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Synthesis and activity of small molecule GPR40 agonists

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Abstract—The first report on the identification and structure–activity relationships of a novel series of GPR40 agonists based on a 3-(4-{[*N*-alkyl]amino}phenyl)propanoic acid template is described. Structural modifications to the original screening hit yielded compounds with a 100-fold increase in potency at the human GPR40 receptor and pEC_{50}s in the low nanomolar range. The carboxylic acid moiety is not critical for activity but typically elicits an agonistic response higher than those observed with carboxamide replacements. These compounds may prove useful in unraveling the therapeutic potential of this receptor for the treatment of Type 2 diabetes.

The G-protein coupled receptor GPR40 is highly expressed in human and rodent pancreatic islets and is activated by long-chain free fatty acids (e.g., linoleic and palmitic acids) resulting in stimulation of downstream signaling pathways which activate protein kinase C (PKC) and elevate intracellular $[Ca^{2+}]$.[1,2] Since both activation of PKC and increasing intracellular $[Ca^{2+}]$ play a key role in insulin exocytosis in pancreatic β-cells,[3] GPR40 may serve as a signaling mechanism through which free fatty acids directly affect insulin secretion. Both linoleic and palmitic acids potentiate glucose-stimulated insulin release in insulinoma cell lines (MIN6 and INS-1E, respectively) but the effects were greatly diminished when the expression of the GPR40 receptor was down-regulated by the addition of interfering RNA.[2,4] Given the need for novel treatments for Type 2 diabetes, GPR40 represents a potentially attractive target.

A FLIPR-based high-throughput screen of the GlaxoSmithKline chemical collection in a HEK293 cell line expressing human GPR40 yielded the small molecule GPR40 agonist **1**.[1] The potency and efficacy of compound **1** was then determined by a ten-point dose–response curve in a CHO cell line expressing human GPR40 using a Gal4/Elk1/luciferase reporter assay.[1] In this assay, compound **1** had a $pEC_{50} = 6.03$ and evoked a maximal response similar to that observed for linoleic acid, indicating that it is a full agonist for the GPR40 receptor as compared to the fatty acid. Compound **1** is an attractive starting point for developing structure–activity relationships (SAR) with GPR40 given the relative ease of product synthesis (i.e., reductive amination reactions) and the commercial availability of starting materials such as aldehydes and anilines. In this manner, several more potent analogs were quickly constructed such as **2A** and **2B** (Fig. 1). Here, the first report on the synthesis and the SAR of a novel series of GPR40 agonists is described.

The desired compounds were prepared by reductive amination coupling reactions as depicted in Scheme 1 between an appropriately substituted aniline intermediate **I** and an aldehyde (commercially available 3-phenoxybenzaldehyde for series A and 4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole-5-carbaldehyde[5] for series B).[6,7] In many cases, the free carboxylic acids were commercially available and used directly, thereby yielding the desired compounds in a single step (compounds **2**–**7A** and **8**–**11**). For others, the carboxylic esters were

Keywords: GPR40; GPR40 agonists; Fatty acid receptor; Type 2 diabetes; GPCR agonist; G-protein coupled receptor agonist; Asymmetric cyclopropanation.
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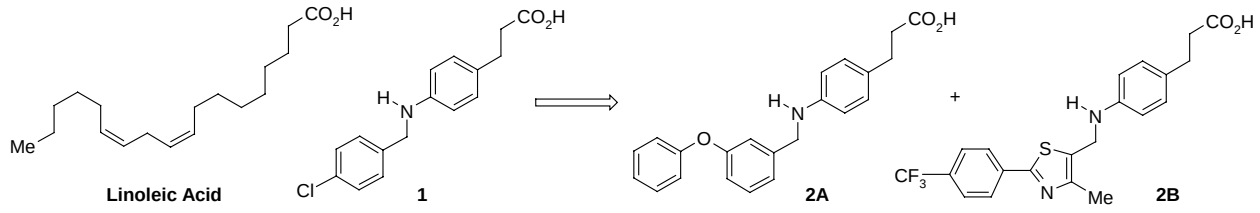
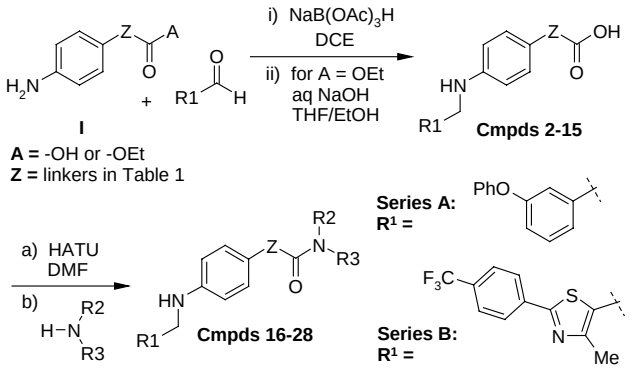


Figure 1. GPR40 agonists identified via high-throughput screening (**1**) and subsequent analog screening (**2A** and **2B**).



Scheme 1. General syntheses of the desired analogs.

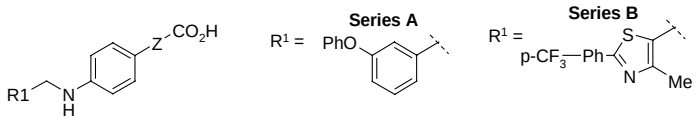
employed which necessitated base-mediated ester hydrolysis as the final step to liberate the acid (compounds **7B** and **12**–**15**).[6,8] The carboxamide derivatives **16**–**28** were prepared via HATU-promoted amide bond formation from the corresponding acid analogs and a variety of amines.[6,9] The potency of a compound was determined via a ten-point dose–response curve in a CHO cell line expressing human GPR40 using a Gal4/Elk1/luciferase reporter assay and is reported as the pEC_{50} value. The efficacy of the compound is shown as a percentage of the maximal agonistic response elicited by the test compound with respect to the maximal response evoked by the internal standard **1** at a dose of 10 μM.

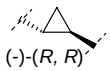
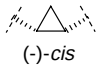
Initial efforts to increase the potency of the screening hit **1** indicated that activity was dependent upon the nature of the acid tether (*Z*).[10] Therefore, an early priority was to examine the optimal spacing between the acid headgroup and the phenyl core in series A and B. A set of analogs was synthesized in which the number of methylene linkers, $Z = (CH_2)_n$, was sequentially increased from $n = 0$–3. Compounds **2**–**5** in both series show a clear preference for the phenethyl-linked acids (compounds **2A** and **2B** where $Z = (CH_2)_{n=2}$) since both the shorter- (e.g., **3** and **4**) and longer chain lengths (e.g., **5**) led to a substantial loss in potency and efficacy (Table 1). Introducing a two-carbon tether in the form of an unsaturated *trans*-cinnamic acid headgroup (compounds **6A** and **6B**) resulted in activities similar to those of the saturated ethyl-linked analogs. Substitution of the two-carbon linker with heteroatoms was also evaluated. The replacement of the benzylic methylene group with an oxygen atom (e.g., **7A** and **7B**) decreased potency though the maximal efficacy was retained. However, the bulkier fibrate headgroup (compound **8A**) completely abolished GPR40 activity. The potency of the sulfur-analog **9A** was slightly decreased but not statistically different from that of the ethyl-linked variant **2A**. As a general rule, a two-carbon tether between the acid- and phenyl units appears optimal for both series.

Structure–activity relationships generated from a solid-phase library highlighted a trend toward increased potency with cyclopropyl-linked acids and therefore the effect of this group was examined in series A and B.[10] Examples **10A** and **10B** show that the racemic mixtures of the *trans*-cyclopropyl acid headgroups significantly increased GPR40 potency. In fact, within series B the *trans*-cyclopropyl modification resulted in a >25-fold increase in potency over the simple ethyl tether (compare $pEC_{50} = 8.61$ for **10B** vs $pEC_{50} = 7.17$ for **2B**). Unfortunately, the cyclopropyl moiety also complicates the overall synthesis in that two new stereogenic centers are introduced. In an effort to eliminate one asymmetric center, the α- and β-methyl analogs **11** and **12** were envisioned. The addition of a methyl group to the benzylic carbon (analogs **12A** and **12B**) resulted in only minor effects on GPR40 activity as compared to the unsubstituted ethyl analogs. Similarly, introduction of a methyl substituent on the carbon adjacent to the acid led to no change in activity for series A (compound **11A**) but did produce a drop in potency in series B (compound **11B**). Although neither the α- nor the β-methyl substituents were overtly detrimental to activity, there was no significant improvement like that observed for the cyclopropyl linker.

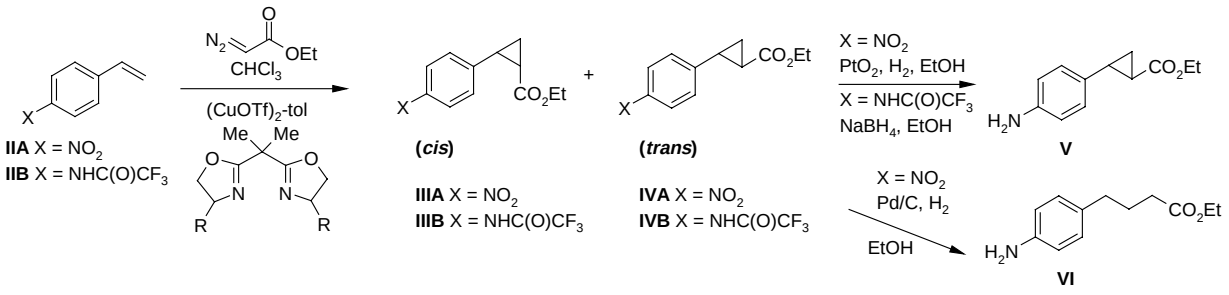
The logical next step was to synthesize and compare the two individual enantiomers of analogs **10**, which required the preparation of both the (*R*,*R*) and (*S*,*S*)-2-(4-aminophenyl)-cyclopropanecarboxylic ethyl esters (**V**). The synthesis was initially accomplished by a slow addition of ethyldiazoacetate to a mixture of 4-nitrostyrene **IIA** and a chiral Cu(I)-bisoxazoline complex as depicted in Scheme 2.[11] The commercially available (*S*,*S*)-bisoxazoline ligand (2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]) produced a mixture of the *cis*-(**IIIA**) and *trans*-(**IVA**) products in an approximate 1:4 ratio which could easily be separated by chromatography on silica gel (Table 2, Entry 1). Unfortunately, the major *trans*-isomer co-eluted with diethylfumarate, a by-product arising from the cross condensation of ethyldiazoacetate, which made determination of the chemical yield difficult but was estimated to be only 24% by ^1H NMR. The nitro group of **IVA** was quantitatively reduced with catalytic PtO_2 and hydrogen (50 psi) in EtOH to afford the aniline **V**, which was isolated in >95% purity. It is worth noting that substituting Pd/C for PtO_2 did not yield the desired intermediate **V** but instead gave the ring-opened adduct **VI**. The enantiomeric

Table 1. SAR for Z-tethered carboxylic acids in series A and B[a]



Compounds	Z =	pEC_{50}[b] ± SD (% max resp.[c] ± SD)[d]	
		Series A	Series B
2A, **2B**	$-(CH_2)_2-$	7.19 ± 0.54 (82 ± 24%)	7.17 ± 0.13 (108 ± 31%)
3A, **3B**	—	<5 (86 ± 18%)	<5 (10%)
4A, **4B**	$-CH_2-$	<5 (36%)	<5 (18%)
5A, **5B**	$-(CH_2)_3-$	5.95 ± 0.07 (59 ± 6%)	<5 (44%)
6A, **6B**	(*E*)-CH=CH–	6.84 ± 0.16 (76 ± 5%)	7.44 ± 0.25 (95 ± 3%)
7A, **7B**	$-OCH_2-$	5.69 ± 0.26 (84 ± 1%)	6.54 (100%)
8A		<5 (14%)	
9A	$-SCH_2-$	6.49 ± 0.30 (84 ± 2%)	
10A, **10B**	 (*Rac*)-*trans*	7.87 ± 0.05 (72 ± 3%)	8.61 ± 0.14 (81 ± 7%)
11A, **11B**	 (*Rac*)	7.00 ± 0.01 (70 ± 1%)	6.45 ± 0.21 (100 ± 15%)
12A, **12B**	 (*Rac*)	6.90 ± 0.14 (83 ± 12%)	7.23 ± 0.15 (109 ± 9%)
13A	 (-)-(*R*, *R*)	6.25 ± 0.02 (64 ± 6%)	
14A, **14B**	 (+)-(*S*, *S*)	7.91 ± 0.25 (88 ± 13%)	8.31 ± 0.27 (89 ± 16%)
15B	 (-)-*cis*		6.52 ± 0.22 (68 ± 26%)

[a] Compound **1** is the internal standard (pEC_{50} = 6.03 ± 0.04).
[b] Negative log of the molar concentration required to elicit a half-maximal response.
[c] The maximal agonistic response elicited by the compound as a percentage of the maximal response evoked by compound **1** at 10 μM.
[d] Reporter assay expressing human GPR40 in a CHO cell line Ref. 1.



Scheme 2. Asymmetric syntheses of (*R*,*R*)- and (*S*,*S*)-2-(4-aminophenyl)cyclopropanecarboxylic ethyl esters **V**.

excess (ee) of compound **V** was determined to be >95% as the (−)-(*R*,*R*)-stereoisomer.[12,13] Overall, the cyclopropanation of 4-nitrostyrene gave comparable results to those reported for styrene both in terms of the diastereo- and enantioselectivity.[11] As expected, the corresponding (+)-(*S*,*S*)-isomer of **V** was obtained via the same two-step sequence with similar enantioselectivity and product distribution using the (*R*,*R*)-*tert*-butyl-bis-

Table 2. Diastereo- and enantioselectivity for the asymmetric cyclopropanation of 4-substituted styrenes

Entry	X =	Chirality of (bis)oxazoline	R =	Ratio of **III/IV**[a]	% Yield of **IV**	Chirality of major enantiomer of **V**[d]	% ee of **V**[e]
1	NO_2	(*S*,*S*)	*t*-Bu	1:4	24[b]	(−)-(*R*,*R*)	95
2	NO_2	(*R*,*R*)	*t*-Bu	1:4	30[b]	(+)-(*S*,*S*)	95
3	NO_2	(*R*,*R*)	Ph	1:5.7	31[b]	(+)-(*S*,*S*)	83
4	$NHC(O)CF_3$	(*R*,*R*)	*t*-Bu	1:2.3	61[c]	(+)-(*S*,*S*)	94
5	$NHC(O)CF_3$	(*R*,*R*)	Bn	1:2.3	na	(+)-(*S*,*S*)	57

na, not determined.
[a] Ratio estimated from ^1H NMR of reaction mixture after workup.
[b] Mixture of **IVA** and diethylfumarate. Yield of **IVA** estimated by ^1H NMR.
[c] Refers to the isolated yield of **IVB** in >95% purity.
[d] The absolute stereochemistry was assigned based on the VCD analysis Ref. 13.
[e] Determined by chiral SFC analysis Ref. 12.

oxazoline ligand (Table 2, entry 2). Unfortunately this ligand is not commercially available and needed to be prepared in three steps from (D)-*tert*-leucine.[14] Since unnaturally occurring (D)-*tert*-leucine is relatively expensive, the use of the commercially available (*R*,*R*)-phenyl-bisoxazoline ligand was also investigated (Table 2, entry 3). The ratio of products **IIIA/IVA** was slightly improved with the phenyl- versus the *tert*-butyl-ligand but the enantiomeric excess of product **V** was significantly worse (83% vs 95% ee, respectively).

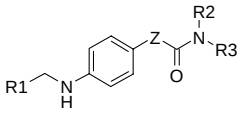
One drawback to the initial cyclopropanation route was the poor isolated yield of compound **V**. It was hypothesized that the nitrostyrene starting material **IIA** might be polymerizing under the reaction conditions and therefore the 4-trifluoroacetamide-styrene **IIB** was subjected to the cyclopropanation procedure described above (Table 2, entry 4). Although the diastereoselectivity of the reaction was a little worse than that observed for substrate **IIA**, the desired *trans*-cyclopropyl analog **IVB** was obtained in a 61% isolated yield, which was a significant improvement. The trifluoroacetamide protecting group was cleaved with $NaBH_4$ in EtOH in an unoptimized 61% yield to afford compound **V** in 94% ee. Although the overall yield is still modest, this method has been used to produce over 30 g of the enantiomerically pure (*S*,*S*)-aniline **V**.[15] The use of the commercially available (*R*,*R*)-benzyl-bisoxazoline ligand was also investigated with substrate **IIB** but the reaction proceeded with poor enantioselectivity (Table 2, entry 5).

Both the (*R*,*R*)- and (*S*,*S*)-anilines of **V** as well as the (−)-*cis*-isomer isolated as the minor product from the cyclopropanation of **IIB** (Table 2, entry 4) were subsequently converted to the final products **13A**, **14A**, **14B**, and **15B** in >95% ee. The (+)-(*S*,*S*)-enantiomer **14A** behaved as a potent, full agonist at the GPR40 receptor with a pEC_{50} = 7.91 (Table 1) and is >45-fold more active than the corresponding (−)-(*R*,*R*)-isomer **13A** (pEC_{50} = 6.25). The (−)-(*R*,*R*)-analog **13A** also appears to be a partial agonist producing a maximal response only 64% of that produced by compound **1**. The (+)-(*S*,*S*)-derivative in series B (compound **14B**) was also active with a pEC_{50} = 8.31, although in neither series was the potency of the enantiomerically pure (*S*,*S*)-isomer statistically different from the potency of the racemic mixture. The (−)-*cis*-isomer **15B** was less active than both the corresponding (+)-(*S*,*S*)-*trans*-isomer **14B** and the simple ethyl-linked analog **2B**.

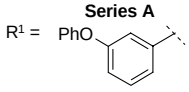
The compounds presented up to this point all contain a carboxylic acid headgroup and thus resemble free fatty acids themselves. The question remained whether this functional group was critical for activity, so a set of amide analogs was prepared. Replacement of the acid would remove the potential for acyl glucuronide formation and perhaps lower binding to plasma proteins, such as albumin, which is typically quite high (>99%) for this class of compounds. The primary amide in series A (**16A**) was equipotent to the corresponding acid **2A**, while in series B the primary amide (**16B**) was more potent than the acid **2B** (Table 3). Simple mono-alkylation with a methyl group (derivative **17A**) or a bulkier isopropyl substituent (compounds **18A** and **18B**) was well tolerated displaying potencies similar to those of the corresponding acids and efficacies similar to those of the primary amides. Though not statistically significant, there does appear to be a drop in maximal efficacy suggesting that the primary and secondary amides may only be partial agonists. This trend was much more pronounced with the tertiary amides (the dimethyl-amide **19A** and the pyrrolidine-amide **20A**) whose maximal efficacy deteriorated to almost half of that elicited by the free carboxylic acid **2A** (e.g., 50% max for **19A** and 46% max for **20A** vs 86% max for **2A**). A similar trend also appeared within the cyclopropyl-linked analogs in series B (**21B**–**23B**). In addition, increasing the bulk of the amide substituent detrimentally affects activity. For instance, changing from the *N*-isopropyl (**24B**) to *N*-cyclobutyl (**25B**) to *N*-(*R*)-phenethylamide (**26B**) resulted in a progressive decrease in efficacy and potency. The more polar analog **27B** was worse still. On the contrary, the smaller hydroxamic acids **28A** and **28B** resemble the free carboxylic acids in both potency and efficacy at GPR40.

In conclusion, a variety of novel compounds that activate GPR40 at low nanomolar concentrations have been identified, the majority of which behave as full agonists as compared to the endogenous long-chain fatty acid ligands. The introduction of the (*S*,*S*)-cyclopropyl acid headgroup led to a significant improvement in potency over the ethyl-linked analogs, while the (*R*,*R*)-cyclopropyl enantiomer was only weakly active. The asymmetric syntheses of the cyclopropyl intermediates were accomplished in high enantiomeric excess and good yield from commercially available 4-aminostyrene. Structure–activity relationships revealed that the acid itself is not critical for activity but typically elicits a higher agonistic response than that observed with the carboxamide

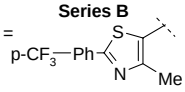
Table 3. SAR for carboxamide analogs in series A and B[a]



Series A



Series B



Compounds	Z =	R^2 =	R^3 =	pEC_{50}[b] ± SD (% max resp.[c] ± SD)[d]	
				Series A	Series B
16A, **16B**	$-(CH_2)_2-$	H	H	7.29 ± 0.15 (68 ± 5%)	7.89 ± 0.20 (88 ± 14%)
17A	$-(CH_2)_2-$	H	Me	7.31 ± 0.27 (67 ± 3%)	
18A, **18B**	$-(CH_2)_2-$	H	*i*-Pr	7.40 ± 0.43 (66 ± 11%)	7.00 ± 0.29 (84 ± 32%)
19A	$-(CH_2)_2-$	Me	Me	6.76 ± 0.13 (50 ± 4%)	
20A	$-(CH_2)_2-$	$-CH_2CH_2CH_2CH_2-$		6.94 ± 0.15 (46 ± 3%)	
21B	(*Rac*)- 	H	H		8.35 ± 0.41 (80 ± 3%)
22A, **22B**	(*Rac*)- 	H	*i*-Pr	7.90 ± 0.17 (62 ± 15%)	7.85 ± 0.09 (69 ± 12%)
23B	(*Rac*)- 	Me	Me		7.18 (49%)
24B	(*S*, *S*)- 	H	*i*-Pr		7.96 ± 0.23 (71 ± 10%)
25B	(*S*, *S*)- 	H	Cyclobutyl		8.04 ± 0.08 (55 ± 9%)
26B	(*S*, *S*)- 	H			7.27 ± 0.14 (42 ± 1%)
27B	(*S*, *S*)- 	H			6.69 ± 0.01 (52 ± 7%)
28A, **28B**	(*S*, *S*)- 	H	OH	7.83 ± 0.17 (90 ± 9%)	8.16 ± 0.08 (78 ± 8%)

[a] Compound **1** is the internal standard (pEC_{50} = 6.03 ± 0.04).
[b] Negative log of the molar concentration required to elicit a half-maximal response.
[c] The maximal agonistic response elicited by the compound as a percentage of the maximal response evoked by compound **1** at 10 μM.
[d] Reporter assay expressing human GPR40 in a CHO cell line Ref. 1.

replacements. The marked increase in activity of these analogs versus the endogenous fatty acid ligands (e.g., linoleic acid) will allow for a better understanding of the role of GPR40 in insulin secretion and as a potential treatment of Type 2 diabetes. A manuscript describing the in vitro effects of compound **2A** on insulin secretion has been submitted and will appear shortly.[16]

Acknowledgments

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6. Compound purity was determined to be >95% by both ^1H NMR and LC/MS spectroscopy; the spectral data were consistent with the reported structures.
7. A typical procedure for the reductive amination coupling reaction is as follows: $NaB(OAc)_3H$ (1.5–2.5 equiv) was added to a solution of aniline (1 equiv) and aldehyde (1 equiv) in dichloroethane (ca. 0.1 M) at rt. The mixture was stirred for 1–16 h and then water and CH_2Cl_2 were added. The crude product was purified on silica gel (hexanes/ethyl acetate).
8. A typical procedure for the hydrolysis of the ester is as follows: aqueous 1–5 N NaOH solution (5–10 equiv) was added to a solution of the ester (1 equiv) in THF (ca. 0.5 M) and EtOH (ca. 0.5 M). The solution was heated to reflux until no ester remains as evident by TLC, then aqueous 1N HCl solution was added until the pH <7. The product was extracted into ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give the pure carboxylic acid.
9. A typical procedure for the synthesis of the amide is as follows: HATU (1.3 equiv) and the carboxylic acid (1 equiv) in DMF (ca. 0.5 M) were stirred at rt for 5 min and then the amine (2 equiv) was added. After 16 h, saturated aqueous $NaHCO_3$ solution and ethyl acetate were added. The crude products were purified on silica gel (hexanes/ethyl acetate).

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12. The enantiomeric excess (ee) of aniline **V** was determined by chiral supercritical fluid chromatography (SFC) using a Berger analytical SFC system with an HP1100 diode array detector. The sample was monitored at 254 nm under the following conditions: 10% MeOH in CO_2, 3000 psi, 40 °C, 2 mL/min on a Diacel Chiralcel OJ-H column, 4.6×250 mm, 5 μ.
13. (a) The absolute stereochemistry of aniline **V** was determined by Vibrational Circular Dichroism (VCD) analysis as described by: Minick, D. J.; Copley, R. C. B.; Szewczyk, J. R.; Rutkowske, R. D.; Miller, L. A. *J. Med. Chem.*, submitted for publication; (b) Dyatkin, A. B.; Freedman, T. B.; Cao, X.; Dukor, R. K.; Maryanoff, B. E.; Maryanoff, C. A.; Matthews, J. M.; Shah, R. D.; Nafie, L. A. *Chirality* **2002**, *14*, 215.
14. Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.
15. A typical procedure for the cyclopropanation of **IIB** is as follows: (2*R*)-4-*tert*-Butyl-2-{1-[(4*R*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-1-methylethyl}-4,5-dihydro-1,3-oxazole (0.12 g, 0.40 mmol) was added to $(CuOTf)_2$–toluene (0.10 g, 0.20 mmol) in $CHCl_3$ (20 mL) at rt. After 1.5 h, the mixture was added to a solution of **IIB** (8.56 g, 39.8 mmol) in $CHCl_3$ (20 mL) followed by a portion (2–3 mL) of a solution of ethyl diazoacetate (4.6 mL, 43.8 mmol) in $CHCl_3$ (100 mL). The mixture was carefully warmed until N_2 gas evolved and the color changed from green to yellow, then the remaining ethyl diazoacetate solution was added dropwise at rt over 2 h. The solvent was evaporated and the residue was purified on silica gel to give 7.56 g (63%) of **IVB** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.46 (d, $J = 8$ Hz, 2H), 7.10 (d, $J = 8$ Hz, 2H), 4.16 (q, $J = 7$ Hz, 2H), 2.50 (m, 1H), 1,87 (m, 1H), 1.60 (m, 1H), 1.28 (m, 1H), 1.27 (t, $J = 7$ Hz, 3H).
16. A manuscript describing the in vitro biology of compound **2A** has been submitted: Briscoe, C. B.; Peat, A. J.; McKeown, S. C.; Corbett, D. F.; Goetz, A. S.; Littleton, T. R.; McCoy, D. C.; Kenakin, T. P.; Andrews, J. L.; Ammala, C.; Fornwald, J. A.; Ignar, D. M., Jenkinson, S. *Br. J. Pharmacol.* Accepted.