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Discovery of +(2-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)acetic acid as potent and selective $\alpha_v\beta_3$ inhibitor: Design, synthesis, and optimization

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Abstract—The integrin $\alpha_v\beta_3$ is expressed in a number of cell types and is thought to play a major role in several pathological conditions. Various small molecules that inhibit the integrin have been shown to suppress tumor growth and retinal angiogenesis. The tripeptide Arg-Gly-Asp (RGD), a common binding motif in several ligands that bind to $\alpha_v\beta_3$, has been depeptidized and optimized in our efforts toward discovering a small molecule inhibitor. We recently disclosed the synthesis and biological activity of several small molecules that did not contain any peptide bond and mimic the tripeptide RGD. The phenethyl group in one of the lead compounds was successfully replaced with a cyclopropyl moiety. The new lead compound was optimized for potency, selectivity, and for its ADME properties. We describe herein the discovery, synthesis, and optimization of cyclopropyl containing analogs that are potent and selective inhibitors of $\alpha_v\beta_3$.

1. Introduction

Integrins are heterodimeric trans-membrane receptors, having α and β subunits, classified broadly according to ligand specificity.[1] The tripeptide sequence Arg-Gly-Asp (RGD), found in extracellular matrix and cell surface proteins such as vitronectin, fibronectin, fibrinogen, thrombospondin, von Willebrand factor, and osteopontin, is recognized by the α_v integrins (β_1, β_3, β_5, β_6, β_8), the platelet glycoprotein receptor (GPIIb/IIIa, $\alpha_{IIb}\beta_3$), and the β_1 integrins, $\alpha_V\beta_1$ and $\alpha_{VIII}\beta_1$. These integrins function in bone remodeling, angiogenesis, and the aggregation of activated platelets. The integrin $\alpha_v\beta_3$ is promiscuous, recognizing several extracellular matrix proteins such as vitronectin and osteopontin that contain RGD. It is expressed on several cell types, including osteoclasts, smooth muscle cells, and endothelial cells, and mediates several biological processes, including adherence to bone matrix, angiogenesis, and the migration of endothelial cells, vascular smooth muscle cells, and tumor cells through the extracellular matrix.[2–9] Integrins are thought to play a role in several pathological conditions, including cancer, arthritis, and pathologic thrombotic events.[10–14] Several anti-integrin drugs are currently being evaluated clinically.[15–18]

We disclosed the discovery of **1** as potent inhibitors of the integrin $\alpha_v\beta_3$, which showed excellent anti-angiogenic properties including its suppression of tumor growth in animal models, through depeptidization and

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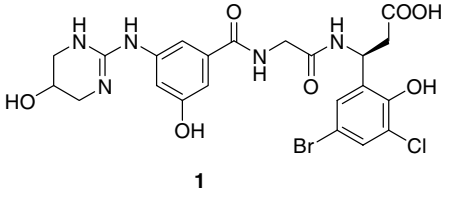
optimization of the peptide RGD.[19–21] We have also recently reported[22] the discovery of **3** as potent inhibitors of the integrin $\alpha_v\beta_3$ (12 nM in Solid Phase Receptor Assay, SPRA) from the modification of **1** via the key compounds **2a** (254 nM) and **2b** (38 nM) as part of a research program to discover new lead molecules that lacked amide bonds while other groups[23] have utilized a different approach in the identification of the lead compound. Our efforts resulted in the determination that the amide bonds and other functionalities could be successfully removed from **1**, the substitutions on the phenyl group of the β-amino acid could be deleted, and that the amino acid glycine could be displaced by a phenyl group. Several recent publications from our laboratories have described the results on replacing the oxyphenyl group in **3** by oxadiazole, thiazole, isoxazole, and pyrazoles, and other heterocycles.[24] The goals of the project have been to improve upon the potency, selectivity against various integrins, and improved absorption, distribution, metabolism, and elimination (ADME) characteristics of **3**. We disclose herein our successful efforts in replacing the phenethyl group in **3** by cyclopropyl moiety as exemplified in **7** which showed improvement in all the desirable properties (Scheme 1).

2. Results and discussion

We initiated a research program to optimize and understand the scope of structure-activity relationships around **3**. Structure based drug design approach was not used as no X-ray crystal structure of the receptor was available during the course of this research. Traditional medicinal chemistry efforts were successfully employed to achieve our goals. Our initial attempts were directed at replacing the phenyl group with different aromatic moieties including heterocycles and alkyl groups to explore spatial and electronic requirements. The pyridyl analog of **3** was targeted toward this goal as shown in Scheme 2. Condensation of methyl nicotinoate (**8**) with *p*-methoxyphenyl acetonitrile (**9**) using sodium methoxide gave the α-cyanoketone **10a**. Attempted hydrolysis of the cyanoketone **10a** with 48% HBr also deprotected the methoxy group to give *p*-hydroxybenzyl 3-pyridyl ketone (**10b**). Wittig reaction of the *O*-acetyl derivative **10c** with (carbethoxymethylene) triphenylphosphorane yielded the olefin as a mixture of isomers. The mixture, without further purification, upon reduction, followed by acidic work up, afforded the phenol **11**. Mitsunobu coupling of the phenol **11** with **14**,[23a] followed by the reduction of the *N*-oxide and saponification, gave **4**. The compound was found to be a potent inhibitor of $\alpha_v\beta_3$ [0.5 nM in solid phase receptor assay (SPRA) vs 8 nM for **3**]. However, the half-life (1.7 h in mice) and plasma concentration (AUC) of the compound in mice were low (see Table 2) and we looked to other substitutions for this position. We explored numerous aromatic substitutions for this position (not reported here) and found them to be unsatisfactory.

We investigated the synthesis of several alkyl substituted analogs of the compound **3**. The 3-methyl compound was chosen as the initial target and was obtained as shown in Scheme 2 by starting from *p*-methoxyphenyl acetone (**12**) and using published procedures.[23] The methyl analog **5** (21 nM in $\alpha_v\beta_3$ SPRA) was less potent than the parent compound and the plasma levels in mice (Table 2, for 20 mpk dose) relatively higher than either of the compounds **3** or **4**. We explored other alkyl substitutions for this position. Simple variations like ethyl and isopropyl moieties resulted in loss of potency. We therefore looked for moieties to replace the methyl group that would mimic its size, but would afford



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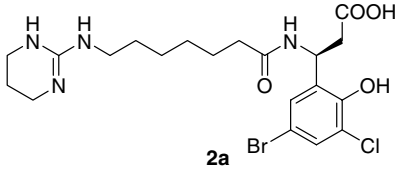

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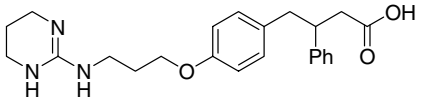

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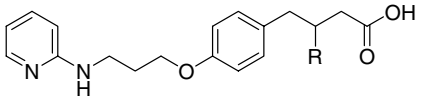
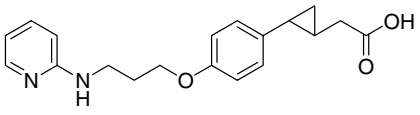


3, R = Ph; **4**, R = 3-Pyridyl; **5**, R = Me



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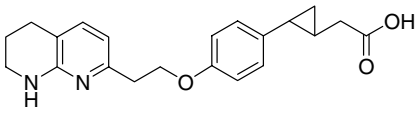

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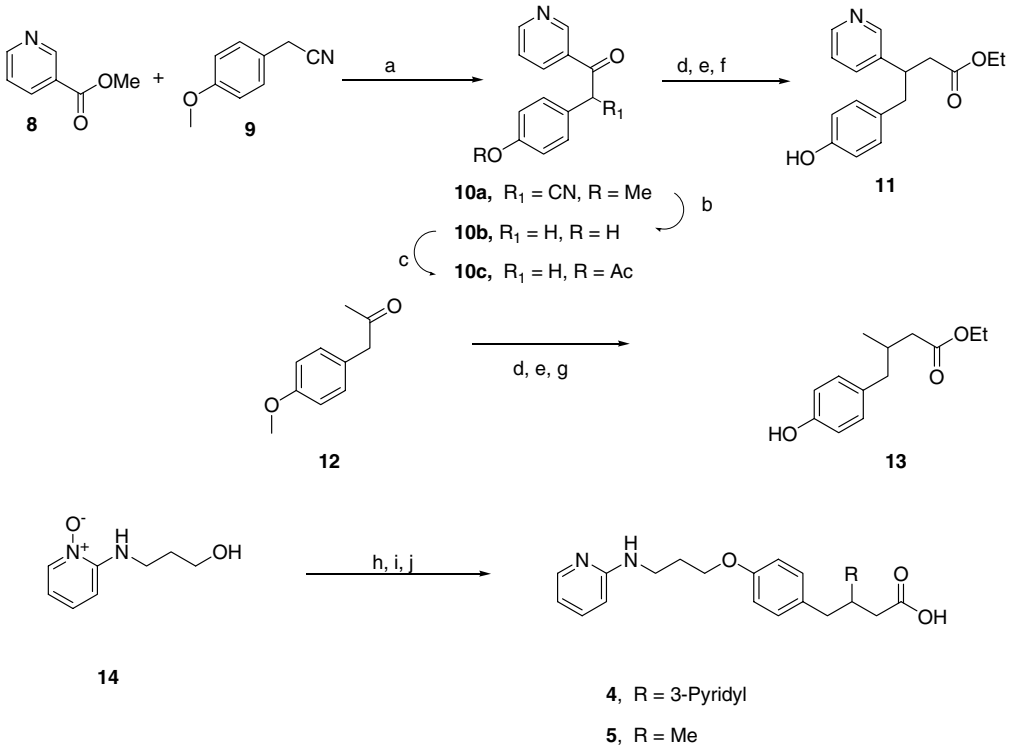
Scheme 1.



Scheme 2. Reagents and conditions: (a) NaOMe, HCl; (b) 48% HBr, reflux, 18 h; (c) Ac_2O, NEt_3; (d) Ph_3P = CHCOOEt; (e) Pd/C, H_2; (f) HCl; (g) BBr_3; (h) PPh_3/DEAD, **11** or **13**; (i) Pd/C, cyclohexene; (j) base, HCl.

Table 1. Potencies of compounds in $\alpha_v\beta_3$ solid phase receptor assay and cell assays

Compound	$\alpha_v\beta_3$/SPRA (nM)	$\alpha_v\beta_1$ 293 cells (nM)	$\alpha_v\beta_3$ 293 cells (nM)	$\alpha_v\beta_5$ 293 cells (nM)	$\alpha_v\beta_6$ HT-29 cells (nM)
3	8	96	29	20	19,800
4	0.5	28	2		25,000
5	21	102	51	33	4360
6	19	234	42		
7	5	64	3	4.4	
(+)**7**	0.6	6	0.6	1.4	2568
(−)**7**	16	297	16	33	10,000
28	7.4		7		20,000
62	0.5	11	11	3	3531
63	2		10		10,000
64	1		0.9	3	9800
67	1900				10,000
69	472		156		
70	1000				
71	776		205		9600
72	954		525		
83	1.3		1.5		10,000
(+)**83**	0.4		0.4	4	1787
(−)**83**	42				10,000
84	12				
92	1.6		1.5		4500
93	3.3		1.7	20	4330
100	2700				
104	36				

Assay data (IC_{50}) for the solid phase receptor assay and cell data for select compounds. Potencies are average of three determinations.

compounds with enhanced potency and pharmacokinetic (PK) properties. We envisioned that the molecules containing cyclopropyl moiety might afford properties similar to those of **5** in both size and polarity. The synthesis of the cyclopropyl compound **6** is shown in Scheme 3.

In general, the cyclopropanation has been achieved using Simmons–Smith reaction with a carbene on an unsaturated alcohol or an amide.[25–31] The starting β,γ-unsaturated acid **16** was synthesized from *p*-anisaldehyde (**15**) and 2-carboxyethylenetriphenylphosphorane.[32,33] The Weinreb amide (**17**) of the acid was then

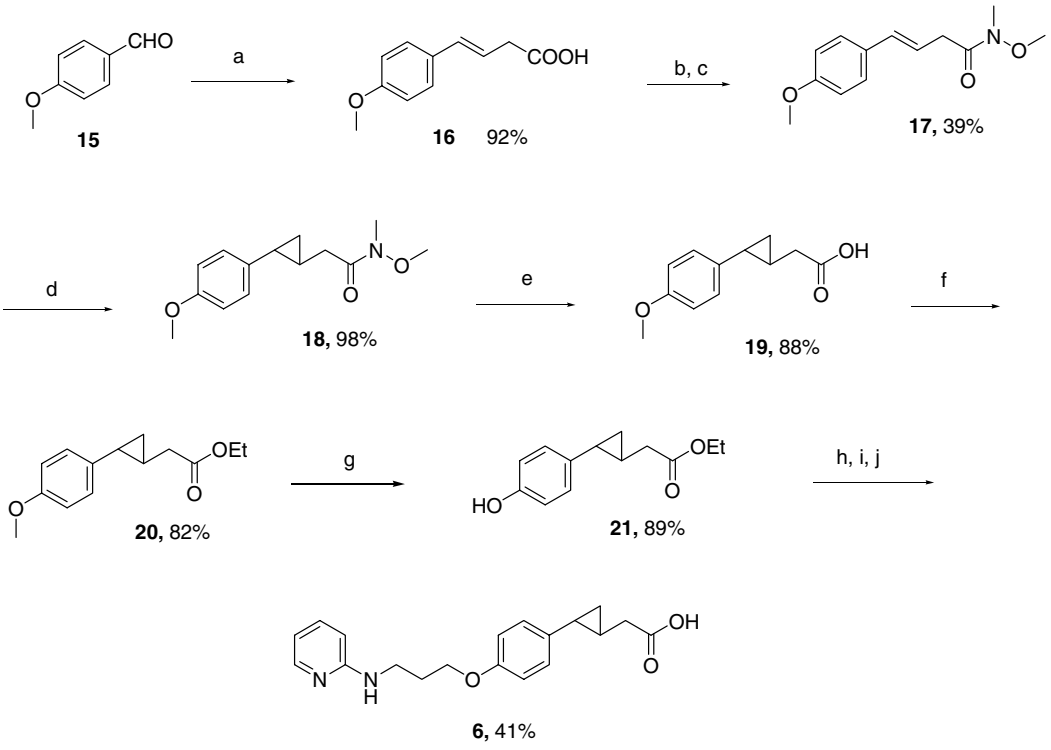
Table 2. Mouse pharmacokinetic data for selected compounds

Compound	AUC (po, μg h/mL)	AUC (iv, μg h/mL)	Dose (mpk)	BA	Half-life (h)
3	2.8	2.3	2	100	4.4
4	0.3	0.2	2	100	1.7
5	195	106	20	92	4.1
6	18.3	14.2	2	79	2.3
7	398	378	2	62	1.6

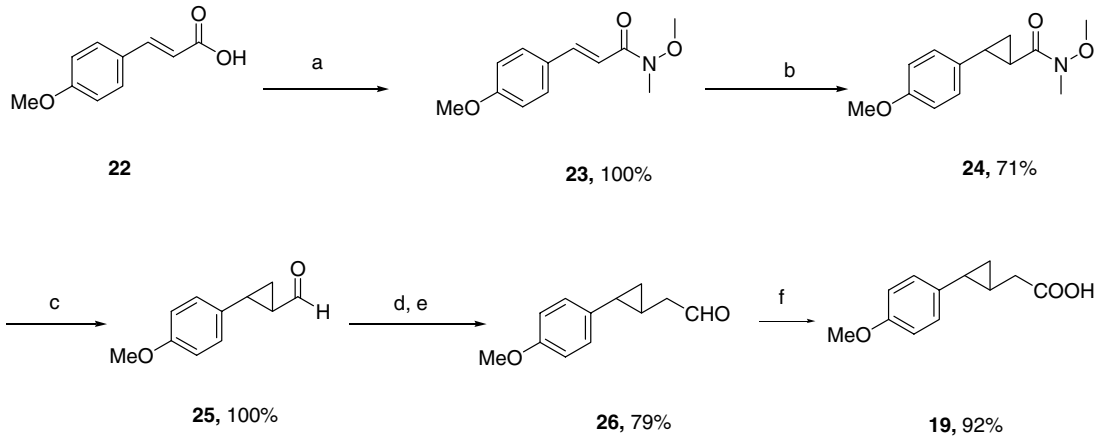
reacted with Simmons–Smith reagent to give the corresponding cyclopropyl compound **18**. The solvent used for Simmons–Smith cyclopropanation, dichloromethane, was found to be unsuitable for the larger scale reactions as a vigorous exotherm was observed during the addition of diethyl zinc to a solution of iodochloromethane. Even on a smaller scale (~1 mmol), a sudden increase in temperature and pressure was noted that had led to expulsion of the rubber septa of the reaction flask and on one occasion, shattering of the reaction vessel. However, addition of dimethoxyethane to the reaction mixture slows down the reaction considerably with no exotherms as also the use of dichloroethane as the solvent for the reaction. Larger scale cyclopropanations have been conducted in our laboratories without any incidents using the earlier modification. The amide **18** was hydrolyzed to the acid **19**, which was esterified to afford **20**.

An alternative method for the synthesis of **19** is described in Scheme 4. The Weinreb amide (**23**) of *p*-methoxycinnamic acid (**22**) was reacted with the sulfur ylide generated by the reaction of sodium hydride and trimethylsulfoxonium iodide.[34] The Weinreb amide of cyclopropyl analog **24** was then reduced with diisobutylaluminum hydride to give the corresponding aldehyde **25**. This aldehyde requires one carbon homologation to get to the acid **19**. Homologation of the aldehyde was accomplished by reacting it with methoxymethyltriphenyl-phosphorane followed by hydrolysis of the enol ether intermediate to give the aldehyde **26**. The aldehyde **26** was oxidized using Tollens reagent to give **19**. Although the overall yield of this reaction sequence is good, the scalability of the reaction described in Scheme 3 is better. The methoxy group in **19** was converted to the ester **20** and was deprotected using BBr_3 to give the key phenolic intermediate, ethyl 1-(*p*-hydroxyphenyl)cyclo-propaneacetate (**21**). Mitsunobu reaction of **21** with *N*-(2-pyridyl-*N*-oxide)-3-aminopropanol[23a] (**14**) followed by the reduction of the *N*-oxide and saponification gave the cyclopropyl compound **6**. The compound **6** was shown to be a potent inhibitor of $\alpha_v\beta_3$ (19 nM in SPRA) compared to **5**, and its PK properties were equally good as measured by the plasma concentration (AUC, Table 2) for both iv and po administration in mice.

We were encouraged by the potency and the pharmacokinetic properties of **6** and we proceeded to optimize each of the regions of the molecule while keeping the other sites constant. We divided the molecule into several regions, the aminopyridine, central phenyl ring, and apical carbon of the cyclopropyl and other carbon atoms of the cyclopropyl moiety for optimization.



Scheme 3. Reagents: (a) $Ph_3P = CHCH_2COOH$; (b) EDC/OBt; (c) *N*,*O*-dimethylhydroxylamine HCl/NEt_3; (d) iodochloromethane/Et_2Zn/CH_2Cl_2, $(CH_2OCH_3)_2$; (e) NaOH, HCl; (f) EtOH/HCl; (g) BBr_3; (h) PPh_3/DEAD and **14**; (i) Pd/C, cyclohexene; (j) base, HCl.



Scheme 4. Reagents: (a) EDC/HOBt/*N*,*O*-dimethylhydroxylamine hydrochloride/NEt_3; (b) Me_3SOI, NaH; (c) DIBAH; (d) Ph_3P = CHOMe; (e) HCl; (f) $AgNO_3$/NaOH.

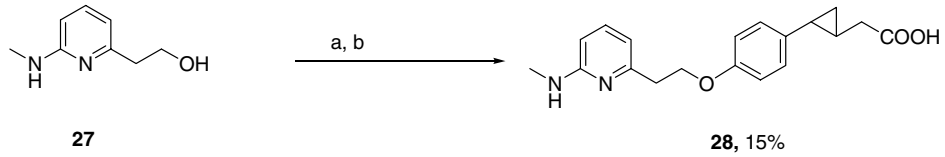
3. Modification of the amino pyridine

The relatively low half-life and AUC for **6** in mice may be attributed to the in vivo N-dealkylation of the aminopyridine moiety. To counter this potential metabolic pathway, we switched the point of attachment of the propyloxy group to the pyridine ring from nitrogen to carbon to give 3-(6-aminomethyl-2-pyridyl)propyl moiety. The chain length was shortened to keep both the nitrogens of aminomethylpyridine in the same general position relative to the phenyl group as in **6**. The synthesis was accomplished by the coupling of **21** with 6-aminomethyl-2-hydroxyethylpyridine (**27**) under Mitsunobu conditions as shown in Scheme 5. The product **28** was shown to be very potent (7.4 nM in the $\alpha_v\beta_3$ SPRA).

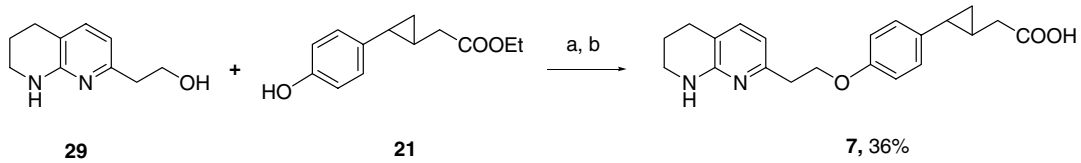
Replacement of the aminopyridine with tetrahydronaphthyridine was then considered. The tetrahydronaphthyridine[23,35–38] **29** was synthesized according to literature procedures starting from 2-aminonicotinaldehyde. The Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) with the phenol **21** (Scheme 6) followed by saponification afforded **7** with improved potency compared to **6** (5 nM in $\alpha_v\beta_3$ SPRA, 3 nM in 293-b3 cell assay) and with excellent PK properties (mouse PK, see Table 2 and rat PK, see Table 3). The product obtained was a mixture of two enantiomers and they were separated at the ester stage (conditions for chiral chromatography are provided in the experimental). Saponification of the separated esters gave the enantiomerically pure isomers. The absolute configuration of the products could not be assigned based on the available data. The designation of the products is based on the sign of the observed optical rotation. The product with the positive rotation (+)**7** was found to be the most potent, (+)**7** $[\alpha]_D$ +34.3 (*c* 0.04, methanol), 0.6 nM and (−)**7** $[\alpha]_D$ −34.0 (*c* 0.07, methanol), 16 nM in the $\alpha_v\beta_3$ assay. The rat pharmacokinetic data indicated a high volume of distribution and low clearance with a half-life of 4 h. Numerous other heterocyclic moieties were synthesized in order to opti-

Table 3. Rat pharmacokinetic data for selected compounds

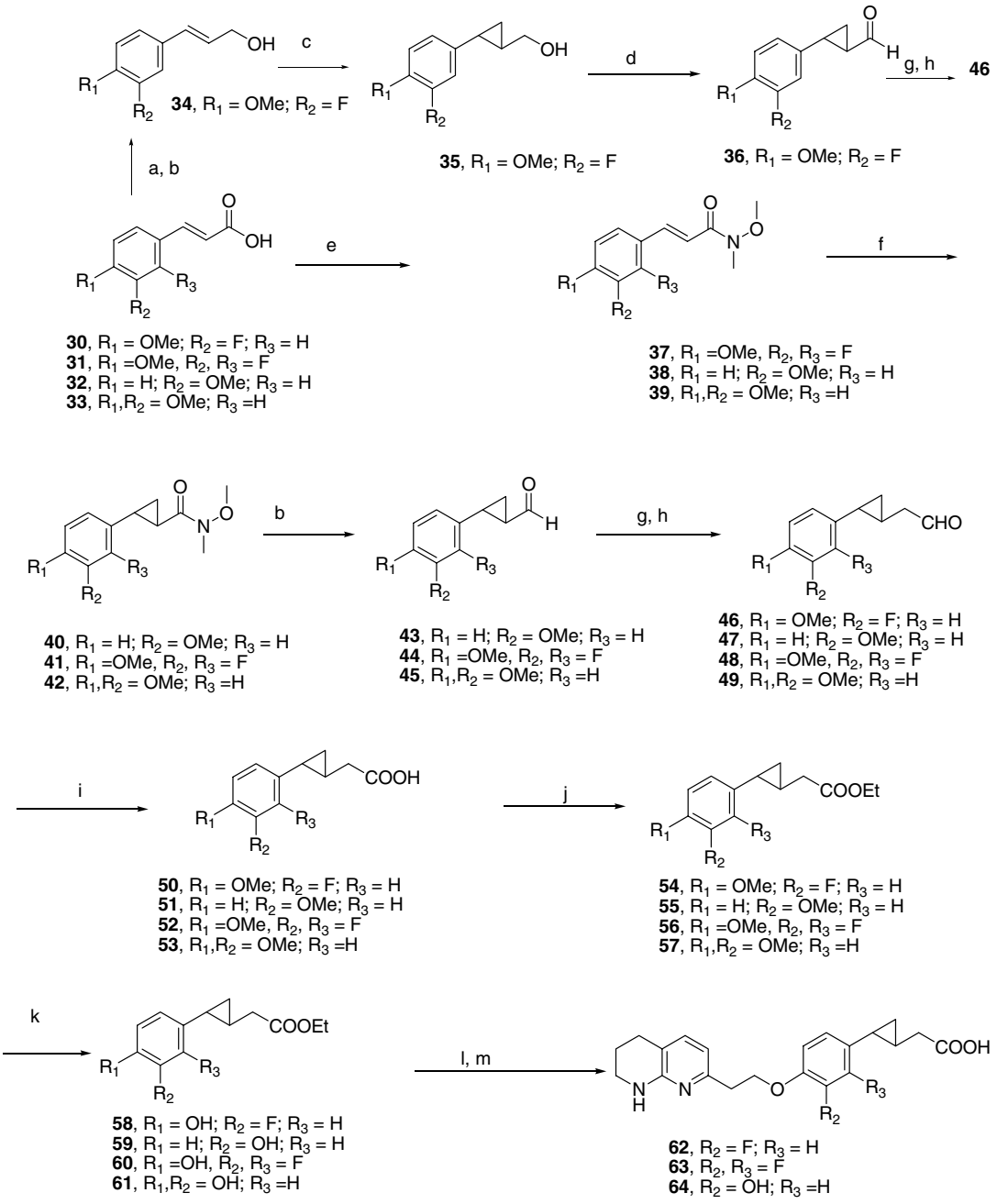
Compound	BA (%)	Half-life (h)	C_{max} (μg/mL)	CL (mL/min/kg)	V_z (mL/kg)
7	62	1.6	24.5	31	221
(+)**7**	100	4	14.8	6.2	915
62	100	3.7	15	5.8	864
83	100	3.5	23.5	1.8	419
(+)**83**	100	5.1	33	0.9	276
92	100	4	17.4	2.2	493



Scheme 5. Reagents: (a) **21**, PPh_3P/DEAD; (b) LiOH, H^+.



Scheme 6. Reagents: (a) PPh_3P/DEAD; (b) LiOH, H^+.



Scheme 7. Reagents: (a) EtOH, HCl; (b) DIBAL; (c) Et_2Zn/iodochloromethane; (d) PCC; (e) EDC/HOBt/*N*,*O*-dimethylhydroxylamine hydrochloride/NEt_3; (f) Me_3SOI, NaH; (g) Ph_3P = CHOMe; (h) HCl; (i) $AgNO_3$/NaOH; (j) EtOH/HCl; (k) BBr_3; (l) **29**/PPh_3P/DEAD; (m) LiOH, H^+.

mize the guanidine surrogate. Some of these heterocycles have been presented in other publications from our laboratories in the context of replacement for the central phenyl ring.[24] Tetrahydronaphthyridine moiety was chosen as an ideal guanidine surrogate in the cyclopropyl containing compounds based on its ease of synthesis.

4. Modifications of the central phenyl ring

We considered several substitutions on the aromatic ring. The synthesis of fluoro, hydroxyl, difluoro substituted compounds was accomplished as shown in Scheme 7. The methodology described in Scheme 7 is similar to the one depicted for the alternate synthesis of **19** (Scheme 4). The monofluoro compound **62** was synthesized by starting from 3-fluoro-4-methoxycinnamic acid **30**. The ethyl ester of **30** was reduced to the allylic alcohol **34** with DIBAL. Cyclopropanation of the allylic alcohol with Simmons–Smith reagent afforded **35**. Homologation of the alcohol was accomplished using the following sequence. The alcohol **35** was oxidized to the aldehyde **36** using pyridinium chlorochromate (PCC). The aldehyde was reacted with methoxymethyltriphenylphosphorane to give the enol ether which was

hydrolyzed with dilute hydrochloric acid to give the homologated aldehyde **46**. The aldehyde was oxidized with Tollens reagent to the acid **50**. The ethyl ester **54** of the acid was treated with BBr_3 to give the phenol **58**, which was converted to **62** using the Mitsunobu conditions described earlier Scheme 5.

The difluoro (**63**) and the hydroxyl (**64**) analogs were synthesized by starting from the corresponding difluoromethoxy (**31**) or dimethoxycinnamic acid (**33**) as shown in Scheme 7. We did not attempt to differentiate the two methoxy groups in **33**, so the *p*-methoxy moiety could be selectively exposed at a latter stage for the Mitsunobu reaction. After considering several possible ways, we chose to start with dimethoxycinnamic acid (**33**) and hoped to separate the two isomeric products by HPLC at the end of the reaction. The dimethoxycinnamic acid (**33**) was converted to ethyl 2-(3,4-dimethoxyphenyl)cyclopropaneacetate (**57**) using the procedure described above. Deprotection of the dimethoxy compound using BBr_3 gave ethyl 2-(3,4-dihydroxyphenyl)cyclopropaneacetate (**61**). Mitsunobu reaction of the dihydroxy compound **61** with tetrahydronaphthyridine-2-ethanol (**29**) afforded a mixture of products from which **64** was isolated in very low yield. The structure was confirmed by NMR experiments. All the compounds synthesized have been shown to be very potent inhibitors of $\alpha_v\beta_3$ (**62**, 0.5 nM; **63**, 2 nM; **64**, 1 nM in the solid phase receptor assay, Table 1). The PK properties of **62** (Table 3) were examined in rat and were found to be very similar to those of (+)**7**. Since the unsubstituted central phenyl ring is easier to synthesize and to scale-up, based on the potency and PK data available, further substitutions on the central phenyl ring were not pursued.

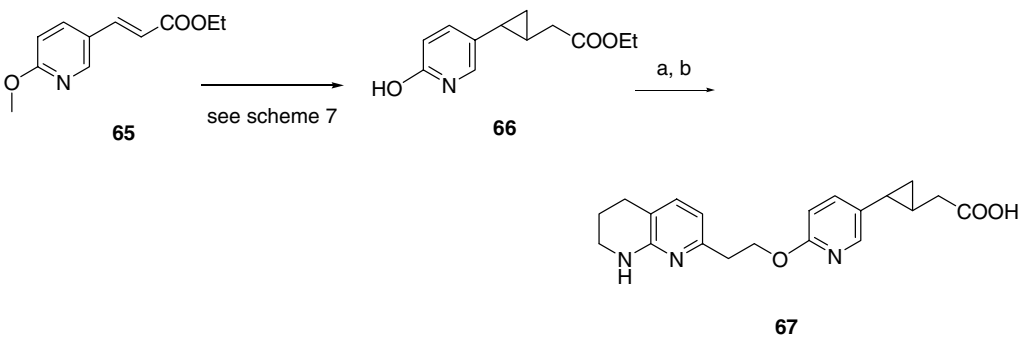
We successfully replaced the central phenyl group in **3** with several heterocycles (thiazoles, oxadiaxoles, pyrazoles, oxazoles, isoxazoles, etc.) with superior potency and pharmacokinetic properties (low clearance, high volume of distribution and half-life).[24] Similar replacements were explored in the cyclopropyl series of compounds. We initiated our optimization efforts starting from replacement by pyridine. The starting material, ethyl 3-(6-methoxypyridyl)acrylate (**65**), was synthesized as reported in the literature.[39] Synthesis of **66** from this intermediate was accomplished in a similar fashion to examples in Scheme 7. Mitsunobu reaction of the deprotected compound **66** with tetrahydro-naphthyridine-2-ethanol (**29**) gave the desired product **67** in very low yield (Scheme 8). The potency of the product in the $\alpha_v\beta_3$ solid phase receptor assay (>100 nM, Table 1) was poor and we did not pursue any other heterocycle replacements in the context of the cyclopropyl containing compounds.

5. Relative distances between key recognition elements

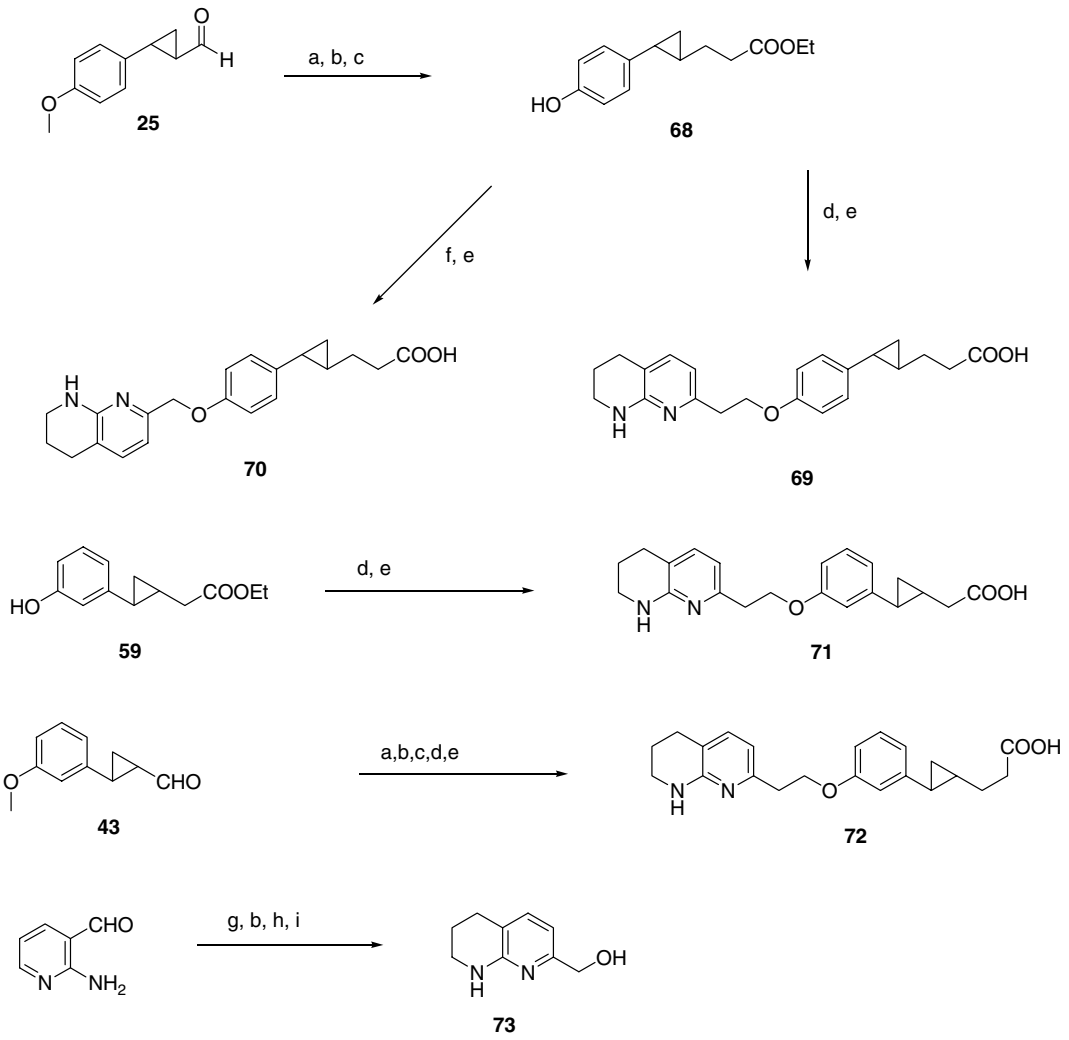
The importance of the relative positions of naphthyridine nitrogens, the phenyl group, and the carboxylic acid moiety in **7** was examined by synthesizing compounds **69** and **70**. The synthesis of these compounds starting from **25** is shown in Scheme 9. Reaction of the aldehyde **25** (see Scheme 4 for the synthesis) with carbethoxymethylenetriphenylphosphorane gave the unsaturated ester. Catalytic reduction of the double bond followed by treatment with BBr_3 afforded the phenolic intermediate **68**. Mitsunobu reaction of **68** with either tetrahydronaphthyridine-2-ethanol (**29**) or tetrahydronaphthyridine-2-methanol[39] (**73**) followed by saponification gave the products **69** and **70**. Both compounds were found to be less potent inhibitors of the integrin $\alpha_v\beta_3$ (470 nM and 1000 nM in the SPRA, respectively). The synthesis of meta analog of **7** was also targeted. The ethyl 2-(3-hydroxyphenyl)cyclopropylacetate (**59**) was synthesized starting from *m*-methoxycinnamic acid (**32**) as shown in Scheme 7 using the Weinreb amide route. Since the meta substitution reduces the overall distance between the nitrogens in tetrahydronaphthyridine and the carboxylic acid, a higher homolog of **71** was also synthesized starting from **43** as described for **69**. Both the analogs **71** (800 nM) and **72** (>1 μM) were shown to be less potent (Table 1). We concluded, based on the data shown, that the 1,4 substitution pattern on the central phenyl ring and the relative distances between the nitrogens, the phenyl ring, and the carboxyl groups as in **7** are crucial for the $\alpha_v\beta_3$ potency.

6. Substitutions on the apical carbon of the cyclopropyl moiety

We considered several substitutions on the apical carbon. In order to reduce the number of optical isomers, we chose to synthesize gem di-substituted analogs.



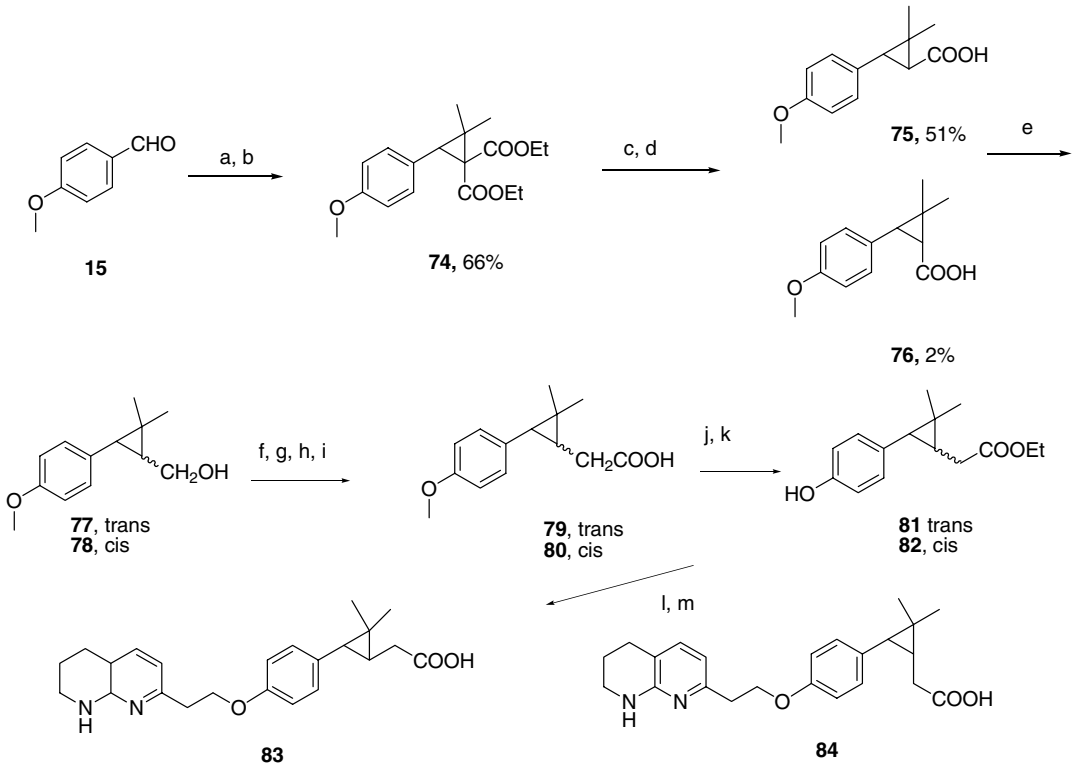
Scheme 8. Reagents: (a) **29**/PPh_3P/DEAD; (b) LiOH, H^+.



Scheme 9. Reagents: (a) Ph_3P = CHCOOEt; (b) Pd/C, H_2; (c) BBr_3; (d) **29**/PPh_3P/DEAD; (e) LiOH, H^+; (f) **73**/PPh_3P/DEAD; (g) pyruvaldehyde; (h) HCl; (i) $NaBH_4$.

gem-Dimethyl, dichloro, and dibromo analogs were targeted for synthesis. The syntheses of *gem*-dimethyl cyclopropyl compounds are well known in the literature.[40–46] Synthesis of the ester of compound **76** as reported by Ahmad et al.,[45] although successful, suffered from low yields and was not amenable for scale up. Tandem Michael addition followed by cyclization for the synthesis of the dimethyl cyclopropyl compound as reported by Babler and Spina[43] was considered next (Scheme 10). Condensation of *p*-anisaldehyde and diethyl malonate with piperidine as base afforded the unsaturated diester.[47] Reaction of this with 2-nitropropane and two equivalents of potassium *tert*-butoxide gave cyclopropyl diester **74**. Removal of the one of the carboxyl groups from the malonyl derivatives has been well documented. The Krapcho conditions[48] using lithium, sodium or potassium chloride and water in DMSO resulted mainly in the opening of the cyclopropyl ring although the desired product was obtained in small amounts. However, heating of the diester **74** in DMSO with several equivalents of potassium cyanide resulted in a mixture of products in which the ester of the *trans*-cyclopropylcarboxylic acid **75** was the major product. The major product was easily purified by chromatography.

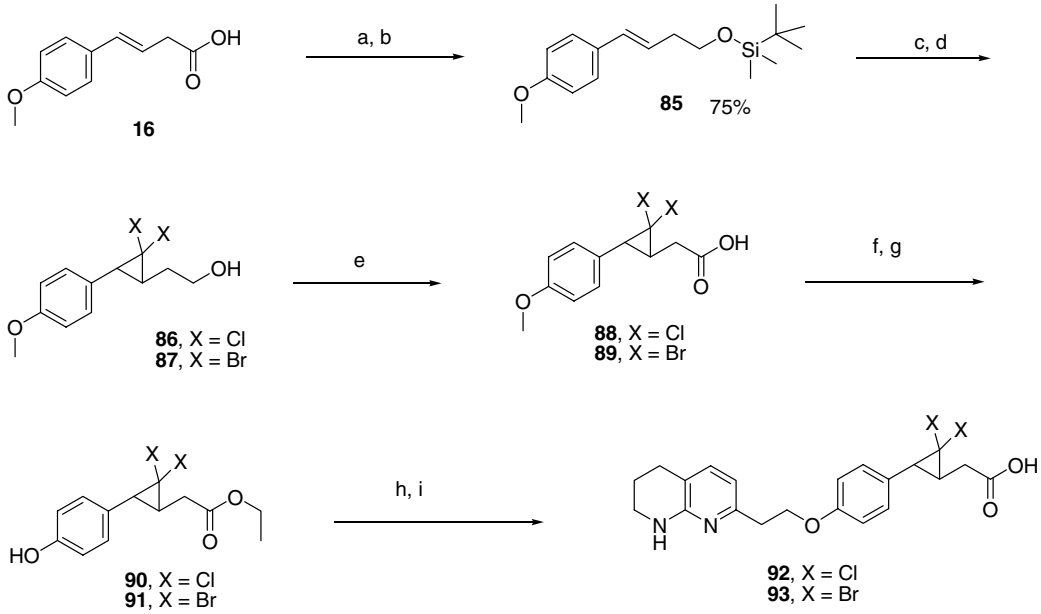
A minor fraction obtained during the purification was a 1:1 mixture of the esters of *trans* (**75**) and *cis* (**76**) products and they were not separable by chromatography. However, we were surprised to find that even with excess base, at room temperature, only the ester of the *trans* isomer was rapidly hydrolyzed to the corresponding acid while it took a long reaction time (24 h) for saponification of the ester of the *cis* isomer. We were able to get quantities of the *cis* isomer by taking advantage of the different rates of saponification. Both the *trans* (**75**) and *cis* (**76**) isomers were carried to the desired final products using standard one carbon homologation, followed by esterification, deprotection, and Mitsunobu reactions as shown in Scheme 10. The structures of both the *cis* and *trans* analogs **84** and **83** were established using NMR experiments. The *trans* isomer (1.3 nM vs $\alpha_v\beta_3$) was found to be a potent inhibitor, while the *cis* isomer (12 nM) was less active. Again, the racemic mixture **83** was separated into its pure enantiomers (+)**83** (0.4 nM) and (−)**83** (42 nM,



Scheme 10. Reagents and conditions: (a) diethyl malonate, HOAc, toluene, reflux; (b) 2-nitropropane, pot. *tert*-butoxide, DMSO; (c) KCN, DMSO, 160 °C, 48 h; (d) NaOH, H^+; (e) BH_3, THF (f) swern oxidation; (g) Ph_3P = CHOMe; (h) HCl; (i) $AgNO_3$/NaOH; (j) EtOH, HCl; (k) BBr_3; (l) **29**/PPh_3P/DEAD; (m) LiOH, H^+.

both in the $\alpha_v\beta_3$ solid phase receptor assay). Both the racemic mixture and the active isomer were examined in the rat for PK properties (Table 3). Although the volume of distribution was lower compared to (+)**7**, the compound was cleared slowly resulting in better half-life for the molecule.

The dichloro and the dibromo compounds were synthesized starting from 4-phenyl-3-butenoic acid (**16**) as shown in Scheme 11. The acid was reduced with LAH to the alcohol and the alcohol was protected as its *tert*-butyldimethylsilyl ether **85**. The protected unsaturated compound was reacted with a dihalocarbene



Scheme 11. Reagents: (a) LAH; (b) TBDMS–Cl, imidazole/DMAP; (c) haloform, NaOH; (d) TBAF; (e) Jones reagent; (f) EtOH/HCl; (g) BBr_3; (h) **29**/PPh_3P/DEAD; (i) LiOH, H^+.

generated by treatment of the haloform with base under phase transfer conditions.[49] The dihalocyclopropanation proceeded in very good yield. The silyl ether protective group was removed using TBAF and the resulting alcohols **86** and **87** were oxidized to the acid **88** and **89** with Jone's reagent. The acid was esterified and the methoxy group was deprotected with BBr_3. Mitsunobu reaction of **90** and **91** with the tetrahydronaphthyridine-2-ethanol (**29**) followed by hydrolysis afforded the desired products **92** and **93**. Both **92** (2.3 nM) and **93** (3.3 nM) are very potent inhibitors of the integrin $\alpha_v\beta_3$ in the solid phase receptor assay (Table 1). The results from these efforts lead us to conclude that the apical position of the cyclopropyl moiety would tolerate substitutions of various sizes.

6.1. Other substitutions on the cyclopropyl group

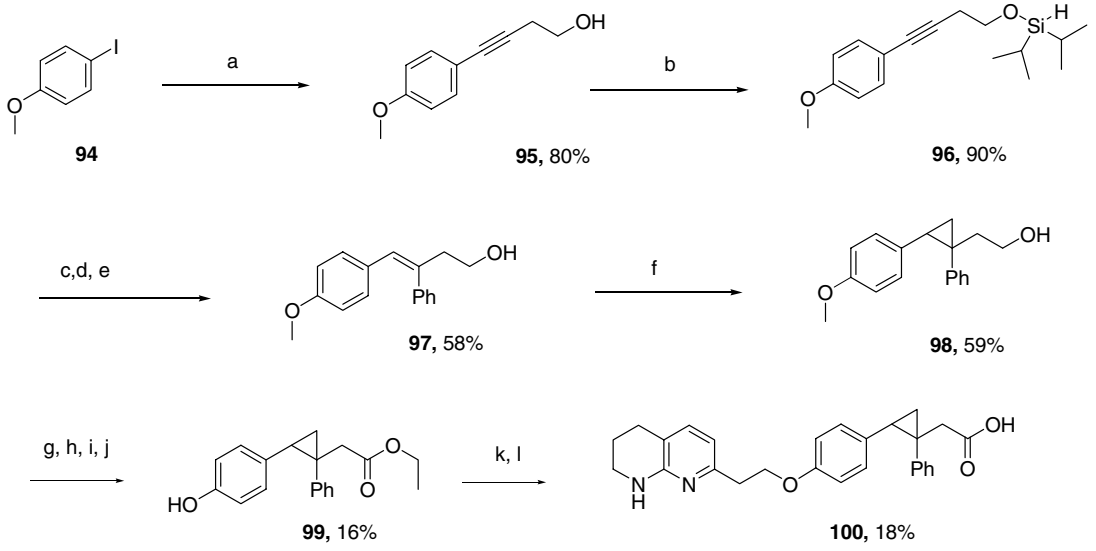
We synthesized compounds with substitutions on the other two carbons of the cyclopropyl moiety to further explore this part of the molecule. The 3-phenyl substituted cyclopropyl compound was chosen as the next target since the 3-methyl-3-phenyl as well as 3,3-gem-dimethyl analogs of **5** were reasonably potent.[50] Methods have been developed for the Palladium mediated cross coupling of vinyl silanes and aryl halides.[51–58] The vinyl silanes in turn have been synthesized by intramolecular hydrosilylation of silyl ethers. We explored this route for the synthesis of phenyl substituted cyclopropyl analogs as shown in Scheme 11. Palladium catalyzed reaction of iodoanisole (**94**) with 3-butyn-1-ol using triethylamine as the solvent afforded 4-(*p*-methoxyphenyl)-3-butyn-1-ol (**95**) in very good yield.[59,60] Reaction of the alcohol with chlorodiisopropylsilane gave the silyl ether **96**. The intramolecular hydrosilylation with Pt(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane [Pt(DVDS)] proceeded smoothly to give the cyclic siloxane. The crude cyclic siloxane without further purification was treated with tetrabutylammonium fluoride to give the vinyl silane, which was reacted in the same pot with iodobenzene and $Pd_2(dba)_3$. The reaction was very slow and use of excess iodobenzene was required to improve the yield of 4-(*p*-methoxyphenyl)-3-phenyl-but-3-en-1-ol (**97**) (Scheme 12).

Other aryl halides required much higher temperatures for the completion of the reaction and 3-iodopyridine did not give the desired product. Cyclopropanation of the unsaturated alcohol **97** was accomplished using modified Simmons–Smith reaction. Jones oxidation of the alcohol **98** to the corresponding carboxylic acid in one step led to mostly decomposition and recovery of some of the starting material. However, stepwise oxidation of the alcohol with pyridiniumchloro chromate to the aldehyde followed by further oxidation with Tollens reagent afforded the carboxylic acid. The acid was converted to the ester and the methoxy group was deprotected using BBr_3 to give the phenol **99**. Mitsunobu reaction of the phenol with tetrahydronaphthyridine-2-ethanol (**29**) followed by hydrolysis gave the desired product **100**. The product was shown to be less potent (>1 μM) in the $\alpha_v\beta_3$ assay. No further analogs were made with modifications at the 3-position.

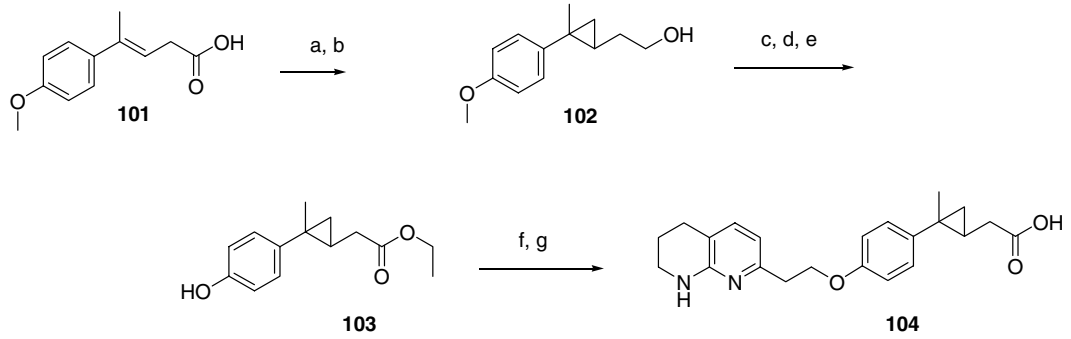
The 4-methyl analog was synthesized as shown in Scheme 13. Reduction of the acid **101**, prepared using literature procedure,[61] with LAH gave the alcohol. Cyclopropanation of the alcohol using Simmons–Smith reagent afforded the **102**. Oxidation of the alcohol to the carboxylic acid has been shown to be very difficult, often resulting in decomposition. Use of $NaClO_2$/NaOCl/TEMPO gave the desired acid. Esterification and deprotection of the methoxyl group to **103** followed by Mitsunobu coupling with **29** gave **104**. This modification also resulted in the loss of potency.

7. Conclusions

The initial cyclopropyl lead compound **6** was divided into several regions and each was optimized for potency against the integrin $\alpha_v\beta_3$, selectivity against various



Scheme 12. Reagents: (a) 3-butyn-1-ol, $Pd(PPh_3)_2Cl_2$, NEt_3; (b) chlorodiisopropylsilane/NEt_3; (c) Pt(DVDS); (d) TBAF; (e) $Pd_2(dba)_3$/iodobenzene; (f) Et_2Zn/iodochloromethane; (g) PCC; (h) $AgNO_3$/NaOH; (i) EtOH, HCl; (j) BBr_3; (k) **29**/DEAD/PPh_3P; (l) LiOH, H^+.



Scheme 13. Reagents: (a) LAH; (b) Et_2Zn/iodochloromethane; (c) $NaClO_2$/NaOCl/TEMPO; (d) EtOH/HCl; (e) BBr_3; (f) **29**/DEAD/PPh_3P; (g) LiOH, H^+.

integrins, and their PK properties. The overall distance between the nitrogens of the naphthyridines and the central phenyl ring as well as the distance between the nitrogens and carboxylic acid moiety has been shown to be crucial. Even though we have shown that the central phenyl ring in **3** could be replaced by other heterocycles with improvements in potency and PK properties, a similar change in cyclopropyl analogs is not tolerated. The tetrahydronaphthyridine has been shown to be a very good guanidine surrogate by others[23] and us. The cyclopropyl moiety has been shown to be an ideal replacement for the methyl group in this class of compounds. The absolute configuration of **7** has not been determined. The compounds have very good selectivity for $\alpha_v\beta_3$ over $\alpha_v\beta_6$. The selectivity versus the integrin $\alpha_v\beta_6$ is crucial due to the physiological effects observed in the b6 knockout mouse.[62] Most of the compounds tested showed very good selectivity (at least 200×) over $\alpha_v\beta_6$. Some of the compounds have been tested for binding to 293 cell lines that express $\alpha_v\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$.[63] In general, good selectivity over $\alpha_v\beta_1$ cell lines was observed. The (+)**7** analog has been scaled up and extensive in vivo studies have been performed and the results will be reported elsewhere.

8. General

Nuclear magnetic resonance spectra were recorded on a Varian XL-400 spectrometer and chemical shifts are reported in ppm relative to TMS as internal standard. Preparative HPLC was performed on a Waters Prep LC 2000 System using a UV detector (Waters 2487 Dual λ absorbance detector) on a Waters Delta pak C18-100A (5 cm × 30 cm column) at a flow rate of 80 mL/min using acetonitrile/water gradient containing 0.01% TFA. All final compounds were analyzed by analytical HPLC (gradient 5–100% acetonitrile in water containing 0.01% TFA) and peaks were monitored at 210 and 254 nM for purity. Mass spectral data were acquired on a Waters ZQ model single quadrupole instrument with an electro spray probe. High resolution data were acquired on a Perception Biosystems Mariner Time of Flight instrument with an electro spray probe. All animal studies were approved by the Pharmacia Institutional Animal Care and Use Committee. Animals were housed in Pharmacia facilities accredited by the Association for Assessment and Accreditaion of Laboratory Animal Care, International. Male Swiss-Webster mice and Sprague–Dawley rats were obtained from Charles River Laboratories (Wilmingotn, MA). All Simmons–Smith reactions were conducted behind a blast shield in the hood.

9. Materials and methods

Human vitronectin receptor $\alpha_v\beta_3$ was purified from human placenta[64] and from fresh frozen plasma[65] as previously described. Biotinylated human vitronectin was prepared by coupling NHS-biotin from Pierce Chemical Company (Rockford, IL) to purified vitronectin.[66] Assay buffer, OPD substrate tablets, and RIA grade BSA were obtained from Sigma (St. Louis, MO). Anti-biotin antibody was obtained from Sigma (St. Luois, MO). Nalge Nunc-Immuno microtiter plates were obtained from Nalge Company (Rochester, NY). Optical rotations were determined on a Rudolph Autopol III Automatic polarimeter with 1 dm cell in methanol.

9.1. Solid phase receptor assays[67]

The purified human vitronectin receptor $\alpha_v\beta_3$ was diluted from stock solutions to 1.0 μg/mL in Tris-buffered saline containing 1.0 mM Ca^{2+}, Mg^{2+}, and Mn^{2+}, pH 7.4 (TBS^{3+}). The diluted receptors were immediately transferred to Nalge Nunc-Immuno microtiter plates at 100 μL/well (100 ng receptor/well). The plates were sealed and incubated overnight at 4 °C to allow the receptors to bind to the wells. All remaining steps were at room temperature. The assay plates were emptied and 200 μL of 1% RIA grade BSA in TBS^{3+} (TBS^{3+}/BSA) was added to block exposed plastic surfaces. Following 2-h incubation, the assay plates were washed with TBS^{3+} using a 96-well plate washer. Logarithmic serial dilution of the test compound and controls was made starting at a stock concentration of 2 mM and using 2 nM biotinylated vitronectin in TBS^{3+}/BSA as the diluent. This premixing of labeled ligand with test (or control) ligand, and subsequent transfer of 50 μL aliquots to the assay plate, was carried out with a CETUS Propette robot; the final concentration of the labeled ligand was 1 nM and the highest concentration of test compound was 1.0×10^{-4} M. The competition occurred

for 2 h after which all wells were washed with a plate washer as before. Affinity-purified horseradish peroxidase labeled goat anti-biotin antibody was diluted 1:2000 in TBS^{3+}/BSA and 125 μL was added to each well. After 45 min, the plates were washed and incubated with OPD/H_2O_2 substrate in 100 mM/L citrate buffer, pH 5.0. The plate was read with a microtiter plate reader at a wavelength of 450 nM and when the maximum-binding control wells reached an absorbance of about 1.0, the final A_{450} were recorded for analysis. The data were analyzed using a macro written for use with the EXCEL spreadsheet program. The mean, standard deviation, and %CV were determined for duplicate concentrations. The mean A_{450} values were normalized to the mean of four maximum-binding controls (no competitor added) (B-MAX). The normalized values were subjected to a four-parameter curve fit algorithm, plotted on a semi-log scale, and the computed concentration corresponding to inhibition of 50% of the maximum binding of biotinylated vitronectin (IC_{50}) and corresponding R^2 were reported for those compounds exhibiting greater than 50% inhibition at the highest concentration tested; otherwise the IC_{50} is reported as being greater than the highest concentration tested. β-[[2-[[5-[(aminoiminomethyl)amino]-1-oxopentyl]amino]-1-oxoethyl]amino]-3-pyridinepropanoic acid which is a potent $\alpha_v\beta_3$ antagonist (IC_{50} in the range 3–10 nM) was included on each plate as a positive control.

9.2. Cell assays for potency and selectivity

While the β_3 subunit of $\alpha_v\beta_3$ is only known to complex with α_v or α_{IIb}, the α_v subunit complexes with multiple β subunits. The three α_v integrins most homologous with $\alpha_v\beta_3$ are $\alpha_v\beta_1$, $\alpha_v\beta_5$, and $\alpha_v\beta_6$, with 43%, 56%, and 47% amino acid identity in the β subunits, respectively. To evaluate the selectivity of compounds between the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_6$, cell-based assays were established using the 293 human embryonic kidney cell line. Two hundred and ninety three cells express $\alpha_v\beta_1$, but little to no detectable $\alpha_v\beta_3$ or $\alpha_v\beta_6$. cDNAs for β_3 and β_6 were transfected separately into 293 cells to generate 293-β3 and 293-β6 cells, respectively. High surface expression of $\alpha_v\beta_3$ and $\alpha_v\beta_6$ was confirmed by flow cytometry. Conditions were established for each cell line in which cell adhesion to immobilized human vitronectin was mediated by the appropriate integrin, as determined by a panel of integrin-specific, neutralizing monoclonal antibodies. Briefly, cells were incubated with inhibitor in the presence of 200 μM Mn^{2+}, allowed to adhere to immobilized vitronectin, washed, and adherent cells are detected by quantifying endogenous alkaline phosphatase and *para*-nitrophenyl phosphate. An 8-point dose–response curve using either 10- or 3-fold dilutions of compound was evaluated by fitting a four-parameter logistic, nonlinear model (using SAS).

To evaluate compound potency for membrane-bound $\alpha_v\beta_6$, a cell-based adhesion assay was established using the HT-29 human colon carcinoma cell line. High surface expression of $\alpha_v\beta_6$ on HT-29 cells was confirmed by flow cytometry. Conditions were established in which cell adhesion to immobilized human latency associated peptide (LAP) was mediated by the $\alpha_v\beta_6$, as determined by a panel of integrin-specific, neutralizing monoclonal antibodies. Briefly, cells were incubated with inhibitor in the presence of 200 μM Mn^{2+}, allowed to adhere to immobilized LAP, washed, and adherent cells are detected by quantifying endogenous alkaline phosphatase using *para*-nitrophenyl phosphate. An 8-point dose–response curve using either 10- or 3-fold dilutions of compound was evaluated by fitting a four-parameter logistic, nonlinear model (using SAS).

9.3. Mouse pharmacokinetics

Test compounds were administered orally (po) or intravenously (iv) as solutions. For iv dosing the compounds were dissolved in normal saline. Compounds for po administration were suspended in 0.5% (w/v) methylcellulose and 0.025% (w/v) polyethylene sorbitan monooleate (Tween 80). Blood samples were collected by cardiac puncture following CO_2 euthanasia, citrated to prevent clotting, and the plasma immediately separated by centrifugation. Plasma samples were stored at −20 °C until assayed for $\alpha_v\beta_3$ inhibitory activity using a solid-phase competitive displacement assay. Pharmacokinetic parameters were calculated using WinNonLin software (Pharsight Corp., Mountain View, CA).

9.4. Rat pharmacokinetic studies

Under isoflurane anesthesia, the femoral artery (all 6 rats) and femoral vein (only 3 of 6 rats) were isolated and cannulated with PE50 tubing and secured with 3.0 silk sutures. The procedure required two catheters, with the venous line being used for infusion of compound (in the group of rats that received compound iv), and the arterial line being used for collection of blood samples. The rats were then placed in restraining cages, which allow minimal movement and allowed to recover from anesthesia for approximately 30 min. At time 0, blood samples (400 μL) were collected from arterial cannula.

One group of rats (three rats per group) received compound via the oral route (18G, 3 in. curved gavage needle) at a dose of 10 mpk (10 mg/mL, dissolved in PEG200: 40%, EtOH: 10%, and saline: 40%), while the other group of rats received compound via the intravenous cannula, at a dose of 2 mpk (10 mg/mL, dissolved in PEG200: 40%, EtOH: 10%, and saline: 40%). The blood samples were collected from the arterial cannula at 10, 30, 60, 120, 240, and 360, 480, 960, and 1440 min with an additional 5 min sample being collected from iv group. After each sample, the cannulas were flushed with PBS containing 10-U/ml heparin. After 24 h, the animals were terminated with excess of anesthesia or by CO_2 asphyxiation. The plasma was obtained by immediate centrifugation and kept frozen (−20 °C) until analyzed. Plasma proteins were precipitated with acetonitrile and subjected to centrifugation. The supernatant containing compound was evaporated under nitrogen and reconstituted in DMSO. To ensure complete extraction, a standard compound at various concentrations was mixed with control rat plasma and extracted (spiked standard curve). The concentration

of the inhibitor present in the plasma was determined using the SPRA (assay described above).

9.4.1. 1-(3-Pyridyl)-2-(*p*-acetoxyphenyl)-ethan-1-one (10). A mixture of *p*-methoxybenzonitrile (**9**, 73.0 g, 0.5 mol) and methyl nicotinoate (68.5 g, 0.5 mmol) in ethanol (400 mL) was added sodium methoxide (270 mL, 25%) at 0 °C and was stirred for 10 min. The reaction mixture was heated at reflux for 2.5 h, then was poured into ice-water mixture (2 L), neutralized with concentrated HCl. The deep yellow solid was filtered, washed with water, and dried to yield 95 g (80%) of the desired product. Hydrobromic acid (48%, 400 mL) was added to the deep yellow product and was heated at reflux for 18 h. Vigorous foaming occurs in the beginning of the reaction. The reaction mixture was poured into ice. The aqueous mixture was neutralized with ammonium hydroxide to afford a precipitate. The precipitate was filtered and dried to give 1-(3-pyridyl)-2-(*p*-hydroxyphenyl)ethan-1-one as a white solid. ^{1}H NMR (CD_3OD) δ 9.11 (s, 1H), 8.67 (m, 1H), 8.37 (m, 1H), 7.52 (m, 1H), 7.06 (d, 2H, J = 8.0 Hz), 6.72 (m, 2H), 4.25 (s, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{11}NO_2$: Mol. wt, 214.0863 (M+H). Found: 214.0836 (M+H). A mixture of 1-(3-pyridyl)-2-(*p*-hydroxyphenyl)ethan-1-one (19.9 g, 0.1 mol), acetic anhydride (10.2 g, 0.1 mol), DMAP (0.20 g), and methylene chloride (250 mL) was heated at reflux for 18 h. The cooled reaction mixture was washed with sodium bicarbonate (100 mL), brine, dried, and concentrated to afford the product as oil (17.4 g, 72%), which solidified upon standing. ^{1}H NMR (CD_3OD) δ 9.17 (s, 1H), 8.72 (m, 1H), 8.23–8.26 (m, 1H), 7.39–7.42 (m, 1H), 7.23 (d, 2H, J = 8.2 Hz), 7.02 (d, 2H, J = 8.2 Hz), 4.26 (s, 2H), 2.0 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{15}H_{13}NO_3$: 256.0968 (M+H). Found: 256.0939 (M+H).

9.4.2. Ethyl 3-(3-pyridyl)-4-(*p*-hydroxyphenyl)butyrate (11). (Carbethoxymethylene)-triphenylphosphorane (30.2 g, 86.63 mmol) was added to the ketone (**10c**, 22.18 g, 86.63 mmol), heated at reflux in toluene (300 mL) for 40 h, and concentrated. Ethyl acetate (200 mL) was added to the residue and was allowed to stand. The precipitate formed was filtered off and the filtrate was concentrated and the residue was purified by chromatography (silica gel, 75% EA in hexane) to yield 16.8 g of the desired product as a complex mixture of three isomers and was subjected to hydrogenation (50 psi) for 4 h. The catalyst was filtered, and the filtrate was concentrated to give a residue. The residue was stirred in saturated ethanol/HCl (200 mL) for 3h and was concentrated. The residue was partitioned between ethyl acetate (400 mL) and sodium bicarbonate (200 mL) and the organic layer was dried ($MgSO_4$). The organic layer was concentrated to afford 12.27 g (84%) of the product as oil. ^{1}H NMR (CD_3OD) δ 8.68 (d, 1H, J = 5.5 Hz), 8.63 (S, 1H), 8.52 (d, 1H, J = 7.8 Hz), 7.80 (t, 1H, J = 6.3 Hz), 6.87 (d, 2H, J = 8.2 Hz), 6.63 (d, 2H, J = 8.2 Hz), 3.95–4.01 (m, 2H), 3.58-3.63 (m, 1H), 2.81–3.17 (m, 4H), 1.11 (t, 3H,J = 7 Hz). HRMS (ES, *m*/*z*) Calcd for $C_{17}H_{19}NO_3$: 286.1438 (M+H). Found: 286.1439 (M+H).

9.4.3. 4-[3-(2-*N*-Pyridyl)amino]-1-propyloxyphenyl-3-(3-pyridyl)butyric acid (4). A solution of DEAD (12.90 g, 74.06 mmol) and *N*-(2-pyridyl-*N*-oxide)-3-aminopropanol[23] (**14**, 12.44 g, 74.06 mmol) in DMF (150 mL) was added to a solution of ethyl 3-(3-pyridyl)-4-(*p*-hydroxyphenyl)butyrate (**13**, 10.0 g, 37.03 mmol) and triphenylphosphine (20.39 g, 74.06mmol) in DMF (150 mL) over a period of 20 min and the reaction mixture was stirred for 24 h. DMF was removed in vacuo and the residue was purified by HPLC (reverse phase C18, 10–100% gradient of acetonitrile in water containing 0.05% TFA) to give 10.8 g of the product as oil. A mixture of the product (10.6 g, 24.37 mmol), palladium/C (3.0 g), and cyclohexene (20 mL) in ethanol (200 mL) was heated at reflux over 24 h. The reaction mixture was filtered, and the residue was washed with additional amount of ethanol (100 mL). The combined filtrates were concentrated. The residue was added ethanol (5 mL) and sodium hydroxide (5 mL, 2.5 N) and stirred for 8 h. The reaction mixture was concentrated and the residue was dissolved in water (5 mL) and the pH was adjusted to 2 by the addition of TFA. This was purified by HPLC (reverse phase C18, 10–100% gradient of acetonitrile in water containing 0.05% TFA) and 6.8 g (36%) of the product was obtained as its TFA salt. ^{1}H NMR (CD_3OD) δ 8.72 (m, 2H), 8.58 (m, 1H), 8.04 (t, 1H, J = 5.8 Hz), 7.8–7.87 (m, 2H), 7.0–7.18 (m, 3H), 6.8–6.91 (m, 3H), 4.08–4.12 (m, 2H), 3.58–3.73 (m, 3H), 3.05–3.2 (m, 1H), 2.87–3.08 (m, 3H), 2.16–2.24 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{23}H_{25}N_3O_3$: 392.1969 (M+H). Found: 392.1990 (M+H).

9.4.4. 4-(*p*-Methoxyphenyl)-but-3-enoic acid (16). A mixture of 3-carboxypropyl-triphenylphosphonium bromide (210 g, 506 mmol) and *p*-anisaldehyde (62.1 mL) in dimethylsulfoxide (600 mL) was added slowly to a suspension of sodium hydride 41 g (60% suspension in mineral oil) in tetrahydrofuran (300 mL). The reaction mixture was stirred mechanically for 18 h, quenched with water (1 L) followed by addition of sodium hydroxide (100 mL, 2.5 M), and extracted with ether. The aqueous layer was acidified to afford oil. The oil was extracted with ethyl acetate (2 L), dried ($MgSO_4$), and concentrated. The residue was added hexane and ethyl acetate and was cooled. The desired product precipitated and filtered and was washed with hexane to yield 90 g (92%) as a yellow crystalline solid. ^{1}H NMR (CD_3OD) δ 7.29 (m, 2H), 6.83 (m, 2H), 6.42 (d, 1H, J = 15.8 Hz), 6.11–6.18 (m, 1H), 3.76 (s, 3H), 3.17 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{11}H_{12}O_3$: 192.0786. Found: 192.1176.

9.4.5. (*N*-Methoxy-*N*-methyl)-4-(*p*-Methoxyphenyl)-but-3-enamide (17). A mixture of 4-(*p*-methoxyphenyl)-but-3-enoic acid (81.51 g, 0.425 mol), HOBt (57.6 g, 0.425 mol), and EDC (81.4 g, 0.425 mol) in dimethylformamide (1.5 L) was stirred mechanically. *N*-Methyl-*O*-methylhydroxylamine hydrochloride (41.5 g, 0.425 mol) was added followed by triethylamine (120 mL) to the reaction mixture and stirring continued for 18 h. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate (1 L) and sodium bicarbonate (saturated solution, 0.75 L). The organic layer was washed with water (1 L), brine (1 L),

dried ($MgSO_4$), and concentrated to give a residue. A solution of the residue was passed through a thick pad of silica gel (40% ethyl acetate in hexane) to yield 40.8 g (39%) of the product. ^1H NMR (CD_3OD) δ 7.29 (m, 2H), 6.83 (m, 2H), 6.44 (d, 1H, $J = 15.8$ Hz), 6.11–6.18 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.35 (m, 2H), 3.19 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{17}NO_3$: 235.1208. Found: 236.1255 (M+H).

9.4.6. *N*-Methoxy-*N*-methyl-1-(*p*-Methoxyphenyl)-2-cyclopropane-acetamide (18). Iodochloromethane (247 g, 102 mL, 1.4 mol) was added to a solution of dimethoxyethane (73 mL) in dichloromethane (1 L) at −15 °C. A solution of diethyl zinc (704 mL, 1 M in hexane) was slowly added maintaining the internal temperature at −15 °C. The reaction mixture was stirred for 20 min and (*N*-methoxy-*N*-methyl)-4-(*p*-methoxyphenyl)-but-3-enamide (**17**, 82.06 g, 0.349 mol) in dichloromethane (500 mL) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. It was quenched with hydrochloric acid (1 N, 1 L). The organic layer was washed with water (1 L), brine (1 L), dried ($MgSO_4$), and concentrated. The residue was passed through a pad of silica gel (30% ethyl acetate in hexane) to yield 89 g (98%) of the product as oil. ^1H NMR (CD_3OD) δ 7.03 (d, 2H, $J = 8.7$ Hz), 6.78 (d, 2H, $J = 8.6$ Hz), 3.75 (s, 3H), 3.66 (s, 3H), 3.18 (s, 3H), 2.40–2.61 (m, 2H), 1.7–1.73 (m, 1H), 1.32–1.37 (m, 1H), 0.88–0.94 (m, 1H), 0.78–0.83 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{14}H_{19}NO_3$: 249.1365. Found: 250.1405 (M+H).

9.4.7. 1-(*p*-Methoxyphenyl)cyclopropane-2-acetic acid (19). Sodium hydroxide (100 mL, 2.5 M) was added to a solution of *N*-methoxy-*N*-methyl-1-(*p*-methoxyphenyl)-2-cyclopropaneacetamide (89 g) in ethanol (300 mL) and was stirred for 24 h at rt. The solvent was removed in vacuo and the residue was partitioned between ether (400 mL) and water (1 L). The aqueous layer was acidified to afford 65 g (88%) of the product as a crystalline powder. ^1H NMR (CD_3OD) δ 7.02 (d, 2H, $J = 8.6$ Hz), 6.79 (d, 2H, $J = 8.6$ Hz), 3.76 (s, 3H), 2.39–2.50 (m, 2H), 1.7–1.76 (m, 1H), 1.29–1.41 (m, 1H), 0.92–0.97 (m, 1H), 0.80–0.84 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0901.

9.4.8. Ethyl 1-(*p*-methoxyphenyl)cyclopropane-2-acetate (20). A mixture of 1-(*p*-methoxyphenyl)cyclopropane-2-acetic acid (65 g, 301 mmol), ethanol (500 mL), and hydrochloric acid (10 mL) was heated at reflux for 18 h. The solvent was removed in vacuo and the residue in ether (500 mL) was washed with saturated bicarbonate (200 mL), dried, and concentrated to afford 60 g (82%) of the product as oil. ^1H NMR (CD_3OD) δ 7.02 (d, 2H, $J = 8.5$ Hz), 6.79 (d, 2H, $J = 8.5$ Hz), 4.14 (q, 2H, $J = 7.2$ Hz), 3.76 (s, 3H), 2.30–2.40 (m, 2H), 1.69–1.73 (m, 1H), 1.23–1.31 (m, 4H), 0.89–0.94 (m, 1H), 0.76–0.81 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 252.1582 (M+NH_4).

9.4.9. Alternative preparation of ethyl 1-(*p*-methoxyphenyl)cyclopropane-2-acetate (20): (2*E*)-*N*-Methoxy-3-(4-methoxyphenyl)-*N*-methylprop-2-enamide (23). To a solution of *trans* 4-methoxycinnamic acid (15 g, 84 mmol) in dry DMF (100 mL), 4-methylmorpholine (11 g, 92 mmol) was added at −5 °C and stirred for 25 min at −5 °C. *iso*-Butylchloroformate (12.6 g, 92 mmol) was added to the above solution and stirred for 10 min at −5 °C followed by the addition of solid N, *O*-dimethylhydroxyamine HCl (9 g, 92 mmol) and 4-methylmorpholine (11 g, 108 mmol). The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with HCl (0.5 N, 200 mL) at 4 °C and was extracted with CH_2Cl_2 (3× 250 mL). The combined organic solution was washed with NaOH (0.5 N, 2× 200 mL), brine (1× 200 mL) and was concentrated. The residue was dissolved in ether (600 mL) and washed with brine, dried over Na_2SO_4, concentrated, and dried to give 19 g oil (quantitative). The crude material was used in the next reaction without further purification. ^1H NMR ($CDCl_3$) δ 7.65 (d, 1H, $J = 15.7$ Hz), 7.5 (m, 2H), 6.9 (m, 3H), 3.8 (s, 3H), 3.75 (s, 3H), 3.3 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{12}H_{15}NO_3$ (M+H): 222.1125. Found: 222.1143.

9.4.10. *N*-Methoxy-2-(4-methoxyphenyl)-*N*-methylcyclopropanecarboxamide (24). Sodium hydride (60% in mineral oil, 7 g, 170 mmol) was added portionwise over 20 min to a solution of trimethylsulfoxonium iodide (38 g, 173 mmol) in DMSO (100 mL) in a water bath. The suspension was stirred for 1 h. A solution of the olefin amide (19 g, 86 mmol) in DMSO (100 mL) was added to the reaction mixture and stirred for 6 h. The reaction mixture was poured into a saturated solution of ammonium chloride (500 mL) and was extracted with CH_2Cl_2 (3×300 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The concentrated residue was purified by chromatography on silica gel (30% ethyl acetate in hexane) to give 14.3 g oil (71%). ^1H NMR ($CDCl_3$) δ 7.1 (m, 2H), 6.8 (m, 2H), 3.8 (s, 3H), 3.7 (s, 3H), 3.2 (s, 3H), 2.4–2.5 (m, 1H), 2.3–2.4 (m, 1H), 1.5–1.6 (m, 1H), 1.2–1.3 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{17}NO_3$ (M+H): 236.1281. Found: 236.1287.

9.4.11. 2-(4-Methoxyphenyl)cyclopropanecarbaldehyde (25). To the cyclopropyl amide (**24**, 15.6 g, 66 mmol) in dry THF (100 mL) under nitrogen at −78 °C, DIBAL (1 M in hexane, 100 mmol) was added. The reaction was complete in 1 h. Reaction mixture was poured into a saturated potassium sodium tartarate (250 mL) and stirred for 1 h and was extracted with ethyl acetate (3× 250 mL). The combined organic solution was washed with brine and dried over Na_2SO_4, concentrated, and dried to give 12 g (quantitative) of white solid. ^1H NMR ($CDCl_3$) δ 9.3 (d, 1H, $J = 4.7$ Hz), 7.0 (m, 2H), 6.8 (m, 2H), 3.8 (s, 3H), 2.6 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H), 1.4 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{11}H_{12}O_2$: Mol. wt, 176.0837. Found: 176.0840.

9.4.12. [2-(4-Methoxyphenyl)cyclopropyl]acetaldehyde (26). To a solution of (methoxymethyl)triphenylphosphonium chloride (24.5 g, 0.071 mol) in dry THF (50 mL) at 4 °C was added lithium bis(trimethylsilyl)amide (1 M in THF, 72 mL). The reaction mixture was stirred for 20 min at 4 °C and a solution of the aldehyde **25** (8.4 g, 0.0477 mol) in THF (100 mL) was added. Ice bath was

removed 30 min later and reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water (350 mL), extracted with ether (3× 200 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (5% ethyl acetate in hexane) to remove the polar spot. Fractions containing top two spots (very close together) were combined, dried to give 9.5 g of the olefin. The resulting methoxy olefin in THF (50 mL) was added HCl (1.5 N, 50 mL) and refluxed for 2 h. The reaction mixture was cooled to room temperature and was neutralized by adding saturated $NaHCO_3$ and extracted with ether. The combined organic solution was concentrated and purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 7.1 g (79%) oil. ^{1}H NMR ($CDCl_3$) δ 9.8 (t, 1H, J = 1.9 Hz), 7.0 (m, 2H), 6.8 (m, 2H), 3.85 (s, 3H), 2.5 (m, 2H), 1.7 (m, 1H), 1.25 (m, 1H), 1.0 (m, 1H), 0.8 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{12}H_{14}O_2$: 190.0994. Found: 190.0990.

9.4.13. [2-(4-Methoxyphenyl)cyclopropyl]acetic acid (19). The aldehyde (**26**, 15.5 g, 0.08 mol) in ethanol (100 mL) was cooled in ice bath and silver nitrate was added (27.4 g in 36 mL of distilled water) followed by NaOH (12.8 g in 36 mL of distilled water). Ice bath was removed 20 min later. The reaction mixture was stirred for 30 min at room temperature. The solid was filtered through Celite and was washed with water (200 mL). The filtrate was concentrated to remove ethanol. The aqueous solution was washed with ether (3× 100 mL) and was acidified (concentrated HCl). The acidified aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to give 15.5 g (92%) yellow solid. ^{1}H NMR (CD_3OD) δ 7.0 (m, 2H), 6.8 (m, 2H), 3.7 (s, 3H), 2.3 (m, 2H), 1.7 (m, 1H), 1.2 (m, 1H), 0.9 (m, 1H), 0.7 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{12}H_{14}O_3$ (M−H): 205.0859. Found: 205.0858.

9.4.14. Ethyl 1-(*p*-hydroxyphenyl)cyclopropane-2-acetate (21). Boron tribromide (246 mL, 1 M) in dichloromethane was added slowly to a solution of ethyl 1-(*p*-methoxyphenyl)cyclopropane-2-acetate (**20**, 60 g, 246 mmol) in dichloromethane (1L) at 0 °C and the reaction mixture was stirred at room temperature for 18 h. It was cooled to 0 °C and was quenched with excess ethanol. The reaction mixture was concentrated and the residue in ethyl acetate (1 L) was washed with saturated sodium bicarbonate (500 mL), washed with brine (500 mL), dried, and concentrated. The residue was purified by passing through a thick pad of silica and eluting with 20% ethyl acetate in hexane to give 50.2 g (89%) of the product. ^{1}H NMR (CD_3OD) δ 6.93 (d, 2H, J = 8.6 Hz), 6.71 (d, 2H, J = 8.6 Hz), 4.15 (q, 2H, J = 7.1 Hz), 2.37 (d, 2H, J = 7.2 Hz), 1.66–1.71 (m, 1H), 1.23–1.28 (m, 4H), 0.87–0.91 (m, 1H), 0.75–0.79 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 238.1410 (M+NH_4).

9.4.15. 2-[4-[3-(2-Pyridinylamino)propoxy]phenyl]cyclopropaneacetic acid, trifluoroacetate (6). Starting from **21** and 2-[(3-hydroxy-1-propyl)amino]pyridine-*N*-oxide (**14**), and following the procedure described for **3**, the desired product was obtained. ^{1}H NMR (CD_3OD) δ 7.82–7.87 (m, 1H), 7.7 (d, 1H, J = 5.9 Hz), 7.02 (d, 1H, J = 9.1 Hz), 6.99 and 6.77 (AB, 4H, J = 8.7 Hz), 6.83 (t, 1H, J = 6.4 Hz), 4.06 (t, 2H, J = 5.9 Hz), 3.55 (t, 2H, J = 6.9 Hz), 2.34 (m, 2H), 2.13 (m, 2H), 1.65–1.71 (m, 1H), 1.16–1.24 (m, 1H), 0.74–0.88 (m, 2H). Anal. Calcd for $C_{19}H_{22}N_2O_3$. TFA C, 57.27; H, 5.26; N, 6.36; Mol. wt, 327.1703 (M+H). Found: C, 57.99; H, 5.44; N, 6.27; Mol. wt, 327.1708 (M+H. HRMS).

9.4.16. [2-(4-{2-[6-(Methylamino)pyridin-2-yl]ethoxy}phenyl)-cyclopropyl]acetic acid trifluoroacetate (28). To a solution of 2-[6-(methylamino)pyridin-2-yl]ethanol (**27**, 1 g, 6.6 mmol) and polymer bound PPh_3 (1.4 g, 9.9 mmol) in dry THF (50 mL) was added ethyl [2-(4-hydroxyphenyl)cyclopropyl]acetate (**21**, 1.4 g, 6.6 mmol) followed by diisopropyl azodicarboxylate (1.5 mL, 7.7 mmol). The reaction mixture was stirred at room temperature. After 18 h, the polymer was filtered through Celite and was washed with excess THF. The filtrate was concentrated and the residue was dissolved in 1:1 acetonitrile/water (40 mL) and was treated with LiOH (1 g). The reaction mixture was heated for 2 h at 55 °C, then cooled to room temperature and was purified on reverse phase HPLC to give 0.45 g (15%) of title compound. ^{1}H NMR (CD_3OD) δ 7.8 (m, 1H), 7.0 (d, 2H, J = 8.6 Hz), 6.9–6.6 (m, 4H), 4.26 (t, 2H, J = 6 Hz), 3.21 (t, 2H, J = 6 Hz), 3.0 (s, 3H), 2.35–2.33 (m, 2H), 1.71–1.67 (m, 1H), 1.21–1.18 (m, 1H), 0.89–0.76 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{19}H_{22}N_2O_3$ (M+H): 327.1703. Found: 327.1677.

9.4.17. (2-{4-[2-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)acetic acid, trifluoroacetate (7). Starting from 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**, 3.9 g, 22 mmol) and the phenol **21**, and following the procedure described for **28**, the ethyl ester of the product was obtained. Yield: 54%. ^{1}H NMR (CD_3OD) δ 7.11 (d, 1H, J = 7.2 Hz), 6.98–6.95 (m, 2H), 6.75 (m, 2H), 6.43 (d, 1H, J = 7.4 Hz), 4.17–4.09 (m, 4H), 3.35 (t, 2H, J = 5.5 Hz), 2.91 (t, 2H, J = 6.8 Hz), 2.68 (t, 2H, J = 6.2 Hz), 2.42–2.29 (m, 2H), 1.88–1.82 (m, 2H), 1.71–1.66 (m, 1H), 1.24–1.13 (m, 4H), 0.88-0.84 (m, 1H), 0.78–0.74 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{23}H_{28}N_2O_3$ (M+H): 381.2173. Found: 381.2193.

The ethyl ester of (3.7 g, 9.8 mmol) was dissolved in 40 mL of 50% acetonitrile in water and LiOH (1.64 g, 39 mmol) was added. The reaction mixture was heated at 50 °C for 2 h, then acidified by adding TFA. The residue was purified on reverse phase HPLC to give 3 g (66%) clear oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H, J = 7.4 Hz), 7.01–6.98 (m, 2H), 6.79–6.76 (m, 2H), 6.70 (d, 1H, J = 7.4 Hz), 4.22 (t, 2H, J = 6.0 Hz), 3.48 (t, 2H, J = 5.71 Hz), 3.10 (t, 2H, J = 5.98 Hz), 2.80 (t, 2H, J = 6.24 Hz), 2.88–2.40 (m, 2H), 1.96–1.90 (m, 2H), 1.71–1.68 (m, 1H), 1.24–1.20 (m, 1H), 0.88–0.85 (m, 1H), 0.76–0.84 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{24}N_2O_3$ (M+H): 353.1865. Found: 353.1876 (M+H).

Separation of diastereomers of ethyl (2-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]-phenyl}cyclopropyl)acetate: the isomeric mixture of ethyl (2-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)acetate (48 g) was separated on ChiralPak AS column (flow rate: 50 mL/min; room temperature, isopropylalcohol/heptane/diethylamine/-30:70:0.1) to give 21 g ethyl ester of isomer A and 20 g ethyl ester of isomer B.

The ethyl ester of isomer A (10 g, 26 mmol) was dissolved in 50% acetonitrile in water (100 mL) and then treated with lithium hydroxide (4.4 g, 104 mmol). The solution was heated at 55 °C for 3 h. The solution was then cooled to room temperature and was acidified by adding TFA. The crude material was purified on reverse phase HPLC to give 11 g TFA salt of isomer A of **7**. The TFA salt was passed through Bio-Rad AG 2-X8 (200–400 Mesh, chloride form, 100 g) column and was eluted with 50% acetonitrile in water to give 9.5 g (94%) HCl salt of isomer A of **7** ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H, J = 7.4 Hz), 7.0 (d, 2H, J = 8.6 Hz), 6.8 (d, 2H, J = 8.6 Hz), 6.71 (d, 1H, J = 7.4 Hz), 4.22 (t, 2H, J = 6.0 Hz), 3.48 (t, 2H, J = 5.6 Hz), 3.10 (t, 2H, J = 5.9 Hz), 2.80 (t, 2H, J = 6.2 Hz), 2.40–2.28 (m, 2H), 1.96–1.90 (m, 2H), 1.71–1.67 (m, 1H), 1.22–1.18 (m, 1H), 0.88–0.84 (m, 1H), 0.76–0.80 (m, 1H). $[\alpha]_D$ +34.3 (*c* 0.04, MeOH). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{24}N_2O_3$ (M+H): 353.1860. Found: 353.1864.

The ethyl ester of isomer B (10 g, 26 mmol) was hydrolyzed and converted to 9.1 g of (89%) HCl salt by using the procedure described above. ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, 1H, J = 7.4 Hz), 7.0 (d, 2H, J = 8.6 Hz), 6.8 (m, 2H), 6.71 (d, 1H, J = 7.4 Hz), 4.22 (t, 2H, J = 6.0 Hz), 3.48 (t, 2H, J = 5.6 Hz), 3.11 (t, 2 H, J = 5.9 Hz), 2.80 (t, 2H, J = 6.2 Hz), 2.40–2.28 (m, 2H), 1.96–1.90 (m, 2H), 1.71–1.67 (m, 1H), 1.22–1.18 (m, 1H), 0.88–0.84 (m, 1H), 0.76-0.80 (m, 1H). $[\alpha]_D$ −34.0 (*c* 0.07, MeOH). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{24}N_2O_3$ (M+H): 353.1860. Found: 353.1862.

9.4.18. (2-{3-Fluoro-4-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylamino)propoxy]-phenyl}cyclopropyl)acetic acid (62). Mitsunobu reaction of 5,6,7,8-tetrahydro-1,8-naphthyridin-2-ethanol (**29**) with the phenol **58** followed by saponification and purification gave **62** (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.34 (1H, br s), 10.02 (1H, s), 7.33 (1H, d), 6.90 (1H, t), 6.80 (1H, d), 6.78 (1H, d), 6.60 (1H, br s), 6.54 (1H, d), 4.31 (2H, t), 3.49 (2H, t), 3.16 (2H, t), 2.74 (2H, t), 2.45 (1H, dd), 2.39 (1H, dd), 1.92 (2H, p), 1.71 (1H, dt), 1.28 (1H, m), 0.93 (1H, dt), 0.84 (1H, dt). Anal Calcd for: $C_{21}H_{23}N_2O_3F$ plus 1.75 TFA. C, 51.63; H, 4.38; N, 4.91. Found: C, 52.01; H, 4.27; N, 4.92.

9.4.19. (2-{2,3-Difluoro-4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]-phenyl}cyclopropyl)acetic acid trifluoroacetate (63). Mitsunobu reaction of 5,6,7,8-tetrahydro-1,8-naphthyridin-2-ethanol (**29**) with the phenol **60** followed by saponification and purification afforded **63** (30% yield). ^{1}HNMR (400 MHz, CD_3OD): δ 7.65 (d, 1H), 6.88 (m, 1H), 6.75 (m, 2H), 4.38 (t, 2H), 3.52 (t, 2H), 3.2 (t, 2H), 2.85 (t, 2H), 2.42 (m, 2H), 2.05 (m, 2H), 1.85 (m, 1H), 1.33 (m, 1H),1.02 (m, 1H), 0.92 (m, 1H). Calcd for $C_{21}H_{22}N_2O_3F_2$. 1TFA, 0.5H_2O: C, 54.01; H, 4.73; N, 5.48. Found: C, 53.99; H, 4.61; N, 5.21.

9.4.20. (2-{3-Hydroxy-4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)acetic acid (64). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) and ethyl [2-(3,4-dihydroxyphenyl)cyclopropyl]-acetate (**61**), followed by saponification and purification by HPLC, afforded the product (<1% yield). Two-dimensional NMR confirmed the structure. ^{1}H NMR (400 MHz, D_2O) δ 7.3 (d, 1H, J = 7.2 Hz), 6.7 (d, 2H, J = 8.7 Hz), 6.4 (m, 3H), 4.2 (t, 2H, J = 6.0 Hz), 3.2 (t, 2H, J = 5.5 Hz), 2.9 (t, 2H, J = 5.7 Hz), 2.5 (t, 2H, J = 5.5 Hz), 2.2 (m, 2H), 1.7 (m, 2H), 1.5 (m, 1H), 1.1 (m, 1H), 0.7 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{24}N_2O_3$ (M+H): 369.1814. Found: 369.1781.

9.4.21. (2-{6-[2-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)ethoxy]pyridin-3-yl}cyclopropyl)acetic acid (67). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) and ethyl [2-(6-hydroxypyridin-3-yl)cyclopropyl]acetate (**66**, prepared from 2-methoxy-5-[(1*E*)-prop-1-enyl]pyridine[39]) and using the procedure described for **28**, followed by purification, gave the product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (m, 1H), 7.65 (m, 1H), 7.42 (m, 1H), 6.79 (m, 2H), 4.1 (q, 2H), 3.45 (t, 2H), 3.12 (t, 2H), 2.91 (t, 2H), 2.2–2.4 (m, 1H), 2.5–2.6 (m, 1H), 1.93 (m, 2H), 1.62–1.8 (m, 1H), 0.95 (m, 1H), 0.84 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{20}H_{23}N_3O_3$: 353.42. Found: 354.1971 (M+H).

9.4.22. Ethyl 3-[2-(4-hydroxyphenyl)cyclopropyl]propionate (68). To the solution of 2-(4-methoxyphenyl)cyclopropanecarbaldehyde (**25**) (5 g, 28 mmol) in toluene (100 mL), (carbethoxymethylene)triphenylphosphorane (12.8 g, 37 mmol) was added. The reaction mixture was refluxed overnight. The reaction mixture was concentrated and the residue was purified by passing through a pad of silica gel eluting with 20% ethyl acetate in hexane to yield 7.6 g of ethyl (2*E*)-3-[2-(4-methoxyphenyl)cyclopropyl]prop-2-enoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.9 (m, 2H), 6.8 (m, 2H), 6.6 (m, 1H), 5.9 (d, 1H), 4.2 (m, 2H), 3.8 (s, 3H), 2.1 (m, 1H), 1.7 (m, 1H), 1.2 (m, 5H). HRMS (ES, *m*/*z*) Calcd for $C_{15}H_{18}O_3$: 246.3061. Found: 246.1256. The product was dissolved in ethyl acetate (100 mL) followed by addition of Rhodium/aluminum powder (1.1 g). The reaction mixture was stirred under $H_{2(g)}$ (50 psi) overnight. The catalyst was filtered through Celite and was washed with excess ethyl acetate. The filtrate was concentrated and dried to afford 3.5 g oil. The crude reduction product was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.9 (m, 2H), 6.8 (m, 2H), 4.1 (m, 2H), 3.7 (s, 3H), 2.4 (t, 2H, J = 7.4 Hz), 1.7 (m, 2H), 1.6 (m, 1H), 1.2 (m, 3H), 1.0 (m, 1H), 0.9 (m, 1H), 0.85 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{15}H_{20}O_3$: 248.3220. Found: 248.1412. To a solution of ethyl 3-[2-(4-methoxyphenyl)cyclopropyl]-propionate (2 g, 8.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added BBr_3 (1 M in CH_2Cl_2, 8 mL). The temperature was kept under 2 °C during the addition. The reaction mixture was slowly warmed up

to room temperature and stirred for 18 h at room temperature. The reaction mixture was quenched with ethanol (10 mL) very slowly and stirred for 1 h at room temperature. The reaction mixture was concentrated and purified by passing through a pad of silica gel eluting with 20% ethyl acetate in hexane to afford 1.0 g oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (m, 2H), 6.70 (m, 2H), 4.11 (m, 2H), 2.42 (t, 2H, J = 7.4 Hz), 1.65 (m, 2H), 1.57 (m, 2H), 1.22 (t, 3H, J = 7.1 Hz), 0.97 (m, 1H), 0.80 (m, 1H), 0.70 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{14}H_{18}O_3$: 234.2960. Found: 234.1256.

9.4.23. 3-{2-[4-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-ylmethoxy)phenyl]-cyclopropyl}propionic acid (70). To a solution of $NaBH_4$ (0.46 g, 12 mmol) in THF (10 mL) was added 5,6,7,8-tetrahydro-1,8-naphthyridine-2-carbaldehyde (2 g, 12 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, quenched with water at 0 °C. The mixture was extracted with ethyl acetate (3× 50 mL). The combined organic solution was dried and concentrated under vacuum to give 1.75 g (87%) of the desired alcohol (**73**) as oil. Mitsunobu reaction of 5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylmethanol with ethyl 3-[2-(4-hydroxyphenyl)-cyclopropyl]propionate (**68**) followed by saponification and purification afforded 47% of the desired product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.6 (d, 1H, J = 7.4 Hz), 7.0 (m, 2H), 6.9 (m, 2H), 6.8 (m, 1H), 5.0 (s, 2H), 3.5 (t, 2H, J = 5.7 Hz), 2.80 (t, 2H, J = 6.2 Hz), 2.40 (t, 2H, J = 7.3 Hz), 2.0 (m, 2H), 1.7 (m, 3H), 1.0 (m, 1H), 0.9 (m, 1H), 0.85 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{24}N_2O_3$ (M+H): 353.1860. Found: 353.1889.

9.4.24. 3-(2-{4-[2-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)-propionic acid (69). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) with ethyl 3-[2-(4-hydroxyphenyl)cyclopropyl]-propionate (**68**) followed by saponification and purification gave 20% of the desired product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H, J = 7.4 Hz), 6.94 (d, 2H, J = 8.7 Hz), 6.75 (d, 2H, J = 8.7 Hz), 6.70 (d, 1H, J = 7.4 Hz), 4.21 (t, 2H, J = 5.9 Hz), 3.48 (t, 2H, J = 5.6 Hz), 3.11 (t, 2H, J = 5.9 Hz), 2.80 (t, 2H, J = 6.3 Hz), 2.40 (t, 2H, J = 7.25 Hz), 1.9 (m, 2H), 1.6 (m, 3H), 0.9 (m, 1H), 0.8 (m, 1H), 0.7 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{22}H_{26}N_2O_3$ (M+H): 367.2016. Found: 367.2017.

9.4.25. (2-{3-[2-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclo-propyl)acetic acid (71). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) and ethyl [2-(3-hydroxyphenyl)cyclopropyl]-acetate(**59**), prepared as described for the *p*-isomer, followed by saponification and purification afforded 63% of the desired product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, 1H, J = 7.4 Hz), 7.11 (t, 1H, J = 7.8 Hz), 6.74–6.63 (m, 4H), 4.26 (t, 2H, J = 5.8 Hz), 3.49 (t, 2H, J = 5.6 Hz), 3.13 (t, 2H, J = 5.8 Hz), 2.82 (t, 2H, J = 6.2 Hz), 2.38–2.35 (m, 2H), 1.98–1.91 (m, 2H), 1.76–1.70 (m, 1H), 1.31–1.25 (m, 1H), 0.97–0.90 (m, 1H), 0.88–0.81 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{24}N_2O_3$ (M+H): 353.1860. Found: 353.1853.

9.4.26. 3-(2-{3-[2-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)propionic acid (72). Starting from the aldehyde **41**, and following the reaction sequence described for the synthesis of **69**, 81% of the desired product was obtained. ^{1}H NMR (400 MHz, CD_3OD) δ 7.6 (d, 1H, J = 7.4 Hz), 7.1 (t, 1H, J = 7.9 Hz), 6.7 (d, 2H, J = 7.4), 6.6 (m, 2H), 6.57 (m, 1H), 4.2 (t, 2H, J = 5.9 Hz), 3.5 (t, 2H, J = 5.6 Hz), 3.10 (t, 2H, J = 5.9 Hz), 2.80 (t, 2H, J = 6.2 Hz), 2.40 (t, 2H, J = 7.3 Hz), 1.90 (m, 2H), 1.7 (m, 3H), 1.05 (m, 1H), 0.9 (m, 1H), 0.8 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{22}H_{26}N_2O_3$ (M+H): 367.2027. Found: 367.2013.

9.4.27. Diethyl 2,2-dimethyl-3-(*p*-methoxyphenyl)cyclopropane-1,1-dicarboxylate (74). A mixture of anisaldehyde (340 g, 2.5 mol), diethylmalonate (400 g, 2.5 mol), acetic acid (150 g), and piperidine (40 g) in dry toluene (2 L) was heated at reflux for 24 h. The solvent was removed in vacuo and the residue was dried to afford 690 g of the product. This was dissolved in dry DMSO (2.5 L) and was added 2-nitropropane (500 mL) and potassium *tert*-butoxide (600 g), and the reaction mixture was stirred using a mechanical stirrer and was heated to 100 °C for 36 h. The pink reaction mixture was poured into ice-water (10 L) and was extracted with ether (10 L overall). The ether layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was passed through a pad of silica (2.5 kg, 30 cm thick) and was eluted with hexane (10 L). Appropriate fractions of hexane eluents were combined and concentrated to yield 523 g (66%) of the product as oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.08 (m, 2H), 6.80 (d, 2H, J = 8.7 Hz), 4.04–4.27 (m, 4H), 3.74 (s, 3H), 2.88 (s, 1H), 1.36 (s, 3H), 1.26 (s, 3H), 1.16 (t, 3H, J = 7.2 Hz). HRMS (ES, *m*/*z*) Calcd for $C_{18}H_{24}O_5$: 320.1624. Found: 320.1616.

9.4.28. Ethyl 2,2-dimethyl-3-(*p*-methoxyphenyl)cyclopropane-1-carboxylate (*trans*-isomer) (75). A mixture of the diester (**74**, 425 g, 1.33 mol), potassium cyanide (392 g, 6 mol) in dry dimethylsulfoxide (1.5 L) was heated at 160 °C for 48 h. The reaction mixture was cooled and was poured into ice-water (6 L) and was extracted with several portions of ether (8 L overall). The ether layer was dried and was concentrated to afford a residue. Chromatography of the residue with 2% hexane in ethyl acetate gave 168 g (51%) of the product as oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (dd, 2H, J = 2.8, 11.1 Hz), 6.82 (m, 2H), 4.15 (q, 2H, J = 7.2 Hz), 3.75 (s, 3H), 2.53 (d, 1H, J = 5.8 Hz), 1.91 (d, 1H, J = 5.8 Hz), 1.32 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz), 0.88 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{15}H_{20}O_3$: 248.1412. Found: 248.1415.

9.4.29. 2,2-Dimethyl-3-(*p*-methoxyphenyl)cyclopropane-1-carboxylic acid (*cis*-isomer) (76). A minor fraction (more polar fraction) obtained from the above was found to be a 1:1 mixture of the cis and trans isomers. The mixture in ethanol (50 mL) was stirred at rt with excess sodium hydroxide (10%, 20 mL). Monitoring by HPLC indicated the disappearance of the *trans* isomer in about 3 h. The reaction mixture was diluted with water and was extracted with ether. The ether layer

was dried and was concentrated to yield a residue. The ester was hydrolyzed with ethanol (200 mL), sodium hydroxide (10%, 50 mL) overnight. The reaction mixture was poured into water and was acidified to afford 6.8 g of the product as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.04 (m, 2H), 6.82 (m, 2H), 3.73 (s, 3H), 2.39 (d, 1H, J = 9.1 Hz), 1.79 (d, 1H, J = 9.1 Hz), 1.31 (s, 3H), 1.23 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 219.1016 (M−H).

9.4.30. [(*cis*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropyl]methanol (78). Borane·THF (40 mL, 40 mmol) was added to a solution of 2,2-dimethyl-(*cis*)-3-(*p*-methoxyphenyl)-cyclopropane-1-carboxylic acid (**76**, 4.0 g, 18 mmol) in THF (40 mL). After 3-h stirring at rt, the reaction mixture was quenched with hydrochloric acid (40 mL, 1 N), diluted with water (200 mL), and extracted with ether (2× 100 mL). The organic layer was washed with water, dried, and concentrated to afford 3.7 g (100%) of the product as oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.08 (m, 2H), 6.79 (m, 2H), 3.73 (s, 3H), 3.68 (m, 1H), 3.33 (m, 1H), 1.89 (d, 1H, J = 9.0 Hz), 1.24 (s, 3H), 1.12 (m, 1H), 0.94 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1316.

9.4.31. [(*cis*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropyl]acetic acid (80). Oxalyl chloride (19.3 mL, 1 M, 19.3 mmol) was added to a solution of DMSO (1.51 g, 38.64 mmol) in dichloromethane (20 mL) at −78 °C. After 15 min, a solution of the alcohol (**78**, 2.0 g, 9.66 mmol) in dichloromethane (5 mL) was added. After 30 min, triethylamine (10 mL) was added to the reaction mixture and was warmed up to ambient temperature. Water (100 mL) was added followed by additional dichloromethane (100 mL). The organic layer was dried and concentrated to give the crude aldehyde. The above crude aldehyde in THF (10 mL) was added to the Wittig reagent [prepared by adding lithium hexamethyldisilazane (21.3 mL, 21.3 mmol) to methoxymethyltriphenylphosphonium chloride (6.62 g, 21.3 mmol) in tetrahydrofuran (40 mL) at 0 °C. After 6h, the reaction mixture was diluted with water (200 mL), extracted with ether (200 mL), dried, and concentrated to afford 2.0 g of the product as a mixture of *E*- and *Z*-isomers. ^{1}H NMR (400 MHz, CD_3OD) δ 7.31–7.33 (m, 1H), 7.06–7.09 (m, 2H), 6.76–6.81 (m, 2H), 6.38–6.41 and 6.02–6.04 (m, 1H), 3.37 and 3.60 (2s, 3H), 3.73 and 3.74 (2s, 3H), 1.9 (m, 1H), 1.2 and 1.21 (2s, 3H), 0.88 and 0.86 (2s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{18}O_2$: 232.1463. Found: 232.1466.

A mixture of the crude 1-methoxy-4-{3-[2-methoxyethenyl]-2,2-dimethylcyclo-propyl}benzene (2.0 g) was heated at reflux in THF (50 mL) and hydrochloric acid (1 N, 5 mL) for 4 h. The reaction mixture was diluted with water, extracted with ether (200 mL), dried, and concentrated to give the aldehyde mixed with triphenylphosphine oxide. The aldehyde in ethanol (100 mL) was added to an aqueous solution of silver nitrate (2.48 g) in water (20 mL) followed by sodium hydroxide (12.4 mL, 1 N) at 0 °C. After 3 h, the reaction mixture was filtered through Celite. The filtrate was diluted with water (100 mL), extracted with ethyl acetate (100 mL), and discarded. The aqueous layer was acidified and then extracted with ether (200 mL), dried, and concentrated to afford 1.40 g (62% overall) of [3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl]acetic acid as oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.04 (m, 2H), 6.81 (m, 2H), 3.74 (s, 3H), 1.97–2.04 and 2.30–2.36 (m, 2H), 1.84 (d, 1H, J = 9 Hz), 1.24 (s, 3H), 1.21 (m, 1H), 0.91 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 233.1154 (M−H).

9.4.32. Ethyl (*cis*)2,2-dimethyl-3-(*p*-hydroxyphenyl)cyclopropaneacetate (82). A solution of [3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl]acetic acid (**80**, 1.40 g) was heated at reflux with ethanol (100 mL) and hydrochloric acid (1 mL) for 3 h. The reaction mixture was concentrated and the residue was dissolved in ether (200 mL). The ether layer was washed with water, dried, and concentrated to afford 1.2 g of the ester. ^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (m, 2H), 6.80 (m, 2H), 4.08–4.16 (m, 2H), 3.74 (s, 3H), 1.99–2.05 and 2.34–2.40 (m, 2H), 1.85 (d, 1H, J = 9 Hz), 1.23 (s, 3H), 1.23 (m, 3H), 1.18 (m, 1H), 0.90 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{16}H_{22}O_3$: 262.1569. Found: 262.1569.

Boron tribromide (1 N, 8 mL) was added to a solution of ethyl (*cis*)2,2-dimethyl-3-(*p*-methoxyphenyl)cyclopropaneacetate (described above, 1.03 g, 3.93 mmol) in dichloromethane (20 mL) at 0 °C and was stirred for 3 h. The reaction mixture was quenched with ethanol (10 mL) and was stirred at rt for 18 h. Diluted with dichloromethane (100 mL) it was washed with sodium bicarbonate (saturated), dried, and concentrated. The residue was purified on silica gel (flash, 40%ethyl acetate in hexane) to yield 0.58 g (39%) of the phenol. ^{1}H NMR (400 MHz, CD_3OD) δ 6.94 (m, 2H), 6.67 (m, 2H), 4.07–4.06 (m, 2H), 1.99–2.05 and 2.34–2.39 (m, 2H), 1.82 (d, 1H, J = 9 Hz), 1.22 (s, 3H), 1.22 (m, 3H), 1.17 (m, 1H), 0.90 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{15}H_{20}O_3$: 248.1412. Found: 248.1415.

9.4.33. 2,2-Dimethyl-3-(*cis*)-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropylacetic acid trifluoroacetate (84). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridyl)-amino ethanol (**29**) and ethyl (*cis*)2,2-dimethyl-3-(*p*-hydroxyphenyl)cyclopropaneacetate (**82**) followed by saponification and purification by HPLC gave 23% of the desired product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, 1H, J = 7.4 Hz), 7.06 (m, 2H), 6.80 (m, 2H), 6.70 (d, 1H, J = 7.3 Hz), 4.24 (t, 2H, J = 5.9 Hz), 3.48 (m, 2H), 3.13 (t, 2H, J = 5.9 Hz), 2.8 (m, 2H), 1.99–2.02 and 2.27–2.33 (m, 2H), 1.93 (m, 2H), 1.83 (d, 1H, J = 9 Hz), 1.23 (s, 3H), 1.18 (m, 1H), 0.89 (s, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{23}H_{28}N_2O_3$: 380.2100. Found: 379.2036 (M−H).

9.4.34. (2,2-dimethyl-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]-phenyl}cyclopropyl)acetic acid (83). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-napthyridin-2-yl)-1-ethanol (**29**) and the cyclopropyl phenol (**81**), prepared from the acid as described for the cis ester, followed by saponification and purification by HPLC, gave

the title compound as yellow solid in a similar yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H), 7.09 (d, 2H), 6.79 (d, 2H), 6.71 (d, 1H), 4.23 (t, 2H), 3.48 (t, 2H), 3.11 (t, 2H), 2.80 (t, 2H), 2.47 (m, 4H), 1.93 (m, 2H), 1.57 (m, 1H), 1.18 (s, 3H), 0.81 (s, 3H). HRMS (ES, *m/z*) Calcd for $C_{23}H_{28}N_2O_3$: 380.2100. Found: 381.2192 (M+H).

9.4.35. Separation of diastereomers of ethyl (2,2-dimethyl-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}cyclopropyl)acetate (83). The isomeric mixture of ethyl (2,2-dimethyl-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}cyclopropyl)-acetate (**83**, 6 g) was separated on ChiralPak AS column (isopropylalcohol/heptane/diethylamine/20:80:0.1, flow rate: 50 mL/min at room temperature) to give 2.5 g ethyl ester of isomer A and 1.5 g ethyl ester of isomer B.

The ethyl ester of isomer A (2.5 g, 6.12 mmol) was dissolved in ethanol (10 mL), water (2 mL) and treated with lithium hydroxide (0.56 g, 13.46 mmol). The solution was heated at 55 °C for 2 h, solvent concentrated, residue dissolved in (10 mL) acetonitrile/water, and acidified by adding TFA. The crude material was purified on reverse phase HPLC to give 1.3 g TFA salt of isomer A of (**83**). The TFA salt was passed through Bio-Rad AG 2-X8 (200–400 Mesh, Chloride form, 13 g) column and was eluted with 50% acetonitrile in water to give 1.02 g (93%) HCl salt of isomer A of (**83**). ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H), 7.09 (d, 2H), 6.79 (d, 2H), 6.71 (d, 1H), 4.23 (t, 2H), 3.48 (t, 2H), 3.11 (t, 2H), 2.80 (t, 2H), 2.47 (m, 4H), 1.93 (m, 2H), 1.57 (m, 1H), 1.18 (s, 3H), 0.81 (s, 3H). $[\alpha]_D$ 12.3 (*c* 0.3, methanol). HRMS (ES, *m/z*) Calcd for $C_{23}H_{28}N_2O_3$: 380.2100. Found: 381.2192 (M+H).

The ethyl ester of isomer B (1.5 g, 3.6 mmol) was hydrolyzed and converted to 1.0 g (92%) HCl salt by using the above procedure. ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H), 7.09 (d, 2H), 6.79 (d, 2H), 6.71 (d, 1H), 4.23 (t, 2H), 3.48 (t, 2H), 3.11 (t, 2H), 2.80 (t, 2H), 2.47 (m, 4H), 1.93 (m, 2H), 1.57 (m, 1H), 1.18 (s, 3H), 0.81 (s, 3H). $[\alpha]_D$ −11.7 (*c* 0.3, methanol). HRMS (ES, *m/z*) Calcd for $C_{23}H_{28}N_2O_3$: 380.2100. Found: 381.2192 (M+H).

9.4.36. *tert*-Butyl{[(3*E*)-4-(4-methoxyphenyl)but-3-enyl]oxy}-dimethylsilane (85). Lithium aluminum hydride (1 M in THF, 4.8 mL) was added slowly to a solution of (3*E*)-4-(4-methoxyphenyl)-but-3-enoic acid (**16**, 14.6 g, 70 mmol) in ether (300 mL) at room temperature. The reaction mixture was stirred for 3 h at room temperature, then quenched slowly with water. The organic layer was separated and water layer was extracted with ether (1× 200 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, concentrated, and dried to afford 7.3 g (58%) of product as solid. The material was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 2H), 6.8 (m, 2H), 6.42 (d, 1H, J = 15.8 Hz), 6.0 (m, 1H), 3.8 (s, 3H), 3.7 (t, 2H, J = 6.2 Hz), 2.4 (m, 2H). HRMS (ES, *m/z*) Calcd for $C_{11}H_{14}O_2$: 178.2310. Found: 178.0994.

To the solution of (3*E*)-4-(4-methoxyphenyl)but-3-en-1-ol (7.3 g, 41 mmol) in DMF (40 mL), *tert*-butyldimethylsilyl chloride (1 M in dichloromethane, 62 mL) and imidazole (5.5 g, 80.1 mmol) were added followed by DMAP (cat.). The reaction mixture was stirred for 18 h at room temperature and was diluted with ether (500 mL). The organic solution was washed with water (2× 200 mL), brine (1× 200 mL), dried over $MgSO_4$, and concentrated to yield 9 g (75%) of oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.8 (m, 2H), 6.35 (d, 1H, J = 15.8 Hz), 6.05 (m, 1H), 3.8 (s, 3H), 3.7 (t, 2H, J = 6.7 Hz), 2.4 (m, 2H), 0.9 (s, 9H), 0.05 (s, 6H). HRMS (ES, *m/z*) Calcd for $C_{17}H_{28}O_2Si$: 292.1859. Found: 292.1851.

9.4.37. 2-[2,2-Dichloro-3-(4-methoxyphenyl)cyclopropyl]ethanol (86). To a solution of *tert*-butyl{[(3*E*)-4-(4-methoxyphenyl)but-3-enyl]oxy}dimethylsilane (**85**, 7.2 g, 24.6 mmol) in chloroform (60 mL), 50% NaOH (30 mL) and benzyltriethylammonium chloride (0.3 g) were added. The reaction mixture was stirred for 4 h at room temperature. Water (100 mL) was added and the reaction mixture was extracted with dichloromethane (2× 250 mL). The organic solution was washed with water (2× 150 mL), brine (1× 150 mL), dried over $MgSO_4$, and concentrated to afford 4.9 g (53%) of brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.14 (m, 2H), 6.87–6.84 (m, 2H), 3.83–3.77 (m, 5H), 2.4 (m, 1H), 2.05–1.96 (m, 2H), 1.84–1.79 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H). To a solution of *tert*-butyl{2-[2,2-dichloro-3-(4-methoxyphenyl)cyclopropyl]ethoxy}dimethylsilane (4.9 g, 13 mmol) in THF (50 mL), tetrabutylammonium flouride (1 M in THF, 69 mL) was added followed by water (2 mL). The reaction mixture was stirred for 3 h at room temperature. Water was added (100 mL). The aqueous solution was extracted with dichloromethane (2× 200 mL). The combined organic solution was washed with water, brine, dried ($MgSO_4$), and concentrated. The concentrated residue was purified by passing through a thick pad of silica gel and eluting with 30% ethyl acetate in hexane to yield 3 g (88%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.15 (m, 2H), 6.88–6.85 (m, 2H), 3.90–3.84 (m, 2H), 3.79 (s, 3H), 2.44 (d, 1H, J = 8.2 Hz), 2.12–2.0 (m, 2H), 1.99–1.85 (m, 1H). HRMS (ES, *m/z*) Calcd for $C_{12}H_{14}O_2Cl_2$: 260.0371. Found: 260.0369.

9.4.38. [2,2-Dichloro-3-(4-methoxyphenyl)cyclopropyl]acetic acid (88). To a solution of 2-[2,2-dichloro-3-(4-methoxyphenyl)cyclopropyl]ethanol (**86**, 0.21 g, 0.8 mmol) in acetone (4 mL), Jone's reagent (2 mL) was added at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 1.5 h. The reaction mixture was quenched with isopropyl alcohol (4 mL), filtered through Celite, and the filtrate was concentrated. Saturated $NaHCO_3$ (20 mL) was added to the concentrated residue and was washed with ether (2× 20 mL). The aqueous solution was acidified and was extracted with ether (3× 20 mL). The combined ether layer was washed with brine, dried ($MgSO_4$), and concentrated to afford 0.09 g (41%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.22 (m, 2H), 6.94–6.81 (m, 2H), 3.79 (s, 3H), 3.01–2.68 (m, 2H), 2.53 (d, 1H, J = 8.3 Hz), 2.25–2.16 (m, 1H). HRMS

(ES, *m*/*z*) Calcd for $C_{12}H_{12}O_3Cl_2$: 274.0163. Found: 274.0155.

9.4.39. Ethyl [2,2-dichloro-3-(4-hydroxyphenyl)cyclopropyl]acetate (90). [2,2-Dichloro-3-(4-methoxyphenyl)cyclopropyl]acetic acid (**88**, 0.1 g, 0.36 mmol) in ethanol (1 mL) was added 4 N HCl (0.5 mL) and the reaction mixture was stirred for 3 h at room temperature and concentrated to give 0.1 g (91%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 8.7 Hz), 6.9 (d, 2H, J = 8.7 Hz), 4.23 (q, 2H, J = 7.1 Hz), 3.83 (s, 3H), 2.96–2.53 (m, 3H), 2.33–2.22 (m, 1H), 1.31 (t, 3H, J = 7.1 Hz). HRMS (ES, *m*/*z*) Calcd for $C_{14}H_{16}O_3Cl_2$: 302.0476. Found: 302.0469. Borontribromide (1 M in CH_2Cl_2, 1 mL) was added to a solution of ethyl [2,2-dichloro-3-(4-methoxyphenyl)cyclopropyl]acetate (0.36 g, 1.2 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 18 h at room temperature and was concentrated. The concentrated residue was purified by passing through a thick pad of silica to afford 0.18 g (53%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.15 (m, 2H), 6.82–6.75 (m, 2H), 4.20 (q, 2H, J = 7.1 Hz), 2.92–2.86 (m, 1H), 2.65–2.59 (m, 1H), 2.51–2.49 (m, 1H), 2.23–2.17 (m, 1H), 1.29–1.24 (m, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{14}O_3Cl_2$: 288.0320. Found: 288.0336 (HRMS).

9.4.40. (2,2-Dichloro-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)acetic acid (92). To a solution of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**, 0.16 g, 0.9 mmol) and polymer bound PPh_3 (0.3 g, 0.9 mmol) in dry THF (6 mL), ethyl [2,2-dichloro-3-(4-hydroxyphenyl)-cyclopropyl]-acetate (**90**, 0.18 g, 0.6 mmol) was added followed by diisopropyl azodicarboxylate (0.2 mL, 1 mmol). The reaction mixture was stirred at room temperature. After 18 h, the reaction mixture was filtered through Celite to remove the polymer and washed with excess THF and the filtrate was concentrated. The residue in 50% acetonitrile in water (4 mL) was added LiOH (0.1 g). The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was acidified with TFA and purified by reverse phase HPLC to afford 0.12 g (36%) of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (d, 1H, J = 8 Hz), 7.26 (d, 2H, J = 8.4 Hz), 6.93 (d, 2H, J = 8.8 Hz), 6.77 (d, 1H, J = 7.6 Hz), 4.32 (t, 2H, J = 6 Hz), 3.53 (t, 2H, J = 5.6 Hz), 3.19 (t, 2H, J = 6 Hz), 2.87–2.59 (m, 5H), 2.32–2.26 (m, 1H), 2.01–1.95 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{22}N_2O_3$ (M+H): 421.1080, Found: 421.1069.

9.4.41. (2,2-Dibromo-3-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropyl)acetic acid (93). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) and ethyl [2,2-dibromo-3-(4-hydroxyphenyl)-cyclopropyl]acetate (**91**), prepared as described for the dichloro compound but starting from bromoform, followed by saponification and purification afforded the desired product in 2% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, 1H, J = 7.4 Hz), 7.21 (d, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.73 (d, 1H, J = 7.2 Hz), 4.27 (t, 2H, J = 6.0 Hz), 3.49 (t, 2H, J = 5.9 Hz), 3.14 (t, 2H, J = 5.9 Hz), 2.82–2.78 (m, 3H), 2.71–2.59 (m, 2H), 2.25–2.19 (m, 1H), 1.97–1.90 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{21}H_{22}N_2O_3$ (M+H): 421.1080, Found: 421.1069 (M+H).

9.4.42. 4-(*p*-Methoxyphenyl)-3-butyn-1-ol (95). A solution of 4-iodoanisole (200 g, 0.8547 mol) and 3-butyn-1-ol (64 mL) in triethylamine (1 L) was degassed and stirred using mechanical stirrer under nitrogen. A mixture of dichlorobis-(triphenylphosphine)palladium (4.80 g) and cuprous iodide (2.46 g) was added to the mixture. The reaction mixture slowly warmed up due to the exotherm and reached the boiling point of triethylamine in 45 min. The reaction mixture was cooled down to room temperature in 90 min and was poured into water (1 L) and ethyl acetate (1.5 L). The organic layer was washed with water (1 L), brine (1 L), dried, and concentrated. The residue was purified using a thick pad of silica gel (30% ethyl acetate in hexane) to afford 120 g (80%) of the product as a crystalline solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (d, 2H, J = 8.7 Hz), 6.82 (d, 2H, J = 8.7 Hz), 3.76 (s, 3H), 3.68 (t, 2H, J = 6.7 Hz), 2.56 (t, 2H, J = 6.8 Hz). HRMS (ES, *m*/*z*) Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0839.

9.4.43. Diisopropyl-[4-(4-methoxyphenyl)-3-butynyloxy]silane (96). Triethylamine (9.1 mL, 64.55 mmol) was added to a solution of 4-(*p*-methoxyphenyl)-3-butyn-1-ol (**95**, 11.25 g, 63.9 mmol) and diisopropylchlorosilane (10.0 g, 64.55 mmol) and DMAP (0.80 g) in dry dichloromethane (100 mL) at 0 °C. After 4h, the reaction mixture was filtered through silica gel (100 g) and the filtrate concentrated to yield 16.9 g (90%) of the product as oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (d, 2H, J = 8.7 Hz), 6.79 (d, 2H, J = 8.7 Hz), 4.18 (s, 1H), 3.87 (t, 2H, J = 7 Hz), 3.78 (s, 3H), 2.63 (t, 2H, J = 6.8 Hz) 1.00–1.08 (m, 14H). HRMS (ES, *m*/*z*) Calcd for $C_{17}H_{26}O_2Si$: 290.1702. Found: 290.1715.

9.4.44. 4-(*p*-Methoxyphenyl)-3-phenyl-3-butene-1-ol (97). A xylene solution (5 mL) of Pt(DVDS) was added to diisopropyl-(4-phenyl-3-butynyloxy)silane (**96**, 20.0 g, 67.91 mmol) in THF (200 mL). A mild exotherm resulted and the reaction mixture was stirred for 2 h. To this tetrabutylammonium fluoride (150 mL, 1 M) in THF was added followed by iodobenzene (8 mL) and $Pd_2(dba)_3$ (6.2 g) was added. Additional amount of iodobenzene (8 mL) was added after 6 h and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was concentrated and the residue was partitioned between ether (500 mL) and water (500 mL). The organic layer was washed with brine and dried and was concentrated to afford a residue. This was purified on a pad of silica (15% EA in hexane) to yield 10.0 g (58%) of the product as crystalline solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43–7.46 (m, 2H), 7.33–7.38 (m, 4H), 7.27–7.30 (m, 1H), 6.88–6.92 (m, 2H), 6.79 (s, 1H), 3.82 (s, 3H), 3.71 (t, 2H, J = 7 Hz), 3.03 (t, 2H, J = 7 Hz). HRMS (ES, *m*/*z*) Calcd for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1321.

9.4.45. 2-(*p*-Methoxyphenyl)-1-phenyl-1-(2-hydroxyethyl)cyclopropane (98). Diethyl zinc (95 mL, 95 mmol) was added to a solution of iodochloromethane (13.87 mL, 190 mmol) in dichloroethane (300 mL) over

30 min at −20 °C. After 20 min, dichloroethane (100 mL) solution of 4-(*p*-methoxyphenyl)-3-phenyl-3-butene-1-ol (**97**, 8.50 g, 33.45 mmol) was added. It was warmed over to rt over 2 h and was stirred for 18 h. The reaction mixture was quenched with hydrochloric acid (200 mL, 1 N). The organic layer was washed with brine (200 mL), dried, and concentrated. The residue was purified by chromatography (20% hexane in ethyl acetate) to give 4.8 g (54%) of the product as oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.37–7.40 (m, 2H), 7.23–7.29 (m, 4H), 7.15–7.20 (m, 1H), 6.88–6.90 (m, 2H), 3.77 (s, 3H), 3.30–3.38 (m, 2H), 2.20–2.22 (m, 1H), 1.69–1.76 (m, 1H), 1.20–1.39 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{18}H_{20}O_2$: 268.1463. Found: 268.1464.

9.4.46. Ethyl 2-(*p*-hydroxyphenyl)-1-phenylcyclopropaneacetate (99). PCC (5.35 g, 24.80 mmol) was added to a suspension of molecular sieves (4A, 10 g) and 2-(*p*-methoxyphenyl)-1-phenyl-1-(2-hydroxyethyl)cyclopropane (**98**, 4.20 g, 16.54 mmol) in dichloromethane (200 mL) and the mixture was stirred for 3 h. The reaction mixture was filtered through Celite and the filtrate was concentrated. The residue in ethyl acetate was then passed through a pad of silica gel. The filtrate was concentrated to provide the aldehyde. An aqueous solution of silver nitrate (5.6 g) was added to a solution of the aldehyde in ethanol (200 mL) followed by sodium hydroxide (28 mL, 2.5 M). The dark reaction mixture was stirred for 2 h at rt and then was filtered through Celite. The solid was washed with ethanol. The filtrate was combined and concentrated. The residue was partitioned between water and ether. The aqueous layer was acidified and was extracted with ether (300 mL). The ether layer was dried and was concentrated to afford 4.0 g of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39–7.41 (m, 2H), 7.23–7.32 (m, 4H), 7.14–7.21 (m, 1H), 6.87–6.89 (m, 2H), 3.77 (s, 3H), 2.46–2.50 (m, 1H), 2.29–2.33 (m, 1H), 1.97–1.98 (m, 1H), 1.52–1.54 (m, 1H), 1.44–1.47 (m, 1H), 1.14–1.17 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{18}H_{18}O_3$: 282.1256. Found: 282.1218.

A mixture of 2-(*p*-methoxyphenyl)-1-phenylcyclopropaneacetic acid (4.0 g), ethanol (200 mL), and hydrochloric acid (2 mL) was heated at reflux for 6 h. The reaction mixture was concentrated. The residue was partitioned between ether and water. The ether layer was dried and was concentrated to afford 4.0 g of ethyl 2-(*p*-methoxy-phenyl)-1-phenyl-cyclopropaneacetate. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39–7.40 (m, 2H), 7.14–7.31 (m, 5H), 6.85–6.87 (m, 2H), 3.85–3.90 (m, 2H), 3.75 (s, 3H), 2.42–2.48 (m, 1H), 2.29–2.33 (m, 1H), 1.99–2.04 (m, 1H), 1.32–1.49 (m, 2H), 1.00–1.04 (m, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{20}H_{22}O_3$: 311.1642 (M+H). Found: 311.1546 (M+H). Borontribromide (10 mL) was added to a solution of ethyl 2-(*p*-methoxyphenyl)-1-phenylcyclopropaneacetate (1.43 g, 4.6 mmol) in dry dichloromethane and stirred for 18 h. The reaction mixture was quenched with ethanol and was concentrated. The residue was purified by chromatography to afford 0.270 g (16% overall) of the product as brown oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36–7.38 (m, 2H), 7.25–7.28 (m, 2H), 7.11–7.17 (m, 3H), 6.73–6.75 (m, 2H), 3.86–3.91 (m, 2H), 2.44–2.48 (m, 1H), 2.27–2.31 (m, 1H), 1.99–2.04 (m, 1H), 1.39–1.47 (m, 2H), 1.01–1.05 (m, 3H). HRMS (ES, *m*/*z*) Calcd for $C_{19}H_{20}O_3$: 296.1412. Found: 296.1361.

9.4.47. 1-Phenyl-2-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]phenyl}-cyclopropylacetic acid (100). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridyl)amino ethanol (**29**) and ethyl 2-(*p*-hydroxyphenyl)-1-phenylcyclo-propaneacetate (**99**) followed by saponification and purification gave the product as its TFA salt. Yield: 18%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, 1H, J = 7.4 Hz), 7.39 (m, 2H), 7.28 (t, 2H, J = 7.4 Hz), 7.22 (d, 2H, J = 8.2 Hz), 7.16 (t, 1H, J = 7.0 Hz), 6.88 (d, 2H, J = 8.2 Hz), 6.72 (d, 1H, J = 7.4 Hz), 4.27 (t, 2H, J = 5.9 Hz), 3.49 (t, 2H, J = 5.6 Hz), 3.14 (t, 2H, J = 5.9 Hz), 2.81 (t, 2H, J = 6.3 Hz), 2.44 and 1.93 (AB q, 2H, J = 16.1 Hz), 2.30 (t, 1H, J = 8.3 Hz), 1.91–1.94 (m, 2H), 1.42–1.54 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{27}H_{28}N_2O_3$: 428.2100. Found: 429.2184 (M+H).

9.4.48. 2-[2-(4-Methoxyphenyl)-2-methylcyclopropyl]ethanol (102). To a solution of $LiAlH_4$ (1 M in THF, 6.17 mL, 6.17 mmol) in THF (20 mL) at 0 °C, a solution of (3*E*)-4-(4-methoxyphenyl)pent-3-enoic acid[61] (**101**, 1.0 g, 4.1 mmol) in THF (20 mL) was slowly added. The reaction mixture was stirred for 3h at room temperature, cooled to 0 °C, and quenched by dropwise addition of 2.5 N NaOH. The solution was stirred at room temperature for few minutes, the solid complex filtered and washed with excess THF. The organic layer washed with sat. NH_4Cl, dried over $MgSO_4$, and concentrated to give white solid in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.88 (m, 2H), 5.72 (m, 1H), 3.8 (s, 3H), 3.7 (t, 2H), 2.29 (m, 2H), 2.02 (m, 3H). To a solution of iodochloromethane (1 mL, 13.52 mmol) in 1,2-dichloroethane (20 mL) at 0 °C, a solution of diethyl zinc (1.0 M in hexane, 6.76 mL, 6.76 mmol) was added dropwise over 10–15 min. A solution of the alcohol (1.0 g, 5.2 mmol) in 1,2-dichloroethane (30 mL) was added dropwise at 0 °C. The solution was then stirred at room temperature for few minutes, heated at 40 °C for 1 h, and stirred at room temperature for 2 days. The solution was cooled at 0 °C and quenched by addition of 1.5 N HCl. The aqueous layer was extracted several times with ethyl acetate, the combined organic layer washed with water, brine, dried over $MgSO_4$, and concentrated to give oil. Yield: 25%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2 (m, 2H), 6.8 (m, 2H), 3.8 (s, 3H), 3.7 (t, 2H), 2.26 (m, 2H), 1.62 (m, 3H), 0.89 (m, 2H), 0.62 (m, 1H). HRMS (ES, *m*/*z*) Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1287 (M+H).

9.4.49. Ethyl [2-(4-hydroxyphenyl)-2-methylcyclopropyl]acetate (103). A solution of alcohol (**102**, 0.25 g, 1.2 mmol), Tempo (0.012 g, 0.08 mmol), and phosphate buffer (4.55 mL, 22.33 mmol) was stirred at room temperature. A solution of $NaClO_2$ (80%, 0.273 g, 2.4 mmol) in water (1 mL) and NaOCl (10–13% chlorine, 0.2 mL, 0.3 mmol, 30 mol%) were added. The solution was heated at 35 °C for 6 h, cooled to room temperature, and adjusted to pH 8 using water and

NaOH. A solution of $Na_2S_2O_3$ in water was added and reaction mixture was stirred for 30 min. Ethyl acetate was added and the solution was acidified using 1.5 N HCl. The aqueous layer was extracted three times with ethyl acetate and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.82 (m, 2H), 3.82 (s, 3H), 3.7 (t, 2H), 2.3–2.7 (m, 2H), 1.92 (m, 1H), 1.02 (m, 1H), 0.82 (m, 1H). To a solution of the acid in ethanol (10 mL), 4 N HCl in dioxane (1 mL) was added. The reaction mixture was stirred for 3 h at room temperature and then concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated to give yellow oil. The crude material was stirred in CH_2Cl_2 (20 mL) at 0 °C and BBr_3 (1.0 M in CH_2Cl_2, 1.6 mL) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, quenched by addition of ethanol, and stirred for 1 h at room temperature. The solvent was concentrated to remove ethanol. The residue was dissolved in ethyl acetate, washed with satd $NaHCO_3$, brine, and dried over Na_2SO_4 to give brown oil. The crude material was used without further purification in the next step. HRMS (ES, *m*/*z*) Calcd for $C_{15}H_{20}O_3$: 266.1751 (M+NH_4). Found: 266.1732 (HRMS, M+NH_4).

9.4.50. (2-Methyl-2-{4-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]-phenyl}cyclopropyl)acetic acid (104). Mitsunobu reaction of 2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethanol (**29**) and **103** followed by saponification and purification afforded the desired product. Yield: 15% ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, 1H), 7.25 (m, 2H), 6.83 (m, 2H), 6.77 (d, 1H), 4.23 (m, 2H), 3.48 (m, 2H), 3.12 (m, 2H), 2.84 (m, 2H), 2.7–2.32 (m, 2H), 2.01–1.90 (m, 2H), 1.3 (m, 3H), 1.05 (m, 1H), 0.8–0.72 (m, 2H). HRMS (ES, *m*/*z*) Calcd for $C_{22}H_{26}N_2O_3$ (M+H): 367.2016. Found: 367.2015.

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