared a series of conformationally restricted pyrazolines (Scheme 7). These pyrazolines were prepared in a manner similar to the nonconformationally restricted analogues; cyclic ketones **24** were condensed with an alkyl or aryl aldehyde to give the requisite chalcone derivatives **25**. Condensation with arylhydrazines **9** gave the desired pyrazolines **26** as predominantly the cis-diastereomer (structure confirmed by nuclear Overhauser effect (NOE) and 2D NMR studies; data not shown). Hydrolysis of the ethyl esters gave the final pyrazoline products (±)-**27a**−**q**. Select examples were then resolved by chiral SFC. X-ray crystallography of pyrazoline **3*R*,3a*R*-27c** confirmed both the relative and absolute stereochemistry of the active enantiomer (Figure 2).

The stereocenter at C4 could be epimerized under basic conditions (Scheme 8). For example, (±)-***cis*-27p** was epimerized with sodium methoxide in methanol at 60 °C to give a mixture of cis and trans diastereomers which were separable by HPLC. Confirmation of stereochemistry for (±)-***cis*-27p** and (±)-***trans*-27p** was obtained by 2D NMR and NOE studies (see Scheme 8), consistent with that observed for **27c**. Furthermore, 1D ^1H NMR was found to be diagnostic for the cis isomer by a δ shift of approximately 0.5−1.0 ppm downfield for the C5 proton relative to that for the trans isomer.

In an effort to take advantage of the acidity of the C4-hydrogen atom, **3*S*,3a*R*-27d** was protected as the methyl ester **28** with trimethylsilyldiazomethane, treated with LDA at −78 °C, and trapped with iodomethane to give the methylated derivative (Scheme 9). Subsequent hydroysis of the methyl ester gave the final product **3*S*,3a*R*-29**. The assigned stereochemistry of **3*S*,3a*R*-29** was confirmed by NOE and 2D NMR experiments (data not shown).

Biological Results. In Vitro Structure−Activity Relationships (SARs). The potency and SAR of pyrazolines as antagonists of

Scheme 4. Synthesis of Pyrazoline Intermediate ***R*-17** and Pyrazoline Lead ***R*-4g**[a]



[a] Reagents and conditions: (a) glyoxylic acid, aq HCl (74%); (b) (i) NBS, DMF, 0 °C to room temp; (ii) 4-fluorostyrene, Et_3N (20%); (c) chiral SFC; (d) 4-carboxyphenylboronic acid, $Pd(PPh_3)_4$, aq Cs_2CO_3, DMF.

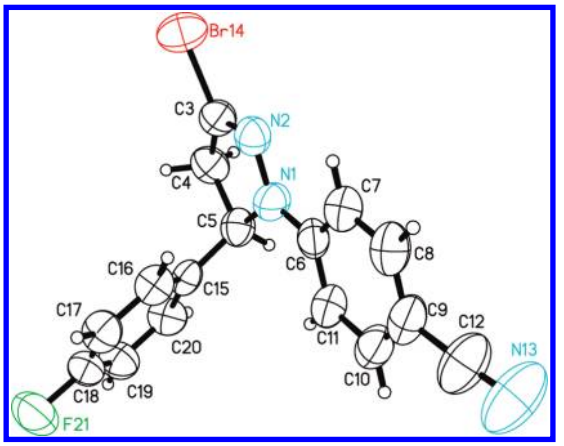
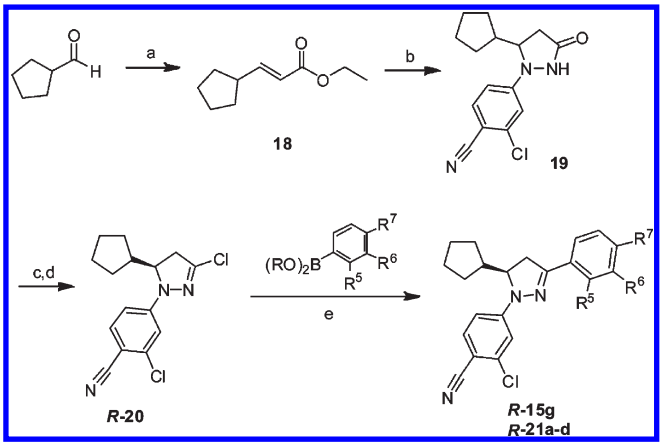


Figure 1. X-ray crystal structure of advanced intermediate ***R*-17**.

MR were evaluated using a functional Gal4-based cellular transcription assay.[12] After considerable effort, the cyano group was identified as the most suitable replacement for the nitro group on the N1 phenyl group (Table 1). The N1 SAR proved to be very narrow as more than 113 non-cyano analogues were made with only 23 having MR $IC_{50} < 1\ \mu M$ (e.g., only *p*-F, *p*-Cl, *p*-Br, and *p*-CO2Et were tolerated but were deemed less desirable than cyano from a druggability standpoint; data not shown). With N1 set as a *p*-benzonitrile, subsequent rounds of exploration around the C3 and C5 groups led to the discovery of compound **4b** wherein the C3 cyclic carbamate group was found to be superior to the phenol, resulting in a 10-fold improvement in potency (MR $IC_{50} = 58$ nM). Furthermore, MR antagonist potency was found to reside primarily in the *R*-enantiomer based on X-ray crystal structures of ***R*-4c** (data not shown) and the ***R*-17** synthetic precursor to pyrazoline ***R*-4g** (Figure 1).

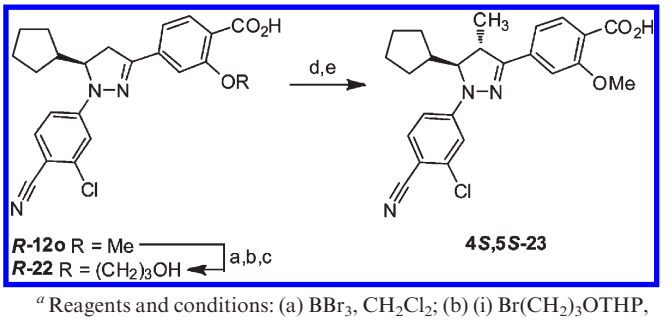
Despite significant advances in potency, it became apparent that early analogues in this compound class suffered from potency on the hERG channel[17] and poor aqueous solubility. An analysis of hERG potential, aqueous solubility, and MR potency is shown in Figure 3. The majority of pyrazolines evaluated had a propensity to inhibit the hERG channel (defined as > 30% inhibition at 10 μM in the dofetilide-Cy3B competitive binding assay[17c]). Of the compounds that passed

Scheme 5. Synthesis of Pyrazoline Intermediate ***R*-20** and Pyrazolines ***R*-15g** and ***R*-21a–d**[a]



[a] Reagents and conditions. (a) $(EtO)_2POCH_2CO_2Et$, NaOEt (87%); (b) **9a**, NaOEt (79%); (c) $POCl_3$, CH_3CN, 80 °C (88%); (d) chiral SFC; (e) (i) $Pd(PPh_3)_4$ or $Pd(dppf)_2Cl_2$, aq Na_2CO_3 or Cs_2CO_3, DME or DMF; if necessary, (ii) NaOH.

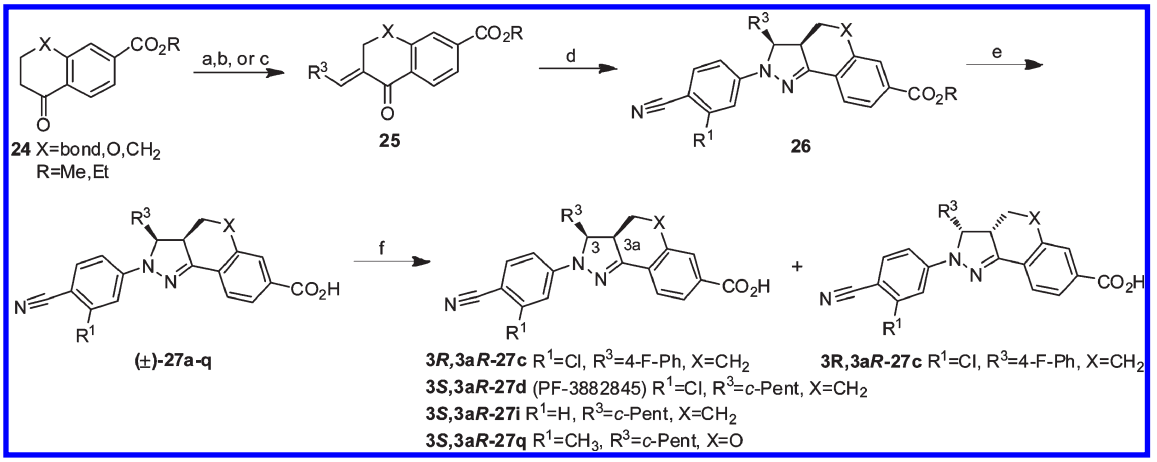
Scheme 6. Synthesis of Pyrazolines **22** and **23**[a]



[a] Reagents and conditions: (a) BBr_3, CH_2Cl_2; (b) (i) $Br(CH_2)_3OTHP$, Cs_2CO_3, DMF, 80 °C; (ii) NaOH; (c) HCl, THF (74% over steps a–c); (d) (i) LDA, THF; (ii) iodomethane; (e) NaOH (60% over steps d and e).

our hERG criteria (< 30% inhibition of dofetilide at 10 μM), only carboxylic acids were found to also have superior aqueous solubility. In fact, all carboxylic acid containing pyrazolines evaluated were inactive in this dofetilide competitive binding assay, regardless of the location of the carboxylate

Scheme 7. Synthesis of Conformationally Restricted Pyrazolines **27a**−**q**[a]



[a] Reagents and conditions: (a) R^3CHO, H_2SO_4 or HCl, EtOH, 80 °C; (b) R^3CHO, pyrrolidine, MeOH; (c) (i) LiHMDS, THF, 0 °C; (ii) R^3CHO; (d) **9a**−**g**·HCl, EtOH, 80 °C; (e) aq NaOH, MeOH, THF; (f) chiral SFC.

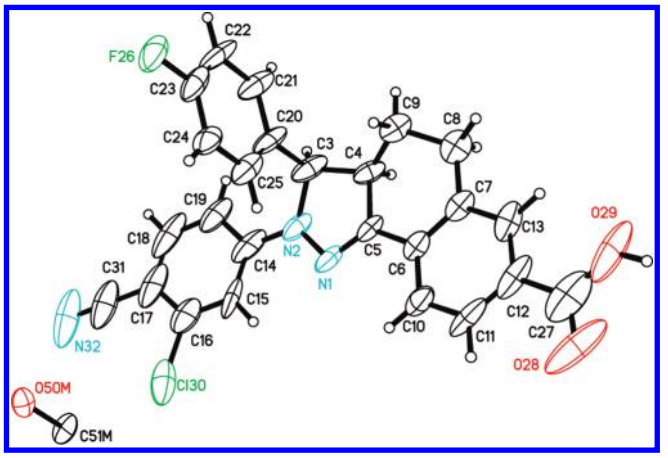


Figure 2. X-ray crystal structure of **3*R*,3a*R*-27c**.

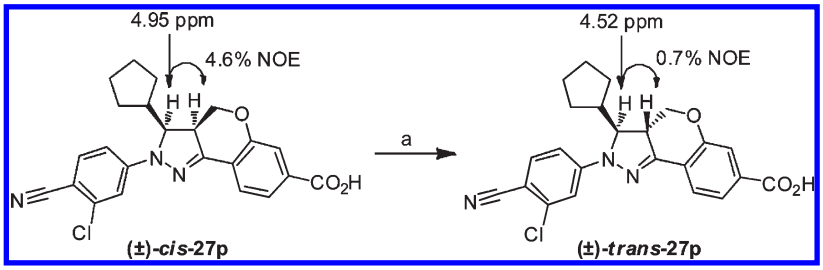
(vide infra). Since most steroidal NRs cannot tolerate a polar carboxylate because of the lipophilic character of their binding sites, we were delighted to find that C3 carboxylate containing pyrazolines were potent MR antagonists. To verify this finding, a series of compounds (e.g., ***R*-4b**, **4d**−**g**) were selected to determine the SAR for each of the three aryl groups for MR potency versus the hERG channel in the patch clamp assay (Table 1). Compounds **4e**−**g** demonstrate that the incorporation of a carboxylate group onto any of the three aryl groups dramatically reduces the hERG potency for these pyrazoline compounds and maintains solubility (aqueous solubility of >30 μM). In addition to maintaining selectivity versus the hERG channel, carboxylic acid **4g** maintains reasonable potency for MR with an IC_{50} of 246 nM. Because of its MR potency (IC_{50} = 101 nM), aqueous solubility, and hERG selectivity, enantiomer ***R*-4g** was selected as a lead with suitable properties for further modification.

Each of the three pyrazoline ring substituents (N1, C3, and C5) was modified simultaneously while keeping the carboxylate fixed (Table 2). As we had observed earlier, the nitrile at R^1 was found to be preferred for MR potency (**4h**−**k**). Deletion of the nitrile group resulted in a 97-fold loss of potency (**4h**). Ethyl ester **4i** was also tolerated in this position, being nearly equipotent to the nitrile, but the corresponding carboxylate **4j** was not, although this could be due to poor cellular permeability. An effort to improve the potency of nitrile-containing N1 resulted in a 2- to 5-fold enhancement in potency when small nonpolar substituents such as cholo, methyl, or trifluoromethyl groups are incorporated in the position ortho to the nitrile (**12c**−**f**). Fluorine substitution (**12a**) or other halogen subtsitution in the position meta to the nitrile (**12b**,**d**) provided negligible or slightly reduced potency for MR. Incorporation of a second nitrile significantly reduced MR potency (**12g**).

Evaluation of C5 (R^4) revealed an extremely tight SAR and a strong preference for 4-fluorophenyl as the preferred aromatic substituent (**12i**−**m**, **15b**,**c**). For example, the 3-fluorophenyl and 3-methoxyphenyl derivatives lost 2-fold and 6-fold potency for MR. Some heterocycles such as furan and thiophene (**12l**−**m**) are tolerated in this position, while incorporation of more basic pyridines significantly reduced MR potency (**12i**−**k**). Replacement of the 4-fluorophenyl group with a benzyl or cyclohexyl group resulted in a 14- and a 5-fold loss in potency, respectivly (**15a**,**d**). Given the sensitivity of the C5 position, it is remarkable to find that incorporation of cyclopentyl in the C5 position (**15e**) gave a slight improvement in potency over 4-fluorophenyl with an IC_{50} of 151 nM. Substitution with an isopropyl group was tolerated (**12h**) but *tert*-butyl resulted in a 10-fold reduction in potency (**15f**). The potency of cyclopentyl analogues was further enhanced by substitution on N1 with a chloro group (**15g**) to 54 nM. Generally speaking, we found the C5 cyclopentyl group to impart a desirable combination of improved MR potency, solubility, and selectivity.

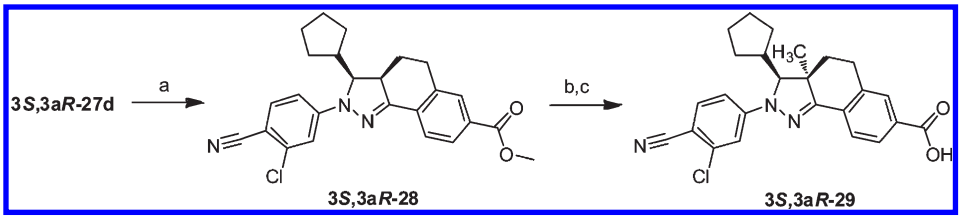
Having identified cyclopentyl and 3-substituted 4-cyanophenyl as the preferred C5 and N1 substituents, a series of C3 substituents were evaluated on the *R*-cyclopentyl scaffold, resulting in further potency enhancements as shown in Table 3. The *R*-enantiomer of **15g** was found to be quite potent for MR with an IC_{50} of 16 nM. The addition of small halogens ortho to the C3 carboxylate (***R*-21a**, ***R*-12n**) was tolerated. Substitution with methoxy groups in either ortho or meta positions results in further increased potency with IC_{50} values of 2−14 nM (***R*-12o**, ***R*-12p**). The ortho alkoxy group could be further enlarged to ethoxy (***R*-21b**) or even hydroxypropyloxy (***R*-22**) without significantly reducing the MR potency. Interestingly, trifluoromethoxy was less well tolerated, resulting in a 6-fold loss of MR potency (***R*-21c**). Extension of the carboxylate itself resulted in nearly a 10-fold loss of MR potency (***R*-21d**). Notably, addition of a

Scheme 8. Epimerization of ***cis*-27p** to ***trans*-27p**[a]



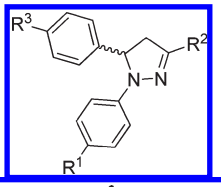
[a] Reagents and conditions: (a) NaOMe, MeOH, THF, 50 °C, 24 h (20%).

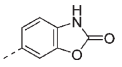
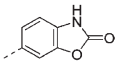
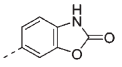
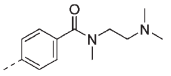
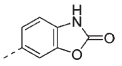
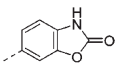
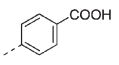
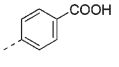
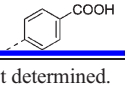
Scheme 9. Synthesis of Methylated Conformationally Restricted Pyrazoline **3*S*,3a*R*-29**[a]



[a] Reagents and conditions: (a) trimethylsilyldiazomethane, THF, MeOH (quant); (b) (i) LiHMDS, THF, −78 °C; (ii) iodomethane, −78 °C; (c) NaOH (31% over steps b and c).

Table 1. Preliminary Hit to Lead SAR for Select Analogues



Cmpd	R^1	R^2	R^3	MR IC_{50} (nM)[a]	hERG IC_{50} (nM)[bc]
eplerenone	--	--	--	122	--
4a	NO_2		F	460	n.d.
4b	CN		F	58	n.d.
***R*-4b**	CN		F	41	29
***S*-4b**	CN		F	2080	n.d.
***R*-4c**	CN		F	32	n.d.
4d	CN		F	83	170
4e	CN		COOH	>10000	>30000
4f	COOH		F	784	>30000
4g	CN		F	246	>30000
***R*-4g**	CN		F	101	n.d.
***S*-4g**	CN		F	8360	n.d.

[a] Reference 12. n ≥ 3. [b] Reference 17d. [c] n.d. = not determined.

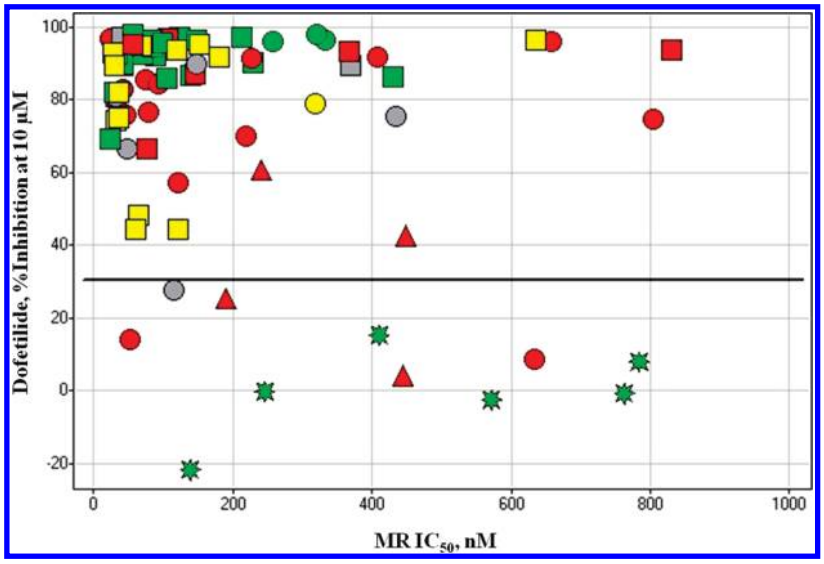
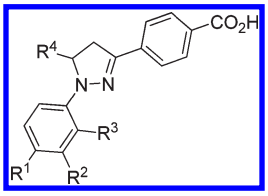


Figure 3. SAR analysis of physical properties, hERG potential, and MR potency in non-conformationally restricted pyrazolines: identification of compound ***R*-4g**. Individual pyrazolines shaped by compound class are amides (■), esters (▲), carboxylic acids (☼), and miscellaneous (e.g., heterocycles, phenols, etc.) (●) and are colored by aqueous solubility: ≤3 μM (red), 3−30 μM (yellow), > 30 μM (green), not determined (gray). Dofetilide = dofetilide-Cy3B competitive binding assay, with % inhibition at 10 μM compound (see ref 17c).

Table 2. N1 and C5 Position SAR of Pyrazoline Carboxylic Acids



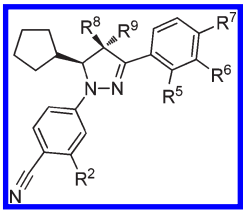
compd	R^1	R^2	R^3	R^4	MR IC_{50} (nM)[a]
***R*-4g**	CN	H	H	4-F-Ph	101
4h	H	H	H	4-F-Ph	9730
4i	CO_2Et	H	H	4-F-Ph	180
4j	COOH	H	H	4-F-Ph	> 10000
4k	OCH_3	H	H	4-F-Ph	1440
12a	CN	F	H	4-F-Ph	243
12b	CN	H	F	4-F-Ph	535
12c	CN	Cl	H	4-F-Ph	56
12d	CN	H	Cl	4-F-Ph	284
12e	CN	CH_3	H	4-F-Ph	56
12f	CN	CF_3	H	4-F-Ph	127
12g	CN	CN	H	4-F-Ph	> 1000
12i	CN	H	H	4-Pyr	> 10000
12j	CN	H	H	3-Pyr	> 10000
12k	CN	H	H	2-Pyr	> 10000
12l	CN	H	H	2-furyl	410
12m	CN	H	H	2-thienyl	763
15a	CN	H	H	Bn	3650
15b	CN	H	H	3-F-Ph	441
15c	CN	H	H	3-MeO-Ph	1590
15d	CN	H	H	*c*-Hex	1290
15e	CN	H	H	*c*-Pent	151
12h	CN	Cl	H	*i*-Pr	383
15f	CN	H	H	*t*-Bu	2530
15g	CN	Cl	H	*c*-Pent	54

[a] Reference 12. n ≥ 3.

methyl group to the pyrazoline core was tolerated but with a 5-fold reduction in potency (**4*S*,5*S*-23**).

Potency data for conformationally restricted pyrazolines **27a**−**q** and **29** are shown in Table 4. Conformational restriction of the benzoic acid with a five-membered ring (***cis*-27a**)

Table 3. SAR of C3 Substituents with Preferred N1 and C5 Groups



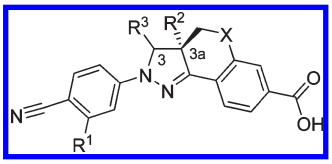
compd	R^2	R^5	R^6	R^7	R^8	R^9	MR IC_{50} (nM)[a]
***R*-15g**	Cl	H	H	COOH	H	H	16
***R*- 21a**	Cl	H	F	COOH	H	H	52
***R*-12n**	Cl	H	Cl	COOH	H	H	26
***R*-12o**	Cl	H	OMe	COOH	H	H	14
***R*-12p**	Cl	MeO	H	COOH	H	H	2
***R*-21b**	Cl	H	OEt	COOH	H	H	6
***R*-22**	Cl	H	$O(CH_2)_3OH$	COOH	H	H	13
***R*-21c**	Cl	H	OCF_3	COOH	H	H	80
***R*-21d**	Cl	H	H	CH_2COOH	H	H	135
4*S*,5*S*-23	Cl	H	OMe	COOH	H	Me	69

[a] Reference 12. n ≥ 3.

resulted in a 18-fold loss of MR potency relative to lead **4g**. In contrast, the six-membered ring restriction (***cis*-27b**) resulted in only a 2-fold loss of MR potency. Incorporation of a chlorine on N1 (***cis*-27c**) further restored potency to 223 nM. As is the case with the nonconformationally restricted pyrazolines, the MR potency lies primarily in one of the two cis-enantiomers. For example, single enantiomer **3*R*,3a*R*-27c** has an IC_{50} of 41 nM versus 3500 nM for its enantiomer **3*S*,3a*S*-27c**. X-ray crystallographic data for **3*R*,3a*R*-27c** confirmed that this is the same preferred orientation of the C5 group observed in the nonconformationally restricted pyrazolines.

Replacement of the 4-fluorophenyl ring in C5 with the preferred cyclopentyl ring resulted in a more dramatic 10-fold potency enhancement (***cis*-27d** versus ***cis*-27c**; IC_{50} = 21 nM and 223 nM, respectively) relative to the nonconformationally restricted series (**15g** versus **12c**; IC_{50} = 54 and 56 nM, respectively). Cyclobutyl (***cis*-27e**) and cyclopentene (***cis*-27f**)

Table 4. Conformationally Restricted SAR



compd	R^1	R^2	R^3	X	MR IC_{50} (nM)[a]
***cis*-27a**	H	H	4-F-Ph	bond	4340
***cis*-27b**	H	H	4-F-Ph	CH_2	553
***cis*-27c**	Cl	H	4-F-Ph	CH_2	223
3*R*,3a*R*-27c	Cl	H	4-F-Ph	CH_2	41
3*S*,3a*S*-27c	Cl	H	4-F-Ph	CH_2	3500
***cis*-27d**	Cl	H	c-Pent	CH_2	21
***cis*-27e**	Cl	H	c-Bu	CH_2	21
***cis*-27f**	Cl	H	cyclopentene	CH_2	15
***cis*-27g**	Cl	H	THF	CH_2	720
***cis*-27 h**	Cl	H	pyran	CH_2	127
***cis*-27i**	H	H	*c*-Pent	CH_2	89
***cis*-27j**	CH_3	H	*c*-Pent	CH_2	4
***cis*-27k**	OCH_3	H	*c*-Pent	CH_2	7
***cis*-27l**	CH_2OCH_3	H	*c*-Pent	CH_2	150
***cis*-27 m**	OBn	H	*c*-Pent	CH_2	488
***cis*-27n**	OH	H	*c*-Pent	CH_2	> 500
***cis*-27o**	Cl	H	4-F-Ph	O	849
***cis*-27p**	Cl	H	*c*-Pent	O	65
***trans*-27p**	Cl	H	*c*-Pent	O	146
***cis*-27q**	CH_3	H	*c*-Pent	O	39
3*S*,3a*R*-29	Cl	CH_3	*c*-Pent	CH_2	25

[a] Reference 12. n ≥ 3.

groups are equipotent to the cyclopentyl group. In contrast, oxygenated varients tetrahydrofuryl and pyranyl resulted in significant losses of potency (***cis*-27g** and ***cis*-27 h**).

Similar to the nonconformationally series, N1 substitution (R^1) with chloro was preferred over hydrogen (***cis*-27d** versus ***cis*-27i**). Methyl and methoxy substitution resulted in an even greater potency enhancement as observed with ***cis*-27j** and ***cis*-27k** with IC_{50} of 4 and 7 nM, respectively. However, incorporation of larger substituents such as CH_2OCH_3 (***cis*-27l**) and benzyloxy (***cis*-27 m**) and polar groups such as hydroxy (***cis*-27n**) resulted in substantial losses of potency.

Chromene derivatives where X = O are also potent MR antagonists (***cis*-27o-q**), albeit 3- to 10-fold less potent than the corresponding hydrocarbon (X = CH_2; ***cis*-27c**,**d**,**j**). As observed for X = CH_2, incorporation of a cyclopentyl group in place of the 4-fluorophenyl group resulted in a dramatic potency enhancement (***cis*-27o**,**27p**). Interestingly, the trans isomer ***trans*-27p** is only 2- to 3-fold less potent than the cis isomer ***cis*-27p**, suggesting that the stereochemistry of the 3a-position is of only marginal importance relative to the 3-position where a dramatic loss of potency was observed for enantiomers in the nonconformationally restricted series (***R*-4g** versus ***S*-4g**). As might be anticipated given the relatively forgiving stereochemistry at this position, a 3a-methyl group is tolerated (**3*S*,3a*R*-29**) resulting in only a 3-fold loss relative to 3a-H analogue **3*S*,3a*R*-27d** (see Table 5).

Molecular Modeling Studies. To understand the potential binding mode for these pyrazolines, an induced-fit model of **3*S*,3a*R*-27d** was prepared using the 1.95 Å MR/corticosterone X-ray crystal structure 2A3I (Figure 4a).[18] In this model, the N1 cyanophenyl group resides in the A-ring pocket, hydrogen-bonding to Q776 and R817, mimicking the A-ring 3-carbonyl group of corticosterone (see Figure 4b). This is consistent with the cyanoaryl binding mode observed in crystal structures for ligands of other nuclear hormone receptors such as the androgen and progesterone receptors.[19] The pendent cyclopentyl group forces the L960 side chain into a higher-energy conformation and displaces the N770 side chain from its normal position, disrupting the hydrogen bonding network stabilized by the 11β-hydroxy group of corticosterone. This feature may be an important component contributing to the antagonism of MR by these pyrazolines, as previous structural studies have suggested that steroidal activation of MR requires (in addition to the C-3 ketone) that the ligand form hydrogen bonds to N770 in helix 3 and to T945 in helix 10.[20] Additionally, the ligand carboxylate displaces the side chains of L848 and particularly F941, opening a channel to solvent under helix 11. This feature is consistent with the activity of extended analogues such as **4d**.

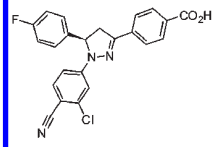
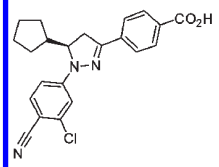
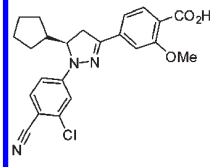
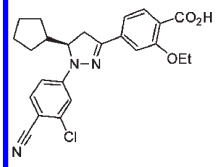
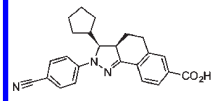
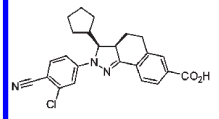
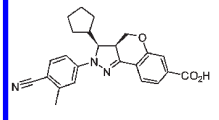
Selectivity and Binding Assays. The antagonist potencies in these functional cell-based assays correlate reasonably well to competitive radioligand binding assays. For example, the binding affinity of **3*S*,3a*R*-27d** for MR is within 4-fold of the functional potency (MR binding IC_{50} = 2.7 nM). Likewise, the binding affinity of **3*S*,3a*R*-27d** for the progesterone receptor (PR) is within 2-fold of the functional PR potency (PR binding IC_{50} = 310 nM). In terms of binding affinity, **3*S*,3a*R*-27d** has a selectivity factor of 115-fold for MR over PR, comparable to spironolactone (MR binding IC_{50} = 8.1 nM vs PR binding IC_{50} = 2440 nM; 301-fold) and eplerenone (MR binding IC_{50} = 138 nM vs PR binding IC_{50} > 10 000 nM; > 72-fold).

MR antagonist selectivity for a select group of enantiomerically pure analogues versus other steroidal nuclear hormone receptors was determined in a similar functional Gal4 cellular assay format (Table 5).[12] These pyrazoline compounds are remarkably selective as a class versus the androgen receptor (AR), glucocorticoid receptor (GR), PR, and estrogen receptor (ER), generally exhibiting selectivities of > 200-fold, with some exceptions for more modest PR selectivities of approximately > 40-fold.

Undesirable side effects of spironolactone-based therapy, such as gynecomastia and menstrual irregularities, have been linked to its progestational and antiandrogenic effects.[5c,7] For example, spironolactone is a PR agonist (in vitro EC_{50} = 2.6 μM)[5c] and an AR antagonist while eplerenone is devoid of PR agonist activity (EC_{50} > 100 μM)[5c] and is selective versus the AR (see Table 5). Importantly, these pyrazolines, including **3*S*,3a*R*-27d**, were also tested for PR agonist activity and were found to be inactive up to concentrations of 100 μM (EC_{50}, data not shown), similar to eplerenone.

Pharmacokinetic Data. Rat pharmacokinetic (PK) data for a select group of enantiomerically pure analogues are shown in Table 6. As a class, both nonconformationally restricted and conformationally restricted pyrazoline carboxylic acids have reasonably low clearance values, modest half-lives, and good bioavailabilities. Replacement of the 4-fluorophenyl C5 group with a cyclopentyl group does result in higher clearance values (e.g., ***R*-12c** CL = 6.9 (mL/min)/kg vs ***R*-15g** CL = 34 (mL/min)/kg). However, conformational restriction of ***R*-15g** results in analogue **3*S*,3a*R*-27d** (CL = 9.8 (mL/min)/kg), a more metabolically stable compound, suggesting that there is some inherent improvement in clearance induced by conformational restriction. Further improvements could be made in reducing clearance by introduction of an oxygen atom to the conformationally restricted series (**3*S*,3a*R*-27d** vs **3*S*,3a*R*-27q**

Table 5. NHR Selectivity[a] for a Select Group of Pyrazoline Carboxylic Acids

Cmpd	MR IC_{50}, nM	AR IC_{50}, nM	GR IC_{50}, nM	PR IC_{50}, nM	ER IC_{50}, nM
spironolactone	13	523	6920	>10000	5702
eplerenone	122	>10000	>8940	>10000	>10000
	31	>8920	>10000	2080	n.d.
***R*-12c**					
	16	>10000	>10000	>4310	n.d.
***R*-15g**					
	14	>10000	>10000	1030	>10000
***R*-12o**					
	6	>10000	>10000	2010	>4960
***R*-21b**					
	38	>10000	>10000	3180	n.d.
3*S*,3a*R*-27i					
	9	>8910	>10000	416	>10000
3*S*,3a*R*-27d					
	26	>10000	>10000	1880	n.d.
3*S*,3a*R*-27q					

[a] Reference 12. n ≥ 3.

CL = 4.6 (mL/min)/kg) or by replacement of the methoxy of ***R*-12o** with the ethoxy group of ***R*-21b**.

Dahl Salt Sensitive Efficacy Model for Hypertension and Nephropathy. On the basis of its potency for MR, selectivity

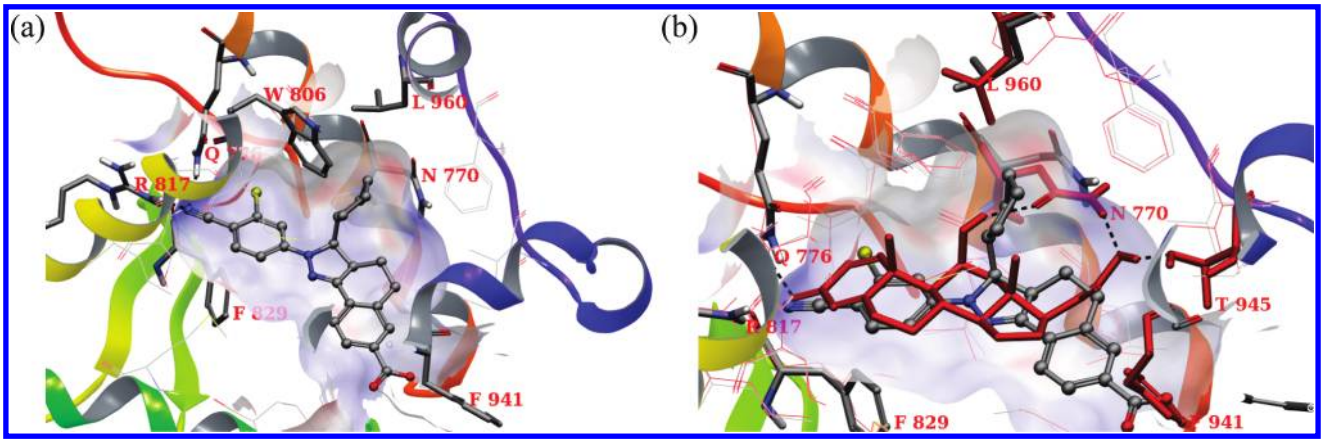


Figure 4. Induced-fit model of **3*S*,3a*R*-27d** in MR: (a) compound **3*S*,3a*R*-27d**, ball and stick, showing residues L960 (helix 12), F941 (helix 11), N770 (helix 3), Q776 and R817 (ketosteroid recognition), and F829, tube; (b) overlay of native crystal MR/corticosterone crystal structure 2A3I (red) with the **3*S*,3a*R*-27d**/MR induced-fit model. The congruence of the cyanophenyl ring with the steroid A/B ring system is apparent, as is the disruption of the N770 and L960 side chains by the cyclopentyl, and the movement of F941 caused by the carboxylate.

Table 6. Rat Pharmacokinetic Data[a] for a Select Group of Pyrazoline Carboxylic Acids

compd	dose, mg/kg	route	CL, (mL/min)/kg	V_{dss}, mL/kg	$t_{1/2}$, h	*F*, %
***R*-12c**	2	iv	6.9	1.5	2.6	
	2	po				46
***R*-15g**	2	iv[b]	34	3.6	1.2	
	2	po[b]				100
***R*-12o**	2	iv	24	3.9	1.9	
	2	po				57
***R*-21b**	1	iv	9.2	2.3	2.5	
	1	po				50
3*S*,3a*R*-27i	2	iv	5.5	0.6	1.3	
	2	po				83
3*S*,3a*R*-27d	2	iv	9.8	1.4	1.7	
	2	po				86
3*S*,3a*R*-27q	2	iv	4.6	0.6	1.6	
	2	po				57

[a] For PK studies, male rats (Sprague−Dawley), $n = 2$, were dosed intravenously (iv) and orally (po) at 1 or 2 mg/kg. Compounds were formulated for solution dosing in 10% ethanol/70% PEG400/20% phosphate buffered saline, pH 7.4. Plasma samples were analyzed by LC/MS/MS. [b] Formulated for solution dosing in 10% ethanol/50% PEG400/40% phosphate buffered saline, pH 7.4.

versus other nuclear receptors, broad target selectivity in the CEREP panel (>100×), and pharmacokinetic properties, the effect of **3*S*,3a*R*-27d** on blood pressure (BP) and kidney injury was tested in male Dahl salt sensitive (SS) rats fed with 4% NaCl. Rats were dosed orally via gavage with wet-milled **3*S*,3a*R*-27d** in vehicle (0.5% methylcellulose/0.1% Tween 80) at 10, 40, and 100 mpk/d, twice a day. For comparison, eplerenone was dosed at 100 mpk/d (dosed in chow because of its very short half-life in rats). Treatment was initiated at the beginning of salt feeding (day 0), and BP was monitored using telemetry units. The results are shown in Figure 5. After 21 days of salt feeding, animals treated with vehicle showed a dramatic increase (40−50 mmHg) in systolic blood pressure (mean 24 h SBP), typical of Dahl SS rats. As has been demonstrated previously, BP increase was much lower in the eplerenone fed group, which represented a significant BP reduction compared to the vehicle group. Similar statistically significant BP reduction was also observed with 10 mpk **3*S*,3a*R*-27d**. Most noticeably, rats dosed with **3*S*,3a*R*-27d** at 40 and 100 mpk had negligible increase in BP over 21 days in the presence of high salt (<5 mmHg), a striking

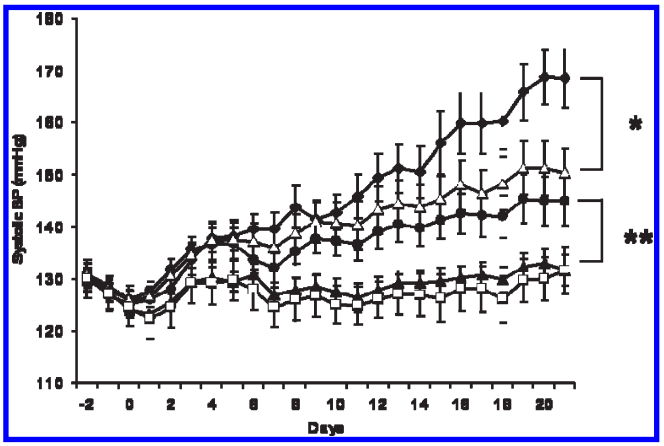


Figure 5. Blood pressure lowering effect of **3*S*,3a*R*-7d** in Dahl SS rats: vehicle (◆); eplerenone, 100 mpk/d, chow (●); **3*S*,3a*R*-27d**, 10 mpk/d, b.i.d. (△); **3*S*,3a*R*-27d**, 40 mpk/d, b.i.d. (▲); **3*S*,3a*R*-27d**, 100 mpk/d, b.i.d. (□). Radiotelemetrized arterial systolic blood pressure (SBP) was measured with the DATAQUEST A.R.T., version 3.0, Gold software. The values represent the average of all data points collected from each animal every 15 min for a 10 s interval over a 24 h period. SBP data were collected continuously over the course of the entire study (days 1−21). $n = 6$ for the **3*S*,3a*R*-27d** 100 mpk group, and $n = 9$ for all other groups: $P < 0.05$ versus vehicle (*); $P < 0.05$ versus eplerenone (**).

reduction of BP compared with the vehicle group and a statistically significantly better BP reduction relative to the eplerenone 100 mpk chow group.

Salt fed Dahl SS rats develop kidney injury and, as a result, increased urinary albumin excretion. Urinary albumin to creatinine ratio (UACR) is a validated clinical biomarker for kidney damage. Since the creatinine levels remain constant and is not affected by salt or compound treatment, 24 h urinary albumin excretion was used as a biomarker to evaluate the effect of **3*S*,3a*R*-27d** on kidney injury at the end of the same study described above. **3*S*,3a*R*-27d** dosed at 10 mpk produced a similar decrease (18−19%) of urinary albumin as compared with eplerenone (Figure 6a). **3*S*,3a*R*-27d** dosed at 40 and 100 mpk achieved 50−60% urinary albumin reduction, which is considered maximum in this model because they matched the levels from rats fed with low salt, as determined previously.

The protection on the kidney was further confirmed by assessing structure changes in the kidney after hematoxylin

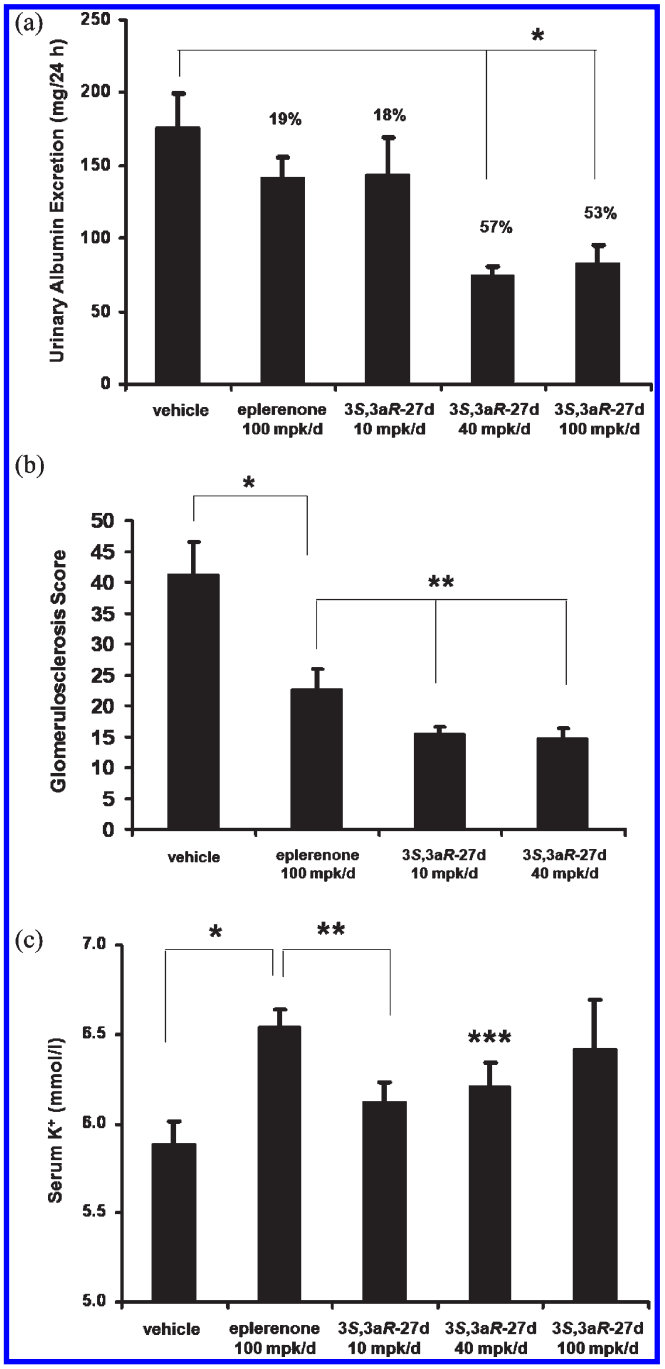


Figure 6. Renal protective effects of **3*S*,3a*R*-27d** in Dahl SS rats. (a) The 24 h urines were collected using metabolic cage. Urinary albumin was analyzed with the Hitachi 912 automated diagnostic clinical chemistry analyzer according to standard procedures: $P < 0.05$ versus vehicle (∗). (b) Glomerulosclerosis was evaluated by assessing 100 glomeruli and scoring severity of individual glomeruli from 0 to 4. The total glomerular score for each animal was calculated as follows: $1X$ (number of glomeruli with severity score 1) + $2X$ (number of glomeruli with severity score 2) + $3X$ (number of glomeruli with severity score 3) + $4X$ (number of glomeruli with severity score 4): $P < 0.05$ versus vehicle (∗); $P < 0.05$ versus eplerenone (∗∗). (c) Effect of **3*S*,3a*R*-27d** on serum potassium (K^+): $P < 0.05$ versus vehicle (∗); $P < 0.05$ versus eplerenone (∗∗); $P = 0.058$ versus eplerenone (∗∗∗).

and eosin, periodic acid Schiff, or trichrome staining. The severity of the glomerular damage was scored from 0 to 4, and 100 glomeruli were assessed for each animal. A total glomerulosclerosis score for each animal was calculated on the basis of severity and the number of glomeruli with each severity score. Eplerenone treatment resulted in a significantly lower mean glomerulosclerosis score compared with the vehicle group, indicative of renal protection by eplerenone (Figure 6b). A further decrease of glomerulosclerosis score was achieved in both 10 and 40 mpk **3*S*,3a*R*-27d** treatment groups, suggesting that **3*S*,3a*R*-27d** afforded significantly better protective effect on the kidney than eplerenone at the doses tested. In addition, **3*S*,3a*R*-27d** appeared to be more potent on glomerulosclerosis than on urinary albumin since 10 mpk **3*S*,3a*R*-27d** treatment reached maximal effect on glomerulosclerosis while 40 mpk was needed to get maximal effect on urinary albumin. Nonetheless, these data together demonstrate that **3*S*,3a*R*-27d** may be a useful renal protective agent.

Serum potassium levels were measured from blood samples taken at the end of the study. As expected, eplerenone treatment resulted in an increase of serum potassium relative to vehicle treatment (Figure 6c). **3*S*,3a*R*-27d** appeared to have a more attenuated effect on serum potassium than eplerenone. The 10 mpk **3*S*,3a*R*-27d** group had significantly lower serum potassium but similar BP reduction compared with the eplerenone group. Moreover, 40 mpk **3*S*,3a*R*-27d** treatment had maximal effect on BP and kidney damage but resulted in a lower, though not statistically significant ($P = 0.058$), serum potassium level relative to eplerenone. These results indicate that **3*S*,3a*R*-27d** may have reduced risk in inducing hyperkalemia in the target patient population.

Conclusion

We have discovered a novel class of nonsteroidal pyrazoline antagonists of MR with excellent potency and good selectivity in cellular transcription assays. Careful modification of the N1, C3, and C5 substituents resulted in leads ***R*-4g** and ***R*-12o**, identifying (1) the meta-substituted para-benzonitrile as the preferred N1 substituent and A-ring mimic, (2) the para-benzoic acid as the preferred C3 group because of its solubility and superior selectivity profile vs the hERG channel, and (3) the cyclopentyl group as the preferred C5 group. Introduction of conformational restriction of the C3 benzoic acid led to the discovery of pyrazoline **3*S*,3a*R*-27d**, a remarkably high affinity selective MR antagonist in vitro. **3*S*,3a*R*-27d** reduces blood pressure, decreases urinary albumin, and protects kidney in Dahl SS rat, a preclinical model of salt induced hypertension and nephropathy, and may have reduced the side effect on serum potassium levels. As a result of its in vitro potency and selectivity, in vivo efficacy, pharmacokinetic properties, and preclinical safety profile, pyrazoline **3*S*,3a*R*-27d** was selected as a clinical candidate for diabetic nephropathy and is currently in clinical studies.

Experimental Section

All materials were obtained from commercial sources and used as purchased. Chromatography solvents were HPLC grade and were used without further purification. Thin layer chromatography (TLC) analysis was performed using Merck silica gel 60 F-254 thin layer plates. LC−MS analyses were performed on Mariner TOF from Perseptive Biosystems. The scan range was m/z 100−1000. The sample was introduced by flow inject from an Agilent 1100 with 100 μL/min MeOH (10 mM ammonium acetate) into the electrospray source. Preparative reverse phase HPLC was performed on a Gilson 215 liquid handler equipped with a Dynamax Microsorb C18 (300 Å) column (41.4 mm × 25 cm,

8 μm) and Gilson 156 variable length UV detector (acetonitrile/water/0.05% TFA). Chiral resolution was performed by supercritical fluid chromatography (SFC) on a Berger SFC MultiGram II system equipped with a Chiralpak AS-H, Chiralpak AD-H, or Chiralcel OJ-H column (Chiral Technologies, 30 mm × 250 mm) and eluted with 20−50% alcohol/CO_2, 50−70 mL/min. Where noted, analytical chiral chromatography was performed on the equivalent Chiralpak AS-H, Chiralpak AD-H, or Chiralcel OJ-H column (Chiral Technologies, 4.6 mm × 100 mm, 3 mL/min). The purity of tested compounds was ≥95% as determined by combustion analysis or by HPLC conducted on an Agilent 1100 system using a reverse phase C8 column with diode array detector unless stated otherwise. NMR spectra were recorded on a Bruker or Varian 400 MHz spectrometer. The signal of the deuterated solvent was used as internal reference. Chemical shifts (δ) are given in ppm and are referenced to residual not fully deuterated solvent signal. Coupling constants (J) are given in Hz.

Preparation of Arylhydrazines: Method A. 2-Chloro-4-hydrazinylbenzonitrile Hydrochloride (9a). A mixture of 2-chloro-4-fluorobenzonitrile (20.0 g, 129 mmol), hydrazine monohydrate (9.4 mL, 193 mmol), and ethanol (80 mL) was refluxed for 4 h. The mixture was diluted with water (200 mL). The precipitate was filtered, washed with water, and dried to give an off-white solid (16.8 g). The solid was suspended in diethyl ether (400 mL) and treated with 2 N hydrogen chloride/diethyl ether (50 mL, 100 mmol). The precipitate was filtered, washed with diethyl ether, and dried to give the title compound as a white solid (16.3 g, 79.9 mmol, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.63 (br s, 3 H), 9.17 (br s, 1 H), 7.74 (d, J = 8.9 Hz, 1 H), 7.13 (d, J = 2.1 Hz, 1 H), 6.92 (dd, J = 8.6, 2.1 Hz, 1 H). ES-MS m/z 168 (M + H).

3-Chloro-4-hydrazinylbenzonitrile Hydrochloride (9b). The title compound was prepared according to method A from 3-chloro-4-fluorobenzonitrile (1.56 g, 10 mmol) at 80 °C to give a pale-pink solid (1.53 g, 7.54 mmol, 75% yield). ES-MS m/z 168 (M + H).

4-Hydrazinyl-2-methylbenzonitrile Hydrochloride (9c). A mixture of 4-fluoro-2-methylbenzonitrile (20.4 g, 151 mmol), hydrazine monohydrate (14.6 mL, 302 mmol), and ethanol (80 mL) was refluxed for 48 h. The mixture was diluted with water (200 mL). The precipitate was filtered, washed with water, and dried to give an off-white solid (16.1 g). The solid was suspended in diethyl ether (400 mL) and treated with 2 N hydrogen chloride/diethyl ether (55 mL, 110 mmol). The precipitate was filtered, washed with diethyl ether, and dried to give **9c** as a white solid (15.6 g, 85.0 mmol, 56% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.42 (br s, 1 H), 8.33 (br s, 3 H), 7.51 (d, J = 8.6 Hz, 1 H), 6.81 (d, J = 1.9 Hz, 1 H), 6.74 (dd, J = 8.6, 2.4 Hz, 1 H), 2.35 (s, 3 H). ES-MS m/z 148 (M + H).

4-Hydrazinyl-2-(trifluoromethyl)benzonitrile Hydrochloride (9d). The title compound was prepared according to method A from 4-fluoro-2-(trifluoromethyl)benzonitrile (1.89 g, 10 mmol) at 80 °C to give an off-white solid (1.89 g, 8.0 mmol, 80% yield). ES-MS m/z 202 (M + H).

4-Hydrazinylphthalonitrile Hydrochloride (9e). The title compound was prepared according to method A from 4-fluorophthalonitrile (1.0 g, 6.8 mmol) at 80 °C to give a pale-yellow solid (949 mg, 4.89 mmol, 72% yield). ES-MS m/z 159 (M + H).

4-Hydrazinyl-2-methoxybenzonitrile Hydrochloride (9f). The title compound was prepared according to method A from 4-fluoro-2-methoxybenzonitrile (4.97 g, 32.9 mmol) refluxing overnight to give the title compound (3.54 g, 17.8 mmol, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.82 (s, 3 H), 6.44 (dd, J = 8.46, 2.01 Hz, 1 H), 6.64 (d, J = 2.15 Hz, 1 H), 7.41 (d, J = 8.32 Hz, 1 H), 7.99 (s, 2 H), 8.40 (s, 1 H). ES-MS m/z 164 (M + H).

4-Hydrazinyl-2-(methoxymethyl)benzonitrile Hydrochloride (9g). A solution of 2-methyl-4-fluorobenzonitrile (3.5 g, 25.9 mmol) in 40 mL of carbon tetrachloride was treated with N-bromosuccinimide (4.6 g, 25.9 mmol) and benzoylperoxide (157 mg, 0.65 mmol). The mixture was heated to reflux for 3 h, cooled to room temperature, and allowed to stir overnight. The solids were filtered off and washed with carbon tetrachloride. The filtrate was condensed and purified by flash column chromatography (5−50% ethyl acetate/hexanes). The second eluting peak was concentrated in vacuo to yield 2-(bromomethyl)-4-fluorobenzonitrile (1.35 g, 0.63 mmol, 25% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.79 (s, 2 H), 7.44 (dt, J = 8.59, 2.69 Hz, 1 H), 7.68 (dd, J = 9.53, 2.55 Hz, 1 H), 8.01 (dd, J = 8.59, 5.64 Hz, 1 H).

A solution of 2-(bromomethyl)-4-fluorobenzonitrile (501 mg, 2.3 mmol) in methanol (5 mL) was treated with sodium methoxide (5.6 mL of 0.5 M solution in methanol, 2.81 mmol) and stirred for 1 h at room temperature and then heated to 55 °C for 2 h. The mixture was cooled to room temperature, condensed to dryness, and purified by flash chromatography (5−60% ethyl acetate/hexanes). Pure fractions were pooled and concentrated in vacuo to yield 4-fluoro-2-(methoxymethyl)benzonitrile (110 mg, 0.66 mmol, 28% yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.97 (dd, J = 8.46, 5.50 Hz, 1 H), 7.46 (dd, J = 9.53, 2.55 Hz, 1 H), 7.39 (td, J = 8.59, 2.69 Hz, 1 H), 4.58 (s, 2 H), 3.37 (s, 3 H).

A mixture of 4-fluoro-2-(methoxymethyl)benzonitrile (110 mg, 0.67 mmol), hydrazine monohydrate (133 mg, 0.13 mL, 2.6 mmol), and ethanol (5 mL) was heated to reflux overnight. The mixture was cooled to room temperature and condensed. The residue was dissolved in methanol and treated with 2.0 N hydrogen chloride in diethyl ether. The solvent was removed and the solid was dried to give **9g** as an off-white solid.

2-(Benzyloxy)-4-hydrazinylbenzonitrile (9h). Benzyl alcohol (3.25 g, 30 mmol) was slowly added to a stirred suspension of sodium hydride (1.15 g, 28.7 mmol) in toluene (50 mL) at room temperature. The mixture was stirred for 30 min. Then 2,4-difluorobenzonitrile was added all at once and stirring continued overnight. The mixture was quenched with water, extracted three times with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and condensed. The crude product was dissolved in hot ethyl acetate and triturated with hexanes to give 2-(benzyloxy)-4-fluorobenzonitrile (5.4 g, 23.8 mmol, 88% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.30 (s, 2 H), 6.99 (td, J = 8.46, 2.42 Hz, 1 H), 7.29−7.51 (m, 6 H), 7.86 (dd, J = 8.59, 6.44 Hz, 1 H).

A solution of 2-(benzyloxy)-4-fluorobenzonitrile (4.8 g, 21 mmol) in ethanol (80 mL) was treated with hydrazine monohydrate (2.6 g, 2.5 mL, 53 mmol) and heated to reflux for 3 days. The mixture was cooled to room temperature and concentrated. Water was added and the residue was extracted three times with ethyl acetate, dried over magnesium sulfate, filtered, and condensed to give **9h** (3.8 g, 15.8 mmol, 75% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.27 (s, 2 H), 5.16 (s, 2 H), 6.36 (dd, J = 8.73, 1.75 Hz, 1 H), 6.61 (d, J = 1.61 Hz, 1 H), 7.30 (d, J = 8.59 Hz, 1 H), 7.32−7.51 (m, 5 H), 7.78 (s, 1 H). ES-MS m/z 240 (M + H).

Preparation of α,β-Unsaturated Ketones: Method B1. The methyl ketone (2 mmol) was dissolved in EtOH (3 mL) and treated with the aldehyde (1.1 equiv) followed by 2.5 N NaOH (15−20 mL). The mixture was stirred at room temperature overnight and neutralized with 1 N HCl. A precipitate formed and was collected by filtration. The crude product was dried in a vacuum oven and used in the next step.

Preparation of α,β-Unsaturated Ketones: Method B2. The methyl ketone (1.0 mmol) was dissolved in N,N-dimethylformamide (1 mL) and treated with the aldehyde (1.0 mmol) followed by tetraethyl orthosilicate (0.5 mmol) and potassium fluoride (1.0 mmol). The solution was heated to 50 °C for 3 h, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. The slurry was filtered and concentrated. Addition of water to residue provided the crude product as a solid which was collected by vacuum filtration.

Preparation of α,β-Unsaturated Ketones: Method B3. A mixture of cyclic aryl ketone **24** (10 mmol) and aldehyde (20 mmol) in methanol (20 mL) was treated with pyrrolidine (1.0 mL, 12 mmol) at room temperature. After 1−6 h, the mixture was cooled to 0 °C, and the precipitate was filtered and washed with cold methanol to give the desired α,β-unsaturated ketone.

Preparation of α,β-Unsaturated Ketones: Method B4. A solution of aldehyde (1.2 equiv) and cyclic aryl ketone **24** (1.0 equiv) in concentrated hydrochloric acid (or 4 N hydrogen chloride in dioxane) and ethanol was refluxed overnight. The mixture was diluted with water, filtered, and dried to give the desired α,β-unsaturated ketone.

Preparation of α,β-Unsaturated Ketones: Method B5. A solution of cyclic aryl ketone **24** (1.9 mmol) in tetrahydrofuran (5 mL) was added dropwise under nitrogen to a 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (2 mL) cooled with an ice bath. After addition was complete the reaction mixture was stirred for 30 min and treated with a solution of aldehyde (2.0 mmol) in tetrahydrofuran (5 mL). The mixture was allowed to warm to room temperature under stirring. After 2 h, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layers were dried over sodium sulfate, concentrated, and the crude product was purified by silica gel flash chromatography (ethyl acetate/heptanes) or reverse-phase HPLC (acetonitrile/water/0.1% trifluoroacetic acid) to give the desired α,β-unsaturated ketone.

4-(3-(4-Fluorophenyl)acryloyl)benzoic Acid (6a). To suspension of 4-fluorobenzaldehyde (13.7 mL, 128 mmol) and 4-acetylbenzoic acid (20 g, 122 mmol) in EtOH (200 mL) was added 2.5 N NaOH (200 mL). The mixture was stirred at room temperature for 1.5 h. The mixture was diluted with acetonitrile (400 mL) and filtered. The resulting precipitate was suspended in water (300 mL) and 1 N HCl (200 mL), and the mixture was stirred for 20 min, filtered, and dried to give 4-(3-(4-fluorophenyl)acryloyl)benzoic acid (25.3 g, 93.6 mmol, 77%). ES-MS *m*/*z* 271 (M + H).

Ethyl 4-(3-(4-Fluorophenyl)acryloyl)benzoate (10a). To **6a** (15 g, 55.5 mmol) in ethanol (250 mL) was added sulfuric acid (5 mL), and the mixture was refluxed overnight. A precipitate formed upon cooling which was collected by vacuum filtration and washed with ethanol to give the title compound as a solid (12.7 g, 42.6 mmol, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 (t, *J* = 7.1 Hz, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 7.13 (t, *J* = 8.6 Hz, 2 H), 7.44 (d, *J* = 15.3 Hz, 1 H), 7.66 (dd, *J* = 8.6, 5.4 Hz, 2 H), 7.79 (d, *J* = 15.8 Hz, 1 H), 8.05 (d, *J* = 8.6 Hz, 2 H), 8.12−8.24 (m, 2 H). ES-MS *m*/*z* 299 (M + H).

Preparation of Pyrazolines: Method C1. The α,β-unsaturated ketone (1 mmol) was dissolved in EtOH (15 mL). The arylhydrazine hydrochloride (1 mmol) was added, and the mixture was heated at 80 °C until the reaction was complete (generally overnight). The solvent was evaporated under vacuum and crude solid was purified by reverse phase HPLC to give the pyrazoline.

Preparation of Pyrazolines Followed by Ester Hydrolysis: Method C2. A solution of the arylhydrazine hydrochloride **9** (1.5 mmol) and α,β-unsaturated ketone **10a** (1.0 mmol) in ethanol (8 mL/mmol) was stirred at 80 °C under nitrogen atmosphere for 2−24 h. The reaction was monitored by LC−MS. Upon completion of the condensation reaction, the mixture was cooled to room temperature, treated with THF (4 mL/mmol) and 2.5 N sodium hydroxide (2 mL/mmol), and stirred overnight. The mixture was concentrated to half the volume under a stream of nitrogen, diluted with water (10−15 mL/mmol), and neutralized with 3 N HCl (1.5 mL/mmol). The resulting precipitate was collected, washed with water, and dried to provide the pyrazoline product.

Preparation of Conformationally Restricted Pyrazolines: Method C3. A mixture of cyclic α,β-unsaturated ketone **25** (1 mmol), arylhydrazine hydrochloride **9** (1.2−1.5 mmol), and absolute ethanol (8 mL) was sparged with argon and stirred at 80 °C for 4−24 h. The reaction mixture was cooled to room temperature and filtered. The resulting solids were washed with ethanol to give the cis isomer of the pyrazoline ester as the major or only diastereomer.

Ester Hydrolysis: Method D. A solution of pyrazoline ester **11** or **26** (1 mmol) in tetrahydrofuran (6 mL) and methanol (2 mL) was treated with 2.5 N sodium hydroxide (2 mL). The mixture was stirred at room temperature until the reaction was complete as determined by reverse-phase HPLC (1−24 h). The resulting mixture was concentrated to approximately half the original volume under a stream of nitrogen and acidified to a pH < 4 with aqueous hydrochloric acid. The mixture was diluted with water and filtered to give the pyrazoline carboxylic acid.

(±)-4-[5-(4-Fluorophenyl)-1-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenol (4a). 1-(4-Hydroxyphenyl)ethanone and 4-fluorobenzaldehyde were reacted according to method B1 to give the chalcone which was reacted with 4-nitrophenylhydrazine according to method C1 to give **4a** (89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.17 (dd, *J* = 17.78, 4.49 Hz, 1 H), 3.93 (dd, *J* = 17.98, 11.72 Hz, 1 H), 5.69 (dd, *J* = 11.72, 4.30 Hz, 1 H), 6.73−6.92 (m, 2 H), 7.01 (d, *J* = 8.99 Hz, 2 H), 7.11−7.21 (m, 2 H), 7.21−7.40 (m, 2 H), 7.64 (d, *J* = 8.99 Hz, 2 H), 8.02 (d, *J* = 9.38 Hz, 2 H). HRMS ($C_{21}H_{16}FN_3O_3$) calcd 378.1248, obsd 378.1254.

(±)-4-[5-(4-Fluorophenyl)-3-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]benzonitrile (4b). 6-Acetylbenzo[*d*]oxazol-2(3*H*)-one (0.164 g, 1.0 mmol) and 4-fluorobenzaldehyde were reacted according to method B1 to give chalcone **6b** (0.630 g, 89%) as a pale-yellow solid: mp 300 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.96−7.89 (m, 4H), 7.81 (br s, 1H), 7.67 (d, *J* = 15.6 Hz, 1H), 7.26 (t, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 1H);. ES-MS *m*/*z* 284 (M + H). The chalcone (0.58 mmol) was reacted with 4-cyanophenylhydrazine hydrochloride according to method C1 to give **4b** (0.228 g, 81%) as a light-yellow solid: mp 179−180 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.73 (d, *J* = 1.4 Hz, 1H), 7.58 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.31−7.27 (m, 2H), 7.17 (app t, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 5.68 (dd, *J* = 12.0, 5.0 Hz, 1H), 3.96 (dd, *J* = 17.3, 12.0 Hz, 1H), 3.17 (dd, *J* = 17.3, 5.0 Hz, 1H). ES-MS *m*/*z* 399 (M + H). Anal. ($C_{23}H_{15}FN_4O_2 \cdot 0.35H_2O$) C, H, N.

4-[(5*R*)-5-(4-Fluorophenyl)-3-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]benzonitrile (*R*-4b) and 4-[(5*S*)-5-(4-Fluorophenyl)-3-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]benzonitrile (*S*-4b). The compounds were obtained by chiral separation of (±)-**4b** on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50% MeOH/CO_2, 70 mL/min flow rate. ***R*-4b**: ES-MS *m*/*z* 399 (M + H), earlier eluting peak, t_R = 5.5 min, >99.5% ee by chiral HPLC. ***S*-4b**: ES-MS *m*/*z* 399 (M + H), later eluting peak, t_R = 7.25 min, >99.5% ee by chiral HPLC.

4-[(5*R*)-3-(2,4-Dimethyl-1,3-thiazol-5-yl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]benzonitrile (*R*-4c). 1-(2,4-Dimethylthiazol-5-yl)ethanone (1.0 mmmol) and 4-fluorobenzaldehyde (1.0 mmmol) were reacted according to method B1 to give the chalcone. The chalcone (1 mmol) was reacted with 4-cyanophenylhydrazine hydrochloride (1.0 mmol) according to method C1 to give crude pyrazoline which was purified by silica gel chromatography (5−50% EtOAc/hexane) to yield (±)-**4c** (53%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H), 2.62 (s, 3 H), 3.17 (dd, *J* = 17.6, 4.9 Hz, 1 H), 4.07 (dd, *J* = 17.6, 12.1 Hz, 1 H), 5.66 (dd, *J* = 11.9, 5.1 Hz, 1 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 7.14−7.24 (m, 2 H), 7.30 (dd, *J* = 8.2, 5.5 Hz, 2 H), 7.57 (d, *J* = 7.9 Hz, 2 H). ES-MS *m*/*z* 377 (M + H). Chiral separation of (±)-**4c** on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50%MeOH/CO_2, 70 mL/min flow afforded ***R*-4c**: later eluting peak, t_R = 8.81 min, >95% ee by chiral HPLC. ES-MS *m*/*z* 377 (M + H).

(±)-4-[1-(4-Cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide Trifluoroacetate (4d). To a solution of acid (±)-**4 g** (1 mmol) in 5 mL of anhydrous DMF under nitrogen at room temperature

was added HBTU (1.1 mmol), followed by *N*,*N*-diisopropylethylamine (1.5 mmol). After the mixture was stirred for 5 min, triethyl-1,2-diamine (1.5 mmol) was added and stirring was continued for another hour. The mixture was then filtered and purified by reverse phase HPLC, eluting with a gradient of acetonitrile in water containing 1% TFA. The fractions containing pure product were combined and lyophilized to give the desired product **4d** (110 mg, 23%). ES-MS *m*/*z* 470 (M + H).

(±)-4-[1-(4-Cyanophenyl)-3-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]benzoic Acid (4e). 6-Acetylbenzo[*d*]oxazol-2(3*H*)-one (0.164 g, 1.0 mmol) and methyl 4-formylbenzoate were reacted according to method B1 to give the chalcone (30%). The chalcone was reacted with 4-cyanophenylhydrazine hydrochloride according method C1 to give **4e** (40 mg, 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.22 (dd, J = 17.99, 5.10 Hz, 1 H), 3.97 (dd, J = 17.72, 12.35 Hz, 1 H), 5.71 (dd, J = 12.08, 5.10 Hz, 1 H), 7.03 (d, J = 8.86 Hz, 2 H), 7.11 (d, J = 8.06 Hz, 1 H), 7.33−7.37 (m, 2 H), 7.51−7.58 (m, 3 H), 7.70 (d, J = 1.34 Hz, 1 H), 7.87−7.92 (m, 2 H), 11.84 (s, 1 H), 12.92 (s, 1 H). HRMS M + H calcd for $C_{24}H_{16}N_4O_4$, 425.1244, obsd 425.1289. Anal. ($C_{24}H_{16}N_4O_4$) Calcd: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.45; H, 3.45; N, 12.87.

(±)-4-[5-(4-Fluorophenyl)-3-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]benzoic Acid (4f). A stirred suspension of chalcone **6b** (0.68 mmol) and 4-hydrazinylbenzoic acid hydrochloride (0.715 mmol) in 3% hydrochloric acid/1-butanol (6.0 mL) was heated at reflux overnight. After this time the precipitate was collected by filtration and triturated with ethanol. The solid was purified by flash column chromatography to provide ethyl 4-[5-(4-fluorophenyl)-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydropyrazol-1-yl]benzoate hydrate (0.231 g, 58%) as a light-yellow solid: mp 237−239 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.86 (s, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 1.4 Hz, 1H), 7.58 (dd, J = 8.1, 1.5 Hz, 1H), 7.31−7.28 (m, 2H), 7.19−7.13 (m, 3H), 7.04 (d, J = 8.9 Hz, 2H), 5.67 (dd, J = 12.0, 5.0 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.95 (dd, J = 17.8, 12.0 Hz, 1H), 3.20 (dd, J = 17.8, 5.0 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H). ES-MS *m*/*z* 446 (M + H). Anal. ($C_{25}H_{20}FN_3O_4 \cdot 0.25H_2O$) C, H, N.

To a stirred suspension of ethyl 4-[5-(4-fluorophenyl)-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydropyrazol-1-yl]benzoate (0.164 g, 0.368 mmol) in methanol/THF (1:1, 8.0 mL) was added potassium hydroxide (5.5 mL of 1.0 M solution in water, 5.50 mmol). After the mixture was stirred for 4 d, 2 M hydrochloric acid was added to adjust the reaction mixture to pH 6 and the precipitate was collected by filtration. The solid was purified by flash column chromatography (95:5 methylene chloride/methanol) to provide **4f** (0.10 g, 65%) as a yellow solid: mp 179−181 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.08 (br s, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 1.4 Hz, 1H), 7.57 (dd, J = 8.1, 1.6 Hz, 1H), 7.31−7.39 (m, 2H), 7.20−7.13 (m, 3H), 7.03 (d, J = 8.9 Hz, 2H), 5.65 (dd, J = 12.0, 5.0 Hz, 1H), 3.95 (dd, J = 17.6, 12.0 Hz, 1H), 3.19 (dd, J = 17.6, 5.0 Hz, 1H). ES-MS *m*/*z* 416 (M − H). Anal. ($C_{23}H_{16}FN_3O_4$) C, H, N.

(±)-4-[1-(4-Cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (4g). 4-Acetylbenzoic acid (5 mmol) and 4-fluorobenzaldehyde were reacted according to method B1 to give **6a**. Chalcone **6a** was reacted with 4-cyanophenylhydrazine hydrochloride according to method C1 to give **4g** (72%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.22 (dd, J = 17.99, 5.10 Hz, 1 H), 3.98 (td, J = 12.35, 5.10 Hz, 1H), 5.71 (dd, J = 12.08, 4.30 Hz, 1 H), 7.08 (d, J = 8.86 Hz, 2 H), 7.15 (tt, J = 8.86, 1.88 Hz, 2 H), 7.28 (td, J = 5.37, 2.15 Hz, 2 H), 7.57 (d, J = 8.86 Hz, 2 H), 7.87 (dd, J = 8.59, 1.88 Hz, 2 H), 7.97 (dd, J = 8.59, 1.88 Hz, 2 H), 13.05 (s, 1 H). ES-MS *m*/*z* 386 (M + H). Anal. ($C_{23}H_{16}FN_3O_2$) C, H, N.

2-(2(4-Cyanophenyl)hydrazone)acetic Acid (16). 4-Cyanophenylhydrazine hydrochloride (3.40 g, 20 mmol) was suspended in aqueous hydrochloric acid (20%, 20 mL), and a solution of glyoxylic acid in water (4 mL) was added. Reaction was stirred at room temperature overnight. The solid was filtered off, washed with water, and dried. Recrystallization from acetonitrile gave pure hydrazone (2.805 g, 74%).

(*R*)-4-(3-Bromo-5-(4-fluorophenyll)-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile (*R*-17). Hydrazone **16** (0.935 g, 5 mmol) was dissolved in DMF (12 mL), and a solution of NBS (1.77 g, 10 mmol) in DMF (12 mL) was added dropwise at 0 °C under nitrogen (*Caution*: exothermic reaction). After addition was complete, the reaction mixture was stirred at room temperature for 1 h. 4-Fluorostyrene (2.5 mL, 20 mmol) was added and then dropwise TEA (0.700 mL, 5 mmol). The mixture was left stirring overnight, then poured into cold water (100 mL) and extracted three times with ether. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under vacuum to give the crude product. Purification by flash chromatography (15% EtOAc/hexane) gave (±)-**17** (690 mg, 20% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 (dd, J = 18.26, 5.91 Hz, 1 H), 3.96 (dd, J = 18.13, 11.95 Hz, 1 H), 5.57 (dd, J = 12.09, 6.18 Hz, 1 H), 6.90 (m, 2 H), 7.20 (m, 2 H), 7.30 (m, 2 H), 7.55 (m, 2 H). ES-MS *m*/*z* 345 (M + H). (±)-**17** was resolved by chiral chromatography on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50% methanol/CO_2, 70 mL/min, to give ***R*-17**: ES-MS *m*/*z* 409 (M + H), later eluting peak, t_R = 8.26 min, >99% ee by chiral HPLC. ***S*-17**: ES-MS *m*/*z* 409 (M + H), earlier eluting peak, t_R = 7.23 min, >99% ee by chiral HPLC.

4-[(5*R*)-1-(4-Cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic acid (*R*-4g). Bromopyrazoline ***R*-17** (0.23 mmol) and 4-carboxyphenylboronic acid (0.25 mmol) were loaded in a vial, and the vial was purged with nitrogen for 15 min. Palladium(0) tetrakis(triphenylphosphine (~10 mg) was added under nitrogen. DMF (3 mL) was added followed by Cs_2CO_3 (2 M aqueous solution, purged, 0.50 mmol). The mixture was heated at 85 °C for 6 h. The solid was filtered off and the remaining filtrate was loaded onto reverse phase HPLC for purification to give ***R*-4g** (116 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.25 (dd, J = 17.8, 5.1 Hz, 1 H), 4.01 (dd, J = 17.9, 12.1 Hz, 1 H), 5.75 (dd, J = 12.1, 4.9 Hz, 1 H), 7.11 (d, J = 8.5 Hz, 2 H), 7.15−7.22 (m, 2 H), 7.31 (dd, J = 8.2, 5.5 Hz, 2 H), 7.60 (d, J = 8.2 Hz, 2 H), 7.87−7.93 (m, 2 H), 7.99 (d, J = 8.2 Hz, 2 H), 13.11 (br s, 1 H). ES-MS *m*/*z* 386 (M + H) . Anal. ($C_{23}H_{16}FN_3O_2 \cdot 0.25H_2O$) C, H, N.

4-[(5*S*)-1-(4-Cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (*S*-4g). Bromopyrazoline ***S*-17** (0.23 mmol) and 4-carboxyphenylboronic acid (0.25 mmol) were reacted as described for ***R*-4g** to give ***S*-4g**. ES-MS *m*/*z* 386 (M + H).

(±)-4-[5-(4-Fluorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (4h). A solution of **6a** (200 mg, 0.74 mmol) and phenylhydrazine (2.22 mmol) in ethanol (6 mL and sulfuric acid (60 μL) was degassed and purged with argon. The mixture was heated to reflux for 1 h and then cooled to room temperature. Diethyl ether was added and the insoluble material filtered off. The filtrate was then concentrated and purified by flash chromatography (0−25% methanol/dichloromethane). The desired fractions were pooled and concentrated to give a yellow solid (90 mg, 0.25 mmol, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.14 (dd, J = 17.45, 6.18 Hz, 1 H), 3.92 (dd, J = 17.45, 12.35 Hz, 1 H), 5.59 (dd, J = 12.49, 6.04 Hz, 1 H), 6.75 (t, J = 7.38 Hz, 1 H), 7.03 (d, J = 7.52 Hz, 2 H), 7.16 (m, 4 H), 7.32 (dd, J = 8.73, 5.50 Hz, 2 H), 7.83 (d, J = 8.59 Hz, 2 H), 7.96 (d, J = 8.86 Hz, 2 H), 12.99 (s, 1 H). ES-MS *m*/*z* 361.2 (M + H). HRMS calcd for $C_{22}H_{17}FN_2O_2$: 361.1347, found 361.1375. Anal. ($C_{22}H_{17}FN_2O_2$) Calcd: C, 73.32; H, 4.76; N, 7.77. Found: C, 73.18; H, 4.31; N, 7.74.

(±)-4-{1-[4-(Ethoxycarbonyl)phenyl]-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}benzoic Acid (4i). 4-Benzoic acid hydrazine (1 mmol) was dissolved in EtOH (5 mL), and molecular sieves were added followed by a catalytic amount of concentrated HCl. The reaction mixture was refluxed overnight, filtered, and concentrated to give crude ethyl 4-hydrazinylbenzoate. Chalcone **6a** (1 mmol) was reacted with ethyl 4-hydrazinylbenzoate according to method C1 using glacial acetic acid in place of HCl to

give crude product purified by HPLC to yield **4i** (46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.06 (br s, 1 H), 7.99 (d, J = 8.20 Hz, 2 H), 7.89 (d, J = 8.20 Hz, 2 H), 7.77 (d, J = 8.98 Hz, 2 H), 7.28−7.34 (m, 2 H), 7.14−7.21 (m, 2 H), 7.09 (d, J = 8.98 Hz, 2 H), 5.74 (dd, J = 12.11, 5.08 Hz, 15 H), 4.19−4.22 (q, J = 7.03 Hz, 2 H), 4.00 (dd, J = 17.58, 12.11 Hz, 1 H), 3.23 (dd, J = 17.77, 4.88 Hz, 1 H), 1.26 (t, J = 7.03 Hz, 3 H). ES-MS m/z 433 (M + H).

(±)-4,4′-[5-(4-Fluorophenyl)-4,5-dihydro-1*H*-pyrazole-1,3-diyl]-dibenzoic Acid (4j). Chalcone **6a** (1 mmol) was reacted with ethyl 4-hydrazinylbenzoate according to method C1. The crude pyrazoline in THF (4 mL) was treated with aqueous NaOH (3 mL) and stirred overnight at room temperature. The mixture was concentrated and then treated with 8 mL of 1 N HCl. The resulting precipitate was filtered and purified by reverse phase HPLC to give **4j** (220 mg, 0.54 mmol, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.22 (dd, J = 17.7, 5.1 Hz, 1 H), 3.99 (dd, J = 17.9, 12.2 Hz, 1 H), 5.73 (dd, J = 12.2, 5.0 Hz, 1 H), 7.08 (d, J = 8.9 Hz, 2 H), 7.14−7.21 (m, 2 H), 7.27−7.35 (m, 2 H), 7.76 (d, J = 8.9 Hz, 2 H), 7.89 (d, J = 8.6 Hz, 2 H), 7.96−8.02 (m, 2 H), 12.70 (br s, 2 H). Anal. ($C_{23}H_{17}FN_2O_4 \cdot 0.25H_2O$) C, H, N.

(±)-4-[5-(4-Fluorophenyl)-1-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (4k). To the chalcone **6a** (300 mg 1.0 mmol) in ethanol (6 mL) was added 4-methoxyphenylhydrazine (1.5 mmol) followed by 2 drops of concentrated HCl. The mixture was heated to 80 °C overnight and then was cooled to room temperature and concentrated to dryness. The residue was purified flash chromatography (0−10% methanol/methylene chloride). The desired fractions were combined and concentrated to give a yellow/orange solid (115 mg, 0.29 mmol, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.10 (dd, J = 17.32, 7.12 Hz, 1 H), 3.64 (s, 3 H), 3.88 (dd, J = 17.32, 12.49 Hz, 1 H), 5.50 (dd, J = 12.35, 6.98 Hz, 1 H), 6.78 (d, J = 9.13 Hz, 2 H), 6.96 (d, J = 9.13 Hz, 2 H), 7.15 (t, J = 8.86 Hz, 2 H), 7.32 (dd, J = 8.73, 5.50 Hz, 2 H), 7.79 (d, J = 8.32 Hz, 2 H), 7.95 (d, J = 8.59 Hz, 2 H), 12.96 (s, 1 H). ES-MS m/z 391 (M + H). Anal. ($C_{23}H_{19}FN_2O_3$) C, H, N.

(±)-4-[1-(4-Cyano-3-fluorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12a). Chalcone **6a** was reacted with 4-cyano-3-fluorophenylhydrazine hydrochloride according to method C1 to give **12a** as a solid (113 mg, 0.28 mmol, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.24−3.31 (m, 1 H), 3.97−4.09 (m, 1 H), 5.77 (dd, J = 12.1, 4.7 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 1 H), 7.04 (d, J = 12.5 Hz, 1 H), 7.18 (t, J = 8.8 Hz, 2 H), 7.28−7.34 (m, 2 H), 7.62 (dd, J = 8.6, 7.8 Hz, 1 H), 7.90−8.01 (m, 4 H), 13.10 (br s, 1 H). ES-MS m/z 404 (M + H). Anal. ($C_{23}H_{15}F_2N_3O_2$) Calcd: C, 68.48; H, 3.75; N, 10.42. Found: C, 68.12; H, 3.37; N, 9.92.

(±)-4-[1-(4-Cyano-2-fluorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12b). Chalcone **6a** was reacted with 4-cyano-2-fluorophenylhydrazine hydrochloride according to method C1 to give **12b** as a solid (69.1 mg, 0.171 mmol, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.32 (dd, J = 17.8, 4.1 Hz, 1 H), 3.97 (dd, J = 17.6, 11.7 Hz, 1 H), 5.89 (dt, J = 11.6, 3.8 Hz, 1 H), 7.10 (t, J = 9.0 Hz, 2 H), 7.16−7.23 (m, 2 H), 7.54 (dd, J = 8.6, 1.6 Hz, 1 H), 7.62 (dd, J = 13.3, 2.0 Hz, 1 H), 7.72 (t, J = 8.6 Hz, 1 H), 7.91 (d, J = 8.6 Hz, 2 H), 7.99 (d, J = 8.6 Hz, 2 H), 13.06 (br s, 1 H). Anal. ($C_{23}H_{15}F_2N_3O_2$) C, H, N.

(±)-4-[1-(3-Chloro-4-cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12c). The title compound was prepared according to method C2. The crude product was recrystallized from DMF/methanol as yellow needles (302 mg, 0.72 mmol, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.24−3.31 (m, 1 H), 4.02 (dd, J = 17.9, 11.9 Hz, 1 H), 5.79 (dd, J = 12.1, 3.8 Hz, 1 H), 6.94 (d, J = 8.6 Hz, 1 H), 7.18 (t, J = 7.9 Hz, 2 H), 7.27−7.35 (m, 3 H), 7.67 (dd, J = 8.6, 1.6 Hz, 1 H), 7.90−8.02 (m, 4 H), 13.10 (s, 1 H). ES-MS m/z 420 (M + H).

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]benzoic Acid (*R*-12c). Chiral separation of (±)-**12c** on a Chiralpak AD-H column (30 mm × 250 mm) eluted with 50% MeOH/CO_2, 50 mL/min flow, afforded ***R*-12c**: first eluting peak, t_R = 3.52 min, >95% ee by chiral HPLC. ES-MS m/z 420 (M + H).

(±)-4-[1-(2-Chloro-4-cyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12d). The title compound was prepared according to method C2. The crude product was dissolved in DMF/methanol and purified by reverse-phase HPLC (40−95% acetonitrile/water/0.05% TFA) to give the title compound as a pale-yellow solid (204 mg, 0.487 mmol, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.39 (dd, J = 17.7, 4.8 Hz, 1 H), 3.98 (dd, J = 17.6, 11.7 Hz, 1 H), 6.14 (dd, J = 11.4, 4.7 Hz, 1 H), 7.06 (t, J = 9.0 Hz, 2 H), 7.21 (dd, J = 8.9, 5.4 Hz, 2 H), 7.64 (d, J = 1.1 Hz, 2 H), 7.83 (t, J = 1.1 Hz, 1 H), 7.91 (d, J = 8.6 Hz, 2 H), 8.00 (d, J = 8.6 Hz, 2 H), 13.05 (br s, 1 H). Anal. ($C_{23}H_{15}ClFN_3O_2$) C, H, N.

(±)-4-[1-(4-Cyano-3-methylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12e). The title compound was prepared according to method C2 as an orange solid (407 mg, 1.02 mmol, quant). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H), 3.23 (dd, J = 18.0, 5.1 Hz, 1 H), 3.99 (dd, J = 17.8, 12.3 Hz, 1 H), 5.73 (dd, J = 12.3, 5.3 Hz, 1 H), 6.81 (dd, J = 8.6, 2.0 Hz, 1 H), 7.13−7.20 (m, 3 H), 7.29 (dd, J = 8.6, 5.5 Hz, 2 H), 7.50 (d, J = 9.0 Hz, 1 H), 7.89 (d, J = 8.6 Hz, 2 H), 7.98 (d, J = 8.2 Hz, 2 H), 13.07 (s, 1 H). Anal. ($C_{24}H_{18}FN_3O_2 \cdot 0.1H_2O$) C, H, N.

(±)-4-{1-[4-Cyano-3-(trifluoromethyl)phenyl]-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}benzoic Acid (12f). The title compound was prepared according to method C2. The crude product was recrystallized from DMF/methanol as yellow needles (411 mg, 0.907 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.33 (dd, J = 18.0, 4.8 Hz, 1 H), 4.06 (dd, J = 18.0, 12.1 Hz, 1 H), 5.85 (dd, J = 11.9, 5.0 Hz, 1 H), 7.15−7.22 (m, 3 H), 7.31−7.36 (m, 2 H), 7.53 (br s, 1 H), 7.85 (d, J = 8.6 Hz, 1 H), 7.92−8.02 (m, 4 H), 13.05 (br s, 1 H). ES-MS m/z 454 (M + H).

(±)-4-[1-(3,4-Dicyanophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12g). The title compound was prepared according to method C2 using AcOH in place of ethanol. The crude ester was filtered, dried, and hydrolyzed with sodium hydroxide as described in method C2. The crude product was recrystallized from DMF/methanol as an orange solid (89.1 mg, 0.217 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.26−3.37 (m, 1 H), 4.05 (dd, J = 18.0, 12.1 Hz, 1 H), 5.81 (dd, J = 12.1, 4.7 Hz, 1 H), 7.13−7.25 (m, 3 H), 7.26−7.35 (m, 2 H), 7.70 (br s, 1 H), 7.82 (d, J = 8.6 Hz, 1 H), 7.90−8.03 (m, 4 H), 13.04 (br s, 1 H). ES-MS m/z 411 (M + H).

(±)-4-[1-(3-Chloro-4-cyanophenyl)-5-isopropyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12h). 12h was prepared as example **12i** using isobutyraldehyde and 3-chloro-4-cyanophenylhydrazine hydrochloride to give the product as a yellow solid (60 mg, 0.19 mmol, 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.55 (d, J = 6.71 Hz, 3 H), 0.94 (d, J = 6.71 Hz, 3 H), 2.22−2.33 (m, 1 H), 3.25−3.40 (m, 2 H), 4.70 (td, 1 H), 7.17 (dd, J = 8.86, 2.15 Hz, 1 H), 7.39 (d, J = 2.15 Hz, 1 H), 7.71 (d, J = 8.59 Hz, 1 H), 7.90 (d, 2 H), 7.97 (d, 2 H). ES-MS m/z 368 (M + H). HRMS ($C_{20}H_{18}N_3O_2$) calcd, 368.1160; found, 368.1189.

(±)-4-[1-(4-Cyanophenyl)-5-pyridin-4-yl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12i). Methyl 4-acetylbenzoate and 4-pyridine carboxaldehyde were reacted according to method B2 to give the chalcone (220 mg, 82%). The chalcone (220 mg, 0.82 mmol) was suspended in ethanol (5 mL), and 4-cyanophenylhydrazine HCl was added followed by one pellet of NaOH. The solution was heated to 80 °C for 3 h. The solution was concentrated to half volume, and the residue was acidified to pH 4 with 1 N HCl and concentrated. The crude material was purified by reverse-phase HPLC (acetonitrile/water/TFA) to provide the title compound as a solid (140 mg, 0.29 mmol, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.30 (dd, J = 17.86, 4.97 Hz, 1 H), 4.05 (dd, J = 17.86, 12.49 Hz, 1 H), 5.82 (dd, J = 12.76, 5.50 Hz, 1 H), 7.08 (d, J = 9.13 Hz, 2 H), 7.40 (d, J = 5.91 Hz, 2 H), 7.60 (d, J = 9.13 Hz, 2 H), 7.87 (d, J = 8.59 Hz, 2 H), 7.97 (d, J = 8.59 Hz, 2 H), 8.60 (d, J = 6.18 Hz, 2 H). ES-MS m/z 369

(M + H). HRMS ($C_{22}H_{16}N_4O_2$) calcd, 396.1346; found, 369.1302. Anal. ($C_{22}H_{16}FN_4O_2 \cdot C_2HF_3O_2$) C, H, N.

(±)-4-[1-(4-Cyanophenyl)-5-pyridin-3-yl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12j). 12j was prepared as example **12i** using 3-pyridinecarboxaldehyde to give the product as a solid (320 mg, 0.79 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.34 (d, J = 5.10 Hz, 1 H), 4.02 (dd, J = 17.86, 12.22 Hz, 1 H), 5.80 (dd, J = 12.22, 4.70 Hz, 1 H), 7.11 (d, J = 8.86 Hz, 2 H), 7.33 (dd, J = 8.32, 5.10 Hz, 1 H), 7.54−7.56 (m, 1 H), 7.58 (d, J = 9.13 Hz, 2 H), 7.88 (d, 2 H), 7.97 (d, J = 8.59 Hz, 2 H), 8.47 (dd, J = 4.70, 1.48 Hz, 1 H), 8.55 (d, J = 2.42 Hz, 1 H), 13.06 (br s, 1 H). ES-MS m/z 369 (M + H). HRMS (M + H) calcd for $C_{22}H_{16}N_4O_2$, 396.1346; found, 369.1342.

(±)-4-[1-(4-Cyanophenyl)-5-pyridin-2-yl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12k). 12k was prepared as example **12i** using 2-pyridinecarboxaldehyde to give **12k** as a solid (83 mg, 0.21 mmol, 45%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.36 (dd, J = 17.86, 5.24 Hz, 1 H), 4.01 (dd, J = 17.99, 12.35 Hz, 1 H), 5.73 (dd, J = 12.49, 5.50 Hz, 1 H), 7.09 (d, J = 8.86 Hz, 2 H), 7.31 (ddd, J = 7.52, 4.83, 1.07 Hz, 1 H), 7.37 (d, J = 7.79 Hz, 1 H), 7.56 (d, J = 9.13 Hz, 2 H), 7.79 (td, J = 7.65, 1.88 Hz, 1 H), 7.88 (d, J = 8.86 Hz, 2 H), 7.97 (d, J = 8.86 Hz, 2 H), 8.53 (ddd, J = 4.83, 1.75, 0.94 Hz, 1 H). ES-MS m/z 369 (M + H). HRMS (M + H) calcd for $C_{22}H_{16}N_4O_2$, 396.1346; found, 369.1334.

(±)-4-[1-(4-Cyanophenyl)-5-(2-furyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12l). 4-Acetylbenzoic acid and 2-furylaldehyde were reacted according to method B1. The chalcone was reacted with 4-cyanophenylhydrazine according to method C1 to give **12l** (4% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.45 (dd, J = 17.59, 4.97 Hz, 1 H), 3.85 (t, J = 12.35 Hz, 1 H), 5.83 (dd, J = 12.22, 4.70 Hz, 1 H), 6.37 (dd, J = 3.22, 1.88 Hz, 1 H), 6.51 (dd, J = 3.22, 0.81 Hz, 1 H), 7.24 (ddd, J = 9.13, 2.42, 2.15 Hz, 2 H), 7.54 (dd, J = 1.88, 0.81 Hz, 1 H), 7.60 (ddd, J = 9.33, 2.28, 2.08 Hz, 2 H), 7.87−7.92 (m, 2 H), 7.96−8.00 (m, 2 H), 13.03 (s, 1 H). HRMS ($C_{21}H_{15}N_3O_3$) calcd, 358.1186; found, 358.1155. Anal. ($C_{21}H_{15}N_3O_3 \cdot 0.5H_2O$) Calcd: C, 68.84; H, 4.41; N, 11.47. Found C, 68.51; H, 3.92; N, 11.37.

(±)-4-[1-(4-Cyanophenyl)-5-(2-thienyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (12m). 4-Acetylbenzoic acid and 2-thiophenecarbaldehyde were reacted according to method B1 to give the chalcone. The chalcone was reacted with 4-cyanophenylhydrazine according to method C1 to give **12m** (30%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.36 (dd, J = 17.72, 4.57 Hz, 1 H), 3.96 (dd, J = 17.72, 11.82 Hz, 1 H), 6.07 (dd, J = 11.68, 4.43 Hz, 1 H), 6.93 (dd, J = 4.83, 3.49 Hz, 1 H), 7.14 (dd, J = 3.49, 1.34 Hz, 1 H), 7.20 (ddd, J = 9.13, 2.42, 2.15 Hz, 2 H), 7.38 (dd, J = 4.97, 1.21 Hz, 1 H), 7.59 (ddd, J = 8.86, 2.42, 1.61 Hz, 2 H), 7.89 (m, J = 8.59, 1.61, 1.61 Hz, 2 H), 7.96−8.00 (m, 2 H), 13.02 (s, 1 H). ES-MS m/z 374 (M + H).

2-Chloro-4-[(5*R*)-1-(3-chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (*R*-12n). 4-Acetyl-2-chlorobenzoic acid and cyclopentylaldehyde were reacted according to method B1. The chalcone was reacted with **9a** according to method C1 to give **(±)-12n** (94 mg). Chiral separation of **(±)-12n** on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50%MeOH/CO_2, 70 mL/min flow, yielded ***R*-12n** as the earlier eluting peak. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.45 (1 H, s), 7.89 (1 H, s), 7.79−7.86 (2 H, m), 7.70 (1 H, d, J = 8.9 Hz), 7.20 (1 H, dd, J = 8.9, 2.1 Hz), 4.90 (1 H, td, J = 7.6, 3.9 Hz), 3.36−3.51 (1 H, m), 3.23 (1 H, m), 2.43 (1 H, m), 1.66−1.81 (1 H, m), 1.18−1.64 (6 H, m), 0.92−1.06 (1 H, m). ES-MS m/z 428 (M + H). Anal. ($C_{22}H_{19}Cl_2N_3O_2$) C, H, N. >99.5% ee by chiral HPLC.

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]-2-methoxybenzoic Acid (*R*-12o). 4-Acetyl-2-methoxybenzoic acid and cyclopentylaldehyde were reacted according to method B1. The chalcone was reacted with **9a** according to method C1 to give **(±)-12o** (92%). Chiral separation of **(±)-12o** on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50%MeOH/CO_2, 70 mL/min flow, yielded ***R*-12o** as the later eluting peak, t_R = 3.67 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.97−1.08 (m, 1 H), 1.22−1.44 (m, 3 H), 1.47−1.65 (m, 3 H), 1.73−1.82 (m, 1 H), 2.42−2.48 (m, 1 H), 3.27 (dd, J = 17.86, 3.63 Hz, 1 H), 3.48 (dd, J = 18.26, 11.55 Hz, 1 H), 3.92 (s, 3 H), 4.91 (ddd, J = 11.41, 3.89, 3.76 Hz, 1 H), 7.22 (dd, J = 8.86, 2.15 Hz, 1 H), 7.41−7.46 (m, 3 H), 7.71 (t, J = 8.86 Hz, 2 H), 12.71 (br s 1 H). ES-MS m/z 424 (M + H).

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]-3-methoxybenzoic Acid (*R*-12p). 4-Acetyl-3-methoxybenzoic acid and cyclopentylaldehyde were reacted according to method B1. The chalcone was reacted with **9a** according to method C1 to give **(±)-12p** (80%). Chiral separation of **(±)-12p** on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50% MeOH/CO_2, 70 mL/min flow, yielded ***R*-12p** as the later eluting peak. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02−1.13 (m, 1 H), 1.18−1.29 (m, 1 H), 1.31−1.62 (m, 5 H), 1.70−1.79 (m, 1 H), 2.38−2.48 (m, 1 H), 3.55 (dd, J = 18.66, 10.98 Hz, 1 H), 3.92 (s, 3 H), 4.80−4.86 (m, 1 H), 7.16 (dd, J = 8.78, 1.46 Hz, 1 H), 7.35 (s, 1 H), 7.56−7.61 (m, 2 H), 7.69 (d, J = 8.78 Hz, 1 H), 7.89 (d, J = 8.05 Hz, 1 H). ES-MS m/z 424 (M + H).

Methyl 4-((2-(4-Cyanophenyl)hydrazono)methyl)benzoate (13a). To a solution of 4-cyanophenylhydrazine hydrochloride (24.4 mmol) in DMF (60 mL) and triethylamine (29.3 mmol) was added methyl 4-formylbenzoate (4.0 g, 24.4 mmol). The mixture was stirred at room temperature for 18 h. Water (100 mL) was added and the resulting yellow solid was collected by vacuum filtration and dried in a vacuum oven to provide **13a** (23.6 mmol, 97%).

Methyl 4-((2-(3-Chloro-4-cyanophenyl)hydrazono)methyl)benzoate (13b). To a solution of 3-chloro-4-cyanophenylhydrazine hydrochloride (24.5 mmol) in DMF (50 mL) and triethylamine (29.4 mmol) was added methyl 4-formylbenzoate (4.0 g, 24.4 mmol). The mixture was stirred at room temperature for 18 h. Water (100 mL) was added and the resulting yellow solid was collected by vacuum filtration and dried in a vacuum oven to provide **13b** (23.6 mmol, 86%).

Methyl 4-(Bromo(2-(4-cyanophenyl)hydrazono)methyl)benzoate (14a). To a suspension of *N*-bromosuccinimide (28.9 mmol) in dichloroethane (30 mL), cooled to 0 °C, was added dimethyl sulfide (57.9 mmol). The mixture was stirred for 15 min, and hydrazone **13a** (19.3 mmol) was added followed by additional dichloroethane (30 mL). The mixture was stirred at room temperature overnight, water (100 mL) was added, and the resulting red solid was collected to provide **14a** (65%).

Methyl 4-(Bromo(2-(3-chloro-4-cyanophenyl)hydrazono)methyl)-benzoate (14b). To a suspension of *N*-bromosuccinimide (14.4 mmol) in dichloroethane (15 mL), cooled to 0 °C, was added dimethyl sulfide (28.8 mmol). The mixture was stirred for 15 min, and then hydrazone **13b** (9.6 mmol) was added followed by additional dichloroethane (15 mL). The mixture was stirred at room temperature overnight, water (100 mL) was added, and the resulting red solid was collected to provide **14b** (97%).

(±)-4-[5-Benzyl-1-(4-cyanophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15a). Step 1. To a solution of **14a** (204 mg, 0.57 mmol) in tetrahydrofuran (2 mL) were added allylbenzene (67 mg, 0.57 mmol) and triethylamine (0.12 mL, 0.85 mmol). The mixture was stirred for 4 h at room temperature. After concentration of solvent, the crude material was purified using normal phase chromatography (ethyl actate/hexane) to provide the intermediate pyrazoline ester (61 mg, 27%).

Step 2. To a solution of the pyrazoline prepared in step 1 (61 mg, 0.15 mmol) in tetrahydrofuran (2 mL) was added 1 N NaOH (1 mL). The mixture was stirred for 18 h at room temperature, concentrated to half volume, and acidified with 1 N HCl to pH 2. The resulting solid was collected by vacuum filtration to provide **15a** as a yellow solid (41 mg, 0.11 mmol, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.70 (dd, J = 13.56, 9.26 Hz, 1 H), 3.01−3.17 (m, 1 H), 3.40 (dd, J = 17.45, 11.01 Hz, 1 H), 4.89−4.97 (m, 2 H), 7.14−7.30 (m, J = 7.25 Hz, 5 H), 7.33 (d, J = 9.13 Hz, 2 H), 7.68 (d, J = 9.13 Hz, 2 H), 7.73 (d, J = 8.32 Hz, 2 H), 7.91 (d, J = 8.59 Hz, 2 H). ES-MS m/z 382 (M + H). HPLC purity 95%. HRMS (M + H) calcd for $C_{24}H_{19}N_3O_2$, 382.1550; found, 382.1575.

(±)-4-[1-(4-Cyanophenyl)-5-(3-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15b). Following the procedure of example **15a**, using 1-fluoro-3-vinylbenzene (83 mg, 0.68 mmol), gave **15b** as a solid (45 mg, 0.11 mmol, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.24 (d, J = 5.10 Hz, 1 H), 4.00 (dd, J = 17.86, 12.22 Hz, 1 H), 5.72 (dd, J = 12.49, 5.24 Hz, 1 H), 7.02−7.13 (m, 5 H), 7.33−7.42 (m, 1 H), 7.58 (d, J = 9.13 Hz, 2 H), 7.87 (d, J = 8.59 Hz, 2 H), 7.93−7.99 (m, 2 H,) 13.06 (s, 1 H). ES-MS m/z 386 (M + H). HRMS (M + H) calcd for $C_{23}H_{16}FN_3O_2$, 386.1299; found, 386.1310. Anal. ($C_{23}H_{16}FN_3O_2 \cdot 0.25H_2O$) Calcd: C, 70.85; H, 4.27; N, 10.78. Found: C, 70.64; H, 3.77; N, 10.70.

(±)-4-[1-(4-Cyanophenyl)-5-(3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15c). Following the procedure of example **15a**, using 1-methoxy-3-vinylbenzene (91 mg, 0.68 mmol), gave **15c** as a solid (97 mg, 0.24 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.22 (dd, J = 17.86, 5.50 Hz, 1 H), 3.68 (s, 3 H), 3.98 (dd, J = 17.72, 12.08 Hz, 1 H), 5.64 (dd, J = 12.35, 5.37 Hz, 1 H), 6.75 (d, J = 8.06 Hz, 1 H), 6.80−6.85 (m, 2 H), 7.09 (d, J = 8.86 Hz, 2 H), 7.24 (dd, J = 8.86, 7.52 Hz, 1 H), 7.57 (d, J = 9.13 Hz, 2 H), 7.87 (d, J = 8.59 Hz, 2 H), 7.96 (d, J = 8.59 Hz, 2 H). ES-MS m/z 398 (M + H). HRMS (M + H) calcd for $C_{24}H_{19}N_3O_3$, 398.1499; found, 398.1484.

(±)-4-[1-(4-Cyanophenyl)-5-cyclohexyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15d. Following the procedure of example **15a**, using vinyl cyclohexane (0.15 mL, 1.1 mmol), gave **15d** as a solid (100 mg, 0.27 mmol, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75−1.24 (m, 6 H), 1.54 (d, J = 9.13 Hz, 1 H), 1.59−1.75 (m, 2 H), 1.84−1.96 (m, 1 H), 3.30−3.36 (m, 2 H), 4.63 (td, J = 9.47, 6.24, 3.09 Hz, 1 H), 7.24 (d, J = 8.86 Hz, 2 H), 7.62 (d, J = 9.13 Hz, 2 H), 7.85 (d, J = 8.59 Hz, 2 H), 7.96 (d, J = 8.59 Hz, 2 H). ES-MS m/z 374 (M + H). HRMS (M + H) calcd for $C_{23}H_{23}N_3O_2$, 374.1863; found, 374.1869.

(±)-4-[1-(4-Cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15e). Following the procedure of example **15a**, using vinyl cyclopentane (0.76 mL, 5.6 mmol), gave **15e** as a solid (127 mg, 0.35 mmol, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.97−1.07 (m, 2 H), 1.19−1.39 (m, 2 H), 1.42−1.63 (m, 3 H), 1.66−1.79 (m, 2 H), 3.18 (dd, J = 18.13, 3.89 Hz, 1 H), 3.43 (dd, J = 17.72, 11.28 Hz, 1 H), 4.82 (td, J = 7.79, 3.49 Hz, 1 H), 7.24 (d, J = 8.86 Hz, 2 H), 7.60 (d, J = 9.13 Hz, 2 H), 7.78 (d, J = 8.32 Hz, 2 H), 7.92 (d, J = 8.32 Hz, 2 H). ES-MS m/z 360 (M + H). HRMS (M + H) calcd for $C_{22}H_{21}N_3O_2$, 360.1707; found, 360.1748

(±)-4-[5-*tert*-Butyl-1-(4-cyanophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15f). Following the procedure of example **15a**, using 3,3-dimethyl-1-butene (0.18 mL, 1.4 mmol), gave **15f** as a solid (26 mg, 0.07 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (s, 9 H), 3.30−3.36 (m, 2 H), 4.52 (dd, J = 9.53, 3.89 Hz, 1 H), 7.34 (d, J = 9.13 Hz, 2 H), 7.59 (d, J = 9.13 Hz, 2 H), 7.90 (d, 2 H), 7.97 (d, 2 H), 13.04 (br s, 1 H). ES-MS m/z 348 (M + H). HRMS (M + H) calcd for $C_{21}H_{21}N_3O_2$, 348.1707; found, 348.1682.

(±)-4-[1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (15g). Step 1. To a solution of **13b** (1.0 g, 2.55 mmol) in tetrahydrofuran (5 mL) were added vinylcyclopentane (0.35 mL, 2.55 mmol) and triethylamine (0.46 mL, 3.31 mmol). The mixture was stirred for 4 h at ambient temperature. After concentration of solvent, the crude material was purified using normal phase chromatography (ethyl actate/hexane) to provide the pyrazoline (61 mg, 27%).

Step 2. To a solution of the pyrazoline prepared in step 1 (61 mg, 0.15 mmol) in tetrahydrofuran (2 mL) was added 1 N NaOH (1 mL), and the mixture was stirred for 18 h at ambient temperature. The solution was concentrated to half volume and acidified with 1 M HCl to pH 2. The resulting solid was collected by vacuum filtration to provide the title compound as a solid (190 mg, 0.48 mmol, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90−1.06 (m, 1 H), 1.16−1.64 (m, 6 H), 1.74 (dd, J = 13.02, 9.80 Hz, 1 H), 2.36−2.46 (m, 1 H), 3.23 (dd, J = 18.13, 3.63 Hz, 1 H), 3.46 (dd, J = 17.86, 11.41 Hz, 1 H), 4.83−4.96 (m, 1 H), 7.18 (dd, J = 9.00, 2.28 Hz, 1 H), 7.39 (d, J = 2.15 Hz, 1 H), 7.70 (d, J = 8.86 Hz, 1 H), 7.86−7.93 (m, 2 H), 7.94−8.01 (m, 2 H), 13.06 (br s, 1 H). ES-MS m/z 394 (M + H). HRMS ($C_{22}H_{20}ClN_3O_2$) calcd, 394.1317; found, 394.1275.

Ethyl 3-Cyclopentylacrylate (18). To a solution of diethyl [(ethoxycarbonyl)methyl]phosphonate (11.7 g, 52.0 mmol) in THF (100 mL) was added 21% sodium ethoxide (20.4 mL, 54.6 mmol) at 0 °C, and the solution was stirred for 20 min. To this solution was added cyclopentanecarbaldehyde (5.00 g, 50.9 mmol), and the mixture was allowed to warm to room temperature overnight. The solution was diluted to 500 mL with hexanes and was washed with water (200 mL). The aqueous layer was extracted with hexane (200 mL) and then hexane (100 mL). The combined organic layer was washed with brine (200 mL), dried over magnesium sulfate, filtered, and evaporated to give a yellow oil. The oil was purified by silica gel chromatography with 10% EA/Hex to give a light-yellow oil (7.52 g, 44.7 mmol, 87.7% yield) containing ~10% of regioisomeric ethyl 3-cyclopentylidenepropanoate. ES-MS m/z 169 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, J = 7.12 Hz, 3 H), 1.29−1.42 (m, 2 H), 1.50−1.70 (m, 4 H), 1.73−1.83 (m, 2 H), 2.55−2.68 (m, 1 H), 4.10 (q, J = 6.98 Hz, 2 H), 5.82 (dd, J = 15.57, 1.34 Hz, 1 H), 6.86 (dd, J = 15.57, 8.06 Hz, 1 H).

2-Chloro-4-(5-cyclopentyl-3-oxopyrazolidin-1-yl)benzonitrile (19). A mixture of **18** (12.41 g, 73.8 mmol) and 2-chloro-4-hydrazinobenzonitrile (20.1 g, 98.5 mmol) in EtOH (260 mL) was treated with 21% sodium ethoxide (83 mL, 220 mmol) under argon. The mixture was heated to 80 °C overnight and was heated another 3 h at reflux. The mixture was cooled to about 40 °C and quenched with 6 M HCl (50 mL). The resulting orange mixture was cooled to room temperature on an ice bath and then poured (slowly) into a stirring solution of water (1200 mL). The cloudy mixture was stirred for 20 min, and a precipitate formed which was collected by vacuum filtration. The solid was dried on the high vacuum overnight over phosphorus pentoxide to give the title compound as an orange solid (17.06 g, 58.9 mmol, 79.8%). ES-MS m/z 290 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14−1.29 (m, 1 H), 1.30−1.44 (m, 1 H), 1.46−1.83 (m, 6 H), 2.01−2.18 (m, 2 H), 2.92 (dd, J = 16.65, 8.59 Hz, 1 H), 4.24 (t, J = 7.92 Hz, 1 H), 6.97 (dd, J = 8.86, 2.42 Hz, 1 H), 7.09 (d, J = 2.42 Hz, 1 H), 7.77 (d, J = 8.86 Hz, 1 H), 10.45 (s, 1 H).

2-Chloro-4-[(5*R*)-3-chloro-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-1-yl]benzonitrile (*R*-20). A mixture of **19** (15.3 g, 52.9 mmol) in acetonitrile (85 mL) was evacuated/purged with argon. Next, phosphorus oxychloride (5.33 mL, 58.2 mmol) was added and the mixture was heated at 80 °C for 2.5 h. The mixture was diluted with dichloromethane (300 mL) and quenched with water (300 mL) and brine (200 mL) (emulsion). The layers were separated and the organic layer was washed with water (300 mL) to give an emulsion which was filtered. The combined aqueous layers were back-extracted with ethyl acetate (300 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to give an oil. The oil was dissolved in 30% EA/Hex and purified by silica gel chromatography with 35−50% EtOAc/hexane to give **(±)-20** as a light-yellow oil (14.5 g, 47.0 mmol, 88.9% yield). ES-MS m/z 308 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12−1.24 (m, 2 H), 1.49−1.74 (m, 5 H), 1.74−1.86 (m, 1 H), 2.43−2.57 (m, 1 H), 2.89 (dd, J = 17.99, 4.30 Hz, 1 H), 3.34 (dd, J = 18.13, 11.41 Hz, 1 H), 4.53−4.65 (m, 1 H), 6.87 (dd, J = 8.73, 2.28 Hz, 1 H), 7.09 (d, J = 2.42 Hz, 1 H), 7.46 (d, J = 8.86 Hz, 1 H). **(±)-20** (14.5 g, 47.0 mmol) was resolved by SFC chiral chromatography on a Chiralpak AD-H column (30 mm × 250 mm) eluted with 20% methanol/CO_2, 70 mL/min, to give ***R*-20** (6.2 g, 43% yield): later eluting peak, t_R = 3.88 min (Chiralpak AD-H;, 20% MeOH/CO_2), >99% ee by chiral HPLC. ES-MS m/z 308 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03−1.23 (m, 2 H), 1.33−1.78 (m, 6 H), 2.33−2.45 (m, 1 H), 2.99 (dd, J = 18.26, 4.03 Hz, 1 H), 3.51 (dd, J = 18.26, 11.28 Hz, 1 H), 4.80−4.92

(m, 1 H), 7.03 (dd, J = 8.86, 2.42 Hz, 1 H), 7.19 (d, J = 2.15 Hz, 1 H), 7.70 (d, J = 8.86 Hz, 1 H). ***S*-20** (5.9 g, 41% yield): ES-MS m/z 308 (M + H); earlier eluting peak, t_R = 3.00 min, >99% ee by chiral HPLC.

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzoic Acid (*R*-15g). A mixture of ***R*-20** (104 mg, 0.338 mmol), (4-carboxyphenyl)boronic acid (76 mg, 0.46 mmol), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.018 mmol), 2 M aqueous sodium carbonate (0.53 mL, 1.06 mmol), and DME (2 mL) was stirred at 80 °C in a vial under Ar for 5 h. The mixture was diluted with ethyl acetate and water. The organic layer was discarded, and the aqueous was acidified with 1 N HCl and extracted twice with ethyl acetate. The combined organic layer was evaporated and the resulting residue was dissolved in DMF and then purified by reverse phase chromatography with 40−95% acetonitrile/water to give the title compound as a yellow solid (86 mg, 0.218 mmol, 64% yield). ES-MS m/z 394 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (d, J = 8.8 Hz, 1 H), 1.20−1.68 (m, 6 H), 1.78 (d, J = 12.4 Hz, 1 H), 2.47 (br s, 1 H), 3.50 (dd, J = 17.9, 10.6 Hz, 1 H), 4.86−4.95 (m, 1 H), 7.21 (d, J = 8.8 Hz, 1 H), 7.42 (s, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.93 (d, J = 8.8 Hz, 2 H), 7.97−8.04 (m, 2 H). HRMS m/z found, 394.1234 (M + H); calcd, 394.1322.

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]-2-fluorobenzoic Acid (*R*-21a). Chloropyrazoline ***R*-20** (1 mmol), 4-borono-2-fluorobenzoic acid (1.1 mmol), and palladium(0) tetrakis(triphenylphosphine) (0.05 mmol) were loaded in a vial. DMF (2 mL) was added, and the vial was purged with nitrogen. A degassed 2 M solution of cesium carbonate (2 equiv) was added under nitrogen, and the reaction mixture was heated at 85 °C for 8 h. The mixture was diluted with additional DMF, filtered, and purified by reverse-phase HPLC to give pure ***R*-21a** (350 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.82−8.00 (m, 1 H), 7.70 (1 H, s), 7.58−7.78 (m, 2 H), 7.43 (s,1 H), 7.20 (d, J = 8.78 Hz, 1 H), 4.80−5.04 (m, 1 H), 3.44 (dd, J = 17.93, 11.35 Hz, 1 H), 3.40 (m, 1 H), 2.40−2.45 (m, 1H), 1.68−1.84 (m, 2 H), 1.43−1.68 (m, 2 H), 1.19−1.43 (m, 2 H), 0.87−1.09 (m, 2 H). Anal. ($C_{22}H_{19}ClFN_3O_2\cdot 0.25H_2O$) Calcd: C, 63.46; H, 4.73; N, 10.09. Found: C, 63.10; H, 4.24; N, 10.05.

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]-2-ethoxybenzoic Acid (*R*-21b). To 4-bromo-2-hydroxybenzoic acid (5.0 g, 23 mmol) and potassium carbonate (12.7 g, 92.2 mmol) in DMF (85 mL) was added ethyl iodide (5.53 mL, 69.1 mmol), and the mixture was heated at 100 °C for 4 h. Another portion of ethyl iodide (5 mL, 62.5 mmol) and potassium carbonate (12 g, 86.8 mmol) was added, and the mixture was heated at 100 °C for another 4 h. The mixture was poured into water (400 mL) and extracted three times with diethyl ether (200 mL). The combined organic layers were washed with brine (200 mL), dried over magnesium sulfate, filtered, and evaporated to give an oil. The oil was purified by silica gel chromatography with 0−30% EA/Hex to give ethyl 4-bromo-2-ethoxybenzoate as a white solid (5.19 g, 19 mmol, 83%). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 1.38 (t, J = 7.12 Hz, 3 H), 1.47 (t, J = 6.98 Hz, 3 H), 4.10 (q, J = 6.98 Hz, 2 H), 4.35 (q, J = 7.25 Hz, 2 H), 7.09−7.13 (m, 2 H), 7.66 (d, J = 8.59 Hz, 1 H). ES-MS m/z 273 (M + H).

To a mixture of ethyl 4-bromo-2-ethoxybenzoate (2.5 g, 9.2 mmol), bis(pinacolato)diboron (2.57 g, 10.1 mmol), and potassium acetate (2.71 g, 27.6 mmol), Pd(dppf)$_2$Cl$_2\cdot$CH$_2$Cl$_2$ complex (225 mg, 0.276 mmol) was added DMF (35 mL). The reaction vial was purged and filled with argon. The mixture was heated at 80 °C overnight. The reaction mixture was diluted with diethyl ether (250 mL), filtered through a pad of Celite, and evaporated to give an oil. The oil was purified by silica gel chromatography with 0−30% EA/Hex to give ethyl 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate as an oil (2.59 g, 8.09 mmol, 88%). ES-MS m/z 321 (M + H).

A mixture ***R*-20** (45 mg, 0.15 mmol), ethyl 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (56 mg, 0.17 mmol), tetrakis(triphenylphosphine)palladium(0) (9.2 mg, 0.008 mmol), 2 M aqueous sodium carbonate (0.22 mL, 0.44 mmol), and DME (1 mL) was stirred at 80 °C in a vial under Ar for 2 h. The mixture was diluted with ethyl acetate, washed with water, and the layers were separated. The organic layer was treated with 3-mercaptopropyl functionalized silica gel to scavenge the palladium catalyst, stirred for 10 min, filtered, and evaporated. The residue was dissolved in 1.5 mL of THF, 1 mL of methanol and treated with 0.5 mL of 1.25 M NaOH, and the solution was stirred overnight. The solution was diluted with ethyl acetate and quenched with 1 N HCl. The organic layer was evaporated to give an oil. The oil was dissolved in DMSO and purified by reverse phase HPLC to give ***R*-21b** as a solid (64 mg, 0.78 mmol, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.91−1.09 (m, 1 H), 1.32 (t, J = 7.0 Hz, 5 H), 1.42−1.64 (m, 3 H), 1.66−1.80 (m, 1 H), 2.34−2.49 (m, 2 H), 3.19−3.33 (m, 1 H), 3.27 (br s, 1 H), 3.43 (dd, J = 17.6, 11.7 Hz, 1 H), 4.08−4.24 (m, 2 H), 4.82−4.92 (m, 1 H), 7.17 (d, J = 7.3 Hz, 1 H), 7.31−7.45 (m, 2 H), 7.65 (dd, J = 15.7, 8.4 Hz, 2 H). HRMS ($C_{24}H_{24}ClN_3O_3$) calcd, 438.1506; found, 438.1569.

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]-2-(trifluoromethoxy)benzoic Acid (*R*-21c). A solution of 4-bromo-2-(trifluoromethoxy)iodobenzene in 25 mL of THF was cooled to −78 °C and treated with 1.1 mL of 2.5 M *n*-BuLi in hexanes (2 equiv, 2.7 mmol). The mixture was stirred at −78 °C for 1.5 h and then treated with fresh small pieces of dry ice (CO_2) and stirred at −78 °C for 30 min. The reaction was quenched with 1 N HCl and extracted 3× with ethyl acetate, dried over magnesiun sulfate, and concentrated to an oil. The oil was dissolved in methylene chloride (10 mL) and treated with 0.5 mL of 98% oxallyl chloride and 1 drop of DMF (bubbling observed). After 1 h, the reaction was quenched by addition of 10 mL of MeOH and then concentrated. The oil was purified by flash chromatography (5−60% ethyl acetate/heptane) to give methyl 4-bromo-2-(trifluoromethoxy)benzoate as a clear oil (292 mg, 72%). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 3.94 (s, 3 H), 7.52 (s, 1 H), 7.55 (dd, J = 8.32, 1.88 Hz, 1 H), 7.86 (d, J = 8.32 Hz, 1 H).

To a mixture of methyl 4-bromo-2-(trifluoromethoxy)-benzoate (280 mg, 0.936 mmol), bis(pinacolato)diboron (262 mg, 1.03 mmol), potassium acetate (276 mg, 2.81 mmol), Pd(dppf)$_2$Cl$_2\cdot$CH$_2$Cl$_2$ complex (38.2 mg, 0.0468 mmol) was added DMF (10 mL), and the reaction vial was purged and filled with argon. The mixture was heated at 80 °C overnight. The mixture was cooled to room temperature, diluted with water, and extracted 3× with ethyl acetate. The organic layer was filtered through Celite, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography, eluting with 2−50% ethyl acetate/hexanes to give a mixture of methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)benzoate and 4-(methoxycarbonyl)-3-(trifluoromethoxy)phenylboronic acid as a semisolid (240 mg, ~74%). ES-MS m/z 321 (M + H). Boronate ester: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 1.36 (s, 12 H), 3.94 (s, 3 H), 7.69−7.74 (m, 1 H), 7.79 (dd, J = 7.72, 1.07 Hz, 1 H), 7.92 (d, J = 7.62 Hz, 1 H). Boronic acid: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 3.98 (s, 3 H), 7.52−7.55 (m, 1 H), 7.62 (dd, J = 8.01, 1.76 Hz, 1 H), 8.09 (d, J = 8.21 Hz, 1 H).

A mixture of ***R*-20** (160 mg, 0.519 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)-benzoate/4-(methoxycarbonyl)-3-(trifluoromethoxy)phenylboronic acid (234 mg, 0.675 mmol), Pd(dppf)$_2$Cl$_2\cdot$CH$_2$Cl$_2$ complex (21.2 mg, 0.026 mmol), 2 M aqueous cesium carbonate (0.519 mL, 1.04 mmol), and DME (5 mL) was degassed and purged with Ar and was stirred at 80 °C for 4 h. The mixture was poured into water and extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and concentrated to give a brown oil. The residue was dissolved in 3 mL of THF, 1 mL of methanol, treated with 1 mL of 2.5 M NaOH, and stirred overnight under Ar. The

solution was diluted with ethyl acetate and quenched with 1 N HCl. The organic layer was evaporated to give an oil. The oil was dissolved in DMSO and purified by reverse phase HPLC to give ***R*-21c** as a yellow-orange solid (112 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95−1.09 (m, 1 H), 1.20−1.67 (m, 6 H), 1.69−1.85 (m, 1 H), 2.39−2.50 (m, 1 H), 3.29 (dd, J = 18.17, 3.91 Hz, 1 H), 3.40−3.55 (m, 1 H), 4.95 (ddd, J = 11.38, 3.96, 3.81 Hz, 1 H), 7.25 (dd, J = 8.79, 2.15 Hz, 1 H), 7.45 (d, J = 2.15 Hz, 1 H), 7.74 (d, J = 8.79 Hz, 1 H), 7.83 (s, 1 H), 7.92 (dd, J = 8.21, 1.56 Hz, 1 H), 7.98−8.02 (m, J = 8.21 Hz, 1 H). ES-MS m/z 478 (M + H).

{4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]phenyl}acetic Acid (*R*-21d). Chloropyrazoline (±)-**20** (0.7 mmol), 4-borono-2-fluorobenzoic acid (0.7 mmol), and palladium(0) tetrakis(triphenylphosphine) (0.05 mmol) were loaded in a vial. DMF (2 mL) was added, and the vial was purged with nitrogen. A degassed 2 M solution of cesium carbonate (2 equiv) was added under nitrogen, and the reaction mixture was heated at 85 °C for 8 h. The mixture was diluted with additional DMF, filtered, and purified by reverse-phase HPLC to give pure (±)-**21d** (230 mg). Chiral separation of (±)-**21d** on a Chiralpak AS-H column (30 mm × 250 mm) eluted with 50%IPA/CO_2, 70 mL/min flow, yielded ***R*-21d** as the later eluting peak. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.38 (br s, 1 H), 7.67−7.91 (m, 4 H), 7.23−7.43 (m, 3 H), 7.15 (dd, J = 8.98, 1.95 Hz, 1 H), 4.85 (ddd, J = 11.13, 3.71, 3.52 Hz, 1 H), 3.63 (s, 2 H), 3.23 (m, 1 H), 2.43 (m, 1 H), 1.76 (dd, J = 11.72, 4.30 Hz, 1 H), 1.59−1.68 (m, 1 H), 1.44−1.59 (m, 1 H), 1.21−1.44 (m, 4 H), 0.95−1.06 (m, 1 H). ES-MS m/z 408 (M + H). t_R = 8.60 min, >99.5% ee by chiral HPLC.

4-[(5*R*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4,5-dihydro-1*H*-pyrazol-3-yl]-2-(3-hydroxypropoxy)benzoic Acid (*R*-22). To a solution of ***R*-12o** (2.94 mmol) in 60 mL of anhydrous methylene chloride in an ice bath under nitrogen was added a solution of 1 M BBr_3 (7.35 mmol) in methylene chloride dropwise. After addition, the mixture was stirred for 1 h. The reaction was then quenched with 10 mL of methanol, and the mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (0−10% MeOH/methylene chloride) to give 958 mg of solid product. A mixture of this solid (0.11 mmol), 2-(3-bromopropoxyl)tetrahydro-2*H*-pyran (0.25 mmol), and cesium carbonate (0.24 mmol) was evacuated and backfilled with Ar several times. Then 1.1 mL of anhydrous DMF was added and the resulting mixture was heated to 80 °C overnight. The mixture was cooled, and 10 mL of methanol was added along with 1 mL of 2.5 N NaOH. The mixture was poured into a diluted solution of HCl and extracted with ethyl acetate. The combined ethyl acetate phase was washed with brine, dried over Na_2SO_4, concentrated, and dried under vacuum. The residue was dissolved in 5 mL of THF, and 0.5 mL of concentrated HCl was added. The resulting mixture was stirred at room temperature for 4 h. The solvents were evaporated and the residue was purified by reverse phase HPLC to give pure ***R*-22** (74%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.97−1.09 (m, 1 H), 1.27−1.37 (m, 3 H), 1.45−1.65 (m, 3 H), 1.71−1.82 (m, 1 H), 1.84−1.95 (m, 2 H), 2.37−2.48 (m, 1 H), 3.21−3.28 (m, 1 H), 3.43−3.52 (m, 1 H), 3.62 (t, J = 6.04 Hz, 2 H), 4.17−4.25 (m, 2 H), 4.84−4.94 (m, 1 H), 7.17−7.25 (m, 1 H), 7.37−7.47 (m, 3 H), 7.64−7.74 (m, 2 H). ES-MS m/z 468 (M + H).

4-[(4*S*,5*S*)-1-(3-Chloro-4-cyanophenyl)-5-cyclopentyl-4-methyl-4,5-dihydro-1*H*-pyrazol-3-yl]-2-methoxybenzoic Acid (4*S*,5*S*-23). To a solution of diisopropylamine (1.4 mmol) in 7 mL of anhydrous THF at −78 °C under nitrogen was added a solution of 2.5 M *n*-BuLi in hexanes (1.4 mmol), and the mixture was stirred for 10 min. Then 1.9 mL of the resulting LDA solution was added dropwise to a mixture of ***R*-12o** (0.14 mmol) in 2.8 mL of anhydrous THF cooled at −78 °C under nitrogen and stirred for 30 min. Iodomethane (0.21 mmol) was then added to the mixture. After 30 min, the mixture was warmed to room temperature and stirred for additional 2.5 h. The mixture was poured into a diluted HCl solution and extracted with ethyl acetate. The combined ethyl acetate phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by reversed-phase HPLC to give **4*S*,5*S*-23** (37 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95−1.08 (m, 1 H), 1.20 (d, J = 7.25 Hz, 3 H), 1.29−1.43 (m, 3 H), 1.44−1.67 (m, 3 H), 1.69−1.79 (m, 1 H), 2.30−2.42 (m, 1 H), 3.68 (ddd, J = 14.03, 7.05, 1.48 Hz, 1 H), 3.92 (s, 3 H), 4.49 (dd, J = 4.30, 1.88 Hz, 1 H), 7.25 (d, J = 8.59 Hz, 1 H), 7.43 (d, J = 1.88 Hz, 1 H), 7.49 (dd, J = 7.79, 1.61 Hz, 1 H), 7.51 (s, 1 H), 7.70 (d, J = 8.06 Hz, 1 H), 7.73 (d, J = 8.86 Hz, 1 H), 12.71 (br s, 1 H). ES-MS m/z 438 (M + H).

Ethyl 6-(4-Fluorobenzylidene)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (25a). The title compound was prepared according to method B4. The isolated crude precipitate was a mixture of ethyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate, **25a**, and 6-(4-fluorobenzylidene)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid. The mixture was combined with 4-fluorobenzaldehyde (0.5 mL), ethanol (40 mL), and 4 N hydrogen chloride/dioxane (10 mL) and was refluxed for 20 h. The solution was poured into 200 mL of water, filtered, and dried to give **25a** as an off-white solid (826 mg, 2.55 mmol, 49% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, J = 7.12 Hz, 3 H), 3.06 (m, 4 H), 4.34 (q, J = 6.98 Hz, 2 H), 7.31 (t, J = 8.86 Hz, 2 H), 7.62 (dd, J = 8.59, 5.64 Hz, 2 H), 7.74 (s, 1 H), 7.94 (m, 2 H), 8.06 (d, J = 8.59 Hz, 1 H). ES-MS m/z 325 (M + H).

Methyl 6-(Cyclopentylmethylene)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (25b). To a solution of methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (3.4 g, 16.7 mmol) in methanol (30 mL) were added cyclopentanecarboxaldehyde (3.3 g, 33.3 mmol) and pyrrolidine (2.78 mL, 33.3 mmol). The solution was stirred for 20 h at ambient temperature. The reaction was recharged with 0.5 mL of cyclopentanecarboxaldehyde. The resulting precipitate was collected by vacuum filtration to provide the title compound as a solid (2.8 g, 60% yield). ES-MS m/z 285 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24−1.39 (m, 2 H), 1.52−1.74 (m, 4 H), 1.76−1.89 (m, 2 H), 2.77 (t, J = 5.77 Hz, 2 H), 2.79−2.90 (m, 1 H), 2.97 (t, J = 6.44 Hz, 2 H), 3.85 (s, 3 H), 6.71 (d, J = 9.94 Hz, 1 H), 7.88 (d, J = 6.44 Hz, 1 H), 7.91 (s, 1 H), 7.98 (d, J = 8.06 Hz, 1 H).

Methyl 6-(Cyclobutylmethylene)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (25c). A solution of methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (600 mg, 2.9 mmol) in tetrahydrofuran (10 mL) was cooled to ice bath temperature and treated with 1.0 M lithium hexamethyldisilazide in tetrahydrofuran (5 mL). After the mixture was stirred for 20 min, cyclobutanecarboxaldehyde[21] (24 mL of 0.5 M solution in tetrahydrofuran) was slowly added and the mixture allowed to warm to room temperature and stirred for 3 days. The mixture was poured into water, extracted three times with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (5−50% ethyl acetate/hexanes). Pure fractions were pooled and concentrated in vacuo to yield the title compound (300 mg, 1.1 mmol, 38% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81−2.03 (m, 4 H), 2.14−2.27 (m, 2 H), 2.71 (t, J = 6.58 Hz, 2 H), 2.93−3.00 (m, 2 H), 3.34−3.44 (m, 1 H), 3.88 (s, 3 H), 6.91 (d, J = 9.13 Hz, 1 H), 7.84−7.95 (m, 2 H), 8.01 (d, J = 8.06 Hz, 1 H). ES-MS m/z 271 (M + H).

Methyl 6-(Cyclopent-1-en-1-ylmethylene)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (25d). To a solution of sodium periodate (28.3 g, 0.13 mol) in water (250 mL) was added an ethyl ether solution (150 mL) of 1,2-cyclohexanediol (12.0 g, 0.10 mol). The solution was stirred for 30 min at ambient temperature. To this solution was added 20% aqueous potassium hydroxide (40 mL), and the solution was stirred for 1 h. The layers were separated, and the organic layer was washed with water and brine and dried over magnesium sulfate. Concentration in vacuo provided cyclopent-1-enecarbaldehyde as a yellow oil (6.0 g, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6)

δ ppm 1.83−1.93 (m, 2 H), 2.36 (td, J = 7.65, 2.15 Hz, 2 H), 2.50−2.59 (m, 2 H), 7.01−7.08 (m, 1 H), 9.73 (s, 1 H). The title compound was prepared from 5-oxo-5,6,7,8-tetrahydronaphtalene-2-carboxylic acid methyl ester (396 mg, 1.9 mmol) and 1-cyclopentene carbaldehyde (220 mg, 2.0 mmol) according to method B5 in 70% yield. ES-MS m/z 283 (M + H).

(±)-Methyl 5-Oxo-6-((tetrahydrofuran-3-yl)methylene)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (25e). To a solution of methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (240 mg, 1.2 mmol) in methanol (3 mL) was added (±)-tetrahydrofuran-3-carboxaldehyde (240 mg, 2.4 mmol) and pyrrolidine (0.20 mL, 2.4 mmol). The solution was stirred for 20 h at ambient temperature and for 4 h at 45 °C. The mixture was concentrated in vacuo. Flash chromatography (ethyl acetate/hexane) provided the title compound as an orange oil (200 mg, 58%). ES-MS m/z 287 (M + H).

Methyl 5-Oxo-6-((tetrahydro-2*H*-pyran-4-yl)methylene)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (25f). A solution of methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (2.9 mmol), tetrahydropyran-4-carbaldehyde (3.2 mmol), and piperidine (3.2 mmol) in 6 mL of methanol was heated to 65 °C overnight. The cooled mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (10−40% ethyl acetate/hexane) to give the desired product (430 mg, 49%). ES-MS m/z 301 (M + H).

Methyl 3-(4-Fluorobenzylidene)-4-oxochroman-7-carboxylate (25g). The title compound was prepared from methyl 4-oxochroman-7-carboxylate and 4-fluorobenzaldehyde according to method B4 using methanol and 4 N hydrogen chloride/dioxane to give an off-white solid (76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.88 (s, 3 H), 5.48 (s, 1 H), 7.35 (t, J = 8.59 Hz, 2 H), 7.50−7.61 (m, 3 H), 7.66 (d, J = 7.25 Hz, 1 H), 7.80 (s, 1 H), 8.01 (d, J = 8.06 Hz, 1 H).

Methyl 3-(Cyclopentylmethylene)-4-oxochroman-7-carboxylate (25h). The title compound was prepared according to method B3 from methyl 4-oxochroman-7-carboxylate[22] and cyclopentanecarboxaldehyde as an off-white solid (2.12 g, 7.42 mmol, 76% yield). ES-MS m/z 287 (M + H).

(±)-*cis*-2-(4-Cyanophenyl)-3-(4-fluorophenyl)-2,3,3a,4-tetrahydroindeno[1,2-*c*]pyrazole-6-carboxylic Acid (27a). A mixture of ethyl 1-oxo-2,3-dihydro-1*H*-indene-5-carboxylate (1.2 mmol) and 4-fluorobenzaldehyde (1.2 mmol) in 5 mL of EtOH containing 0.5 mL of concentrated H_2SO_4 was heated to 80 °C overnight. After the mixture was cooled, the solid was filtered, washed with cold EtOH, and dried to give 285 mg of solid chalcone product (0.92 mmol, 77%). A mixture of the chalcone (0.42 mmol) and 4-cyanophenylhydrazine hydrochloride (0.42 mmol) in 4.2 mL of EtOH was heated to 80 °C overnight. The mixture was cooled, filtered, washed with cold EtOH, and dried. The solid was suspended in 6 mL of THF, 2 mL of MeOH, and 2 mL of 2.5 N NaOH and stirred at room temperature overnight. The mixture was concentrated and purified by reverse-phase chromatography (56 mg, 0.14 mmol, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (dd, J = 16.25, 7.65 Hz, 1 H), 3.06 (dd, J = 16.51, 9.26 Hz, 1 H), 4.43 (ddd, J = 11.01, 8.86, 7.79 Hz, 1 H), 6.03 (d, J = 11.01 Hz, 1 H), 6.98−7.18 (m, 6 H), 7.58 (d, J = 9.13 Hz, 2 H), 7.82 (d, J = 8.06 Hz, 1 H), 7.87 (s, 1 H), 7.93 (dd, J = 7.92, 1.48 Hz, 1 H), 13.10 (br s, 1 H). HRMS ($C_{24}H_{17}FN_3O_2$) calcd, 398.1299; found, 398.1303.

(±)-(3*RS*,3a*RS*)-2-(4-Cyanophenyl)-3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27b). The title compound was prepared from **25a** (324 mg, 1.0 mmol) and 4-hydrazinylbenzonitrile hydrochloride (254 mg, 1.5 mmol) according to method C3 and method D as a solid (294 mg, 0.72 mmol, 72% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.70−0.88 (m, 1 H), 1.74−1.84 (m, 1 H), 2.82−3.01 (m, 2 H), 3.86−3.99 (m, 1 H), 5.87 (d, J = 11.28 Hz, 1 H), 7.13 (s, 6 H), 7.57 (d, J = 9.14 Hz, 2 H), 7.74 (s, 1 H), 7.78−7.83 (m, 1 H), 8.05 (d, J = 8.33 Hz, 1 H). ES-MS m/z 412 (M + H).

(±)-(3*RS*,3a*RS*)-Ethyl 2-(3-chloro-4-cyanophenyl)-3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylate (26a). The title compound was prepared from **25a** (324 mg, 1.0 mmol) and 2-chloro-4-hydrazinylbenzonitrile hydrochloride (306 mg, 1.5 mmol) according to method C3 as a yellow solid (394 mg, 0.830 mmol, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (m, 1 H), 1.31 (t, J = 7.12 Hz, 3 H), 1.79 (m, 1 H), 2.95 (m, 2 H), 3.97 (ddd, J = 13.49, 11.21, 4.83 Hz, 1 H), 4.31 (q, J = 6.98 Hz, 2 H), 5.94 (d, J = 11.28 Hz, 1 H), 7.15 (m, 6 H), 7.66 (d, J = 8.86 Hz, 1 H), 7.80 (s, 1 H), 7.85 (dd, J = 8.19, 1.75 Hz, 1 H), 8.16 (d, J = 8.06 Hz, 1 H). ES-MS m/z 474 (M + H).

(±)-(3*RS*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (*cis*-27c). The title compound was prepared from **26a** (330 mg, 0.696 mmol) according to method D as a yellow solid (297 mg, 0.666 mmol, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (m, 1 H), 1.79 (m, 1 H), 2.93 (m, 2 H), 3.96 (m, 1 H), 5.93 (d, J = 11.01 Hz, 1 H), 7.15 (m, 6 H), 7.66 (d, J = 8.59 Hz, 1 H), 7.78 (s, 1 H), 7.83 (dd, J = 8.19, 1.48 Hz, 1 H), 8.14 (d, J = 8.06 Hz, 1 H), 13.07 (s, 1 H). ES-MS m/z 446 (M + H).

(3*R*,3a*R*)-2-(3-Chloro-4-cyanophenyl)-3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (3*R*,3a*R*-27c). The title compound was obtained by chiral resolution of (±)-*cis*-**27c** (Chiralcel OJ-H 30 mm × 250 mm, 50% ethanol/carbon dioxide, 70 mL/min). First eluting peak: chiral HPLC t_R = 2.3 min (Chiralcel OJ-H 4.6 mm × 250 mm, 50% ethanol/carbon dioxide, 3 mL/min). Anal. ($C_{25}H_{17}ClFN_3O_2$) C, H, N.

(3*S*,3a*S*)-2-(3-Chloro-4-cyanophenyl)-3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic acid (3*S*,3a*S*-27c). The title compound was obtained by chiral resolution of (±)-*cis*-**27c** (Chiralcel OJ-H 30 mm × 250 mm, 50% ethanol/carbon dioxide, 70 mL/min). Second eluting peak: chiral HPLC t_R = 4.0 min (Chiralcel OJ-H 4.6 mm × 250 mm, 50% ethanol/carbon dioxide, 3 mL/min). Anal. ($C_{25}H_{17}ClFN_3O_2 \cdot 0.25H_2O$) Calcd: C, 66.01; H, 3.88; N, 9.24. Found: C, 66.36; H, 3.42; N, 9.02.

(±)-(3*SR*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27d). 25b (2.8 g, 9.9 mmol) was suspended in ethanol (100 mL), and **9a** (2.6 g, 12.8 mmol) was added. The solution was heated to 80 °C for 8 h. The solution was returned to ambient temperature. The resulting solid was collected by vacuum filtration and washed with cold ethanol to provide only the cis isomer of the methyl ester (3.75 g, 87% yield). ES-MS m/z 434 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06−1.54 (m, 6 H), 1.62−1.74 (m, 1 H), 1.73−1.87 (m, 1 H), 1.99−2.09 (m, 1 H), 2.21 (dd, J = 7.79, 2.15 Hz, 1 H), 2.82−2.94 (m, 2 H), 3.09 (d, J = 16.92 Hz, 1 H), 3.54−3.66 (m, 1 H), 3.84 (s, 3 H), 4.95 (dd, J = 9.67, 5.64 Hz, 1 H), 7.19 (dd, J = 9.26, 1.75 Hz, 1 H), 7.39 (d, J = 2.15 Hz, 1 H), 7.67 (d, J = 8.86 Hz, 1 H), 7.82 (d, J = 8.32 Hz, 1 H), 7.86 (s, 1 H), 8.10 (d, J = 8.06 Hz, 1 H).

To a solution of the methyl ester (3.75 g, 8.6 mmol) in methanol (10 mL) and tetrahydrofuran (30 mL) was added 10% aqueous sodium hydroxide (10 mL). The solution was stirred for 20 h at ambient temperature. The resulting slurry was concentrated to half volume and acidified to pH 2 with 1 M hydrochloric acid. The resulting solid was collected by vacuum filtration to provide (±)-**27d** as a yellow solid (3.79 g, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10−1.55 (m, 6 H), 1.64−1.75 (m, 2 H), 1.75−1.87 (m, 1 H), 1.99−2.09 (m, 1 H), 2.15−2.23 (m, 1 H), 2.78−2.91 (m, 2 H), 3.00 (d, J = 16.11 Hz, 1 H), 4.89 (dd, J = 9.26, 5.77 Hz, 1 H), 7.14 (dd, J = 9.00, 1.75 Hz, 1 H), 7.34 (d, J = 1.88 Hz, 1 H), 7.63 (d, J = 8.86 Hz, 1 H), 7.73 (s, 1 H), 7.76 (s, 1 H), 7.94 (d, J = 7.79 Hz, 1 H). ES-MS m/z 420 (M + H). HRMS ($C_{24}H_{22}ClN_3O_2$) calcd, 420.1473; found, 420.1449. Anal. ($C_{24}H_{22}ClN_3O_2$) C, H, N.

(3*S*,3a*R*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (3*S*,3a*R*-27d). The title compound was obtained by chiral resolution of (±)-**27d** (Chiralpak AD-H 21 mm × 250 mm, 50% *n*-butanol/carbon

dioxide, 50 mL/min). Second eluting peak: chiral HPLC t_R = 4.0 min (Chiralpak AD-H 4.6 mm × 250 mm, 50% *n*-butanol/carbon dioxide, 3 mL/min).

(±)-(3*RS*,3a*SR*)-2-(3-Chloro-4-cyanophenyl)-3-cyclobutyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27e). The title compound was prepared according to method C3 and method D from **25c** and **9a** to give only the cis diastereomer (150 mg, 0.36 mmol, 65% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.56−1.77 (m, 4 H), 1.77−1.98 (m, 3 H), 2.07−2.18 (m, 1 H), 2.51−2.59 (m, 1 H), 2.80−2.93 (m, 1 H), 2.97−3.07 (m, 1 H), 3.44−3.56 (m, 1 H), 4.88 (dd, J = 9.40, 6.98 Hz, 1 H), 7.22 (dd, J = 8.86, 1.88 Hz, 1 H), 7.42 (d, J = 2.15 Hz, 1 H), 7.67 (d, J = 8.86 Hz, 1 H), 7.75−7.83 (m, 2 H), 8.01 (d, J = 8.06 Hz, 1 H). ES-MS m/z 420 (M + H).

(±)-(3*RS*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentenyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27f). The title compound was prepared from **25d** (268 mg, 1.0 mmol) and **9a** (303 mg, 1.5 mmol) according to method C3 and method D (20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 (dd, J = 13.09, 5.67 Hz, 1 H), 1.73 (dt, J = 17.59, 6.64 Hz, 2 H), 1.85 (m, 1 H), 1.90−2.00 (m, 1H), 2.07 (s, 1 H), 2.10 (dt, J = 5.86, 3.71 Hz, 1 H), 2.22 (br s, 2 H), 2.99−3.06 (m, 2H), 3.71−3.77 (m, 1H), 5.48 (d, J = 10.55 Hz, 1 H), 5.69 (br s, 1 H), 7.72 (d, J = 8.60 Hz, 1 H), 7.83 (d, J = 8.21 Hz, 1 H), 7.85 (s, 1 H), 8.09 (d, J = 8.21 Hz, 1 H). ES-MS m/z 418 (M + H). HRMS ($C_{24}H_{21}ClN_3O_2$) calcd, 418.1317; found, 418.1298.

(±)-(3*RS*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-((*R*)-tetrahydrofuran-3-yl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid and (±)-(3*RS*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-((*S*)-tetrahydrofuran-3-yl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27g). The title compounds were prepared as a mixture of diastereomers according to method C3 and method D from **25e** and **9a** as a yellow solid (167 mg, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51−1.99 (m, 3 H), 2.11−2.27 (m, 1 H), 2.91 (dd, J = 12.35, 4.03 Hz, 1 H), 3.03−3.13 (m, 1 H), 3.38−3.47 (m, 1 H), 3.49−3.57 (m, 1 H), 3.58−3.69 (m, 1 H), 3.73 (t, J = 8.06 Hz, 1 H), 3.77−3.85 (m, 1 H), 4.75−4.83 (m, 1 H), 4.99 (dd, J = 9.40, 6.71 Hz, 1 H), 7.18 (td, J = 8.59, 2.15 Hz, 1 H), 7.39 (dd, J = 18.80, 2.15 Hz, 1 H), 7.69 (dd, J = 8.86, 5.10 Hz, 1 H), 7.80 (d, J = 8.06 Hz, 1 H), 7.84 (s, 1 H), 8.08 (d, J = 8.32 Hz, 1 H), 13.07 (br s, 1 H). ES-MS m/z 422 (M + H). HRMS ($C_{23}H_{20}ClN_3O_3$) calcd, 422.1266; found, 422.1257.

(±)-(3*SR*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-(tetrahydro-2*H*-pyran-4-yl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27h). The title compound was prepared from **25f** and **9a** according to method C3 and method D (250 mg, 0.57 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24−1.33 (m, 2 H), 1.40 (ddd, J = 24.57, 12.08, 4.70 Hz, 1 H), 1.50−1.57 (m, 1 H), 1.86−1.99 (m, 2 H), 2.25−2.32 (m, 1 H), 2.85−2.95 (m, 1 H), 3.07−3.20 (m, 3 H), 3.61−3.79 (m, 3 H), 4.83 (dd, J = 9.67, 3.76 Hz, 1 H), 7.21 (d, J = 8.86 Hz, 1 H), 7.44 (d, J = 1.61 Hz, 1 H), 7.71 (d, J = 8.59 Hz, 1 H), 7.83 (dd, J = 8.32, 1.34 Hz, 1 H), 7.87 (s, 1 H), 8.09 (d, J = 8.32 Hz, 1 H), 13.07 (s, 1 H). HRMS m/z 436.1445 (M + H).

(±)-(3*SR*,3a*RS*)-2-(4-Cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27i). The title compound was prepared from **25b** and 4-hydrazinylbenzonitrile hydrochloride according to method C3 and method D (205 mg, 0.53 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18−1.54 (m, 7 H), 1.65−1.74 (m, 1 H), 1.77−1.89 (m, 1 H), 2.04−2.12 (m, 1 H), 2.20−2.28 (m, 1 H), 2.83−2.95 (m, 1 H), 3.05−3.14 (m, 1 H), 3.55−3.63 (m, 1 H), 4.91 (dd, J = 9.53, 5.50 Hz, 1 H), 7.29 (d, J = 8.86 Hz, 2 H), 7.60 (d, J = 8.86 Hz, 2 H), 7.82 (dd, J = 8.19, 1.48 Hz, 1 H), 7.86 (s, 1 H), 8.06 (d, J = 8.06 Hz, 1 H), 12.99 (br s, 1 H). HRMS m/z 386.1838 (M + H).

(3*S*,3a*R*)-2-(4-Cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (3*S*,3a*R*-27i). The title compound was obtained by chiral resolution of (±)-**27i** (Chiralcel OJ-H 21 mm × 250 mm, 50% methanol/carbon dioxide, 50 mL/min). First eluting peak: chiral HPLC t_R = 3.6 min (Chiralcel OJ-H 4.6 mm × 250 mm, 50% methanol/carbon dioxide, 3 mL/min).

(±)-(3*SR*,3a*RS*)-2-(4-Cyano-3-methylphenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27j). The title compound was prepared from **25b** (310.5 mg, 1.09 mmol) and **9c** (265 mg, 1.45 mmol) according to method C3 and method D (hydrolysis conducted at 60 °C). The crude precipitate was purified by reverse phase chromatography with 60−95% acetonitrile/water to give the title compound as a yellow solid (280 mg, 0.563 mmol, 64% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12−1.56 (m, 7 H), 1.64−1.74 (m, 1 H), 1.76−1.92 (m, J = 12.89, 4.30 Hz, 1 H), 2.01−2.14 (m, 1 H), 2.18−2.29 (m, 1 H), 2.41 (s, 3 H), 2.81−2.96 (m, 1 H), 3.04−3.14 (m, 1 H), 3.51−3.63 (m, 1 H), 4.89 (dd, J = 9.67, 5.37 Hz, 1 H), 7.09 (dd, J = 8.59, 2.15 Hz, 1 H), 7.22 (d, J = 1.88 Hz, 1 H), 7.52 (d, J = 8.59 Hz, 1 H), 7.82 (dd, J = 8.19, 1.48 Hz, 1 H), 7.85 (s, 1 H), 8.07 (d, J = 8.06 Hz, 1 H), 13.01 (s, 1 H). ES-MS m/z 400 (M + H).

(±)-(3*SR*,3a*RS*)-2-(4-Cyano-3-methoxyphenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27k). The title compound was prepared from **25b** (310 mg, 1.09 mmol) and **9f** (282 mg, 1.42 mmol) according to method C3 (methanol was used in place of ethanol as solvent) and method D. The crude precipitate was purified by reverse phase chromatography with 40−95% acetonitrile/water to give the title compound as a yellow solid (220 mg, 0.53 mmol, 49% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (m, 7 H), 1.65−1.90 (m, 2 H), 1.99−2.12 (m, 1 H), 2.18−2.27 (m, 1 H), 2.82−2.95 (m, 1 H), 3.04−3.13 (m, 1 H), 3.52−3.63 (m, 1 H), 3.90 (s, 3 H), 4.94 (dd, J = 9.67, 5.37 Hz, 1 H), 6.80 (dd, J = 8.59, 1.88 Hz, 1 H), 6.90 (d, J = 1.61 Hz, 1 H), 7.45 (d, J = 8.59 Hz, 1 H), 7.81 (dd, J = 8.19, 1.48 Hz, 1 H), 7.85 (s, 1 H), 8.08 (d, J = 8.06 Hz, 1 H), 13.02 (s, 1 H). ES-MS m/z 416 (M + H). Anal. ($C_{25}H_{25}N_3O_3$) C, H, N.

(±)-(3*RS*,3a*SR*)-2-(4-Cyano-3-(methoxymethyl)phenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27l). A mixture of **9g**, **25b** (209 mg, 0.73 mmol), and ethanol (4 mL) was stirred under argon at 80 °C for 4 h. The mixture was cooled to room temperature and concentrated to give the pyrazoline ester as a yellow solid. The ester was suspended in tetrahydrofuran (4 mL), methanol (1 mL) and treated with 2.5 N sodium hydroxide (1 mL) at room temperature. After 4 h the mixture was concentrated to half the original volume, treated with 6 N hydrogen chloride (2 mL), dimethyl sulfoxide (24 mL) and purified by reversed-phase HPLC (acetonitrile/water/0.05% trifluoroacetic acid) to give the title compound (65 mg, 0.015 mmol, 18%) as a yellow-orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.04 (s, 1 H), 8.07 (d, J = 8.06 Hz, 1 H), 7.80−7.87 (m, 2 H), 7.60 (d, J = 8.86 Hz, 1 H), 7.35 (d, J = 2.15 Hz, 1 H), 7.18 (dd, J = 8.86, 2.15 Hz, 1 H), 4.92 (dd, J = 9.80, 5.51 Hz, 1 H), 4.50 (s, 2 H), 3.59 (ddd, J = 13.83, 9.40, 4.70 Hz, 1 H), 3.36 (s, 3 H), 3.06−3.15 (m, 1 H), 2.82−2.96 (m, 1 H), 2.19−2.29 (m, 1 H), 2.00−2.13 (m, 1 H), 1.65−1.89 (m, 2 H), 1.14−1.54 (m, 7 H). ES-MS m/z 430 (M + H).

(±)-(3*RS*,3a*SR*)-2-(3-(Benzyloxy)-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (27m). The title compound was obtained from **25b** and **9h** according to method C3 followed by method D as a yellow-orange solid (90 mg, 0.18 mmol, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03−1.51 (m, 7 H), 1.57−1.69 (m, 1 H), 1.74−1.89 (m, 1 H), 1.95−2.07 (m, 1 H), 2.18−2.29 (m, 1 H), 2.82−2.96 (m, 1 H), 3.03−3.14 (m, 1 H), 3.57 (ddd, J = 13.70, 9.40, 4.30 Hz, 1 H), 4.91 (dd, J = 9.53, 5.50 Hz, 1 H), 5.31 (q, J = 12.35 Hz, 2 H), 6.84 (d, J = 8.86 Hz, 1 H), 6.96 (s, 1 H), 7.35 (t, J = 7.25 Hz, 1 H), 7.40−7.53 (m, 5 H), 7.81−7.88 (m, 2 H), 8.09 (d, J = 8.06 Hz, 1 H), 13.03 (s, 1 H). ES-MS m/z 492 (M + H).

(±)-(3*RS*,3a*SR*)-Methyl 2-(3-(Benzyloxy)-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylate (27n). A mixture of **27m** (70 mg, 0.14 mmol), ethyl acetate, tetrahydrofuran, and methanol was treated with 10% palladium on carbon (10 mg) and hydrogenated for 4 h at 30 psi of hydrogen.

The mixture was filtered through Celite and concentrated to give the title compound (57 mg, 0.14 mmol, quant) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10−1.58 (m, 8 H), 1.61−1.75 (m, 1 H), 1.74−1.90 (m, 1 H), 2.00−2.12 (m, 1 H), 2.16−2.30 (m, 1 H), 2.79−2.96 (m, 1 H), 3.09 (d, J = 16.11 Hz, 1 H), 3.57 (ddd, J = 13.76, 9.47, 4.70 Hz, 1 H), 4.76 (dd, J = 9.67, 5.37 Hz, 1 H), 6.69 (dd, J = 8.86, 1.61 Hz, 1 H), 6.82 (s, 1 H), 7.36 (d, J = 8.59 Hz, 1 H), 7.82−7.90 (m, 2 H), 8.00 (d, J = 8.06 Hz, 1 H), 10.70 (s, 1 H). ES-MS m/z 402 (M + H).

(±)-(3*SR*,3a*SR*)-2-(3-Chloro-4-cyanophenyl)-3-(4-fluorophenyl)-2,3,3a,4-tetrahydrochromeno[4,3-*c*]pyrazole-7-carboxylic Acid (27o). The title compound was prepared from **25g** (155 mg, 0.50 mmol) and **9a** (153 mg, 0.75 mmol) according to method C3 and method D. The crude product was purified by reverse-phase HPLC (acetonitrile/water/0.05% trifluoroacetic acid) to give the title compound (41 mg, 0.09 mmol, 18%). ES-MS m/z 448 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.16 (dd, J = 12.9, 10.5 Hz, 1 H), 4.20−4.31 (m, 1 H), 4.38 (dd, J = 10.5, 5.9 Hz, 1 H), 5.96 (d, J = 11.5 Hz, 1 H), 6.95−7.26 (m, 5 H), 7.39 (d, J = 1.6 Hz, 1 H), 7.55−7.63 (m, 3 H), 7.98 (d, J = 8.1 Hz, 1 H), 13.17 (s, 1 H).

(±)-(3*RS*,3a*SR*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-2,3,3a,4-tetrahydrochromeno[4,3-*c*]pyrazole-7-carboxylic Acid (*cis*-27p). The title compound was prepared from **25h** (573 mg, 2.0 mmol) and **9a** (612 mg, 3.0 mmol) according to method C3 and method D. The crude precipitate was recrystallized from dimethylformamide and methanol to give the title compound as yellow crystals (237 mg, 0.563 mmol, 28% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.20 (s, 1 H), 7.98 (d, J = 8.2 Hz, 1 H), 7.70 (d, J = 9.0 Hz, 1 H), 7.58 (dd, J = 8.2, 1.6 Hz, 1 H), 7.47 (d, J = 1.2 Hz, 1 H), 7.41 (d, J = 2.0 Hz, 1 H), 7.20 (dd, J = 8.8, 2.1 Hz, 1 H), 4.95 (dd, J = 9.4, 7.0 Hz, 1 H), 4.78 (dd, J = 10.2, 5.9 Hz, 1 H), 4.31 (dd, J = 13.3, 10.5 Hz, 1 H), 4.00 (ddd, J = 13.2, 9.7, 5.7 Hz, 1 H), 2.03−2.16 (m, 1 H), 1.13−1.68 (m, 8 H). ES-MS m/z 422 (M + H).

(±)-(3*RS*,3a*RS*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-2,3,3a,4-tetrahydrochromeno[4,3-*c*]pyrazole-7-carboxylic Acid (*trans*-27p). The title compound was prepared by epimerization of ***cis*-27p** (131 mg) in a solution of 0.5 M sodium methoxide/methanol (4 mL) and tetrahydrofuran (2 mL) at 50 °C. After 24 h, the mixture was concentrated under a stream of nitrogen and purified by reverse-phase HPLC (60 to 90% acetonitrile/water/0.05% trifluoroacetic acid) to give the trans diastereomer of the title compound as a yellow solid (26.7 mg, 0.0634 mmol, 20% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.16 (br s, 1 H), 7.82 (d, J = 8.2 Hz, 1 H), 7.75 (d, J = 9.0 Hz, 1 H), 7.56 (dd, J = 7.8, 1.6 Hz, 1 H), 7.43 (d, J = 1.6 Hz, 1 H), 7.38 (d, J = 2.3 Hz, 1 H), 7.18 (dd, J = 9.0, 2.3 Hz, 1 H), 4.63 (dd, J = 10.5, 5.9 Hz, 1 H), 4.52 (dd, J = 8.2, 4.7 Hz, 1 H), 4.26 (dd, J = 12.5, 10.5 Hz, 1 H), 3.54−3.62 (m, 1 H), 2.68−2.85 (m, 1 H), 1.79−1.91 (m, 1 H), 1.20−1.71 (m, 7 H). ES-MS m/z 422 (M + H). Anal. ($C_{23}H_{20}ClN_3O_3 \cdot 0.2H_2O$) C, H, N.

(±)-(3*RS*,3a*SR*)-2-(4-Cyano-3-methylphenyl)-3-cyclopentyl-2,3,3a,4-tetrahydrochromeno[4,3-*c*]pyrazole-7-carboxylic Acid (27q). The title compound was prepared according to method C3 and method D from **25h** and **9c** to give only the cis diastereomer as a yellow solid (301 mg, 0.751 mmol, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.15 (s, 1 H), 7.94 (d, J = 8.2 Hz, 1 H), 7.58 (dd, J = 8.2, 1.6 Hz, 1 H), 7.53 (d, J = 9.0 Hz, 1 H), 7.46 (d, J = 1.6 Hz, 1 H), 7.21 (d, J = 2.0 Hz, 1 H), 7.08 (dd, J = 8.8, 2.1 Hz, 1 H), 4.89 (dd, J = 9.8, 7.0 Hz, 1 H), 4.78 (dd, J = 10.2, 5.9 Hz, 1 H), 4.30 (dd, J = 12.9, 10.5 Hz, 1 H), 3.97 (ddd, J = 13.0, 9.9, 5.7 Hz, 1 H), 2.41 (s, 3 H), 2.01−2.16 (m, 1 H), 1.13−1.67 (m, 8 H). ES-MS m/z 402 (M + H). Anal. ($C_{24}H_{23}N_3O_3$) Calcd: C, 71.80; H, 5.78; N, 10.47. Found: C, 71.90; H, 5.28; N, 10.19.

(3*S*,3a*R*)-2-(4-Cyano-3-methylphenyl)-3-cyclopentyl-2,3,3a,4-tetrahydrochromeno[4,3-*c*]pyrazole-7-carboxylic Acid (3*S*,3a*R*-27q). The title compound was obtained by chiral resolution of (±)-**27q** (Chiralcel OJ-H 30 mm × 250 mm, 50% methanol/carbon dioxide, 70 mL/min). First eluting peak: chiral HPLC t_R = 3.2 min (Chiralcel OJ-H 4.6 mm × 250 mm, 50% methanol/carbon dioxide, 3 mL/min).

(3*S*,3a*R*)-Methyl 2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylate (28). A solution of (trimethylsilyl)diazomethane (2.0 M in diethyl ether, 0.286 mL, 0.572 mmol) was added to a solution of **3*S*,3a*R*-27d** (200 mg, 0.476 mmol) in tetrahydrofuran (3 mL) and methanol (1 mL). After 90 min, the mixture was concentrated to give the crude methyl ester as a yellow solid (217 mg, quant.). ES-MS m/z 434 (M + H).

(3*S*,3a*R*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3a-methyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic Acid (3*S*,3a*R*-29). To a solution of diisopropylamine (0.0772 mL, 0.551 mmol) in tetrahydrofuran (1.5 mL) at −78 °C was added *n*-butyllithium (2.5 M in hexanes, 0.206 mL, 0.514 mmol). After 10 min, a solution of **28** (159 mg, 0.367 mmol) in tetrahydrofuran (3.0 mL) was added dropwise. After 1 h at −78 °C, iodomethane (0.0343 mL, 0.551 mmol) was added. The mixture was kept at −78 °C and monitored by LCMS. After 2 h, another 0.015 mL of iodomethane was added. Lithium hexamethyldisilazide (1.0 M in tetrahydrofuran, 0.100 mL, 0.100 mmol) was added, followed by another 0.015 mL iodomethane. The mixture was allowed to slowly warm to room temperature overnight. The mixture was treated with 0.5 mL of methanol and 0.5 mL of 2.5 N NaOH. After 4 h, the reaction mixture was neutralized with 0.5 mL of 3 N hydrogen chloride and concentrated under a stream of nitrogen. The residue was dissolved in dimethylformamide/methanol, filtered through a syringe filter, and purified by reverse-phase HPLC (60−95% acetonitrile/water/0.05% trifluoroacetic acid) to give the title compound as a yellow solid and a single stereoisomer (48.6 mg, 0.112 mmol, 30.5% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.06 (br s, 1 H), 8.10 (d, J = 8.2 Hz, 1 H), 7.87 (s, 1 H), 7.81 (d, J = 7.8 Hz, 1 H), 7.69 (d, J = 9.0 Hz, 1 H), 7.43 (s, 1 H), 7.23 (d, J = 9.0 Hz, 1 H), 4.57 (d, J = 5.9 Hz, 1 H), 3.01−3.10 (m, 2 H), 1.91−2.11 (m, 3 H), 1.71−1.82 (m, 1 H), 1.09−1.56 (m, 7 H), 1.06 (s, 3 H). ES-MS m/z 434 (M + H). HPLC purity 85%.

Biological Assays. Cell-Based Gal4 Response Element-Controlled Luciferase Reporter Assays. MR Luciferase Reporter Antagonist Assay. HUH7 human hepatocyte cells were maintained in RPMI 1640 plus 10% FBS and transfected with Gal4-MRLBD construct and a luciferase reporter under Gal4 control. After transfection, compounds were added in RPMI 1640 media plus 10% heat-inactivated and charcoal dextran stripped FBS (Hyclone) with and without 1 nM aldosterone. Cells were harvested 20 h later for reporter activity as previously described.[12] IC_{50} values were obtained through curve-fitting of dose response plots ($n \geq 3$/concentration, 6−10 concentrations) using the four-parameter logistic model. Standard error of the IC_{50} was generally less than 30%. Selectivity against other steroid receptors were assayed in the same manner using Gal4-driven luciferase as reporter.

Radioligand Binding Assay. Test compound affinity was expressed as IC_{50} value, defined as the concentration of test compound required to decrease [^{3}H]aldosterone binding by 50%. MR binding assays were performed in a final volume of 50 μL containing 1 nM MR (GST-LBD fusion, expressed in SF9 insect cells) and 1 nM [^{3}H]aldosterone (PerkinElmer, NET419) plus varying concentrations of test compound or vehicle. Briefly, assays were prepared at 4 °C in 384-well plate (Costar, 3657) containing 1 μL of test compound in DMSO (or DMSO as vehicle). Assays were initiated by addition of 24 μL of 2 nM [^{3}H]aldosterone followed by 25 μL of 2 nM GST-MR in binding-wash buffer (50 mM HEPES (pH 7.5), 50 mM KCl, 2 mM EDTA, 10% glycerol, and 5 mM DTT). The mixture was incubated at 4 °C for 4 h, then was transferred to a 384-well glass fiber filtration plate (Millipore, MZFCN0W50) previously treated with 0.5% PEI. The mixture was suctioned dry with vacuum and immediately washed three times with 100 μL of 4 °C binding-wash buffer. The plates were allowed to air-dry overnight at room temperature, and 7 μL of Ready Safe liquid scintillant (Beckman, 141349) was added to each well. The amount

of receptor−ligand complex was determined by liquid scintillation counting using a 1450 Microbeta Trilux (Wallac). Radioligand binding filtration format assays for progesterone receptor (PR) were performed in an identical manner as described for MR except 4 nM (final concentration) full length PR (Invitrogen, P2835) was substituted for MR and 1 nM (final concentration) [^{3}H]progesterone (PerkinElmer, NET381) was substituted for radiolabeled aldosterone.

Dahl Salt Sensitive Rat Model of Hypertension and Nephropathy.[11] All animals were outfitted with radiotelemetry units (Data Sciences Inc., St. Paul, MN) for conscious, unrestricted SBP measurements. After recovery from surgery, baseline SBP was measured and all animals were then randomized into various treatment groups and compounds were continued for 21 days. The vehicle group received 0.5% methylcellulose/0.1% Tween 80. All compounds given to the treatment groups were dissolved in 0.5% methylcellulose/0.1% Tween 80. For compound treated groups, animals were dosed with the compounds daily, via gavage. For eplerenone treated groups, eplerenone was incorporated into the 4% NaCl rodent chow at various concentrations (Research Diets, Inc., New Brunswick, NJ). Radiotelemetrized arterial SBP was measured with the DATAQUEST A.R.T., version 3.0, Gold software (Data Sciences International, St. Paul, MN).

Twenty-four hours prior to the termination of the study, animals were placed in metabolism caging and urine was collected at 24 h. Animals were not fasted for the 24 h period. After 21 days of treatment, animals were exsanguinated using a 20 gauge needle inserted into the abdominal aorta. Blood samples were immediately transferred into Vacutainer collection tubes (Becton-Dickinson and Co., Franklin Lakes, NJ) and placed on wet ice. Blood was centrifuged for 15 min at 3000 rpm, 4 °C, and plasma collected and frozen at −80 °C until further analysis. Plasma and urine chemistries (e.g., albumin, creatine, and electrolytes) were analyzed with the Hitachi 912 automated diagnostic clinical chemistry analyzer (Roche Diagnostics Corp., Indianapolis, IN) according to standard procedures. Pathlogy scoring was conducted, as reported in ref 23.

The St. Louis Pfizer Institutional Animal Care and Use Committee reviewed and approved the animal use in these studies. The animal care and use program is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Molecular Modeling Studies. Molecular modeling was conducted using the Schrodinger Suite 2006 and 2009 (Schrodinger Suite 2009 Induced Fit Docking protocol, Glide version 5.5, Prime version 2.1, Jaguar version 7.6; Schrodinger LLC, New York, NY). The 1.95 Å MR structure with bound corticosterone (PDB code 2A3I)[18] was prepared by removal of waters, addition of hydrogens, and restrained energy minimization. Conformationally restricted pyrazoline **3*S*,3a*R*-27d** was geometry-optimized using Jaguar (B3LYP/6-31G**//B3LYP/6-31G**) prior to docking into the receptor model. The induced fit docking protocol[24] used defaults except for trimming residues N770, L848, and F941 for the initial Glide docking; Prime side chain refinement out to 7.5 Å from docked poses (omitting Q776 and R817); and use of XP scoring on the redock step. No hydrogen bonding or other constraints were used. The top-scoring pose obtained was subjected to restrained energy minimization to produce the model shown. Pictures were generated using Maestro 9.0.211 (Schrodinger LLC).

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Supporting Information Available: X-ray crystallographic data for compounds ***R*-17** and **3*R*,3a*R*-27c** and combustion analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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