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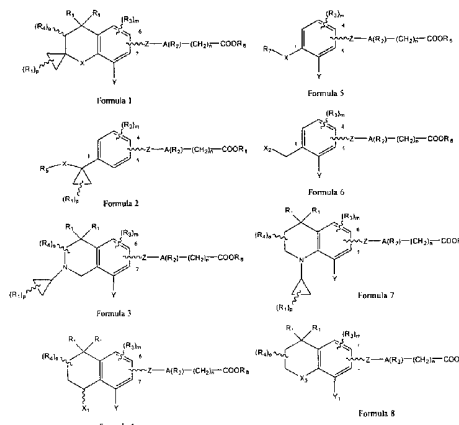
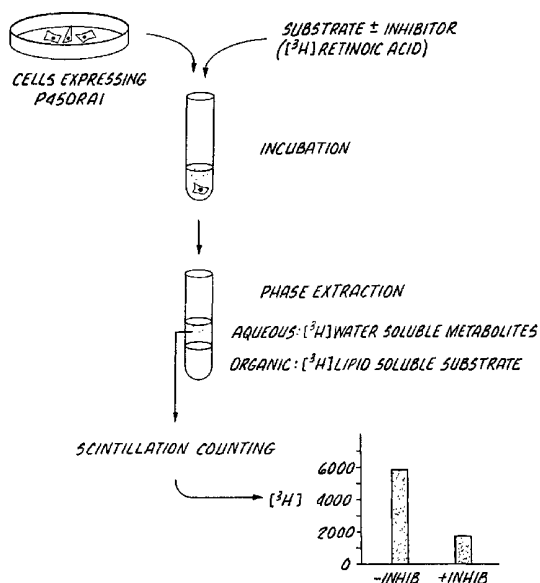
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(54) Title: COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF CYTOCHROME P450RAI





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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

1 COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF  
2 CYTOCHROME P450RAI

3 BACKGROUND OF THE INVENTION

4 1. Field of the Invention

5 The present invention is directed to novel compounds which inhibit  
6 the enzyme cytochrome P450RAI. More particularly, the present invention  
7 is directed to compounds many of which are derivatives of phenylacetic or  
8 heteroarylacetic acid, and which inhibit the enzyme cytochrome P450RAI.  
9 Several compounds of the invention that have an inhibitory effect on the  
10 enzyme cytochrome P450RAI include a cyclopropyl aryl, cyclopropyl-  
11 heteroaryl, cyclopropylaminoaryl, or (1-imidazolyl) methylaryl structure.

12 BACKGROUND ART

13 Compounds which have retinoid-like activity are well known in the  
14 art, and are described in numerous United States and other patents and in  
15 scientific publications. It is generally known and accepted in the art that  
16 retinoid-like activity is useful for treating animals of the mammalian species,  
17 including humans, for curing or alleviating the symptoms and conditions of  
18 numerous diseases and conditions. In other words, it is generally accepted  
19 in the art that pharmaceutical compositions having a retinoid-like compound  
20 or compounds as the active ingredient are useful as regulators of cell  
21 proliferation and differentiation, and particularly as agents for treating  
22 skin-related diseases, including, actinic keratoses, arsenic keratoses,  
23 inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other  
24 keratinization and hyperproliferative disorders of the skin, eczema, atopic  
25 dermatitis, Darriers disease, lichen planus, prevention and reversal of  
26 glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin  
27 anti-pigmentation agents and to treat and reverse the effects of age and  
28 photo damage to the skin. Retinoid compounds are also useful for the  
29 prevention and treatment of cancerous and precancerous conditions,

1 including, premalignant and malignant hyperproliferative diseases such as  
2 cancers of the breast, skin, prostate, cervix, uterus, colon, bladder,  
3 esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic system,  
4 metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the  
5 mucous membranes and in the treatment of Kaposi's sarcoma. In addition,  
6 retinoid compounds can be used as agents to treat diseases of the eye,  
7 including, without limitation, proliferative vitreoretinopathy (PVR), retinal  
8 detachment, dry eye and other corneopathies, as well as in the treatment and  
9 prevention of various cardiovascular diseases, including, without limitation,  
10 diseases associated with lipid metabolism such as dyslipidemias, prevention  
11 of post-angioplasty restenosis and as an agent to increase the level of  
12 circulating tissue plasminogen activator (TPA). Other uses for retinoid  
13 compounds include the prevention and treatment of conditions and diseases  
14 associated with human papilloma virus (HPV), including warts and genital  
15 warts, various inflammatory diseases such as pulmonary fibrosis, ileitis,  
16 colitis and Krohn's disease, neurodegenerative diseases such as Alzheimer's  
17 disease, Parkinson's disease and stroke, improper pituitary function,  
18 including insufficient production of growth hormone, modulation of  
19 apoptosis, including both the induction of apoptosis and inhibition of T-Cell  
20 activated apoptosis, restoration of hair growth, including combination  
21 therapies with the present compounds and other agents such as Minoxidil<sup>R</sup>,  
22 diseases associated with the immune system, including use of the present  
23 compounds as immunosuppressants and immunostimulants, modulation of  
24 organ transplant rejection and facilitation of wound healing, including  
25 modulation of chelosis. Retinoid compounds have relatively recently been  
26 also discovered to be useful for treating type II non-insulin dependent  
27 diabetes mellitus (NIDDM).

28 Several compounds having retinoid-like activity are actually

1 marketed under appropriate regulatory approvals in the United States of  
2 America and elsewhere as medicaments for the treatment of several diseases  
3 responsive to treatment with retinoids. Retinoic acid (RA) itself is a natural  
4 product, biosynthesized and present in a multitude of human and  
5 mammalian tissues and is known to play an important rule in the regulation  
6 of gene expression, tissue differentiation and other important biological  
7 processes in mammals including humans. Relatively recently it has been  
8 discovered that a catabolic pathway in mammals, including humans, of  
9 natural retinoic acid includes a step of hydroxylation of RA catalyzed by the  
10 enzyme Cytochrome P450RAI (retinoic acid inducible).

11 Several inhibitors of CP450RAI have been synthesized or discovered  
12 in the prior art, among the most important ones ketoconazole, liarozole and  
13 R116010 are mentioned. The chemical structures of these prior art  
14 compounds are provided below. It has also been noted in the prior art, that  
15 administration to mammals, including humans, of certain inhibitors of CP-  
16 450RAI results in significant increase in endogeneous RA levels, and  
17 further that treatment with CP450RAI inhibitors, for example with liarozole,  
18 gives rise to effects similar to treatment by retinoids, for example  
19 amelioration of psoriasis.

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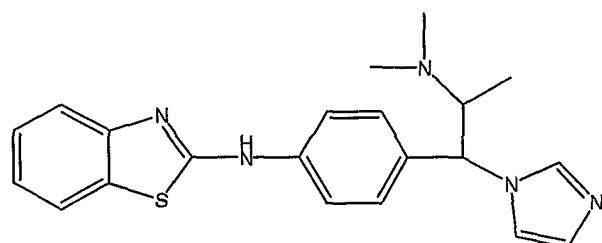
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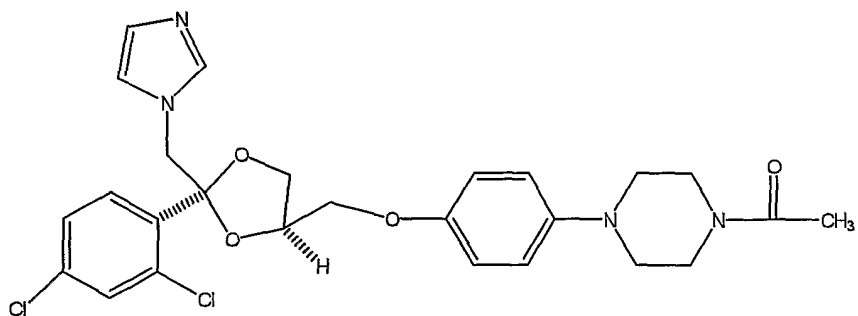
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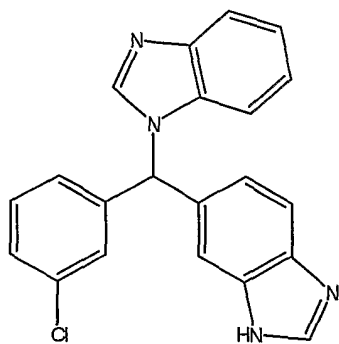
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R116010



KETOCONAZOLE



LIARAZOLE

1           The following publications describe or relate to the above-  
2 summarized role of CP450RAI in the natural catabolism of RA, to inhibitors  
3 of CP-450RAI and to *in vitro* and *in vivo* experiments which demonstrate  
4 that inhibition of CP450RAI activity results in a increases endogeneous RA  
5 levels and potential therapeutic benefits:  
6 *Kuijpers, et al.*, "The effects of oral liarozole on epidermal proliferation and  
7 differentiation in severe plaque psoriasis are comparable with those of  
8 acitretin", British Journal of Dermatology, (1998) **139**: pp 380-389.  
9 *Kang, et al.*, "Liarozole Inhibits Human Epidermal Retinoid Acid 4-  
10 Hydroxylase Activity and Differentially Augments Human Skin Responses  
11 to Retinoic Acid and Retinol *In Vivo*", The Journal of Investigative  
12 Dermatology, (August 1996) **Vol. 107**, No. 2: pp 183-187.  
13 *VanWauwe, et al.*, "Liarozole, an Inhibitor of Retinoic Acid Metabolism,  
14 Exerts Retinoid-Mimetic Effects *in Vivo*", The Journal of Pharmacology and  
15 Experimental Therapeutics, (1992) **Vol. 261**, No 2: pp 773-779.  
16 *De Porre, et al.*, "Second Generation Retinoic Acid Metabolism Blocking  
17 Agent (Ramba) R116010: Dose Finding in Healthy Male Volunteers",  
18 University of Leuven, Belgium, pp 30.  
19 *Wauwe, et al.*, "Ketoconazole Inhibits the *in Vitro* and *in Vivo* Metabolism of  
20 All-*Trans*-Retinoic Acid", The Journal of Pharmacology and Experimental  
21 Therapeutics, (1988) **Vol. 245**, No. 2: pp 718-722.  
22 *White, et al.*, "cDNA Cloning of Human Retinoic Acid-metabolizing  
23 Enzyme (hP450RAI) Identifies a Novel Family of Cytochromes P450  
24 (CYP26)\*", The Journal of Biological Chemistry, (1997) **Vol. 272**, No. 30,  
25 Issue of July 25 pp 18538-18541.  
26 *Hanzlik, et al.*, "Cyclopropylamines as Suicide Substrates for Cytochromes  
27 P450RAI", Journal of Medicinal Chemistry (1979), **Vol. 22**, No. 7, pp 759-

1 761.

2 *Ortiz de Montellano*, "Topics in Biology - The Inactivation of Cytochrome  
3 P450RAI", Annual Reports in Medicinal Chemistry, (1984), Chapter 20, pp  
4 201-210.

5 *Hanzlik, et al.* "Suicidal Inactivation of Cytochrome P450RAI by  
6 Cyclopropylamines> Evidence for Cation-Radical Intermediates", J. Am.  
7 Chem. Soc., (1982), **Vol. 104**, No. 107, pp. 2048-2052.

8 The present invention provides several new chemical compounds  
9 which act as inhibitors of CP450RAI, and as such potentially provide  
10 therapeutic benefit in the treatment or prevention of the diseases and  
11 conditions which respond to treatment by retinoids and or which in healthy  
12 mammals, including humans, are controlled by natural retinoic acid. The  
13 perceived mode of action of these compounds is that by inhibiting the  
14 enzyme CP450RAI that catabolyzes natural RA, endogenous RA level is  
15 elevated to a level where desired therapeutic benefits are attained. The  
16 chemical structures of the compounds of the invention are summarized by  
17 **Formulas 1** through **8** which are provided in the Summary Section of this  
18 application for patent. Based on these chemical structures the following art  
19 is of interest as background to the novel structures.

20 U.S. Patent Nos. 5,965,606; 6,025,388; 5,773,594; 5,675,024;  
21 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,089,509; 5,616,712;  
22 5,134,159; 5,346,895; 5,346,915; 5,149,705; 5,399,561; 4,980,369;  
23 5,015,658; 5,130,335; 4,740,519; 4,826,984; 5,037,825; 5,466,861;  
24 WO 85/00806; EP 0 130,795; DE 3316932; DE 3708060; *Dawson, et al.*  
25 "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,  
26 Inc., (1990), pages 324-356; are of interest to compounds of **Formula 1**.

27 U.S. Patent Nos. 5,965,606; 5,534,641; 5,663,357; 5,013,744;  
28 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468;

1 4,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;  
2 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;  
3 EP 0 619 116; DE 3524199; Derwent JP6072866; *Dawson, et al.*  
4 “Chemistry and Biology of Synthetic Retinoids”, published by CRC Press,  
5 Inc., 1990, pages 324-356; are of interest to compounds of **Formula 2.**

6 *Dawson, et al.* “Chemistry and Biology of Synthetic Retinoids”,  
7 published by CRC Press, Inc., (1990), pages 324-356; is of interest to  
8 compounds of **Formula 3.**

9 U.S. Patent Nos. 5,965,606; 5,773,594; 5,675,024; 5,663,347;  
10 5,023,341; 5,264,578; 5,089,509; 5,149,705; 5,130,335; 4,740,519;  
11 4,826,969; 4,833,240; 5,037, 825; 5,466,861; 5,559,248; WO 85/00806;  
12 WO 92/06948; WO 95/04036; WO 96/05165; EP 0 098 591; EP 0 170 105;  
13 EP 0 176 034; EP 0 253,302; EP 0 303 915; EP 0 514 269; EP 0 617 020;  
14 EP 0 619 116; EP 0 661 259; DE 3316932; DE 3602473; DE 3715955; UK  
15 application GB 2190378; *Eyrolles et al.*, J. Med. Chem., (1994), **37**, 1508-  
16 1517; *Graupner et al.* Biochem. and Biophysical Research  
17 Communications, (1991), 1554-1561; *Kagechika, et al.*, J. Med. Chem.,  
18 (1988), **31**, 2182-2192; *Dawson, et al.* “Chemistry and Biology of Synthetic  
19 Retinoids”, published by CRC Press, Inc., (1990), pages 324-356; are of  
20 interest to compounds of **Formula 4.**

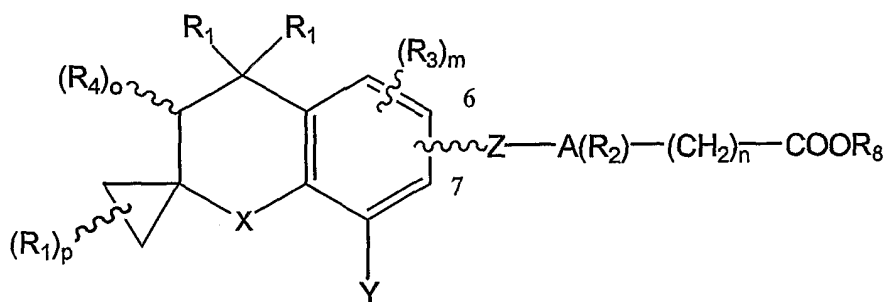
21 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;  
22 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795;  
23 4,992,468; 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;  
24 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;  
25 EP 0 619 116; DE 3524199; Derwent JP6072866; *Dawson, et al.*  
26 “Chemistry and Biology of Synthetic Retinoids”, published by CRC Press,  
27 Inc., (1990), pages 324-356; are of interest to compounds of **Formula 5.**

28 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;

1 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795;  
2 4,992,468; 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;  
3 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;  
4 EP 0 619 116; DE 3524199; Derwert JP6072866; *Dawson, et al.*  
5 “Chemistry and Biology of Synthetic Retinoids”, published by CRC Press,  
6 Inc., (1990), pages 324-356; is of interest to compounds of **Formula 6.**  
7 U.S. Patent Nos. 6,048,873; 5,663,347; 5,045,551; 5,023,341;  
8 5,739,338; 5,264,578; 5,089,509; 5,616,712; 5,399,561; 4,826,984;  
9 5,037,825; EP 0 130 795; DE 3316932; *Dawson, et al.* “Chemistry and  
10 Biology of Synthetic Retinoids”, published by CRC Press, Inc., (1990),  
11 pages 324-356; are of interest to compounds of **Formula 7.**  
12 U.S. Patent Nos. 5,965,606; 5,998,471; 5,773,594; 5,675,024;  
13 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,134,159; 5,346,895;  
14 5,346,915; 5,149,705; 5,399,561; 4,980,369; 5,130,335; 4,326,055;  
15 4,539,154; 4,740,519; 4,826,969; 4,826,984; 4,833,240; 5,037,825;  
16 5,466,861; 5,559,248; WO 85/00806; WO 92/06948; WO 95/04036;  
17 WO 96/05165; EP 0 098 591; EP 0 130 795; EP 0 176 034; EP 0 253 302;  
18 EP 0 303 915; EP 0 514 269; EP 0 617 020; EP 0 619 116; EP 0 661 259;  
19 DE 3316932; DE 3602473; DE 3708060; DE 3715955; U.K. application  
20 GB 2190378; *Eyrolles et al.*, J. Med. Chem., (1994), **37** 1508, 1517;  
21 *Graupner et al.*, Biochem. and Biophysical Research Communications,  
22 (1991) 1554-1561; *Kagechika, et al.*, J. Med. Chem., (1988), **31**, 2182-  
23 2192; *Dawson, et al.* “Chemistry and Biology of Synthetic Retinoids”,  
24 published by CRC Press, Inc., (1990), pages 324-356; are of interest to  
25 compounds of **Formula 8.**

## SUMMARY OF THE INVENTION

The present invention relates to compounds of **Formula 1**



Formula 1

wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two **R<sub>2</sub>** groups;

**X** is O, S or NR where **R** is H, alkyl of 1 to 6 carbons or benzyl;

**Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

**Z** is -C≡C-,

-(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

-CO-NR<sub>1</sub>-,

NR<sub>1</sub>-CO-;

-CO-O-,

-O-CO-,

-CS-NR<sub>1</sub>-,

1  $\text{NR}_1\text{-CS-}$ ,

2  $\text{-CO-S-}$ ,

3  $\text{-S-CO-}$ ,

4  $\text{-N=N-}$ ;

5  $\text{R}_1$  is independently H or alkyl of 1 to 6 carbons;

6  $p$  is an integer having the values of 0 to 4;

7  $\text{R}_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I,  $\text{CF}_3$ ,  
8 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or  
9 alkylthio of 1 to 6 carbons;

10  $\text{R}_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
11 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
12 alkylthio of 1 to 6 carbons or benzyl;

13  $m$  is an integer having the values 0 to 2;

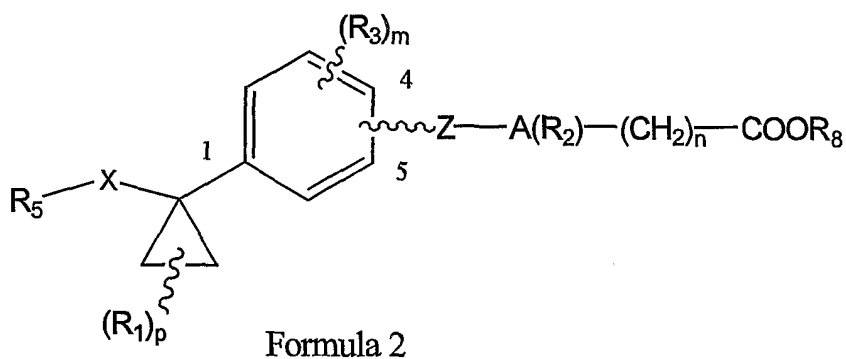
14  $\text{R}_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
15 alkyl of 1 to 6 carbons, or halogen;

16  $o$  is an integer having the values of 0 to 2;

17  $n$  is an integer having the values of 0 to 4, and

18  $\text{R}_8$  is H, alkyl of 1 to 6 carbons,  $\text{-CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
19 pharmaceutically acceptable base.

20 The present invention also relates to compounds of **Formula 2**



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from  
 2 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 3 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
 4 heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

5 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

6 Z is  $-C\equiv C-$ ,

7  $-(CR_1=CR_1)_n$ , where n' is an integer having the value 1 - 5,

8  $-CO-NR_1-$ ,

9  $NR_1-CO-$ ,

10  $-CO-O-$ ,

11  $-O-CO-$ ,

12  $-CS-NR_1-$ ,

13  $NR_1-CS-$ ,

14  $-CO-S-$ ,

15  $-S-CO-$ ,

16  $-N=N-$ ;

17  $R_1$  is independently H or alkyl of 1 to 6 carbons;

18 p is an integer having the values of 0 to 4;

19  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 20 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
 21 to 6 carbons;

22  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 23 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
 24 alkylthio of 1 to 6 carbons or benzyl;

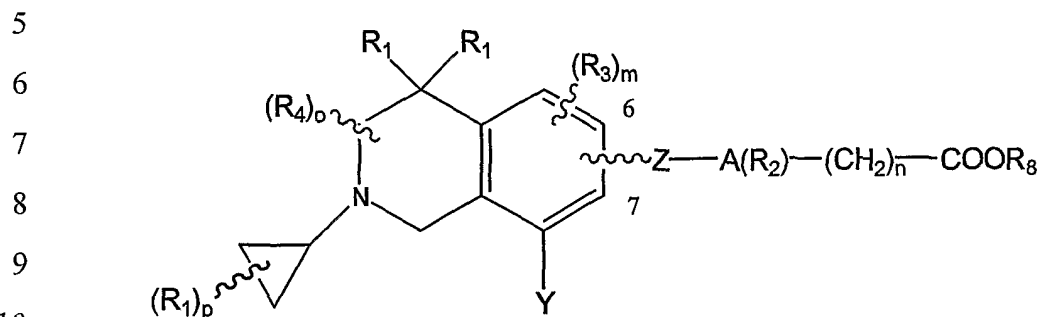
25 m is an integer having the values 0 to 4;

26  $R_5$  is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6  
 27 carbons, benzyl, or lower alkyl or halogen substituted benzyl;

1  $n$  is an integer having the values of 0 to 4, and

2  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
3 pharmaceutically acceptable base.

4 The present invention relates to compounds of **Formula 3**



12 **Formula 3**

13 wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from  
14 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
15 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
16 heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

17  $Y$  is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
18 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of  
19 3 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br,  
20 or I;

21  $Z$  is  $-\text{C}\equiv\text{C}-$ ,

22  $-(\text{CR}_1=\text{CR}_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,

23  $-\text{CO}-\text{NR}_1-$ ,

24  $\text{NR}_1-\text{CO}-$ ,

25  $-\text{CO}-\text{O}-$ ,

26  $-\text{O}-\text{CO}-$ ,

27  $-\text{CS}-\text{NR}_1-$ ,

1                   NR<sub>1</sub>-CS-,

2                   -CO-S-,

3                   -S-CO-,

4                   -N=N-;

5           R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

6           p is an integer having the values of 0 to 5;

7           R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

8 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
9 to 6 carbons;

10          R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

11 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,

12 alkylthio of 1 to 6 carbons or benzyl;

13          m is an integer having the values 0 to 2;

14          R<sub>4</sub> is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted

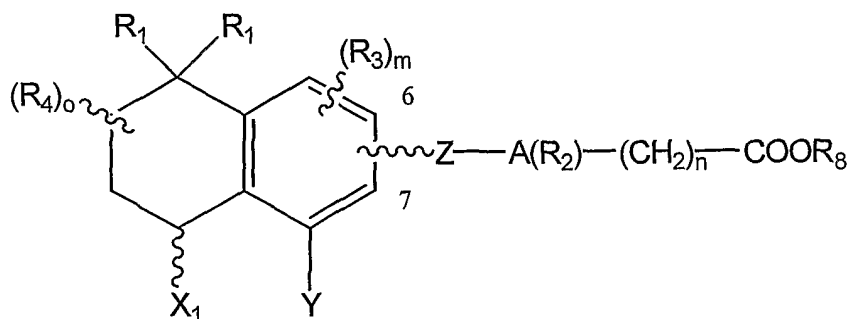
15 alkyl of 1 to 6 carbons, or halogen;

16          o is an integer having the values of 0 to 4;

17          n is an integer having the values of 0 to 4, and

18          R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
19 pharmaceutically acceptable base.

The present invention also relates to compounds of **Formula 4**



Formula 4

wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two **R<sub>2</sub>** groups;

**X<sub>1</sub>** is 1-imidazolyl, or lower alkyl or halogen substituted 1-imidazolyl, **OR**, **SR**, **NRR<sub>6</sub>** where **R** is H, alkyl of 1 to 6 carbons or benzyl;

**Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

**Z** is  $-C\equiv C-$ ,  
 $-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,  
 $-CO-NR_1-$ ,  
 $NR_1-CO-$ ,  
 $-CO-O-$ ,  
 $-O-CO-$ ,  
 $-CS-NR_1-$ ,

1                   NR<sub>1</sub>-CS-,

2                   -CO-S-,

3                   -S-CO-,

4                   -N=N-;

5           R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

6           R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
7 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
8 to 6 carbons;

9           R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
10 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
11 alkylthio of 1 to 6 carbons or benzyl;

12           m is an integer having the values 0 to 2;

13           R<sub>4</sub> is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
14 alkyl of 1 to 6 carbons, or halogen;

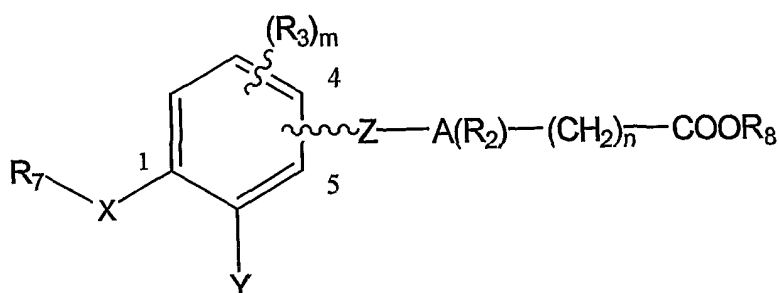
15           o is an integer having the values of 0 to 4;

16           R<sub>6</sub> is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl  
17 substituted cycloalkyl of 3 to 6 carbons;

18           n is an integer having the values of 0 to 4, and

19           R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
20 pharmaceutically acceptable base, with the proviso that when Y is H, A is  
21 phenyl and X<sub>1</sub> is OH then n is 1 to 4.

22           The present invention also relates to compounds of **Formula 5**



Formula 5

wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

X is O, S or NR where R is H, alkyl of 1 to 6 carbons,  $C_{1-6}$ -trialkylsilyl or benzyl;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

Z is  $-C\equiv C-$ ,  
 $-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,  
 $-CO-NR_1-$ ,  
 $NR_1-CO-$ ,  
 $-CO-O-$ ,  
 $-O-CO-$ ,  
 $-CS-NR_1-$ ,  
 $NR_1-CS-$ ,  
 $-CO-S-$ ,  
 $-S-CO-$ ,  
 $-N=N-$ ;

1  $R_1$  is independently H or alkyl of 1 to 6 carbons;

2  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
3 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
4 to 6 carbons;

5  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
6 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
7 alkylthio of 1 to 6 carbons or benzyl;

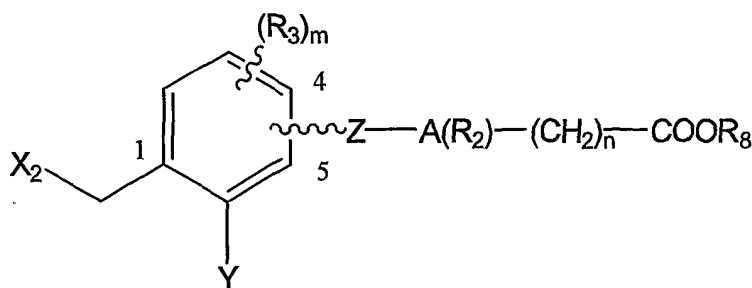
8  $m$  is an integer having the values 0 to 3;

9  $R_7$  is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower  
10 alkyl substituted cycloalkyl of 1 to 6 carbons;

11  $n$  is an integer having the values of 1 to 4, and

12  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
13 pharmaceutically acceptable base.

14 The present invention also relates to compounds of **Formula 6**



21 **Formula 6**

22 wherein  $A$  is a phenyl or naphthyl group, or heteroaryl selected from  
23 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
25 heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

26  $X_2$  is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,  
27  $\text{OR}_7$ ,  $\text{SR}_7$  or  $\text{NRR}_7$  where  $R$  is H, alkyl of 1 to 6 carbons or benzyl;

1           Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 2 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of  
 3 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,  
 4 or I;

5           Z is     $-C\equiv C-$ ,  
 6                    $-(CR_1=CR_1)_n$ , where n' is an integer having the value 1 - 5,  
 7                    $-CO-NR_1-$ ,  
 8                    $NR_1-CO-$ ,  
 9                    $-CO-O-$ ,  
 10                   $-O-CO-$ ,  
 11                   $-CS-NR_1-$ ,  
 12                   $NR_1-CS-$ ,  
 13                   $-CO-S-$ ,  
 14                   $-S-CO-$ ,  
 15                   $-N=N-$ ;

16            $R_1$  is independently H or alkyl of 1 to 6 carbons;

17            $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 18 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
 19 to 6 carbons;

20            $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 21 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
 22 alkylthio of 1 to 6 carbons or benzyl;

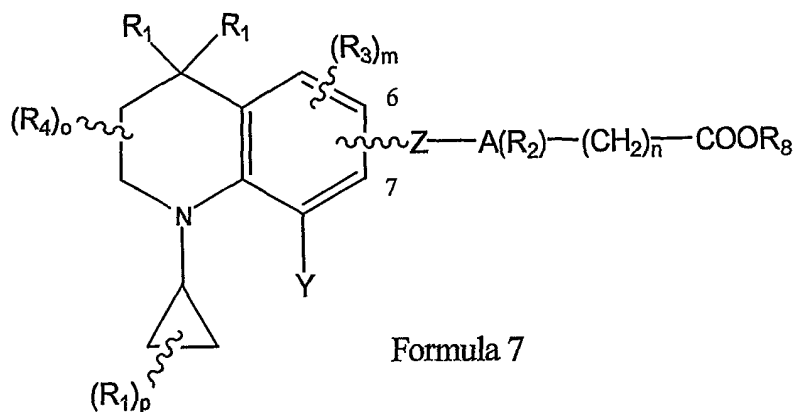
23           m is an integer having the values 0 to 3;

24            $R_7$  is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower  
 25 alkyl substituted cycloalkyl of 3 to 6 carbons or  $C_{1-6}$ -trialkylsilyl.

26           n is an integer having the values of 0 to 4, and

27            $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a  
 28 pharmaceutically acceptable base.

The present invention also relates to compounds of **Formula 7**



wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two **R<sub>2</sub>** groups;

**Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl, Br, or I;

**Z** is  $-C\equiv C-$ ,

$-(CR_1=CR_1)_{n'}$ , where  $n'$  is an integer having the value 1 - 5,

$-CO-NR_1-$ ,

$NR_1-CO-$ ,

$-CO-O-$ ,

$-O-CO-$ ,

$-CS-NR_1-$ ,

$NR_1-CS-$ ,

$-CO-S-$ ,

$-S-CO-$ ,

1                    -N=N-;

2                     $R_1$  is independently H or alkyl of 1 to 6 carbons;

3                     $p$  is an integer having the values of 0 to 5;

4                     $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,  
5 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or  
6 alkylthio of 1 to 6 carbons;

7                     $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro  
8 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
9 alkylthio of 1 to 6 carbons or benzyl;

10                    $m$  is an integer having the values 0 to 2;

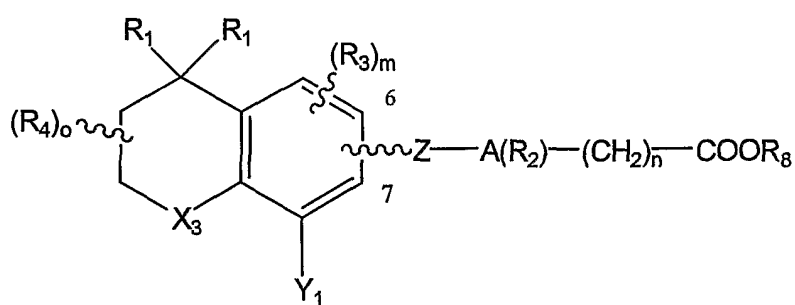
11                    $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
12 alkyl of 1 to 6 carbons, or halogen;

13                    $o$  is an integer having the values of 0 to 4;

14                    $n$  is an integer having the values of 0 to 4, and

15                    $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a  
16 pharmaceutically acceptable base.

17                   The present invention also relates to compounds of **Formula 8**



24                   **Formula 8**

25                   wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from  
26 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
27 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and

- 1 heteroaryl groups being optionally substituted with one or two  $R_2$  groups;
- 2  $X_3$  is S, or O,  $C(R_1)_2$ , or CO;
- 3  $Y_1$  is H, lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons,
- 4 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;
- 5  $Z$  is  $-C\equiv C-$ ,
- 6  $-(CR_1=CR_1)_n$ , where  $n'$  is an integer having the value 1 - 5,
- 7  $-CO-NR_1-$ ,
- 8  $NR_1-CO-$ ,
- 9  $-CO-O-$ ,
- 10  $-O-CO-$ ,
- 11  $-CS-NR_1-$ ,
- 12  $NR_1-CS-$ ,
- 13  $-CO-S-$ ,
- 14  $-S-CO-$ ,
- 15  $-N=N-$ ;
- 16  $R_1$  is independently H or alkyl of 1 to 6 carbons;
- 17  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,
- 18 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or
- 19 alkylthio of 1 to 6 carbons;
- 20  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro
- 21 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
- 22 alkylthio of 1 to 6 carbons or benzyl;
- 23  $m$  is an integer having the values 0 to 2;
- 24  $R_4$  is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
- 25 alkyl of 1 to 6 carbons, or halogen;
- 26  $o$  is an integer having the values of 0 to 4;
- 27  $n$  is an integer having the values of 0 to 4, and
- 28  $R_8$  is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a

1 pharmaceutically acceptable base, the compound meeting at least one of the  
2 provisos selected from the group consisting of:

3  $Y_1$  is cycloalkyl,  
4 when  $Y_1$  is not cycloalkyl then  $X_3$  is O or S and  $n$  is 1,  
5 when  $Y_1$  is not cycloalkyl then  $X_3$  is CO, and  $n$  is 1,  
6 when  $Y_1$  is not cycloalkyl then  $X_3$  is CO and the moiety A is  
7 substituted with at least one F group.

8 In a second aspect, this invention relates to the use of the compounds  
9 of **Formula 1** through **Formula 8** for the prevention or treatment of  
10 diseases and conditions in mammals, including humans, which diseases or  
11 conditions are prevented, treated, ameliorated, or the onset of which is  
12 delayed by administration of retinoid compounds or by the mammalian  
13 organism's naturally occurring retinoic acid. Because the compounds act as  
14 inhibitors of the breakdown of retinoic acid, the invention also relates to the  
15 use of the compounds of **Formula 1** through **Formula 8** in conjunction  
16 with retinoic acid or other retinoids. In this regard it is noted that retinoids  
17 are useful for the treatment of skin-related diseases, including, without  
18 limitation, actinic keratoses, arsenic keratoses, inflammatory and  
19 non-inflammatory acne, psoriasis, ichthyoses and other keratinization and  
20 hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers  
21 disease, lichen planus, prevention and reversal of glucocorticoid damage  
22 (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation  
23 agents and to treat and reverse the effects of age and photo damage to the  
24 skin. The retinoids are also useful for the prevention and treatment of  
25 metabolic diseases such as type II non-insulin dependent diabetes mellitus  
26 (NIDDM) and for prevention and treatment of cancerous and precancerous  
27 conditions, including, premalignant and malignant hyperproliferative  
28 diseases such as cancers of the breast, skin, prostate, cervix, uterus, colon,

1 bladder, esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic  
2 system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of  
3 the mucous membranes and in the treatment of Kaposi's sarcoma. Retinoids  
4 can also be used as agents to treat diseases of the eye, including, without  
5 limitation, proliferative vitreoretinopathy (PVR), retinal detachment, dry eye  
6 and other corneopathies, as well as in the treatment and prevention of  
7 various cardiovascular diseases, including, without limitation, diseases  
8 associated with lipid metabolism such as dyslipidemias, prevention of  
9 post-angioplasty restenosis and as an agent to increase the level of  
10 circulating tissue plasminogen activator (TPA). Other uses for retinoids  
11 include the prevention and treatment of conditions and diseases associated  
12 with human papilloma virus (HPV), including warts and genital warts,  
13 various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis and  
14 Krohn's disease, neurodegenerative diseases such as Alzheimer's disease,  
15 Parkinson's disease and stroke, improper pituitary function, including  
16 insufficient production of growth hormone, modulation of apoptosis,  
17 including both the induction of apoptosis and inhibition of T-Cell activated  
18 apoptosis, restoration of hair growth, including combination therapies with  
19 the present compounds and other agents such as Minoxidil<sup>®</sup>, diseases  
20 associated with the immune system, including use of the present compounds  
21 as immunosuppressants and immunostimulants, modulation of organ  
22 transplant rejection and facilitation of wound healing, including modulation  
23 of chelosis.

24       This invention also relates to a pharmaceutical formulation  
25 comprising one or more compounds of **Formula 1** through **Formula 8** in  
26 admixture with a pharmaceutically acceptable excipient, said formulation  
27 being adapted for administration to a mammal, including a human being, to  
28 treat or alleviate the conditions which were described above as treatable by

1 retinoids, or which are controlled by or responsive to the organism's native  
2 retinoic acid. These formulations can also be co-administered with retinoids  
3 to enhance or prolong the effects of medications containing retinoids or of  
4 the organism's native retinoic acid.

#### 5 BRIEF DESCRIPTION OF THE DRAWING FIGURE

6 Figure 1 is a schematic representation of the P450RAI cell based  
7 assay utilized to evaluate the ability of the compounds of the invention to  
8 inhibit the Cytochrome P450RAI enzyme.

#### 9 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

##### 10 P450RAI-1 Cell-Based Inhibitor Assay:

11 **Figure 1** shows a schematic diagram of the P450RAI-1 cell based  
12 assay. P450RAI-1 stably transfected HeLa cells are maintained in 100  
13 millimolar tissue culture dishes in Modified Eagle's Medium (MEM)  
14 containing 10 % Fetal Bovine Serum (FBS) and 100 µg/ml hygromycin.  
15 Exponentially growing cells are harvested by incubating in trypsin. Cells are  
16 then washed with 1X Phosphate Buffered Saline (PBS) and plated in a 48-  
17 well plate at  $5 \times 10^5$  cells in 0.2 ml MEM medium containing 10 % FBS and  
18 0.05 µCi [ $^3\text{H}$ ]-RA in the presence or absence of increasing concentrations of  
19 the test compounds. The compounds are diluted in 100% DMSO and then  
20 added in triplicate wells at either 10, 1 or 0.1 µM final concentration. As a  
21 positive control for RA metabolism inhibition, cells are also incubated with  
22 ketoconazole at 100, 10 and 1 µM. Cells are incubated for 3 hours at 37°C.  
23 The retinoids are then extracted using the procedure of *Bligh et al.* (1959)  
24 Canadian Journal of Biochemistry 37, 911-917, modified by using  
25 methylenechloride instead of chloroform. The publication *Bligh et al.*  
26 (1959) Canadian Journal of Biochemistry 37, 911-917 is specifically  
27 incorporated herein by reference. The water soluble radioactivity is

1 quantified using a  $\beta$ -scintillation counter.  $IC_{50}$  values represent the  
2 concentration of inhibitor required to inhibit all-*trans*-RA metabolism by 50  
3 percent and are derived manually from log-transformed data. The  $IC_{50}$   
4 values obtained in this assay for several preferred compounds of the  
5 invention are disclosed in **Table 1** below.

6 Assays of Retinoid-like or Retinoid Antagonist and Inverse Agonist-  
7 like Biological Activity

8 Assays described below measure the ability of a compound to bind  
9 to, and/or activate various retinoid receptor subtypes. When in these assays  
10 a compound binds to a given receptor subtype and activates the transcription  
11 of a reporter gene through that subtype, then the compound is considered an  
12 **agonist** of that receptor subtype. Conversely, a compound is considered an  
13 **antagonist** of a given receptor subtype if in the below described  
14 co-transfection assays the compound does not cause significant  
15 transcriptional activation of the receptor regulated reporter gene, but  
16 nevertheless binds to the receptor with a  $K_d$  value of less than approximately  
17 1 micromolar. In the below described assays the ability of the compounds to  
18 bind to  $RAR_{\alpha}$ ,  $RAR_{\beta}$ ,  $RAR_{\gamma}$ ,  $RXR_{\alpha}$ ,  $RXR_{\beta}$  and  $RXR_{\gamma}$  receptors, and the  
19 ability or inability of the compounds to activate transcription of a reporter  
20 gene through these receptor subtypes can be tested.

21 As far as specific assays are concerned, a **chimeric receptor**  
22 **transactivation assay** which tests for agonist-like activity in the  $RAR_{\alpha}$ ,  
23  $RAR_{\beta}$ , and  $RAR_{\gamma}$  receptor subtypes, and which is based on work published  
24 by Feigner P. L. and Holm M. (1989) Focus, 112 is described in detail in  
25 United States Patent No. 5,455,265. The specification of United States  
26 Patent No. 5,455,265 is hereby expressly incorporated by reference. The  
27 numeric results obtained with several preferred compounds of this

1 invention in this assay are shown below in **Table 1**. These data demonstrate  
2 that generally speaking the compounds are not agonists (or only weak  
3 agonists) of RAR retinoic receptors, and also that they do not bind, or in  
4 some cases bind only weakly to RAR retinoid receptors.

5       A **holoreceptor transactivation assay** and a **ligand binding assay**  
6 which measure the antagonist/agonist like activity of the compounds of the  
7 invention, or their ability to bind to the several retinoid receptor subtypes,  
8 respectively, are described in published PCT Application No. WO  
9 WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published on June  
10 24, 1993, the specification of which is also incorporated herein by reference.  
11 A detailed experimental procedure for holoreceptor transactivations has  
12 been described by *Heyman et al. Cell* 68, 397 - 406, (1992); *Allegretto et*  
13 *al. J. Biol. Chem.* 268, 26625 - 26633, and *Mangelsdorf et al. The*  
14 *Retinoids: Biology, Chemistry and Medicine*, pp 319 - 349, Raven Press  
15 Ltd., New York, which are expressly incorporated herein by reference. The  
16 results obtained in this assay are expressed in EC<sub>50</sub> numbers, as they are  
17 also in the **chimeric receptor transactivation assay**. The results of **ligand**  
18 **binding assay** are expressed in K<sub>d</sub> numbers. (See *Cheng et al. Biochemical*  
19 *Pharmacology* Vol. 22 pp 3099-3108, expressly incorporated herein by  
20 reference.)

21       The results of the ligand binding assay for several preferred  
22 compounds of the invention are included in **Table 1**. In the **holoreceptor**  
23 **transactivation assay**, tested for RXR<sub>α</sub>, RXR<sub>β</sub>, and RXR<sub>γ</sub> receptors, the  
24 compounds of the present invention are, generally speaking, entirely devoid  
25 of activity, demonstrating that the compounds of the invention do not act as  
26 RXR agonists.

TABLE 1

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Compound #	General Formula	Table # <sup>1</sup>	RAR EC <sub>50</sub> /(EFFICACY)/K <sub>d</sub> nM			P450RAI INHIBITION DATA
			$\alpha$	$\beta$	$\gamma$	INTACT HELA IC <sub>50</sub> $\mu$ M
110	2	3	NA 2058	74 (44) 409	262 (42) >10K	>10
112	2	3	NA 5853	335 (37) 704	NA 685	>10
3	4	5	280 (28) 145	4.8 (54) 0.8	9.8 (52) 158	3
114	2	3	NA >10K	NA >10K	NA >10K	>10
108	2	3	6.6 (15) 21K	283 (36) 547	141 (10) 13K	>10
116	2	3	NA 3269	WA 732	NA 886	>10
77	2	3	NA 2207	WA 225	NA 16	>10
78	2	3	NA >10K	NA >10K	NA >10K	>10
40	1	2	33 (207) 69	1.2 (126) 1.3	6.8 (140) 363	1.7
42	1	2	NA 15K	NA 3636	NA >10K	0.19

1	28	8	9	NA 21K	NA 4272	NA >10K	0.34
2	70	2	3	NA >10K	NA >10K	NA >10K	>10
3	69	2	3	313 (10) 469	12 (50) 133	52.6 (31) 501	>10
4	73	2	3	WA 486	22.5 (39) 26	91 (24) 351	>10
5	74	2	3	NA 11K	NA 14K	NA >10K	3.5
6	30	8	9	14	2.2	84	0.28
7	44	1	2	49 (138) 37	1.7 (100) 1.9	7.5 (116) 392	0.27
8	82	2	3	NA >10K	NA >10K	NA >10K	>10
9	81	2	3	NA 4210	490 (80) 846	183 (67) 1058	>10
10	89	2	3	268 (20) 3407	26 (50) 980	12 (46) 475	>10
11	90	2	3	NA >10K	NA >10K	NA >10K	0.95
12	94	2	3	NA >10K	NA >10K	NA >10K	>10

1	93	2	3	4821 (114) 3450	20 (39) 554	10 (55) 358	>10
2	5	8	9	NA 9148	11 (36) 2815	NA >10K	0.55
3	8	4	5	NA 10K	363 (96) 3781	NA 25K	0.4
4	86	2	3	NA >10K	NA >10K	NA >10K	1.4
5	85	2	3	976 (60) 1861	3.5 (77) 240	2.5 (65) 302	>10
6	98	2	3	NA	NA	NA	0.8
7	13	4	5	NA	3.2 (6.6)	116 (9)	3.1
8	10	8	9	57 (146)	0.3 (86)	6 (94)	0.7
9	36	8	9	13K	4896	492	0.033
10	38	8	9	10K	5317	2884	0.025
11	34	8	9	61.5	15	2.5	0.13
12	119	6	7	>10K	>10K	>10K	0.4

1	121	6	7				0.18
				>10K	>100K	>100K	
2	46	8	9				2.2
				>10K	>10K	>10K	
3	20	8	9				>10
4	18	4	5				1.1
5	32	8	9				0.18
				27K	4225	13K	
6	139	4	5				0.05
7	22	3	4				1.6
8	24	3	4				3
9	137	4	5				0.1
10	26	4	5				10
11	127	6	7				0.4
12	126	6	7				0.09
13	48	1	2				0.03
14	50	1	2				0.014
15	52	1	2				0.05
16	54	1	2				0.022

1	62	7	8				>10
2	56	8	9				0.13
3	134	6	7				5
4	58	1	2				0.18
5	60	1	2				1.6
6	143						0.8
7	145						0.2

8  
9 <sup>1</sup>The "Table #" refers to the Table provided below where the compound is  
10 identified with reference to a corresponding specific formula of **Formulas 9**  
11 through **16**.

## TOPICAL SKIN IRRITATION TESTS

As is known the topical retinoid all-trans-retinoic acid (ATRA) and oral retinoids such as 13-cis RA and etretinate are known to induce substantial skin irritation in humans. This irritation is a direct result of activation of the RAR nuclear receptors. Analysis of retinoid topical irritation is also a highly reproducible method of determining *in vivo* retinoid potency. The SKH1-*hr*BR or hairless mouse provides a convenient animal model of topical irritation, since retinoid-induced skin flaking and abrasion can be readily scored by eye (*Standeven et al.*, "Specific antagonist of retinoid toxicity in mice." Toxicol. Appl. Pharmacol., **138**:169-175, (1996); *Thacher, et al.*, "Receptor specificity of retinoid-induced hyperplasia. Effect of RXR-selective agonists and correlation with topical irritation". J. Pharm. Exp. Ther., **282**:528-534, (1997)). As is demonstrated below the topical application of P450RAI inhibitors of the present invention also causes an increase in the endogenous levels of ATRA that results in ATRA-induced irritation in skin of hairless mice. The attached data table discloses the retinoid-mimetic effects of some P450RAI inhibitor compounds of the present invention on the skin of hairless mice.

## Methods

Female hairless mice (Crl:SKH1-*hr*BR), 5-7 weeks old, were obtained from Charles River Breeding Labs (Wilmington, MA). Animals were about 6 weeks old at the start of the experiments. Food (Purina Rodent Chow 5001) and reverse osmosis water were provided *ad libitum*. Mice were housed individually throughout the dosing period. In some experiments, mice that fit within a defined weight range, *e.g.*, 21-25g, were selected from the available stock and then randomly assigned to the various treatment groups, using body weight as the randomization variable.

The compounds to be tested were dissolved in acetone for application

1 to the backs of the mice.

2 Mice were treated topically on the back in a volume of 4.0 ml/kg  
3 (0.07-0.12ml) adjusted daily so as to deliver a fixed dose of test compound  
4 per g body weight. Doses are disclosed as nmol/25g.

5 Unless indicated otherwise, mice were treated with retinoids once  
6 daily on days 1 through 5 and observed on days 2, 3, 4, 5, 6, 7 and 8.

7 The mice were weighed daily and the dorsal skin was graded daily  
8 using separate semi-quantitative scales to determine flaking and abrasion.  
9 These flaking and abrasion scores were combined with weight change (if  
10 any) to create a cutaneous toxicity score (Blackjack score).

#### 11 Cutaneous Toxicity Score

12 A visual grading scale was used for characterizing topical irritation  
13 on a daily basis. The grading scale used is as follows:

14	<b><u>Flaking</u></b>	<b><u>Abrasions</u></b>
15	0 = none	0 = none
16	1 = slight (small flakes, <50%	1 = slight (one or two abrasions
17	coverage)	with a light pink color)
18	2 = mild (small flakes, 50%	2 = mild (several abrasions with a
19	coverage)	pink color)
20	3 = moderate (small flakes, >50%	3 = moderate (one or two deep
21	coverage & large flakes, <25%	abrasions with red color, <25%
22	coverage)	coverage)
23	4 = severe (small flakes, >50%	4 = severe (multiple deep abrasions
24	coverage & large flakes, 25-50%	with red color, >25% coverage)
25	coverage)	
26	5 = very severe (large flakes, >50%	
27	coverage)	

28

# 1 Topical Toxicity Score

2       The flaking and abrasion observations were combined with body  
3 weight observations to calculate a single, semiquantitative topical or  
4 cutaneous "toxicity score" as detailed below. The toxicity score (also  
5 known as "blackjack score" since the theoretical maximum is 21) takes into  
6 account the maximal severity, and the time of onset of skin flaking and  
7 abrasions and the extent of weight between the first and last days of the  
8 experiment. Below are listed the seven numerical components of the  
9 toxicity score and an explanation of how those values are combined to  
10 calculate the toxicity score.

## 11       1. Flaking-Maximal Severity:

12           Highest flaking score attained during observation period.

## 13       2. Flaking-Day of Onset of grade 2 or worse:

14           0 - > 8 days

15           1 - day 8

16           2 - day 6 or 7

17           3 - day 4 or 5

18           4 - day 2 or 3

## 19       3. Flaking-Average Severity:

20           Flaking severity scores are summed and divided by the number  
21 of observation days.

## 22       4. Abrasion-Maximal Severity:

23           Highest abrasion score attained during observation period.

## 24       5. Abrasion-Day of Onset of grade 2 or worse:

25           Same scale as (2) above.

## 26       6. Abrasion-Average Severity:

27           Abrasion severity scores are summed and divided by the  
28 number of observation days.

1           7.     Systemic Toxicity (weight loss):

2                   0 - <1g

3                   1 - 1 to 2g

4                   2 - 2 to 4g

5                   3 - 4 to 6g

6                   4 - >6g or dead

7     Calculation of Composite Flaking Score

8           Flaking onset score (2) and average severity score (3) are summed  
9     and divided by two. The quotient is added to the maximal severity score (1).  
10    Composite flaking scores are calculated for each individual animal in a  
11    group, averaged, and rounded to the nearest integer. Values can range from  
12    0-9.

13    Calculation of Composite Abrasion Score

14           Abrasion onset score (5) and average severity score (6) are summed  
15    and divided by two. The quotient is added to the maximal severity score (4).  
16    Composite abrasion scores are calculated for each individual animal in a  
17    group, averaged and rounded to the nearest integer. Values can range from  
18    0-8.

19    Calculation of Toxicity Score

20           Composite flaking score, composite abrasion score, and systemic  
21    toxicity score are summed to give the "toxicity score." Toxicity scores are  
22    calculated for each individual animal in a group, averaged, and rounded to  
23    the nearest integer. Values can range from 0-21 and are expressed in Table  
24    1A below as the mean  $\pm$  SD of the values for a group.

25    Calculation of Percentage Change in Body Weight

26           The body weight at the time of the last weighing (day 8, 11, or 12)  
27    was subtracted from the initial body weight. The difference was divided by  
28    the initial body weight, multiplied by 100%, and rounded to the nearest

integer. Values were calculated for each individual animal and the mean and standard deviation for each group are shown.

TABLE 1A

Compound No.	Cutaneous Toxicity Score (Blackjack Score)		
	100 nmole	300 nmole	1000 nmole
5	0		6±3
15	1 ± 1		5 ± 2
36	1 ± 1		11 ± 0
38	1 ± 1		10 ± 1
8	5 ± 2	8 ± 3	12 ± 1
22	0 ± 0	0 ± 0	1 ± 1
137	1 ± 1	1 ± 1	5 ± 2
48	1 ± 1	3 ± 1	7 ± 2
50	1 ± 0	3 ± 2	8 ± 2
58	0 ± 0	0 ± 0	0 ± 0
131	1 ± 1	0 ± 1	1 ± 1
127	0 ± 0	0 ± 0	0 ± 0
18	0 ± 0	5 ± 2	10 ± 2

#### Modes of Administration

The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations. Thus, in the treatment of dermatoses, it will

1 generally be preferred to administer the drug topically, though in certain  
2 cases such as treatment of severe cystic acne or psoriasis, oral administration  
3 may also be used. Any common topical formulation such as a solution,  
4 suspension, gel, ointment, or salve and the like may be used. Preparation of  
5 such topical formulations are well described in the art of pharmaceutical  
6 formulations as exemplified, for example, by Remington's Pharmaceutical  
7 Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. For  
8 topical application, these compounds could also be administered as a  
9 powder or spray, particularly in aerosol form. If the drug is to be  
10 administered systemically, it may be confectioned as a powder, pill, tablet or the  
11 like or as a syrup or elixir suitable for oral administration. For intravenous  
12 or intraperitoneal administration, the compound will be prepared as a  
13 solution or suspension capable of being administered by injection. In  
14 certain cases, it may be useful to formulate these compounds by injection.  
15 In certain cases, it may be useful to formulate these compounds in  
16 suppository form or as extended release formulation for deposit under the  
17 skin or intramuscular injection.

18 Other medicaments can be added to such topical formulation for such  
19 secondary purposes as treating skin dryness; providing protection against  
20 light; other medications for treating dermatoses; medicaments for preventing  
21 infection, reducing irritation, inflammation and the like.

22 Treatment of dermatoses or any other indications known or  
23 discovered to be susceptible to treatment by retinoic acid-like compounds,  
24 or to control by naturally occurring retinoic acid will be effected by  
25 administration of the therapeutically effective dose of one or more  
26 compounds of the instant invention. A therapeutic concentration will be  
27 that concentration which effects reduction of the particular condition, or  
28 retards its expansion. In certain instances, the compound potentially may be

1 used in prophylactic manner to prevent onset of a particular condition.

2 A useful therapeutic or prophylactic concentration will vary from  
3 condition to condition and in certain instances may vary with the severity of  
4 the condition being treated and the patient's susceptibility to treatment.  
5 Accordingly, no single concentration will be uniformly useful, but will  
6 require modification depending on the particularities of the disease being  
7 treated. Such concentrations can be arrived at through routine  
8 experimentation. However, it is anticipated that in the treatment of, for  
9 example, acne, or similar dermatoses, that a formulation containing between  
10 0.01 and 1.0 milligrams per milliliter of formulation will constitute a  
11 therapeutically effective concentration for total application. If administered  
12 systemically, an amount between 0.01 and 5 mg per kg of body weight per  
13 day would be expected to effect a therapeutic result in the treatment of many  
14 diseases for which these compounds are useful.

15 In some applications pharmaceutical formulations containing the CP-  
16 450RAI inhibitory compounds of the invention may be co-administered  
17 with formulations containing retinoids.

## 18 GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY

### 19 Definitions

20 The term alkyl refers to and covers any and all groups which are  
21 known as normal alkyl and branched-chain alkyl. Unless specified  
22 otherwise, lower alkyl means the above-defined broad definition of alkyl  
23 groups having 1 to 6 carbons in case of normal lower alkyl, and 3 to 6  
24 carbons for lower branch chained alkyl groups. A pharmaceutically  
25 acceptable salt may be prepared for any compound in this invention having a  
26 functionality capable of forming a salt, for example an acid functionality. A  
27 pharmaceutically acceptable salt is any salt which retains the activity of the  
28 parent compound and does not impart any deleterious or untoward effect on

1 the subject to which it is administered and in the context in which it is  
2 administered.

3       Pharmaceutically acceptable salts may be derived from organic or  
4 inorganic bases. The salt may be a mono or polyvalent ion. Of particular  
5 interest are the inorganic ions, sodium, potassium, calcium, and magnesium.  
6 Organic salts may be made with amines, particularly ammonium salts such  
7 as mono-, di- and trialkyl amines or ethanol amines. Salts may also be  
8 formed with caffeine, tromethamine and similar molecules. Where there is a  
9 nitrogen sufficiently basic as to be capable of forming acid addition salts,  
10 such may be formed with any inorganic or organic acids or alkylating agent  
11 such as methyl iodide. Preferred salts are those formed with inorganic acids  
12 such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a  
13 number of simple organic acids such as mono-, di- or tri- acid may also be  
14 used.

15       Some compounds of the present invention may have *trans* and *cis* (E  
16 and Z) isomers. Unless specific orientation of substituents relative to a  
17 double bond or a ring is indicated in the name of the respective compound,  
18 and/or by specifically showing in the structural formula the orientation of  
19 the substituents relative to the double bond or ring the invention covers  
20 *trans* as well as *cis* isomers.

21       Some of the compounds of the present invention may contain one or  
22 more chiral centers and therefore may exist in enantiomeric and  
23 diastereomeric forms. The scope of the present invention is intended to  
24 cover all isomers *per se*, as well as mixtures of *cis* and *trans* isomers,  
25 mixtures of diastereomers and racemic mixtures of enantiomers (optical  
26 isomers) as well. A bond drawn with a wavy line indicates that the carbon  
27 to which the bond is attached can be in any of the applicable possible  
28 configurations.

## 1 General Synthetic Methodology

2       The compounds of the invention are encompassed by the general  
3 **Formulas 1** through **8** provided above. As it can be seen, in each of these  
4 formulas a linker or tethering group designated **Z** covalently connects an  
5 aromatic or heteroaromatic moiety designated  $A(R_2)-CH_2)_n-COOR_8$  and  
6 another cyclic moiety which in accordance with these formulas is a  
7 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,  
8 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety.  
9 Generally speaking a compound such as  $X_4-A(R_2)-CH_2)_n-COOR_8$  is  
10 commercially available, or can be made in accordance with the chemical  
11 literature, or with such modification of known chemical processes which are  
12 within the skill of the practicing organic chemist. The group  $X_4$  represents a  
13 reactive group, which is suitable for coupling the  $X_4-A(R_2)-CH_2)_n-COOR_8$   
14 compound to a derivative of the substituted phenyl, substituted  
15 tetrahydronaphthalene, substituted chroman, thiochroman,  
16 tetrahydroquinoline or tetrahydroisoquinoline moiety so that as a result of  
17 the coupling the linker or tether moiety **Z** is formed. In many instances the  
18 group  $X_4$  is a leaving group such as halogen, or  
19 trifluoromethanesulfonyloxy, or a group capable of participating in a *Wittig*  
20 or *Horner Emmons* reaction. In some instances the group  $X_4$  is an ethynyl  
21 group capable of undergoing a coupling reaction with a leaving group (such  
22 as a halogen or a trifluoromethanesulfonyloxy group) attached to the  
23 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,  
24 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety. The  
25 group  $X_4$  can also represent an OH or an  $NH_2$  group that forms an ester  
26 (COO) or amide (CONH) linker, respectively, when reacted with an  
27 activated carboxyl derivative of the substituted phenyl, substituted  
28 tetrahydronaphthalene, substituted chroman, thiochroman,

1 tetrahydroquinoline or tetrahydroisoquinoline moiety. Examples for the  
2 compounds of formula  $X_4A(R_2)-CH_2)_n-COOR_8$  are provided in the  
3 specific examples below. Further examples where the  $X_4$  group is halogen  
4 are ethyl 4-iodobenzoate, ethyl 6-iodonicotinate, ethyl 5-iodofuran-3-  
5 carboxylate, ethyl 5-iodothiophen-3-carboxylate, ethyl 5-iodofuran-2-  
6 carboxylate, ethyl 5-iodothiophen-2-carboxylate, and analogous halogenated  
7 derivatives of the respective pyridazine, pyrazine and other heteroaryl  
8 carboxylic acid esters. The analogous aryl and heteroaryl hydroxyl  
9 compounds and amines, wherein the halogen of the above-listed compounds  
10 is replaced by OH or  $NH_2$  respectively, also serve as additional examples for  
11 the reagents of the formula  $X_4A(R_2)-CH_2)_n-COOR_8$ . In these examples  
12  $X_4$  is OH or  $NH_2$ , respectively.

13       Still further in accordance with the general synthetic methodology to  
14 provide the compounds of the present invention, a derivative of the  
15 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,  
16 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety is  
17 synthesized first, having a covalently attached  $X_5$  group. The  $X_5$  group  
18 reacts with the  $X_4$  group of the reagent  $X_4A(R_2)-CH_2)_n-COOR_8$  to form  
19 the linker designated **Z** in **Formulas 1** through **8**. The  $X_5$  group is one that  
20 is capable of participating in a catalyzed coupling reaction, (such as an  
21 ethynyl group when  $X_4$  is a leaving group), or a leaving group (such as  
22 halogen or trifluoromethanesulfonyloxy when  $X_4$  is an ethynyl group), or  
23 an activated carboxylic acid function (when  $X_4$  is OH or  $NH_2$ ). The  $X_5$   
24 group can also be an OH, SH or  $NH_2$  group when the  $X_4$  group is an  
25 activated carboxylic acid function. Specific examples for substituted  
26 phenyl, substituted tetrahydronaphthalene, substituted chroman,  
27 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline intermediates  
28 having an  $X_5$  functionality are provided below, and are also available in the

1 chemical scientific and patent literature. Generally speaking, for reagents  
2 and reactions covalently joining a substituted tetrahydronaphthalene,  
3 substituted chroman, thiochroman, or tetrahydroquinoline intermediate with  
4 a substituted aryl or heteroaryl group, such as  $X_4-A(R_2)-CH_2)_n-COOR_8$ , to  
5 form a compound including the linker designated **Z**, reference is made to  
6 United States Patent Nos. 5,648,503; 5,723,666 and 5,952,345 the  
7 specification of each of which are expressly incorporated herein by  
8 reference.

9       The substituted phenyl, tetrahydronaphthalene, chroman,  
10 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety of the  
11 novel compounds of the invention are derivatized in a manner to include the  
12 specific substituents (such as for example the cycloalkyl substituents)  
13 encompassed within the scope of the invention, either before or after the -  
14  $A(R_2)-CH_2)_n-COOR_8$  moiety has been attached and the linker **Z** has  
15 formed, as illustrated by the below described specific examples.  
16 The  $-CH_2)_n-COOR_8$  moiety of the compounds of the invention can be  
17 modified in order to obtain still further compounds of the invention. One  
18 such modification is saponification of compounds where the  $R_8$  group is an  
19 alkyl or  $-CH_2O(C_{1-6}\text{-alkyl})$  group. Another modification is esterification of  
20 the carboxylic acid function when the  $R_8$  group is H or a cation. Such  
21 saponification and esterification reactions are well known in the art and  
22 within the skill of the practicing organic chemist. Still another modification  
23 of the compounds of the invention (or of the intermediates  $X_4-A(R_2)-$   
24  $CH_2)_n-COOR_8$ , or of precursors to these intermediates) is the  
25 homologation of the  $(CH_2)_n$  group. The latter can be accomplished, for  
26 example, by the well known *Arndt-Eistert* method of homologation, or other  
27 known methods of homologation.

## SPECIFIC EMBODIMENTS

2 With reference to the symbol **A** in **Formulas 1** through **8**, the  
3 preferred compounds of the invention are those where **A** is phenyl, naphthyl,  
4 pyridyl, thienyl or furyl. Even more preferred are compounds where **A** is  
5 phenyl. As far as substitutions on the **A** (phenyl) and **A** (pyridyl) groups  
6 are concerned, compounds are preferred where the phenyl group is 1,4  
7 (*para*) substituted and where the pyridine ring is 2,5 substituted.  
8 (Substitution in the 2,5 positions in the "pyridine" nomenclature corresponds  
9 to substitution in the 6-position in the "nicotinic acid" nomenclature.) In the  
10 presently preferred compounds of the invention either there is no **R**<sub>2</sub>  
11 substituent on the **A** group, or the **R**<sub>2</sub> substituent is preferably a fluoro  
12 group that is preferably located on the aromatic carbon adjacent (*ortho*) to  
13 the carbon bearing the  $-(\text{CH}_2)_n\text{-COOR}_8$  group.

As far as the  $-(\text{CH}_2)_n-\text{COOR}_8$  is concerned compounds are preferred where  $n$  is 0, 1 or 2, and even more preferred where  $n$  is 1. In **Formulas 5** and **8** only compounds where  $n$  is 1 or 2 are preferred, with  $n=1$  being most preferred. For the  $\text{R}_8$  group H, lower alkyl of 1 to 3 carbons, and  $-\text{CH}_2\text{O}(\text{C}_1\text{-}_6\text{-alkyl})$  groups are preferred, as well as the pharmaceutically acceptable salts of the free acids when  $\text{R}_8$  is H. Among the lower alkyl and  $-\text{CH}_2\text{O}(\text{C}_1\text{-}_6\text{-alkyl})$  groups ethyl and  $\text{OCH}_2\text{CH}_3$ , respectively, are presently most preferred.

22 The linker group **Z** in all the compounds of the invention is  
23 preferably ethynyl  
24 (-C≡C-), ester (CO-O), ethenyl, (-CR<sub>1</sub>=CR<sub>1</sub>-) or amide (CONR<sub>1</sub>).  
25 Among these the ethynyl (-C≡C-) and ester (CO-O) linkers are most  
26 preferred. Moreover, in the preferred compounds of the invention the linker  
27 **Z** is attached to the 6 position in **Formula 1**, to the 4 position in **Formula 2**.

1 to the 6 position in **Formula 3**, to the 6 position in **Formula 4**, to the 4  
2 position in **Formula 5**, to the 4 position in **Formula 6**, to the 6 position in  
3 **Formula 7**, and to the 6 position in **Formula 8**. These positions are  
4 indicated by arabic numerals in **Formulas 1** through **8**.

5 The **R<sub>1</sub>** group substituting the non-aromatic rings in **Formulas 1, 3**,  
6 **4, 7** and **8** is preferably alkyl, more preferably alkyl of 1 to 3 carbons, and  
7 most preferably methyl. The **R<sub>1</sub>** group substituting the cyclopropane ring in  
8 **Formulas 1, 2, 3** and **7** is preferably non-existent (**p** is 0), or is alkyl of 1 to  
9 3 carbons, even more preferably methyl.

10 The **X** group in **Formulas 1** and **5** is preferably O, and in **Formula 2**  
11 **X** is preferably O or NR.

12 The **X<sub>1</sub>** group in **Formula 4** is preferably 1-imidazolyl, substituted 1-  
13 imidazolyl, or **NRR<sub>6</sub>**, where **R<sub>6</sub>** is preferably cyclopropyl or branched-chain  
14 alkyl. The **X<sub>2</sub>** group in **Formula 6** is preferably 1-imidazolyl or substituted  
15 1-imidazolyl.

16 The **X<sub>3</sub>** group in **Formula 8** is preferably O or C=O.

17 The **Y** group is preferably H, lower alkyl of 1 to 3 carbons,  
18 cycloalkyl, lower alkyl substituted cycloalkyl, or halogen. Among these, H,  
19 Cl, and cyclopropyl are most preferred.

20 The **Y<sub>1</sub>** group of **Formula 8** is preferably H, lower alkyl of 1 to 3  
21 carbons, cycloalkyl, or lower alkyl substituted cycloalkyl. Among these H,  
22 ethyl and cyclopropyl are presently most preferred.

23 The most preferred compounds of the invention are disclosed in  
24 **Tables 2** through **9** with reference to **Formulas 9** through **16**. The  
25 compounds specifically shown in **Tables 2** through **9** are carboxylic acids,  
26 but it should be understood that the C<sub>1-3</sub>alkyl esters, methoxymethyl  
27 (OCH<sub>2</sub>CH<sub>3</sub>) esters and pharmaceutically acceptable salts of the acids shown

1 in these tables are also highly preferred.

2 It should also be apparent that the preferred compounds shown in  
3 **Table 2** with reference to the more specific **Formula 9** are within the scope  
4 of **Formula 1**.

5 Similarly, the preferred compounds shown in **Table 3** with reference  
6 to the more specific **Formula 10** are within the scope of **Formula 2**;

7 the preferred compounds shown in **Table 4** with reference to the  
8 more specific **Formula 11** are within the scope of **Formula 3**;

9 the preferred compounds shown in **Table 5** with reference to the  
10 more specific **Formula 12** are within the scope of **Formula 4**;

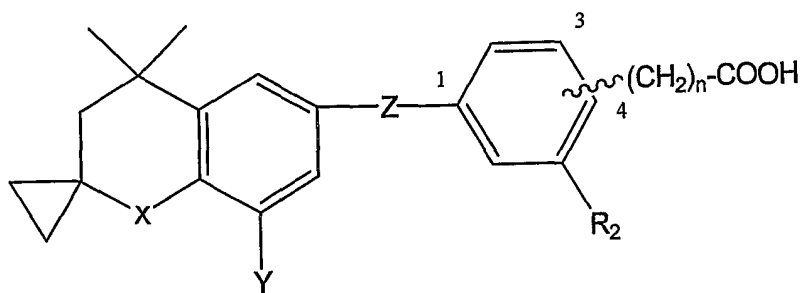
11 the preferred compounds shown in **Table 6** with reference to the  
12 more specific **Formula 13** are within the scope of **Formula 5**;

13 the preferred compounds shown in **Table 7** with reference to the  
14 more specific **Formula 14** are within the scope of **Formula 6**;

15 the preferred compounds shown in **Table 8** with reference to the  
16 more specific **Formula 15** are within the scope of **Formula 7**, and

17 the preferred compounds shown in **Table 9** with reference to the  
18 more specific **Formula 16** are within the scope of **Formula 8**.

46

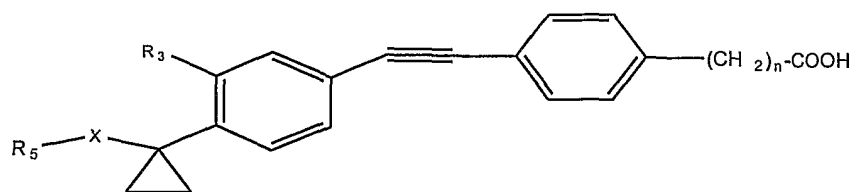


Formula 9

TABLE 2

Compound No.	X	Y	Z	R <sub>2</sub>	n	Position of (CH <sub>2</sub> ) <sub>n</sub> COOH
40	O	H	-C≡C-	H	0	4
42	O	H	-C≡C-	H	1	4
44	O	H	-C≡C-	F	0	4
48	O	cyclopropyl	-C≡C-	H	1	4
50	O	cyclopropyl	-C≡C-	F	1	4
52	O	cyclopropyl	-C≡C-	H	0	4
54	O	cyclopropyl	-C≡C-	F	0	4
58	O	cyclopropyl	-CO-O-	H	1	4
60	O	cyclopropyl	-CO-O-	H	1	3
66	CH <sub>3</sub> N	H	-C≡C-	H	0	4

47

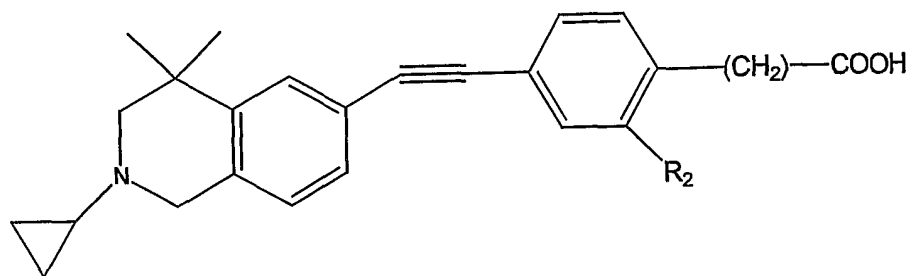


Formula 10

TABLE 3

Compound No.	R <sub>5</sub>	X	R <sub>3</sub>	n
110	n-propyl	(n-propyl)N	H	0
112	benzyl	NH	H	0
114	benzyl	(n-benzyl)N	H	0
108	n-propyl	NH	H	0
116	benzyl	methylN	H	0
77	benzyl	O	H	0
78	benzyl	O	H	1
70	methyl	O	H	1
69	methyl	O	H	0
73	isopropyl	O	H	0
74	isopropyl	O	H	1
82	benzyl	O	methyl	1
81	benzyl	O	methyl	0
89	(CH <sub>3</sub> ) <sub>3</sub> C-CH <sub>2</sub> -	O	methyl	0
90	(CH <sub>3</sub> ) <sub>3</sub> C-CH <sub>2</sub> -	O	methyl	1
94	benzyl	O	ethyl	1
93	benzyl	O	ethyl	0
86	isopropyl	O	methyl	1
85	isopropyl	O	methyl	0
105	ethyl	O	<i>t</i> -butyl	0
106	ethyl	O	<i>t</i> -butyl	1
98	isopropyl	O	ethyl	1

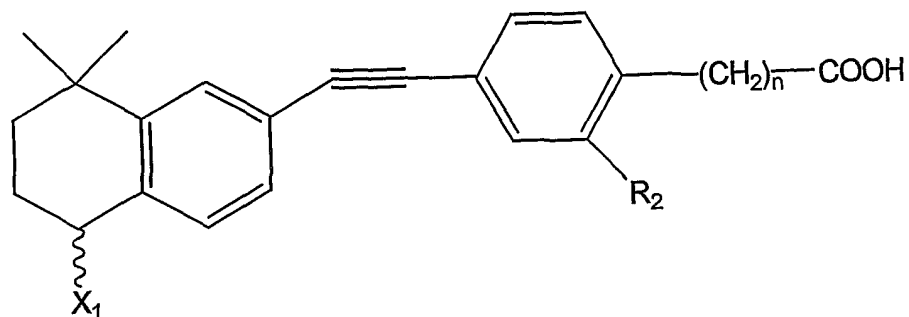
48



Formula 11

TABLE 4

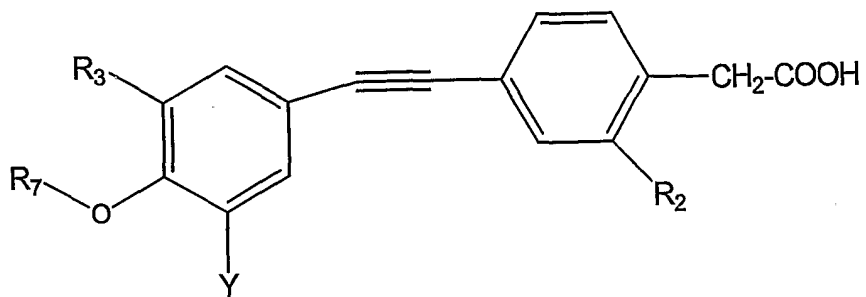
Compound No.	$R_2$
22	F
24	H



Formula 12

TABLE 5

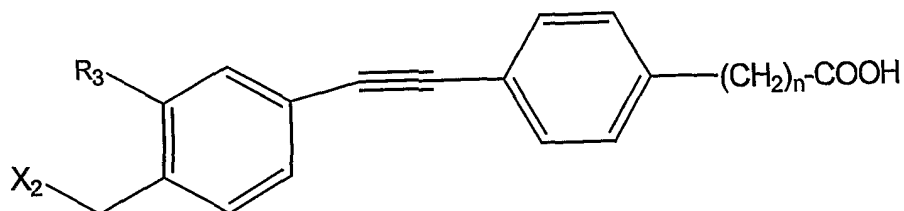
Compound No.	$X_1$	$R_2$	n
3	methyl,cyclopropyl-N	H	0
8	methyl,cyclopropyl-N	H	1
13	methyl,cyclopropyl-N	F	0
18	methyl,cyclopropyl-N	F	1
139	1-imidazolyl	H	0
137	1-imidazolyl	H	1
26	methyl,isopropyl-N	H	0



Formula 13

TABLE 6

Compound No.	$R_2$	$R_7$	Y	$R_3$
143	H	methyl	<i>t</i> -butyl	<i>t</i> -butyl
145	F	methyl	<i>t</i> -butyl	<i>t</i> -butyl

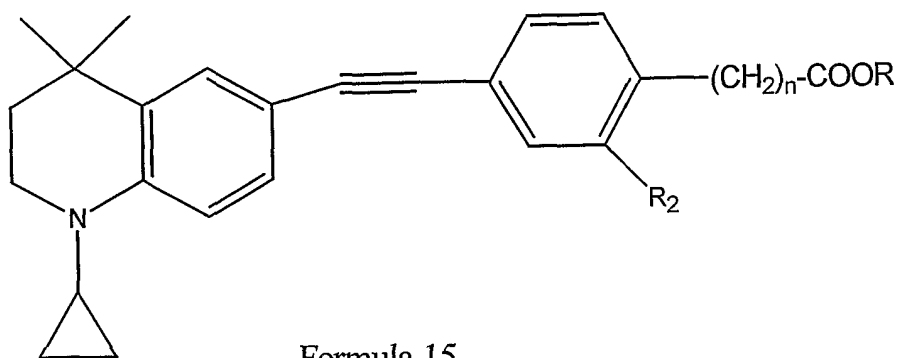


Formula 14

TABLE 7

Compound No.	$X_2$	$R_3$	n
119	1-imidazolyl	methyl	0
121	1-imidazolyl	methyl	1
127	1-imidazolyl	iso-propyl	1
126	1-imidazolyl	iso-propyl	0
134	ethyl,cyclopropyl-N	iso-propyl	0
130	ethyl,cyclopropyl-N	methyl	0
131	ethyl,cyclopropyl-N	methyl	1
141	(1-methyl)cyclopropyl-oxy	iso-propyl	1

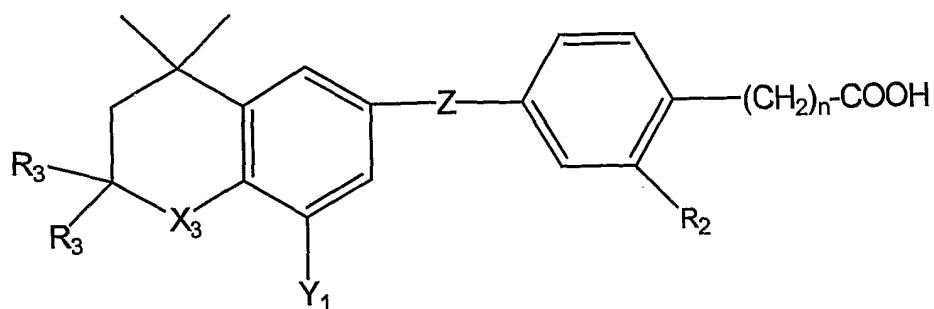
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Formula 15

TABLE 8

Compound No.	R	R <sub>2</sub>	n
62	H	H	0
63	Me	H	1



Formula 16

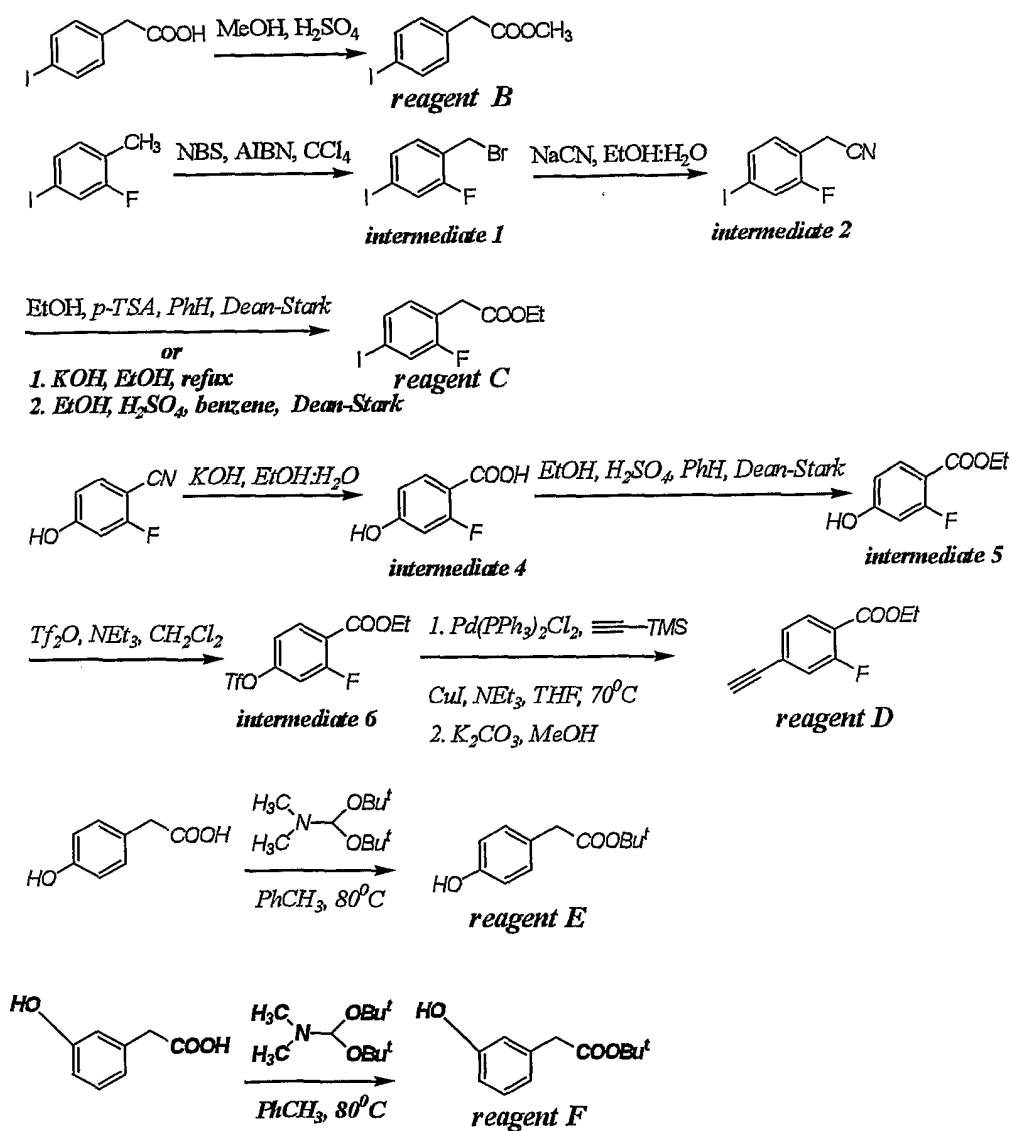
TABLE 9

Compound No.	X <sub>3</sub>	Y <sub>1</sub>	R <sub>3</sub>	Z	R <sub>2</sub>	n
28	O	H	methyl	-C≡C-	H	1
30	O	H	methyl	-C≡C-	F	0
5	CO	H	H	-C≡C-	H	1
10	CO	H	H	-C≡C-	F	0
36	O	cyclopropyl	methyl	-C≡C-	H	1
38	O	cyclopropyl	methyl	-C≡C-	F	1
46	O	H	methyl	-CO-O-	H	1
20	CO	H	H	-CO-O-	H	1
32	O	H	methyl	-C≡C-	F	1
56	O	ethyl	methyl	-C≡C-	H	1
34	O	cyclopropyl	methyl	-C≡C-	H	0
15	CO	H	H	-C≡C-	F	1

1       The compounds of the invention can be synthesized by applying the  
2   general synthetic methodology described above, and by such modifications  
3   of the hereinafter described specific synthetic routes which will become  
4   readily apparent to the practicing synthetic organic chemist in light of this  
5   disclosure and in view of general knowledge available in the art. The  
6   hereinafter disclosed specific reaction schemes are directed to the synthesis  
7   of exemplary and preferred compounds of the invention. Whereas each of  
8   the specific and exemplary synthetic routes shown in these schemes may  
9   describe specific compounds of the invention only within the scope of one  
10   or two of the general **Formulas 1** through **8**, the synthetic processes and  
11   methods used therein are adaptable within the skill of the practicing organic  
12   chemist and can be used with such adaptation for the synthesis of  
13   compounds of the invention which are not specifically described herein as  
14   examples.

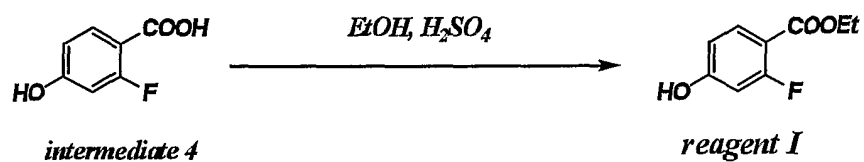
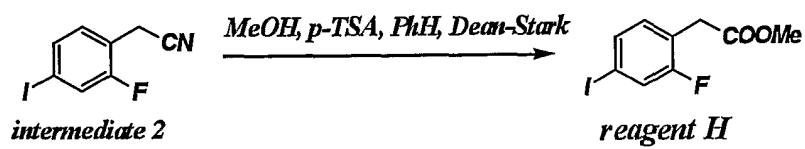
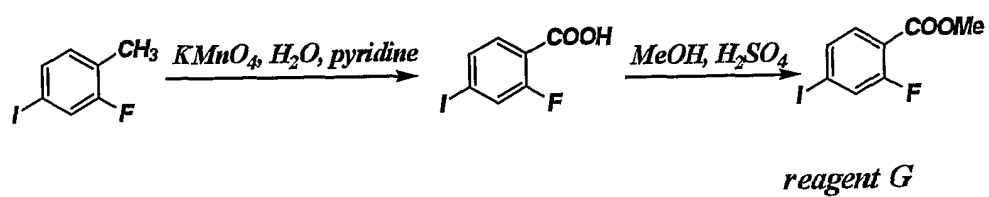
15       **Reaction Scheme 1** discloses a presently preferred synthetic route to  
16   certain intermediates or reagents having the general formula  $X_4-A(R_2)-$   
17    $CH_2)_n-COOR_g$ , where the symbol **A** represents a di-, or tri-substituted  
18   phenyl moiety. These intermediates are utilized in the synthesis of the  
19   compounds of the invention.

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REACTION SCHEME 1

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*REACTION SCHEME 1 CONTINUED*

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3       **Reaction Scheme 2** discloses presently preferred synthetic routes to  
4 obtain exemplary and preferred tetrahydronaphthalenone compounds of the  
5 invention within the scope of **Formula 8** where the the symbol  $X_3$   
6 represents a C=O group, **Z** represents an ethynyl moiety or a -COO- (ester)  
7 function, and **A** is a substituted phenyl moiety.

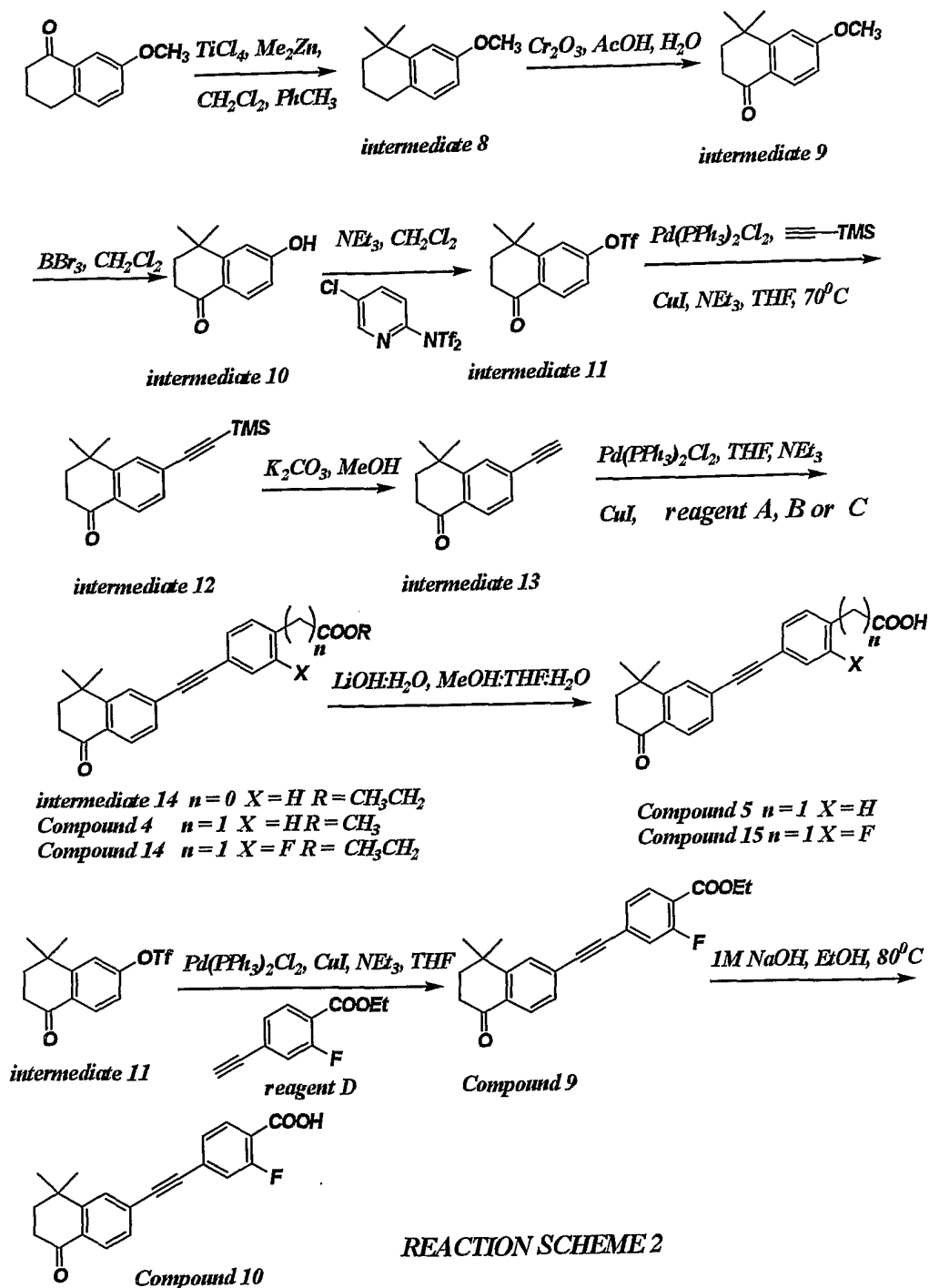
8       **Reaction Scheme 3** discloses presently preferred synthetic routes to  
9 obtain exemplary and preferred tetrahydronaphthalene compounds of the  
10 invention within the scope of **Formula 4** where  $X_1$  represents a dialkyl  
11 substituted nitrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl  
12 moiety.

13       **Reaction Scheme 4** discloses presently preferred synthetic routes to  
14 obtain exemplary and preferred isoquinoline compounds of the invention  
15 within the scope of **Formula 3** where the symbol **Y** represents hydrogen, **Z**  
16 is an ethynyl moiety and **A** is a substituted phenyl moiety.

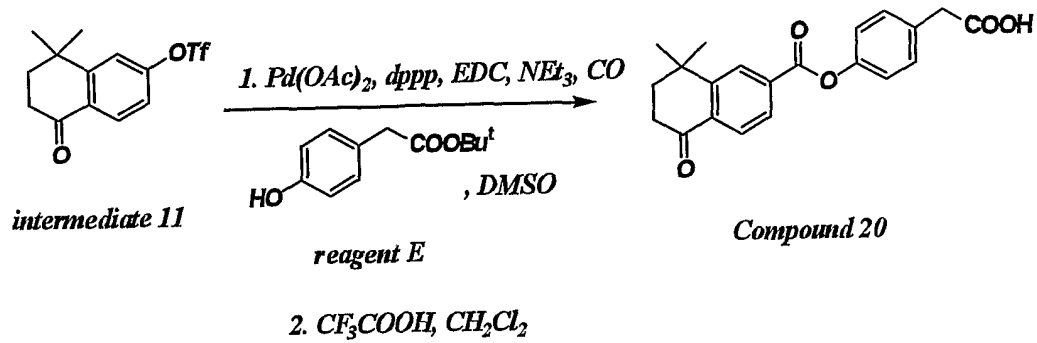
17       **Reaction Scheme 5** discloses presently preferred synthetic routes to  
18 obtain exemplary and preferred chroman compounds of the invention within  
19 the scope of **Formula 8** where the symbol  $Y_1$  represents hydrogen, **Z** is an  
20 ethynyl moiety or an ester (COO) function, and **A** is a substituted phenyl  
21 moiety.

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**REACTION SCHEME 2 CONTINUED**

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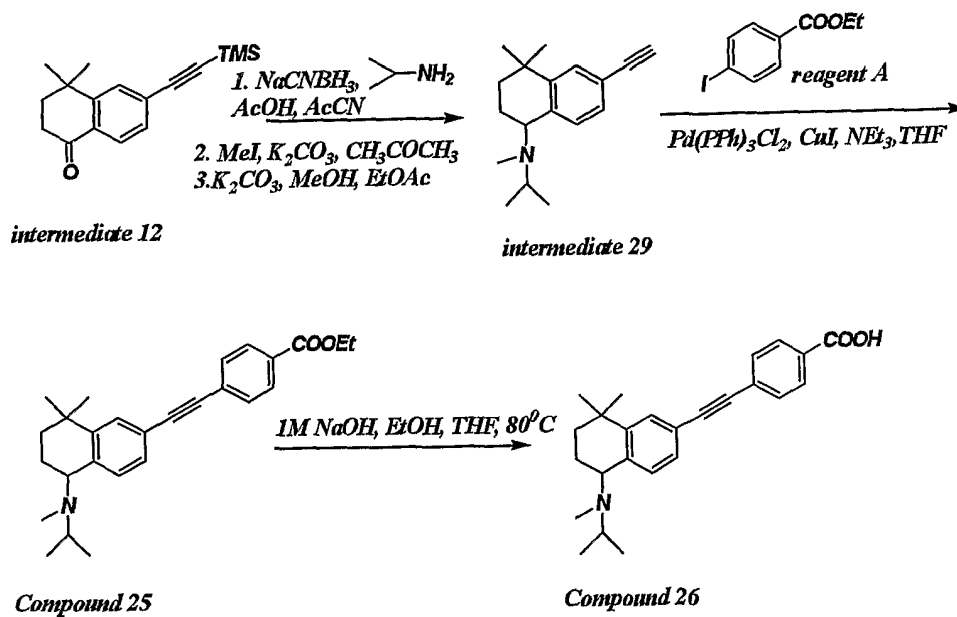
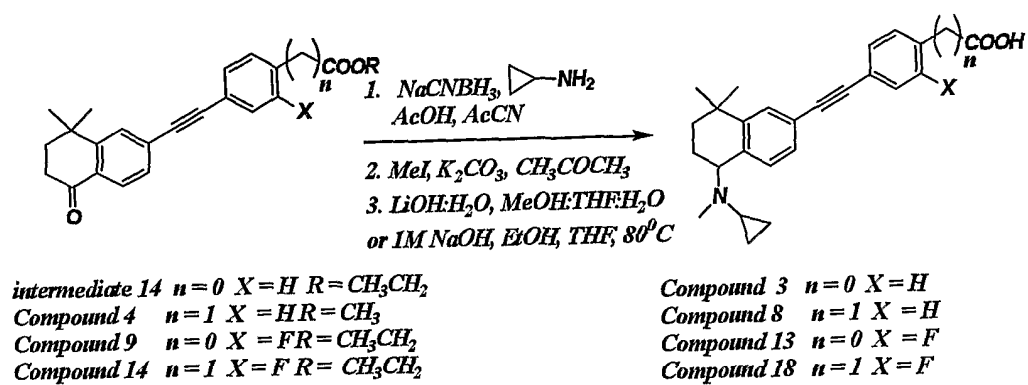
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## REACTION SCHEME 3

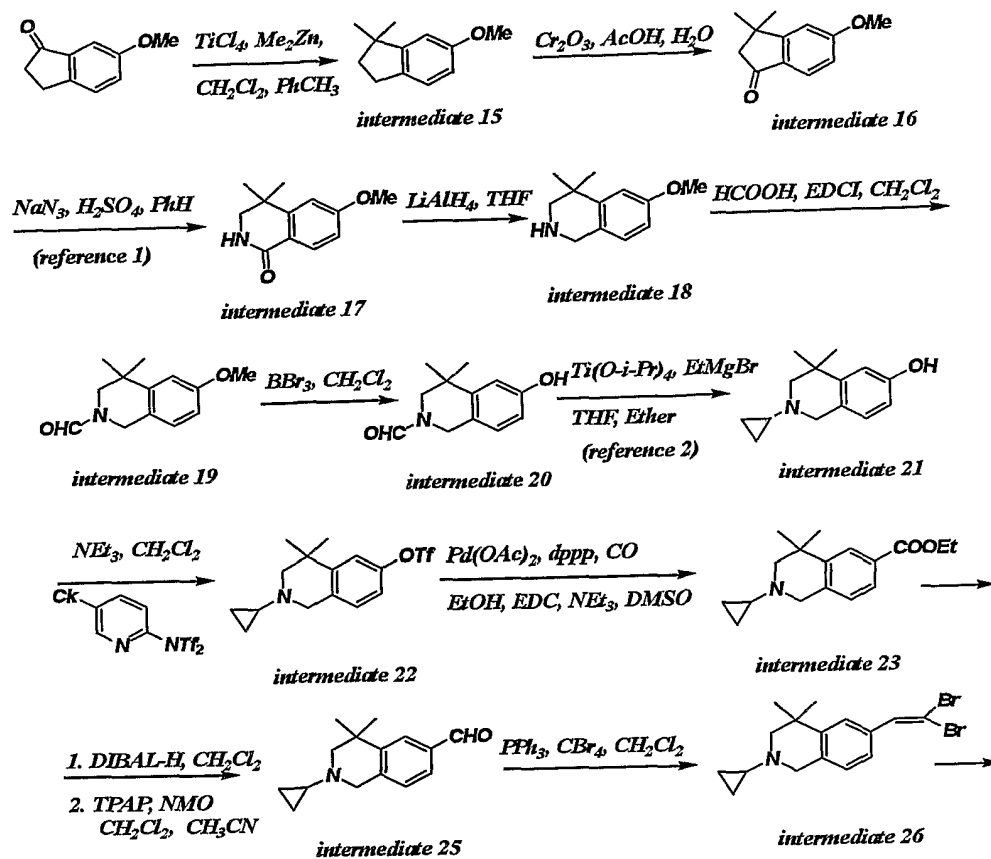
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TPAP = tetra-*n*-propyl ammonium perruthenate  
 NMO = *N*-methylmorpholine *N*-oxide

reference 1 Tomita et al. *J. Chem. Soc. (c)*, 1969, 183-188  
 reference 2 Chaplinski et al. *Angew. Chem. Int. Edn. Engl.*, 1996, 35, 413-414

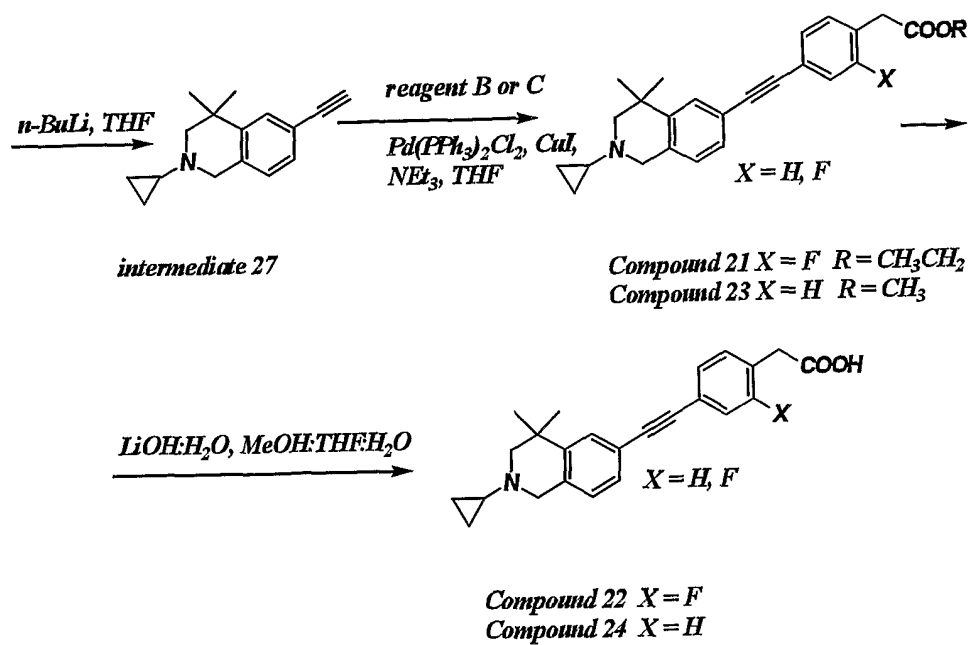
## REACTION SCHEME 4

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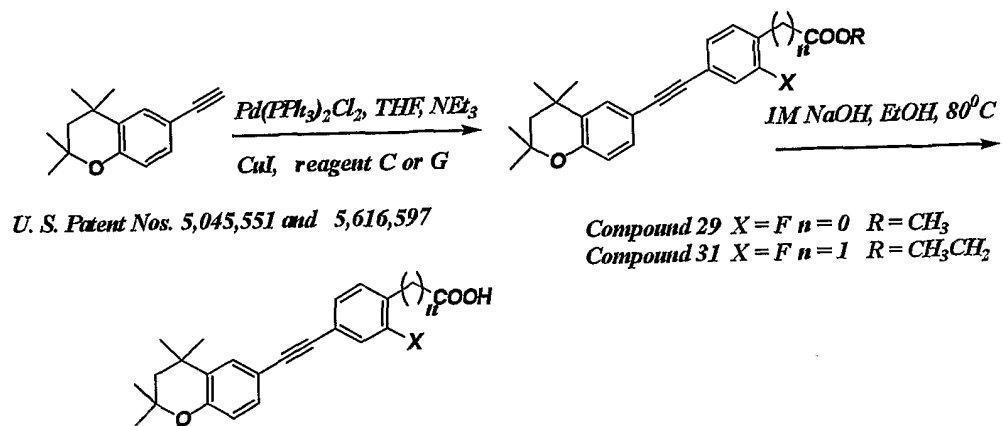
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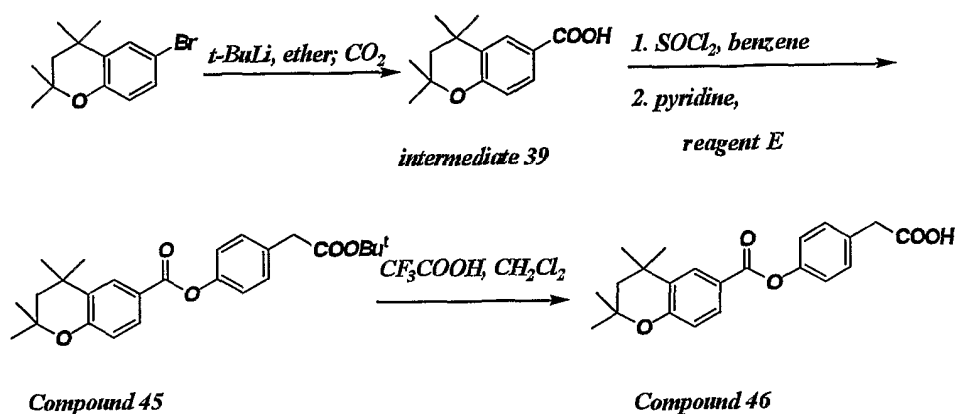


## REACTION SCHEME 4 CONTINUED

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Compound 30  $X = F$   $n = 0$   
 Compound 32  $X = F$   $n = 1$



## REACTION SCHEME 5

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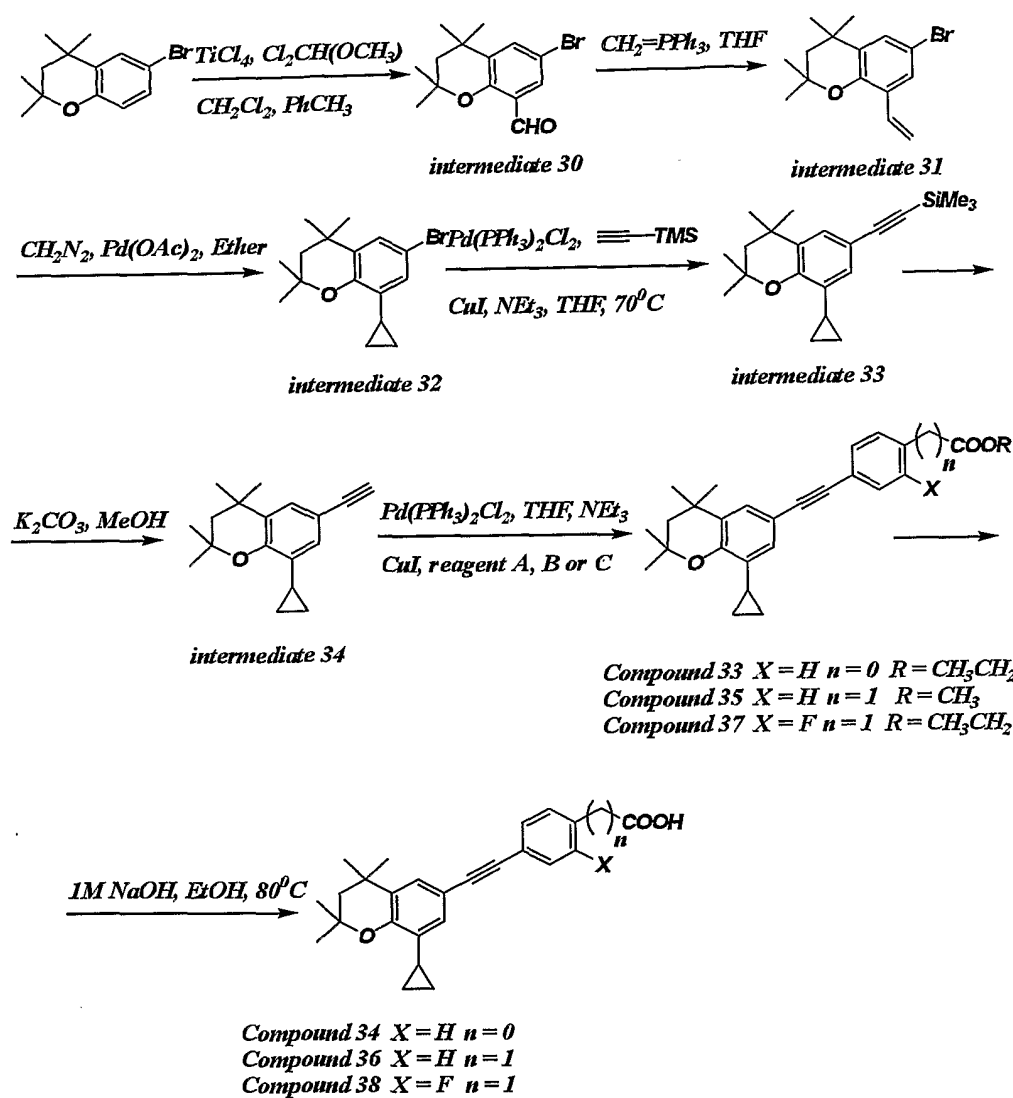
1           **Reaction Scheme 6** discloses presently preferred synthetic routes to  
2 obtain other exemplary and preferred chroman compounds of the invention  
3 within the scope of **Formula 8** where the symbol **Y<sub>1</sub>** represents a  
4 cyclopropyl group, **Z** is an ethynyl moiety and **A** is a substituted phenyl  
5 moiety.

6           **Reaction Scheme 7** discloses presently preferred synthetic routes to  
7 obtain exemplary and preferred chroman compounds of the invention within  
8 the scope of **Formula 1** where the symbol **X** represents oxygen (O), **Y**  
9 represents hydrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl  
10 moiety.

11           **Reaction Scheme 8** discloses presently preferred synthetic routes to  
12 obtain other exemplary and preferred chroman compounds of the invention  
13 within the scope of **Formula 1** where the symbol **X** represents oxygen (O),  
14 **Y** represents a cyclopropyl group, **Z** is an ethynyl moiety and **A** is a  
15 substituted phenyl moiety.

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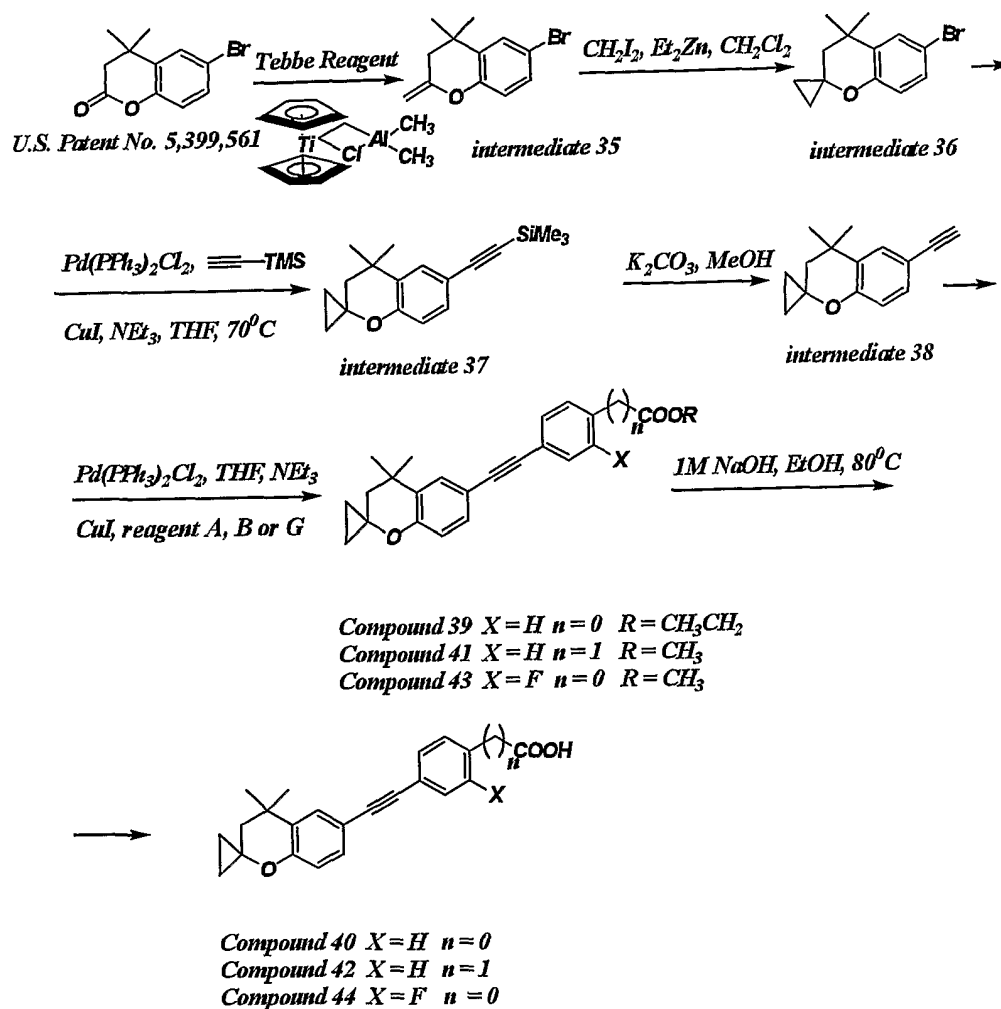


REACTION SCHEME 6

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REACTION SCHEME 7

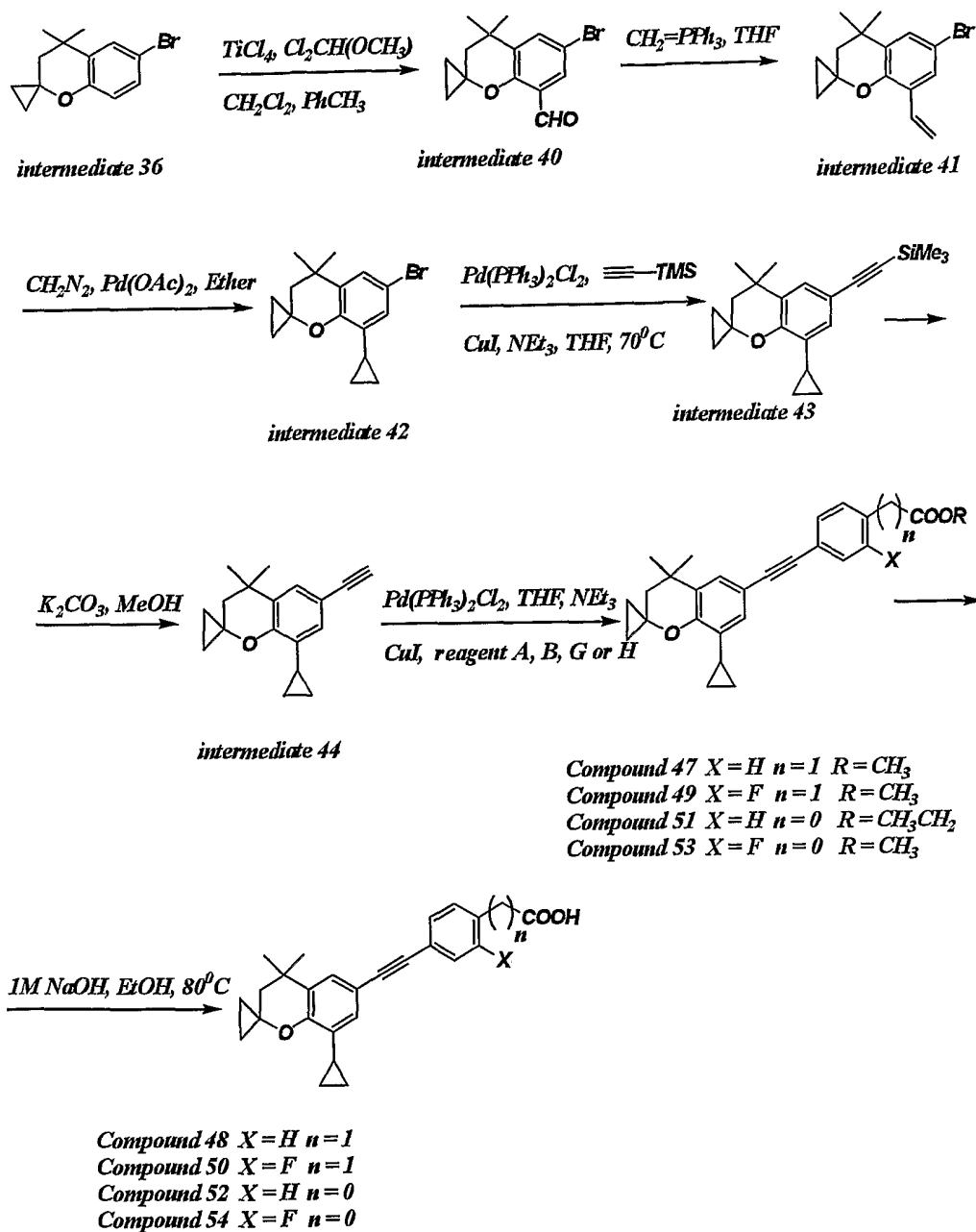
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REACTION SCHEME 8

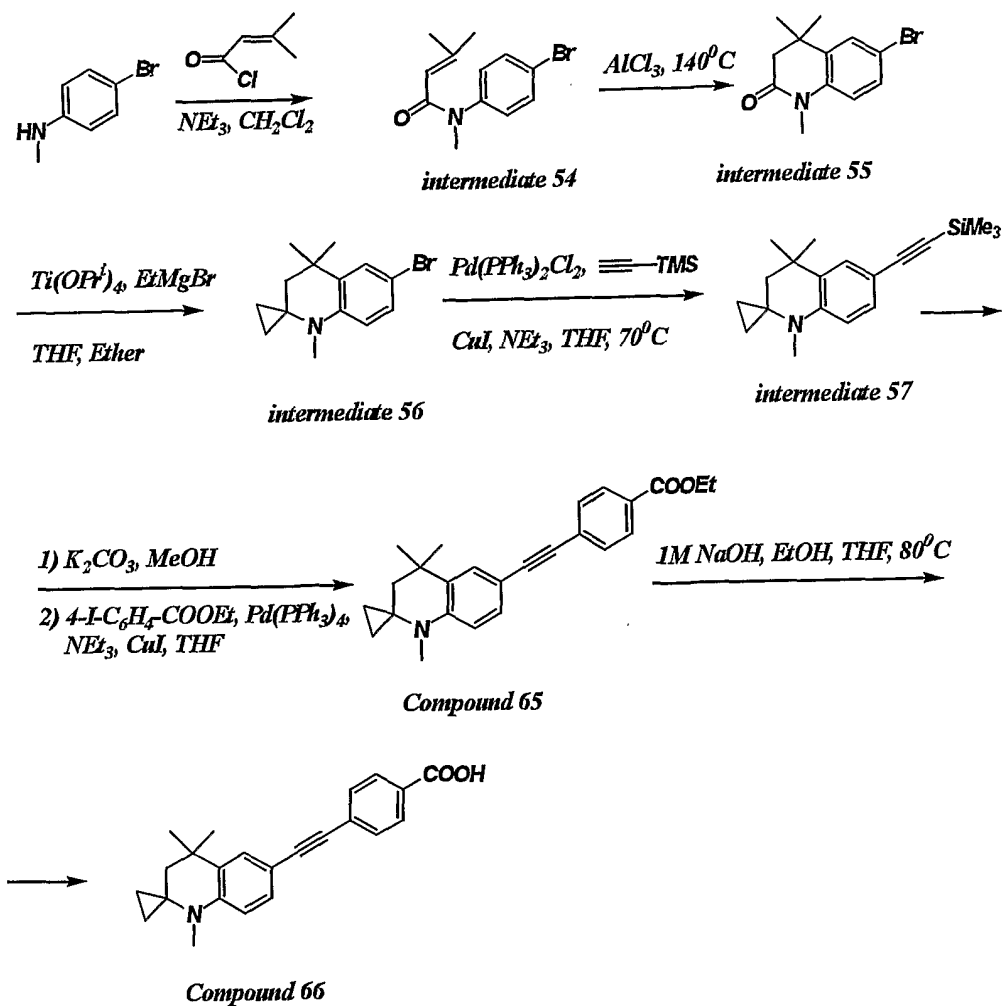
1        **Reaction Scheme 9** discloses presently preferred synthetic routes to  
2 obtain exemplary and preferred tetrahydroquinoline compounds of the  
3 invention within the scope of **Formula 1** where the symbol **X** represents an  
4 alkyl substituted nitrogen (alkyl-N), **Y** represents hydrogen, **Z** is an ethynyl  
5 moiety and **A** is a substituted phenyl moiety.

6        **Reaction Schemes 10 and 11** disclose presently preferred synthetic  
7 routes to obtain exemplary and preferred phenyl compounds of the invention  
8 within the scope of **Formula 2** where the symbol **X** represents oxygen (O),  
9 **R<sub>5</sub>** is alkyl or benzyl, **Z** is an ethynyl moiety and **A** is a substituted phenyl  
10 moiety.

11       **Reaction Scheme 12** discloses presently preferred synthetic routes to  
12 obtain exemplary and preferred phenyl compounds of the invention within  
13 the scope of **Formula 2** where the symbol **R<sub>5</sub>-X** represents an alkyl, dialkyl,  
14 benzyl or dibenzyl substituted nitrogen, **Z** is an ethynyl moiety and **A** is a  
15 substituted phenyl moiety.

16       **Reaction Schemes 13 and 14** disclose presently preferred synthetic  
17 routes to obtain exemplary and preferred phenyl compounds of the invention  
18 within the scope of **Formula 6** where the symbol **X<sub>2</sub>** represents a (1-  
19 imidazolyl) moiety, **Z** is an ethynyl moiety and **A** is a substituted phenyl  
20 moiety.

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REACTION SCHEME 9

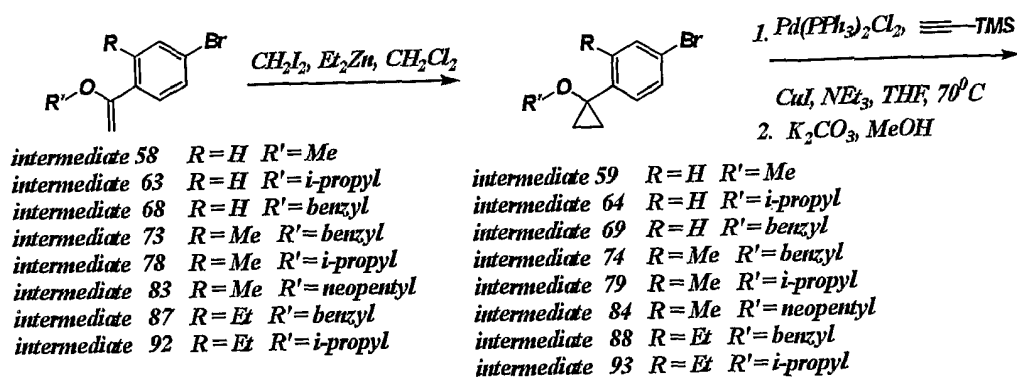
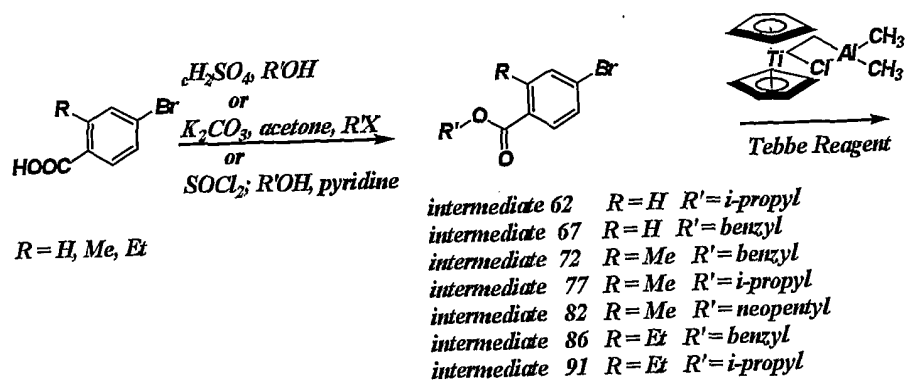
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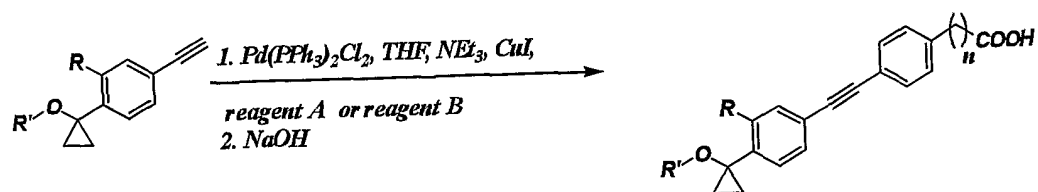
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REACTION SCHEME 10

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*intermediate 61*     $R=H$     $R'=Me$   
*intermediate 66*     $R=H$     $R'=i\text{-propyl}$   
*intermediate 71*     $R=H$     $R'=benzyl$   
*intermediate 76*     $R=Me$     $R'=benzyl$   
*intermediate 81*     $R=Me$     $R'=i\text{-propyl}$   
*intermediate 85*     $R=Me$     $R'=neopentyl$   
*intermediate 90*     $R=Et$     $R'=benzyl$   
*intermediate 95*     $R=Et$     $R'=i\text{-propyl}$

*Compound 69*     $n=0$     $R=H$     $R'=methyl$   
*Compound 70*     $n=1$     $R=H$     $R'=methyl$   
*Compound 73*     $n=0$     $R=H$     $R'=i\text{-propyl}$   
*Compound 74*     $n=1$     $R=H$     $R'=i\text{-propyl}$   
*Compound 77*     $n=0$     $R=H$     $R'=benzyl$   
*Compound 78*     $n=1$     $R=H$     $R'=benzyl$   
*Compound 81*     $n=0$     $R=Me$     $R'=benzyl$   
*Compound 82*     $n=1$     $R=Me$     $R'=benzyl$   
*Compound 85*     $n=0$     $R=Me$     $R'=i\text{-propyl}$   
*Compound 86*     $n=1$     $R=Me$     $R'=i\text{-propyl}$   
*Compound 89*     $n=0$     $R=Me$     $R'=neopentyl$   
*Compound 90*     $n=1$     $R=Me$     $R'=neopentyl$   
*Compound 93*     $n=0$     $R=Et$     $R'=benzyl$   
*Compound 94*     $n=1$     $R=Et$     $R'=benzyl$   
*Compound 97*     $n=0$     $R=Et$     $R'=i\text{-propyl}$   
*Compound 98*     $n=1$     $R=Et$     $R'=i\text{-propyl}$

## REACTION SCHEME 10 CONTINUED

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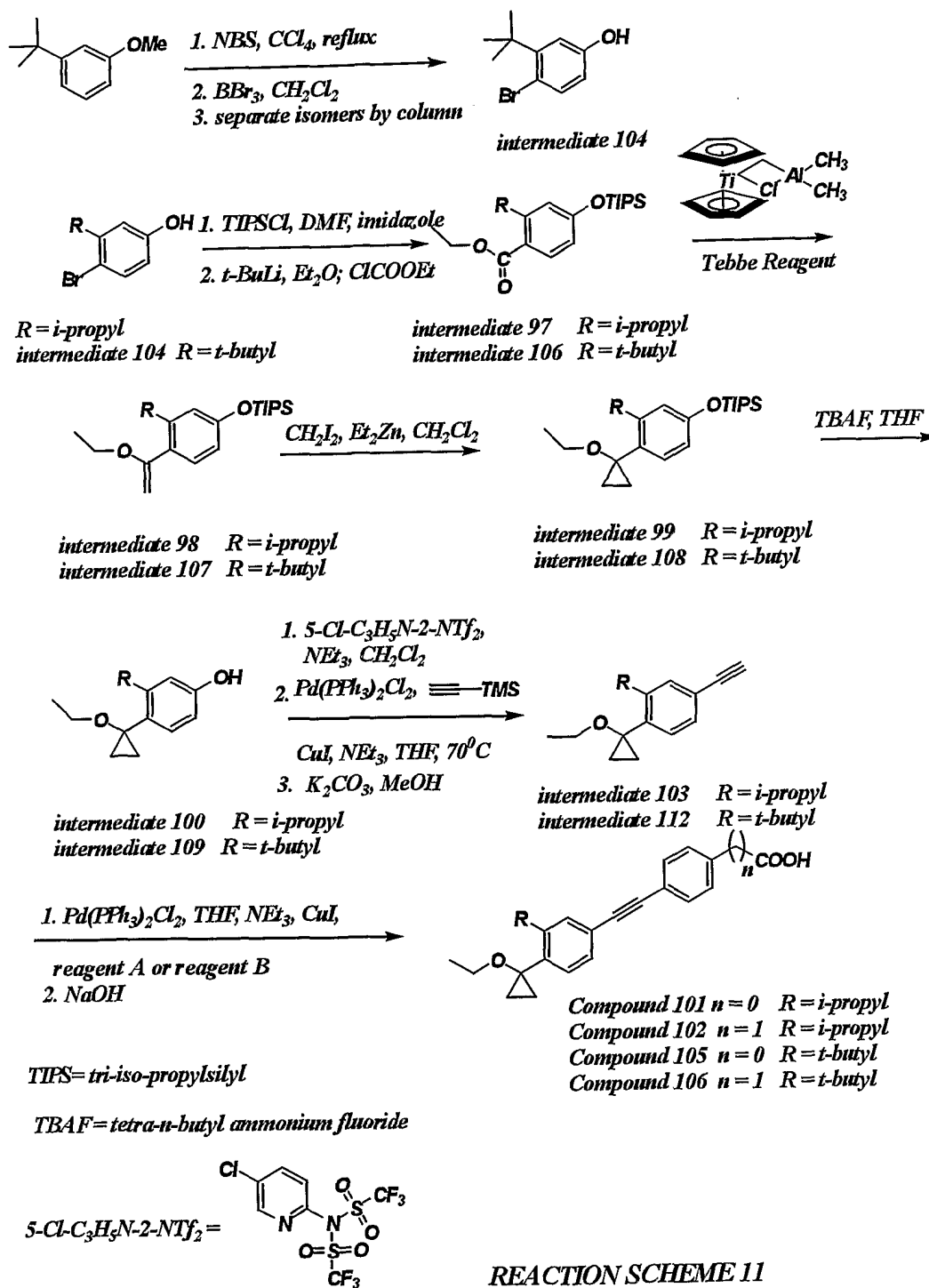
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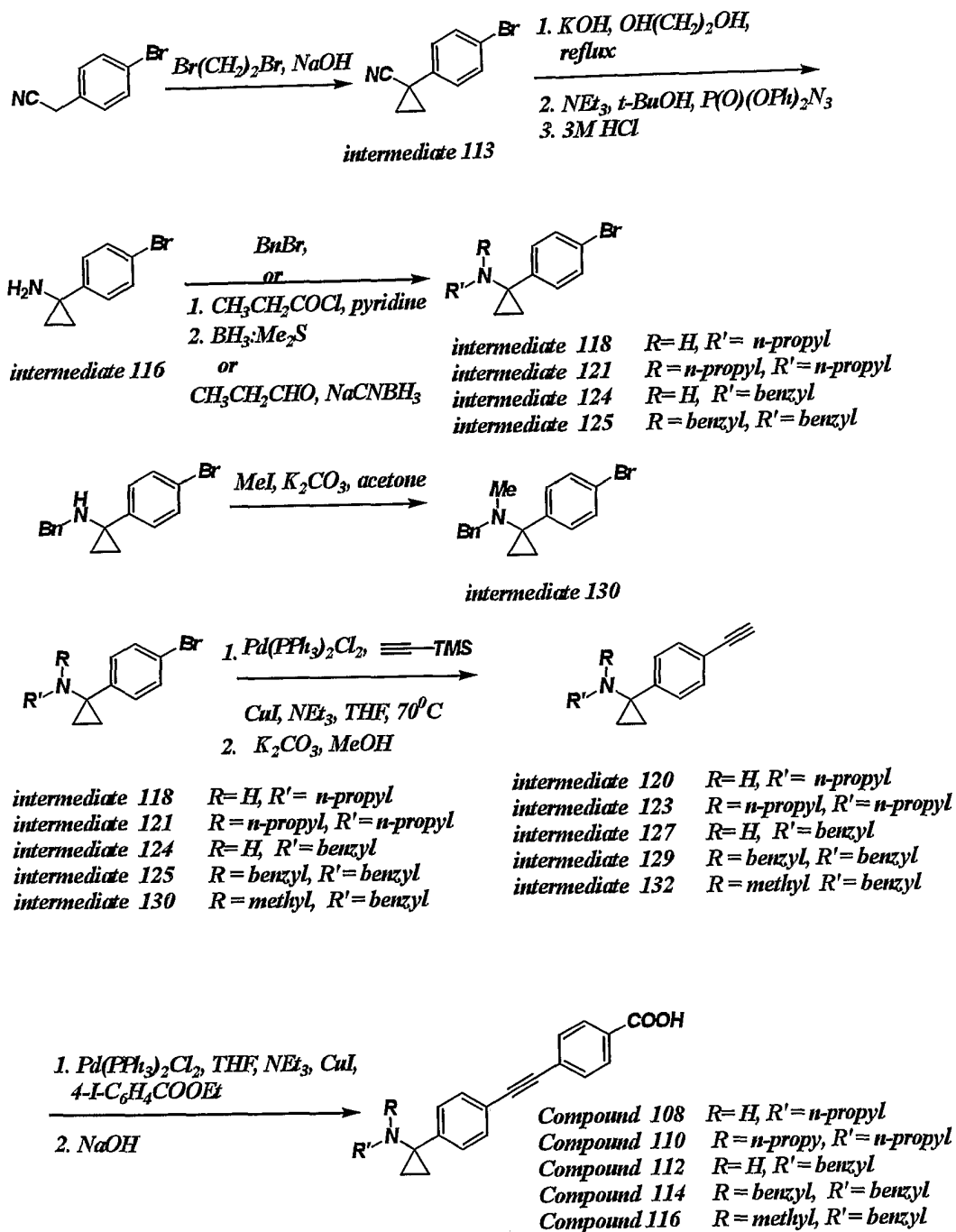
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REACTION SCHEME 11

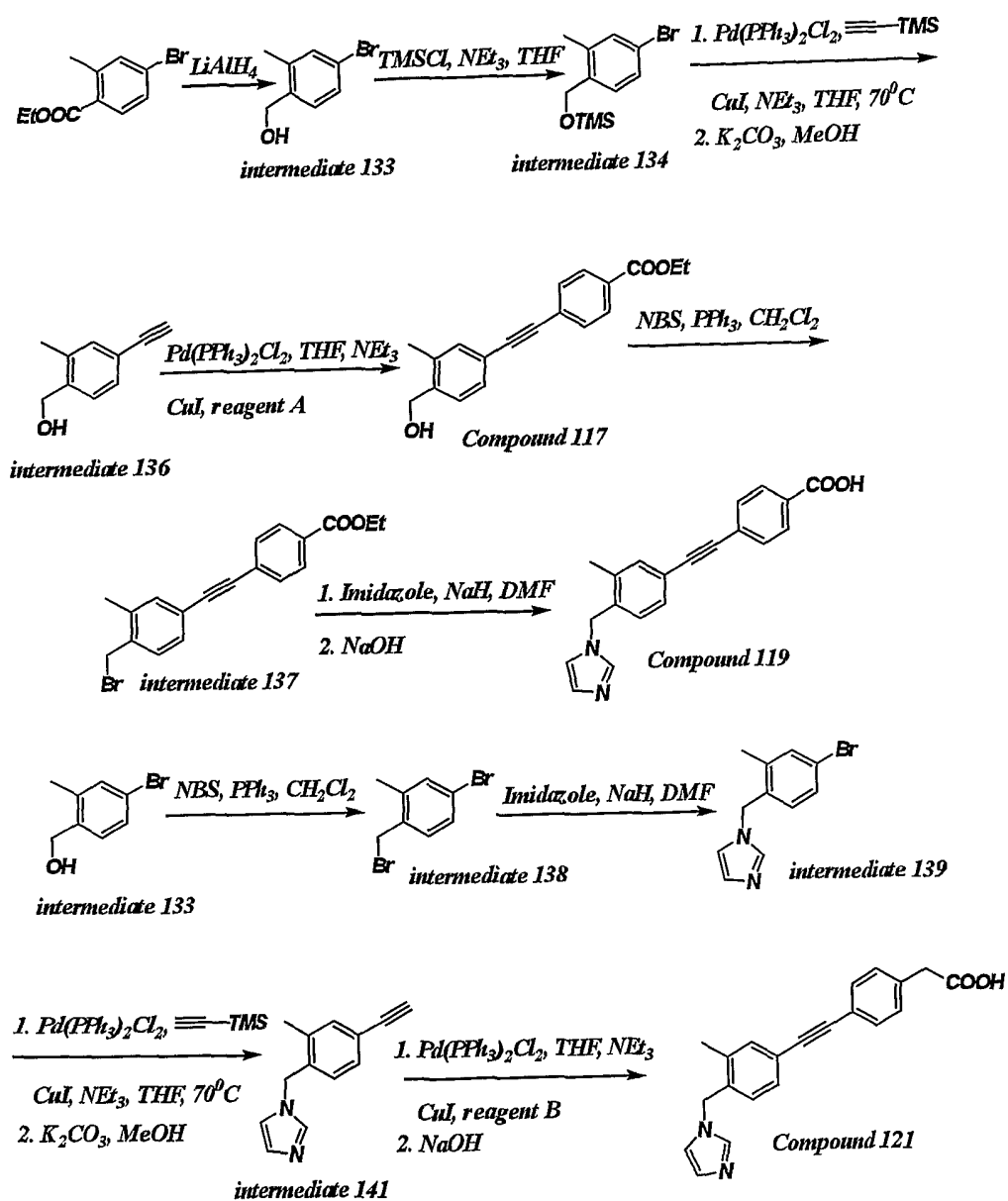
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REACTION SCHEME 12

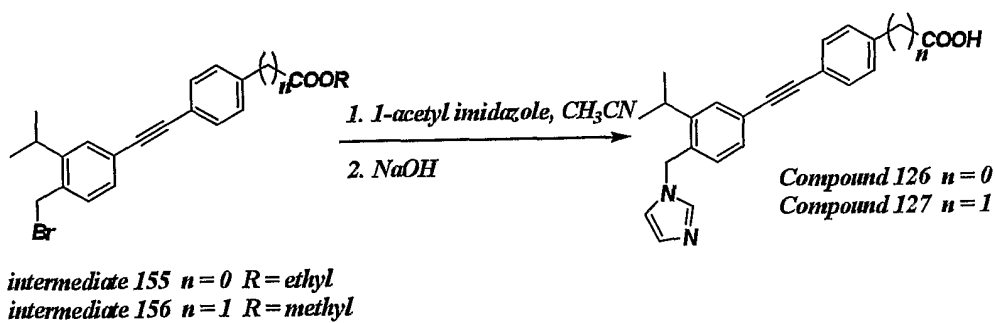
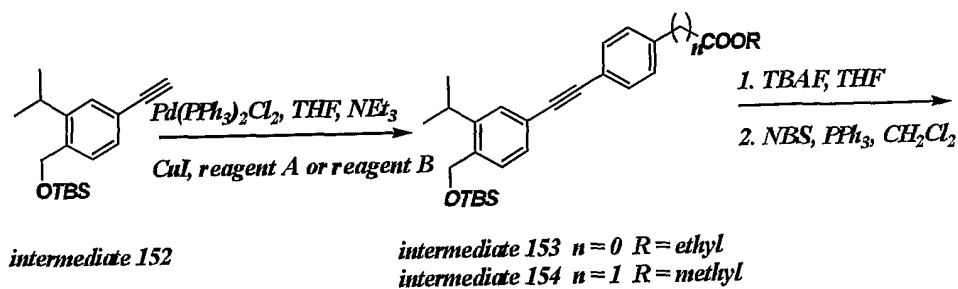
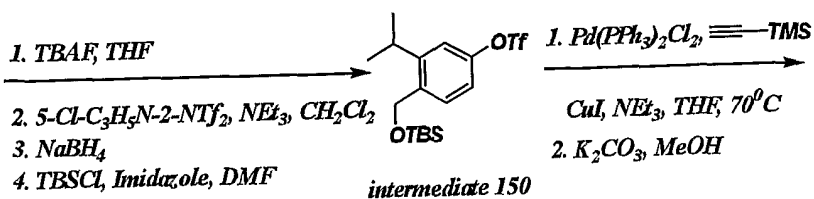
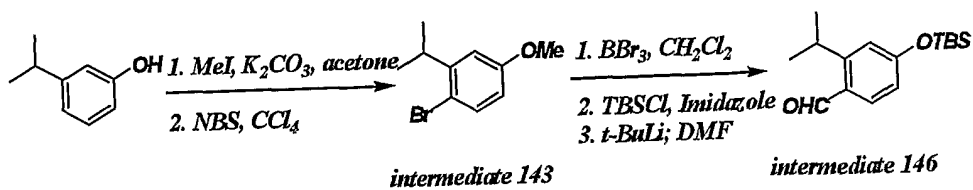
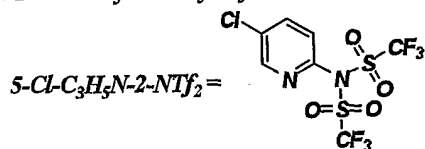
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REACTION SCHEME 13

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TBS = *t*-butyldimethylsilyl

REACTION SCHEME 14

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1        **Reaction Scheme 15** disclose presently preferred synthetic routes to  
2 obtain exemplary and preferred phenyl compounds of the invention within  
3 the scope of **Formula 6** where  $X_2$  represents an alkyl and cyclopropyl  
4 substituted nitrogen ( $X_2 = (\text{alkyl, cycloalkyl})N$ ),  $Y$  represents hydrogen,  $Z$   
5 is an ethynyl moiety and  $A$  is a substituted phenyl moiety.

6        **Reaction Scheme 16** discloses presently preferred synthetic routes to  
7 obtain exemplary and preferred tetrahydronaphthalene compounds of the  
8 invention within the scope of **Formula 4** where the symbol  $X_1$  represents a  
9 (1-imidazolyl) moiety,  $Y$  represents hydrogen,  $Z$  is an ethynyl moiety and  $A$   
10 is a substituted phenyl moiety.

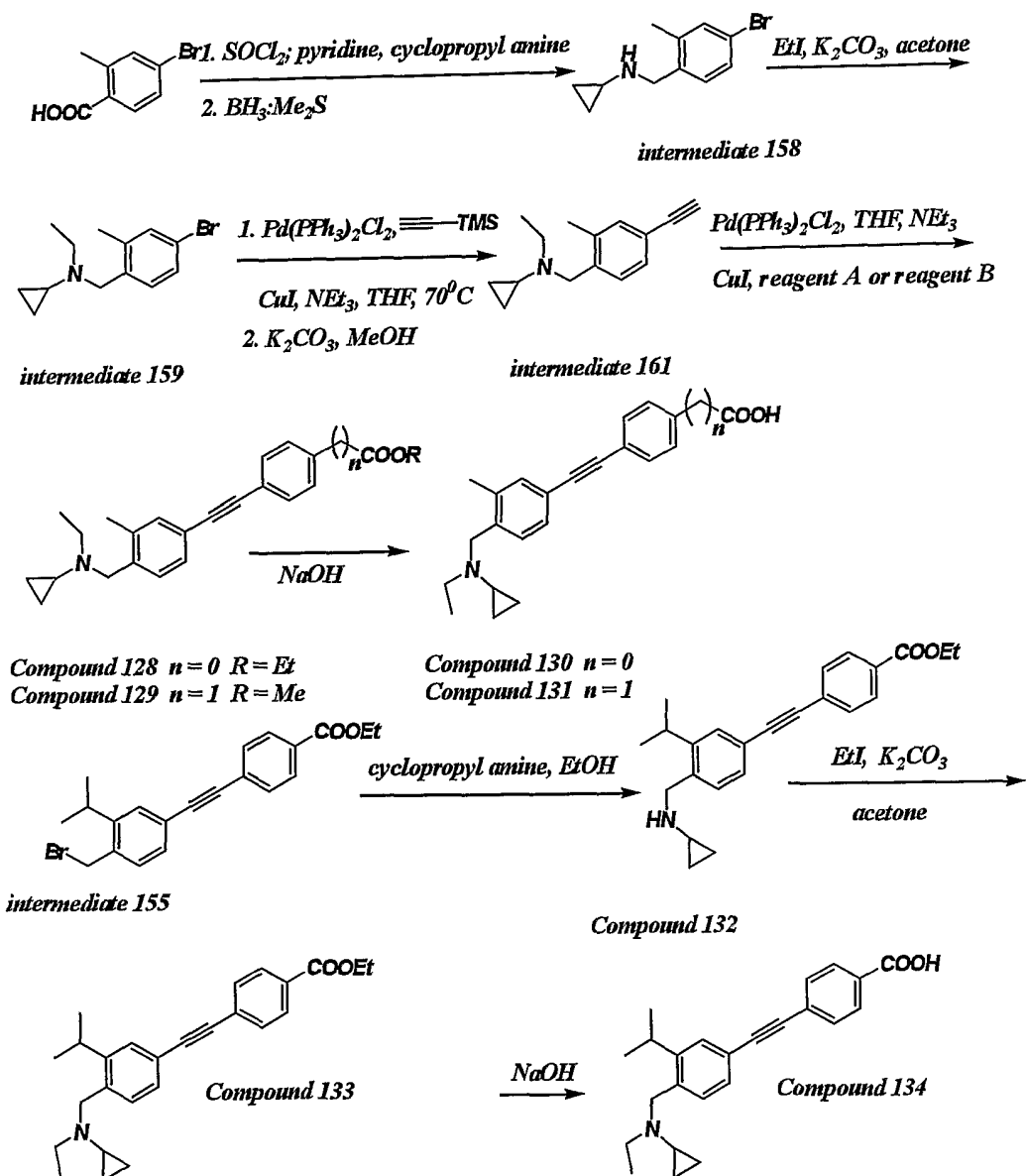
11       **Reaction Scheme 17** discloses presently preferred synthetic routes to  
12 obtain exemplary and preferred phenyl compounds of the invention within  
13 the scope of **Formula 6** where the symbol  $X_2$  represents a 1-methyl-  
14 cyclopropoxy moiety,  $Y$  represents hydrogen,  $Z$  is an ethynyl moiety and  $A$   
15 is a substituted phenyl moiety.

16       **Reaction Scheme 18** discloses presently preferred synthetic routes to  
17 obtain exemplary and preferred phenyl compounds of the invention within  
18 the scope of **Formula 5** where the symbol  $X$  represents oxygen (O),  $Y$   
19 represents a *tertiary*-butyl group,  $Z$  is an ethynyl moiety and  $A$  is a  
20 substituted phenyl moiety.

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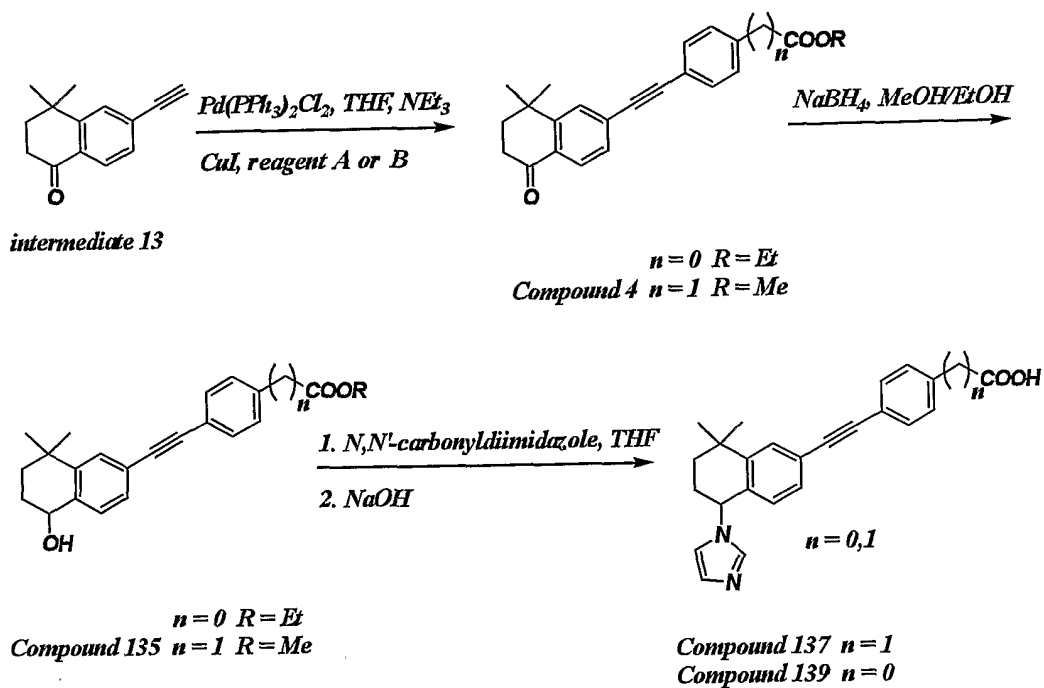
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**REACTION SCHEME 15**

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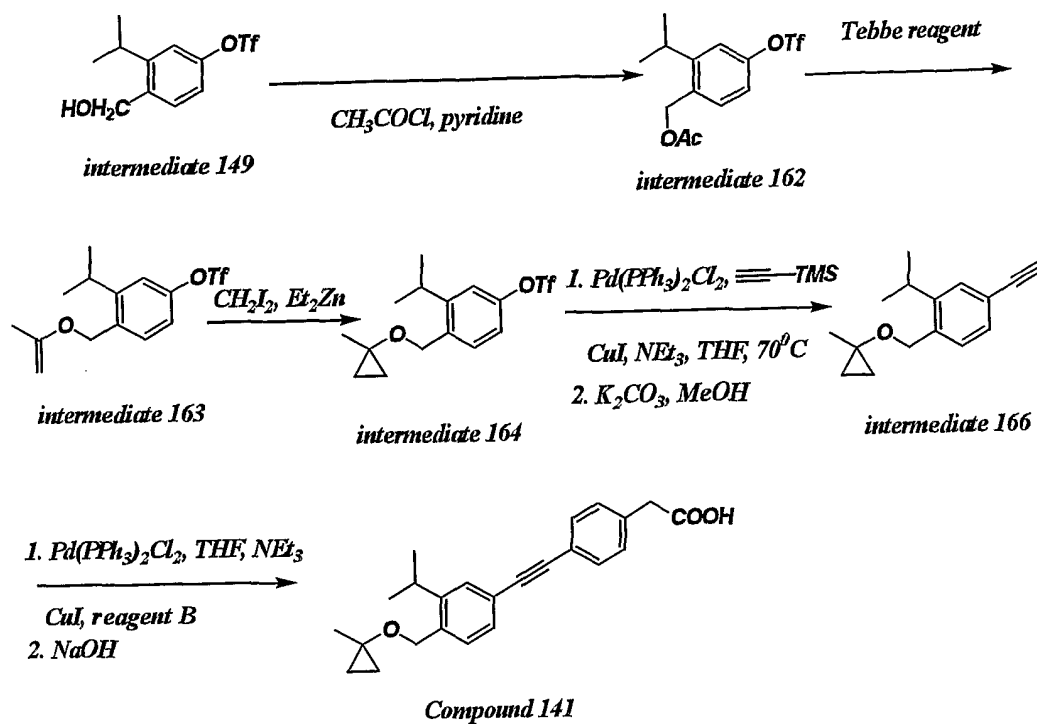
REACTION SCHEME 16

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REACTION SCHEME 17

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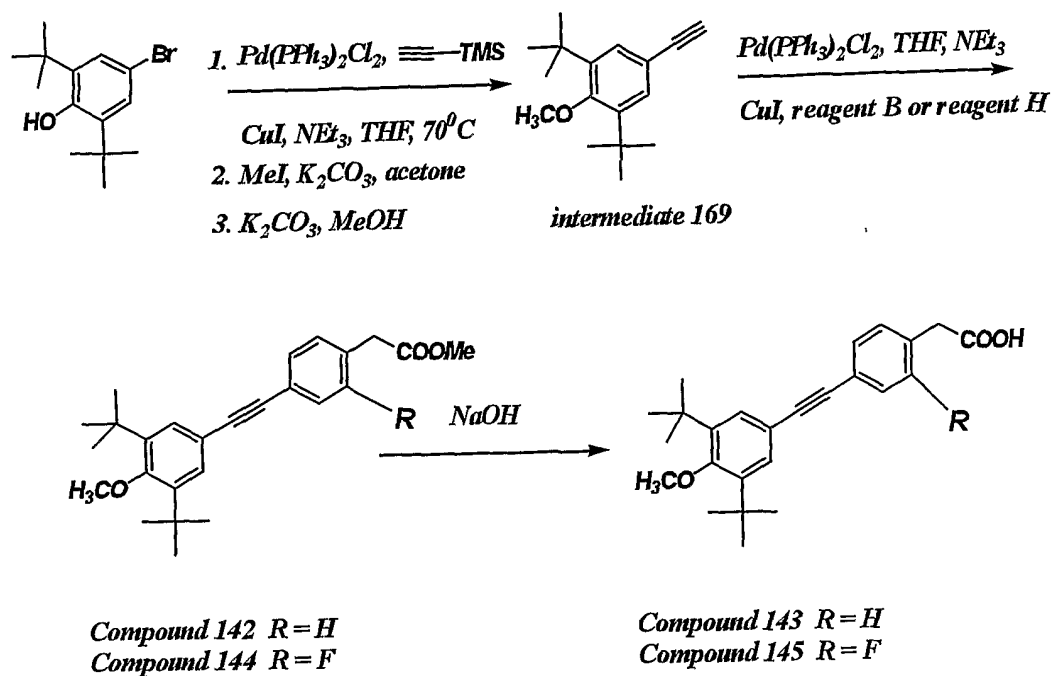
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## REACTION SCHEME 18

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## SPECIFIC EXAMPLES

2 4-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent E)

3 A stirred suspension of 4-hydroxy-phenyl acetic acid (0.152g,  
4 1mmol) in anhydrous toluene (5mL) was heated at 80°C and N,N-dimethyl  
5 formamide-di-*t*-butyl acetal (1mL, 4.17mmol) was added when the solution  
6 became homogenous. After 0.5h, the reaction mixture was cooled to  
7 ambient temperature and the volatiles were distilled off in *vacuo*. The  
8 residue was diluted with water and extracted with diethyl ether (x2). The  
9 combined organic extract was dried over anhydrous sodium sulfate, filtered  
10 and evaporated in *vacuo* to afford an oil which was subjected to flash  
11 column chromatography over silica gel (230-400 mesh) using 16% ethyl  
12 acetate in hexane as the eluent to afford the title compound as a solid (0.11g,  
13 56%).

14 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.44(s, 9H), 3.45(s, 2H), 6.55(s, 1H), 6.69(d,  
15 *J* = 8.8Hz, 2H), 7.06(d, *J* = 8.5Hz, 2H).

16 3-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent F)

A stirred suspension of 3-hydroxy-phenyl acetic acid (1.52g, 10mmol) in anhydrous toluene (20mL) was heated at 80°C and N,N-dimethyl formamide-di-*t*-butyl acetal (9.6mL, 40mmol) was added when the solution became homogenous. After 0.5h, the reaction mixture was cooled to ambient temperature and the volatiles were distilled off in *vacuo*. The residue was diluted with water and extracted with diethyl ether (x2). The combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an oil which was subjected to flash column chromatography over silica gel (230-400 mesh) using 16% ethyl acetate in hexane as the eluent to afford the title compound as a solid (1.17g, 56%).

1 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.47(s, 9H), 3.49(s, 2H), 6.30(s, 1H), 6.70-  
2 6.79 (m, 2H), 6.81(d, *J* = 7.6Hz, 1H), 7.16(t, *J* = 7.7Hz, 1H).

3 Methyl-2-fluoro-4-iodo benzoate (Reagent G)

4 A solution of 2-fluoro-4-iodo toluene (5g, 26.6mmol) in pyridine  
5 (2mL) and water (20mL) was treated with potassium permanganate (16.6g,  
6 105mmol) and heated at 150°C overnight. The reaction mixture was then  
7 cooled to room temperature and filtered and the filtrate was extracted with  
8 hexane. The aqueous phase was acidified with 10% hydrochloric acid and  
9 extracted with ethyl acetate. The organic phase was dried over anhydrous  
10 sodium sulfate, filtered and evaporated in *vacuo*. The residue was dissolved  
11 in 20mL of methanol, treated with concentrated sulfuric acid (1mL) and  
12 refluxed overnight. The volatiles were distilled off in *vacuo* and the residue  
13 was dissolved in diethyl ether, washed with brine, dried over anhydrous  
14 sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash column  
15 chromatography over silica gel (230-400 mesh) using 10% ethyl acetate in  
16 hexane as the eluent afforded the title compound as an oil (0.26g, 5%).

17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.60 (m, 4H), 3.93 (s, 3H).

18 Ethyl-2-fluoro-4-hydroxy benzoate (Reagent I)

19 A solution of 2-fluoro-4-hydroxy benzoic acid (**Intermediate 4**, 3g,  
20 19.2mmol) in ethanol (65mL) and benzene (90mL) was treated with  
21 concentrated sulfuric acid (1.5mL) and heated at reflux overnight using a  
22 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the  
23 residue was diluted with water and diethyl ether. The phases were separated  
24 and the organic phase was washed with saturated aqueous sodium  
25 bicarbonate (x1), water (x1) and brine (x1), dried over anhydrous  
26 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title  
27 compound as a solid (3.07g, 86%).

1  $^1\text{H-NMR}$  (300 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  1.34 (t,  $J = 7.1\text{Hz}$ , 3H), 4.32 (q,  $J =$   
2 7.1Hz, 2H), 6.66(dd,  $J = 2.6, 10.9\text{Hz}$ , 1H), 6.76 (dd,  $J = 2.3, 8.5\text{Hz}$ , 1H),  
3 7.83(d,  $J = 8.4\text{Hz}$ , 1H), 9.91 (s, 1H).

4 Ethyl-2-fluoro-4-trifluoromethylsulfonyloxy-benzoate (**Intermediate 6**)

5 A stirred, cooled (ice bath) solution of ethyl-2-fluoro-4-hydroxy-  
6 benzoate (**Intermediate 5**, 0.368g, 2mmol) and 2,6-di-*tert*-butyl-4-methyl-  
7 pyridine (0.81g, 8mmol) in 8mL of dichloromethane was treated with  
8 trifluoromethanesulfonic anhydride (0.1g, 4mmol). The reaction mixture  
9 was allowed to warm to ambient temperature and stirred overnight. The  
10 reaction mixture was subjected to flash column chromatography over silica  
11 gel (230-400 mesh) using 5-10% ethyl acetate in hexane as the eluent to  
12 afford the title compound (0.53g, 85%).

13  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.41 (t,  $J = 7.3\text{Hz}$ , 3H), 4.42 (q,  $J = 7.1\text{Hz}$ ,  
14 2H), 7.12-7.20(m, 2H), 8.08(t,  $J = 8.3\text{Hz}$ , 1H).

15 Ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate (**Intermediate 7**)

16 A solution of ethyl-2-fluoro-4- trifluoromethylsulfonyloxy-benzoate  
17 (**Intermediate 6**, 1.82g, 6mmol) in triethyl amine (12mL) and anhydrous  
18 tetrahydrofuran (30mL) was treated with copper(I)iodide (0.12g, 0.6mmol)  
19 and sparged with argon. Dichlorobis(triphenylphosphine)palladium(II)  
20 (0.43g, 0.6mmol) was added followed by (trimethylsilyl)acetylene (3.6mL,  
21 24mmol) and the resulting reaction mixture was heated at 70°C overnight. It  
22 was then cooled to ambient temperature, diluted with diethyl ether and  
23 filtered over a bed of celite. The filtrate was evaporated in *vacuo* to an oil  
24 which was subjected to flash column chromatography over silica gel (230-  
25 400 mesh) using 5% ethyl acetate in hexane as the eluent to afford the title  
26 compound as an orange oil (1.5g, quantitative).

27  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): $\delta$  0.011 (s, 9H), 1.13(t,  $J = 7.1\text{Hz}$ , 3H), 4.13 (q,

1  $J = 7.1\text{Hz}$ , 2H), 6.93-7.02(m, 2H), 7.07 (s, 1H), 7.61(t,  $J = 7.9\text{Hz}$ , 1H).

2 Ethyl-4-ethynyl-2-fluoro benzoate (Reagent D)

3 A solution of ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate  
4 (**Intermediate 7**, 1.5g, 6mmol) in ethanol (16mL) was treated with  
5 potassium carbonate (1.485g, 10.74mmol) and stirred overnight at room  
6 temperature. The reaction mixture was then diluted with water and extracted  
7 with diethyl ether (x2). The combined organic phase was dried over  
8 anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford an  
9 orange oil. Flash column chromatography over silica gel (230-400 mesh)  
10 using 5% ethyl acetate in hexane as the eluent afforded the title compound  
11 (1g, 86%).

12  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.39 (t,  $J = 7.1\text{Hz}$ , 3H), 3.26 (s, 1H), 4.39 (q,  
13  $J = 7.1\text{Hz}$ , 2H), 7.22-7.33 (m, 2H), 7.88(t,  $J = 7.7\text{Hz}$ , 1H).

14 Methyl-4-iodo-phenyl acetate (Reagent B)

15 A solution of 4-iodo phenyl acetic acid (5g, 19mmol) in methanol was  
16 treated with concentrated sulfuric acid (0.5mL) and refluxed overnight. The  
17 volatiles were distilled off in *vacuo* and the residue was dissolved in ethyl  
18 acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and  
19 evaporated in *vacuo* to an oil which was subjected to flash column  
20 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in  
21 hexane as the eluent to afford the title compound as a clear oil (5g, 95%).

22  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.63 (d, 2H,  $J = 8.5\text{Hz}$ ), 7.01 (d, 2H,  $J =$   
23 8.0Hz), 3.67 (s, 3H), 3.55 (s, 2H).

24 2-Fluoro-4-iodo-phenyl acetonitrile (Intermediate 2)

25 A solution of 2-fluoro-4-iodo-benzyl bromide (**Intermediate 1**,  
26 2.56g, 8.15mmol) in ethanol (55mL and water (10mL) was treated with  
27 sodium cyanide (2.15g, 43.86mmol) and refluxed for 0.5h. The volatiles

1 were distilled off in *vacuo* and the residue was diluted with water and  
2 extracted with diethyl ether (x2). The combined organic extract was washed  
3 with water (x1) and brine (x1), dried over anhydrous magnesium sulfate,  
4 filtered and evaporated in *vacuo* to afford the title compound as a pale  
5 yellow solid (2.05g, 96%).

6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.71(s, 3H), 7.16(t, *J* = 8.2Hz, 1H), 7.45(dd,  
7 *J* = 1.7, 9.1Hz, 1H), 7.51(dd, *J* = 1.5, 8.2Hz, 1H).

8 2-Fluoro-4-iodo-phenyl acetic acid (**Intermediate 3**)

9 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (**Intermediate 2**,  
10 2.05g, 7.83mmol) in ethanol (50mL) and water (15mL) was treated with  
11 potassium hydroxide (3.4g, 60.7mmol) and refluxed for 4h. The volatiles  
12 were distilled off in *vacuo* and the residue was diluted with water and poured  
13 into cold, dilute hydrochloric acid and the precipitated solid was filtered.  
14 The solid was dissolved in diethyl ether, and the organic solution was dried  
15 over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to  
16 afford the title compound a pale yellow solid (1.75g, 79%).

17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.64 (s, 2H), 6.98(t, *J* = 7.9Hz, 1H), 7.25-  
18 7.46 (m, 2H), 9.60-10.40(br s, 1H).

19 Ethyl-2-fluoro-4-iodo-phenyl acetate (**Reagent C**)

20 A solution of 2-fluoro-iodo-phenyl acetic acid (**Intermediate 3**,  
21 1.75g, 6.22mmol) in ethanol (50mL) and benzene (100mL) was treated with  
22 concentrated sulfuric acid (1.4mL) and heated at reflux overnight using a  
23 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the  
24 residue was diluted with water and diethyl ether. The phases were separated  
25 and the organic phase was washed with saturated aqueous sodium  
26 bicarbonate (x1), water (x1) and brine (x1), dried over anhydrous  
27 magnesium sulfate, filtered and evaporated in *vacuo* to afford an oil which

1 was subjected to flash column chromatography over silica gel (230-400  
2 mesh) using 5%-10% ethyl acetate in hexane as the eluent to afford the title  
3 compound as a pale yellow solid (1.4g, 73%).  
4 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25 (t, *J* = 7.1Hz, 3H), 3.60 (s, 2H), 4.16 (q,  
5 *J* = 7.1Hz, 2H), 6.99(t, *J* = 8.0Hz, 1H), 7.39-7.44(m, 2H).

6 Methyl-2-fluoro-4-iodo-phenyl acetate (Reagent H)

7 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (**Intermediate 2**,  
8 3g, 11.45mmol) in methanol (50mL) and benzene (50mL) was treated with  
9 *p*-toluene sulfonic acid (2.5g, 13.15mmol) and heated at reflux overnight  
10 using a Dean-Stark water trap. The volatiles were distilled off in *vacuo* and  
11 the residue was diluted with water and diethyl ether. The phases were  
12 separated and the organic phase was washed with saturated aqueous sodium  
13 bicarbonate (x1), water (x1) and brine (x1), dried over anhydrous  
14 magnesium sulfate, filtered and evaporated in *vacuo* to afford an oil which  
15 was subjected to flash column chromatography over silica gel (230-400  
16 mesh) using 6% ethyl acetate in hexane as the eluent to afford the title  
17 compound as a colorless oil (2.7g, 80%).  
18 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.62 (s, 2H), 3.70 (s, 3H), 6.99(t, *J* = 7.9Hz,  
19 1H), 7.39-7.45(m, 2H).

20 GENERAL PROCEDURE A: 7-Methoxy-1,1-dimethyl-1,2,3,4-  
21 tetrahydronaphthalene (Intermediate 8)

22 A stirred, cooled (-40°C) solution of titanium tetrachloride in  
23 anhydrous dichloromethane (1M, 20mL) under argon, was treated with a  
24 solution of dimethyl zinc (2M, 40mL) in toluene. After 0.5h, a solution of 7-  
25 methoxy-1-tetralone (1.76g, 10mmol) in anhydrous dichloromethane (5mL)  
26 was cannulated into the reaction mixture and the resulting solution was  
27 allowed to warm to ambient temperature and stirred overnight. The reaction

1 mixture was then cooled to  $-40^{\circ}\text{C}$  and cautiously quenched with methanol  
2 (11mL). It was diluted with dichloromethane and saturated aqueous  
3 ammonium chloride solution. The phases were separated and the aqueous  
4 phase was extracted with dichloromethane (x2mL). The combined organic  
5 phase was dried over anhydrous sodium sulfate, filtered and evaporated in  
6 *vacuo* to the title compound (1.75g, 92%) as an oil.

7  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): $\delta$  1.33(s, 6H), 1.67-1.71(m, 2H), 1.79-1.90(m,  
8 2H), 2.75(t,  $J = 6.2\text{Hz}$ , 2H), 3.83(s, 3H), 6.72(dd,  $J = 2.6, 8.3\text{Hz}$ , 1H),  
9 6.93(d,  $J = 2.6\text{Hz}$ , 1H), 7.02(d,  $J = 8.3\text{Hz}$ , 1H).

10 GENERAL PROCEDURE B: 6-Methoxy-4,4-dimethyl-1,2,3,4-  
11 tetrahydronaphthalene-1-one (**Intermediate 9**)

12 A solution of 7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene  
13 (**Intermediate 8**, 1.65g, 8.7 mmol) in 7.5mL of glacial acetic acid was  
14 cooled to  $0^{\circ}\text{C}$  and treated with a solution of chromium trioxide (2g, 20mmol)  
15 in 8mL of acetic acid and 7mL of water. The reaction mixture was then  
16 allowed to warm to ambient temperature and stirred overnight. It was  
17 diluted with water and extracted with diethyl ether (x2). The combined  
18 organic phase was washed with water (x1), saturated aqueous sodium  
19 bicarbonate (x1) and brine (x1), dried over anhydrous magnesium sulfate,  
20 filtered and evaporated in *vacuo* to afford the title compound (1.64g, 93%) as  
21 a yellow oil.

22  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): $\delta$  1.34(s, 6H), 1.96(t,  $J = 7.1\text{Hz}$ , 2H), 2.64(t,  $J$   
23  $= 7.1\text{Hz}$ , 2H), 3.83(s, 3H), 6.77(dd,  $J = 2.6, 8.7\text{Hz}$ , 1H), 6.83(d,  $J = 2.5\text{Hz}$ ,  
24 1H), 7.98(d,  $J = 8.7\text{Hz}$ , 1H).

25 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-one  
26 (**Intermediate 10**)

1 A stirred, cooled (-78°C) solution of 6-methoxy-4,4-dimethyl-1,2,3,4-  
2 tetrahydronaphthalene-1-one (**Intermediate 9**, 0.8, 3mmol) under argon was  
3 treated with a 1M solution of boron tribromide (10mL). The reaction  
4 mixture was allowed to warm to ambient temperature and stirred overnight.  
5 The reaction mixture was cooled to -78°C, quenched and diluted with  
6 saturated aqueous sodium bicarbonate solution and the aqueous phase was  
7 extracted with dichloromethane (x2). The combined organic phase was  
8 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an  
9 oil. Flash column chromatography over silica gel (230-400 mesh) using  
10 30% ethyl acetate in hexane as the eluent afforded the title compound (0.3g,  
11 52%) as a yellow viscous oil.

12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.33(s, 6H), 1.97(t, *J* = 6.8Hz, 2H), 2.71(t, *J*  
13 = 6.7Hz, 2H), 6.81(dd, *J* = 2.3, 8.5Hz, 1H), 6.94(d, *J* = 2.3Hz, 1H), 7.98(d,  
14 *J* = 8.7Hz, 1H), 9.35(s, 1H).

15 GENERAL PROCEDURE C: 4,4-Dimethyl-6-trifluoromethylsulfonyloxy-  
16 1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 11**)

17 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-  
18 tetrahydronaphthalene-1-one (**Intermediate 10**, 0.3g, 1.6mmol) in anhydrous  
19 dichloromethane (10mL) was treated with 4-(dimethylamino)pyridine  
20 (0.36g, 3.27mmol) followed by 2-[N,N'-bis(trifluoromethylsulfonyl)amino]-  
21 5-chloropyridine (0.79g, 2mmol). After stirring at ambient temperature for  
22 0.75h, the reaction mixture was diluted with dichloromethane and washed  
23 with water (x1). The organic phase was dried over anhydrous sodium  
24 sulfate, filtered and evaporated in *vacuo* to an oil. Flash column  
25 chromatography over silica gel (230-400 mesh) using 8-10% ethyl acetate in  
26 hexane as the eluent afforded the title compound (0.462g, 90%) as an off-  
27 white solid.

1 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.36(s, 6H), 2.01(t, *J* = 6.8Hz, 2H), 2.70(t, *J*  
2 = 6.7Hz, 2H), 7.15(dd, *J* = 2.5, 8.7Hz, 1H), 7.28(d, *J* = 2.4Hz, 1H), 8.06(d,  
3 *J* = 8.7Hz, 1H).

4 GENERAL PROCEDURE D: 4,4-Dimethyl-6-trimethylsilanyl-ethynyl-  
5 1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 12**)

6 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-  
7 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.46g, 1.43mmol) in triethyl  
8 amine (3mL) and anhydrous tetrahydrofuran (8mL) was treated with  
9 copper(I)iodide (0.1g, 0.53mmol) and sparged with argon for 5 minutes.  
10 Trimethylsilyl acetylene (0.85mL, 6mmol) was then added followed by  
11 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol). The  
12 resulting reaction mixture was heated at 70°C for 17h. It was then cooled to  
13 ambient temperature, diluted with diethyl ether and filtered over a bed of  
14 celite. The filtrate was evaporated *vacuo* to an oil which was subjected to  
15 flash column chromatography over silica gel (230-400 mesh) using 5% ethyl  
16 acetate in hexane as the eluent to afford the title compound (0.28g, 72%).  
17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.26(s, 9H), 1.36(s, 6H), 1.99(t, *J* = 6.8Hz,  
18 2H), 2.69(t, *J* = 6.7Hz, 2H), 7.35(dd, *J* = 1.7, 8.2Hz, 1H), 7.49 (unresolved  
19 d, 1H), 7.93(d, *J* = 8.1Hz, 1H).

20 GENERAL PROCEDURE E: 6-Ethynyl-4,4-dimethyl-1,2,3,4-  
21 tetrahydronaphthalene-1-one (**Intermediate 13**)

22 A solution of 4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-  
23 tetrahydronaphthalene-1-one (**Intermediate 12**, 0.28g, 1.03mmol) in  
24 methanol (10mL) was treated with potassium carbonate (0.74g, 5.35mmol)  
25 and stirred at ambient temperature for 4h. The volatiles were distilled off in  
26 *vacuo* and the residue was diluted with water and extracted with diethyl ether  
27 (x2). The combined organic extract was dried over anhydrous magnesium

1 sulfate, filtered and evaporated in *vacuo* to afford the title compound (0.19g,  
2 89%) as an oil that solidified on standing.

3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.33(s, 6H), 1.96(t, *J* = 6.8Hz, 2H), 2.67(t, *J*  
4 = 6.8Hz, 2H), 3.25(s, 1H), 7.33(dd, *J* = 1.5, 8.1Hz, 1H), 7.49 (d, *J* = 1.5Hz,  
5 1H), 7.13(d, *J* = 8.1Hz, 1H).

6 GENERAL PROCEDURE F: 4-(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-  
7 naphthalene-2-yl-ethynyl)-benzoic acid ethyl ester (Intermediate 14)

8 A solution of 6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-  
9 1-one (**Intermediate 13**, 0.23g, 1.1mmol) and ethyl-4-iodo benzoate  
10 (**Reagent A**, 0.36g, 1.3mmol) in triethyl amine (7mL) and anhydrous  
11 tetrahydrofuran (3mL) was treated with copper(I)iodide (0.114g, 0.6mmol)  
12 and sparged with argon for 5 minutes.

13 Dichlorobis(triphenylphosphine)palladium(II) (0.23g, 0.33mmol) was added  
14 and the reaction mixture was stirred overnight at room temperature. It was  
15 diluted with diethyl ether and filtered over a bed of celite. The filtrate was  
16 evaporated in *vacuo* to a brown oil that was subjected to flash column  
17 chromatography over silica gel (230-400 mesh) using 6-7% ethyl acetate in  
18 hexane as the eluent to afford the title compound (0.29g, 72%) as a pale  
19 brown solid.

20 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.3(t, *J* = 7.1Hz, 3H), 1.37(s, 6H), 1.80 (t, *J*  
21 = 6.8Hz, 2H), 2.69(t, *J* = 6.8Hz, 2H), 4.35(q, *J* = 7.1Hz, 2H), 7.40(dd, *J* =  
22 1.5, 8.2Hz, 1H), 7.51 (d, *J* = 1.6Hz, 1H), 7.57 (d, *J* = 8.3Hz, 2H), 7.96(d, *J*  
23 = 8.2Hz, 1H), 7.99(d, *J* = 8.5Hz, 2H).

24 GENERAL PROCEDURE G 4-(5-Cyclopropylamino-8,8-dimethyl-5,6,7,8-  
25 tetrahydro-naphthalene-2yl-ethynyl)-benzoic acid ethyl ester (Compound 1,  
26 **General Formula 4)**

1       A solution of 4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-  
2 2-ylethynyl)-benzoic acid ethyl ester (**Intermediate 14**, 0.14g, 0.4mmol) in  
3 3mL of dichloromethane and 2mL of acetonitrile was treated with  
4 cyclopropyl amine(1mL, 14.45mmol). After 5 minutes, acetic acid (1mL)  
5 was added followed by sodium cyanoborohydride (0.13g, 2mmol). The  
6 reaction was stirred overnight at ambient temperature. It was then diluted  
7 with water and saturated aqueous sodium carbonate solution and extracted  
8 with dichloromethane (x2). The combined organic extract was dried over  
9 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash  
10 column chromatography over silica gel (230-400 mesh) using 20% ethyl  
11 acetate in hexane as the eluent afforded the title compound (0.1g, 62%) as a  
12 pale yellow solid.

13 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.30-0.60(m, 4H), 1.28(s, 3H), 1.35 (s, 3H),  
14 1.30(t, *J* = 7.1Hz, 3H), 1.55-1.61(m, 1H), 1.83-2.05(m, 3H), 2.25 (quintet, *J*  
15 = 3.0 Hz, 1H), 3.80 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.27-7.36(m,  
16 2H), 7.52 (s, 1H), 7.55(d, *J* = 8.3Hz, 2H), 8.03(d, *J* = 8.5Hz, 2H).

17 GENERAL PROCEDURE H 4-[(5-Cyclopropyl-methyl-amino)-8,8-  
18 dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl  
19 ester (Compound 2, General Formula 4)

20       A solution of 4-(5-cyclopropylamino-8,8-dimethyl-5,6,7,8-tetrahydro-  
21 naphthalene-2-ylethynyl)-benzoic acid ethyl ester (**Compound 1**, 0.064g,  
22 0.16mmol) in acetone (2mL) was treated with potassium carbonate (0.6g,  
23 4.34mmol) and methyl iodide (1mL, 16mmol) and stirred overnight at  
24 ambient temperature. The volatiles were distilled off in *vacuo* and the  
25 residue was diluted with water and extracted with dichloromethane (x2).  
26 The combined organic extract was dried over anhydrous sodium sulfate,  
27 filtered and evaporated in *vacuo* to afford the title compound (0.065g, 99%).

1 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.28-0.49 (m, 4H), 1.21(s, 3H), 1.26 (s, 3H),  
2 1.33 (t, *J* = 7.1Hz, 3H), 1.58-1.73 (m, 2H), 1.83-1.89 (m, 2H), 2.02-2.08 (m,  
3 1H), 2.06 (s, 3H), 3.88 (t, *J* = 8.1Hz, 1H), 4.32(q, *J* = 7.1Hz, 2H), 7.20(d, *J*  
4 = 7.8Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 7.8Hz, 1H), 7.52(d, *J* = 8.4Hz, 2H),  
5 8.03(d, *J* = 8.3Hz, 2H).

6 GENERAL PROCEDURE I: 4-[(5-Cyclopropyl-methyl-amino)-8,8-  
7 dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid  
8 (**Compound 3, General Formula 4**) A solution of 4-[(5-cyclopropyl-  
9 methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-  
10 benzoic acid ethyl ester (**Compound 2**, 0.065g, 0.158mmol) in ethanol  
11 (1mL) and tetrahydrofuran (1mL) was treated with 1M aqueous sodium  
12 hydroxide solution (1mL) and heated at 80°C for 1h. The volatiles were  
13 distilled off in *vacuo* and the residue was diluted with saturated aqueous  
14 ammonium chloride solution and extracted with ethyl acetate (x2). The  
15 combined organic extract was dried over anhydrous sodium sulfate, filtered  
16 and evaporated in *vacuo* to afford a solid that was washed with  
17 dichloromethane and dried to afford the title compound (0.029g, 38%) as a  
18 white solid.

19 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 0.35-0.51(m, 4H), 1.26(s, 3H), 1.29 (s,  
20 3H), 1.60-1.82(m, 2H), 1.88-2.02(m, 2H), 2.02-2.15 (m, 1H), 2.10 (s, 3H),  
21 3.93 (t, *J* = 8.0Hz, 1H), 7.26(dd, *J* = 1.5, 8.2Hz, 1H), 7.51 (d, *J* = 1.5Hz,  
22 1H), 7.52(d, *J* = 8.2Hz, 1H), 7.62(d, *J* = 8.5Hz, 2H), 8.02(d, *J* = 8.2Hz, 2H).  
23 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-  
24 phenyl]-acetic acid methyl ester (**Compound 4, General Formula 8**)

25 Following general procedure F and using 6-ethynyl-4,4-dimethyl-  
26 1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 13**, 0.312g, 1.5mmol),  
27 4-iodo phenyl acetic acid methyl ester (**Reagent B**, 0.50g, 1.8mmol), triethyl

1 amine (7mL), anhydrous tetrahydrofuran (3mL), copper(I)iodide (0.04g,  
2 0.2mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.15g,  
3 0.213mmol) followed by flash column chromatography over silica gel (230-  
4 400 mesh) using 16-20% ethyl acetate in hexane as the eluent, the title  
5 compound was obtained as a pale yellow solid (0.42g, 76%).  
6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.42(s, 6H), 2.04(t, *J* = 6.7Hz, 2H), 2.74(t, *J*  
7 = 6.7Hz, 2H), 3.66(s, 2H), 3.71(s, 3H), 7.29 (d, *J* = 8.2Hz, 2H), 7.43(dd, *J* =  
8 1.5, 7.9Hz, 1H), 7.52 (d, *J* = 8.2Hz, 2H), 7.57 (d, *J* = 1.5Hz, 1H), 8.00(d, *J*  
9 = 8.2Hz, 1H).

10 GENERAL PROCEDURE J: 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-  
11 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (**Compound 5, General**  
12 **Formula 8**)

13 A solution of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-  
14 2-ylethynyl)-phenyl]-acetic acid methyl ester (**Compound 4**, 0.1g,  
15 0.28mmol) in a mixture of methanol (2mL), tetrahydrofuran (3.5mL) and  
16 water (1.5mL) was treated with lithium hydroxide monohydrate (0.11g,  
17 2.62mmol) and the resulting reaction mixture was stirred at ambient  
18 temperature for 3h. The volatiles were distilled off in *vacuo* and the residue  
19 was diluted with water and dilute hydrochloric acid and extracted with ethyl  
20 acetate (x3). The combined organic phase was dried over anhydrous sodium  
21 sulfate, filtered and evaporated in *vacuo* to afford the title compound as a  
22 pale yellow solid (0.088g, 92%).  
23 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.41(s, 6H), 2.02(t, *J* = 6.7Hz, 2H), 2.74(t, *J*  
24 = 6.8Hz, 2H), 3.68(s, 2H), 7.28 (d, *J* = 8.2Hz, 2H), 7.42(dd, *J* = 1.5, 8.2Hz,  
25 1H), 7.52 (d, *J* = 8.2Hz, 2H), 7.56 (d, *J* = 1.5Hz, 1H), 7.99(d, *J* = 8.2Hz,  
26 1H).

1 4-[(5-(Cyclopropyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-  
2 yl-ethynyl)-phenyl]-acetic acid methyl ester (Compound 6, General  
3 **Formula 4)**

4       Following general procedure G and using 4-[(8,8-dimethyl-5-oxo-  
5 5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester  
6 (**Compound 4**, 0.2g, 0.54mmol), dichloromethane (4mL), acetonitrile(2mL),  
7 cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and sodium  
8 cyanoborohydride (0.16g, 2.54mmol) followed by flash column  
9 chromatography over silica gel (230-400 mesh) using 30% ethyl acetate in  
10 hexane as the eluent the title compound was obtained as a pale yellow oil  
11 (0.22g, 99%).

12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.38-0.60 (m, 4H), 1.26(s, 3H), 1.33(s, 3H),  
13 1.50-1.59(m, 1H), 1.79-2.10 (m, 3H), 2.25(m, 1H), 3.63(s, 2H), 3.69(s, 3H),  
14 3.79(t, *J* = 4.8Hz, 1H), 7.20-7.32 (m, 4H), 7.47(s, 1H), 7.58(d, *J* = 8.2Hz,  
15 2H).

16 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
17 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester (Compound 7,  
18 **General Formula 4)**

19       Following general procedure H and using 4-[(5-(cyclopropyl-amino)-  
20 8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-phenyl]-acetic  
21 acid methyl ester (**Compound 6**, 0.15g, 0.37mmol), acetone (5mL),  
22 potassium carbonate (1.1g, 7.95mmol) and methyl iodide (1mL, 16mmol),  
23 the following work-up was used. The volatiles were distilled off in *vacuo*  
24 and the residue was diluted with water and extracted with dichloromethane  
25 (x2). The combined organic extract was dried over anhydrous sodium  
26 sulfate, filtered and evaporated in *vacuo* to afford the title compound  
27 (0.148g, 97%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.38-0.58(m, 4H), 1.27(s, 3H), 1.31 (s, 3H), 1.68-1.81(m, 2H), 1.85-1.98(m, 2H), 2.08-2.15 (m, 1H), 2.12 (s, 3H), 3.62(s, 2H), 3.69(s, 3H), 3.94 (t, *J* = 7.9Hz, 1H), 7.24(d, *J* = 8.2Hz, 1H), 7.24 (d, *J* = 8.2Hz, 2H), 7.44-7.51(m, 4H).

4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 8, General Formula 4)

Following general procedure J and using 4-[(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-phenyl]-acetic acid methyl ester (**Compound 7**, 0.148g, 0.357mmol), methanol (2mL), tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate (0.25g, 5.95mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 30-75% ethyl acetate in hexane as the eluent, the title compound was obtained as a white solid (0.08g, 56%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s, 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H), 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.24(dd, *J* = 1.5, 8.2Hz, 1H), 7.26 (d, *J* = 8.2Hz, 2H), 7.43 (d, *J* = 8.2Hz, 1H), 7.47(s, 1H), 7.47(d, *J* = 8.2Hz, 2H), 10.37(br s, 1H).

2-Fluoro-4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl]benzoic acid ethyl ester (Compound 9, General Formula 8)

A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 11**, 0.3g, 0.9mmol), copper(I)iodide (0.057g, 0.3mmol) and ethyl-2-fluoro-4-ethynyl-benzoate (**Reagent D**, 0.44g, 2.27mmol) in triethyl amine (2mL) and tetrahydrofuran (3mL) was sparged with argon for 5 minutes and treated with dichlorobis(triphenylphosphine)palladium(II) (0.135g, 0.192mmol) and

1 stirred at room temperature overnight and then refluxed for 2h. It was then  
2 cooled to ambient temperature, diluted with diethyl ether and filtered over a  
3 bed of celite. The filtrate was evaporated in *vacuo* to an oil which was  
4 subjected to flash column chromatography over silica gel (230-400 mesh)  
5 using 10-15% ethyl acetate in hexane as the eluent to afford the title  
6 compound as a yellow solid (0.22g, 67%).

7 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.38 (t, *J* = 7.0Hz, 3H), 1.39(s, 6H), 2.01(t, *J*  
8 = 6.7Hz, 2H), 2.71(t, *J* = 6.7Hz, 2H), 4.37(q, *J* = 7Hz, 2H), 7.28(dd, *J* = 0.9,  
9 10Hz, 1H), 7.34(dd, *J* = 0.9, 8.2Hz, 1H), 7.41 (dd, *J* = 1.5, 8.2Hz, 1H),  
10 7.57(d, *J* = 0.9Hz), 7.90(t, *J* = 7.9Hz, 1H), 7.93 (d, *J* = 7.9Hz, 1H).

11 2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2yl-ethynyl)-  
12 benzoic acid (Compound 10, General Formula 8)

13 A solution of 2-fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-  
14 naphthalen-2-ylethynyl)benzoic acid ethyl ester (**Compound 9**, 0.1g,  
15 0.274mmol) in ethanol(4mL), methanol (2mL) and tetrahydrofuran (2mL)  
16 was treated with 1M aqueous sodium hydroxide solution and heated at 70°C  
17 for 1h. The volatiles were distilled off in *vacuo* and the residue was diluted  
18 with water and dilute hydrochloric acid and extracted with ethyl acetate (x2).  
19 The combined organic extract was dried over anhydrous sodium sulfate,  
20 filtered and evaporated in *vacuo* to afford a solid that was recrystallized from  
21 hot aqueous acetonitrile to afford the title compound (0.025g, 27%).

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.43(s, 6H), 2.05(t, *J* = 6.9Hz, 2H), 2.76(t, *J*  
23 = 6.9Hz, 2H), 7.26-7.47(m, 3H), 7.60(d, *J* = 1.1Hz, 1H), 7.99-8.05(m, 2H).

24 4-[5-(Cyclopropyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-  
25 yl-ethynyl]-2-fluoro-benzoic acid ethyl ester (Compound 11, General  
26 Formula 4)

27 Following general procedure G and using 2-fluoro-4-(8,8-dimethyl-5-  
28 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-benzoic acid ethyl ester

1 (Compound 9, 0.132g, 0.3mmol), dichloromethane (4mL),  
2 acetonitrile(2mL), cyclopropyl amine(1mL, 14.45mmol), acetic acid  
3 (1mL)and sodium cyanoborohydride (0.18g, 2.86mmol) followed by flash  
4 column chromatography over silica gel (230-400 mesh) using 16-20% ethyl  
5 acetate in hexane as the eluent, the title compound was obtained as a pale  
6 yellow oil (0.1g, 82%).  
7 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.36-0.54 (m, 4H), 1.27(s, 3H), 1.33(s, 3H),  
8 1.40(t, *J* = 7.0Hz, 3H), 1.54-1.61(m, 2H), 1.82-2.05 (m, 2H), 2.26(m, 1H),  
9 3.79 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.26-7.50(m, 4H), 7.87(s,  
10 1H), 7.92 (t, *J* = 7.9Hz, 1H).  
11 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
12 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid ethyl ester (Compound 12,  
13 **General Formula 4)**  
14 Following general procedure H and using 4-[5-(cyclopropyl-methyl-  
15 amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-  
16 benzoic acid ethyl ester (Compound 11, 0.1g, 0.246mmol), acetone (4mL),  
17 potassium carbonate (0.917g, 6.63mmol) and methyl iodide (0.8mL,  
18 11mmol), the following work-up was used. The volatiles were distilled off  
19 in *vacuo* and the residue was diluted with water and extracted with  
20 dichloromethane (x2). The combined organic extract was dried over  
21 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash  
22 column chromatography over silica gel (230-400 mesh) using 8-10% ethyl  
23 acetate in hexane as the eluent afforded the title compound as a pale yellow  
24 oil (0.102g, 98%).  
25 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.39-0.62 (m, 4H), 1.29(s, 3H), 1.34(s, 3H),  
26 1.42(t, *J* = 6.9Hz, 3H), 1.65-1.82(m, 2H), 1.85-2.02 (m, 2H), 2.02-2.10(m,

1H), 2.15(s, 3H), 3.97(t,  $J = 7.7\text{Hz}$ , 1H), 4.42(q,  $J = 7.0\text{Hz}$ , 2H), 7.28-7.36  
(m, 3H), 7.59(s, 1H), 7.55(d,  $J = 7.9\text{Hz}$ , 2H), 7.92 (t,  $J = 7.5\text{Hz}$ , 1H).  
4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-  
naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid (Compound 13, General  
Formula 4)

Following general procedure I and using 4-[(5-cyclopropyl-methyl-  
amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-  
benzoic acid ethyl ester (**Compound 12**, 0.102g, 0.23mmol), ethanol (4mL)  
and 1M aqueous sodium hydroxide solution (2mL) followed by flash  
column chromatography over silica gel (230-400 mesh) 30% ethyl acetate in  
hexane as the eluent, the title compound was obtained as an off-white  
solid(0.015g, 16%).

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.54-0.65 (m, 4H), 1.29 (s, 3H), 1.32 (s, 3H),  
1.68-1.83 (m, 2H), 1.97-2.05 (m, 2H), 2.18-2.25 (m, 1H), 2.25 (s, 3H), 4.13  
(t,  $J = 6.7\text{Hz}$ , 1H), 7.26-7.30 (m, 2H), 7.34 (dd,  $J = 1.5, 7.9\text{Hz}$ , 1H), 7.48 (d,  
 $J = 1.8\text{Hz}$ , 1H), 7.60 (d,  $J = 8.5\text{Hz}$ , 1H), 7.95 (t,  $J = 7.9\text{Hz}$ , 1H).  
[2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-  
ethynyl)-phenyl]acetic acid ethyl ester (Compound 14, General Formula  
8)

Following general procedure F and using 6-ethynyl-4,4-dimethyl-  
1,2,3,4-tetrahydro-naphthalene-1-one (**Intermediate 13**, 0.298g, 1.43mmol),  
2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**, 0.44g,  
1.43mmol), triethyl amine (**Intermediate 13**, 3mL), anhydrous  
tetrahydrofuran (7mL), copper(I)iodide (0.04g, 0.2mmol) and  
dichlorobis(triphenylphosphine)palladium(II) (0.15g, 0.213mmol) followed  
by flash column chromatography over silica gel (230-400 mesh) using 14-

1 16% ethyl acetate in hexane as the eluent, the title compound was obtained  
2 as an oil (0.43g, 77%).

3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.26(t, *J* = 7.2Hz, 3H), 1.41(s, 6H), 2.04(t, *J*  
4 = 6.7Hz, 2H), 2.74(t, *J* = 6.7Hz, 2H), 3.68(s, 2H), 4.18(q, *J* = 7.1Hz, 2H),  
5 7.23-7.57(m, 4H), 7.59 (d, *J* = 1.5Hz, 1H), 7.99(d, *J* = 7.9Hz, 1H).

6 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-  
7 ethynyl)phenyl]-acetic acid (Compound 15, General Formula 8)

8 Following general procedure J and using [2-fluoro-4-(8,8-dimethyl-5-  
9 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)phenyl]acetic acid methyl  
10 ester (**Compound 14**, 0.18g, 0.48mmol), methanol (4mL), tetrahydrofuran  
11 (8mL), water (2mL) and lithium hydroxide monohydrate (0.2g, 4.76mmol)  
12 followed by flash column chromatography over silica gel (230-400 mesh)  
13 using 50- 100% ethyl acetate in hexane as the eluent, the title compound was  
14 obtained as a dirty white solid (0.068g, 41%).

15 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.41(s, 6H), 2.03(t, *J* = 6.7Hz, 2H), 2.74(t, *J*  
16 = 6.8Hz, 2H), 3.73(s, 2H), 7.24-7.32(m, 3H), 7.42(dd, *J* = 1.5, 7.9Hz, 1H),  
17 7.56 (s, 1H), 7.99(d, *J* = 7.9Hz, 1H), 9.40-10.00 (br s, 1H).

18 [4-(5-(Cyclopropyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-  
19 yl-ethynyl)-2-fluoro-phenyl] acetic acid ethyl ester (Compound 16,  
20 **General Formula 4)**

21 Following general procedure G and using [2-fluoro-4-(8,8-dimethyl-  
22 5-oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl) phenyl]acetic acid ethyl  
23 ester (**Compound 14**, 0.258g, 0.68mmol), dichloromethane (4mL),  
24 acetonitrile(2mL), cyclopropyl amine(1mL, 14.45mmol), acetic acid  
25 (1mL)and sodium cyanoborohydride (0.266g, 4.23mmol) followed by flash  
26 column chromatography over silica gel (230-400 mesh) using 16-20-25%

1 ethyl acetate in hexane as the eluent, the title compound was obtained as a  
2 pale yellow oil (0.21g, 73%).  
3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.35-0.54 (m, 4H), 1.25(t, *J* = 7.1Hz, 3H),  
4 1.26(s, 3H), 1.32(s, 3H), 1.53-1.64(m, 1H), 1.82-2.05 (m, 3H), 2.21-2.28(m,  
5 1H), 3.65(s, 2H), 3.78(t, *J* = 5.0Hz, 1H), 4.17(q, *J* = 7.1Hz, 2H), 7.19-7.41  
6 (m, 5H), 7.47(d, *J* = 1.5Hz, 1H).

7 [4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-  
8 naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid ethyl ester  
9 **(Compound 17, General Formula 8)**

10 Following general procedure H and using [4-((5-cyclopropyl-amino)-  
11 8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-2-fluoro-  
12 phenyl]acetic acid ethyl ester (**Compound 16**, 0.21g, 0.5mmol), acetone  
13 (5mL), potassium carbonate (1.13g, 8.17mmol) and methyl iodide (0.5mL,  
14 8mmol), the following work-up was used. The volatiles were distilled off in  
15 *vacuo* and the residue was diluted with water and extracted with  
16 dichloromethane (x2). The combined organic extract was dried over  
17 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an oil.  
18 Flash column chromatography over silica gel (230-400 mesh) using 8% ethyl  
19 acetate in hexane as the eluent afforded the title compound (0.15g, 69%).  
20 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.39-0.53(m, 4H), 1.27(s, 3H), 1.31 (s, 3H),  
21 1.66-1.81(m, 2H), 1.89-2.05(m, 2H), 2.08-2.13 (m, 1H), 2.13 (s, 3H), 3.62(s,  
22 2H), 3.94 (t, *J* = 8.0Hz, 1H), 4.16(q, *J* = 7.1Hz, 2H), 7.20-7.29(m, 4H),  
23 7.44(d, *J* = 1.5Hz, 1H), 7.51 (d, *J* = 8.2Hz, 1H).

24 [4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-  
25 naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid (**Compound 18,**  
26 **General Formula 4)**

27 Following general procedure J and using [4-(5-(cyclopropyl-methyl-  
28 amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-2-fluoro-

1 phenyl]-acetic acid ethyl ester (**Compound 17**, 0.025g, 0.059mmol),  
2 methanol (1mL), tetrahydrofuran (1mL), water (0.5mL) and lithium  
3 hydroxide monohydrate (0.060g, 1.43mmol), the title compound was  
4 obtained as a white solid (0.023g, 95%).  
5 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s,  
6 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H),  
7 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.19-7.28(m, 4H), 7.45 (d, *J*  
8 = 1.5Hz, 1H), 7.49(d, *J* = 8.2Hz, 1H), 8.80-9.20(br s, 1H).

9 GENERAL PROCEDURE K: 8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalene-  
10 1-one-2-carboxylic acid-4-(tert-butoxycarbonylmethyl)phenyl ester  
11 **Compound 19, General Formula 8)**

12 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-  
13 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.14g, 0.434mmol), *t*-butyl-  
14 4-hydroxy-phenyl acetate (**Reagent E**, 0.14g, 0.673mmol), palladium acetate  
15 (0.054g, 0.24mmol) and 1,3-bis(diphenylphosphino)propane (0.082g,  
16 0.2mmol) in a mixture of dimethylsulfoxide (1mL), 1,2-dichloroethane  
17 (1.5mL) and triethyl amine (1mL) was heated at 70°C under an atmosphere  
18 of carbon monoxide overnight. The volatiles were distilled off in *vacuo* and  
19 the residue was diluted with water and extracted with diethyl ether (x3). The  
20 combined organic extract was dried over anhydrous magnesium sulfate,  
21 filtered and evaporated in *vacuo* to an oil which was subjected to flash  
22 column chromatography over silica gel (230-400 mesh) using 15% ethyl  
23 acetate in hexane as the eluent to afford the title compound (0.11g, 53%).  
24 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.44(s, 3H), 1.44(s, 9H), 1.46 (s, 3H), 2.07(t,  
25 *J* = 6.9Hz, 2H), 2.76(t, *J* = 6.8Hz, 2H), 3.55(s, 2H), 7.17 (d, *J* = 8.5Hz, 2H),  
26 7.35(d, *J* = 8.5Hz, 2H), 8.05-8.13(m, 2H), 8.25 (d, *J* = 1.5Hz, 1H).

1 8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-  
2 (carboxymethyl)phenyl ester (Compound 20, General Formula 8)

3 A solution of 8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-  
4 carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (**Compound 19**,  
5 0.11g, 0.229mmol) in dichloromethane (2mL) was treated with  
6 trifluoroacetic acid (0.85mL and stirred at ambient temperature for 2.5h.  
7 The volatiles were distilled off in *vacuo* and the residue was diluted with  
8 water and extracted with ethyl acetate (x3). The combined organic phase  
9 was dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to  
10 afford a solid which was subjected to flash column chromatography over  
11 silica gel (230-400 mesh) using ethyl acetate as the eluent to afford the title  
12 compound (0.024g, 25%).

13 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.46 (s, 6H), 2.08(t, *J* = 6.7Hz, 2H), 2.80(t, *J*  
14 = 6.7Hz, 2H), 3.70(s, 2H), 7.20(d, *J* = 8.5Hz, 2H), 7.37(d, *J* = 8.5Hz, 2H),  
15 8.08(dd, *J* = 1.4, 8.2Hz, 1H), 8.14 (d, *J* = 8.2Hz, 1H), 8.24 (d, *J* = 1.2Hz,  
16 1H). 5-Methoxy-3,3-dimethyl-indane (Intermediate 15)

17 Following general procedure A and using titanium tetrachloride  
18 (5.5mL, 50mmol), anhydrous dichloromethane (80mL), 2M solution  
19 dimethyl zinc (50mL) in toluene and a solution of 6-methoxy-indane-1-one  
20 (4.05g, 25mmol) in dichloromethane (10mL) the title compound was  
21 obtained as an oil (3.13g, 71%).

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.37 (s, 6H), 2.04(t, *J* = 7.2Hz, 2H), 2.94(t, *J*  
23 = 7.2Hz, 2H), 3.89(s, 3H), 6.82(d, *J* = 2.1Hz, 1H), 7.28(dd, *J* = 2.1, 7.0Hz,  
24 1H), 7.35 (d, *J* = 7.0Hz, 1H).

25 5-Methoxy-3,3-dimethyl-indane-1-one (Intermediate 16)

26 Following general procedure B and using 5-methoxy-3,3-dimethyl  
27 indane (**Intermediate 15**, 3.13g, 17.78mmol) in 20mL of glacial acetic acid

1 and a solution of chromium trioxide (3.91g, 39.1mmol) in 20mL of acetic  
2 acid and 20mL of water the title compound was obtained as a viscous yellow  
3 oil (3.3g, 97%).

4 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.37 (s, 6H), 2.54 (s, 2H), 3.87(s, 3H), 6.86-  
5 6.87 (m, 2H), 7.60 (d, *J* = 7.0Hz, 1H).

6 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-1-one  
7 (**Intermediate 17**)

8 A solution of 5-methoxy-3,3-dimethyl-indane-1-one (**Intermediate**  
9 **16**, 3.3g, 17.4mmol) in benzene (50mL) was treated with concentrated  
10 sulfuric acid (10mL) and heated to 60°C. Sodium azide (1.95g, 30mmol)  
11 was added in small portions and after the addition was complete, the reaction  
12 mixture was heated further for 4h. It was then cooled, diluted with water and  
13 extracted with chloroform (x3). The combined organic phase was dried over  
14 anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford the  
15 title compound as a brown solid (3.5g, quantitative by weight).

16 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.31 (s, 6H), 3.28 (s, 2H), 3.83(s, 3H), 6.78  
17 (d, *J* = 2.6Hz, 1H), 6.82(dd, *J* = 2.6Hz, 8.5Hz, 1H), 7.59 (s, 1H), 8.02 (d, *J* =  
18 8.2Hz, 1H).

19 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 18**)

20 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-  
21 isoquinoline-1-one (**Intermediate 17**, 3.5g, 17mmol) in 100mL of  
22 anhydrous tetrahydrofuran was treated with lithium aluminum hydride (1.3g,  
23 34.25mmol) in small portions and the resulting suspension was refluxed for  
24 3 hours under argon. The reaction mixture was then cooled in an ice bath  
25 and cautiously quenched with saturated aqueous sodium sulfate solution and  
26 the resulting slurry was filtered and the filter-cake washed well with ethyl  
27 acetate. The filtrate and washings were evaporated in *vacuo* to a brown oil

1 which was dissolved in chloroform, the solution was dried over anhydrous  
2 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title  
3 compound (3.2g, ~100%).  
4 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.27 (s, 6H), 2.22 (s, 1H), 2.84 (s, 2H), 3.79  
5 (s, 3H), 3.95 (s, 2H), 6.68(dd, *J* = 2.4Hz, 8.3Hz, 1H), 6.86(d, *J* = 2.4Hz, 1H),  
6 6.91 (d, *J* = 8.3Hz, 1H).

7 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde  
8 **(Intermediate 19)**

9 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline  
10 **(Intermediate 18, 3.2g, 16.7mmol)** in anhydrous dichloromethane (40mL)  
11 was treated with formic acid (1mL, 26.5mmol) followed 1-(3-  
12 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.9g, 20.34mmol)  
13 and the resulting solution was stirred at ambient temperature overnight. It  
14 was then diluted with chloroform and washed with water (x1) and brine (x1),  
15 dried over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to  
16 afford the title compound as pale brown viscous oil (3.26g, 90%).  
17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.28 (s, 6H), 3.32 (s, 0.7H), 3.54 (s, 0.3H),  
18 3.79(s, 3H), 4.54 (s, 0.3H), 4.66(s, 0.7H), 6.71(dd, *J* = 2.6Hz, 8.2Hz, 1H),  
19 6.85-6.97(m, 1H), 7.02-7.27(m, 1H), 8.15(s, 0.7H), 8.34(s, 0.3H), 8.40-8.80  
20 (br s, 1H).

21 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde  
22 **(Intermediate 20)** A stirred, cooled (-78°C) solution of 6-methoxy-4,4-  
23 dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde **(Intermediate 19,**  
24 **3.26g, 15mmol)** in anhydrous dichloromethane (15mL) was treated with 1M  
25 solution of boron tribromide in dichloromethane (50mL) stirred at ambient  
26 temperature for 3h. It was then cooled again to 78°C and quenched carefully  
27 with saturated aqueous sodium carbonate solution, diluted with water and the  
28 aqueous phase was extracted with ethyl acetate (x2). The combined organic

1 extract was dried over anhydrous sodium sulfate, filtered and evaporated in  
2 *vacuo* to afford the title compound as a solid foam (3g, 99%).

3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.23 (s, 6H), 3.31 (s, 0.7H), 3.54 (s, 0.3H),  
4 4.51 (s, 0.3H), 4.64 (s, 0.7H), 6.70-6.75(m, 1H), 6.84-6.90(m, 2H), 7.50-  
5 7.80(br s, 1H), 8.12(s, 0.7H), 8.32(s, 0.3H).

6 2-Cyclopropyl-6-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline  
7 **(Intermediate 21)**

8 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-  
9 tetrahydro-isoquinoline-2-carbaldehyde (**Intermediate 20**, 2.3g, 11.21mmol)  
10 in anhydrous tetrahydrofuran (40mL) under argon was treated with titanium  
11 tetra-*iso*-propoxide (8.28mL, 28mmol) followed by 3M solution of ethyl  
12 magnesium bromide in diethyl ether (18.7mL) and the reaction mixture was  
13 then heated at 55°C overnight. It was then cooled in an ice-bath, quenched  
14 with saturated aqueous ammonium chloride solution and extracted with  
15 diethyl ether (x2). The combined organic phase was dried over anhydrous  
16 sodium sulfate, filtered and evaporated in *vacuo* to afford a yellow oily solid.  
17 Flash column chromatography over silica gel (230-400 mesh) using 10-20%  
18 ethyl acetate in hexane as the eluent afforded the title compound as a pale  
19 yellow solid (1.55g, 63%).

20 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 0.016-0.16(m, 4H), 0.847 (s, 6H), 1.37  
21 (m, 1H), 2.20(s, 2H), 3.25 (s, 2H), 6.22(dd, *J* = 2.4, 8.2Hz, 1H), 6.41(d, *J* =  
22 2.6Hz, 1H), 6.47(d, *J* = 8.2Hz, 1H), 7.62(s, 1H).

23 2-Cyclopropyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-  
24 tetrahydro-isoquinoline (**Intermediate 22**)

25 Following general procedure C and using 2-cyclopropyl-6-hydroxy-  
26 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 21**, 1.5g,  
27 6.9mmol) in anhydrous dichloromethane (30mL), triethyl amine (1.5mL,  
28 10.39mmol) and [N,N'-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine

(2.75g, 7mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 8% ethyl acetate in hexane as the eluent the title compound was obtained (2.23g, 92%) as oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.42-0.54(m, 4H), 1.25(s, 6H), 1.76(m, 1H), 2.62(s, 2H), 3.74(s, 2H), 6.98(dd, *J* = 2.3, 8.4Hz, 1H), 7.16(d, *J* = 8.2Hz, 1H), 7.14(d, *J* = 2.3Hz, 1H).

Ethyl-2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (**Intermediate 23**)

Following general procedure K and using 2-cyclopropyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 22**, 1.6g, 4.6mmol), palladium acetate (0.127g, 0.56mmol), 1,3-bis(diphenylphosphino)propane (0.160g, 0.39mmol), dimethylsulfoxide (2mL), 1,2-dichloroethane (5mL), triethyl amine (2mL), ethanol (5mL) and an atmosphere of carbon monoxide followed by flash column chromatography over silica gel (230-400 mesh) using 10% ethyl acetate in hexane as the eluent the title compound was obtained as an oil (1g, 79%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.44-0.54(m, 4H), 1.27(s, 6H), 1.38 (t, *J* = 7Hz, 3H), 1.73(m, 1H), 2.62(s, 2H), 3.76(s, 2H), 4.35 (q, *J* = 7.1Hz, 2H), 7.04(d, *J* = 7.9Hz, 1H), 7.74 (dd, *J* = 1.7, 7.9Hz, 1H), 7.97(d, *J* = 1.8Hz, 1H).

2-Cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (**Intermediate 24**)

A stirred cooled (-78°C) solution of ethyl-2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro isoquinoline-6-carboxylate (**Intermediate 23**, 1g, 3.66mmol) in anhydrous dichloromethane (20mL) under argon was treated with a 1M solution of di-*iso*-butyl aluminum hydride in dichloromethane (10mL) and the reaction mixture was warmed to -20°C over 1h. It was then quenched with saturated aqueous ammonium chloride solution and diluted

1 with dichloromethane and filtered over a bed of celite. The phases were  
2 separated and the aqueous phase was extracted with dichloromethane (x1).  
3 The combined organic extract was dried over anhydrous sodium sulfate,  
4 filtered and evaporated in *vacuo* to afford the title compound as a viscous oil  
5 (0.74g, 87%).

6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.45-0.53(m, 4H), 1.25(s, 6H), 1.72-1.82(m,  
7 2H), 2.61(s, 2H), 3.73(s, 2H), 4.61 (d, *J* = 5Hz, 2H), 6.98(d, *J* = 7.9Hz, 1H),  
8 7.07 (dd, *J* = 1.5, 7.6Hz, 1H), 7.27(s, 1H).

9 2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde  
10 **(Intermediate 25)**

11 A solution of 2-cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-  
12 tetrahydroisoquinoline (**Intermediate 24**, 0.74g, 3.2mmol) in  
13 dichloromethane (10mL) and acetonitrile (2.5mL) was treated sequentially  
14 with 4A<sup>0</sup> molecular sieves powder (1.06g), tetra-*n*-propyl ammonium  
15 perruthenate (0.050g, 0.14mmol) and N-methyl morpholine N-oxide (1.1g,  
16 9.8mmol). After stirring at ambient temperature for 0.5h, it was diluted with  
17 5mL of hexane and subjected to flash column chromatography over silica gel  
18 (230-400 mesh) using 10% ethyl acetate in hexane as the eluent to afford  
19 the title compound as an oil (0.27g, 37%).

20 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 0.44-0.56(m, 4H), 1.30(s, 6H), 1.79(m, 1H),  
21 2.66(s, 2H), 3.82(s, 2H), 7.17(d, *J* = 7.9Hz, 1H), 7.60 (dd, *J* = 1.6, 7.9Hz,  
22 1H), 7.82(d, *J* = 1.8Hz, 1H), 9.95 (s, 1H).

23 6-(2,2-Dibromo-vinyl)-2-cyclopropyl-4,4-dimethyl-1,2,3,4-  
24 tetrahydroisoquinoline (**Intermediate 26**)

25 A stirred, cooled (ice-bath) solution of triphenyl phosphine (0.53g,  
26 2mmol) in anhydrous dichloromethane was treated with carbon tetrabromide  
27 (0.35g, 1mmol) under argon. After 0.5h, a solution of 2-cyclopropyl-4,4-  
28 dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde (**Intermediate**

1 **25**, 0.13g, 0.57mmol) in dichloromethane (2mL) was cannulated into the  
2 reaction mixture. After 1.5h between 0°C and 10°C, the reaction mixture  
3 was subjected to flash column chromatography over silica gel (230-400  
4 mesh) using 3-5% ethyl acetate in hexane as the eluent to afford the title  
5 compound as a viscous, pale yellow oil (0.18g, 82%).

6 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.49-0.57(m, 4H), 1.31(s, 6H), 1.80(m, 1H),  
7 2.67(s, 2H), 3.77(s, 2H), 7.04(d, *J* = 7.9Hz, 1H), 7.29 (dd, *J* = 1.7, 7.9Hz,  
8 1H), 7.49 (s, 1H), 7.50(d, *J* = 1.7Hz, 1H).

9 2-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

10 (**Intermediate 27**)

11 A stirred, cooled (-78°C) solution of 6-(2,2-dibromo-vinyl)-2-  
12 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde  
13 (**Intermediate 26**, 0.18g, 0.47mmol) in tetrahydrofuran (2mL) was treated  
14 with 1.6M solution of *n*-butyl lithium (0.6mL, 0.96mmol) under argon. The  
15 reaction mixture was allowed to warm to -20°C over 1.5h, quenched with  
16 saturated aqueous ammonium chloride solution and extracted with diethyl  
17 ether (x2). The combined organic phase was dried over anhydrous  
18 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title  
19 compound as an oil (0.1g, 94%).

20 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.47-0.55(m, 4H), 1.28(s, 6H), 1.77(m, 1H),  
21 2.63(s, 2H), 3.05(s, 1H), 3.67(s, 2H), 6.98(d, *J* = 7.6Hz, 1H), 7.26 (dd, *J* =  
22 1.5, 7.9Hz, 1H), 7.46(d, *J* = 1.5Hz, 1H).

23 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-

24 2-fluoro-phenyl]-acetic acid ethyl ester (**Compound 21, General Formula**

25 **3**)

26 Following general procedure F and using 2-cyclopropyl-6-ethynyl-  
27 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,

1 0.571mmol), 2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**,  
2 0.16g, 0.52mmol), triethyl amine (0.8mL), anhydrous tetrahydrofuran (2mL),  
3 copper(I)iodide (0.051g, 0.27mmol) and  
4 dichlorobis(triphenylphosphine)palladium(II) (0.1g, 0.14mmol) followed by  
5 flash column chromatography over silica gel (230-400 mesh) using 10%  
6 ethyl acetate in hexane as the eluent, 0.1g of the title compound was obtained  
7 as an oil. It was further purified by preparative normal phase HPLC on a  
8 partisil-10 silica column using 10% ethyl acetate in hexane as the mobile  
9 phase (0.055g, 24%).

10 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.42-0.51(m, 4H), 1.26(t, *J* = 7.3Hz, 3H),  
11 1.27(s, 6H), 1.75(m, 1H), 2.61(s, 2H), 3.66(s, 2H), 3.74(s, 2H), 4.18 (q, *J* =  
12 7.3Hz, 2H), 6.97 (d, *J* = 7.9Hz, 1H), 7.20-7.29(m, 4H), 7.45(d, *J* = 1.5Hz,  
13 1H).

14 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
15 2-fluoro-phenyl]-acetic acid (**Compound 22, General Formula 3**)

16 Following general procedure J and using [4-(2-cyclopropyl-4,4-  
17 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-ylethynyl)-2-fluoro-phenyl]-acetic  
18 acid ethyl ester (**Compound 21**, 0.055g, 0.135mmol), methanol (2mL),  
19 tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate  
20 (0.117g, 2.97mmol) the title compound was obtained as a pale yellow solid  
21 foam (0.040g, 78%).

22 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.52-0.65(m, 4H), 1.27(s, 6H), 1.84(m, 1H),  
23 2.71(s, 2H), 3.61(s, 2H), 3.85(s, 2H), 6.98(d, *J* = 7.9Hz, 1H), 7.06 (t, *J* =  
24 7.6Hz, 1H), 7.17-7.25(m, 3H), 7.43(d, *J* = 1.2Hz, 1H), 8.60-9.00(br s, 1H).

25 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
26 phenyl]-acetic acid methyl ester (**Compound 23, General Formula 3**)

1       Following general procedure F and using 2-cyclopropyl-4,4-dimethyl-  
2 6-ethynyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,  
3 0.571mmol), 4-iodo phenyl acetic acid methyl ester (**Reagent B**, 0.16g,  
4 0.58mmol), triethyl amine (0.5mL), anhydrous tetrahydrofuran (2mL),  
5 copper(I)iodide (0.04g, 0.21mmol) and  
6 dichlorobis(triphenylphosphine)palladium(II) (0.12g, 0.17mmol) followed by  
7 flash column chromatography over silica gel (230-400 mesh) using 10%  
8 ethyl acetate in hexane as the eluent, 0.05g of the title compound was  
9 obtained as an oil. It was further purified by preparative normal phase  
10 HPLC on a partisil-10 silica column using 10% ethyl acetate in hexane as the  
11 mobile phase (0.01g, 6%).

12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.42-0.58(m, 4H), 1.29(m, 6H), 1.79(m, 1H),  
13 2.64(s, 2H), 3.67(s, 3H), 3.72(s, 2H), 3.77(s, 2H), 7.09 (d, *J* = 7.9Hz, 1H),  
14 7.28(dd, *J* = 1.5, 7.9Hz, 1H), 7.36 (d, *J* = 7.9Hz, 2H), 7.50 (d, *J* = 1.6Hz,  
15 1H), 7.51(d, *J* = 7.9Hz, 2H).

16 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
17 phenyl]-acetic acid (**Compound 24, General Formula 3**)

18       Following general procedure J and using [4-(2-cyclopropyl-4,4-  
19 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6ylethynyl)-phenyl]-acetic acid  
20 methyl ester (**Compound 23**, 0.01g, 0.027mmol), methanol (1mL),  
21 tetrahydrofuran (1mL), water (0.5mL) and lithium hydroxide monohydrate  
22 (0.042g, 1mmol) the title compound was obtained as a pale yellow solid  
23 foam (0.0065g, 68%).

24 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.35-0.52(m, 4H), 1.24(s, 6H), 1.74(m, 1H),  
25 2.59(s, 2H), 3.64(s, 2H), 3.71(s, 2H), 7.03 (d, *J* = 8.2Hz, 1H), 7.22(dd, *J* =  
26 1.4, 7.9Hz, 1H), 7.33 (d, *J* = 8.2Hz, 2H), 7.46 (d, *J* = 8.2Hz, 2H), 7.47(s,  
27 1H).

1 1-(*Iso*-propyl-methyl-amino)-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-  
2 tetrahydro-naphthalene (Intermediate 28)

3       Following general procedure G and using a solution of 4,4-dimethyl-  
4 6-trimethylsilanylethynyl-1,2,3,4-tetrahydro-naphthalene 2-one  
5 (**Intermediate 12**, 0.2g, 0.78mmol), dichloromethane (4mL), acetonitrile  
6 (2mL), acetic acid (1mL), isopropyl amine (1mL, 11.74mmol) and sodium  
7 cyanoborohydride (0.19g, 3.02mmol), after 15 days of reaction time and work  
8 up afforded an intermediate (0.14g, 60%, 0.47mmol) which was used  
9 following general procedure H along with acetone (2mL), potassium  
10 carbonate (0.6g, 4.34mmol) and methyl iodide (0.5mL, 8mmol). The crude  
11 product after work up was subjected to flash column chromatography over  
12 silica gel (230-400 mesh) using 15% ethyl acetate in hexane as the eluent to  
13 afford the title compound as a pale yellow oil (0.14g, 95%).

14 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.001(s, 9H), 0.85 (d, *J* = 6.4Hz, 6H), 0.98  
15 (s, 3H), 1.03 (s, 3H), 1.32-1.60 (m, 4H), 1.81(s, 3H), 2.64(heptet, *J* = 6.4Hz,  
16 1H), 3.65 (dd, *J* = 6.1, 9.4Hz, 1H), 6.97 (dd, *J* = 1.7, 7.9Hz, 1H), 7.13 (d, *J*  
17 = 1.7Hz, 1H), 7.82 (d, *J* = 7.9Hz, 1H).

18 6-Ethynyl-1-(*iso*-propyl-methyl-amino)-4,4-dimethyl-1,2,3,4-tetrahydro-  
19 naphthalene (Intermediate 29)

20       Following general procedure E and using 1-(methyl-*iso*-  
21 propylamino)-4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-tetrahydro-  
22 naphthalene (**Intermediate 28**, 0.14g, 0.45mmol), methanol (5mL),  
23 potassium carbonate (0.61g, 4.41mmol) and ethyl acetate the title compound  
24 (0.092g, 80%) was obtained as an oil.

25 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.11(d, *J* = 6.4Hz, 6H), 1.23(s, 3H), 1.28(s,  
26 3H), 1.51-1.87 (m, 4H), 2.09(s, 3H), 2.90 (heptet, *J* = 6.4Hz, 1H), 3.00(s,  
27 1H), 3.91 (dd, *J* = 5.8, 10.0Hz, 1H), 7.25(dd, *J* = 1.7, 8.2Hz, 1H), 7.41 (d, *J*  
28 = 1.7Hz, 1H), 7.70(d, *J* = 8.2Hz, 1H).

1 4-[5-(*Iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-  
2 naphthalene-2-yl-ethynyl)]-benzoic acid ethyl ester (Compound 25,  
3 **General Formula 4)**

4       Following general procedure F and 6-ethynyl-1-(*iso*-propyl-methyl-  
5 amino)-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalene (**Intermediate 29**,  
6 0.092g, 0.36mmol), ethyl-4-iodo benzoate (**Reagent A**, 0.12g, 0.48mmol),  
7 triethyl amine (1mL), tetrahydrofuran (2mL), copper(I)iodide (0.028g,  
8 0.14mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.075g,  
9 0.11mmol) followed by flash column chromatography over silica gel (230-  
10 400 mesh) using 10-15% ethyl acetate in hexane as the eluent the title  
11 compound was obtained (0.04g, 27%).

12 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.12 (d, *J* = 6.5Hz, 6H), 1.27 (s, 3H), 1.31 (s,  
13 3H), 1.40 (t, *J* = 7.0Hz, 3H), 1.62-1.89 (m, 4H), 2.10(s, 3H), 2.92 (heptet, *J*  
14 = 6.4Hz, 1H), 3.94(dd, *J* = 6.1, 9.7Hz, 1H), 4.38(q, *J* = 7.1Hz, 2H), 7.31(dd,  
15 *J* = 1.4, 8.2Hz, 1H), 7.46 (d, *J* = 1.7Hz, 1H), 7.58 (d, *J* = 8.2Hz, 2H),  
16 7.75(d, *J* = 8.2Hz, 1H), 8.01(d, *J* = 8.2Hz, 2H).

17 4-[5-(*Iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-  
18 naphthalene-2-yl-ethynyl)]-benzoic acid (Compound 26, General Formula  
19 **4)**

20       Following general procedure I and using 4-[5-(*iso*-propyl-methyl-  
21 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)]-benzoic  
22 acid ethyl ester (**Compound 25**, 0.04g, 0.01mmol), ethanol (2mL),  
23 tetrahydrofuran (1mL) and 1M aqueous sodium hydroxide solution (1mL)  
24 followed by recrystallization from diethylether-hexane, the title compound  
25 was obtained as an off-white solid (0.010g, 27%).

26 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.30(d, *J* = 6.0Hz, 6H), 1.31(s, 9H), 1.67-  
27 1.98(m, 4H), 2.35 (s, 3H), 3.19 (heptet, *J* = 6.4Hz, 1H), 4.36 (t, *J* = 7.6Hz,

1H), 7.28(dd,  $J = 1.4, 8.2\text{Hz}$ , 1H), 7.48 (d,  $J = 1.4\text{Hz}$ , 1H), 7.55 (d,  $J = 8.2\text{Hz}$ , 2H), 7.81 (d,  $J = 8.2\text{Hz}$ , 1H), 8.05 (d,  $J = 8.2\text{Hz}$ , 2H).  
3 [4-(2,2,4,4-Tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid methyl  
4 ester (Compound 27, General Formula 8)

5 Following general procedure F and using 6-ethynyl-2,2,4,4-  
6 tetramethylchroman (synthesis described in U.S. Patent Nos. 5,045,551 and  
7 5,616,597 incorporated herein by reference) (0.060g, 0.28mmol), methyl-4-  
8 iodo phenyl acetate (**Reagent B**, 0.078g, 0.28mmol), triethyl amine (4mL),  
9 tetrahydrofuran (4mL), copper(I)iodide (0.030g, 0.16mmol) and  
10 dichlorobis(triphenylphosphine)palladium(II) (0.11g, 0.16mmol) followed by  
11 flash column chromatography over silica gel (230-400 mesh) using 5-10 %  
12 ethyl acetate in hexane as the eluent the title compound was obtained  
13 (0.047g, 46%).

14  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.48-7.45 (m, 3H), 7.25-7.23 (m, 3H), 6.75  
15 (d, 1H,  $J = 8.2\text{Hz}$ ), 3.70 (s, 3H), 3.62 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35  
16 (s, 6H).

17 GENERAL PROCEDURE L: [4-(2,2,4,4-Tetramethyl-chroman-6-yl-  
18 ethynyl) phenyl] acetic acid (Compound 28, General Formula 8)

19 A solution of [4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl]  
20 acetic acid methyl ester (**Compound 27**, 0.047g, 0.13mmol) in 5mL of  
21 methanol was treated with 1M sodium hydroxide solution (2mL) and heated  
22 at 55°C for 2h. The volatiles were distilled off in *vacuo* and the residue was  
23 acidified with 10% hydrochloric acid and extracted with ethyl acetate (x2).  
24 The combined organic phase was washed with brine (x1), dried over  
25 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue  
26 which was purified by preparative reverse phase HPLC using 10% water in  
27 acetonitrile as the mobile phase to afford the title compound (0.034g, 82%).

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.49-7.45 (m, 3H), 7.26-7.22 (m, 3H), 6.75  
2 (d, 1H, *J* = 8.2Hz), 3.65 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35 (s, 6H).  
3 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl  
4 ester (Compound 29, General Formula 8)  
5 Following general procedure F and using 6-ethynyl-2,2,4,4-  
6 tetramethylchroman (0.11g, 0.51mmol), methyl-2-fluoro-4-iodo-benzoate  
7 (**Reagent G**, 0.14g, 0.51mmol), triethyl amine (5mL),  
8 tetrahydrofuran(10mL), copper(I)iodide(0.030g, 0.16mmol) and  
9 dichlorobis(triphenylphosphine)palladium(II) (0.110g, 0.16mmol) followed  
10 by flash column chromatography over silica gel (230-400 mesh) using 5-10  
11 % ethyl acetate in hexane as the eluent, the title compound was obtained  
12 (0.14g, 79%).

13 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.82 (t, 1H, *J* = 7.9Hz), 7.39 (d, 1H, *J* =  
14 1.8Hz), 7.25-7.16 (m, 3H), 6.69 (d, 1H, *J* = 8.2Hz), 3.85 (s, 3H), 1.77 (s,  
15 2H), 1.29 (s, 6H), 1.28 (s, 6H).

16 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid  
17 (Compound 30, General Formula 8)

18 Following general procedure L and using 2-fluoro-4-(2,2,4,4-  
19 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl ester (**Compound**  
20 **29**, 0.14g, 0.4mmol), 5mL of methanol and 1M sodium hydroxide solution  
21 (2mL) followed by recrystallization from ethyl acetate, the title compound  
22 was obtained (0.083g, 58%).

23 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.00 (t, 1H, *J* = 7.8Hz), 7.63 (d, 1H, *J* =  
24 2.1Hz), 7.45 (dd, 1H, *J* = 1.5, 7.9Hz), 7.38 (dd, 1H, *J* = 1.5, 11.4Hz), 7.32  
25 (dd, 1H, *J* = 2.1, 8.2Hz), 6.81 (d, 1H, *J* = 8.5Hz), 1.92 (s, 2H), 1.41 (s, 6H),  
26 1.38 (s, 6H).

1 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
2 ethyl ester (Compound 31, General Formula 8)

3       Following general procedure F and using 6-ethynyl-2,2,4,4-  
4 tetramethylchroman (0.204g, 0.95mmol), ethyl-2-fluoro-4-iodo phenyl  
5 acetate (**Reagent C**, 0.263g, 0.86mmol), triethyl amine, tetrahydrofuran,  
6 copper(I)iodide (0.025g, 0.13mmol) and  
7 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed  
8 by flash column chromatography over silica gel (230-400 mesh) using 5-10  
9 % ethyl acetate in hexane as the eluent, the title compound was obtained  
10 (0.21g, 62%).

11 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 1H, *J* = 2.1Hz), 7.25-7.21 (m, 4H),  
12 6.69 (d, 1H, *J* = 8.5Hz), 4.16 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 1.82 (s, 2H),  
13 1.35 (s, 6H), 1.35 (s, 6H), 1.24 (t, 3H, *J* = 7.2Hz).

14 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
15 (Compound 32, General Formula 8)

16       Following general procedure L and using [2-fluoro-4-(2,2,4,4-  
17 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid ethyl ester  
18 (**Compound 31**, 0.21g, 0.58mmol), 5mL of methanol and 1M sodium  
19 hydroxide solution (2mL) followed by flash column chromatography over  
20 silica gel (230-400 mesh) using 50% ethyl acetate in hexane, the title  
21 compound was obtained as a solid (0.184g, 93%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 11.40 (br s, 1H), 7.48 (d, 1H, *J* = 1.8Hz),  
23 7.46-7.16 (m, 4H), 6.76 (d, 1H, *J* = 8.2Hz), 3.69 (s, 2H), 1.82 (s, 2H), 1.34  
24 (s, 12H).

25 3-Methyl-but-2-enoic acid 4-bromo-phenyl ester:

26       To a stirred, cooled (ice bath) suspension of sodium hydride (2.4g,  
27 100mmol) in anhydrous tetrahydrofuran (200mL), 4-bromo phenol (17.3g,  
28 100mmol) was added followed by 3,3,-dimethyl acryloyl chloride (11.14mL,

1 100mmol). After 4hours at ambient temperature, the reaction mixture was  
2 poured into brine and extracted with diethyl ether (x2). The combined  
3 organic phase was dried over anhydrous sodium sulfate, filtered and  
4 evaporated in *vacuo* to afford an oil which was subjected to flash column  
5 chromatography over silica gel (230-400 mesh) using 2% ethyl acetate in  
6 hexane as the eluent to afford the title compound (15g, 59%).

7 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 2.00(s, 3H), 2.23(s, 3H), 5.89(s, 1H), 7.00(d,  
8 *J* = 8.8Hz, 2H), 7.49(d, *J* = 8.8Hz, 2H).

9 6-Bromo-4,4-dimethyl-chroman-2-one:

10 A solution of 3-methyl-but-2-enoic acid 4-bromo-phenyl ester (7g,  
11 27.6mmol) in anhydrous dichloromethane (200mL) was cooled (ice bath)  
12 and treated with aluminum chloride (6.6g, 49.6mmol) and the reaction  
13 mixture was stirred overnight at ambient temperature. The reaction mixture  
14 was quenched with saturated aqueous sodium bicarbonate solution and  
15 extracted with diethyl ether (x2). The combined organic extract was washed  
16 with brine (x1), dried over anhydrous sodium sulfate, filtered and  
17 evaporated in *vacuo* to afford an oil which was purified by flash column  
18 chromatography over silica gel (230-400 mesh) using 2.5% ethyl acetate in  
19 hexane as the eluent to afford the title compound (4.2g, 57%).

20 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.36(s, 6H), 2.62(s, 2H), 6.95(d, *J* = 8.5Hz,  
21 1H), 7.37(dd, *J* = 2.4, 8.5Hz, 1H), 7.43(d, *J* = 2.3Hz, 1H).

22 4-Bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol:

23 A solution of 6-bromo-4,4-dimethyl-chroman-2-one (1g, 3.92mmol)  
24 in anhydrous tetrahydrofuran (20mL) was treated with 3M solution of ethyl  
25 magnesium bromide (2.6mL) and stirred at ambient temperature for 2hours.  
26 The reaction mixture was poured into cold dilute hydrochloric acid and  
27 extracted with ethyl acetate (x2). The combined organic extract was dried

1 over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a  
2 residue which was subjected to flash column chromatography over silica gel  
3 (230-400 mesh) using 10% ethyl acetate in hexane as the eluent to afford the  
4 title compound as a pale yellow solid (1.1g, 100%).

5 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.14(s, 6H), 1.44(s, 6H), 2.20(s, 2H), 6.49(d,  
6 *J* = 8.4Hz, 1H), 7.15(dd, *J* = 2.4, 8.5Hz, 1H), 7.37(d, *J* = 2.4Hz, 1H).

7 6-Bromo-2,2,4,4-tetramethyl-chroman:

8 A solution of 4-bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol  
9 (1.1g, 3.92mmol) and *p*-toluene sulfonic acid (0.744g, 3.92mmol) in benzene  
10 (20mL) was refluxed overnight. The reaction mixture cooled to ambient  
11 temperature, filtered on silica gel and washed with 10% ethyl acetate in  
12 hexane. The filtrate and washings were evaporated in *vacuo* to an oil which  
13 was subjected to flash column chromatography over silica gel (230-400  
14 mesh) using 5% ethyl acetate in hexane as the eluent to afford the title  
15 compound as a pale yellow oil (0.84g, 80%).

16 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):δ 1.34(s, 6H), 1.35(s, 6H), 1.82(s, 2H), 6.68(d,  
17 *J* = 8.4Hz, 1H), 7.16(dd, *J* = 2.7, 8.7Hz, 1H), 7.37(d, *J* = 2.6Hz, 1H).

18 The synthesis of this compound, as described here, is in close analogy  
19 to the synthesis of 6-bromo-2,2,4,4-tetramethylthiochroman, as described in  
20 United States Patent No. 5,045,551

21 2,2,4,4-tetramethyl-6-(2-trimethylsilyl)ethynyl chroman:

22 Following general procedure D and using 6-bromo-2,2,4,4-  
23 tetramethyl chroman (0.5g, 1.87mmol), triethyl amine (5mL), anhydrous  
24 tetrahydrofuran (15mL), copper(I)iodide (0.107g, 0.156mmol), trimethylsilyl  
25 acetylene (1.84g, 18.7mmol) and  
26 dichlorobis(triphenylphosphine)palladium(II) (0.39g, 0.56mmol) the title  
27 compound was obtained as a brown oil (0.61g, 100%).

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.43 (d, 1H, *J* = 2.1Hz), 7.23 (dd, 1H, *J* =  
2 7.9, 2.1Hz), 6.73 (d, 1H, *J* = 8.2Hz), 1.83 (s, 2H), 1.36 (s, 12H), 0.28 (s, 9H).

3 6-Ethynyl-2,2,4,4-tetramethyl chroman:

4 Following general procedure E and using 2,2,4,4-tetramethyl-6-(2-  
5 trimethylsilyl)ethynyl chroman (0.61g, 1.87mmol), potassium carbonate  
6 (1.9g, 13.74mmol) and methanol the title compound was obtained (0.4g,  
7 90%).

8 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* =  
9 7.9, 2.1Hz), 6.76 (d, 1H, *J* = 8.2Hz), 3.01 (s, 1H), 1.85 (s, 2H), 1.37 (s, 6H),  
10 1.36 (s, 6H).

11 An alternative synthesis for this compound is described in United  
12 States Patent Nos. 5,045,551 and 5,616,597

13 GENERAL PROCEDURE M: 6-Bromo-2,2,4,4-tetramethyl-chroman-8-  
14 carbaldehyde (Intermediate 30)

15 A stirred, cooled (ice bath) solution of 6-bromo-2,2,4,4-tetramethyl  
16 chroman, (0.5g, 1.865mmol) in anhydrous dichloromethane (5mL) was  
17 treated with a 1M solution (1.86mL, 1.86mmol) of titanium tetrachloride in  
18 dichloromethane followed by α,α-dichloro methyl ether (0.214g,  
19 1.865mmol). The reaction mixture was allowed to warm to ambient  
20 temperature for 4h. The reaction mixture was diluted with diethyl ether,  
21 washed with brine (x1) and dried over anhydrous sodium sulfate, filtered and  
22 evaporated in *vacuo* to a residue which was subjected to flash column  
23 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in  
24 hexane to afford the title compound as a yellow solid (0.52g, 94%).

25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.38 (s, 1H), 7.72 (d, 1H, *J* = 2.6Hz), 7.57  
26 (d, 1H, *J* = 2.6Hz), 1.88 (s, 2H), 1.41 (s, 6H), 1.36 (s, 6H).

1 GENERAL PROCEDURE N: 6-Bromo-8-vinyl -2,2,4,4-tetramethyl-  
2 chroman (Intermediate 31)

3 A solution of methylenetriphenyl phosphorane [generated from  
4 methyl triphenylphosphonium bromide (7g, 20mmol) and (11.8mL, 19mmol)  
5 of a 1.6M solution of *n*-butyl lithium in hexanes ] was added 6-bromo-  
6 2,2,4,4-tetramethyl chroman-8-carbaldehyde (**Intermediate 30**, 0.52g,  
7 1.75mmol). After 1h the reaction mixture was diluted with hexane, washed  
8 with brine (x1), dried over anhydrous sodium sulfate, filtered and evaporated  
9 in *vacuo* to a clear oil which was subjected to flash column chromatography  
10 over silica gel (230-400 mesh) using 2% ethyl acetate in hexane as the eluent  
11 to afford the title compound as a clear oil (0.37g, 72%).

12 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 1H, *J* = 2.5Hz), 7.33 (d, 1H, *J* =  
13 2.5Hz), 7.03 (dd, 1H, *J* = 11.3, 17.9Hz), 5.75 (dd, 1H, *J* = 1.4, 17.9Hz), 5.30  
14 (dd, 1H, *J* = 1.4, 11.3Hz), 1.85 (s, 2H), 1.39 (s, 6H), 1.37 (s, 6H).

15 GENERAL PROCEDURE O: 6-Bromo-8-cyclopropyl-2,2,4,4-tetramethyl  
16 chroman (Intermediate 32)

17 A stirred, cooled (-30°C) solution of 6-bromo-8-vinyl-2,2,4,4-  
18 tetramethyl chroman (**Intermediate 31**, 0.37g, 1.26mmol) in diethyl ether  
19 was treated with a solution of diazomethane in diethyl ether and catalytic  
20 amount of palladium (II)acetate (~30mg). The reaction mixture was allowed  
21 to warm to ambient temperature and subjected to flash column  
22 chromatography over silica gel (230-400 mesh) using 2% ethyl acetate in  
23 hexane as the eluent to afford the title compound as a clear, pale yellow oil  
24 (0.376g, 97%).

25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.17 (d, 1H, *J* = 2.3Hz), 6.73 (d, 1H, *J* =  
26 2.6Hz), 2.19-2.16 (m, 1H), 1.83 (s, 2H), 1.37 (s, 6H), 1.33 (s, 6H), 0.94-0.88  
27 (m, 2H), 0.64-0.59 (m, 2H).

1 8-Cyclopropyl-6-trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman

2 **(Intermediate 33)**

3       Following general procedure D and using 6-bromo-8-cyclopropyl-  
4 2,2,4,4-tetramethyl chroman (**Intermediate 32**, 0.376g, 1.22mmol),  
5 (trimethylsilyl)acetylene (4mL, 28mmol), triethyl amine (3mL), anhydrous  
6 tetrahydrofuran (5mL), copper(I)iodide (0.025g, 0.13mmol) and  
7 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title  
8 compound was obtained as an oil (0.173g, 43%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.36 (d, 1H, *J* = 2.2Hz), 6.90 (d, 1H, *J* =  
10 1.9Hz), 2.31-2.22 (m, 1H), 1.96 (s, 2H), 1.49 (s, 6H), 1.46 (s, 6H), 1.05-0.88  
11 (m, 2H), 0.78-0.72 (m, 2H), 0.37 (s, 9H).

12 8-Cyclopropyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 34**)

13       Following general procedure E and using 8-cyclopropyl-6-  
14 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 33**,  
15 0.17g, 0.68mmol), methanol and potassium carbonate (0.2g, 1.47mmol) the  
16 title compound was obtained as an oil (0.064g, 47%).

17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.38 (d, 1H, *J* = 1.9Hz), 6.92 (d, 1H, *J* =  
18 1.9Hz), 3.08 (s, 1H), 2.32-2.23 (m, 1H), 1.96 (s, 2H), 1.50 (s, 6H), 1.46 (s,  
19 6H), 1.05-0.99 (m, 2H), 0.77-0.72 (m, 2H).

20 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid  
21 ethyl ester (**Compound 33, General Formula 8**)

22       Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
23 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.1g, 0.38mmol), ethyl-4-  
24 iodo-benzoate (**Reagent A**, 0.1g, 0.34mmol), triethyl amine (5mL),  
25 tetrahydrofuran(10mL), copper(I)iodide(0.025g, 0.13mmol) and  
26 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed  
27 by flash column chromatography over silica gel (230-400 mesh) using 5-10

1 % ethyl acetate in hexane as the eluent, the title compound was obtained  
2 (0.135g, 89%).  
3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* =  
4 8.2Hz), 7.30 (d, 1H, *J* = 1.8Hz), 6.84 (d, 1H, *J* = 2.0Hz), 4.38 (q, 2H, *J* =  
5 6.9Hz), 2.22-2.12 (m, 1H), 1.85 (s, 2H), 1.40 (t, 3H, *J* = 6.9Hz), 1.38 (s, 6H),  
6 1.36 (s, 6H), 0.92-0.88 (m, 2H), 0.67-0.62 (m, 2H).

7 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid  
8 **(Compound 34, General Formula 8)**

9 Following general procedure L and using 4-(8-cyclopropyl-2,2,4,4-  
10 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid ethyl ester (**Compound 33**,  
11 0.135g, 0.34mmol), 5mL of methanol and 1M sodium hydroxide solution  
12 (2mL) followed by preparative reverse phase HPLC using 10% water in  
13 acetonitrile as the mobile phase, the title compound was obtained as a solid  
14 (0.093g, 73%).

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 11.26 (br s, 1H), 8.08 (d, 2H, *J* = 8.2Hz),  
16 7.59 (d, 2H, *J* = 8.2Hz), 7.31 (d, 1H, *J* = 1.8Hz), 6.85 (d, 1H, *J* = 2.1Hz),  
17 2.22-2.13 (m, 1H), 1.85 (s, 2H), 1.38 (s, 6H), 1.36 (s, 6H), 0.95-0.87 (m,  
18 2H), 0.68-0.63 (m, 2H).  
19 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic  
20 acid methyl ester (**Compound 35, General Formula 8**)

21 Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
22 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.096g, 0.38mmol), methyl-  
23 4-iodo phenyl acetate (**Reagent B**, 0.094g, 0.34mmol), triethyl amine (3mL),  
24 tetrahydrofuran (3mL), copper(I)iodide (0.025g, 0.13mmol) and  
25 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title  
26 compound was obtained (0.137g, 90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47  
27 (d, 2H, *J* = 7.9Hz), 7.29 (d, 1H, *J* = 1.8Hz), 7.24 (d, 2H, *J* = 7.9 Hz), 6.82 (d,

1 1H,  $J = 2.1\text{Hz}$ ), 3.70 (s, 3H), 3.63 (s, 2H), 2.22-2.13 (m, 1H), 1.85 (s, 2H),  
2 1.38 (s, 6H), 1.36 (s, 6H), 0.94-0.86 (m, 2H), 0.68-0.63 (m, 2H).  
3 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic  
4 acid (Compound 36, General Formula 8)

5 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-  
6 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester  
7 (**Compound 35**, 0.137g, 0.30mmol), 5mL of methanol and 1M sodium  
8 hydroxide solution (2mL) followed by preparative reverse phase HPLC  
9 using 10% water in acetonitrile as the mobile phase, the title compound was  
10 obtained as a solid (0.11g, 80%).  
11  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.56 (br s, 1H), 7.47 (d, 2H,  $J = 8.9\text{Hz}$ ),  
12 7.28 (d, 1H,  $J = 1.9\text{Hz}$ ), 7.23 (d, 2H,  $J = 8.5\text{Hz}$ ), 6.82 (d, 1H,  $J = 1.9\text{Hz}$ ),  
13 3.62 (s, 2H), 2.21-2.12 (m, 1H), 1.83 (s, 2H), 1.36 (s, 6H), 1.34 (s, 6H), 0.93-  
14 0.82 (m, 2H), 0.72-0.62 (m, 2H).

15 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-  
16 fluorophenyl] acetic acid ethyl ester (Compound 37, General Formula 8)

17 Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
18 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.096g, 0.38mmol), ethyl-2-  
19 fluoro-4-iodo phenyl acetate (**Reagent C**, 0.104g, 0.34mmol), triethyl amine  
20 (3mL), tetrahydrofuran (3mL), copper(I)iodide (0.020g, 0.1mmol) and  
21 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) the title  
22 compound was obtained (0.14g, 85%).  
23  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.31 (d, 1H,  $J = 1.9\text{Hz}$ ), 7.29-7.21 (m, 3H),  
24 6.85 (d, 1H,  $J = 1.9\text{Hz}$ ), 4.20 (q, 2H,  $J = 7.1\text{Hz}$ ), 3.68 (s, 2H), 2.24-2.14 (m,  
25 1H), 1.87 (s, 2H), 1.40 (s, 6H), 1.38 (s, 6H), 1.28 (t, 3H,  $J = 7.1\text{Hz}$ ), 0.96-  
26 0.85 (m, 2H), 0.70-0.64 (m, 2H).

1 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-  
2 fluorophenyl] acetic acid (Compound 38, General Formula 8)

3       Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-  
4 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid ethyl ester  
5 (**Compound 37**, 0.14g, 0.323mmol), 5mL of methanol and 1M sodium  
6 hydroxide solution (2mL) followed by reverse phase HPLC using 10% water  
7 in acetonitrile as the mobile phase, the title compound was obtained as a  
8 solid (0.110g, 80%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 (d, 1H, *J* = 2.1Hz), 7.27-7.17 (m, 3H),  
10 6.82 (d, 1H, *J* = 1.8Hz), 3.70 (s, 2H), 2.21-2.11 (m, 1H), 1.84 (s, 2H), 1.37  
11 (s, 6H), 1.35 (s, 6H), 0.94-0.87 (m, 2H), 0.67-0.62 (m, 2H).

12 GENERAL PROCEDURE P: 6-Bromo-4,4-dimethyl-2-methylene chroman  
13 (**Intermediate 35**)

14       A stirred, cooled (ice bath) solution of 6-bromo-4,4-dimethyl-  
15 chroman-2-one available in accordance with U.S. Patent No. 5,399,561  
16 incorporated herein by reference (1g, 3.92mmol) in 8mL of anhydrous  
17 tetrahydrofuran was treated with a 0.5 M solution of  $\mu$ -chloro- $\mu$ -methylene-  
18 [bis(cyclopentadienyl)titanium]dimethylaluminum (Tebbe reagent) in  
19 toluene (8.23mL, 4.12mmol). After 10 minutes, the reaction mixture was  
20 poured into ice-water mixture containing 50mL of 1M sodium hydroxide and  
21 extracted with hexane. The hexane extract was washed with brine (x1),  
22 filtered over a bed of celite and evaporated in *vacuo* to an oil which was  
23 subjected to flash column chromatography over silica gel (230-400 mesh)  
24 using hexane as the eluent to afford the title compound (0.74g, 74%) as a  
25 clear oil.

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.34 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =  
2 2.3, 8.5Hz), 6.77 (d, 1H, *J* = 8.0Hz), 4.61 (d, 1H, *J* = 0.73Hz), 4.17 (d, 1H, *J*  
3 = 0.73Hz), 2.33 (s, 2H), 1.27 (s, 6H).

4 GENERAL PROCEDURE Q: 6-Bromo-3,4-dihydro-4,4-dimethylspiro[2H-  
5 1-benzopyran-2,1'-cyclopropane] (**Intermediate 36**)

6 A solution of diethyl zinc in hexane (1M, 7.1mL) was treated with  
7 diiodomethane (1.89g, 7.1mmol). After 5 minutes, a solution of 6-bromo-  
8 4,4-dimethyl-2-methylene chroman (**Intermediate 35**, 0.44g, 1.77mmol) in  
9 3mL of hexane was added and the solution was refluxed for 1h. The  
10 reaction mixture was then cooled to ambient temperature, diluted with  
11 hexane, washed with brine (x1), dried over anhydrous sodium sulfate,  
12 filtered and evaporated in *vacuo* to a residue which was subjected to flash  
13 column chromatography over silica gel (230-400 mesh) using hexane as the  
14 eluent to obtain the title compound (0.44g, 93%).

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =  
16 2.3, 8.5Hz), 6.70 (d, 1H, *J* = 8.0Hz), 1.96 (s, 2H), 1.47 (s, 6H), 1.09-1.05 (m,  
17 2H), 0.74-0.70 (m, 2H).

18 3,4-Dihydro-4,4-dimethyl-6-(trimethylsilanyl)ethynylspiro[2H-1-  
19 benzopyran-2,1'-cyclopropane] (**Intermediate 37**)

20 Following general procedure D and using 6-bromo-3,4-dihydro-4,4-  
21 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 36**,  
22 0.44g, 1.65mmol), triethyl amine (4mL), anhydrous tetrahydrofuran (5mL),  
23 copper(I)iodide (0.95g, 0.5mmol), trimethylsilyl acetylene (1.62g,  
24 16.5mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.4g,  
25 0.56mmol), the title compound was obtained as a brown oil (0.4g, 86%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* = 2.1, 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 1.87 (s, 2H), 1.37 (s, 6H), 1.01-0.97 (m, 2H), 0.65-0.61 (m, 2H), 0.26 (s, 9H).

6-Ethynyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**)

Following general procedure E and using 3,4-dihydro-4,4-dimethyl-6-(trimethylsilyl)ethynylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 37**, 0.4g, 1.42mmol), potassium carbonate (0.98g, 7.1mmol) and methanol, the title compound was obtained as a yellow oil (0.3g, 100%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* = 2.1, 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 2.97 (s, 1H), 1.86 (s, 2H), 1.37 (s, 6H), 1.00-0.95 (m, 2H), 0.64-0.59 (m, 2H).

Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 39, General Formula 1**)

Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, 0.06g, 0.28mmol), ethyl-4-iodo-benzoate (**Reagent A**, 0.086g, 0.31mmol), triethyl amine (4mL), tetrahydrofuran(4mL), copper(I)iodide(0.032g, 0.17mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.118g, 0.17mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 5-10 % ethyl acetate in hexane as the eluent, the title compound was obtained (0.07g, 70%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.01 (d, 2H, *J* = 8.2Hz), 7.56 (d, 2H, *J* = 8.5Hz), 7.49 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* = 2.1, 8.5Hz), 6.70 (d, 1H, *J* = 8.5Hz), 4.38 (q, 2H, *J* = 7.1Hz), 1.89 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* = 7.0Hz), 1.02-0.98 (m, 2H), 0.67-0.62 (m, 2H).

1 Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
2 cyclopropane]-6-yl)ethynyl]- (**Compound 40, General Formula 1**)

3 Following general procedure L and using benzoic acid, 4-[(3,4-dihydro-4,4-  
4 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester  
5 (**Compound 39**, 0.07g, 0.196mmol), 5mL of ethanol and 1M sodium  
6 hydroxide solution (2mL) followed by preparative reverse phase HPLC  
7 using 10% water in acetonitrile as the mobile phase, the title compound was  
8 obtained as a solid (0.034g, 52%).

9 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.05 (d, 2H, *J* = 8.2Hz), 7.64 (d, 2H, *J* =  
10 8.2Hz), 7.60 (d, 1H, *J* = 2.1Hz), 7.28 (dd, 1H, *J* = 2.1, 8.5Hz), 6.73 (d, 1H, *J* =  
11 8.5Hz), 1.95 (s, 2H), 1.43 (s, 6H), 0.96-0.92 (m, 2H), 0.74-0.71 (m, 2H).

12 Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
13 2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 41, General**  
14 **Formula 1**)

15 Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-  
16 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, ,  
17 0.060g, 0.28mmol), methyl-4-iodo phenyl acetate (**Reagent B**, 0.078g,  
18 0.28mmol), triethyl amine (4mL), tetrahydrofuran (4mL), copper(I)iodide  
19 (0.032g, 0.17mmol) and dichlorobis(triphenylphosphine)palladium(II)  
20 (0.118g, 0.17mmol) followed by flash column chromatography over silica  
21 gel (230-400 mesh) using 5 % ethyl acetate in hexane as the eluent, the title  
22 compound was obtained (0.084g, 84%).

23 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.48-7.45 (m, 3H), 7.26-7.20 (m, 3H), 6.67  
24 (d, 1H, *J* = 8.5Hz), 3.70 (s, 3H), 3.63 (s, 2H), 1.89 (s, 2H), 1.40 (s, 3H), 1.40  
25 (s, 3H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).

26 Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
27 2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 42, Formula 1**)

1           A solution of benzeneacetic acid, 4-[(3,4-dihydro-4,4-  
2 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl  
3 ester (**Compound 41**, 0.084g, 0.24mmol) in 5mL of methanol was treated  
4 with 1M sodium hydroxide solution (2mL) and heated at 55°C for 2h. The  
5 volatiles were distilled off in *vacuo* and the residue was acidified with 10%  
6 hydrochloric acid and extracted with ethyl acetate (x2). The combined  
7 organic phase was washed with brine (x1), dried over anhydrous sodium  
8 sulfate, filtered and evaporated in *vacuo* to a residue which was purified by  
9 preparative reverse phase HPLC using 10% water in acetonitrile as the  
10 mobile phase to afford the title compound (0.080g, 100%).  
11 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 7.49-7.46 (m, 3H), 7.25 (d, 2H, *J*=  
12 8.2Hz), 7.22 (dd, 1H *J*= 2.1, 8.5Hz), 6.68 (d, 1H, *J*= 8.5Hz), 3.66 (s, 2H),  
13 1.88 (s, 2H), 1.44 (s, 6H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).  
14 2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-  
15 2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 43, General**  
16 **Formula 1**)  
17           Following general procedure F and 6-ethynyl-3,4-dihydro-4,4-  
18 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**,  
19 0.050g, 0.23mmol), methyl-2-fluoro-4-iodo-benzoate (**Reagent G**, 0.069g,  
20 0.24mmol), triethyl amine (5mL), tetrahydrofuran(5mL),  
21 copper(I)iodide(0.013g, 0.07mmol) and  
22 dichlorobis(triphenylphosphine)palladium(II) (0.049g, 0.07mmol) followed  
23 by flash column chromatography over silica gel (230-400 mesh) using 5-10  
24 % ethyl acetate in hexane as the eluent, the title compound was obtained  
25 (0.080g, 100%).  
26 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.90 (t, 1H, *J*= 7.9Hz), 7.63 (d, 1H, *J*=  
27 1.8Hz), 7.32 (dd, 1H, *J*= 1.5, 8.2Hz), 7.26 (dd, 1H, *J*= 1.5, 11.4Hz), 7.24

1 (dd, 1H,  $J = 2.1, 8.5\text{Hz}$ ), 6.71 (d, 1H,  $J = 8.5\text{Hz}$ ), 1.97 (s, 2H), 1.44 (s, 6H),  
2 0.98-0.94 (m, 2H), 0.76-0.71 (m, 2H).  
3 2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
4 2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 44, General Formula 1)  
5 Following general procedure L and using 2-fluoro-benzoic acid, 4-  
6 [(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-  
7 yl)ethynyl]-methyl ester (**Compound 43**, 0.08g, 0.23mmol), 5mL of  
8 methanol and 2M sodium hydroxide solution (1mL) followed by flash  
9 column chromatography over silica gel (230-400 mesh) using ethyl acetate  
10 as the eluent, the title compound was obtained (0.020g, 25%).  
11  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  7.99 (t, 1H,  $J = 7.9\text{Hz}$ ), 7.63 (d, 1H,  $J =$   
12 2.1Hz), 7.44 (dd, 1H,  $J = 1.5, 7.9\text{Hz}$ ), 7.37 (dd, 1H,  $J = 1.5, 11.4\text{Hz}$ ), 7.31  
13 (dd, 1H,  $J = 2.1, 8.5\text{Hz}$ ), 6.75 (d, 1H,  $J = 8.2\text{Hz}$ ), 1.97 (s, 2H), 1.44 (s, 6H),  
14 0.98-0.94 (m, 2H), 0.76-0.71 (m, 2H).

15 GENERAL PROCEDURE R: 2,2,4,4-Tetramethyl-chroman-6-carboxylic  
16 acid (Intermediate 39)

17 A stirred, cooled ( $-78^\circ\text{C}$ ) solution of 6-bromo-2,2,4,4-tetramethyl  
18 chroman (1.2g, 4.47mmol) in 15mL of anhydrous tetrahydrofuran was  
19 treated with a 1.7M solution of *tert*-butyl lithium solution in pentane (  
20 5.27mL, 8.9mmol). After 10 minutes at  $-78^\circ\text{C}$ , carbon dioxide (generated  
21 from dry ice) was bubbled into the reaction mixture. The reaction mixture  
22 was allowed to warm to ambient temperature. The reaction mixture was  
23 diluted with ethyl acetate, washed with brine, dried over anhydrous sodium  
24 sulfate, filtered and evaporated in *vacuo* to a residue which was subjected to  
25 flash column chromatography over silica gel (230-400 mesh) using ethyl  
26 acetate as the eluent to afford the title compound as a white solid (1.1g,  
27 92%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 12.17 (br s, 1H), 8.09 (d, 1H, *J* = 2.1Hz), 7.85 (dd, 1H, *J* = 2.1, 8.5Hz), 6.83 (d, 1H, *J* = 8.2Hz), 1.87 (s, 2H), 1.39 (s, 6H), 1.37 (s, 6H).

2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (**Compound 45, General Formula 8**)

A solution of 2,2,4,4-tetramethyl chroman-6-carboxylic acid (0.1g, 0.43mmol) in thionyl chloride (10mL) was refluxed for 2h. The thionyl chloride was evaporated under reduced pressure and the residue was dissolved in 5mL of dichloromethane and treated with triethyl amine (5mL) followed by *tert*-butyl-4-hydroxy phenyl acetate (**Reagent E**, 0.088g, 0.427mmol). After 0.5h, the reaction mixture was subjected to flash column chromatography over silica gel (230-400 mesh) using 5-10% ethyl acetate in hexane as the eluent to afford the title compound (0.1g, 55%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.15 (d, 1H, *J* = 2.1Hz), 7.93 (dd, 1H, *J* = 2.1, 8.5Hz), 7.33 (d, 2H, *J* = 8.8Hz), 7.16 (d, 2H, *J* = 8.8Hz), 6.88 (d, 1H, *J* = 8.5Hz), 3.54 (s, 2H), 1.89 (s, 2H), 1.45 (s, 9H), 1.41 (s, 6H), 1.40 (s, 6H).

2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl ester (**Compound 46, General Formula 8**)

A solution of 2,2,4,4-tetramethyl-chroman-6-carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (**Compound 45**, 0.1g, 0.23mmol) was treated with 5mL of trifluoroacetic acid and stirred at ambient temperature for 1h. The trifluoroacetic acid was distilled off under reduced pressure and the residue was subjected to preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase to afford the title compound as a white solid (0.045g, 50%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.13 (d, 1H, *J* = 2.1Hz), 7.92 (dd, 1H, *J* = 2.3, 8.5Hz), 7.35 (d, 2H, *J* = 8.8Hz), 7.17 (d, 2H, *J* = 8.5Hz), 6.87 (d, 1H, *J* = 8.5Hz), 3.68 (s, 2H), 1.89 (s, 2H), 1.41 (s, 6H), 1.39 (s, 6H).

6-Bromo-8-carbaldehyde-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 40**)

Following general procedure M and using 6-bromo-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 36**, 2.3g, 8.65mmol), anhydrous dichloromethane (25mL), 1M solution (8.65mL, 8.65mmol) of titanium tetrachloride in dichloromethane and α,α-dichloromethyl ether (1.09g, 9.52mmol) followed by flash column chromatography using 10% ethyl acetate in hexane as the eluent, the title compound was obtained as a yellow solid (2.06g, 81%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.20 (s, 1H), 7.69 (d, 1H, *J* = 2.6Hz), 7.58 (d, 1H, *J* = 2.6Hz), 1.92 (s, 2H), 1.40 (s, 6H), 1.09-1.04 (m, 2H), 0.73-0.69 (m, 2H).

6-Bromo-3,4-dihydro-4,4-dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 41**)

Following general procedure N and using A solution of methylenetriphenyl phosphorane [generated from methyl triphenylphosphonium bromide (7g, 20mmol) and 1.6M solution of *n*-butyl lithium in hexanes (11.8mL, 19mmol)], 6-bromo-8-carbonyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 40**, 2.06g, 7mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title compound was obtained as a clear oil (1.36g, 66%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.36 (d, 1H, *J* = 2.3Hz), 7.28 (d, 1H, *J* = 2.6Hz), 6.80 (dd, 1H, *J* = 11.1, 17.9Hz), 5.63 (dd, 1H, *J* = 1.2, 17.9Hz), 5.19

1 (dd, 1H,  $J = 1.2, 11.1\text{Hz}$ ), 1.84 (s, 2H), 1.35 (s, 6H), 0.97 (t, 2H,  $J = 6.3\text{Hz}$ ),  
2 0.62 (d, 1H,  $J = 5.3\text{Hz}$ ), 0.60 (d, 1H,  $J = 6.2\text{Hz}$ ).

3 6-Bromo-8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
4 2,1'-cyclopropane] (**Intermediate 42**)

5 Following general procedure O and using A 6-bromo-3,4-dihydro-  
6 4,4-dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
7 (**Intermediate 41**, 1.36g, 4.6mmol), a solution of diazomethane in diethyl  
8 ether and palladium (II)acetate (~30mg) followed by flash column  
9 chromatography over silica gel (230-400 mesh) using hexane as the eluent,  
10 the title compound was obtained as a clear oil (1.38g, 100%).

11  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.19 (d, 1H,  $J = 2.2\text{Hz}$ ), 6.71 (d, 1H,  $J =$   
12 2.2Hz), 1.99-1.92 (m, 1H), 1.87 (s, 2H), 1.35 (s, 6H), 1.00-0.95 (m, 2H),  
13 0.90-0.82 (m, 2H), 0.65-0.54 (m, 4H).

14 8-Cyclopropyl-3,4-dihydro-4,4-dimethyl-6-  
15 (trimethylsilyl)ethynylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
16 (**Intermediate 43**)

17 Following general procedure D and 6-bromo-8-cyclopropyl-3,4-  
18 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
19 (**Intermediate 42**, 0.74g, 2.4mmol), (trimethylsilyl)acetylene (4mL,  
20 28mmol), triethyl amine (8mL), anhydrous tetrahydrofuran, copper(I)iodide  
21 (0.050g, 0.26mmol) and dichlorobis(triphenylphosphine)palladium(II)  
22 (0.15g, 0.22mmol), followed by flash column chromatography over silica gel  
23 (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title  
24 compound was obtained as an oil (0.62g, 80%).

25  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.28 (d, 1H,  $J = 1.9\text{Hz}$ ), 6.77 (d, 1H,  $J =$   
26 1.9Hz), 2.03-1.94 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.05-0.98 (m, 2H),  
27 0.95-0.83 (m, 2H), 0.69-0.59 (m, 4H), 0.27 (s, 9H).

1 8-Cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-  
2 2,1'-cyclopropane] (**Intermediate 44**)

3       Following general procedure E, and 8-cyclopropyl-3,4-dihydro-4,4-  
4 dimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-benzopyran-2,1'-  
5 cyclopropane] (**Intermediate 43**, 0.62g, 1.9mmol), methanol and potassium  
6 carbonate (0.5g, 3.6mmol) followed by flash column chromatography over  
7 silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent,  
8 the title compound was obtained as an oil (0.5g, 100%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.30 (d, 1H, *J* = 1.8Hz), 6.80 (d, 1H, *J* =  
10 2.0Hz), 2.97 (s, 1H), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.39 (s, 6H), 1.20-0.90  
11 (m, 2H), 0.90-0.84 (m, 2H), 0.75-0.58 (m, 4H).

12 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
13 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 47**,  
14 **General Formula 1**)

15       Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
16 3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
17 (**Intermediate 44**, 0.11g, 0.43mmol), methyl-4-iodo phenyl acetate  
18 (**Reagent B**, 0.114g, 0.41mmol), triethyl amine (5mL), tetrahydrofuran  
19 (3mL), copper(I)iodide (0.025g, 0.13mmol) and  
20 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title  
21 compound was obtained as a clear oil (0.096g, 56%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (d, 2H, *J* = 8.0Hz), 7.31 (d, 1H, *J* =  
23 1.9Hz), 7.24 (d, 2H, *J* = 8.2Hz), 6.81 (d, 1H, *J* = 1.9Hz), 3.69 (s, 3H), 3.62  
24 (s, 2H), 2.04-1.95 (m, 1H), 1.90 (s, 2H), 1.39 (s, 6H), 1.03-0.99 (m, 2H),  
25 0.90-0.83 (m, 2H), 0.68-0.59 (m, 4H).

1 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
2 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 48, General**  
3 **Formula 1**)

4       Following general procedure L and using benzeneacetic acid, 4-[(8-  
5 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
6 cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 47**, 0.96g, 0.24mmol),  
7 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by  
8 flash column chromatography over silica gel (230-400 mesh) using 15%  
9 methanol in dichloromethane as the eluent, the title compound was obtained  
10 as a solid (0.084g, 91%).

11 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.27 (br s, 1H), 7.46 (d, 2H, *J* = 8.2Hz),  
12 7.30 (d, 1H, *J* = 1.8Hz), 7.23 (d, 2H, *J* = 8.2Hz), 6.80 (d, 1H, *J* = 1.5Hz),  
13 3.63 (s, 2H), 2.07-1.94 (m, 1H), 1.89 (s, 2H), 1.39 (s, 6H), 1.03-0.98 (m,  
14 2H), 0.89-0.82 (m, 2H), 0.73-0.59 (m, 4H).

15 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
16 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester  
17 (**Compound 49, General Formula 1**)

18       Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
19 3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
20 (**Intermediate 44**, 0.125g, 0.5mmol), methyl-2-fluoro-4-iodo phenyl acetate  
21 (**Reagent H**, 0.14g, 0.5mmol), triethyl amine (3mL), tetrahydrofuran (3mL),  
22 copper(I)iodide (0.020g, 0.1mmol) and  
23 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed  
24 by preparative normal phase HPLC using 10% ethyl acetate in hexane as the  
25 mobile phase, the title compound was obtained (0.096g, 46%).

26 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.30 (d, 1H, *J* = 2.1Hz), 7.26-7.18 (m, 3H),  
27 6.80 (d, 1H, *J* = 1.8Hz), 3.71 (s, 3H), 3.67 (s, 2H), 2.04-1.94 (m, 1H), 1.90

1 (s, 2H), 1.40 (s, 6H), 1.18-0.99 (m, 2H), 0.90-0.83 (m, 2H), 0.68-0.59 (m,  
2 4H).  
3 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-  
4 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid (**Compound 50**,

5 **General Formula 1)**

6 Following general procedure L and using 4-[(8-cyclopropyl-3,4-  
7 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-  
8 yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester (**Compound 49**,  
9 0.096g, 0.23mmol), 5mL of methanol and 1M sodium hydroxide solution  
10 (2mL) followed by flash column chromatography over silica gel (230-400  
11 mesh) using 15% methanol in dichloromethane as the eluent, the title  
12 compound was obtained as a solid (0.093g, 100%).  
13 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.50 (br s, 1H), 7.27 (d, 1H, *J* = 2.1Hz), 7.24-  
14 7.15 (m, 3H), 6.77 (d, 1H, *J* = 1.5Hz), 3.67 (s, 2H), 2.01-1.91 (m, 1H), 1.87  
15 (s, 2H), 1.36 (s, 6H), 1.01-0.96 (m, 2H), 0.87-0.80 (m, 2H), 0.65-0.56 (m,  
16 4H).

17 Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-  
18 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 51**,

19 **General Formula 1)**

20 Following general procedure F and using 8-cyclopropyl-6-ethynyl-  
21 3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]  
22 (**Intermediate 44**, 0.05g, 0.2mmol), ethyl-4-iodo-benzoate (**Reagent A**,  
23 0.055g, 0.2mmol), triethyl amine (3mL), tetrahydrofuran(3mL),  
24 copper(I)iodide(0.020g, 0.1mmol) and  
25 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol), the title  
26 compound was obtained (0.06g, 75%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* = 8.2Hz), 7.33 (d, 1H, *J* = 1.8Hz), 6.83 (d, 1H, *J* = 2.1Hz), 4.38 (q, 2H, *J* = 7.1Hz), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* = 7.0Hz), 1.05-0.95 (m, 2H), 0.91-0.84 (m, 2H), 0.69-0.61 (m, 4H).

Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 52, General Formula 1**)

Following general procedure L and using benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 51**, 0.06g, 0.15mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase, the title compound was obtained as a solid (0.040g, 72%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.08 (d, 2H, *J* = 8.8Hz), 7.60 (d, 2H, *J* = 8.8Hz), 7.34 (d, 1H, *J* = 1.9Hz), 6.84 (d, 1H, *J* = 1.9Hz), 2.05-1.96 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.05-0.95 (m, 2H), 0.92-0.83 (m, 2H), 0.75-0.60 (m, 4H).

4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid methyl ester (**Compound 53, General Formula 1**)

Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 44**, 0.03g, 0.11mmol), methyl-2-fluoro-4-iodo-benzoate (**Reagent G**, 0.025g, 0.09mmol), triethyl amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.020g, 0.1mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by preparative normal phase HPLC using 10% ethyl acetate in hexane as the

1 mobile phase, the title compound was obtained as a white solid (0.019g,  
2 40%).  
3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.97 (t, 1H, *J* = 7.8Hz), 7.34 (d, 1H, *J* =  
4 1.9Hz), 7.32-7.25 (m, 2H), 6.83 (d, 1H, *J* = 1.9Hz), 3.95 (s, 3H), 2.06-1.96  
5 (m, 1H), 1.93 (s, 2H), 1.42 (s, 6H), 1.06-1.02 (m, 2H), 0.91-0.86 (m, 2H),  
6 0.71-0.61 (m, 4H).

7 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
8 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid (Compound 54,  
9 **General Formula 1)**

10 Following general procedure L and using 4-[(8-cyclopropyl-3,4-  
11 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-  
12 yl)ethynyl]-2-fluoro-benzoic acid methyl ester (**Compound 53**, 0.019g,  
13 0.047mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL)  
14 followed by preparative reverse phase HPLC using 10% water in acetonitrile  
15 as the mobile phase, the title compound was obtained as a solid (0.01g,  
16 56%).

17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (t, 1H, *J* = 8.0Hz), 7.36 -7.28 (m, 3H),  
18 6.83 (d, 1H, *J* = 1.9Hz), 2.18-1.95 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.06-  
19 1.01 (m, 2H), 0.96-0.83 (m, 2H), 0.76-0.60 (m, 4H).

20 8-Acetyl-6-bromo-2,2,4,4-tetramethyl chroman (Intermediate 45)

21 A stirred, cooled (ice bath) suspension of aluminum chloride (0.99g,  
22 7.46mmol) in anhydrous dichloromethane (20 mL) was treated with acetyl  
23 chloride (0.58g, 7.46mmol). After 5 minutes, a solution of 6-bromo-2,2,4,4-  
24 tetramethyl chroman (1g, 3.73mmol) in dichloromethane was added. The  
25 reaction was allowed to warm to ambient temperature and stirred for 2h.  
26 The reaction mixture was then poured into ice containing 10% hydrochloric  
27 acid and extracted with diethyl ether (x2). The combined organic phase was  
28 washed with saturated aqueous sodium bicarbonate solution, dried over

1 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue  
2 which was subjected to flash column chromatography over silica gel (230-  
3 400 mesh) using 5% ethyl acetate in hexane as the eluent to afford the title  
4 compound as a pale yellow oil (0.95g, 83%). It was used as such for the next  
5 step without any characterization.

6 6-Bromo-8-ethyl-2,2,4,4-tetramethyl chroman (**Intermediate 46**)

7 A stirred, cooled (ice bath) solution of 8-acetyl-6-bromo-2,2,4,4-  
8 tetramethyl chroman (**Intermediate 45**, 0.95g, 3.1mmol) in trifluoroacetic  
9 acid (10mL) was treated with triethylsilane (10mL) and the resulting reaction  
10 mixture was allowed to warm to ambient temperature and stirred overnight.  
11 The volatiles were distilled off in *vacuo* and the residue was diluted with  
12 water and extracted with hexane (x2). The combined organic phase was  
13 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an  
14 oil which was subjected to flash column chromatography over silica gel  
15 (230-400 mesh) using hexane as the eluent to afford the title compound as a  
16 clear oil, contaminated with a small amount of triethylsilane (0.51g, 56%).  
17 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.23 (d, 1H, *J* = 2.3Hz), 7.08 (d, 1H, *J* =  
18 2.3Hz), 2.58 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.34 (s, 6H), 1.33 (s, 6H), 1.17  
19 (t, 3H, *J* = 7.6Hz).

20 8-Ethyl-6-trimethylsilyl-ethynyl-2,2,4,4-tetramethyl chroman  
21 (**Intermediate 47**)

22 Following general procedure D and using 6-bromo-8-ethyl-2,2,4,4-  
23 tetramethyl chroman (**Intermediate 46**, 0.5g, 1.61mmol),  
24 (trimethylsilyl)acetylene (1.57g, 16.1mmol), triethyl amine (8mL), anhydrous  
25 tetrahydrofuran (10mL), copper(I)iodide (0.025g, 0.13mmol) and  
26 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), followed  
27 by flash column chromatography over silica gel (230-400 mesh) using 5%

1 ethyl acetate in hexane as the eluent, the title compound was obtained as an  
2 oil (0.137g, 27%).

3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.27 (d, 1H, *J* = 2.1Hz), 7.10 (d, 1H, *J* =  
4 2.1Hz), 2.55 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.33 (s, 6H), 1.32 (s, 6H), 1.15  
5 (t, 3H, *J* = 7.6Hz), 0.24 (s, 9H).

6 8-Ethyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 48**)

7 Following general procedure E and using 8-ethyl-6-  
8 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 47**,  
9 0.137g, 0.44mmol), methanol and potassium carbonate (0.1g, 0.72mmol)  
10 followed by flash column chromatography over silica gel (230-400 mesh)  
11 using 5% ethyl acetate in hexane as the eluent, the title compound was  
12 obtained as an oil (0.066g, 62%).

13 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.33 (d, 1H, *J* = 2.2Hz), 7.15 (d, 1H, *J* =  
14 1.6Hz), 2.99 (s, 1H), 2.59 (q, 2H, *J* = 7.6Hz), 1.84 (s, 2H), 1.37 (s, 6H), 1.35  
15 (s, 6H), 1.19 (t, 3H, *J* = 7.6Hz).

16 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
17 methyl ester (**Compound 55, General Formula 8**)

18 Following general procedure F and using 8-ethyl-6-ethynyl-2,2,4,4-  
19 tetramethylchroman (**Intermediate 48**, 0.033g, 0.136mmol), methyl-4-iodo  
20 phenyl acetate (**Reagent B**, 0.034g, 0.12mmol), triethyl amine (2mL),  
21 tetrahydrofuran (2mL), copper(I)iodide (0.025g, 0.13mmol) and  
22 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title  
23 compound was obtained (0.035g, 73%).

24 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.49 (d, 2H, *J* = 7.9Hz), 7.35 (d, 1H, *J* =  
25 1.8Hz), 7.26 (d, 2H, *J* = 7.9Hz), 7.18 (d, 1H, *J* = 1.9Hz), 3.72 (s, 3H), 3.65  
26 (s, 2H), 2.61 (q, 2H, *J* = 7.5Hz), 1.85 (s, 2H), 1.38 (s, 12H), 1.21 (t, 3H, *J* =  
27 7.5Hz).

1 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid  
2 **(Compound 56, General Formula 8)**

3       Following general procedure L and using [4-(8-ethyl-2,2,4,4-  
4 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester  
5 **(Compound 55, 0.035g, 0.1mmol)**, 5mL of methanol and 1M sodium  
6 hydroxide solution (1mL) followed by preparative reverse phase HPLC  
7 using 10% water in acetonitrile as the mobile phase, the title compound was  
8 obtained as a solid (0.11g, 25%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.48 (d, 2H, *J* = 8.0Hz), 7.33 (d, 1H, *J* =  
10 1.9Hz), 7.25 (d, 2H, *J* = 8.0Hz), 7.15 (d, 1H, *J* = 1.9Hz), 3.65 (s, 2H), 2.59  
11 (q, 2H, *J* = 7.5Hz), 1.83 (s, 2H), 1.35 (s, 12H), 1.18 (t, 3H, *J* = 7.4Hz).

12 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-  
13 cyclopropyl-3,4-dihydro-4,4-dimethyl- **(Intermediate 49)**

14       Following general procedure R and using 6-bromo-8-cyclopropyl-3,4-  
15 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]  
16 **(Intermediate 42, 0.45g, 1.48mmol)**, anhydrous tetrahydrofuran (5mL),  
17 1.7M solution of *tert*-butyl lithium solution in pentane ( 1.74mL, 2.96mmol)  
18 and carbon dioxide generated from dry ice, followed by flash column  
19 chromatography over silica gel (230-400 mesh) using 50% ethyl acetate in  
20 hexane as the eluent, the title compound was obtained as a white solid  
21 (0.34g, 85%).

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 12.43 (br s, 1H), 7.94 (d, 1H, *J* = 2.1Hz),  
23 7.42 (d, 1H, *J* = 1.8Hz), 2.06-1.96 (m, 1H), 1.92 (s, 2H), 1.42 (s, 6H), 1.12-  
24 0.97 (m, 2H), 0.95-0.81 (m, 2H), 0.77-0.60 (m, 4H).

25 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-  
26 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(*tert*-butoxycarbonylmethyl)phenyl  
27 ester **(Compound 57, General Formula 1)**

1       A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-  
2   carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**,  
3   0.06g, 0.22mmol) in anhydrous dichloromethane (5mL) was treated with  
4   *tert*-butyl-4-hydroxy phenyl acetate (**Reagent E**, 0.05g, 0.22mmol) followed  
5   by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.11g,  
6   0.22mmol) and 4-dimethylaminopyridine (0.028g, 0.22mmol). The resulting  
7   solution was stirred at ambient temperature overnight. The reaction mixture  
8   was subjected to flash column chromatography over silica gel (230-400  
9   mesh) using 7% ethyl acetate in hexane as the eluent to afford the title  
10   compound as a clear oil that solidified on standing (0.048g, 48%).  
11   <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.91 (d, 1H, *J* = 2.1Hz), 7.41 (d, 1H, *J* =  
12   1.8Hz), 7.24 (d, 2H, *J* = 8.8Hz), 7.05 (d, 2H, *J* = 8.5Hz), 3.46 (s, 2H), 1.97-  
13   1.90 (m, 1H), 1.87 (s, 2H), 1.37 (s, 9H), 1.36 (s, 6H), 1.04-0.90 (m, 2H),  
14   0.87-0.75 (m, 2H), 0.65-0.56 (m, 4H).  
15   Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-  
16   cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester  
17   (**Compound 58, General Formula 1**)

18       A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-  
19   carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(*tert*-  
20   butoxycarbonylmethyl)phenyl ester (**Compound 57**, 0.048g, 0.105mmol)  
21   was treated with 2mL of trifluoroacetic acid and stirred at ambient  
22   temperature for 2h. The trifluoroacetic acid was distilled off under reduced  
23   pressure and the residue was subjected to preparative reverse phase HPLC  
24   using 10% water in acetonitrile as the mobile phase to afford the title  
25   compound as a white solid (0.029g, 55%).  
26   <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (d, 1H, *J* = 2.2Hz), 7.48 (d, 1H, *J* =  
27   1.9Hz), 7.34 (d, 2H, *J* = 8.5Hz), 7.16 (d, 2H, *J* = 8.5Hz), 3.67 (s, 2H), 2.07-

1 1.97 (m, 1H), 1.95 (s, 2H), 1.44 (s, 6H), 1.09-1.04 (m, 2H), 0.93-0.85 (m,  
2 2H), 0.79-0.64 (m, 4H).

3 Spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-  
4 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(tert-butoxycarbonylmethyl)phenyl  
5 ester (Compound 59, General Formula 1)

6 A solution of spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-  
7 carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**,  
8 0.05g, 0.18mmol) in anhydrous dichloromethane (5mL) was treated with  
9 *tert*-butyl-3-hydroxy phenyl acetate (**Reagent F**, 0.04g, 0.18mmol) followed  
10 by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.029g,  
11 0.1mmol) and 4-dimethylaminopyridine (0.022g, 0.18mmol). The resulting  
12 solution was stirred at ambient temperature overnight. The reaction mixture  
13 was subjected to flash column chromatography over silica gel (230-400  
14 mesh) using 7% ethyl acetate in hexane as the eluent to afford the title  
15 compound as a clear oil that solidified on standing (0.020g, 23%).  
16 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.98 (d, 1H, *J* = 1.9Hz), 7.48 (d, 1H, *J* =  
17 2.2Hz), 7.38 (t, 1H, *J* = 7.7Hz), 7.19-7.11 (m, 3H), 3.68 (s, 2H), 2.05-1.94  
18 (m, 1H), 1.95 (s, 2H), 1.44 (s, 15H), 1.09-1.04 (m, 2H), 0.96-0.82 (m, 2H),  
19 0.73-0.64 (m, 4H).

20 Spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-  
21 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester  
22 (**Compound 60, General Formula 1**)

23 A solution of spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-  
24 carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(*tert*-  
25 butoxycarbonylmethyl)phenyl ester (**Compound 59**, 0.020g, 0.04mmol) was  
26 treated with 2mL of trifluoroacetic acid and stirred at ambient temperature  
27 for 2h. The trifluoroacetic acid was distilled off under reduced pressure and  
28 the residue was subjected to preparative reverse phase HPLC using 10%

1 water in acetonitrile as the mobile phase to afford the title compound as a  
2 white solid (0.0125g, 62%).  
3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (d, 1H, *J* = 2.1Hz), 7.49 (d, 1H, *J* =  
4 2.1Hz), 7.36 (t, 1H, *J* = 7.8Hz), 7.18-7.08 (m, 3H), 3.56 (s, 2H), 2.06-1.95  
5 (m, 1H), 1.95 (s, 2H), 1.45 (s, 6H), 1.09-1.05 (m, 2H), 0.96-0.84 (m, 2H),  
6 0.74-0.65 (m, 4H).

7 6-Bromo-4,4-dimethyl-1,2,3,4-tetrahydro-quinoline-1-carbaldehyde  
8 **(Intermediate 50)**

9 A solution of 6-bromo-4,4-dimethyl-1,2,3,4-tetrahydroquinoline,  
10 available in accordance with United States Patent No. 5,089,509, the  
11 specification of which is incorporated herein by reference (1.8g, 7.5mmol) in  
12 10mL of formic acid was refluxed for 3h. The reaction mixture was then  
13 cooled to ambient temperature and poured into ice-cold saturated aqueous  
14 sodium bicarbonate solution and extracted with diethyl ether (x2). The  
15 combined organic phase was dried over anhydrous sodium sulfate, filtered  
16 and evaporated in *vacuo* to a residue which was subjected to flash column  
17 chromatography over silica gel (230-400 mesh) using 15-25% ethyl acetate  
18 in hexane as the eluent to afford the title compound as a pale yellow solid  
19 (1.8g, 90%).

20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.71 (s, 1H), 7.45 (d, 1H, *J* = 2.2Hz), 7.28  
21 (dd, 1H, *J* = 2.2, 8.5Hz), 6.98 (d, 1H, *J* = 8.5Hz), 3.78 (t, 2H, *J* = 6.3Hz),  
22 1.74 (t, 2H, *J* = 6.3Hz), 1.28 (s, 6H).

23 6-Bromo-1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline  
24 **(Intermediate 51)**

25 A stirred, cooled (0°C) solution of 6-bromo-4,4-dimethyl-1,2,3,4-  
26 tetrahydro-quinoline-1-carbaldehyde (**Intermediate 50**, 21.8, 6.7mmol) in  
27 anhydrous tetrahydrofuran (20mL) under argon was treated with titanium  
28 tetra-*iso*-propoxide (2.15mL, 7.39mmol) followed by 3M solution of ethyl

1 magnesium bromide in diethyl ether (5.6mL, 16.8mmol) and the reaction  
2 mixture was then heated at 50°C overnight. It was then cooled in an ice-  
3 bath, quenched with saturated aqueous ammonium chloride solution and  
4 extracted with diethyl ether (x2). The combined organic phase was dried  
5 over anhydrous sodium sulfate, filtered over celite and evaporated in *vacuo*  
6 to residue which was subjected to flash column chromatography over silica  
7 gel (230-400 mesh) using 5% ethyl acetate in hexane as the eluent to afford  
8 the title compound as an oil (1.2g, 64%).

9 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.24 (d, 1H, *J* = 2.5Hz), 7.12 (dd, 1H, *J* =  
10 2.2, 8.8Hz), 7.01 (d, 1H, *J* = 8.8Hz), 3.20 (t, 2H, *J* = 6.0Hz), 2.27-2.20 (m,  
11 1H), 1.68 (t, 2H, *J* = 5.9Hz), 1.24 (s, 3H), 1.23 (s, 3H), 0.83-0.77 (m, 2H),  
12 0.60-0.55 (m, 2H).

13 1-Cyclopropyl-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydro-  
14 quinoline (Intermediate 52)

15 Following general procedure D and using 6-bromo-1-cyclopropyl-4,4-  
16 dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 51**, 0.8g, 2.86mmol),  
17 (trimethylsilyl)acetylene (5mL, 35mmol), triethyl amine (10mL), anhydrous  
18 tetrahydrofuran, copper(I)iodide (0.080g, 0.42mmol) and  
19 dichlorobis(triphenylphosphine)palladium(II) (0.240g, 0.34mmol), the title  
20 compound was obtained as an oil (0.67g, 79%).

21 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.33 (d, 1H, *J* = 1.8Hz), 7.22 (dd, 1H, *J* =  
22 2.1, 8.5Hz), 7.06 (d, 1H, *J* = 8.5Hz), 3.27 (t, 2H, *J* = 5.9Hz), 2.37-2.31 (m,  
23 1H), 1.70 (t, 2H, *J* = 6.0Hz), 1.28 (s, 6H), 0.89-0.82 (m, 2H), 0.66-0.60 (m,  
24 2H), 0.28 (s, 9H).

25 1-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline:  
26 (Intermediate 53)

27 Following general procedure E and using 1-cyclopropyl-6-  
28 trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline

1 (**Intermediate 52**, 0.40g, 1.34mmol), methanol and potassium carbonate  
2 (0.2g, 1.47mmol) followed by flash column chromatography over silica gel  
3 (230-400 mesh) using 2% ethyl acetate in hexane as the eluent, the title  
4 compound was obtained as an oil (0.17g, 56%).

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.38 (d, 1H, *J* = 2.1Hz), 7.27 (dd, 1H, *J* =  
6 2.1, 8.5Hz), 7.11 (d, 1H, *J* = 8.5Hz), 3.30 (t, 2H, *J* = 6.0Hz), 3.02 (s, 1H),  
7 2.40-2.34 (m, 1H), 1.74 (t, 2H, *J* = 6.0Hz), 1.30 (s, 6H), 0.93-0.85 (m, 2H),  
8 0.70-0.63 (m, 2H).

9 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-  
10 benzoic acid ethyl ester (**Compound 61, General Formula 7**)

11 Following general procedure F and using 1-cyclopropyl-6-ethynyl-  
12 4,4-dimethyl-1,2,3,4-tetrahydro quinoline (**Intermediate 53**, 0.11g,  
13 0.43mmol), ethyl-4-iodo-benzoate (**Reagent A**, 0.11g, 0.9mmol), triethyl  
14 amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.02g, 0.1mmol) and  
15 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed  
16 by flash column chromatography over silica gel (230-400 mesh) using 5-  
17 10% ethyl acetate in hexane as the eluent, the title compound was obtained  
18 (0.05g, 31%).

19 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 (d, 2H, *J* = 8.2Hz), 7.54 (d, 2H, *J* =  
20 8.2Hz), 7.37 (d, 1H, *J* = 2.1Hz), 7.26 (dd, 1H, *J* = 2.1, 8.5Hz), 7.10 (d, 1H, *J* =  
21 8.8Hz), 4.37 (q, 2H, *J* = 7.1Hz), 3.28 (t, 2H, *J* = 6.0Hz), 2.40-2.33 (m,  
22 1H), 1.71 (t, 2H, *J* = 5.8Hz), 1.40 (t, 3H, *J* = 7.0Hz), 1.27 (s, 6H), 0.94-0.82  
23 (m, 2H), 0.65-0.60 (m, 2H).

24 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-  
25 benzoic acid (**Compound 62, General Formula 7**)

26 Following general procedure L and using 4-(1-cyclopropyl-4,4-  
27 dimethyl-1,2,3,4-tetrahydro-quinolin-6-ylethynyl)-benzoic acid ethyl ester

1 (Compound 61, 0.05g, 0.13mmol), 5mL of ethanol and 5M sodium  
2 hydroxide solution (2mL) followed by recrystallization from hot ethyl  
3 acetate, the title compound was obtained as a solid (0.030g, 64%).  
4 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 7.92 (d, 2H, *J* = 8.2Hz), 7.57 (d, 2H, *J* =  
5 8.2Hz), 7.33 (d, 1H, *J* = 1.9Hz), 7.23 (dd, 1H, *J* = 1.9, 8.5Hz), 7.06 (d, 1H, *J*  
6 = 8.8Hz), 3.25 (t, 2H, *J* = 5.8Hz), 2.41-2.34 (m, 1H), 1.64 (t, 2H, *J* = 5.6Hz),  
7 1.21 (s, 6H), 0.87-0.81 (m, 2H), 0.59-0.54 (m, 2H).  
8 [4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-  
9 ethynyl)phenyl] acetic acid methyl ester (Compound 63, General Formula  
10 7)

11 Following general procedure F and using 1-cyclopropyl-6-ethynyl-  
12 4,4-dimethyl-1,2,3,4-tetrahydro quinoline (Intermediate 53, 0.05g,  
13 0.22mmol), methyl-4-iodo-phenyl acetate (Reagent B, 0.055g, 0.2mmol),  
14 triethyl amine (5mL), tetrahydrofuran, copper(I)iodide(0.025g, 0.13mmol)  
15 and dichlorobis(triphenylphosphine)palladium(II) (0.75g, 0.11mmol)  
16 followed preparative normal phase HPLC using 10 % ethyl acetate in hexane  
17 as the mobile phase, the title compound was obtained (0.089g, 100%).  
18 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (d, 2H, *J* = 8.8Hz), 7.45 (d, 1H, *J* =  
19 1.8Hz), 7.35-7.22 (m, 2H), 7.10 (d, 2H, *J* = 8.8Hz), 3.70 (s, 3H), 3.63 (s,  
20 2H), 3.27 (t, 2H, *J* = 6.0Hz), 2.37-2.31 (m, 1H), 1.71 (t, 2H, *J* = 6.0Hz), 1.27  
21 (s, 6H), 0.89-0.81 (m, 2H), 0.65-0.60 (m, 2H).  
22 [4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-2-  
23 fluoro-phenyl] acetic acid ethyl ester (Compound 64, General Formula 7)

24 Following general procedure F and using 1-cyclopropyl-6-ethynyl-  
25 4,4-dimethyl-1,2,3,4-tetrahydro quinoline (Intermediate 53, 0.11g,  
26 0.49mmol), ethyl-2-fluoro-4-iodo-phenyl acetate (Reagent C, 0.11g,  
27 0.9mmol), triethyl amine (3mL), tetrahydrofuran(3mL),

1 copper(I)iodide(0.06g, 0.32mmol) and  
2 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol) followed by  
3 flash column chromatography over silica gel (230-400 mesh) using 10 %  
4 ethyl acetate in hexane as the eluent, the title compound was obtained (0.1g,  
5 51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.34 (d, 1H, *J* = 2.1Hz), 7.25-7.17 (m,  
6 3H), 7.09 (d, 2H, *J* = 8.8Hz), 4.17 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 3.27 (t,  
7 2H, *J* = 6.0Hz), 2.38-2.31 (m, 1H), 1.69 (t, 2H, *J* = 6.0Hz), 1.27 (s, 6H), 1.25  
8 (t, 3H, *J* = 7.1Hz), 0.88-0.81 (m, 2H), 0.65-0.59 (m, 2H).

9 N-(4-Bromophenyl)-N-methyl-3-methyl-2-butenamide (Intermediate 54)

10 3,3-Dimethylacryloyl chloride (3mL, 27mmol) was added to a  
11 solution of 4-bromo-N-methyl-aniline (4.55g, 25mmol) in 150mL of  
12 dichloromethane followed after 5 minutes by triethyl amine (5mL, 33mmol).  
13 After 2.5h at ambient temperature, the reaction mixture was washed with  
14 water and the organic phase was dried over anhydrous sodium sulfate and  
15 evaporated in vacuo to afford the title product as a brown oil in quantitative  
16 yield.

17 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): d 1.71 (s, 3H), 2.11(s, 3H), 3.28(s, 3H), 5.47(s,  
18 1H), 7.05(d, *J* = 8.5Hz, 2H), 7.50(d, *J* = 8.2Hz, 2H).

19 6-Bromo-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (Intermediate  
20 **55)**

21 N-(4-bromophenyl)-N-methyl-3-methyl-2-butenamide  
22 (**Intermediate 54**, 6.42g, 24mmol) was heated to 130°C and aluminum  
23 chloride (5g, 37.4mmol) was added in portions over 0.5h. The reaction  
24 mixture was stirred for 1 hour at the same temperature and then cooled to  
25 room temperature. Ice was added cautiously to the solid, followed by  
26 ~200mL of iced water. The reaction mixture was then extracted with ether  
27 (x2) and dichloromethane (x1) and the combined organic phase was dried  
28 over anhydrous magnesium sulfate and evaporated in *vacuo* to yield a brown

1 solid. The solid was treated with hexane-dichloromethane and filtered to  
2 afford 1.7g of product. The mother liquor was evaporated and purified by  
3 flash column chromatography on silica gel (230-400 mesh) to afford 2.9g of  
4 the title compound as a solid (total 72%).

5 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.29(s, 6H), 2.49(s, 2H), 3.36(s, 3H), 6.87(d,  
6 *J* = 8.2Hz, 1H), 7.36(dd, *J* = 2.0, 8.5Hz, 1H), 7.39(d, *J* = 2.0Hz, 1H).

7 6-Bromo-1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-  
8 cyclopropane] (**Intermediate 56**)

9 A stirred, cooled (-78°C) 3M solution of ethyl magnesium bromide in  
10 ether (8.1mL, 24.25mmol) under argon was treated with anhydrous  
11 tetrahydrofuran (20mL) followed by a solution of titanium tetra-*iso*-  
12 propoxide (3.15mL, 10.2mmol) in tetrahydrofuran (10mL). A solution of 6-  
13 bromo-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (**Intermediate 55**,  
14 2.6g, 9.7mmol) was cannulated into the reaction mixture and the solution  
15 was allowed to warm to room temperature overnight. It was then cooled in  
16 an ice-bath, quenched with saturated aqueous ammonium chloride solution,  
17 filtered over celite and the aqueous phase was extracted with diethyl ether  
18 (x2). The combined organic phase was dried over anhydrous magnesium  
19 sulfate, filtered and evaporated in *vacuo* to afford an orange oil. Flash  
20 column chromatography over silica gel (230-400 mesh) using 2-4% ethyl  
21 acetate in hexane as the eluent afforded the title compound as an oil which  
22 was ~70% pure (1.7g, 63%) and 0.5g of recovered starting material.

23 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.58(t, *J* = 6.0Hz, 2H), 0.91(t, *J* = 6.0Hz,  
24 2H), 1.35 (s, 6H), 1.70(s, 2H), 2.68 (s, 3H), 6.59 (d, *J* = 8.8Hz, 1H), 7.16(dd,  
25 *J* = 2.3, 8.8Hz, 1H), 7.33(d, *J* = 2.3Hz, 1H).

26 1,4,4-Trimethyl-6-(trimethylsilanyl)ethynylspiro[2*H*-1-1,2,3,4-  
27 tetrahydroquinoline-2,1'-cyclopropane] (**Intermediate 57**)

1       Following general procedure D and using 6-bromo-1,4,4-  
2 trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]  
3 (**Intermediate 56**, 0.56g, 2mmol), (trimethylsilyl)acetylene (1.13mL,  
4 8mmol), triethyl amine (4mL), anhydrous tetrahydrofuran (5mL),  
5 copper(I)iodide (0.08g, 0.4mmol) and  
6 dichlorobis(triphenylphosphine)palladium(II) (0.28g, 0.4mmol), followed by  
7 flash column chromatography over silica gel (230-400 mesh) using hexane-  
8 2% ethyl acetate in hexane as the eluent, the title compound was obtained as  
9 an oil (0.42g, 70%).

10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.023(s, 9H), 0.33(t, *J* = 6.1Hz, 2H), 0.71(t, *J*  
11 = 6.1Hz, 2H), 1.10(s, 6H), 1.45(s, 2H), 2.41 (s, 3H), 6.31(d, *J* = 8.5Hz, 1H),  
12 6.96 (dd, *J* = 2.1, 8.5Hz, 1H), 7.10(d, *J* = 2.1Hz, 1H).

13 Benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-  
14 2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 65**, **General**  
15 **Formula 1**)

16       Following general procedure E and using a solution of 1,4,4-  
17 trimethyl-6-(trimethylsilanyl)ethynylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-  
18 2,1'-cyclopropane] (**Intermediate 57**, 0.416g, 1.4mmol), methanol (10mL),  
19 ethyl acetate (2mL) and potassium carbonate (1.08g, mmol) a silyl  
20 deprotected acetylenic intermediate was obtained which was used directly  
21 for the next step (0.25g, 79%). Following general procedure F and using part  
22 of the acetylenic intermediate obtained as above (0.11g, 0.5mmol), ethyl-4-  
23 iodo benzoate (**Reagent A**, 0.112g, 0.4mmol), triethyl amine (1mL),  
24 tetrahydrofuran (2.5mL), copper(I)iodide (0.050g, 0.26mmol) and  
25 tetrakis(triphenylphosphine)palladium(0) (0.096g, 0.17mmol) followed by  
26 flash column chromatography over silica gel (230-400 mesh) using 8% ethyl  
27 acetate in hexane as the eluent and preparative HPLC on Partisil 10 silica

1 column using 10% ethyl acetate in hexane as the mobile phase, the title  
2 compound was obtained as a yellow oil (0.048g, 26%).  
3 <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.60 (t, *J* = 6.1Hz, 2H), 0.99(t, *J* = 6.1Hz,  
4 2H), 1.37(s, 6H), 1.42(t, *J* = 7.0Hz, 3H), 1.73(s, 2H), 2.68(s, 3H), 4.40 (q, *J*  
5 = 7.0Hz, 2H), 6.61(d, *J* = 8.8Hz, 1H), 7.28 (dd, *J* = 2.1, 8.5Hz, 1H), 7.42 (d,  
6 *J* = 2.1Hz, 1H), 7.57(d, *J* = 8.2Hz, 2H), 8.01(d, *J* = 8.2Hz, 2H).

7 Benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-  
8 2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 66, General Formula 1**)

9       Following general procedure I and using benzoic acid, 4-[(1,4,4-  
10 trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]-6-  
11 yl)ethynyl]-ethyl ester (**Compound 65**, 0.03g, 0.08mmol), ethanol (2mL),  
12 tetrahydrofuran (2mL) and 1M aqueous sodium hydroxide solution (1mL),  
13 the title compound was obtained as a yellow solid (0.020g, 67%).  
14 <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 0.60 (t, *J* = 5.8Hz, 2H), 1.03(t, *J* =  
15 5.8Hz, 2H), 1.34(s, 6H), 1.74(s, 2H), 2.69(s, 3H), 6.60(d, *J* = 8.5Hz, 1H),  
16 7.23 (dd, *J* = 2.0, 8.4Hz, 1H), 7.39 (d, *J* = 2.0Hz, 1H), 7.58(d, *J* = 8.2Hz,  
17 2H), 8.01(d, *J* = 8.2Hz, 2H).

#### 18 **Esterification Methods:**

##### 19 **Method A:**

20       The carboxylic acid was combined with a solution of the desired  
21 alcohol and concentrated sulfuric acid (20 to 1 v/v) and the resulting  
22 mixture or solution (0.75 to 1.0 M) heated to reflux overnight. The solution  
23 was cooled to room temperature, diluted with Et<sub>2</sub>O, and washed with H<sub>2</sub>O,  
24 saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried  
25 over MgSO<sub>4</sub>. Concentration of the dry solution under reduced pressure  
26 afforded the desired carboxylic ester of sufficient purity to be used directly  
27 in the next reaction.

1 **Method B:**

2 To a solution (0.67 to 1.0M) of the carboxylic acid in acetone was  
3 added 1.1 equivalents of the desired alkyl halide and 1.0 equivalents of solid  
4 potassium carbonate. The resulting mixture was heated to reflux for 2h and  
5 then allowed to stir at room temperature overnight. The mixture was filtered  
6 and the filtrate concentrated under reduced pressure. The product was  
7 isolated from the residue by column chromatography using silica gel as the  
8 solid phase.

9 **Method C:**

10 A solution (1M) of the carboxylic acid in thionyl chloride was heated  
11 at reflux until analysis of a reaction aliquot by IR spectroscopy showed the  
12 absence of the aryl carboxylic acid carbonyl band ( 1705 - 1680  $\text{cm}^{-1}$ ). The  
13 solution was cooled to room temperature and concentrated under reduced  
14 pressure to give the crude acyl chloride.

15 The acyl chloride was dissolved in  $\text{CH}_2\text{Cl}_2$  and the resulting solution  
16 (0.5 to 0.75M) treated with 1.1 equivalents the desired alcohol and 2.0  
17 equivalents of pyridine. After stirring overnight at room temperature the  
18 solution was diluted with  $\text{Et}_2\text{O}$  and washed with  $\text{H}_2\text{O}$ , 10% aqueous HCl,  
19 saturated aqueous  $\text{NaHCO}_3$ , and saturated aqueous NaCl before being dried  
20 over  $\text{Na}_2\text{SO}_4$ . Concentration of the dry solution under reduced pressure  
21 followed by column chromatography afforded the desired ester.

22 **GENERAL PROCEDURE 1 (preparation of Enol ethers):**

23 A solution (0.35 M) of the aryl ester in anhydrous THF was cooled to  
24 0 °C and treated with 1.0 equivalents of Tebbe's Reagent ( $[\mu\text{-chloro-}\mu\text{-}$   
25  $\text{methylene[bis(cyclopentadienyl)titanium]-dimethylaluminum}]$  0.5 M in  
26 toluene). After 30 minutes the solution was warmed to room temperature  
27 and stirred for 30 minutes before being carefully added to a 0.1 N NaOH  
28 solution at 0 °C. This mixture was treated with hexanes and the solids

1 removed by filtration through a pad of Celite. The solids were washed with  
2 hexanes and the filtrate passed through a second pad of Celite to remove any  
3 newly formed solids. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and  
4 concentrated under reduced pressure. The desired enol ether was isolated  
5 from the residue by column chromatography using 1-2% of  $\text{Et}_3\text{N}$  added to  
6 the eluant. (note: prolonged exposure of the product to the column can  
7 result in hydrolysis and formation of the corresponding methyl ketone.)

8 GENERAL PROCEDURE 2 (cyclopropanation of the enol ethers):

9 To a solution (0.3 M) of the enol ether in anhydrous  $\text{Et}_2\text{O}$  was added  
10 2.0 equivalent of  $\text{Et}_2\text{Zn}$  (as a solution in hexanes) and 2.0 equivalents of  
11  $\text{CH}_2\text{I}_2$ . The resulting solution was heated to reflux until analysis of a  
12 reaction aliquot (by TLC or  $^1\text{H}$  NMR) indicated that all of the starting enol  
13 ether had been consumed. (note: Additional equal amounts of  $\text{Et}_2\text{Zn}$  and  
14  $\text{CH}_2\text{I}_2$  can be added to drive the reaction to completion.) Upon cooling to  
15 room temperature the reaction was carefully quenched by the addition of  
16 saturated aqueous  $\text{NH}_4\text{Cl}$ . The resulting mixture is extracted with  $\text{Et}_2\text{O}$  and  
17 the combined organic layers washed with  $\text{H}_2\text{O}$  and saturated aqueous  $\text{NaCl}$   
18 before being dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  
19 The product is isolated from the residue by column chromatography.

20 1-Bromo-4-(1-methoxyvinyl)-benzene: (Intermediate 58)

21 Using General Procedure 1; methyl 4-bromo-benzoate (600.0 mg,  
22 2.78 mmols), and 5.6 mL of Tebbe's Reagent (794.0 mg, 2.78 mmols)  
23 afforded 420.0 mg (70%) of the title compound as a colorless oil after  
24 column chromatography (100% hexanes).  
25  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.48 - 7.45 (4H, m), 4.64 (1H, d,  $J = 2.9$  Hz), 4.23 (1H,  
26 d,  $J = 2.9$  Hz), 3.73 (3H, s).

27 1-Bromo-4-(1-methoxycyclopropyl)-benzene (Intermediate 59)

28 Using General Procedure 2; 1-bromo-4-(1-methoxyvinyl)-benzene

1 (Intermediate 58, 410.0 mg, 1.92 mmols), Et<sub>2</sub>Zn (711.3 mg, 5.76 mmols),  
2 and CH<sub>2</sub>I<sub>2</sub> (1.54 g, 5.76 mmols) in 4.0 mL Et<sub>2</sub>O afforded 300.0 mg (69%) of  
3 the title compound as a colorless oil after chromatography (0-3% EtOAc -  
4 hexanes).

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.5 Hz), 7.18 (2H, d, J = 8.5 Hz), 3.21  
6 (3H, s), 1.19 (2H, m), 0.94 (2H, m).

7 [4-(1-Methoxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate  
8 **60)**

9 Using General Procedure D; 1-bromo-4-(1-methoxycyclopropyl)-  
10 benzene (Intermediate 59, 300.0 mg, 1.32 mmol) in triethylamine (4 mL)  
11 and anhydrous tetrahydrofuran (4 mL) was treated with copper(I)iodide  
12 (93.0 mg, 0.13 mmol) and then sparged with argon for 5 minutes.  
13 Trimethylsilyl acetylene (1.39 g, 14.2 mmols) was then added followed by  
14 dichlorobis(triphenylphosphine)palladium(II) (93.0 mg, 0.13 mmol). The  
15 resulting reaction mixture was heated to 70 °C for 60h. The title compound  
16 (286.0 mg, 90%) was isolated by chromatography (0 - 3% EtOAc -  
17 hexanes).

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.35 (2H, d, J = 7.2 Hz), 7.14 (2H, d, J = 7.2 Hz), 3.14  
19 (3H, s), 1.14 (2H, m), 0.88 (2H, m), 0.17 (9H, s).

20 1-Ethynyl-4-(1-methoxycyclopropyl)-benzene (Intermediate 61)

21 Using General Procedure E; [4-(1-methoxycyclopropyl)-  
22 phenylethynyl]-trimethylsilane (Intermediate 60, 285.0 mg, 1.18 mmols) in  
23 methanol (10mL) was treated with potassium carbonate (100.0 mg, 0.72  
24 mmol) and stirred overnight at ambient temperature. The crude alkyne (220  
25 mg, 100%) was used directly in the next reaction.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.2 Hz), 3.23  
27 (3H, s), 3.06 (1H, s), 1.22 (2H, m), 0.98 (2H, m).

1 Ethyl 4-[4-(1-methoxycyclopropyl)-phenylethynyl]-benzoate (**Compound**  
2 **67, General Formula 2**)

3       Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-  
4 benzene (**Intermediate 61**, 100.0 mg, 0.47 mmol) and ethyl-4-iodo  
5 benzoate (**Reagent A**, 141.0 mg, 0.51 mmol) in triethyl amine (6 mL) was  
6 treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon  
7 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (109 mg, 0.16  
8 mmol) was added and the reaction mixture was stirred overnight at room  
9 temperature. Column chromatography (2-5% EtOAc - hexanes) afforded  
10 135.0 mg (90%) of the title compound as an orange solid.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.52  
12 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.25  
13 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.23 (2H, m), 1.00 (2H, m).

14 Methyl {4-[4-(1-methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate  
15 (**Compound 68, General Formula 2**)

16       Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-  
17 benzene (**Intermediate 61**, 120.0 mg, 0.56 mmol) and methyl-(4-  
18 iodophenyl)-acetate (**Reagent B**, 154.0 mg, 0.56 mmol) in triethyl amine (6  
19 mL) was treated with copper(I)iodide (35.0 mg, 0.19 mmol) and sparged  
20 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
21 (130 mg, 0.19 mmol) was added and the reaction mixture was stirred  
22 overnight at room temperature. Column chromatography (2-8% EtOAc -  
23 hexanes) afforded 140.0 mg (78%) of the title compound as an orange solid.  
24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50 (4H, d, J = 8.1 Hz), 7.28 (4H, d, J = 8.1 Hz), 3.76  
25 (3H, s), 3.64 (2H, s), 3.25 (3H, s), 1.22 (2H, m), 0.99 (2H, m).

26 4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound 69,**  
27 **General Formula 2**)

1       Using General Procedure I; a solution of ethyl 4-[4-(1-  
2 methoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 67**, 110.0 mg,  
3 0.34 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
4 NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred  
5 overnight at room temperature. Work-up afforded 85.0 mg (86%) of the  
6 title compound as an orange solid.

7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.05 (2H), 7.66 (2H), 7.56 (2H, d, J = 8.5 Hz), 7.35  
8 (2H, d, J = 8.6 Hz), 3.22 (3H, s), 1.21 (2H, m), 1.01 (2H, m).

9 {4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid  
10 (**Compound 70, General Formula 2**)

11       Using General Procedure I; a solution of methyl {4-[4-(1-  
12 methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 68**,  
13 100.0 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
14 treated with NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution)  
15 and stirred overnight at room temperature. Work-up afforded 80.0 mg  
16 (84%) of the title compound as an orange solid.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (4H), 7.27 (4H), 3.66 (2H, s), 3.25 (3H, s), 1.22  
18 (2H, m), 0.99 (2H, m).

19 Isopropyl 4-bromobenzoate (**Intermediate 62**)

20       Using General Esterification Procedure A; 4-bromobenzoic acid  
21 (1.50 g, 7.46 mmols) was combined with isopropyl alcohol to give 1.76 g  
22 (97%) of the title compound as a colorless oil.

23 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.90 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5  
24 Hz), 5.24 (1H, septet, J = 6.2 Hz), 1.37 (6H, d, J = 6.2 Hz).

25 1-Bromo-4-(1-isopropoxyvinyl)-benzene (**Intermediate 63**)

26       Using General Procedure 1; isopropyl 4-bromobenzoate  
27 (**Intermediate 62**, 780.0 mg, 3.20 mmols) and 6.4 mL of Tebbe's Reagent

1 (910.7 mg, 3.20 mmols) afforded 328.0 mg (43%) of the title compound as a  
2 colorless oil after column chromatography (100% hexanes).

3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (4H, m), 4.66 (1H, d, J = 2.6 Hz), 4.40 (1H, septet,  
4 J = 6.2 Hz), 4.21 (1H, d, J = 2.6 Hz), 1.34 (6H, d, J = 6.2 Hz).

5 1-Bromo-4-(1-isopropoxycyclopropyl)-benzene (Intermediate 64)

6 Using General Procedure 2; 1-bromo-4-(1-isopropoxyvinyl)-benzene  
7 (**Intermediate 63**, 328.0 mg, 1.36 mmols), Et<sub>2</sub>Zn (335.9 mg, 2.72 mmols),  
8 and CH<sub>2</sub>I<sub>2</sub> (728.0 mg, 2.72 mmols) in 4.0 mL Et<sub>2</sub>O afforded 240.0 mg (70%)  
9 of the title compound as a colorless oil after chromatography (3% EtOAc -  
10 hexanes).

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (2H, d, J = 8.5 Hz), 7.27 (2H, d, J = 8.5 Hz), 3.70  
12 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.06 (6H, d, J = 6.2 Hz), 0.91 (2H,  
13 m).

14 [4-(1-Isopropoxycyclopropyl)-phenylethynyl]-trimethylsilane

15 (**Intermediate 65**)

16 Using General Procedure D; 1-bromo-4-(1-isopropoxycyclopropyl)-  
17 benzene (**Intermediate 64**, 240.0 mg, 0.94 mmol) in triethylamine (8 mL)  
18 was treated with copper(I)iodide (18.0 mg, 0.094 mmol) and then sparged  
19 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was  
20 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (66.0  
21 mg, 0.094 mmol). The resulting reaction mixture was heated to 70 °C for 5  
22 days. The title compound (250.0 mg, 98%) was isolated by chromatography  
23 (0 - 3% EtOAc - hexanes) as an orange oil.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 3.70  
25 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.05 (6H, d, J = 6.2 Hz), 0.93 (2H,  
26 m), 0.94 (9H, s).

27 1-Ethynyl-4-(1-isopropoxycyclopropyl)-benzene (Intermediate 66)

1 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-  
2 phenylethynyl]-trimethylsilane (**Intermediate 65**, 260.0 mg, 0.96 mmol) in  
3 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72  
4 mmol) and stirred overnight at ambient temperature. The crude alkyne (220  
5 mg, 100%) was used directly in the next reaction.

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.45 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.8 Hz), 3.72  
7 (1H, septet, J = 6.2 Hz), 3.06 (1H, s), 1.20 (2H, m), 1.07 (6H, d, J = 6.2 Hz),  
8 0.95 (2H, m).

9 Ethyl 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-benzoate  
10 (**Compound 71, General Formula 2**)

11 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-  
12 benzene (**Intermediate 66**, 114.0 mg, 0.57 mmol) and ethyl-4-iodo  
13 benzoate (**Reagent A**, 731.0 mg, 0.63 mmol) in triethylamine (8 mL) was  
14 treated with copper(I)iodide (36.0 mg, 0.19 mmol) and sparged with argon  
15 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (133 mg, 0.19  
16 mmol) was added and the reaction mixture was stirred overnight at room  
17 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
18 151.0 mg (76%) of the title compound as an orange solid.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 7.6 Hz), 7.58 (2H, d, J = 7.6 Hz), 7.50  
20 (2H, d, J = 7.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.74  
21 (1H, septet, J = 6.2 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.22 (2H, m), 1.08 (6H, d,  
22 J = 6.2 Hz), 0.97 (2H, m).

23 Methyl {4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate  
24 (**Compound 72, General Formula 2**)

25 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-  
26 benzene (**Intermediate 66**, 95.0 mg, 0.45 mmol) and methyl-(4-  
27 iodophenyl)-acetate (**Reagent B**, 131.0 mg, 0.45 mmol) in triethylamine (6

1 mL) was treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged  
2 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
3 (111 mg, 0.16 mmol) was added and the reaction mixture was stirred  
4 overnight at room temperature. Column chromatography (2-8% EtOAc -  
5 hexanes) afforded 110.0 mg (70%) of the title compound as an orange oil.  
6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.20 (4H), 7.08 (2H, d, J = 7.0 Hz), 6.97 (2H, d, J = 7.9  
7 Hz), 3.45 (1H, septet, J = 6.2 Hz), 3.41 (3H, s), 3.35 (2H, s), 0.91 (2H, m),  
8 0.79 (6H, d, J = 6.2 Hz), 0.68 (2H, m).

9 4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound**  
10 **73, General Formula 2**)

11 Using General Procedure I; a solution of ethyl 4-[4-(1-  
12 isopropoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 71**, 110.0  
13 mg, 0.32 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated  
14 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and  
15 stirred overnight at room temperature. Work-up afforded 89.0 mg (88%) of  
16 the title compound as a yellow solid.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.55  
18 (2H, d, J = 8.2 Hz), 7.46 (2H, d, J = 8.2 Hz), 3.73 (1H, septet, J = 6.2 Hz),  
19 1.18 (2H, m), 1.04 (6H, d, J = 6.2 Hz), 0.99 (2H, m).

20 {4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid  
21 (**Compound 74, General Formula 2**)

22 Using General Procedure I; a solution of methyl {4-[4-(1-  
23 isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 72**,  
24 80.0 mg, 0.23 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
25 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
26 and stirred overnight at room temperature. Work-up afforded 48.0 mg  
27 (56%) of the title compound as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.20 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.09 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.2 Hz), 3.46 (1H, septet, J = 6.2 Hz), 3.37 (2H, s), 0.92 (2H, m), 0.79 (6H, d, J = 6.2 Hz), 0.67 (2H, m).

**Benzyl 4-bromobenzoate (Intermediate 67)**

Using General Esterification Method B; 4-bromobenzoic acid (2.01 g, 10.0 mmols), benzyl bromide (1.89 g, 11.1 mmols), and K<sub>2</sub>CO<sub>3</sub> (1.40 g, 10.0 mmols) afforded 2.33 g (80%) of the title compound as a colorless solid after column chromatography (3-10% EtOAc - hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.89 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.5 Hz), 7.43 - 7.31 (5H), 5.33 (2H, s).

**1-Bromo-4-(1-benzyloxyvinyl)-benzene (Intermediate 68)**

Using General Procedure 1; benzyl 4-bromobenzoate (**Intermediate 67**, 920.0 mg, 3.16 mmols) and 6.3 mL of Tebbe's Reagent (897.0 mg, 3.16 mmols) afforded 640.0 mg (70%) of the title compound after column chromatography (100% hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.55 - 7.35 (9H), 4.95 (2H, s), 4.73 (1H, d, J = 2.9 Hz), 4.34 (1H, d, J = 2.9 Hz).

**1-Bromo-4-(1-benzyloxycyclopropyl)-benzene (Intermediate 69)**

Using General Procedure 2; 1-bromo-4-(1-benzyloxyvinyl)-benzene (**Intermediate 68**, 280.0 mg, 0.97 mmol), Et<sub>2</sub>Zn (247.0 mg, 2.0 mmols), and CH<sub>2</sub>I<sub>2</sub> (536.0 mg, 2.0 mmols) in 2.0 mL Et<sub>2</sub>O afforded 159.0 mg (53%) of the title compound as a colorless solid after chromatography (2-5% EtOAc - hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 - 7.24 (9H), 4.41 (2H, s), 1.29 (2H, m), 1.00 (2H, m).

**[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate 70)**

1       Using General Procedure D; 1-bromo-4-(1-benzyloxycyclopropyl)-  
2 benzene (**Intermediate 69**, 160.0 mg, 0.53 mmol) in triethylamine (5 mL)  
3 was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged  
4 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was  
5 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (37.0  
6 mg, 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d.  
7 The title compound (150.0 mg, 83%) was isolated by chromatography (0 -  
8 3% EtOAc - hexanes) as a pale-yellow oil.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.21 (3H, m), 7.09 - 7.01 (6H, m), 4.18 (2H, s), 1.07  
10 (2H, m), 0.79 (2H, m), 0.02 (9H, s).

11 1-Ethynyl-4-(1-benzyloxycyclopropyl)-benzene (**Intermediate 71**)

12       Using General Procedure E; [4-(1-benzyloxycyclopropyl)-  
13 phenylethynyl]-trimethylsilane (**Intermediate 70**, 150.0 mg, 0.47 mmols) in  
14 methanol (6 mL) was treated with potassium carbonate (100.0 mg, 0.72  
15 mmol) and stirred overnight at ambient temperature. The crude alkyne (115  
16 mg, 100%) was used directly in the next reaction.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.67 - 7.50 (2H, d, J = 8.2 Hz), 7.34 - 7.26 (7H, m),  
18 4.43 (2H, s), 3.07 (1H, s), 1.32 (2H, m), 1.04 (2H, m).

19 Ethyl 4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-benzoate (**Compound**  
20 **75, General Formula 2**)

21       Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-  
22 benzene (**Intermediate 71**, 60.0 mg, 0.24 mmol) and ethyl-4-iodo benzoate  
23 (**Reagent A**, 72.0 mg, 0.26 mmol) in triethylamine (4 mL) was treated with  
24 copper(I)iodide (17.0 mg, 0.09 mmol) and sparged with argon for 5 minutes.  
25 Dichlorobis(triphenylphosphine)palladium(II) (61 mg, 0.09 mmol) was  
26 added and the reaction mixture was stirred overnight at room temperature.  
27 Column chromatography (2-4% EtOAc - hexanes) afforded 85.0 mg (91%)

1 of the title compound as an orange oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.62-7.54 (4H, m), 7.39-7.26  
3 (7H, m), 4.47 (2H, s), 4.40 (2H, q, J = 7.1 Hz), 1.42 (3H, t, J = 7.1 Hz), 1.36  
4 (2H, m), 1.07 (2H, m).

5 Methyl {4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate

6 (**Compound 76, General Formula 2**)

7 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-  
8 benzene (**Intermediate 71**, 60.0 mg, 0.20 mmol) and methyl-(4-  
9 iodophenyl)-acetate (**Reagent B**, 66.0 mg, 0.24 mmol) in triethylamine (5  
10 mL) was treated with copper(I)iodide (15.0 mg, 0.08 mmol) and sparged  
11 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (56  
12 mg, 0.08 mmol) was added and the reaction mixture was stirred overnight at  
13 room temperature. Column chromatography (2-7% EtOAc - hexanes)  
14 afforded 64.0 mg (81%) of the title compound as a yellow oil.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.52-7.47 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s),  
16 3.70 (3H, s), 3.64 (2H, s), 1.32 (2H, m), 1.06 (2H, m).

17 4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-benzoic acid (**Compound**  
18 **77, General Formula 2**)

19 Using General Procedure I; a solution of ethyl 4-[4-(1-  
20 benzyloxycyclopropyl)-phenylethynyl]-benzoate (**Compound 75**, 78.0 mg,  
21 0.20 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
22 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred  
23 overnight at room temperature. Work-up afforded 65.0 mg (89%) of the  
24 title compound as a solid.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.97 (2H, d, J = 8.5 Hz), 7.67 (2H, d, J = 8.7 Hz), 7.58  
26 (2H, d, J = 8.5 Hz), 7.41-7.28 (7H, m), 4.44 (2H, s), 1.33 (2H, m), 1.12 (2H,  
27 m).

1 {4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid

2 **(Compound 78, General Formula 2)**

3       Using General Procedure I; a solution of methyl {4-[4-(1-  
4 benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 76**,  
5 45.0 mg, 0.11 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
6 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
7 and stirred overnight at room temperature. Work-up afforded 35.0 mg  
8 (81%) of the title compound as a pale-yellow solid.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s), 3.66  
10 (2H, s), 1.32 (2H, m), 1.05 (2H, m).

11 Benzyl 4-bromo-2-methylbenzoate (Intermediate 72)

12       Using General Esterification Method C; 2-methyl-4-bromo-benzoic  
13 acid (2.15 g, 10.0 mmols) was refluxed for 3h with 10 mL SOCl<sub>2</sub>. The  
14 resulting solution concentrated under reduced pressure and the crude acyl  
15 chloride was combined with benzyl alcohol (1.08 g, 10.0mmols) and  
16 pyridine (1.6 mL, 20.0 mmols) to give the title compound (2.4 g, 80%) after  
17 work-up and column chromatography (2-5% EtOAc - hexanes) as a  
18 colorless oil.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.81 (1H, d, J = 8.5 Hz), 7.41-7.33 (7H, m), 5.32 (2H,  
20 s), 2.57 (3H, s).

21 4-Bromo-1-(1-benzyloxyvinyl)-2-methylbenzene (Intermediate 73)

22       Using General Procedure 1; benzyl 4-bromo-2-methylbenzoate  
23 (**Intermediate 72**, 840.0 mg, 2.77 mmols) and 5.4 mL of Tebbe's Reagent  
24 (788.0 mg, 2.77 mmols) afforded 640.0 mg (76%) of the title compound  
25 after column chromatography (100% hexanes).

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38-7.19 (8H, m), 4.88 (2H, s), 4.45 (1H, d, J = 2.6  
27 Hz), 4.25 (2H, d, J = 2.6 Hz), 2.35 (3H, s).

1 4-Bromo-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (**Intermediate 74**)

2       Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-methyl-  
3 benzene (**Intermediate 73**, 400.0 mg, 1.32 mmols), Et<sub>2</sub>Zn (325.0 mg, 2.63  
4 mmols), and CH<sub>2</sub>I<sub>2</sub> (704.0 mg, 2.63 mmols) in 4 mL Et<sub>2</sub>O afforded 380.0 mg  
5 (90%) of the title compound as a colorless oil after chromatography (2-5%  
6 EtOAc - hexanes).

7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42-7.20 (8H, m), 4.31 (2H, s), 2.58 (3H, s), 1.25 (2H,  
8 m), 0.94 (2H, m).

9 [4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane  
10 (**Intermediate 75**)

11       Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-  
12 methyl-benzene (**Intermediate 74**, 320.0 mg, 1.00 mmol) in triethylamine  
13 (8 mL) was treated with copper(I)iodide (19.0 mg, 0.1 mmol) and then  
14 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1  
15 mmols) was then added followed by dichlorobis-  
16 (triphenylphosphine)palladium(II) (70.0 mg, 0.05 mmol). The resulting  
17 reaction mixture was heated to 70 °C for 5d. The title compound (300.0 mg,  
18 89%) was isolated by chromatography (0 - 2% EtOAc - hexanes).

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.34-7.13 (8H, m), 4.24 (2H, s), 2.52 (3H, s), 1.20  
20 (2H, m), 0.88 (2H, m), 0.25 (9H, s).

21 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (**Intermediate**  
22 **76**)

23       Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-methyl-  
24 phenylethynyl]-trimethylsilane (**Intermediate 75**, 300.0 mg, 0.95 mmols) in  
25 methanol (6 mL) was treated with potassium carbonate (120.0 mg, 0.87  
26 mmol) and stirred overnight at ambient temperature. The crude alkyne (185  
27 mg, 79%) was used directly in the next reaction.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.16 (8H, m), 4.27 (2H, s), 3.07 (1H, s), 2.55  
2 (3H, s), 1.21 (2H, m), 0.92 (2H, m).

3 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate  
4 **(Compound 79, General Formula 2)**

5 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
6 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and ethyl-4-iodo  
7 benzoate (**Reagent A**, 95.0 mg, 0.34 mmol) in triethylamine (6 mL) was  
8 treated with copper(I)iodide (23.0 mg, 0.12 mmol) and sparged with argon  
9 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11  
10 mmol) was added and the reaction mixture was stirred overnight at room  
11 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
12 68.0 mg (54%) of the title compound.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz),  
14 7.33-7.16 (8H, m), 4.39 (2H, q, J = 7.1 Hz), 4.29 (2H, s), 2.57 (3H, s), 1.40  
15 (3H, t, J = 7.1 Hz), 1.22 (2H, m), 0.93 (2H, m).

16 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-  
17 acetate (Compound 80, General Formula 2)

18 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
19 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and methyl-(4-  
20 iodophenyl)-acetate (**Reagent B**, 95.0 mg, 0.34 mmol) in triethylamine (5  
21 mL) was treated with copper(I)iodide (22.0 mg, 0.11 mmol) and sparged  
22 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80  
23 mg, 0.11 mmol) was added and the reaction mixture was stirred overnight at  
24 room temperature. Column chromatography (2-4% EtOAc - hexanes)  
25 afforded 90.0 mg (71%) of the title compound as a pale-yellow oil.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.32-7.16 (10H, m), 4.28  
27 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 2.56 (3H, s), 1.22 (2H, m), 0.92 (2H, m).

1 4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid

2 **(Compound 81, General Formula 2)**

3       Using General Procedure I; a solution of ethyl 4-[4-(1-  
4 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 79**,  
5 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
6 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)  
7 and stirred overnight at room temperature. Work-up afforded 48.0 mg  
8 (76%) of the title compound as a solid.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.10 (2H, d, J = 8.1 Hz), 7.63 (2H, d, J = 8.1 Hz), 7.44-  
10 7.16 (8H, m), 4.29 (2H, m), 2.58 (3H, s), 1.24 (2H, m), 0.94 (2H, m).

11 {4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic  
12 acid (Compound 82, General Formula 2)

13       Using General Procedure I; a solution of methyl {4-[4-(1-  
14 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate  
15 (**Compound 80**, 75.0 mg, 0.18 mmol) in ethanol (3 mL) and  
16 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0  
17 mL of a 1N aqueous solution) and stirred overnight at room temperature.  
18 Work-up afforded 30.0 mg (40%) of the title compound.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.51 (2H, d, J = 8.2 Hz), 7.42 (1H, s), 7.33-7.17 (9H,  
20 m), 4.36 (2H, s), 3.67 (2H, s), 2.57 (3H, s), 1.23 (2H, m), 0.94 (2H, m).

21 Isopropyl 3-methyl-4-bromobenzoate (Intermediate 77)

22       Using General Esterification Procedure A; 4-bromo-2-methylbenzoic  
23 acid (1.6 g, 7.4 mmols) was combined with isopropyl alcohol to give 1.5 g  
24 (79%) of the title compound as a colorless oil.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.76 (1H, d, J = 8.2 Hz), 7.40 (1H, d, J = 7.4 Hz), 7.37  
26 (1H, dd, J = 1.4, 8.2 Hz), 5.23 (1H, septet, J = 6.2 Hz), 2.57 (3H, s), 1.37  
27 (6H, d, J = 6.2 Hz).

1 4-Bromo-1-(1-isopropoxyvinyl)-2-methyl-benzene (Intermediate 78)

2       Using General Procedure 1; isopropyl 2-methyl-4-bromobenzoate  
3 (**Intermediate 77**, 800.0 mg, 3.11 mmols) and 6.2 mL of Tebbe's Reagent  
4 (885.2 mg, 3.11 mmols) afforded 595.0 mg (75%) of the title compound as a  
5 colorless oil after column chromatography (100% hexanes).

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31-7.25 (2H, m), 7.16 (1H, d, J = 8.2 Hz), 4.34 (1H,  
7 septet, J = 6.0 Hz), 4.31 (1H, d, J = 2.1 Hz), 4.18 (1H, d, J = 2.1 Hz), 2.33  
8 (3H, s), 1.31 (6H, d, J = 6.0 Hz).

9 4-Bromo-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (Intermediate  
10 **79)**

11       Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-  
12 methyl-benzene (**Intermediate 78**, 389.0 mg, 1.53 mmols), Et<sub>2</sub>Zn (376.6  
13 mg, 3.05 mmols), and CH<sub>2</sub>I<sub>2</sub> (817.0 mg, 3.05 mmols) in 3.0 mL Et<sub>2</sub>O  
14 afforded 340.0 mg (84%) of the title compound as a colorless oil after  
15 chromatography (3% EtOAc - hexanes).

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.33 (1H, d, J = 2.3 Hz), 7.24 (1H, dd, J = 2.3, 8.2 Hz),  
17 7.13 (1H, d, J = 8.2 Hz), 3.57 (1H, septet, J = 6.1 Hz), 2.49 (3H, s), 1.00  
18 (2H, m), 0.97 (6H, d, J = 6.1 Hz), 0.82 (2H, m).

19 [4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane  
20 (**Intermediate 80)**

21       Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-  
22 2-methyl-benzene (**Intermediate 79**, 250.0 mg, 0.95 mmol) in triethylamine  
23 (8 mL) was treated with copper(I)iodide (19.0 mg, 0.10 mmol) and then  
24 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1  
25 mmols) was then added followed by dichlorobis-  
26 (triphenylphosphine)palladium(II) (70.0 mg, 0.1 mmol). The resulting  
27 reaction mixture was heated to 70 °C for 5d. The title compound (250.0 mg,

1 91%) was isolated by chromatography (0 - 3% EtOAc - hexanes).

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32-7.17 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.48

3 (3H, s), 1.00 (2H, m), 0.95 (6H, d, J = 6.2 Hz), 0.83 (2H, m), 0.24 (9H, s).

4 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (**Intermediate**  
5 **81**)

6 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-methyl-  
7 phenylethynyl]-trimethylsilane (**Intermediate 80**, 250.0 mg, 0.87 mmol) in  
8 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72  
9 mmol) and stirred overnight at ambient temperature. The crude alkyne (180  
10 mg, 98%) was used directly in the next reaction.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.23 (2H, m), 3.57 (1H, septet, J = 6.2  
12 Hz), 3.05 (1H, s), 2.50 (3H, s), 1.11 (2H, m), 0.96 (6H, d, J = 6.2 Hz), 0.83  
13 (2H, m).

14 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate  
15 (**Compound 83, General Formula 2**)

16 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-  
17 3-methyl-benzene (**Intermediate 81**, 80.0 mg, 0.13 mmol) and ethyl-4-iodo  
18 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was  
19 treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with argon  
20 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (91 mg, 0.13  
21 mmol) was added and the reaction mixture was stirred overnight at room  
22 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
23 75.0 mg (56%) of the title compound as an orange solid.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.2 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.39  
25 (1H, s), 7.29-7.20 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.60 (1H, septet, J = 6.2  
26 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87  
27 (2H, m).

1 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-  
2 acetate (Compound 84, General Formula 2)

3       Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-  
4 3-methyl-benzene (**Intermediate 81**, 100.0 mg, 0.47 mmol) and methyl-(4-  
5 iodophenyl)-acetate (**Reagent B**, 129.0 mg, 0.45 mmol) in triethylamine (6  
6 mL) was treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged  
7 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
8 (110 mg, 0.16 mmol) was added and the reaction mixture was stirred  
9 overnight at room temperature. Column chromatography (2-4% EtOAc -  
10 hexanes) afforded 120.0 mg (71%) of the title compound.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.5 Hz), 7.36 (1H, s), 7.29-7.22 (4H,  
12 m), 3.70 (3H, s), 3.63 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.52 (3H, s),  
13 1.09 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.86 (2H, m).

14 4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid  
15 (Compound 85, General Formula 2)

16       Using General Procedure I; a solution of ethyl 4-[4-(1-  
17 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 83**,  
18 60.0 mg, 0.17 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was  
19 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
20 and stirred overnight at room temperature. Work-up afforded 38.0 mg  
21 (69%) of the title compound as a colorless solid.

22 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz),  
23 7.42 (1H, s), 7.35 (2H, m), 3.59 (1H, septet, J = 6.2 Hz), 2.52 (3H, s), 1.07  
24 (2H, m), 0.93 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

25 {4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic  
26 acid (Compound 86, General Formula 2)

27       Using General Procedure I; a solution of methyl {4-[4-(1-

1 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate  
2 (**Compound 84**, 100.0 mg, 0.28 mmol) in ethanol (3 mL) and  
3 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0  
4 mL of a 1N aqueous solution) and stirred overnight at room temperature.  
5 Work-up afforded 60.0 mg (62%) of the title compound as a colorless solid.  
6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 7.6 Hz), 7.36 (1H, s), 7.25 (4H, m),  
7 3.65 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.51 (3H, s), 1.12 (2H, m), 0.97  
8 (6H, d, J = 6.2 Hz), 0.86 (2H, m).

9 2,2-Dimethylpropyl 2-methyl-4-bromobenzoate (**Intermediate 82**)

10 Using General Esterification Method C; 2-methyl-4-bromo-benzoic  
11 acid (1.82 g, 8.47 mmols) was refluxed for 3h with 10 mL SOCl<sub>2</sub>. The  
12 resulting solution was concentrated under reduced pressure and the crude  
13 acyl chloride combined with 2,2-dimethylpropanol (0.75 g, 8.47 mmols) and  
14 pyridine (1.4 mL, 16.9 mmols) to give the title compound (1.64 g, 68%)  
15 after work-up and column chromatography (2-5% EtOAc - hexanes) as a  
16 colorless oil.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.81 (1H, d, J = 8.2 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.39  
18 (1H, dd, J = 2.0, 8.2 Hz), 3.99 (2H, s), 2.60 (3H, s), 1.03 (9H, s).

19 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-vinyl]-2-methyl-benzene  
20 (**Intermediate 83**)

21 Using General Procedure 1; 2,2-dimethylpropyl 2-methyl-4-  
22 bromobenzoate (**Intermediate 82**, 820.0 mg, 2.87 mmols) and 5.8 mL of  
23 Tebbe's Reagent (817.0 mg, 2.87 mmols) afforded 800.0 mg (98%) of the  
24 title compound as a colorless oil after column chromatography (100%  
25 hexanes). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J =  
26 2.0, 8.2 Hz), 7.18 (1H, d, J = 8.2 Hz), 4.27 (1H, d, J = 2.1 Hz), 4.10 (1H, d,  
27 J = 2.1 Hz), 3.43 (2H, s), 2.33 (3H, s), 0.98 (9H, s).

1 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene  
2 **(Intermediate 84)**

3 Using General Procedure 2; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-  
4 cyclopropyl]-2-methyl-benzene (**Intermediate 83**, 400.0 mg, 1.43 mmols),  
5 Et<sub>2</sub>Zn (353.2 mg, 2.86 mmols), and CH<sub>2</sub>I<sub>2</sub> (760.0 mg, 2.86 mmols) in 3.0  
6 mL Et<sub>2</sub>O afforded 370.0 mg (87%) of the title compound as a colorless oil  
7 after chromatography (3% EtOAc - hexanes).

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.36 (1H, s), 7.27 (1H, d, J = 8.5 Hz), 7.09 (1H, d, J =  
9 7.9 Hz), 2.86 (2H, s), 2.52 (3H, s), 1.08 (2H, m), 0.83 (2H, m), 0.80 (9H, s).  
10 [4-[1-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]]-  
11 trimethylsilane (Intermediate 84a)

12 Using General Procedure D; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-  
13 cyclopropyl]-2-methyl-benzene (**Intermediate 84**, 255.0 mg, 0.86 mmol) in  
14 triethylamine (8 mL) was treated with copper(I)iodide (17.0 mg, 0.09 mmol)  
15 and then sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g,  
16 7.1 mmols) was then added followed by dichlorobis-  
17 (triphenylphosphine)palladium(II) (63.0 mg, 0.09 mmol). The resulting  
18 reaction mixture was heated to 70 °C for 5d. The title compound (220.0 mg,  
19 81%) was isolated by chromatography (1-2% EtOAc - hexanes).  
20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.30 (1H, s), 7.21 (1H, d, J = 7.6 Hz), 7.12 (1H, d, J =  
21 8.6 Hz), 2.80 (2H, s), 2.47 (3H, s), 1.05 (2H, m), 0.82 (2H, m), 0.75 (9H, s),  
22 0.24 (9H, s).

23 4-Ethynyl-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene  
24 **(Intermediate 85)**

25 Using General Procedure E; [4-[1-[1-(2,2-dimethylpropyloxy)-  
26 cyclopropyl]]-3-methyl-phenylethynyl]-trimethylsilane (**Intermediate 84a**,  
27 220.0 mg, 0.83 mmol) in methanol (10 mL) was treated with potassium

1 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient  
2 temperature. The crude alkyne (155 mg, 76%) was used directly in the next  
3 reaction.

4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.24 (1H, d, J = 7.1 Hz), 7.15 (1H, d, J =  
5 7.1 Hz), 3.04 (1H, s), 2.83 (2H, s), 2.49 (3H, s), 1.06 (2H, m), 0.83 (2H, m),  
6 0.76 (9H, s).

7 Ethyl 4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-  
8 phenylethynyl]-benzoate (Compound 87, General Formula 2)

9 Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-  
10 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and  
11 ethyl-4-iodo benzoate (**Reagent A**, 86.0 mg, 0.31 mmol) in triethylamine (5  
12 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged  
13 with argon for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II)  
14 (78 mg, 0.11 mmol) was added and the reaction mixture was stirred  
15 overnight at room temperature. Column chromatography (2-4% EtOAc -  
16 hexanes) afforded 60.0 mg (50%) of the title compound as an orange solid.  
17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.38  
18 (1H, s), 7.30 (1H, dd, J = 1.1, 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 4.38 (2H, q,  
19 J = 7.1 Hz), 2.84 (2H, s), 2.52 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.07 (2H, m),  
20 0.84 (2H, m), 0.77 (9H, s).

21 Methyl {4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-  
22 phenylethynyl]-phenyl}-acetate (Compound 88, General Formula 2)

23 Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-  
24 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and  
25 methyl-(4-iodophenyl)-acetate (**Reagent B**, 86.0 mg, 0.31 mmol) in  
26 triethylamine (6 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol)  
27 and sparged with argon for 5 minutes.

1 Dichlorobis(triphenylphosphine)palladium(II) (78 mg, 0.11 mmol) was  
2 added and the reaction mixture was stirred overnight at room temperature.  
3 Column chromatography (2-4% EtOAc - hexanes) afforded 100.0 mg (83%)  
4 of the title compound.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 7.9 Hz), 7.36-7.24 (4H, m), 7.18 (1H,  
6 d, J = 7.9 Hz), 3.70 (3H, s), 3.63 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07  
7 (2H, m), 0.83 (2H, m), 0.77 (9H, s).

8 4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-  
9 benzoic acid (Compound 89, General Formula 2)

10 Using General Procedure I; a solution of ethyl 4-[4-[1-(2,2-  
11 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-benzoate  
12 (Compound 87, 60.0 mg, 0.15 mmol) in ethanol (3 mL) and  
13 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0  
14 mL of a 1N aqueous solution) and stirred overnight at room temperature.  
15 Work-up afforded 24.0 mg (43%) of the title compound as a colorless solid.  
16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.06 (2H, d, J = 7.9 Hz), 7.65 (2H, d, J = 7.9 Hz), 7.42  
17 (1H, s), 7.33 (2H, m), 2.89 (2H, s), 2.53 (3H, s), 1.07 (2H, m), 0.90 (2H, m),  
18 0.77 (9H, s).

19 {4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-  
20 phenyl}-acetic acid (Compound 90, General Formula 2)

21 Using General Procedure I; a solution of methyl {4-[4-[1-(2,2-  
22 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetate  
23 (Compound 88, 95.0 mg, 0.24 mmol) in ethanol (3 mL) and  
24 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0  
25 mL of a 1N aqueous solution) and stirred overnight at room temperature.  
26 Work-up afforded 49.0 mg (53%) of the title compound as a colorless solid.  
27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.36 (1H, s), 7.27 (3H, m),

1 7.18 (1H, d,  $J = 7.9$  Hz), 3.66 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07 (2H,  
2 m), 0.83 (2H, m), 0.77 (9H, s).

3 Benzyl 4-bromo-2-ethyl-benzoate (**Intermediate 86**)

4 Using General Esterification Method B; 4-bromo-2-ethyl-benzoic  
5 acid (0.98 g, 4.25 mmols), benzyl bromide (0.80 g, 4.68 mmols), and  $K_2CO_3$   
6 (0.64 g, 4.68 mmols) afforded 1.0 g (74%) of the title compound after  
7 column chromatography (0-3% EtOAc - hexanes).

8  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 7.76 (1H, d,  $J = 8.5$  Hz), 7.41-7.33 (7H, m), 5.32 (2H,  
9 s), 2.95 (2H, q,  $J = 7.6$  Hz), 1.20 (3H, t,  $J = 7.6$  Hz).

10 4-Bromo-1-(1-benzyloxyvinyl)-2-ethyl-benzene (**Intermediate 87**)

11 Using General Procedure 1; benzyl 4-bromo-2-ethylbenzoate  
12 (**Intermediate 86**, 1.20 g, 3.78 mmols) and 7.6 mL of Tebbe's Reagent  
13 (1.08 g, 3.78 mmols) afforded 800.0 mg (66%) of the title compound after  
14 column chromatography (100% hexanes).

15  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 7.37-7.17 (8H, m), 4.88 (2H, s), 4.43 (1H, d,  $J = 2.1$   
16 Hz), 4.25 (1H, d,  $J = 2.1$  Hz), 2.71 (2H, q,  $J = 7.6$  Hz), 1.18 (3H, t,  $J = 7.6$   
17 Hz).

18 4-Bromo-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (**Intermediate 88**)

19 Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-ethyl-  
20 benzene (**Intermediate 87**, 330.0 mg, 1.04 mmols),  $Et_2Zn$  (257.0 mg, 2.08  
21 mmols), and  $CH_2I_2$  (557.0 mg, 2.08 mmols) in 4 mL  $Et_2O$  afforded 241.0 mg  
22 (70%) of the title compound as a colorless oil after chromatography (2-5%  
23 EtOAc - hexanes).

24  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 7.43-7.15 (8H, m), 4.27 (2H, s), 3.00 (2H, q,  $J = 7.6$   
25 Hz), 1.29-1.21 (5H, m), 0.90 (2H, m).

26 [4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane  
27 (**Intermediate 89**)

1       Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-  
2 ethyl-benzene (**Intermediate 88**, 220.0 mg, 0.66 mmol) in triethylamine (8  
3 mL) was treated with copper(I)iodide (14.0 mg, 0.07 mmol) and then  
4 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1  
5 mmols) was then added followed by dichlorobis-  
6 (triphenylphosphine)palladium(II) (50.0 mg, 0.07 mmol). The resulting  
7 reaction mixture was heated to 70 °C for 5d. The title compound was  
8 isolated by chromatography (0 - 2% EtOAc - hexanes).

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41-7.13 (8H, m), 4.24 (2H, s), 2.98 (2H, q, J = 7.6  
10 Hz), 1.25 (3H, t, J = 7.6 Hz), 1.20 (2H, m), 0.90 (2H, m), 0.26 (9H, s).

11 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (**Intermediate 90**)

12       Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-ethyl-  
13 phenylethynyl]-trimethylsilane (**Intermediate 89**, 240 mg, 0.69 mmol) in  
14 methanol (6 mL) was treated with potassium carbonate (10.0 mg, 0.72  
15 mmol) and stirred overnight at ambient temperature. The crude alkyne (190  
16 mg, 99%) was used directly in the next reaction. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43-  
17 7.15 (8H, m), 4.27 (2H, s), 3.08 (1H, s), 3.01 (2H, q, J = 7.6 Hz), 1.26 (3H,  
18 t, J = 7.6 Hz), 1.22 (2H, m), 0.92 (2H, m).

19 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate  
20 (**Compound 91**, General Formula 2)

21       Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
22 ethyl-benzene (**Intermediate 90**, 90.0 mg, 0.33 mmol) and ethyl-4-iodo  
23 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was  
24 treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged with argon  
25 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (77 mg, 0.11  
26 mmol) was added and the reaction mixture was stirred overnight at room  
27 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded

1 100.0 mg (72%) of the title compound.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (2H, d, J = 7.9 Hz), 7.49  
3 (1H, s), 7.36-7.16 (7H, m), 4.38 (2H, q, J = 7.1 Hz), 4.28 (2H, s), 3.04 (2H,  
4 q, J = 7.6 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H,  
5 m), 0.94 (2H, m).

6 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-  
7 acetate (Compound 92, General Formula 2)

8 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-  
9 ethyl-benzene (**Intermediate 90**, 107.0 mg, 0.39 mmol) and methyl-(4-  
10 iodophenyl)-acetate (**Reagent B**, 110.0 mg, 0.39 mmol) in triethylamine (5  
11 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged  
12 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91  
13 mg, 0.13 mmol) was added and the reaction mixture was stirred overnight at  
14 room temperature. Column chromatography (2-4% EtOAc - hexanes)  
15 afforded 130.0 mg (79%) of the title compound as a pale-yellow oil.  
16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (3H, m), 7.32-7.16 (9H, m), 4.28 (2H, s), 3.71  
17 (3H, s), 3.64 (2H, s), 3.03 (2H, q, J = 7.6 Hz), 1.32-1.23 (5H, m), 0.94 (2H,  
18 m).

19 4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid  
20 (Compound 93, General Formula 2)

21 Using General Procedure I; a solution of ethyl 4-[4-(1-  
22 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 91**,  
23 100.0 mg, 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
24 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
25 and stirred overnight at room temperature. Work-up and purification by  
26 HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded the title compound as a  
27 colorless solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.10 (2H, d, J = 8.5 Hz), 7.64 (2H, d, J = 8.5 Hz), 7.50 (1H, s), 7.35-7.16 (7H, m), 4.29 (2H, s), 3.04 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J = 7.6 Hz), 1.25 (2H, m), 0.95 (2H, m).

{4-[4-(1-Benzoyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid  
(**Compound 94, General Formula 2**)

Using General Procedure I; a solution of methyl {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate (**Compound 92**, 130.0 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred overnight at room temperature. Work-up and purification by HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (3H, m), 7.31-7.16 (9H, m), 4.28 (2H, s), 3.66 (2H, s), 3.02 (2H, q, J = 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H, m), 0.94 (2H, m).

Isopropyl 2-ethyl-4-bromobenzoate (**Intermediate 91**)

Using General Esterification Procedure A; 4-bromo-2-ethyl-benzoic acid (2.25 g, 9.9 mmols) was combined with isopropyl alcohol to give the title compound as a colorless oil after column chromatography (2% EtOAc-hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.69 (1H, d, J = 8.5 Hz), 7.41 (1H, s), 7.36 (1H, d, J = 8.5 Hz), 5.23 (1H, septet, J = 6.2 Hz), 2.95 (2H, q, J = 7.6 Hz), 1.37 (6H, d, J = 6.2 Hz), 1.23 (3H, t, J = 7.6 Hz).

4-Bromo-1-(1-isopropoxyvinyl)-2-ethyl-benzene (**Intermediate 92**)

Using General Procedure 1; isopropyl 2-ethyl-4-bromobenzoate (**Intermediate 91**, 1.21 g, 4.46 mmols) and 8.9 mL of Tebbe's Reagent (1.27 g, 4.46 mmols) afforded 570.0 mg (75%) of the title compound after column chromatography (100% hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.36 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J = 2.0, 8.0 Hz), 7.17 (1H, d, J = 8.0 Hz), 4.39 (1H, septet, J = 6.2 Hz), 4.31 (1H, d, J = 2.1 Hz), 4.26 (1H, d, J = 2.1 Hz), 2.73 (2H, q, J = 7.6 Hz), 1.35 (6H, d, J = 6.2 Hz), 1.24 (3H, t, J = 7.6 Hz).

4-Bromo-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (Intermediate 93)

Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-ethyl-benzene (**Intermediate 92**, 570.0 mg, 2.11 mmols), Et<sub>2</sub>Zn (521.0 mg, 4.22 mmols), and CH<sub>2</sub>I<sub>2</sub> (1.13 g, 4.22 mmols) in 7.0 mL Et<sub>2</sub>O afforded 500.0 mg (85%) of the title compound as a colorless oil after chromatography (3% EtOAc - hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (1H, d, J = 2.1 Hz), 7.25 (1H, dd, J = 2.1, 8.1 Hz), 7.15 (1H, d, J = 8.1 Hz), 3.59 (1H, septet, J = 6.2 Hz), 2.97 (2H, q, J = 7.6 Hz), 1.27 (3H, t, J = 7.6 Hz), 1.11 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.83 (2H, m).

[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane (Intermediate 94)

Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (**Intermediate 93**, 300.0 mg, 1.07 mmol) in triethylamine (8 mL) was treated with copper(I)iodide (20.0 mg, 0.11 mmol) and then sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added followed by dichlorobis-(triphenylphosphine)palladium(II) (75.0 mg, 0.11 mmol). The resulting reaction mixture was heated to 70 °C for 5d. The title compound (320.0 mg, 99%) was isolated by chromatography (0 - 2% EtOAc - hexanes) as an orange oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.21 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.96 (2H, q, J = 7.6 Hz), 1.27 (3H, t, J = 7.6 Hz), 1.10 (2H, m), 0.94 (6H, d, J =

1 6.2 Hz), 0.84 (2H, m), 0.25 (9H, s).

2 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (Intermediate 95)

3 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-ethyl-  
4 phenylethynyl]-trimethylsilane (**Intermediate 94**, 330.0 mg, 1.10 mmols) in  
5 methanol (10 mL) was treated with potassium carbonate (150.0 mg, 1.10  
6 mmol) and stirred overnight at ambient temperature. The crude alkyne (238  
7 mg, 95%) was used directly in the next reaction.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.40-7.22 (3H, m), 3.59 (1H, septet, J = 6.2 Hz), 3.07  
9 (1H, s), 2.97 (2H, q, J = 7.6 Hz), 1.28 (3H, t, J = 7.6 Hz), 1.12 (2H, m), 0.96  
10 (6H, d, J = 6.2 Hz), 0.85 (2H, m).

11 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate  
12 (**Compound 95, General Formula 2**)

13 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-  
14 3-ethyl-benzene (**Intermediate 95**, 108.0 mg, 0.47 mmol) and ethyl-4-iodo  
15 benzoate (**Reagent A**, 130.0 mg, 0.47 mmol) in triethylamine (5 mL) was  
16 treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon  
17 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (110 mg, 0.16  
18 mmol) was added and the reaction mixture was stirred overnight at room  
19 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
20 125.0 mg (71%) of the title compound as an oil.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.46  
22 (1H, s), 7.33-7.26 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.62 (1H, septet, J = 6.2  
23 Hz), 3.01 (2H, q, J = 7.6 Hz), 1.41 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1  
24 Hz), 1.14 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

25 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-  
26 acetate (Compound 96, General Formula 2)

27 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-

1 3-ethyl-benzene (**Intermediate 95**, 130.0 mg, 0.57 mmol) and methyl-(4-  
2 iodophenyl)-acetate (**Reagent B**, 157.0 mg, 0.57 mmol) in triethylamine (5  
3 mL) was treated with copper(I)iodide (36.0 mg, 0.19 mmol) and sparged  
4 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
5 (133 mg, 0.19 mmol) was added and the reaction mixture was stirred  
6 overnight at room temperature. Column chromatography (2-5% EtOAc -  
7 hexanes) afforded 150.0 mg (70%) of the title compound as an orange oil.  
8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50-7.44 (3H, m), 7.27 (4H, m), 3.70 (3H, s), 3.64  
9 (2H, s), 3.62 (1H, septet, J = 6.2 Hz), 3.00 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J  
10 = 7.6 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87 (2H, m).

11 4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid  
12 (**Compound 97, General Formula 2**)

13 Using General Procedure I; a solution of ethyl 4-[4-(1-  
14 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 95**,  
15 110.0 mg, 0.29 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
16 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
17 and stirred overnight at room temperature. Work-up and isolation by HPLC  
18 (partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded the title compound as a  
19 colorless solid.

20 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz),  
21 7.49 (1H, s), 7.40-7.34 (2H, m), 3.61 (1H, septet, J = 6.2 Hz), 3.01 (2H, q, J  
22 = 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.08 (2H, m), 0.93 (6H, d, J = 6.2 Hz),  
23 0.88 (2H, m).

24 {4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic  
25 acid (**Compound 98, General Formula 2**)

26 Using General Procedure I; a solution of methyl {4-[4-(1-  
27 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate

1 (Compound 96, 156.0 mg, 0.41 mmol) in ethanol (3 mL) and  
2 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0  
3 mL of a 1N aqueous solution) and stirred overnight at room temperature.  
4 Work-up and isolation by HPLC (partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN)  
5 afforded 85.0 mg (57%) of the title compound.

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.54-7.48 (3H, m), 7.34-7.27 (4H, m), 3.68 (2H, s),  
7 3.66 (1H, septet, J = 6.2 Hz), 3.03 (2H, q, J = 7.6 Hz), 1.33 (2H, t, J = 7.6  
8 Hz), 1.17 (2H, m), 1.01 (6H, d, J = 6.2 Hz), 0.90 (2H, m).

9 (4-Bromo-3-isopropyl-phenoxy)-triisopropyl-silane (Intermediate 96)

10 To a solution of 4-bromo-3-isopropylphenol (880.0 mg, 4.09 mmols)  
11 and imidazole (417.0 mg, 6.13 mmols) in 10 mL DMF was added chloro-  
12 triisopropylsilane (946.0 mg, 4.90 mmols). After stirring overnight at room  
13 temperature the solution was diluted with H<sub>2</sub>O and extracted with EtOAc.  
14 The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous  
15 NaCl before being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure.  
16 The title compound, 1.30 g (92%), was isolated by column chromatography  
17 (1-2% EtOAc-hexanes) as a colorless oil.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.34 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 2.9 Hz), 6.59  
19 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.33-1.21 (3H, m),  
20 1.24 (6H, d, J = 7.0 Hz), 1.13 (18H, d, J = 7.0 Hz).

21 Ethyl 2-isopropyl-4-triisopropylsilanyloxy-benzoate (Intermediate 97)

22 To a solution of (4-bromo-3-isopropyl-phenoxy)-triisopropyl-silane  
23 (Intermediate 96, 1.3 g, 3.8 mmols) in 15 mL Et<sub>2</sub>O cooled to -78 °C was  
24 added 4.9 mL of *tert*-butyllithium in pentane (532.0 mg, 8.3 mmols; 1.7 M).  
25 After stirring for 30 minutes ethyl chloroformate (832.0 mg, 7.8 mmols) was  
26 added. The resulting solution was warmed to room temperature and  
27 quenched by the addition of saturated aqueous NH<sub>4</sub>Cl. The mixture was

1 extracted with EtOAc and the combined organic layers dried (MgSO<sub>4</sub>)  
2 concentrated under reduced pressure and the residue chromatographed (4%  
3 EtOAc-hexanes) to give 1.09 g (85%) of the title compound as a colorless  
4 oil.  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.72 (1H, d, J = 8.5 Hz), 6.87 (1H, d, J = 2.3 Hz), 6.69  
6 (1H, dd, J = 2.3, 8.5 Hz), 3.88 (1H, septet; J = 7.1 Hz), 4.30 (2H, q, J = 7.1  
7 Hz), 1.36 (3H, t, J = 7.1 Hz), 1.31-1.17 (9H, m), 1.09 (18H).  
8 [4-(1-Ethoxyvinyl)-3-isopropyl-phenoxy]-triisopropyl-silane (Intermediate  
9 **98)**

10 Using General Procedure 1; ethyl 2-isopropyl-4-  
11 triisopropylsilanyloxy-benzoate (**Intermediate 97**, 450.0 mg, 1.34 mmols)  
12 and 2.0 mL of Tebbe's Reagent (398.0 mg, 1.40 mmols) afforded the title  
13 compound after column chromatography (100% hexanes).  
14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.11 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 2.3 Hz), 6.63  
15 (1H, dd, J = 2.3, 8.2 Hz), 4.23 (1H, d, J = 1.7 Hz), 4.10 (1H, d, J = 1.7 Hz),  
16 3.86 (2H, q, J = 7.0 Hz), 3.16 (1H, septet, J = 7.0 Hz), 1.35 (3H, t, J = 7.1  
17 Hz), 1.28-1.19 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.11 (18H).  
18 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenoxy]-triisopropyl-silane  
19 (**Intermediate 99)**

20 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-isopropyl-  
21 phenoxy]-triisopropyl-silane (**Intermediate 98**, 300.0 mg, 0.83 mmols),  
22 Et<sub>2</sub>Zn (325.0 mg, 2.63 mmols), and CH<sub>2</sub>I<sub>2</sub> (704.0 mg, 2.63 mmols) in 5.0  
23 mL Et<sub>2</sub>O afforded 270.0 mg (86%) of the title compound as a colorless oil  
24 after chromatography (0.5-2.5% EtOAc - hexanes).  
25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.06 (1H, d, J = 8.2 Hz), 6.81 (1H, d, J = 2.6 Hz), 6.59  
26 (1H, dd, J = 2.6, 8.2 Hz), 3.76 (1H, septet, J = 7.0 Hz), 3.25 (2H, q, J = 7.0  
27 Hz), 1.30-1.20 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.10 (18H),

1 1.02 (2H, t, J = 7.0 Hz), 0.82 (2H, m).

2 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenol (**Intermediate 100**)

3 To a solution of [4-(1-ethoxycyclopropyl)-3-isopropyl-phenoxy]-  
4 triisopropyl-silane (**Intermediate 99**, 360.0 mg, 0.96mmol) in 3 mL THF at  
5 0 °C was added tetrabutylammonium fluoride (625.0 mg, 2.39 mmols, 2.4  
6 mL of a 1 M solution in THF). The solution was stirred at 0 °C for 30  
7 minutes and then quenched by the addition of H<sub>2</sub>O. The mixture was  
8 extracted with EtOAc and the combined organic layers were washed with  
9 H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and  
10 concentrated under reduced pressure. The title compound (180 mg, 86%)  
11 was isolated from the residue by column chromatography (4-10% EtOAc-  
12 hexanes) as a colorless solid.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.13 (1H, d, J = 8.2 Hz), 6.79 (1H, d, J = 2.6 Hz), 6.57  
14 (1H, dd, J = 2.6, 8.2 Hz), 5.48 (1H, s), 3.79 (1H, septet, J = 7.0 Hz), 3.32  
15 (2H, q, J = 7.0 Hz), 1.21 (6H, d, J = 7.0 Hz), 1.12 (2H, m), 1.05 (3H, t, J =  
16 7.0 Hz), 0.84 (2H, m).

17 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenyl 1,1,1-trifluoromethanesulfonate  
18 (**Intermediate 101**)

19 A solution of 4-(1-ethoxycyclopropyl)-3-isopropyl-phenol  
20 (**Intermediate 100**, 172.0 mg, 0.78 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to  
21 0 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-  
22 chloropyridine (321.0 mg, 0.82 mmol) and triethylamine (240.0 mg, 2.4  
23 mmols). The resulting solution was warmed to room temperature and stirred  
24 overnight. The reaction was quenched by the addition of H<sub>2</sub>O and the  
25 mixture extracted with EtOAc and the combined organic layers were washed  
26 with 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and saturated  
27 aqueous NaCl. The solution was dried (MgSO<sub>4</sub>) and concentrated under

1 reduced pressure. The title compound was isolated by column  
2 chromatography (2-4% EtOAc-hexanes) as a colorless oil, 240.0 mg, 87%.  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.00  
4 (1H, dd, J = 2.6, 8.6 Hz), 3.87 (1H, septet, J = 7.0 Hz), 2.38 (2H, q, J = 7.0  
5 Hz), 1.24 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.04 (3H, t, J = 7.0 Hz), 0.86  
6 (2H, m).

7 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-trimethylsilane  
8 **(Intermediate 102)**

9 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-isopropyl-  
10 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 101**, 240.0 mg, 0.68  
11 mmol) in triethylamine (2 mL) and DMF (6 mL) was sparged with argon for  
12 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added  
13 followed by dichlorobis-(triphenylphosphine)palladium(II) (38.0 mg, 0.05  
14 mmol). The resulting reaction mixture was heated to 95 °C for 5d. The title  
15 compound, 200.0 mg (99%), was isolated by chromatography (0 - 2%  
16 EtOAc - hexanes) as an orange oil.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (1H, d, J = 1.7 Hz), 7.25 (1H, dd, J = 1.7, 7.9 Hz),  
18 7.16 (1H, d, J = 7.9 Hz), 3.80 (1H, septet, J = 6.8 Hz), 3.26 (2H, q, J = 7.0  
19 Hz), 1.24 (6H, d, J = 6.8 Hz), 1.24-1.10 (2H, m), 1.03 (3H, t, J = 7.0 Hz),  
20 0.87 (2H, s), 0.26 (9H, s).

21 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**)

22 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-isopropyl-  
23 phenylethynyl]-trimethylsilane (**Intermediate 102**, 210.0 mg, 0.70 mmol) in  
24 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72  
25 mmol) and stirred overnight at ambient temperature. The crude alkyne was  
26 used directly in the next reaction.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (1H, d, J = 1.7 Hz), 7.23 (1H, dd, J = 1.7, 7.6 Hz),

1 7.19 (1H, d, J = 7.6 Hz), 3.80 (1H, septet, J = 7.0 Hz), 3.27 (1H, q, J = 7.0  
2 Hz), 3.07 (1H, s), 1.23 (6H, d, J = 7.0 Hz), 1.13 (2H, m), 1.03 (3H, t, J = 7.0  
3 Hz), 0.85 (2H, m).

4 Ethyl 4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate  
5 **(Compound 99, General Formula 2)**

6 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-  
7 isopropylbenzene (**Intermediate 103**, 50.0 mg, 0.22 mmol) and ethyl-4-iodo  
8 benzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL) was  
9 treated with copper(I)iodide (14.0 mg, 0.07 mmol) and sparged with argon  
10 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (51 mg, 0.07  
11 mmol) was added and the reaction mixture was stirred overnight at room  
12 temperature. Column chromatography (1-2% EtOAc - hexanes) afforded  
13 28.0 mg (34%) of the title compound.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.51  
15 (1H, d J = 1.7 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz), 7.21 (1H, d, J = 7.9 Hz),  
16 4.38 (2H, q, J = 7.1 Hz), 3.83 (1H, septet, J = 6.7 Hz), 3.29 (2H, q, J = 7.0  
17 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J = 6.7 Hz), 1.14 (2H, m), 1.04  
18 (3H, t, J = 7.0 Hz), 0.87 (2H, m).

19 Methyl {4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-  
20 acetate (**Compound 100, General Formula 2**)

21 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-  
22 isopropylbenzene (**Intermediate 103**, 120.0 mg, 0.52 mmol) and methyl-(4-  
23 iodophenyl)-acetate (**Reagent B**, 150.0 mg, 0.52 mmol) in triethylamine (8  
24 mL) was treated with copper(I)iodide (32.0 mg, 0.17 mmol) and sparged  
25 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
26 (121 mg, 0.17 mmol) was added and the reaction mixture was stirred  
27 overnight at room temperature. Column chromatography (2-5% EtOAc -  
28 hexanes) afforded 140.0 mg (71%) of the title compound as a pale-yellow

1 oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.53 (3H, m), 7.31-7.23 (4H, m), 3.86 (1H, septet, J =  
3 6.7 Hz), 3.73 (3H, s), 3.67 (2H, s), 3.33 (2H, q, J = 7.0 Hz), 1.30 (6H, d, J =  
4 6.7 Hz), 1.15 (2H, m), 1.08 (3H, t, J = 7.0 Hz), 0.90 (2H, m).

5 4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoic acid

6 **(Compound 101, General Formula 2)**

7 Using General Procedure I; A solution of ethyl 4-[4-(1-  
8 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate (**Compound 99**,  
9 28.0 mg, 0.07 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was  
10 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
11 and stirred overnight at room temperature. Work-up afforded 24 mg (92%)  
12 the title compound as a pale-yellow solid.

13 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz),  
14 7.58 (1H, s), 7.33 (2H, m), 3.87 (1H, m), 2.27 (2H, q, J = 7.0 Hz), 1.26 (6H,  
15 d, J = 6.7 Hz), 1.09 (2H, m), 0.99 (3H, t, J = 7.0 Hz), 0.88 (2H, m).

16 {4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetic  
17 acid (**Compound 102, General Formula 2**)

18 Using General Procedure I; a solution of methyl {4-[4-(1-  
19 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetate  
20 (**Compound 100**, 130.0 mg, 0.35 mmol) in ethanol (5 mL) and  
21 tetrahydrofuran (5 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0  
22 mL of a 1N aqueous solution) and stirred at 50 °C for 4h. Work-up and  
23 isolation by HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded 88.0 mg  
24 (70%) of the title compound.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50 (3H, m), 7.28-7.19 (4H, m), 3.82 (1H, m), 3.65  
26 (2H, s), 3.29 (2H, q, J = 7.0 Hz), 1.25 (6H, d, J = 6.7 Hz), 1.14 (2H, m),  
27 1.04 (3H, t, J = 7.0 Hz), 0.86 (2H, m).

1 4-Bromo-3-*tert*-butylphenol (Intermediate 104)

2 To a mixture of 3-*tert*-butyl-methoxy benzene (1.00 g, 6.09 mmols)  
3 in CCl<sub>4</sub> (20 mL), molecular sieves, and silica gel was added *N*-  
4 bromosuccinimide (1.19 g, 6.70 mmols). This mixture was stirred at 55 °C  
5 for 48h. The resulting mixture was cooled to room temperature, filtered to  
6 remove the solids, and the filtrate diluted with EtOAc. This solution was  
7 washed with H<sub>2</sub>O, 10% aqueous HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub> and  
8 saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated under  
9 reduced pressure. Column chromatography (2.5% EtOAc-hexanes)  
10 afforded 1.15 g (78%) of a 3 to 1 mixture of 1-bromo-2-*tert*-butyl methoxy  
11 benzene and 1-bromo-2-methoxy-4-*tert*-butyl benzene as a colorless oil.

12 A solution of the isomeric methoxy compounds in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>  
13 was cooled to 0 °C and treated with a solution (18.5 mL) of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>  
14 (4.63 g, 18.5 mmols). After 10 minutes the solution was warmed to room  
15 temperature, stirred for 1h, and then quenched with H<sub>2</sub>O. The mixture was  
16 extracted with EtOAc and the combined organic layers washed with  
17 saturated aqueous NaCl, dried (MgSO<sub>4</sub>), and concentrated under reduced  
18 pressure. The title compound was isolated, 1.17 g (59%), by column  
19 chromatography (2.5-5% EtOAc-hexanes).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (1H, d, J = 8.5 Hz), 6.96 (1H, d, J = 2.9 Hz), 6.54  
21 (1H, dd, J = 2.9, 8.5 Hz), 1.46 (9H, s).

22 (4-Bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane (Intermediate 105)

23 To a solution of 4-bromo-3-*tert*-butylphenol (Intermediate 104, 1.17  
24 g, 5.10 mmols) and imidazole (520.0 mg, 7.65 mmols) in 10 mL DMF was  
25 added chloro-triisopropylsilane (1.18 g, 6.10 mmols). After stirring  
26 overnight at room temperature the solution was diluted with H<sub>2</sub>O and  
27 extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O

1 and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated  
2 under reduced pressure. The title compound, 1.80 g (92%), was isolated by  
3 column chromatography (0-1.5% EtOAc-hexanes) as a colorless oil.  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 2.9 Hz), 6.56  
5 (1H, dd, J = 2.9, 8.5 Hz), 1.47 (9H, s), 1.29-1.24 (3H, m), 1.09 (18H, d, J =  
6 6.7 Hz).

7 Ethyl 2-*tert*-butyl-4-triisopropylsilanyloxy-benzoate (**Intermediate 106**)

8 To a solution of (4-bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane  
9 (**Intermediate 105**, 1.00 g, 2.60 mmols) in 15 mL Et<sub>2</sub>O cooled to -78 °C  
10 was added 3.6 mL of *tert*-butyllithium, 1.7 M in pentane (395.0 mg, 6.2  
11 mmols). After stirring for 30 minutes ethyl chloroformate (607.6 mg, 5.6  
12 mmols) was added. The resulting solution was warmed to room temperature  
13 and quenched by the addition of saturated aqueous NH<sub>4</sub>Cl. The mixture was  
14 extracted with EtOAc and the combined organic layers dried (MgSO<sub>4</sub>)  
15 concentrated under reduced pressure. The residue was chromatographed (2-  
16 5% EtOAc-hexanes) to give 1.23 g (88%) of the title compound as a  
17 colorless oil.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.24 (1H, d, J = 8.2 Hz), 6.97 (1H, d, J = 2.6 Hz), 6.69  
19 (1H, dd, J = 2.6, 8.2 Hz), 4.33 (2H, q, J = 7.1 Hz), 1.39 (9H, s), 1.37 (3H, t,  
20 J = 7.1 Hz), 1.29-1.21 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

21 [4-(1-Ethoxyvinyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane (**Intermediate**  
22 **107**)

23 Using General Procedure 1; ethyl 2-*tert*-butyl-4-  
24 triisopropylsilanyloxy-benzoate (**Intermediate 106**, 1.30 g, 3.44 mmols)  
25 and 7.2 mL of Tebbe's Reagent (1.03 g, 3.61 mmols) were reacted. The  
26 reaction required 7 days at room temperature to go to completion. The  
27 standard work-up afforded 1.29 g (78%) of the title compound after column

1 chromatography (1-2% EtOAc-hexanes).

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.05 (1H, d, J = 8.2 Hz), 6.94 (1H, d, J = 2.6 Hz), 6.63  
3 (1H, dd, J = 2.6, 8.2 Hz), 4.20 (1H, d, J = 1.7 Hz), 4.08 (1H, d, J = 1.7 Hz),  
4 3.83 (2H, q, J = 7.1 Hz), 1.37 (9H, s), 1.36 (3H, t, J = 7.1 Hz), 1.27-1.20  
5 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

6 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane  
7 (**Intermediate 108**)

8 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-*tert*-butyl-  
9 phenoxy]-triisopropyl-silane (**Intermediate 107**, 320.0 mg, 0.85 mmols),  
10 Et<sub>2</sub>Zn (325.0 mg, 2.63 mmols), and CH<sub>2</sub>I<sub>2</sub> (704.0 mg, 2.63 mmols) in 5.0  
11 mL Et<sub>2</sub>O afforded 257.0 mg (66%) of the title compound as a colorless oil  
12 after chromatography (1-2.5% EtOAc - hexanes).  
13 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.24 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 2.6 Hz), 6.60  
14 (1H, dd, J = 2.6, 8.5 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.50 (9H, s), 1.29-1.21  
15 (3H, m), 1.11 (18H, d, J = 6.7 Hz), 1.04 (3H, t, J = 7.1 Hz).

16 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenol (**Intermediate 109**)

17 To a solution of [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-  
18 triisopropyl-silane (**Intermediate 108**, 600.0 mg, 1.54 mmol) in 3 mL THF  
19 at 0 °C was added tetrabutylammonium fluoride (802.8.0 mg, 3.07 mmols;  
20 3.1 mL of a 1 M solution in THF). The solution was stirred at 0 °C for 30  
21 minutes and then quenched by the addition of H<sub>2</sub>O. The mixture was  
22 extracted with EtOAc and the combined organic layers were washed with  
23 H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and  
24 concentrated under reduced pressure. The title compound (400 mg, 88%)  
25 was isolated from the residue by column chromatography (4-10% EtOAc-  
26 hexanes) as a colorless solid.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.29 (1H, d, J = 8.2 Hz), 7.01 (1H, d, J = 2.6 Hz), 6.57

1 (1H, dd, J = 2.6, 8.2 Hz), 3.29 (2H, q, J = 7.1 Hz), 1.59 (9H, s), 1.08-1.04  
2 (7H, m).

3 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenyl 1,1,1-trifluoromethanesulfonate  
4 (**Intermediate 110**)

5 A solution of 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenol  
6 (**Intermediate 109**, 400.0 mg, 1.71 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled  
7 to 0 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-  
8 chloropyridine (705.0 mg, 1.79 mmol) and triethylamine (522.0 mg, 5.1  
9 mmols). The resulting solution was warmed to room temperature and stirred  
10 overnight. The reaction was quenched by the addition of H<sub>2</sub>O and the  
11 mixture extracted with EtOAc and the combined organic layers were washed  
12 with 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and saturated  
13 aqueous NaCl. The solution was dried (MgSO<sub>4</sub>) and concentrated under  
14 reduced pressure. The title compound was isolated by column  
15 chromatography (2-4% EtOAc-hexanes) as a colorless oil, 542.0 mg (87%).  
16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (1H, d, J = 8.5 Hz), 7.39 (1H, d, J = 2.6 Hz), 7.01  
17 (1H, dd, J = 2.6, 8.5 Hz), 3.26 (2H, q, J = 7.1 Hz), 1.52 (9H, s), 1.12 (2H,  
18 bs), 1.08-1.04 (5H, m).

19 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-trimethylsilane  
20 (**Intermediate 111**)

21 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-  
22 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 110**, 260.0 mg, 0.71  
23 mmol) in triethylamine (4 mL) and DMF (6 mL) was sparged with argon for  
24 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added  
25 followed by dichlorobis-(triphenylphosphine)palladium(II) (40.0 mg, 0.06  
26 mmol). The resulting reaction mixture was heated to 95 °C for 18 hours.  
27 The title compound, 215.0 mg (96%), was isolated by chromatography (0 -

1 2% EtOAc - hexanes) as an orange oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.63 (1H, d, J = 1.7 Hz), 7.32 (1H, d, J = 7.9 Hz), 7.19  
3 (1H, dd, J = 1.7, 7.9 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.51 (9H, s), 1.10 (2H,  
4 bs), 1.06-1.01 (5H, m), 0.25 (9H, s).

5 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-*tert*-butylbenzene (**Intermediate 112**)

6 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-  
7 phenylethynyl]-trimethylsilane (**Intermediate 111**, 215.0 mg, 0.69 mmol) in  
8 methanol (10 mL) was treated with potassium carbonate (80.0 mg, 0.58  
9 mmol) and stirred overnight at ambient temperature. The crude alkyne, 169  
10 mg, was used directly in the next reaction.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.68 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.23  
12 (1H, dd, J = 1.8, 7.9 Hz), 3.26 (2H, q, J = 7.1 Hz), 3.06 (1H, s), 1.51 (9H, s),  
13 1.11 (2H, bs), 1.07-1.02 (5H, m).

14 Ethyl 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate  
15 (**Compound 103, General Formula 2**)

16 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-  
17 *tert*-butylbenzene (**Intermediate 112**, 70.0 mg, 0.30 mmol) and ethyl-4-iodo  
18 benzoate (**Reagent A**, 85.0 mg, 0.30 mmol) in triethylamine (5 mL) was  
19 treated with copper(I)iodide (19.0 mg, 0.01 mmol) and sparged with argon  
20 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (70 mg, 0.01  
21 mmol) was added and the reaction mixture was stirred overnight at room  
22 temperature. Column chromatography (1-2% EtOAc - hexanes) afforded  
23 70.0 mg (73%) of the title compound.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.8 Hz), 7.72 (1H, d, J = 1.7 Hz), 7.59  
25 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz),  
26 4.39 (2H, q, J = 7.1 Hz), 3.28 (2H, q, J = 7.1 Hz), 1.55 (9H, s), 1.40 (3H, t,  
27 J = 7.1 Hz), 1.12 (2H, bs), 1.08-1.04 (5H, m).

1 Methyl {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-  
2 acetate (Compound 104, General Formula 2)

3       Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-  
4 *tert*-butylbenzene (**Intermediate 112**, 95.0 mg, 0.39 mmol) and methyl-(4-  
5 iodophenyl)-acetate (**Reagent B**, 108.0 mg, 0.39 mmol) in triethylamine (8  
6 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged  
7 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91  
8 mg, 0.13 mmol) was added and the reaction mixture was stirred overnight at  
9 room temperature. Column chromatography (2-5% EtOAc - hexanes)  
10 afforded 100.0 mg (72%) of the title compound.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.70 (1H, d, J = 1.5 Hz), 7.50 (2H, d, J = 7.9 Hz), 7.38  
12 (1H, d, J = 7.9 Hz), 7.27 (3H, m), 3.70 (3H, s), 3.64 (2H, s), 3.28 (2H, q, J =  
13 7.1 Hz), 1.54 (9H, s), 1.12 (2H, bs), 1.08-1.03 (5H, m).

14 4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoic acid  
15 (Compound 105, General Formula 2)

16       Using General Procedure I; a solution of ethyl 4-[4-(1-  
17 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate (**Compound 103**,  
18 70.0 mg, 0.18 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
19 treated with NaOH (240.0 mg, 6.0 mmols, 3.0 mL of a 2N aqueous solution)  
20 and stirred overnight at room temperature. Work-up afforded 40 mg (62%)  
21 the title compound as a pale-yellow solid.

22 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.06 (2H, d, J = 8.7 Hz), 7.76 (1H, d, J = 1.8 Hz),  
23 7.67 (2H, d, J = 8.7 Hz), 7.50 (1H, d, J = 7.9 Hz), 7.33 (1H, dd, J = 1.8, 7.9  
24 Hz), 3.28 (2H, q, J = 7.3 Hz), 1.54 (9H, s), 1.13 (2H, bs), 1.10 (2H, m), 1.02  
25 (3H, t, J = 7.3 Hz).

26 {4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetic  
27 acid (Compound 106, General Formula 2)

1       Using General Procedure I; a solution of methyl {4-[4-(1-  
2 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetate  
3 (**Compound 104**, 100.0 mg, 0.26 mmol) in ethanol (4 mL) and  
4 tetrahydrofuran (4 mL) was treated with NaOH (240.0 mg, 6.0 mmols, 3.0  
5 mL of a 2N aqueous solution) and stirred at 50 °C for 4h. Work-up and  
6 isolation by HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded 70.0 mg  
7 (73%) of the title compound.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.73 (1H, d, J = 1.3 Hz), 7.53 (2H, d, J = 7.9 Hz), 7.41  
9 (1H, d, J = 7.9 Hz), 7.28 (3H, m), 3.69 (2H, s), 3.31 (2H, q, J = 7.1 Hz),  
10 1.56 (9H, s), 1.15 (2H, bs), 1.11-1.05 (5H, m).

11 1-(4-Bromophenyl)-cyclopropanecarbonitrile (**Intermediate 113**)

12       To a 50% aqueous NaOH solution (40.0 g, wt/wt) was added benzyl  
13 triethylammonium chloride (1.0 g, 4.4 mmols), 4-bromobenzonitrile (19.6 g,  
14 0.10 mol), and 1,2-dibromoethane (56.4 g, 0.30 mol). The mixture was  
15 stirred overnight at room temperature and then diluted with 100 mL of H<sub>2</sub>O.  
16 This mixture was extracted with EtOAc and the combined extracts were  
17 washed with saturated aqueous NaHS<sub>2</sub>O<sub>3</sub>, H<sub>2</sub>O, and saturated aqueous NaCl  
18 before being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure.  
19 Bulb-to-bulb distillation afforded 18.8 g (85%) of the title compound as a  
20 colorless solid.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 8.6 Hz), 1.75  
22 (2H, dd, J = 5.2, 7.6 Hz), 1.39 (2H, dd, J = 5.2, 7.6 Hz).

23 1-(4-Bromophenyl)-cyclopropanecarboxylic acid (**Intermediate 114**)

24       To a solution of KOH (6.06 g, 0.11 mol) in 10 mL of H<sub>2</sub>O was added  
25 40 mL of ethylene glycol and 1-(4-bromophenyl)-cyclopropanecarbonitrile  
26 (**Intermediate 113**, 10.0 g, 0.45 mol). This solution was heated to 135-140  
27 °C for 4h, cooled to room temperature, and then poured into a mixture of

1 100 mL ice and 10% aqueous HCl. The resulting mixture was allowed to  
2 stand overnight at 5 °C, the solid was collected by filtration and washed  
3 with H<sub>2</sub>O. The colorless solid was dried under reduced pressure to give  
4 10.6 g (97%) of the title compound.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 1.68  
6 (2H, dd, J = 4.0, 7.1 Hz), 1.24 (2H, dd, J = 4.0, 7.1 Hz).

7 *Tert*-butyl [1-(4-bromophenyl)-cyclopropyl]-carbamate (Intermediate 115)

8 A solution of 1-(4-bromophenyl)-cyclopropanecarboxylic acid  
9 (**Intermediate 114**, 2.32 g, 9.62 mmols), diphenylphosphoryl azide (2.65 g,  
10 9.62 mmols), triethylamine (973.0 mg, 9.62 mmols) in 40 mL *tert*-BuOH  
11 (distilled from Na<sup>o</sup>) was heated to reflux for 17h. The solution was  
12 concentrated under reduced pressure and the residue dissolved in EtOAc  
13 and washed with 5% aqueous HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and  
14 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Concentration of  
15 the dry solution under reduced pressure and column chromatography (5-  
16 10% EtOAc - hexanes) afforded 2.01 g (67%) of the title compound as a  
17 colorless solid.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.3 Hz), 5.35  
19 (1H, bs), 1.43 (9H, s), 1.26 (2H, m), 1.17 (2H, m).

20 1-(4-Bromophenyl)-cyclopropylamine (Intermediate 116)

21 To a solution of *tert*-butyl [1-(4-bromophenyl)-cyclopropyl]-  
22 carbamate (**Intermediate 115**, 1.08 g, 3.40 mmols) in 20 mL MeOH and 20  
23 mL THF was added 20 mL of 3M aqueous HCl. The solution was warmed  
24 to 35 °C for 3 hours and then stirred for 17h at 25 °C. The reaction was  
25 quenched by adjusting the pH of the solution to 12 with 3M aqueous NaOH.  
26 The mixture was extracted with Et<sub>2</sub>O and the combined organic layers were  
27 washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>)

1 and concentrated under reduced pressure. The title compound 613 mg  
2 (85%) was used without further purification.  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 1.89  
4 (2H, bs), 1.07 (2H, m), 0.95 (2H, m).

5 *N*-[1-(4-bromophenyl)-cyclopropyl]-propionamide (Intermediate 117)

6 To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**  
7 **116**, 84 mg, 0.4 mmol) in 4 mL CH<sub>2</sub>Cl<sub>2</sub> at room temperature was added  
8 propionyl chloride (43.0 mg, 0.47 mmol) and pyridine (56.0 mg, 0.71  
9 mmol). After stirring 17 hours at room temperature the reaction was  
10 quenched by the addition of H<sub>2</sub>O and extracted with EtOAc. The combined  
11 extracts were washed with 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>,  
12 and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated  
13 under reduced pressure. The title compound 85.0 mg (67%), was isolated  
14 by column chromatography (20-50% EtOAc-hexanes) as a colorless solid.  
15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 6.40  
16 (1H, s), 2.19 (2H, q, J = 7.2 Hz), 1.18-1.24 (4H, m), 1.12 (3H, t, J = 7.2 Hz).  
17 [1-(4-Bromophenyl)-cyclopropyl]-propylamine (Intermediate 118)

18 To a solution of *N*-[1-(4-bromophenyl)-cyclopropyl]-propionamide  
19 (**Intermediate 117**, 85.0 mg, 0.32 mmol) in THF (5 mL) at 0 °C was added  
20 BH<sub>3</sub>-Me<sub>2</sub>S (48.0 mg, 0.63 mmol; 0.31 mL of a 2M solution in THF). The  
21 solution was heated to 55 °C for 17 hours, cooled to room temperature,  
22 saturated aqueous NaHCO<sub>3</sub> was added and the resulting mixture was stirred  
23 for 2 hours. This mixture was extracted with EtOAc and the combined  
24 organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl before  
25 being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The title  
26 compound was isolated by column chromatography (10-30% EtOAc-  
27 hexanes).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 2.46 (2H, t, J = 7.3 Hz), 1.40 (2H, m), 0.98 (2H, m), 0.86 (5H, m).

Propyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
(**Intermediate 119**)

Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-propylamine (**Intermediate 118**, 100.0 mg, 0.39 mmol) in triethylamine (8 mL) was treated with copper(I)iodide (13.0 mg, 0.06 mmol) and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was then added followed by dichlorobis(triphenylphosphine)palladium(II) (48.0 mg, 0.06 mmol). The resulting reaction mixture was heated to 70 °C for 5 days. The title compound (80.0 mg, 75%) was isolated by chromatography (0 - 10% EtOAc - hexanes) as an orange oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 2.45 (2H, t, J = 7.3 Hz), 1.39 (2H, m), 0.98 (2H, m), 0.87 (2H, m), 0.84 (3H, t, J = 7.3 Hz), 0.24 (9H, s).

[1-(4-Ethynylphenyl)-cyclopropyl]-propylamine (**Intermediate 120**)

Using General Procedure E; propyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine (**Intermediate 119**, 80.0 mg, 0.30 mmols) in methanol (8 mL) was treated with potassium carbonate (80.0 mg, 0.59 mmol) and stirred overnight at ambient temperature. The crude alkyne (58 mg, 100%) was used directly in the next reaction.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.44 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 3.05 (1H, s), 2.46 (2H, t, J = 7.3 Hz), 1.41 (2H, m), 1.00 (2H, m), 0.90 (2H, m), 0.86 (3H, t, J = 7.3 Hz).

Ethyl 4-[4-(1-propylamino-cyclopropyl)-phenylethynyl]-benzoate  
(**Compound 107, General Formula 2**)

1       Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-  
2 propylamine (**Intermediate 120**, 38.0 mg, 0.19 mmol) and ethyl-4-iodo  
3 benzoate (**Reagent A**, 58.0 mg, 0.21 mmol) in triethyl amine (6 mL) was  
4 treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with argon  
5 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04  
6 mmol) was added and the reaction mixture was stirred overnight at room  
7 temperature. Column chromatography (5-15% EtOAc - hexanes) afforded  
8 40.0 mg (61%) of the title compound as an orange oil.  
9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.49  
10 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.49  
11 (2H, t, J = 7.3 Hz), 1.46 (2H, m), 1.41 (3H, t, J = 7.1 Hz), 1.01 (2H, m), 0.89  
12 (2H, m), 0.87 (3H, t, J = 7.3 Hz).

13 4-[4-(1-Propylamino-cyclopropyl)-phenylethynyl]-benzoic acid  
14 (**Compound 108, General Formula 2**)

15       Using General Procedure I; a solution of ethyl 4-[4-(1-propylamino-  
16 cyclopropyl)-phenylethynyl]-benzoate (**Compound 107**, 40.0 mg, 0.12  
17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
18 NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred  
19 overnight at room temperature. Work-up afforded 25.0 mg (69%) of the  
20 title compound as a solid.

21 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.97 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz),  
22 7.50 (2H, d, J = 8.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 2.39 (2H, t, J = 7.3 Hz),  
23 1.37 (2H, m), 1.00 (2H, m), 0.93 (2H, m), 0.84 (3H, t, J = 7.3 Hz).

24 [1-(4-Bromophenyl)-cyclopropyl]-dipropylamine (**Intermediate 121**)

25       To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**  
26 **116**) in CH<sub>3</sub>CN / HOAc (5 mL, 9:1, v/v) and THF 3 mL at 0 °C was added  
27 propionaldehyde (277.0 mg, 4.95 mmols) and NaCNBH<sub>3</sub> (153.0 mg, 2.47

1 mmols). The reaction was warmed to room temperature and after 5 hours  
2 quenched with H<sub>2</sub>O. The pH of the solution was adjusted to 8-9 using  
3 aqueous NaOH and extracted with EtOAc. The combined extracts were  
4 washed with H<sub>2</sub>O and saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and  
5 concentrated under reduced pressure. The title compound, 190.0 mg (56%),  
6 was isolated by column chromatography (2-5% EtOAc-hexanes).  
7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 2.39  
8 (4H, t, J = 7.3 Hz), 1.62-1.40 (4H, m), 0.96 (2H, m), 0.86 (6H, t, J = 7.3  
9 Hz), 0.80 (2H, m).

10 Dipropyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
11 **(Intermediate 122)**

12 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-  
13 dipropylamine (**Intermediate 121**, 150.0 mg, 0.50 mmol) in triethylamine  
14 (5 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then  
15 sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1  
16 mmols) was then added followed by  
17 dichlorobis(triphenylphosphine)palladium(II) (35.0 mg, 0.05 mmol). The  
18 resulting reaction mixture was heated to 70 °C for 5d. The title compound  
19 was isolated by chromatography (0 - 3% EtOAc - hexanes).  
20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.35 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 2.39  
21 (4H, t, J = 7.3 Hz), 1.55-1.42 (4H, m), 0.96 (2H, m), 0.88-0.79 (8H, m), 0.25  
22 (9H, s).

23 [1-(4-Ethynylphenyl)-cyclopropyl]-dipropylamine (**Intermediate 123**)

24 Using General Procedure E; dipropyl-[1-(4-trimethylsilanylethynyl-  
25 phenyl)-cyclopropyl]-amine (**Intermediate 122**, 45.0 mg, 0.14 mmols) in  
26 methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37  
27 mmol) and stirred overnight at ambient temperature. The crude alkyne (34

1 mg, 100%) was used directly in the next reaction.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.3 Hz),  
3 2.40(4H, t, J = 7.3 Hz), 1.53-1.40 (4H, m), 0.96 (2H, m), 0.90-0.79 (8H, m).

4 Ethyl 4-[4-(1-dipropylamino-cyclopropyl)-phenylethynyl]-benzoate

5 **(Compound 109, General Formula 2)**

6 Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-  
7 dipropylamine (**Intermediate 123**, 34.0 mg, 0.16 mmol) and ethyl-4-iodo  
8 benzoate (**Reagent A**, 59.0 mg, 0.21 mmol) in triethyl amine (6 mL) was  
9 treated with copper(I)iodide (13.0 mg, 0.07 mmol) and sparged with argon  
10 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (49 mg, 0.07  
11 mmol) was added and the reaction mixture was stirred overnight at room  
12 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded  
13 the title compound as a yellow oil.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.49  
15 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.2 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.43  
16 (4H, t, J = 7.3 Hz), 1.52-1.42 (4H, m), 1.41 (3H, t, J = 7.1 Hz), 0.99 (2H,  
17 m), 0.88-0.83 (8H, m).

18 4-[4-(1-Dipropylamino-cyclopropyl)-phenylethynyl]-benzoic acid

19 **(Compound 110, General Formula 2)**

20 Using General Procedure I; a solution of ethyl 4-[4-(1-  
21 dipropylamino-cyclopropyl)-phenylethynyl]-benzoate (**Compound 109**,  
22 51.0 mg, 0.13 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
23 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
24 and stirred overnight at room temperature. Work-up afforded 32.0 mg  
25 (70%) of the title compound as a colorless solid.

26 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.98 (2H, d, J = 8.3 Hz), 7.67 (6H, m), 3.05-2.89  
27 (4H, m), 1.98 (2H, m), 1.72 (4H, m), 1.23 (2H, m), 0.88 (6H, t, J = 7.3 Hz).

1 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (Intermediate 124) and  
2 Dibenzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (Intermediate 125)

3 A solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**  
4 **116**, 244.0 mg, 1.15 mmols) and benzyl bromide (255.0 mg, 1.50 mmols) in  
5 4 mL DMF was stirred at 85 °C for 6 hours, cooled to room temperature and  
6 stirred overnight. The solution was diluted with H<sub>2</sub>O and the pH adjusted to  
7 8-9 with aqueous NaOH. The solution was extracted with EtOAc and the  
8 combined organic layers were washed with H<sub>2</sub>O and saturated aqueous  
9 NaCl, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Column  
10 chromatography (5-10% EtOAc-Hexanes) afforded 110 mg (32%) of the *N*-  
11 benzyl amine.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (2H, d, J = 8.4 Hz), 7.30-7.23 (7H, m), 3.68 (2H,  
13 s), 1.07 (2H, m), 0.93 (2H, m); and 100 mg (22%) of the *N,N*-dibenzyl  
14 amine, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.55 (2H, d, J = 8.3 Hz), 7.40-7.19 (12H, m),  
15 3.61 (4H, s), 0.87 (2H, m), 0.71 (2H, m).

16 Benzyl-[1-(4-trimethylsilyl-ethynyl-phenyl)-cyclopropyl]-amine  
17 **(Intermediate 126)**

18 Using General Procedure D; benzyl-[1-(4-bromophenyl)-  
19 cyclopropyl]-amine (**Intermediate 124**, 110.0 mg, 0.36 mmol) in  
20 triethylamine (8 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol)  
21 and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g,  
22 7.1 mmols) was then added followed by  
23 dichlorobis(triphenylphosphine)palladium(II) (38.0 mg, 0.05 mmol). The  
24 resulting reaction mixture was heated to 70 °C for 5d. The title compound  
25 85 mg (74%) was isolated by chromatography (1 - 10% EtOAc - hexanes).  
26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.3 Hz), 7.31-7.22 (7H, m), 3.67 (2H,  
27 s), 1.06 (2H, m), 0.94 (2H, m), 0.26 (9H, s).

1 Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (Intermediate 127)

2       Using General Pcedure E; benzyl-[1-(4-trimethylsilanylethynyl-  
3 phenyl)-cyclopropyl]-amine (**Intermediate 126**, 85.0 mg, 0.27 mmol) in  
4 methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37  
5 mmol) and stirred overnight at ambient temperature. The crude alkyne (65  
6 mg, 100%) was used directly in the next reaction.

7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.23  
8 (5H, m), 3.68 (2H, s), 3.08 (1H, s), 1.07 (2H, m), 0.95 (2H, m).

9 Ethyl 4-[4-(1-benzylamino-cyclopropyl)-phenylethynyl]-benzoate  
10 (**Compound 111, General Formula 2**)

11       Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-  
12 cyclopropyl]-amine (**Intermediate 127**, 65.0 mg, 0.27 mmol) and ethyl-4-  
13 iodo benzoate (**Reagent A**, 68.0 mg, 0.27 mmol) in triethyl amine (8 mL)  
14 was treated with copper(I)iodide (16.0 mg, 0.08 mmol) and sparged with  
15 argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (58 mg,  
16 0.08 mmol) was added and the reaction mixture was stirred overnight at  
17 room temperature. Column chromatography (2-5% EtOAc - hexanes)  
18 afforded 90 mg (90%) of the title compound as an orange solid.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.05 (2H, d, J = 8.3 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.55  
20 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.32-7.22 (5H, m), 4.40 (2H, q,  
21 J = 7.1 Hz), 3.72 (2H, s), 1.42 (2H, t, J = 7.1 Hz), 1.01 (2H, m), 0.99 (2H,  
22 m).

23 4-[4-(1-Benzylamino-cyclopropyl)-phenylethynyl]-benzoic acid  
24 (**Compound 112, General Formula 2**)

25       Using General Procedure I; a solution of ethyl 4-[4-(1-benzylamino-  
26 cyclopropyl)-phenylethynyl]-benzoate (**Compound 111**, 75.0 mg, 0.19  
27 mmol) in ethanol (4 mL) and tetrahydrofuran (4 mL) was treated with

200

1 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred  
2 overnight at room temperature. Work-up afforded 35.0 mg (50%) of the  
3 title compound as a colorless solid.

4  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$ : 7.93 (2H, d,  $J = 8.3$  Hz), 7.61-7.51 (6H, m), 7.32-7.23  
5 (5H, m), 3.98 (2H, s), 1.33 (2H, m), 1.19 (2H, m).

6 Dibenzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine  
7 (**Intermediate 128**)

8 Using General Procedure D; dibenzyl-[1-(4-bromophenyl)-  
9 cyclopropyl]-amine (**Intermediate 125**, 45.0 mg, 0.11 mmol) in  
10 triethylamine (8 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol)  
11 and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.35 g,  
12 3.6 mmols) was then added followed by  
13 dichlorobis(triphenylphosphine)palladium(II) (35.0 mg, 0.05 mmol). The  
14 resulting reaction mixture was heated to 70 °C for 5d. The title compound  
15 40 mg (88%) was isolated by chromatography (hexanes).

16  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.52 (2H, d,  $J = 8.3$  Hz), 7.36-7.24 (12H, m), 3.60 (4H,  
17 s), 0.87 (2H, m), 0.67 (2H, m), 0.29 (9H, s).

18 Dibenzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (**Intermediate 129**)

19 Using General Procedure E; dibenzyl-[1-(4-trimethylsilanylethynyl-  
20 phenyl)-cyclopropyl]-amine (**Intermediate 128**, 100.0 mg, 0.26 mmol) in  
21 methanol (5 mL) was treated with potassium carbonate (60.0 mg, 0.44  
22 mmol) and stirred overnight at ambient temperature. The crude alkyne (80  
23 mg, 99%) was used directly in the next reaction.

24  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.53 (2H, d,  $J = 7.9$  Hz), 7.36 (2H, d,  $J = 7.9$  Hz), 7.28-  
25 7.25 (10H, m), 3.62 (4H, s), 3.11 (1H, s), 0.88 (2H, m), 0.68 (2H, m).

26 Ethyl 4-[4-(1-dibenzylamino-cyclopropyl)-phenylethynyl]-benzoate  
27 (**Compound 113, General Formula 2**)

1       Using General Procedure F; dibenzyl-[1-(4-ethynylphenyl)-  
2 cyclopropyl]-amine (**Intermediate 129**, 40.0 mg, 0.12 mmol) and ethyl-4-  
3 iodo benzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL)  
4 was treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with  
5 argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (27 mg,  
6 0.04 mmol) was added and the reaction mixture was stirred overnight at  
7 room temperature. Column chromatography (2-5% EtOAc - hexanes)  
8 afforded the title compound as an oil.  
9 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.04 (2H, d, J = 8.5 Hz), 7.79 (4H, m), 7.42 (2H, d, J =  
10 7.9 Hz), 7.29-7.17 (10H, m), 4.40 (2H, q, J = 7.1 Hz), 3.63 (4H, s), 1.42  
11 (3H, t, J = 7.1 Hz), 0.88 (2H, m), 0.73 (2H, m).

12 4-[4-(1-Dibenzylamino-cyclopropyl)-phenylethynyl]-benzoic acid  
13 (**Compound 114, Formula 2**)

14       Using General Procedure I; a solution of ethyl 4-[4-(1-  
15 dibenzylamino-cyclopropyl)-phenylethynyl]-benzoate (**Compound 113**,  
16 48.0 mg, 0.10 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was  
17 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)  
18 and stirred overnight at room temperature. Work-up afforded 42.0 mg  
19 (93%) of the title compound as a colorless solid.

20 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.98 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz),  
21 7.64 (2H, d, J = 7.9 Hz), 7.47 (2H, d, J = 7.9 Hz), 7.28-7.20 (10H, m), 3.57  
22 (4H, s), 0.84 (2H, m), 0.69 (2H, m).

23 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-methylaniline (**Intermediate 130**)

24       To a solution of benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine  
25 (**Intermediate 124**, 100.0 mg, 0.33 mmol) in 5 mL of acetone was added  
26 K<sub>2</sub>CO<sub>3</sub> (91 mg, 0.66 mmol) and iodomethane (2.28 g, 16.1 mmols). The  
27 resulting mixture was stirred at 25 °C for 20 hours, diluted with Et<sub>2</sub>O, and

1 washed with H<sub>2</sub>O and saturated aqueous NaCl. The solution was dried  
2 (MgSO<sub>4</sub>) and concentrated under reduced pressure to give 90 mg (86%) of  
3 the title compound.

4 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (2H, d, J = 8.5 Hz), 7.29-7.18 (7H, m), 3.53 (2H,  
5 s), 2.07 (3H, s), 1.07 (2H, m), 0.86 (2H, m).

6 Benzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-methylaniline  
7 (**Intermediate 131**)

8 Using General Procedure D; benzyl-[1-(4-bromophenyl)-  
9 cyclopropyl]-methylaniline (**Intermediate 130**, 90.0 mg, 0.28 mmol) in  
10 triethylamine (8 mL) was treated with copper(I)iodide (6.0 mg, 0.03 mmol)  
11 and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g,  
12 7.1 mmols) was then added followed by  
13 dichlorobis(triphenylphosphine)palladium(II) (20.0 mg, 0.03 mmol). The  
14 resulting reaction mixture was heated to 70 °C for 5 days. The title  
15 compound 80 mg (84%) was isolated by chromatography (0-2% EtOAc-  
16 hexanes).

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (2H, d, J = 8.2 Hz), 7.32-7.18 (7H, m), 3.52 (2H,  
18 s), 2.06 (3H, s), 1.06 (2H, m), 0.87(2H, m), 0.26 (9H, s).

19 Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-methylaniline (**Intermediate**  
20 **132**)

21 Using General Procedure E; benzyl-[1-(4-trimethylsilanylethynyl-  
22 phenyl)-cyclopropyl]-methylaniline (**Intermediate 131**, 80.0 mg, 0.24 mmol)  
23 in methanol (5 mL) was treated with potassium carbonate (80.0 mg, 0.59  
24 mmol) and stirred overnight at ambient temperature. The crude alkyne (60  
25 mg, 99%) was used directly in the next reaction.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.33-7.21 (7H, m), 3.55 (2H,  
27 s), 3.08 (1H, s), 2.08 (3H, s), 1.07 (2H, m), 0.89 (2H, m).

1 Ethyl 4-{4-[1-(benzyl-methylamino)-cyclopropyl]-phenylethynyl}-benzoate

2 **(Compound 115, General Formula 2)**

3       Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-  
4 cyclopropyl]-methylamine (**Intermediate 132**, 70.0 mg, 0.28 mmol) and  
5 ethyl-4-iodo benzoate (**Reagent A**, 77.0 mg, 0.28 mmol) in triethylamine (5  
6 mL) was treated with copper(I)iodide (18.0 mg, 0.10 mmol) and sparged  
7 with argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II)  
8 (65 mg, 0.10 mmol) was added and the reaction mixture was stirred  
9 overnight at room temperature. Column chromatography (2-5% EtOAc -  
10 hexanes) afforded 86 mg (75%) of the title compound as an oil.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.53  
12 (2H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.39 (2H, q, J =  
13 7.1 Hz), 3.57 (2H, s), 2.10 (3H, s), 1.41 (3H, t, J = 7.1 Hz), 1.10 (2H, m),  
14 0.92 (2H, m).

15 4-[4-(1-Benzylmethylamino-cyclopropyl)-phenylethynyl]-benzoic acid

16 **(Compound 116, General Formula 2)**

17       Using General Procedure I; a solution of ethyl 4-{4-[1-(benzyl-  
18 methylamino)-cyclopropyl]-phenylethynyl}-benzoate (**Compound 115**, 65.0  
19 mg, 0.16 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated  
20 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and  
21 stirred overnight at room temperature. Work-up afforded 45.0 mg (75%) of  
22 the title compound as a solid.

23 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.96 (2H, d, J = 8.3 Hz), 7.66 (2H, d, J = 8.3 Hz),  
24 7.58 (2H, d, J = 8.2 Hz), 7.42 (2H, d, J = 8.2 Hz), 7.29-7.18 (5H, m), 3.52  
25 (2H, s), 2.00 (3H, s), 1.02 (2H, m), 0.87 (2H, m).

26 (4-Bromo-2-methyl-phenyl)-methanol (**Intermediate 133**)

27       A solution of methyl 4-bromo-2-methyl-benzoate (1.05 g, 4.58

1 mmols) in 10 mL of Et<sub>2</sub>O was cooled to 0 °C and treated with LiAlH<sub>4</sub>  
2 (177.0 mg, 4.58 mmols), stirred for 3 hours, and then carefully quenched  
3 with H<sub>2</sub>O. The mixture was extracted with Et<sub>2</sub>O and the combined organic  
4 layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, dried (MgSO<sub>4</sub>),  
5 and concentrated under reduced pressure. The title compound, 830.0 mg  
6 (90%), was isolated by column chromatography (10-30% EtOAc-hexanes)  
7 as a colorless oil.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.30 (2H, m), 7.18 (1H, d, J = 8.8 Hz), 4.57 (2H, d, J =  
9 5.5 Hz), 2.27 (3H, s), 2.13 (1H, t, J = 5.5 Hz).

10 (4-Bromo-2-methyl-benzyloxy)-trimethylsilane (**Intermediate 134**)

11 To a solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate**  
12 **133**, 500.0 mg, 2.48 mmols), in 10 mL THF was added triethylamine (374.0  
13 mg, 3.70 mmols) and chlorotrimethylsilane (297.0 mg, 2.70 mmols). The  
14 resulting solution was stirred for 17 hours at 25 °C and then treated with  
15 H<sub>2</sub>O and extracted with Et<sub>2</sub>O. The combined organic layers were washed  
16 with H<sub>2</sub>O, 10% aqueous HCl, saturated NaHCO<sub>3</sub>, and saturated NaCl before  
17 being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The title  
18 compound, 550.0 mg (81%), was isolated by column chromatography (5%  
19 EtOAc-hexanes) as a colorless oil.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.35-7.28 (3H, m), 4.64 (2H, s), 2.29 (3H, s), 0.20 (9H,  
21 s).

22 2-Methyl-4-trimethylsilyl-ethynyl-1-trimethylsilyloxymethyl-benzene  
23 (**Intermediate 135**)

24 Using General Procedure D; (4-bromo-2-methyl-benzyloxy)-  
25 trimethylsilane (**Intermediate 134**, 550.0 mg, 2.01 mmol) in triethylamine  
26 (8 mL) was treated with copper(I)iodide (38.0 mg, 0.20 mmol) and then  
27 sparged with argon for 5 minutes. Trimethylsilyl acetylene (1.05 g, 10.6

1 mmols) was then added followed by  
2 dichlorobis(triphenylphosphine)palladium(II) (142.0 mg, 0.20 mmol). The  
3 resulting reaction mixture was heated to 70 °C for 5 days. The title  
4 compound (380.0 mg, 65%) was isolated by chromatography (0 - 2% EtOAc  
5 - hexanes) as an orange oil.

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.31 (3H, m), 4.64 (2H, s), 2.24 (3H, s), 0.24 (9H, s),  
7 0.15 (9H, s).

8 (4-Ethynyl-2-methyl-phenyl)-methanol (**Intermediate 136**)

9 Using General Procedure E; 2-methyl-4-trimethylsilanylethynyl-1-  
10 trimethylsilanyloxymethyl-benzene (**Intermediate 135**, 380.0 mg, 1.30  
11 mmols) in methanol (10 mL) was treated with potassium carbonate (180.0  
12 mg, 1.3 mmol) and stirred overnight at ambient temperature. The crude  
13 alkyne was purified by column chromatography (5-20% EtOAc-hexanes) to  
14 give 100.0 mg (34%) of the title compound.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.06 (3H, m), 4.42 (2H, d, J = 5.2 Hz), 2.81 (1H, s),  
16 2.05 (3H, s), 1.59 (1H, t, J = 5.2 Hz).

17 Ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-benzoate (**Compound**  
18 **117, General Formula 6**)

19 Using General Procedure F; (4-ethynyl-2-methyl-phenyl)-methanol  
20 (**Intermediate 136**, 100.0 mg, 0.44 mmol) and ethyl-4-iodo benzoate  
21 (**Reagent A**, 125.0 mg, 0.45 mmol) in triethyl amine (4 mL) was treated  
22 with copper(I)iodide (29 mg, 0.15 mmol) and sparged with argon for 5  
23 minutes. Dichlorobis(triphenylphosphine)palladium(II) (102 mg, 0.15  
24 mmol) was added and the reaction mixture was stirred overnight at room  
25 temperature. Column chromatography (20-40% EtOAc - hexanes) afforded  
26 130.0 mg (99%) of the title compound as an orange solid.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.98 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.36

1 (3H, m), 4.65 (2H, s), 4.36 (2H, q,  $J = 7.1$  Hz), 2.40 (1H, s), 2.30 (3H, s),  
2 1.39 (3H, t,  $J = 7.1$  Hz).

3 Ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate (**Intermediate**  
4 **137**)

5 A solution of ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-  
6 benzoate (**Compound 117**, 130.0 mg, 0.44 mmol) and triphenylphosphine  
7 (150.0 mg, 0.57 mmol) in 5 mL  $\text{CH}_2\text{Cl}_2$  was cooled to 0 °C and *N*-  
8 bromosuccinimide (101.0 mg, 0.57 mmol) was added in 5 portions over 20  
9 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The  
10 reaction was quenched by the addition of dilute aqueous  $\text{NaHCO}_3$ . The  
11 resulting mixture was extracted with  $\text{Et}_2\text{O}$  and the combined organic layers  
12 were washed with  $\text{H}_2\text{O}$  and saturated aqueous  $\text{NaCl}$  before being dried  
13 ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The title compound,  
14 120.0 mg (76%), was isolated by column chromatography (2-5%  $\text{EtOAc}$ -  
15 hexanes) as a colorless solid.  
16  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.01 (2H, d,  $J = 8.1$  Hz), 7.56 (2H, d,  $J = 8.1$  Hz), 7.32  
17 (3H, m), 4.48 (2H, s), 4.38 (2H, q,  $J = 7.1$  Hz), 2.40 (3H, s), 1.39 (3H, t,  $J =$   
18 7.1 Hz).

19 Ethyl 4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoate  
20 (**Compound 118, General Formula 6**)

21 A solution of imidazole (30.0 mg, 0.44 mmol) in 2 mL DMF was  
22 treated with  $\text{NaH}$  (11.0 mg, 0.44 mmol) and heated to 90 °C. After 1h a  
23 solution of ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate  
24 (**Intermediate 137**, 120.0 mg, 0.34 mmol) in 2 mL DMF was added and  
25 stirring at 90 °C continued for 1 hour. The solution was cooled to room  
26 temperature and concentrated under reduced pressure. The title compound,  
27 90.0 mg (71%) was isolated by column chromatography (20-100%  $\text{EtOAc}$ -

1 hexanes) as a colorless solid.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.02 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.51  
3 (1H, s), 7.40 (1H, s), 7.36 (1H, dd, J = 1.2, 7.9 Hz), 7.10 (1H, s), 6.93 (1H,  
4 d, J = 7.9 Hz), 6.88 (1H, t, J = 1.7 Hz), 5.12 (2H, s), 4.38 (2H, q, J = 7.1  
5 Hz), 2.27 (3H, s), 1.40 (3H, t, J = 7.1 Hz).

6 4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoic acid

7 **(Compound 119, General Formula 6)**

8 Using General Procedure I; a solution of ethyl 4-(4-imidazol-1-  
9 ylmethyl-3-methyl-phenylethynyl)-benzoate (**Compound 118**, 82.0 mg,  
10 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with  
11 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred  
12 overnight at room temperature. Work-up afforded 51.0 mg (68%) of the  
13 title compound as a solid.

14 <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 9.20 (1H, s), 7.97 (2H, d, J = 8.2 Hz), 7.73 (2H, m),  
15 7.65 (2H, d, J = 8.2 Hz), 7.52 (1H, s), 7.46 (1H, d, J = 7.9 Hz), 7.13 (1H, d,  
16 J = 7.9 Hz), 5.50 (2H, s), 2.32 (3H, s).

17 4-Bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**)

18 A solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate**  
19 **133**, 319.0 mg, 1.58 mmol) and triphenylphosphine (466.0 mg, 1.74 mmol)  
20 in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and *N*-bromosuccinimide (309.0 mg,  
21 1.74 mmol) was added in 5 portions over 20 minutes. The solution was  
22 warmed to 25 °C and stirred for 17 hours. The reaction was quenched by  
23 the addition of dilute aqueous NaHCO<sub>3</sub>. The resulting mixture was  
24 extracted with Et<sub>2</sub>O and the combined organic layers were washed with H<sub>2</sub>O  
25 and saturated aqueous NaCl before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated  
26 under reduced pressure. The title compound, 350.0 mg (84%), was isolated  
27 by column chromatography (2-3% EtOAc-hexanes) as a colorless oil.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, d, J = 2.0 Hz), 7.29 (1H, dd, J = 2.0, 7.9 Hz),  
2 7.15 (1H, d, J = 7.9 Hz), 4.43 (2H, s), 2.37 (3H, s).

3 1-(4-Bromo-2-methyl-benzyl)-1H-imidazole (**Intermediate 139**)

4 A solution of imidazole (58.0 mg, 0.86 mmol) in 3 mL DMF was  
5 treated with NaH (20.0 mg, 0.86 mmol) and heated to 90 °C. After 1h a  
6 solution of 4-bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**,  
7 190.0 mg, 0.72 mmol) in 3 mL DMF was added and stirring at 90 °C  
8 continued for 1hour. The solution was cooled to room temperature and  
9 concentrated under reduced pressure. The title compound, 160.0 mg (88%)  
10 was isolated by column chromatography (5% MeOH-EtOAc) as a colorless  
11 solid.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.46 (1H, s), 7.34 (1H, dd, J = 1.8 Hz), 7.30 (1H, dd, J  
13 = 1.8, 8.2 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.83 (1H, t, J = 1.2 Hz), 6.80 (1H, d,  
14 J = 8.2 Hz), 5.03 (2H, s), 2.23 (3H, s).

15 1-(2-Methyl-4-trimethylsilanylethynyl-benzyl)-1H-imidazole (**Intermediate**  
16 **140**)

17 Using General Procedure D; 1-(4-bromo-2-methyl-benzyl)-1H-  
18 imidazole (**Intermediate 139**, 160.0 mg, 0.64 mmol) in triethylamine (8  
19 mL) was treated with copper(I)iodide (12.0 mg, 0.07 mmol) and then  
20 sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 0.71  
21 mmols) was then added followed by  
22 dichlorobis(triphenylphosphine)palladium(II) (45.0 mg, 0.07 mmol). The  
23 resulting reaction mixture was heated to 70 °C for 5 days. The title  
24 compound (140.0 mg, 82%) was isolated by chromatography (5% MeOH-  
25 EtOAc ) as an orange oil.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.53 (1H, s), 7.38 (1H, s), 7.34 (1H, d, J = 8.0 Hz),  
27 7.15 (1H, s), 6.94 (1H, s), 6.91 (1H, d, J = 8.0 Hz), 5.14 (2H, s), 2.29 (3H,

1 s), 0.31 (9H, s).

2 1-(4-Ethynyl-2-methyl-benzyl)-1H-imidazole (Intermediate 141)

3 Using General Procedure E; 1-(2-methyl-4-trimethylsilanylethynyl-  
4 benzyl)-1H-imidazole (**Intermediate 140**, 140.0 mg, 0.53 mmols) in  
5 methanol (5 mL) was treated with potassium carbonate (100.0 mg, 0.72  
6 mmol) and stirred overnight at ambient temperature. The crude alkyne (105  
7 mg, 100%) was used directly in the next reaction.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (1H, s), 7.35 (1H, s), 7.31 (1H, dd, J = 1.7, 7.9  
9 Hz), 7.10 (1H, s), 6.69 (1H, d, J = 7.9 Hz), 6.85 (1H, t, J = 1.2 Hz), 5.14  
10 (2H, s), 3.08 (1H, s), 2.26 (3H, s).

11 Methyl [4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetate  
12 (**Compound 120, General Formula 6**)

13 Using General Procedure F; 1-(4-ethynyl-2-methyl-benzyl)-1H-  
14 imidazole (**Intermediate 141**, 101.0 mg, 0.53 mmol) and methyl-(4-  
15 iodophenyl)-acetate (**Reagent B**, 145.0 mg, 0.53 mmol) in triethylamine (5  
16 mL) was treated with copper(I)iodide (34.0 mg, 0.18 mmol) and sparged  
17 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
18 (124 mg, 0.18 mmol) was added and the reaction mixture was stirred  
19 overnight at room temperature. Column chromatography (5% MeOH-  
20 EtOAc) afforded 45.0 mg (25%) of the title compound as an orange oil.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (3H, m), 7.35 (3H, m), 7.27 (3H, m), 6.91 (1H, d,  
22 J = 7.3 Hz), 5.11 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 2.26 (3H, s).

23 [4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetic acid  
24 (**Compound 121, General Formula 6**)

25 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-  
26 ylmethyl-3-methyl-phenylethynyl)-phenyl]-acetate (**Compound 120**, 45.0  
27 mg, 0.13 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was treated

1 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and  
2 stirred overnight at room temperature. Work-up afforded 30.0 mg (70%) of  
3 the title compound as a pale-orange solid.  
4 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 8.97 (1H, s), 7.60 (2H, d J = 8.8 Hz), 7.47 (3H, m),  
5 7.41 (1H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz), 7.23 (1H, d, J = 7.9 Hz),  
6 5.51 (2H, s), 3.64 (2H, s), 2.33 (3H, s).

7 1-Isopropyl-3-methoxy-benzene (Intermediate 142)

8 To a solution of 3-isopropyl-phenol (5.00 g, 36.2 mmols) in 50 mL of  
9 acetone was added K<sub>2</sub>CO<sub>3</sub> (7.50 g, 54.3 mmols) and iodomethane (10.3 g,  
10 72.5 mmols). The resulting solution was heated to 50 °C and stirred for 18  
11 hours, cooled to room temperature, and concentrated under reduced  
12 pressure. The residual oil was dissolved in Et<sub>2</sub>O and washed with H<sub>2</sub>O,  
13 saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried  
14 (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude methyl ether  
15 was used without further purification.  
16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.22 (1H, t, J = 8.1 Hz), 6.84-6.72 (3H, m), 3.81 (3H,  
17 s), 2.88 (1H, septet, J = 7.0 Hz), 1.25 (6H, d, J = 7.0 Hz).

18 1-Bromo-2-isopropyl-4-methoxy-benzene (Intermediate 143)

19 A mixture of 1-isopropyl-3-methoxy-benzene (Intermediate 142,  
20 3.50 g, 23.3 mmols), molecular sieves, and silica gel in 150 mL CCl<sub>4</sub> was  
21 treated with *N*-bromosuccinimide (4.98 g, 28.0 mmols) at 35 °C for 18  
22 hours. An additional portion of *N*-bromosuccinimide (830.0 mg, 4.46  
23 mmols) was added and stirring continued for 6 hours. The mixture was  
24 cooled to room temperature, H<sub>2</sub>O was added, and the mixture was filtered to  
25 remove the solids. The mixture was extracted with E<sub>2</sub>O and the combined  
26 organic layers were washed with 10% aqueous HCl, H<sub>2</sub>O, saturated aqueous  
27 NaHCO<sub>3</sub>, and saturated NaCl before being dried (MgSO<sub>4</sub>) and concentrated

1 under reduced pressure. Column chromatography (2.5% EtOAc-hexanes)  
2 afforded 4.34 g (81%) of the title compound as a pale-yellow oil.  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41 (1H, d, J = 8.8 Hz), 6.82 (1H, d, J = 2.6 Hz), 6.61  
4 (1H, dd, J = 2.6, 8.8 Hz), 3.79 (3H, s), 3.31 (1H, septet, J = 6.7 Hz), 1.23  
5 (6H, d, J = 6.7 Hz).

6 4-Bromo-3-isopropyl-phenol (**Intermediate 144**)

7 To a solution of 1-bromo-2-isopropyl-4-methoxy-benzene  
8 (**Intermediate 143**, 2.20 g, 9.60 mmols) in 50 mL CH<sub>2</sub>Cl<sub>2</sub> at -78 °C was  
9 added BBr<sub>3</sub> (4.81 g, 19.2 mmols; 19.2 mL of a 1M solution in CH<sub>2</sub>Cl<sub>2</sub>).  
10 After stirring for 3 hours at -78 °C the solution was warmed to 0 °C for 3  
11 hours and then at 25 °C for 1 hour before being quenched with H<sub>2</sub>O. The  
12 mixture was diluted with Et<sub>2</sub>O and washed with H<sub>2</sub>O and saturated aqueous  
13 NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column  
14 chromatography (2.5-10% EtOAc-hexanes) afforded the title compound as a  
15 colorless oil.  
16 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.38 (1H, d, J = 8.5 Hz), 6.79 (1H, d, J = 2.9 Hz), 6.57  
17 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.22 (6H, d, J = 7.0  
18 Hz).

19 (4-Bromo-3-isopropyl-phenoxy)-tert-butyl-dimethyl-silane (**Intermediate**  
20 **145**)

21 A solution of 4-bromo-3-isopropyl-phenol (**Intermediate 144**, 1.13  
22 g, 5.25 mmols), chloro-*tert*-butyl-dimethylsilane (0.95 g, 6.30 mmols), and  
23 imidazole (428.0 mg, 6.3 mmols) in 10 mL DMF was stirred at 25 °C for 3  
24 hours. The solution was diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O and the  
25 combined organic layers were washed with H<sub>2</sub>O, saturated aqueous NaCl,  
26 and dried (MgSO<sub>4</sub>) before being concentrated under reduced pressure.  
27 Column chromatography (1-2% EtOAc-hexanes) afforded 1.50 g (87%) of

1 the title compound as a colorless oil.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, d, J = 8.8 Hz), 6.73 (1H, d, J = 3.0 Hz), 6.52  
3 (1H, dd, J = 3.0, 8.8 Hz), 3.26 (1H, septet, J = 6.7 Hz), 1.19 (6H, d, J = 6.7  
4 Hz), 0.96 (9H, s), 0.17 (6H, s).

5 4-(*Tert*-butyl-dimethyl-silanyloxy)-2-isopropyl-benzaldehyde

6 (**Intermediate 146**)

7 A solution of (4-bromo-3-isopropyl-phenoxy)-*tert*-butyl-dimethyl-  
8 silane (**Intermediate 145**, 1.03 g, 3.13 mmols) in 25 mL E<sub>2</sub>O was cooled to  
9 -78 °C and treated with *tert*-butyllithium (401.0 mg, 6.26 mmols; 3.7 mL of  
10 a 1.7M solution in pentane). After 30 minutes the reaction was quenched  
11 with DMF (913.0 mg, 12.5 mmols) and warmed to room temperature. The  
12 solution was diluted with H<sub>2</sub>O, extracted with Et<sub>2</sub>O and the combined  
13 organic layers washed with H<sub>2</sub>O and saturated aqueous NaCl before being  
14 dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Column  
15 chromatography (2% EtOAc-hexanes) afforded 480.0 mg (55%) of the title  
16 compound as a colorless oil.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.19 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J =  
18 2.3 Hz), 6.77 (1H, dd, J = 2.3, 8.5 Hz), 3.97 (1H, septet, J = 6.7 Hz), 1.27  
19 (6H, d, J = 6.7 Hz), 1.00 (9H, s), 0.25 (6H, s).

20 4-Hydroxy-2-isopropyl-benzaldehyde (**Intermediate 147**)

21 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-isopropyl-  
22 benzaldehyde (**Intermediate 146**, 880.0 mg, 3.17 mmols) in 6 mL THF at 0  
23 °C was added tetrabutylammonium fluoride (1.66 g, 6.33 mmols; 6.3 mL of  
24 a 1M solution in THF). The pale-yellow solution was stirred for 30 minutes  
25 and quenched by the addition of ice cold H<sub>2</sub>O. The mixture was extracted  
26 with Et<sub>2</sub>O and the combined organic layers were washed with H<sub>2</sub>O and  
27 saturated aqueous NaCl before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under

1 reduced pressure. Column chromatography (20% EtOAc-hexanes) afforded  
2 500.0 mg (96%) of the title compound as a colorless solid.  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.15 (1H, s), 7.79 (1H, d, J = 8.5 Hz), 6.95 (1H, d, J =  
4 2.3 Hz), 6.86 (1H, dd, J = 2.3, 8.5 Hz), 3.96 (1H, septet, J = 6.7 Hz), 1.29  
5 (6H, d, J = 6.7 Hz).

6 4-Formyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate  
7 **(Intermediate 148)**

8 A solution of 4-hydroxy-2-isopropyl-benzaldehyde (**Intermediate**  
9 **147**, 300.0 mg, 1.83 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and to it  
10 was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine  
11 (754.0 mg, 1.92 mmol) and triethylamine (592.0 mg, 5.85 mmols). The  
12 resulting solution was warmed to room temperature and stirred for 4.5  
13 hours. The reaction was quenched by the addition of H<sub>2</sub>O and the mixture  
14 extracted with EtOAc and the combined organic layers were washed with  
15 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, and saturated aqueous  
16 NaCl. The solution was dried (MgSO<sub>4</sub>) and concentrated under reduced  
17 pressure. The title compound was isolated by column chromatography (5-  
18 10% EtOAc-hexanes) as a colorless oil, 470.0 mg (87%).  
19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.37 (1H, s), 7.94 (1H, d, J = 8.5 Hz), 7.33 (1H, d, J =  
20 2.3 Hz), 7.26 (1H, dd, J = 2.3, 8.5 Hz), 4.00 (1H, septet, J = 6.7 Hz), 1.33  
21 (6H, d, J = 6.7 Hz),

22 4-Hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate  
23 **(Intermediate 149)**

24 To a solution of 4-formyl-3-isopropyl-phenyl 1,1,1-trifluoro-  
25 methansulfonate (**Intermediate 148**, 540.0 mg, 1.82 mmols) in 7 mL  
26 MeOH at 0 °C was added NaBH<sub>4</sub> (72.0 mg, 1.91 mmols). After stirring 2  
27 hours at 0 °C the reaction was carefully quenched with H<sub>2</sub>O and extracted

1 with Et<sub>2</sub>O. The combined organic layers were washed with H<sub>2</sub>O and  
2 saturated aqueous NaCl, dried (MgSO<sub>4</sub>), and concentrated under reduced  
3 pressure. The title compound was isolated by column chromatography (5-  
4 10% EtOAc-hexanes) as a colorless oil, 355.0 mg (90%).  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.45 (1H, d, J = 8.5 Hz), 7.17 (1H, d, J = 2.7 Hz), 7.08  
6 (1H, dd, J = 2.7, 8.5 Hz), 4.74 (2H, d, J = 5.3 Hz), 3.21 (1H, septet, J = 7.0  
7 Hz), 2.12 (1H, t, J = 5.3 Hz), 1.24 (6H, d, J = 7.0 Hz).  
8 4-(Tert-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-phenyl 1,1,1-  
9 trifluoro-methansulfonate (**Intermediate 150**)

10 A solution of 4-hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-  
11 methansulfonate (**Intermediate 149**, 760.0 mg, 2.55 mmols), chloro-*tert*-  
12 butyl-dimethylsilane (470.0 mg, 3.18 mmols), and imidazole (225.0 mg,  
13 3.25 mmols) in 6 mL DMF was stirred at 25 °C for 17 hours. The solution  
14 was diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O and the combined organic  
15 layers were washed with 10% aqueous HCl, saturated aqueous NaHCO<sub>3</sub>,  
16 H<sub>2</sub>O, and saturated aqueous NaCl, and dried (MgSO<sub>4</sub>) before being  
17 concentrated under reduced pressure. Column chromatography (2-5%  
18 EtOAc-hexanes) afforded 970.0 mg (92%) of the title compound as a  
19 colorless oil.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 2.3 Hz), 7.06  
21 (1H, dd, J = 2.3, 8.5 Hz), 4.75 (2H, s), 3.10 (1H, septet, J = 6.7 Hz), 1.21  
22 (6H, d, J = 6.7 Hz), 0.93 (9H, s), 0.10 (6H, s).  
23 1-(Tert-butyl-dimethyl-silanyloxymethyl)-2-isopropyl-4-  
24 trimethylsilanylethynyl-benzene (**Intermediate 151**)

25 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-  
26 isopropyl-phenyl 1,1,1-trifluoro-methansulfonate (**Intermediate 150**, 970.0  
27 mg, 2.35 mmols) in triethylamine (2 mL) and 6 mL DMF was sparged with

1 argon for 15 minutes. Trimethylsilyl acetylene (1.00 g, 10.6 mmols) was  
2 then added followed by dichlorobis(triphenylphosphine)palladium(II) (66.0  
3 mg, 0.09 mmol). The resulting reaction mixture was heated to 95 °C for 20  
4 hours. The solution was cooled to room temperature and concentrated under  
5 reduced pressure. The title compound (200.0 mg, 78%) was isolated by  
6 chromatography (0-25% EtOAc-hexanes) as an orange oil.  
7 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.37-7.25 (3H, m), 4.75 (2H, s), 3.08 (1H, septet, J =  
8 7.0 Hz), 1.21 (6H, d, J = 7.0 Hz), 0.92 (9H, s), 0.25 (9H, s), 0.09 (6H, s).

9 *Tert*-butyl-(4-ethynyl-2-isopropyl-benzyloxy)-dimethyl-silane

10 **(Intermediate 152)**

11 Using General Procedure E; 1-(*tert*-butyl-dimethyl-  
12 silanyloxymethyl)-2-isopropyl-4-trimethylsilanylethynyl-benzene  
13 **(Intermediate 151**, 850.0 mg, 2.36 mmols) in methanol (25 mL) was  
14 treated with potassium carbonate (250.0 mg, 1.81 mmols) and stirred  
15 overnight at ambient temperature. The crude alkyne (650 mg, 95%) was  
16 used directly in the next reaction.

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.41-7.25 (3H, m), 4.77 (2H, s), 3.07 (1H, septet, J =  
18 7.0 Hz), 3.05 (1H, s), 1.22 (6H, d, J = 7.0 Hz), 0.94 (9H, s), 0.11 (6H, s).

19 Ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-  
20 phenylethynyl]-benzoate **(Intermediate 153)**

21 Using General procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-  
22 benzyloxy)-dimethyl-silane **(Intermediate 152**, 300.0 mg, 1.04 mmols) and  
23 ethyl-4-iodo benzoate **(Reagent A**, 287.0 mg, 1.04 mmols) in triethylamine  
24 (8mL) was treated with copper(I)iodide (50.0 mg, 0.26 mmol) and sparged  
25 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
26 (182 mg, 0.26 mmol) was added and the reaction mixture was stirred  
27 overnight at room temperature. Column chromatography (2-4% EtOAc -

1 hexanes) afforded 310.0 mg (68%) of the title compound as an orange solid.  
2 .  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.48-  
4 7.37 (3H, m), 4.80 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.14 (1H, septet, J = 6.8  
5 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.27 (6H, d, J = 6.8 Hz), 0.96 (9H, s), 0.12  
6 (6H, s).

7 Methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-  
8 phenylethynyl]-phenyl}-acetate (Intermediate 154)

9 Using General Procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-  
10 benzyloxy)-dimethyl-silane (**Intermediate 152**, 355.0 mg, 1.26 mmols) and  
11 methyl-(4-iodophenyl)-acetate (**Reagent B**, 349.0 mg, 1.26 mmols) in  
12 triethylamine (8 mL) was treated with copper(I)iodide (60.0 mg, 0.32 mmol)  
13 and sparged with argon for 5 minutes.  
14 Dichlorobis(triphenylphosphine)palladium(II) (222 mg, 0.32 mmol) was  
15 added and the reaction mixture was stirred overnight at room temperature.  
16 Column chromatography (2-5% EtOAc-hexanes) afforded 288.0 mg (66%)  
17 of the title compound as an orange oil.  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.5 Hz), 7.43-7.35 (3H, m), 7.25 (2H,  
19 d, J = 8.5 Hz), 4.77 (2H, s), 3.69 (3H, s), 3.63 (2H, s), 3.11 (1H, septet, J =  
20 6.7 Hz), 1.25 (6H, d, J = 6.7 Hz), 0.94 (9H, s), 0.10 (6H, s).

21 Ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-benzoate  
22 (Compound 122, General Formula 6)

23 To a solution of ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-  
24 isopropyl-phenylethynyl]-benzoate (**Intermediate 153**, 310.0 mg, 0.71  
25 mmol) in 4 mL THF at 0 °C was added tetrabutylammonium fluoride (371.0  
26 mg, 1.42 mmols; 1.4 mL of a 1M solution in THF). The pale-yellow  
27 solution was stirred for 10 minutes and quenched by the addition of ice cold

1 H<sub>2</sub>O. The mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
2 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
3 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column  
4 chromatography (20-30% EtOAc-hexanes) afforded 200.0 mg (87%) of the  
5 title compound as a colorless solid.

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.98 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.48  
7 (1H, s), 7.35 (2H, m), 4.71 (2H, s), 4.35 (2H, q, J = 7.1 Hz), 3.19 (1H,  
8 septet, J = 7.0 Hz), 2.51 (1H, s), 1.39 (3H, t, J = 7.1 Hz), 1.25 (6H, d, J = 7.0  
9 Hz).

10 Methyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate  
11 **(Compound 123, General Formula 6)**

12 To a solution of methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-  
13 3-isopropyl-phenylethynyl]-phenyl}-acetate (**Intermediate 154**, 288.0 mg,  
14 0.66 mmol) in 5 mL THF at 0 °C was added tetrabutylammonium fluoride  
15 (471.0 mg, 1.80 mmols; 1.8 mL of a 1M solution in THF). The pale-yellow  
16 solution was stirred for 15 minutes and quenched by the addition of ice cold  
17 H<sub>2</sub>O. The mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
18 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
19 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column  
20 chromatography (5-10% EtOAc-hexanes) afforded 180.0 mg (85%) of the  
21 title compound as a colorless solid.

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (3H, m), 7.32 (2H, m), 7.24 (2H, d, J = 8.5 Hz),  
23 4.69 (2H, s), 3.68 (3H, s), 3.62 (2H, s), 3.18 (1H, septet, J = 7.0 Hz), 2.21  
24 (1H, s), 1.25 (6H, d, J = 7.0 Hz).

25 Ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-benzoate  
26 **(Intermediate 155)**

27 A solution of ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-

1 benzoate (**Compound 122**, 200.0 mg, 0.62 mmol) and triphenylphosphine  
2 (211.0 mg, 0.81 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C and *N*-  
3 bromosuccinimide (144.0 mg, 0.81 mmol) was added in 5 portions over 20  
4 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The  
5 reaction was quenched by the addition of dilute aqueous NaHCO<sub>3</sub>. The  
6 resulting mixture was extracted with Et<sub>2</sub>O and the combined organic layers  
7 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried  
8 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The title compound,  
9 220.0 mg (93%), was isolated by column chromatography (5% EtOAc-  
10 hexanes) as a pale-yellow solid.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.48  
12 (1H, s), 7.31 (2H, m), 4.55 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.29 (1H, septet,  
13 J = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.30 (6H, d, J = 7.0 Hz).

14 Methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate  
15 (**Intermediate 156**)

16 A solution of methyl [4-(4-hydroxymethyl-3-isopropyl-  
17 phenylethynyl)-phenyl]-acetate (**Compound 123**, 180.0 mg, 0.56 mmol) and  
18 triphenylphosphine (190.0 mg, 0.73 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0  
19 °C and *N*-bromosuccinimide (130.0 mg, 0.73 mmol) was added in 5 portions  
20 over 20 minutes. The solution was warmed to 25 °C and stirred for 17  
21 hours. The reaction was quenched by the addition of dilute aqueous  
22 NaHCO<sub>3</sub>. The resulting mixture was extracted with Et<sub>2</sub>O and the combined  
23 organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl before  
24 being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The title  
25 compound, 212.0 mg (98%), was isolated by column chromatography (5-  
26 10% EtOAc-hexanes) as a pale-yellow oil.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.48 (3H, m), 7.28 (4H, m), 4.55 (2H, s), 3.69 (3H, s),

1 3.63 (2H, s), 3.28 (1H, septet,  $J = 7.0$  Hz), 1.30 (6H, d,  $J = 7.0$  Hz).

2 Ethyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-  
3 benzoate (**Compound 124, General Formula 6**)

4 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-  
5 benzoate (**Intermediate 155**, 120.0 mg, 0.31 mmol) and 1-acetylimidazole  
6 (36.0 mg, 0.33 mmol) in 5 mL  $\text{CH}_3\text{CN}$  was heated at 65 °C for 4 hours and  
7 then at 55 °C for 16 hours. The solution was cooled to room temperature,  
8 diluted with  $\text{H}_2\text{O}$  and made basic by addition of  $\text{Na}_2\text{CO}_3$ , and extracted with  
9 EtOAc. The combined organic layers were washed with  $\text{H}_2\text{O}$  and saturated  
10 aqueous NaCl, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure.  
11 Column chromatography (1%  $\text{Et}_3\text{N}$  in 5% MeOH-EtOAc) afforded 75.0 mg  
12 (65%) of the title compound as a colorless solid.

13  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.03 (2H, d,  $J = 8.5$  Hz), 7.60 (2H, d,  $J = 8.5$  Hz), 7.53  
14 (1H, d,  $J = 1.5$  Hz), 7.49 (1H, s), 7.35 (1H, dd,  $J = 1.5, 7.9$  Hz), 7.09 (1H,  
15 bs), 6.98 (1H, d,  $J = 7.9$  Hz), 6.85 (1H, bs), 5.19 (2H, s), 4.39 (2H, q,  $J = 7.1$   
16 Hz), 3.08 (1H, septet,  $J = 6.8$  Hz), 1.40 (3H, t,  $J = 7.1$  Hz), 1.20 (6H, d,  $J =$   
17 6.8 Hz).

18 Methyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-  
19 acetate (**Compound 125, General Formula 6**)

20 A solution of methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-  
21 phenyl]-acetate (**Intermediate 156**, 72.0 mg, 0.19 mmol) and 1-  
22 acetylimidazole (22.0 mg, 0.20 mmol) in 5 mL  $\text{CH}_3\text{CN}$  was heated at 65 °C  
23 for 8h and then at 55 °C for 16 hours. The solution was cooled to room  
24 temperature, diluted with  $\text{H}_2\text{O}$  and made basic by addition of  $\text{Na}_2\text{CO}_3$ , and  
25 extracted with EtOAc. The combined organic layers were washed with  $\text{H}_2\text{O}$   
26 and saturated aqueous NaCl, dried ( $\text{MgSO}_4$ ), and concentrated under  
27 reduced pressure. Column chromatography (0.5%  $\text{Et}_3\text{N}$  in 5% MeOH-

1 EtOAc) afforded 40.0 mg (58%) of the title compound as a colorless solid.  
2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (4H, m), 7.33 (1H, dd, J = 1.5, 7.9 Hz), 7.28 (2H,  
3 d, J = 8.5 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.95 (1H, d, J = 7.9 Hz), 6.84 (1H, t,  
4 J = 1.2 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 3.06 (1H, septet, J = 6.8  
5 Hz), 1.20 (6H, d, J = 6.8 Hz).

6 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-benzoic  
7 acid (Compound 126, General Formula 6)

8 Using General Procedure I; a solution of ethyl [4-(4-imidazol-1-  
9 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-benzoate (**Compound 124**,  
10 75.0 mg, 0.20 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was  
11 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)  
12 and stirred overnight at room temperature. Work-up afforded 68.0 mg  
13 (88%) of the title compound as a colorless solid.

14 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 9.01 (1H, s), 8.01 (2H, d, J = 8.2 Hz), 7.63-7.57  
15 (5H, m), 7.44 (1H, d, J = 7.9 Hz), 7.29 (1H, d, J = 7.9 Hz), 5.59 (2H, s),  
16 3.17 (1H, septet, J = 6.8 Hz), 1.20 (6H, d, J = 6.8 Hz).

17 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-acetic acid  
18 (Compound 127, General Formula 6)

19 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-  
20 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate (**Compound 125**, 40.0  
21 mg, 0.11 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was treated  
22 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and  
23 stirred overnight at room temperature. Work-up afforded 22.0 mg (52%) of  
24 the title compound as a colorless solid.

25 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 9.02 (1H, bs), 7.62 (1H, t, J = 1.4 Hz), 7.58 (2H, m),  
26 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.31 (3H, m), 5.58  
27 (2H, s), 3.68 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.18 (6H, d, J = 6.7 Hz).

1 4-Bromo-*N*-cyclopropyl-2-methyl-benzamide (**Intermediate 157**)

2       A solution of 4-bromo-2-methylbenzoic acid and SOCl<sub>2</sub> was refluxed  
3 for 3 hours, cooled to room temperature and concentrated under reduced  
4 pressure. The residue was dissolved in 30 mL CH<sub>2</sub>Cl<sub>2</sub> and combined with  
5 cyclopropyl amine (810.0 mg, 14.3 mmols) and pyridine (2.05 g, 26.0  
6 mmols). The solution was stirred for 18 hours and then diluted with EtOAc  
7 before being washed with 5% aqueous HCl, saturated NaHCO<sub>3</sub>, and  
8 saturated aqueous NaCl. The solution was dried (MgSO<sub>4</sub>) and concentrated  
9 under reduced pressure leaving the title compound as a colorless solid.  
10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.34 (1H, d, J = 2.3 Hz), 7.28 (1H, dd, J = 2.3, 8.2 Hz),  
11 7.13 (1H, d, J = 8.2 Hz), 6.10 (1H, bs), 2.85 (1H, m), 2.37 (3H, s), 0.85 (2H,  
12 m), 0.59 (2H, m).

13 (4-Bromo-2-methyl-benzyl)-cyclopropyl-amine (**Intermediate 158**)

14       To a solution of 4-bromo-*N*-cyclopropyl-2-methyl-benzamide  
15 (**Intermediate 157**, 1.81 g, 7.12 mmols) in THF (12 mL) was added  
16 BH<sub>3</sub>•SMe<sub>2</sub> (1.08 g, 14.24 mmols). The solution was heated to 60 °C for 6  
17 hours, cooled to room temperature and carefully treated with saturated  
18 aqueous Na<sub>2</sub>CO<sub>3</sub> (30 mL) and stirred for 17 hours. This mixture was  
19 extracted with EtOAc and the combined organic layers were washed with  
20 H<sub>2</sub>O, saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and concentrated  
21 under reduced pressure. The title compound was isolated by column  
22 chromatography (10-15% EtOAc-hexanes).  
23 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.26 (2H, m), 7.12 (1H, d, J = 7.9 Hz), 3.76 (2H, s),  
24 2.31 (3H, s), 2.14 (1H, m), 0.44 (2H, m), 0.36 (2H, m).

25 (4-Bromo-2-methyl-benzyl)-cyclopropyl-ethyl-amine (**Intermediate 159**)

26       A mixture of (4-bromo-2-methyl-benzyl)-cyclopropyl-amine  
27 (**Intermediate 158**, 600.0 mg, 2.49 mmols), ethyl iodide (1.56 g, 10.0

1 mmols), and  $K_2CO_3$  (690.0 mg, 5.00 mmols) in 10 mL acetone was heated at  
2 60 °C for 18 hours. The mixture was cooled to room temperature, diluted  
3 with  $H_2O$ , and extracted with EtOAc. The combined organic layers were  
4 washed with  $H_2O$  and saturated aqueous NaCl before being dried ( $MgSO_4$ )  
5 and concentrated under reduced pressure. The title compound was isolated  
6 by column chromatography (2.5% EtOAc-hexanes).  
7  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 7.23 (2H, m), 7.12 (1H, d,  $J = 7.6$  Hz), 3.62 (2H, s),  
8 2.56 (2H, q,  $J = 7.3$  Hz), 2.29 (3H, s), 1.75 (1H, m), 1.04 (3H, t,  $J = 7.3$  Hz),  
9 0.39 (2H, m), 0.30 (2H, m).

10 Cyclopropyl-ethyl-(2-methyl-4-trimethylsilanylethynyl-benzyl)-amine  
11 **(Intermediate 160)**

12 Using General Procedure D; (4-bromo-2-methyl-benzyl)-  
13 cyclopropyl-ethyl-amine (**Intermediate 159**, 620.0 mg, 2.31 mmols) in  
14 triethylamine (8 mL) was treated with copper(I)iodide (44.0 mg, 0.23 mmol)  
15 and then sparged with argon for 15 minutes. Trimethylsilylacetylene (1.04  
16 g, 10.6 mmols) was then added followed by dichlorobis-  
17 (triphenylphosphine)palladium(II) (162.0 mg, 0.23 mmol). The resulting  
18 reaction mixture was heated to 70 °C for 5 days. The title compound (650.0  
19 mg, 98%) was isolated by chromatography (1-4% EtOAc - hexanes).  
20  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 7.32 (1H, s), 7.20 (2H, m), 3.65 (2H, s), 2.55 (2H, q,  $J$   
21 = 7.3 Hz), 2.28 (3H, s), 1.74 (1H, m), 1.03 (3H, t,  $J = 7.3$  Hz), 0.36 (2H, m),  
22 0.27 (2H, m), 0.24 (9H, s).

23 Cyclopropyl-ethyl-(4-ethynyl-2-methyl-benzyl)-amine (**Intermediate 161**)

24 Using General Procedure E; cyclopropyl-ethyl-(2-methyl-4-  
25 trimethylsilanylethynyl-benzyl)-amine (**Intermediate 160**, 650.0 mg, 2.30  
26 mmols) in methanol (10mL) was treated with potassium carbonate (100.0  
27 mg, 0.72 mmol) and stirred overnight at ambient temperature. The crude

1 alkyne (495 mg, 99%) was used directly in the next reaction.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.32 (1H, s), 7.21 (2H, m), 3.66 (2H, s), 3.01 (1H, s),  
3 2.56 (2H, q, J = 7.3 Hz), 2.29 (3H, s), 1.76 (1H, m), 1.04 (3H, t, J = 7.3 Hz),  
4 0.40 (2H, m), 0.29 (2H, m).

5 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-  
6 benzoate (**Compound 128, General Formula 6**)

7 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-  
8 benzyl)-amine (**Intermediate 161**, 190.0 mg, 0.89 mmol) and ethyl-4-iodo  
9 benzoate (**Reagent A**, 245.0 mg, 0.89 mmol) in triethylamine (5 mL) was  
10 treated with copper(I)iodide (56.0 mg, 0.30 mmol) and sparged with argon  
11 for 15 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (208 mg,  
12 0.30 mmol) was added and the reaction mixture was stirred overnight at  
13 room temperature. Column chromatography (3-5% EtOAc - hexanes)  
14 afforded the title compound.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.31-  
16 7.24 (3H, m), 4.38 (2H, q, J = 7.1 Hz), 3.68 (2H, s), 2.58 (2H, q, J = 7.3  
17 Hz), 2.32 (3H, s), 1.77 (1H, m), 1.39 (3H, t, J = 7.1 Hz), 1.05 (3H, t, J = 7.3  
18 Hz), 0.39 (2H, m), 0.31 (2H, m).

19 Methyl (4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-  
20 phenyl)-acetate) (**Compound 129, General Formula 6**)

21 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-  
22 benzyl)-amine (**Intermediate 161**, 300.0 mg, 1.41 mmols) and methyl-(4-  
23 iodophenyl)-acetate (**Reagent B**, 388.0 mg, 1.41 mmols) in triethylamine (8  
24 mL) was treated with copper(I)iodide (67.0 mg, 0.35 mmol) and sparged  
25 with argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II)  
26 (246 mg, 0.35 mmol) was added and the reaction mixture was stirred  
27 overnight at room temperature. Column chromatography (5-7% EtOAc -

1 hexanes) afforded 270.0 mg (53%) of the title compound as a pale-yellow  
2 oil.

3 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.47 (2H, d, J = 7.9 Hz), 7.30-7.22 (5H, m), 3.70 (3H,  
4 s), 3.68 (2H, s), 3.63 (2H, s), 2.58 (2H, q, J = 7.3 Hz), 2.32 (3H, s), 1.77  
5 (1H, m), 1.05 (3H, t, J = 7.3 Hz), 0.39 (2H, m), 0.30 (2H, m).

6 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoic  
7 acid: (Compound 130, General Formula 6)

8 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-  
9 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoate (**Compound 128**,  
10 130.0 mg, 0.36 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was  
11 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)  
12 and stirred overnight at room temperature. Work-up afforded 115.0 mg  
13 (96%) of the title compound as a colorless solid.

14 <sup>1</sup>H NMR (d<sub>6</sub>-acetone) δ: 8.05 (2H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.2 Hz),  
15 7.32 (3H, m), 3.73 (2H, s), 2.59 (2H, q, J = 7.3 Hz), 2.35 (3H, s), 1.83 (1H,  
16 m), 1.05 (3H, t, J = 7.3 Hz), 0.38 (2H, m), 0.27 (2H, m).

17 (4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-  
18 phenyl)-acetic acid (Compound 131, General Formula 6)

19 Using General Procedure I; a solution of methyl (4-{4-[(cyclopropyl-  
20 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-acetate (**Compound**  
21 **129**, 140.0 mg, 0.39 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL)  
22 was treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous  
23 solution) and stirred overnight at room temperature. Work-up followed by  
24 HPLC (Partisil-10 pac 10% H<sub>2</sub>O-CH<sub>3</sub>CN) afforded the title compound.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.45 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.16 (2H, m),  
26 3.82 (2H, s), 3.56 (2H, s), 2.75 (2H, q, J = 7.3 Hz), 2.30 (3H, s), 1.86 (1H,  
27 m), 1.14 (3H, t, J = 7.3 Hz), 0.54 (2H, m), 0.46 (2H, m).

1 Ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-phenylethynyl)}-benzoate  
2 **(Compound 132, General Formula 6)**

3 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-  
4 benzoate (**Intermediate 155**, 110.0 mg, 0.29 mmol) and cyclopropylamine  
5 (420.0 mg, 7.4 mmols) in EtOH (5 mL) was stirred at 25 °C for 6 hours and  
6 then concentrated under reduced pressure. The residue was dissolved in  
7 EtOAc and washed with saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O and saturated  
8 aqueous NaCl. The solution was dried (MgSO<sub>4</sub>) and concentrated under  
9 reduced pressure to give 103 mg (99%) of the title compound as an orange  
10 oil.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.47  
12 (1H, s), 7.30 (2H, m), 4.38 (2H, q, J = 7.1 Hz), 3.89 (2H, s), 3.26 (1H,  
13 septet, J = 7.0 Hz), 2.17 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J =  
14 7.0 Hz), 0.45 (2H, m), 0.39 (2H, m).

15 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-  
16 benzoate (**Compound 133, General Formula 6**)

17 To a solution of ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-  
18 phenylethynyl)}-benzoate (**Compound 132**, 103.0 mg, 0.29 mmol) in 6 mL  
19 of acetone was added ethyl iodide (67.0 mg, 0.43 mmol) and K<sub>2</sub>CO<sub>3</sub> (79.0  
20 mg, 0.57 mmol). The mixture was stirred at 60 °C for 6 hours, cooled to  
21 room temperature and quenched by the addition of H<sub>2</sub>O. The mixture was  
22 extracted with EtOAc and the combined organic layers were washed with  
23 H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and  
24 concentrated under reduced pressure. Column chromatography (4-5%  
25 EtOAc - hexanes) afforded 68.0 mg (59%) of the title compound.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.01 (2H, d, J = 8.6 Hz), 7.58 (2H, d, J = 8.6 Hz), 7.44  
27 (1H, s), 7.28 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.73 (2H, s), 3.55 (1H,

1 septet,  $J = 6.6$  Hz), 2.57 (2H, q,  $J = 7.3$  Hz), 1.75 (1H, m), 1.40 (3H, t,  $J =$   
2 7.1 Hz), 1.22 (6H, d,  $J = 6.6$  Hz), 1.05 (3H, t,  $J = 7.3$  Hz), 0.37 (2H, m), 0.28  
3 (2H, m).

4 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-  
5 benzoic acid (**Compound 134, General Formula 6**)

6 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-  
7 ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-benzoate (**Compound**  
8 **133**, 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
9 treated with NaOH (600.0 mg, 15.0 mmols, 3.0 mL of a 5N aqueous  
10 solution) and stirred overnight at room temperature and then at 55 °C for 9  
11 hours. Work-up followed by crystallization of the solid residue from hot  
12 CH<sub>3</sub>CN afforded 45.0 mg (72%) of the title compound as a pale-yellow  
13 solid.

14 <sup>1</sup>H NMR (d<sub>6</sub>-acetone)  $\delta$ : 8.05 (2H, d,  $J = 8.1$  Hz), 7.66 (2H, d,  $J = 8.1$  Hz),  
15 7.49 (1H, s), 7.32 (2H, m), 3.78 (2H, s), 3.44 (1H, septet,  $J = 6.7$  Hz), 2.59  
16 (2H, q,  $J = 7.3$  Hz), 1.80 (1H, m), 1.21 (6H, d,  $J = 6.7$  Hz), 1.05 (3H, t,  $J =$   
17 7.3 Hz), 0.40 (2H, m), 0.26 (2H, m).

18 Methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
19 phenyl]-acetate (**Compound 4, General Formula 8**)

20 Using General Procedure F; 6-ethynyl-4,4-dimethyl-3,4-dihydro-2H-  
21 naphthalen-1-one (**Intermediate 13**, 190.0 mg, 0.96 mmol) and methyl-(4-  
22 iodophenyl)-acetate (**Reagent B**, 245.0 mg, 0.96 mmol) in triethyl amine (8  
23 mL) was treated with copper(I)iodide (46 mg, 0.24 mmol) and sparged with  
24 argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (168  
25 mg, 0.24 mmol) was added and the reaction mixture was stirred overnight at  
26 room temperature. Column chromatography (10-20% EtOAc - hexanes)  
27 afforded 250.0 mg (75%) of the title compound as a pale-yellow solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.99 (1H, d, J = 7.9 Hz), 7.57 (1H, d, J = 1.5 Hz), 7.51 (2H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.29 (2H, d, J = 8.5 Hz), 3.70 (3H, s), 3.65 (2H, s), 2.73 (2H, t, J = 7.0 Hz), 2.04 (2H, t, J = 7.0 Hz), 1.41 (6H, s).

Methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-phenyl]-acetate (Compound 135, General Formula 4)

To a solution of methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-phenyl]-acetate (**Compound 4**) in 5 mL MeOH at 0 °C was added NaBH<sub>4</sub> (18.0 mg, 0.48 mmol). The reaction was stirred at 0 °C for 2 hours and then quenched by the addition of H<sub>2</sub>O. The solution was diluted with Et<sub>2</sub>O and washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried (MgSO<sub>4</sub>) and the solvents were removed under reduced pressure. Column chromatography (20-40% EtOAc-hexanes) afforded 140.0 mg (87%) of the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (3H, m), 7.39 (1H, d, J = 7.9 Hz), 7.31 (1H, dd, J = 1.5, 7.9 Hz), 7.25 (2H, d, J = 8.2 Hz), 4.58 (1H, bs), 3.68 (3H, s), 3.62 (2H, s), 2.05 (1H, m), 1.79 (2H, m), 1.60 (1H, m), 1.33 (3H, s), 1.26 (3H, s).

Methyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ylethynyl)-phenyl]-acetate (Compound 136, General Formula 4)

A solution of methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-ylethynyl)-phenyl]-acetate (**Compound 135**, 140.0 mg, 0.40 mmol) and carbonyldiimidazole (136.0 mg, 0.84 mmol) in 5 mL THF was heated to 65 °C for 48 hours. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in Et<sub>2</sub>O and washed with 5% aqueous NaOH, H<sub>2</sub>O, and saturated aqueous NaCl before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column chromatography (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 50.0 mg (31%) of

1 the title compound as a colorless solid.

2 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.57 (1H, d, J = 1.5 Hz), 7.52-7.45 (3H, m), 7.27 (3H,  
3 m), 7.08 (1H, s), 6.81 (2H, m), 5.30 (1H, t, J = 5.8 Hz), 3.71 (3H, s), 3.65  
4 (2H, s), 2.20 (2H, m), 1.75 (2H, m), 1.40 (3H, s), 1.36 (3H, s).

5 [4-(5-Imidazol-1-yl)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-  
6 ethynyl]-phenyl]-acetic acid (**Compound 137, General Formula 4**)

7 Using General Procedure I; a solution of methyl [4-(5-imidazol-1-yl-  
8 8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-phenyl]-acetate  
9 (**Compound 136**, 50.0 mg, 0.13 mmol) in ethanol (4 mL) was treated with  
10 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred  
11 overnight at room temperature. Work-up afforded 40.0 mg (83%) of the title  
12 compound as a pale-orange solid.

13 <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 8.93 (1H, s), 7.68 (1H, s), 7.61 (1H, s), 7.54 (1H, s),  
14 7.47 (2H, d, J = 8.2 Hz), 7.31 (3H, m), 6.95 (1H, d, J = 8.2 Hz), 5.83 (1H, t, J  
15 = 5.8 Hz), 3.68 (1H, s), 3.63 (1H, s), 2.38 (1H, m), 2.26 (1H, m), 1.76 (2H,  
16 m), 1.45 (3H, s), 1.36 (3H, s).

17 Ethyl [4-(5-imidazol-1-yl)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-  
18 ethynyl]-benzoate (**Compound 138, General Formula 4**)

19 A solution of ethyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-  
20 naphthalen-2-yl-ethynyl)-benzoate (180.0 mg, 0.52 mmol) and  
21 carbonyldiimidazole (176.0 mg, 1.08 mmol) in 5 mL THF was heated to 65  
22 °C for 21 hours. The solution was cooled to room temperature and  
23 concentrated under reduced pressure. The residue was dissolved in Et<sub>2</sub>O and  
24 washed with 5% aqueous NaOH, H<sub>2</sub>O, and saturated aqueous NaCl before  
25 being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Column  
26 chromatography (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 50.0 mg (24%) of the title  
27 compound as a colorless solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (3H, m), 7.46 (1H, s), 7.29 (1H, dd, J = 1.5, 8.3 Hz), 7.09 (1H, s), 6.82 (1H, d, J = 8.2 Hz), 6.81 (1H, s), 5.31 (1H, t, J = 5.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.20 (2H, m), 1.75 (2H, m), 1.40 (9H, m).

[4-(5-Imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoic acid (**Compound 139, General Formula 4**)

Using General Procedure I; a solution of ethyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoate (**Compound 138**, 50.0 mg, 0.13 mmol) in ethanol (3 mL) and tetrahydrofuran (1 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred overnight at room temperature. Work-up afforded 40.0 mg (87%) of the title compound as a colorless solid. <sup>1</sup>H NMR (d<sub>4</sub>-MeOH) δ: 8.92 (1H, s), 8.04 (2H, d, J = 8.2 Hz), 7.74 (1H, d, J = 1.5 Hz), 7.62 (3H, m), 7.57 (1H, t, J = 1.5 Hz), 7.38 (1H, dd, J = 1.5, 7.9 Hz), 6.97 (1H, d, J = 7.9 Hz), 5.83 (1H, t, J = 5.8 Hz), 2.33 (2H, m), 1.78 (2H, m), 1.47 (3H, s), 1.39 (3H, s).

2-Isopropyl-4-trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate 162**)

To a solution of 4-hydroxymethyl-3-isopropylphenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 149**, 190.0 mg, 0.64 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was added acetyl chloride (75.0 mg, 0.96 mmol) and pyridine (101.0 mg, 1.38 mmols). After stirring for 3 hours at 25 °C the reaction was quenched by the addition of H<sub>2</sub>O and the resulting mixture extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The title compound, 182 mg (84%), was isolated from the residual oil by column chromatography (5 - 10% EtOAc-hexanes) as a colorless oil.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (1H, d, J = 8.7 Hz), 7.19 (1H, d, J = 2.7 Hz), 7.09  
2 (1H, dd, J = 2.7, 8.5 Hz), 5.17 (2H, s), 3.18 (1H, septet, J = 6.7 Hz), 2.10  
3 (3H, s), 1.26 (6H, d, J = 6.7 Hz).

4 4-Isopropenyloxymethyl-3-isopropyl-phenyl 1,1,1-  
5 trifluoromethanesulfonate (**Intermediate 163**)

6 Using General Procedure 1; 2-isopropyl-4-  
7 trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate 162**, 182.0 mg,  
8 0.54 mmols), and 1.1 mL of Tebbe's Reagent (159.0 mg, 0.56 mmols)  
9 afforded 130.0 mg (72%) of the title compound as a colorless oil after  
10 column chromatography (2-5% EtOAc-hexanes).

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.43 (1H, d, J = 8.5 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.09  
12 (1H, dd, J = 2.6, 8.5 Hz), 4.75 (2H, s), 3.98 (2H, s), 3.12 (1H, septet, J = 6.7  
13 Hz), 1.88 (3H, s), 1.25 (6H, d, J = Hz).

14 3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenyl 1,1,1-  
15 trifluoromethanesulfonate (**Intermediate 164**)

16 Using General Procedure 2; 4-isopropenyloxymethyl-3-  
17 isopropylphenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 163**, 130.0  
18 mg, 0.39 mmol), Et<sub>2</sub>Zn (272.0 mg, 2.2 mmols), and CH<sub>2</sub>I<sub>2</sub> (702.0 mg, 2.6  
19 mmols) in 3.0 mL Et<sub>2</sub>O afforded 120.0 mg (89%) of the title compound as a  
20 colorless oil after column chromatography (4-5% EtOAc - hexanes).

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.39 (1H, d, J = 8.5 Hz), 7.13 (1H, d, J = 2.7 Hz), 7.05  
22 (1H, dd, J = 2.7, 8.5 Hz), 4.54 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.47  
23 (3H, s), 1.24 (6H, d, J = 6.7 Hz), 0.86 (2H, m), 0.48 (2H, m).

24 [3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-  
25 trimethylsilane (**Intermediate 165**)

26 Using General Procedure D; 3-isopropyl-4-(1-methyl-  
27 cyclopropoxymethyl)-phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate**

1 **164**, 120.0 mg, 0.34mmol) in triethylamine (2 mL) and anhydrous DMF (5  
2 mL) was sparged with argon for 5 minutes. Trimethylsilyl acetylene (700.0  
3 mg, 0.71 mmol) was then added followed by  
4 dichlorobis(triphenylphosphine)palladium(II) (24.0 mg, 0.03 mmol). The  
5 resulting reaction mixture was heated to 95 °C for 60 hours. The title  
6 compound 110.0 mg, (99%) was isolated by chromatography (0-1% EtOAc  
7 - hexanes).

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.36 (1H, s), 7.24 (2H, bs), 4.53 (2H, s), 3.11 (1H,  
9 septet, J = 6.7 Hz), 1.45 (3H, s), 1.22 (6H, d, J = 6.7 Hz), 0.85 (2H, m), 0.44  
10 (2H, m), 0.25 (9H, s).

11 4-Ethynyl-2-isopropyl-1-(1-methyl-cyclopropoxymethyl)-benzene  
12 (**Intermediate 166**)

13 Using General Procedure E; [3-isopropyl-4-(1-methyl-  
14 cyclopropoxymethyl)-phenylethynyl]-trimethylsilane (**Intermediate 165**,  
15 110.0 mg, 0.37 mmol) in methanol (6 mL) was treated with potassium  
16 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient  
17 temperature. The crude alkyne (84 mg, 100%) was used directly in the next  
18 reaction.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.55 (1H, s), 7.41 (2H, m), 4.68 (2H, s), 3.26 (1H,  
20 septet, J = 6.8 Hz), 3.18 (1H, s), 1.60 (3H, s), 1.37 (6H, d, J = 6.8 Hz), 0.99  
21 (2H, m), 0.59 (2H, m).

22 Methyl {4-[3-isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-  
23 phenyl}-acetate (**Compound 140, General Formula 6**)

24 Using General Procedure F; 4-ethynyl-2-isopropyl-1-(1-methyl-  
25 cyclopropoxymethyl)-benzene (**Intermediate 166**, 78.0 mg, 0.34 mmol) and  
26 methyl-(4-iodophenyl)-acetate (**Reagent B**, 94.0 mg, 0.34 mmol) in  
27 triethylamine (8 mL) was treated with copper(I)iodide (22.0 mg, 0.11 mmol)

1 and sparged with argon for 5 minutes.  
2 Dichlorobis(triphenylphosphine)palladium(II) (79 mg, 0.11 mmol) was  
3 added and the reaction mixture was stirred at room temperature for 3.5  
4 hours. Column chromatography (2-5% EtOAc - hexanes) afforded 77.0 mg  
5 (60%) of the title compound as a yellow oil.

6 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, d, J = 1.5 Hz), 7.33-  
7 7.24 (4H, m), 4.55 (2H, s), 3.70 (3H, s), 3.63 (2H, s), 3.14 (1H, septet, J =  
8 6.8 Hz), 1.47 (3H, s), 1.25 (6H, d, J = 6.8 Hz), 0.86 (2H, m), 0.46 (2H, m).

9 {4-[3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-  
10 acetic acid (Compound 141, Formula 6)

11 Using General Procedure I; a solution methyl {4-[3-isopropyl-4-(1-  
12 methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetate (**Compound**  
13 **140**, 70.0 mg, 0.19 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was  
14 treated with NaOH (240.0 mg, 6.0 mmols, 2.0 mL of a 3N aqueous solution)  
15 and stirred overnight at room temperature. Work-up and purification by  
16 HPLC (Partisil 10-pac, 10% H<sub>2</sub>O/CH<sub>3</sub>CN) afforded of the title compound as  
17 a colorless solid.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.50 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.33-7.24 (4H,  
19 m), 4.55 (2H, s), 3.65 (2H, s), 3.14 (1H, septet, J = 6.7 Hz), 1.47 (3H, s),  
20 1.25 (6H, d, J = 6.7 Hz), 0.87 (2H, m), 0.46 (2H, m).

21 2,6-Di-*tert*-butyl-4-trimethylsilanylethynyl-phenol: (Intermediate 167)

22 Following General Procedure D and using 4-bromo-2,6-di-*t*-butyl-  
23 phenol (1.43g, 5mmol), triethyl amine (15mL), anhydrous tetrahydrofuran  
24 (15mL), copper(I)iodide (0.06g, 0.31mmol), trimethylsilyl acetylene (4.9g,  
25 50mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.18g,  
26 0.26mmol) followed by flash column chromatography over silica gel (230-  
27 400 mesh) using hexane as eluent, the title compound was obtained (1.35g,

1 90%).

2 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.29 (s, 2H), 5.35 (s, 1H), 1.42 (s, 18H), 0.24  
3 (s, 9H).

4 (3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-trimethyl-silane:

5 **(Intermediate 168)**

6 A solution 2,6-di-*tert*-butyl-4-trimethylsilanylethynyl-phenol  
7 **(Intermediate 167**, 0.302g, 1mmol) in acetone (5mL) was treated with  
8 potassium carbonate (0.138g, 1mmol) and methyl iodide (0.142g, 1mmol)  
9 and stirred overnight at room temperature. The volatiles were distilled off *in*  
10 *vacuo* and the residue was purified by flash column chromatography on  
11 silica gel (230-400 mesh) using ethyl acetate as the eluent to afford the title  
12 compound as a white solid (0.28g, 90%).

13 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41 (s, 2H), 3.70 (s, 3H), 1.49 (s, 18H), 0.30  
14 (s, 9H).

15 1,3-Di-*tert*-butyl-5-ethynyl-2-methoxy-benzene: (Intermediate 169)

16 Following General Procedure E and (3,5-di-*tert*-butyl-4-methoxy-  
17 phenylethynyl)-trimethyl-silane **(Intermediate 168**, 0.28g, 0.9mmol),  
18 potassium carbonate (0.98g, 7.1mmol) and methanol (10mL) followed by  
19 flash column chromatography over silica gel (230-400 mesh) using hexane  
20 as the eluent, the title compound was obtained (0.23g, 100%).

21 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (s, 2H), 3.75 (s, 3H), 3.05 (s, 1H), 1.49  
22 (s, 18H).

23 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid methyl  
24 ester: (Compound 142, General Formula 5)

25 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-  
26 2-methoxy-benzene **(Intermediate 169**, 0.094g, 0.36mmol), methyl-4-iodo  
27 phenyl acetate **(Reagent B**, 0.09g, 0.32mmol), triethyl amine (5mL),

1 anhydrous tetrahydrofuran (5mL), copper(I)iodide (0.02g, 0.1mmol) and  
2 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed  
3 by flash column chromatography over silica gel (230-400 mesh) using 10 %  
4 ethyl acetate in hexane as the eluent, the title compound (0.114g, 81%) was  
5 obtained as an oil.

6 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.52 (d, 2H, *J* = 8.0Hz), 7.46 (s, 2H), 7.28 (d,  
7 2H, *J* = 8.2Hz), 3.72 (s, 3H), 3.71(s, 3H), 3.66 (s, 2H), 1.47 (s, 18H).

8 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid:

9 **(Compound 143, General Formula 5)**

10 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-  
11 methoxy-phenylethynyl)-phenyl]-acetic acid methyl ester (**Compound 142**,  
12 0.114g, 0.29mmol), 5M aqueous sodium hydroxide solution (2mL) and  
13 ethanol (4mL), followed by preparative reverse phase HPLC using 10%  
14 water in acetonitrile as the mobile phase, the title compound was obtained as  
15 a white solid (0.097g, 88%).

16 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.55(d, 2H, *J* = 8.0Hz), 7.48 (s, 2H), 7.30 (d,  
17 2H, *J* = 8.2Hz), 3.74 (s, 3H), 3.69 (s, 2H), 1.49 (s, 18H).

18 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid

19 methyl ester: (**Compound 144, General Formula 5**)

20 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-  
21 2-methoxy-benzene (**Intermediate 169**, 0.087g, 0.33mmol), methyl-2-  
22 fluoro-4-iodo phenyl acetate (**Reagent H**, 0.088g, 0.30mmol), triethyl amine  
23 (5mL), anhydrous tetrahydrofuran (10mL), copper(I)iodide (0.02g, 0.1mmol)  
24 and dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol)  
25 followed by flash column chromatography over silica gel (230-400 mesh)  
26 using 10 % ethyl acetate in hexane as the eluent, the title compound (0.122g,  
27 89%) was obtained.

1 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.46 (s, 2H), 7.33-7.24 (m, 3H), 3.75 (s, 3H),  
2 3.73(s, 3H), 3.72 (s, 2H), 1.48 (s, 18H).

3 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic  
4 acid: (Compound 145, General Formula 5)

5       Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-  
6 methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid methyl ester  
7 (**Compound 144**, 0.122g, 0.29mmol), 5M aqueous sodium hydroxide  
8 solution (1mL) and ethanol (4mL), followed preparative reverse phase  
9 HPLC using 10% water in acetonitrile as the mobile phase, the title  
10 compound was obtained as a white solid (0.077g, 65%).

11 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.42 (s, 2H), 7.29-7.19 (m, 3H), 3.71 (s, 2H),  
12 3.69 (s, 3H), 1.43 (s, 18H).

## 1 WHAT IS CLAIMED IS:

2 1. A compound of the formula

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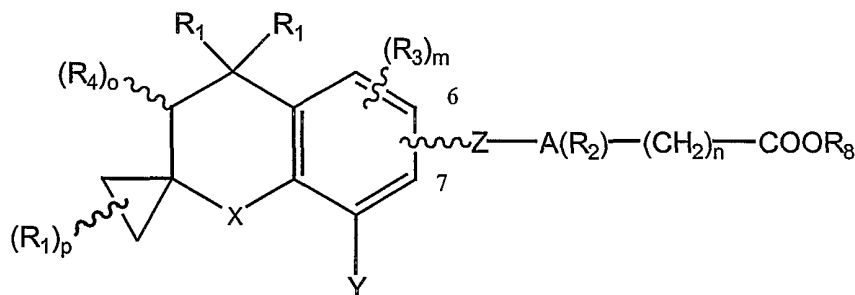
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10 wherein A is a phenyl or naphthyl group, or heteroaryl selected from  
 11 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 12 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
 13 heteroaryl groups being optionally substituted with one or two **R<sub>2</sub>** groups;

14 **X** is O, S or NR where **R** is H, alkyl of 1 to 6 carbons or benzyl;

15 **Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 16 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of  
 17 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,  
 18 or I;

19 **Z** is -C≡C-,

20 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,

21 -CO-NR<sub>1</sub>-,

22 NR<sub>1</sub>-CO-;

23 -CO-O-,

24 -O-CO-,

25 -CS-NR<sub>1</sub>-,

26 NR<sub>1</sub>-CS-,

27 -CO-S-,

1                   -S-CO-,

2                   -N=N-;

3           **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;

4           **p** is an integer having the values of 0 to 4;

5           **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
6 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or  
7 alkylthio of 1 to 6 carbons;

8           **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
9 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
10 alkylthio of 1 to 6 carbons or benzyl;

11           **m** is an integer having the values 0 to 2;

12           **R<sub>4</sub>** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
13 alkyl of 1 to 6 carbons, or halogen;

14           **o** is an integer having the values of 0 to 2;

15           **n** is an integer having the values of 0 to 4, and

16           **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
17 pharmaceutically acceptable base.

18           2. A compound in accordance with Claim 1 where A is phenyl,  
19 naphthyl, pyridyl, thienyl or furyl.

20           3. A compound in accordance with Claim 1 where **n** is 0, 1 or 2.

21           4. A compound in accordance with Claim 1 where Z is -C≡C-, -CO-  
22 NR<sub>1</sub>-,

23 -CO-O-, or -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where **n'** is 1.

24           5. A compound in accordance with Claim 1 where the Z group is  
25 attached to the 6-position of the bicyclic moiety.

26           6. A compound in accordance with Claim 1 where X is O.

27           7. A compound in accordance with Claim 1 where Y is H, lower

1 alkyl of 1 to 3 carbons or cyclopropyl.

2 8. A compound in accordance with Claim 1 where A is phenyl.

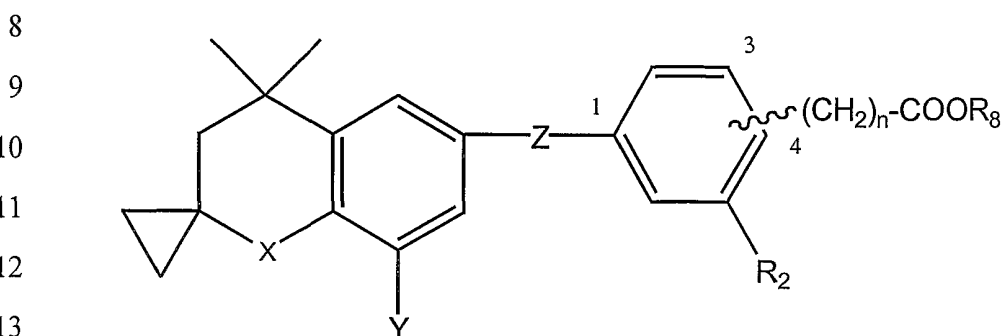
3 9. A compound in accordance with Claim 8 where Z is  $-C\equiv C-$ , or -

4 CO-O-.

5 10. A compound in accordance with Claim 9 where Y is H or

6 cyclopropyl.

7 11. A compound of the formula



15 where X is O or  $CH_3N$ ;

16 Y is H or cyclopropyl;

17 Z is  $-C\equiv C-$  or  $-CO-O-$ ;

18  $R_2$  is H or F;

19 n is 0 or 1, and

20  $R_8$  is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically

21 acceptable base.

22 12. A compound in accordance with Claim 11 where X is O.

23 13. A compound in accordance with Claim 12 where Y is H and Z is

24  $-C\equiv C-$ .

25 14. A compound in accordance with Claim 13 where the -

26  $(CH_2)_nCOOR_8$  group is in the 4 position of the phenyl ring.

27 15. A compound in accordance with Claim 14, which is selected

28 from the group consisting of:

1        benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-  
2    2,1'-cyclopropane]-6-yl)ethynyl]-, benzeneacetic acid, 4-[(3,4-dihydro-4,4-  
3    dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- and 2-  
4    fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-  
5    2,1'-cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically  
6    acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

7        **16.** A compound in accordance with Claim 12 where **Y** is  
8    cyclopropyl and **Z** is -C≡C-.

9        **17.** A compound in accordance with Claim 16 where the -  
10    (CH<sub>2</sub>)<sub>n</sub>COOR<sub>8</sub> group is in the 4 position of the phenyl ring.

11       **18.** A compound in accordance with Claim 17, which is selected  
12    from the group consisting of:

13       benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-  
14    dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-, 4-[(8-  
15    cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
16    cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid, benzoic acid, 4-  
17    [(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-  
18    cyclopropane]-6-yl)ethynyl]- and 4-[(8-cyclopropyl-3,4-dihydro-4,4-  
19    dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-  
20    benzoic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
21    ester of said compound.

22       **19.** A compound in accordance with Claim 12 where **Y** is  
23    cyclopropyl and **Z** is -CO-O-.

24       **20.** A compound in accordance with Claim 19 where the -  
25    (CH<sub>2</sub>)<sub>n</sub>COOR<sub>8</sub> group is in the 4 position of the phenyl ring.

26       **21.** A compound in accordance with Claim 20 which is spiro[2*H*-1-  
27    benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-3,4-  
28    dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester or a salt with a

1 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

2       **22.** A compound in accordance with Claim 19 where the -

3 (CH<sub>2</sub>)<sub>n</sub>COOR<sub>8</sub> group is in the 3 position of the phenyl ring.

4       **23.** A compound in accordance with Claim 22 which is spiro[2*H*-1-

5 benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-3,4-

6 dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester or a salt with a

7 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

8       **24.** A compound in accordance with Claim 11 where X is CH<sub>3</sub>N, Y

9 is H and Z is -C≡C-.

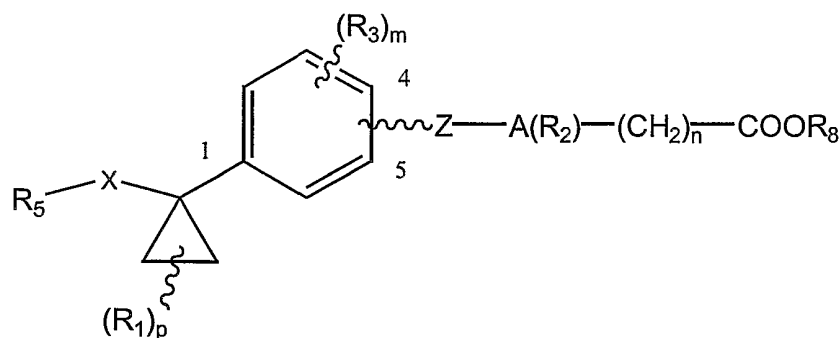
10       **25.** A compound in accordance with Claim 22 which is benzoic acid,

11 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-

12 cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically acceptable

13 base or a C<sub>1-6</sub> alkyl ester of said compound.

14       **26.** A compound of the formula



22       wherein A is a phenyl or naphthyl group, or heteroaryl selected from

23 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,

24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and

25 heteroaryl groups being optionally substituted with one or two R<sub>2</sub> groups;

26

- 1        **X** is O, S or NR where **R** is H, alkyl of 1 to 6 carbons or benzyl;
- 2        **Z** is     $-C\equiv C-$ ,
- 3             $-(CR_1=CR_1)_n$ , where  $n'$  is an integer having the value 1 - 5,
- 4             $-CO-NR_1-$ ,
- 5             $NR_1-CO-$ ,
- 6             $-CO-O-$ ,
- 7             $-O-CO-$ ,
- 8             $-CS-NR_1-$ ,
- 9             $NR_1-CS-$ ,
- 10           $-CO-S-$ ,
- 11           $-S-CO-$ ,
- 12           $-N=N-$ ;
- 13        **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;
- 14        **p** is an integer having the values of 0 to 4;
- 15        **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
- 16 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
- 17 to 6 carbons;
- 18        **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
- 19 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
- 20 alkylthio of 1 to 6 carbons or benzyl;
- 21        **m** is an integer having the values 0 to 4;
- 22        **R<sub>5</sub>** is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6
- 23 carbons, benzyl, or lower alkyl or halogen substituted benzyl;
- 24        **n** is an integer having the values of 0 to 4, and
- 25        **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a
- 26 pharmaceutically acceptable base.
- 27        **27.** A compound in accordance with Claim 26 where A is phenyl,
- 28 naphthyl, pyridyl, thienyl or furyl.

1           **28.** A compound in accordance with Claim 26 where **n** is 0, 1 or 2.

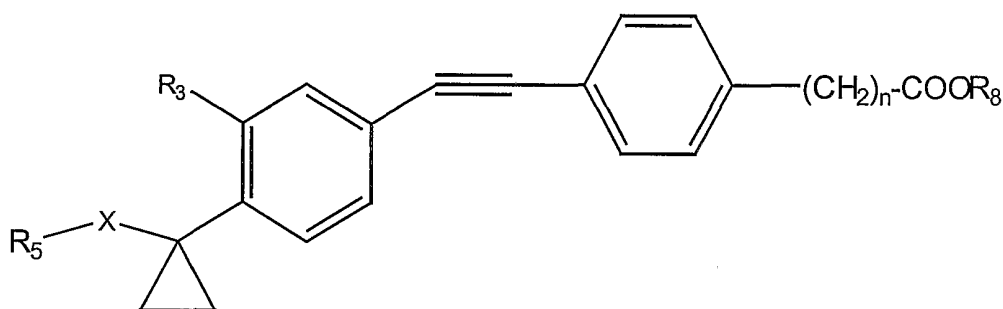
2           **29.** A compound in accordance with Claim 26 where **Z** is  $-\text{C}\equiv\text{C}-$ , -  
3  $\text{CO}-\text{NR}_1-$ ,  $-\text{CO}-\text{O}-$ , or  $-(\text{CR}_1=\text{CR}_1)_n$ , where **n'** is 1.

4           **30.** A compound in accordance with Claim 26 where the **Z** group is  
5 attached to the 4-position of the phenyl moiety.

6           **31.** A compound in accordance with Claim 26 where **X** is O.

7           **32.** A compound in accordance with Claim 26 where **X** is NR.

8           **33.** A compound of the formula



9           where **X** is O, NR where **R** is H, *n*-propyl or benzyl;

10          **R<sub>3</sub>** is H or lower alkyl of 1 to 6 carbons;

11          **R<sub>5</sub>** is benzyl or lower alkyl of 1 to 6 carbons;

12          **n** is 0 or 1, and

13          **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
14 acceptable base.

15          **34.** A compound in accordance with Claim 33 where **X** is NR.

16          **35.** A compound in accordance with Claim 34 where **R** is *n*-propyl  
17 and **R<sub>5</sub>** is *n*-propyl.

18          **36.** A compound in accordance with Claim 35 which is 4-[4-(1-  
19 dipropylamino-cyclopropyl)-phenylethynyl]-benzoic acid or a salt with a  
20 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

21          **37.** A compound in accordance with Claim 34 where **R** is H and **R<sub>5</sub>**

1 is *n*-propyl or benzyl.

2       **38.** A compound in accordance with Claim 37 which is selected from  
3 the group consisting of 4-[4-(1-propylamino-cyclopropyl)-phenylethynyl]-  
4 benzoic acid and 4-[4-(1-benzylamino-cyclopropyl)-phenylethynyl]-benzoic  
5 acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of  
6 said compound.

7       **39.** A compound in accordance with Claim 34 where **R** is benzyl or  
8 methyl and **R<sub>5</sub>** is benzyl.

9       **40.** A compound in accordance with Claim 39 which is selected from  
10 the group consisting of 4-[4-(1-dibenzylamino-cyclopropyl)-  
11 phenylethynyl]-benzoic acid and 4-[4-(1-benzylmethylamino-cyclopropyl)-  
12 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable  
13 base or a C<sub>1-6</sub> alkyl ester of said compound.

14       **41.** A compound in accordance with Claim 33 where **X** is O.

15       **42.** A compound in accordance with Claim 41 where **R<sub>5</sub>** is benzyl  
16 and **n** is 0.

17       **43.** A compound in accordance with Claim 42 which is selected from  
18 the group consisting of 4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-  
19 benzoic acid, 4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-  
20 benzoic acid and 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-  
21 benzoic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub>  
22 alkyl ester of said compound.

23       **44.** A compound in accordance with Claim 41 where **R<sub>5</sub>** is benzyl  
24 and **n** is 1.

25       **45.** A compound in accordance with Claim 44 which is selected from  
26 the group consisting of {4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-  
27 phenyl}-acetic acid, {4-[4-(1-benzyloxycyclopropyl)-3-methyl-  
28 phenylethynyl]-phenyl}-acetic acid and {4-[4-(1-benzyloxycyclopropyl)-3-

1 ethyl-phenylethynyl]-phenyl}-acetic acid or a salt with a pharmaceutically  
2 acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

3       **46.** A compound in accordance with Claim 41 where **R<sub>5</sub>** is methyl,  
4 ethyl, *iso*-propyl, or (CH<sub>3</sub>)<sub>3</sub>-CH<sub>2</sub>- and **n** is 0.

5       **47.** A compound in accordance with Claim 46 which is selected from  
6 the group consisting of 4-[4-(1-methoxycyclopropyl)-phenylethynyl]-  
7 benzoic acid, 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-benzoic acid,  
8 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid, 4-  
9 [4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-  
10 benzoic acid and 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-  
11 benzoic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
12 ester of said compound.

13       **48.** A compound in accordance with Claim 41 where **R<sub>5</sub>** is methyl,  
14 ethyl, *iso*-propyl, or (CH<sub>3</sub>)<sub>3</sub>-CH<sub>2</sub>- and **n** is 1.

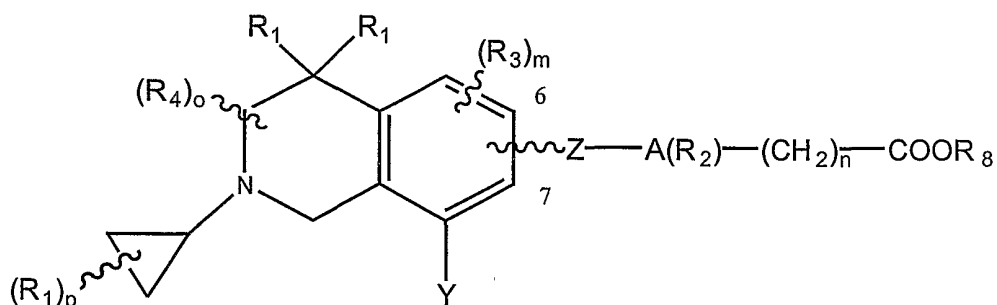
15       **49.** A compound in accordance with Claim 48 which is selected from  
16 the group consisting of {4-[4-(1-methoxycyclopropyl)-phenylethynyl]-  
17 phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-  
18 phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-3-methyl-  
19 phenylethynyl]-phenyl}-acetic acid, {4-[4-[1-(2,2-dimethylpropyloxy)-  
20 cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-  
21 benzyloxy-cyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid, {4-[4-  
22 (1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid and  
23 {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetic acid  
24 or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said  
25 compound.

26

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28

1      **50.** A compound of the formula



2            wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from  
3            a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
4            pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
5            heteroaryl groups being optionally substituted with one or two **R<sub>2</sub>** groups;

6           Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
7 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of  
8 3 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br,  
9 or I;

10            **Z** is    -C≡C-,  
11                    -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,  
12                    -CO-NR<sub>1</sub>-,  
13                    NR<sub>1</sub>-CO-,  
14                    -CO-O-,  
15                    -O-CO-,  
16                    -CS-NR<sub>1</sub>-,  
17                    NR<sub>1</sub>-CS-,  
18                    -CO-S-,  
19                    -S-CO-,  
20                    -N=N-;

1        **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;

2        **p** is an integer having the values of 0 to 5;

3        **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
4 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
5 to 6 carbons;

6        **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
7 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
8 alkylthio of 1 to 6 carbons or benzyl;

9        **m** is an integer having the values 0 to 2;

10       **R<sub>4</sub>** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
11 alkyl of 1 to 6 carbons, or halogen;

12       **o** is an integer having the values of 0 to 4;

13       **n** is an integer having the values of 0 to 4, and

14       **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
15 pharmaceutically acceptable base.

16       **51.** A compound in accordance with Claim 50 where A is phenyl,  
17 naphthyl, pyridyl, thienyl or furyl.

18       **52.** A compound in accordance with Claim 50 where **n** is 0, 1 or 2.

19       **53.** A compound in accordance with Claim 50 where Z is -C≡C-, -  
20 CO-NR<sub>1</sub>-,

21 -CO-O-, or -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where **n'** is 1.

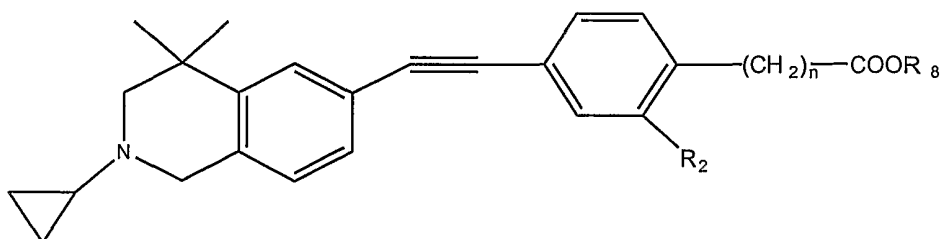
22       **54.** A compound in accordance with Claim 50 where the Z group is  
23 attached to the 6-position of the bicyclic moiety.

24       **55.** A compound in accordance with Claim 50 where Y is H, lower  
25 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or  
26 halogen.

27       **56.** A compound in accordance with Claim 50 where A is phenyl.

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1        **57.** A compound of the formula



7        where  $R_2$  is H or halogen;

8         $n$  is 0 or 1 and

9         $R_8$  is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
10 acceptable base.

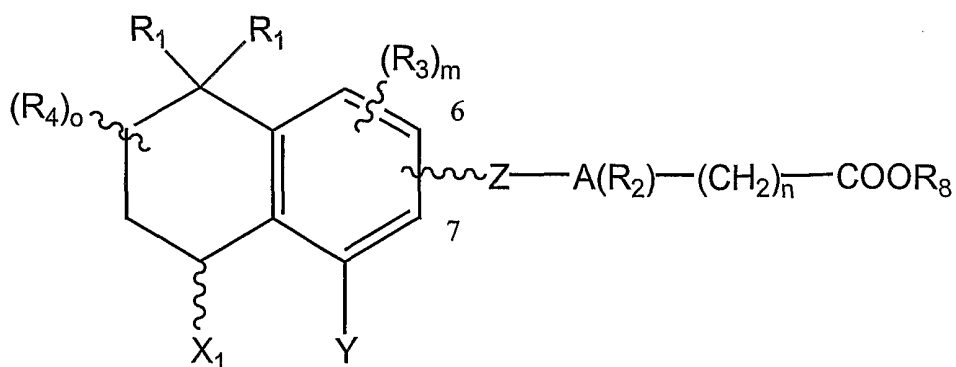
11        **58.** A compound in accordance with Claim 57 where  $n$  is 1 and  $R_2$  is  
12 F.

13        **59.** A compound in accordance with Claim 58 which is [4-(2-  
14 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-2-  
15 fluoro-phenyl]-acetic acid or a salt with a pharmaceutically acceptable base.

16        **60.** A compound in accordance with Claim 57 where  $n$  is 1 and  $R_2$  is  
17 H.

18        **61.** A compound in accordance with Claim 60 which is [4-(2-  
19 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-  
20 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base.

21        **62.** A compound of the formula



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from  
 2 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 3 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
 4 heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

5  $X_1$  is 1-imidazolyl, or lower alkyl or halogen substituted 1-  
 6 imidazolyl, OR, SR,  $NRR_6$  where R is H, alkyl of 1 to 6 carbons or benzyl;

7 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 8 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of  
 9 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,  
 10 or I;

11 Z is  $-C\equiv C-$ ,  
 12  $-(CR_1=CR_1)_n$ , where n' is an integer having the value 1 - 5,  
 13  $-CO-NR_1-$ ,  
 14  $NR_1-CO-$ ,  
 15  $-CO-O-$ ,  
 16  $-O-CO-$ ,  
 17  $-CS-NR_1-$ ,  
 18  $NR_1-CS-$ ,  
 19  $-CO-S-$ ,  
 20  $-S-CO-$ ,  
 21  $-N=N-$ ;

22  $R_1$  is independently H or alkyl of 1 to 6 carbons;

23  $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 24 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
 25 to 6 carbons;

26  $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 27 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,

1 alkylthio of 1 to 6 carbons or benzyl;

2 **m** is an integer having the values 0 to 2;

3 **R<sub>4</sub>** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
4 alkyl of 1 to 6 carbons, or halogen;

5 **o** is an integer having the values of 0 to 4;

6 **R<sub>6</sub>** is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl  
7 substituted cycloalkyl of 3 to 6 carbons;

8 **n** is an integer having the values of 0 to 4, and

9 **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
10 pharmaceutically acceptable base, with the proviso that when **Y** is H, **A** is  
11 phenyl and **X<sub>1</sub>** is OH then **n** is 1 to 4.

12 **63.** A compound in accordance with Claim 62 where **A** is phenyl,  
13 naphthyl, pyridyl, thienyl or furyl.

14 **64.** A compound in accordance with Claim 62 where **n** is 0, 1 or 2.

15 **65.** A compound in accordance with Claim 62 where **Z** is -C≡C-, -  
16 CO-NR<sub>1</sub>-,  
17 -CO-O-, or -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where **n'** is 1.

18 **66.** A compound in accordance with Claim 62 where the **Z** group is  
19 attached to the 6-position of the bicyclic moiety.

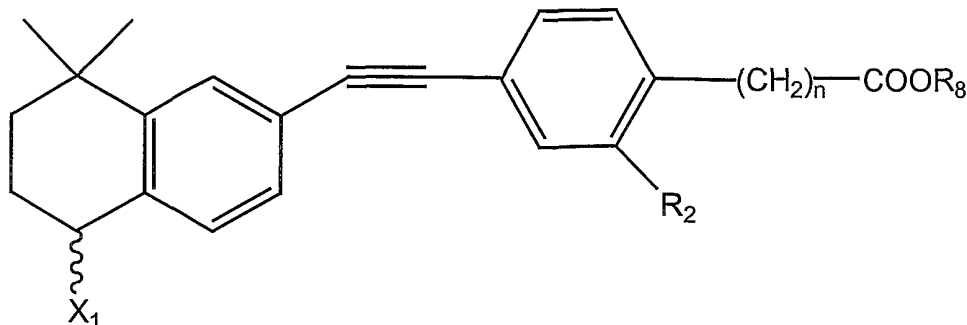
20 **67.** A compound in accordance with Claim 62 where **X<sub>1</sub>** is 1-  
21 imidazolyl, halogen or C<sub>1-6</sub> substituted 1-imidazolyl, or NRR<sub>6</sub>, where **R<sub>6</sub>** is  
22 preferably cyclopropyl or branched-chain alkyl of 1 to 6 carbons.

23 **68.** A compound in accordance with Claim 62 where **Y** is H, lower  
24 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or  
25 halogen.

26

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1        **69.** A compound of the formula



9        wherein  $X_1$  is 1-imidazolyl, or dialkyl-N or alkyl,cyclopropyl-N

10        where the alkyl group has 1 to 6 carbons;

11         $R_2$  is H or halogen;

12         $n$  is 0 or 1, and

13         $R_8$  is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
14        acceptable base.

15        **70.** A compound in accordance with Claim 69 where  $X_1$  is  
16        methyl,cyclopropyl-N and  $n$  is 0.

17        **71.** A compound in accordance with Claim 70 which is selected from  
18        the group consisting of 4-[(5-cyclopropyl-methyl-amino)-8,8-dimethyl-  
19        5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid and 4-[5-  
20        (cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-  
21        2-yl-ethynyl]-2-fluoro benzoic acid or a salt with a pharmaceutically  
22        acceptable base or a  $C_{1-6}$  alkyl ester of said compound.

23        **72.** A compound in accordance with Claim 69 where  $X_1$  is  
24        methyl,cyclopropyl-N and  $n$  is 1.

25        **73.** A compound in accordance with Claim 72 which is selected from  
26        the group consisting of 4-[(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-  
27        5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [4-(5-

1 (cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-  
 2 yl-ethynyl)-2-fluoro-phenyl]-acetic acid or a salt with a pharmaceutically  
 3 acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

4 **74.** A compound in accordance with Claim 69 where X<sub>1</sub> is  
 5 methyl, *iso*-propyl-N.

6 **75.** A compound in accordance with Claim 74 which is 4-[5-(*iso*-  
 7 propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-  
 8 ethynyl]-benzoic acid or a salt with a pharmaceutically acceptable base or a  
 9 C<sub>1-6</sub> alkyl ester of said compound.

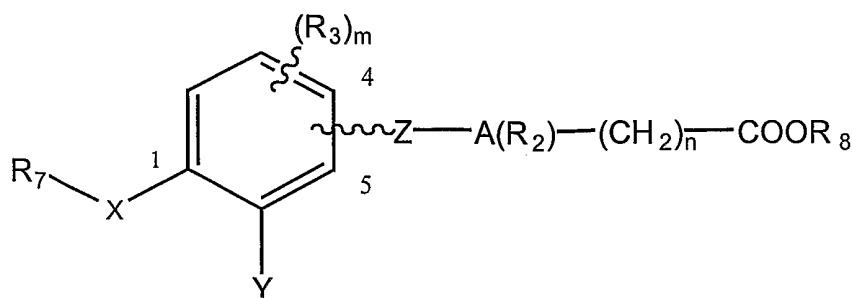
10 **76.** A compound in accordance with Claim 69 where X<sub>1</sub> is 1-  
 11 imidazolyl and *n* is 0.

12 **77.** A compound in accordance with Claim 76 which is [4-(5-  
 13 imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
 14 benzoic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl  
 15 ester of said compound.

16 **78.** A compound in accordance with Claim 69 where X<sub>1</sub> is 1-  
 17 imidazolyl and *n* is 1.

18 **79.** A compound in accordance with Claim 78 which is [4-(5-  
 19 imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-  
 20 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base or a C<sub>1-6</sub>  
 21 alkyl ester of said compound.

22 **80.** A compound of the formula



1        wherein A is a phenyl or naphthyl group, or heteroaryl selected from  
2        a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
3        pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
4        heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

5        X is O, S or NR where R is H, alkyl of 1 to 6 carbons,  $C_{1-6}$ -  
6        trialkylsilyl or benzyl; Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl  
7        or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons,  
8        cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6  
9        carbons, Cl, Br, or I;

10       Z is     $-C\equiv C-$ ,  
11                $-(CR_1=CR_1)_n$ , where n' is an integer having the value 1 - 5,  
12                $-CO-NR_1-$ ,  
13                $NR_1-CO-$ ,  
14                $-CO-O-$ ,  
15                $-O-CO-$ ,  
16                $-CS-NR_1-$ ,  
17                $NR_1-CS-$ ,  
18                $-CO-S-$ ,  
19                $-S-CO-$ ,  
20                $-N=N-$ ;

21         $R_1$  is independently H or alkyl of 1 to 6 carbons;

22         $R_2$  is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
23        substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
24        to 6 carbons;

25         $R_3$  is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
26        substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
27        alkylthio of 1 to 6 carbons or benzyl;

1 **m** is an integer having the values 0 to 3;

2 **R<sub>7</sub>** is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower  
3 alkyl substituted cycloalkyl of 1 to 6 carbons;

4 **n** is an integer having the values of 1 to 4, and

5 **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
6 pharmaceutically acceptable base.

7 **81.** A compound in accordance with Claim 80 where A is phenyl,  
8 naphthyl, pyridyl, thienyl or furyl.

9 **82.** A compound in accordance with Claim 80 where **n** is 0, 1 or 2.

10 **83.** A compound in accordance with Claim 80 where Z is -C≡C-, -  
11 CO-NR<sub>1</sub>-,  
12 -CO-O-, or -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where **n'** is 1.

13 **84.** A compound in accordance with Claim 80 where the **Z** group is  
14 attached to the 4-position of the phenyl moiety.

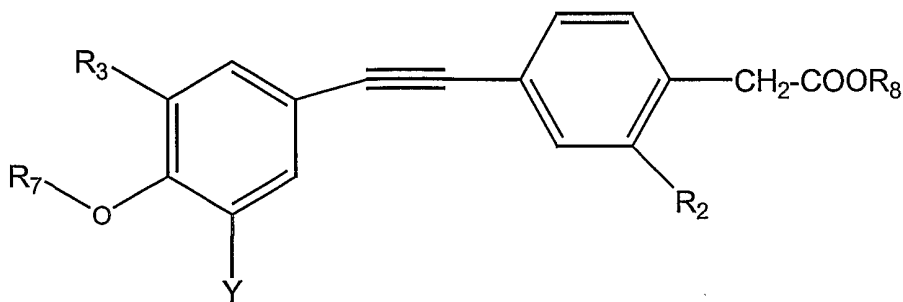
15 **85.** A compound in accordance with Claim 80 where **X** is O.

16 **86.** A compound in accordance with Claim 80 where **Y** is H, lower  
17 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or  
18 halogen.

19 **87.** A compound in accordance with Claim 80 where A is phenyl.

20 **88.** A compound in accordance with Claim 80 where **n** is 1.

21 **89.** A compound of the formula



1 wherein Y is branched-chain alkyl of 3 to 6 carbons;  
 2  $R_2$  is H or F;  
 3  $R_3$  is branched-chain alkyl of 3 to 6 carbons;  
 4  $R_7$  is lower alkyl of 1 to 6 carbons, and  
 5  $R_8$  is H, alkyl of 1 to 6 carbons,  $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$ , or a cation of a  
 6 pharmaceutically acceptable base.

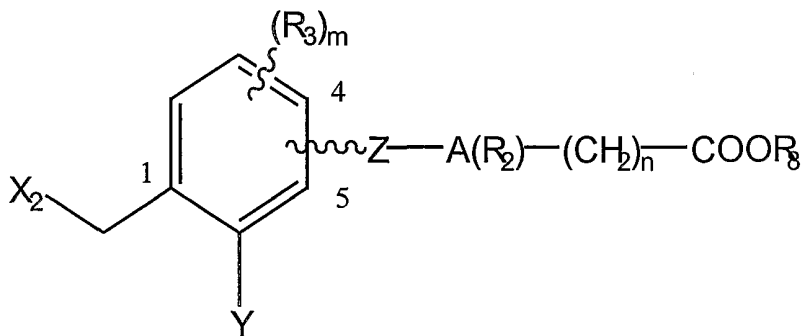
7 **90.** A compound in accordance with Claim 89 where Y is *t*-butyl.

8 **91.** A compound in accordance with Claim 90 where  $R_3$  is *t*-butyl.

9 **92.** A compound in accordance with Claim 91 where  $R_7$  is methyl.

10 **93.** A compound in accordance with Claim 92 which is selected from  
 11 the group consisting of [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-  
 12 phenyl]-acetic acid and [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-2-  
 13 fluoro-phenyl]-acetic acid or a salt of said compound with a  
 14 pharmaceutically acceptable base.

15 **94.** A compound of the formula



23 wherein A is a phenyl or naphthyl group, or heteroaryl selected from  
 24 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 25 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
 26 heteroaryl groups being optionally substituted with one or two  $R_2$  groups;  
 27  $X_2$  is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,

- 1  $OR_7$ ,  $SR_7$  or  $NRR_7$  where **R** is H, alkyl of 1 to 6 carbons or benzyl;  
 2 **Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 3 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of  
 4 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,  
 5 or I;  
 6 **Z** is  $-C\equiv C-$ ,  
 7  $-(CR_1=CR_1)_n$ , where  $n'$  is an integer having the value 1 - 5,  
 8  $-CO-NR_1-$ ,  
 9  $NR_1-CO-$ ,  
 10  $-CO-O-$ ,  
 11  $-O-CO-$ ,  
 12  $-CS-NR_1-$ ,  
 13  $NR_1-CS-$ ,  
 14  $-CO-S-$ ,  
 15  $-S-CO-$ ,  
 16  $-N=N-$ ;  
 17 **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;  
 18 **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro  
 19 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1  
 20 to 6 carbons;  
 21 **R<sub>3</sub>** is alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1  
 22 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio of 1 to 6 carbons  
 23 or benzyl;  
 24 **m** is an integer having the values 0 to 3;  
 25 **R<sub>7</sub>** is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower  
 26 alkyl substituted cycloalkyl of 3 to 6 carbons or C<sub>1-6</sub>-trialkylsilyl.  
 27 **n** is an integer having the values of 0 to 4, and  
 28 **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons,  $-CH_2O(C_{1-6}\text{-alkyl})$ , or a cation of a

1 pharmaceutically acceptable base.

2       **95.** A compound in accordance with Claim 94 where A is phenyl,  
3 naphthyl, pyridyl, thienyl or furyl.

4       **96.** A compound in accordance with Claim 94 where **n** is 0, 1 or 2.

5       **97.** A compound in accordance with Claim 94 where Z is  $-C\equiv C-$ , -  
6  $CO-NR_1-$ ,

7  $-CO-O-$ , or  $-(CR_1=CR_1)_n$ , where **n'** is 1.

8       **98.** A compound in accordance with Claim 94 where the Z group is  
9 attached to the 4-position of the phenyl moiety.

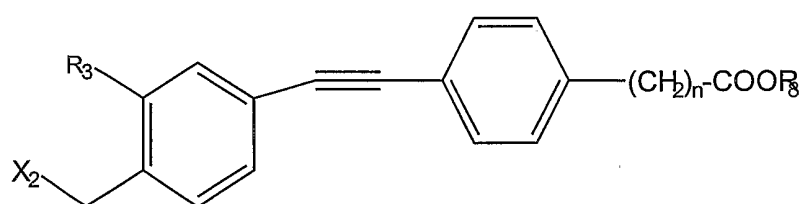
10       **99.** A compound in accordance with Claim 94 where **X**<sub>2</sub> is 1-  
11 imidazolyl, lower alkyl or halogen substituted 1-imidazolyl.

12       **100.** A compound in accordance with Claim 94 where **Y** is H, lower  
13 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or  
14 halogen.

15       **101.** A compound in accordance with Claim 94 where A is phenyl.

16       **102.** A compound in accordance with Claim 94 where **n** is 1.

17       **103.** A compound of the formula



23       wherein **R**<sub>3</sub> is alkyl of 1 to 6 carbons;

24       **X**<sub>2</sub> is 1-imidazolyl, OR<sub>7</sub>, or NRR<sub>7</sub> where **R** is alkyl of 1 to 6 carbons  
25 or cyclopropyl, and **R**<sub>7</sub> is alkyl of 1 to 6 carbons, cyclopropyl or lower alkyl  
26 substituted cyclopropyl;

27       **n** is 0 or 1, and

1            **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
2 acceptable base.

3            **104.** A compound in accordance with Claim 103 wherein **X<sub>2</sub>** is 1-  
4 imidazolyl.

5            **105.** A compound in accordance with Claim 104 wherein **n** is 0.

6            **106.** A compound in accordance with Claim 105 which is selected  
7 from the group consisting of 4-(4-imidazol-1-yl-methyl-3-methyl-  
8 phenylethynyl)-benzoic acid and [4-(4-imidazol-1-yl-methyl-3-isopropyl-  
9 phenylethynyl)-phenyl]-benzoic acid or a salt of said compound with a  
10 pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said compound.

11           **107.** A compound in accordance with Claim 104 wherein **n** is 1.

12           **108.** A compound in accordance with Claim 107 which is selected  
13 from the group consisting of [4-(4-imidazol-1-yl-methyl-3-methyl-  
14 phenylethynyl)-phenyl]-acetic acid and [4-(4-imidazol-1-yl-methyl-3-  
15 isopropyl-phenylethynyl)-phenyl]-acetic acid or a salt of said compound  
16 with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of said  
17 compound.

18           **109.** A compound in accordance with Claim 103 where **X<sub>2</sub>** is  
19 ethyl,cyclopropyl-N-.

20           **110.** A compound in accordance with Claim 109 wherein **n** is 0.

21           **111.** A compound in accordance with Claim 110 which is selected  
22 from the group consisting of 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-  
23 methyl-phenylethynyl}-benzoic and 4-{4-[(cyclopropyl-ethyl-amino)-  
24 methyl]-3-isopropyl-phenylethynyl}-benzoic acid or a salt of said  
25 compound with a pharmaceutically acceptable base or a C<sub>1-6</sub> alkyl ester of  
26 said compound.

27           **112.** A compound in accordance with Claim 109 wherein **n** is 1.

28           **113.** A compound in accordance with Claim 112 which is (4-{4-

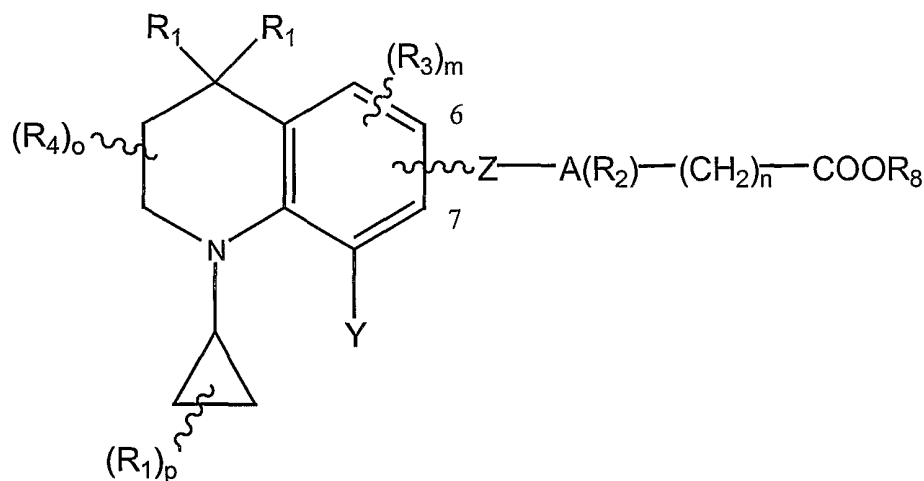
1 [(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-acetic  
 2 acid or a salt of said compound with a pharmaceutically acceptable base or a  
 3 C<sub>1-6</sub> alkyl ester of said compound.

4 **114.** A compound in accordance with Claim 103 where X<sub>2</sub> is (1-  
 5 methyl)cyclopropyl-oxy.

6 **115.** A compound in accordance with Claim 114 wherein n is 1.

7 **116.** A compound in accordance with Claim 115 which is {4-[3-  
 8 isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetic  
 9 acid or a salt of said compound with a pharmaceutically acceptable base or a  
 10 C<sub>1-6</sub> alkyl ester of said compound.

11 **117.** A compound of the formula



22 wherein A is a phenyl or naphthyl group, or heteroaryl selected from  
 23 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
 25 heteroaryl groups being optionally substituted with one or two R<sub>2</sub> groups;

26 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen  
 27 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of

- 1 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl,  
2 Br, or I;
- 3 **Z** is -C≡C-,  
4 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where n' is an integer having the value 1 - 5,  
5 -CO-NR<sub>1</sub>-,  
6 NR<sub>1</sub>-CO-,  
7 -CO-O-,  
8 -O-CO-,  
9 -CS-NR<sub>1</sub>-,  
10 NR<sub>1</sub>-CS-,  
11 -CO-S-,  
12 -S-CO-,  
13 -N=N-;
- 14 **R<sub>1</sub>** is independently H or alkyl of 1 to 6 carbons;  
15 **p** is an integer having the values of 0 to 5;
- 16 **R<sub>2</sub>** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
17 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or  
18 alkylthio of 1 to 6 carbons;
- 19 **R<sub>3</sub>** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
20 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
21 alkylthio of 1 to 6 carbons or benzyl;
- 22 **m** is an integer having the values 0 to 2;
- 23 **R<sub>4</sub>** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
24 alkyl of 1 to 6 carbons, or halogen;
- 25 **o** is an integer having the values of 0 to 4;
- 26 **n** is an integer having the values of 0 to 4, and
- 27 **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
28 pharmaceutically acceptable base.

1           **118.** A compound in accordance with Claim 117 where A is phenyl,  
2 naphthyl, pyridyl, thienyl or furyl.

3           **119.** A compound in accordance with Claim 117 where **n** is 0, 1 or  
4 2.

5           **120.** A compound in accordance with Claim 117 where Z is  $-C\equiv C-$ , -  
6  $CO-NR_1-$ ,  
7  $-CO-O-$ , or  $-(CR_1=CR_1)_n$ , where **n'** is 1.

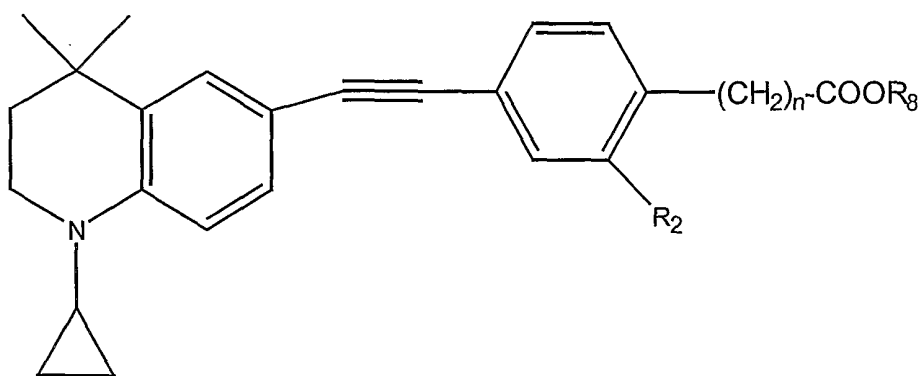
8           **121.** A compound in accordance with Claim 117 where the **Z** group  
9 is attached to the 6-position of the bicyclic moiety.

10           **122.** A compound in accordance with Claim 117 where **Y** is H,  
11 lower alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl,  
12 or halogen.

13           **123.** A compound in accordance with Claim 117 where **A** is phenyl.

14           **124.** A compound in accordance with Claim 117 where **n** is 1.

15           **125.** A compound of the formula



25           wherein **R<sub>2</sub>** is hydrogen, alkyl of 1 to 6 carbons, or halogen

26           **n** is 0 or 1, and

27           **R<sub>8</sub>** is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
28 acceptable base.

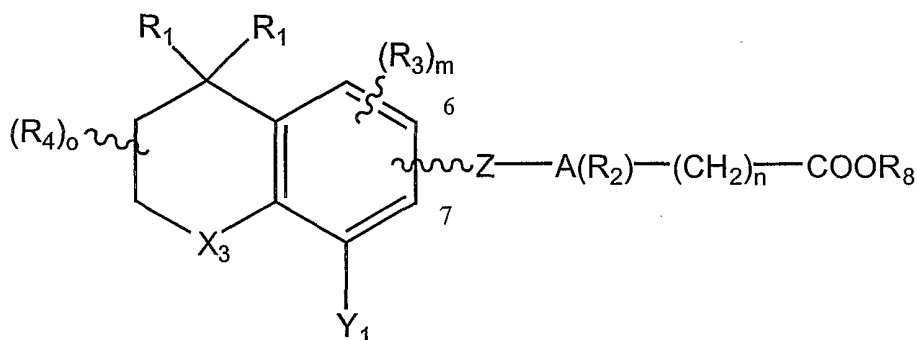
1        **126.** A compound in accordance with Claim 125 wherein **n** is 0.

2        **127.** A compound in accordance with Claim 126 which is 4-(1-  
3 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-benzoic  
4 acid or a salt of said compound with a pharmaceutically acceptable base or a  
5 C<sub>1-6</sub> alkyl ester of said compound.

6        **128.** A compound in accordance with Claim 125 wherein **n** is 1.

7        **129.** A compound in accordance with Claim 128 which is [4-(1-  
8 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)phenyl]  
9 acetic acid methyl ester.

10       **130.** A compound of the formula



18       wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from  
19 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
20 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
21 heteroaryl groups being optionally substituted with one or two **R**<sub>2</sub> groups;

22       **X**<sub>3</sub> is S, or O, C(**R**<sub>1</sub>)<sub>2</sub>, or CO;

23       **Y**<sub>1</sub> is H, lower alkyl of 1 to 3 carbons, cycloalkyl of 3 to 6 carbons,  
24 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

25       **Z** is -C≡C-,

26       -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>, where **n**' is an integer having the value 1 - 5,

27       -CO-NR<sub>1</sub>-,

1           NR<sub>1</sub>-CO-,

2           -CO-O-,

3           -O-CO-,

4           -CS-NR<sub>1</sub>-,

5           NR<sub>1</sub>-CS-,

6           -CO-S-,

7           -S-CO-,

8           -N=N-;

9           R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;

10          R<sub>2</sub> is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
11 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or  
12 alkylthio of 1 to 6 carbons;

13          R<sub>3</sub> is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
14 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,  
15 alkylthio of 1 to 6 carbons or benzyl;

16          m is an integer having the values 0 to 2;

17          R<sub>4</sub> is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted  
18 alkyl of 1 to 6 carbons, or halogen;

19          o is an integer having the values of 0 to 4;

20          n is an integer having the values of 0 to 4, and

21          R<sub>8</sub> is H, alkyl of 1 to 6 carbons, -CH<sub>2</sub>O(C<sub>1-6</sub>-alkyl), or a cation of a  
22 pharmaceutically acceptable base, the compound meeting at least one of the  
23 provisos selected from the group consisting of:

24           Y<sub>1</sub> is cycloalkyl,

25           when Y<sub>1</sub> is not cycloalkyl then X<sub>3</sub> is O or S and n is 1,

26           when Y<sub>1</sub> is not cycloalkyl then X<sub>3</sub> is CO, and n is 1,

27           when Y<sub>1</sub> is not cycloalkyl then X<sub>3</sub> is CO and the moiety A is

28 substituted with at least one F group.

1        **131.** A compound in accordance with Claim 130 where A is phenyl,  
 2 naphthyl, pyridyl, thienyl or furyl.

3        **132.** A compound in accordance with Claim 130 where n is 0, 1 or  
 4 2.

5        **133.** A compound in accordance with Claim 130 where Z is  $-C\equiv C-$ , -  
 6  $CO-NR_1-$ ,  
 7  $-CO-O-$ , or  $-(CR_1=CR_1)_n$ , where n' is 1.

8        **134.** A compound in accordance with Claim 130 where the Z group  
 9 is attached to the 6-position of the bicyclic moiety.

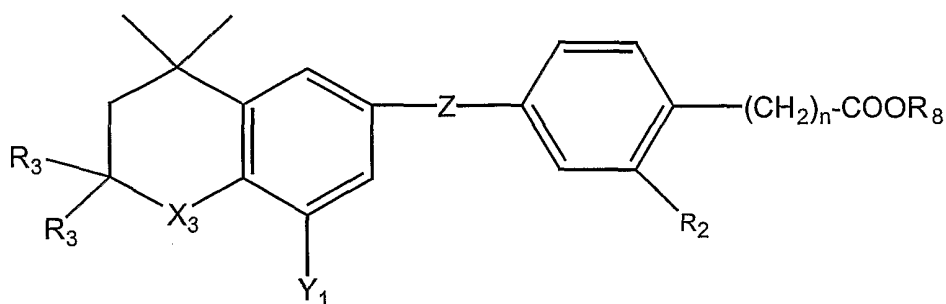
10       **135.** A compound in accordance with Claim 130 where  $Y_1$  is H,  
 11 lower alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl.

12       **136.** A compound in accordance with Claim 130 where A is phenyl.

13       **137.** A compound in accordance with Claim 130 where n is 1.

14       **138.** A compound in accordance with Claim 130 where  $X_3$  is O or  
 15 CO.

16       **139.** A compound of the formula



24       wherein  $R_2$  is H or F;

25        $R_3$  is H or lower alkyl of 1 to 6 carbons;

26        $X_3$  is O or CO;

27        $Y_1$  is H, alkyl of 1 to 6 carbons, or cyclopropyl;

1           **Z** is -C≡C- or -CO-O-;

2           **n** is 0 or 1, and

3           **R<sub>g</sub>** is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically  
4 acceptable base, the compound meeting at least one of the provisos selected  
5 from the group consisting of:

6                   **Y<sub>1</sub>** is cyclopropyl,

7                   when **Y<sub>1</sub>** is not cyclopropyl then **X<sub>3</sub>** is O and **n** is 1,

8                   when **Y<sub>1</sub>** is not cyclopropyl then **X<sub>3</sub>** is CO, and **n** is 1,

9                   when **Y<sub>1</sub>** is not cyclopropyl then **X<sub>3</sub>** is CO and the moiety **A** is  
10 substituted with at least one F group.

11           **140.** A compound in accordance with Claim 139 wherein **Z** is -C≡C-  
12 .

13           **141.** A compound in accordance with Claim 140 wherein **X<sub>3</sub>** is CO,  
14 **Y<sub>1</sub>** is H and **n** is 0.

15           **142.** A compound in accordance with Claim 141 which is 2-fluoro-  
16 4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoic  
17 acid or a salt of said compound with a pharmaceutically acceptable base or a  
18 C<sub>1-6</sub> alkyl ester of said compound.

19           **143.** A compound in accordance with Claim 140 wherein **X<sub>3</sub>** is CO,  
20 **Y<sub>1</sub>** is H and **n** is 1.

21           **144.** A compound in accordance with Claim 143 which is selected  
22 from the group consisting of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-  
23 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [2-fluoro-4-(8,8-  
24 dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)phenyl]-acetic  
25 acid or a salt of said compound with a pharmaceutically acceptable base or a  
26 C<sub>1-6</sub> alkyl ester of said compound.

27           **145.** A compound in accordance with Claim 140 wherein **X<sub>3</sub>** is O,

1  $Y_1$  is H and  $n$  is 0.

2 **146.** A compound in accordance with Claim 145 which is 2-fluoro-  
3 4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a salt of said  
4 compound with a pharmaceutically acceptable base or a  $C_{1-6}$  alkyl ester of  
5 said compound.

6 **147.** A compound in accordance with Claim 140 wherein  $X_3$  is O,  
7  $Y_1$  is H or ethyl and  $n$  is 1.

8 **148.** A compound in accordance with Claim 147 which is selected  
9 from the group consisting of [4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)  
10 phenyl] acetic acid, [2-fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)  
11 phenyl] acetic acid and [4-(8-ethyl-2,2,4,4-tetramethyl-chroman-6-yl-  
12 ethynyl) phenyl] acetic acid or a salt of said compound with a  
13 pharmaceutically acceptable base or a  $C_{1-6}$  alkyl ester of said compound.

14 **149.** A compound in accordance with Claim 140 wherein  $X_3$  is O,  
15  $Y_1$  is cyclopropyl and  $n$  is 0.

16 **150.** A compound in accordance with Claim 149 which is 4-(8-  
17 cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a  
18 salt of said compound with a pharmaceutically acceptable base or a  $C_{1-6}$   
19 alkyl ester of said compound.

20 **151.** A compound in accordance with Claim 140 wherein  $X_3$  is O,  
21  $Y_1$  is cyclopropyl and  $n$  is 1.

22 **152.** A compound in accordance with Claim 151 which is selected  
23 from the group consisting of [4-(8-cyclopropyl-2,2,4,4-tetramethyl-  
24 chroman-6-yl-ethynyl) phenyl] acetic acid and [4-(8-cyclopropyl-2,2,4,4-  
25 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid or a salt of  
26 said compound with a pharmaceutically acceptable base or a  $C_{1-6}$  alkyl ester  
27 of said compound.

28 **153.** A compound in accordance with Claim 139 where  $Z$  is -CO-O-,

1  $X_3$  is CO and  $n$  is 1.

2       **154.** A compound in accordance with Claim 153 which is 8,8-  
3 dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-  
4 (carboxymethyl)phenyl ester or a salt of said compound with a  
5 pharmaceutically acceptable base or a  $C_{1-6}$  alkyl ester of said compound.

6       **155.** A compound in accordance with Claim 139 where  $Z$  is -CO-O-,  
7  $X_3$  is O and  $n$  is 1.

8       **156.** A compound in accordance with Claim 155 which is 2,2,4,4-  
9 tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl ester or a  
10 salt of said compound with a pharmaceutically acceptable base or a  $C_{1-6}$   
11 alkyl ester of said compound.

