



(86) Date de dépôt PCT/PCT Filing Date: 2002/10/31

(87) Date publication PCT/PCT Publication Date: 2003/05/08

(85) Entrée phase nationale/National Entry: 2004/04/29

(86) N° demande PCT/PCT Application No.: GB 2002/004933

(87) N° publication PCT/PCT Publication No.: 2003/037321

(30) Priorité/Priority: 2001/10/31 (0126157.7) GB

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 31/235

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(54) Titre : DERIVES D'ALCANE-DIOLS UTILISES COMME AGENTS THERAPEUTIQUES POUR LE TRAITEMENT DE
PATHOLOGIES OSSEUSES

(54) Title: ALKANE DIOL DERIVATIVES AS THERAPEUTIC AGENTS FOR THE TREATMENT OF BONE CONDITIONS

(57) **Abrégé/Abstract:**

The present invention pertains to certain alkane diol derivatives (including, e.g., mono- and di-esters) of the formula $R^1-O-A-O-R^2$, wherein: A is a C_{2-10} alkylene group; R^1 is independently a first hydroxy protecting group (e.g., an ester group); and, R^2 is independently -H or a second hydroxy protecting group (e.g., an ester group); and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrug thereof, which, inter alia, inhibit osteoclast survival, formation, and/or activity; and/or inhibit bone resorption. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both in vitro and in vivo, to inhibit osteoclast survival, formation, and/or activity, and to inhibit conditions mediated by osteoclasts and/or characterised by bone resorption, such as osteoporosis, rheumatoid arthritis, cancer associated bone disease, Paget's disease, and the like; and/or conditions associated with inflammation or activation of the immune system.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 May 2003 (08.05.2003)

PCT

(10) International Publication Number
WO 03/037321 A1

(51) International Patent Classification⁷: **A61K 31/235**

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(21) International Application Number: PCT/GB02/04933

(22) International Filing Date: 31 October 2002 (31.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0126157.7 31 October 2001 (31.10.2001) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

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.

(54) Title: ALKANE DIOL DERIVATIVES AS THERAPEUTIC AGENTS FOR THE TREATMENT OF BONE CONDITIONS

(57) Abstract: The present invention pertains to certain alkane diol derivatives (including, e.g., mono- and di-esters) of the formula R¹-O-A-O-R², wherein: A is a C₂₋₁₀alkylene group; R¹ is independently a first hydroxy protecting group (e.g., an ester group); and, R² is independently -H or a second hydroxy protecting group (e.g., an ester group); and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrug thereof, which, *inter alia*, inhibit osteoclast survival, formation, and/or activity; and/or inhibit bone resorption. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit osteoclast survival, formation, and/or activity, and to inhibit conditions mediated by osteoclasts and/or characterised by bone resorption, such as osteoporosis, rheumatoid arthritis, cancer associated bone disease, Paget's disease, and the like; and/or conditions associated with inflammation or activation of the immune system.



WO 03/037321 A1

ALKANE DIOL DERIVATIVES AS THERAPEUTIC AGENTS FOR THE TREATMENT OF BONE CONDITIONS

RELATED APPLICATION

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This application is related to (and where permitted by law, claims priority to) United Kingdom patent application number GB 0126157.7 filed 31 October 2001, the contents of which are incorporated herein by reference in their entirety.

10

TECHNICAL FIELD

The present invention pertains generally to the field of therapeutic compounds for treating bone conditions, and more specifically to certain alkane diol derivatives which, *inter alia*, inhibit osteoclast survival, formation, and/or activity; and/or inhibit bone resorption. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit osteoclast survival, formation, and/or activity, and to inhibit conditions mediated by osteoclasts and/or characterised by bone resorption, such as osteoporosis, rheumatoid arthritis, cancer associated bone disease, Paget's disease, and the like; and/or conditions associated with inflammation or activation of the immune system.

BACKGROUND

25 Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

30

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context

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clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

5 Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiments.

10

Functions of Bone

The function of bone is to provide mechanical support for joints, tendons and ligaments, to protect vital organs from damage and to act as a reservoir for
15 calcium and phosphate in the preservation of normal mineral homeostasis. Diseases of bone compromise these functions, leading to clinical problems such as bone pain, bone deformity, fracture and abnormalities of calcium and phosphate homeostasis.

20 Types of Bone

The normal skeleton contains two types of bone; cortical or compact bone, which makes up most of shafts (diaphysis) of the long bones such as the femur and tibia, and trabecular or spongy bone which makes up most of the vertebral
25 bodies and the ends of the long bones.

Trabecular bone has a greater surface area than cortical bone and because of this is remodeled more rapidly. This means that conditions associated with increased bone turnover tend to affect trabecular bone more quickly and more
30 profoundly than cortical bone. Cortical bone is arranged in so-called Haversian systems which consists of a series of concentric lamellae of collagen fibres surrounding a central canal that contains blood vessels. Nutrients reach the

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central parts of the bone by an interconnecting system of canaliculi that run between osteocytes buried deep within bone matrix and lining cells on the bone surface. Trabecular bone has a similar structure, but here the lamellae run in parallel to the bone surface, rather than concentrically as in cortical bone.

5

Bone Composition

The organic component of bone matrix comprises mainly of type I collagen; a fibrillar protein formed from three protein chains, wound together in a triple helix.

10 Collagen type I is laid down by bone forming cells (osteoblasts) in organised parallel sheets (lamellae) and subsequently the collagen chains become cross-linked by specialised covalent bonds which help to give bone its tensile strength.

When bone is formed rapidly (for example in Paget's disease, or in bone metastases), the lamellae are laid down in a disorderly fashion giving rise to
15 "woven bone", which is mechanically weak and easily fractured. Bone matrix also contains small amounts of other collagens and several non-collagenous proteins and glycoproteins. Some of these, such as osteocalcin, are specific to bone, whereas others, such as osteopontin and fibronectin and various peptide growth factors are also found in other connective tissues. The function of non-
20 collagenous bone proteins is unclear, but it is thought that they are involved in mediating the attachment of bone cells to bone matrix, and in regulating bone cell activity during the process of bone remodelling. The organic component of bone forms a framework upon which mineralisation occurs. During bone formation, osteoblasts lay down uncalcified bone matrix (osteoid) which contains
25 the components described above and small amounts of other proteins, which are adsorbed from extracellular fluid. After a lag phase of about 10 days, the matrix becomes mineralised, as hydroxyapatite ($(\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) crystals are deposited in the spaces between collagen fibrils. Mineralisation confers upon bone the property of mechanical rigidity, which complements the tensile strength,
30 and elasticity derived from bone collagen.

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Bone cell function and bone remodelling

The mechanical integrity of the skeleton is maintained by the process of bone remodelling, which occurs throughout life, in order that damaged bone can be replaced by new bone. Remodelling can be divided into four phases; resorption; reversal, formation and quiescence (see, e.g., Raisz, 1988; Mundy, 1996). At any one time approximately 10% of bone surface in the adult skeleton is undergoing active remodeling whereas the remaining 90% is quiescent.

10 Osteoclast formation and Differentiation

Remodelling commences with attraction of bone resorbing cells (osteoclasts) to the site, which is to be resorbed. These are multinucleated phagocytic cells, rich in the enzyme tartrate-resistant acid phosphatase, which are formed by fusion of precursors derived from the cells of monocyte/macrophage lineage. Recent work has identified several molecules that are of key importance in the regulation of osteoclast differentiation (see, e.g., Ralston, 1997). The transcription factor *PU-1* which is expressed in early osteoclast precursors is necessary for the initial stages of osteoclast and monocyte differentiation, whereas other transcription factors including *c-fos* and *NFkB* play an essential role in stimulating differentiation of committed precursors to mature osteoclasts. Osteoclast formation and activation is also dependent on close contact between osteoclast precursors and bone marrow stromal cells. Stromal cells secrete the cytokine *M-CSF* (macrophage colony stimulating factor), which is essential for differentiation of both osteoclasts and macrophages from a common precursor. Stromal cells also express a molecule called *RANK ligand (RANKL)* on the cell surface, which interacts with another cell surface receptor present on osteoclast precursors called *RANK (Receptor Activator of Nuclear Factor Kappa B)* to promote differentiation of osteoclast precursors to mature osteoclasts. The *RANK-RANKL* interaction is blocked by another molecule called Osteoprotegerin (*OPG*), which is a "decoy" ligand for RANK and which acts a potent inhibitor of osteoclast formation (see, e.g., Kong et al., 1999; Yasuda et al., 1998). Recent

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work suggests that many of the factors that promote osteoclast formation and bone resorption do so by regulating expression of these molecules.

5 Mature osteoclasts form a tight seal over the bone surface and resorb bone by secreting hydrochloric acid and proteolytic enzymes through the "ruffled border" into a space beneath the osteoclast (Howship's lacuna). Formation of this ruffled border is critically dependent on the presence of *c-src*, a cell membrane associated signalling protein. The hydrochloric acid secreted by osteoclasts dissolves hydroxyapatite and allows proteolytic enzymes (mainly Cathepsin K and matrix metalloproteinases) to degrade collagen and other matrix proteins. 10 Molecules which have been identified as being important in regulating osteoclast activity include; carbonic anhydrase II (Ca-II) which catalyses formation of hydrogen ions within osteoclasts; TCIRG1, which encodes a subunit of the osteoclast proton pump, and Cathepsin K which degrades collagen and other non-collagenous proteins. 15 Deficiency of these proteins causes osteopetrosis which is a disease associated with increased bone density and osteoclast dysfunction. After resorption is completed osteoclasts undergo programmed cell death (apoptosis), in the so-called reversal phase which heralds the start of bone formation. It has recently been discovered that many of the drugs, which are 20 used clinically to inhibit bone resorption, such as bisphosphonates and oestrogen do so by promoting osteoclast apoptosis (see, e.g., Hughes et al., 1997).

Osteoblast Formation and Differentiation

25 Bone formation begins with attraction of osteoblast precursors, which are derived from mesenchymal stem cells in the bone marrow, to the bone surface. Although these cells have the potential to differentiate into many cell types including adipocytes, myocytes, and chondrocytes it is now known that the key trigger for osteoblast differentiation is expression of a regulatory molecule called *Cbfa1* in 30 pre-osteoblasts (see, e.g., Rodan et al., 1997). *Cbfa1* is a transcription factor that activates co-ordinated expression of genes characteristic of the osteoblast phenotype such as osteocalcin, type I collagen and alkaline phosphatase. In

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contrast, expression of the transcription factor PPAR γ promotes the cells towards adipocyte differentiation. It is currently thought that some cases of osteoporosis may occur because there is an imbalance between the rate of osteoblast and adipocyte differentiation in bone. Mature osteoblasts are plump cuboidal cells, which are responsible for the production of bone matrix. They are rich in the enzyme alkaline phosphatase and the protein osteocalcin, which are used clinically as serum markers of osteoblast activity. Osteoblasts lay down bone matrix which is initially unmineralised (osteoid), but which subsequently becomes calcified after about 10 days to form mature bone. During bone formation, some osteoblasts become trapped within the matrix and differentiate into osteocytes, whereas others differentiate into flattened "lining cells" which cover the bone surface. Osteocytes connect with one another and with lining cells on the bone surface by an intricate network of cytoplasmic processes, running through canaliculi in bone matrix. Osteocytes appear to act as sensors of mechanical strain in the skeleton, and release signalling molecules such as prostaglandins and nitric oxide (NO), which modulate the function of neighbouring bone cells.

Regulation of Bone Remodelling

Bone remodelling is a highly organised process, but the mechanisms which determine where and when remodelling occurs are poorly understood. Mechanical stimuli and areas of micro-damage are likely to be important in determining the sites at which remodelling occurs in the normal skeleton. Increased bone remodelling may result from local or systemic release of inflammatory cytokines like interleukin-1 and tumour necrosis factor in inflammatory diseases. Calciotropic hormones such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D, act together to increase bone remodelling on a systemic basis allowing skeletal calcium to be mobilised for maintenance of plasma calcium homeostasis. Bone remodelling is also increased by other hormones such as thyroid hormone and growth hormone, but suppressed by oestrogen, androgens and calcitonin.

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Common Bone Diseases

Osteoporosis is a common disease characterized by reduced bone density, deterioration of bone tissue and increase risk of fracture. Many factors contribute to the pathogenesis of osteoporosis including poor diet, lack of exercise, smoking and excessive alcohol intake. Osteoporosis may also arise in association with inflammatory diseases such as rheumatoid arthritis, endocrine diseases such as thyrotoxicosis and with certain drug treatments such as glucocorticoids. However one of the most important factors in the pathogenesis of osteoporosis is heredity.

10

Paget's disease of bone is a common condition of unknown cause, characterized by increased bone turnover and disorganized bone remodeling, with areas of increased osteoclastic and osteoblast activity. Although Pagetic bone is often denser than normal, the abnormal architecture causes the bone to be mechanically weak, resulting in bone deformity and increased susceptibility to pathological fracture.

15

Multiple Myeloma is a cancer of plasma cells. In contrast to most other haematological malignancies, the tumour cells do not circulate in the blood, but accumulate in the bone marrow where they give rise to high levels of cytokines that activate osteoclastic bone resorption (e.g., interleukin-6). The disease accounts for approximately 20% of all haematological cancers and is mainly a disease of elderly people.

20

Bone Resorption Inhibitors

25

Several common diseases, such as osteoporosis and rheumatoid arthritis, are characterised by bone loss due to excess bone resorption by osteoclasts. At present the most commonly used types of drugs used to suppress osteoclast activity in these diseases are bisphosphonates (BPs) and non-steroidal anti-inflammatory drugs (NSAIDs).

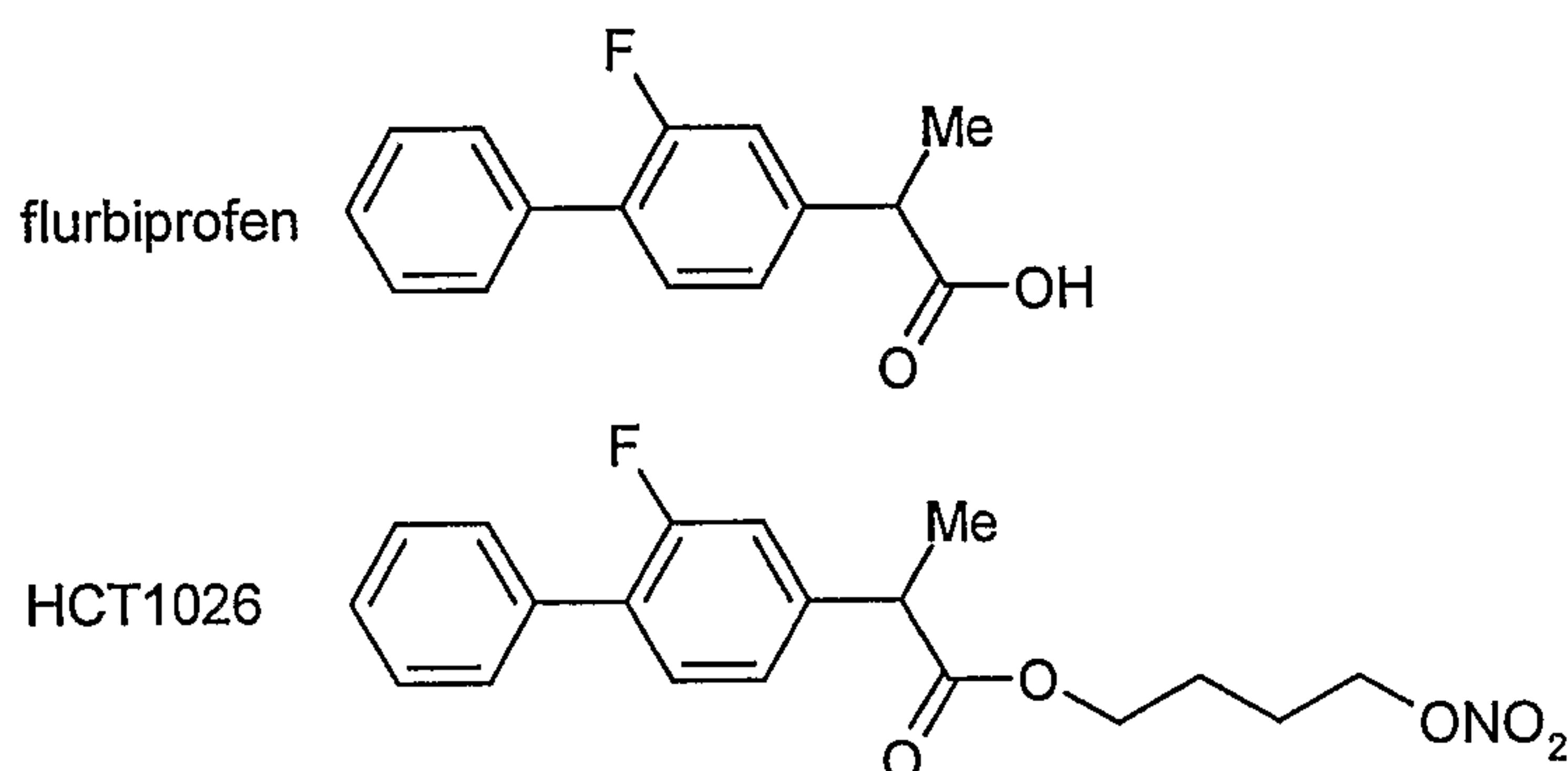
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Bisphosphonates (also known as diphosphonates) are an important class of drugs used in the treatment of bone diseases involving excessive bone destruction or resorption, e.g., Paget's disease, tumour-associated osteolysis, and post-menopausal osteoporosis. Bisphosphonates are structural analogues of naturally occurring pyrophosphate. Whereas pyrophosphate consists of two phosphate groups linked by an oxygen atom (P-O-P), bisphosphonates have two phosphate groups linked by a carbon atom (P-C-P). This makes bisphosphonates very stable and resistant to degradation. Furthermore, like pyrophosphate, bisphosphonates have very high affinity for calcium and therefore target to bone mineral *in vivo*. The carbon atom that links the two phosphate groups has two side chains attached to it, which can be altered in structure. This gives rise to a multitude of bisphosphonate compounds with different anti-resorptive potencies. Bone resorption is mediated by highly specialised, multinucleated osteoclast cells. Bisphosphonate drugs specifically inhibit the activity and survival of these cells. Firstly, after intravenous or oral administration, the bisphosphonates are rapidly cleared from the circulation and bind to bone mineral. As the mineral is then resorbed and dissolved by osteoclasts, it is thought that the drug is released from the bone mineral and is internalised by osteoclasts. Intracellular accumulation of the drugs inhibits the ability of the cells to resorb bone (probably by interfering with signal transduction pathways or cellular metabolism) and causes osteoclast apoptosis.

NSAIDs are widely used in the treatment of inflammatory diseases, but often cause severe gastro-intestinal (GI) side effects. NSAIDs developed by Nicox SA (Sophia Antipolis, France), that contain a nitric oxide (NO)-donor group (NO-NSAID) exhibit anti-inflammatory properties without causing GI side effects. An example of such a compound is HCT 1026, which is a nitrosylated derivative of the NSAID flurbiprofen (see, for example, Armour et al., 2001).

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There is a recognized need for more and better treatments for these and other bone-related diseases, which offer, for example, one or more the following

- 5 benefits:
- (a) improved activity;
 - (b) improved efficacy;
 - (c) improved specificity;
 - (d) reduced toxicity (e.g., cytotoxicity);
 - 10 (e) complement the activity of other treatments (e.g., chemotherapeutic agents);
 - (f) reduced intensity of undesired side-effects;
 - (g) fewer undesired side-effects;
 - (h) simpler methods of administration (e.g., route, timing, compliance);
 - (i) reduction in required dosage amounts;
 - 15 (j) reduction in required frequency of administration;
 - (k) increased ease of synthesis, purification, handling, storage, etc.;
 - (l) reduced cost of synthesis, purification, handling, storage, etc.

Thus, one aim of the present invention is the provision of active compounds
20 which offer one or more of the above benefits.

SUMMARY OF THE INVENTION

One aspect of the invention pertains to a method of inhibiting osteoclast survival,
25 formation, and activity, *in vitro* or *in vivo*, comprising contacting an osteoclast with an effective amount of an active compound, as described herein.

- 10 -

Another aspect of the invention pertains to a method of inhibiting bone resorption, *in vitro* or *in vivo*, comprising contacting cells in the bone microenvironment with a therapeutically-effective amount of an active compound, as described herein.

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Another aspect of the present invention pertains to a method for the treatment of a condition mediated by osteoclasts and/or characterised by bone resorption, as described herein, comprising administering to a subject suffering from said condition a therapeutically-effective amount of an active compound, as described
10 herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to a method for the treatment of a condition associated with inflammation or activation of the immune system, as described herein, comprising administering to a subject suffering from said
15 condition a therapeutically-effective amount of an active compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the
20 treatment of a condition mediated by osteoclasts and/or characterised by bone resorption, as described herein.

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the
25 treatment of a condition mediated by osteoclasts, as described herein.

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition characterised by bone resorption, as described herein.
30

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the

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treatment of osteoporosis, rheumatoid arthritis, cancer associated bone disease, or Paget's disease.

Another aspect of the present invention pertains to use of an active compound,
5 as described herein, for the manufacture of a medicament for use in the treatment of a condition associated with inflammation or activation of the immune system, as described herein.

Another aspect of the present invention pertains to an active compound as
10 described herein for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition mediated by
15 osteoclasts and/or characterised by bone resorption, as described herein, of the human or animal body by therapy.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition mediated by
20 osteoclasts, as described herein, of the human or animal body by therapy.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition characterised by bone resorption, as described herein, of the human or animal body by therapy.
25

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment of osteoporosis, rheumatoid arthritis, cancer associated bone disease, or Paget's disease of the human or animal body by therapy.
30

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition associated with

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inflammation or activation of the immune system, as described herein, of the human or animal body by therapy.

Another aspect of the invention pertains to active compounds, specifically,
5 certain alkane diol derivatives (e.g., esters of alkane diols) as described herein.

Another aspect of the invention pertains to a composition comprising an active compound as described herein and a pharmaceutically acceptable carrier or diluent.

10

Another aspect of the present invention pertains to a kit comprising (a) an active compound, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and
15 (b) instructions for use, for example, written instructions on how to administer the active compound.

20

Another aspect of the present invention pertains to compounds *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to compounds *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

25 Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

Another aspect of the present invention pertains to the use of such novel
30 intermediates, as described herein, in the methods of synthesis described herein.

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As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspect of the invention.

5 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of macrophage viability, as measured by the MTT and Alamar Blue macrophage J774 viability assays, expressed as % of control, after 72 hour exposure to ABD-0028 (4T) ("28") and ABD-0042 (4BPA) ("42") as a function of
10 concentration of compound.

Figure 2 is a bar graph showing the number of osteoclasts, expressed as a % of control value, after three days exposure to compound, for the murine co-culture system, for several examples of biphenylcarboxy (BP), trityl (T), and ibuprofenyl
15 (I) compounds: ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), ABD-0054 (6BP), ABD-0028 (4T), ABD-0037 (3I), ABD-0036 (4I), ABD-0038 (5I), and ABD-0039 (6I). All compounds were tested at 100 μ M concentration. Each value represents an average of 3 experiments, each of which had 5 data points.

20 Figure 3 is a graph showing the effects of compounds on osteoclast and J774 survival, for both the murine co-culture system (A) and the MTT macrophage J774 viability assay (B), for several examples of biphenylcarboxy (BP), trityl (T), and ibuprofenyl (I) compounds, and some others. For co-culture (A), the graph shows number of osteoclasts, expressed as a % of control value. For
25 macrophages (B), the graph shows viability as measured by the MTT assay, expressed as % of control. All compounds were tested at 100 μ M concentration.

Figure 4 is a graph of macrophage viability, as measured by the MTT macrophage J774 viability assay, expressed as % of control, after 24 hour
30 exposure to compound, for several examples of biphenylcarboxy (BP) compounds: ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), ABD-0054 (6BP). Unless shown, error bars are less than 20%.

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Figure 5 is a graph of macrophage viability, as measured by the MTT macrophage J774 viability assay, expressed as % of control, after 24 hour exposure to compound, for several examples of ibuprofenyl (I) compounds:
5 ABD-0035 (BuI), ABD-0037 (3I), ABD-0036 (4I), ABD-0038 (5I), ABD-0039 (6I). Unless shown, error bars are less than 20%.

Figure 6 is a graph of macrophage viability, as measured by the MTT macrophage J774 viability assay, expressed as % of control, after 24 hour
10 exposure to compound, for several examples of trityl (T) compounds: ABD-0028 (4T), ABD-0030 (5T), ABD-0031 (6T). Unless shown, error bars are less than 20%.

Figure 7 is a graph of macrophage viability, as measured by the MTT
15 macrophage J774 viability assay, expressed as % of control, after 24 hour exposure to compound, for several examples of biphenylacetyl (BPA) compounds: ABD-0040 (BuBPA), ABD-0041 (3BPA), ABD-0042 (4BPA), ABD-0043 (5BPA), ABD-0044 (6BPA). Unless shown, error bars are less than 20%.

20
Figure 8 is a graph of macrophage viability, as measured by the MTT macrophage J774 viability assay, expressed as % of control, after 24 hour exposure to compound, for several examples of butanediol compounds: ABD-0042 (4BPA), ABD-0028 (4T), ABD-0056 (4BP), ABD-0036 (4I).

25
Figure 9 is a graph of macrophage viability, as measured by the Alamar Blue macrophage J774 viability assay, expressed as % of control, after 72 hour exposure to compound, for several examples of butanediol compounds: ABD-0042 (4BPA), ABD-0028 (4T), ABD-0056 (4BP), ABD-0036 (4I).

30
Figure 10 is a graph of macrophage viability, as measured by the Alamar Blue macrophage J774 viability assay, expressed as % of control, after 72 hour

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exposure to compound, for ABD-0098 ("2NO₂"), ABD-0100 ("4F"), ABD-0099 ("2F"), ABD-0089 ("Xyl"), and ABD-0102 ("4Br").

Figure 11 is a graph of macrophage viability, as measured by the Alamar Blue
5 macrophage J774 viability assay, expressed as % of control, after 72 hour exposure to compound, for ABD-0072 ("OH"), ABD-0089 ("Dimethyl"), ABD-0070 ("Methyl"), ABD-0094 ("Ethyl"), and ABD-0097 ("Methoxy").

Figure 12 is a graph of macrophage viability, as measured by the Alamar Blue
10 macrophage J774 viability assay, expressed as % of control, after 72 hour exposure to compound, for ABD-0085 (10F) and ABD-0077 (5F).

Figure 13 is a graph showing the effects of compounds in the rabbit osteoclast culture system, and is a plot of the number of rabbit osteoclasts, expressed as a
15 % of control value, after three days exposure to compound, as a function of compound concentration, for several examples of biphenylcarboxy (BP) derivatives: ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), ABD-0054 (6BP).

Figure 14 is a graph showing the effects of compounds in the rabbit osteoclast culture system, and is a plot of resorption pit area expressed as a % of control, after three days exposure to compound, as a function of compound concentration, for several examples of biphenylcarboxy (BP) derivatives:
20 ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP),
25 ABD-0054 (6BP). Each value represents an average of 3 experiments, each of which had 5 data points.

Figure 15 is a graph showing the effects of compounds in the murine co-culture system, and is a plot of the number of murine osteoclasts, expressed as a % of
30 control value as a function of compound concentration, for ABD-0056 (4BP). The compound is added at Day 2 and there is a complete medium refresh after Day 4 to remove the compound. The experiment is terminated at Day 10 and the

- 16 -

number of osteoclasts ascertained by TRAcP staining. Each value represents an average of 3 experiments, each of which had 5 data points.

Figure 16 is a graph showing the effects of compounds in the murine co-culture system, and is a plot of resorption pit area expressed as a % of control value as a function of compound concentration, for ABD-0056 (4BP). The compound is added at Day 2 and there is a complete medium refresh after Day 4 to remove the compound. The experiment is terminated at Day 10 and the amount of resorption measured by reflected light microscopy. Each value represents an average of 3 experiments, each of which had 5 data points.

Figure 17 is a graph showing the effects of compounds in the murine co-culture system, and is a plot of the number of murine osteoclasts, expressed as a % of control value, after three days exposure to compound added at Day 7, as a function of compound concentration, for several examples of biphenylcarboxy (BP) derivatives: ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), ABD-0054 (6BP).

Figure 18 is a graph showing the effects of compounds in the murine co-culture system, and is a plot of resorption pit area expressed as a % of control, after three days exposure to compound added at Day 7, as a function of compound concentration, for several examples of biphenylcarboxy (BP) derivatives: ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), ABD-0054 (6BP). Each value represents an average of 3 experiments, each of which had 5 data points.

Figure 19 is a graph of osteoclast number and resorption pit area for the murine co-culture system, where ABD-0056 (4BP) was added at Day 7, and incubation continued until Day 10 (mature osteoclasts).

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DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention pertains to compounds which may be described as alkane diol derivatives, and their surprising and unexpected
 5 osteoclast-inhibitory and resorption-inhibitory effects.

Alkane Diol Derivatives

One aspect of the present invention pertains to compounds which may be described as derivatives of the alkane diols described above (i.e., alkane diol
 10 derivatives), and which have the following formula:



wherein:

A is a C₂₋₁₀alkylene group;
 R¹ is independently a first hydroxy protecting group; and,
 15 R² is independently -H or a second hydroxy protecting group;
 and pharmaceutically acceptable salts, solvates, amides, esters, ethers,
 chemically protected forms, or prodrugs thereof.

In one embodiment, R² is not -H, and the compound is di-protected.
 20

In one embodiment, R² is not -H, and R¹ and R² are the same.

In one embodiment, R² is not -H, and R¹ and R² are different.

In one embodiment, R² is -H, the compound is mono-protected, and has the
 25 following formula:



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Alkane Diols

The compounds of the present invention may be described as alkane diol derivatives. In this context, the alkane diols have the following formula:



5 wherein A is a C₂₋₁₀alkylene group, and is optionally substituted.

The Alkylene Group, A

10 The alkylene group, A, is a C₂₋₁₀alkylene group, and is optionally substituted.

The term "C₂₋₁₀alkylene," as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, either both from the same carbon atom, or one from each of two different carbon atoms, of a hydrocarbon compound having from 2 to 10 carbon atoms, which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. The prefix (i.e., "C₂₋₁₀") denotes the number of carbon atoms in the moiety.

In one embodiment, the alkylene group is unsubstituted.

20 In one embodiment, the two hydrogen atoms are removed from different carbon atoms.

In one embodiment, the two hydrogen atoms are removed from different carbon atoms, and these carbon atoms are not adjacent.

25

In one embodiment, the alkylene group is C₃₋₁₀alkylene group.

In one embodiment, the alkylene group is C₄₋₁₀alkylene group.

In one embodiment, the alkylene group is C₂₋₈alkylene group.

In one embodiment, the alkylene group is C₃₋₈alkylene group.

30 In one embodiment, the alkylene group is C₄₋₈alkylene group.

In one embodiment, the alkylene group is C₂₋₇alkylene group.

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In one embodiment, the alkylene group is C₃₋₇alkylene group.

In one embodiment, the alkylene group is C₄₋₇alkylene group.

In one embodiment, the alkylene group is C₂₋₆alkylene group.

In one embodiment, the alkylene group is C₃₋₆alkylene group.

5 In one embodiment, the alkylene group is C₄₋₆alkylene group.

In one embodiment, the alkylene group is C₃alkylene group.

In one embodiment, the alkylene group is C₄alkylene group.

In one embodiment, the alkylene group is C₅alkylene group.

In one embodiment, the alkylene group is C₆alkylene group.

10

In one embodiment, the alkylene group is an aliphatic group.

In one embodiment, the alkylene group is a branched group.

15 In one embodiment, the alkylene group is a linear group.

In one embodiment, the alkylene group is a partially unsaturated aliphatic group.

In one embodiment, the alkylene group is a fully saturated aliphatic group.

20

In one embodiment, the alkylene group is a partially unsaturated branched group. Examples of such groups include, but are not limited to, the following:

-C(Me)=CH-, -CH=C(Me)-, -C(Me)=C(Me)-,

-C(Et)=CH-, -CH=C(Et)-, -C(Et)=C(Et)-,

25 -C(Me)=CH-CH₂-, -CH=C(Me)-CH₂-, -CH=CH-CH(Me)-,

-C(Et)=CH-CH₂-, -CH=C(Et)-CH₂-, -CH=CH-CH(Et)-,

-C(Me)=CH-CH₂CH₂-, -CH=C(Me)-CH₂CH₂-, -CH=CH-CH(Me)CH₂-,

-C(Et)=CH-CH₂CH₂-, -CH=C(Et)-CH₂CH₂-, and -CH=CH-CH(Et)CH₂-.

30 In one embodiment, the alkylene group is a fully saturated branched group.

Examples of such groups include, but are not limited to, the following:

-CH(Me)-, -CH(Et)-,

- 20 -

- CH(Me)CH₂-, -CH(Et)CH₂-, -CH₂CH(Me)-, -CH₂CH(Et)-,
 -CH(Me)CH₂CH₂-, -CH₂CH(Me)CH₂-, -CH₂CH₂CH(Me)-,
 -CH(Et)CH₂CH₂-, -CH₂CH(Et)CH₂-, -CH₂CH₂CH(Et)-,
 -CH(Me)CH₂CH₂CH₂-, -CH₂CH(Me)CH₂CH₂-,
 5 -CH(Et)CH₂CH₂CH₂-, and -CH₂CH(Et)CH₂CH₂-.

In one embodiment, the alkylene group is a partially unsaturated linear group.
 Examples of such groups include, but are not limited to, the following:

- CH=CH- (vinylene),
 10 -CH=CH-CH₂-, -CH₂-CH=CH-,
 -CH=CH-CH₂-CH₂-, -CH₂-CH-CH=CH-, -CH=CH-CH=CH-,
 -CH=CH-CH₂-CH₂-CH₂-, -CH=CH-CH=CH-CH₂-, -CH=CH-CH₂-CH=CH-,
 -CH=CH-CH=CH-CH₂-CH₂-, and -CH=CH-CH₂-CH₂-CH=CH-.

- 15 In one embodiment, the alkylene group is a fully saturated linear group.
 Examples of such groups include, but are not limited to, groups of the formula
 -(CH₂)_n- where n is an integer from 2 to 10, for example, -(CH₂)₂- (ethylene),
 -(CH₂)₃- (propylene), -(CH₂)₄- (butylene), -(CH₂)₅- (pentylene), -(CH₂)₆-
 (hexylene), -(CH₂)₇- (heptylene), -(CH₂)₈- (octylene), -(CH₂)₉- (nonylene), and
 20 -(CH₂)₁₀- (decylene).

In one embodiment, the alkylene group is -(CH₂)_n- where n is an integer from 3 to 10.

- In one embodiment, the alkylene group is -(CH₂)_n- where n is an integer from 4 to
 25 10.

In one embodiment, the alkylene group is -(CH₂)_n- where n is an integer from 2 to 8.

In one embodiment, the alkylene group is -(CH₂)_n- where n is an integer from 3 to 8.

- 30 In one embodiment, the alkylene group is -(CH₂)_n- where n is an integer from 4 to 8.

- 21 -

In one embodiment, the alkylene group is $-(CH_2)_n-$ where n is an integer from 2 to 7.

In one embodiment, the alkylene group is $-(CH_2)_n-$ where n is an integer from 3 to 7.

5 In one embodiment, the alkylene group is $-(CH_2)_n-$ where n is an integer from 4 to 7.

In one embodiment, the alkylene group is $-(CH_2)_n-$ where n is an integer from 2 to 6.

10 In one embodiment, the alkylene group is $-(CH_2)_n-$ where n is an integer from 3 to 6.

In one embodiment, the alkylene group is $-(CH_2)_n-$ where n is an integer from 4 to 6.

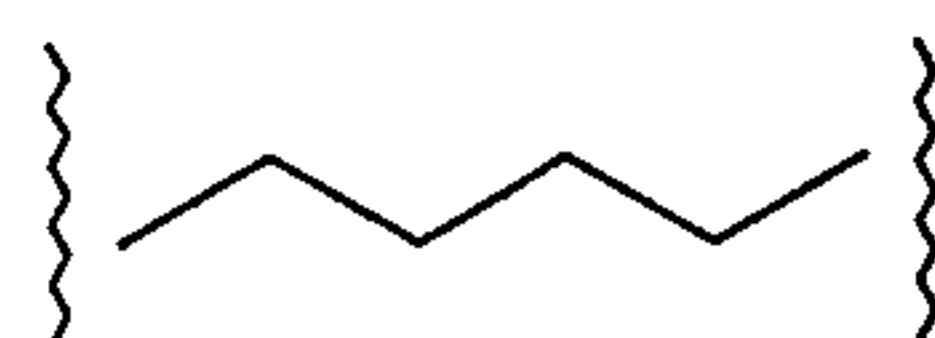
In one embodiment, the alkylene group is $-(CH_2)_3-$.

In one embodiment, the alkylene group is $-(CH_2)_4-$.

15 In one embodiment, the alkylene group is $-(CH_2)_5-$.

In one embodiment, the alkylene group is $-(CH_2)_6-$.

In one especially preferred embodiment, the alkylene group is $-(CH_2)_4-$:



20

In one embodiment, the alkylene group is substituted, for example, with one or more substituents selected from: halogen, hydroxy, ether (e.g., C_{1-7} alkoxy), amino, and amido.

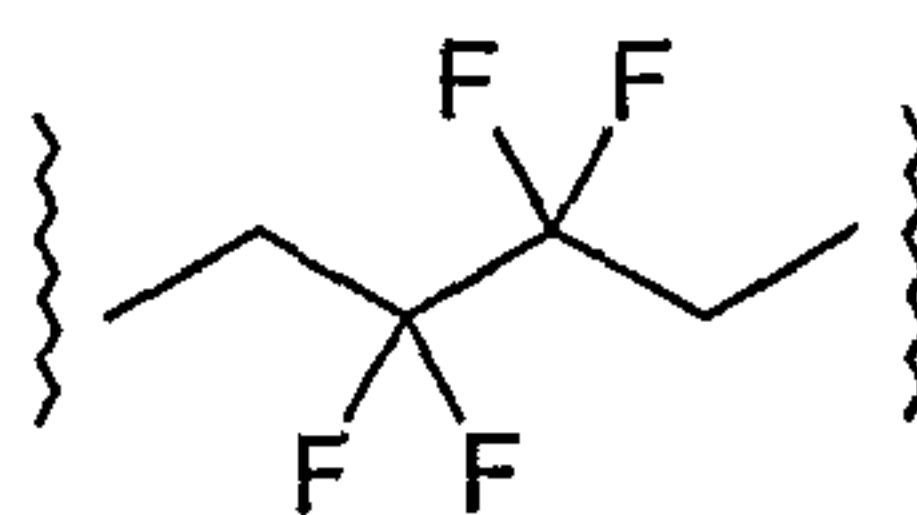
25 In one embodiment, the alkylene group is substituted, for example, with one or more substituents selected from: $-F$, $-Cl$, $-Br$, and $-I$.

In one embodiment, the alkylene group is substituted, for example, with one or more $-F$ groups.

30

In one embodiment, the alkylene group is:

- 22 -



The Hydroxy Groups, -OH, of the Alkane Diol

- 5 The hydroxy groups, -OH, of the alkane diol may be primary, secondary, or tertiary.

In one embodiment, the hydroxy groups are primary or secondary.

- 10 In one embodiment, at least one of the hydroxy groups is a primary hydroxy group.

In one embodiment, each of the hydroxy groups is a primary hydroxy group.

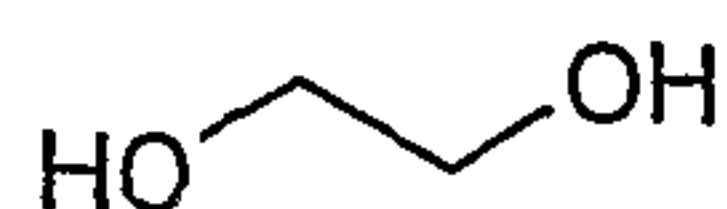
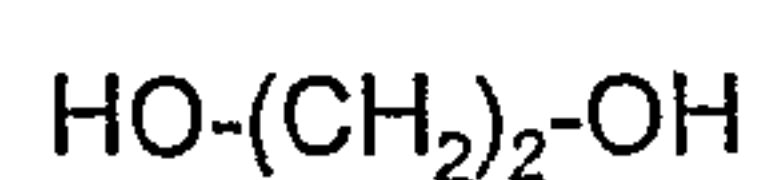
- 15 In one embodiment, the hydroxy groups are not geminal.

In one embodiment, the hydroxy groups are not geminal, and are not vicinal.

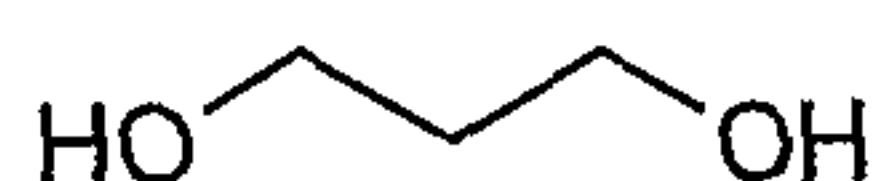
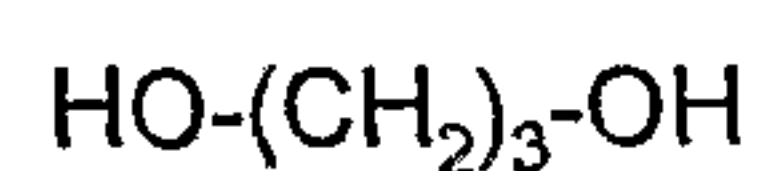
Some Preferred Alkane Diols

20

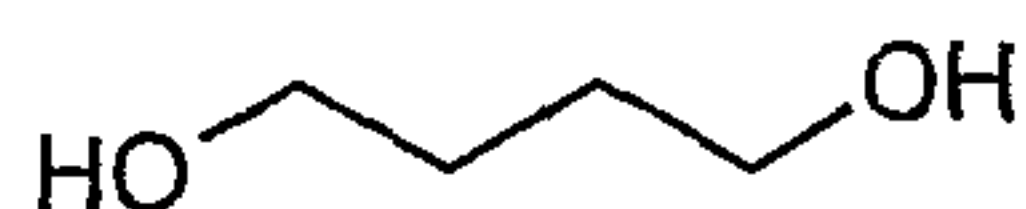
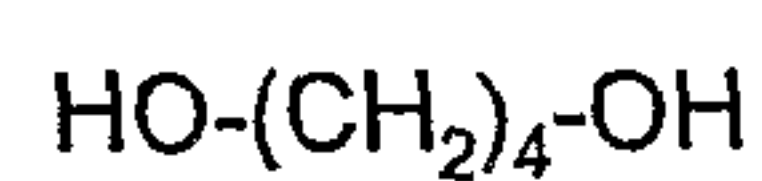
In one embodiment, the alkane diol has the formula $\text{HO}-(\text{CH}_2)_n-\text{OH}$, where n is an integer from 2 to 10.



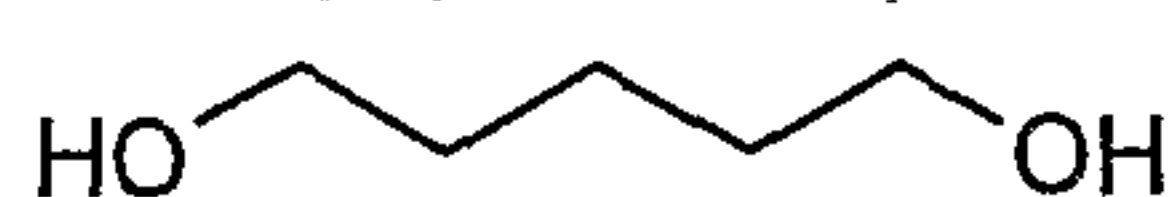
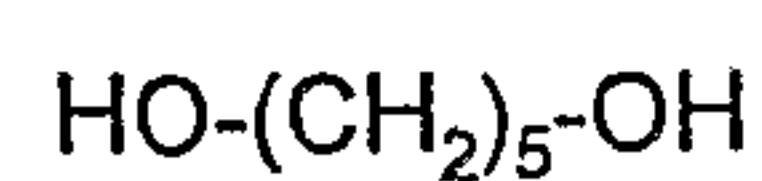
1,2-ethanediol



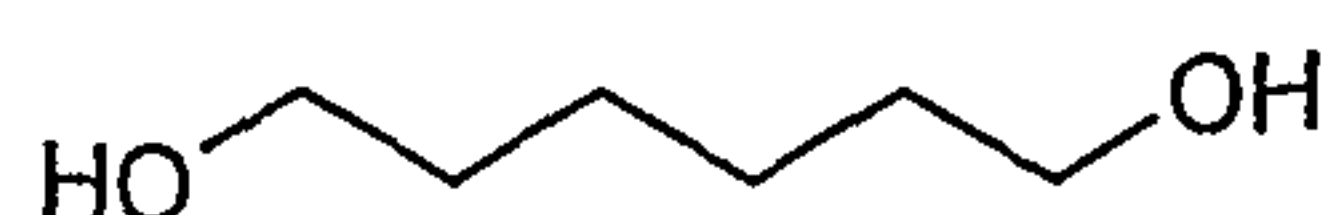
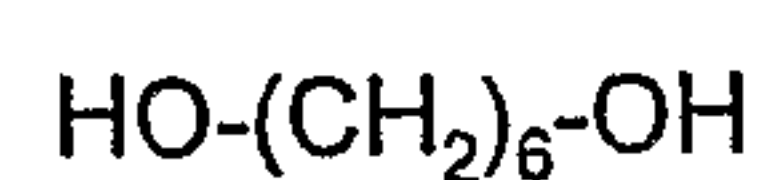
1,3-propanediol



1,4-butanediol

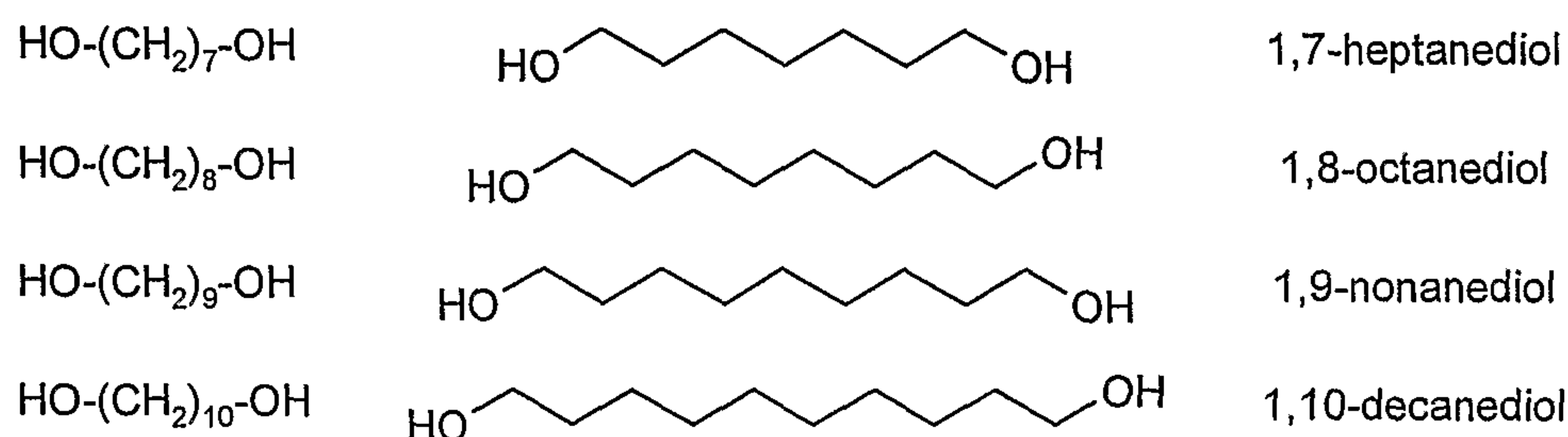


1,5-pentanediol



1,6-hexanediol

- 23 -



In one embodiment, the alkane diol is 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, or 1,6-hexanediol.

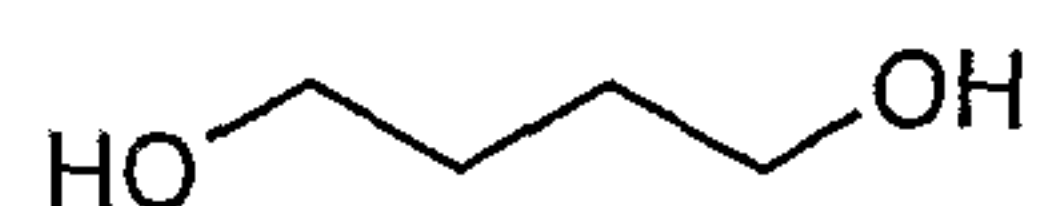
5

In one embodiment, the alkane diol is 1,4-butanediol, 1,5-pentanediol, or 1,6-hexanediol.

In one embodiment, the alkane diol is 1,4-butanediol or 1,6-hexanediol.

10

In one especially preferred embodiment, the alkane diol is 1,4-butanediol:



Hydroxy Protecting Groups

15

Without wishing to be bound by any particular theory, it is believed that the hydroxy protecting group (or, if there are two such groups, one of them, or each of them) additionally conveys one or more advantageous properties (e.g., solubility, lipophilicity, targeting) to the resulting compound.

20

For example, the compound is preferably sufficiently soluble in the relevant media (e.g., water, culture media, *in vivo*) so that, for example, its beneficial therapeutic properties may be realised. Thus, in one embodiment, the hydroxy protecting group (or, if there are two such groups, one of them, or each of them) is selected so that the resulting compound has acceptable solubility properties.

25

Similarly, the compound is preferably readily able to cross cell membranes, and more specifically, the membranes of cells for which treatment is sought. Thus, in

- 24 -

one embodiment, the hydroxy protecting group (or, if there are two such groups, one of them, or each of them) is selected to be, or to comprise, a hydrophobic group, so that the resulting compound is better able to cross cell membranes.

5

Also, in one embodiment, the compound is targeted to bone and/or the bone environment. Thus, in one embodiment, the hydroxy protecting group (or, if there are two such groups, one of them, or each of them) is selected to be, or to comprise, a bone-targeting group.

10

The term "bone-targeting group," as used herein, pertains to a chemical moiety which has an affinity for bone and/or the bone environment, and which, when attached to compound, acts as a targeting moiety, and so aids in the delivery of that compound to the bone and/or bone environment. Examples of such bone-targeting groups include phosphonic acid groups, and salts, esters, and amides thereof, as discussed below.

15

Esters as Hydroxy Protecting Groups

20 In one embodiment, the hydroxy protecting group (or, if there are two such groups, one of them, or each of them) is an acyl group (i.e., $R^A-C(=O)-$), and the protected hydroxy group is an ester group (i.e., $R^A-C(=O)-O-$). More specifically, the hydroxy group is protected as an ester group.

25 In one embodiment, R^2 is not -H, and each of the hydroxy protecting groups are acyl groups ($R^{A1}-C(=O)-$ and $R^{A2}-C(=O)-$, respectively), which may be the same or different, and the compound has the following formula (also referred to herein as a "di-ester" of the alkane diol):



30 In one embodiment, R^2 is not -H, and R^{A1} and R^{A2} are the same.

- 25 -

In one embodiment, R^2 is not -H, and R^{A1} and R^{A2} are different.

In one embodiment, R^2 is -H, the hydroxy protecting group is an acyl group (i.e., R^{A1} -C(=O)-), and the compound has the following formula (also referred to
5 herein as a "mono-ester" of the alkane diol):



Acyl Groups, R^{A1} -C(=O)- and R^{A2} -C(=O)-

In one embodiment, R^{A1} is independently a C_{1-7} alkyl group, a C_{3-20} heterocyclyl
10 group, or a C_{5-20} aryl group, and is optionally substituted; and, R^{A2} , if present, is independently, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, and is optionally substituted.

In one especially preferred embodiment, R^{A1} is independently a C_{3-20} heterocyclyl
15 group, or a C_{5-20} aryl group, and is optionally substituted

In one especially preferred embodiment, R^{A1} is independently an optionally substituted C_{5-20} aryl group, as described below.

20 As discussed above, one or both of the moieties R^{A1} and R^{A2} may be selected so that the resulting compound (a) has improved solubility, (b) is better able to cross cell membranes, (c) is, or comprises, a bone-targeting moiety; or a combination thereof

25 R^{A1} as Optionally Substituted Aryl

In one embodiment, R^{A1} (and optionally also R^{A2}) is independently an optionally substituted C_{5-20} aryl group.

- 26 -

In one embodiment, R^{A1} (and optionally also R^{A2}) is independently an optionally substituted phenyl, naphthyl, pyridyl, furanyl, thiofuranyl, indolyl, pyrrolyl, imidazolyl, naphthyl, quinoliny, benzimidazolyl, benzothiofuranyl, fluorenyl, acridinyl, or carbazolyl.

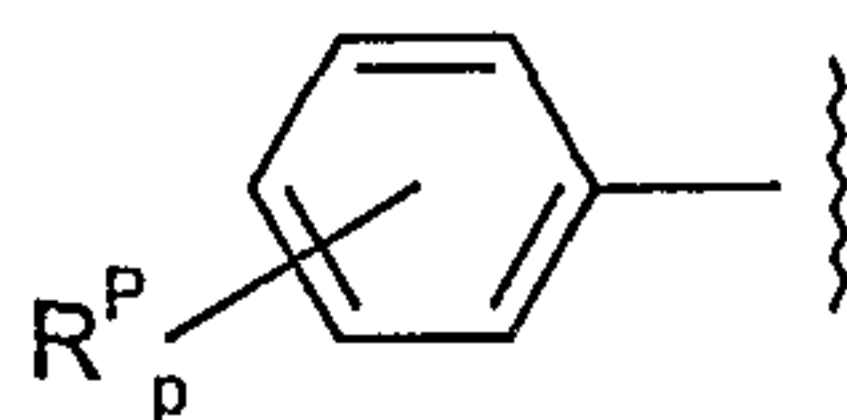
5

In one embodiment, R^{A1} (and optionally also R^{A2}) is independently an optionally substituted C_{5-6} aryl group.

10 In one embodiment, R^{A1} (and optionally also R^{A2}) is independently an optionally substituted phenyl, pyridyl, furanyl, thiofuranyl, indolyl, pyrrolyl, or imidazolyl.

R^{A1} as Optionally Substituted Phenyl

15 In one embodiment, R^{A1} (and optionally also R^{A2}) is independently an optionally substituted phenyl group of the following formula:



wherein each R^P is independently a phenyl substituent, and p is an integer from 0 to 5.

20 In one embodiment, p is an integer from 0 to 4.

In one embodiment, p is an integer from 0 to 3.

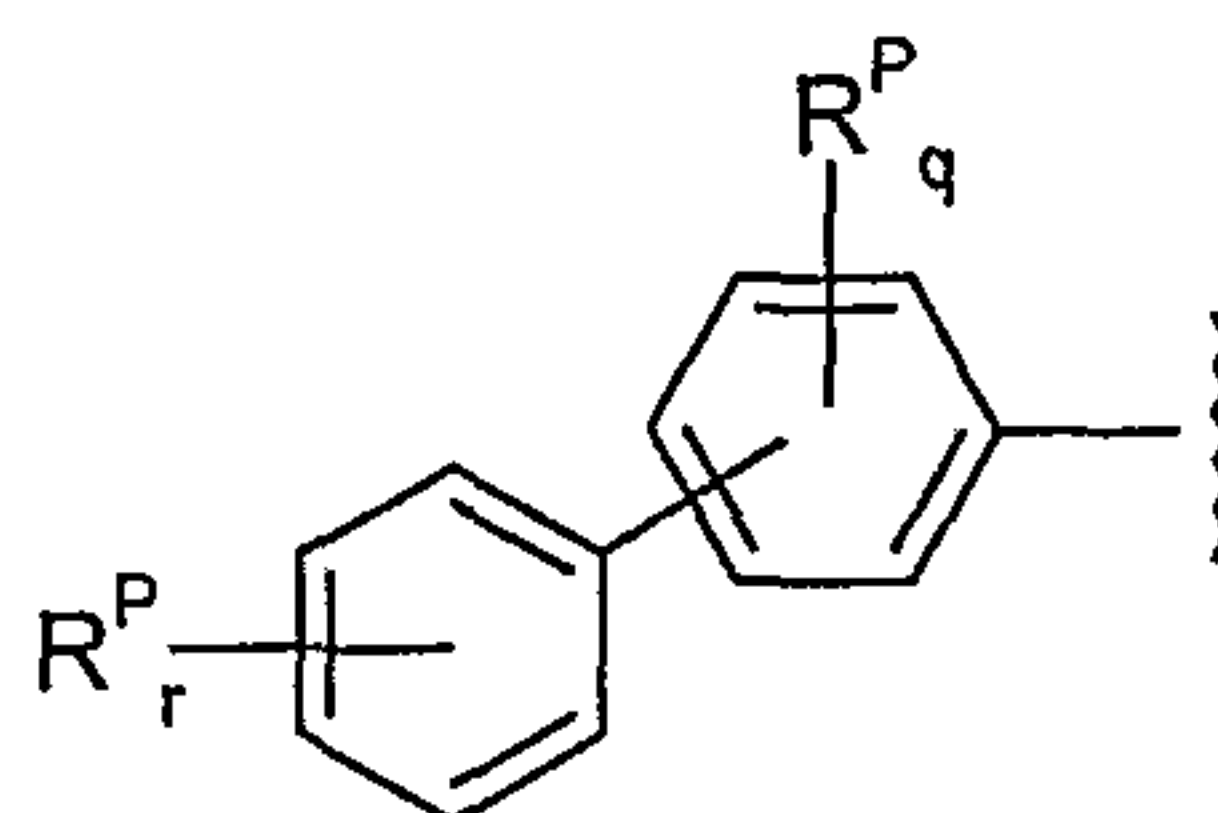
In one embodiment, p is an integer from 0 to 2.

In one embodiment, p is 0 or 1.

25 R^{A1} as Optionally Substituted Biphenyl

In one embodiment, R^{A1} (and optionally also R^{A2}) is independently an optionally substituted biphenyl group of the following formula:

- 27 -



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and r is an integer from 0 to 5.

In one embodiment, q is an integer from 0 to 3.

5 In one embodiment, q is an integer from 0 to 2.

In one embodiment, q is 0 or 1.

In one embodiment, q is 0.

In one embodiment, r is an integer from 0 to 4.

In one embodiment, r is an integer from 0 to 3.

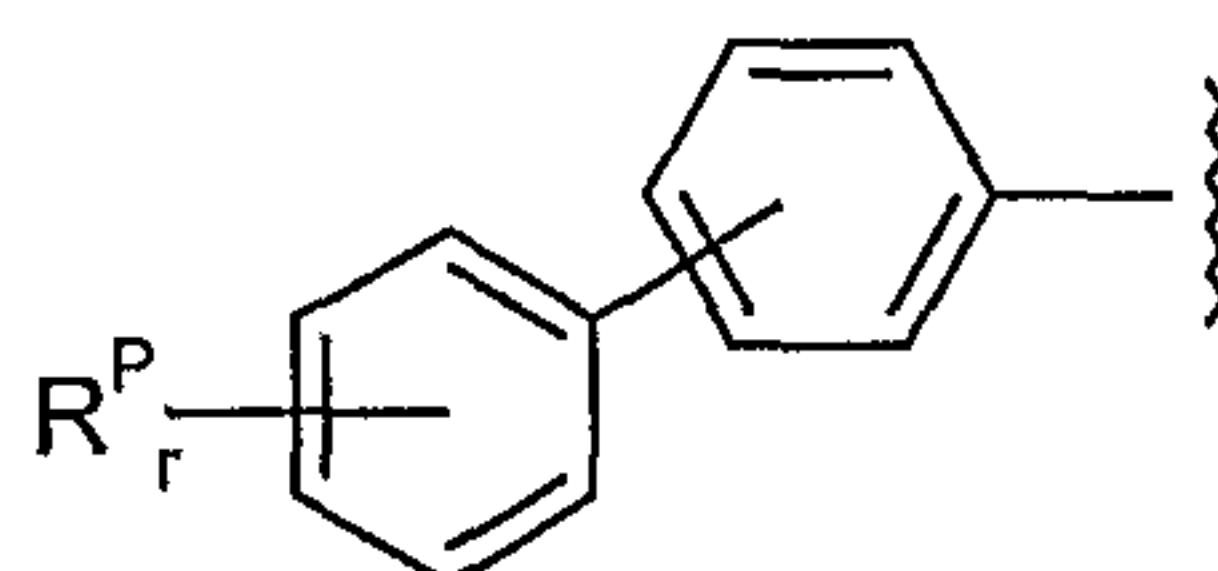
10 In one embodiment, r is an integer from 0 to 2.

In one embodiment, r is 0 or 1.

In one embodiment, r is 0.

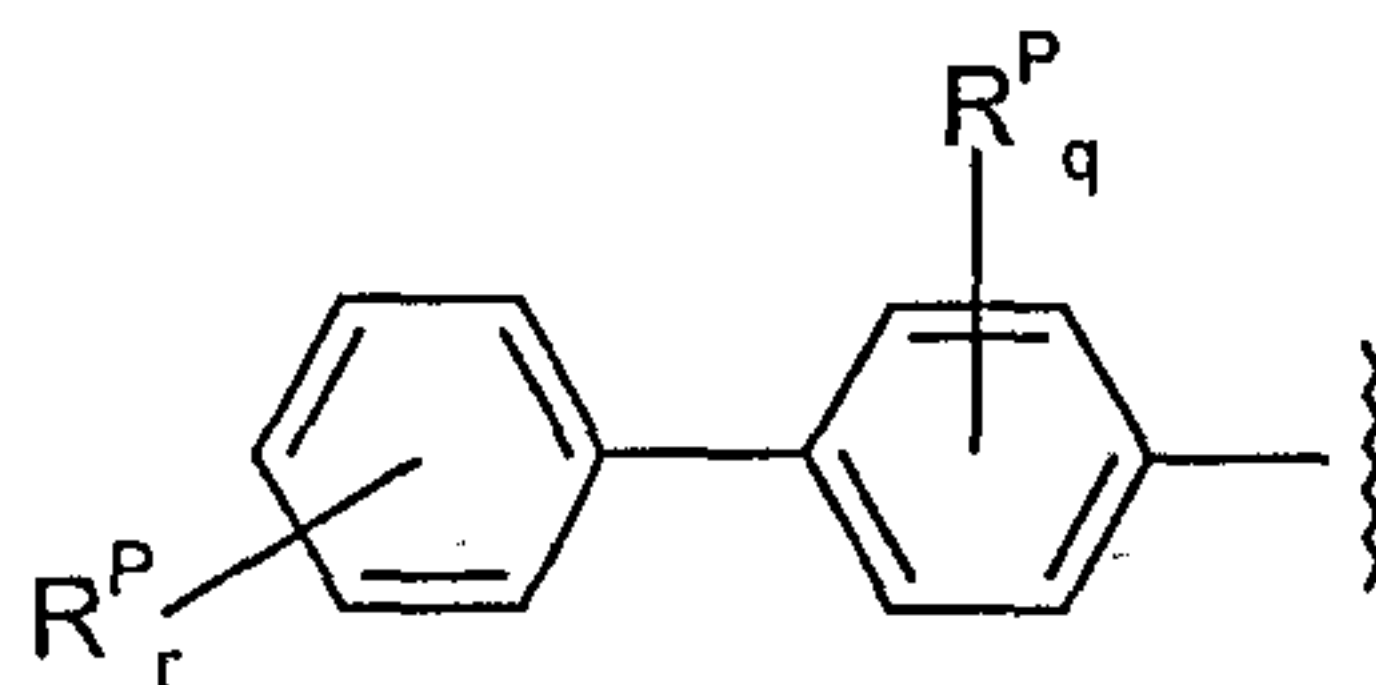
In one embodiment, q is 0, and R^{A1} (and optionally also R^{A2}) is an optionally substituted biphenyl group of the following formula:

15



R^{A1} as Optionally Substituted Biphenyl-4-yl

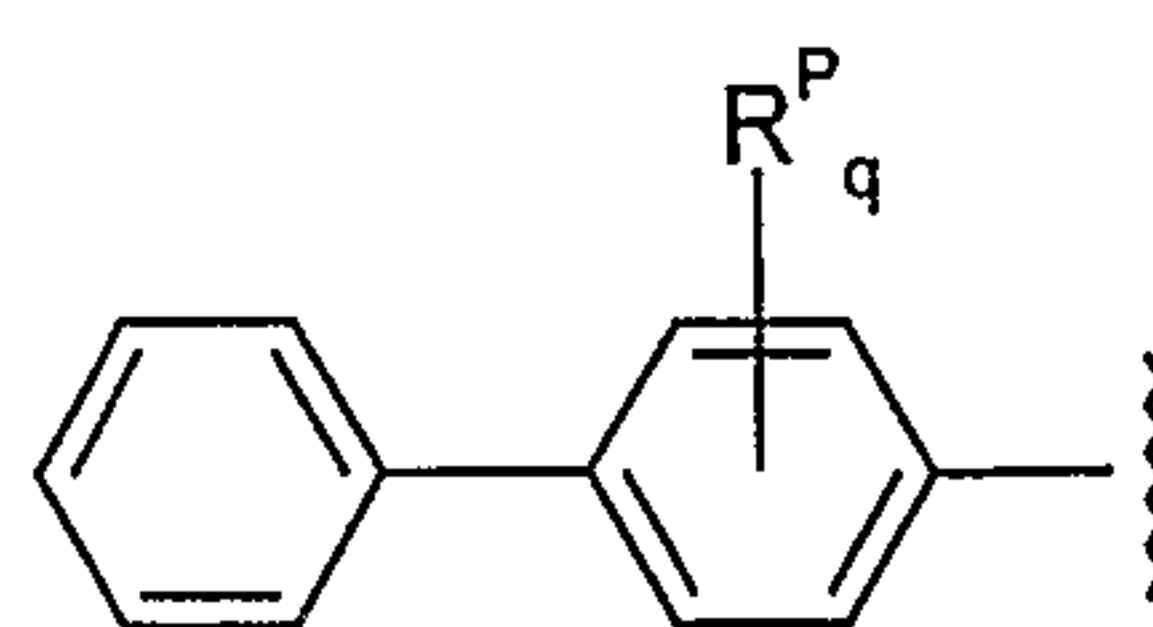
20 In one embodiment, R^{A1} (and optionally also R^{A2}) is an optionally substituted biphenyl-4-yl group of the following formula:



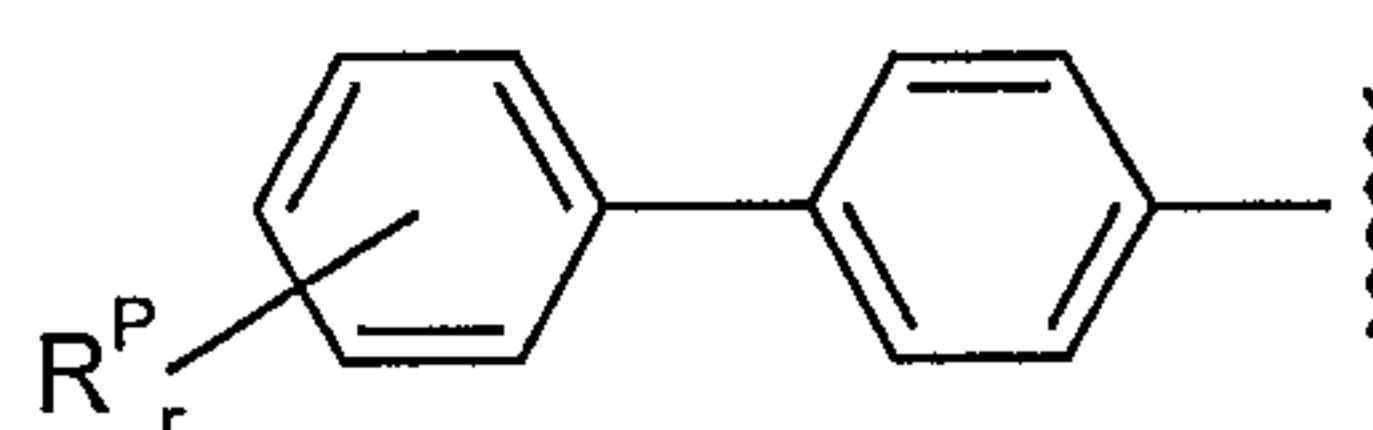
In one embodiment, R^{A1} (and optionally also R^{A2}) is an optionally substituted biphenyl-4-yl group of the following formula:

25

- 28 -



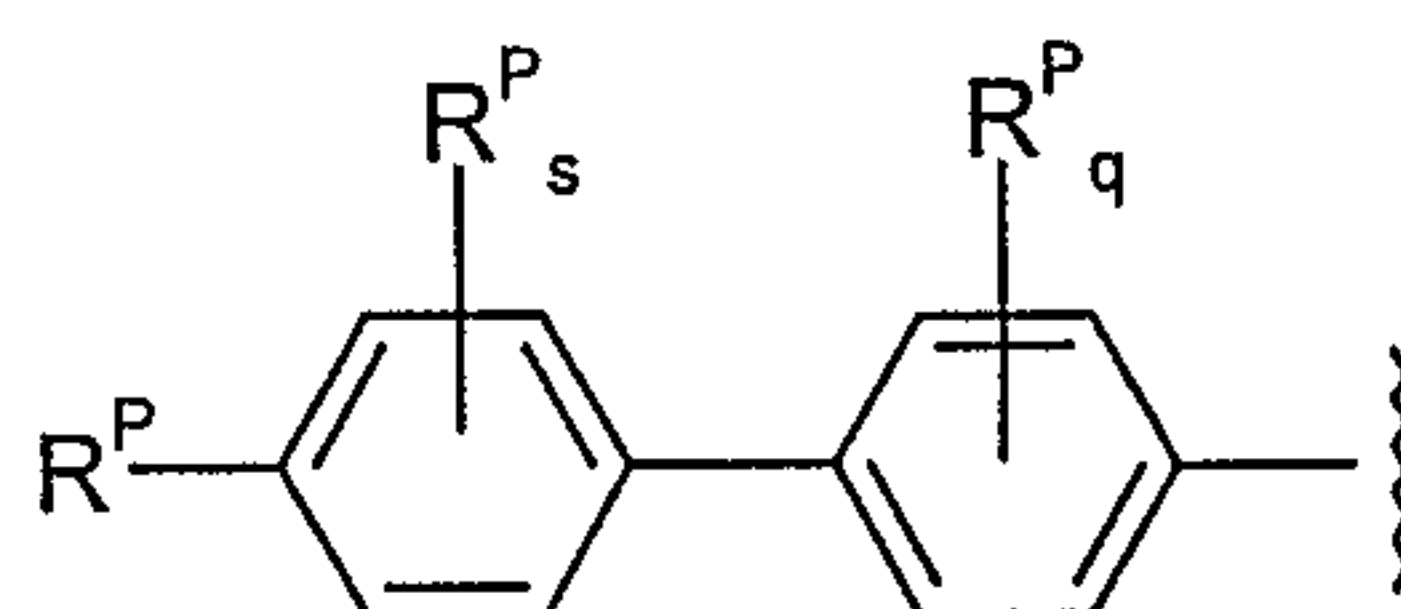
In one embodiment, R^{A1} (and optionally also R^{A2}) is an optionally substituted biphenyl-4-yl group of the following formula:



5

R^{A1} as 4'-Substituted Biphenyl-4-yl

10 In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



wherein s is an integer from 0 to 4.

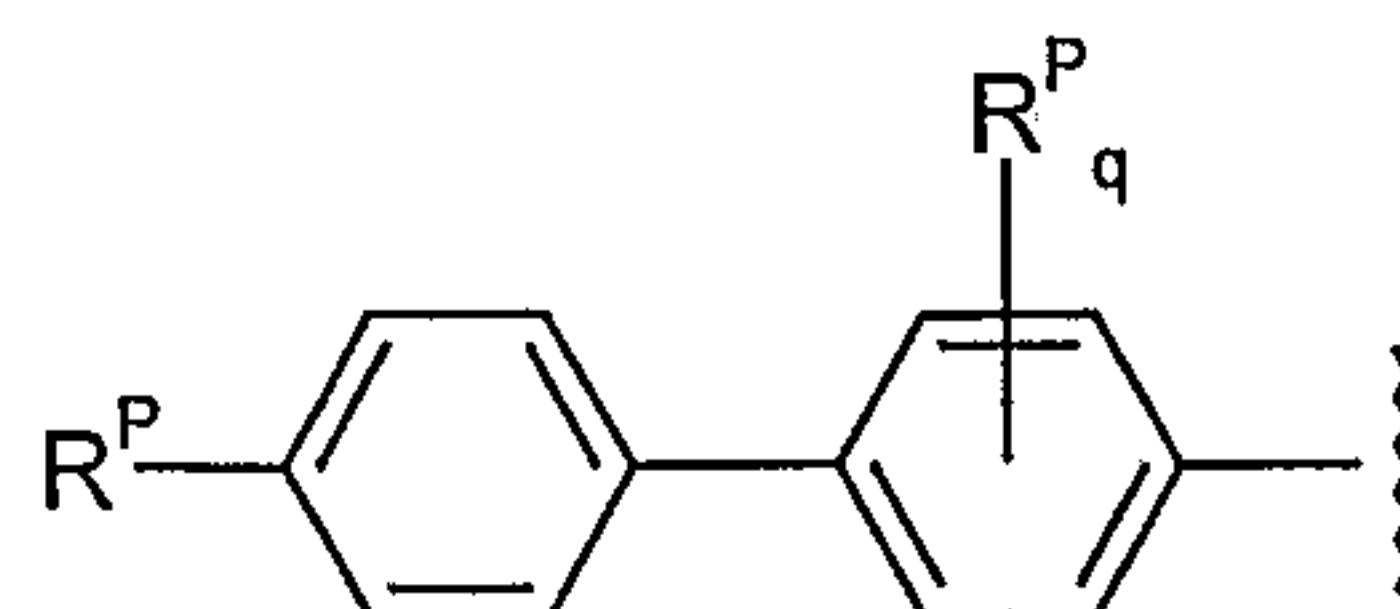
In one embodiment, s is an integer from 0 to 3.

In one embodiment, s is an integer from 0 to 2.

15 In one embodiment, s is 0 or 1.

In one embodiment, s is 0.

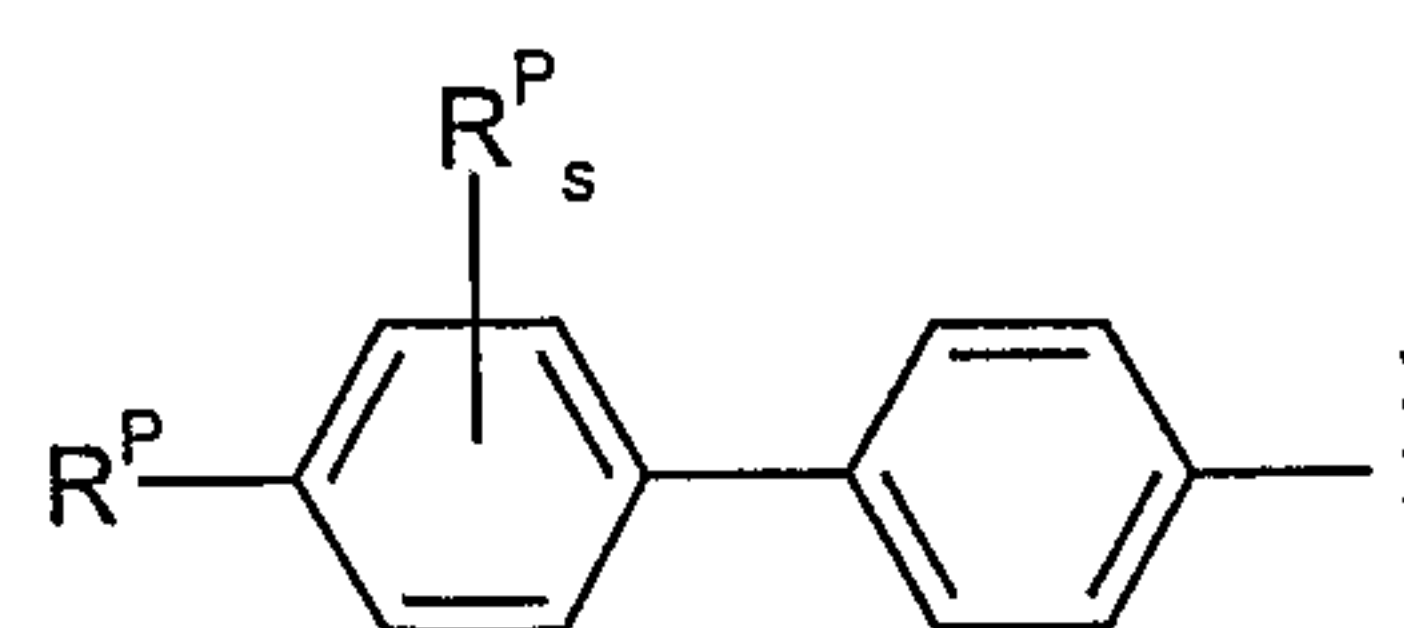
In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



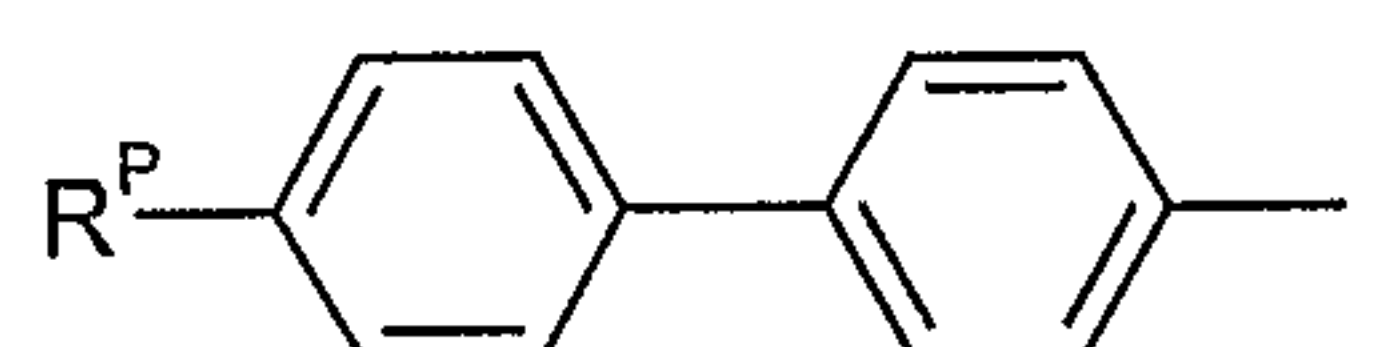
20

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

- 29 -



In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

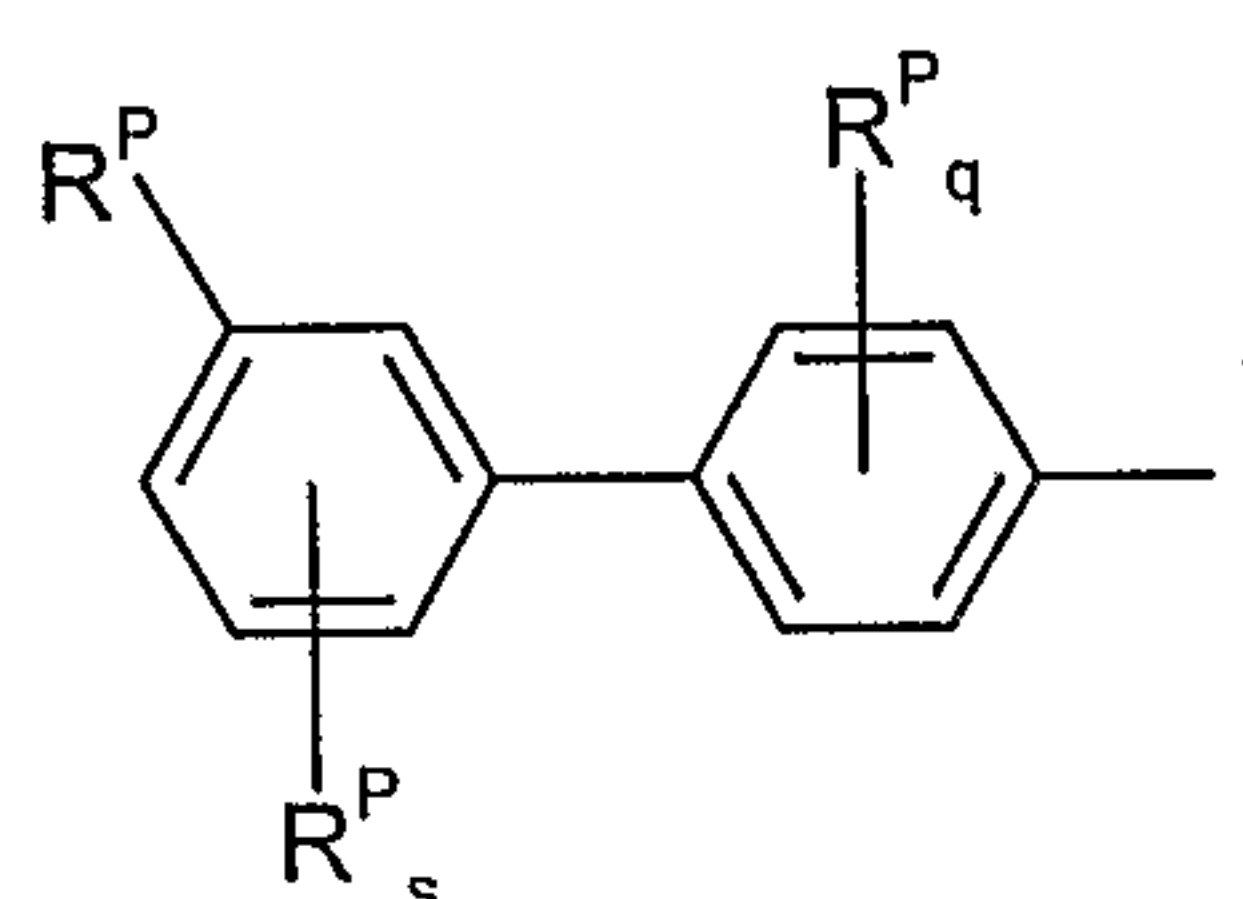


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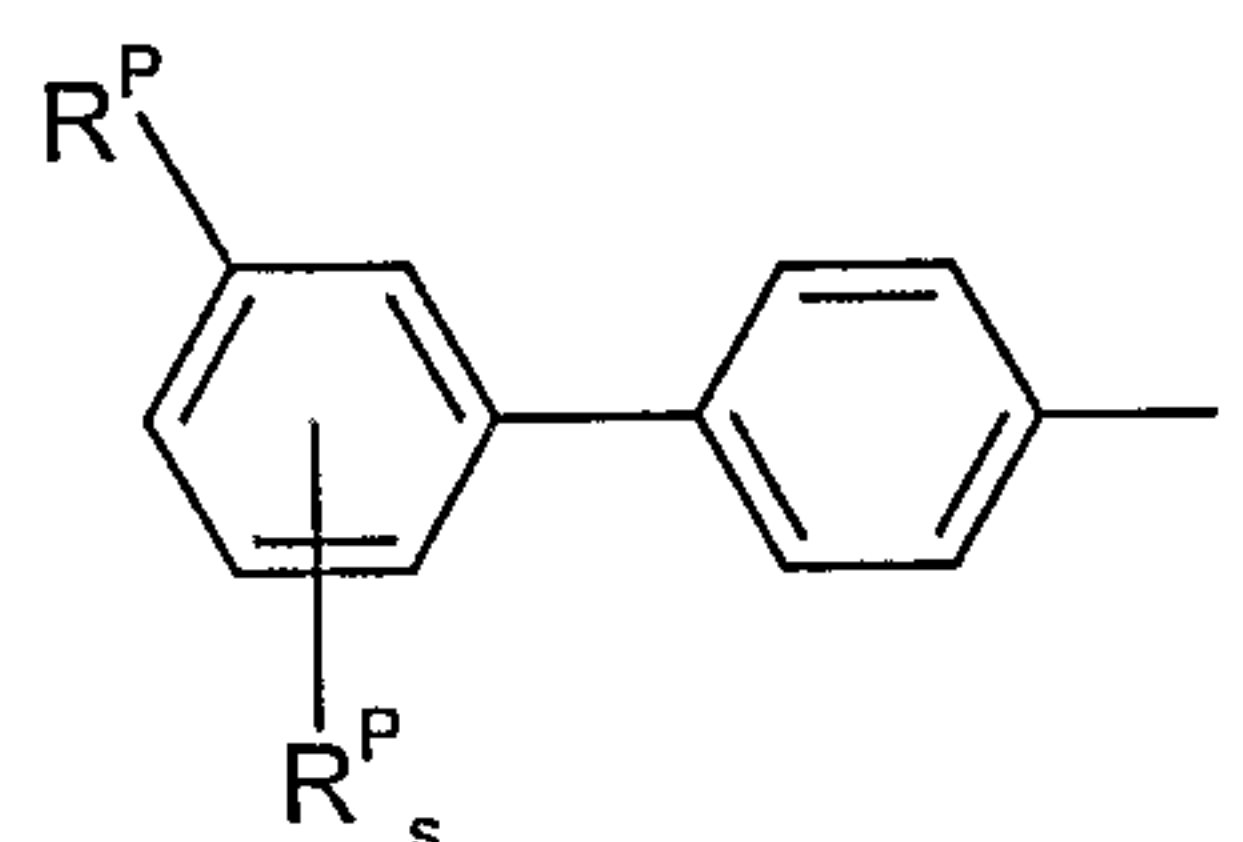
R^{A1} as 3'-Substituted Biphenyl-4-yl

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

10

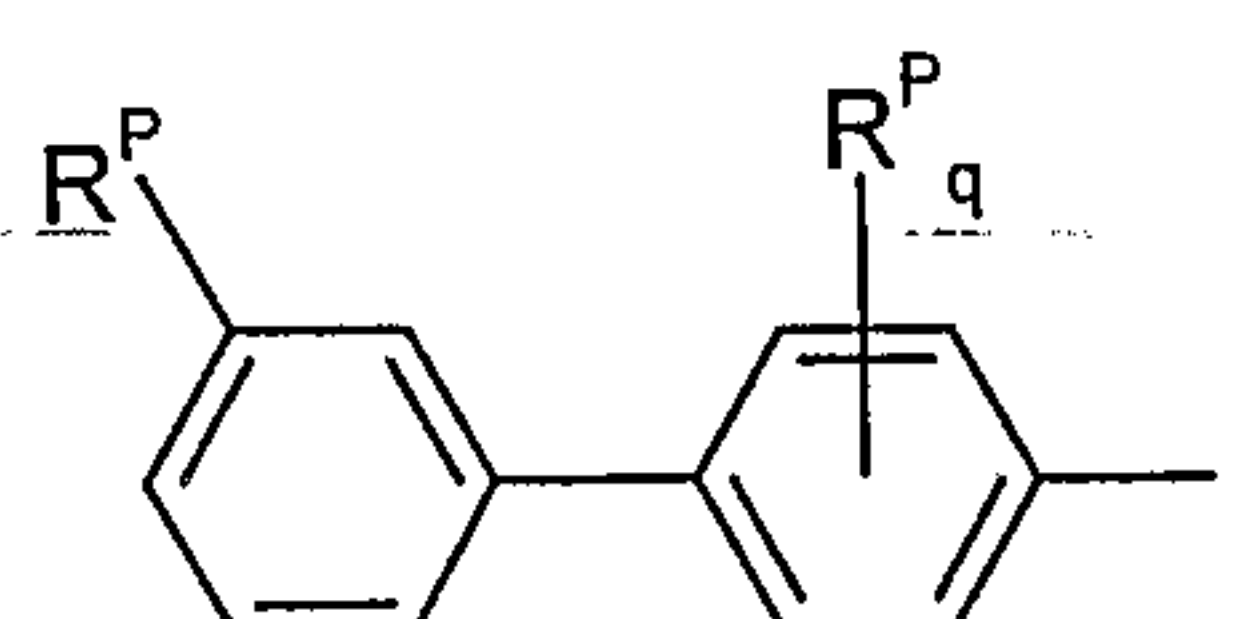


In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



15

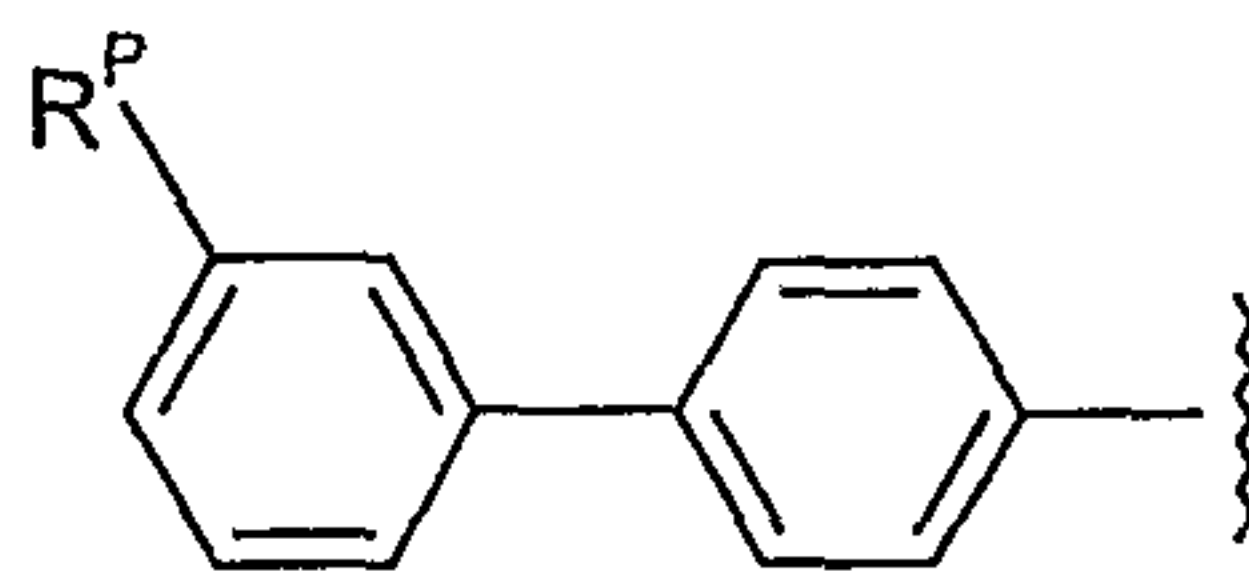
In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



20

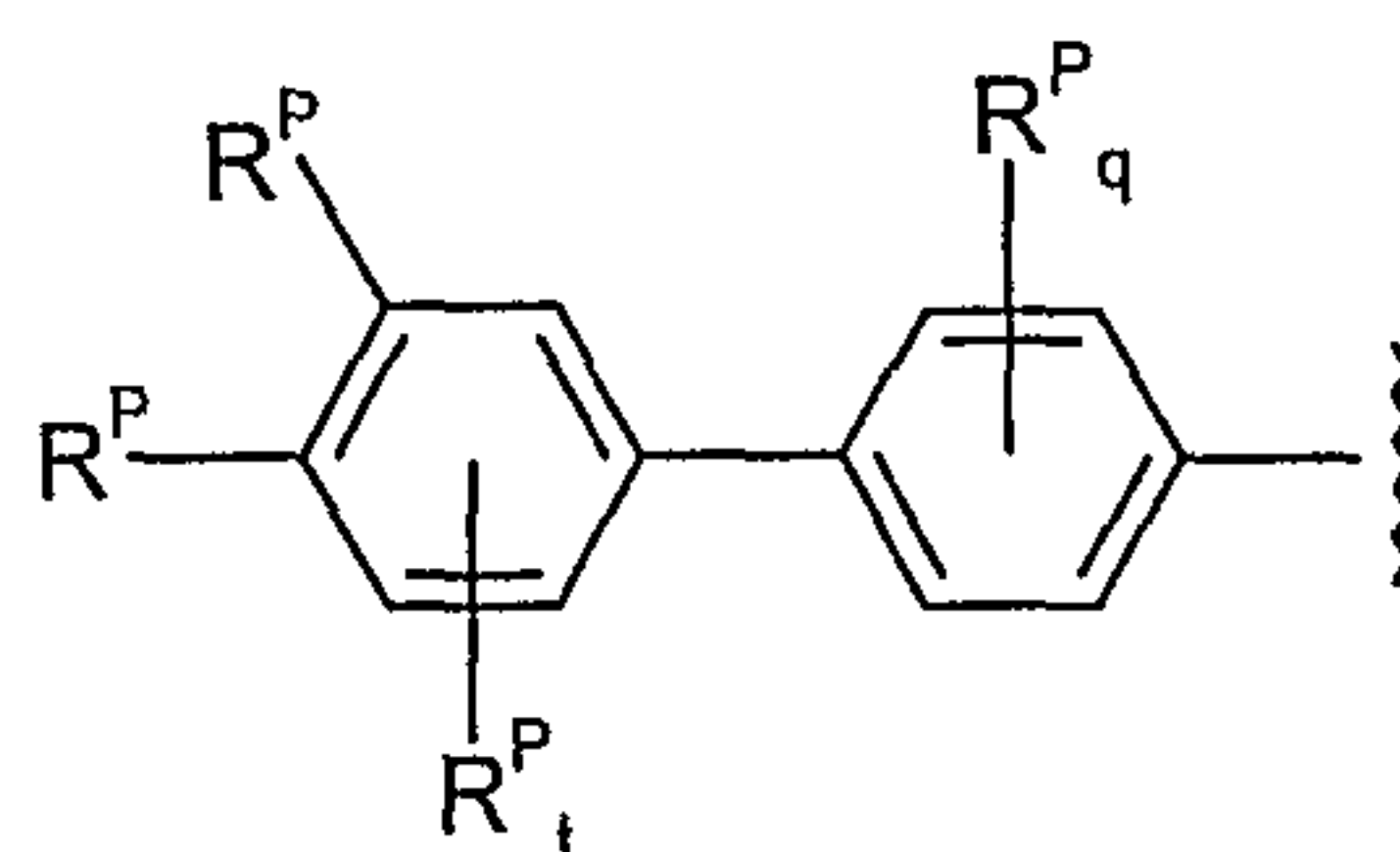
- 30 -

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



5 R^{A1} as 3',4'-Disubstituted Biphenyl-4-yl

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



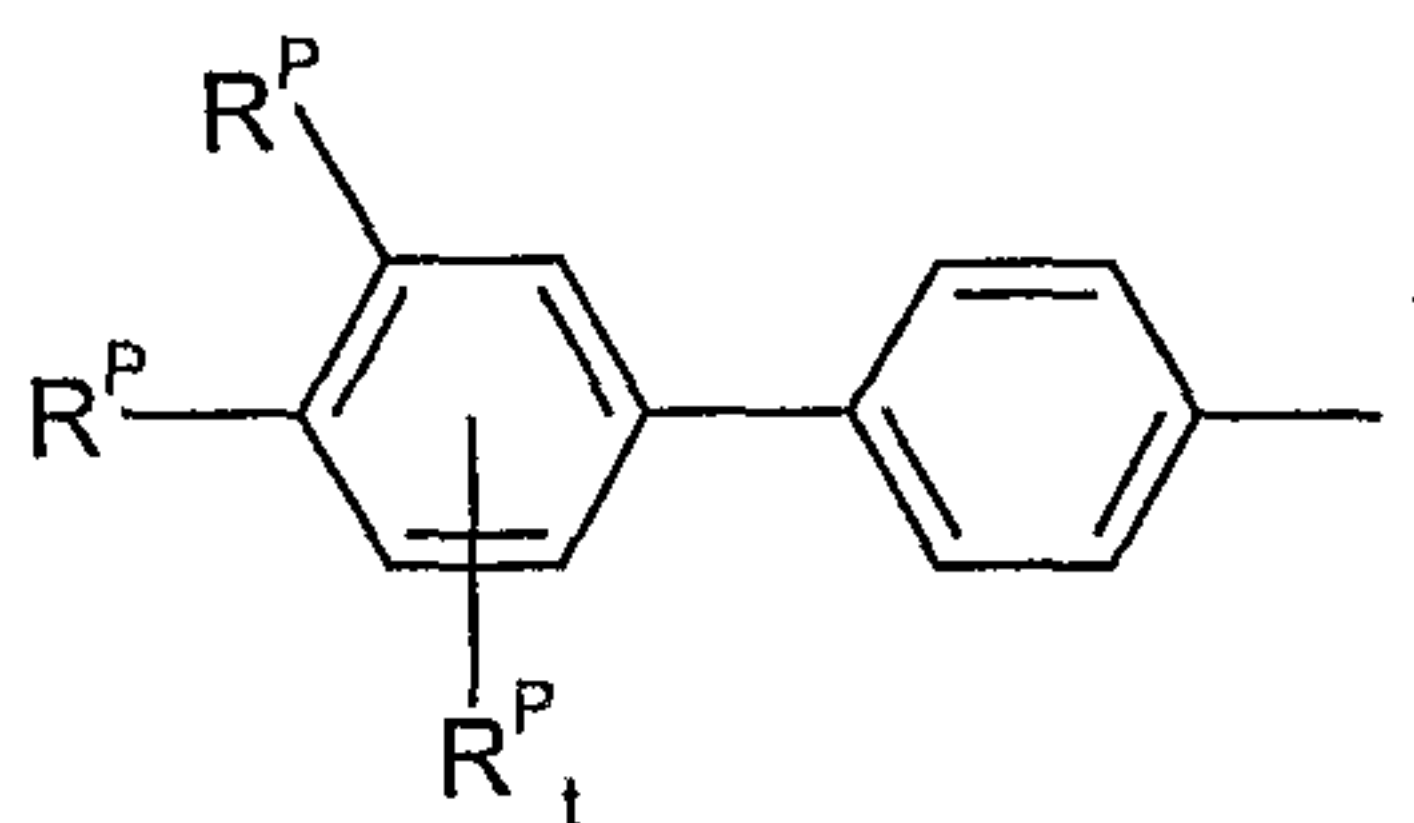
10 wherein t is an integer from 0 to 3.

In one embodiment, t is an integer from 0 to 2.

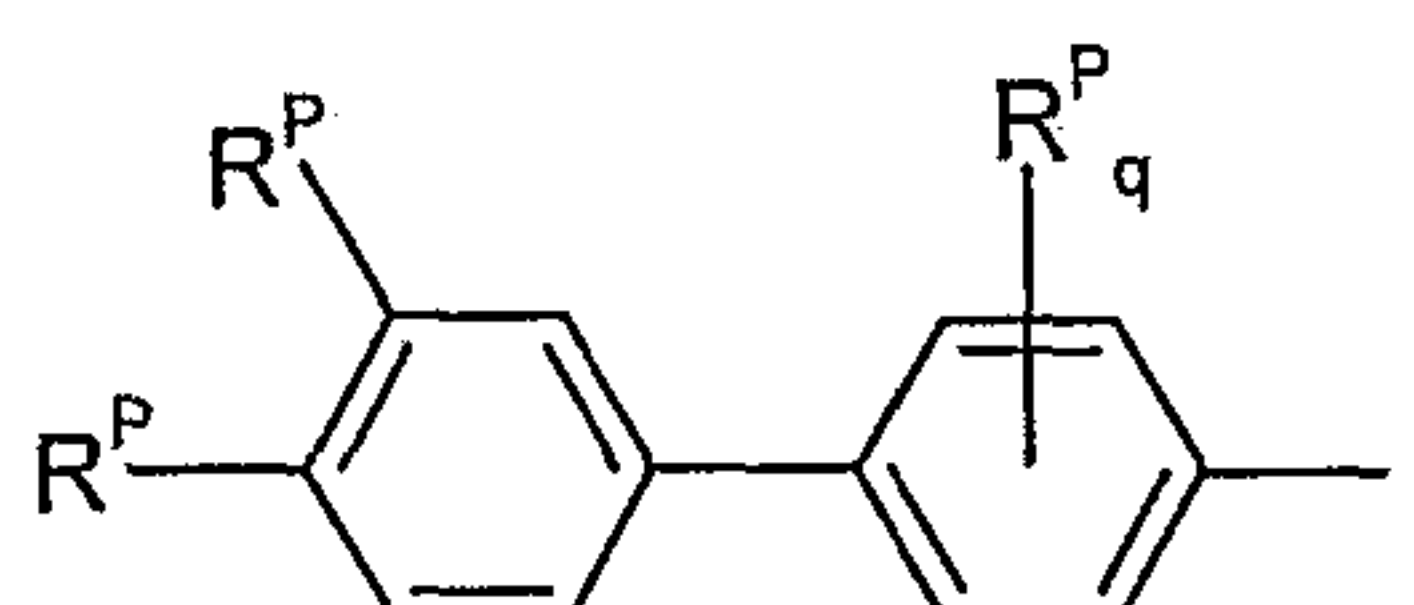
In one embodiment, t is 0 or 1.

In one embodiment, t is 0.

15 In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

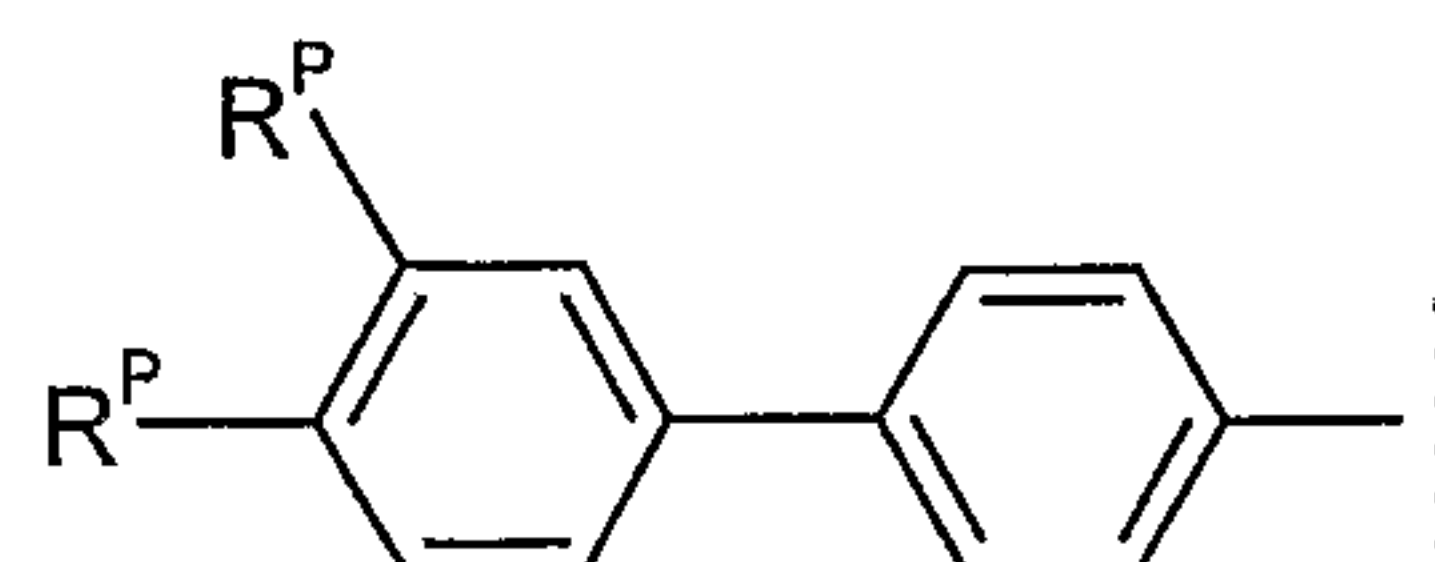


20 In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



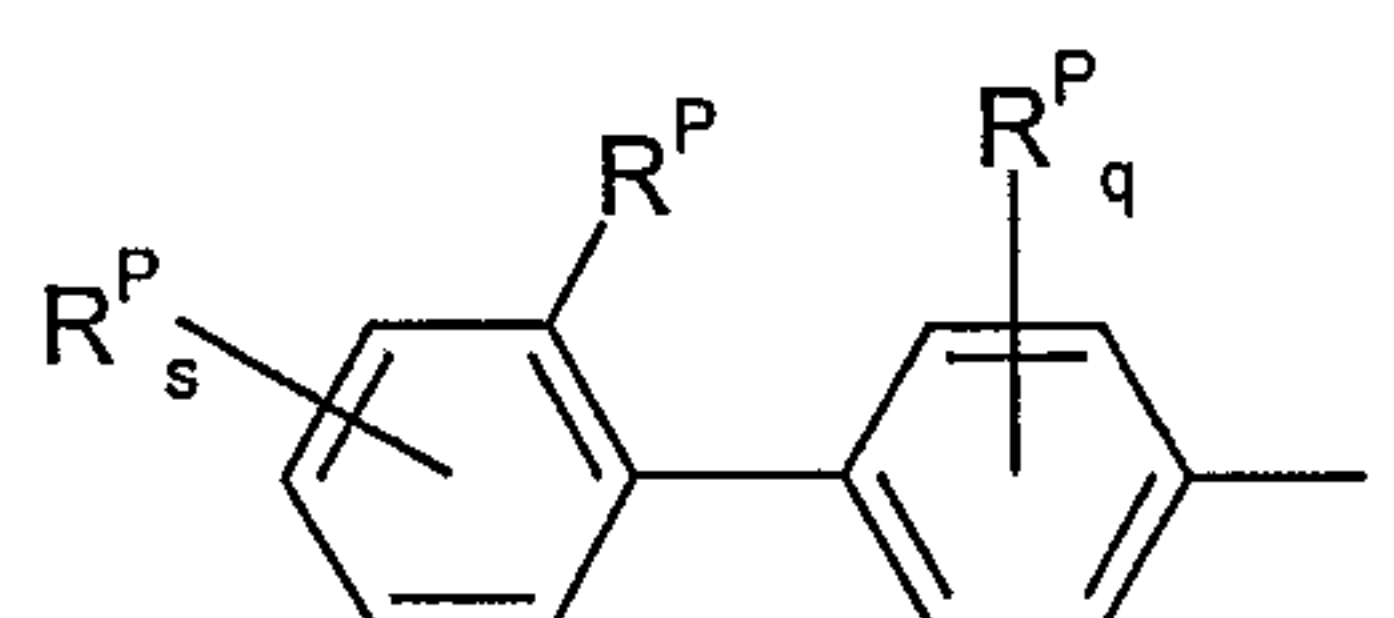
- 31 -

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



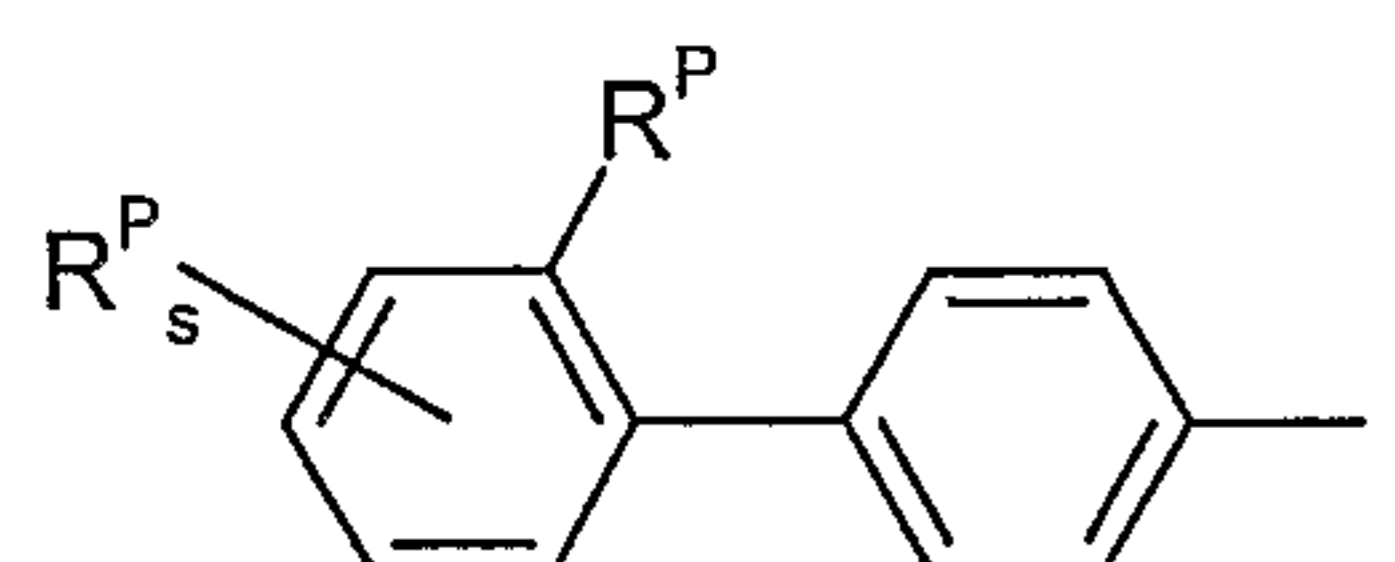
5 R^{A1} as 2'-Substituted Biphenyl-4-yl

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

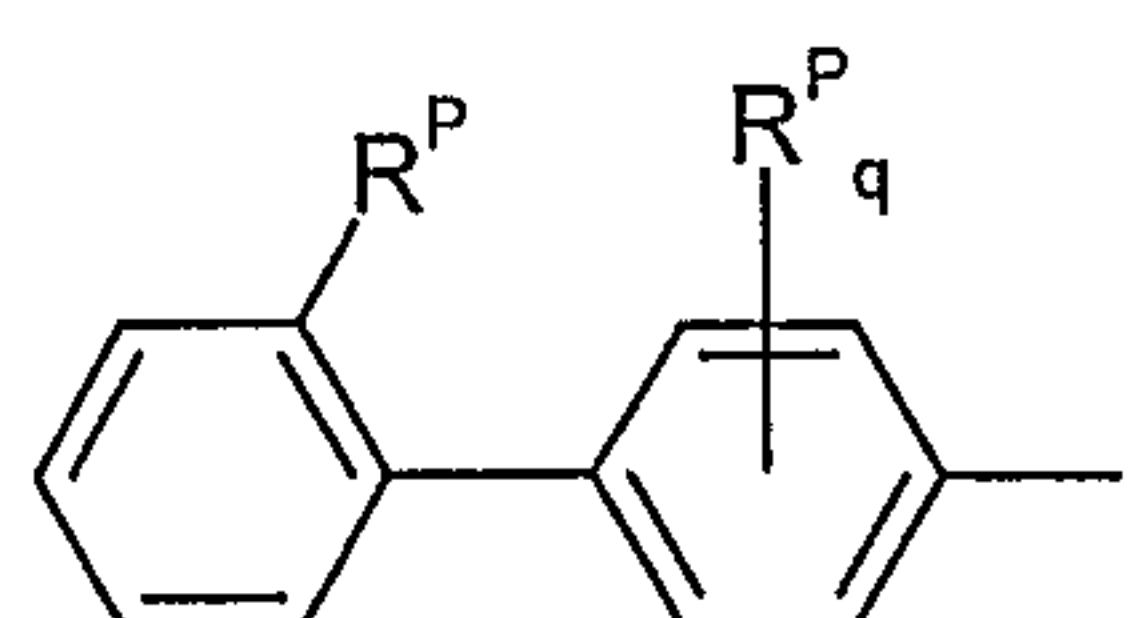


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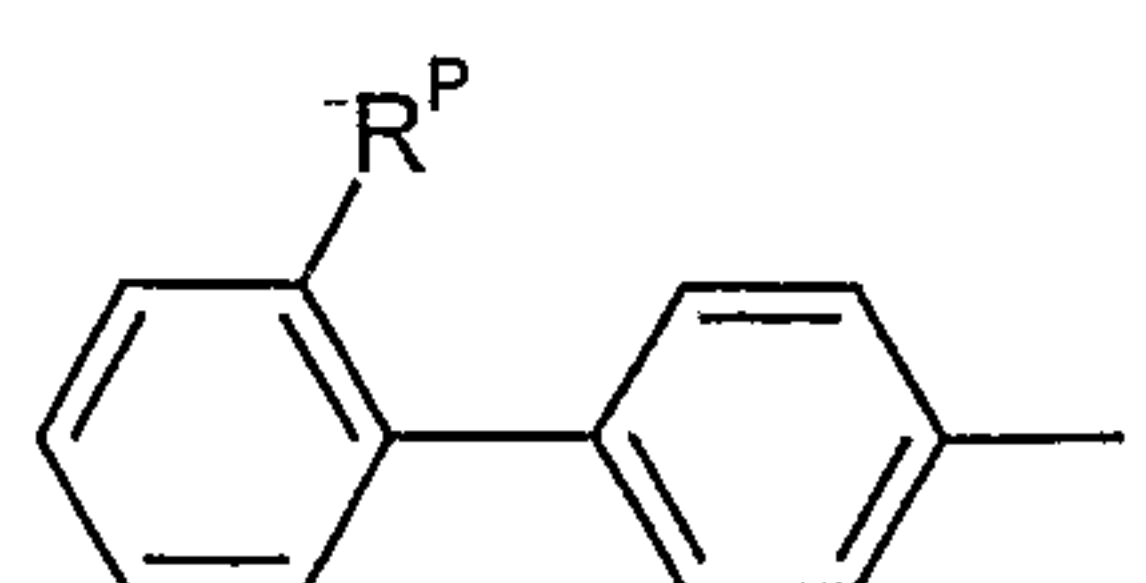
In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



15 In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



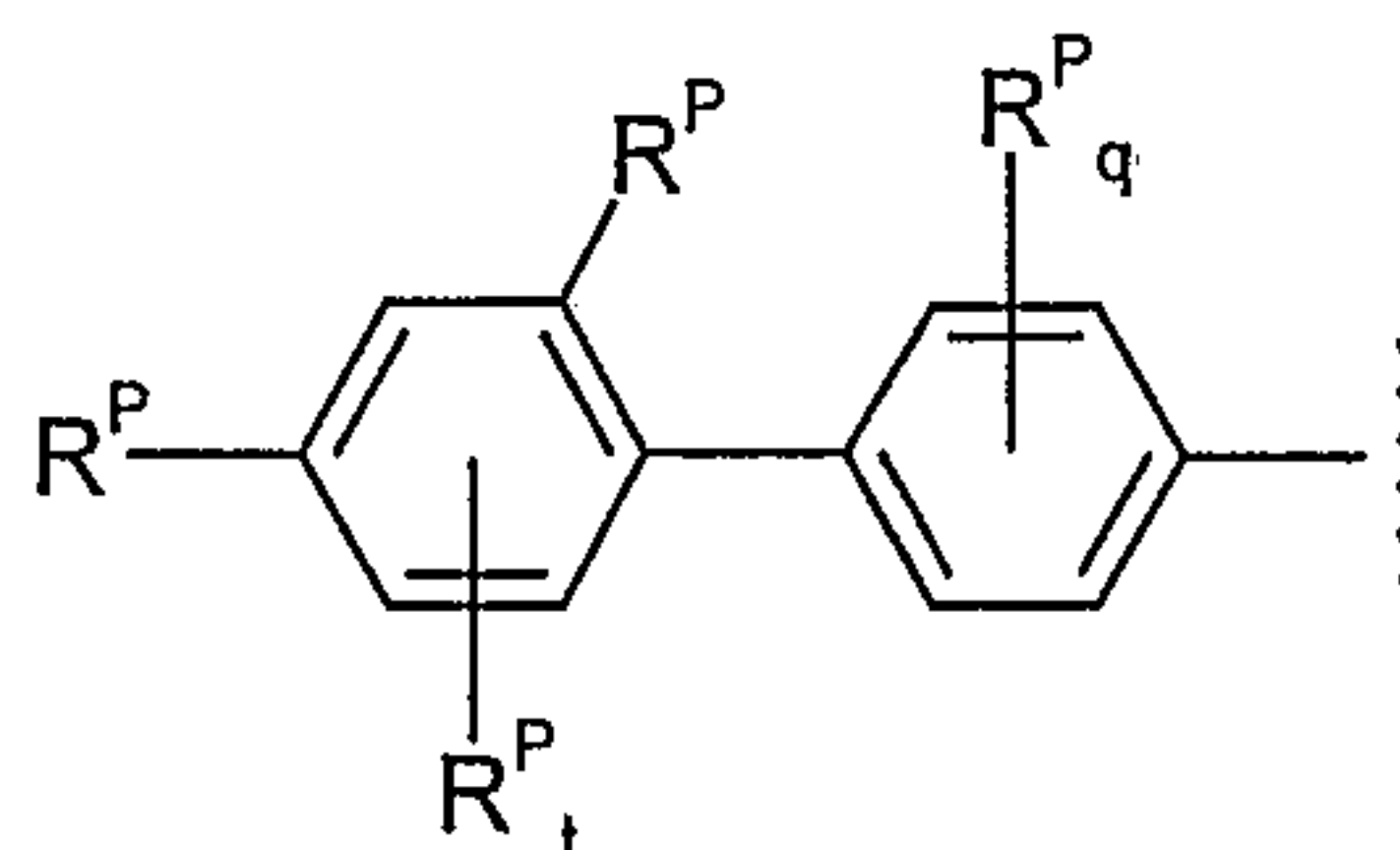
20 In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



- 32 -

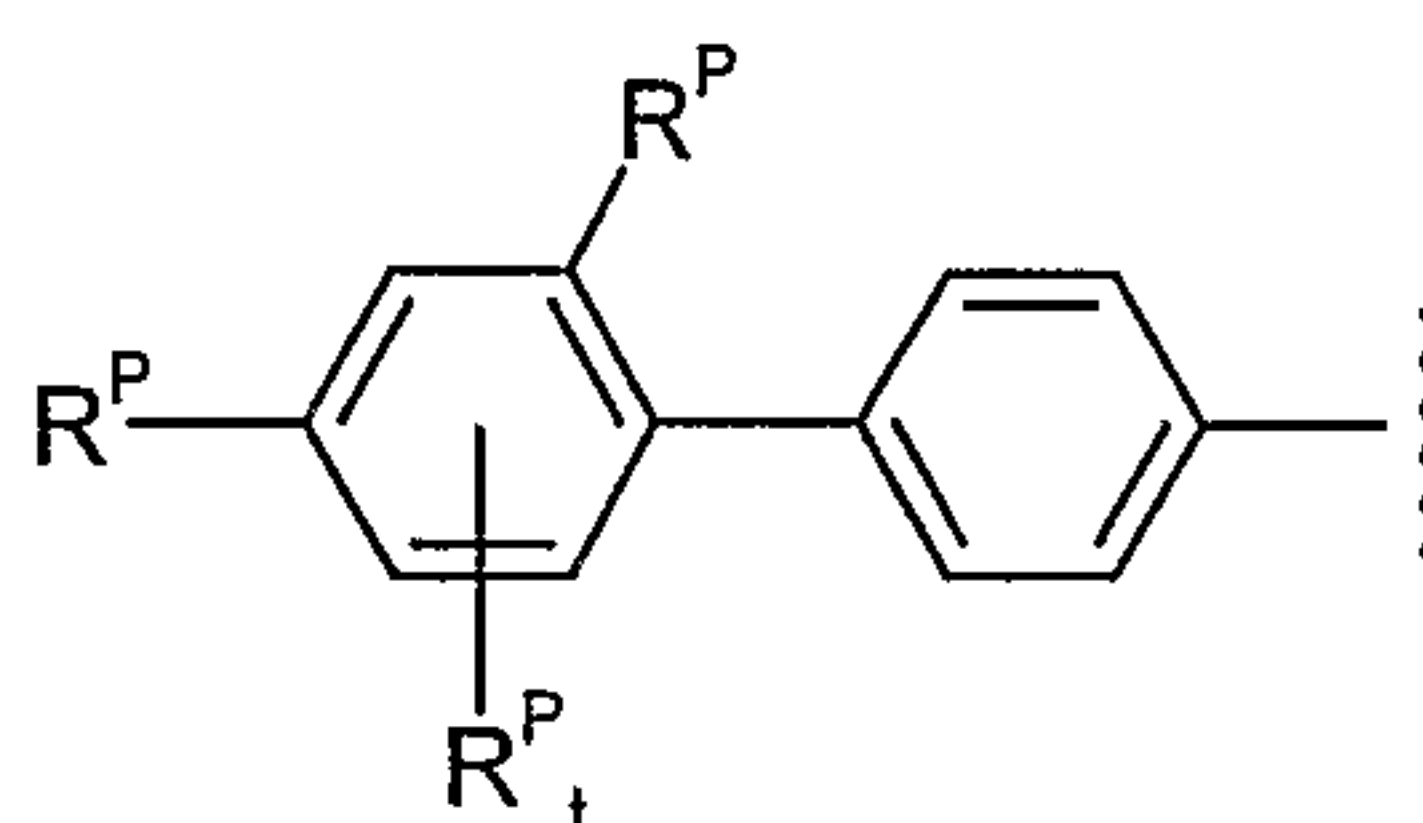
R^{A1} as 2',4'-Disubstituted Biphenyl-4-yl

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



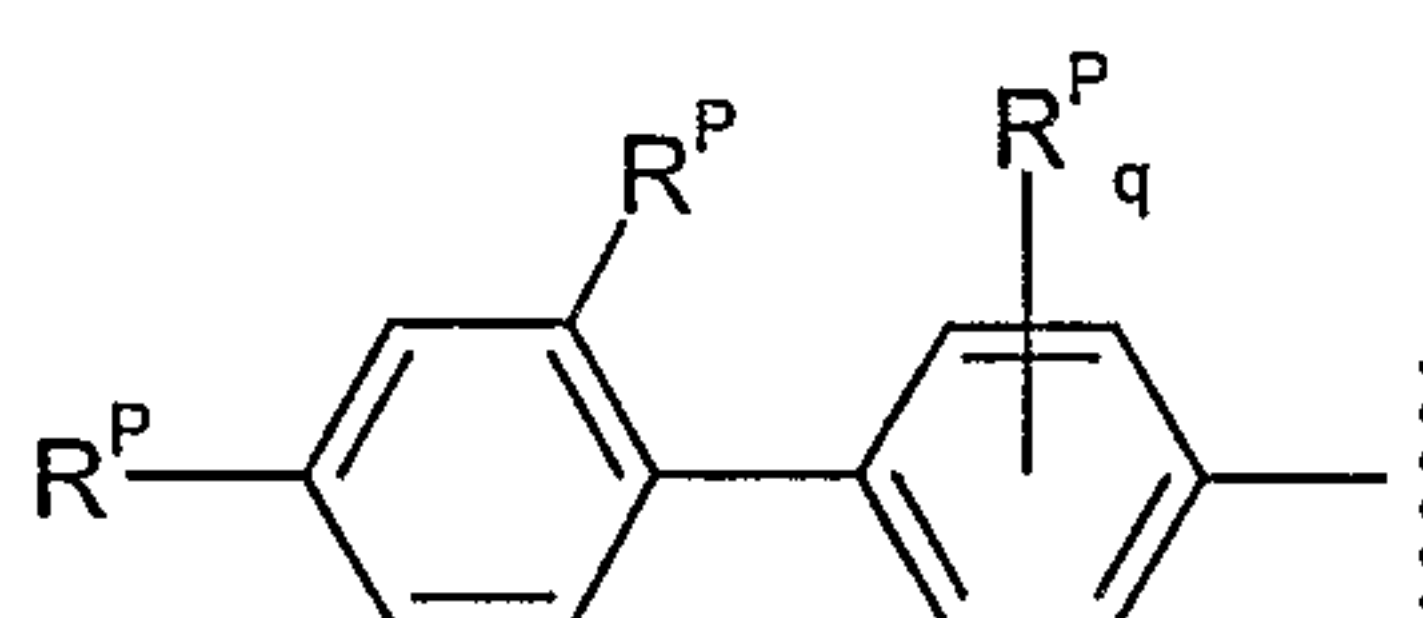
5

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

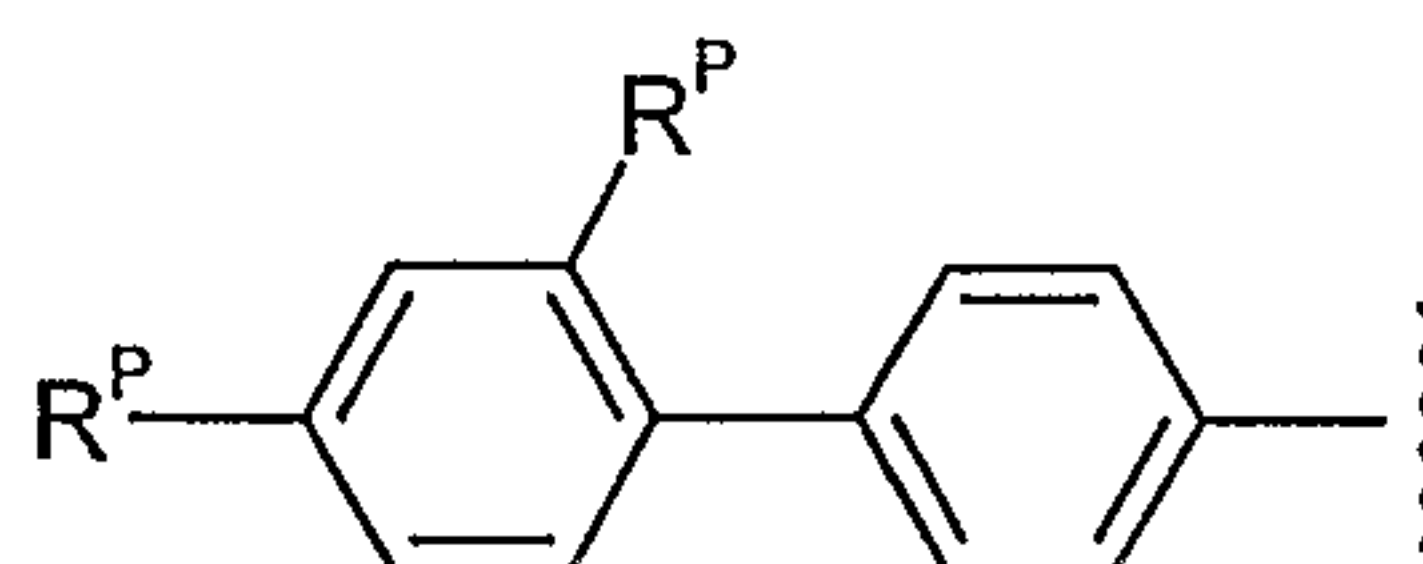


10

In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:



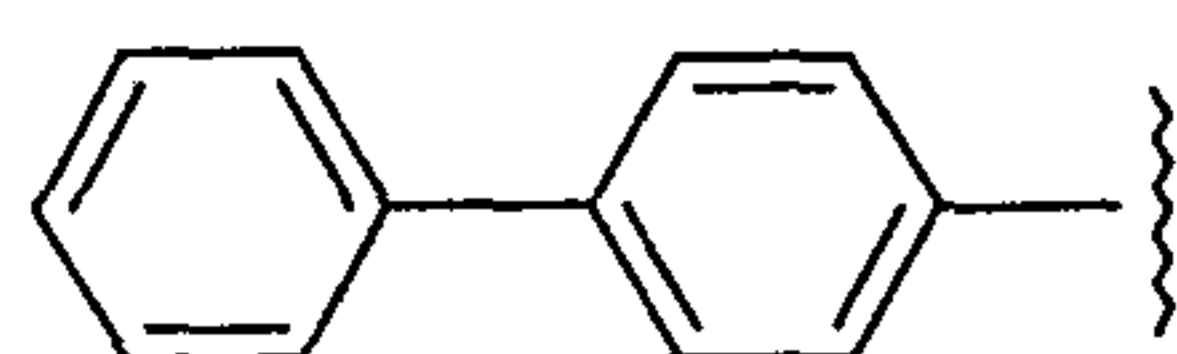
15 In one embodiment, R^{A1} (and optionally also R^{A2}) is a substituted biphenyl-4-yl group of the following formula:

R^{A1} as Unsubstituted Biphenyl-4-yl

20

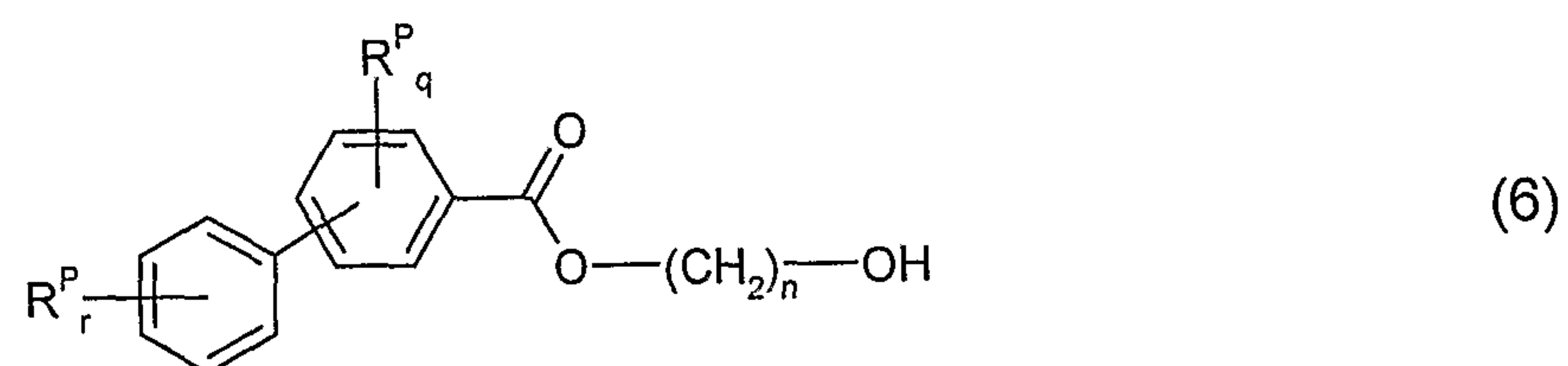
In one embodiment, R^{A1} (and optionally also R^{A2}) is an unsubstituted biphenyl-4-yl group of the following formula:

- 33 -

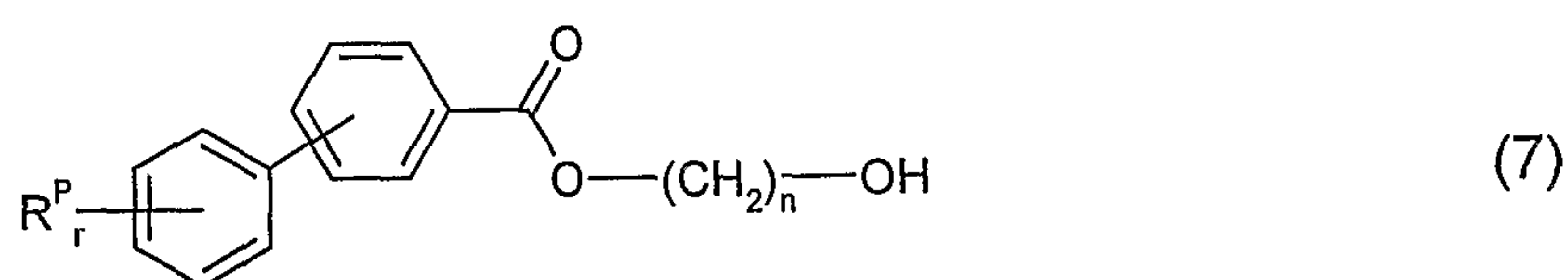


Some examples of preferred alkane diol derivatives, wherein R^{A2} is -H, are shown below.

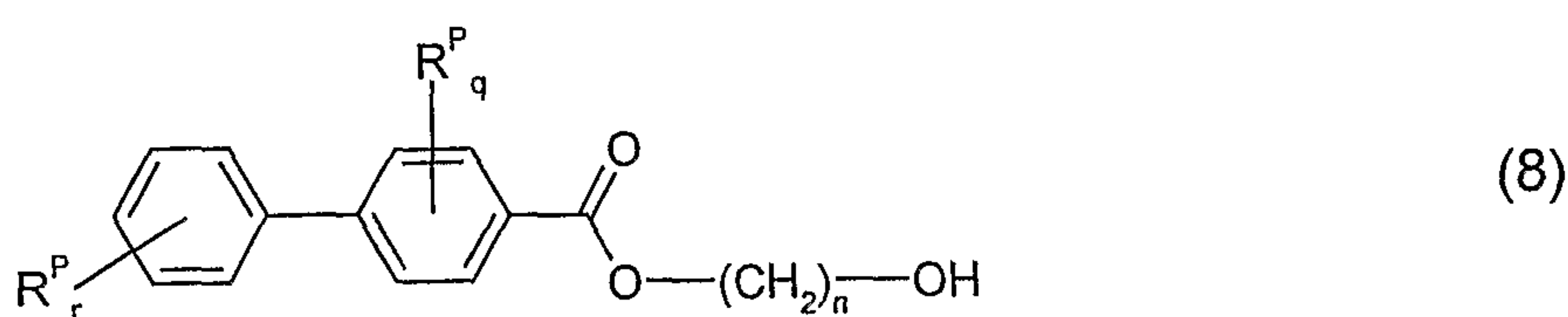
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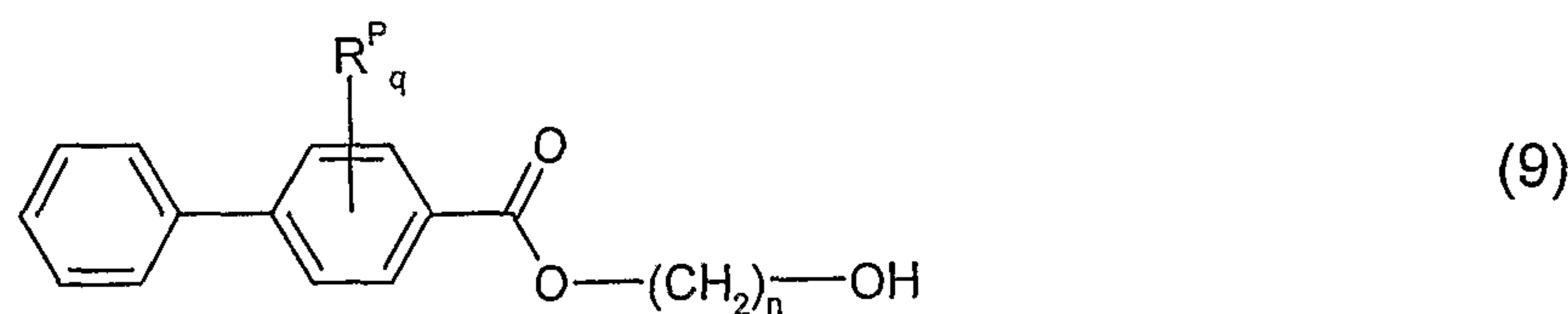
(6)



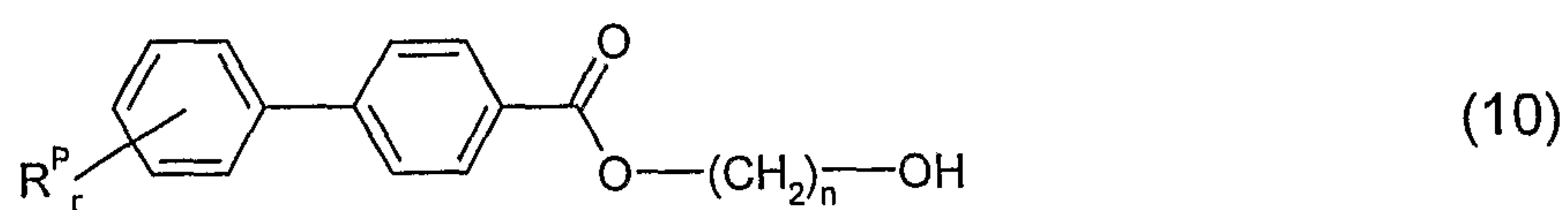
(7)



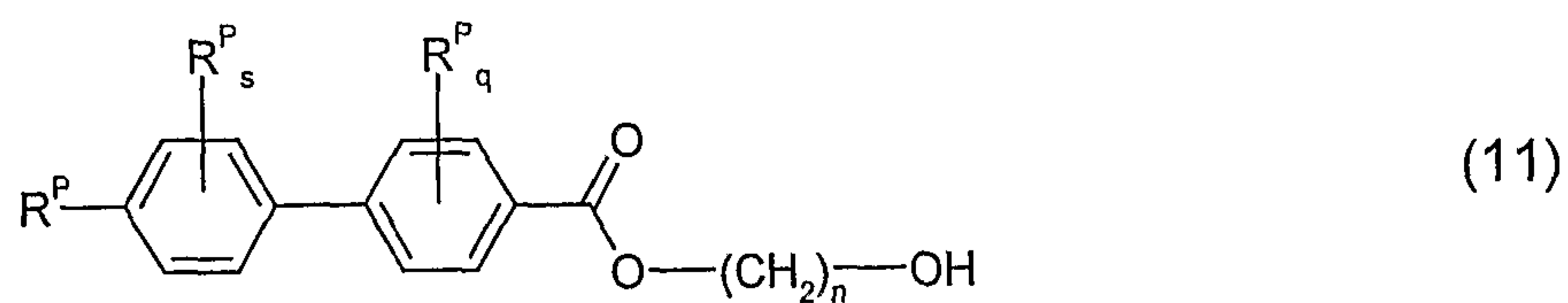
(8)



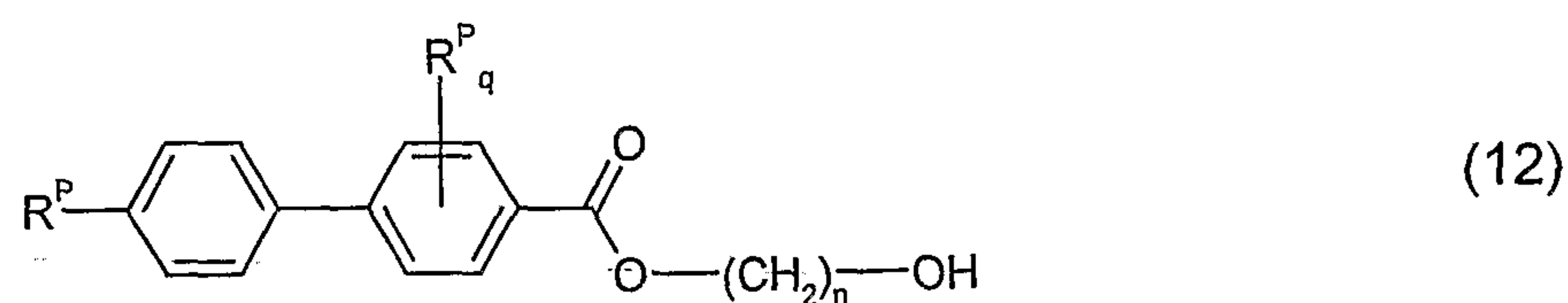
(9)



(10)

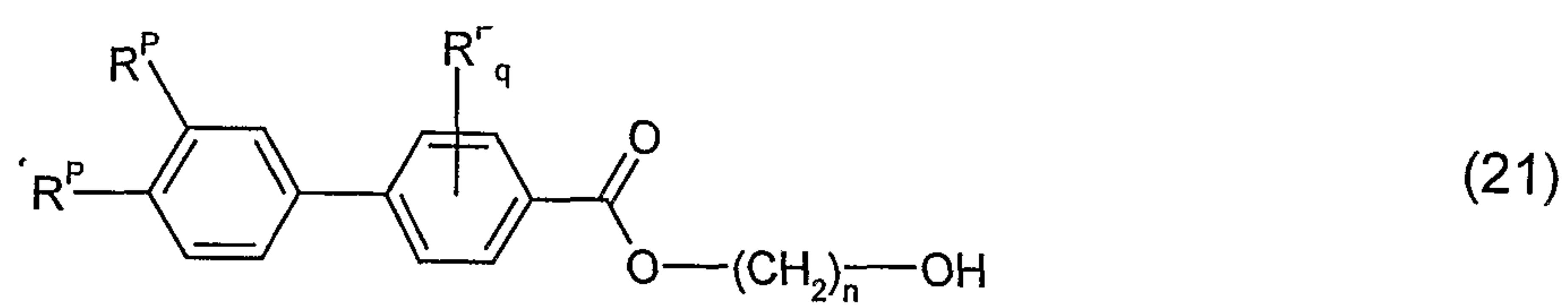
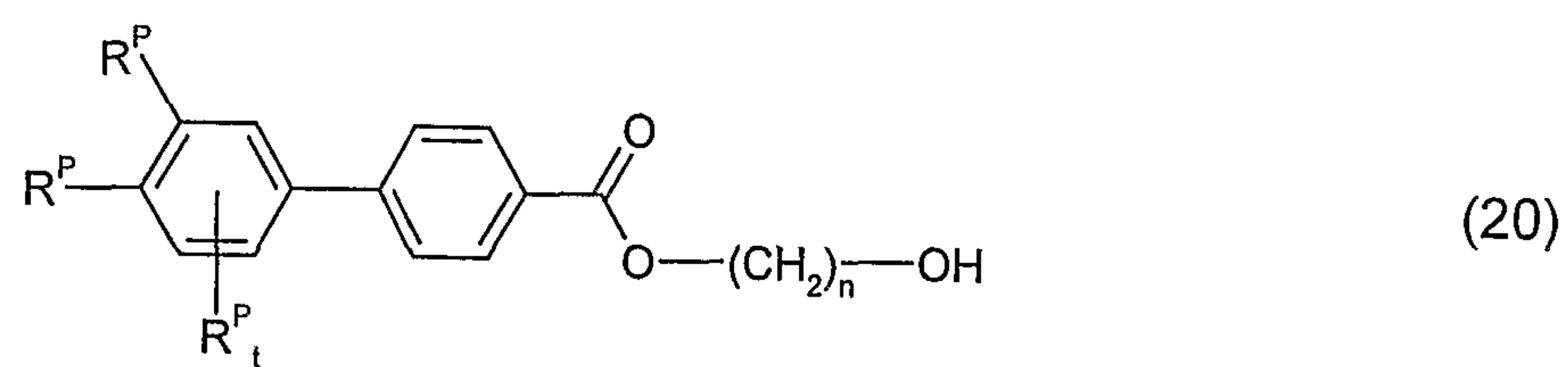
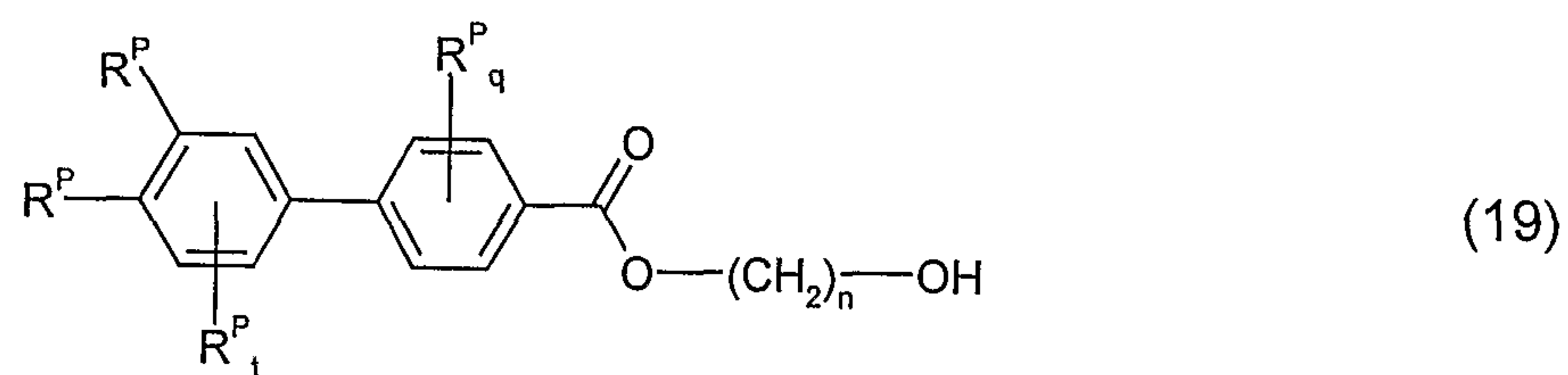
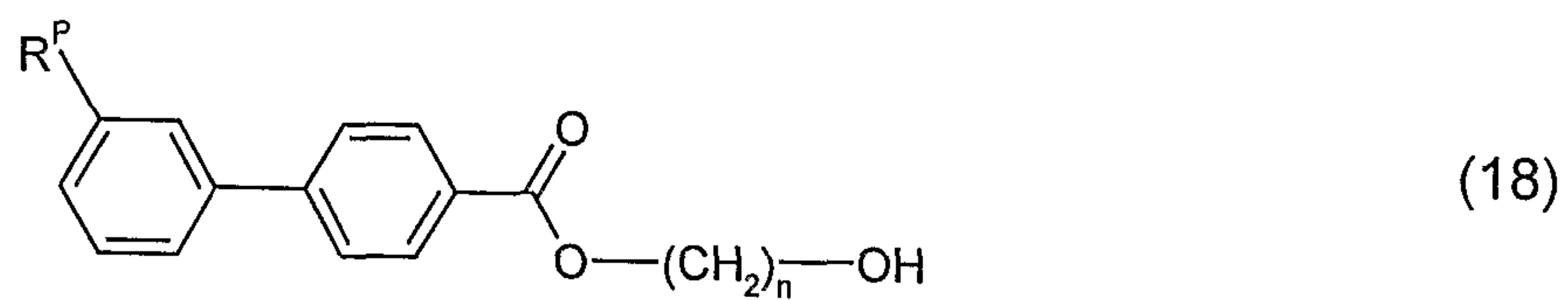
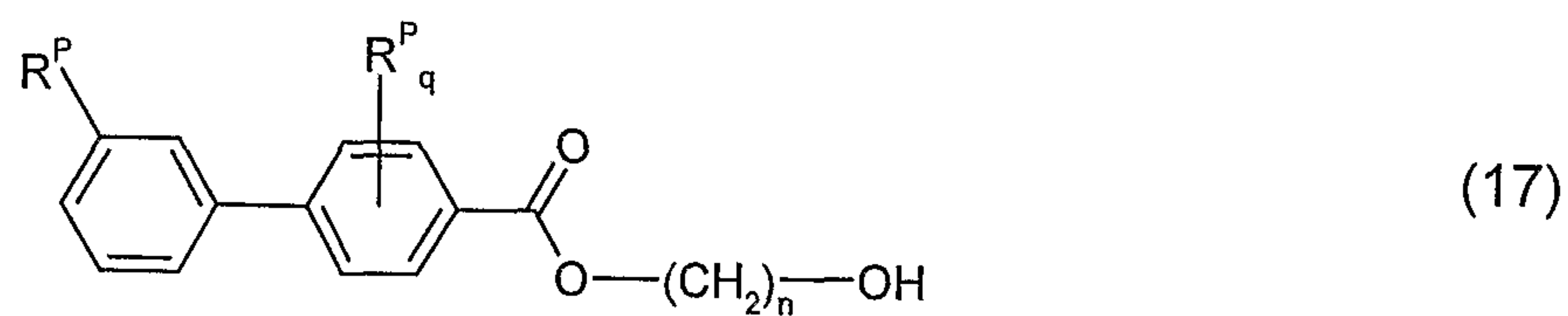
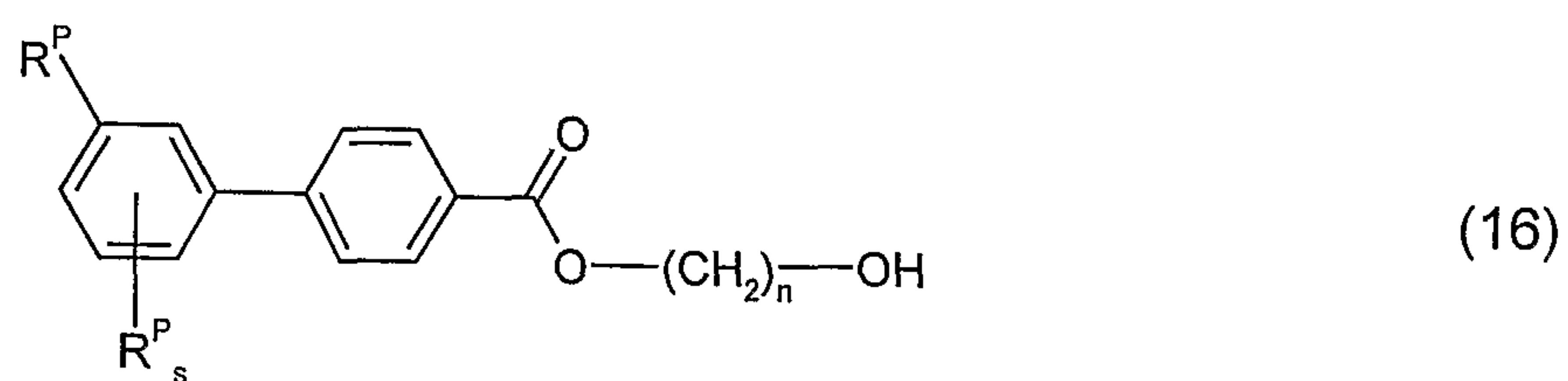
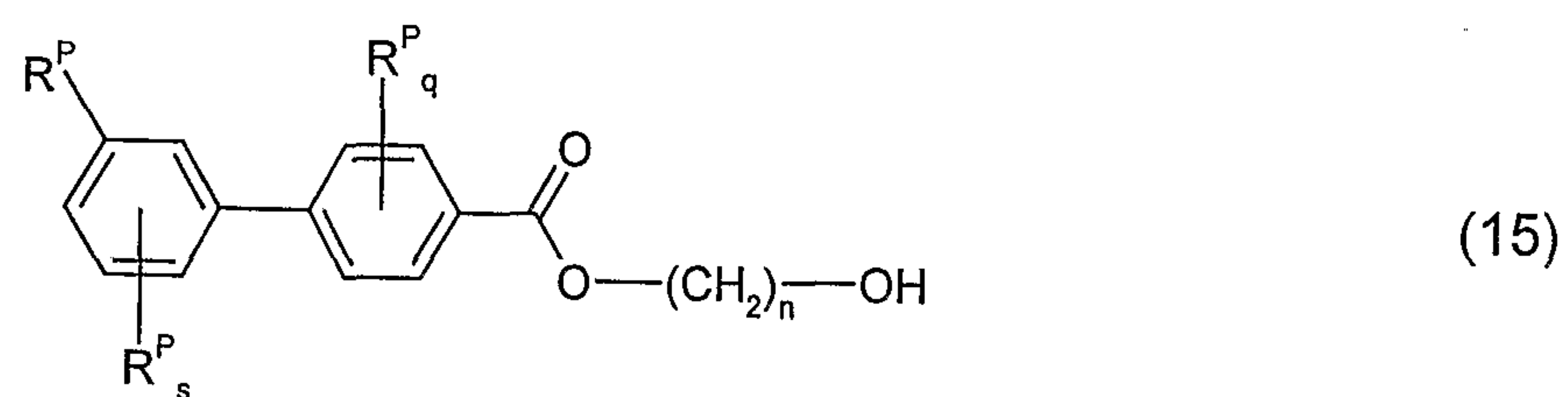
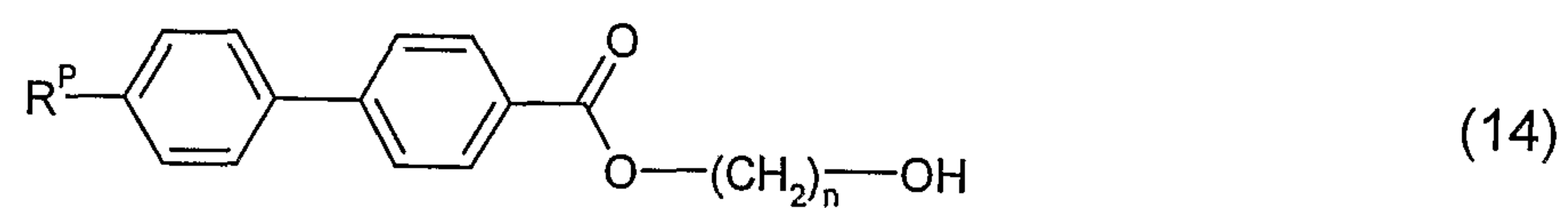
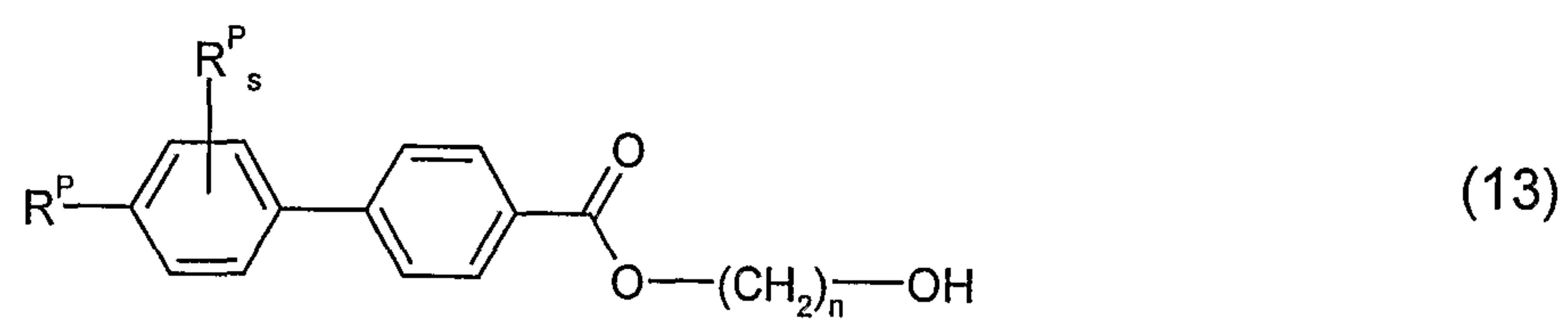


(11)

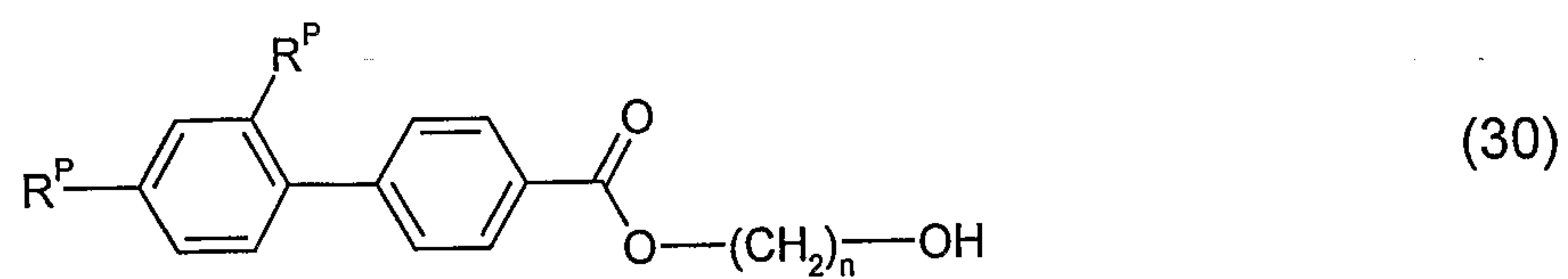
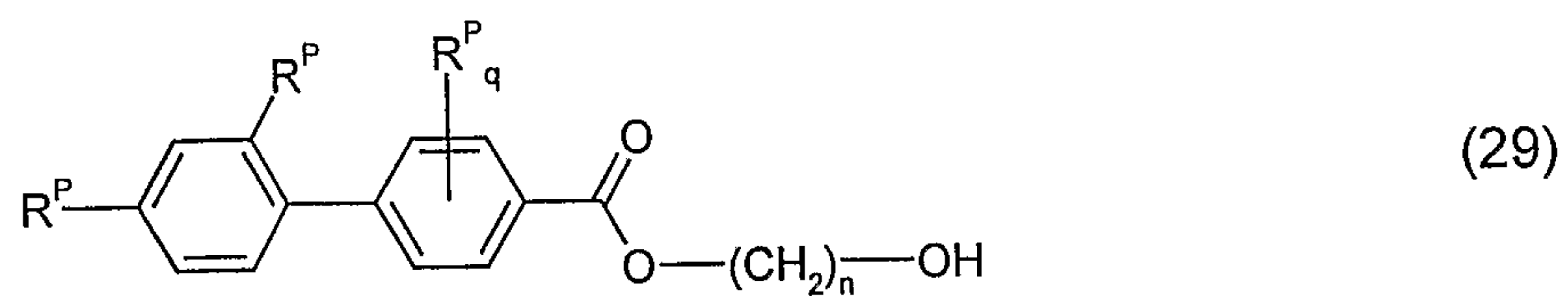
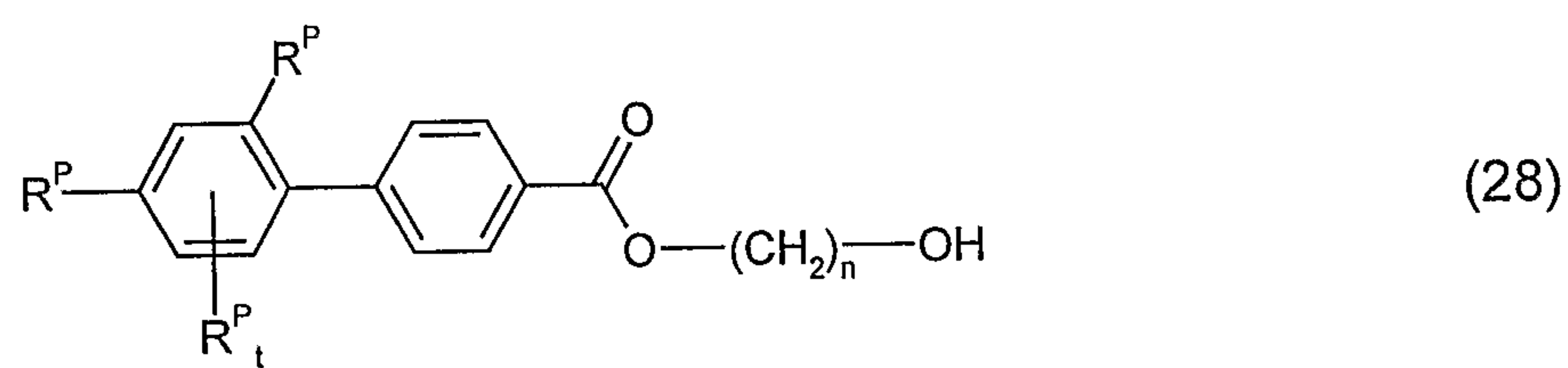
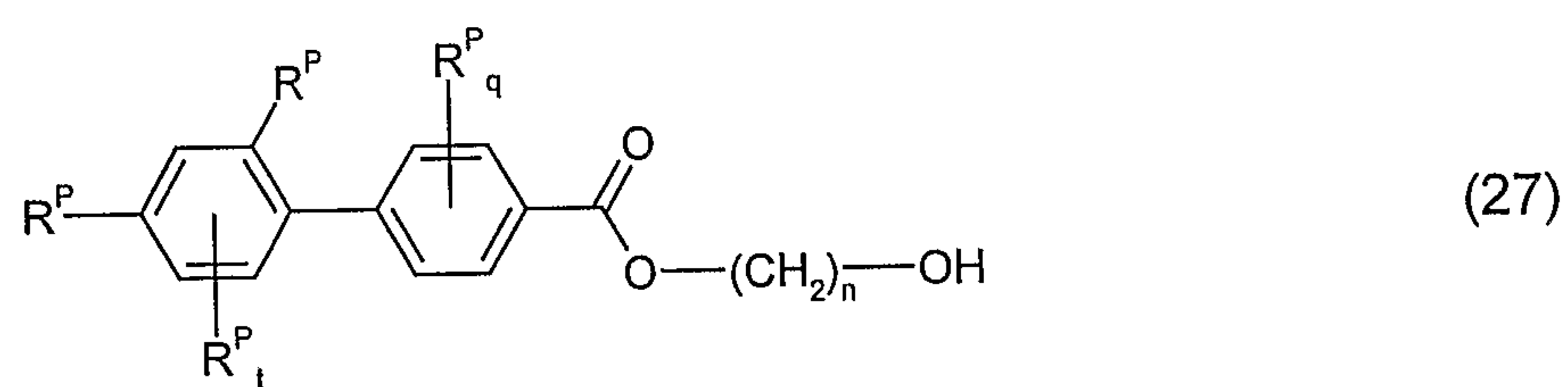
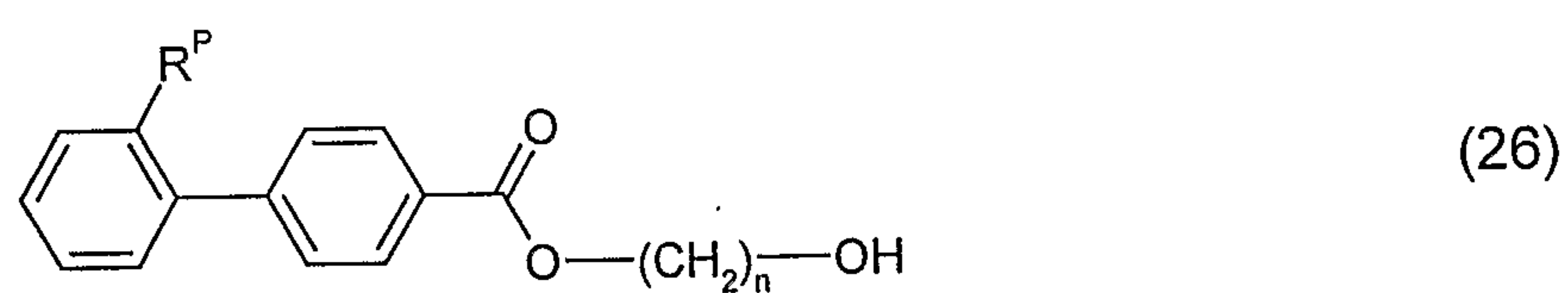
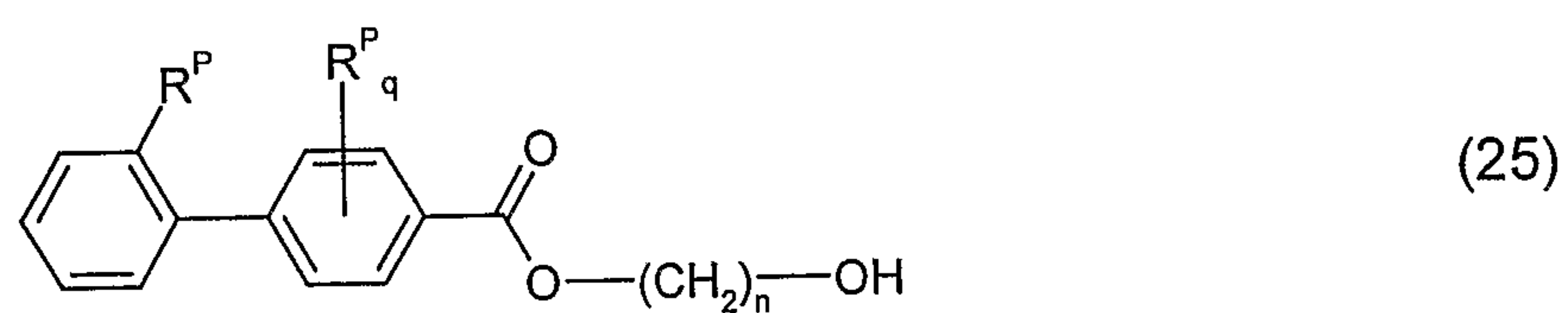
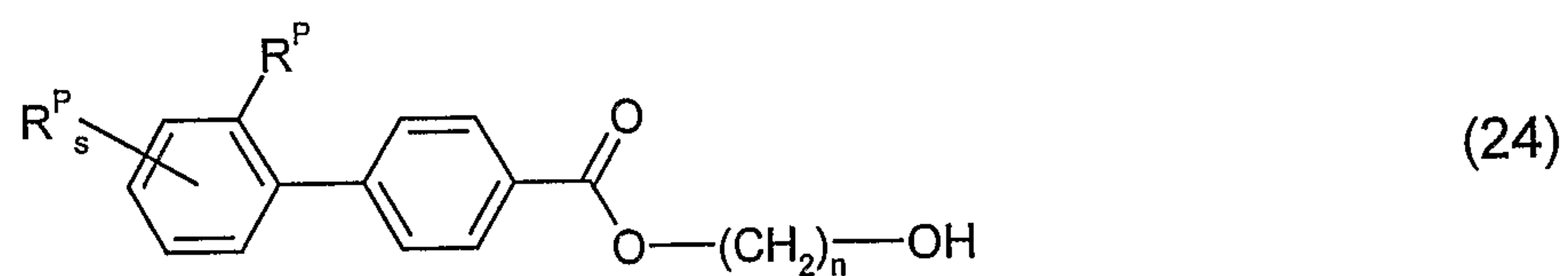
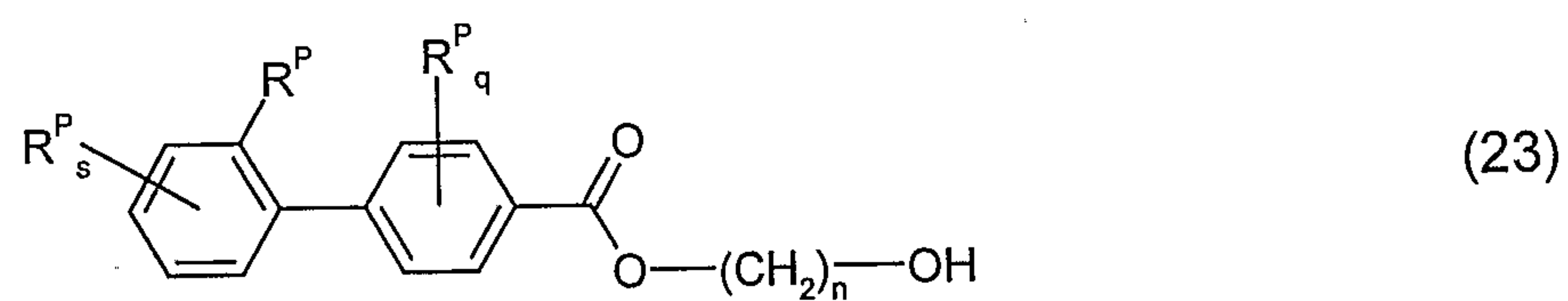
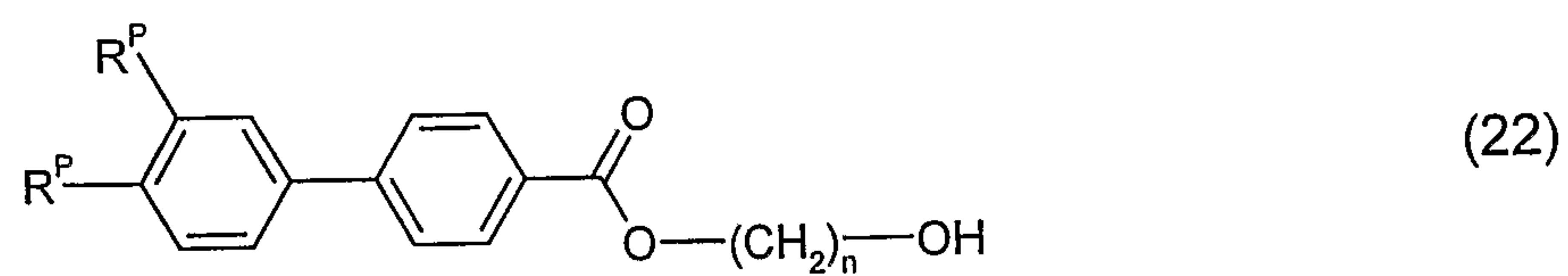


(12)

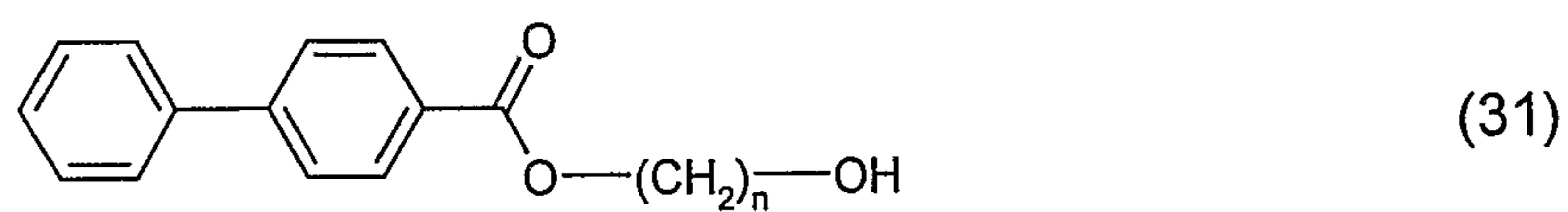
- 34 -



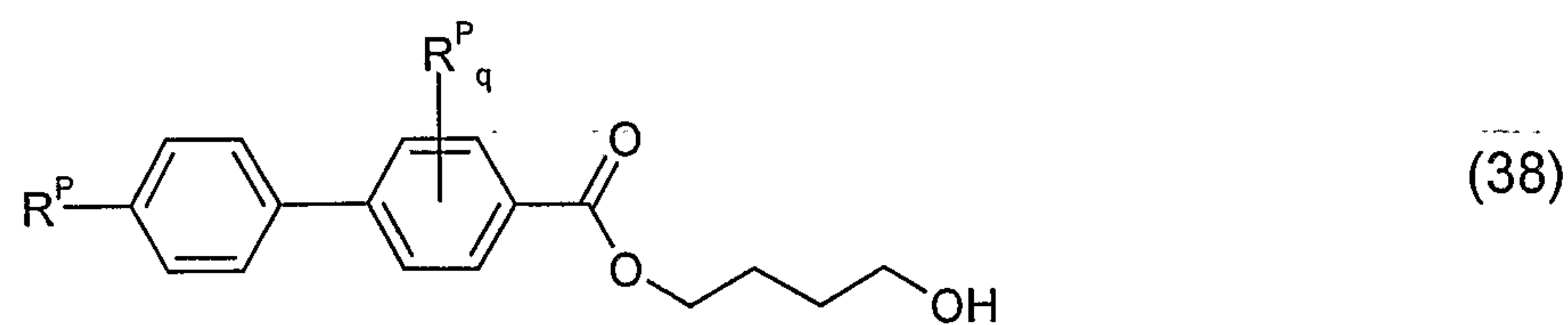
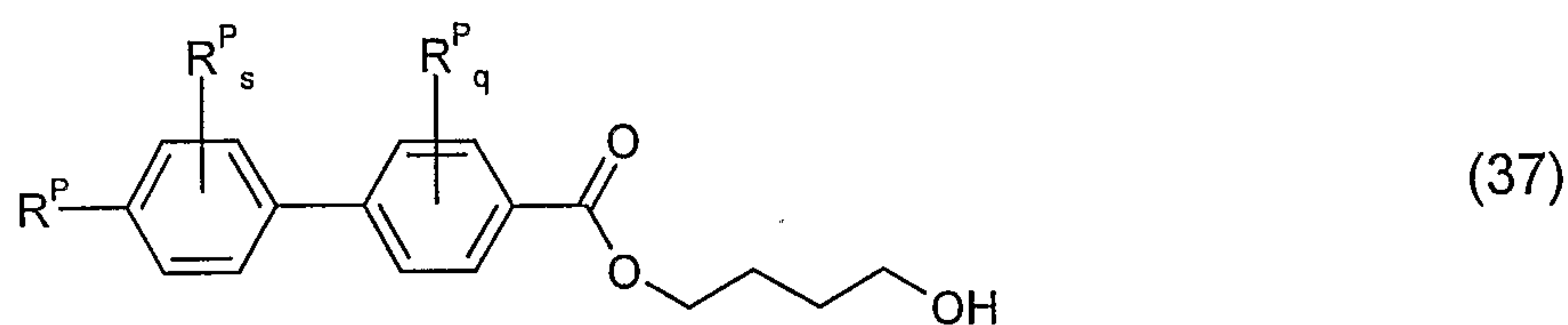
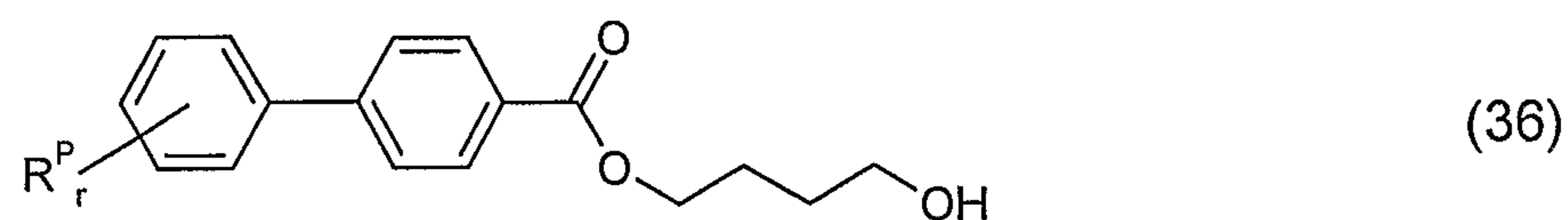
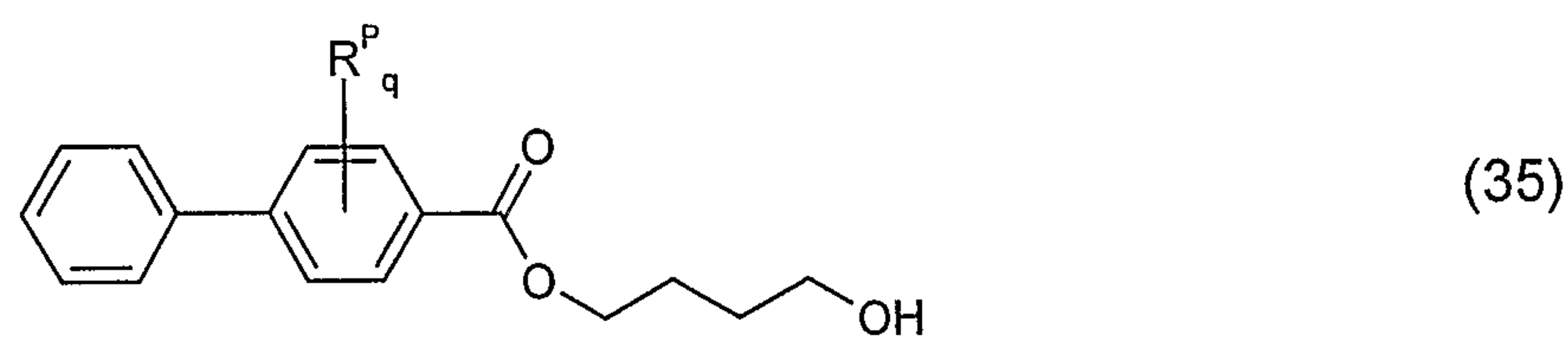
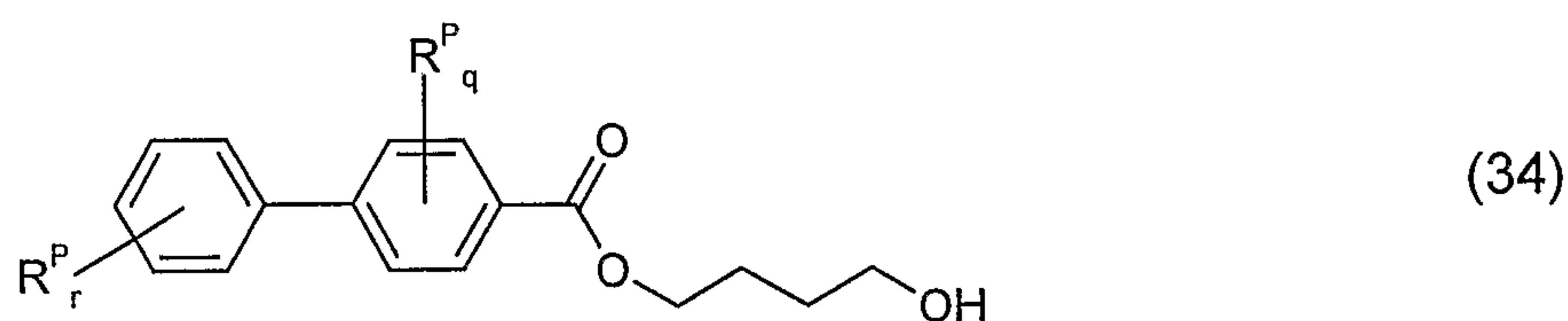
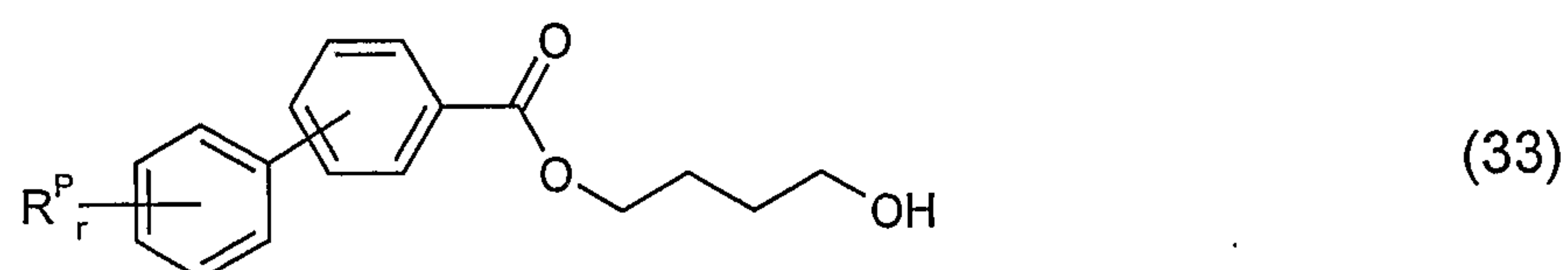
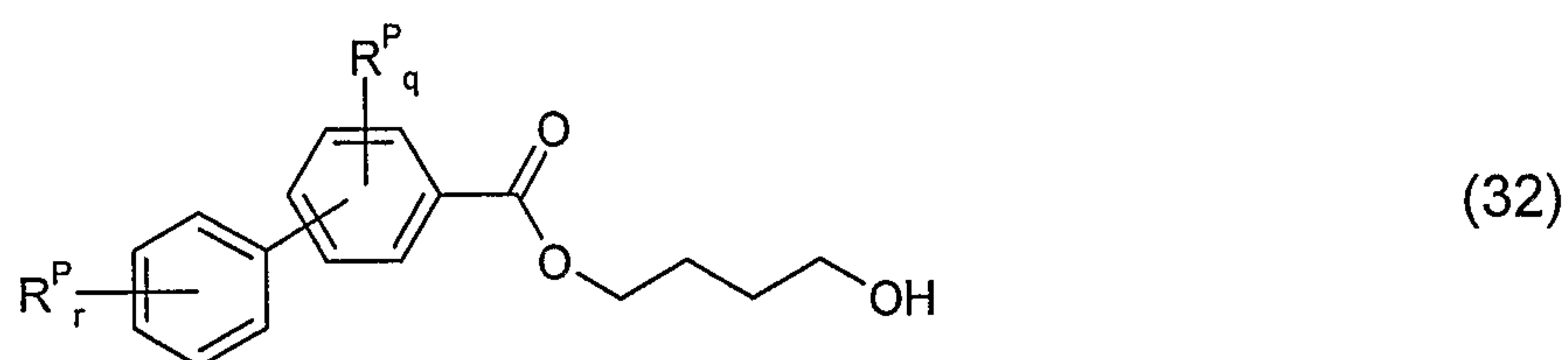
- 35 -



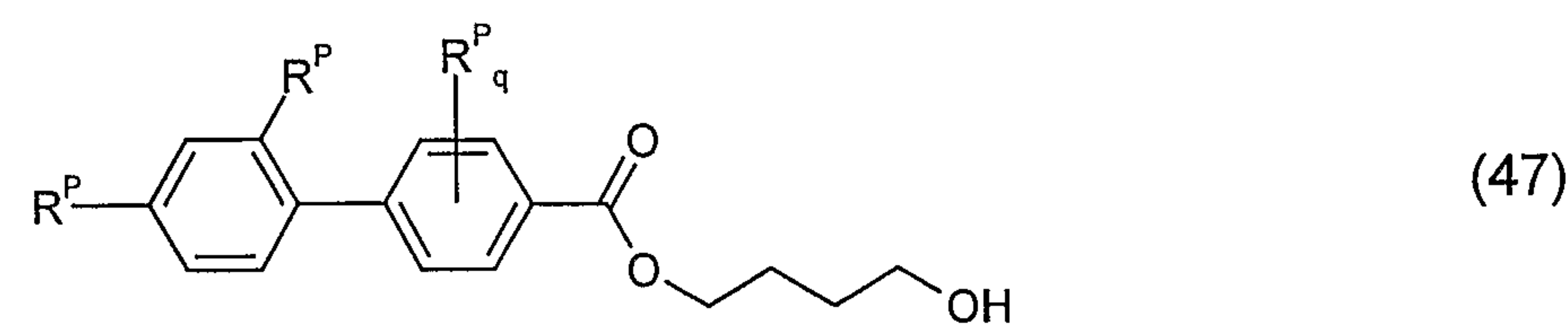
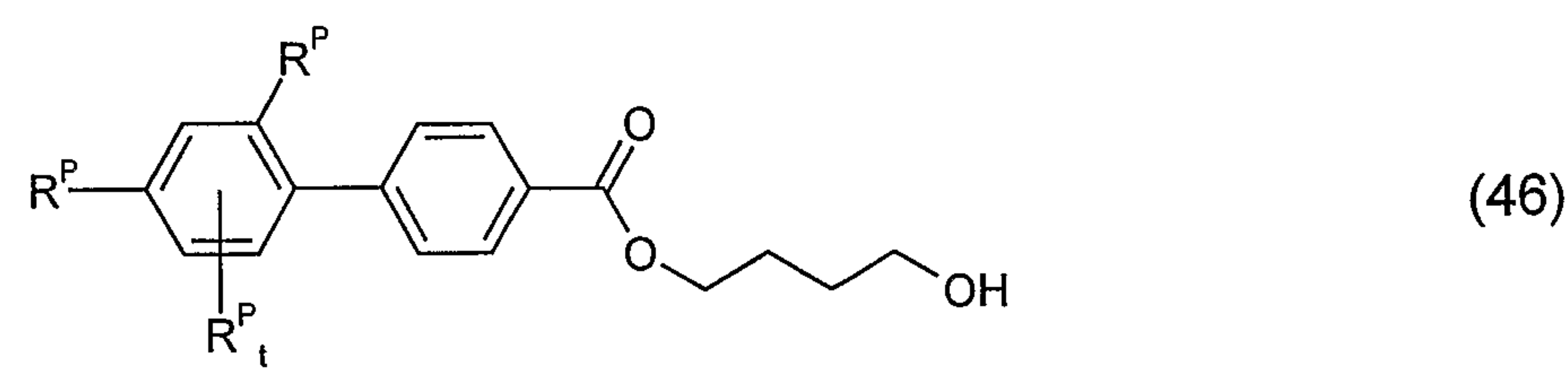
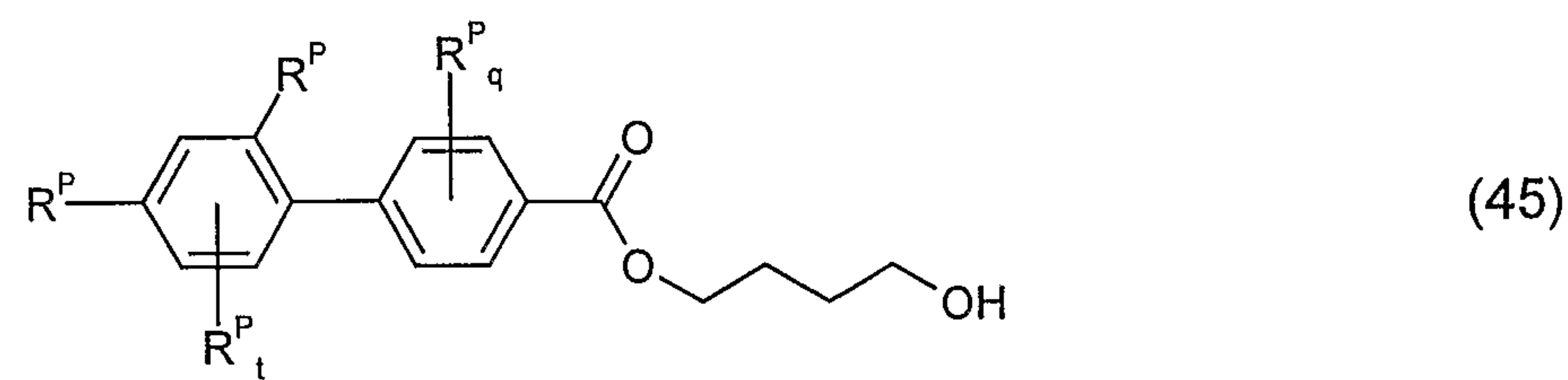
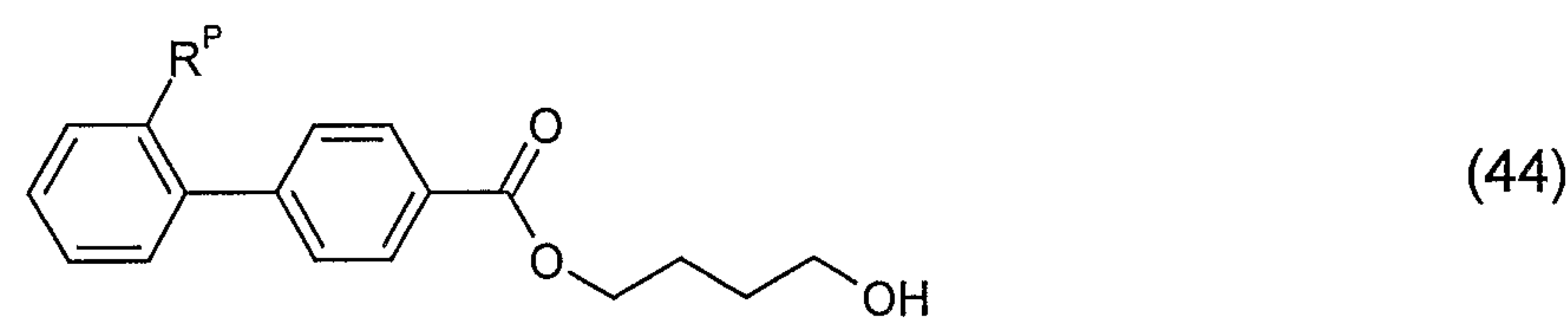
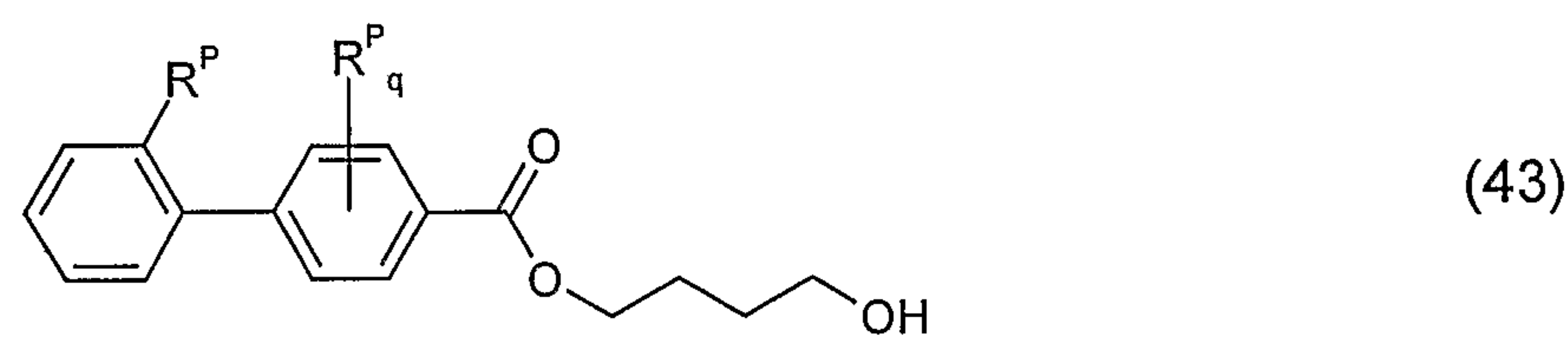
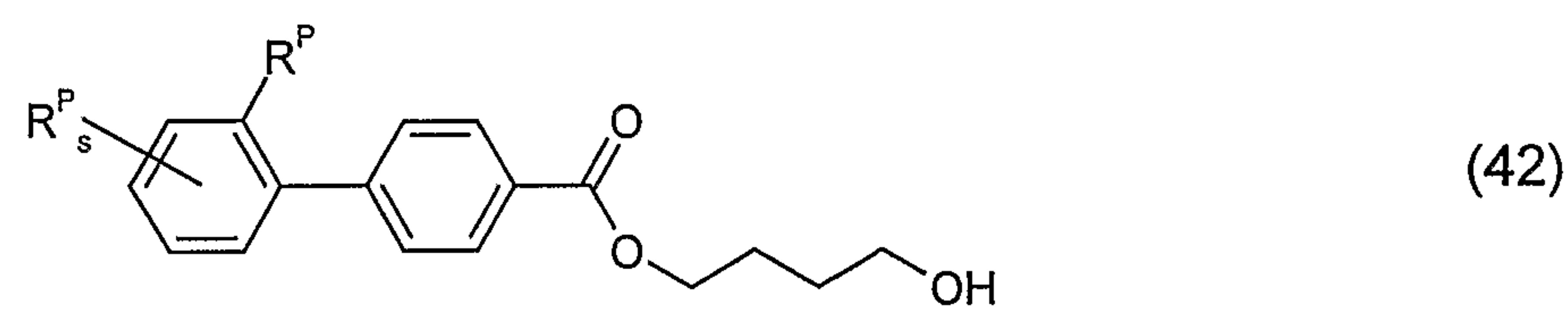
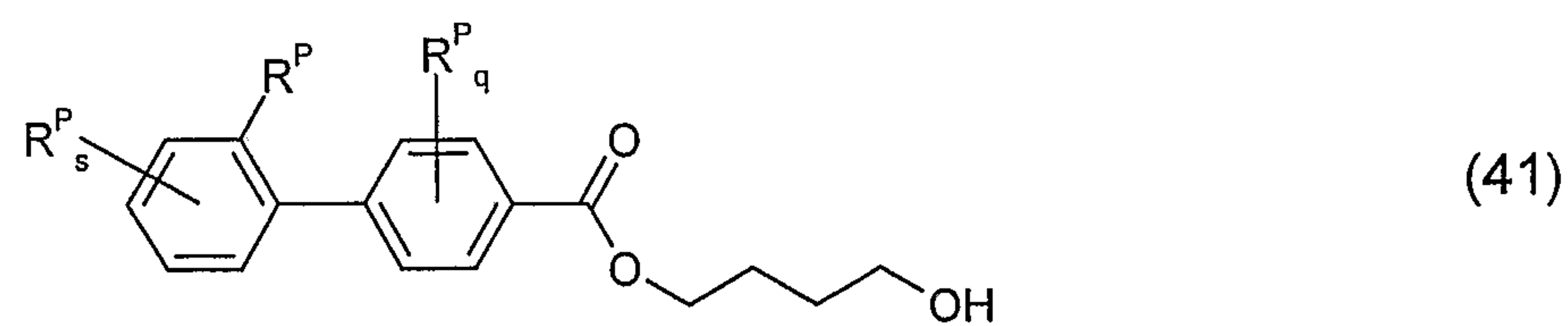
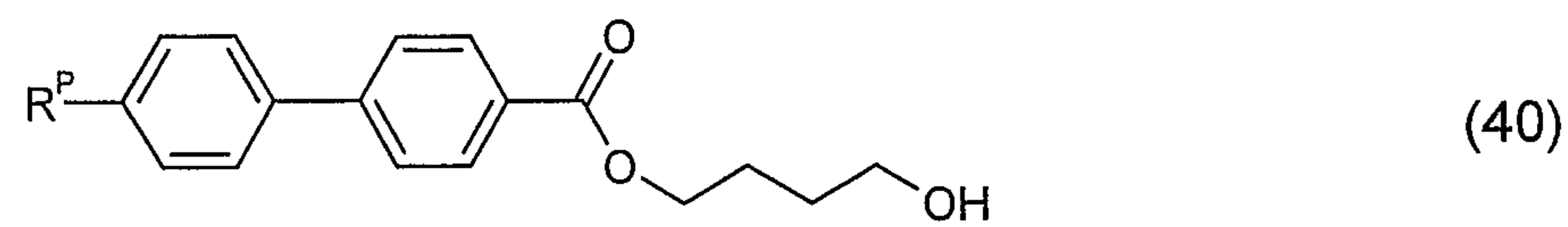
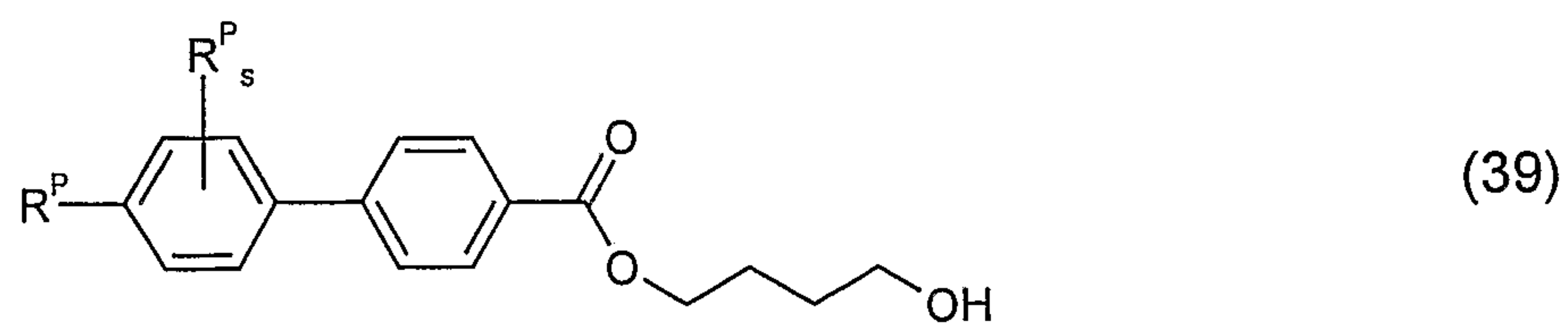
- 36 -



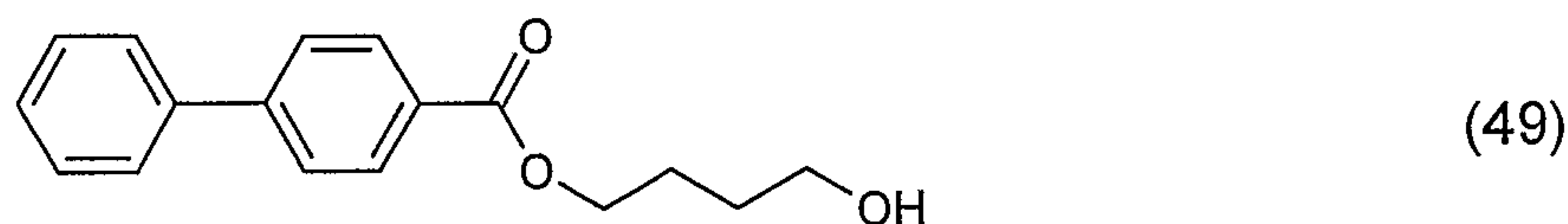
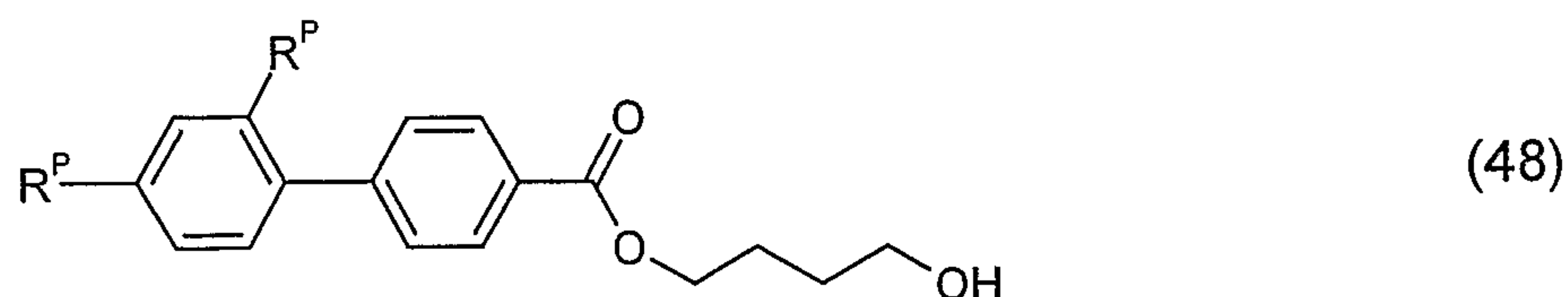
Some examples of preferred alkane diol derivatives, wherein $\text{R}^{\text{A}2}$ is -H and the alkane diol is 1,4-butanediol, are shown below.



- 37 -



- 38 -



Phenyl Substituents, R^P

Examples of phenyl substituents, R^P, include, but are not limited to, those
 5 described below under the heading "substituents."

Examples of some preferred phenyl substituents, R^P, include, but are not limited to, the following:

- C₁₋₇alkyl (optionally substituted) (including, e.g., unsubstituted C₁₋₇alkyl,
- 10 C₁₋₇haloalkyl, C₁₋₇hydroxyalkyl, C₁₋₇carboxyalkyl, C₁₋₇aminoalkyl, C₅₋₂₀aryl-C₁₋₇alkyl);
- C₃₋₂₀heterocyclyl (optionally substituted);
- C₅₋₂₀aryl group (optionally substituted) (including, e.g., C₅₋₂₀carboaryl, C₅₋₂₀heteroaryl, C₁₋₇alkyl-C₅₋₂₀aryl and C₅₋₂₀haloaryl);
- 15 halo;
- hydroxy;
- ether (e.g., C₁₋₇alkoxy);
- acyl (e.g., C₁₋₇alkylacyl, C₅₋₂₀arylacyl);
- carboxy;
- 20 ester;
- acyloxy;
- oxycarboxyloxy;
- amido;
- acylamido;
- 25 thioamido;
- tetrazolyl;

- 39 -

amino;

nitro;

cyano;

sulfhydryl;

5 thioether (e.g., C₁₋₇alkylthio);

sulfonic acid;

sulfonate; and

sulfonamido.

10 In one embodiment, the phenyl substituents, R^P, are selected from:C₁₋₇alkyl (optionally substituted);C₃₋₂₀heterocyclyl (optionally substituted);C₅₋₂₀aryl group (optionally substituted);

halo;

15 hydroxy;

ether (e.g., C₁₋₇alkoxy);acyl (e.g., C₁₋₇alkylacyl, C₅₋₂₀arylacyl);

carboxy;

ester;

20 acyloxy;

amido;

acylamido;

amino;

nitro;

25 cyano; and,

sulfonate.

In one embodiment, the phenyl substituents, R^P, are selected from:-Me, -Et, -iPr, -nPr, -tBu;

30 -Ph;

-F, -Cl, -Br, -I;

-OH;

- 40 -

- OMe, -OEt, -O(iPr), -O(nPr), -O(tBu), -OPh, -OBn;
 -C(=O)OH;
 -C(=O)OMe, -C(=O)OEt, -C(=O)O(tBu), -C(=O)OPh;
 -OC(C=O)Me, -OC(C=O)Et, -OC(C=O)(tBu), -OC(C=O)Ph;
 5 -OC(C=O)OMe, -OC(C=O)OEt, -OC(C=O)O(tBu), -OC(C=O)OPh;
 -C(=O)NH₂, -C(=O)NHMe, -C(=O)NMe₂, -C(=O)NHPh;
 -NHC(=O)Me, -NHC(=O)Et, -NHC(=O)Ph;
 -NH₂, -NHMe, -NMe₂, -NHEt, -NEt₂;
 -NO₂;
 10 -CN; and,
 -S(=O)₂OMe, -S(=O)₂OEt, -S(=O)₂OPh.

In one embodiment, the phenyl substituents, R^P, are selected from:
 -Me, -F, -Cl, -Br, -I, -OH, -OMe, -NH₂, -NMe₂, -NO₂, and -CN.

15

In one embodiment, the phenyl substituents, R^P, are selected from:
 -Me, -F, -Cl, -OH, -OMe, -NH₂, -NMe₂, -NO₂, and -CN.

In one embodiment, the phenyl substituents, R^P, are selected from:

20 -F, -Cl, -Br, -I, -NO₂, and -OH.

In one embodiment, the phenyl substituents, R^P, are selected from:
 -F, -Cl, -Br, and -I, -NO₂.

25 In one embodiment, the phenyl substituents, R^P, are selected from:
 -F, -Cl, -Br, -I.

In one embodiment, the phenyl substituents, R^P, are selected from:
 -F and -Br.

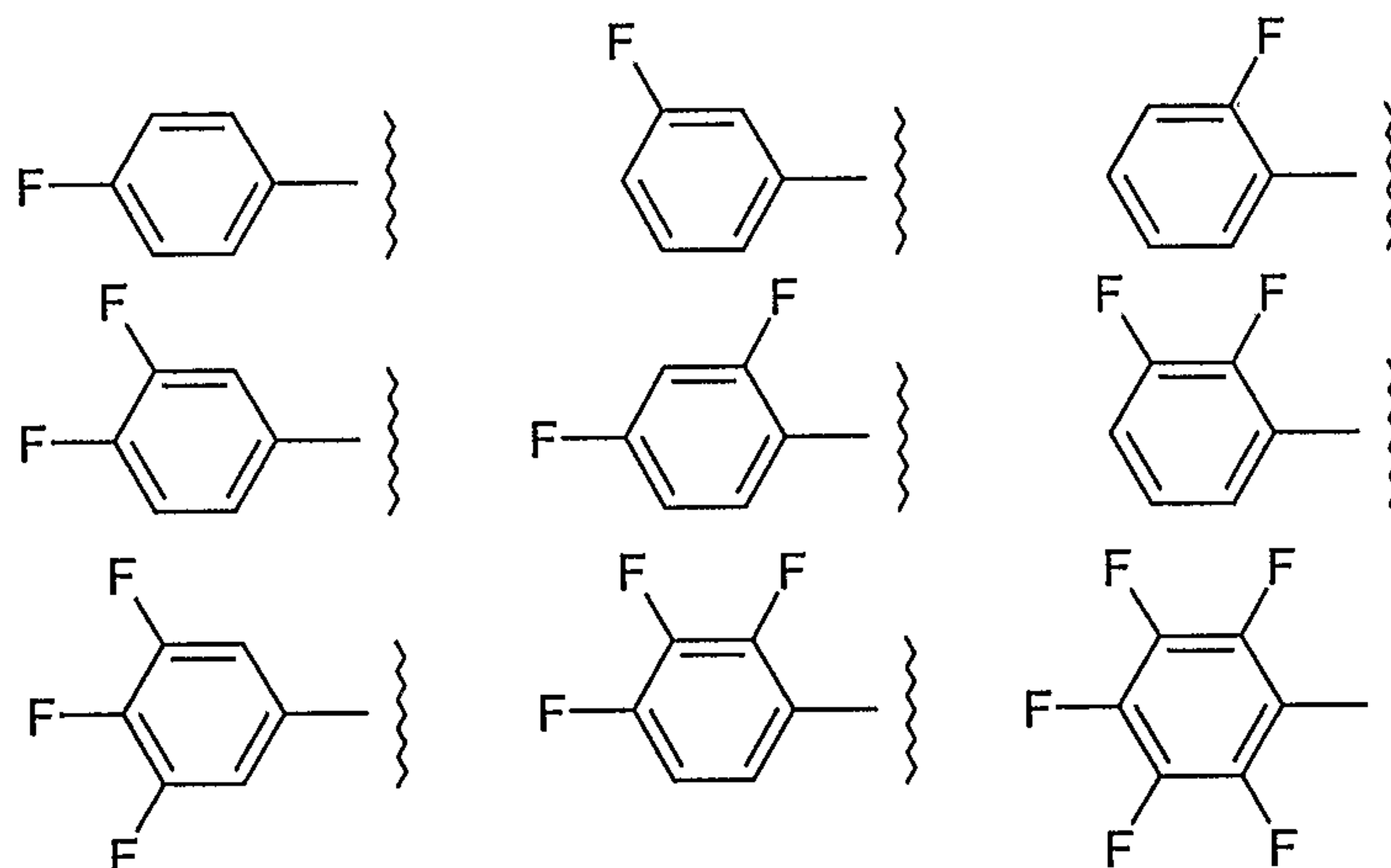
30

In one embodiment, the phenyl substituents, R^P, are -F.

- 41 -

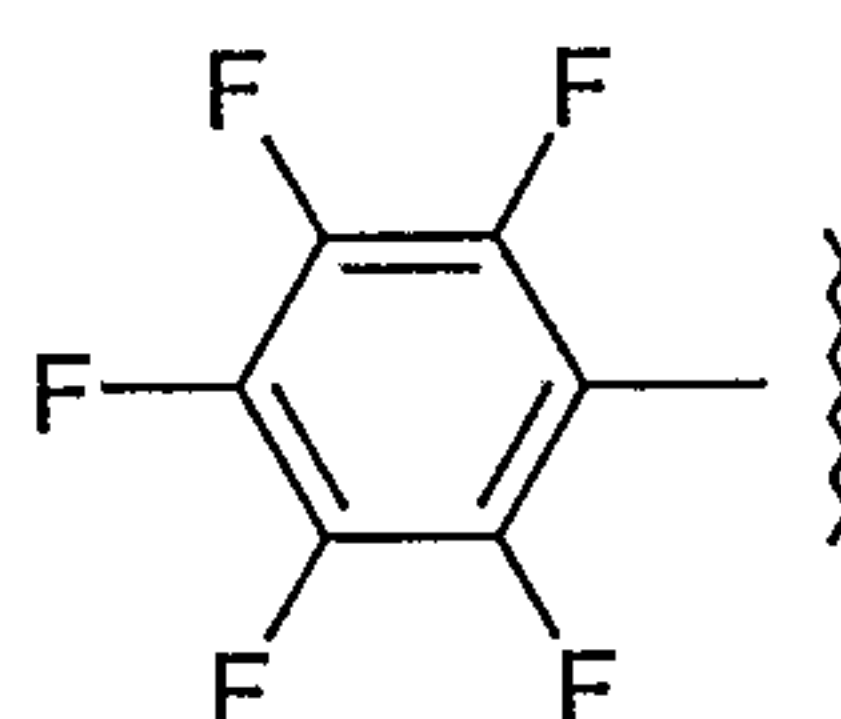
Examples of Some Preferred Fluoro-Substituted Phenyl R^{A1} Groups

Some examples of substituted phenyl groups, suitable as R^{A1}
(and optionally also R^{A2}) include the following:



5

One especially preferred substituted phenyl group, suitable as R^{A1}
(and optionally also R^{A2}) is:

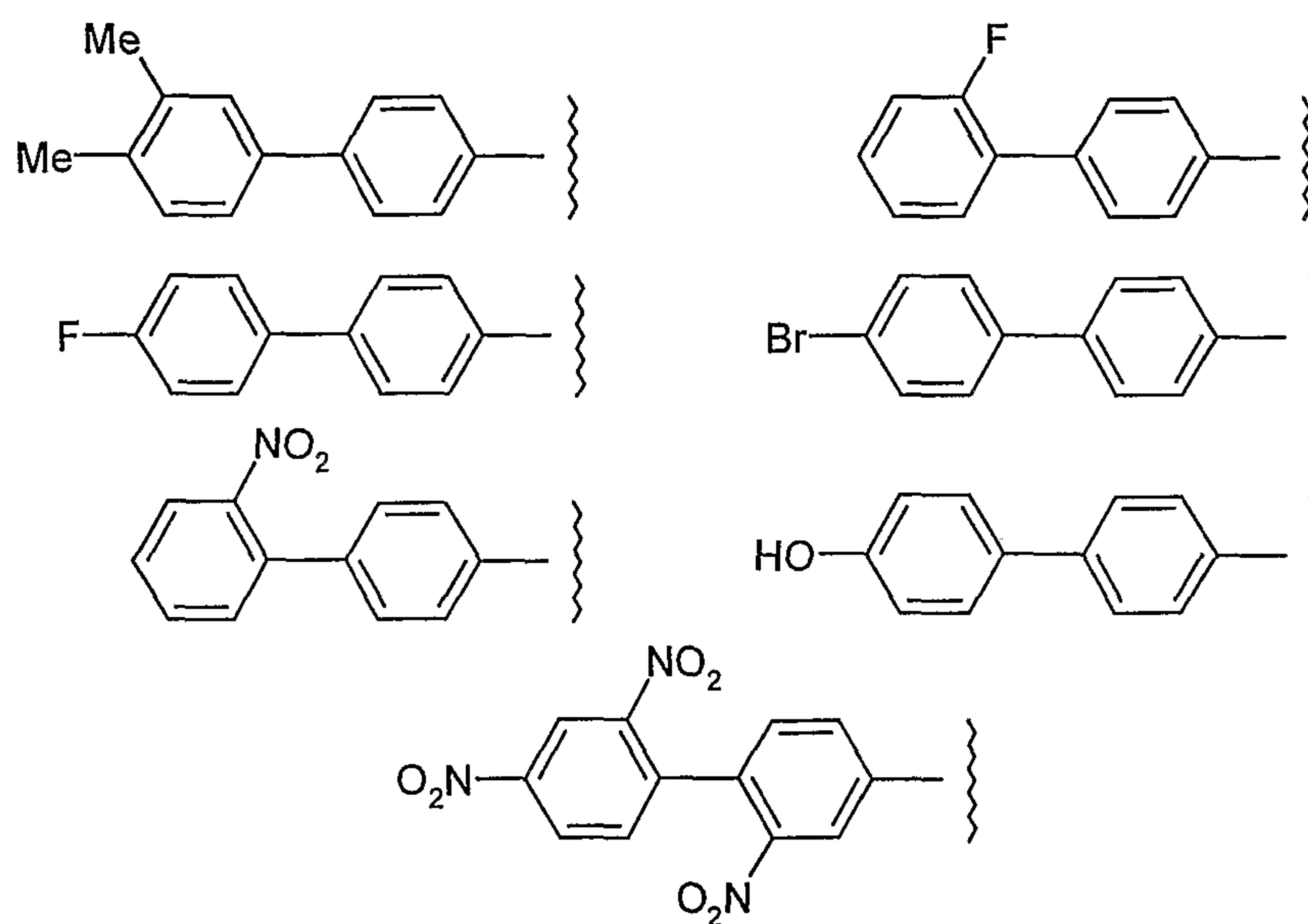


10

Examples of Some Preferred Substituted Biphenyl-4-yl R^{A1} Groups

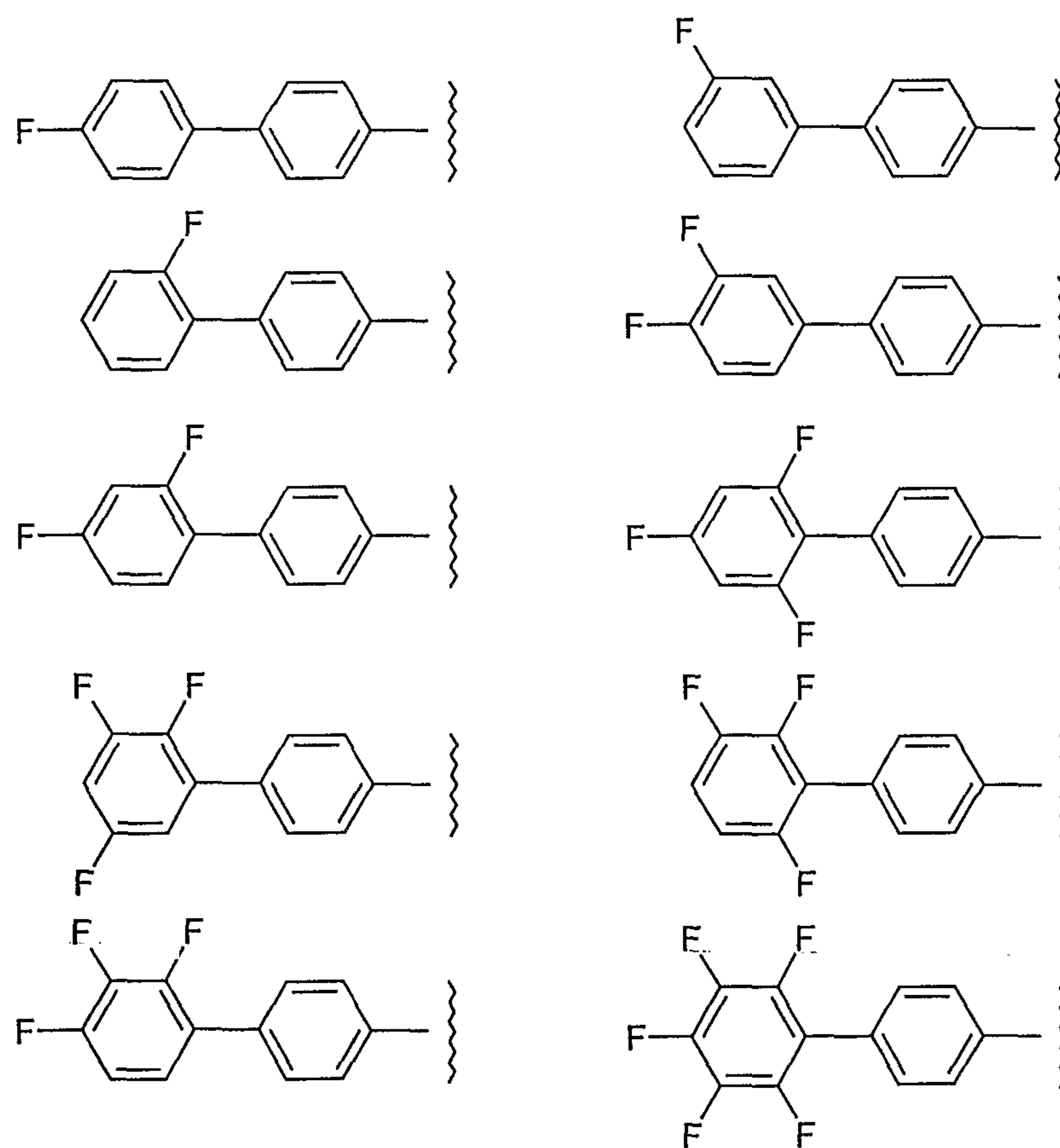
Some examples of substituted biphenyl-4-yl groups, suitable as R^{A1} (and
optionally also R^{A2}) include the following:

- 42 -

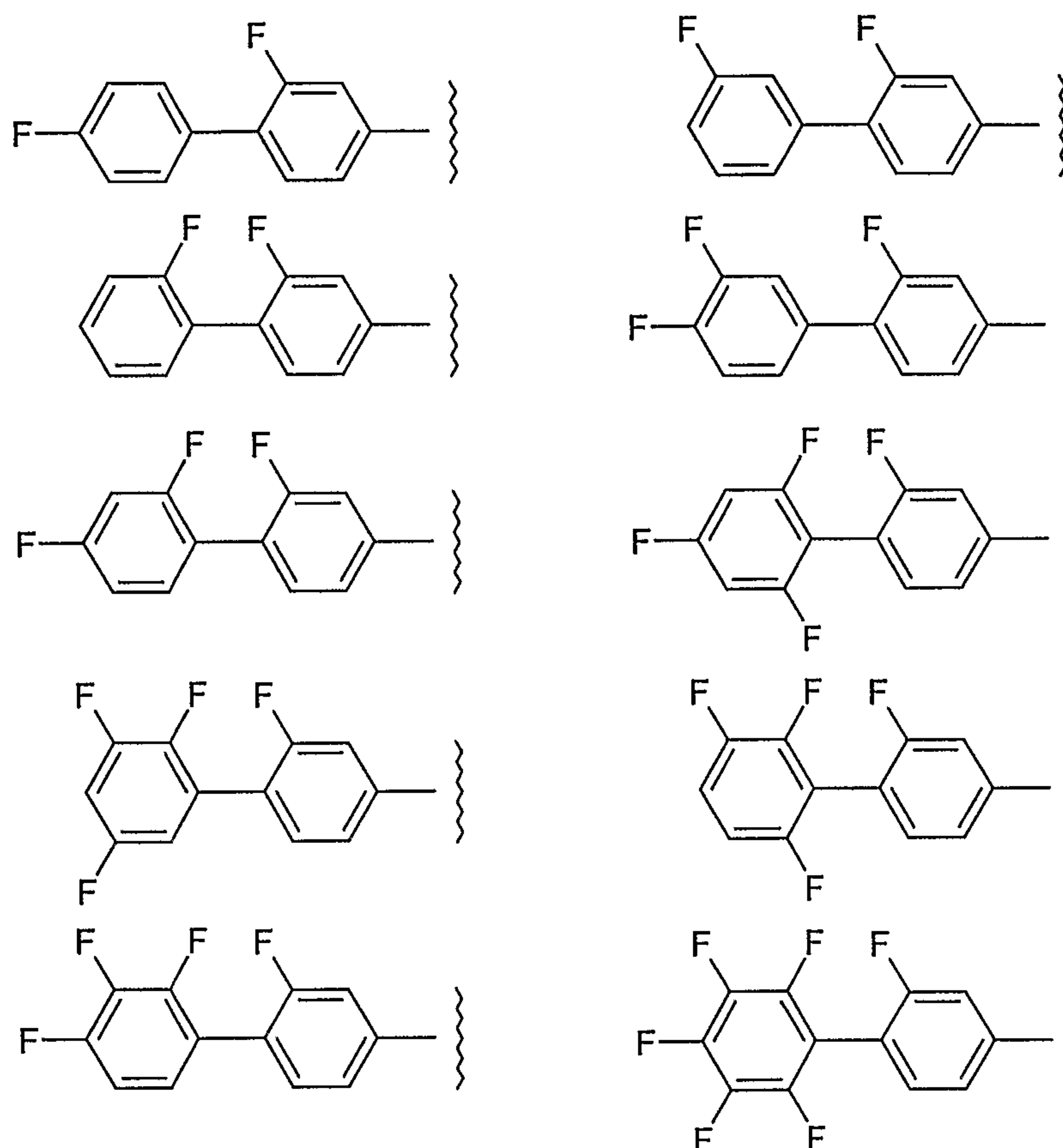


Examples of Some Preferred Fluoro-Substituted Biphenyl-4-yl R^{A1} Groups

- 5 Some examples of substituted biphenyl-4-yl groups, suitable as R^{A1} (and optionally also R^{A2}) include the following:



- 43 -



R^A as Optionally Substituted Aryl-Alkyl

5

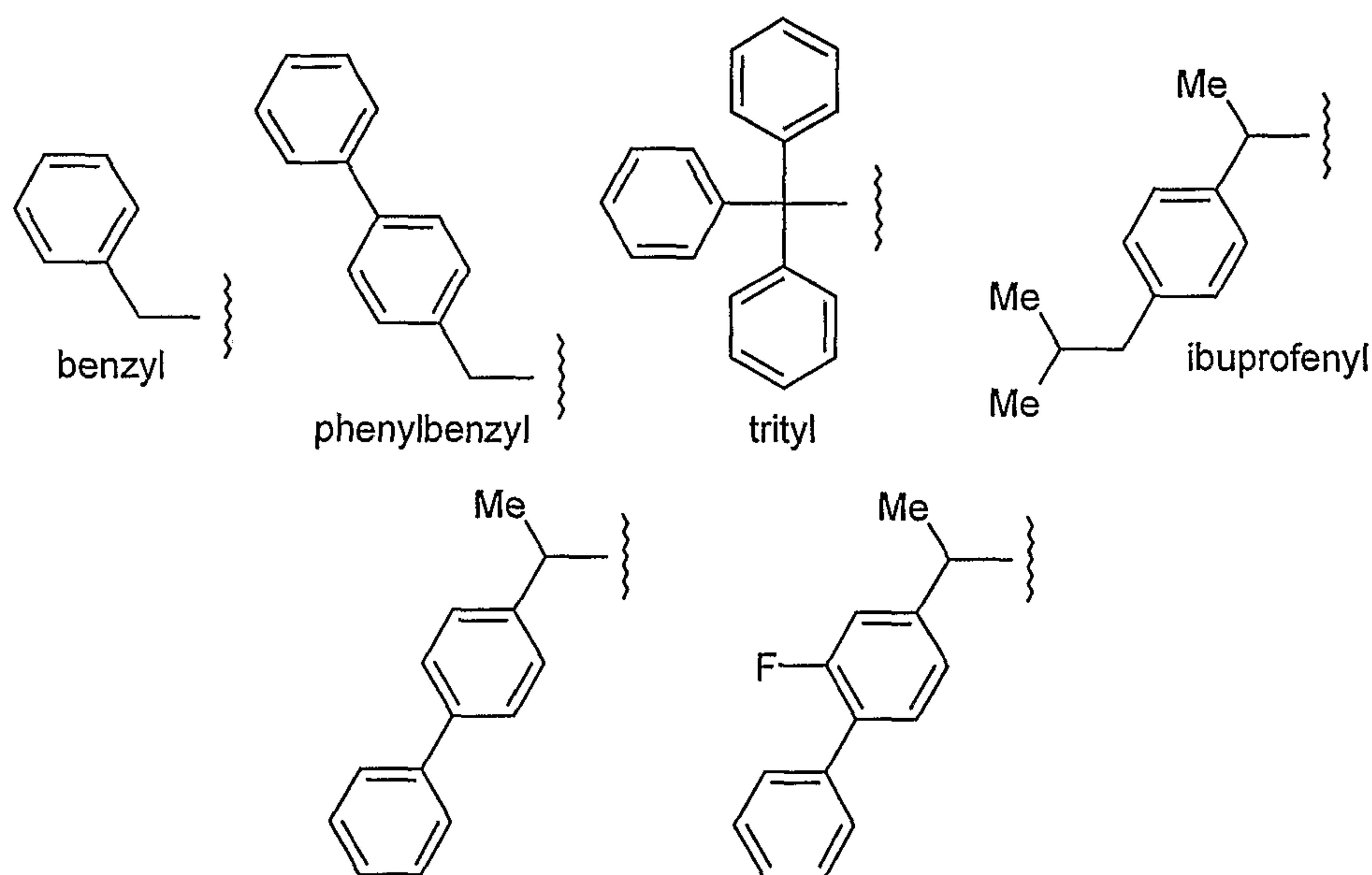
In one embodiment, R^{A1} alone, R^{A2} alone, or each of R^{A1} and R^{A2}, is an optionally substituted C₅₋₂₀aryl-C₁₋₇alkyl group.

10 In one embodiment, R^{A1} alone, R^{A2} alone, or each of R^{A1} and R^{A2}, is an optionally substituted C₅₋₆aryl-C₁₋₇alkyl group.

In one embodiment, R^{A1} alone, R^{A2} alone, or each of R^{A1} and R^{A2}, is an optionally substituted C₅₋₆aryl-C₁₋₃alkyl group.

15 Examples of such groups include, but are not limited to, the following:

- 44 -



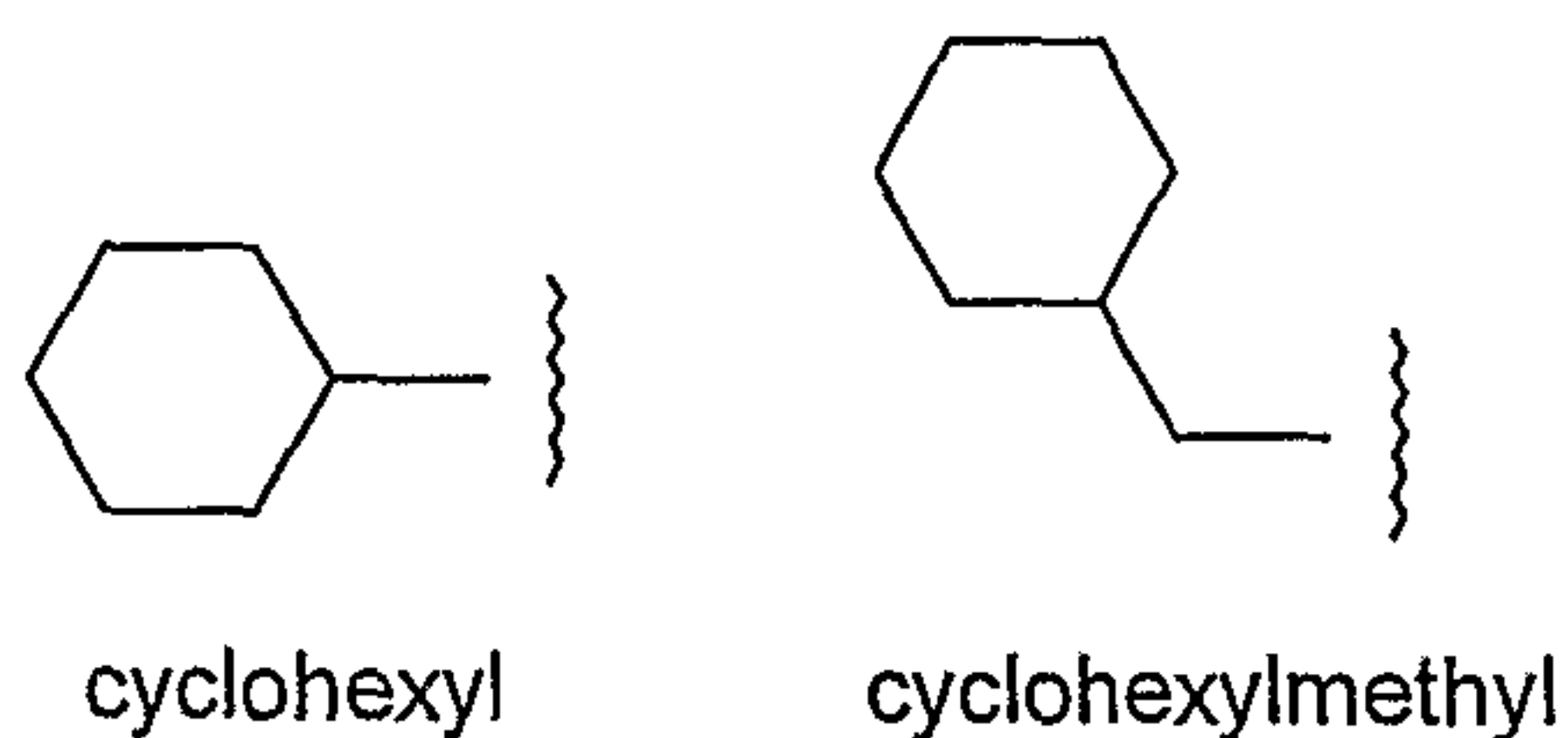
R^A Comprising Optionally Substituted Cycloalkyl

5

In one embodiment, R^{A1} alone, R^{A2} alone, or each of R^{A1} and R^{A2}, is or comprises an optionally substituted C₃₋₇cycloalkyl group.

10 In one embodiment, R^{A1} alone, R^{A2} alone, or each of R^{A1} and R^{A2}, is an optionally substituted C₃₋₇cycloalkyl group or optionally substituted C₃₋₇cycloalkyl-C₁₋₇alkyl group.

Examples of such groups include, but are not limited to, the following:



15

R^{A2} Comprising a Phosphonic Acid Group: Bone Targeting Moieties

In one embodiment, R^{A2} independently is, or comprises, a phosphonic acid group.

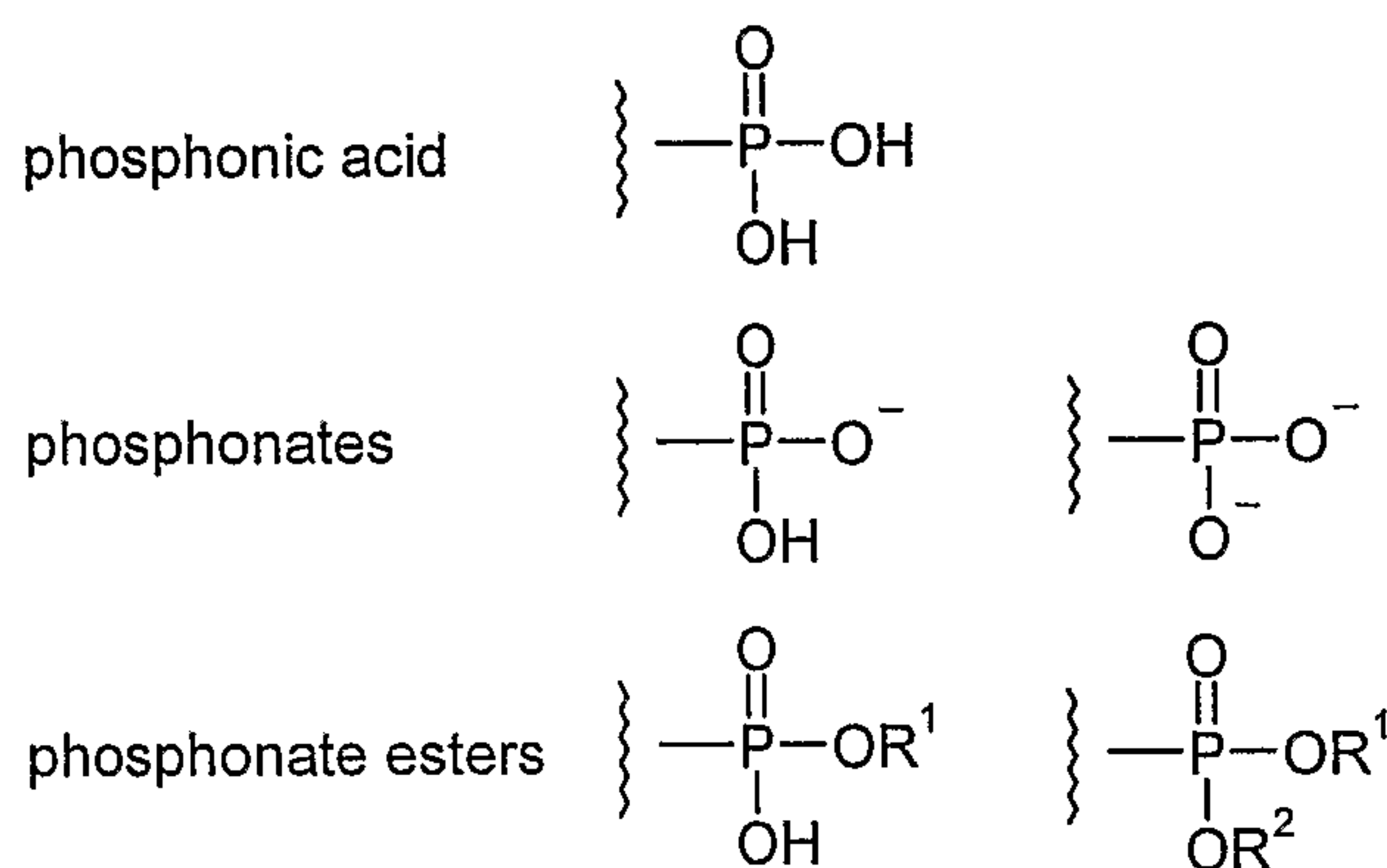
20

- 45 -

In one embodiment, R^{A2} independently is, or comprises, a phosphonic acid group selected from phosphonic acid, and salts (e.g. phosphonates) and esters (e.g., phosphonate esters) thereof.

- 5 Without wishing to be bound by any particular theory, it is believed that such groups act as bone targeting moieties, and improve delivery of the compound to the bone environment.

- 10 Examples of such substituents are shown below. For the phosphonate esters, the groups R^1 and R^2 are independently C_{1-7} alkyl, C_{3-20} heterocyclyl, or C_{5-20} aryl, preferably C_{1-7} alkyl.

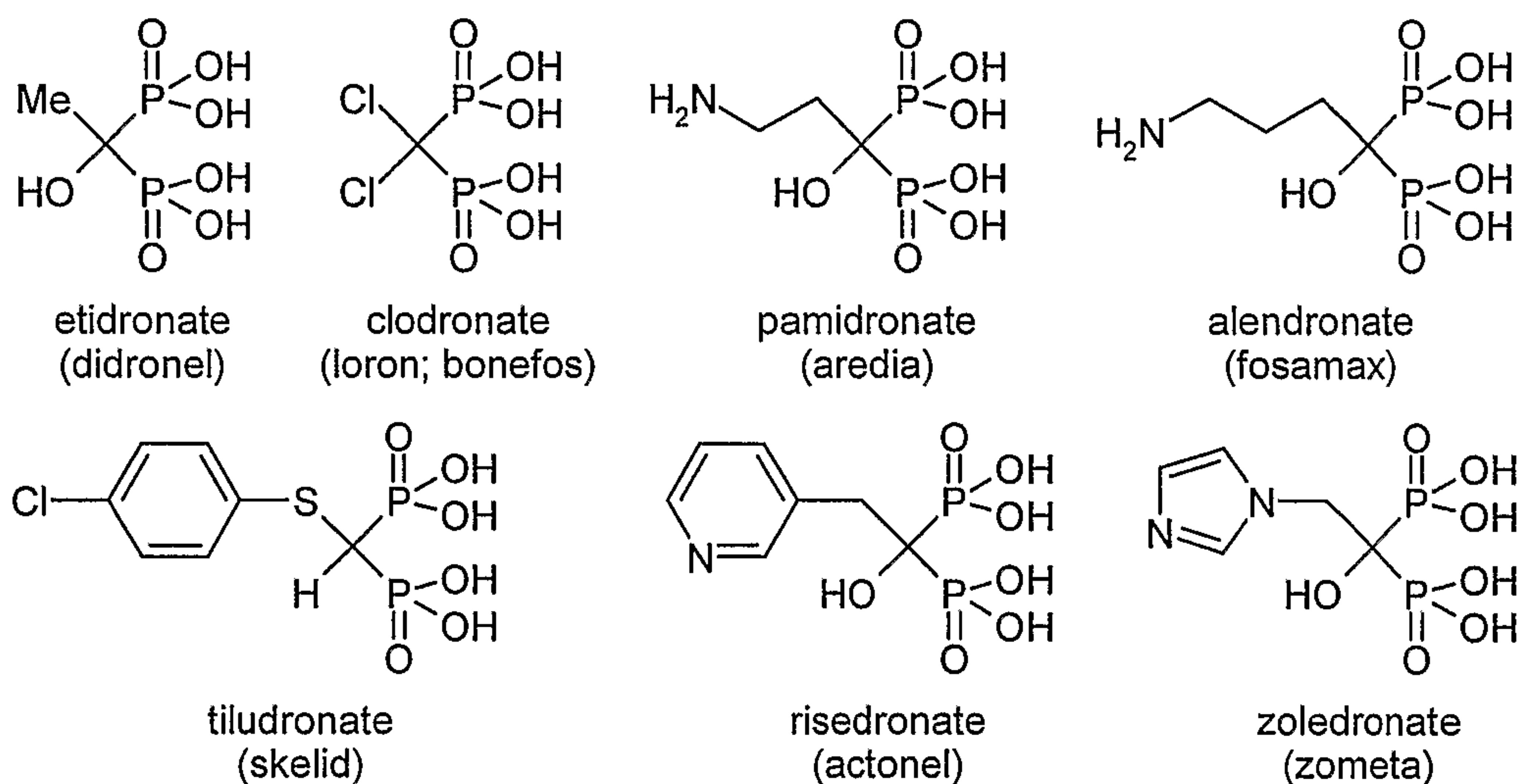


- 15 Where the group is a phosphonate bearing a charge of (-1) or (-2), it will be associated with a suitable number of cation or cations of suitable charge. Examples of suitable cations are discussed below.

Thus, in one embodiment, R^{A2} is, or comprises, a substituted C_{1-7} alkyl group derived from a bisphosphonate compound.

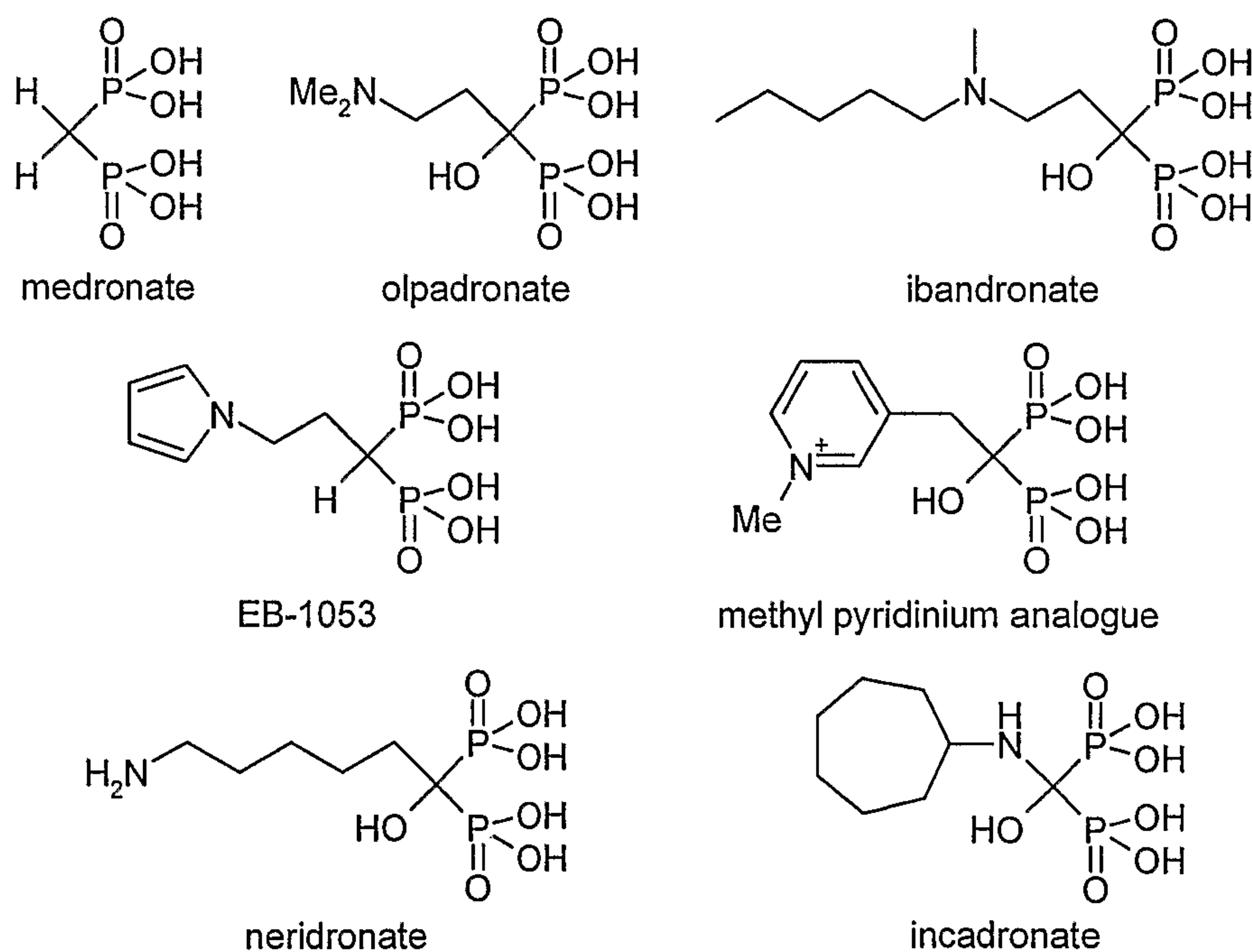
- 46 -

Examples of bisphosphonate compounds currently in use for the treatment of osteoporosis, Paget's disease, and cancer associated bone disease include the following:



5

Examples of bisphosphonate compounds currently in development include the following:



10

In one embodiment, R^{A2} independently is, or comprises, a C_{1-7} alkyl group substituted with one or more groups independently selected from phosphonic acid, and salts (e.g. phosphonates) and esters (e.g., phosphonate esters) thereof.

15

- 47 -

In one embodiment, R^{A2} independently is, or comprises, a C_{1-7} alkyl group substituted with *one* group independently selected from phosphonic acid, and salts (e.g. phosphonates) and esters (e.g., phosphonate esters) thereof.

5

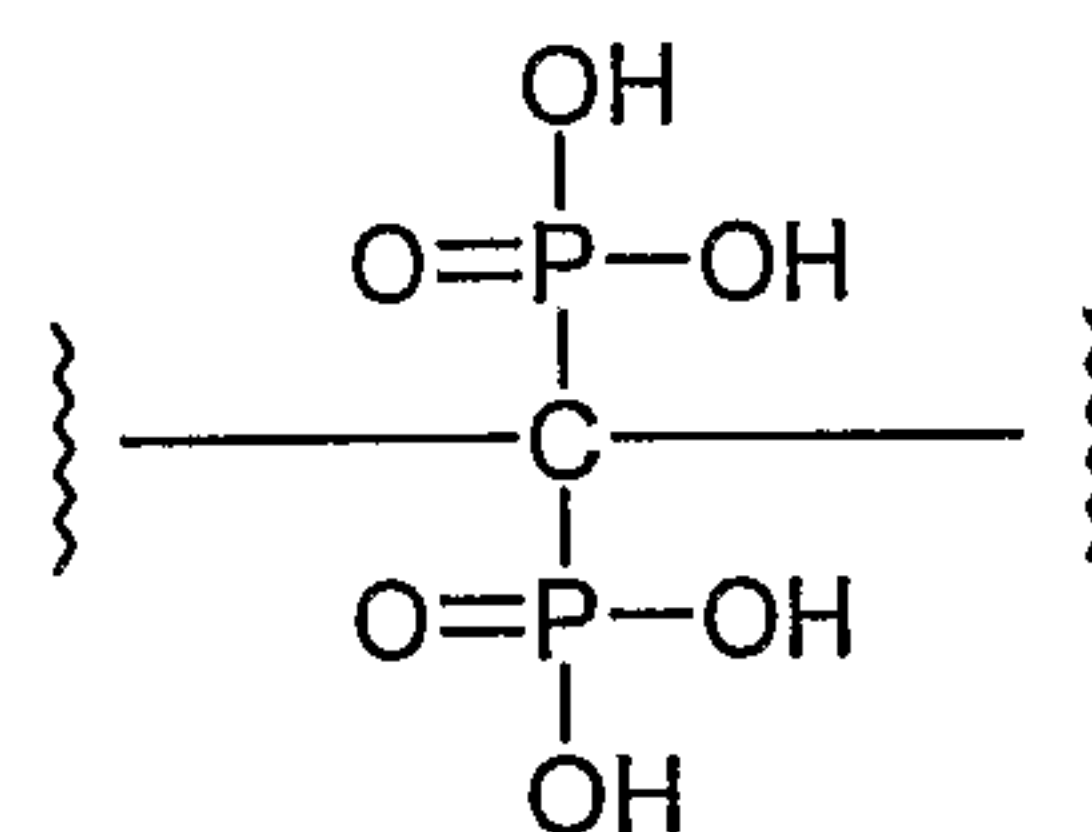
In one embodiment, R^{A2} independently is, or comprises, a C_{1-7} alkyl group substituted with *two* groups independently selected from phosphonic acid, and salts (e.g. phosphonates) and esters (e.g., phosphonate esters) thereof.

10 In one embodiment, R^{A2} independently is, or comprises, a C_{1-7} alkyl group which is substituted with a bisphosphonic acid group, or a salt or ester thereof.

The C_{1-7} alkyl group may optionally be additionally substituted with one or more other groups.

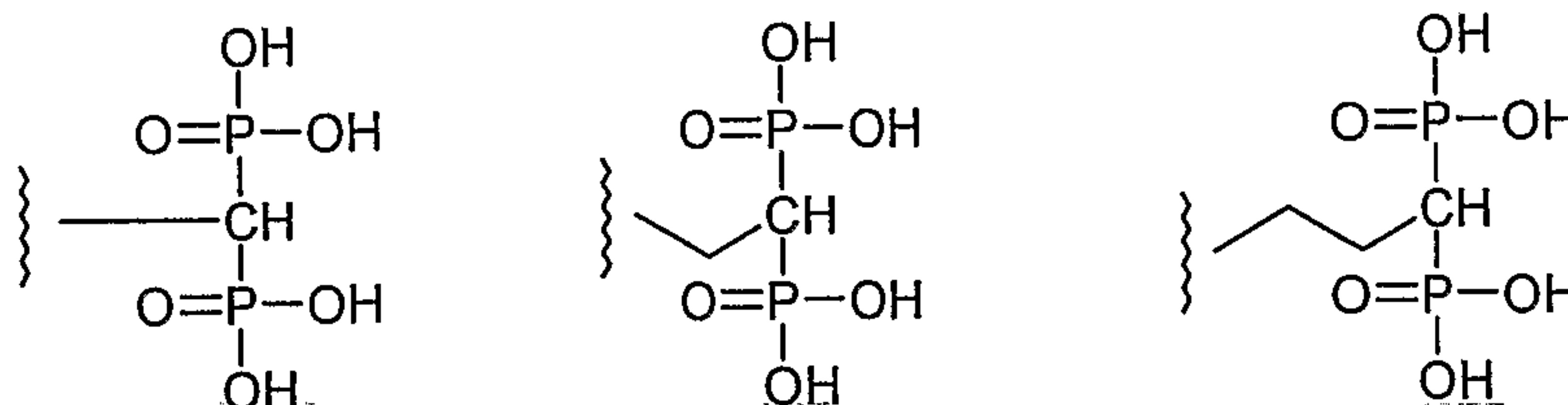
15

In one embodiment, R^{A2} independently is, or comprises, a C_{1-7} alkyl group which comprises a bisphosphonic acid group of the following formula, or a salt or ester thereof:



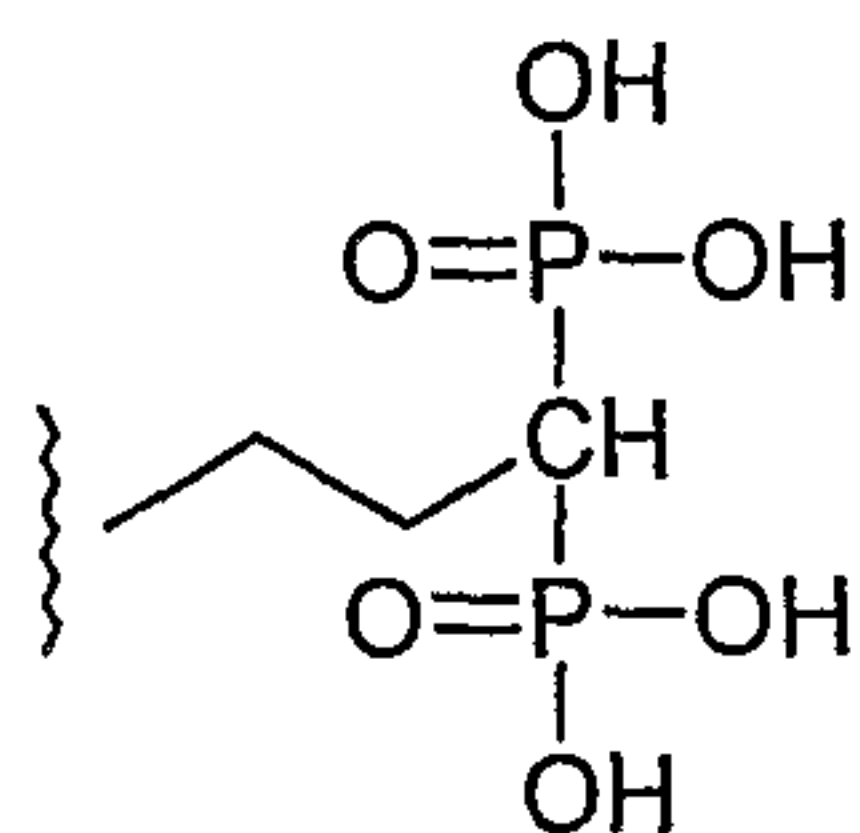
20

In one embodiment, R^{A2} , is independently a group selected from groups of the following formula, or a salt or ester thereof:

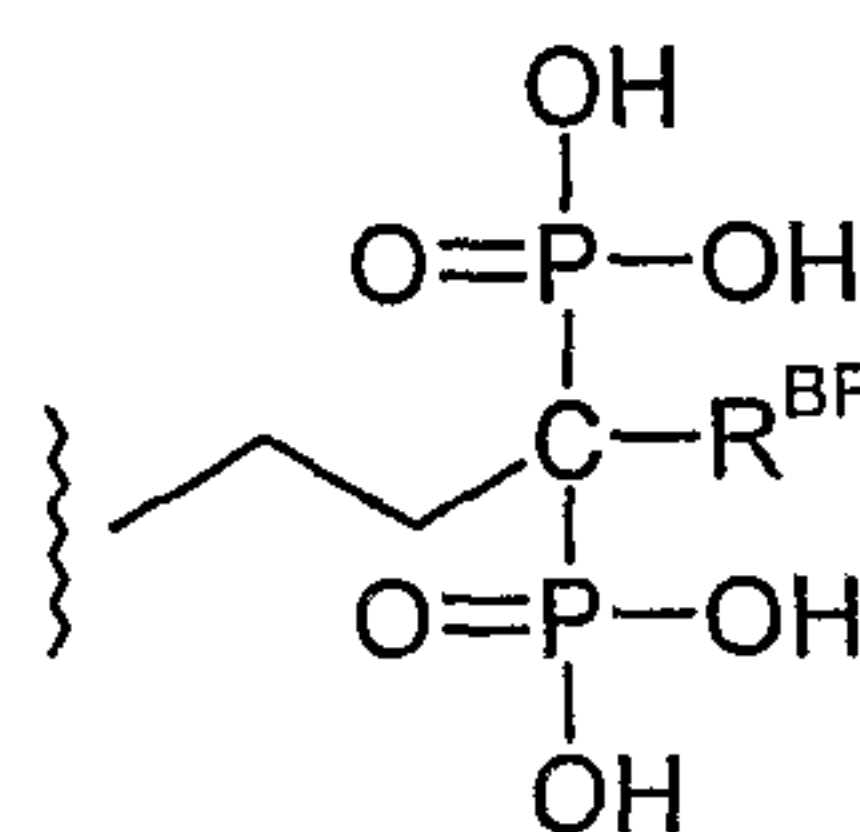


- 48 -

In one embodiment, R^{A2} , is independently a group of the following formula, or a salt or ester thereof:

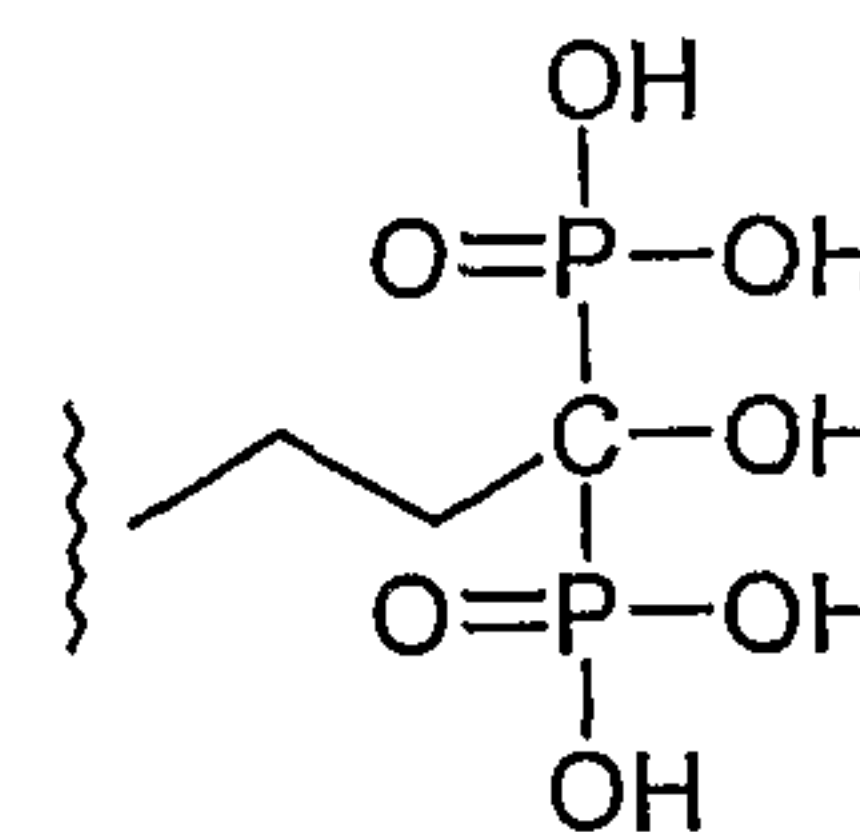


- 5 In one embodiment, R^{A2} is independently a group of the following formula, or a salt or ester thereof, wherein R^{BP} is a bisphosphonate substituent, for example, -H, -OH, -Cl, and C_{1-7} alkyl (including, e.g., unsubstituted C_{1-7} alkyl, C_{1-7} haloalkyl, C_{1-7} hydroxyalkyl, C_{1-7} alkoxyalkyl, C_{1-7} carboxyalkyl, C_{1-7} aminoalkyl, C_{5-20} aryl- C_{1-7} alkyl).



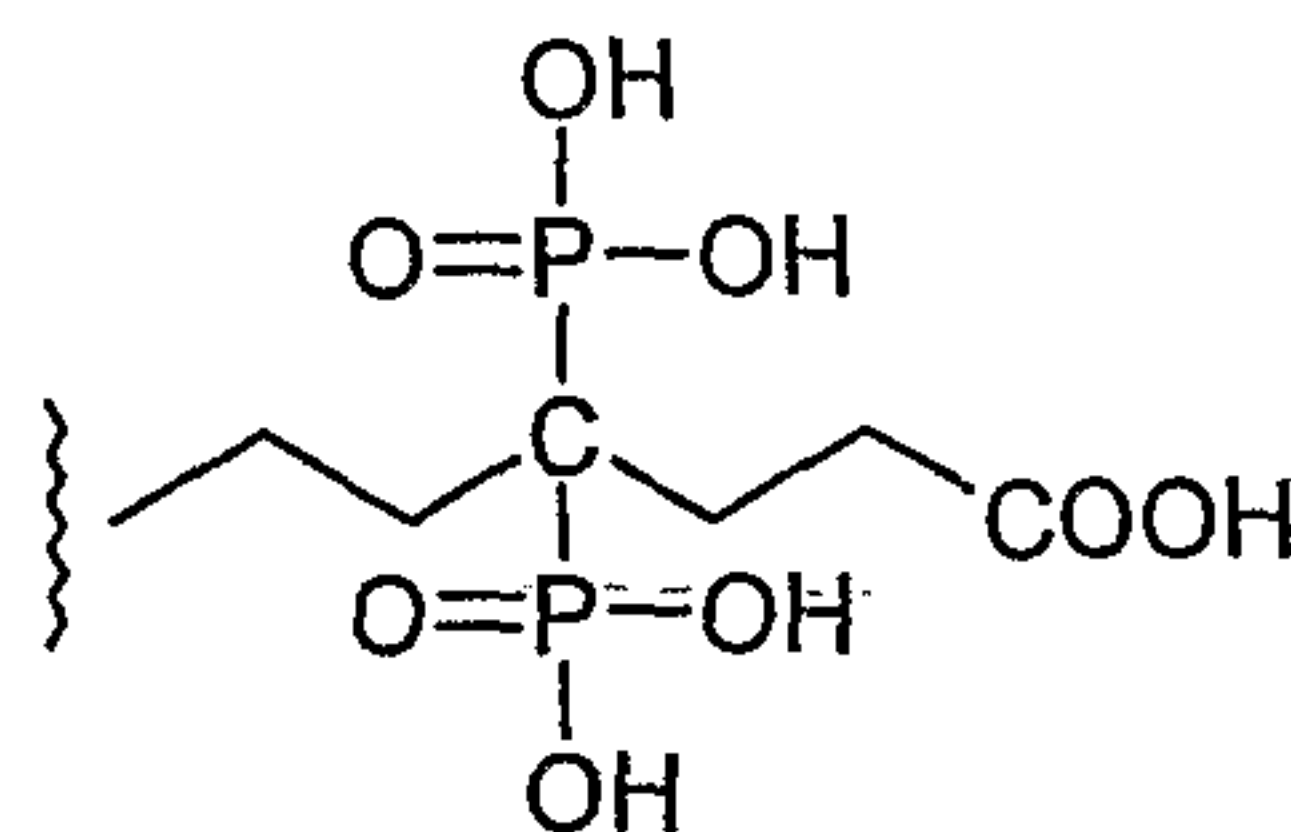
10

In one embodiment, R^{A2} is independently a group of the following formula, or a salt or ester thereof:



15

In one embodiment, R^{A2} is independently a group of the following formula, or a salt or ester thereof:



- 49 -

R^{A2} Comprising a Ca²⁺ Binding Group: Bone Targeting Moieties

In one embodiment, R^{A2} independently is or comprises a Ca²⁺ binding group.

- 5 The term "Ca²⁺ binding group," as used herein, pertains to a moiety which binds (e.g., complexes) one or more Ca²⁺ ions. Without wishing to be bound by any particular theory, it is believed that such Ca²⁺ binding groups act as bone targeting moieties, and improve delivery of the compound to the bone environment.

10

Examples of Ca²⁺ binding groups include, but are not limited to, those derived from tetracyclin.

Combination Derivatives of Alkane Diols

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In one embodiment, both R¹ and R² are not -H; R¹ and R² are different; and each of R¹ and R² is independently a (non -H) group as described above. Such compounds may be conveniently referred to as "asymmetric" compounds.

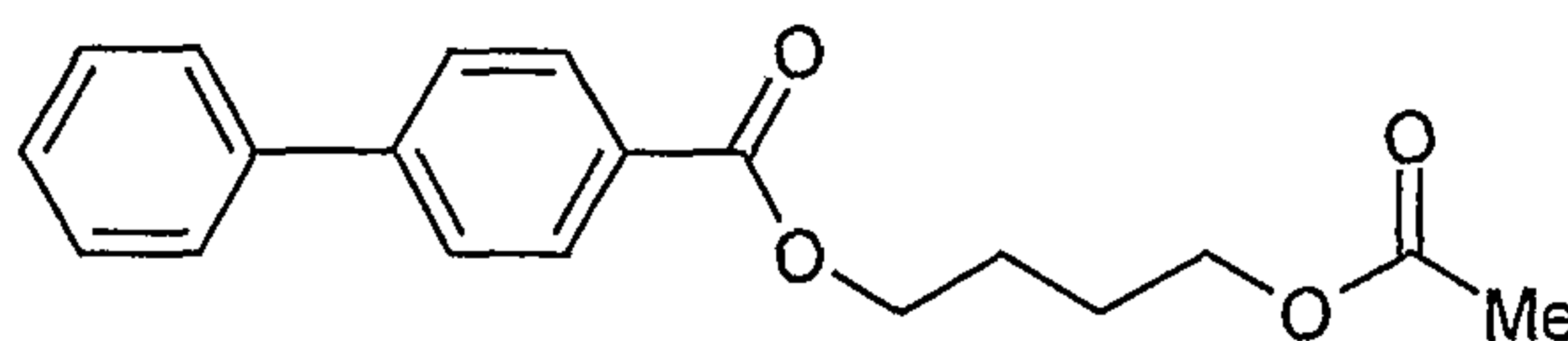
- 20 In one embodiment, both R¹ and R² are not -H; R¹ and R² are different; R¹ is a group of the formula -C(=O)R^{A1}, where R^{A1} is an optionally substituted aryl group, as described above; and, R² is independently a (non -H) group, as described above.

- 25 In one embodiment, both R¹ and R² are not -H; R¹ and R² are different; R¹ is a group of the formula -C(=O)R^{A1}, where R^{A1} is an optionally substituted aryl group, as described above; and, R² is a group of the formula -C(=O)R^{A2}, where R^{A2} is as described above (e.g., a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, and is optionally substituted).

30

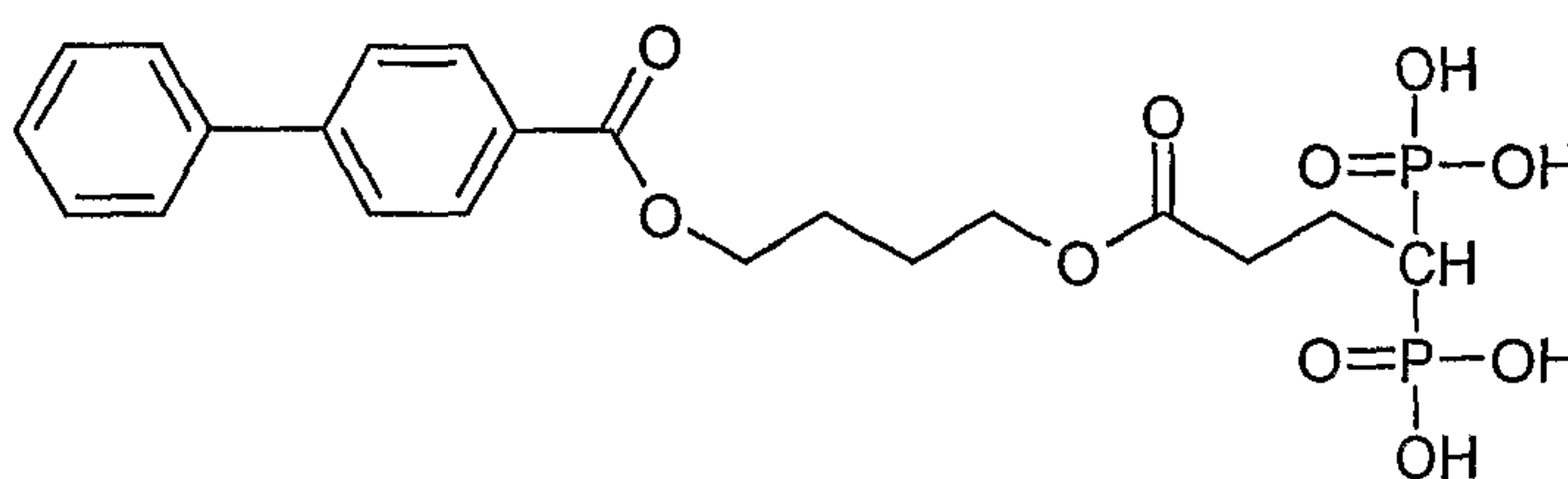
For example, in one embodiment, R^{A1} is an optionally substituted aryl and R^{A2} is a C₁₋₇alkyl group. An example of such an embodiment is:

- 50 -



In one embodiment, both R^1 and R^2 are not -H; R^1 and R^2 are different; R^1 is a group of the formula $-C(=O)R^{A1}$, where R^{A1} is an optionally substituted aryl group, as described above; and, R^2 is a group of the formula $-C(=O)R^{A2}$, where R^{A2} comprises a bone targeting moiety, for example, phosphonic acid group or a Ca^{2+} binding group, as described above.

For example, in one embodiment, the compound has the following formula, or is a salt or ester thereof:



Other Derivatives of Alkane Diols

In one embodiment, the compounds are as described herein, except that the group $-OR^2$ is replaced with another group.

Thus, one aspect of the present invention pertains to compounds which have the following formula:



wherein R^1 and A are as described above, and J is independently selected from hydrogen; halogen; nitrooxy ($-ONO_2$); ether groups (e.g., C_{1-7} alkoxy); groups which are, or comprise, a phosphonic acid group (as described above); and groups which are, or comprise, a Ca^{2+} binding group (as described above); and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, or prodrugs thereof.

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In one embodiment, the compound has the following formula:



wherein R^{A1} , A, and J are as described above.

In one embodiment, J is selected from: hydrogen, halogen, nitrooxy ($-\text{ONO}_2$), and
5 C_{1-7} alkoxy.

In one embodiment, J is selected from: -H, -F, -Cl, -Br, -I, $-\text{ONO}_2$, -OMe, and
-OEt.

10 In one embodiment, J is -H.

In one embodiment, J is selected from: -F, -Cl, -Br, and -I.

In one embodiment, J is $-\text{ONO}_2$.

15

In one embodiment, J is C_{1-7} alkoxy.

In one embodiment, J is selected from: -OMe and -OEt.

20 In one embodiment, J is selected from groups which are, or comprise,
a phosphonic acid group (as described above).

In one embodiment, J is selected from groups which are, or comprise,
a Ca^{2+} binding group (as described above).

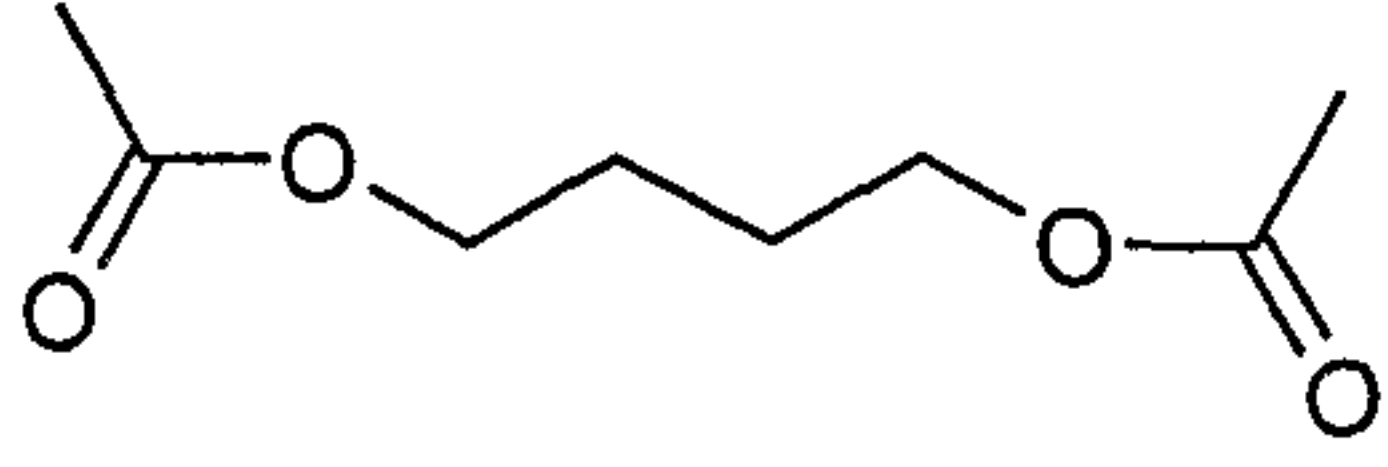
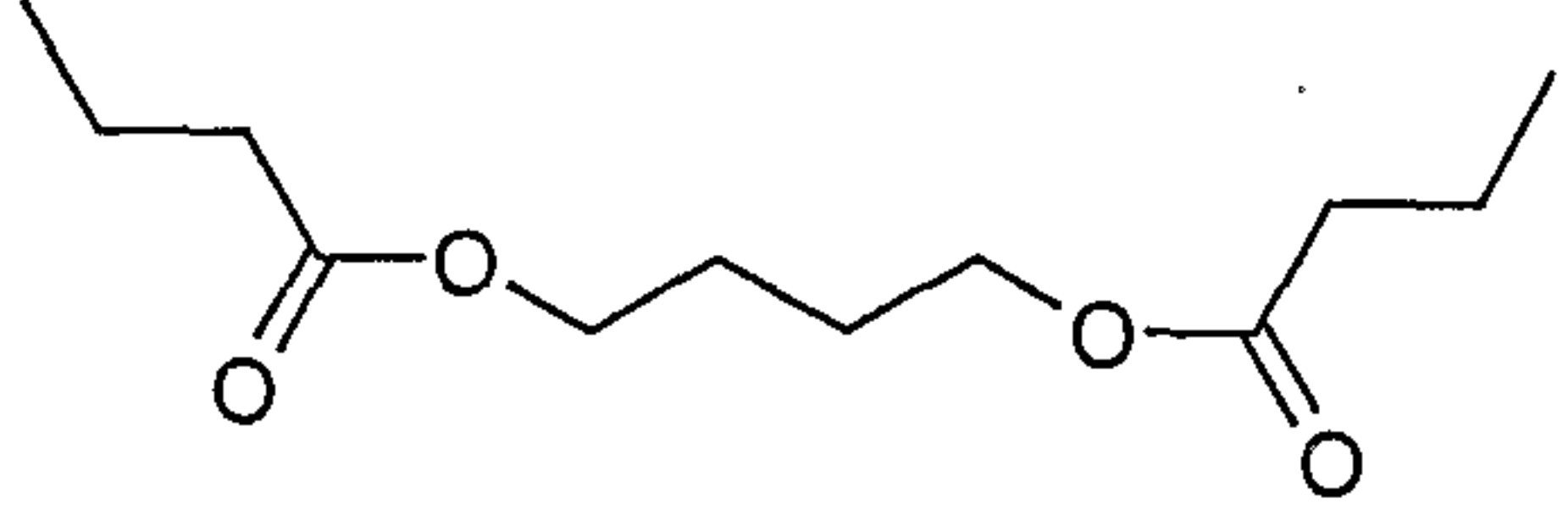
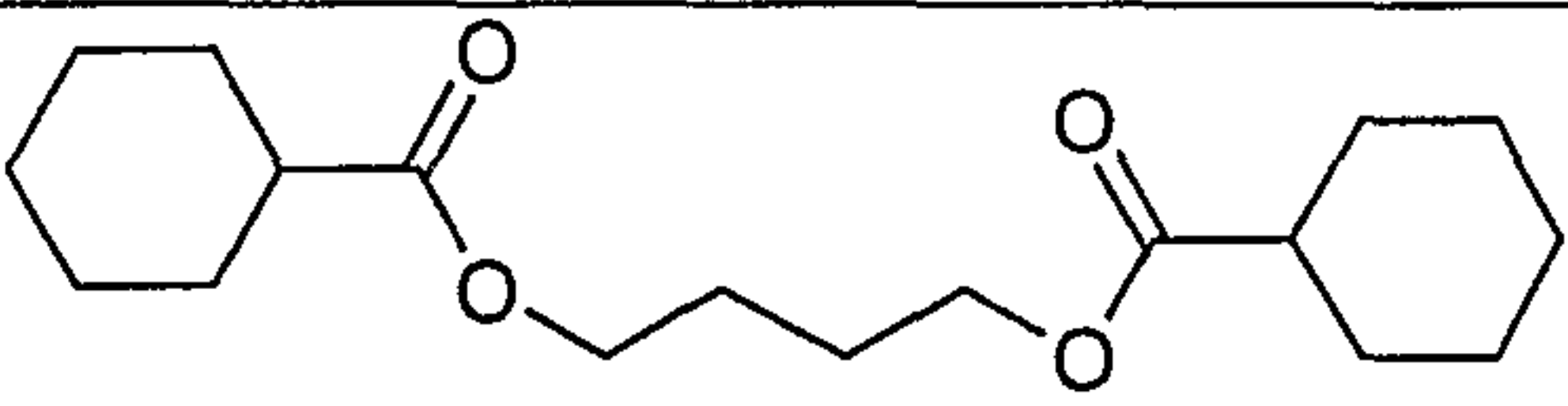
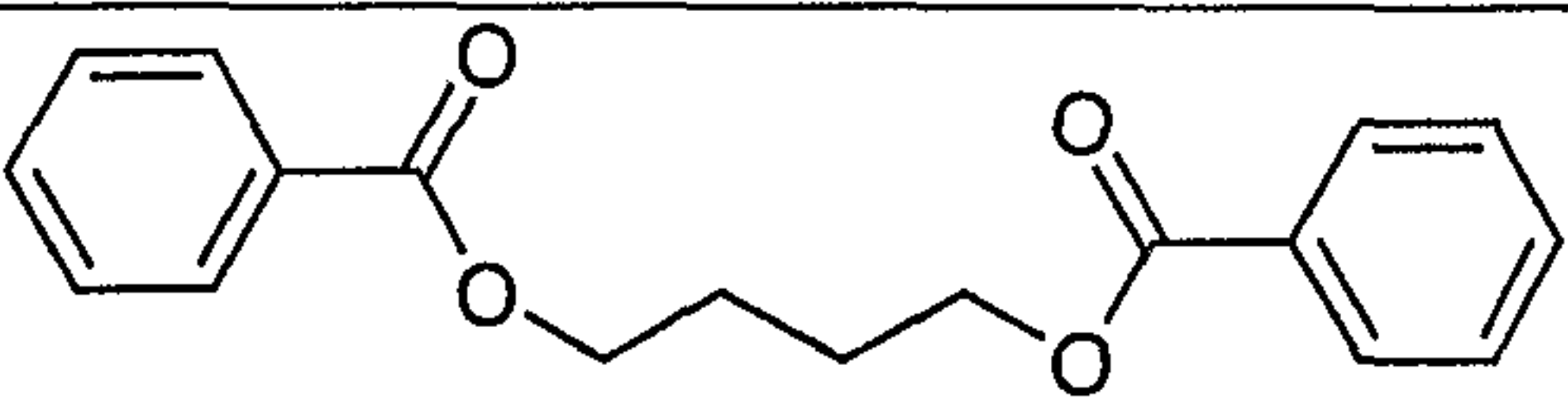
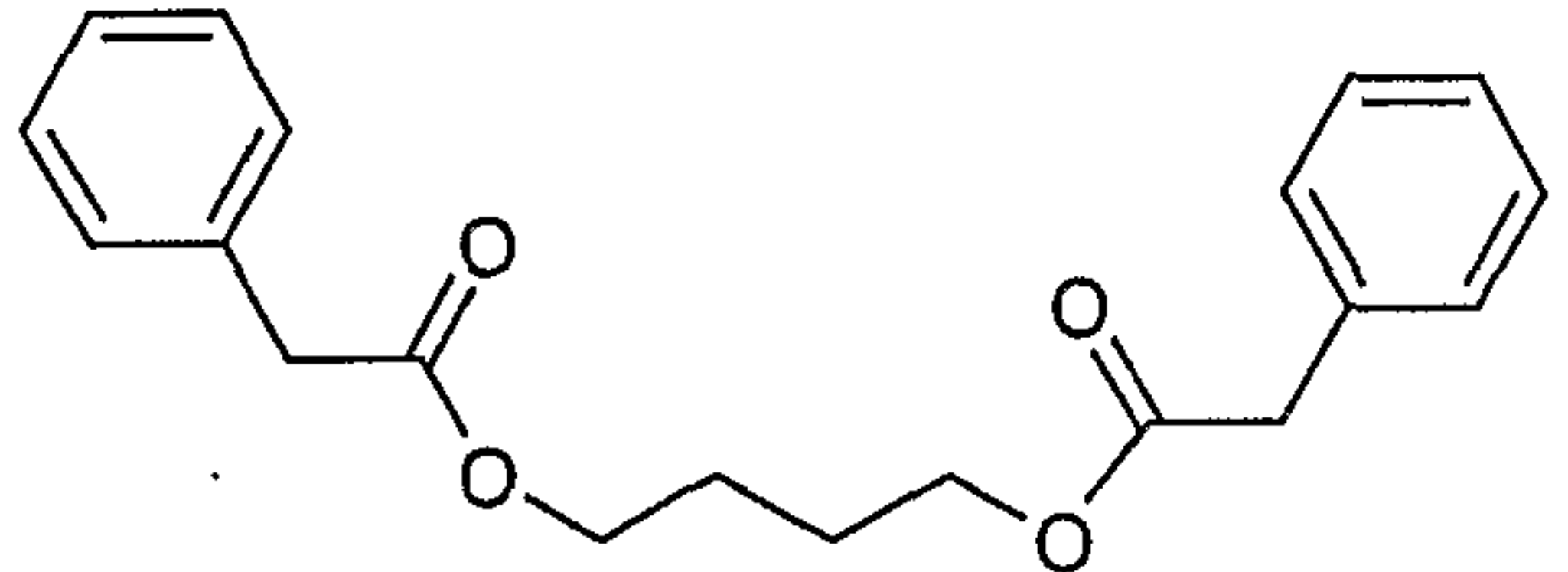
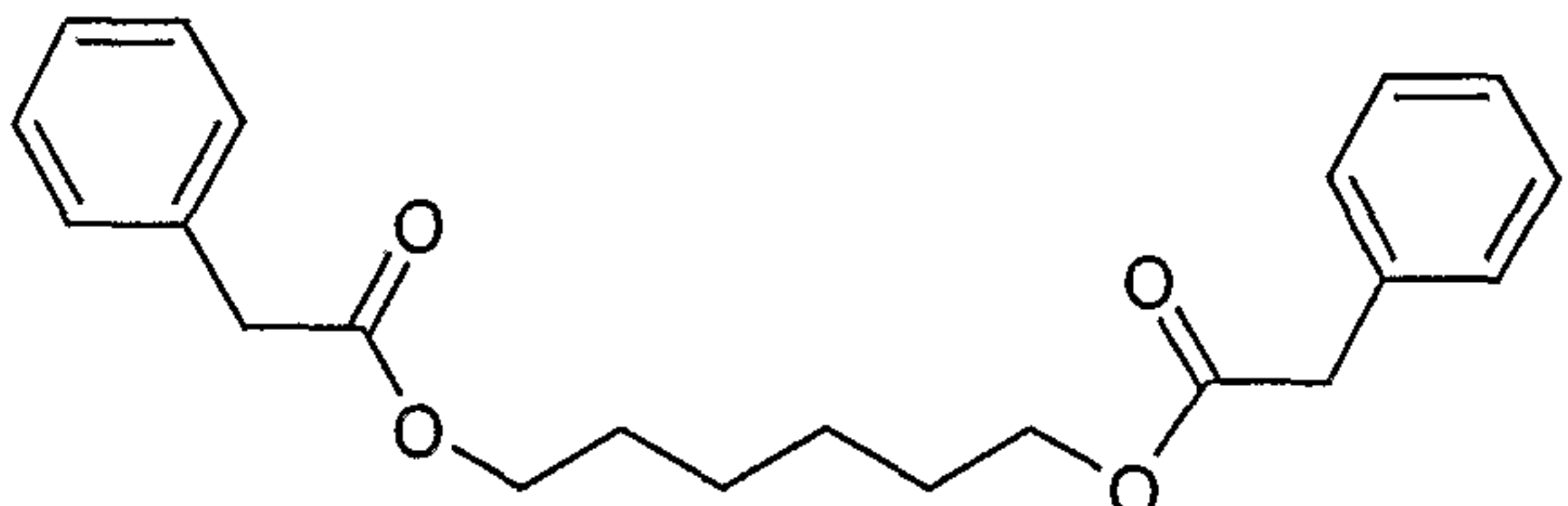
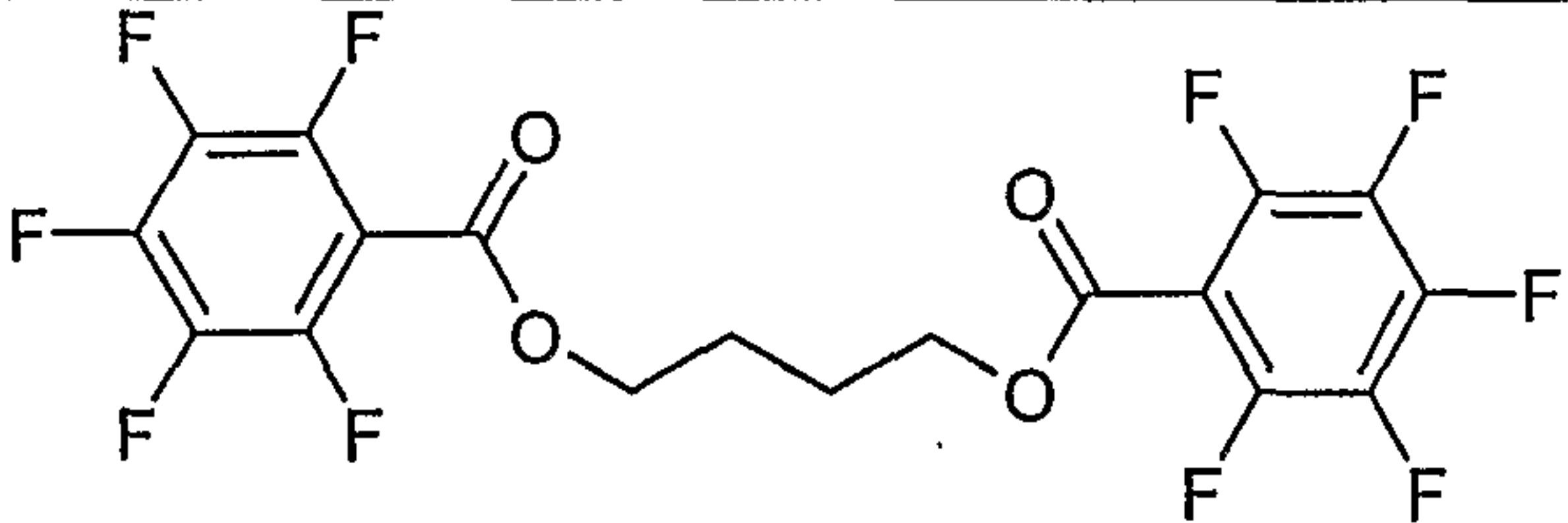
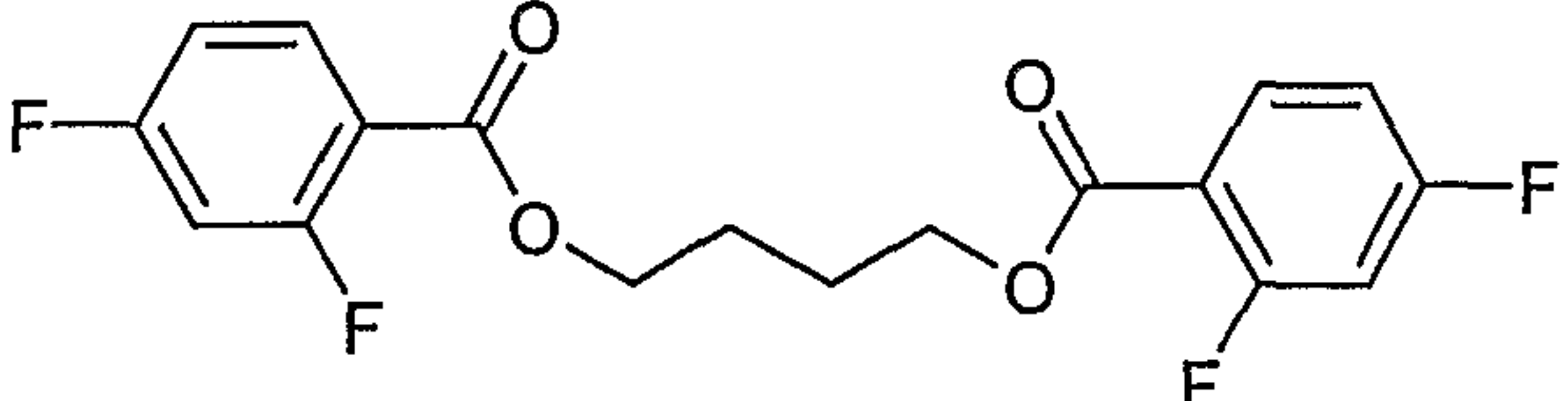
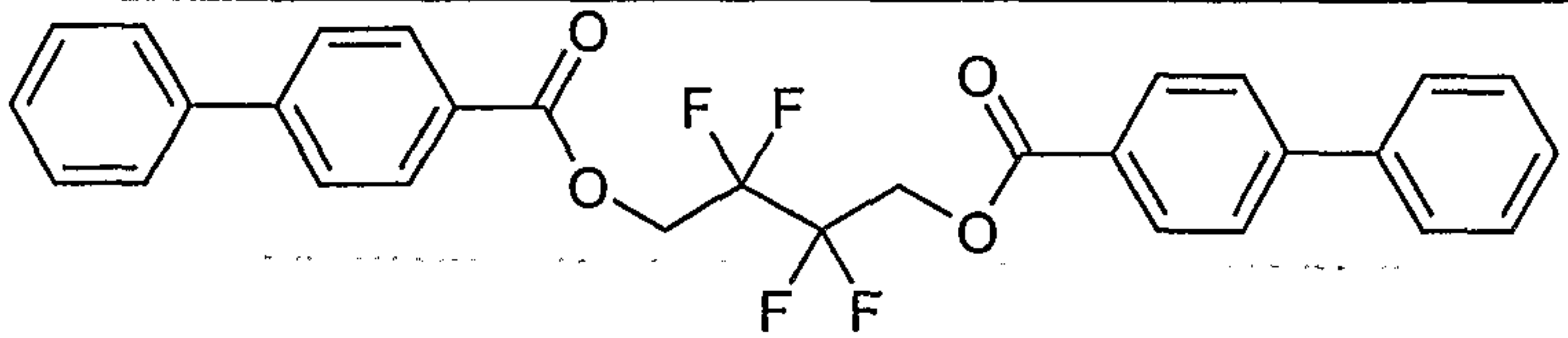
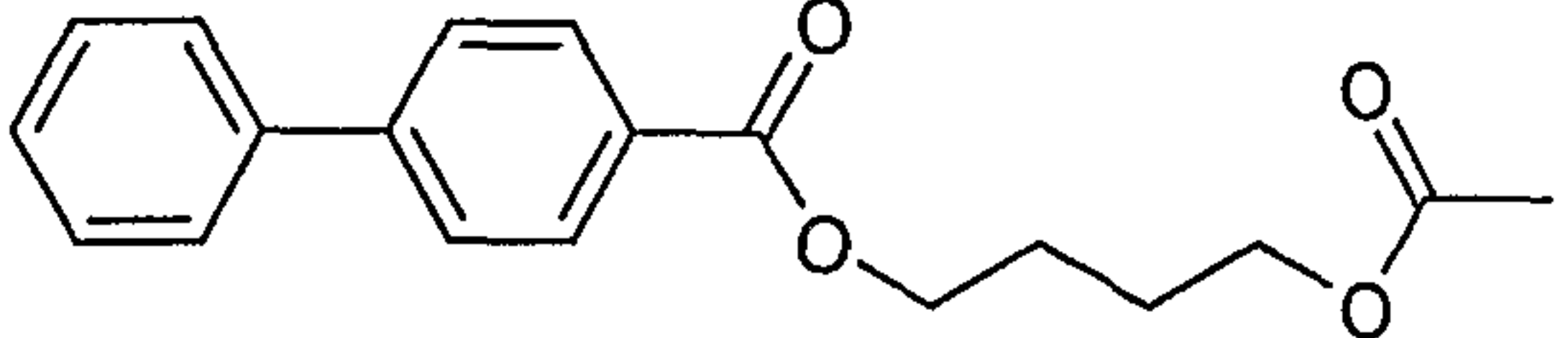
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Examples of Specific Embodiments

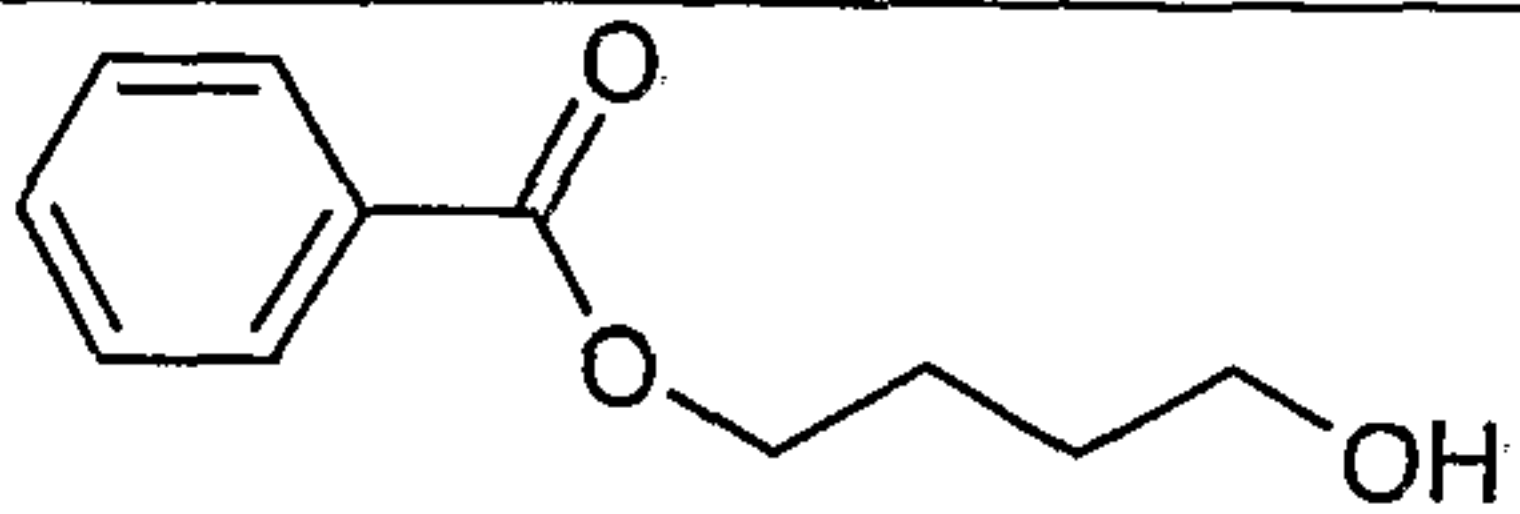
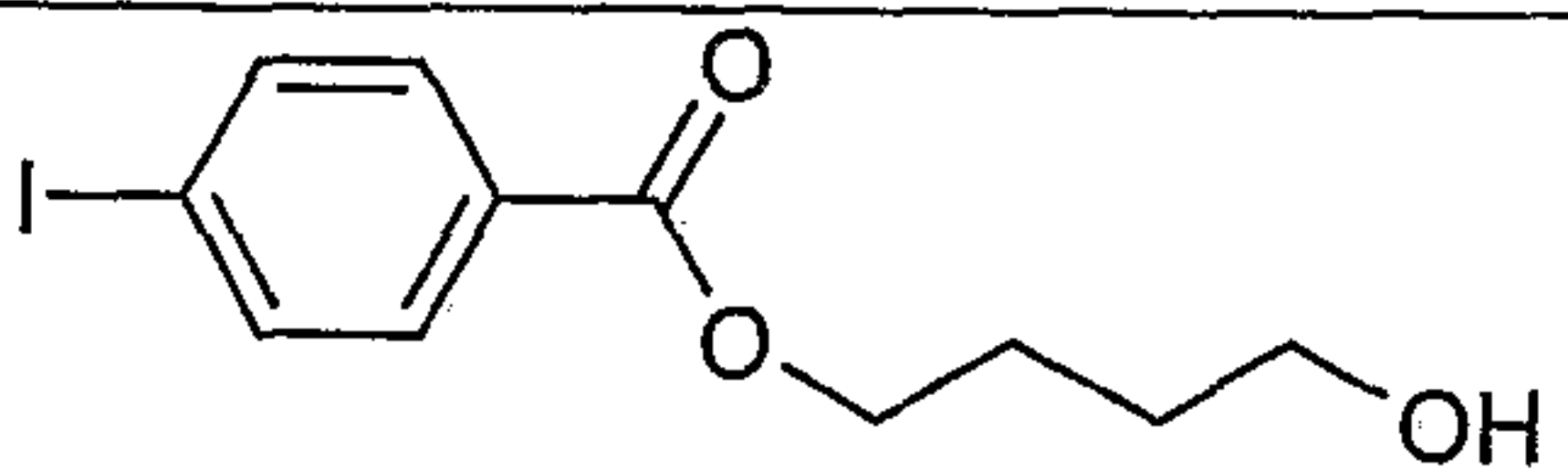
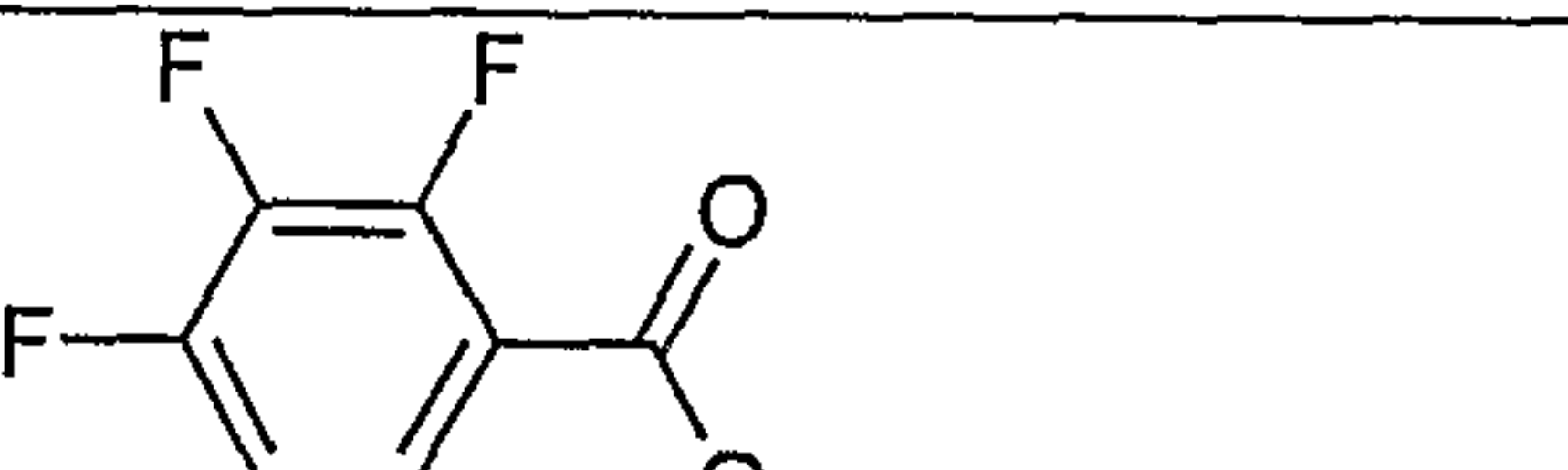
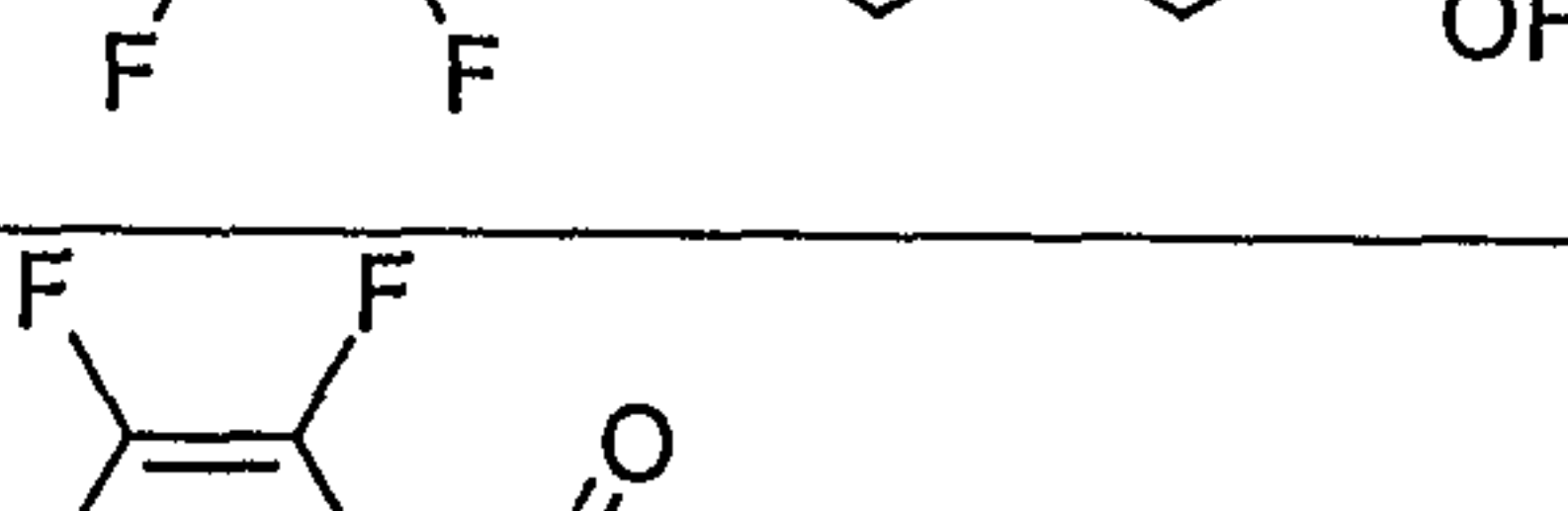
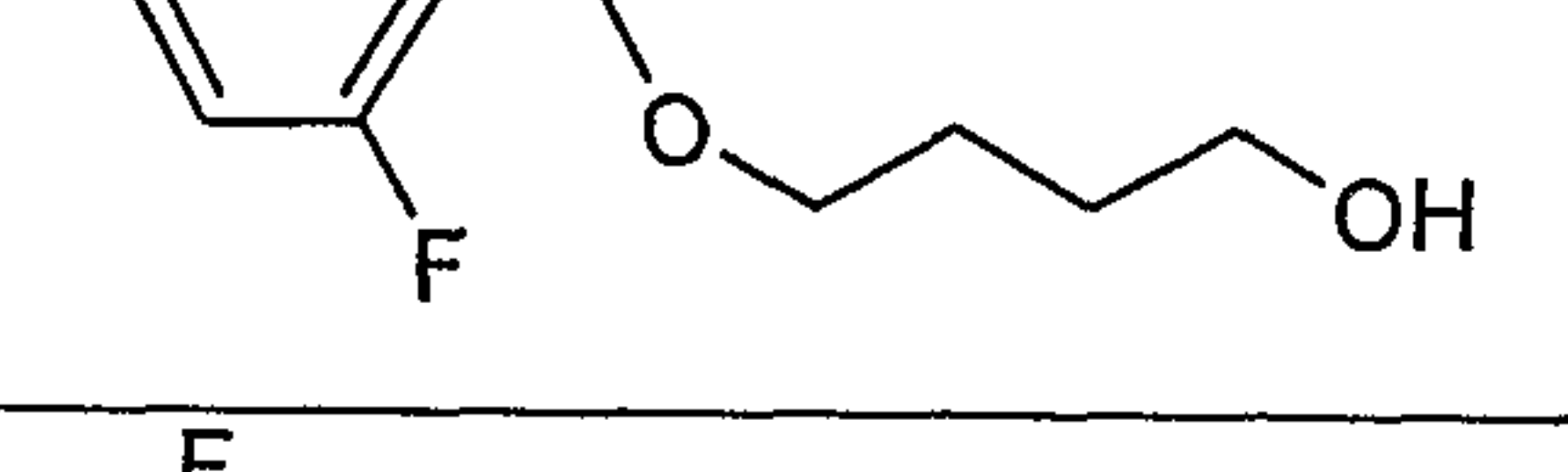
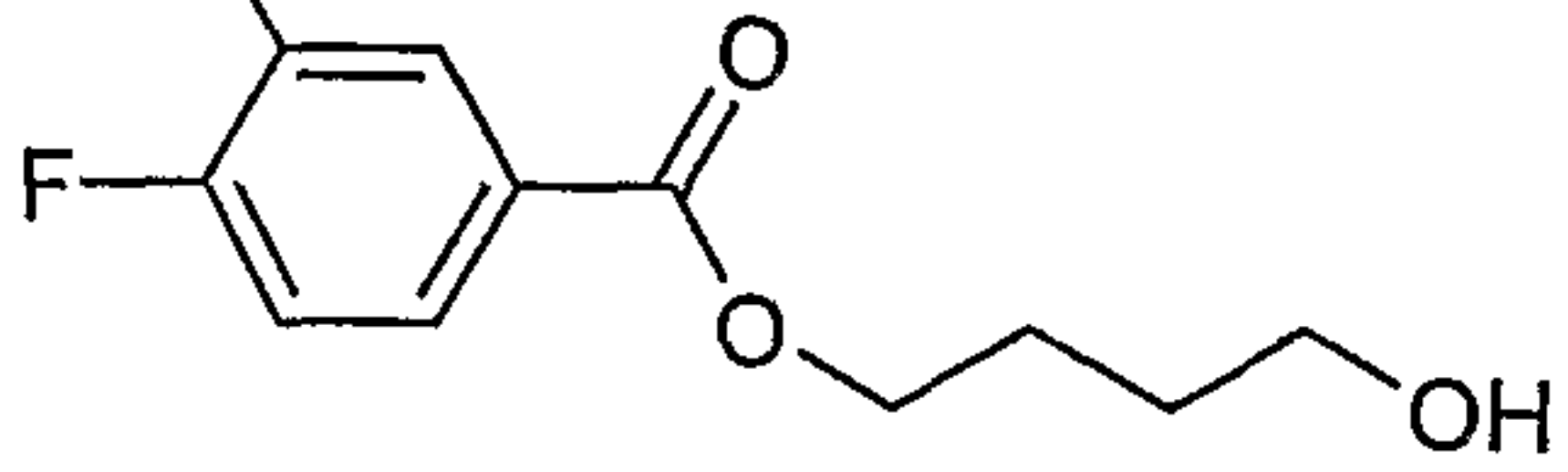
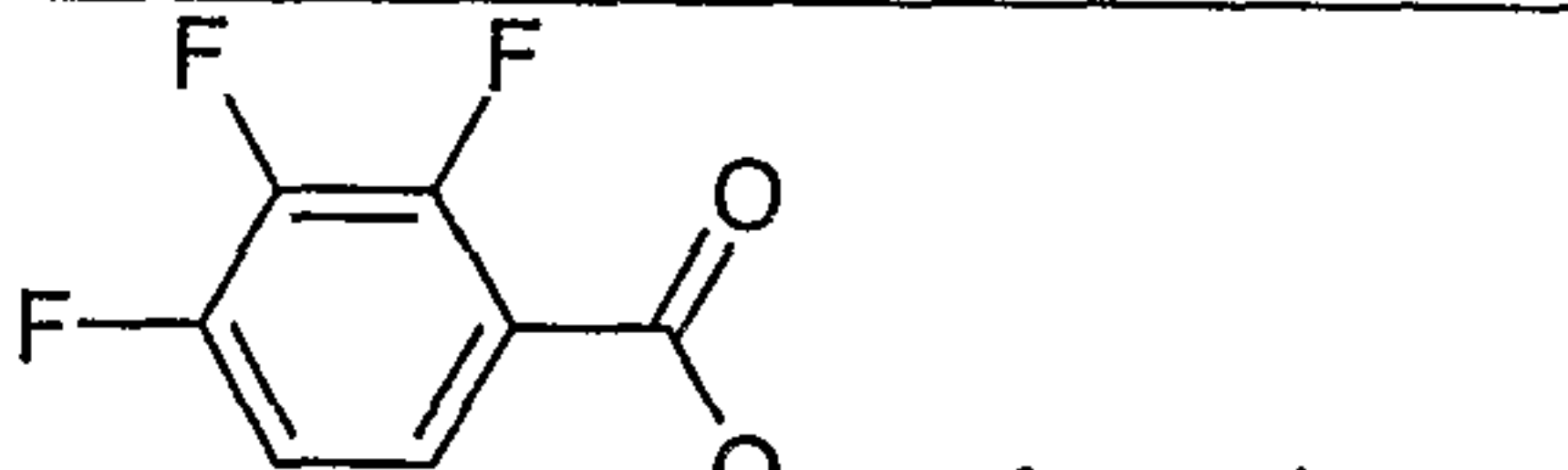
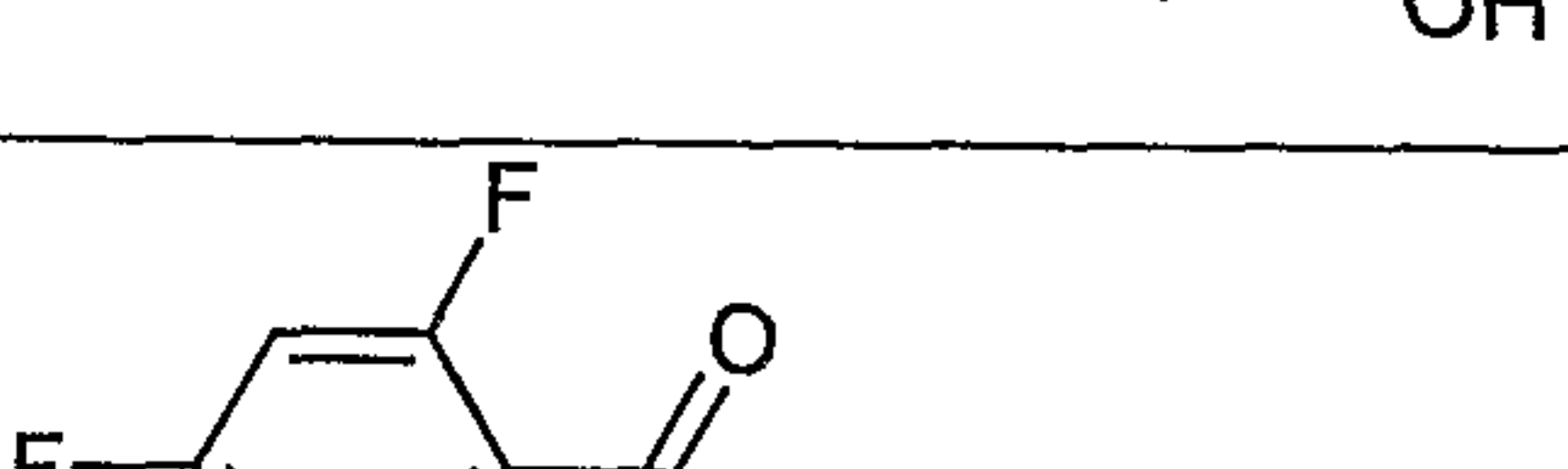
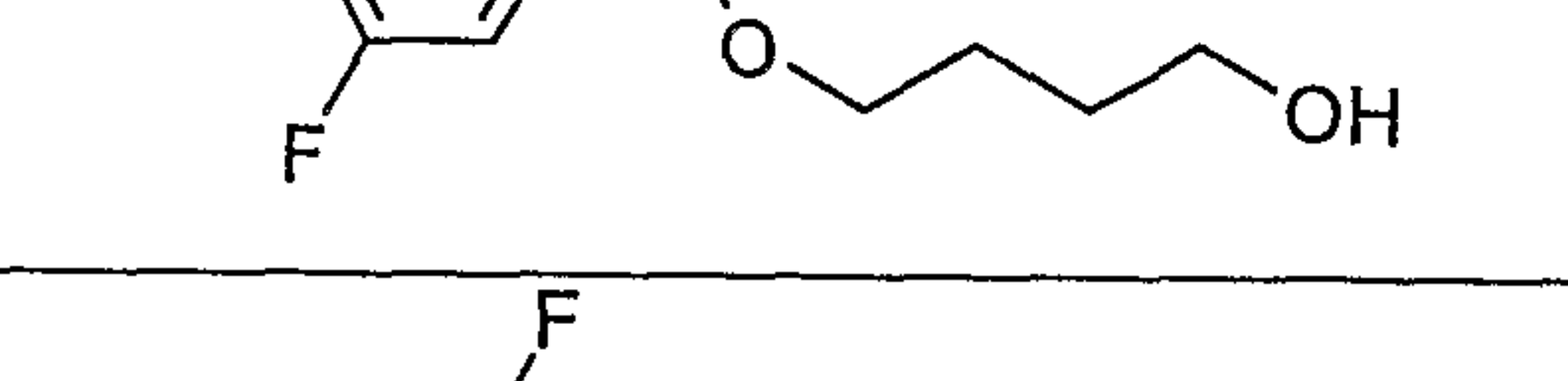
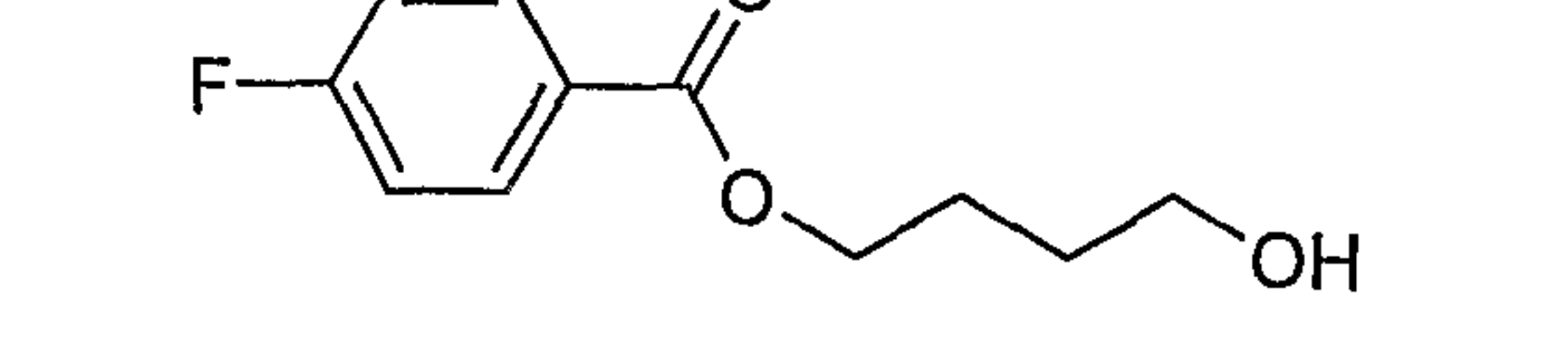
Some individual embodiments of the present invention include the following
compounds.

30

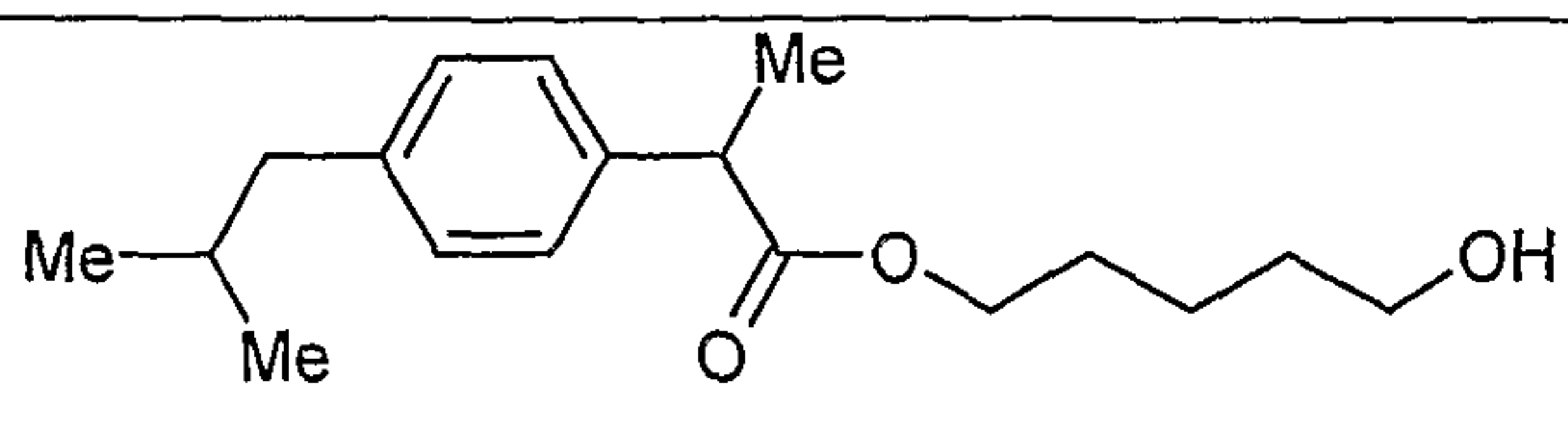
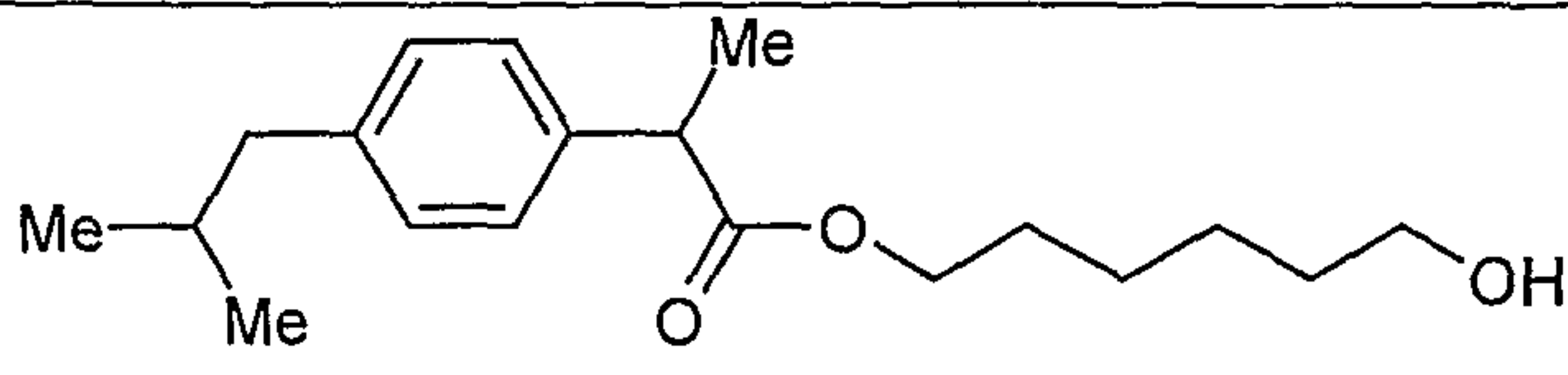
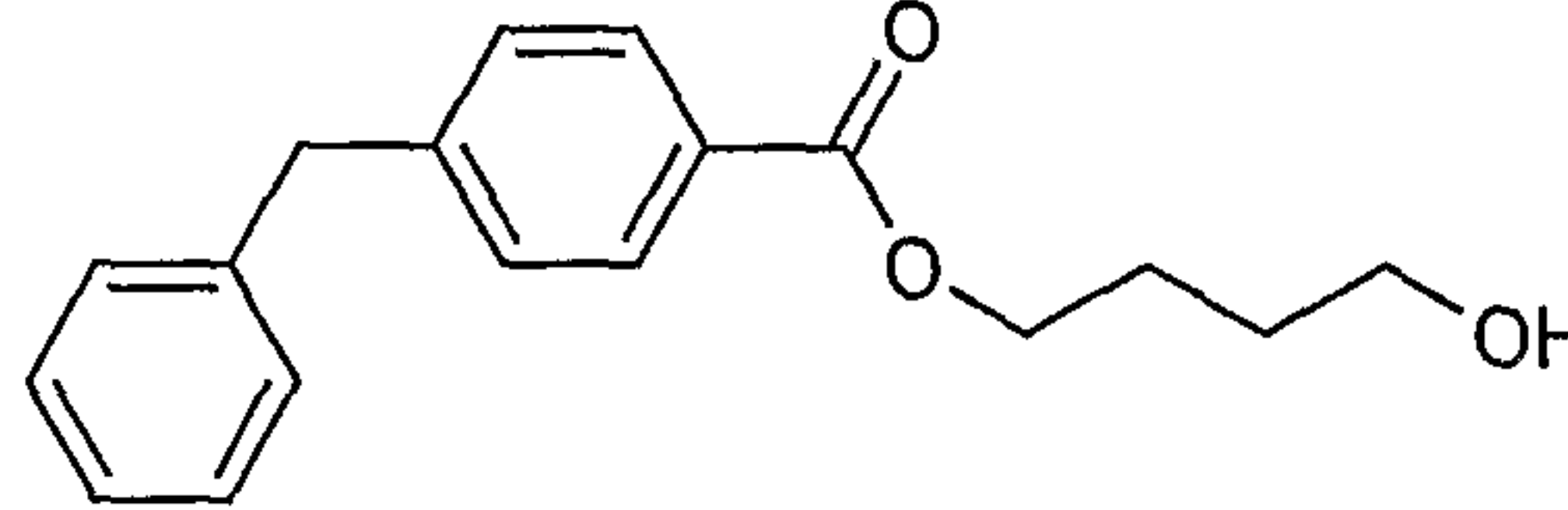
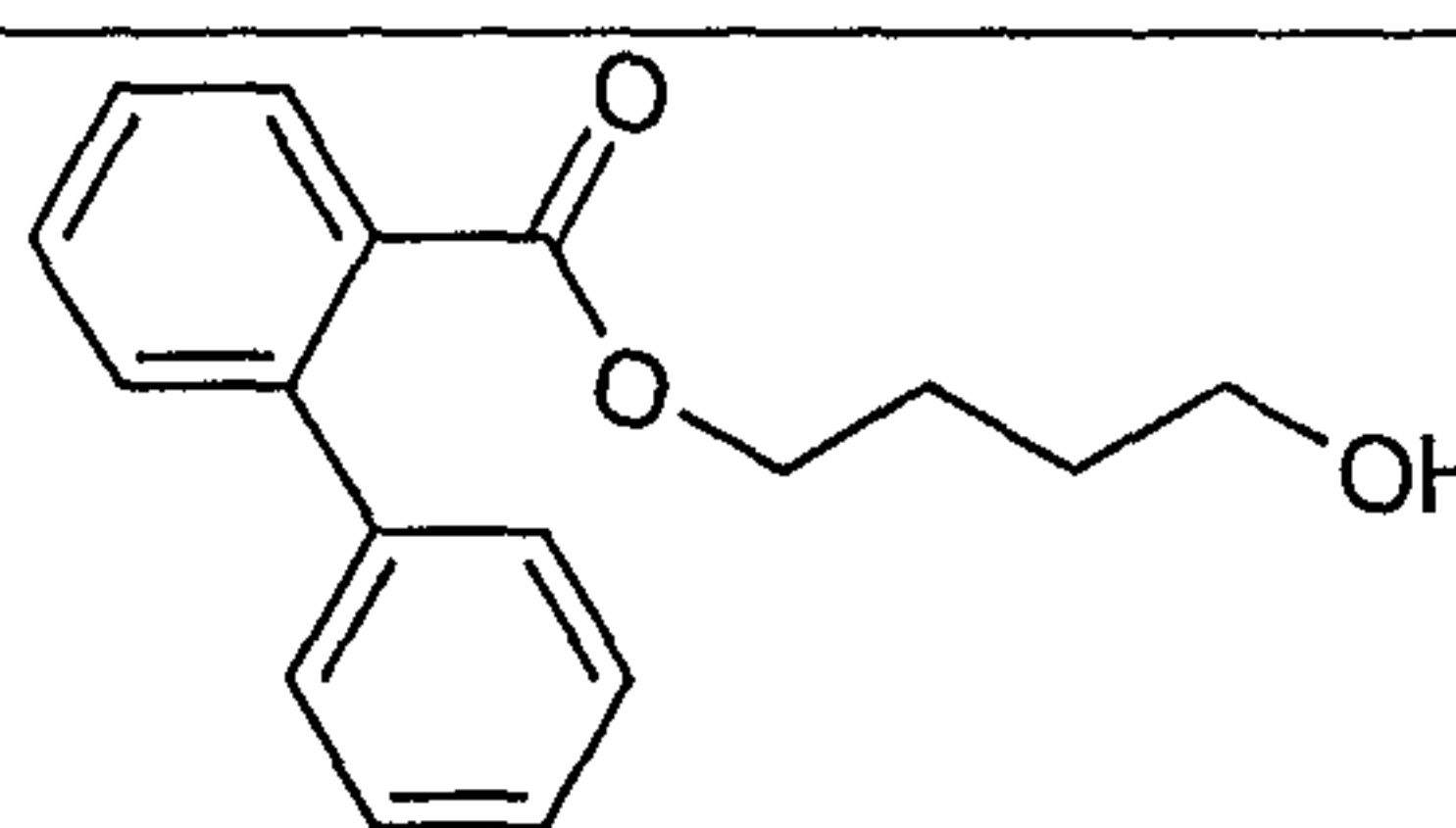
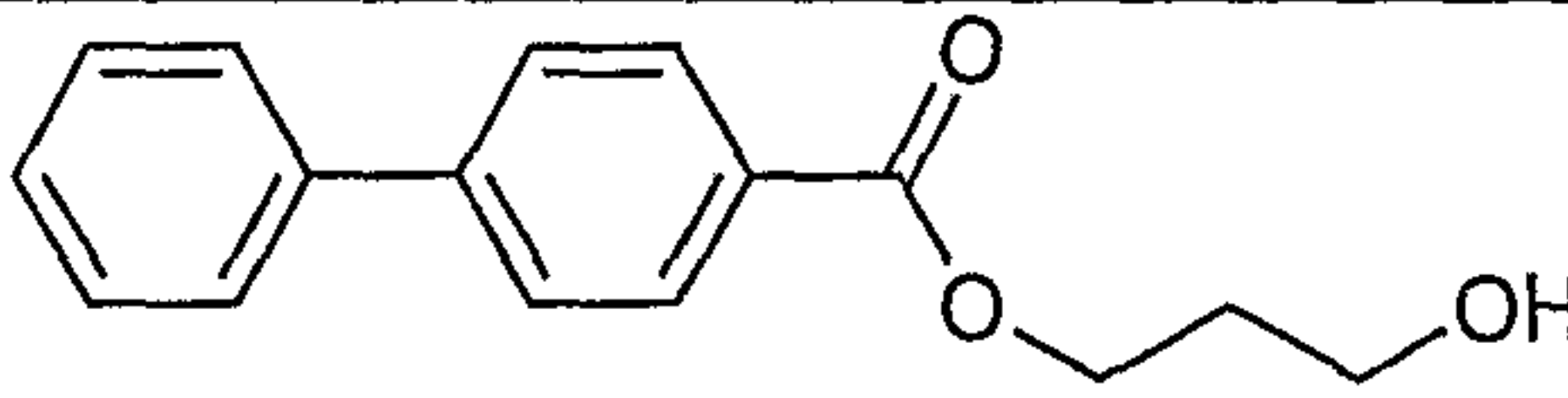
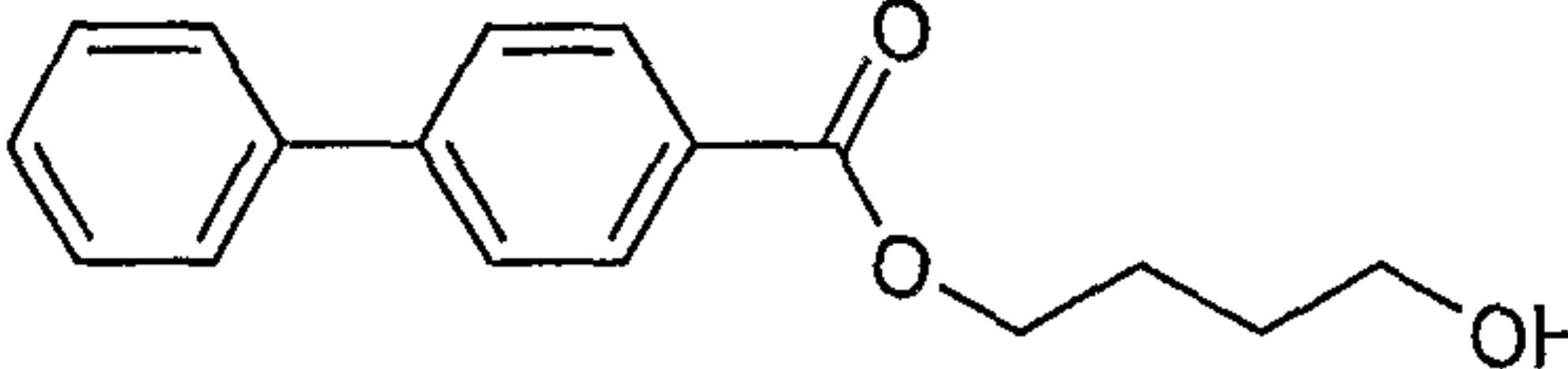
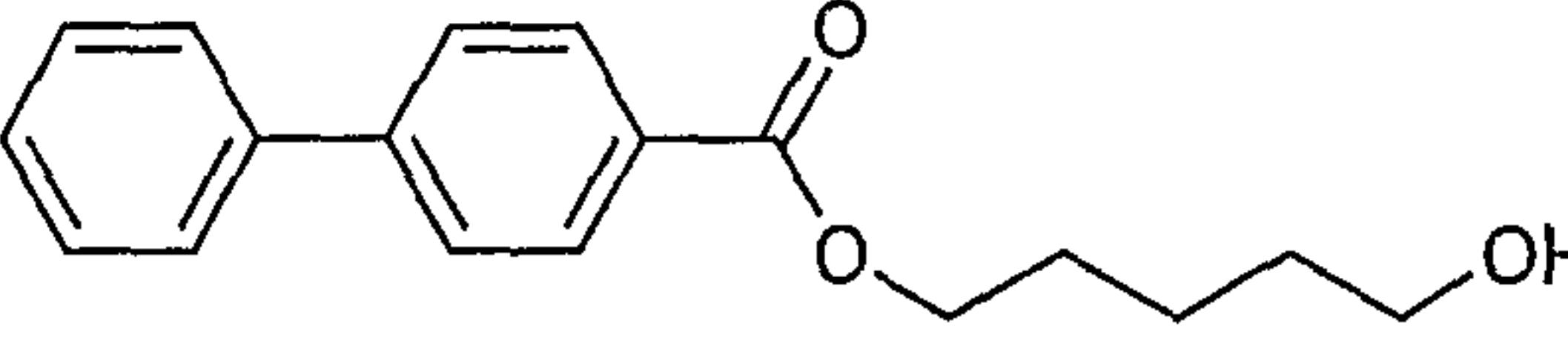
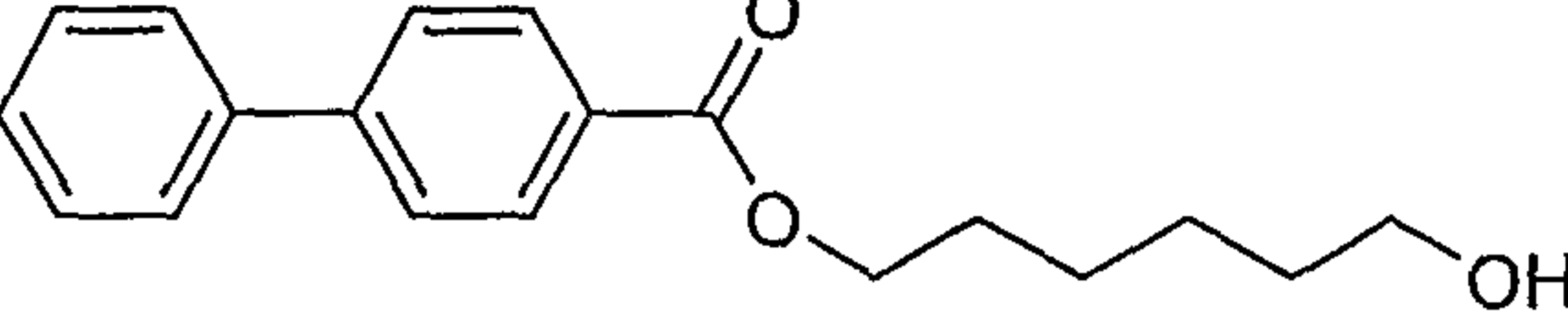
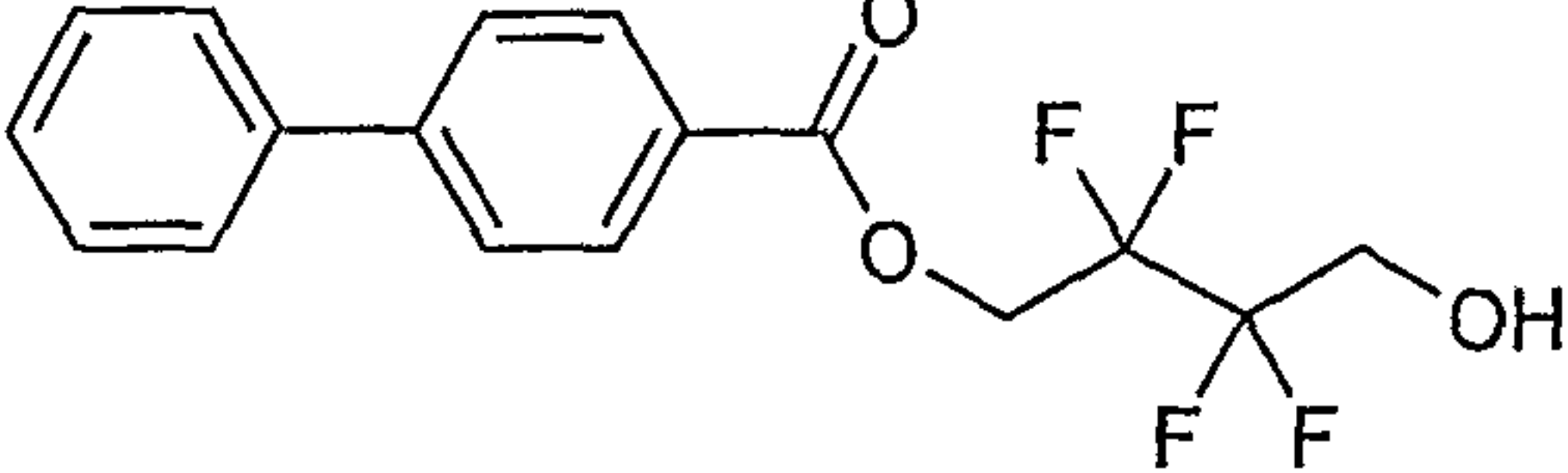
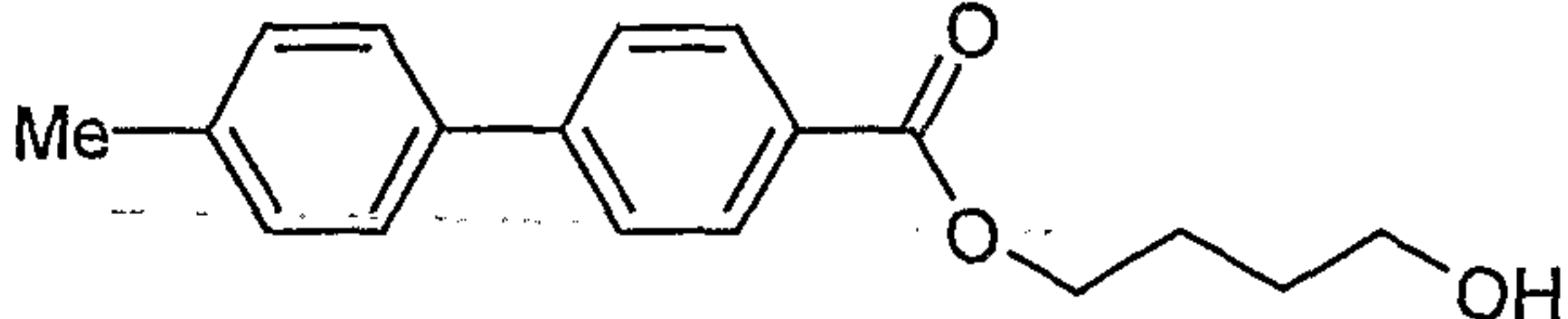
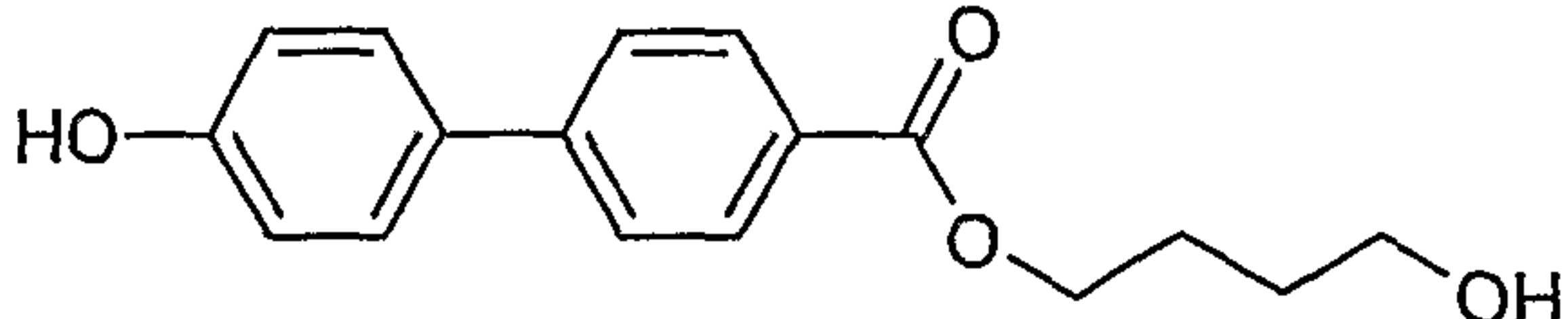
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2	ABD-0007 4BU	
3	ABD-0019 4C	
4	ABD-0009 4B	
5	ABD-0014 4P	
6	ABD-0017 6P	
7	ABD-0085 10F	
8	ABD-0111 D2,4FB	
9	ABD-0096 DBP-4F	
10	ABD-0049 4BP-acetate	

- 53 -

11	ABD-0008 4MB	
12	ABD-0069 4IB	
13	ABD-0077 4FB	
14	ABD-0106 2,3,6-FB	
15	ABD-0107 3,4-FB	
16	ABD-0108 2,3,4-FB	
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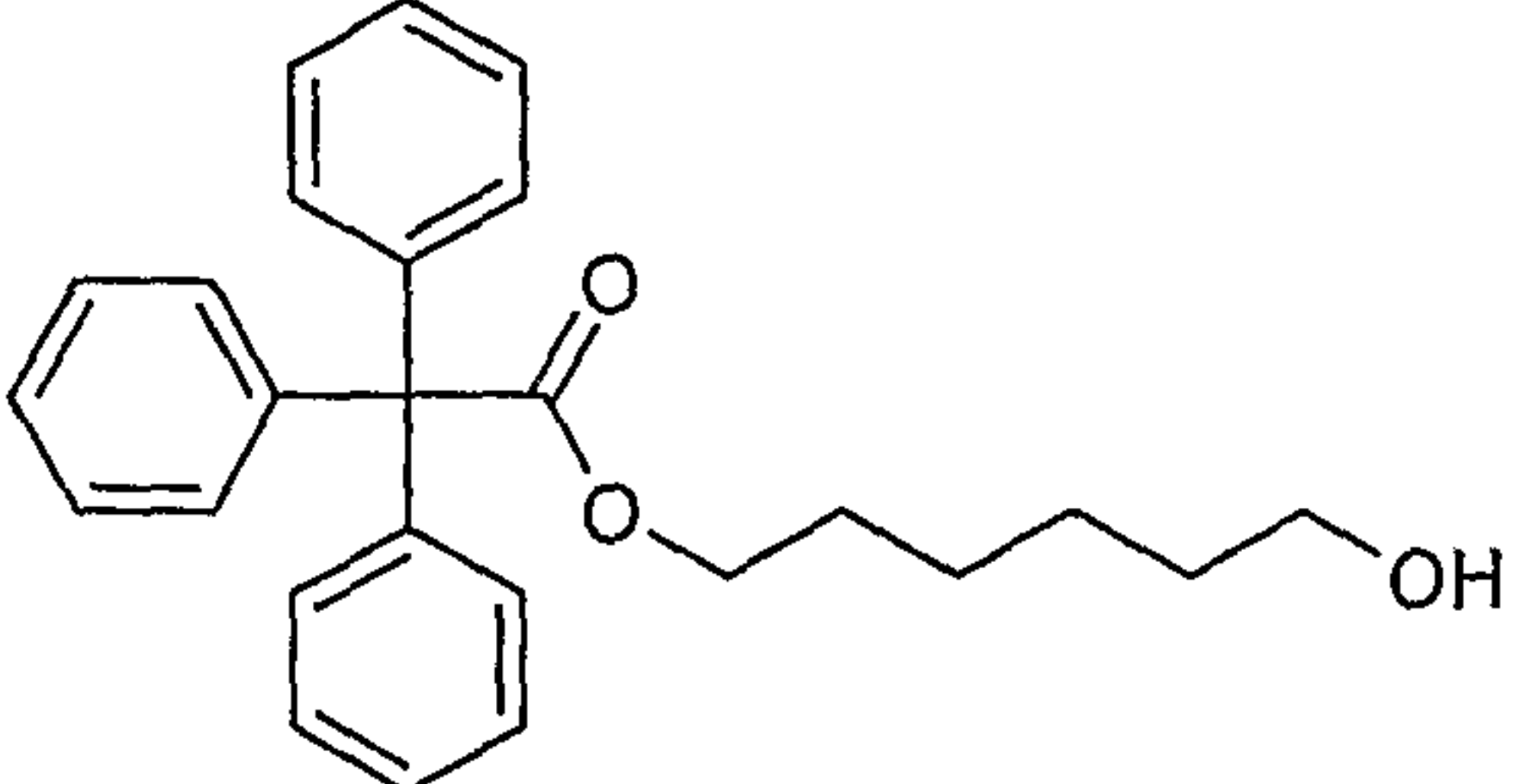
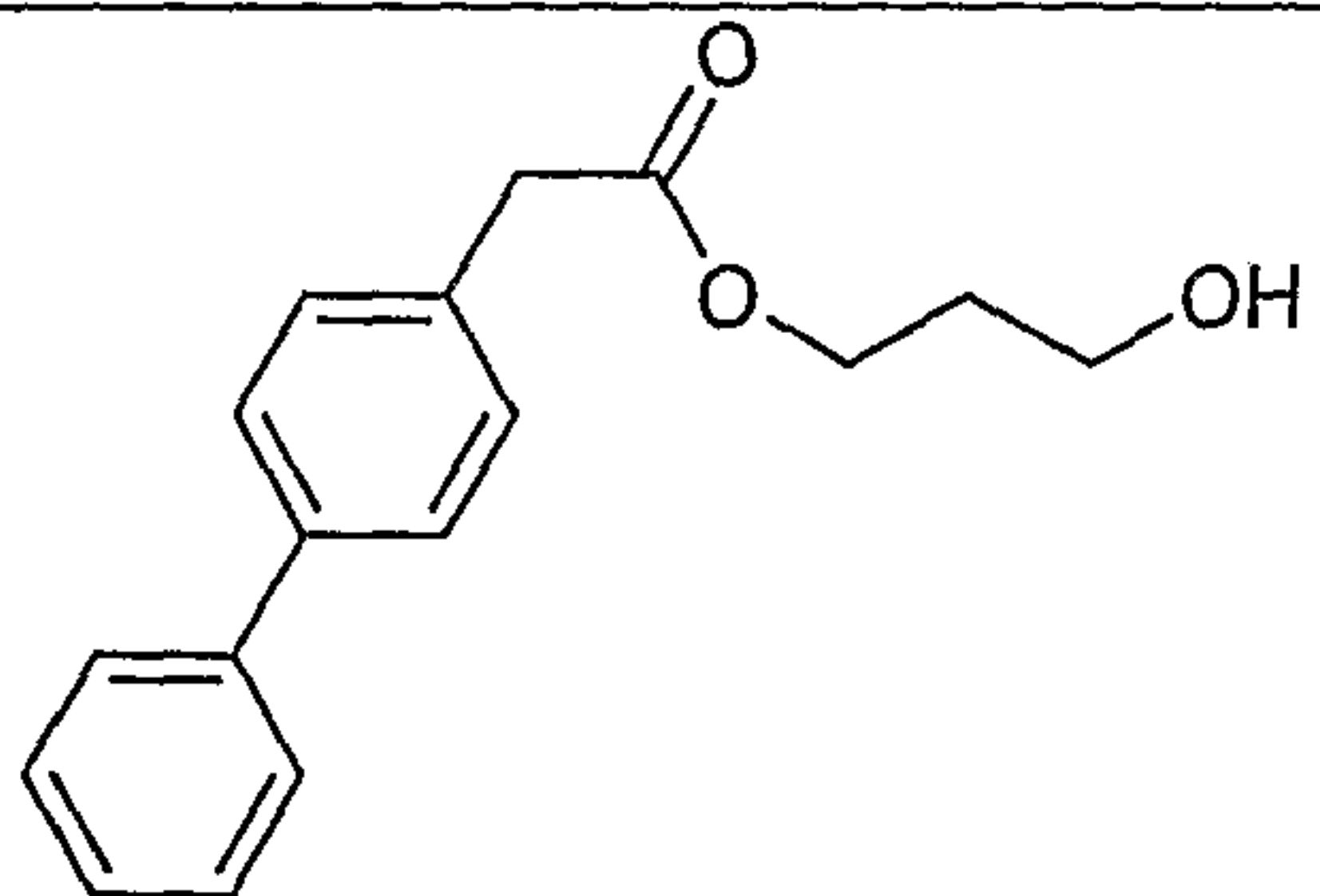
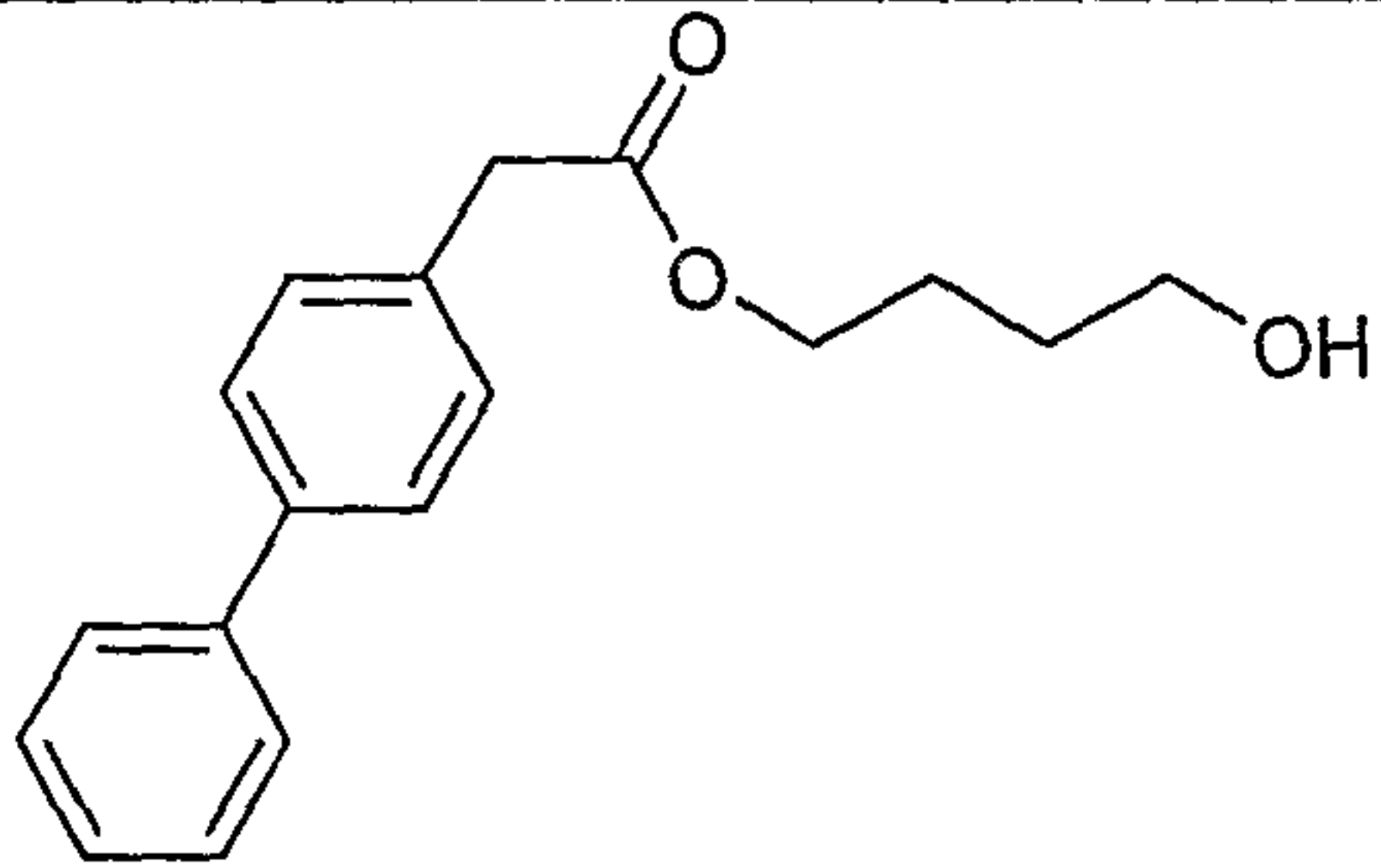
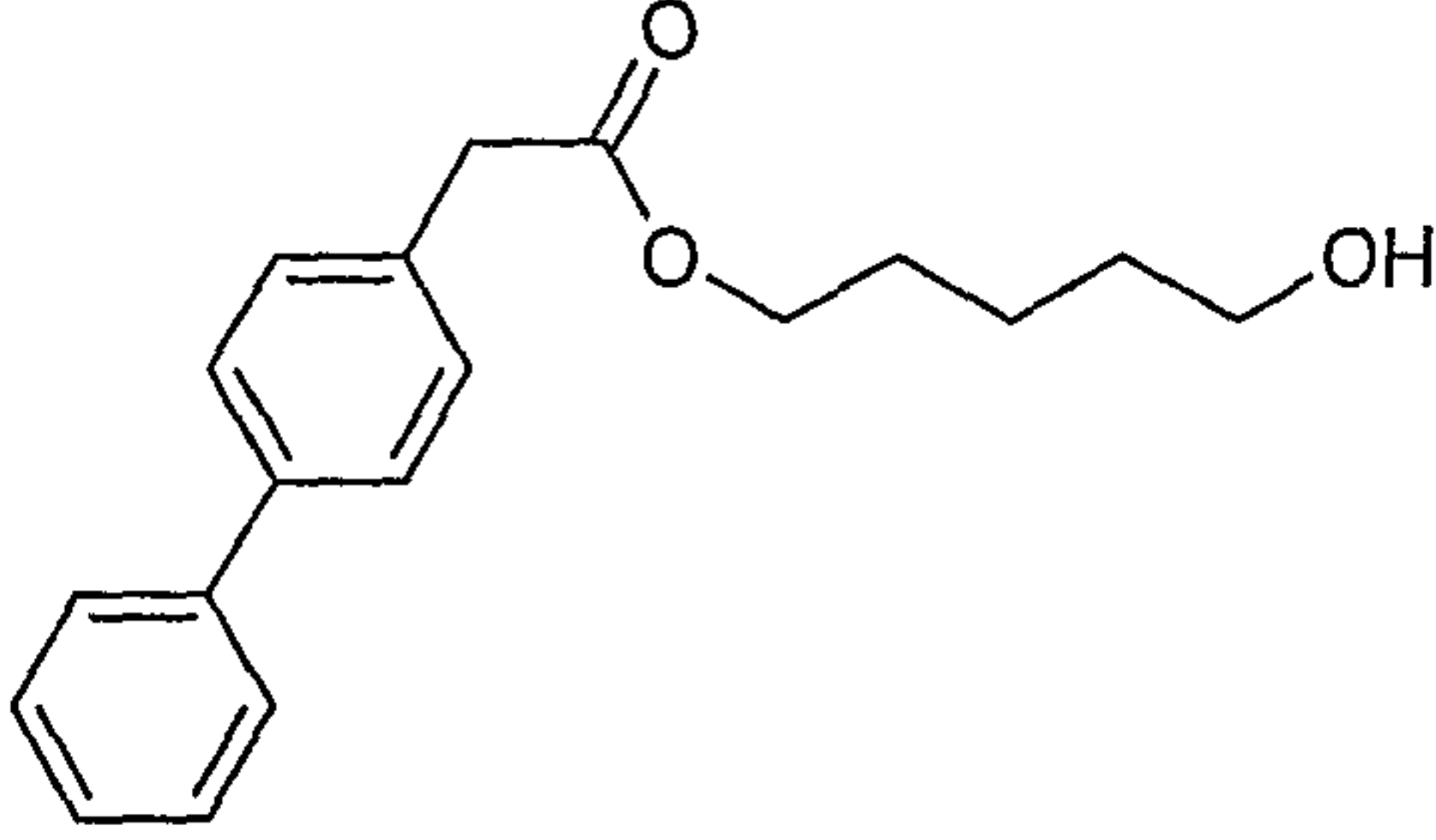
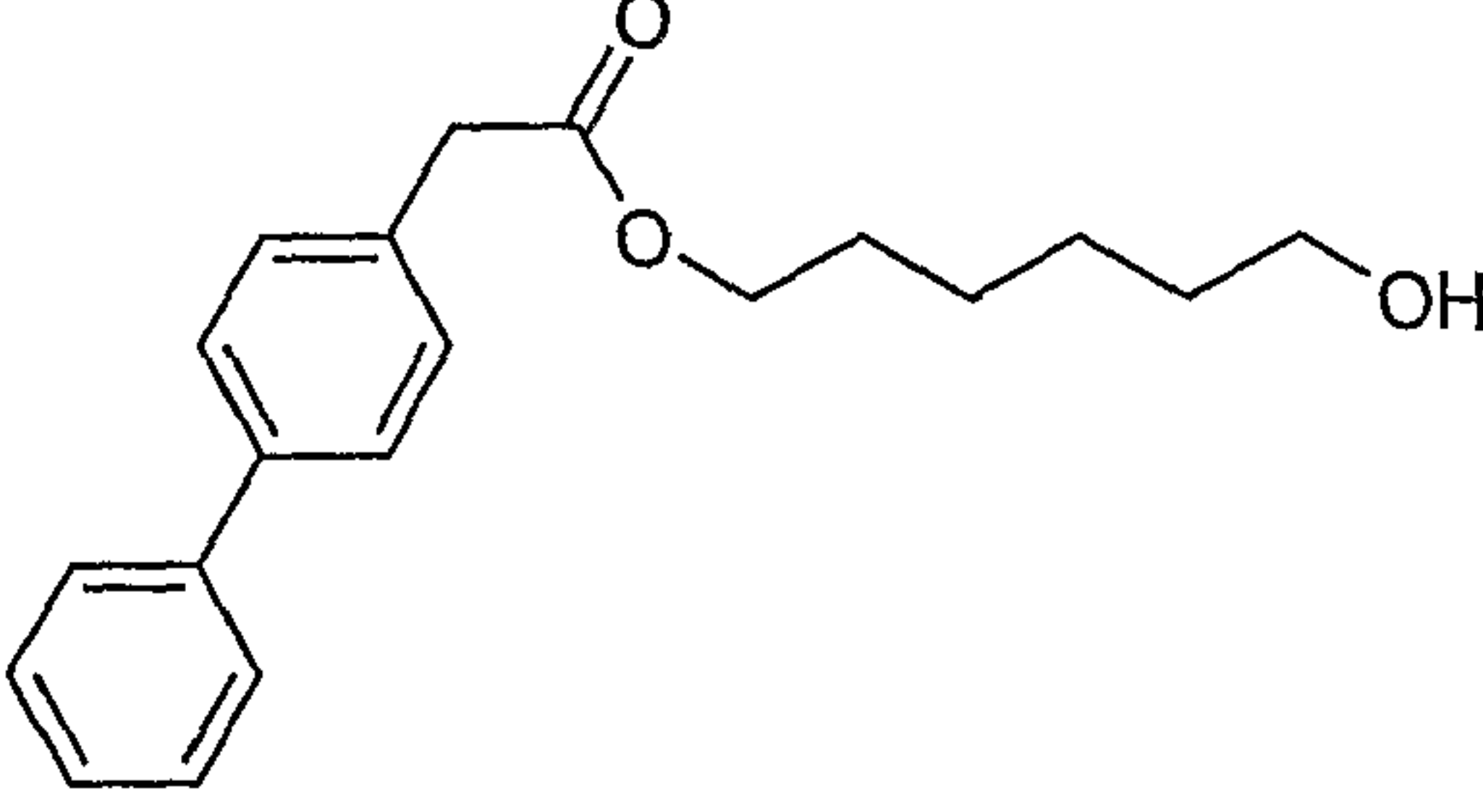
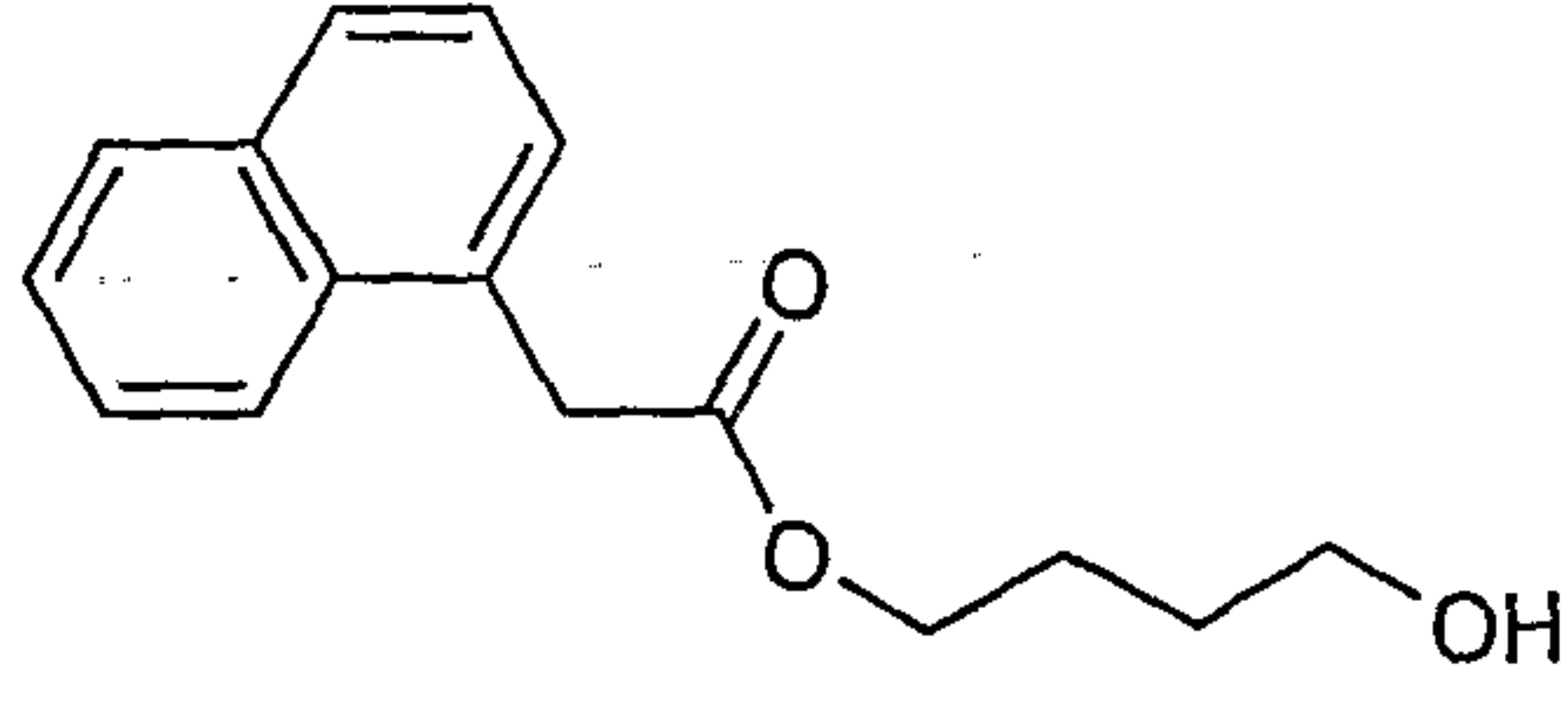
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26	ABD-0056 4BP	
27	ABD-0055 5BP	
28	ABD-0054 6BP	
29	ABD-0095 BP-4F	
30	ABD-0070 Me4BP	
31	ABD-0072 HO4BP	

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32	ABD-0089 Xy4BP	
33	ABD-0094 Et4BP	
34	ABD-0097 4-OMeBP	
35	ABD-0098 2-NO2BP	
36	ABD-0099 2-FBP	
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40	ABD-0030 5T	

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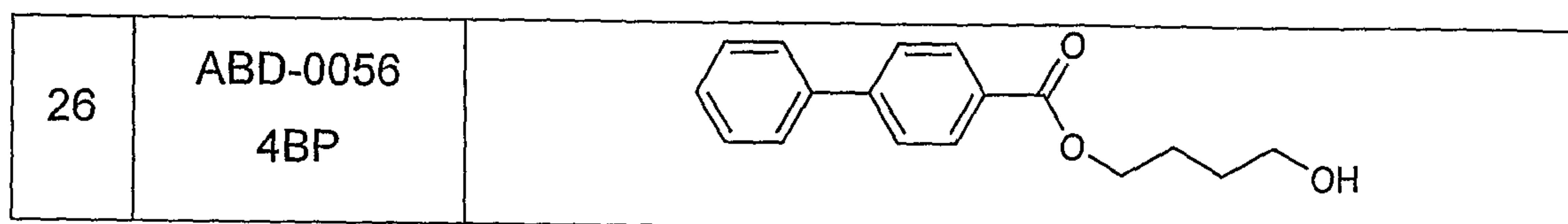
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46	ABD-0032 4N	

- 57 -

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50	ABD-0053 BuBP	
51	ABD-0090 PBP	
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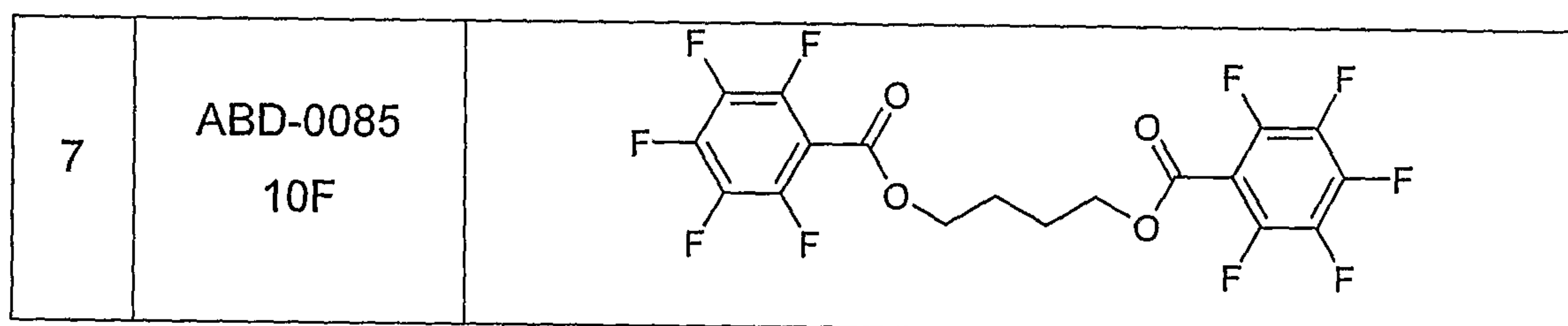
- 58 -

An especially preferred embodiment of the present invention is:



Another especially preferred embodiment of the present invention is:

5



Chemical Terms

10 The term "carbo," "carbyl," "hydrocarbo," and "hydrocarbyl," as used herein, pertain to compounds and/or groups which have only carbon and hydrogen atoms (but see "carbocyclic" below).

15 The term "hetero," as used herein, pertains to compounds and/or groups which have at least one heteroatom, for example, multivalent heteroatoms (which are also suitable as ring heteroatoms) such as boron, silicon, nitrogen, phosphorus, oxygen, sulfur, and selenium (more commonly nitrogen, oxygen, and sulfur) and monovalent heteroatoms, such as fluorine, chlorine, bromine, and iodine.

20 The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

25 The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

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The term "aliphatic," as used herein, pertains to compounds and/or groups which are linear or branched, but not cyclic (also known as "acyclic" or "open-chain" groups).

- 5 The term "ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms, yet more preferably 5 to 6 covalently linked atoms. A ring may be an alicyclic ring or an aromatic ring. The term "alicyclic ring," as used herein, pertains to a ring which is not an aromatic ring.

10

The term "carbocyclic ring," as used herein, pertains to a ring wherein all of the ring atoms are carbon atoms.

- 15 The term "heterocyclic ring," as used herein, pertains to a ring wherein at least one of the ring atoms is a multivalent ring heteroatom, for example, nitrogen, phosphorus, silicon, oxygen, or sulfur, though more commonly nitrogen, oxygen, or sulfur. Preferably, the heterocyclic ring has from 1 to 4 heteroatoms.

- 20 The term "cyclic compound," as used herein, pertains to a compound which has at least one ring. The term "cyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a cyclic compound.

- 25 Where a cyclic compound has two or more rings, they may be fused (e.g., as in naphthalene), bridged (e.g., as in norbornane), spiro (e.g., as in spiro[3.3]heptane), or a combination thereof. Cyclic compounds with one ring may be referred to as "monocyclic" or "mononuclear," whereas cyclic compounds with two or more rings may be referred to as "polycyclic" or "polynuclear."

- 30 The term "carbocyclic compound," as used herein, pertains to a cyclic compound which has only carbocyclic ring(s).

- 60 -

The term "heterocyclic compound," as used herein, pertains to a cyclic compound which has at least one heterocyclic ring.

5 The term "aromatic compound," as used herein, pertains to a cyclic compound which has at least one aromatic ring.

The term "carboaromatic compound," as used herein, pertains to a cyclic compound which has only carboaromatic ring(s).

10 The term "heteroaromatic compound," as used herein, pertains to a cyclic compound which has at least one heteroaromatic ring.

The term "monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment.

15

The term "monovalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, via a single bond. Examples of such substituents include halo, hydroxy, and alkyl.

20 The term "multivalent monodentate substituents," as used herein, pertains to substituents which have one point of covalent attachment, but through a double bond or triple bond. Examples of such substituents include oxo, imino, alkylidene, and alkylidyne.

25 The term "bidentate substituents," as used herein, pertains to substituents which have two points of covalent attachment, and which act as a linking group between two other moieties. Examples of such substituents include alkylene and arylene.

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Substituents

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

5

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group.

10 A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

The substituents are described in more detail below.

15 Alkyl: The term "alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl,
20 cycloalkyl, etc., discussed below.

In this context, the prefixes (e.g., C₁₋₄, C₁₋₇, C₁₋₂₀, C₂₋₇, C₃₋₇, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C₁₋₄alkyl," as used herein, pertains to an alkyl group having from 1 to 4
25 carbon atoms. Examples of groups of alkyl groups include C₁₋₄alkyl ("lower alkyl"), C₁₋₇alkyl, and C₁₋₂₀alkyl.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), propyl (C₃), butyl (C₄), pentyl (C₅), hexyl (C₆), heptyl (C₇),
30 octyl (C₈), nonyl (C₉), decyl (C₁₀), n-undecyl (C₁₁), dodecyl (C₁₂), tridecyl (C₁₃), tetradecyl (C₁₄), pentadecyl (C₁₅), and eicoddecyl (C₂₀).

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Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), n-propyl (C₃), n-butyl (C₄), n-pentyl (amyl) (C₅), n-hexyl (C₆), and n-heptyl (C₇).

- 5 Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C₃), iso-butyl (C₄), sec-butyl (C₄), tert-butyl (C₄), iso-pentyl (C₅), and neo-pentyl (C₅).

10 Cycloalkyl: The term "cycloalkyl," as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

- 15 Examples of (unsubstituted) saturated cylcoalkyl groups include, but are not limited to, those derived from: cyclopropane (C₃), cyclobutane (C₄), cyclopentane (C₅), cyclohexane (C₆), cycloheptane (C₇), norbornane (C₇), norpinane (C₇), adamantane (C₁₀), and decalin (decahydronaphthalene) (C₁₀).

- 20 Examples of (substituted) saturated cycloalkyl groups, which are also referred to herein as "alkyl-cycloalkyl" groups, include, but are not limited to, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, and dimethylcyclohexyl.

25

- Examples of (substituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "alkyl-cycloalkenyl" groups, include, but are not limited to, methylcyclopropenyl, dimethylcyclopropenyl, methylcyclobutenyl, dimethylcyclobutenyl, methylcyclopentenyl, dimethylcyclopentenyl, 30 methylcyclohexenyl, and dimethylcyclohexenyl.

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Examples of (substituted) cycloalkyl groups, with one or more other rings fused to the parent cycloalkyl group, include, but are not limited to, those derived from: indene (C₉), indan (e.g., 2,3-dihydro-1H-indene) (C₉), tetraline (1,2,3,4-tetrahydronaphthalene (C₁₀), fluorene (C₁₃), phenalene (C₁₃). For example, 2H-inden-2-yl is a C₅cycloalkyl group with a substituent (phenyl) fused thereto.

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C₂₋₄alkenyl, C₂₋₇alkenyl, C₂₋₂₀alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH₂), 1-propenyl (-CH=CH-CH₃), 2-propenyl (allyl, -CH-CH=CH₂), isopropenyl (-C(CH₃)=CH₂), butenyl (C₄), pentenyl (C₅), and hexenyl (C₆).

Examples of (unsubstituted) unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C₃), cyclobutenyl (C₄), cyclopentenyl (C₅), and cyclohexenyl (C₆).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C₂₋₄alkynyl, C₂₋₇alkynyl, C₂₋₂₀alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH₂-C≡CH).

Alkylidene: The term "alkylidene," as used herein, pertains to a divalent monodentate moiety obtained by removing two hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated.

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Examples of groups of alkylidene groups include C₁₋₄alkylidene, C₁₋₇alkylidene, C₁₋₂₀alkylidene.

5 Examples of alkylidene groups include, but are not limited to, methyldene (=CH₂), ethyldene (=CH-CH₃), vinylidene (=C=CH₂), and isopropylidene (=C(CH₃)₂).

Alkylidyne: The term "alkylidyne," as used herein, pertains to a trivalent monodentate moiety obtained by removing three hydrogen atoms from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless
10 otherwise specified), which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated. Examples of groups of alkylidyne groups include C₁₋₄alkylidyne, C₁₋₇alkylidyne, C₁₋₂₀alkylidyne.

15 Examples of alkylidyne groups include, but are not limited to, methyldidyne ($\equiv$ CH) and ethyldidyne ($\equiv$ C-CH₃).

Carbocyclyl: The term "carbocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a carbocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise
20 specified). Preferably, each ring has from 3 to 7 ring atoms.

In this context, the prefixes (e.g., C₃₋₂₀, C₃₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms. For example, the term
25 "C₅₋₆carbocyclyl," as used herein, pertains to a carbocyclyl group having 5 or 6 ring atoms. Examples of groups of carbocyclyl groups include C₃₋₂₀carbocyclyl, C₃₋₁₀carbocyclyl, C₅₋₁₀carbocyclyl, C₃₋₇carbocyclyl, and C₅₋₇carbocyclyl.

30 Examples of carbocyclic groups include, but are not limited to, those described above as cycloalkyl groups; those described below as carboaryl groups.

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Heterocyclyl: The term "heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has
5 from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g., C₃₋₂₀, C₃₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆heterocyclyl," as used herein, pertains to a
10 heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C₃₋₂₀heterocyclyl, C₃₋₇heterocyclyl, C₅₋₇heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

15

N₁: aziridine (C₃), azetidine (C₄), pyrrolidine (tetrahydropyrrole) (C₅), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C₅), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C₅), piperidine (C₆), dihydropyridine (C₆), tetrahydropyridine (C₆), azepine (C₇);

20

O₁: oxirane (C₃), oxetane (C₄), oxolane (tetrahydrofuran) (C₅), oxole (dihydrofuran) (C₅), oxane (tetrahydropyran) (C₆), dihydropyran (C₆), pyran (C₆), oxepin (C₇);

25

S₁: thiirane (C₃), thietane (C₄), thiolane (tetrahydrothiophene) (C₅), thiane (tetrahydrothiopyran) (C₆), thiepane (C₇);

O₂: dioxolane (C₅), dioxane (C₆), and dioxepane (C₇);

30

O₃: trioxane (C₆);

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N₂: imidazolidine (C₅), pyrazolidine (diazolidine) (C₅), imidazoline (C₅), pyrazoline (dihydropyrazole) (C₅), piperazine (C₆);

5 N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅), tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine (C₆), tetrahydrooxazine (C₆), dihydrooxazine (C₆), oxazine (C₆);

N₁S₁: thiazoline (C₅), thiazolidine (C₅), thiomorpholine (C₆);

10 N₂O₁: oxadiazine (C₆);

O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and,

N₁O₁S₁: oxathiazine (C₆).

15

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include saccharides, in cyclic form, for example, furanoses (C₅), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C₆), such as allopyranose, altropyranose, glucopyranose, mannopyranose, 20 gulopyranose, idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

25 Aryl: The term "aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

30 In this context, the prefixes (e.g., C₃₋₂₀, C₅₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆aryl," as used herein, pertains to an aryl group

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having 5 or 6 ring atoms. Examples of groups of aryl groups include C₃₋₂₀aryl, C₃₋₁₂aryl, C₅₋₁₂aryl, C₅₋₇aryl, and C₅₋₆aryl.

5 The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g., C₅₋₂₀carboaryl).

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C₆), naphthalene (C₁₀), azulene (C₁₀), anthracene (C₁₄), phenanthrene (C₁₄), naphthacene (C₁₈), and pyrene (C₁₆).

10

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C₉), isoindene (C₉), and fluorene (C₁₃).

15 Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups" (e.g., C₅₋₂₀heteroaryl).

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

20 N₁: pyrrole (azole) (C₅), pyridine (azine) (C₆);

O₁: furan (oxole) (C₅);

S₁: thiophene (thiole) (C₅);

N₁O₁: oxazole (C₅), isoxazole (C₅), isoxazine (C₆);

N₂O₁: oxadiazole (furazan) (C₅);

25 N₃O₁: oxatriazole (C₅);

N₁S₁: thiazole (C₅), isothiazole (C₅);

N₂: imidazole (1,3-diazole) (C₅), pyrazole (1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆), pyrimidine (1,3-diazine) (C₆) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C₆);

30 N₃: triazole (C₅), triazine (C₆); and,

N₄: tetrazole (C₅).

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Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C₉heterocyclic groups (with 2 fused rings) derived from benzofuran (O₁), isobenzofuran (O₁), indole (N₁), isoindole (N₁), purine (N₄) (e.g., adenine, guanine), benzimidazole (N₂), benzoxazole (N₁O₁), benzisoxazole (N₁O₁), benzodioxole (O₂), benzofurazan (N₂O₁), benzotriazole (N₃), benzothiofuran (S₁), benzothiazole (N₁S₁), benzothiadiazo (N₂S);

C₁₀heterocyclic groups (with 2 fused rings) derived from benzodioxan (O₂), quinoline (N₁), isoquinoline (N₁), benzoxazine (N₁O₁), benzodiazine (N₂), pyridopyridine (N₂), quinoxaline (N₂), quinazoline (N₂), phthalazine (N₂), pteridine (N₄);

C₁₃heterocyclic groups (with 3 fused rings) derived from carbazole (N₁), dibenzofuran (O₁), dibenzothiophene (S₁); and,

C₁₄heterocyclic groups (with 3 fused rings) derived from acridine (N₁), xanthene (O₁), phenoxathiin (O₁S₁), phenazine (N₂), phenoxazine (N₁O₁), phenothiazine (N₁S₁), thianthrene (S₂), phenanthridine (N₁), phenanthroline (N₂), phenazine (N₂).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methylpyrrole. Examples of N-substitutents include, but are not limited to C₁₋₇alkyl, C₃₋₂₀heterocyclyl, C₅₋₂₀aryl, and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as -N(→O)= (also denoted -N⁺(→O⁻)=). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

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Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

C₅: cyclopentanone, cyclopentenone, cyclopentadienone;

5 C₆: cyclohexanone, cyclohexenone, cyclohexadienone;

O₁: furanone (C₅), pyrone (C₆);

N₁: pyrrolidone (pyrrolidinone) (C₅), piperidinone (piperidone) (C₆),
piperidinedione (C₆);

N₂: imidazolidone (imidazolidinone) (C₅), pyrazolone (pyrazolinone) (C₅),

10 piperazinone (C₆), piperazinedione (C₆), pyridazinone (C₆), pyrimidinone (C₆)
(e.g., cytosine), pyrimidinedione (C₆) (e.g., thymine, uracil), barbituric acid (C₆);

N₁S₁: thiazolone (C₅), isothiazolone (C₅);

N₁O₁: oxazolinone (C₅).

15 Polycyclic examples of such groups include, but are not limited to, those derived from:

C₉: indenedione;

C₁₀: tetralone, decalone;

N₁: oxindole (C₉);

20 O₁: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C₁₀);

N₁O₁: benzoxazolinone (C₉), benzoxazolinone (C₁₀);

N₂: quinazolinedione (C₁₀);

N₄: purinone (C₉) (e.g., guanine).

25 Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride (C₅), succinic anhydride (C₅), and glutaric anhydride (C₆);

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C₅)

30 and 1,2-propylene carbonate (C₅);

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C₅), maleimide (C₅), phthalimide, and glutarimide (C₆);

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lactones (cyclic esters, $-O-C(=O)-$ in a ring), including, but not limited to, β -propiolactone, γ -butyrolactone, δ -valerolactone (2-piperidone), and ϵ -caprolactone;

lactams (cyclic amides, $-NR-C(=O)-$ in a ring), including, but not limited to, β -propiolactam (C_4), γ -butyrolactam (2-pyrrolidone) (C_5), δ -valerolactam (C_6), and ϵ -caprolactam (C_7);

cyclic carbamates ($-O-C(=O)-NR-$ in a ring), such as 2-oxazolidone (C_5);

cyclic ureas ($-NR-C(=O)-NR-$ in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

10

The above alkyl, alkylidene, alkylidyne, heterocyclyl, and aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

15

Hydrogen: $-H$. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at that position.

20 Halo: $-F$, $-Cl$, $-Br$, and $-I$.

Hydroxy: $-OH$.

Ether: $-OR$, wherein R is an ether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkoxy group, discussed below), a C_{3-20} heterocyclyl group (also referred to as a C_{3-20} heterocyclyloxy group), or a C_{5-20} aryl group (also referred to as a C_{5-20} aryloxy group), preferably a C_{1-7} alkyl group.

C_{1-7} alkoxy: $-OR$, wherein R is a C_{1-7} alkyl group. Examples of C_{1-7} alkoxy groups include, but are not limited to, $-OMe$ (methoxy), $-OEt$ (ethoxy), $-O(nPr)$ (n -propoxy), $-O(iPr)$ (isopropoxy), $-O(nBu)$ (n -butoxy), $-O(sBu)$ (sec-butoxy), $-O(iBu)$ (isobutoxy), and $-O(tBu)$ (tert-butoxy).

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- Acetal: $-\text{CH}(\text{OR}^1)(\text{OR}^2)$, wherein R^1 and R^2 are independently acetal substituents, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group, or, in the case of a "cyclic" acetal group, R^1 and R^2 , taken together with the two oxygen atoms to which they are attached, and the carbon atoms to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of acetal groups include, but are not limited to, $-\text{CH}(\text{OMe})_2$, $-\text{CH}(\text{OEt})_2$, and $-\text{CH}(\text{OMe})(\text{OEt})$.
- 10 Hemiacetal: $-\text{CH}(\text{OH})(\text{OR}^1)$, wherein R^1 is a hemiacetal substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of hemiacetal groups include, but are not limited to, $-\text{CH}(\text{OH})(\text{OMe})$ and $-\text{CH}(\text{OH})(\text{OEt})$.
- 15 Ketal: $-\text{CR}(\text{OR}^1)(\text{OR}^2)$, where R^1 and R^2 are as defined for acetals, and R is a ketal substituent other than hydrogen, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples ketal groups include, but are not limited to, $-\text{C}(\text{Me})(\text{OMe})_2$, $-\text{C}(\text{Me})(\text{OEt})_2$, $-\text{C}(\text{Me})(\text{OMe})(\text{OEt})$, $-\text{C}(\text{Et})(\text{OMe})_2$, $-\text{C}(\text{Et})(\text{OEt})_2$, and
- 20 $-\text{C}(\text{Et})(\text{OMe})(\text{OEt})$.
- Hemiketal: $-\text{CR}(\text{OH})(\text{OR}^1)$, where R^1 is as defined for hemiacetals, and R is a hemiketal substituent other than hydrogen, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group.
- 25 Examples of hemiacetal groups include, but are not limited to, $-\text{C}(\text{Me})(\text{OH})(\text{OMe})$, $-\text{C}(\text{Et})(\text{OH})(\text{OMe})$, $-\text{C}(\text{Me})(\text{OH})(\text{OEt})$, and $-\text{C}(\text{Et})(\text{OH})(\text{OEt})$.

Oxo (keto, -one): $=\text{O}$.

- 30 Thione (thioketone): $=\text{S}$.

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Imino (imine): $=NR$, wherein R is an imino substituent, for example, hydrogen, C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $=NH$, $=NMe$, $=NEt$, and $=NPh$.

5

Formyl (carbaldehyde, carboxaldehyde): $-C(=O)H$.

Acyl (keto): $-C(=O)R$, wherein R is an acyl substituent, for example, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-20} heterocyclyl group (also referred to as C_{3-20} heterocyclylacyl), or a C_{5-20} aryl group (also referred to as C_{5-20} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl), $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (t-butyryl), and $-C(=O)Ph$ (benzoyl, phenone).

15 Carboxy (carboxylic acid): $-C(=O)OH$.

Thiocarboxy (thiocarboxylic acid): $-C(=S)SH$.

Thiolocarboxy (thiolocarboxylic acid): $-C(=O)SH$.

20

Thionocarboxy (thionocarboxylic acid): $-C(=S)OH$.

Imidic acid: $-C(=NH)OH$.

25 Hydroxamic acid: $-C(=NOH)OH$.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): $-C(=O)OR$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and $-C(=O)OPh$.

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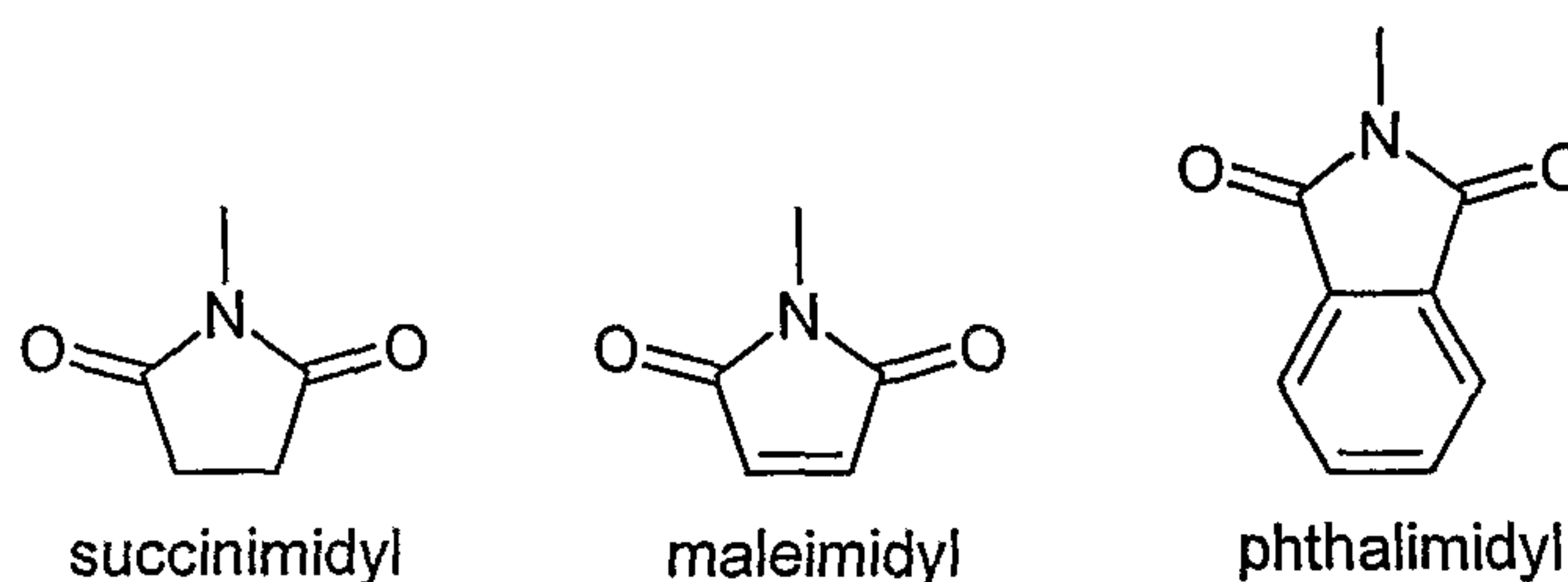
Acyloxy (reverse ester): $-\text{OC}(=\text{O})\text{R}$, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of acyloxy groups include, but are not limited to, $-\text{OC}(=\text{O})\text{CH}_3$ (acetoxy), $-\text{OC}(=\text{O})\text{CH}_2\text{CH}_3$, $-\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$,
 5 $-\text{OC}(=\text{O})\text{Ph}$, and $-\text{OC}(=\text{O})\text{CH}_2\text{Ph}$.

Oxycarboxyloxy: $-\text{OC}(=\text{O})\text{OR}$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to,
 10 $-\text{OC}(=\text{O})\text{OCH}_3$, $-\text{OC}(=\text{O})\text{OCH}_2\text{CH}_3$, $-\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$, and $-\text{OC}(=\text{O})\text{OPh}$.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-\text{C}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-\text{C}(=\text{O})\text{NH}_2$,
 15 $-\text{C}(=\text{O})\text{NHCH}_3$, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})\text{NHCH}_2\text{CH}_3$, and $-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, as well as amido groups in which R^1 and R^2 , together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

20

Acylamido (acylamino): $-\text{NR}^1\text{C}(=\text{O})\text{R}^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group,
 25 preferably hydrogen or a C_{1-7} alkyl group. Examples of acylamide groups include, but are not limited to, $-\text{NHC}(=\text{O})\text{CH}_3$, $-\text{NHC}(=\text{O})\text{CH}_2\text{CH}_3$, and $-\text{NHC}(=\text{O})\text{Ph}$. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



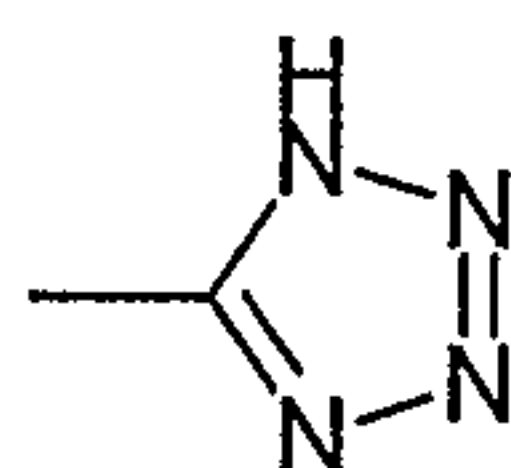
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Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)N(CH_3)_2$, and
 5 $-C(=S)NHCH_2CH_3$.

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl
 10 group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, $-NHCONHMe$, $-NHCONHEt$, $-NHCONMe_2$, $-NHCONEt_2$, $-NMeCONH_2$, $-NMeCONHMe$, $-NMeCONHEt$, $-NMeCONMe_2$, and $-NMeCONEt_2$.

15 Guanidino: $-NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



20

Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di- C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2 , taken
 25 together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NHR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and $-NHPh$. Examples
 30 of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

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Amidine (amidino): $-C(=NR)NR_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group. Examples of amidine groups include,
5 but are not limited to, $-C(=NH)NH_2$, $-C(=NH)NMe_2$, and $-C(=NMe)NMe_2$.

Nitro: $-NO_2$.

Nitroso: $-NO$.

10

Azido: $-N_3$.

Cyano (nitrile, carbonitrile): $-CN$.

15 Isocyano: $-NC$.

Cyanato: $-OCN$.

Isocyanato: $-NCO$.

20

Thiocyano (thiocyanato): $-SCN$.

Isothiocyano (isothiocyanato): $-NCS$.

25 Sulfhydryl (thiol, mercapto): $-SH$.

Thioether (sulfide): $-SR$, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkylthio group), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of
30 C_{1-7} alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

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Disulfide: $-SS-R$, wherein R is a disulfide substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group (also referred to herein as C_{1-7} alkyl disulfide). Examples of C_{1-7} alkyl disulfide groups include, but are not limited to, $-SSCH_3$ and $-SSCH_2CH_3$.

5

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

Sulfonate (sulfonic acid ester): $-S(=O)_2OR$, wherein R is a sulfonate substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonate groups include, but are not limited to, $-S(=O)_2OCH_3$ and $-S(=O)_2OCH_2CH_3$.

10

Sulfinic acid: $-S(=O)OH$, $-SO_2H$.

Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ and $-S(=O)OCH_2CH_3$.

15

Sulfate: $-OS(=O)_2OR$; wherein R is a sulfate substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfate groups include, but are not limited to, $-OS(=O)_2OCH_3$ and $-SO(=O)_2OCH_2CH_3$.

20

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group, for example, a fluorinated or perfluorinated C_{1-7} alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonafllyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl),

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4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

5 Sulfine (sulfinyl, sulfoxide): $-S(=O)R$, wherein R is a sulfine substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfine groups include, but are not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

10 Sulfonyloxy: $-OS(=O)_2R$, wherein R is a sulfonyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ (mesylate) and $-OS(=O)_2CH_2CH_3$ (esylate).

15 Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

20 Sulfamino: $-NR^1S(=O)_2OH$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-NHS(=O)_2OH$ and $-N(CH_3)S(=O)_2OH$.

25 Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

30 Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group.

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Examples of sulfinamino groups include, but are not limited to, -NHS(=O)CH_3 and $\text{-N(CH}_3\text{)S(=O)C}_6\text{H}_5$.

5 Sulfamyl: $\text{-S(=O)NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, -S(=O)NH_2 , $\text{-S(=O)NH(CH}_3\text{)}$, $\text{-S(=O)N(CH}_3\text{)}_2$, $\text{-S(=O)NH(CH}_2\text{CH}_3\text{)}$, $\text{-S(=O)N(CH}_2\text{CH}_3\text{)}_2$, and -S(=O)NHPh .

10 Sulfonamido: $\text{-S(=O)}_2\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $\text{-S(=O)}_2\text{NH}_2$, $\text{-S(=O)}_2\text{NH(CH}_3\text{)}$, $\text{-S(=O)}_2\text{N(CH}_3\text{)}_2$, $\text{-S(=O)}_2\text{NH(CH}_2\text{CH}_3\text{)}$, $\text{-S(=O)}_2\text{N(CH}_2\text{CH}_3\text{)}_2$, and $\text{-S(=O)}_2\text{NHPh}$.

15 Phosphino (phosphine): -PR_2 , wherein R is a phosphino substituent, for example, -H , a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H , a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples of phosphino groups include, but are not limited to, -PH_2 , $\text{-P(CH}_3\text{)}_2$, $\text{-P(CH}_2\text{CH}_3\text{)}_2$, -P(t-Bu)_2 , and -P(Ph)_2 .

20 Phospho: -P(=O)_2 .

Phosphinyl (phosphine oxide): -P(=O)R_2 , wherein R is a phosphinyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group or a C_{5-20} aryl group. Examples of phosphinyl groups include, but are not limited to, $\text{-P(=O)(CH}_3\text{)}_2$, $\text{-P(=O)(CH}_2\text{CH}_3\text{)}_2$, -P(=O)(t-Bu)_2 ,
25 and -P(=O)(Ph)_2 .

Phosphonic acid (phosphono): -P(=O)(OH)_2 .

30 Phosphonate (phosphono ester): -P(=O)(OR)_2 , where R is a phosphonate substituent, for example, -H , a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H , a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples

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of phosphonate groups include, but are not limited to, $-P(=O)(OCH_3)_2$, $-P(=O)(OCH_2CH_3)_2$, $-P(=O)(O-t-Bu)_2$, and $-P(=O)(OPh)_2$.

Phosphoric acid (phosphonooxy): $-OP(=O)(OH)_2$.

5

Phosphate (phosphonooxy ester): $-OP(=O)(OR)_2$, where R is a phosphate substituent, for example, -H, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H, a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples of phosphate groups include, but are not limited to, $-OP(=O)(OCH_3)_2$,

10 $-OP(=O)(OCH_2CH_3)_2$, $-OP(=O)(O-t-Bu)_2$, and $-OP(=O)(OPh)_2$.

Phosphorous acid: $-OP(OH)_2$.

Phosphite: $-OP(OR)_2$, where R is a phosphite substituent, for example, -H, a
15 C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H, a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples of phosphite groups include, but are not limited to, $-OP(OCH_3)_2$, $-OP(OCH_2CH_3)_2$, $-OP(O-t-Bu)_2$, and $-OP(OPh)_2$.

Phosphoramidite: $-OP(OR^1)-NR^2_2$, where R^1 and R^2 are phosphoramidite
20 substituents, for example, -H, a (optionally substituted) C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H, a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples of phosphoramidite groups include, but are not limited to, $-OP(OCH_2CH_3)-N(CH_3)_2$, $-OP(OCH_2CH_3)-N(i-Pr)_2$, and $-OP(OCH_2CH_2CN)-N(i-Pr)_2$.

25

Phosphoramidate: $-OP(=O)(OR^1)-NR^2_2$, where R^1 and R^2 are phosphoramidate
substituents, for example, -H, a (optionally substituted) C_{1-7} alkyl group, a
 C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H, a C_{1-7} alkyl group, or a
 C_{5-20} aryl group. Examples of phosphoramidate groups include, but are not
30 limited to, $-OP(=O)(OCH_2CH_3)-N(CH_3)_2$, $-OP(=O)(OCH_2CH_3)-N(i-Pr)_2$, and
 $-OP(=O)(OCH_2CH_2CN)-N(i-Pr)_2$.

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In many cases, substituents may themselves be substituted. For example, a C₁₋₇alkyl group may be substituted with, for example, hydroxy (also referred to as a C₁₋₇hydroxyalkyl group), C₁₋₇alkoxy (also referred to as a C₁₋₇alkoxyalkyl group), amino (also referred to as a C₁₋₇aminoalkyl group), halo (also referred to as a C₁₋₇haloalkyl group), carboxy (also referred to as a C₁₋₇carboxyalkyl group), and C₅₋₂₀aryl (also referred to as a C₅₋₂₀aryl-C₁₋₇alkyl group).

Similarly, a C₅₋₂₀aryl group may be substituted with, for example, hydroxy (also referred to as a C₅₋₂₀hydroxyaryl group), halo (also referred to as a C₅₋₂₀haloaryl group), amino (also referred to as a C₅₋₂₀aminoaryl group, e.g., as in aniline), C₁₋₇alkyl (also referred to as a C₁₋₇alkyl-C₅₋₂₀aryl group, e.g., as in toluene), and C₁₋₇alkoxy (also referred to as a C₁₋₇alkoxy-C₅₋₂₀aryl group, e.g., as in anisole).

These and other specific examples of such substituted-substituents are described below.

C₁₋₇haloalkyl group: The term "C₁₋₇haloalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a halogen atom (e.g., F, Cl, Br, I). If more than one hydrogen atom has been replaced with a halogen atom, the halogen atoms may independently be the same or different. Every hydrogen atom may be replaced with a halogen atom, in which case the group may conveniently be referred to as a C₁₋₇perhaloalkyl group." Examples of C₁₋₇haloalkyl groups include, but are not limited to, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CBr₃, -CH₂CH₂F, -CH₂CHF₂, and -CH₂CF₃.

C₁₋₇haloalkoxy: -OR, wherein R is a C₁₋₇haloalkyl group. Examples of C₁₋₇haloalkoxy groups include, but are not limited to, -OCF₃, -OCHF₂, -OCH₂F, -OCCl₃, -OCBr₃, -OCH₂CH₂F, -OCH₂CHF₂, and -OCH₂CF₃.

C₁₋₇hydroxyalkyl: The term "C₁₋₇hydroxyalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom has been replaced with a

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hydroxy group. Examples of C₁₋₇hydroxyalkyl groups include, but are not limited to, -CH₂OH, -CH₂CH₂OH, and -CH(OH)CH₂OH.

5 C₁₋₇carboxyalkyl: The term "C₁₋₇carboxyalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom has been replaced with a carboxy group. Examples of C₁₋₇carboxyalkyl groups include, but are not limited to, -CH₂COOH and -CH₂CH₂COOH.

10 C₁₋₇aminoalkyl: The term "C₁₋₇aminoalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom has been replaced with an amino group. Examples of C₁₋₇aminoalkyl groups include, but are not limited to, -CH₂NH₂, -CH₂CH₂NH₂, and -CH₂CH₂N(CH₃)₂.

15 C₁₋₇aminoalkylamino: The term "C₁₋₇aminoalkylamino," as used herein, pertains to an amino group, -NR¹R², in which one of the substituents, R¹ or R², is itself a C₁₋₇aminoalkyl group (-C₁₋₇alkyl-NR¹R²). The C₁₋₇aminoalkylamino may be represented, for example, by the formula -NR¹-C₁₋₇alkyl-NR¹R². Examples of amino-C₁₋₇alkylamino groups include, but are not limited to, groups of the formula -NR¹(CH₂)_nNR¹R², where n is 1 to 6, for example, -NHCH₂NH₂, -NH(CH₂)₂NH₂,
20 -NH(CH₂)₃NH₂, -NH(CH₂)₄NH₂, -NH(CH₂)₅NH₂, -NH(CH₂)₆NH₂, -NHCH₂NH(Me), -NH(CH₂)₂NH(Me), -NH(CH₂)₃NH(Me), -NH(CH₂)₄NH(Me), -NH(CH₂)₅NH(Me), -NH(CH₂)₆NH(Me), -NHCH₂NH(Et), -NH(CH₂)₂NH(Et), -NH(CH₂)₃NH(Et), -NH(CH₂)₄NH(Et), -NH(CH₂)₅NH(Et), and -NH(CH₂)₆NH(Et).

25 C₃₋₇cycloalkyl-C₁₋₇alkyl: The term "," as used herein, describes certain C₁₋₇alkyl groups which have been substituted with a C₃₋₇cycloalkyl group. Examples of such groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl.

30 C₃₋₇cycloalkenyl-C₁₋₇alkyl: The term "," as used herein, describes certain C₁₋₇alkyl groups which have been substituted with a C₃₋₇cycloalkenyl group.

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Examples of such groups include, but are not limited to, cyclopropenylmethyl and cyclohexenylmethyl.

5 C₁₋₇alkyl-C₅₋₂₀aryl: The term "C₁₋₇alkyl-C₅₋₂₀aryl," as used herein, describes certain C₅₋₂₀aryl groups which have been substituted with a C₁₋₇alkyl group. Examples of such groups include, but are not limited to, tolyl (as in toluene), xylyl (as in xylene), mesityl (as in mesitylene), styryl (as in styrene), and cumenyl (as in cumene).

10 C₁₋₇alkyl-C₅₋₂₀aryloxy: The term "C₁₋₇alkyl-C₅₋₂₀aryloxy," as used herein, describes certain C₅₋₂₀aryloxy groups which have been substituted with a C₁₋₇alkyl group. Examples of such groups include, but are not limited to, tolyloxy, xylyloxy, mesityloxy, and cumenyloxy.

15 C₅₋₂₀aryl-C₁₋₇alkyl: The term "C₅₋₂₀aryl-C₁₋₇alkyl," as used herein, describes certain C₁₋₇alkyl groups which have been substituted with a C₅₋₂₀aryl group. Examples of such groups include, but are not limited to, benzyl (phenylmethyl), tolylmethyl, phenylethyl, triphenylmethyl (trityl), and cinnamyl (3-phenyl-2-propenyl, C₆H₅-CH=CH-CH₂-).

20

C₅₋₂₀aryl-C₁₋₇alkoxy: The term "C₅₋₂₀aryl-C₁₋₇alkoxy," as used herein, describes certain C₁₋₇alkoxy groups which have been substituted with a C₅₋₂₀aryl group. Examples of such groups include, but are not limited to, benzyloxy, tolylmethoxy, and phenylethoxy.

25

C₅₋₂₀haloaryl: The term "C₅₋₂₀haloaryl," as used herein, describes certain C₅₋₂₀aryl groups which have been substituted with one or more halo groups. Examples of such groups include, but are not limited to, halophenyl (e.g., fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl, whether ortho-, meta-, or para-substituted), dihalophenyl, trihalophenyl, tetrahalophenyl, and pentahalophenyl.

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Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to
5 carboxylic acid (-COOH) also includes the anionic (carboxylate) form (-COO⁻), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form (-N⁺HR¹R²), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a
10 hydroxyl group also includes the anionic form (-O⁻), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

Isomers, Salts, Solvates, Protected Forms, and Prodrugs

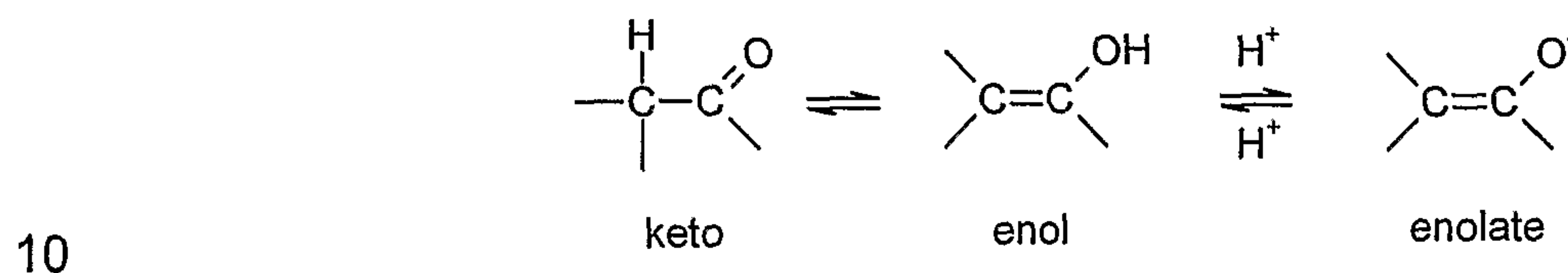
15 Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and
20 enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

25 Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy
30 group, -OCH₃, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, -CH₂OH. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally

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isomeric forms falling within that class (e.g., C₁₋₇alkyl includes n-propyl and isopropyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

- 5 The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ¹H, ²H (D), and ³H (T); C may be in any isotopic form, including ¹²C, ¹³C, and ¹⁴C; O may be in any isotopic form, including ¹⁶O and ¹⁸O; and the like.

15

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

20

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

25

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in

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Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be
5 anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable
cation. Examples of suitable inorganic cations include, but are not limited to,
alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and
 Mg^{2+} , and other cations such as Al^{+3} . Examples of suitable organic cations
include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted
10 ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some
suitable substituted ammonium ions are those derived from: ethylamine,
diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine,
ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine,
choline, meglumine, and tromethamine, as well as amino acids, such as lysine
15 and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic
(e.g., -NH_2 may be -NH_3^+), then a salt may be formed with a suitable anion.
Examples of suitable inorganic anions include, but are not limited to, those
20 derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic,
sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived
from the following organic acids: 2-acetoxybenzoic, acetic, ascorbic, aspartic,
25 benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic,
ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic,
hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic,
malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic,
phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic,
30 sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric
organic anions include, but are not limited to, those derived from the following
polymeric acids: tannic acid, carboxymethyl cellulose.

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It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

25

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other

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functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester
 5 (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal
 10 (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

15 For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyloxy amide (-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide
 20 (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

25

For example, a carboxylic acid group may be protected as an ester for example, as: an C₁₋₇alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇haloalkyl ester (e.g., a C₁₋₇trihaloalkyl ester); a triC₁₋₇alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀aryl-C₁₋₇alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for
 30 example, as a methyl amide.

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For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised (e.g., *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

10

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula

20 -C(=O)OR wherein R is:

C₁₋₇alkyl

(e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);

C₁₋₇aminoalkyl

(e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and

25 acyloxy-C₁₋₇alkyl

(e.g., acyloxymethyl;

acyloxyethyl;

pivaloyloxymethyl;

acetoxymethyl;

30 1-acetoxyethyl;

1-(1-methoxy-1-methyl)ethyl-carboxyloxyethyl;

1-(benzoyloxy)ethyl; isopropoxy-carboxyloxymethyl;

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- 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;
5 (4-tetrahydropyranyloxy) carbonyloxymethyl;
1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).
- 10 Also, some prodrugs are activated enzymatically to yield the active compound, or
a compound which, upon further chemical reaction, yields the active compound
(for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug
may be a sugar derivative or other glycoside conjugate, or may be an amino acid
ester derivative.

15

Acronyms

For convenience, many chemical moieties are represented using well known
abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr),
20 iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu),
n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn),
naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known
25 abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH),
iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et₂O),
acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile
(ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran
(THF), and dimethylsulfoxide (DMSO).

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Synthesis of Alkane Diols Derivatives

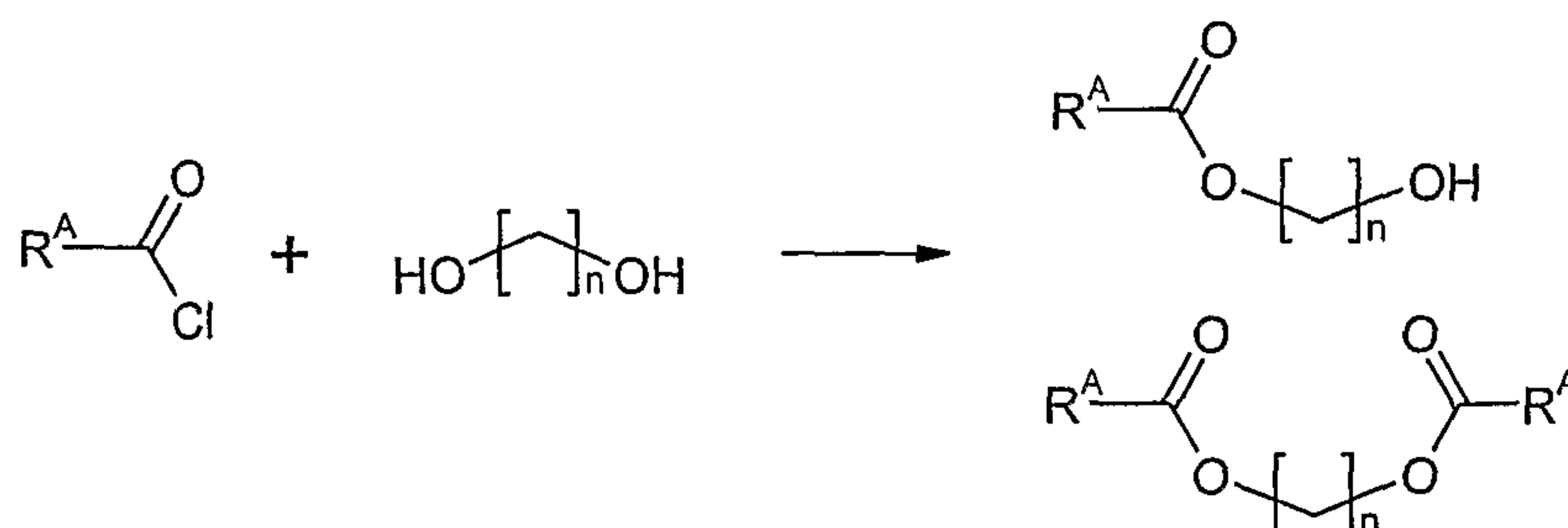
Compounds suitable for use in the present invention may be synthesised using known methods. Suitable reagents and intermediates are commercially available. Additionally, several methods for the chemical synthesis of suitable compounds (e.g., alkane diol esters) for use in present invention are described herein. These methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds suitable for use in the present invention.

10

Examples of some suitable methods for the synthesis of alkane diol monoesters are described below.

In one method, esters of alkane diols are prepared by the reaction of the alkane diol with acyl halide (e.g., acyl chloride), optionally in the presence of a base (e.g., pyridine). For example, the alkane diol may first be dissolved in pyridine, and then the acyl halide added. If an excess of alkane diol is used, the mono-protected product is predominant; if an excess of acyl halide is used, the di-protected product is predominant. An example of such a method is illustrated in the following scheme.

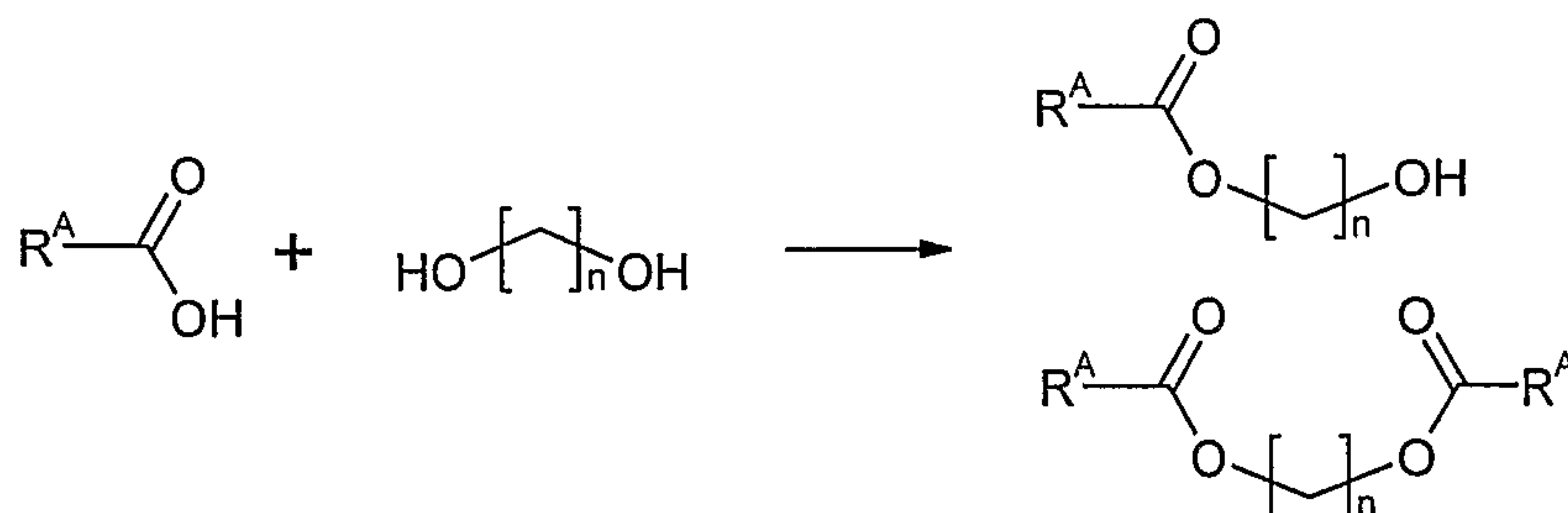
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Scheme 1

25 In another method, esters of alkane diols are prepared by the reaction of the alkane diol with a carboxylic acid, in the presence of a strong acid (e.g., H₂SO₄). For example, a small (catalytic) amount of strong acid may be used. If an excess of alkane diol is used, the mono-protected product is predominant; if an excess

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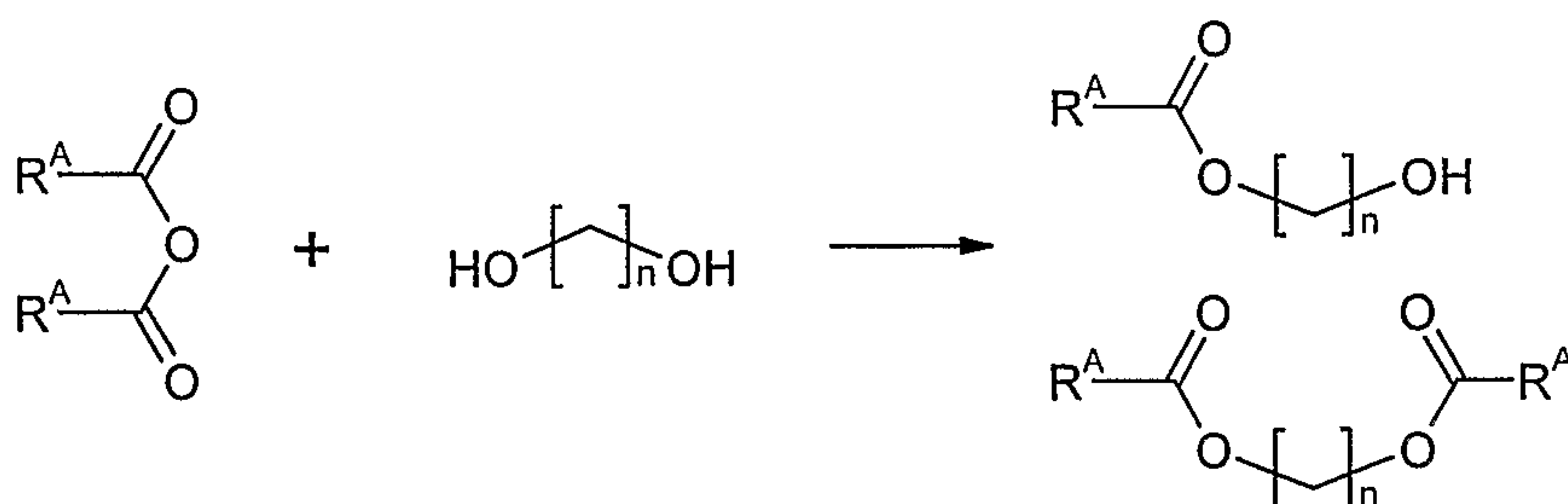
of carboxylic acid is used, the di-protected product is predominant. An example of such a method is illustrated in the following scheme.

Scheme 2

5

In another method, esters of alkane diols are prepared by the reaction of the alkane diol with an excess of acyl anhydride, in the presence of a base (e.g., pyridine). If an excess of alkane diol is used, the mono-protected product is predominant; if an excess of acyl anhydride is used, the di-protected product is predominant. An example of such a method is illustrated in the following scheme.

10

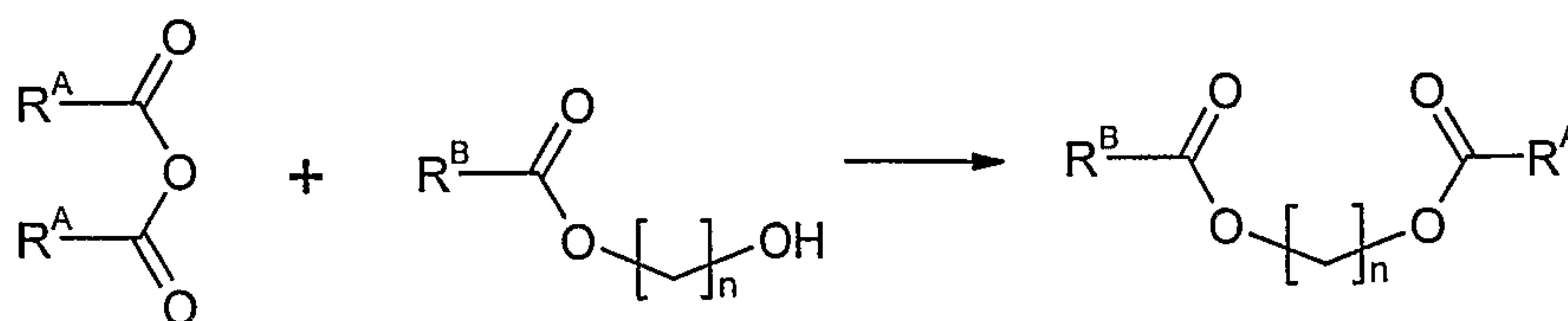
Scheme 3

15

In another method, mixed esters of alkane diols are prepared by reaction of a mono-ester with an excess of acyl anhydride, in the presence of a base (e.g., pyridine). An example of such a method is illustrated in the following scheme.

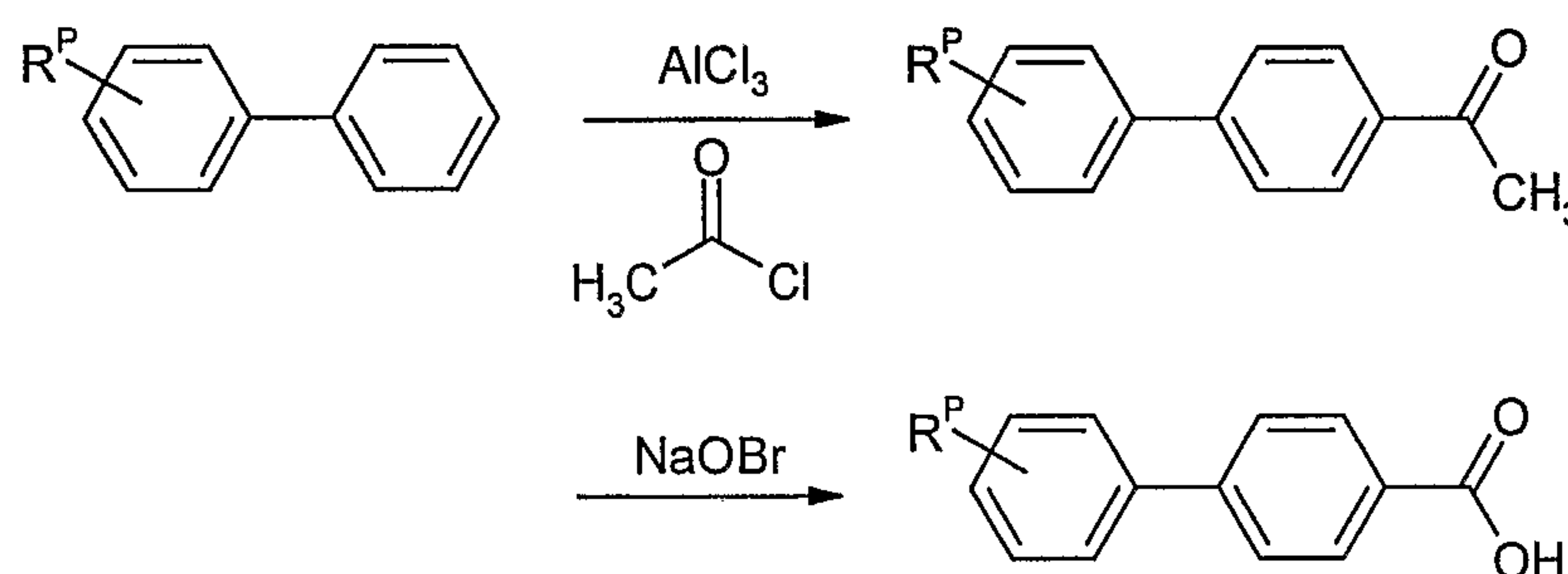
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Scheme 4

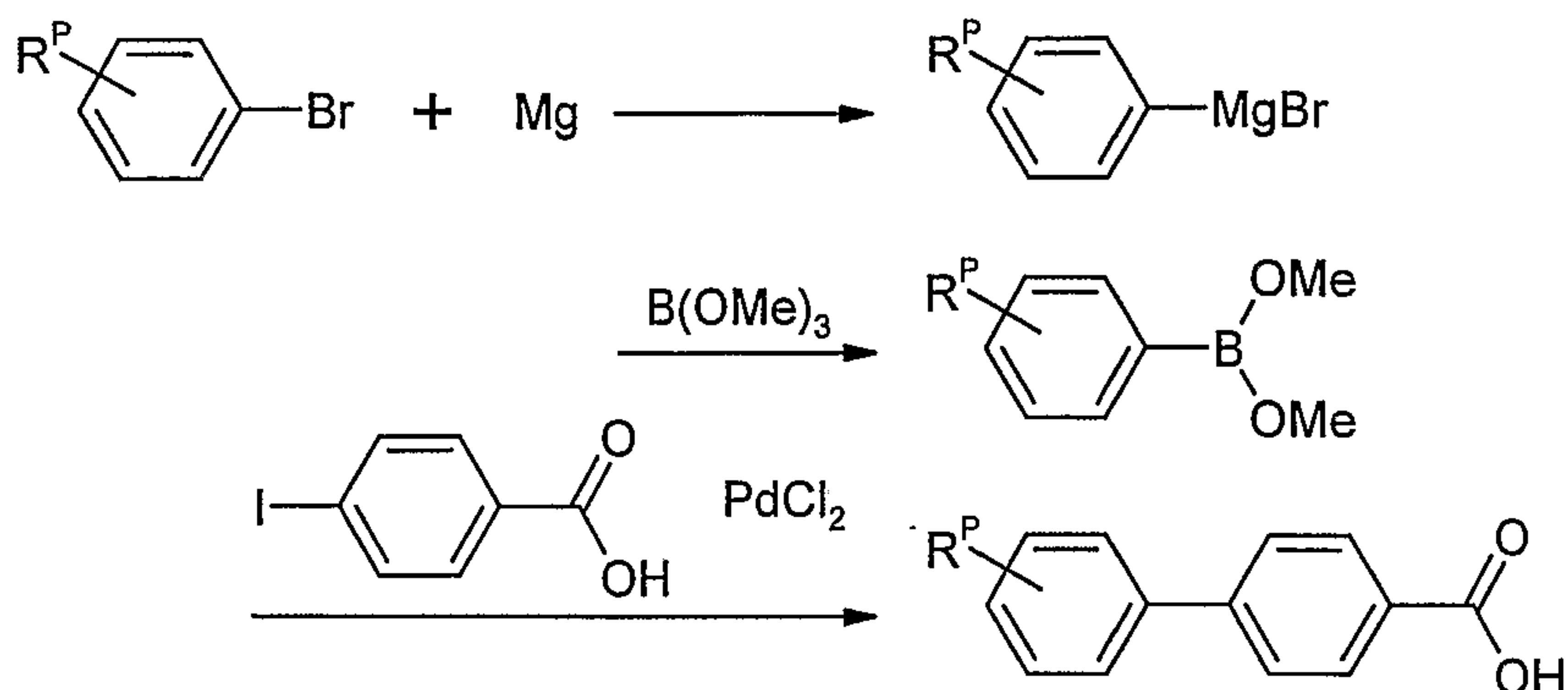
Suitable carboxylic acids may be prepared, for example, by reaction with
 5 aluminium trichloride ($AlCl_3$) and acetyl chloride (CH_3COCl) to give the
 corresponding methyl ketone, which is then reacted with $NaOBr$ (formed by
 reaction of Br_2 with $NaOH$) to give the corresponding carboxylic acid. An
 example of such a method is illustrated in the following scheme.

10

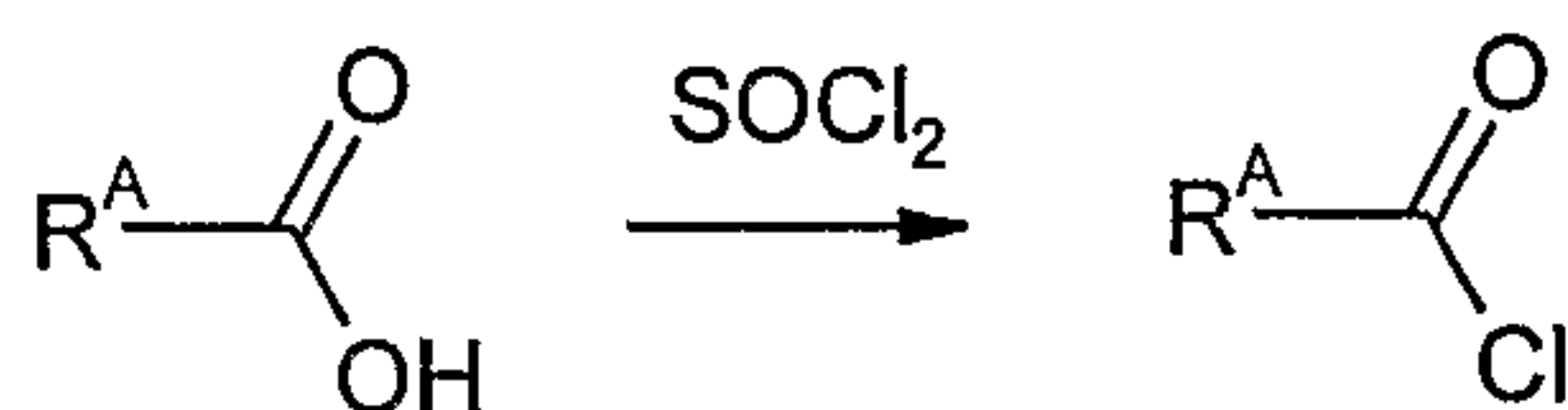
Scheme 5

Suitable carboxylic acids may also be prepared by forming a Grignard reagent,
 15 which is then reacted with a borate, e.g., $B(OMe)_3$ to form a borane, which is
 then reacted with a suitable halide compound, in the presence of a suitable
 catalyst, e.g., $PdCl_2$, to yield the desired carboxylic acid. An example of such a
 method is illustrated in the following scheme.

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Scheme 6

Suitable acyl halides may be prepared, for example, by reaction of the
 5 corresponding carboxylic acid with sulfonyl halide, e.g., sulfonyl chloride (SOCl₂).
 An example of such a method is illustrated in the following scheme.

Scheme 7

10

1,4-Butanediol mono(fluorobiphenyl-4-carboxylic acid)esters can be synthesized
 by an analogous method, using a commercially available boronic acid (e.g., a
 fluorinated phenylboronic acid) and an iodobenzoic acid.

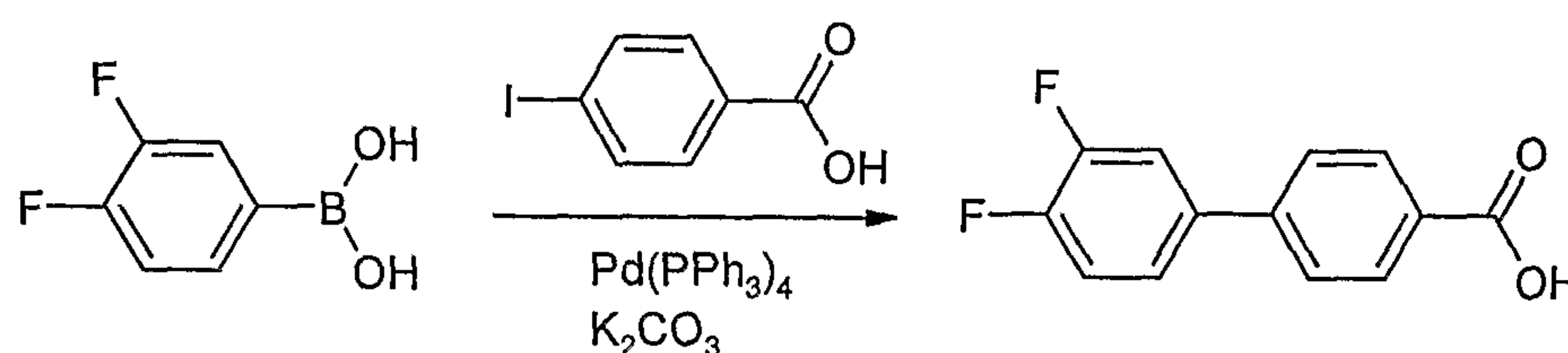
15 Commercially available fluorinated phenylboronic acids include, but are not
 limited to, 2,3-difluoro-; 2,4-difluoro-; 2,5-difluoro-; 2,6-difluoro-; 3,4-difluoro-;
 3,5-difluoro-; 2,3,6-trifluoro-; and 2,4,6-trifluoro-phenylboronic acid (Sigma-
 Aldrich); as well as 2-fluoro-4-iodo-; 4-fluoro-3-methyl-; and 3,5-dibromo-
 phenylboronic acid (Lancaster). An example of such a method is illustrated in
 20 the following scheme. In one method, iodobenzoic acid (1.75 mmol),
 3,4-difluorophenylboronic acid (3.5 mmol) and K₂CO₃ (2.6 mmol) are stirred in
 toluene (17 ml). Pd(PPh₃)₄ (0.05 mmol) is added and the mixture stirred for 2
 hours at 85°C. After cooling, the mixture is diluted with ethyl acetate (17 ml),
 washed with saturated Na₂CO₃ (20 ml), water (20 ml), 10% citric acid (20 ml),
 25 water (20 ml) and saturated NaCl (20 ml). The solvent is evaporated and the

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product is purified by column chromatography. In another method, a suspension of $\text{Pd}(\text{PPh}_3)_4$ (0.05 mmol) in dimethoxyethanol (20 ml) is prepared. Iodobenzoic acid (2 mmol) is added and the mixture is stirred for 10 minutes.

3,4-Difluorophenylboronic acid (3 mmol) in ethanol (2 ml) is added followed by
 5 2 M Na_2CO_3 (4 mmol). The mixture is refluxed for 18 hours, filtered and evaporated. The residue is washed with saturated NaCl (20 ml) and product is purified by column chromatography. See, for example, Miyaura et al., 1995.

Scheme 8

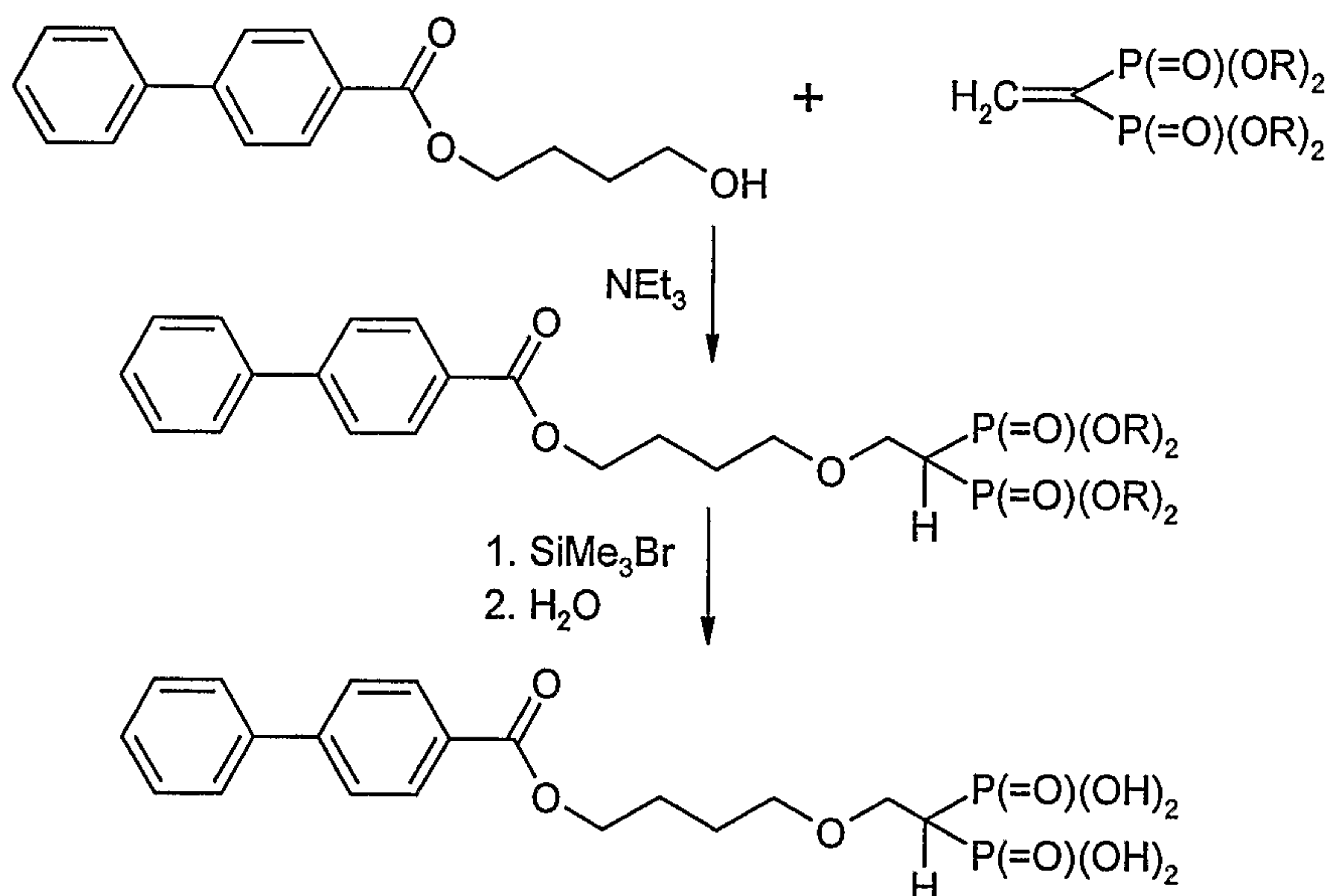


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Methods for the preparation of compounds having a phosphonic acid group, include, for example, those described below.

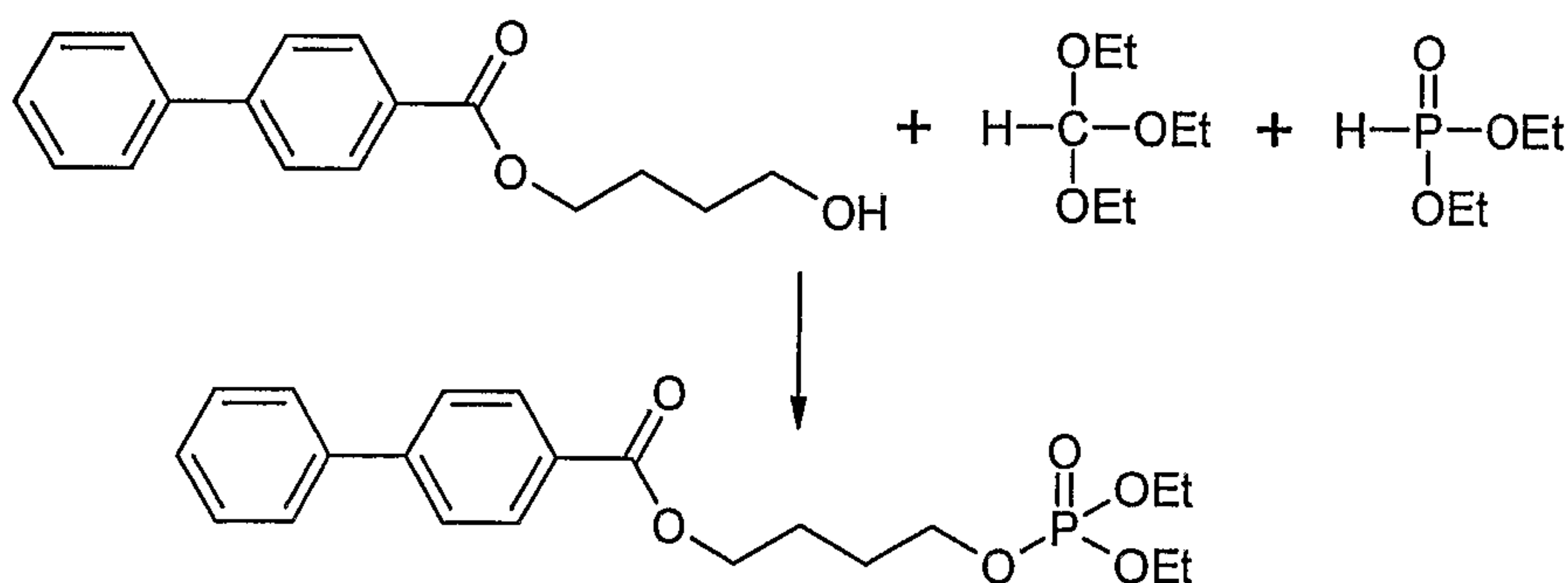
15 In one method, ethenylidenebisphosphonate ($\text{CH}_2=\text{C}(\text{P}(=\text{O})(\text{OR})_2)_2$) is prepared from paraformaldehyde, diethylamine and a tetraalkyl methylene bisphosphonate ($\text{H}_2\text{C}(\text{P}(=\text{O})(\text{OR})_2)_2$), using, for example, the method described by Degenhardt and Burdsall, 1986. The ethenylidene-bisphosphonate is then reacted with, for example, ABD-0056 (4BP), in methylene chloride, in the presence of
 20 triethylamine, using, for example, the method described by Herczegh et al., 2002. The phosphate ester groups, e.g., ethyl groups, are removed e.g., with trimethylsilylbromide or left in place. An example of such a method is illustrated in the following scheme.

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Scheme 9

In another method, ABD-0056, for example, is heated with triethylorthoformate and diethyl phosphite ($\text{HP}(\text{=O})(\text{OEt})_2$) using, for example, the method described by Herczegh et al., 2002. Again, the phosphate ester groups, e.g., ethyl groups, are removed e.g., with trimethylsilylbromide or left in place. An example of such a method is illustrated in the following scheme.

10

Scheme 10

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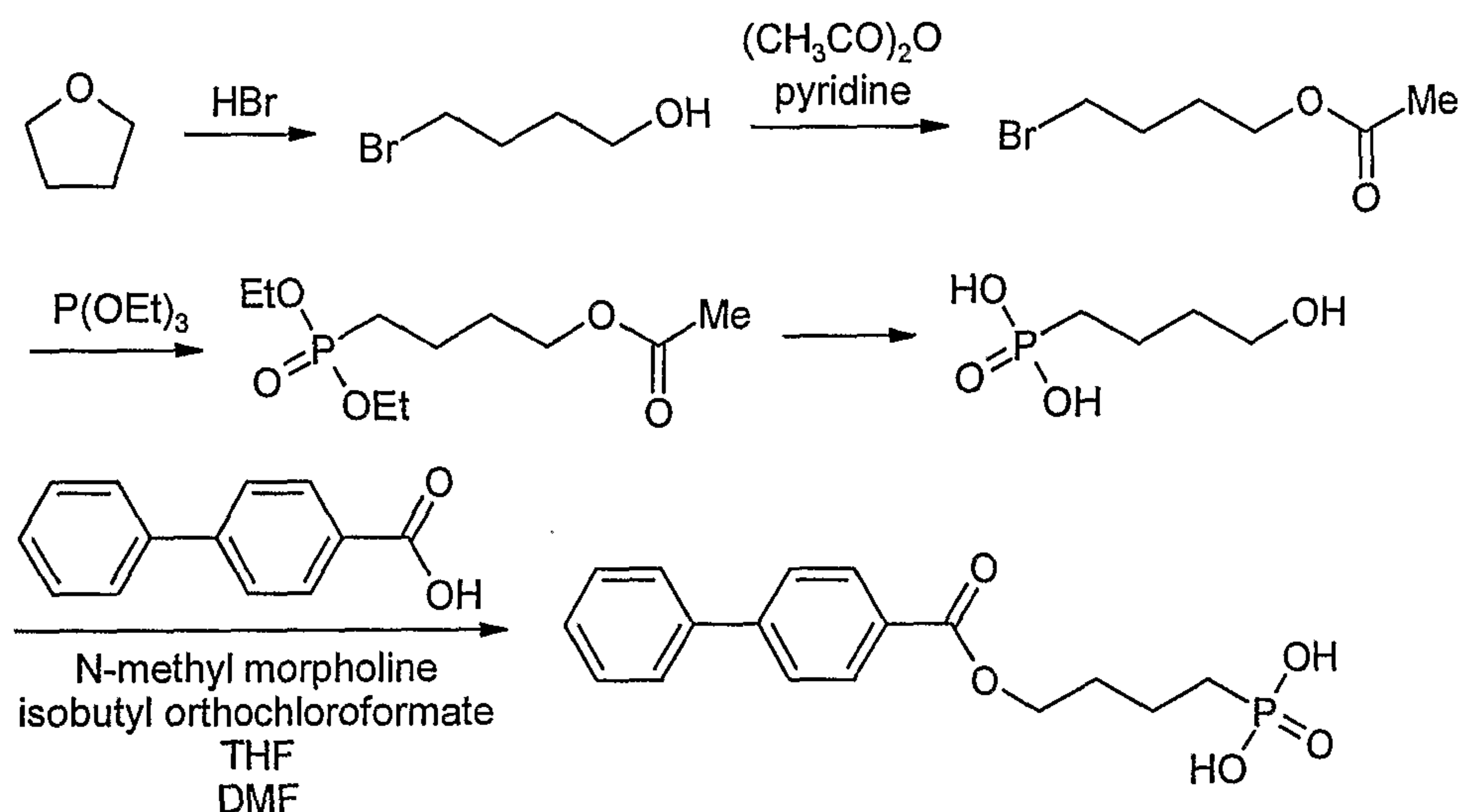
In another method, 4-bromobutanol (prepared, for example, by Method 9 described herein) is acetylated in acetic anhydride/pyridine. The resultant 4-acetoxybutylbromide is then heated with triethylphosphite to give diethyl-4-acetoxybutyl phosphonate using, for example, the method described by Eberhard and Westheimer, 1965. Hydrolysis with sulphuric acid removes the acetyl and ethyl groups to give the 4-hydroxybutylphosphonate. This is then linked to

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biphenyl-4-carboxylic acid using N-methyl morpholine and isobutyl chloroformate in a mixture of tetrahydrofuran and dimethylformamide. An example of such a method is illustrated in the following scheme.

5

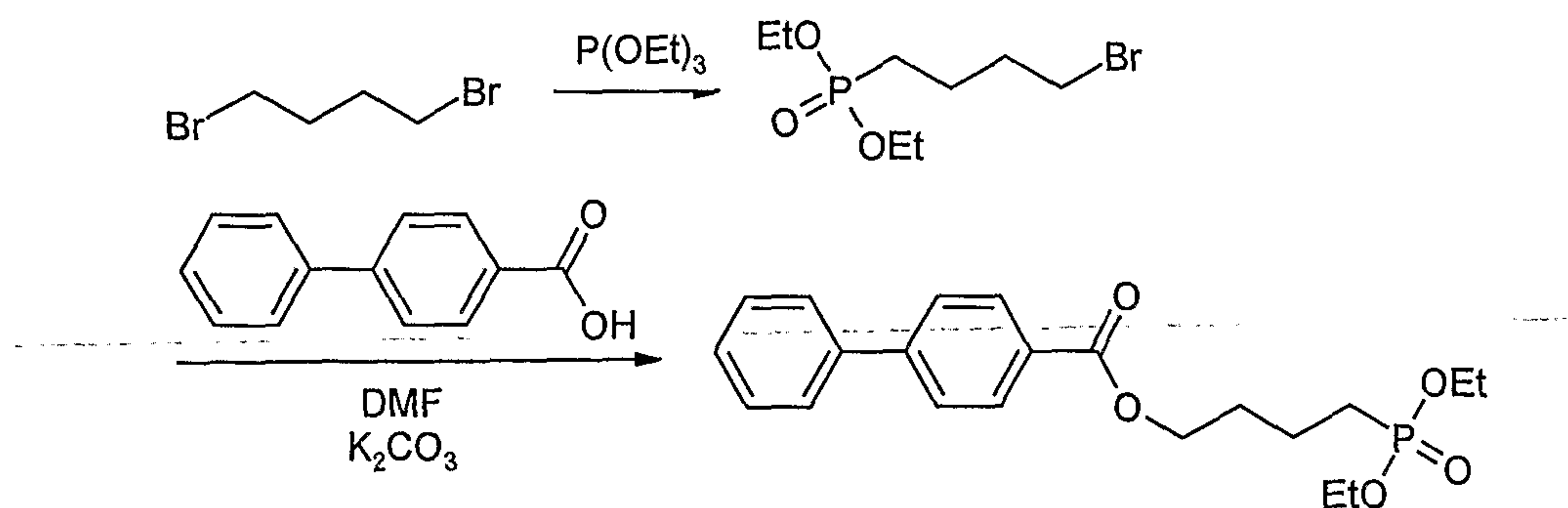
Scheme 11



In another method, 1,4-dibromobutane is heated with triethylphosphite to give diethyl-4-bromobutylphosphonate, for example, as described by Eberhard and Westheimer, 1965. The resultant bromide is then reacted with, for example, biphenyl-4-carboxylic acid in dimethylformamide, in the presence of potassium carbonate. Again, the phosphate ester groups, e.g., ethyl groups, are removed e.g., with trimethylsilylbromide or left in place. An example of such a method is illustrated in the following scheme.

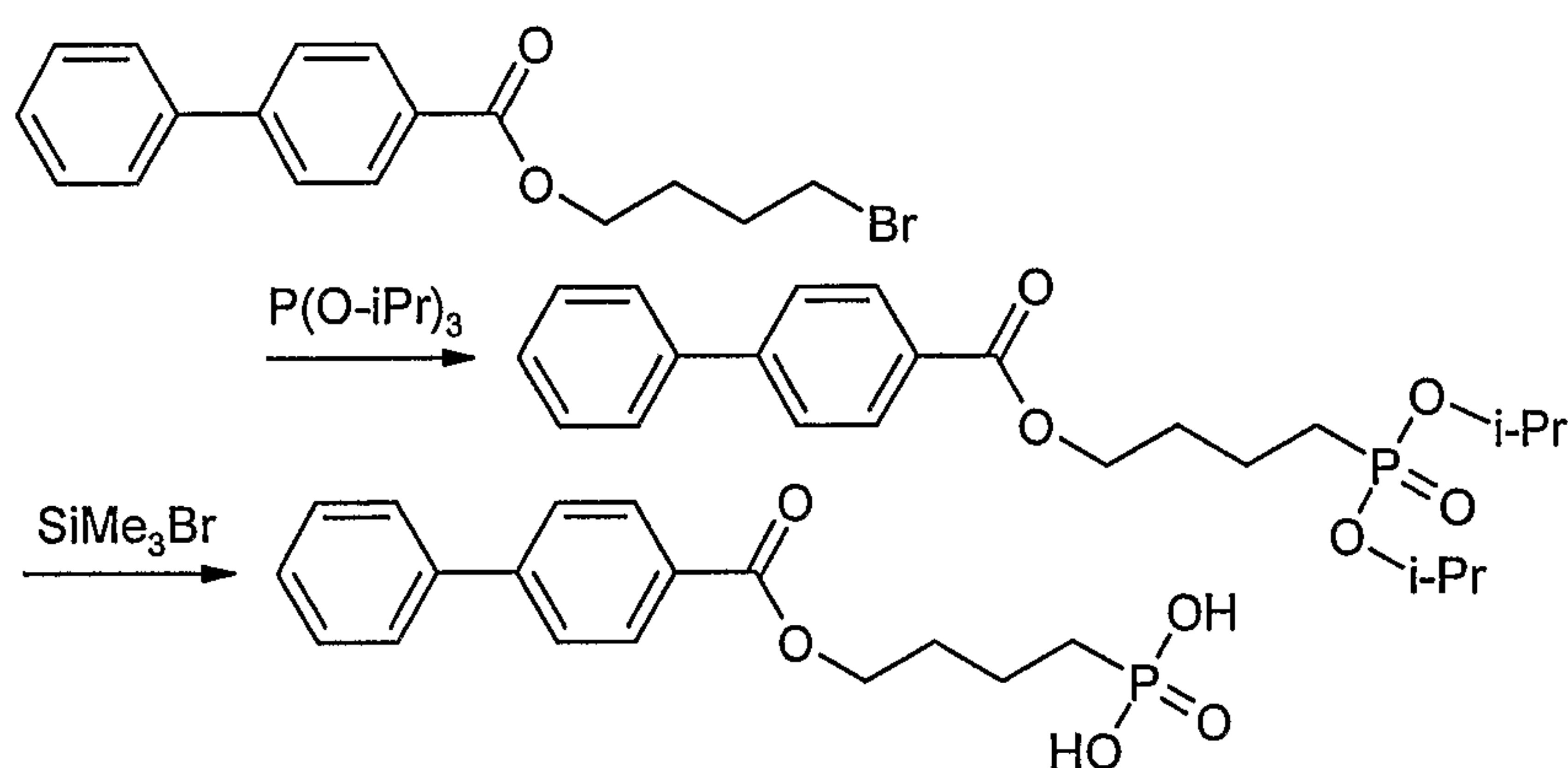
15

Scheme 12



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In another method, ABD-0086 (4BP-Br), for example, is gently refluxed with triisopropylphosphite to give the phosphonylated product. Remaining triisopropylphosphite is removed by distillation under reduced pressure and the residue is purified by column chromatography to give a clear oil. The isopropyl groups are removed using trimethylsilylbromide in dichloromethane, or left in place. An example of such a method is illustrated in the following scheme.

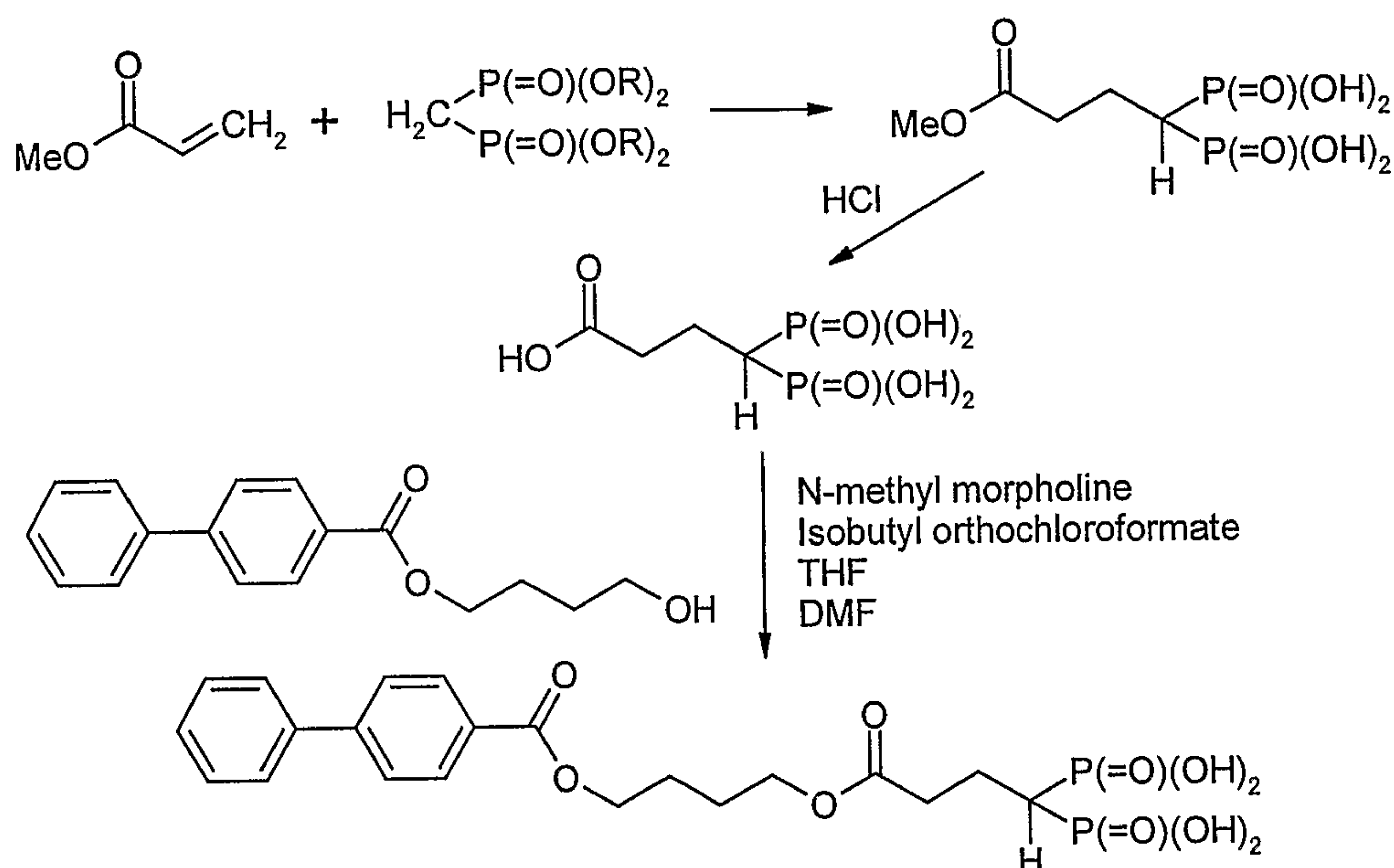
Scheme 13

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In another method, acrylic acid methyl ester (methyl acrylate) and methylene diphosphonic acid tetraethyl ester are mixed and saturated sodium ethanolate solution is added dropwise. The mixture is heated (e.g., to 90°C for 2 hours) and the product obtained by distillation under reduced pressure. The ester groups were removed by hydrolysis in conc. HCl. See, e.g., Blum et al., 1978. An example of such a method is illustrated in the following scheme.

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Scheme 14

The products may be purified, for example, by column chromatography.

5

Use of Alkane Diol Derivatives

The present invention provides active compounds, specifically, active alkane diol derivatives (e.g., esters of alkane diols), as described herein, which inhibit osteoclasts, for example, inhibit of the survival, formation, and/or activity of osteoclasts, and/or which inhibit bone resorption. The compounds may therefore be referred to as "osteoclast inhibitors" and/or "bone resorption inhibitors."

The term "active," as used herein, pertains to compounds which are capable of inhibiting the survival, formation, and/or activity of osteoclasts, and/or inhibiting bone resorption, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits the survival, formation, and/or activity of osteoclasts and/or inhibits bone resorption. For example, suitable methods which may

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conveniently be used in order to assess the inhibitory effects offered by a particular compound are described in the examples below.

5 The compounds of the present invention are also useful in the treatment of conditions mediated by osteoclasts (as "osteoclast inhibitors"), and/or conditions characterised by bone resorption (as "bone resorption inhibitors"). Examples of such conditions include, but are not limited to, the following:

10 Diseases of the skeleton, including but not limited to, pathologically low bone mineral density, such as osteoporosis (including, e.g., steroid induced osteoporosis); osteopetrosis; osteoarthritis; ectopic bone formation; Paget's disease of bone (osteitis deformans); and rheumatoid arthritis.

15 Neoplasia of bones, both as a primary tumour and as metastases, including but not limited to, osteosarcoma and osteoma (Zheng et al., 1998, J. Cell Biochem., Vol. 70, p. 121) and cancer associated bone disease (e.g., multiple myeloma).

20 Examples of preferred conditions include osteoporosis, rheumatoid arthritis, cancer associated bone disease, and Paget's disease.

The compounds of the present invention have also macrophage inhibitory effects, and so are useful in the treatment of conditions associated with inflammation or activation of the immune system. Examples of such conditions include, but are not limited to, the following:

25 Diseases with an inflammatory or autoimmune component, including allergic diseases, such as atopy, allergic rhinitis, atopic dermatitis, anaphylaxis, allergic bronchopulmonary aspergillosis, and hypersensitivity pneumonitis (pigeon breeders disease, farmer's lung disease, humidifier lung disease, malt workers' lung disease); allergies, including flea allergy dermatitis in mammals such as
30 domestic animals, e.g., dogs and cats, contact allergens including mosquito bites or other insect sting allergies, poison ivy, poison oak, poison sumac, or other skin

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allergens; autoimmune disorders, including, but not limited to, type I diabetes, Crohn's disease, multiple sclerosis, arthritis, rheumatoid arthritis (Ogata et al., 1997, J. Pathol., Vol. 182, p. 106); Gong et al., 1997, J. Exp. Med., Vol 186, p. 131), systemic lupus erythematosus, autoimmune (Hasimoto's) thyroiditis, 5 autoimmune liver diseases such as hepatitis and primary biliary cirrhosis, hyperthyroidism (Graves' disease; thyrotoxicosis), insulin-resistant diabetes, autoimmune adrenal insufficiency (Addison's disease), autoimmune oophoritis, autoimmune orchitis, autoimmune hemolytic anemia, paroxysmal cold hemoglobinuria, Behcet's disease, autoimmune thrombocytopenia, autoimmune 10 neutropenia, pernicious anemia, pure red cell anemia, autoimmune coagulopathies, myasthenia gravis, experimental allergic encephalomyelitis, autoimmune polyneuritis, pemphigus and other bullous diseases, rheumatic carditis, Goodpasture's syndrome, postcardiotomy syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, and scleroderma; disease states 15 resulting from inappropriate inflammation, either local or systemic, for example, irritable or inflammatory bowel syndrome (Mazzucchelli et al., 1996, J. Pathol., Vol. 178, p. 201), skin diseases such as psoriasis and lichen planus, delayed type hypersensitivity, chronic pulmonary inflammation, e.g., pulmonary alveolitis and pulmonary granuloma, gingival inflammation or other periodontal disease, 20 and osseous inflammation associated with lesions of endodontic origin (Volejnikova et al., 1997, Am. J. Pathol., Vol. 150, p. 1711), hypersensitivity lung diseases such as hypersensitivity pneumonitis (Sugiyama et al., 1995, Eur. Respir. J., Vol. 8, p. 1084), and inflammation related to histamine release from basophils (Dvorak et al., 1996, J. Allergy Clin. Immunol., Vol. 98, p. 355), such as 25 hay fever, histamine release from mast cells (Galli et al., 1989, Ciba Foundation Symposium, Vol. 147, p. 53), or mast cell tumors, types of type 1 hypersensitivity reactions (anaphylaxis, skin allergy, hives, allergic rhinitis, and allergic gastroenteritis); ulcerative colitis.

30 Thus, one aspect of the invention pertains to a method of inhibiting osteoclast survival, formation, and activity, *in vitro* or *in vivo*, comprising contacting an osteoclast with an effective amount of an active compound, as described herein.

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Another aspect of the invention pertains to a method of inhibiting bone resorption, *in vitro* or *in vivo*, comprising contacting cells in the bone microenvironment with a therapeutically-effective amount of an active compound,
5 as described herein.

The term "cells in the bone microenvironment," as used herein, pertains to cells such as osteoblasts, osteoclasts, osteocytes and bone marrow stromal cells, which are located in close proximity to bone (e.g., within one hundred
10 micrometers of the bone surface).

Another aspect of the present invention pertains to a method for the treatment of a condition mediated by osteoclasts and/or characterised by bone resorption, as described herein, comprising administering to a subject suffering from said
15 condition a therapeutically-effective amount of an active compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to a method for the treatment of a condition associated with inflammation or activation of the immune system, as
20 described herein, comprising administering to a subject suffering from said condition a therapeutically-effective amount of an active compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to an active compound as
25 described herein for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition mediated by
30 osteoclasts and/or characterised by bone resorption, as described herein, of the human or animal body by therapy.

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Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition mediated by osteoclasts, as described herein, of the human or animal body by therapy.

- 5 Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition characterised by bone resorption, as described herein, of the human or animal body by therapy.

- 10 Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment of osteoporosis, rheumatoid arthritis, cancer associated bone disease, or Paget's disease of the human or animal body by therapy.

- 15 Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment a condition associated with inflammation or activation of the immune system, as described herein, of the human or animal body by therapy.

- 20 Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition mediated by osteoclasts and/or characterised by bone resorption, as described herein.

- 25 Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition mediated by osteoclasts, as described herein.

- 30 Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition characterised by bone resorption, as described herein.

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Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of osteoporosis, rheumatoid arthritis, cancer associated bone disease, or Paget's disease.

5

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a condition associated with inflammation or activation of the immune system, as described herein.

10

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and
15 includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included.

20

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

25

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g.,
drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in
30 photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

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Active compounds may also be used as cell culture additives to inhibit osteoclasts, for example, to inhibit the survival, formation, and/or activity of osteoclasts.

- 5 Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

- 10 Active compounds may also be used as a standard, for example, in an assay, in order to identify other active compounds, other osteoclast inhibitors, etc.

Kits

- 15 One aspect of the invention pertains to a kit comprising (a) an active compound as described herein, or a composition comprising an active compound as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the active compound or composition.

- 20 The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Routes of Administration

- 25 The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).
- 30 Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal

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spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, 5 intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

10 The Subject

The subject may be a chordate, a vertebrate, a mammal, a bird, a reptile (e.g., snakes, lizards, crocodiles), an amphibian (e.g., frogs, toads), a bony fish (e.g., salmon, plaice, eel, lungfish), a cartilaginous fish (e.g., sharks, rays), or a jawless 15 fish (e.g., lampreys, hagfish).

The subject may be a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph 20 (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

25 Furthermore, the subject may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject is a human.

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Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one active compound, as defined above, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the active compound.

The term "pharmaceutically acceptable" as used herein pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th

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edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994.

5 The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

10

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

15 Formulations may suitably be in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, e.g., coated tablets), granules, powders, lozenges, pastilles, capsules (including, e.g., hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, 20 lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more active compounds and optionally one or more other pharmaceutically acceptable ingredients, 25 including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

The active compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The active compound may 30 be presented in a liposome or other microparticulate which is designed to target the active compound, for example, to blood components or one or more organs.

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Formulations suitable for oral administration (e.g, by ingestion) include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

5

Formulations suitable for buccal administration include mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Lozenges typically comprise the active compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the active

10 compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia.

Mouthwashes typically comprise the active compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, lozenges, pastilles, capsules, and pills.

15

Formulations suitable for oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

20

Formulations suitable for non-oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive

25 plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

30

Tablets may be made by conventional means, e.g., compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be

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prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium
5 hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and
10 sweeteners. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the
15 desired release profile. Tablets may optionally be provided with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the active compound and a paraffinic or a
20 water-miscible ointment base.

Creams are typically prepared from the active compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having
25 two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas.
---Examples of such dermal penetration enhancers include dimethylsulfoxide and
30 related analogues.

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Emulsions are typically prepared from the active compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

10

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

25

Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

30

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size,

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for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

- 5 Formulations suitable for pulmonary administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide, or other suitable gases.
- 10 Formulations suitable for ocular administration include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.
- 15 Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.
- 20 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.
- 25 Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the active compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additional contain other pharmaceutically acceptable ingredients, such as
- 30 anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of

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excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the liquid is from
5 about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection
10 solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

15 It will be appreciated by one of skill in the art that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including,
20 but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of
25 compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

30 Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration

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are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian,
5 or clinician.

In general, a suitable dose of the active compound is in the range of about 100 µg to about 250 mg (more typically about 100 µg to about 25 mg) per kilogram body weight of the subject per day. Where the active compound is a salt, an
10 ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLES

15

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

The identity and purity of the compounds was proven using ^{13}C and ^1H nmr in
20 comparison with model literature compounds (ABD-0006 and ABD-0009) (4A and 4B), for which accurate melting or boiling points can also be obtained. The identity of many compounds was also ascertained using gas chromatography-mass spectroscopy (GC-MS).

25 General Methods

Method 1: Esterification using an acid chloride and an alcohol

The alcohol (0.1 mol) was dissolved in dry pyridine (50 ml) and chilled in an ice
30 bath. The acid chloride (0.02 mol) was added dropwise with vigorous stirring and the mixture stirred overnight at room temperature. The mixture was poured into water (200 ml) and extracted with methylene chloride (100 ml). The organic

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phase was washed sequentially with 2 M HCl (3 x 100 ml), water, saturated NaHCO₃ and water. The solution was dried over Na₂SO₄ and evaporated to an oil or amorphous solid. The product was dissolved in methylene chloride (< 5 ml), absorbed onto a column (silica gel 60, Merck) and purified using a mixture of
5 light petroleum and ethyl acetate (usually a 1:1 mixture was satisfactory). Evaporation of the solvent gave an oil or a solid.

Method 2: Esterification using an acid and an alcohol

10 The alcohol (0.2 mol) was heated in a boiling water bath. The acid (0.02 mol) was added followed by 20 drops of concentrated H₂SO₄ with vigorous stirring. Stirring was continued for 3 hours or until all of the acid had dissolved. The solution was poured into water (200 ml) and extracted with methylene chloride. The organic phase was washed with water, saturated NaHCO₃ and water. The
15 solution was dried over Na₂SO₄ and purified as described in Method 1.

Method 3: Esterification using an acid anhydride and an alcohol

Pyridine (25 ml) and acetic anhydride (25 ml) were stirred at 0°C. The alcohol (4
20 mmol) in pyridine (10 ml) was added dropwise. The mixture was stirred overnight at room temperature and then in a boiling water bath for 2 hours. The mixture was then poured into water (200 ml) and extracted with methylene chloride (100 ml). The organic phase was washed sequentially with water, 2 M HCl (2 x 100 ml), water, saturated NaHCO₃ (100 ml) and water. The organic phase was dried
25 over Na₂SO₄, evaporated and purified by column chromatography (light petroleum:ethyl acetate, 3:1).

Method 4: Preparation of biphenylcarboxylates by Friedel-Crafts acylation

30 The biphenyl (0.03 mol) was added to 1 M AlCl₃ in nitrobenzene (40 ml, 0.04 mol) with chilling in an ice bath. Acetyl chloride (0.06 mol) was added dropwise and the mixture stirred overnight at room temperature. The dark

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solution was poured into a mixture of crushed ice (150 ml), water (25 ml) and conc. HCl (50 ml). The organic phase was separated and the nitrobenzene removed by steam distillation to give a dark low melting solid. The solid was recrystallised from aqueous methanol.

5

Method 5: Oxidation of acetate group to free acid

NaOH (7 g) was dissolved in water (25 ml) and cooled in an ice bath. Bromine (7.8 g) was added dropwise to give a solution of NaOBr. The biphenyl acetate from Method 4 (0.01 mol) was dissolved in dioxane (35 ml) and warmed to 50°C in a water bath. The NaOBr solution was added slowly to the stirred solution of the biphenyl acetate and stirring continued at 50°C for a further 20 minutes. The solution was allowed to cool and a solution of sodium metabisulphite ($\text{Na}_2\text{S}_2\text{O}_5$) (8 g in 40 ml water) was added followed by water (170 ml). 50 ml of the liquid was evaporated under reduced pressure with heating. The remainder was acidified with conc. HCl (5 ml) and a white precipitate formed upon cooling. The precipitate was filtered and recrystallised from acetic acid.

Method 6: Preparation of biphenyls by Suzuki coupling

20

The substituted benzylbromide (e.g., 4-bromotoluene) (16 mmol) was dissolved in dry ether (15 ml) and reacted with magnesium (0.4 g, 16 mmol) to form the Grignard reagent. Gentle heating may be required to initiate the reaction. Trimethylborate (0.42 g, 4 mmol) was dissolved in ether (5 ml). The Grignard reagent was added dropwise to this solution with vigorous stirring. The reaction mixture was boiled for 15 minutes to give the aryl borane. A solution containing NaOH (2 g), 4-iodobenzoic acid (10 mmol), and PdCl_2 (0.1 mmol) in water (70 ml) was prepared and added dropwise to the aryl borane with vigorous stirring. Following addition, the mixture was boiled for 1 hour, allowed to cool and extracted with ether. The aqueous was extracted with methylene chloride. The aqueous was then acidified with HCl and extracted with methylene chloride followed by diethyl ether. These final two fractions were washed with saturated

25
30

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NaHCO₃ solution and water. All four fractions were combined, dried over Na₂SO₄ and evaporated to an amorphous solid. Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave the desired product as a white powder.

5

Method 7: Acetylation

The alcohol (10 mmol) was dissolved in pyridine (25 ml) and acetic anhydride (10 ml) was added dropwise. The mixture was stirred overnight, poured into water (200 ml) and extracted with methylene chloride (100 ml). The organic phase was washed sequentially with water, 2M HCl (2 x 100 ml), water, saturated NaHCO₃ (100 ml) and water. The organic phase was dried over Na₂SO₄, evaporated and purified by column chromatography (light petroleum:ethyl acetate, 3:1).

15 Method 8: Preparation of acid chloride

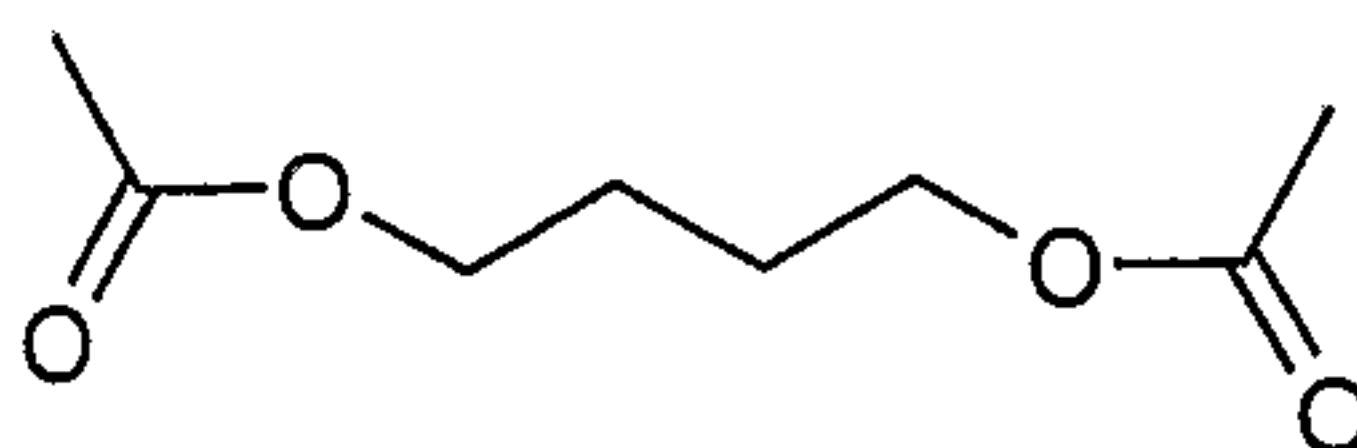
The acid (10 mmol) was dissolved in thionyl chloride (SOCl₂) (30 ml) and refluxed for 3 hours. The mixture was poured into acetic acid (100 ml) and left to stand until bubbling ceased. Volatile components were removed under vacuum and the mixture left to crystallise overnight. The desired acid chloride was collected by filtration.

Method 9: Preparation of 4-bromobutanol

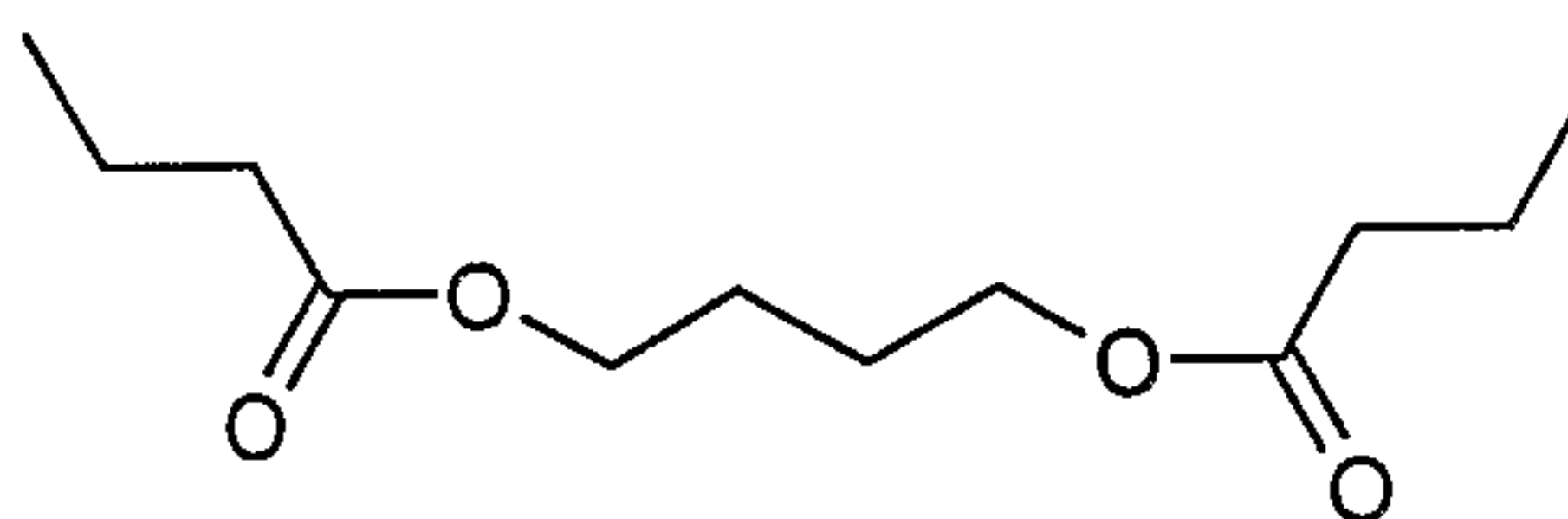
25 48% Hydrobromic acid (200 ml) was added to refluxing tetrahydrofuran (400 ml) over a period of 1 hour. Reflux was continued for 4 hours. The solution was allowed to cool, excess HBr was neutralised with NaHCO₃ and partitioned with water. The organic phase was separated, washed with brine and dried over MgSO₄. Evaporation of the solvent gave 4-bromobutanol as an oil.

30

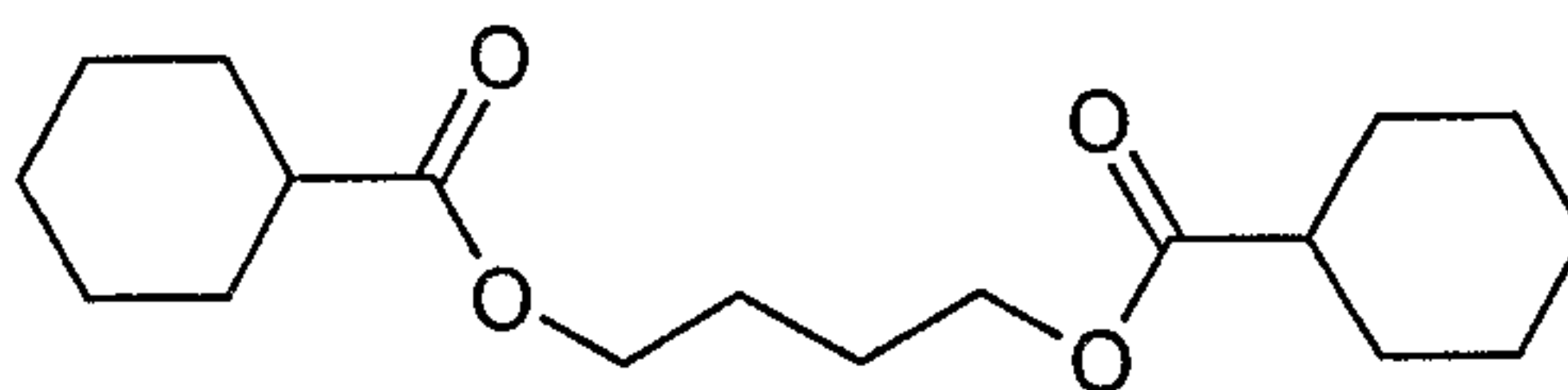
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Example 11,4-Butanediol di(acetic acid)ester (**ABD-0006**) (**4A**)

The title compound was prepared from acetic anhydride and 1,4-butanediol using Method 3, and was purified by distillation under reduced pressure to give a clear oil (yield 60%). δ_C (CDCl₃, 62.9 MHz): 20.96, 25.3, 63.9 and 171.1. δ_H (CDCl₃, 250 MHz): 1.70 (4H, m), 2.02 (6H, m) and 4.10 (4H, m).

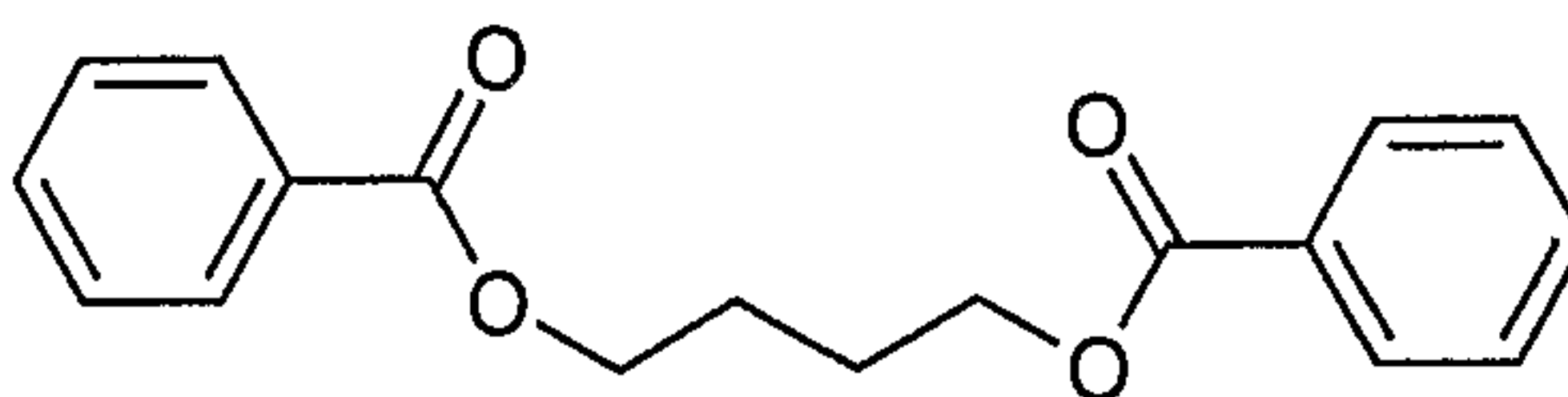
Example 210 1,4-Butanediol di(butanoic acid)ester (**ABD-0007**) (**4BU**)

The title compound was prepared from butyric acid and 1,4-butanediol using Method 2, to give a clear oil (yield 85%). δ_C (CDCl₃, 62.9 MHz): 13.6, 18.4, 25.4, 36.2, 63.7 and 173.7. δ_H (CDCl₃, 250 MHz): 0.92 (6H, t, *J* 7.3), 1.58-1.70 (8 H, m), 2.26 (4H, t, *J* 7.3) and 4.07 (4 H, m).

Example 31,4-Butanediol di(cyclohexanecarboxylic acid)ester (**ABD-0019**) (**4C**)

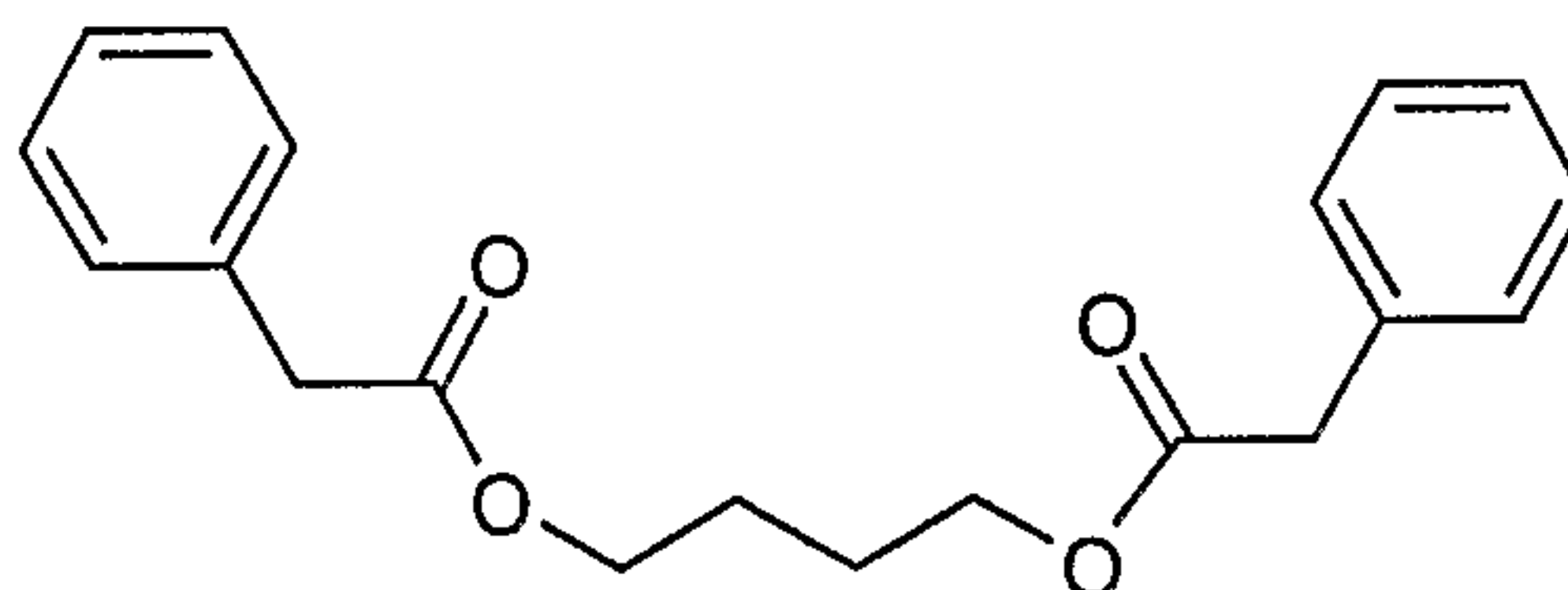
20 The title compound was prepared from cyclohexanecarbonyl chloride and 1,4-butanediol using Method 1 to give a clear oil which solidified over time (yield 30%). δ_C (CDCl₃, 62.9 MHz): 25.5, 25.8, 29.0, 43.2, 63.6 and 176.1.

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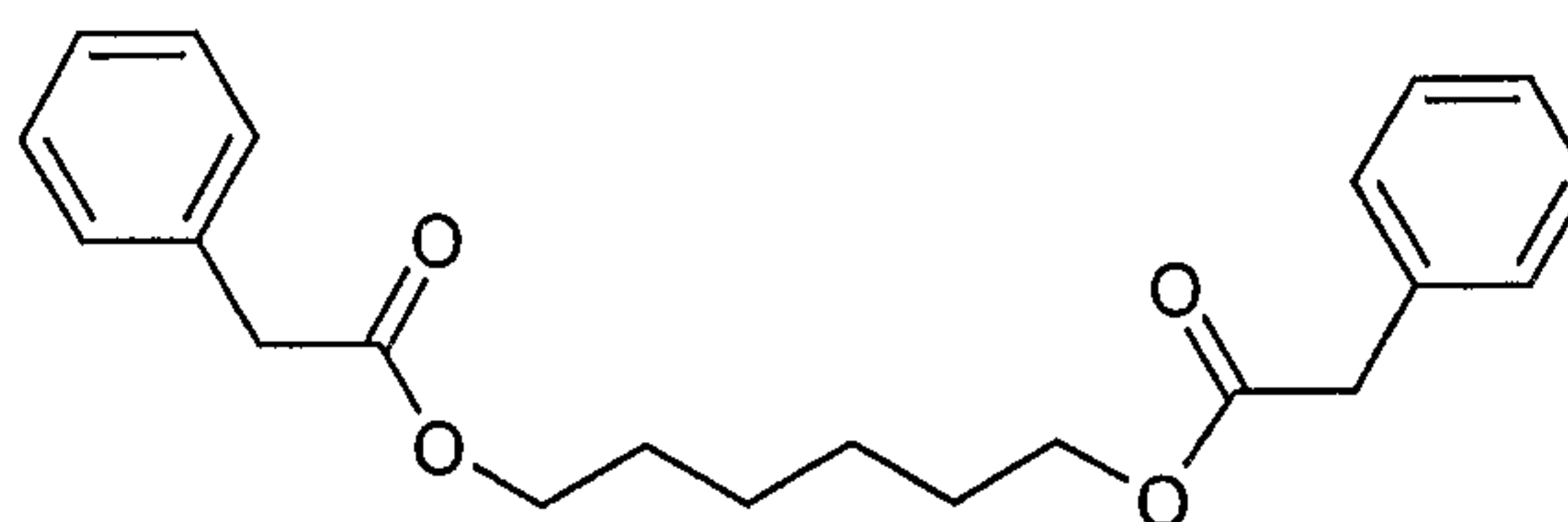
Example 41,4-Butanediol di(benzoic acid)ester (**ABD-0009**) (**4B**)

5 The title compound was prepared from benzoic acid and 1,4-butanediol using Method 2, to give a white crystalline solid (yield 80%). δ_C (CDCl₃, 62.9 MHz): 25.6, 64.5, 128.4, 129.6, 130.3, 133.0 and 166.6. δ_H (CDCl₃, 250 MHz): 1.95 (4H, m), 4.40 (4H, m), 7.43 (4H, t, J 7.3), 7.54 (2H, d, J 7.0) and 8.04 (4H, d, J 7.0).

10

Example 51,4-Butanediol di(phenylacetic acid)ester (**ABD-0014**) (**4P**)

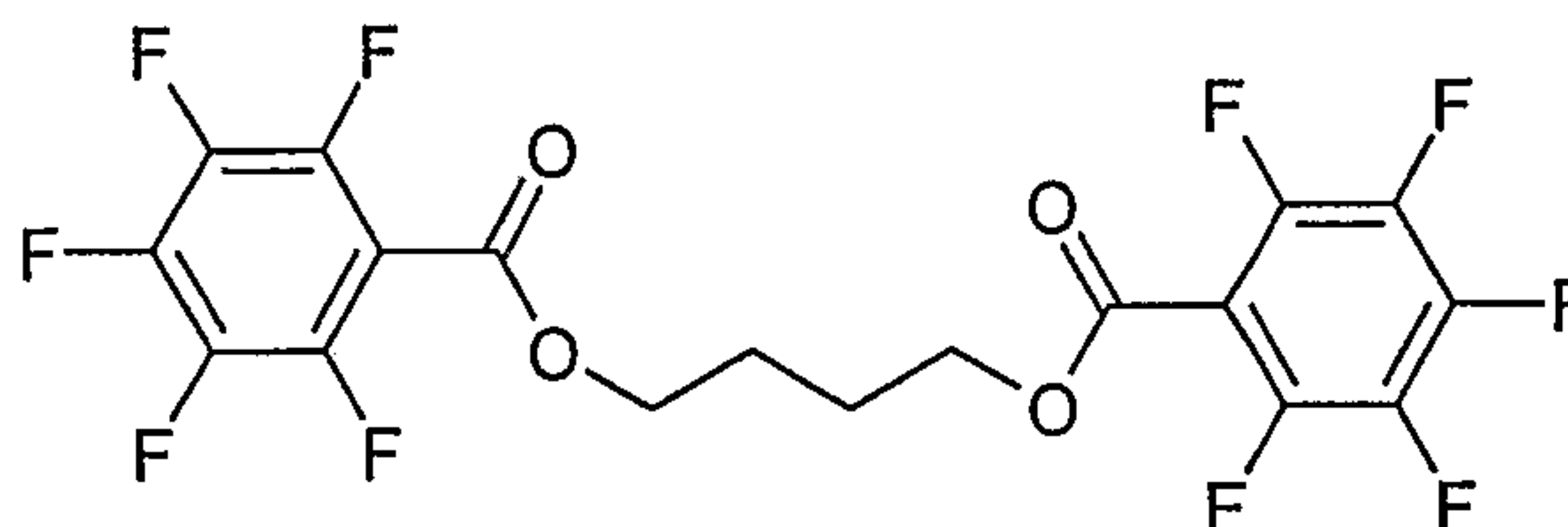
15 The title compound was prepared from phenylacetic acid and 1,4-butanediol using Method 2, to give a white solid (yield 50%). δ_C (CDCl₃, 62.9 MHz): 19.8, 23.8, 36.3, 57.1, 59.5, 121.9, 123.4, 124.1, 128.9, 157.4 and 166.5. δ_H (CDCl₃, 250 MHz): 1.64 (4H, m), 3.61 (4H, s), 4.08 (4H, m) and 7.29 (10H, m).

Example 61,6-Hexanediol di(phenylacetic acid)ester (**ABD-0017**) (**6P**)

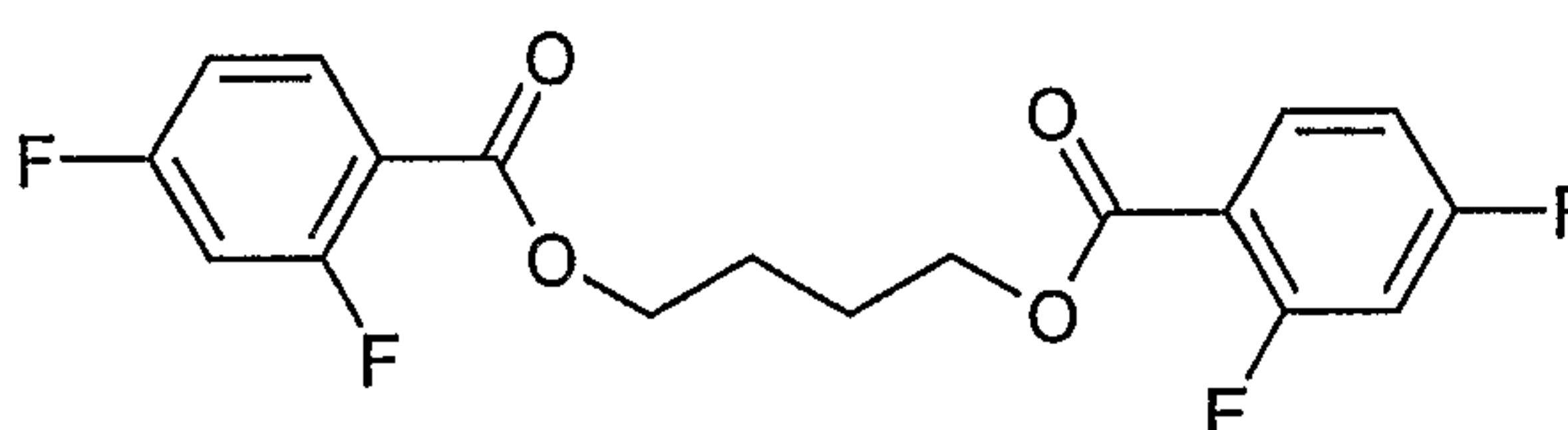
20

The title compound was prepared from phenylacetic acid and 1,6-hexanediol using Method 2 to give a clear oil (yield 90%). δ_C (CDCl₃, 62.9 MHz): 25.5, 28.4, 41.5, 64.7, 127.1, 128.6, 129.3, 134.2, and 171.6.

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Example 71,4-Butanediol di(pentafluorobenzoic acid)ester (**ABD-0085**) (**10F**)

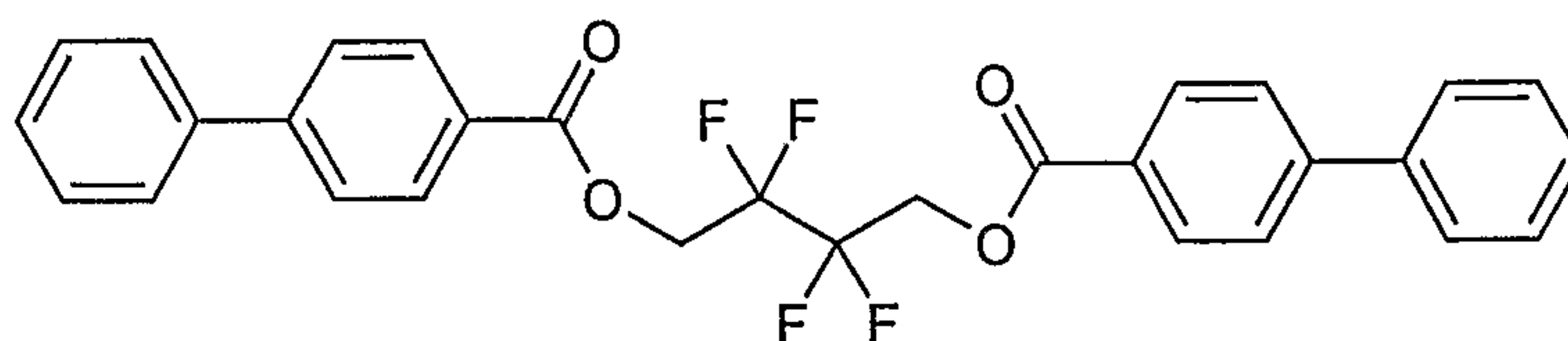
The title compound was prepared from pentafluorobenzoyl chloride and
 5 1,4-butanediol using Method 1 to give a white solid. Column chromatography
 gave the title compound as the first fraction (yield 20%). δ_C (CDCl₃, 62.9 MHz):
 25.0 and 66.0.

Example 810 1,4-Butanediol di(2,4-difluorobenzoic acid)ester (**ABD-0111**) (**D2,4FB**)

The title compound was prepared from 2,4-difluorobenzoyl chloride and
 1,4-butanediol using Method 1, to give a clear oil. Column chromatography gave
 the title compound as the first fraction (yield 20%). δ_C (CDCl₃, 62.9 MHz): 25.4,
 15 64.9, 105.2 (t, *J* 26.4), 111.6 (dd, *J* 21.5, 2.9) and 133.9 (d, *J* 10.7).

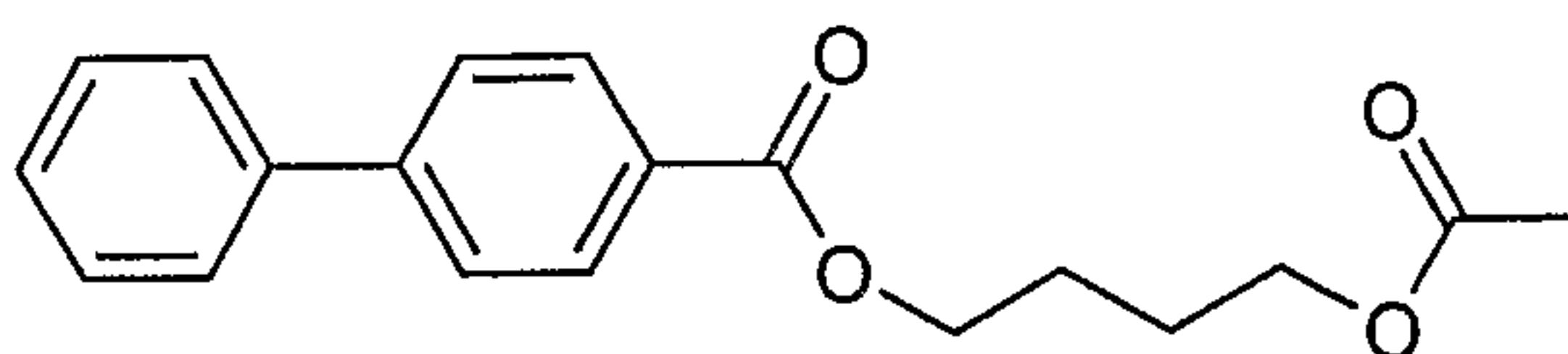
Example 9

2,2,3,3-tetrafluorobutan-1,4-diol di(biphenyl-4-carboxylic acid)ester (**ABD-0096**)
 (**DBP-4F**)



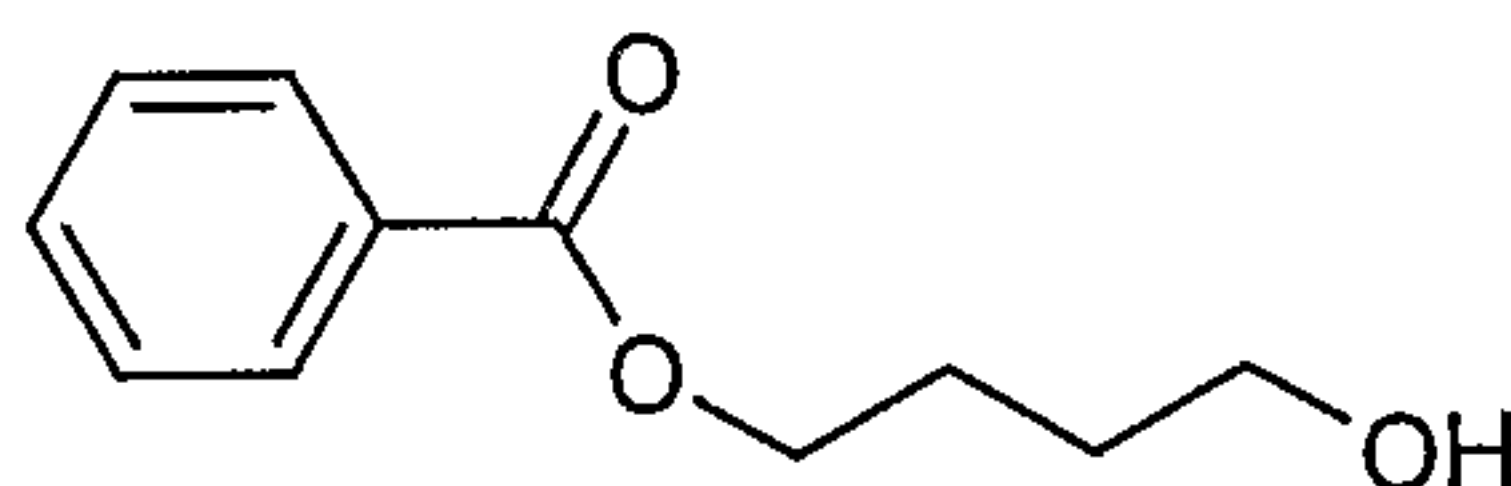
20 The title compound was prepared from 2,2,3,3-tetrafluorobutane-1,4-diol and
 biphenylcarbonyl chloride using Method 1 to give a white (yield 20%).
 Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave
 the title compound as the first fraction. δ_C (CDCl₃, 62.9 MHz): 127.3, 127.3,
 25 128.4, 129.0, 130.6, 139.8, 146.5 and 165.4.

- 120 -

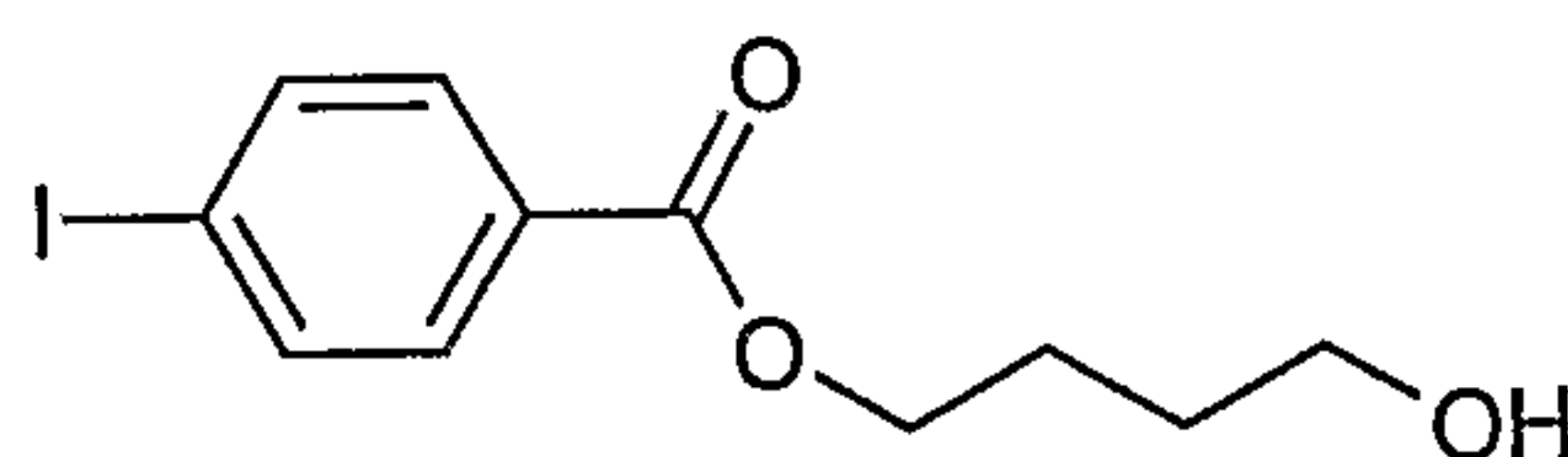
Example 10Biphenyl-4-carboxylic acid (4-acetoxy)butyl ester (**ABD-0049**) (**4BP-acetate**)

- 5 The title compound was prepared from **ABD-0056** using Method 7 to give a white solid (yield 90%). δ_C (CDCl₃, 62.9 MHz): 21.0, 25.4, 25.5, 64.0, 64.5, 127.1, 127.3, 128.2, 129.0, 130.1, 140.0, 145.7, 166.5 and 171.2. δ_H (CDCl₃, 250 MHz): 1.8 (4H, s, 2xCH₂), 2.0 (3H, s, COCH₃), 4.1 (2H, t, *J* 6.3), 4.4 (2H, t, *J* 6.3), 7.4 (3H, m), 7.6 (4H, 2 x d) and 8.1 (2H, d, *J* 8.8).

10

Example 111,4-Butanediol mono(benzoic acid)ester (**ABD-0008**) (**4MB**)

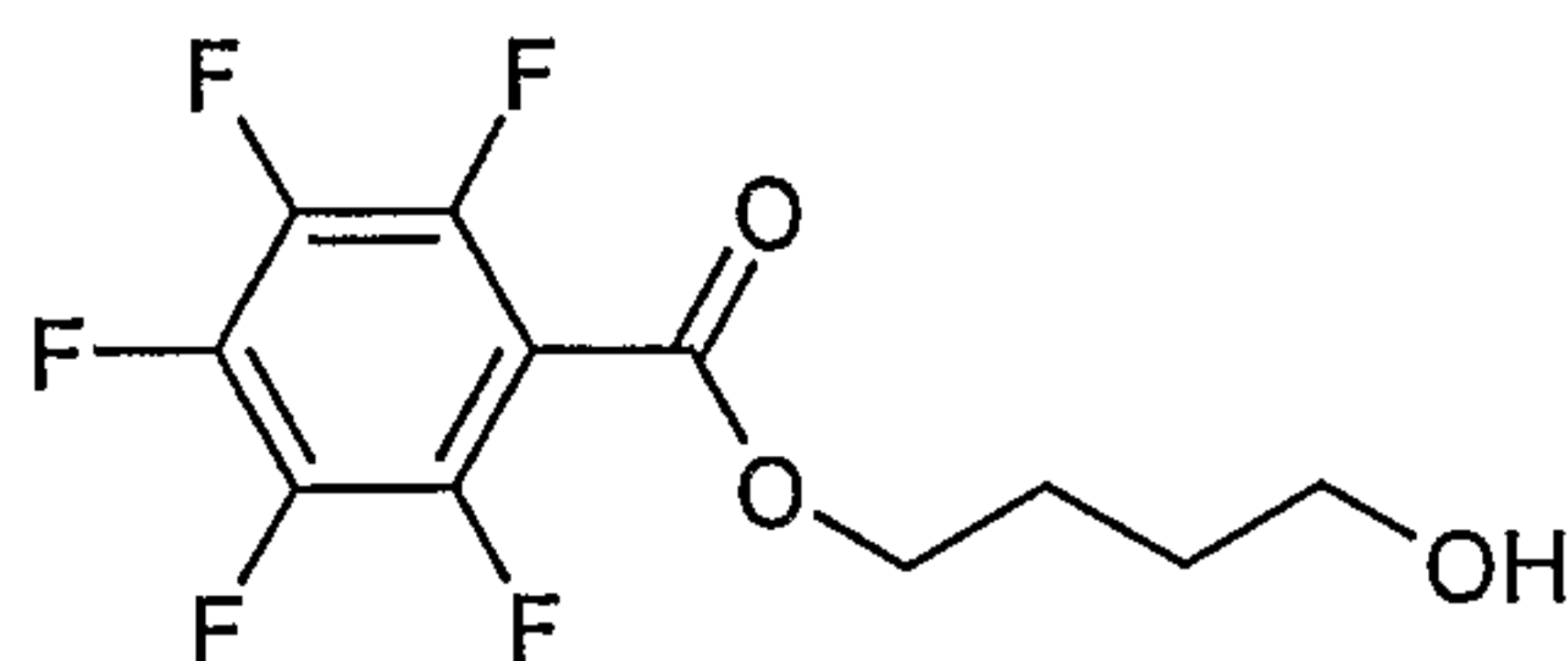
- 15 The title compound was prepared from benzoyl chloride and 1,4-butanediol using Method 1 to give a pale oil (yield 40%). δ_C (CDCl₃, 62.9 MHz): 25.2, 29.1, 62.4, 64.8, 128.4, 129.6, 132.9, 133.0, and 164.1.

Example 121,4-Butanediol mono(4-iodobenzoic acid)ester (**ABD-0069**) (**4IB**)

20

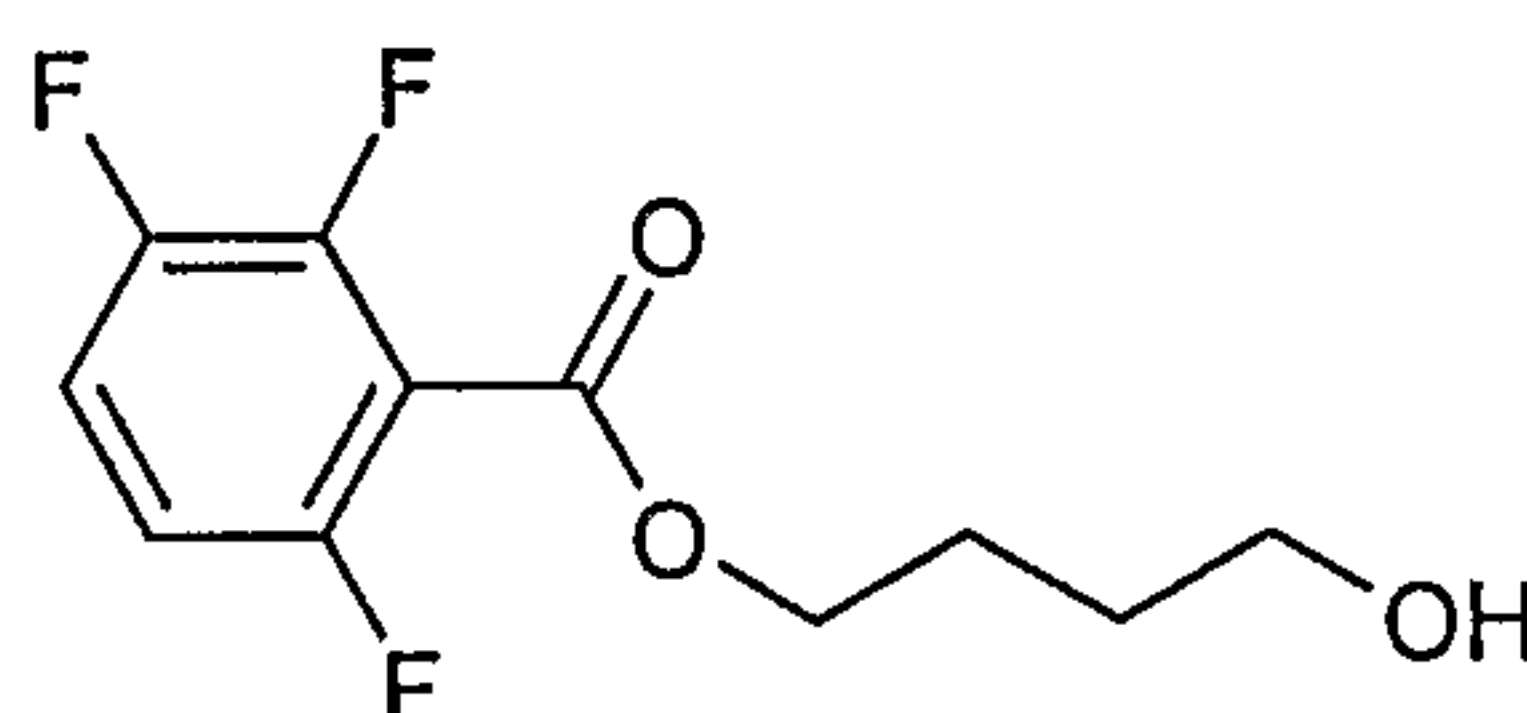
The title compound was prepared from 4-iodobenzoyl chloride and 1,4-butanediol using Method 1 to give a clear oil (yield 90%). δ_C (CDCl₃, 62.9 MHz): 25.2, 29.2, 62.3, 65.1, 100.7, 129.8, 131.0, 137.7 and 166.2.

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Example 131,4-Butanediol mono(pentafluorobenzoic acid)ester (**ABD-0077**) (**4FB**)

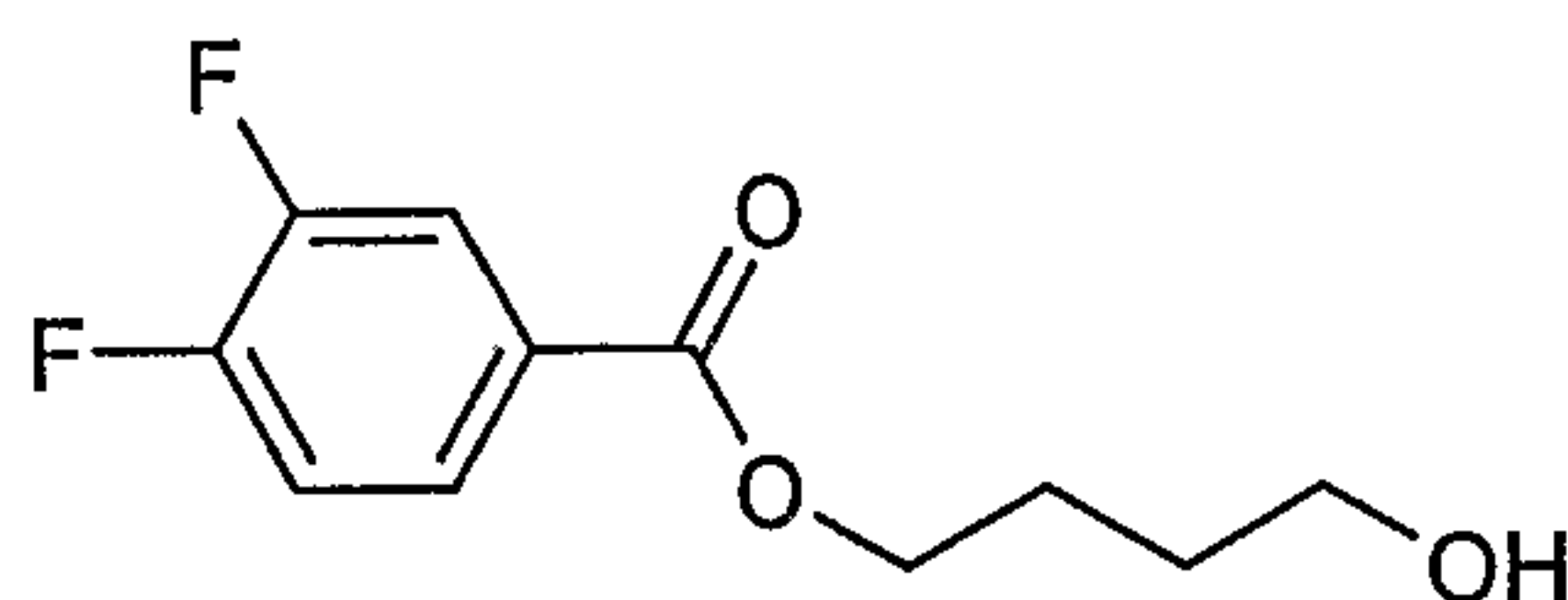
The title compound was prepared from pentafluorobenzoyl chloride and
 5 1,4-butanediol using Method 1 to give a clear oil. Column chromatography gave
 the title compound as the second fraction (yield 55%). δ_C (CDCl₃, 62.9 MHz):
 25.0, 28.9, 62.2 and 66.7. δ_H (CDCl₃, 250 MHz): 1.46 (1H, s, OH), 1.72 (2H, m),
 1.86 (2H, m), 3.73 (2H, t, *J* 6.4) and 4.42 (2H, t, *J* 6.4).

10

Example 141,4-Butanediol mono(2,3,6-trifluorobenzoic acid)ester (**ABD-0106**) (**2,3,6-FB**)

15

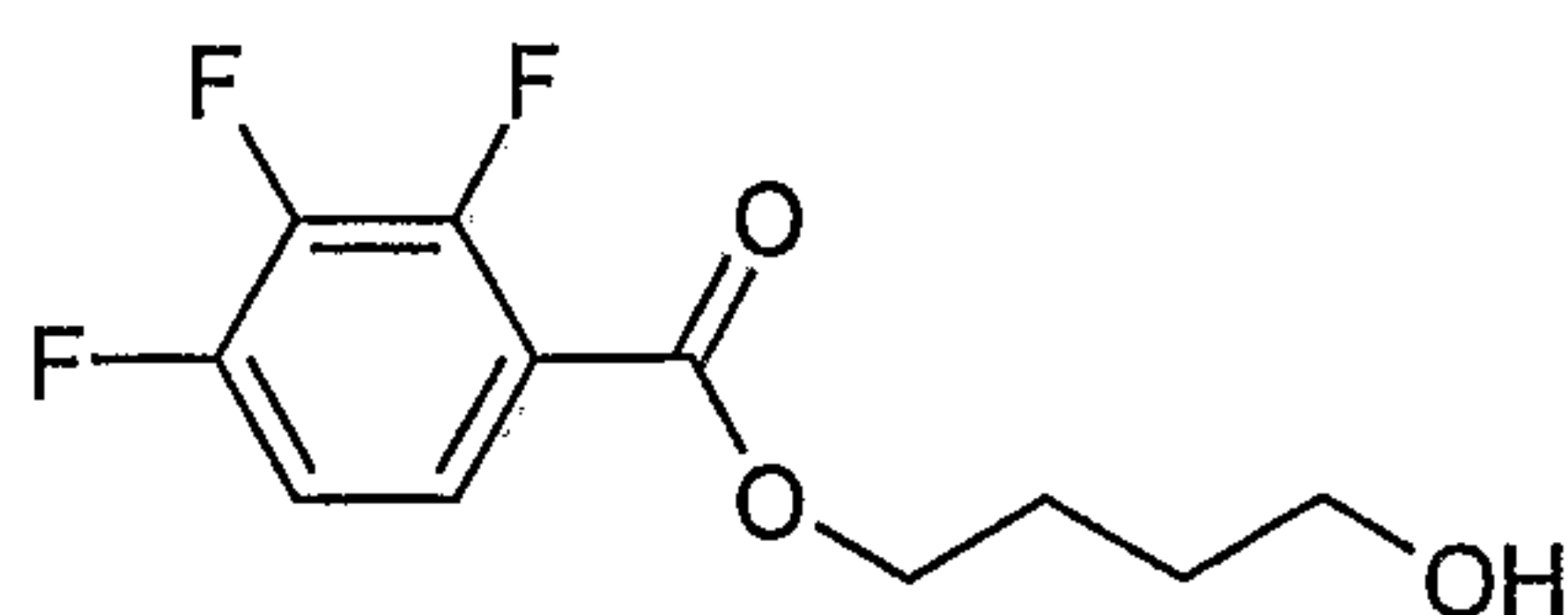
The title compound was prepared from 2,3,6-trifluorobenzoic acid and
 1,4-butanediol using Method 2, to give a clear oil. Column chromatography gave
 the title compound as the second fraction (yield 60%). δ_C (CDCl₃, 62.9 MHz):
 25.0, 29.0, 62.3, 66.2, 111.6 and 119.6.

Example 151,4-Butanediol mono(3,4-difluorobenzoic acid)ester (**ABD-0107**) (**3,4-FB**)

20

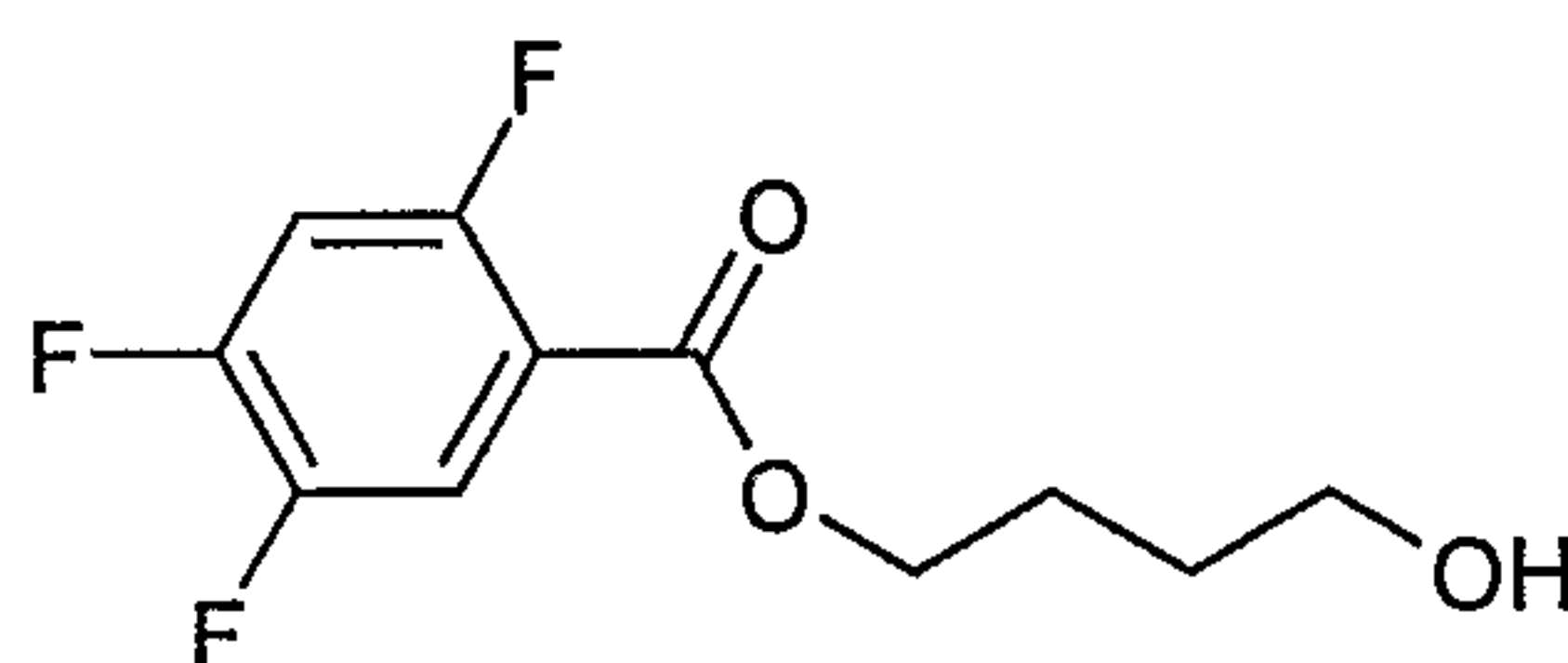
The title compound was prepared from 3,4-difluorobenzoyl chloride and
 1,4-butanediol using Method 1, to give a clear oil. Column chromatography gave
 the title compound as the second fraction (yield 70%). δ_C (CDCl₃, 62.9 MHz):
 25.2, 29.1, 62.3, 65.4, 117.4 (d, *J* 17.6), 118.9 (d, *J* 18.6), 126.5 (d, *J* 3.9) and
 25 127.3.

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Example 161,4-Butanediol mono(2,3,4-trifluorobenzoic acid)ester (**ABD-0108**) (**2,3,4-FB**)

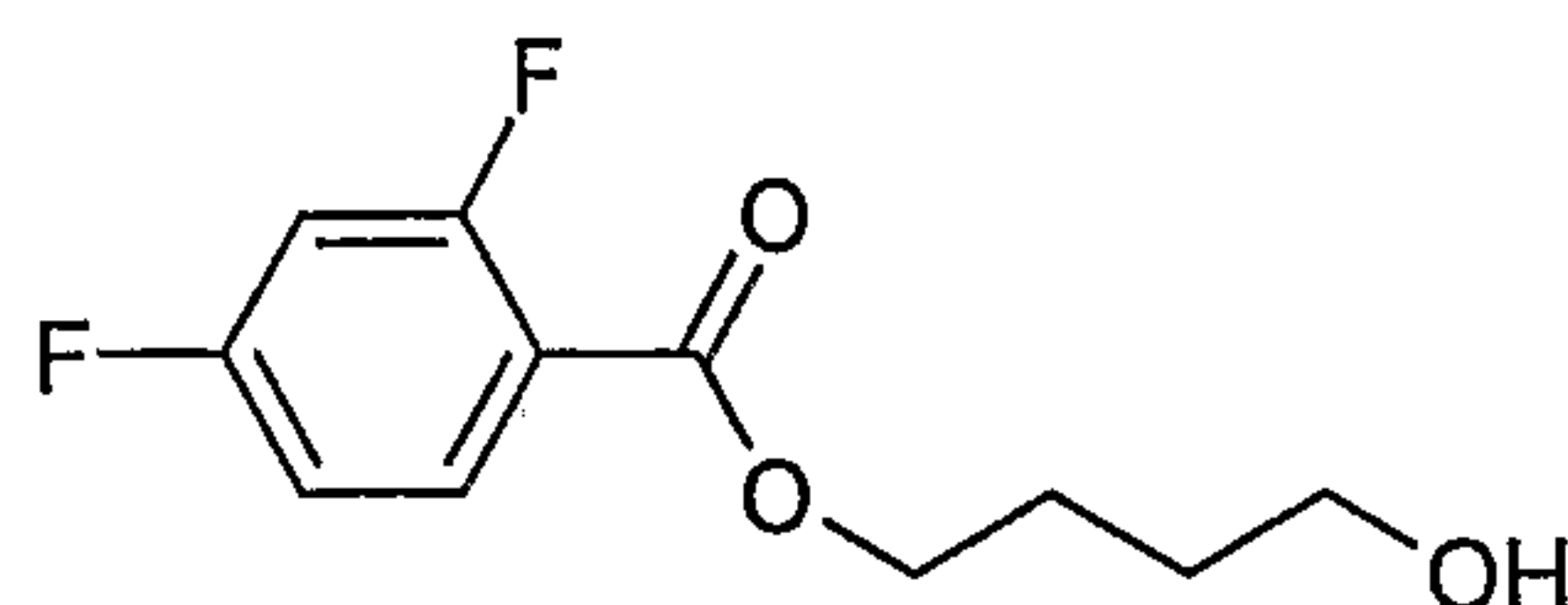
- 5 The title compound was prepared from 2,3,4-trifluorobenzoic acid and 1,4-butanediol using Method 2, to give a clear oil. Column chromatography gave the title compound as the second fraction (yield 85%). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.1, 62.3, 65.7, 112.3 and 126.1.

10

Example 171,4-Butanediol mono(2,4,5-trifluorobenzoic acid)ester (**ABD-0109**) (**2,4,5-FB**)

- The title compound was prepared from 2,4,5-trifluorobenzoyl chloride and 1,4-butanediol using Method 1, to give a white solid. Column chromatography gave the title compound as the second fraction (yield 65%). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.0, 62.1, 65.7, 107.1 and 120.0.

15

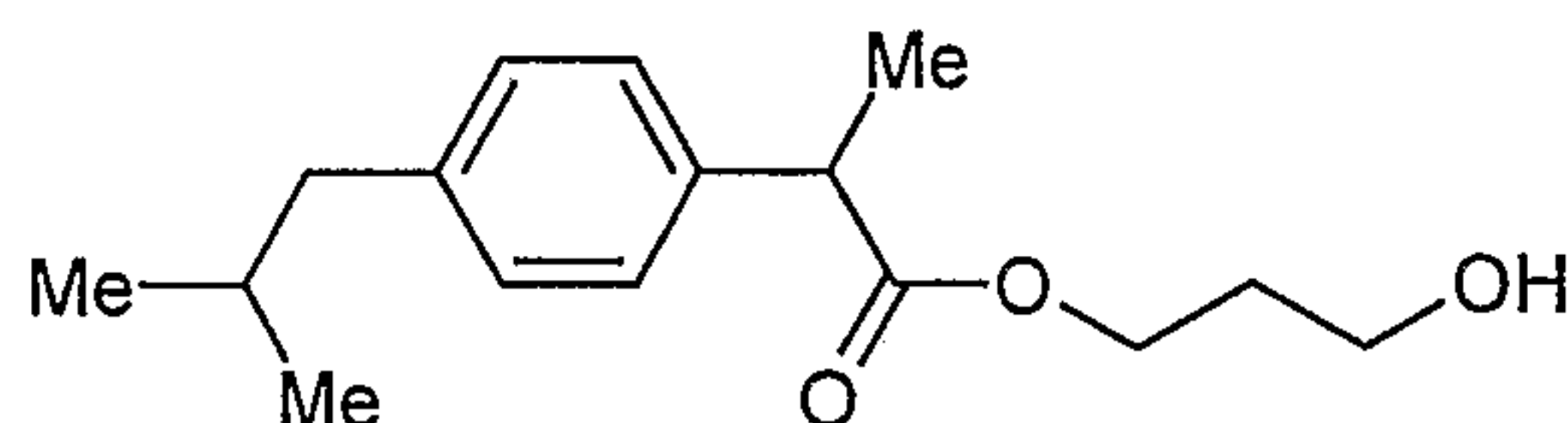
Example 181,4-Butanediol mono(2,4-difluorobenzoic acid)ester (**ABD-0110**) (**2,4-FB**)

20

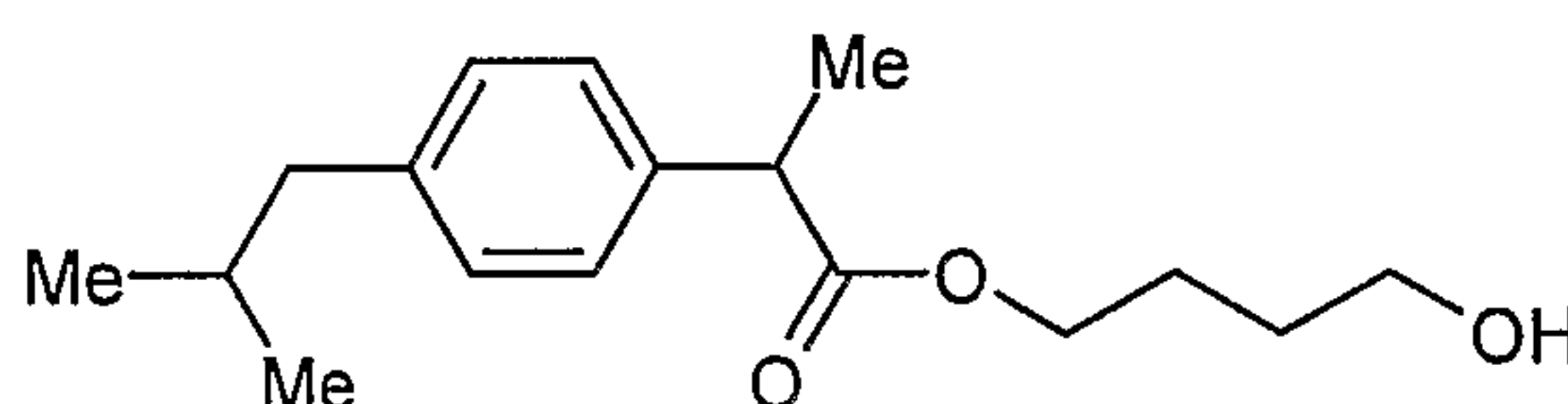
- The title compound was prepared from 2,4-difluorobenzoyl chloride and 1,4-butanediol using Method 1, to give a clear oil. Column chromatography gave the title compound as the second fraction (yield 70%). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.2, 62.3, 65.3, 105.2 (t, *J* 26.4), 111.6 (dd, *J* 21.5, 2.9) and 133.9 (d, *J* 10.7).

25

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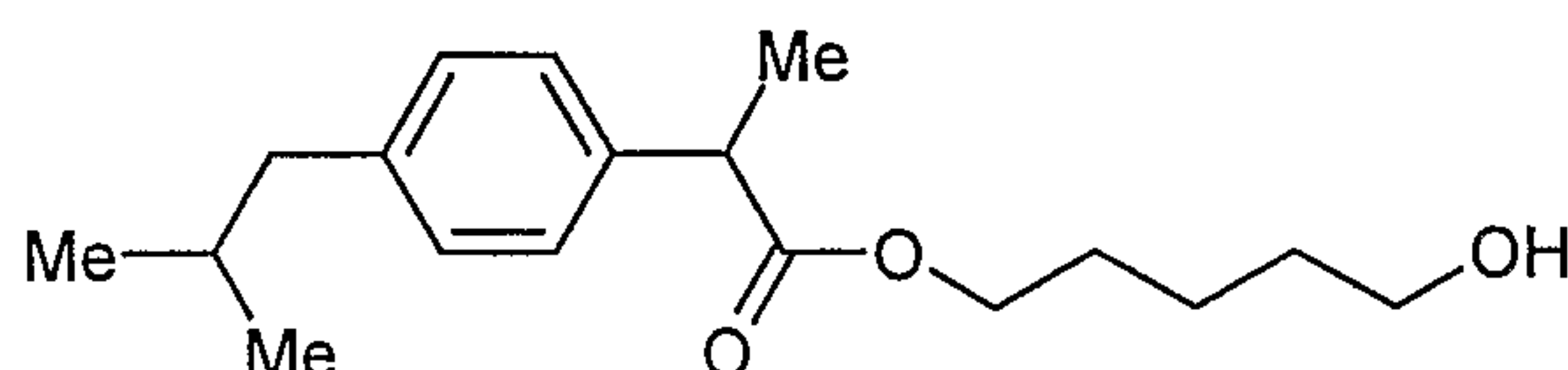
Example 191,3-Propanediol mono[2-(4-isobutylphenyl)propionic acid]ester (**ABD-0037**) (**3I**)

- 5 The title compound was prepared from ibuprofen and 1,3-propanediol using Method 2 to give a clear oil (yield 70%). δ_c (CDCl₃, 62.9 MHz): 18.4, 22.4, 30.2, 31.7, 45.0, 45.2, 59.1, 61.7, 127.1, 129.4, 137.7, 140.7 and 175.3.

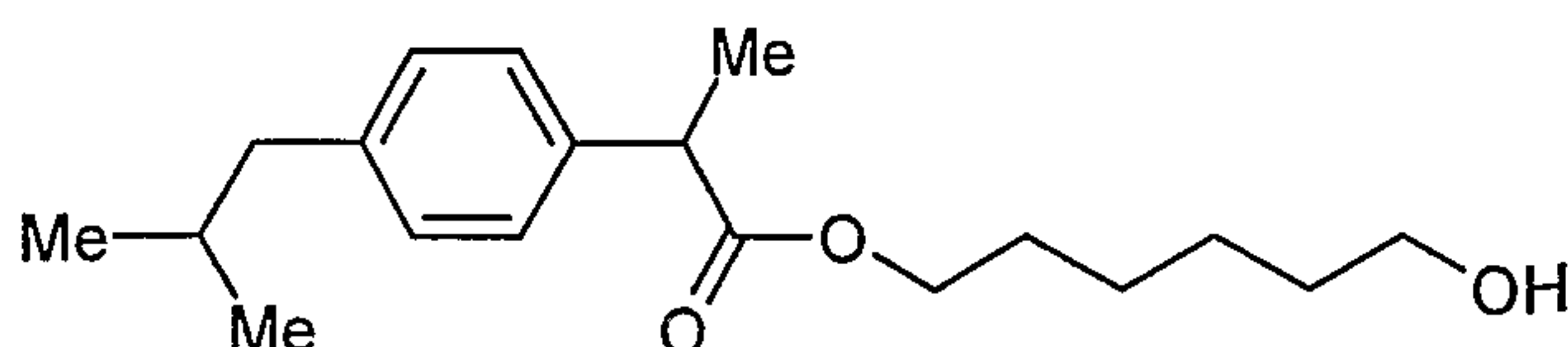
Example 2010 1,4-Butanediol mono[2-(4-isobutylphenyl)propionic acid]ester (**ABD-0036**) (**4I**)

The title compound was prepared from ibuprofen and 1,4-butanediol using Method 2 to give a clear oil (yield 75%). δ_c (CDCl₃, 62.9 MHz): 18.4, 22.4, 25.0, 29.0, 30.2, 45.0, 62.2, 64.5, 127.2, 129.3, 137.8, 140.6 and 174.9.

15

Example 211,5-Pentanediol mono[2-(4-isobutylphenyl)propionic acid]ester (**ABD-0038**) (**5I**)

- 20 The title compound was prepared from ibuprofen and 1,5-pentanediol using Method 2 to give a clear oil (yield 70%). δ_c (CDCl₃, 62.9 MHz): 18.5, 22.1, 22.4, 28.3, 30.2, 32.2, 45.0, 45.2, 62.7, 64.6, 127.2, 129.3, 137.9, 140.5 and 174.9.

Example 221,6-Hexanediol mono[2-(4-isobutylphenyl)propionic acid]ester (**ABD-0039**) (**6I**)

25

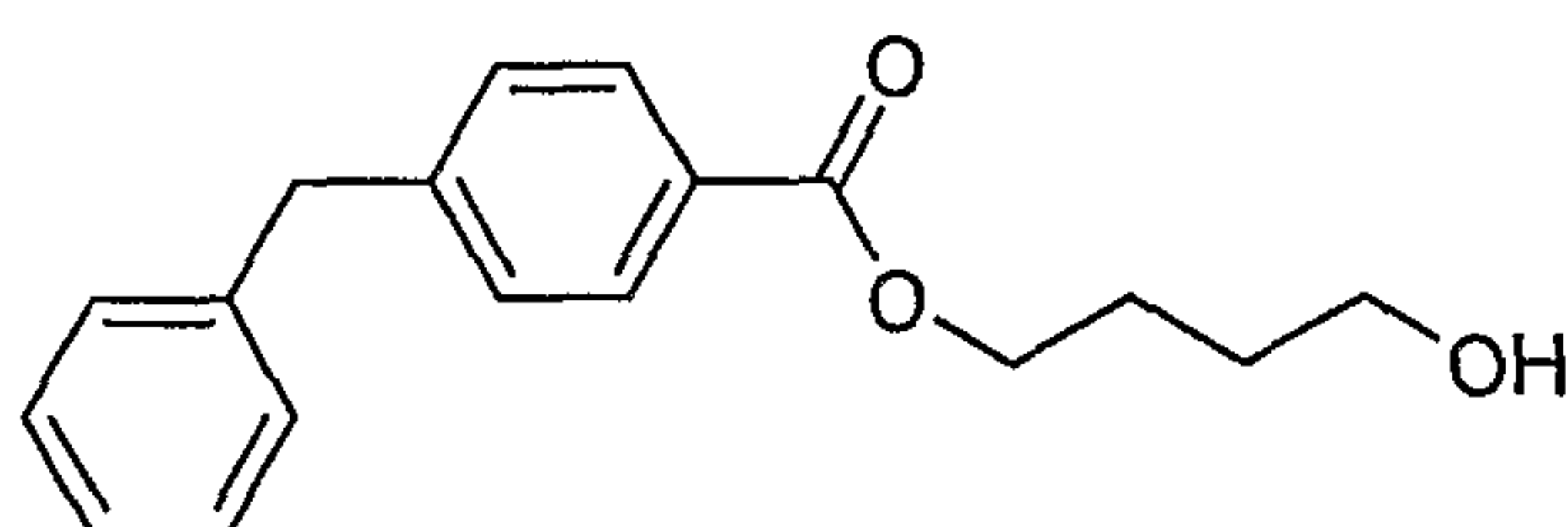
- 124 -

The title compound was prepared from ibuprofen and 1,6-hexanediol using Method 2 to give a clear oil (yield 75%). δ_c (CDCl₃, 62.9 MHz): 18.5, 22.4, 25.3, 25.6, 28.5, 30.2, 32.5, 45.0, 45.2, 62.7, 64.6, 127.2, 129.3, 137.9, 140.5 and 174.9.

5

Example 23

1,4-Butanediol mono(4-benzylbenzoic acid)ester (**ABD-0034**) (**4PT**)

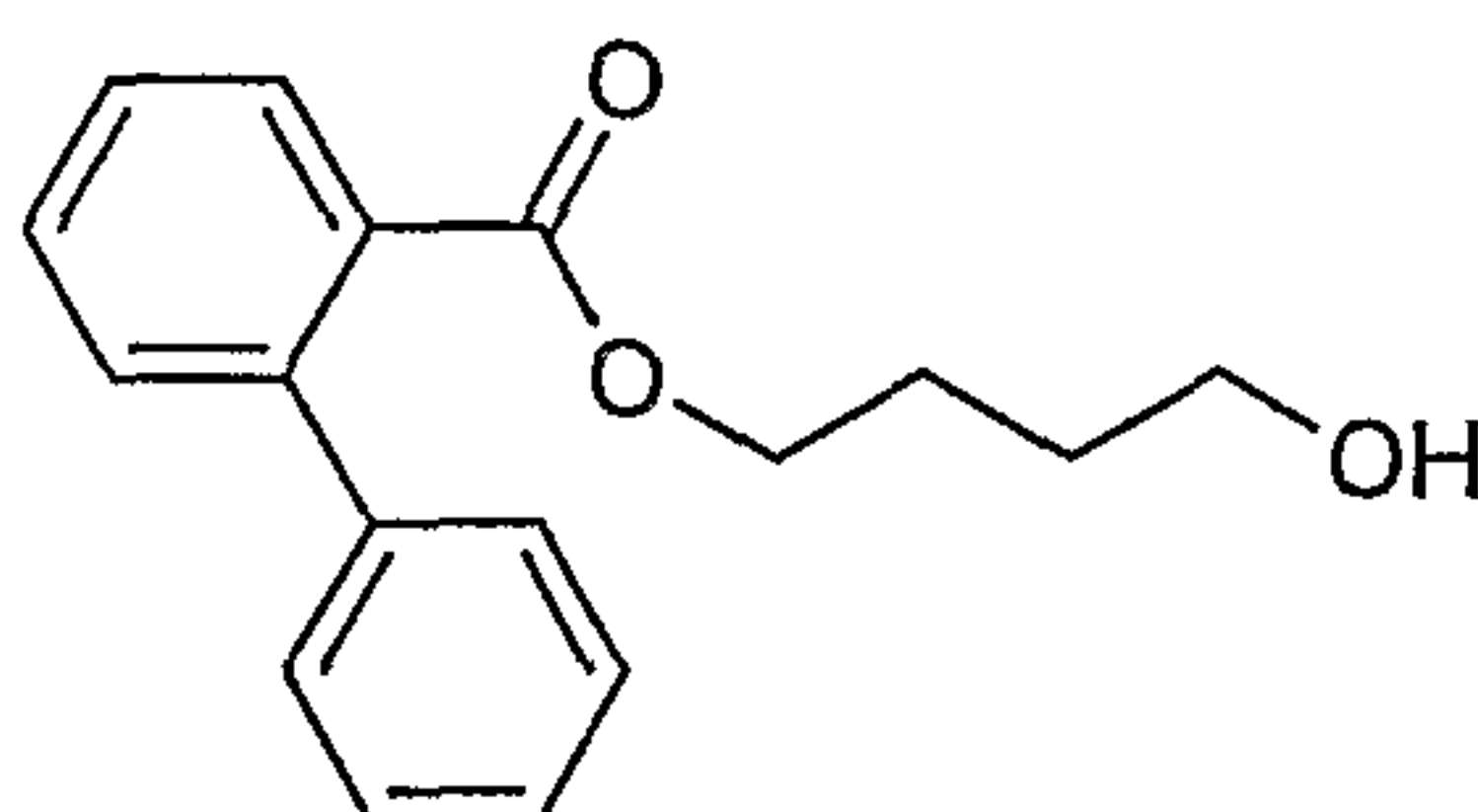


The title compound was prepared from 4-benzylbenzoic acid and 1,4-butanediol using Method 2, to give a clear oil (yield 45%). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.1, 39.7, 62.4, 64.8, 126.0, 128.9, 129.1, 131.7, 132.9, 130.1, 140.8, 143.4 and 172.8.

10

Example 24

15 1,4-Butanediol (biphenyl-2-carboxylic acid) ester (**ABD-0059**) (**4BPX**)



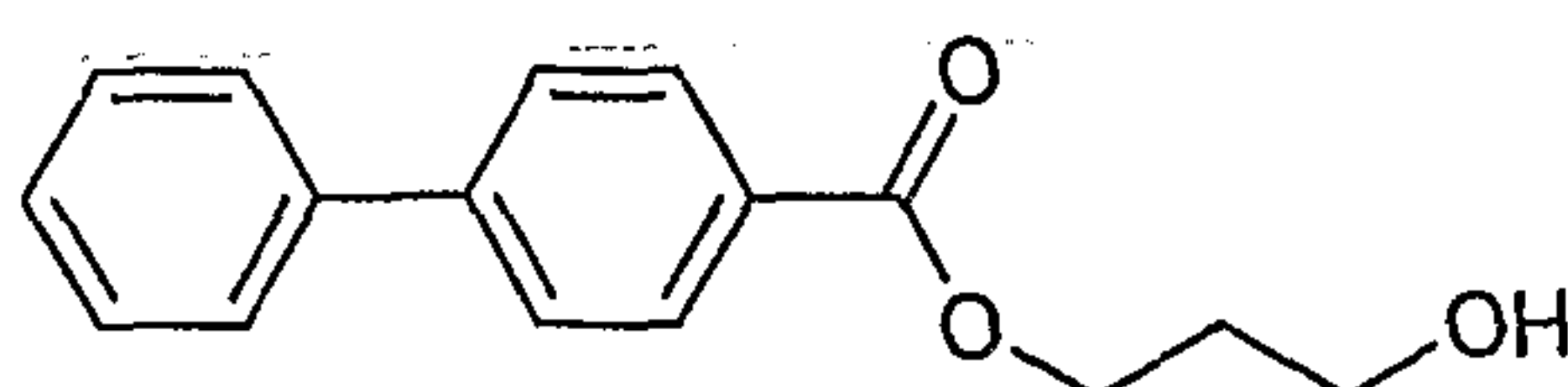
15

The title compound was prepared from biphenyl-2-carboxylic acid and 1,4-butanediol using Method 2 to give a clear oil (yield 40%). δ_c (CDCl₃, 62.9 MHz): 24.6, 28.9, 62.3, 64.9, 127.3, 128.1, 128.5, 129.9, 130.6, 130.7, 131.2, 131.9, 141.2, 141.7, 142.3, 143.2 and 169.2.

20

Example 25

1,3-Propanediol mono(biphenyl-4-carboxylic acid)ester (**ABD-0057**) (**3BP**)



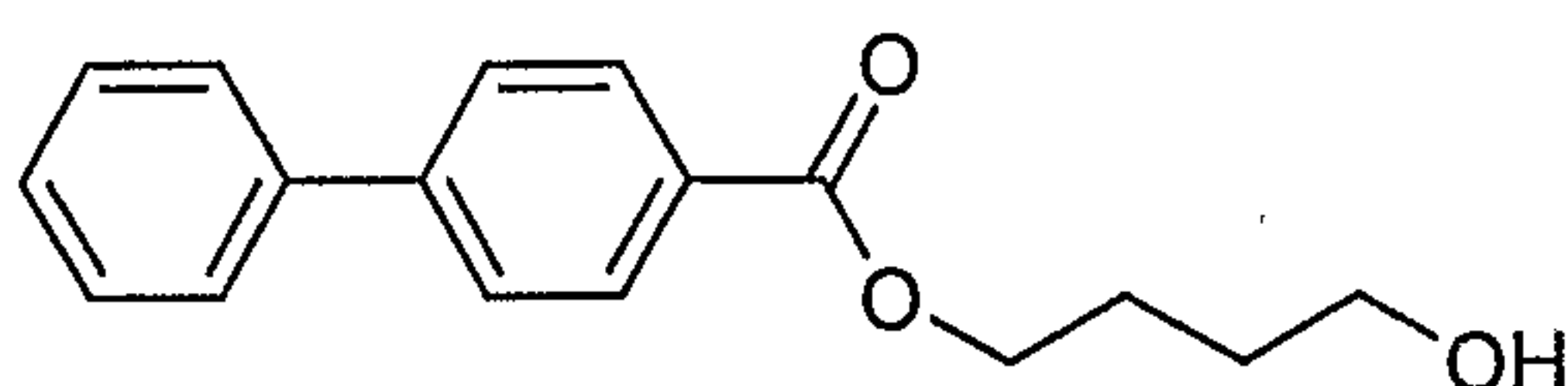
- 125 -

The title compound was prepared from biphenyl-4-carbonyl chloride and 1,3-propanediol using Method 1 to give a white solid (yield 80%). δ_c (CDCl₃, 62.9 MHz): 14.2, 30.9, 32.0, 127.1, 127.3, 128.2, 129.3, 130.1, 140.0, 145.8 and 166.9.

5

Example 26

1,4-Butanediol mono(biphenyl-4-carboxylic acid)ester (**ABD-0056**) (**4BP**)

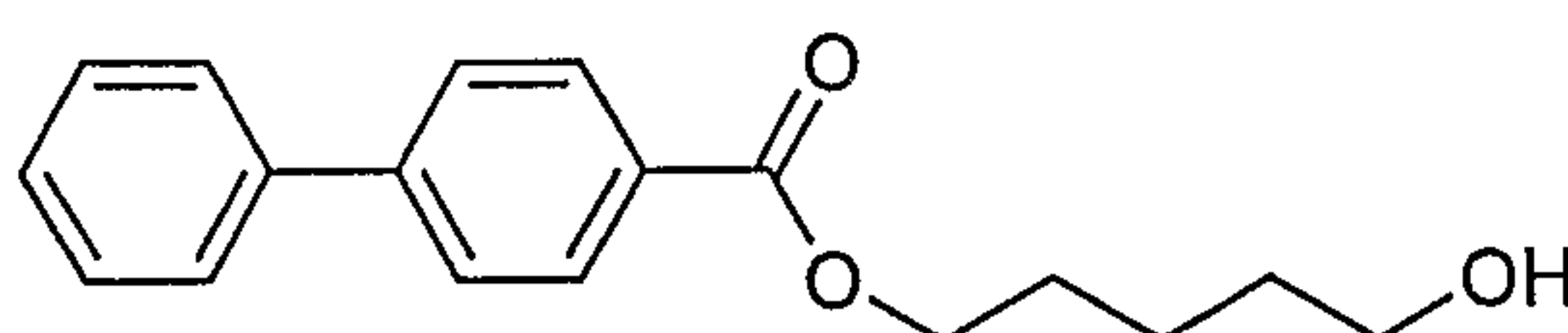


The title compound was prepared from biphenyl-4-carbonyl chloride and 1,4-butanediol using Method 1 to give a white solid (yield 85%). δ_c (CDCl₃, 62.9 MHz): 25.3, 29.3, 62.4, 64.8, 127.1, 127.3, 128.2, 129.0, 129.1, 130.1, 130.7, 140.0, 145.7 and 166.6. δ_H (CDCl₃, 250 MHz): 1.74-1.77 (2H, m), 1.86-1.89 (2H, m), 2.63 (1H, s, OH), 3.74 (2H, t, *J* 6.3), 4.38 (2H, t, *J* 6.3), 7.45 (3H, m), 7.63 (4H, m) and 8.10 (2H, d, *J* 8.5). *m/z* (Found M, 270. C₁₇H₁₈O₃ requires 270).

15

Example 27

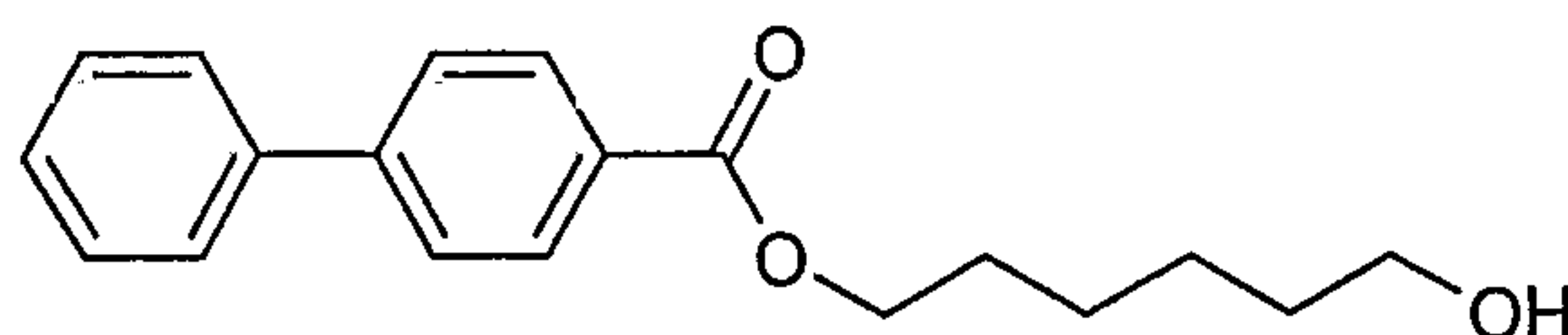
1,5-Pentanediol mono(biphenyl-4-carboxylic acid)ester (**ABD-0055**) (**5BP**)



The title compound was prepared from biphenyl-4-carbonyl chloride and 1,5-pentanediol using Method 1 to give a white solid (yield 80%). δ_c (CDCl₃, 62.9 MHz) 22.4, 28.6, 32.4, 62.7, 65.0, 127.1, 127.3, 128.2, 129.0, 129.1, 130.1, 140.0, 145.6 and 166.7; *m/z* (Found M, 284. C₁₈H₂₀O₃ requires 284).

Example 28

25 1,6-Hexanediol mono(biphenyl-4-carboxylic acid)ester (**ABD-0054**) (**6BP**)



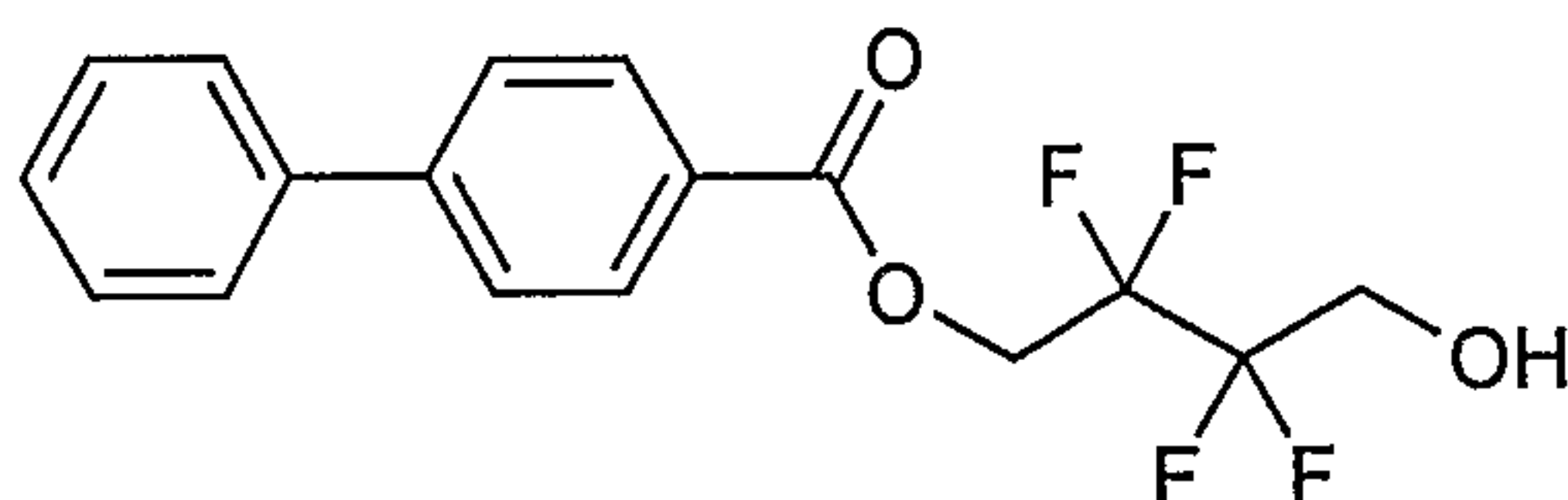
The title compound was prepared from biphenyl-4-carbonyl chloride and 1,6-hexanediol using Method 1 to give a white solid (yield 85%). δ_c (CDCl₃, 62.9

- 126 -

MHz) 25.5, 25.9, 28.8, 32.7, 62.9, 65.0, 127.1, 127.3, 128.2, 129.0, 129.2, 130.1, 140.1, 145.7 and 166.7. m/z (Found M, 298. $C_{19}H_{22}O_3$ requires 298).

Example 29

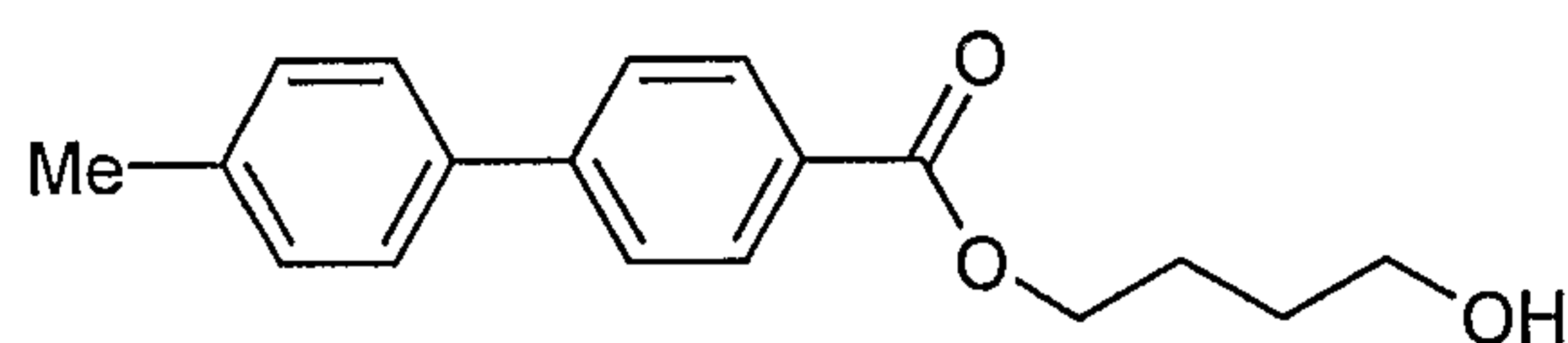
- 5 2,2,3,3-Tetrafluoro-butane-1,4-diol mono(biphenyl-4-carboxylic acid)ester
(ABD-0095) (BP-4F)



- The title compound was prepared from biphenyl-4-carbonyl chloride and 2,2,3,3-tetrafluorobutane-1,4-diol using Method 1 to give a clear oil (yield 65%).
- 10 Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave the title compound as the second fraction. δ_C ($CDCl_3$, 62.9 MHz): 60.4 (t, J 26.4), 127.3, 127.3, 128.4, 129.0, 130.6, 139.8, 146.5 and 165.4.

Example 30

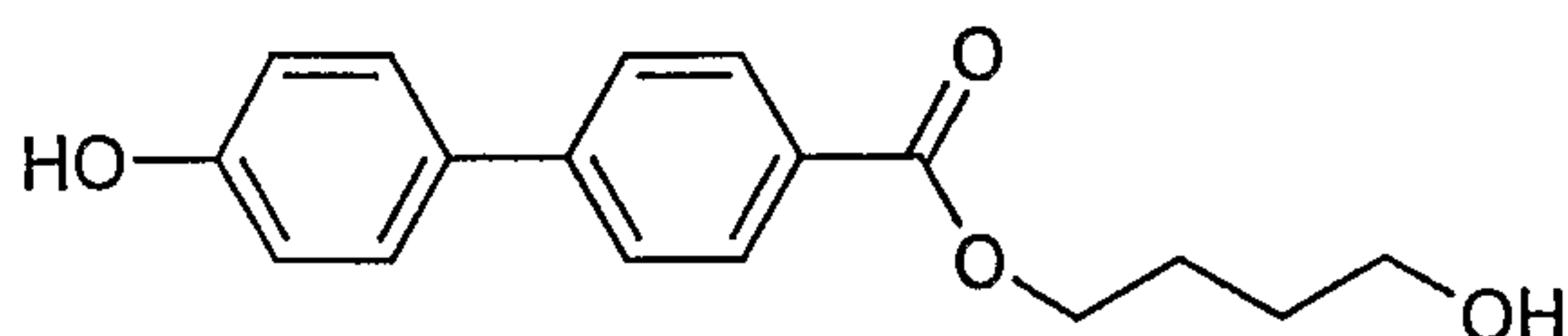
- 15 1,4-Butanediol mono(4'-methyl-biphenyl-4-carboxylic acid)ester (ABD-0070)
(Me4BP)



- The title compound was prepared from 4'-methyl-biphenyl-4-carboxylic acid (prepared from 4-bromotoluene using Method 6) and 1,4-butanediol using
- 20 Method 2 to give a white solid (yield 20%). δ_C ($CDCl_3$, 62.9 MHz): 21.2, 25.3, 29.3, 62.4, 64.8, 126.8, 127.1, 128.8, 129.7, 130.1, 137.1, 138.2, 145.6 and 166.7.

Example 31

- 25 1,4-Butanediol mono(4'-hydroxy-biphenyl-4-carboxylic acid)ester (ABD-0072)
(HO4BP)



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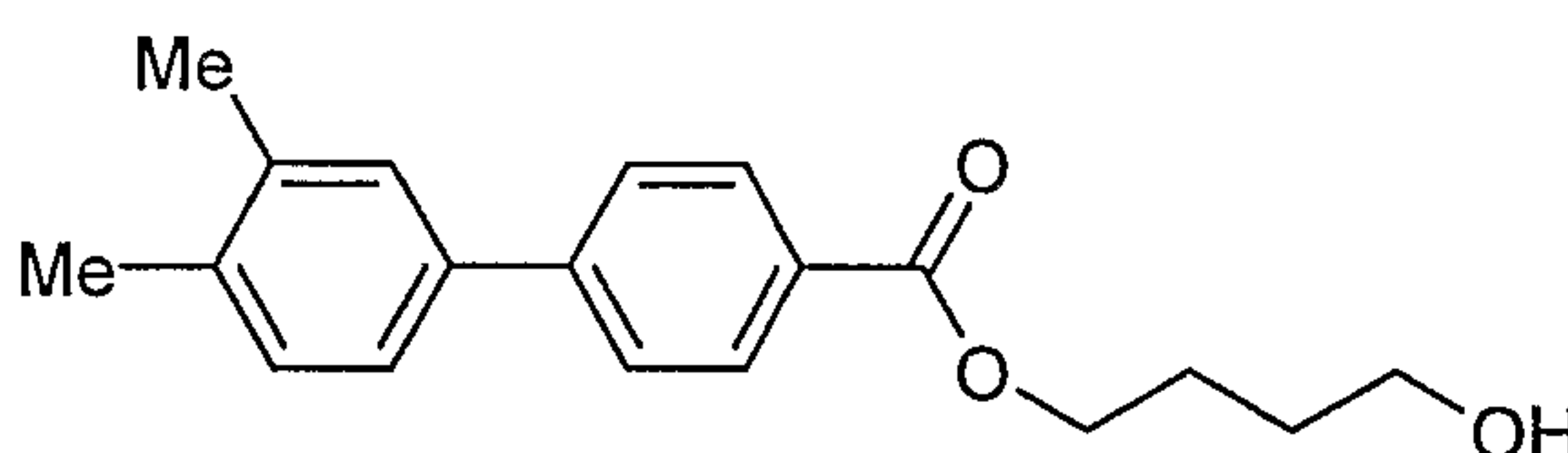
The title compound was prepared from 4'-hydroxy-biphenyl-4-carboxylic acid (which was first protected as the 4'-tertiarybutylchlorodiphenylsilyl ether) and 1,4-butanediol using Method 2 (the silyl protecting group was removed during the reaction) to give the title product as a white powder (yield 15%). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.0, 60.3, 64.6, 115.9, 126.0, 127.6, 128.2, 129.5, 144.7, 158.0 and 165.7.

The protected acid was prepared as follows: 4'-Hydroxy-biphenyl-4-carboxylic acid (4.2 g, 20 mmol) was dissolved in pyridine (50 ml). Tertiarybutylchlorodiphenylsilane (TBDPSi-Cl) (11 g, 40 mmol) was added dropwise, followed by a catalytic amount of 4-dimethylaminopyridine (0.1 g). The solution was left to stir overnight, then poured into water (200 ml) and extracted with methylene chloride (100 ml). The organic phase was washed with 2 M HCl (100 ml) which caused the precipitation of an acid. The acid was collected by filtration, dissolved in diethyl ether and washed with water. The methylene chloride layer was washed with water, the two organic phases combined and dried over Na₂SO₄. Evaporation and purification by column chromatography (light petroleum:ethyl acetate, 2:1) gave the silylated product as a white solid.

20

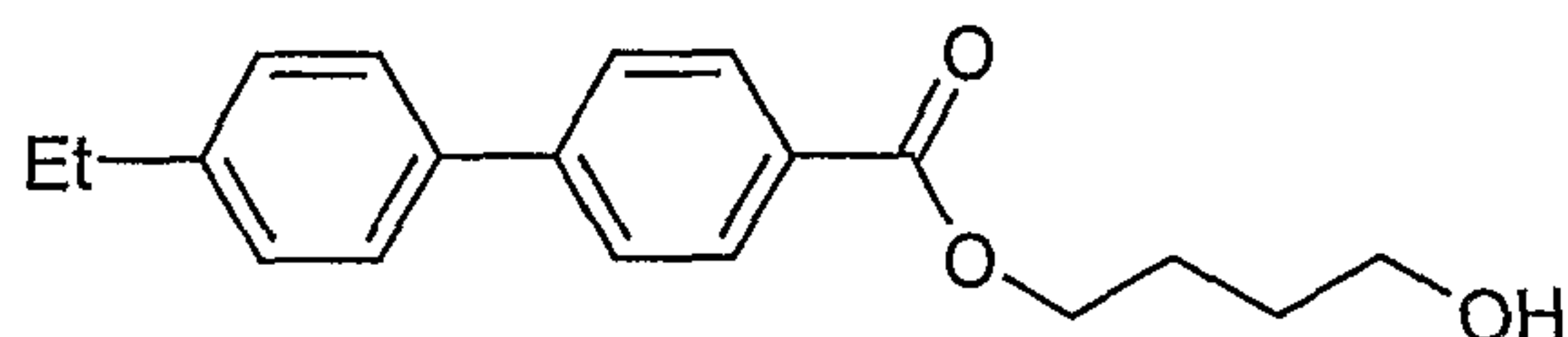
Example 32

1,4-Butanediol mono(3',4'-dimethyl-biphenyl-4-carboxylic acid)ester (**ABD-0089**)
(**Xy4BP**)



The title compound was prepared from 3',4'-dimethyl-biphenyl-4-carboxylic acid (prepared from 4-bromo-o-xylene using Method 6) and 1,4-butanediol using Method 2 to give a clear oil (yield 15%). δ_c (CDCl₃, 62.9 MHz): 19.5, 20.0, 25.3, 29.2, 62.3, 64.8, 124.6, 126.8, 128.5, 128.6, 130.0, 130.2, 136.8, 137.2, 137.5, 145.8 and 166.8.

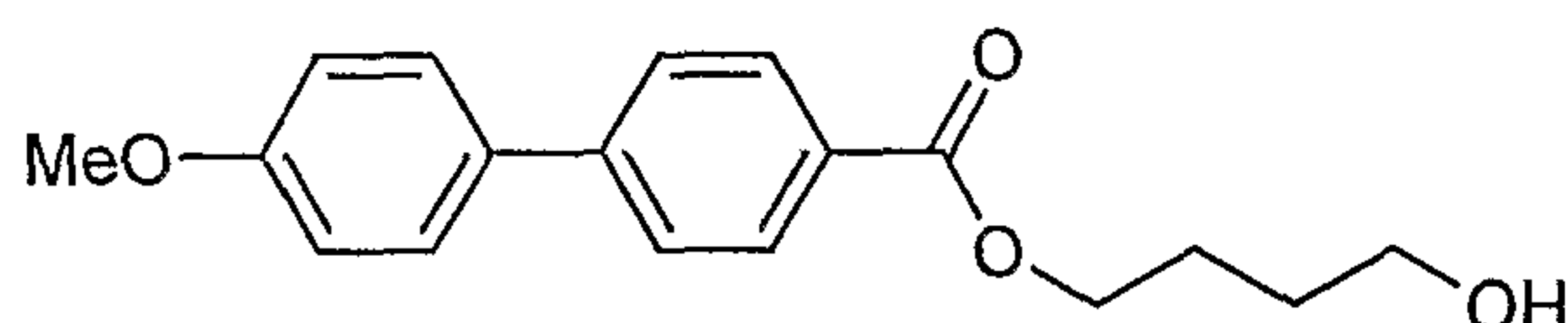
- 128 -

Example 331,4-Butanediol mono(4'-ethyl-biphenyl-4-carboxylic acid)ester (**ABD-0094**)**(Et4BP)**

- 5 The title compound was prepared from 4'-ethyl-biphenyl-4-carboxylic acid (prepared from 4-bromo-ethylbenzene using Method 6) and 1,4-butanediol using Method 2 to give a white powder (yield 25 %). δ_C (CDCl₃, 62.9 MHz): 15.6, 25.3, 28.6, 29.3, 62.4, 64.8, 126.9, 127.2, 128.5, 128.8, 130.1, 137.3, 144.5, 145.6 and 166.7. δ_H (CDCl₃, 250 MHz): 1.27 (3H, t, *J* 7.6), 1.76 (2H, m), 1.86 (2H, m),
- 10 2.43 (1H, br s), 2.70 (2H, q, *J* 7.6), 3.74 (2H, t, *J* 6.4), 4.38 (2H, t, *J* 6.4), 7.29 (2H, d, *J* 8.2), 7.54 (2H, d, *J* 8.2), 7.64 (2H, d, *J* 8.2), 8.08 (2H, d, *J* 8.2).

Example 341,4-Butanediol mono(4'-methoxy-biphenyl-4-carboxylic acid)ester (**ABD-0097**)

15

(4-OMeBP)

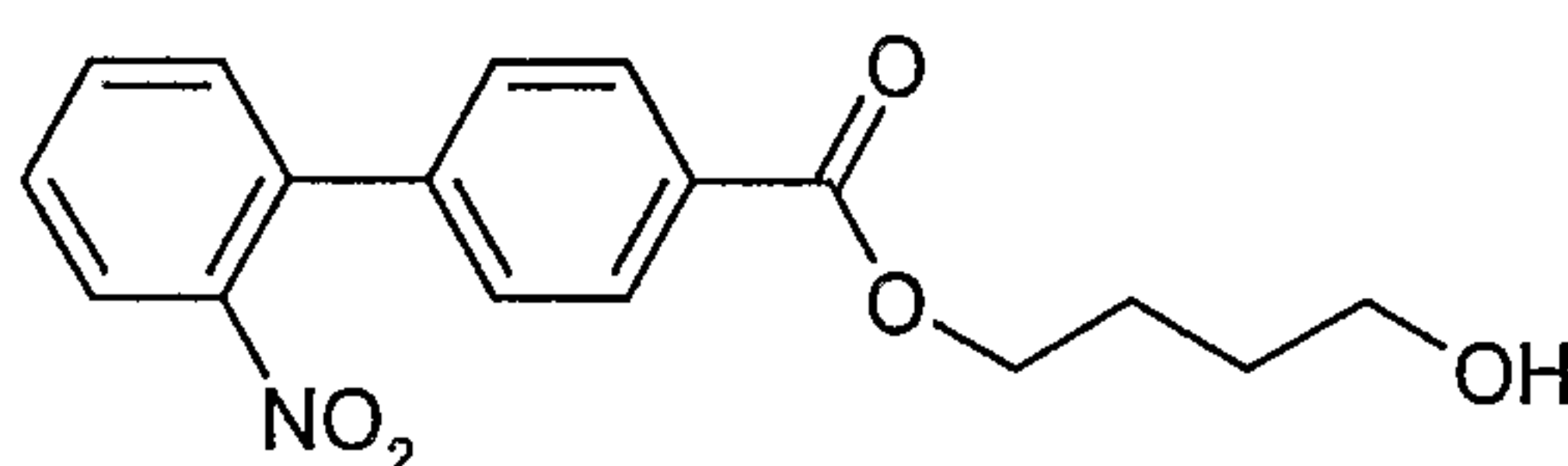
- The title compound was prepared from 4'-methoxy-biphenyl-4-carboxylic acid (prepared from 4-methoxybiphenyl using Methods 4 and 5) and 1,4-butanediol using Method 2. Purification by column chromatography (ethyl acetate:light
- 20 petroleum 1:1) gave the title compound as a white powder (yield 45 %). δ_C (CDCl₃, 62.9 MHz): 25.3, 29.3, 55.4, 62.3, 64.8, 114.4, 126.5, 128.4, 130.1, 132.4, 145.2, 159.8 and 166.7. δ_H (CDCl₃, 250 MHz): 1.60 (1H, s, OH), 1.76 (2H, m), 1.85 (2H, m), 3.73 (2H, t, *J* 6.4), 3.85 (3H, s, OMe), 4.37 (2H, t, *J* 6.4), 6.98 (2H, d, *J* 8.8), 7.56 (2H, d, *J* 8.8), 7.61 (2H, d, *J* 8.2) and 8.06 (2H, d, *J* 8.5).

25

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Example 35

1,4-Butanediol mono(2'-nitro-biphenyl-4-carboxylic acid)ester (**ABD-0098**)
(**2-NO₂BP**)

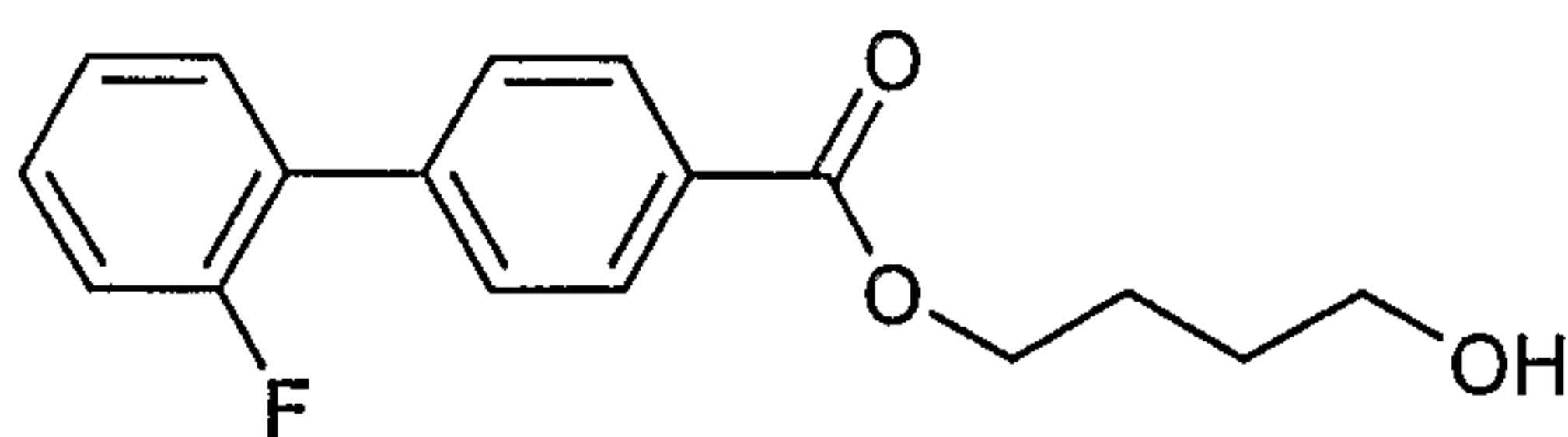


- 5 The title compound was prepared from 2'-nitro-biphenyl-4-carboxylic acid (prepared from 2-nitrobiphenyl using Methods 4 and 5) and 1,4-butanediol using Method 2. Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave the title compound as a pale yellow oil (yield 15%). δ_c (CDCl₃, 62.9 MHz): 25.3, 29.2, 62.4, 65.0, 124.4, 128.0, 128.9, 129.9, 130.1, 131.8, 132.7,
10 135.6, 142.2, 149.0 and 166.2. δ_H (CDCl₃, 250 MHz): 1.62 (1H, s, OH), 1.76 (2H, m), 1.85 (2H, m), 3.73 (2H, t, *J* 6.4), 4.38 (2H, t, *J* 6.4), 7.37 (2H, d, *J* 8.5), 7.41 (1H, dd, *J* 7.9, 1.5), 7.52 (1H, *J* 7.9, 1.5), 7.64 (1H, td, *J* 7.6, 1.2), 7.91 (1H, d, 8.2) and 8.10 (2H, d, *J* 8.5).

15

Example 36

1,4-Butanediol mono(2'-fluoro-biphenyl-4-carboxylic acid)ester (**ABD-0099**)
(**2-FBP**)

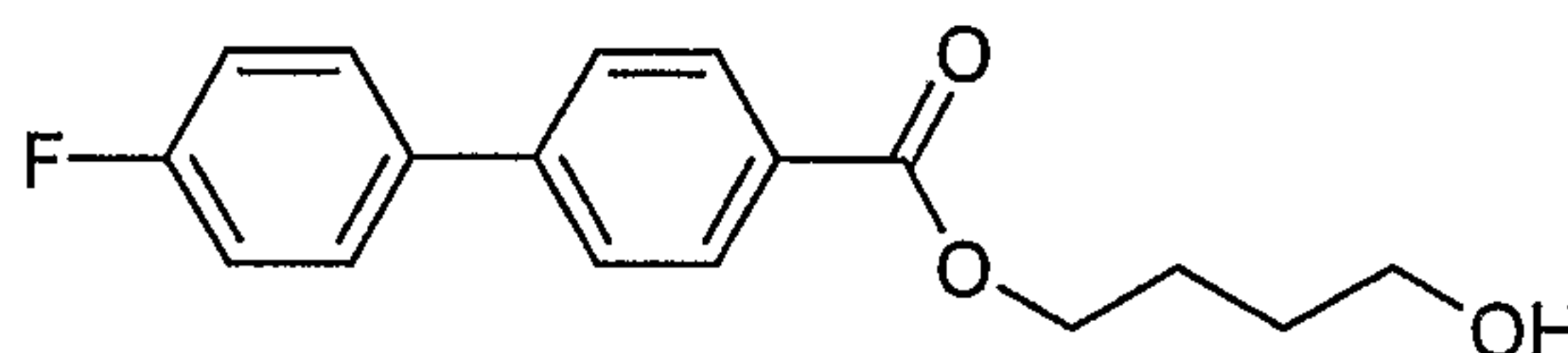


- The title compound was prepared from 2'-fluoro-biphenyl-4-carboxylic acid
20 (prepared from 2-fluorobiphenyl using Methods 4 and 5) and 1,4-butanediol using Method 2. Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave the product as a clear oil (yield 25 %). δ_c (CDCl₃, 62.9 MHz): 25.3, 29.2, 62.4, 64.9, 116.3 (d, *J* 23.4), 124.5, (d, *J* 2.9), 128.0 (d, *J* 13.7), 129.0 (d, *J* 2.0), 129.4, 129.7, 129.8 (d, *J* 13.7), 130.6 (d, *J* 2.0), 140.4, 159.6 (d, *J* 249.0) and 166.6. δ_H (CDCl₃): 1.67 (1H, s, OH), 1.76 (2H, m), 1.88 (2H, m),
25 3.73 (2H, t, *J* 6.4), 4.38 (2H, t, *J* 6.4), 7.16 (1H, m), 7.24 (1H, dd *J* 8.8, 1.2), 7.33 (1H, m), 7.44 (1H, dt, *J* 7.6, 1.8) 7.61 (2H, dd, *J* 8.5, 1.8) and 8.10 (2H, d, *J* 8.5).

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Example 37

1,4-Butandiol mono(4'-fluoro-biphenyl-4-carboxylic acid)ester (**ABD-0100**)
(**4-FBP**)

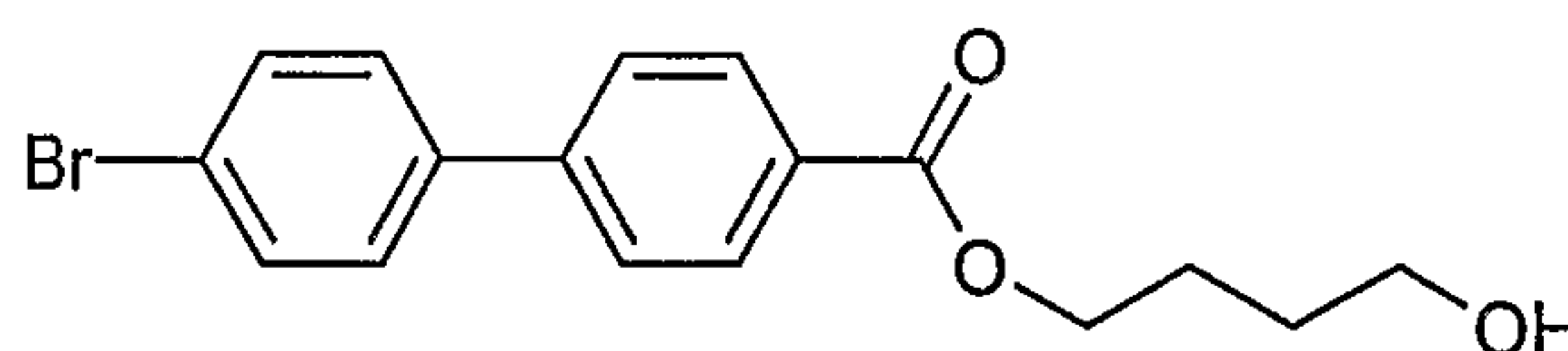


- 5 The title compound was prepared from 4'-fluoro-biphenyl-4-carboxylic acid (prepared from 4-fluorobiphenyl using Methods 4 and 5) and 1,4-butanediol using Method 2. Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave the title compound as a white solid (yield 50%). δ_c (CDCl₃, 62.9 MHz): 25.3, 29.2, 62.4, 64.9, 115.9 (d, *J* 22.5), 126.9, 128.9 (d, *J* 8.8),
10 129.1, 130.2, 136.1 (d, *J* 2.9), 144.6, 163.0 (d, *J* 248.0) and 166.6. δ_H (CDCl₃, 250 MHz): 1.58 (1H, s, OH), 1.74 (2H, m), 1.86 (2H, m), 3.74 (2H, t, *J* 6.4), 4.38 (2H, t, *J* 6.4), 7.14 (2H, t, *J* 8.8), 7.56 (2H, d, *J* 8.8), 7.59 (2H, dd, *J* 8.2) and 8.08 (2H, d, *J* 8.5).

15

Example 38

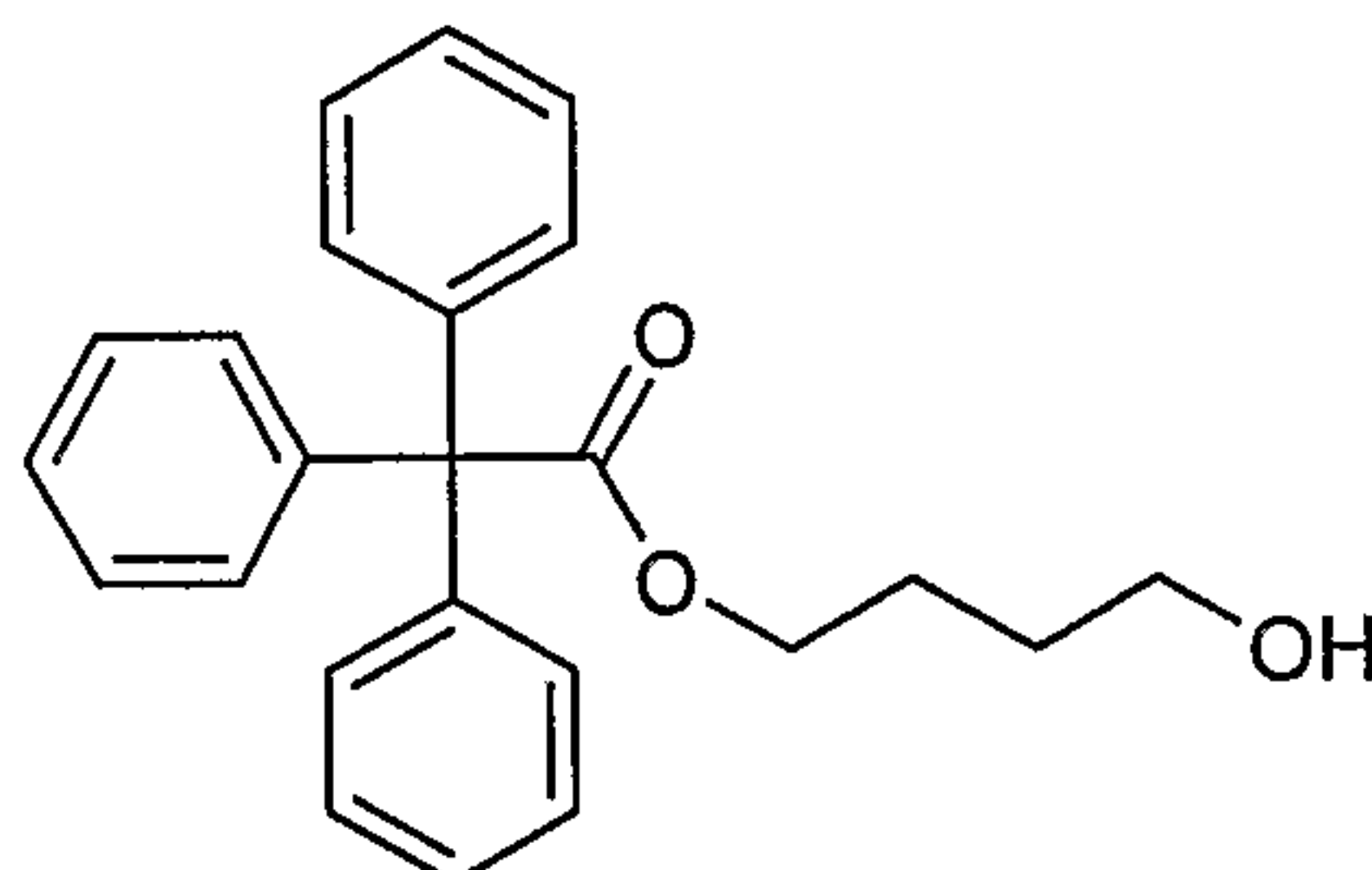
1,4-Butanediol mono(4'-bromo-biphenyl-4-carboxylic acid)ester (**ABD-0102**)
(**4-BrBP**)



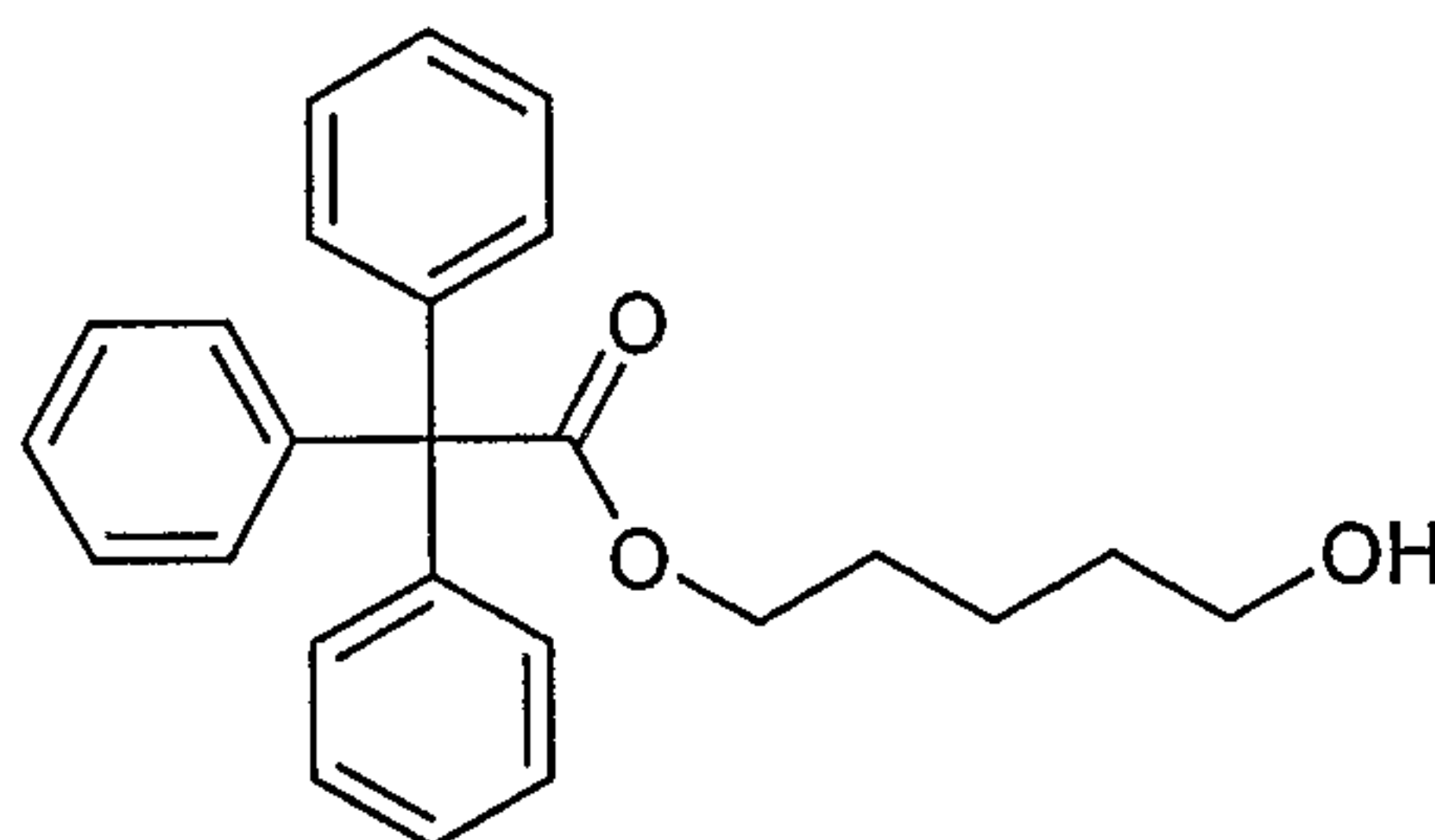
- The title compound was prepared from 4'-bromo-biphenyl-4-carboxylic acid
20 (prepared from 4-bromobiphenyl using Methods 4 and 5) and 1,4-butanediol using Method 2. Purification by column chromatography (ethyl acetate:light petroleum, 1:1) gave the title compound as a white solid (yield 30%). δ_c (DMSO, 62.9 MHz): 25.3, 29.3, 62.4, 64.9, 122.6, 126.9, 128.9, 129.4, 130.2, 132.1, 138.0, 144.4 and 166.4.

25

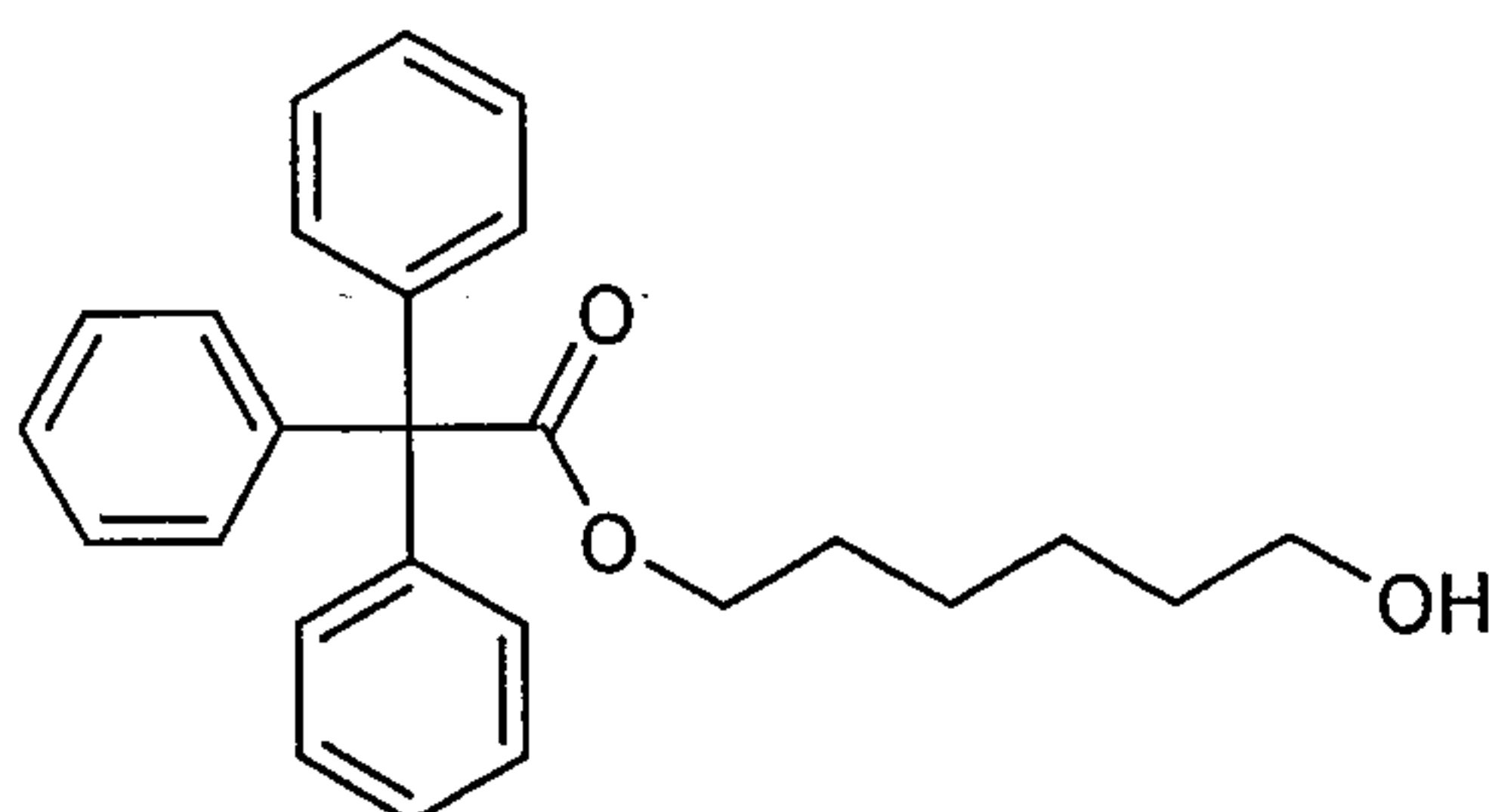
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Example 391,4-Butandiol mono(triphenylacetic acid)ester (**ABD-0028**) (**4T**)

The title compound was prepared from triphenylacetyl chloride (prepared by from
5 triphenylacetic acid using Method 8) and 1,4-butanediol using Method 1, to give
the title compound as a white powder (yield 45%). δ_C (CDCl₃, 62.9 MHz): 24.8,
29.0, 62.2, 65.5, 67.6, 126.9, 127.8, 130.3, 143.0 and 173.7.

Example 4010 1,5-Pentandiol mono(triphenylacetic acid)ester (**ABD-0030**) (**5T**)

The title compound was prepared from triphenylacetyl chloride (prepared by from
triphenylacetic acid using Method 8) and 1,5-pentanediol using Method 1, to give
the title compound as a white powder (yield 35%). δ_C (CDCl₃, 62.9 MHz): 22.1,
15 28.1, 32.1, 62.6, 65.6, 67.6, 126.9, 127.7, 130.3, 143.0 and 173.7.

Example 411,6-Hexandiol mono(triphenylacetic acid)ester (**ABD-0031**) (**6T**)

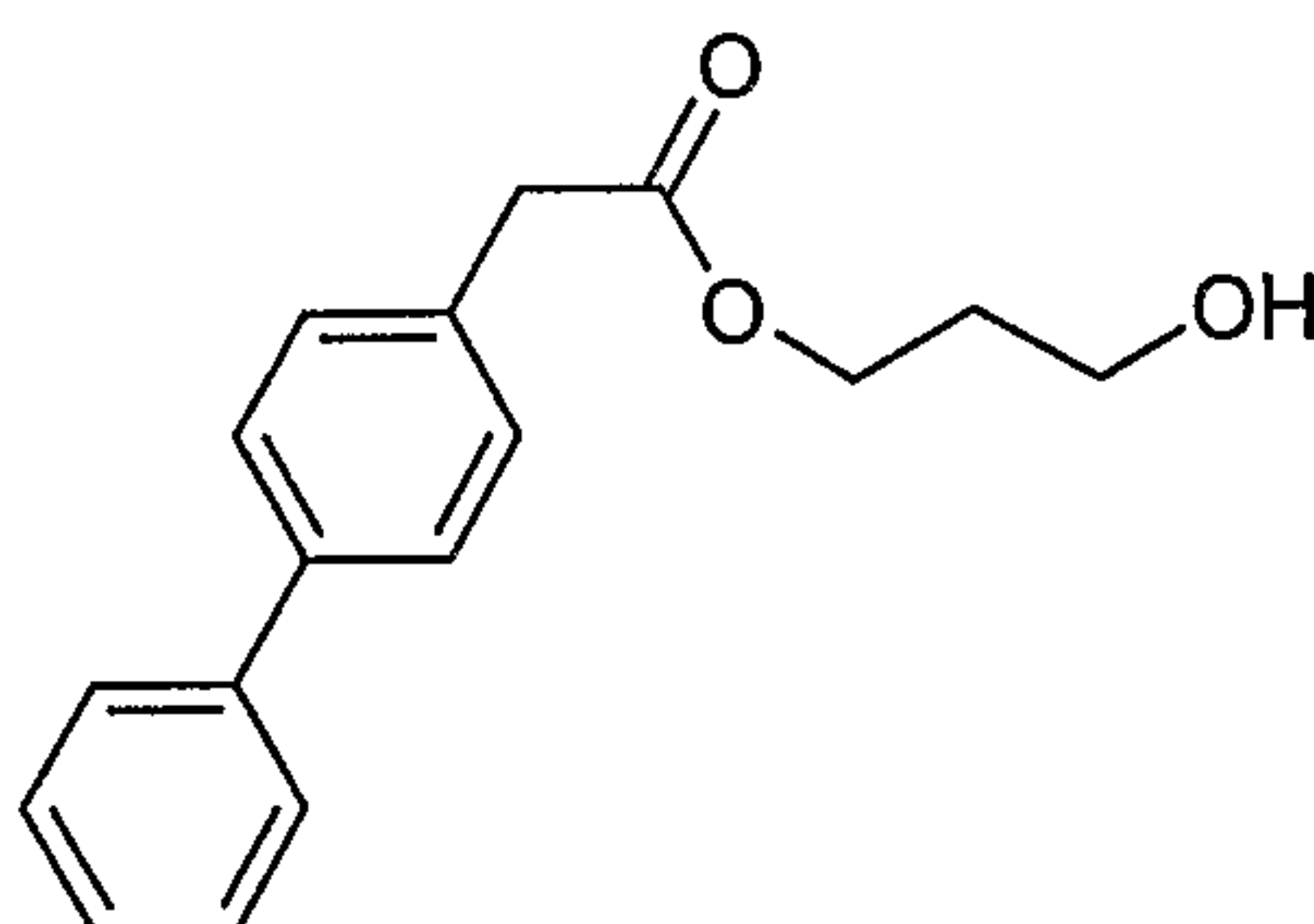
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The title compound was prepared from triphenylacetyl chloride (prepared by from triphenylacetic acid using Method 8) and 1,6-Hexanediol using Method 1, to give the title compound as a white powder (yield 35%). δ_c (CDCl₃, 62.9 MHz): 25.2, 25.6, 28.3, 32.5, 62.8, 65.6, 67.6, 126.9, 127.7, 130.3, 143.0 and 173.7.

5

Example 42

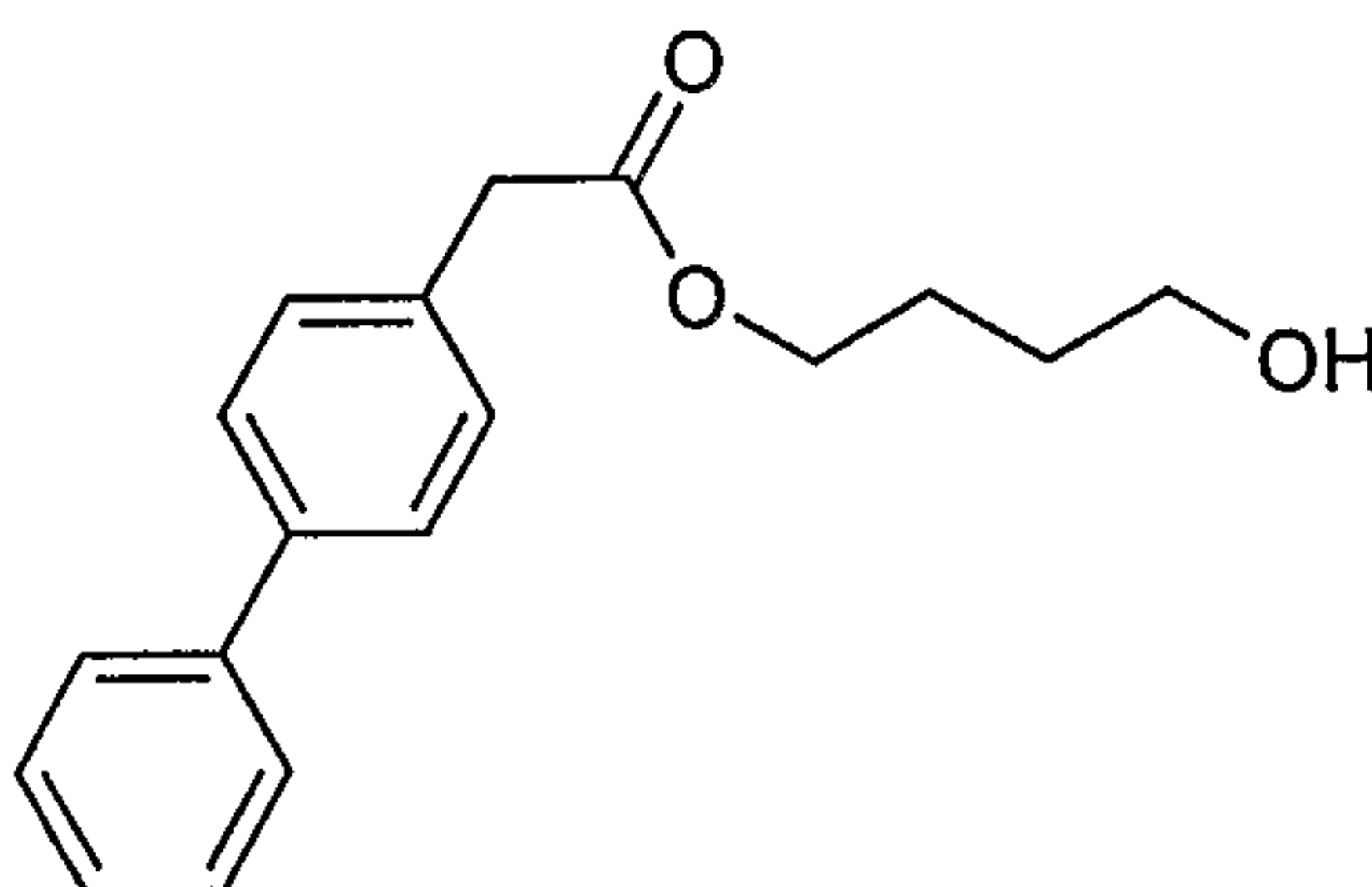
1,3-Propanediol mono(biphenyl-4-yl-acetic acid)ester (**ABD-0041**) (**3BPA**)



The title compound was prepared from biphenyl-4-yl-acetic acid and 1,3-propanediol using Method 2 to give a white solid (yield 75%). δ_c (CDCl₃, 62.9 MHz): 31.7, 41.1, 59.1, 62.0, 127.1, 127.4, 128.8, 129.7, 133.0, 140.2, 140.8 and 172.1.

Example 43

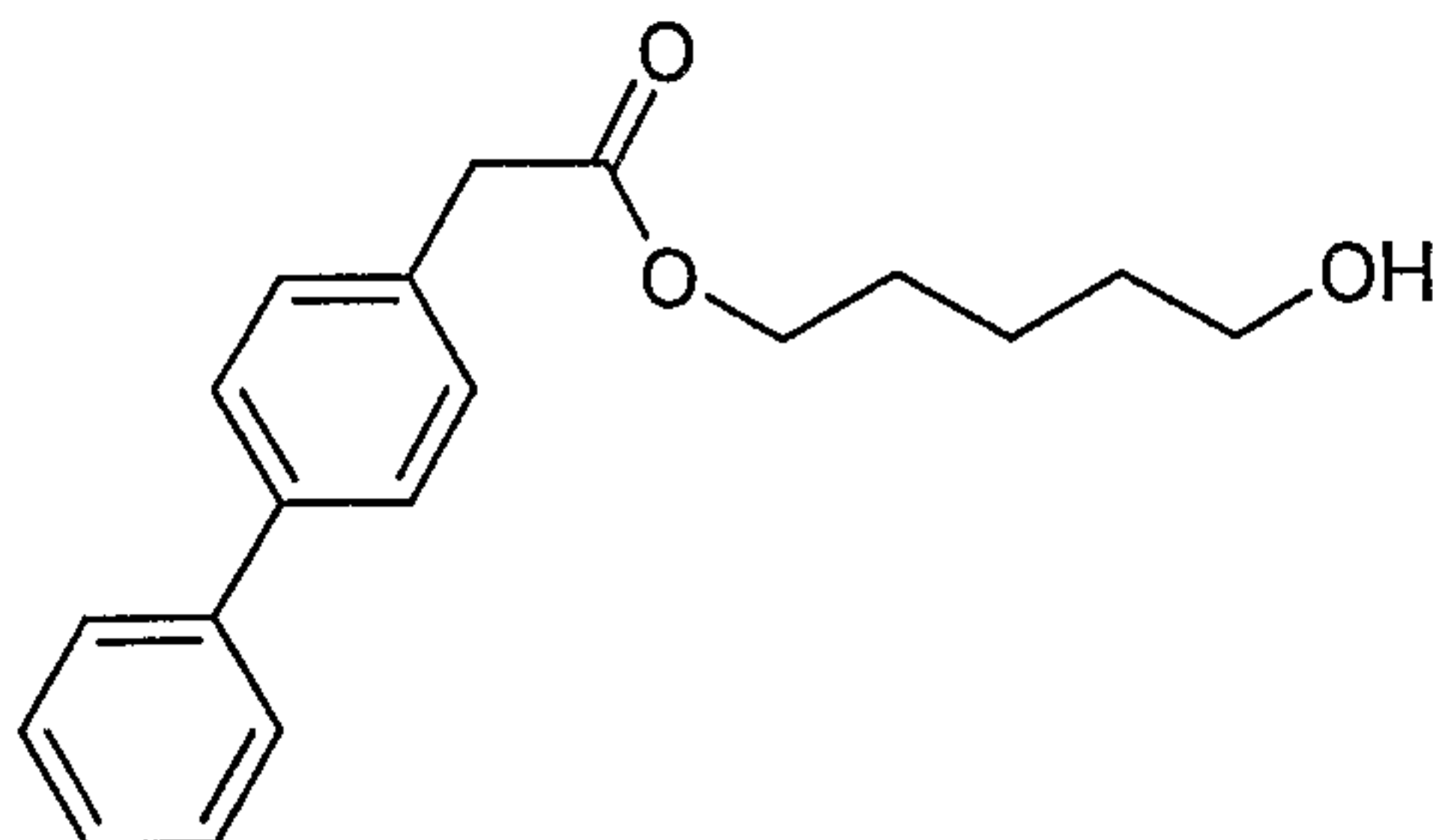
1,4-Butanediol mono(biphenyl-4-yl-acetic acid)ester (**ABD-0042**) (**4BPA**)



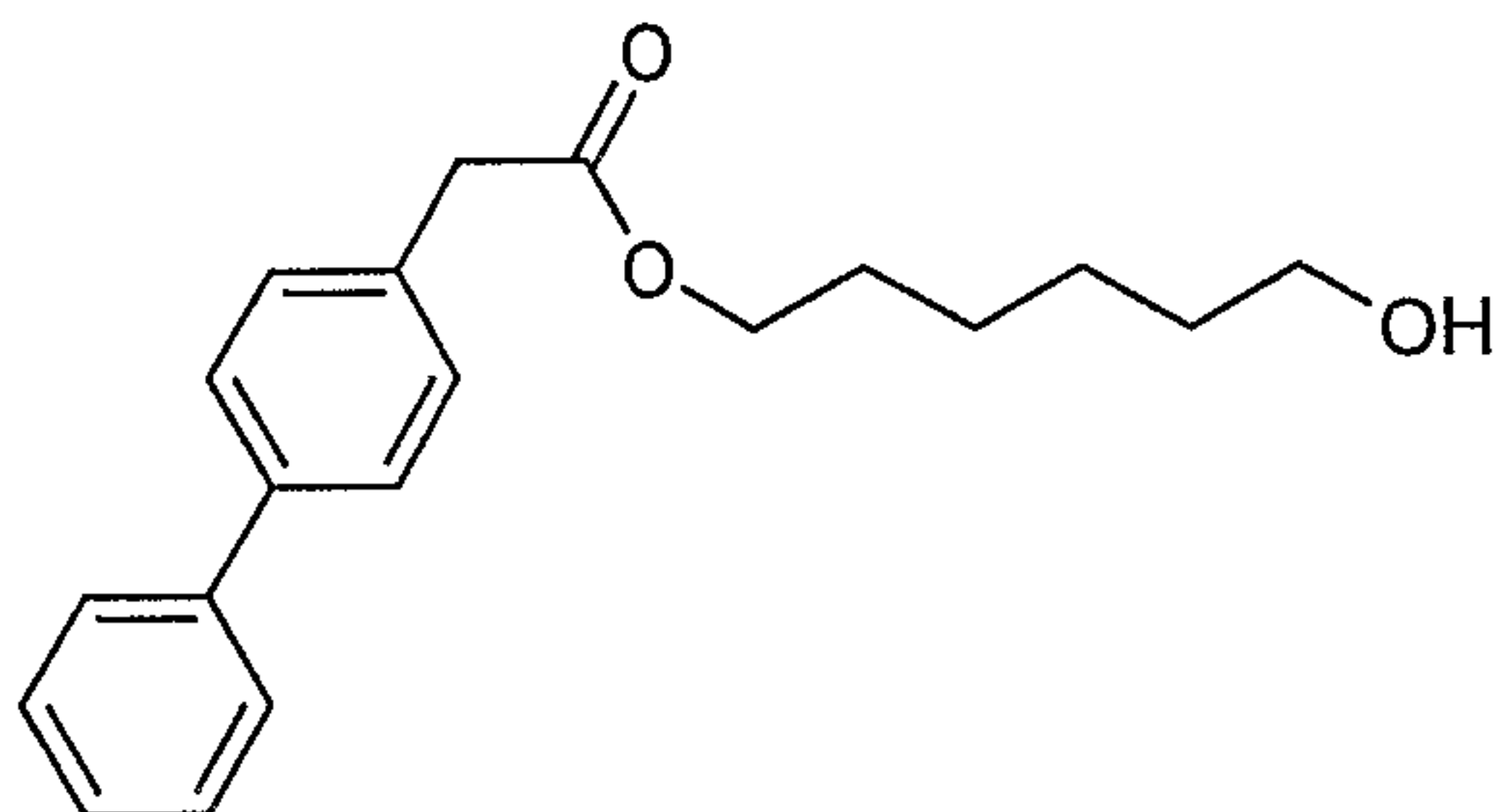
The title compound was prepared from biphenyl-4-yl-acetic acid and 1,4-butanediol using Method 2 to give a white solid (yield 80 %). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.1, 41.1, 62.3, 64.8, 127.1, 127.4, 128.8, 129.7, 133.1, 140.1, 140.8 and 171.8. m/z (Found M, 284. C₁₈H₂₀O₃ requires 284).

20

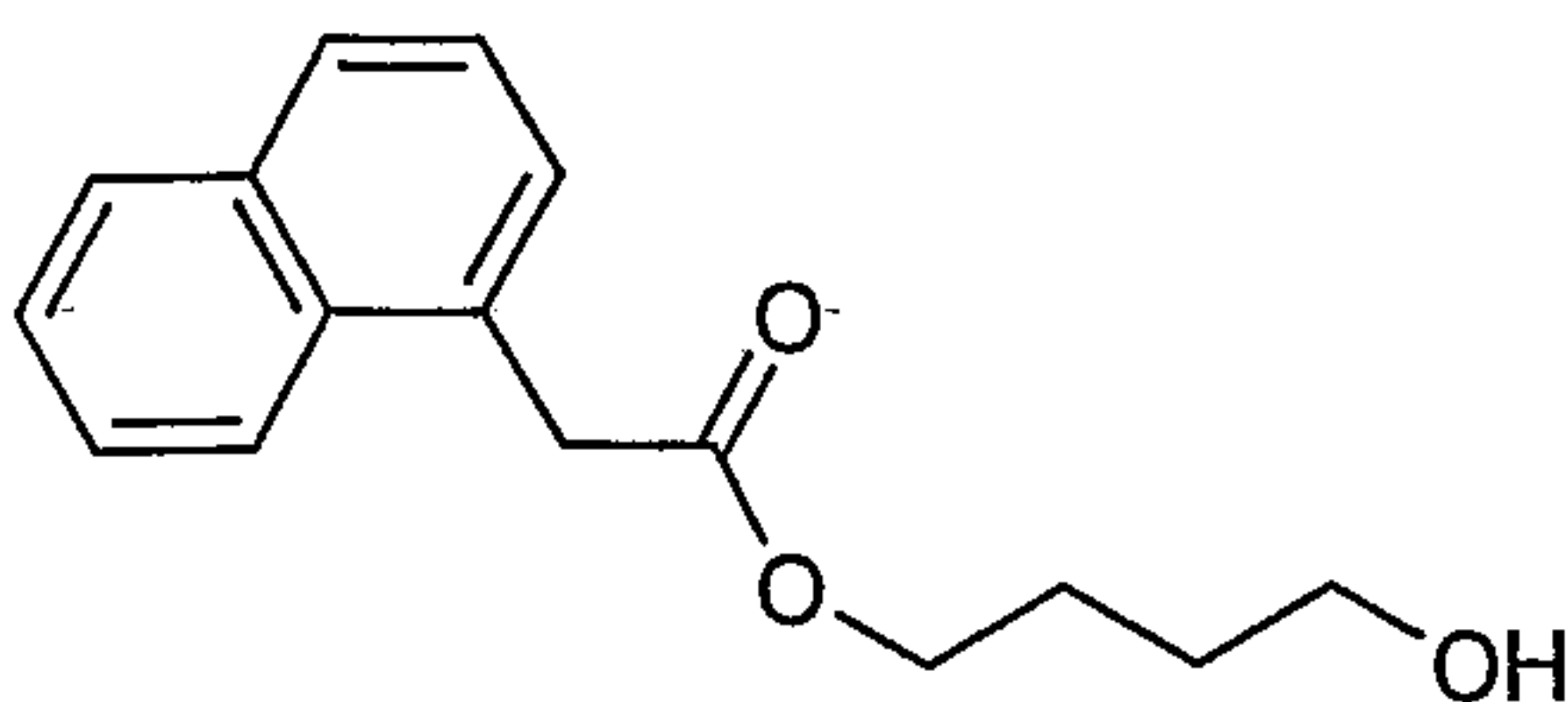
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Example 441,5-Pentanediol mono(biphenyl-4-yl-acetic acid)ester (**ABD-0043**) (**5BPA**)

5 The title compound was prepared from biphenyl-4-yl-acetic acid and 1,5-pentanediol using Method 2 to give a white solid (yield 75%). δ_c (CDCl₃, 62.9 MHz): 22.2, 28.4, 32.3, 41.1, 62.6, 65.0, 127.1, 127.3, 128.8, 129.7, 133.2, 140.1, 140.8 and 171.8.

Example 4510 1,6-Hexanediol mono(biphenyl-4-yl-acetic acid)ester (**ABD-0044**) (**6BPA**)

The title compound was prepared from biphenyl-4-yl-acetic acid and 1,6-hexanediol using Method 2 to give a white solid (yield 70%). δ_c (CDCl₃, 62.9 MHz): 25.4, 25.7, 28.6, 32.6, 41.1, 62.8, 65.0, 127.1, 127.3, 128.8, 129.7, 133.2, 15 140.0, 140.8 and 171.8.

Example 461,4-Butanediol mono(naphth-1-yl-acetic acid)ester (**ABD-0032**) (**4N**)

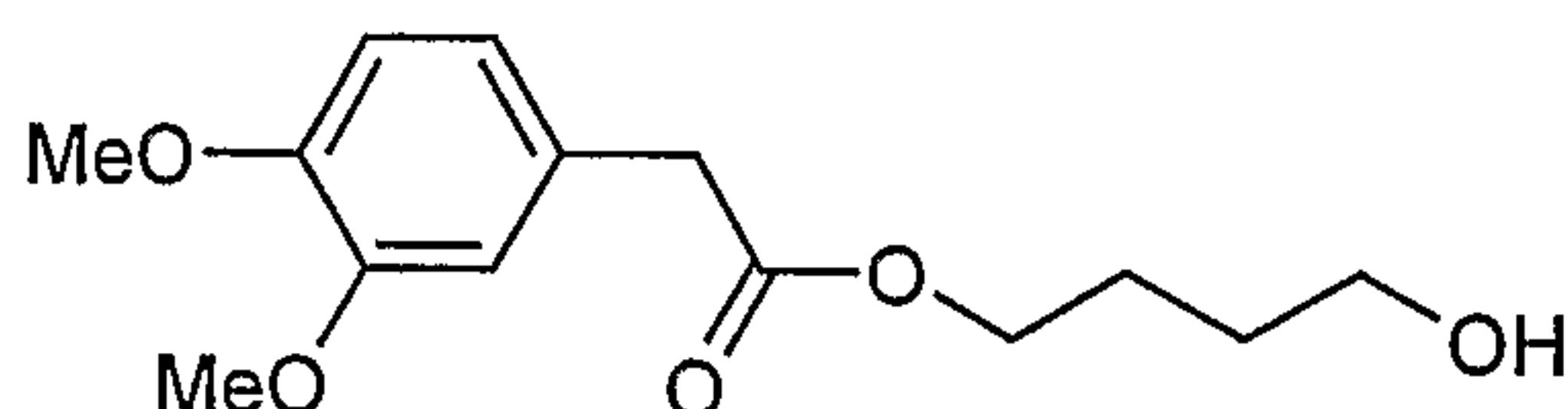
20 The title compound was prepared from naphth-1-yl acetic acid and 1,4-butanediol using Method 2, to give a clear oil (yield 70%). δ_c (CDCl₃): 25.0,

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29.0, 39.3, 62.1, 64.8, 123.8, 125.6, 125.8, 126.4, 128.1, 128.1, 128.9, 130.7, 132.1, 133.8 and 171.8.

Example 47

5 1,4-Butanediol mono(homoveratric acid)ester (**ABD-0033**) (**4H**)

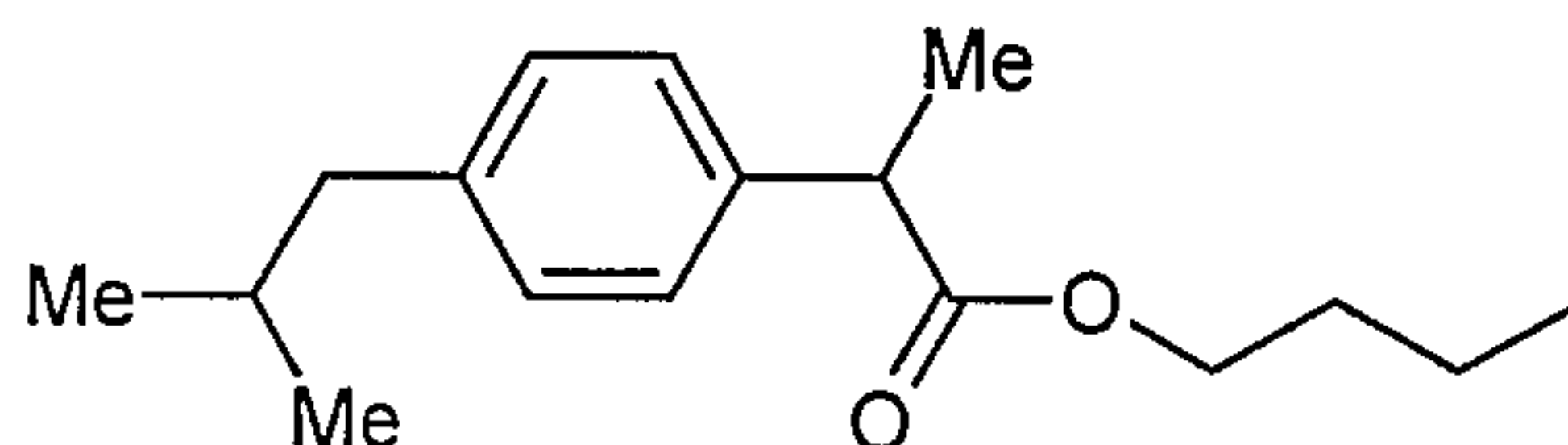


The title compound was prepared from homoveratric acid and 1,4-butanediol using Method 2 to give a clear oil (yield 90%). δ_c (CDCl₃, 62.9 MHz): 25.1, 29.0, 41.0, 55.9, 62.2, 64.7, 111.2, 112.4, 121.4, 126.5, 148.1, 148.9 and 172.0.

10

Example 48

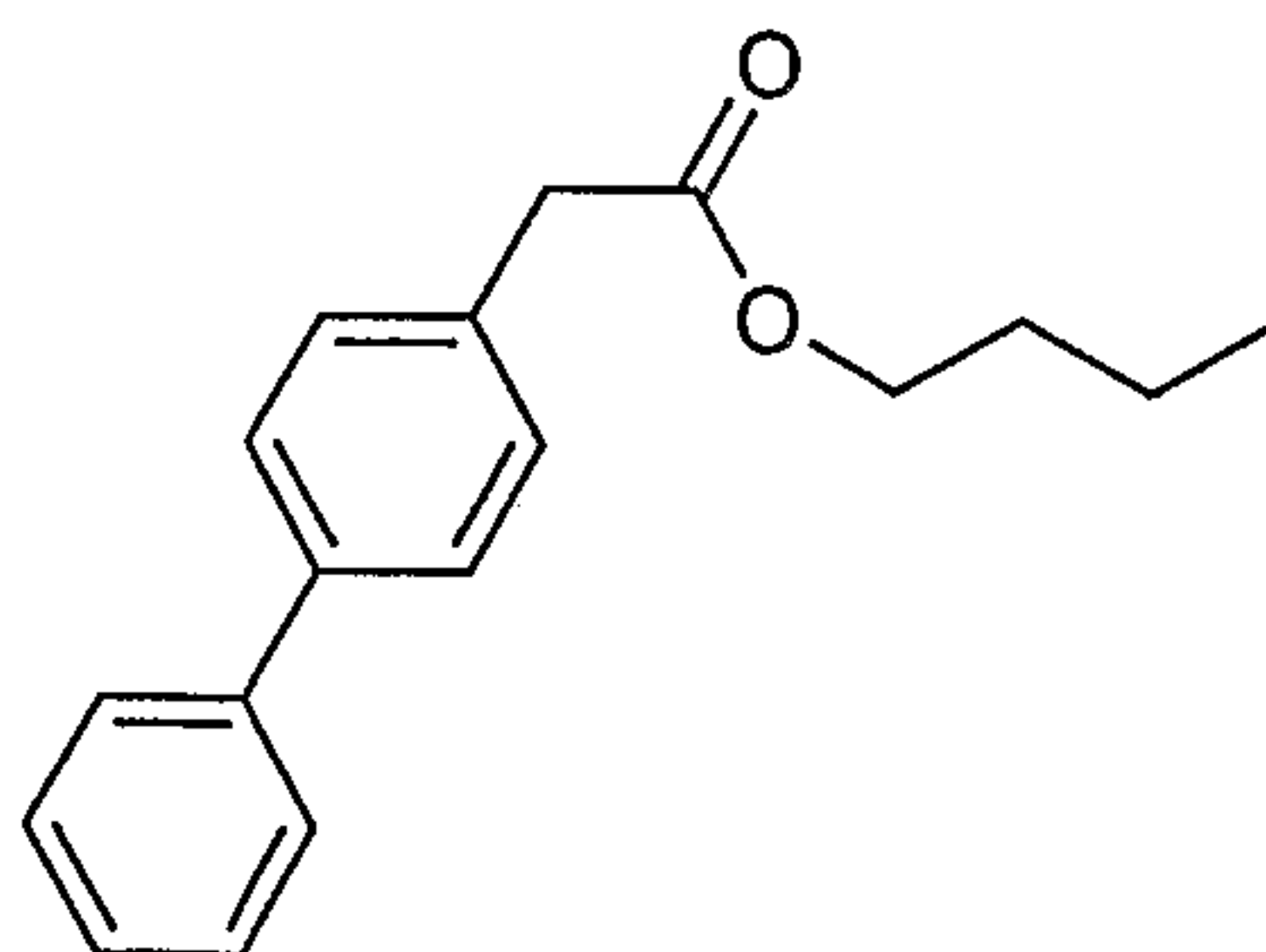
Butyl [2-(4-isobutylphenyl)propionic acid] ester (**ABD-0035**) (**Bul**)



15 The title compound was prepared from ibuprofen and butanol using Method 2 to give a clear oil (yield 85%). δ_c (CDCl₃, 62.9 MHz): 13.7, 18.5, 19.0, 22.4, 30.2, 30.6, 45.1, 45.2, 64.6, 127.2, 129.3, 137.9, 140.5 and 174.9

Example 49

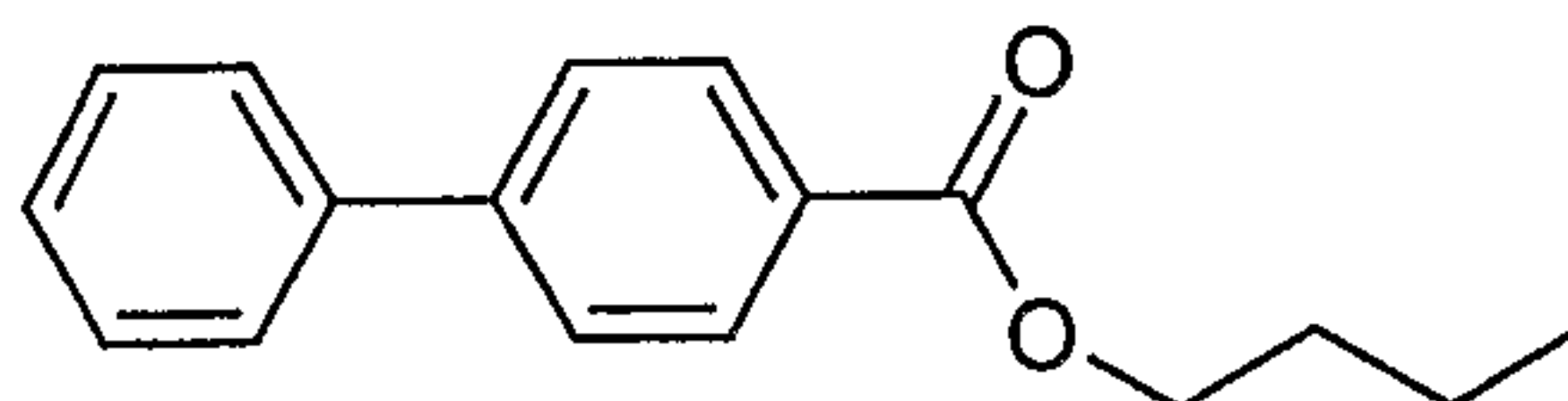
Butyl (biphenyl-4-yl-acetic acid) ester (**ABD-0040**) (**BuBPA**)



20

The title compound was prepared from biphenylacetic acid and butanol using Method 2 to give a clear oil (yield 70%). δ_c (CDCl₃, 62.9 MHz): 13.8, 19.1, 30.7, 41.1, 64.9, 127.1, 127.3, 128.8, 129.7, 133.3, 140.0, 140.9 and 171.7.

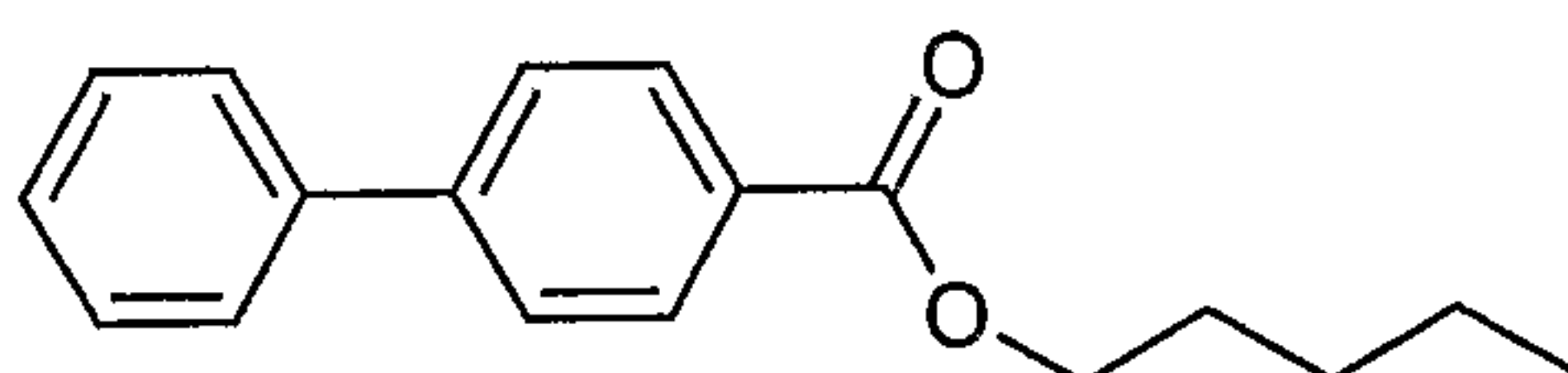
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Example 50Butyl (biphenyl-4-carboxylic acid) ester (**ABD-0053**) (**BuBP**)

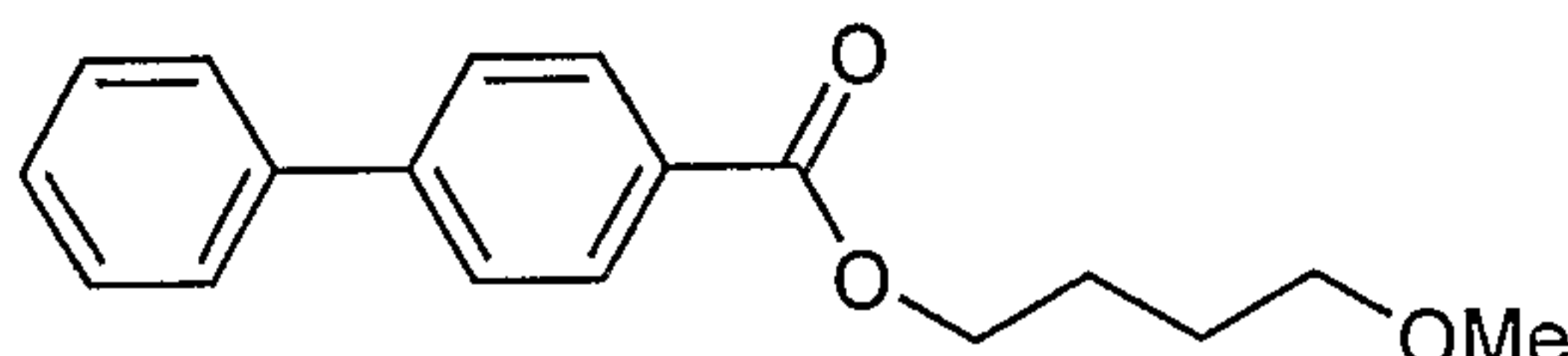
The title compound was prepared from biphenyl-4-carbonyl chloride and butanol
 5 using Method 1 to give a white solid (yield 85%). δ_c (CDCl₃, 62.9 MHz) 13.8,
 19.3, 30.9, 64.9, 127.1, 127.3, 128.1, 129.0, 130.1, 140.1, 145.6 and 166.6; m/z
 (Found M, 254. C₁₇H₁₈O₂ requires 254).

Example 51

10 Pentyl (biphenyl-4-carboxylic acid) ester (**ABD-0090**) (**PBP**)



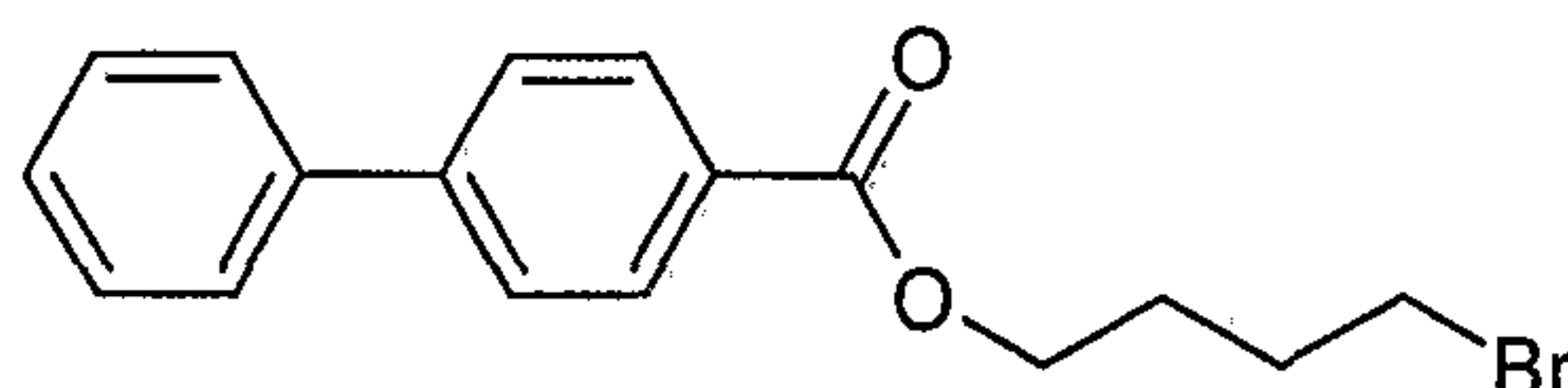
The title compound was prepared from biphenyl-4-carbonyl chloride and
 pentanol using Method 1 to give a clear oil (yield 85%). δ_c (CDCl₃, 62.9 MHz):
 14.1, 22.4, 28.3, 28.5, 65.2, 127.1, 127.3, 128.1, 128.9, 129.3, 130.1, 140.1,
 15 145.6 and 166.6.

Example 524-Methoxybutyl (biphenyl-4-carboxylic acid) ester (**ABD-0050**) (**4BP-OMe**)

20 **ABD-0056** (7 mmol) was dissolved in acetone (20 ml) containing powdered
 NaOH (1.5 g). Dimethyl sulphate (1.5 g, 12 mmol) was added dropwise and the
 mixture stirred overnight to give a slurry. The slurry was poured into water (200
 ml) and washed with methylene chloride (100 ml). The organic phase was
 washed with water until it became clear. The organic phase was dried over
 25 Na₂SO₄, the solvent evaporated and the title compound obtained by column
 chromatography (light petroleum:ethyl acetate, 1:1, followed by a repeat using
 light petroleum:ethyl acetate, 5:1) as a yellow oil (yield 50%). δ_c (CDCl₃, 62.9
 MHz): 25.6, 26.3, 58.7, 64.8, 72.2, 127.1, 127.3, 128.2, 129.0, 129.2, 130.1,

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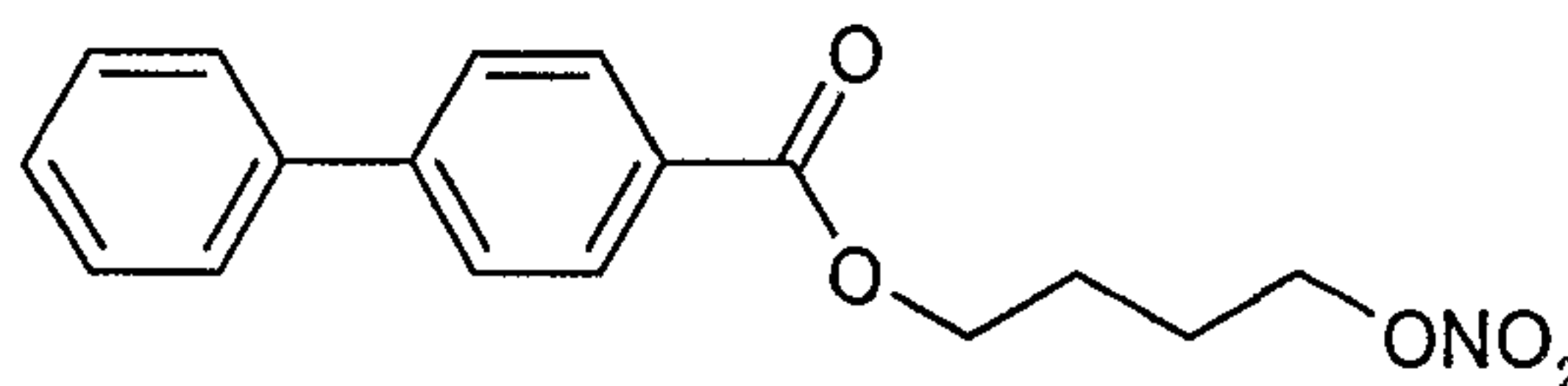
140.0, 145.6 and 166.6.

Example 534-Bromobutyl (biphenyl-4-carboxylic acid) ester (**ABD-0086**) (**4BP-Br**)

5

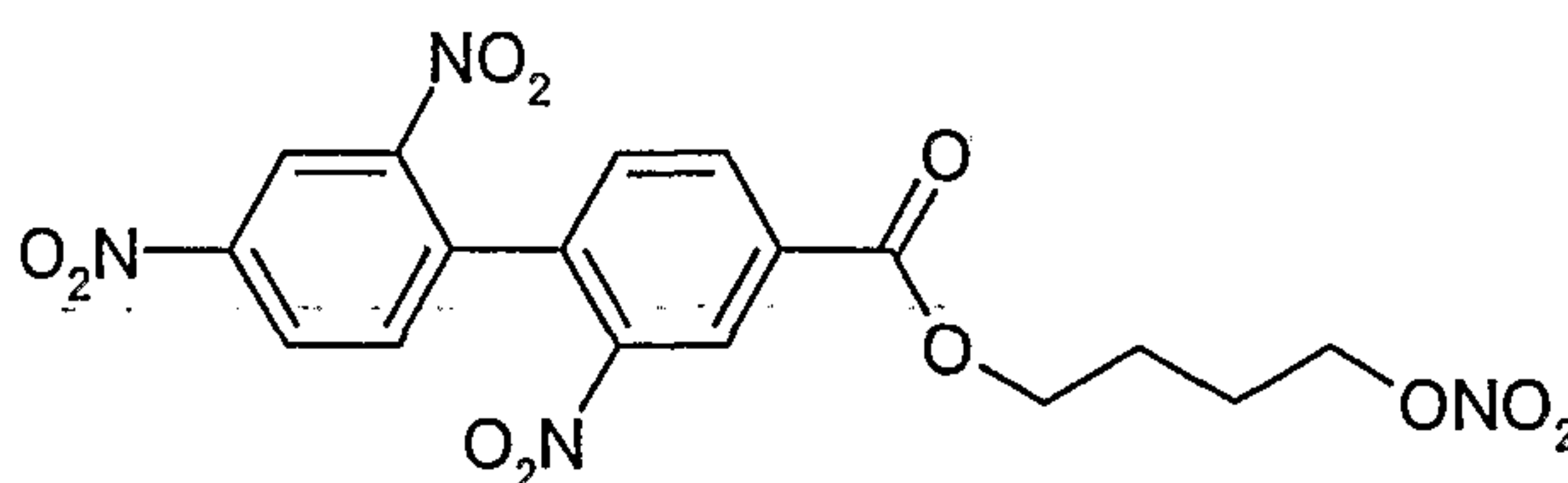
The title compound was prepared from biphenyl-4-carbonyl chloride and 4-bromobutanol (prepared using Method 9) using Method 1, to give the title compound as a pale brown oil (yield 20 %). δ_c (CDCl₃, 62.9 MHz): 26.2, 29.3, 44.6, 64.2, 127.1, 127.3, 128.2, 129.0, 130.1, 140.0, 145.7 and 166.5

10

Example 544-Nitrooxybutyl (biphenyl-4-carboxylic acid) ester (**ABD-0087**) (**4BP-NO₂**)

The title compound was prepared from **ABD-0086** (5 mmol) by stirring with AgNO₃ (25 mmol) in acetonitrile (50 ml) for 24 hours. The mixture was filtered, the filtrate evaporated and purified by column chromatography (light petroleum:ethyl acetate, 4:1) to give the title compound as pale yellow oil (yield 55%). δ_c (CDCl₃, 62.9 MHz): 23.8, 25.2, 64.0, 72.7, 127.1, 127.3, 128.2, 128.8, 129.0, 130.1, 139.9, 145.8 and 166.4.

20

Example 554-Nitrooxybutyl (2,2',4'-trinitro-biphenyl-4-carboxylic acid) ester (**ABD-0088**) (**4xNO₂-BP**)

ABD-0056 (10 mmol) was stirred in nitric acid (50 ml) and the temperature slowly increased to 80°C for 5 hours. The mixture was poured into water (250 ml) and

25

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extracted with methylene chloride (100 ml). The organic phase was washed with water, saturated NaHCO_3 and water, dried with Na_2SO_4 and evaporated.

Column chromatography (ethyl acetate:light petroleum, 1:1) gave the title compound as a thick yellow oil (yield 20%). δ_{C} (CDCl_3 , 62.9 MHz): 23.7, 25.1, 65.3, 72.4, 120.6, 126.2, 127.9, 130.7, 131.9, 132.4, 134.5, 136.5, 139.7, 146.7, 147.0, 148.0 and 163.7. δ_{H} (CDCl_3 , 250 MHz): 1.95 (4H, m), 4.47 (2H, m), 4.54 (2H, m), 7.40 (1H, d, J 7.9), 7.54 (1H, d, J 8.5), 8.38 (1H, dd, J 7.9, 1.8), 8.55 (1H, dd, J 8.5, 2.4), 8.90 (1H, d, J 1.5) and 9.10 (1H, d, J 2.4).

10 Biological Studies

Initial screening of candidate compounds was performed using viability assays, on cultures of the macrophage cell line J774, which have been used before as a model system for osteoclast survival (see, e.g., Luckman et al., 1998). The assay is based on the survival of the J774 macrophage cell line; macrophages are closely related to osteoclasts, and contain similar high levels of esterase activity.

MTT Macrophage J774 Viability Assay

20

J774 cells were plated at 10^4 cells per well in 150 μL αMEM (α Modified Eagle Medium) in 96-well plates and grown overnight. The next day, compounds were added to the cultures, and culture was continued for another 72 hours. At the end of the culture period cell survival was determined using the tetrazolium dye-based MTT assay as previously described (see, e.g., MacPherson et al., 1999).

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) has an orange colour and is soluble in the medium used for cell culture. The mitochondrial enzyme succinate dehydrogenase acts upon MTT in living cells to produce the insoluble purple coloured formazan. The amount of formazan produced, as measured by UV/visible spectroscopy, is proportional to the

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number of viable cells.

Briefly, MTT (5 mg/ml MTT in α MEM) was added to each well (1:10 v/v, 15 μ L) and the cells incubated for 4 hours. The medium was carefully removed using a
5 needle without dislodging the crystal layer. 100 μ L acidified isopropanol (4 M HCl 1:100 v/v in isopropanol) was added to each well and the purple crystals allowed to dissolve. The absorbance was measured in a plate reader at 540 nm, with 690 nm as reference. The controls were a deep purple colour, indicating a high number of live cells. The results for each test compound were
10 expressed as a % of the average control value.

Addition of Compounds. All of the compounds studied were made up as 100 mM solutions in DMSO. These stock solutions were then diluted 100 x in culture medium. From these 1 mM solutions, convenient quantities (3-15 μ L) were
15 added directly to the wells so as to give the desired final compound concentration.

Alamar Blue Macrophage J774 Viability Assay

20 J774 cells were plated at 10^4 cells per well in 150 μ L α MEM (α Modified Eagle Medium) in 96-well plates and grown overnight. The next day, compounds were added to the cultures, and culture was continued for another 72 hours. At the end of the culture period cell survival was determined using an Alamar Blue assay as previously described (see, e.g., Nociari et al., 1998).

25

Alamar Blue is an oxidation-reduction sensitive indicator. The dye itself is in the oxidised state, which is blue and non-fluorescent. The dye can accept electrons from reducing species, such as NADPH and FADH, to form a reduced dye species, which is red and fluorescent. Thus the transformation from oxidised
30 form to reduced form can be measured by fluorimetric or colourimetric means. For fluorescence measurements, 530-560 nm excitation and 590 nm emission wavelengths are typically used. For colourimetric measurements, absorbance is

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measured at 570 nm (reduced form) and 600 nm (oxidised form) and a simple calculation performed to determine the relative quantities of the two species.

5 A high ratio of the reducing species, NADPH and FADH, to the corresponding oxidised species, NADP and FAD, is an indicator that cells are proliferating and viable. A low ratio indicates cells that are quiescent or non-viable.

10 Briefly, Alamar Blue (Biosource International) was added undiluted to the each well (1:10 v/v, 15 μ L). The plate was incubated at 37°C for 3-4 hours and the fluorescence was measured at 570 nm, with a 25 nm bandwidth. A high reading indicated cells with normal viability, and a low reading indicates cells that have been damaged and are no longer proliferating normally. The controls gave a high fluorescence reading, indicating a high number of live, healthy cells.

15 A potent test compound gave a low fluorescence reading. The average results for each test compound (n=5) were expressed as a % of the average control value.

Addition of Compounds. All of the compounds studied were made up as 100 mM solutions in DMSO. These stock solutions were then diluted 100 or 1000 x in 20 culture medium (α MEM). From these 1 mM or 100 μ M solutions, convenient quantities (3-15 μ L) were added directly to the wells so as to give the desired final compound concentration.

25 This assay offers numerous advantages over other assays, including MTT assays: it permits a higher throughput; it is more sensitive; it is non-damaging to the cells; it is faster; it generally gives an identical result to MTT assay. A comparison is shown in Figure 1, which is a graph of the macrophage J774 viability, as measured by the MTT and Alamar Blue macrophage J774 viability assays, expressed as % of control, after 72 hours exposure to ABD-0028 and 30 ABD-0042, as a function of concentration of compound. Only one compound (ABD-0056) showed significant difference between the MTT and Alamar Blue assays.

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Additional Studies

Some compounds were further evaluated in two model systems of true
5 osteoclasts: (a) the murine co-culture system, and (b) the rabbit osteoclast culture system.

Murine Co-Culture System

10 The first model system, the murine co-culture system, studies the formation of osteoclasts from precursors present in the bone marrow. The number of osteoclasts and the amount of dentine resorption was measured.

Osteoclast formation and activity was studied using an adaptation (see, e.g.,
15 van't Hof & Ralston, 1997) of the osteoblast-bone marrow co-culture assay originally described by Takahashi et al., 1988.

Co-Culture Methods. Co-culture (see, e.g., Van't Hof et al., 1997) is a method to study the formation of osteoclasts from their precursors. In this assay,
20 osteoblasts were obtained from the calvaria of 2-3 day old neonatal mice. These were plated on dentine, stimulated with 1,25-dihydroxy vitamin D₃ to stimulate RANKL and M-CSF expression. Early osteoclast precursors were present in the bone marrow of adult mice. The bone marrow suspension was purified to remove the red blood cells and the remainder cultured on top of the osteoblast
25 layer. The stimulatory factors then allowed the osteoclast precursors to differentiate into mature osteoclasts. At the end of the culture osteoclasts were identified by TRAcP staining and the resorption activity was measured in the same manner as for rabbit osteoclasts.

30 Although it is possible to generate osteoclasts from bone marrow cells alone by treating the cultures with RANKL and M-CSF, the co-culture system is still regarded as one of the most reliable and reproducible available. It is useful for

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studying the effects of drugs on both osteoclast progenitors and mature osteoclasts.

Preparation of Dentine. The dentine was elephant ivory, preferred to bone because of its uniform surface, which facilitates easy visualisation of resorption pits. It was cut into slices of approximately 200 µm thickness using a Buehler Isomet low speed saw with a diamond wafering blade (series 15 HC). These slices were polished by hand, to a high degree, until one side was shiny. Out of these slices, discs were punched that fit the wells of a 96 well plate, using a paper puncher. Excess residues from the polish were removed by sonication. The discs were then stored in 70% ethanol until required. These discs were then dried and placed shiny side up in the wells of a 96 well plate. Cells were seeded onto the dentine. Following completion of the culture, these dentine slices were carefully removed from the plate and studied under the microscope.

Osteoblast Isolation. Briefly, osteoblasts were isolated from the calvarial bones of 2-day-old mice by sequential collagenase digestion (type I collagenase, Sigma) and cultured in αMEM supplemented with 10% FCS (foetal calf serum) and penicillin and streptomycin at 37°C in 5% CO₂.

More specifically, osteoblasts were obtained from a collagenase digestion of the calvaria (skull bones) of 2-3 day old neo-natal MF1 mice. At this stage in their development these are soft and easily removed. The calvaria from 5-6 mice were carefully dissected and washed in HBSS (Hank's balanced saline solution). The calvaria were placed in a 15 ml tube and shaken at 37°C in 4 ml collagenase (10 mg/ml) for 10 minutes. This removes the excess unwanted tissue. The liquid was disposed of and a further 4 ml collagenase (10 mg/ml) added to the tube. The calvaria were then digested for a further 30 minutes. After this the supernatant (F1) was removed and retained. The calvaria were washed with a 2 x 4 ml PBS and this was added to F1. 4 ml EDTA (ethylenediamine tetraacetic acid) (4 mM in PBS) was then added to complex the calcium and allow further extraction of osteoblasts. This was shaken for 10 minutes at

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37°C. The supernatant was removed and retained (F2). The calvaria were again washed with 2 x 4 ml HBSS and this was added to F2. The final 4 ml of collagenase (10 mg/ml) was added to the tube and this was again shaken at 37°C for 30 minutes. Whilst this was being done, F1 and F2 were spun down at 5 300 g for 3 minutes, brake 3. The pellets were re-suspended in 1 ml medium (α MEM supplemented with 10% FCS (foetal calf serum) and penicillin and streptomycin), combined and added to 10 ml medium in two 75 cm² flasks. The liquid from the final collagenase digestion was collected (F3), the calvaria washed and the combined liquid extracts spun down in the centrifuge. The pellet 10 was re-suspended in 1 ml medium and added in equal proportions to the flasks containing F1 and F2. The flasks were left for 4-6 hours at 37°C and then the medium was changed to remove any non-adherent cells. These flasks may be left for up to 4 days at 37°C, 5% CO₂.

15 *Osteoblast Plating.* The medium was removed from the flasks and the cells washed with PBS. 2 ml Trypsin was added to the cells and these were incubated at 37°C for 2 minutes. The flasks usually required gentle agitation to fully loosen the cells. 4 ml medium supplemented with 10% FCS was added to stop the enzymatic action. The cells were removed and the flask washed out with 20 medium. The cell suspension was spun down at 300 g for 3 minutes, the medium removed and the pellet re-suspended in 1 ml medium. The cells were counted and then seeded in a 96 well plated containing dentine slices, at 8 x 10³ cells per well in 100 μ l medium containing 1000 x dilution of stock 1,25-dihydroxyvitamin D₃ (final conc. 10 nM/well) to stimulate the expression of 25 RANKL and cultured overnight.

Isolation of Bone Marrow Cells. Briefly, bone marrow cell populations containing osteoclast precursors were isolated from the long bones of 3-5 month old mice and erythrocytes were removed by Ficoll-Hypaque density gradient 30 centrifugation. The resulting bone marrow cells were washed with PBS (phosphate buffered saline) and re-suspended in culture medium.

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More specifically, the femurs and tibia were dissected from 2-3 adult MF1 mice (3-6 months old) and the surrounding tissue was removed. The bones were trimmed to allow access to the bone marrow. The marrow was flushed out using a 25G needle and HBSS + 10% FCS. A single cell suspension is obtained by
5 repeatedly squeezing the cell suspension through needles of decreasing size (start with 19G, end with 25G). 5 ml Ficoll was added to a 15 ml tube and the cell suspension carefully placed on top of this with the minimum amount of mixing between the layers. The density centrifugation was performed at 600 g, 25 min, brake off. This was sufficient to allow the red blood cells to congregate
10 at the bottom of the tube, fats to remain at the top of the liquid and the desired bone marrow cells to collect at the interface. The cloudy layer from the interface was collected with a pipette, placed in a fresh 15 ml tube and made up to 12 ml with HBSS. The cell suspension was spun down at 300 g for 3 minutes. The pellet was collected and re-suspended in 1 ml medium. The bone marrow cells
15 were counted and then added to the 96 well plate containing the osteoblasts at 2×10^5 cells/well in 50 μ L medium.

Osteoblast Precursor Studies. To investigate the effects of a drug on osteoclast precursors the timetable was as follows:

- 20 Day 0 - Plate osteoblasts.
Day 1 - Plate bone marrow cells
Day 2 - Add test compound.
Day 4 - 100% medium refresh + 1,25-dihydroxyvitamin D₃ (final conc. 10 nm/well)
Day 6 - Add IL1 (10 u/ml) and 1,25-dihydroxyvitamin D₃ (final conc. 10 nm/well)
25 Day 10 - Fix cells.

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Mature Osteoclast Studies. To investigate the effects of a drug on mature osteoclasts the timetable was as follows:

Day 0 - Plate osteoblasts.

Day 1 - Plate bone marrow cells.

5 Day 6 - 50% medium refresh + 10 nM IL1 and 1,25-dihydroxyvitamin D₃.

Day 7 - Add drugs and remove and fix day 7 control slices.

Day 10 - Fix cells.

At the conclusion of a study, the cells were fixed in 4% formaldehyde for
10 10 minutes and washed in PBS. Fixed cells were either stained and kept in 70%
ethanol or refrigerated in water or PBS. The 50% medium refresh involved the
addition of 150 µL fresh medium containing a 500 x dilution of
1,25-dihydroxyvitamin D₃ and a 250 x dilution of IL1 (interleukin 1). This was left
for 15 minutes and then 150 µL medium carefully removed. The medium refresh
15 must be done very carefully, because the confluent layer of osteoblasts can be
quite easily disturbed, and detached. This would result in a total absence of
osteoclasts. Usually the first osteoclasts and resorption pits appeared on day 6.
Reasonable numbers of osteoclasts were present between day 7-10.

20 At the end of the culture, the osteoclasts were identified by staining for tartrate-
resistant acid phosphatase (TRAcP) staining and resorption pit area was
quantified by reflected light microscopy as described previously (see, e.g., van't
Hof & Ralston, 1997).

25 *TRAcP Staining.* Osteoclasts express very high levels of the enzyme tartrate
resistant acid phosphatase (TRAcP) and can therefore be easily visualised by
staining for this enzyme, for example, by the following method. Two staining
solutions, (1) and (2), were made up freshly as follows:

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Solution 1. 300 μ L Naphthol-AS-BI-phosphate stock.
1.5 ml Veronal buffer.
1.8 ml Acetate buffer.
1.8 ml Acetate buffer with 100 mM tartrate.

5

Solution 2. 240 μ L Pararosaniline.
240 μ L NaNO_2 (4% stock solution).

10 Naphthol-AS-BI-phosphate stock: 10 mg/ml Naphthol-AS-BI-phosphate in dimethylformamide.

Veronal buffer: 1.17 g anhydrous Sodium Acetate; 2.94 g Veronal (sodium barbiturate); dissolved in 100 ml distilled water.

15 Acetate buffer 0.1 M, pH 5.2: solution (a): 0.82 g Sodium Acetate anhydrous dissolved in 100 ml distilled water; solution (b): 0.6 ml Acetic acid glacial made up to 100 ml with distilled water; pH of solution (a) adjusted to pH 5.2 with solution (b).

20 Pararosaniline: 1g Pararosaniline in 20 ml distilled water. 5 ml concentrated hydrochloric acid was added, the solution was heated carefully in a water bath while stirring. The solution was allowed to cool and then filtered.

Solutions (1) and (2) were mixed and filtered to give the staining solution. The PBS from the wells was removed and at least 50 μ L of staining solution added.
25 The cells were incubated at 37°C for about 45 min, or until the dentine slices appeared sufficiently red. To determine what passes as sufficient it was necessary to remove the dentine slice and check under a light microscope that the osteoclasts were suitably stained. The staining solution was then removed and replaced with 70% ethanol. The dentine slices were stored in a refrigerator.
30

Osteoclast Counting. This was done using a light microscope to determine the number of TRAcP positive multinucleated cells on each dentine slice. The slices

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were carefully removed from the 96-well plate, avoiding disturbance of the cell layer, and placed on a glass slide. A few drops of 70% ethanol were put on each slice followed by a glass coverslip. Working across the dentine the number of multinucleated, red-stained cells were counted. There were usually a large
5 number of small red mononucleated cells. These were osteoclast precursors and these were not counted. The numbers of osteoclasts on the control slices can range from 300 up to 1000. For each compound or concentration studied, the average of the values for the 5 slices was taken and expressed as a % of the average value for the controls. Any obvious outlying values were ignored. The
10 most common reason for this was when there were no cells of any kind, usually indicating that the osteoblast layer has detached during handling.

Quantification of Resorption Area. After the osteoclasts were stained and counted it was necessary for the dentine slice to be thoroughly cleaned. The
15 slices were rubbed on a suitable surface, a piece of blue roll proved ideal for this purpose. In order to clean the slices properly it may be necessary to wash them in dilute HClO for a few seconds to loosen the cell debris. The resorption pits can be visualised either by staining with dyes such as Toluidine blue or Coomassie blue, by scanning electron microscopy or by reflected light
20 microscopy. Here, reflected light microscopy was used, because it is easy to perform, the slices needed only thorough cleaning and no staining, and the image obtained could be fairly easily quantified using image analysis. Because the slices need to be completely flat for the reflected light microscopy, they were glued glass slides under pressure of a 0.5 kg metal weight. These may then be
25 easily stored. A Zeiss reflected light microscope was used, fitted with a 2.5x lens, wide field c-mount adapter, and Diagnostics Instruments Insight B/W large chip digital camera. This set-up allowed the capture of an entire bone slice in one image at sufficient resolution to identify and measure the resorption pits. The image analysis software package was developed using the Aphelion ActiveX
30 image analysis toolkit from ADCIS (ADCIS SA, Hérrouville-Saint-Clair, France). The dentine slices appeared as a bright shiny surface littered with dark resorption pits. The software calculated the resorption areas for each slice. When

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determining the effects of the compounds in co-cultures, it was necessary to use both the values obtained for slices removed at the time when the drugs were added (e.g., Day 7), as well as the controls from the end of the study (e.g., Day 10).

5

Rabbit Osteoclast Culture System

The second model system was the rabbit osteoclast system, where mature, functional osteoclasts were isolated from the long bones of rabbits and cultured
10 on dentine slices.

Osteoclast Isolation. Osteoclasts were isolated from the long bones of 2-10 day-old rabbits, as described previously (see, e.g., reference Coxon et al., 2000). All 4 limbs were removed from the rabbits and placed in ice-cold PBS. Soft
15 tissue and cartilage were removed and the bones transferred into fresh PBS. The bones were minced in α MEM (without FCS), using a scalpel. All the medium and fragments were transferred to a 50 ml tube, vortexed for 3 x 10 seconds and left to stand for 1 minute. The supernatant was removed and made up to 50 ml/rabbit with medium and FCS so as to give a final concentration of 10%
20 FCS.

Osteoclast Plating. The cells were plated onto dentine slices in a 96 well plate, at 100 μ L/well (medium: α MEM supplemented with 10% FCS and penicillin and streptomycin) and left for 4 hours to allow adherence to the dentine. After this
25 period the medium was removed, and with it the non-adherent cells. Fresh medium was then added. The remaining population was highly enriched in osteoclasts.

Culturing. -At this point, test compounds to be studied were added and the cells
30 cultured at 37°C in 5% CO₂ for 48 hours. At the end of the culture, the osteoclasts were identified by staining for tartrate-resistant acid phosphatase (TRAcP) staining. A good number of osteoclasts in the controls was 100-200.

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The results were expressed as a % of the average number of osteoclasts seen in the controls. The resorption pit area was quantified by reflected light microscopy as described previously (see, e.g., van't Hof & Ralston, 1997) and again the results expressed as a % of the control values.

5

Biological Data

1,4-butanediol was tested for its ability to inhibit osteoclast formation and activity in the murine co-culture system; it had no detected effect on the osteoclasts.

10

A number of monoesters of alkane diols were prepared, and IC₅₀ values for macrophage J774 viability assays for many of these are summarised in Table 1. The most potent compounds, ABD-0056 (4BP) and ABD-0085 (10F), are almost an order of magnitude more active than any of the other compounds studied.

15

Table 1				
#	Compound		IC ₅₀ (μM)	
			MTT	Alamar Blue
1	ABD-0006	4A	>100	-
2	ABD-0007	4Bu	>100	-
3	ABD-0008	4MB	>100	-
4	ABD-0009	4B	>100	-
5	ABD-0014	4P	>100	-
6	ABD-0017	6P	>100	-
7	ABD-0019	4C	>100	-
8	ABD-0028	4T	20	30
9	ABD-0030	5T	40	-
10	ABD-0031	6T	40	-
11	ABD-0032	4N	>100	-
12	ABD-0033	4H	>100	-
13	ABD-0034	4PT	>100	-
14	ABD-0035	BuI	72	-
15	ABD-0036	4I	52	-
16	ABD-0037	3I	72	-
17	ABD-0038	5I	68	-
18	ABD-0039	6I	72	-
19	ABD-0040	BuBPA	>100	-
20	ABD-0041	3BPA	75	-
21	ABD-0042	4BPA	45	45
22	ABD-0043	5BPA	>100	-

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Table 1				
#	Compound		IC ₅₀ (μM)	
			MTT	Alamar Blue
23	ABD-0044	6BPA	28	-
24	ABD-0049	4BP-Ac	-	50
25	ABD-0050	4BP-Ome	-	>100
26	ABD-0053	BuBP	>100	-
27	ABD-0054	6BP	35	-
28	ABD-0055	5BP	65	-
29	ABD-0056	4BP	3.5	18
30	ABD-0057	3BP	>100	-
31	ABD-0059	4BPX	>100	-
32	ABD-0069	4IB	-	90
33	ABD-0070	Me-4BP	-	>100
34	ABD-0072	HO-4BP	-	45
35	ABD-0077	5F	-	25
36	ABD-0085	10F	-	4
37	ABD-0086	4BP-Br	-	>100
38	ABD-0087	4BP-NO ₂	-	30
39	ABD-0088	4xNO ₂ -BP	-	35
40	ABD-0089	Xyl	-	9
41	ABD-0090	PBP	-	45
42	ABD-0094	Et-4BP	-	>100
43	ABD-0095	BP-4F	-	40
44	ABD-0096	DBP-4F	-	-
45	ABD-0097	4OMe-BP	-	>100
46	ABD-0098	2NO ₂ -BP	-	17
47	ABD-0099	2F-BP	-	14
48	ABD-0100	4F-BP	-	14
49	ABD-0102	4Br-BP	-	14
50	ABD-0106	2,3,6-FB	-	>100
51	ABD-0107	3,4-FB	-	>100
52	ABD-0108	2,3,4-FB	-	>100
53	ABD-0109	2,4,5-FB	-	>100
54	ABD-0110	2,4-FB	-	>100
55	ABD-0111	D2,4-FB	-	>100

Some compounds were also evaluated using the murine co-culture system and rabbit osteoclasts.

- At a concentration of 100 μM, all of the biphenylcarboxy (BP), trityl (T), and ibuprofenyl (I) compounds tested were found to be potent inhibitors of osteoclast formation and activity in the murine co-culture system, as illustrated in Figure 2.

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Figure 3 shows that at 100 μ M, survival of macrophage J774 cells is comparable to that of genuine osteoclasts. All compounds which were effective in macrophages were also effective in the murine co-culture, and no compounds were found to be solely effective in one system. Only one compound, ABD-0057 (3BP), showed a significant difference in response between the two systems.

Some compounds were also evaluated over a range of concentrations, using the MTT and Alamar Blue macrophage J774 viability assays.

10 The results for the biphenylcarboxy compounds, ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), and ABD-0054 (6BP), using the MTT macrophage J774 viability assay, are illustrated in Figure 4.

Compound ABD-0056 (4BP) is the most active of the BP compounds, with an
15 IC_{50} of 3.5 μ M. This is substantially lower than any of the other BP derivatives, or indeed any other derivatives yet encountered (other than ABD-0085 (10F)). The next most active BP compound is ABD-0054 (6BP). The butanol compound ABD-0053 (BuBP) (which lacks a terminal hydroxyl group) showed very little activity, suggesting that the biphenylcarboxy (BP) group itself is not toxic. The
20 biphenylcarboxylic acid was not active.

The results for the ibuprofenyl (I) compounds, ABD-0035 (BuI), ABD-0037 (3I), ABD-0036 (4I), ABD-0038 (5I), and ABD-0039 (6I), using the MTT macrophage J774 viability assay, are illustrated in Figure 5.

25

Again the butanediol derivative, compound ABD-0036 (4I), was the most active, but by a less significant margin. But note that ibuprofen itself may be having a significant effect on the proliferation and survival of the macrophages.

30 The results for various trityl compounds, ABD-0028 (4T), ABD-0030 (5T), and ABD-0031 (6T), using the MTT macrophage J774 viability assay, are illustrated in Figure 6.

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All of the trityl compounds were found to inhibit macrophage function to a high degree, suggesting the high toxicity of the triphenylacetyl group. The butanediol derivative, compound ABD-0028 (4T), is more potent than compound ABD-0030
5 (5T) and compound ABD-0031 (6T).

The results for various biphenylacetyl (BPA) compounds, ABD-0040 (BuBPA), ABD-0041 (3BPA), ABD-0042 (4BPA), ABD-0043 (5BPA), and ABD-0044 (6BPA), using the MTT macrophage J774 viability assay, are illustrated in
10 Figure 7.

Again, the butanediol derivative, compound ABD-0042 (4BPA), is very active, as is the hexanediol derivative, compound ABD-0044 (6BPA). Since BPA (4-biphenyl acetic acid; also known as Felbinac), like ibuprofen, is a COX
15 inhibitor, some of the effects may be due to suppression of prostaglandin synthesis.

The results for various butanediol derivatives, ABD-0042 (4BPA), ABD-0028 (4T), ABD-0056 (4BP), ABD-0036 (4I), using the MTT macrophage J774 viability
20 assay, are also illustrated in Figure 8.

The results for various butanediol derivatives, ABD-0042 (4BPA), ABD-0028 (4T), ABD-0056 (4BP), ABD-0036 (4I), using the Alamar Blue macrophage J774 viability assay, are also illustrated in Figure 9.
25

The results for various substituted biphenyl (BP) compounds, ABD-0098 ("2NO₂"), ABD-0100 ("4F"), ABD-0099 ("2F"), ABD-0089 ("Xyl"), and ABD-0102 ("4Br"), using the Alamar Blue macrophage J774 viability assay, are illustrated in
Figure 10.

30 The results for various substituted biphenyl (BP) compounds, ABD-0072 ("OH"), ABD-0089 ("Dimethyl"), ABD-0070 ("Methyl"), ABD-0094 ("Ethyl"), and

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ABD-0097 ("Methoxy"), using the Alamar Blue macrophage J774 viability assay, are illustrated in Figure 11.

5 The results for two fluoro-substituted phenyl compounds, ABD-0085 ("10F") and ABD-0077 ("5F"), using the Alamar Blue macrophage J774 viability assay, are illustrated in Figure 12.

10 Various butanediol derivatives (ABD-0053 (BuBP), ABD-0057 (3BP), ABD-0056 (4BP), ABD-0055 (5BP), ABD-0054 (6BP)) were further evaluated using the murine co-culture system and the rabbit osteoclast culture system, and osteoclast number and resorption pit area recorded as a function of compound concentration.

15 The results for osteoclast number for the rabbit osteoclast culture system are illustrated in Figure 13.

The results for resorption pit area for the rabbit osteoclast culture system are illustrated in Figure 14.

20 It was possible to investigate the effects of compounds upon the osteoclast precursors by adding the test compounds at the Day 2 stage of the co-culture procedure. The test compounds were added and left in contact with the cell culture for 2 days. A 100% medium change was then performed, as it is desirable to remove all of the test compound. This must be done very carefully
25 without touching or disturbing the cell layer. Were any compound to remain then it would complicate the results by potentially killing osteoclasts as well as their precursors and not give an accurate indication of the toxicity specifically towards precursors.

30 The results for osteoclast number for the murine co-culture system, where test compound was added at Day 2, removed at Day 4 and incubation continued until Day 10 (osteoclast precursors), are illustrated in Figure 15.

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The results for resorption pit area for the murine co-culture system, where test compound was added at Day 2, removed at Day 4 and incubation continued until Day 10 (osteoclast precursors), are illustrated in Figure 16.

5

Figure 15 shows that ABD-0056 (4BP) is even more effective against osteoclast precursor formation than against mature osteoclasts. As a potential treatment for disorders involving excess bone removal, this suggests ABD-0056 (4BP) is a very potent drug capable of strongly inhibiting the formation of osteoclasts, and then demonstrating a high degree of toxicity towards those that do develop. The same pattern is demonstrated by studies on the levels of osteoclast-induced resorption, as shown in Figure 16. At all concentrations tested, there is virtually no resorption seen.

15 The results for osteoclast number for the murine co-culture system, where test compound was added at Day 7, and incubation continued until Day 10 (mature osteoclasts), are illustrated in Figure 17.

The results for resorption pit area for the murine co-culture system, where test compound was added at Day 7, and incubation continued until Day 10 (mature osteoclasts), are illustrated in Figure 18.

Compounds ABD-0056 (4BP) and ABD-0054 (6BP) significantly reduced rabbit osteoclast numbers and resorption activity. Additionally, ABD-0056 (4BP) showed a significant effect at concentrations down to 10 μ M. Compounds ABD-0056 (4BP) and ABD-0054 (6BP) also significantly inhibited osteoclast formation in the murine co-culture system.

The effects on resorption pit area were more pronounced in the murine co-culture than in the rabbit osteoclast system. In the rabbit system, mature, resorbing osteoclasts are present from the start and may resorb bone for some time, until the compound starts affecting the cells. The co-culture system,

30

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however, depends on the actual formation of osteoclasts from non-resorbing precursors.

The results for osteoclast number and resorption pit area for the murine
5 co-culture system, where test compound (ABD-0056) (4BP) was added at Day 7, and incubation continued until Day 10 (mature osteoclasts), are illustrated in Figure 19.

The results show that the 1,4-butanediol ester of biphenylcarboxylic acid
10 (compound ABD-0056 (4BP)) is a potent inhibitor of osteoclast survival, formation and activity, and is 10 times more effective than any compounds of this class (other than ABD-0085 (10F)).

In a comparable study on J774 survival (see, e.g., reference Luckman et al.,
15 1998), the bisphosphonates alendronate and pamidronate had IC50 values that were 10 and 8 times higher respectively.

Without wishing to be bound by any particular theory, it is believed that the biphenylcarboxylic acid conveys the lipophilicity needed for the compound to
20 pass across the cell membrane.

Additional esters of 1,4-butanediol were prepared and tested, specifically, the naphth-1-ylacetyl (compound ABD-0032 (4N)), homoveratryl (compound ABD-0033 (4H)), 2-biphenylcarboxy (compound ABD-0059 (4BPX)) and
25 4-phenyltoluyl (compound ABD-0034 (4PT)) derivatives. These compounds showed little activity at 100 µM concentration.

Without wishing to be bound to any particular theory, it is believed that the activity of the compounds is related to the overall shape of the molecule.
30 The I, BP and BPA derivatives can be regarded as broadly linear, whereas the BPX and N derivatives are bent out of the linear plane. That the H and PT derivatives are inactive suggests that the molecular target will only accommodate

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a specific size of compound, and that the homoveratrate compound is too small or insufficiently lipophilic and the phenyltoluate compound is too long or too flexible.

- 5 It is believed that one preferred class of compounds will be of a generally rigid, cylindrical shape, and be based on the biphenyl structure. A sub-class of such compounds are those with a further 4'-substituent on the biphenyl group. Another sub-class of such compounds are those with further 2'- and 4'-substituents on the biphenyl group. Another sub-class of such compounds are
10 those with further 2-, 2'- and 4'-substituents on the biphenyl group.

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the
15 above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention as defined by the appended claims.

20

REFERENCES

A number of patents and publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these
25 references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

Armour K.J., et al., 2001, "Inhibition of bone resorption in vitro and prevention of
30 ovariectomy-induced bone loss in vivo by flurbiprofen nitroxybutylester (HCT1026), " Arthritis Rheum., Vol. 44, No. 9, pp. 2185-2192.

- 156 -

- Blum, H., et al., 1978, "Diphosphonoalkane Carboxylic Acids, Process of Preparation and Methods of Use," U.S. Patent No. 4,077,997.
- Coxon, F.P., Helfrich, M.H., Van't Hof, R., Sehti, S., Ralston, S.H., Hamilton, A., and Rogers, M.J., 2000, "Protein geranylgeranylation is required for
5 osteoclast formation, function, and survival: inhibition by bisphosphonates and GGTI-298," J. Bone Miner. Res., Vol. 15, pp. 1467-1476.
- Degenhardt and Burdsall, 1986, "Synthesis of Ethenylidenebis(phosphonic acid) and its Tetraalkyl Esters," J. Org. Chem., Vol. 51, pp. 3488-3490.
- Eberhard and Westheimer, 1965, "Hydrolysis of Phostonates," J. Amer. Chem.
10 Soc., Vol. 87, pp. 252-260.
- Herczegh et al, 2002, "Osteoadsorptive Bisphosphonate Derivatives of Fluoroquinolone Antibacterials," J. Med. Chem., Vol. 45, pp. 2338-2341.
- Hughes, D.E., Boyce, B.F., 1997, "Apoptosis in bone physiology and disease," Molecular Pathology, Vol. 50, pp. 132-137.
- 15 Kong, Y.Y., Yoshida, H., Sarosi, I., Tan, H.L., Timms, E., Capparelli, C., et al, 1999, "OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis," Nature, Vol. 397, pp. 315-323.
- Luckman, S.P., Coxon, F.P., Ebetino, F.H., Russell, R.G., and Rogers, M.J.,
20 1998, "Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: evidence from structure- activity relationships in J774 macrophages," J. Bone Miner. Res., Vol. 13, pp. 1668-1678.
- Luckman, S.P.; Coxon, F.P.; Ebetino, F.H.; Russell, R.G.; Rogers, M.J., 1998,
25 "Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: evidence from structure-activity relationships in J774 macrophages," J. Bone Miner. Res., Vol. 13, pp. 1668-1678, 1998.
- MacPherson, H; Noble, B.S.; Ralston, S.H., 1999, "Expression and functional
30 role of nitric oxide synthase isoforms in human osteoblast-like cells," Bone, Vol. 24, pp. 179-185.

- 157 -

- Miyaura, N. and Suzuki, A., 1995, "Palladium-catalysed cross-coupling reactions of organoboron compounds," Chem. Rev., Vol. 95, No. 7, pp. 2457-2483.
- Mundy, G.R., 1996, Bone Remodelling and its disorders (2nd edition), London: Martin Dunitz.
- 5 Nociari, M.N., et al., 1998, "A Novel one-step, highly sensitive fluorimetric assay to evaluate cell-mediated cytotoxicity," Journal of Immunological Methods, Vol. 213, pp. 157-167.
- Raisz, L.G., 1988, "Local and systemic factors in the pathogenesis of osteoporosis," N. Engl. J. Med., Vol. 318, pp. 818-828.
- 10 Ralston, S.H., 1997, "Science, Medicine and the Future: Osteoporosis," Br. Med. J., Vol. 315, pp. 469-472.
- Rodan, G.A., Harada, S., 1997, "The missing bone," Cell, Vol. 89, pp. 677-680.
- Takahashi, N.; Akatsu, T.; Udagawa, N.; Sasaki, T.; Yamaguchi, A.; Moseley, J.M.; Martin, T.J.; Suda, T., 1988, "Osteoblastic cells are involved in
- 15 osteoclast formation," Endocrinology, Vol. 123, pp. 2600-2602, 1988.
- van't Hof, R.J., and Ralston, S.H., 1997, "Cytokine-induced nitric oxide inhibits bone resorption by inducing apoptosis of osteoclast progenitors and suppressing osteoclast activity," J. Bone Miner. Res., Vol. 12, pp. 1797-804.
- 20 Yasuda, H., Shima, N., Nakagawa, N., Mochizuki, S.I., Yano, K., Fujise, N., et al, 1998, "Identity of osteoclastogenesis inhibitory factor (OCIF) and osteoprotegerin (OPG): a mechanism by which OPG/OCIF inhibits osteoclastogenesis in vitro," Endocrinology, Vol. 139, pp. 1329-1337.

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CLAIMS

1. Use of a compound for the manufacture of a medicament for use in the treatment of a condition mediated by osteoclasts and/or characterised by bone resorption, wherein the compound is selected from compounds of the following formulae:



wherein:

A is a C₂₋₁₀alkylene group;

R^{A1} is independently a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, and is optionally substituted;

R^{A2} is independently, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, and is optionally substituted; and,

J is independently selected from:

hydrogen;

ether groups;

groups which are, or comprise, a phosphonic acid group; and,

groups which are, or comprise, a Ca²⁺ binding group;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

* * *

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2. Use according to claim 1, wherein the compound is selected from compounds of the following formula:



wherein:

A is a C₂₋₁₀alkylene group;

R^{A1} is independently a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, and is optionally substituted; and,

R^{A2} is independently, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, and is optionally substituted;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

3. Use according to claim 2, wherein R^{A1} and R^{A2} are the same.
4. Use according to claim 2, wherein R^{A1} and R^{A2} are different.
5. Use according to claim 4, wherein R^{A2} is, or comprises, a bone targeting moiety.
6. Use according to claim 4, wherein R^{A2} independently comprises a phosphonic acid group.
7. Use according to claim 4, wherein R^{A2} independently comprises a phosphonic acid group selected from phosphonic acid, and salts and esters thereof.
8. Use according to claim 4, wherein R^{A2} independently is, or comprises, a C₁₋₇alkyl group substituted with one or more groups independently selected from phosphonic acid, and salts and esters thereof.

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9. Use according to claim 4, wherein R^{A2} independently is, or comprises, a C_{1-7} alkyl group which comprises a bisphosphonic acid group, or a salt or ester thereof.
10. Use according to claim 4, wherein R^{A2} comprises a Ca^{2+} binding group.
11. Use according to claim 4, wherein R^{A2} comprises a Ca^{2+} binding group derived from tetracyclin.

* * *

12. Use according to claim 1, wherein the compound is selected from compounds of the following formula:



wherein:

A is a C_{2-10} alkylene group;

R^{A1} is independently a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, and is optionally substituted;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

* * *

13. Use according to claim 1, wherein the compound is selected from compounds of the following formula:



wherein:

A is a C_{2-10} alkylene group;

R^{A1} is independently a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, and is optionally substituted;

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J is independently selected from:

hydrogen;

ether groups;

groups which are, or comprise, a phosphonic acid group; and,

groups which are, or comprise, a Ca^{2+} binding group;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

14. Use according to claim 13, wherein J is -H.
15. Use according to claim 13, wherein J is C_{1-7} alkoxy.
16. Use according to claim 13, wherein J is selected from: -OMe and -OEt.
17. Use according to claim 13, wherein J is selected from groups which are, or comprise, a phosphonic acid group.
18. Use according to claim 13, wherein J is selected from groups which are, or comprise, Ca^{2+} binding groups.

* * *

19. Use according to any one of claims 1 to 18, wherein A is an unsubstituted C_{2-10} alkylene group.
20. Use according to any one of claims 1 to 19, wherein A is a C_{3-8} alkylene group.
21. Use according to any one of claims 1 to 19, wherein A is a C_{4-6} alkylene group.

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22. Use according to any one of claims 1 to 19, wherein A is a C₄alkylene group.
23. Use according to any one of claims 1 to 19, wherein A is a C₅alkylene group.
24. Use according to any one of claims 1 to 19, wherein A is a C₆alkylene group.

* * *

25. Use according to any one of claims 1 to 24, wherein A is an aliphatic group.
26. Use according to any one of claims 1 to 24, wherein A is a linear group.
27. Use according to any one of claims 1 to 24, wherein A is a fully saturated aliphatic group.

* * *

28. Use according to any one of claims 1 to 18, wherein A is a group of the formula -(CH₂)_n- where n is an integer from 2 to 10.
29. Use according to any one of claims 1 to 18, wherein A is a group of the formula -(CH₂)_n- where n is an integer from 3 to 8.
30. Use according to any one of claims 1 to 18, wherein A is a group of the formula -(CH₂)_n- where n is an integer from 4 to 6.
31. Use according to any one of claims 1 to 18, wherein A is a group of the formula -(CH₂)₄-.

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32. Use according to any one of claims 1 to 18, wherein A is a group of the formula $-(CH_2)_5-$.
33. Use according to any one of claims 1 to 18, wherein A is a group of the formula $-(CH_2)_6-$.

* * *

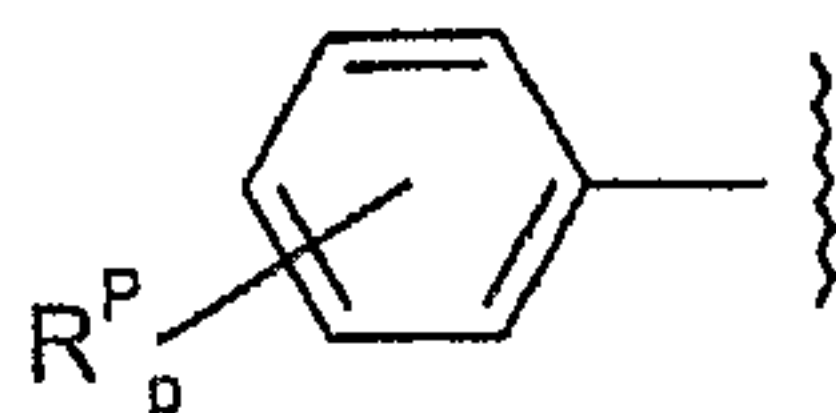
34. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, and is optionally substituted
35. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted C_{5-20} aryl group.
36. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted phenyl, naphthyl, pyridyl, furanyl, thiofuranyl, indolyl, pyrrolyl, imidazolyl, naphthyl, quinoliny, benzimidazolyl, benzothiofuranyl, fluorenyl, acridinyl, or carbazolyl.
37. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted C_{5-6} aryl group.
38. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted substituted phenyl, pyridyl, furanyl, thiofuranyl, indolyl, pyrrolyl, or imidazolyl.

* * *

39. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted phenyl group.

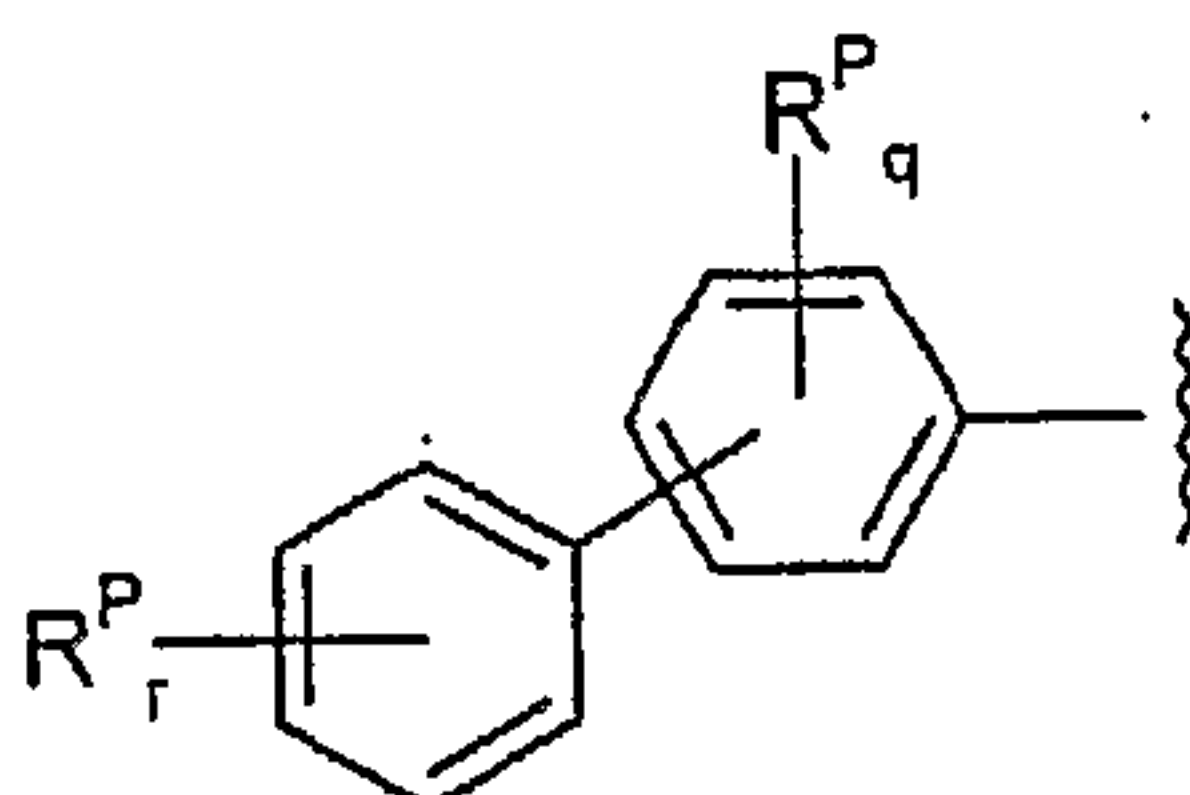
- 164 -

40. Use according to any one of claims 1 to 33, wherein R^{A1} is independently optionally substituted phenyl group of the following formula:



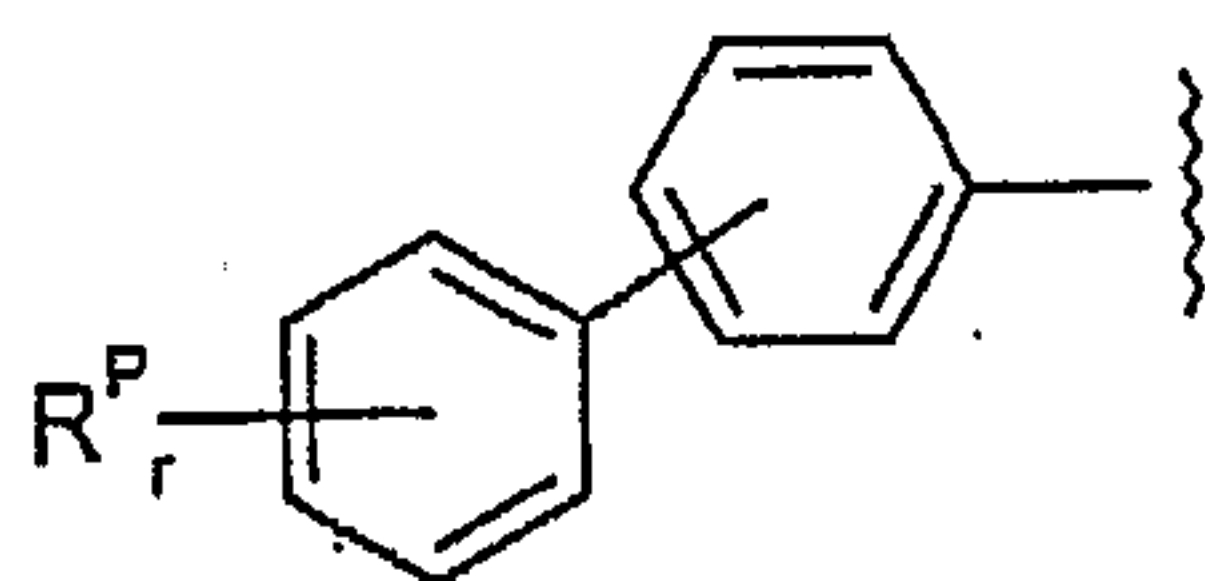
wherein each R^p is independently a phenyl substituent, and p is an integer from 0 to 5.

41. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted biphenyl group of the following formula:



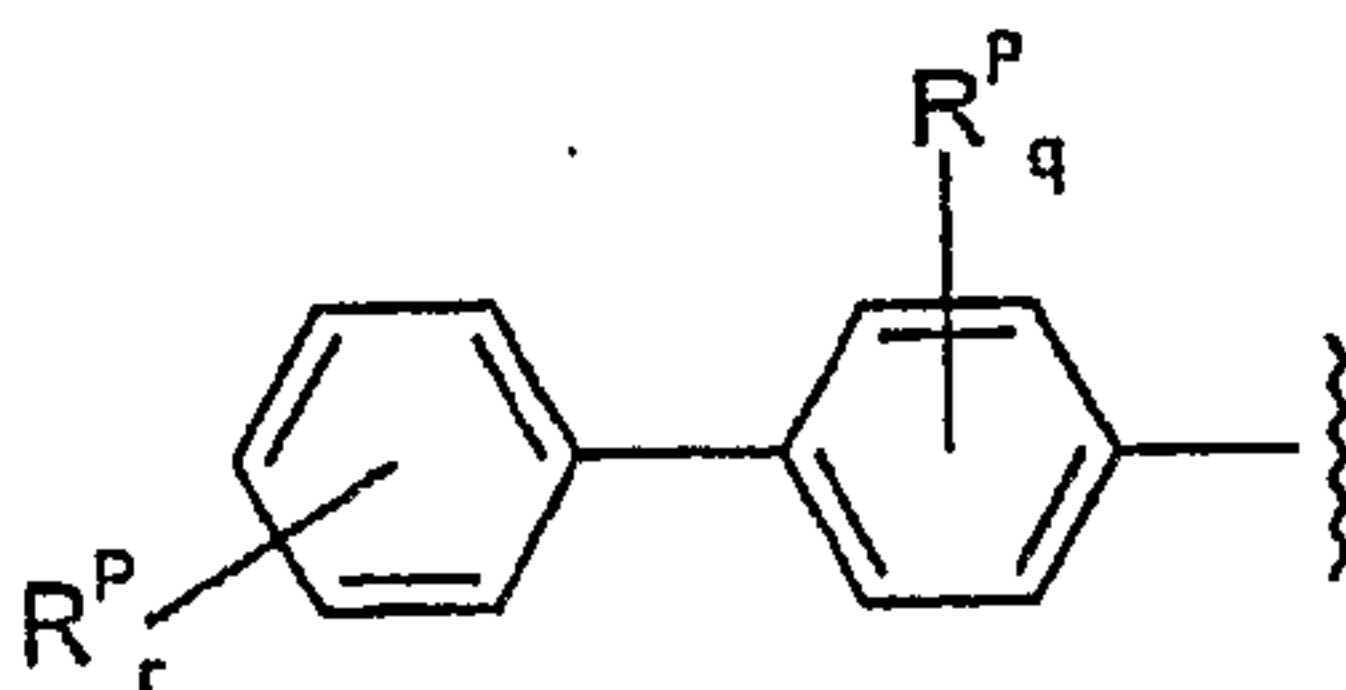
wherein each R^p is independently a phenyl substituent, q is an integer from 0 to 4, and r is an integer from 0 to 5.

42. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted biphenyl group of the following formula:



wherein each R^p is independently a phenyl substituent, and r is an integer from 0 to 5.

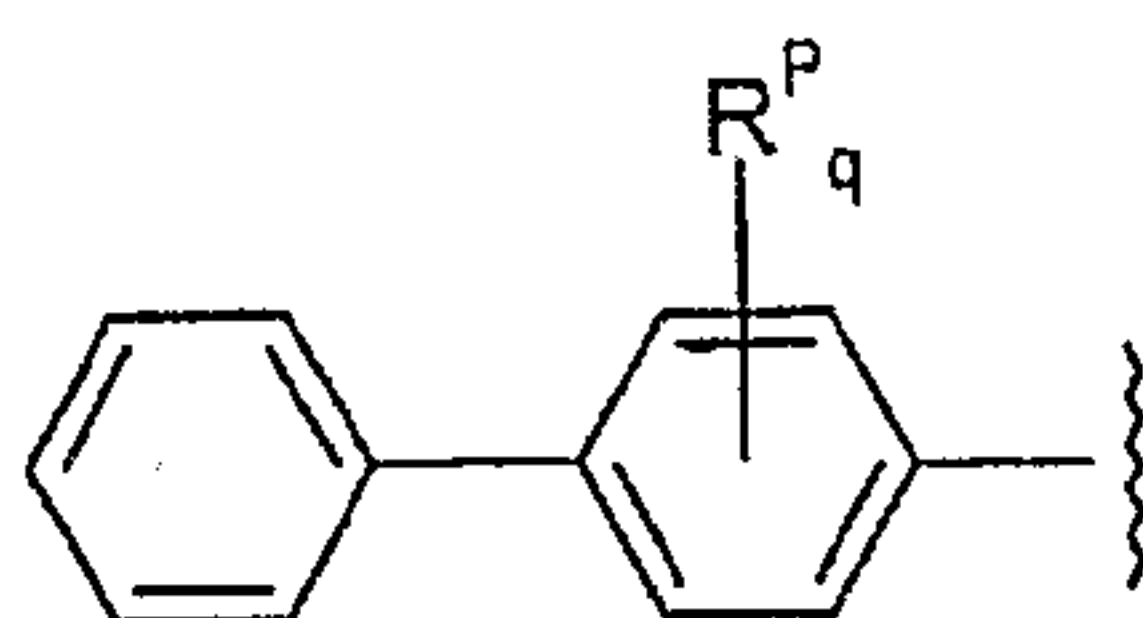
43. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted biphenyl-4-yl group of the following formula:



wherein each R^p is independently a phenyl substituent, q is an integer from 0 to 4, and r is an integer from 0 to 5.

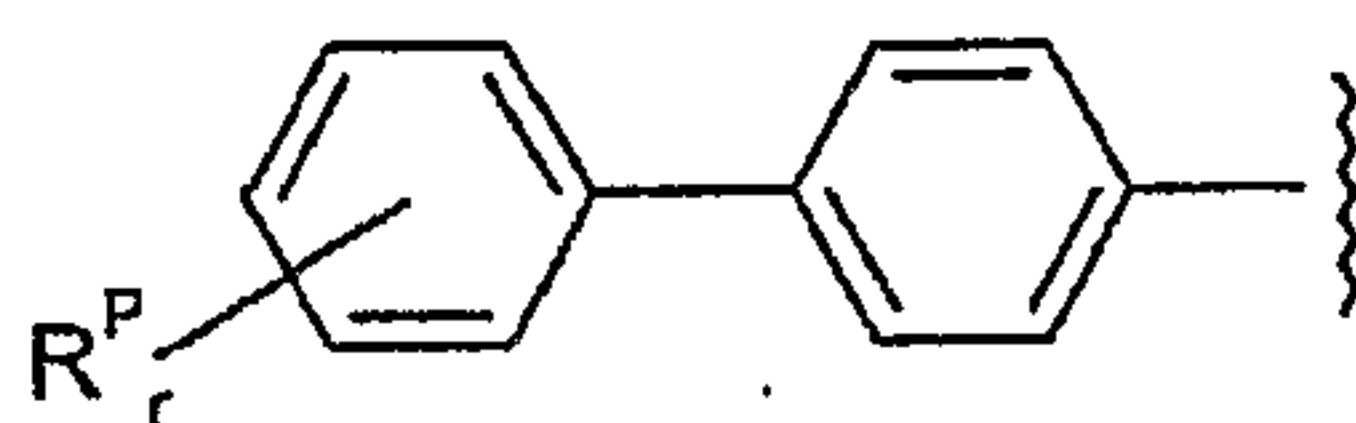
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44. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted biphenyl-4-yl group of the following formula:



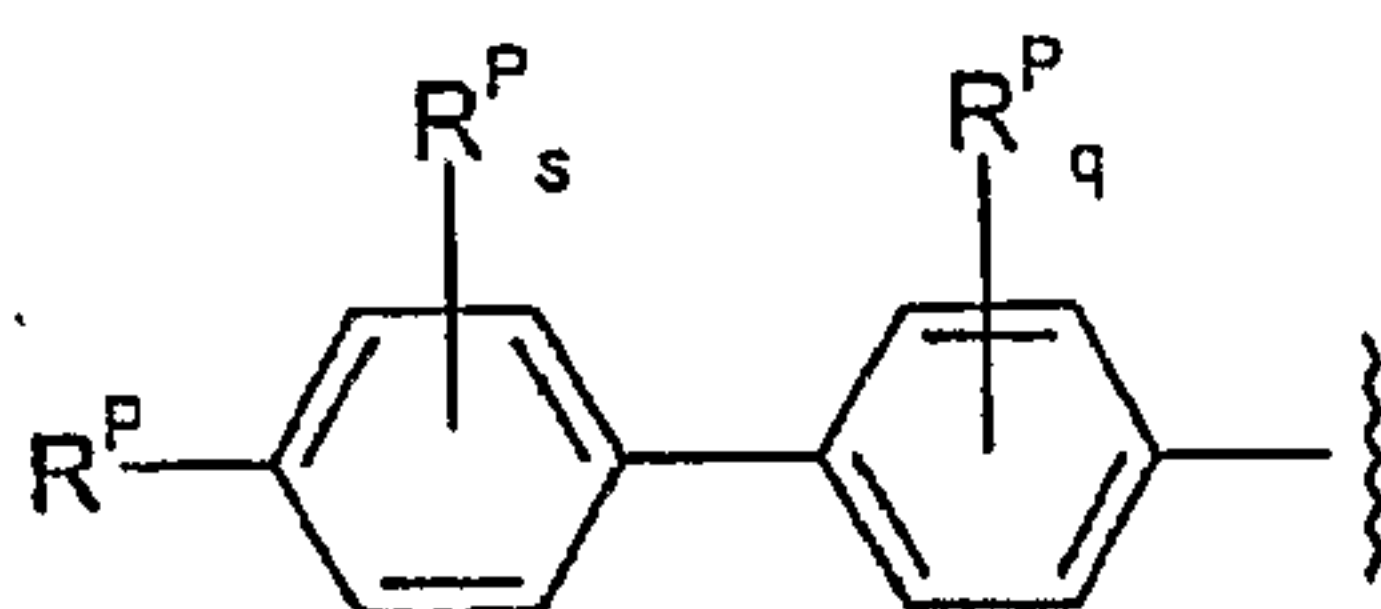
wherein each R^P is independently a phenyl substituent, and q is an integer from 0 to 4.

45. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted biphenyl-4-yl group of the following formula:



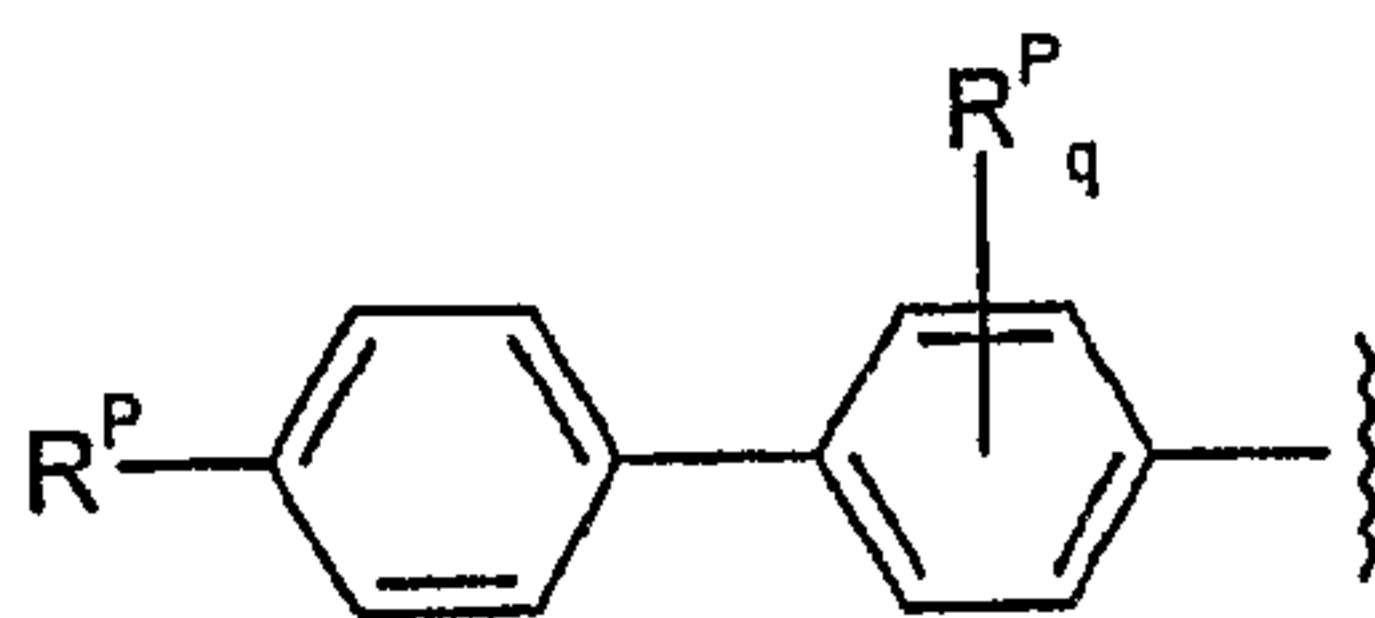
wherein each R^P is independently a phenyl substituent, and r is an integer from 0 to 5.

46. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and s is an integer from 0 to 4.

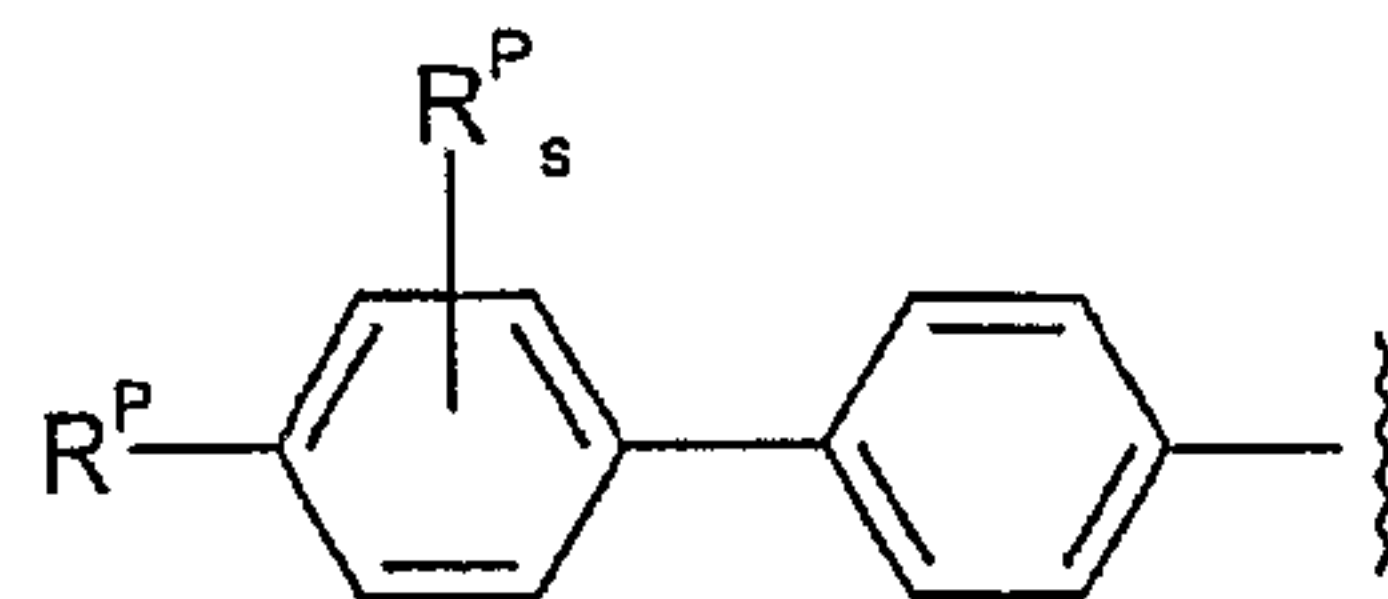
47. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and q is an integer from 0 to 4.

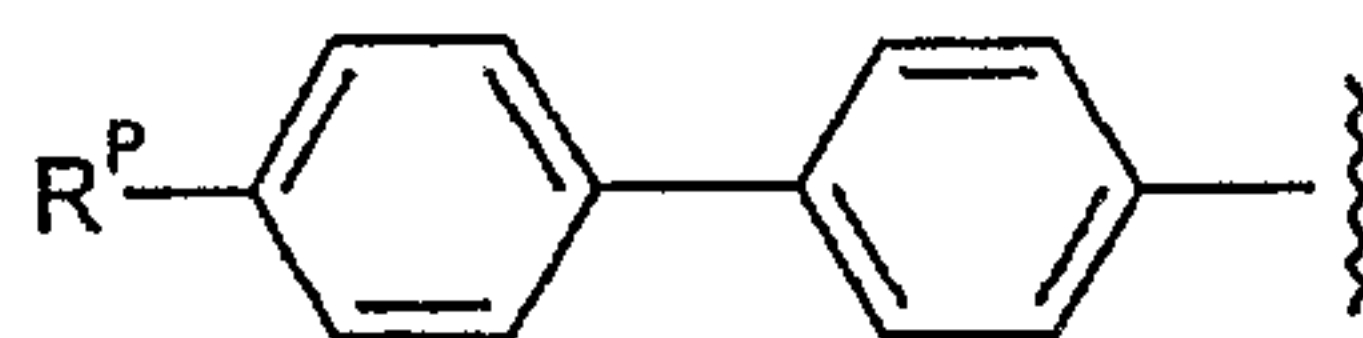
- 166 -

48. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



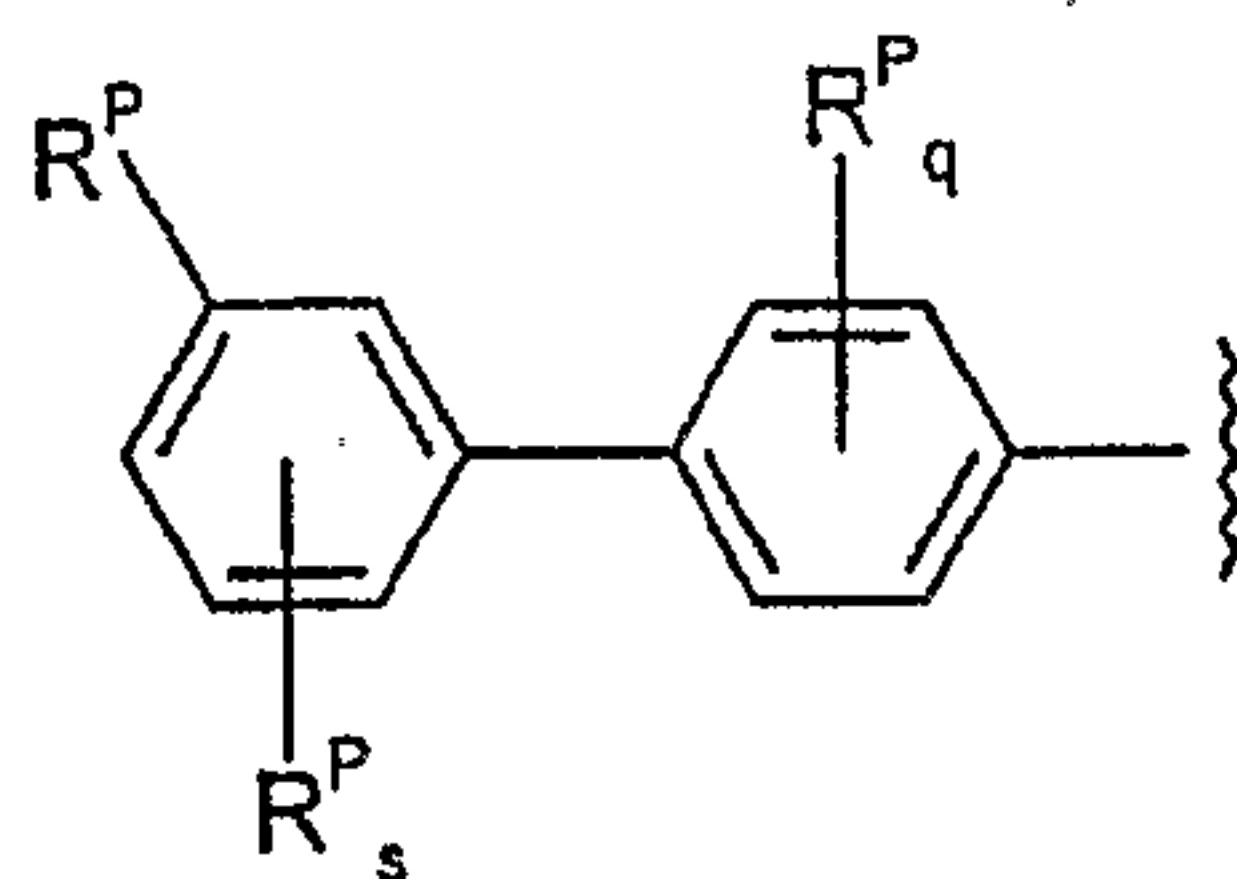
wherein each R^P is independently a phenyl substituent, and s is an integer from 0 to 4.

49. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



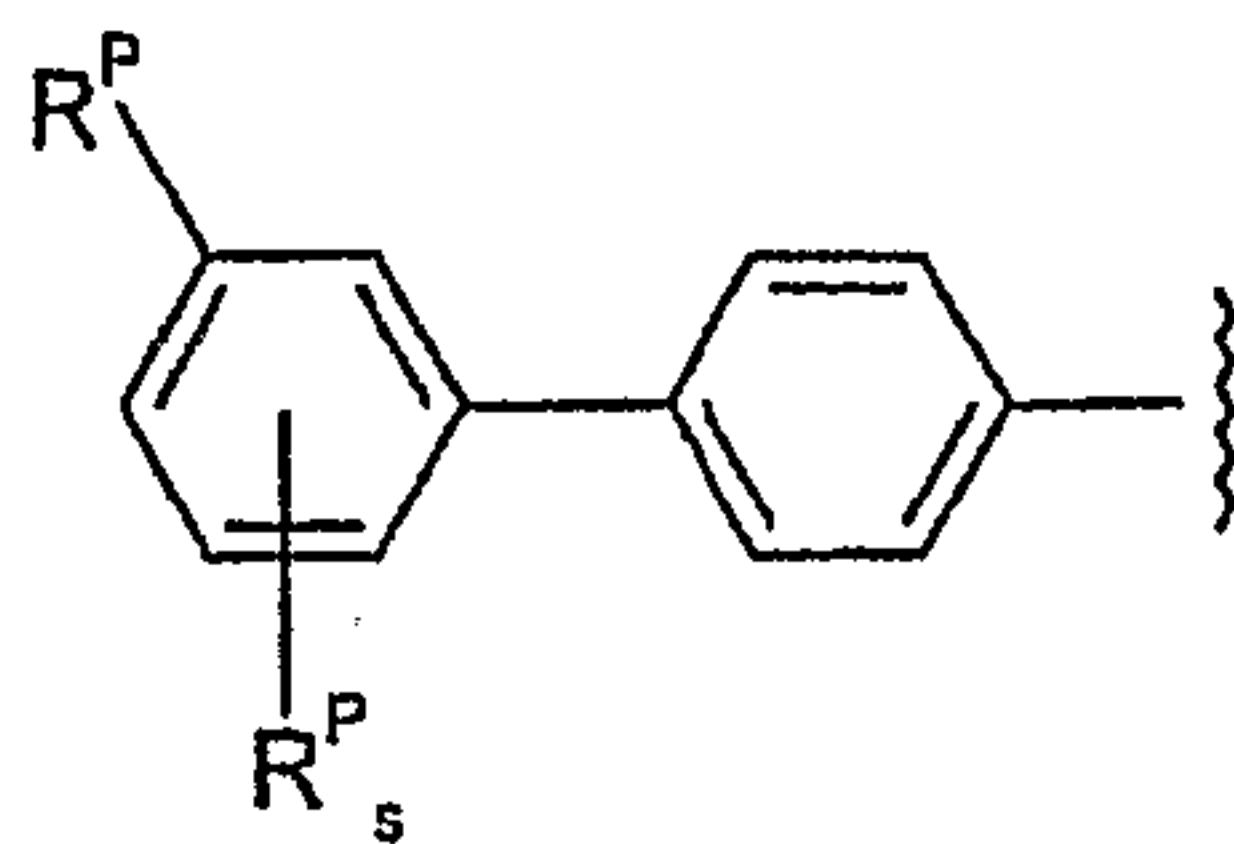
wherein R^P is independently a phenyl substituent.

50. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and s is an integer from 0 to 4.

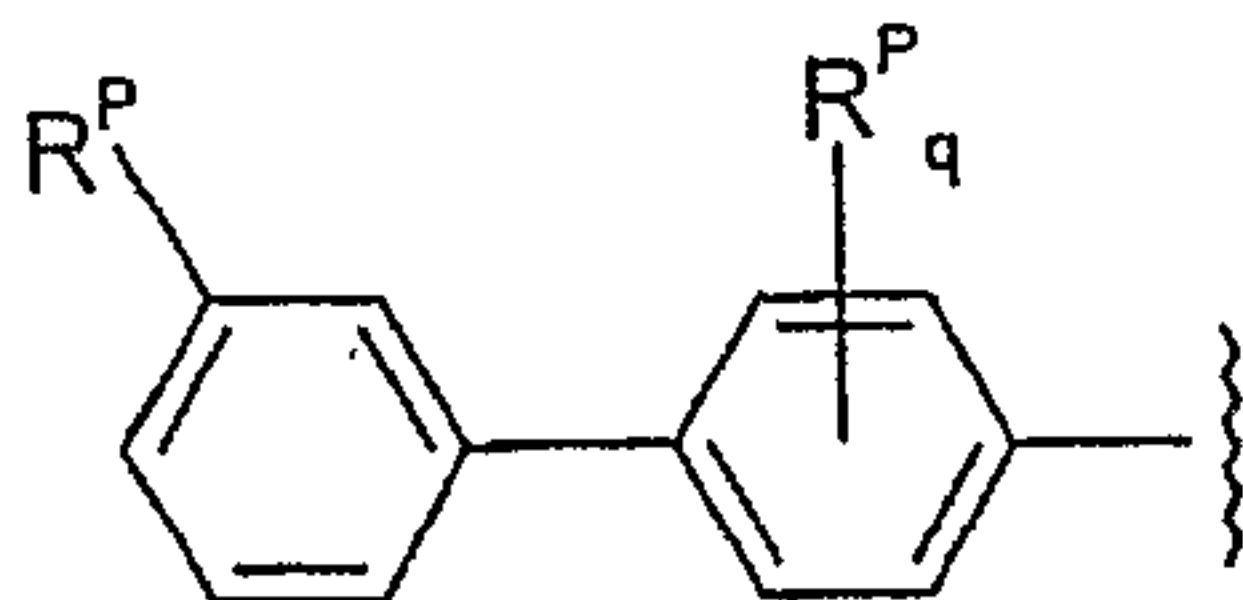
51. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and s is an integer from 0 to 4.

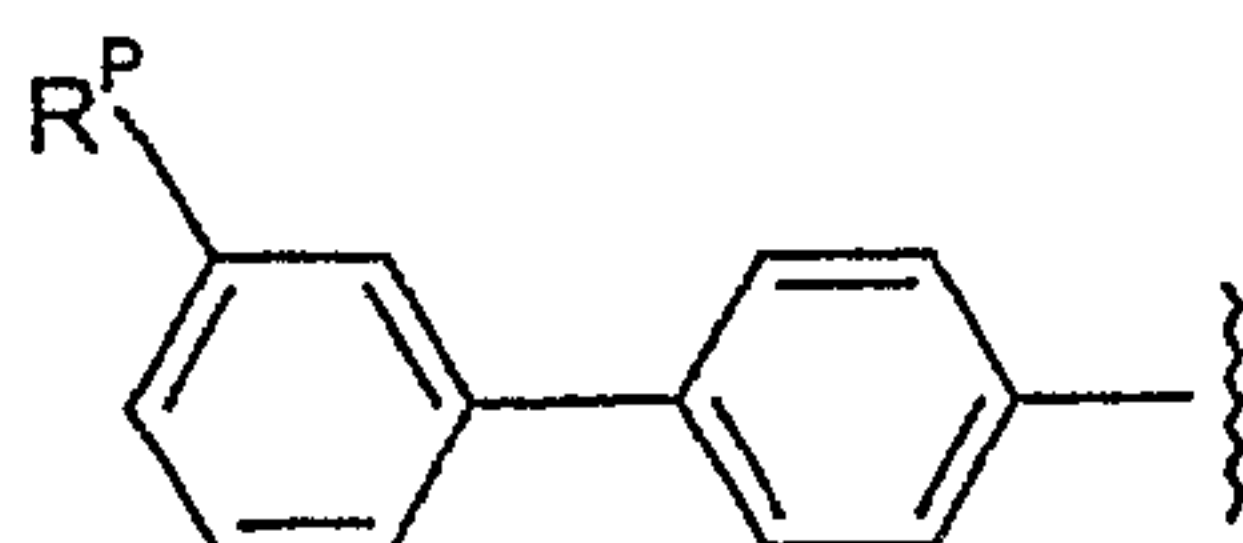
- 167 -

52. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



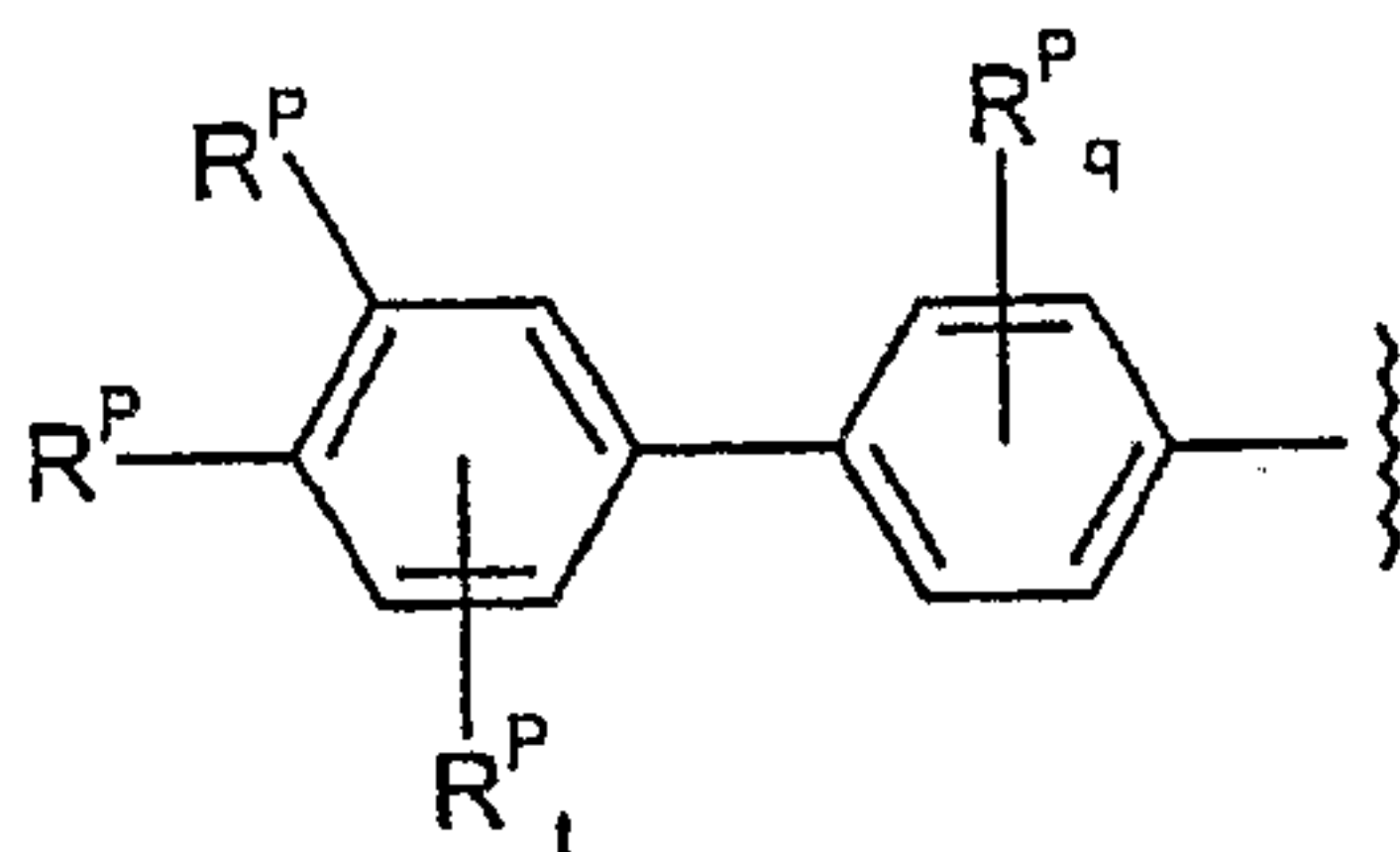
wherein each R^P is independently a phenyl substituent, and q is an integer from 0 to 4.

53. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



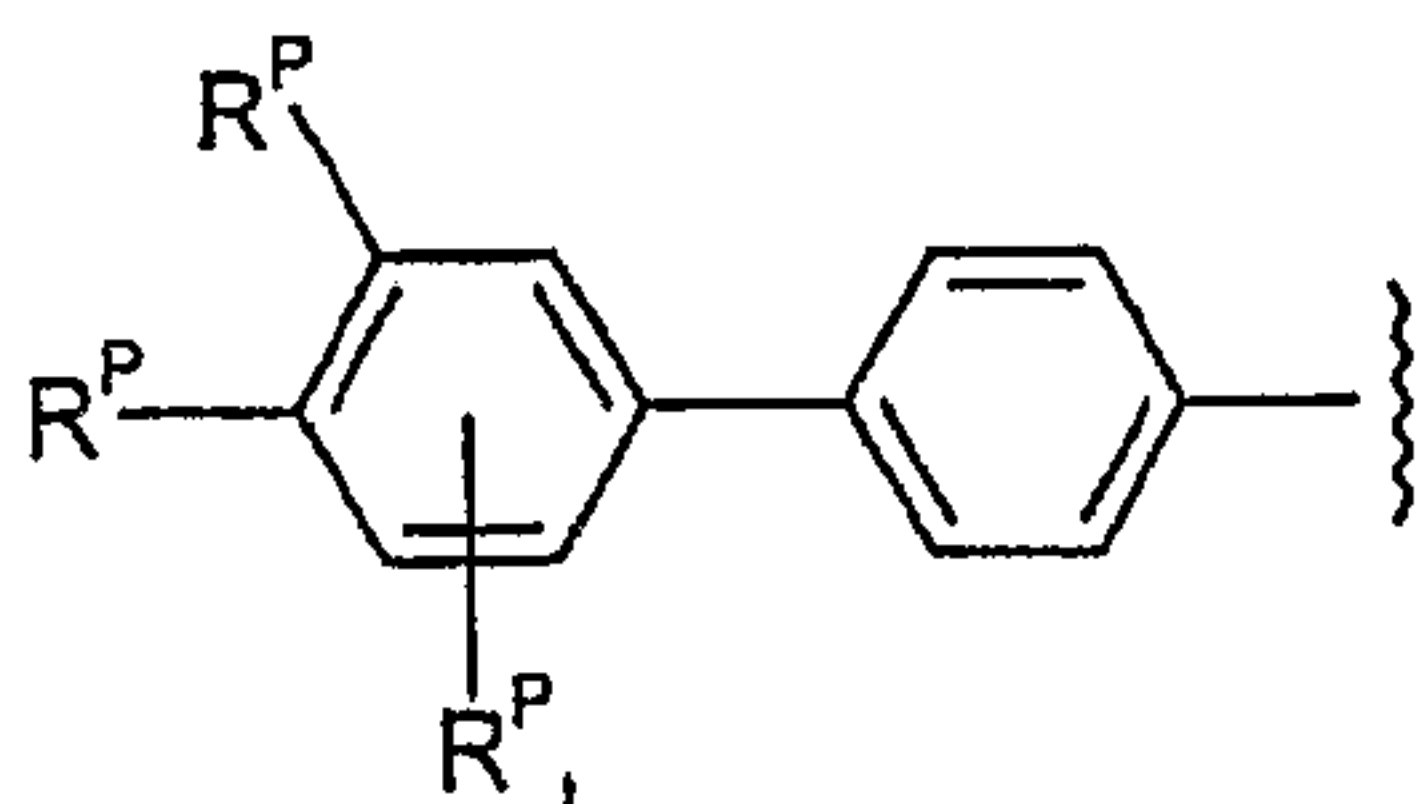
wherein R^P is independently a phenyl substituent.

54. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and t is an integer from 0 to 3.

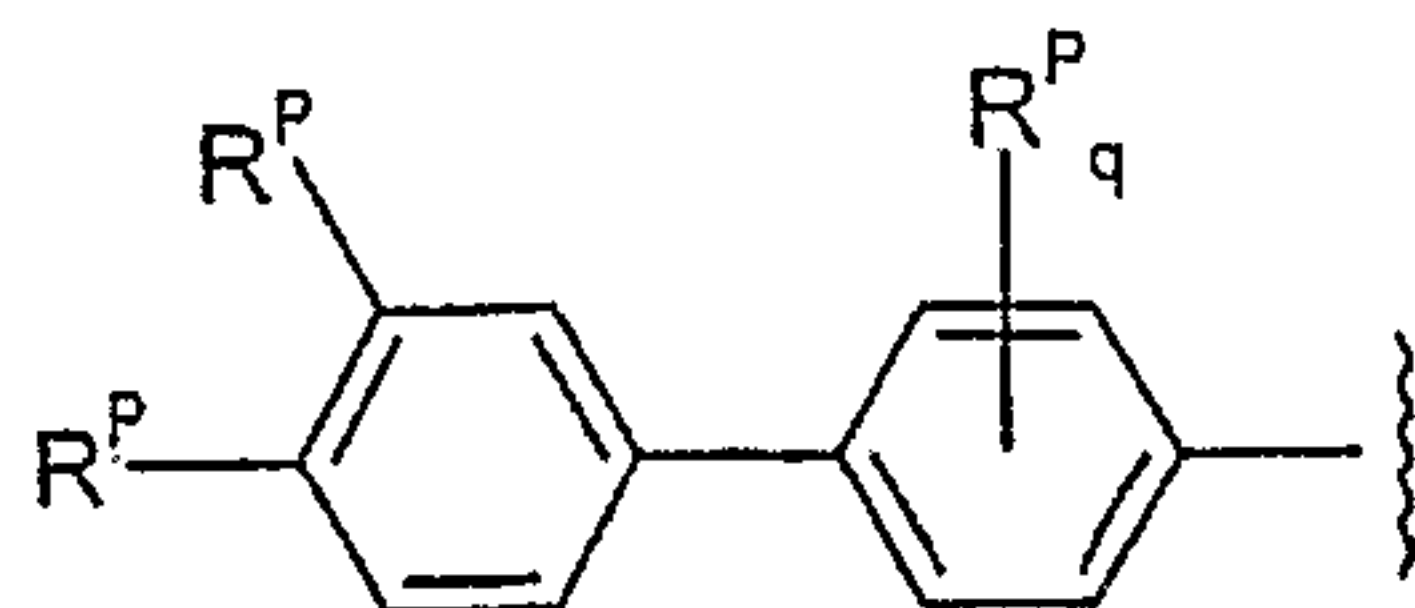
55. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and t is an integer from 0 to 3.

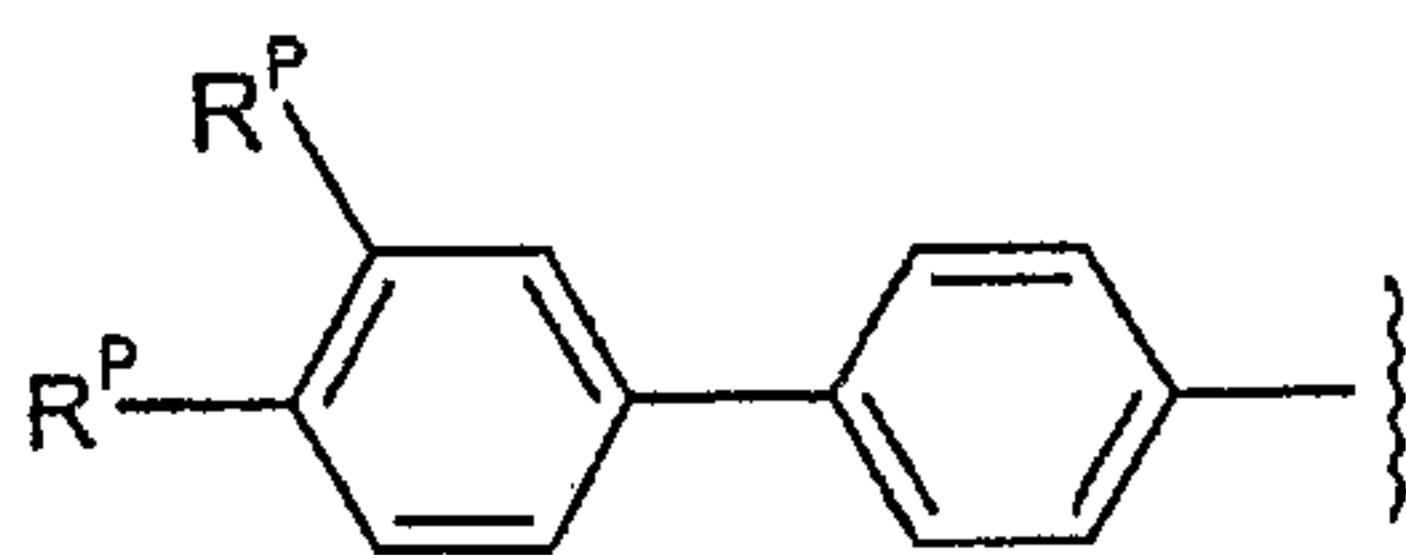
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56. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



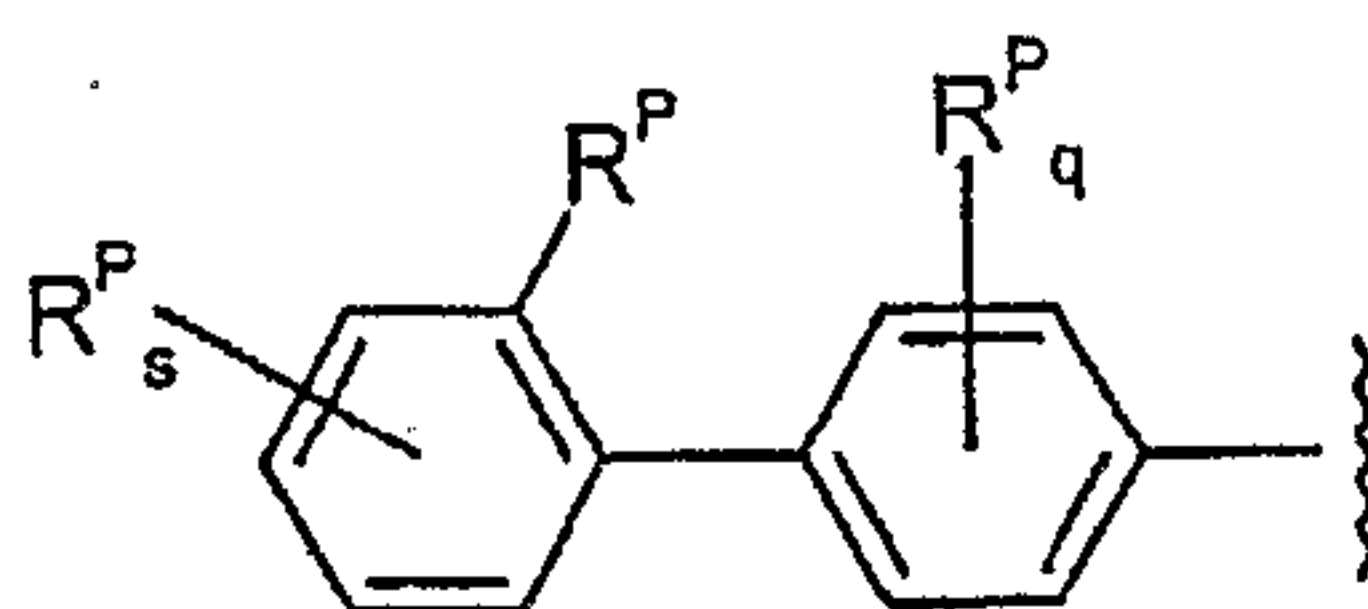
wherein each R^P is independently a phenyl substituent, and q is an integer from 0 to 4.

57. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



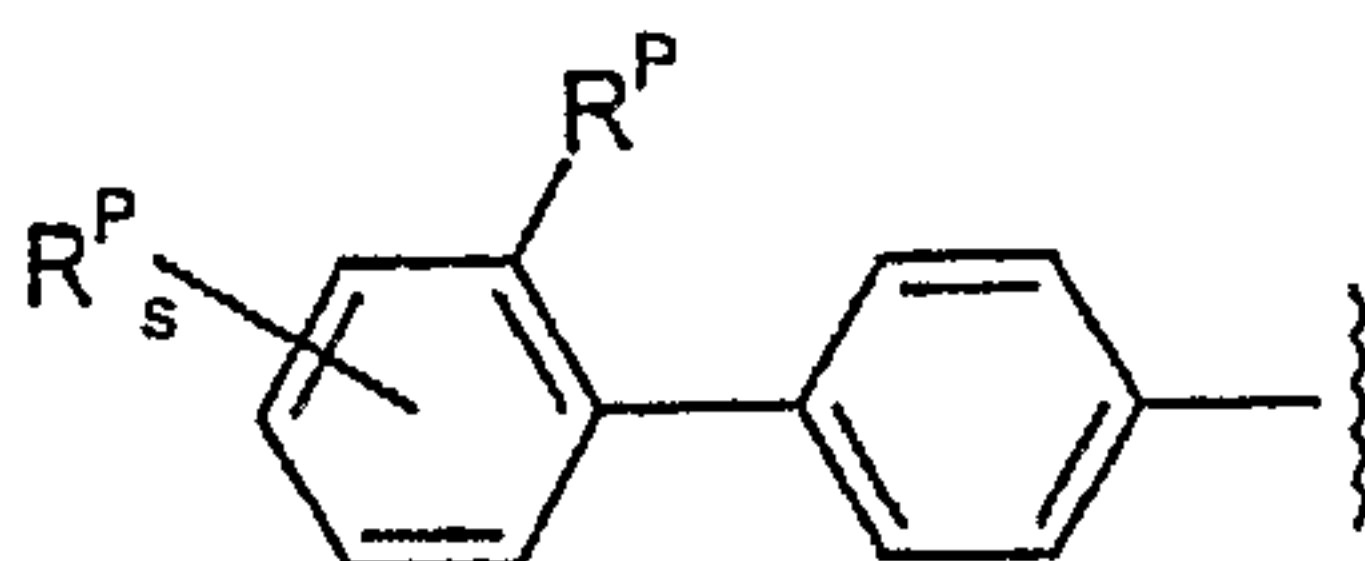
wherein each R^P is independently a phenyl substituent.

58. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and s is an integer from 0 to 4.

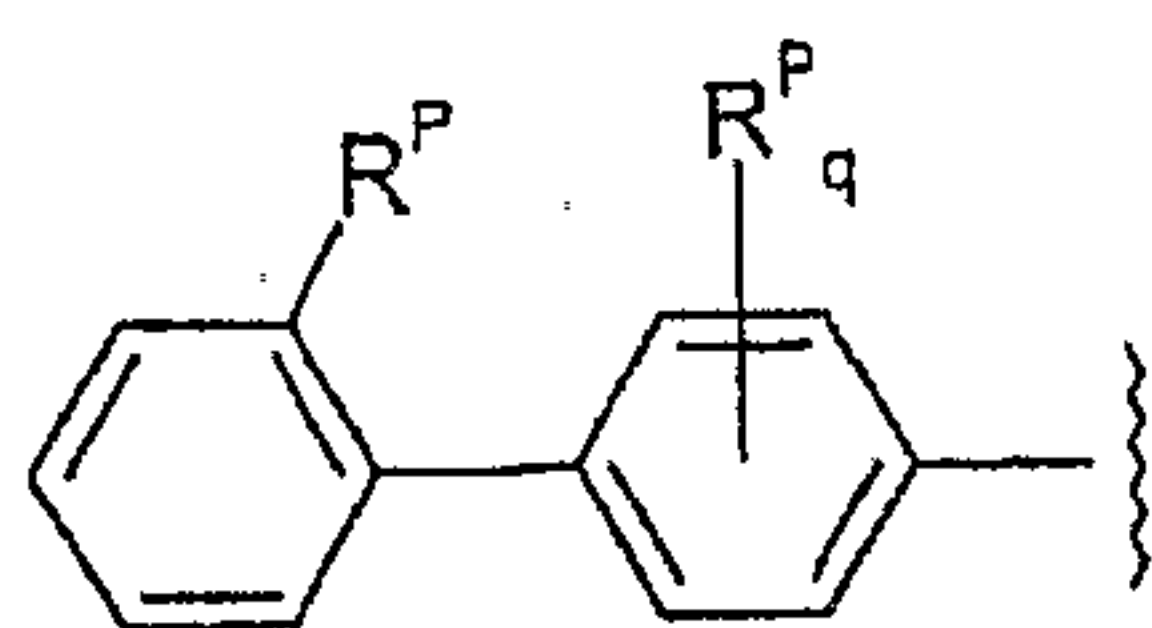
59. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and s is an integer from 0 to 4.

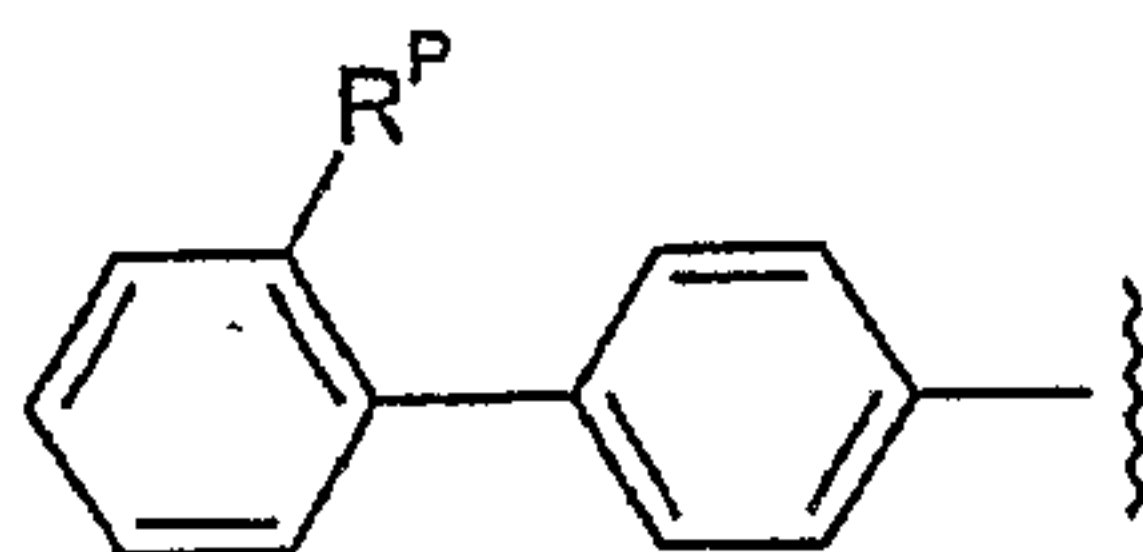
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60. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



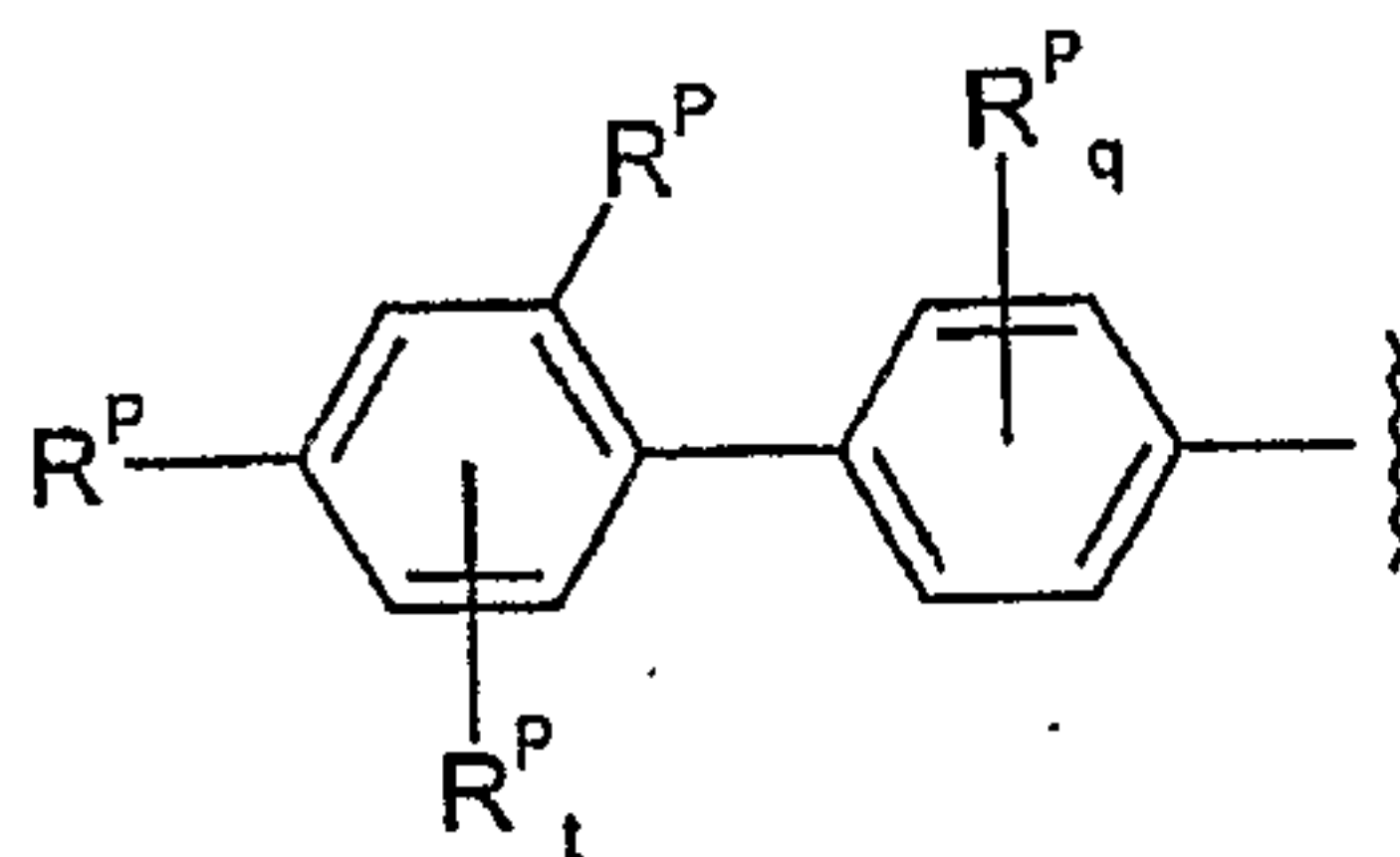
wherein each R^P is independently a phenyl substituent, and q is an integer from 0 to 4.

61. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



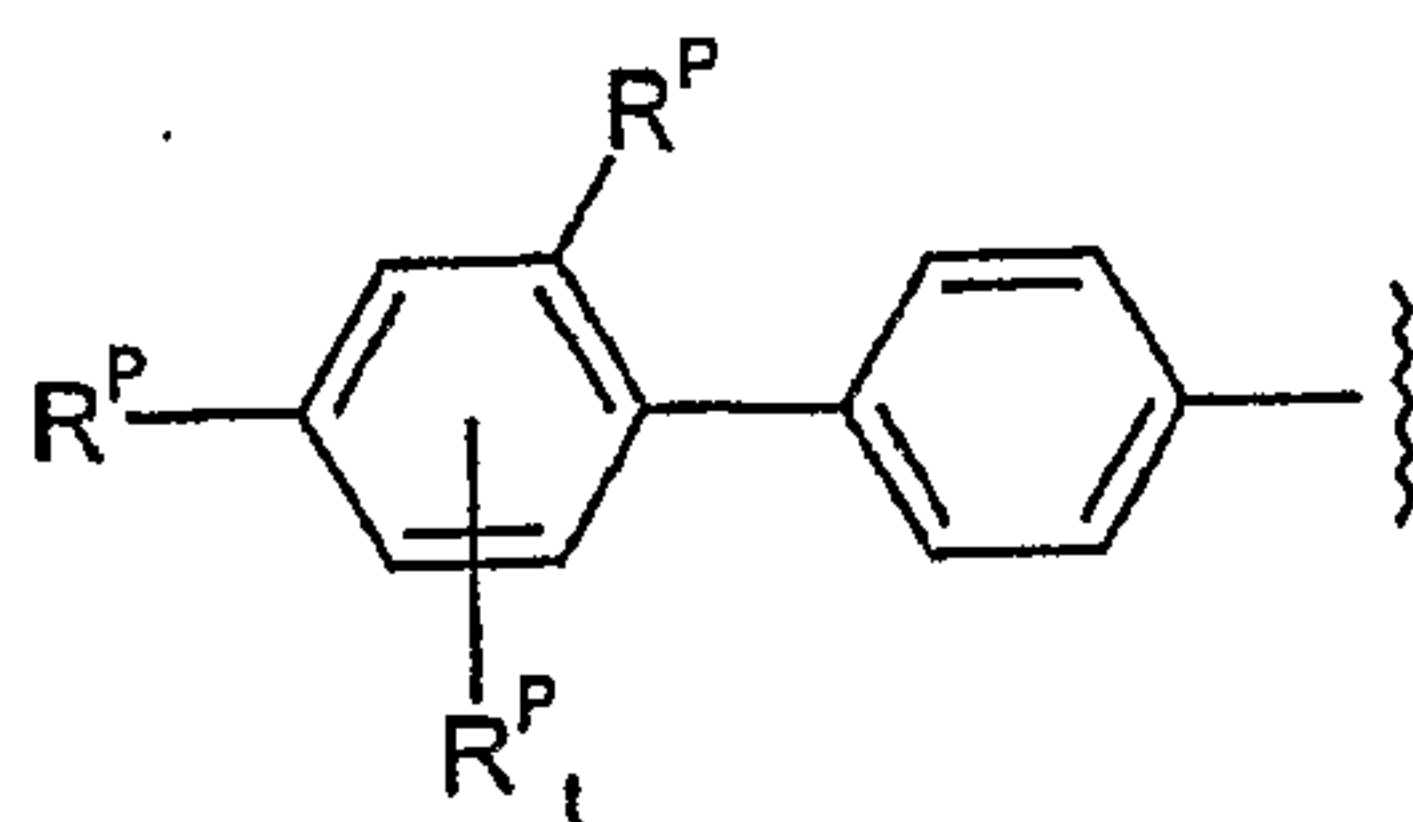
wherein R^P is independently a phenyl substituent.

62. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and t is an integer from 0 to 3.

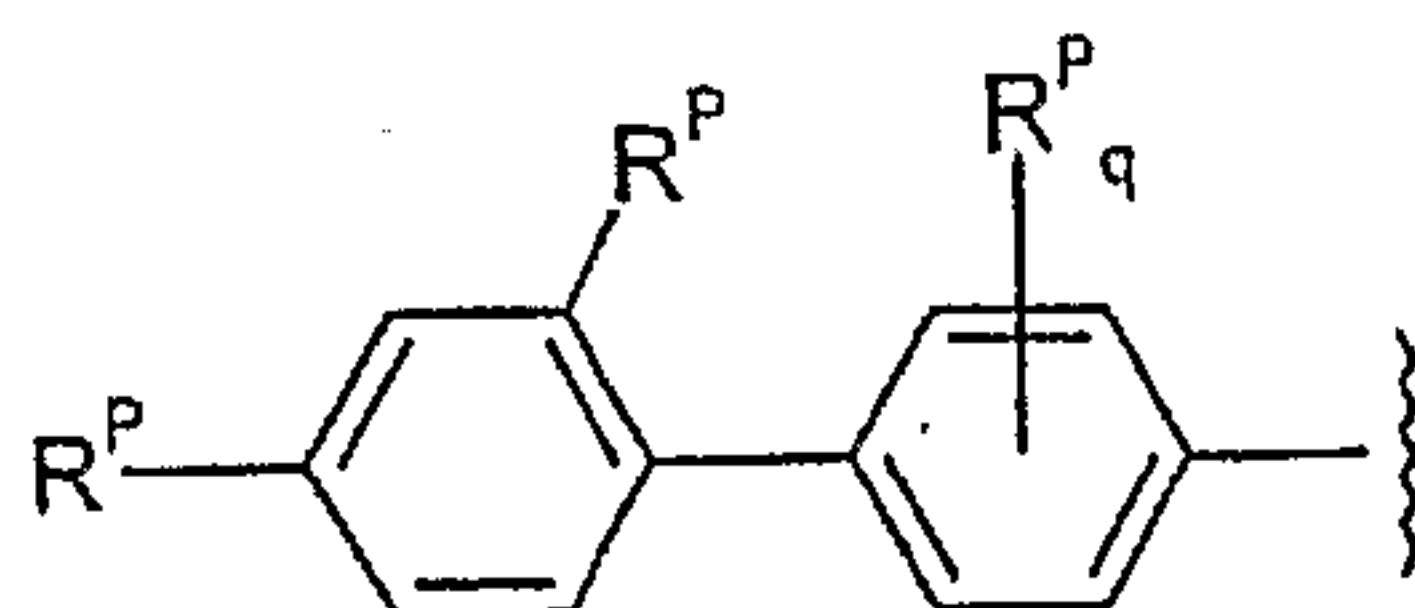
63. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and t is an integer from 0 to 3.

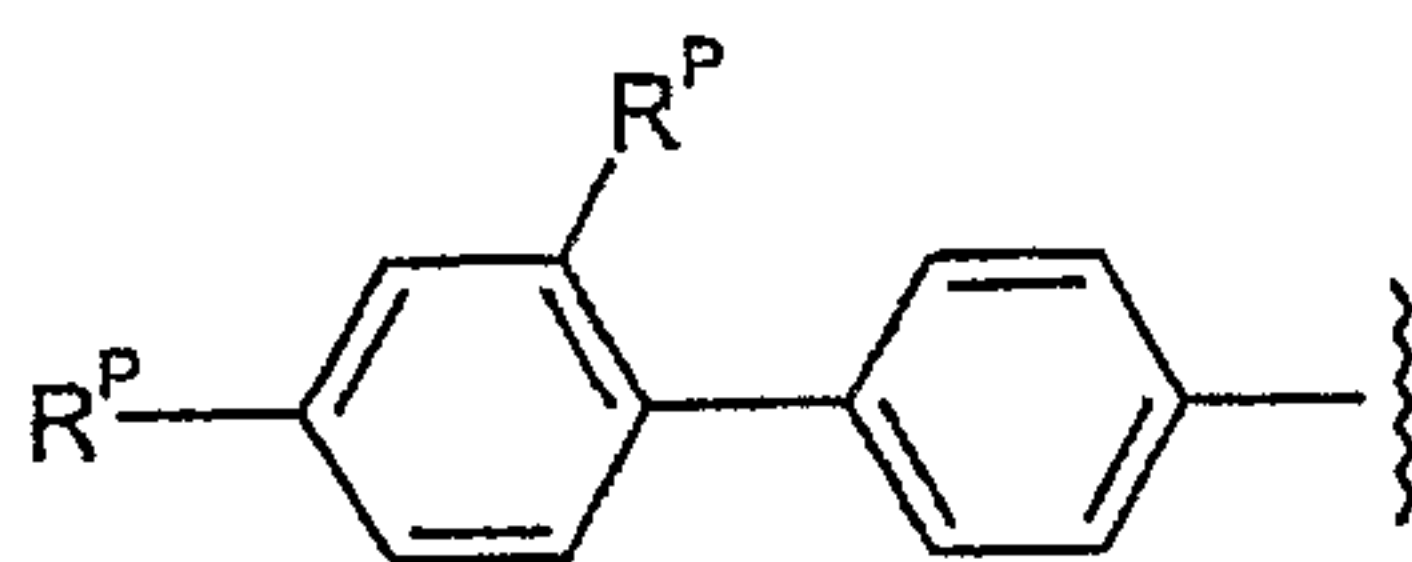
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64. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



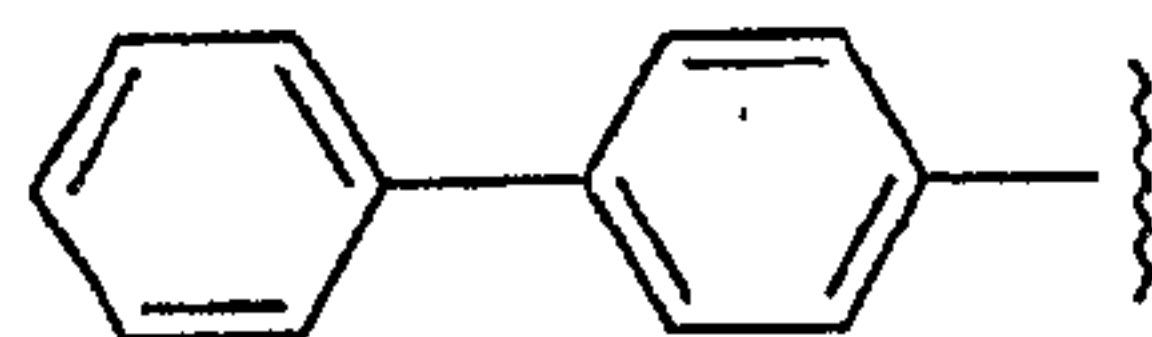
wherein each R^P is independently a phenyl substituent, and q is an integer from 0 to 4.

65. Use according to any one of claims 1 to 33, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent.

66. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an unsubstituted biphenyl-4-yl group of the following formula:



* * *

67. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from:

C_{1-7} alkyl (optionally substituted); C_{3-20} heterocyclyl (optionally substituted); C_{5-20} aryl group (optionally substituted); halo; hydroxy; ether; acyl; carboxy; ester; acyloxy; amido; acylamido; amino; nitro; cyano; and, sulfonate.

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68. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from:

-Me, -Et, -iPr, -nPr, -tBu;
-Ph;
-F, -Cl, -Br, -I;
-OH;
-OMe, -OEt, -O(iPr), -O(nPr), -O(tBu), -OPh, -OBn;
-C(=O)OH;
-C(=O)OMe, -C(=O)OEt, -C(=O)O(tBu), -C(=O)OPh;
-OC(C=O)Me, -OC(C=O)Et, -OC(C=O)(tBu), -OC(C=O)Ph;
-OC(C=O)OMe, -OC(C=O)OEt, -OC(C=O)O(tBu), -OC(C=O)OPh;
-C(=O)NH₂, -C(=O)NHMe, -C(=O)NMe₂, -C(=O)NHPh;
-NHC(=O)Me, -NHC(=O)Et, -NHC(=O)Ph;
-NH₂, -NHMe, -NMe₂, -NH₂Et, -NEt₂;
-NO₂;
-CN; and,
-S(=O)₂OMe, -S(=O)₂OEt, -S(=O)₂OPh.

69. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from: -Me, -F, -Cl, -Br, -I, -OH, -OMe, -NH₂, -NMe₂, -NO₂, and -CN.

70. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from: -Me, -F, -Cl, -OH, -OMe, -NH₂, -NMe₂, -NO₂, and -CN.

71. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from: -F, -Cl, -Br, -I, -NO₂, and -OH.

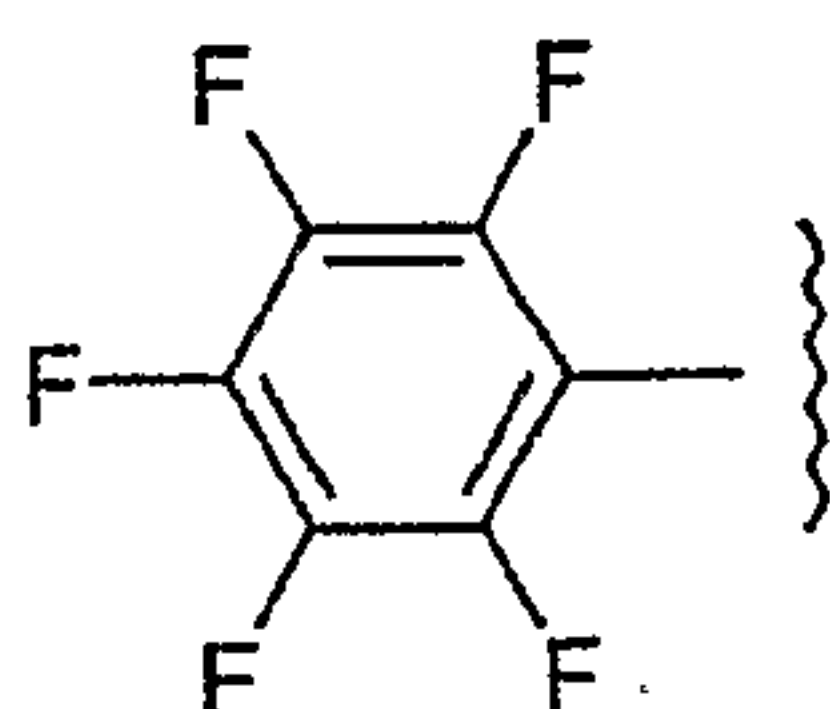
72. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from: -F, -Cl, -Br, and -I, -NO₂.

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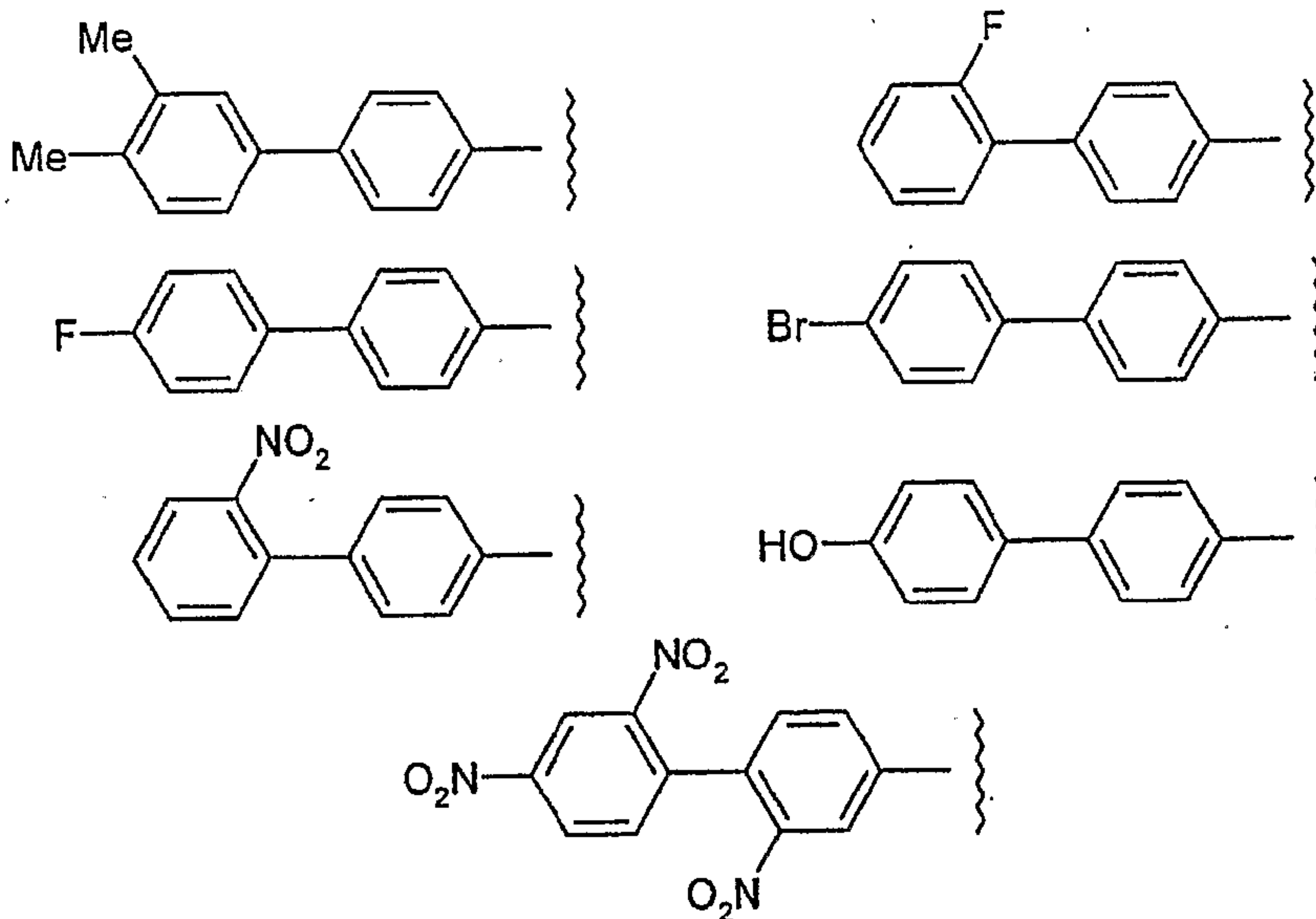
73. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from: -F, -Cl, -Br, -I.

74. Use according to any one of claims 40 to 65, wherein each of the phenyl substituents, R^P , is independently selected from: -F and -Br.

75. Use according to any one of claims 1 to 33, wherein R^{A1} is independently:



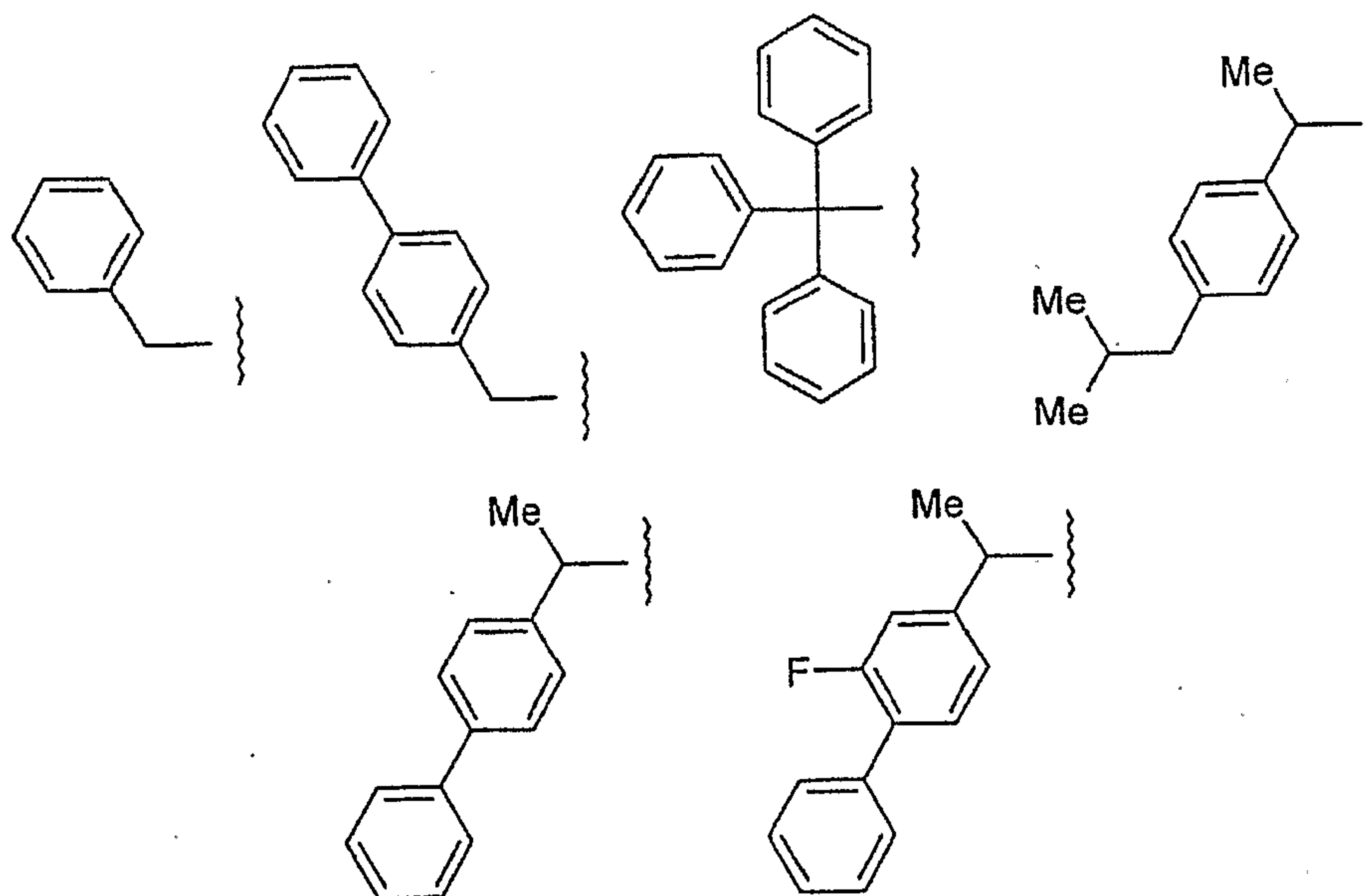
76. Use according to any one of claims 1 to 33, wherein R^{A1} is independently selected from the following:



* * *

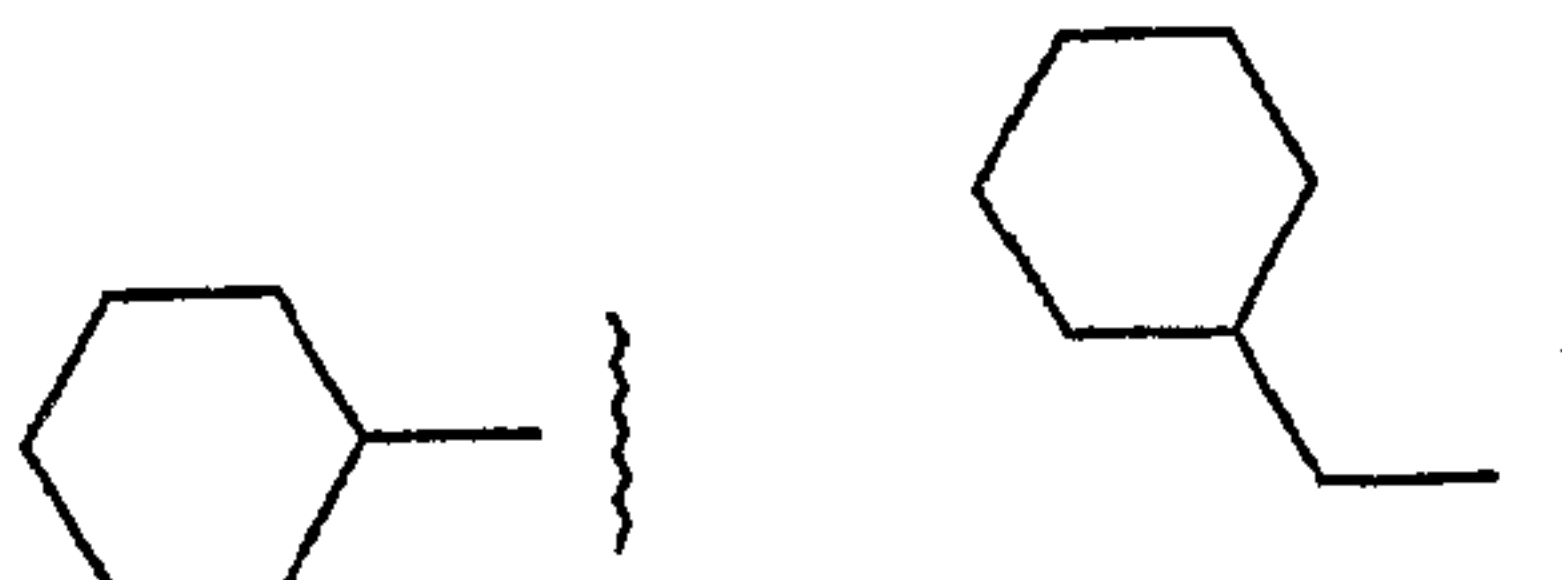
77. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted C_{5-20} aryl- C_{1-7} alkyl group.

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* * *

80. Use according to any one of claims 1 to 33, wherein R^{A1} is independently an optionally substituted C₃₋₇cycloalkyl or optionally substituted C₃₋₇cycloalkyl-C₁₋₇alkyl.
81. Use according to any one of claims 1 to 33, wherein R^{A1} is independently selected from:



* * *

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82. Use according to claim 1, wherein the compound is selected from the following compounds, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:

ABD-0006 (4A);
ABD-0007 (4BU);
ABD-0019 (4C);
ABD-0009 (4B);
ABD-0014 (4P);
ABD-0017 (6P);
ABD-0085 (10F);
ABD-0111 (D2,4FB);
ABD-0096 (DBP-4F);
ABD-0049 (4BP-acetate);
ABD-0008 (4MB);
ABD-0069 (4IB);
ABD-0077 (4FB);
ABD-0106 (2,3,6-FB);
ABD-0107 (3,4-FB);
ABD-0108 (2,3,4-FB);
ABD-0109 (2,4,5-FB);
ABD-0110 (2,4-FB);
ABD-0037 (3I);
ABD-0036 (4I);
ABD-0038 (5I);
ABD-0039 (6I);
ABD-0034 (4PT);
ABD-0059 (4BPX);
ABD-0057 (3BP);
ABD-0056 (4BP);
ABD-0055 (5BP);
ABD-0054 (6BP);
ABD-0095 (BP-4F);

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ABD-0070 (Me4BP);
ABD-0072 (HO4BP);
ABD-0089 (Xy4BP);
ABD-0094 (Et4BP);
ABD-0097 (4-OMeBP);
ABD-0098 (2-NO₂BP);
ABD-0099 (2-FBP);
ABD-0100 (4-FBP);
ABD-0102 (4-BrBP);
ABD-0028 (4T);
ABD-0030 (5T);
ABD-0031 (6T);
ABD-0041 (3BPA);
ABD-0042 (4BPA);
ABD-0043 (5BPA);
ABD-0044 (6BPA);
ABD-0032 (4N);
ABD-0033 (4H);
ABD-0035 (BuI);
ABD-0040 (BuBPA);
ABD-0053 (BuBP);
ABD-0090 (PBP);
ABD-0050 (4BP-OMe);
ABD-0086 (4BP-Br);
ABD-0087 (4BP-NO₂); and
ABD-0088 (4xNO₂-BP).

* * *

83. Use according to any one of claims 1 to 82, wherein the condition is a condition mediated by osteoclasts.

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84. Use according to any one of claims 1 to 82, wherein the condition is a condition characterised by bone resorption.
85. Use according to any one of claims 1 to 82, wherein the condition is osteoporosis, rheumatoid arthritis, cancer associated bone disease, or Paget's disease.

* * *

86. Use of a compound for the manufacture of a medicament for use in the treatment of a condition associated with inflammation or activation of the immune system, wherein the compound is a compound as described in any one of claims 1 to 82.

* * *

87. A method of inhibiting osteoclast survival, formation, and activity, *in vitro* or *in vivo*, comprising contacting an osteoclast with an effective amount of a compound as described in any one of claims 1 to 82.
88. A method of inhibiting bone resorption, *in vitro* or *in vivo*, comprising contacting cells in the bone microenvironment with a therapeutically-effective amount of a compound as described in any one of claims 1 to 82.
89. A method for the treatment of a condition mediated by osteoclasts and/or characterised by bone resorption, comprising administering to a subject suffering from said condition a therapeutically-effective amount of a compound as described in any one of claims 1 to 82.

* * *

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90. A method for the treatment of a condition associated with inflammation or activation of the immune system, comprising administering to a subject suffering from said condition a therapeutically-effective amount of a compound as described in any one of claims 1 to 82.

* * *

91. A compound as described in any one of claims 1 to 82, for use in a method of treatment of the human or animal body by therapy.

* * *

92. A compound as described in any one of claims 1 to 82, for use in a method of treatment a condition mediated by osteoclasts and/or characterised by bone resorption of the human or animal body by therapy.

93. A compound as described in any one of claims 1 to 82, for use in a method of treatment a condition mediated by osteoclasts of the human or animal body by therapy.

94. A compound as described in any one of claims 1 to 82, for use in a method of treatment a condition characterised by bone resorption of the human or animal body by therapy.

95. A compound as described in any one of claims 1 to 82, for use in a method of treatment of osteoporosis, rheumatoid arthritis, cancer associated bone disease, or Paget's disease of the human or animal body by therapy.

* * *

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96. A compound as described in any one of claims 1 to 82, for use in a method of treatment a condition associated with inflammation or activation of the immune system of the human or animal body by therapy.

* * *

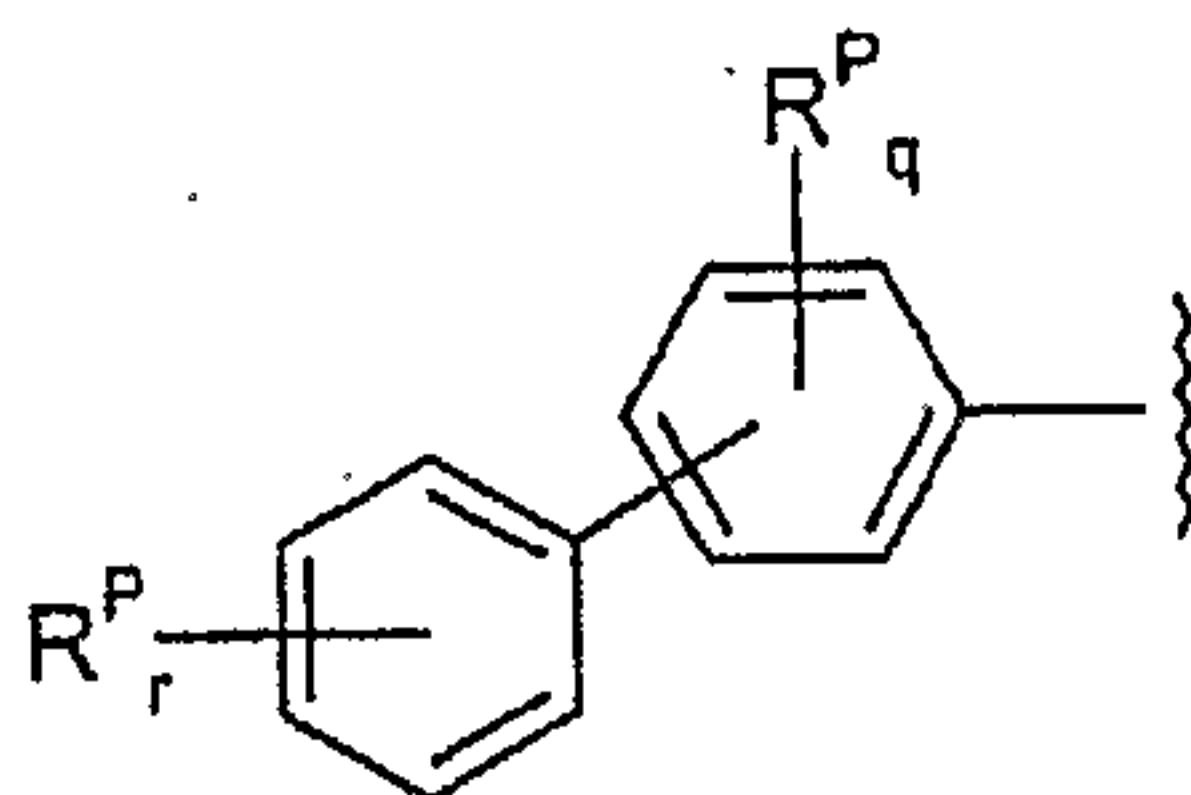
97. A compound selected from compounds of the following formula:



wherein:

A is a C₂₋₁₀alkylene group;

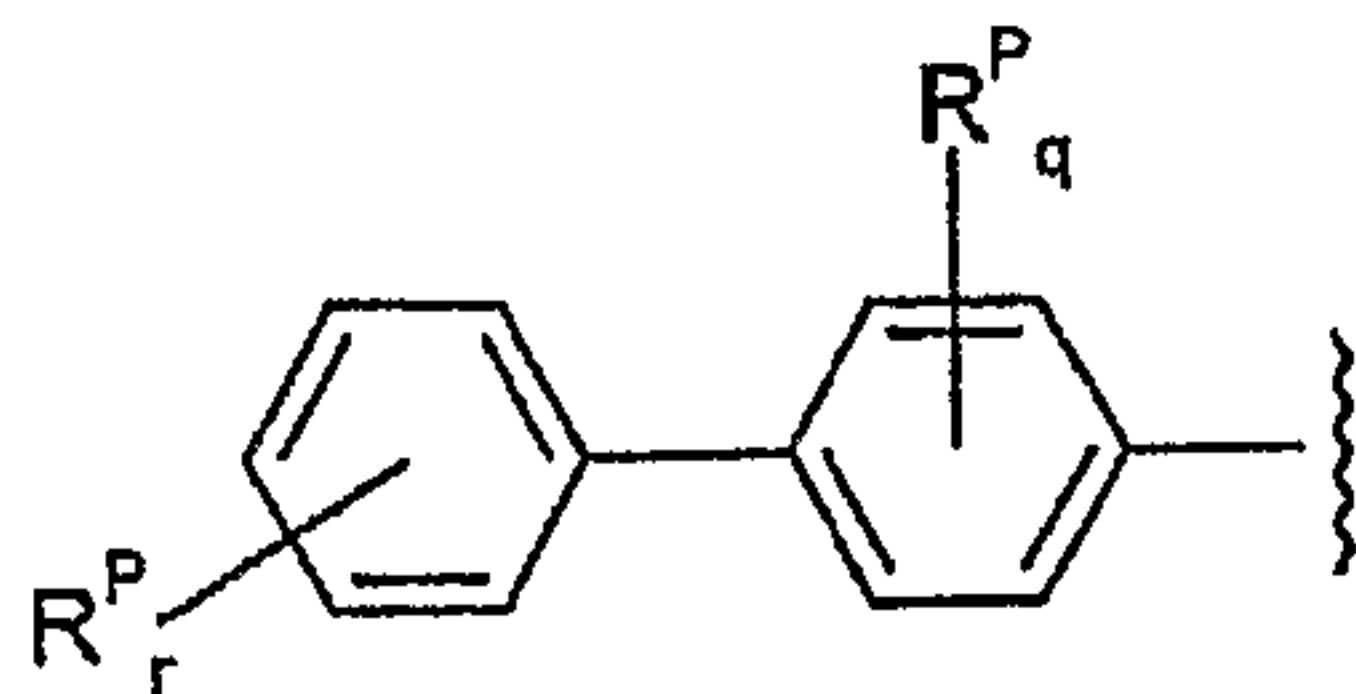
R^{A1} is independently an optionally substituted biphenyl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and r is an integer from 0 to 5;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

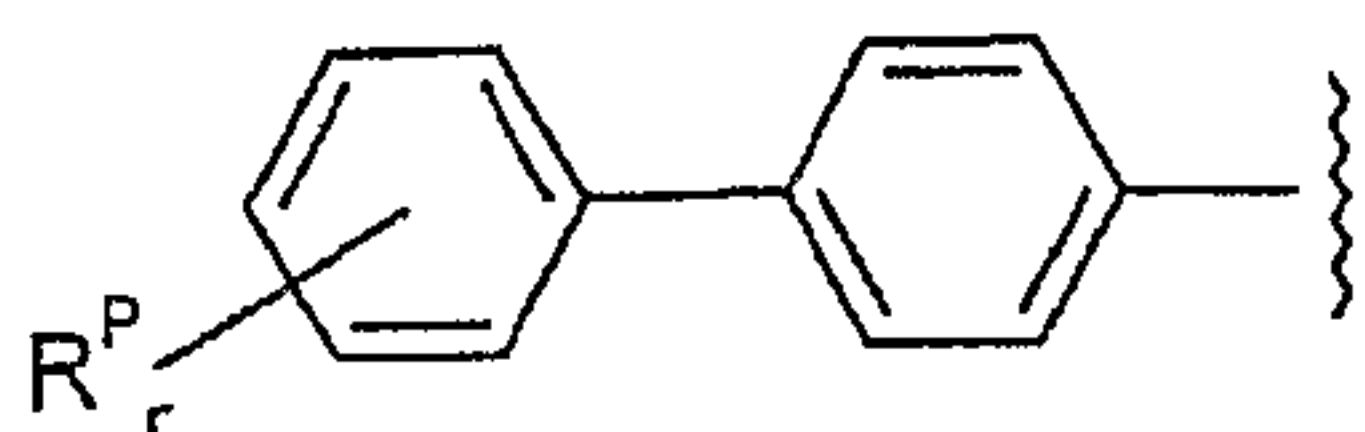
98. A compound according to claim 97, wherein R^{A1} is independently an optionally substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, q is an integer from 0 to 4, and r is an integer from 0 to 5.

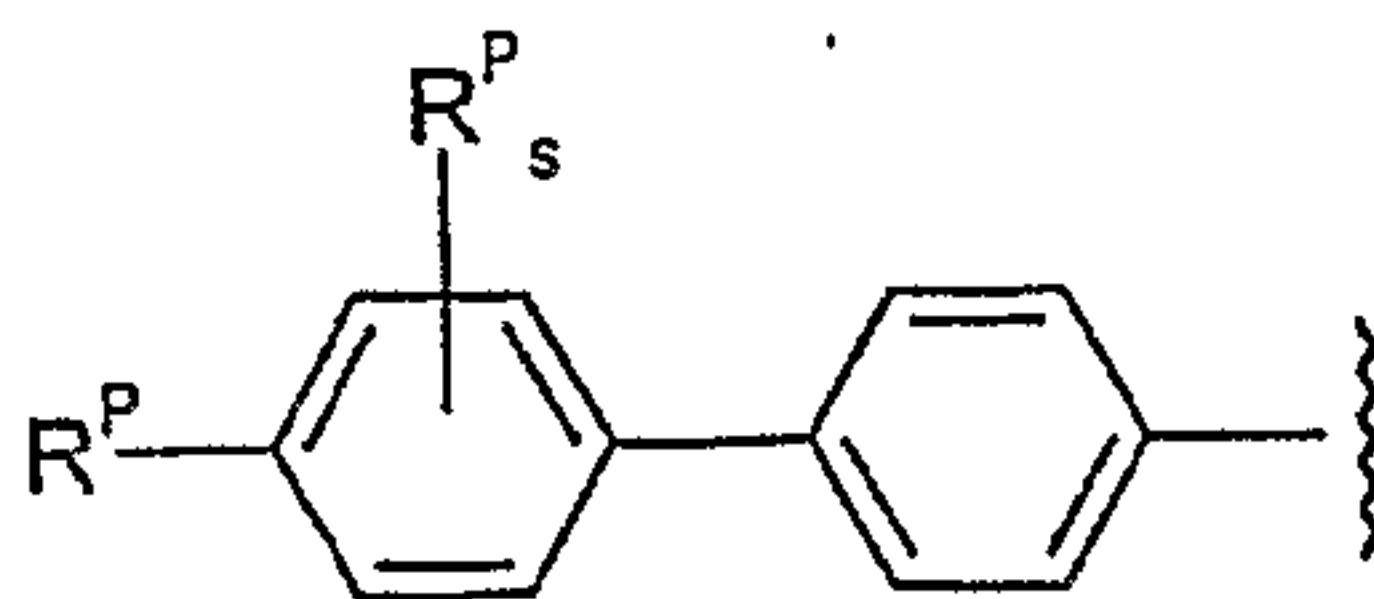
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99. A compound according to claim 97, wherein R^{A1} is independently an optionally substituted biphenyl-4-yl group of the following formula:



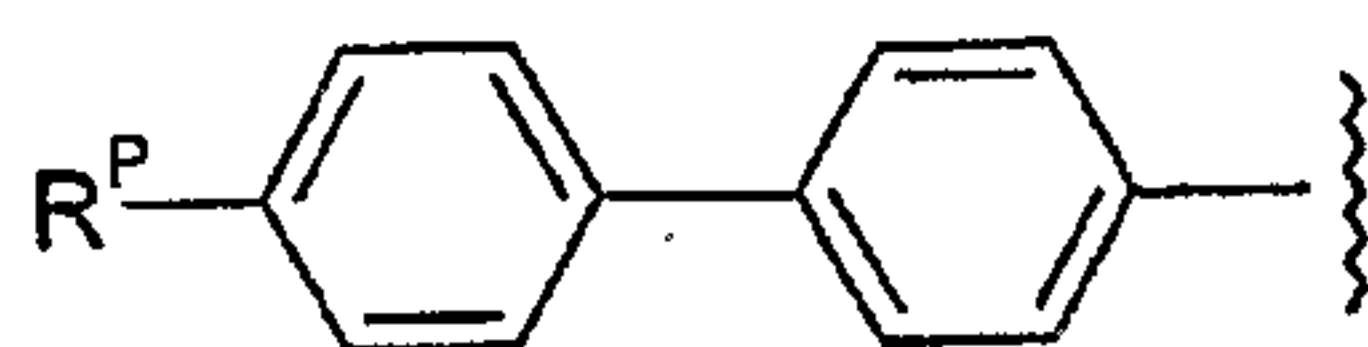
wherein each R^P is independently a phenyl substituent, and r is an integer from 0 to 5.

100. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



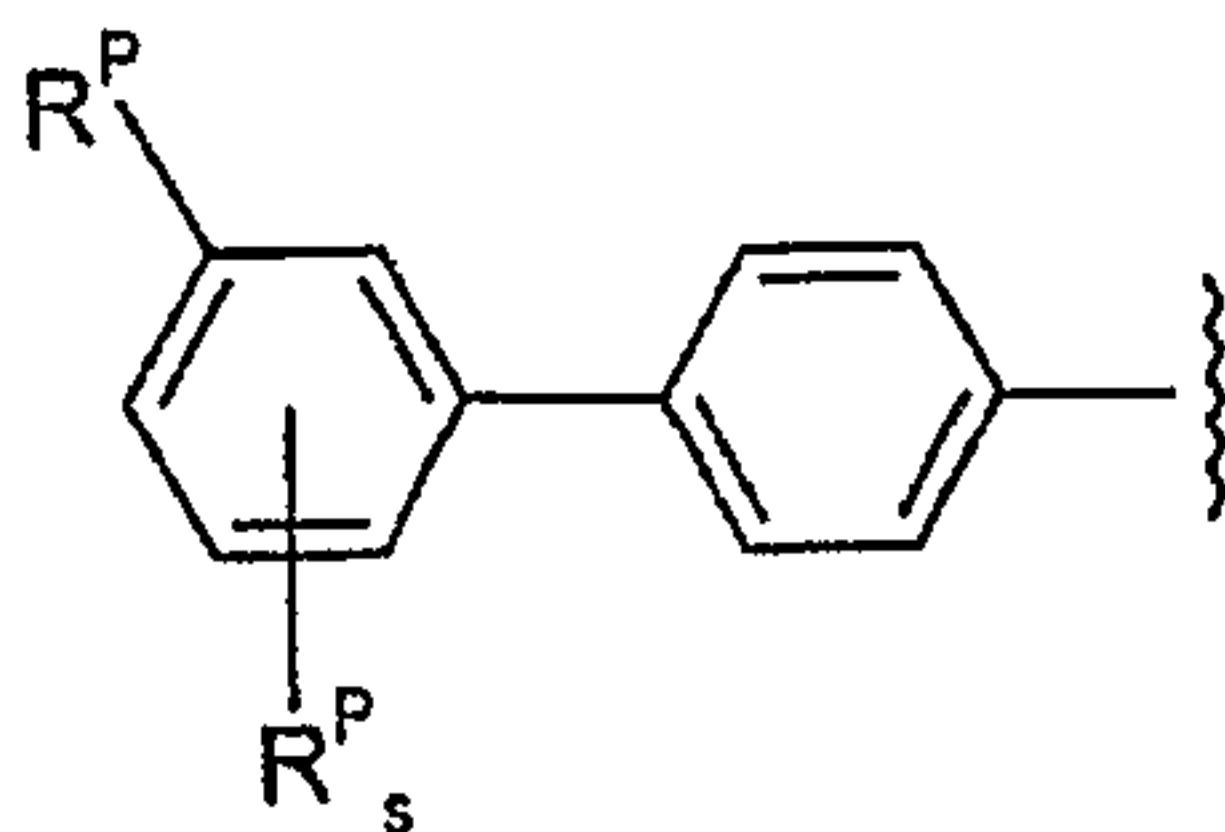
wherein each R^P is independently a phenyl substituent, and s is an integer from 0 to 4.

101. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein R^P is independently a phenyl substituent.

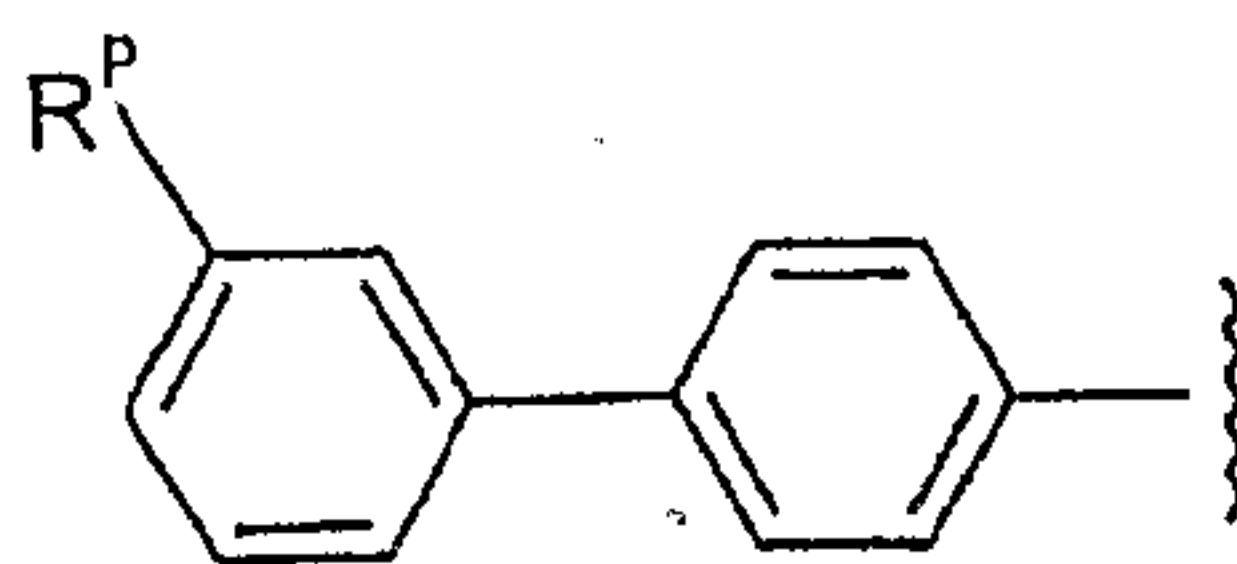
102. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and s is an integer from 0 to 4.

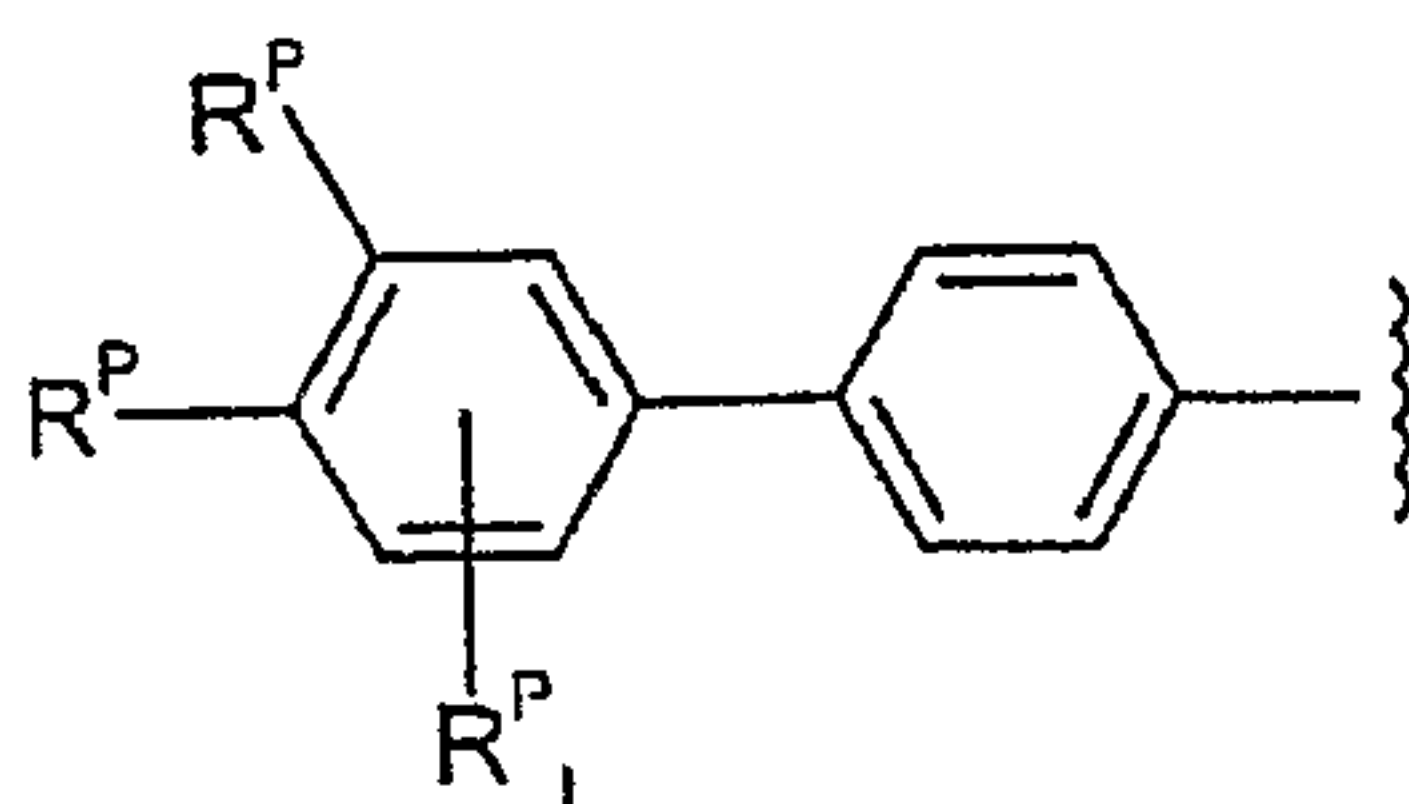
- 180 -

103. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



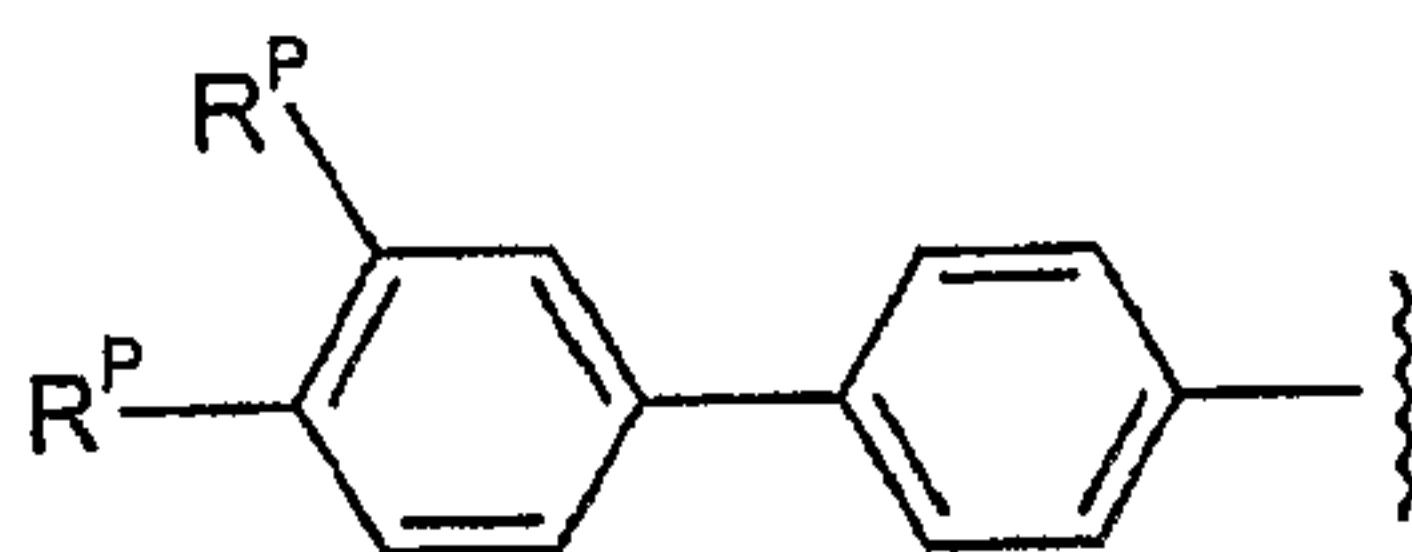
wherein R^P is independently a phenyl substituent.

104. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



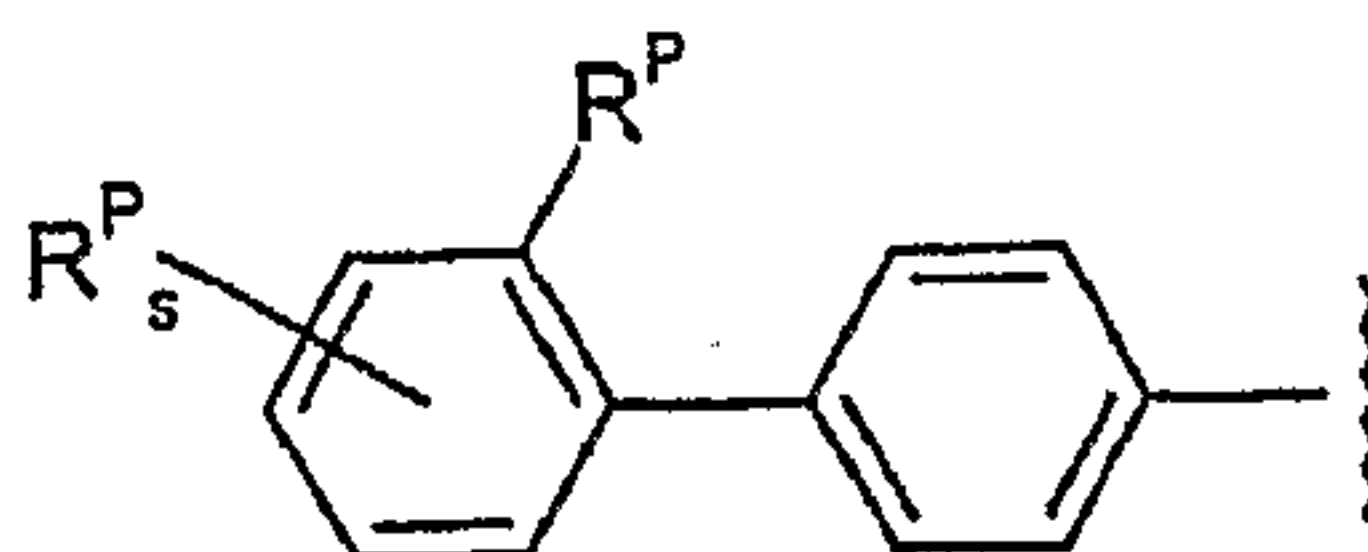
wherein each R^P is independently a phenyl substituent, and t is an integer from 0 to 3.

105. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent.

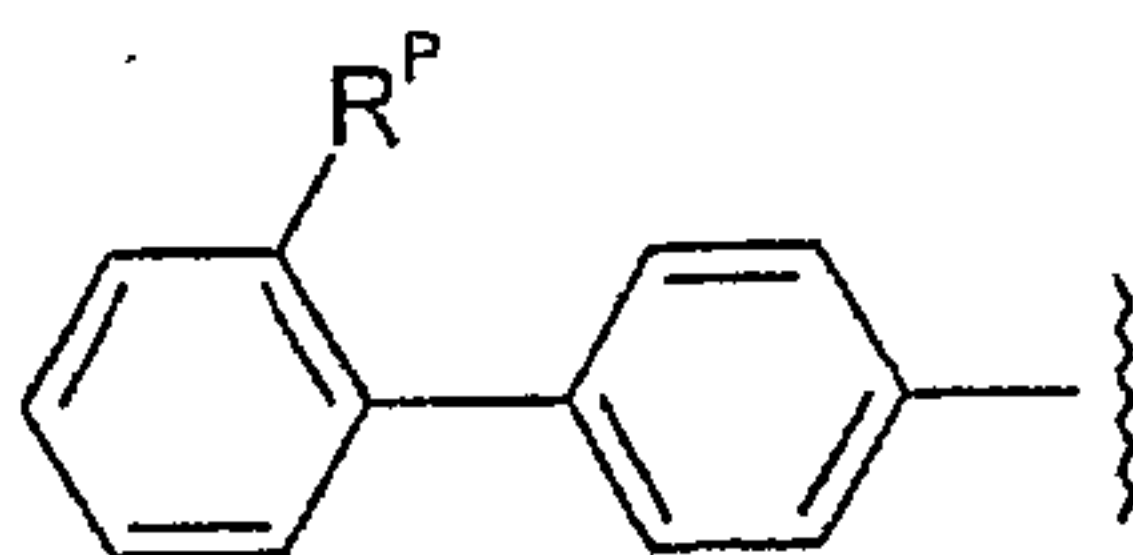
106. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent, and s is an integer from 0 to 4.

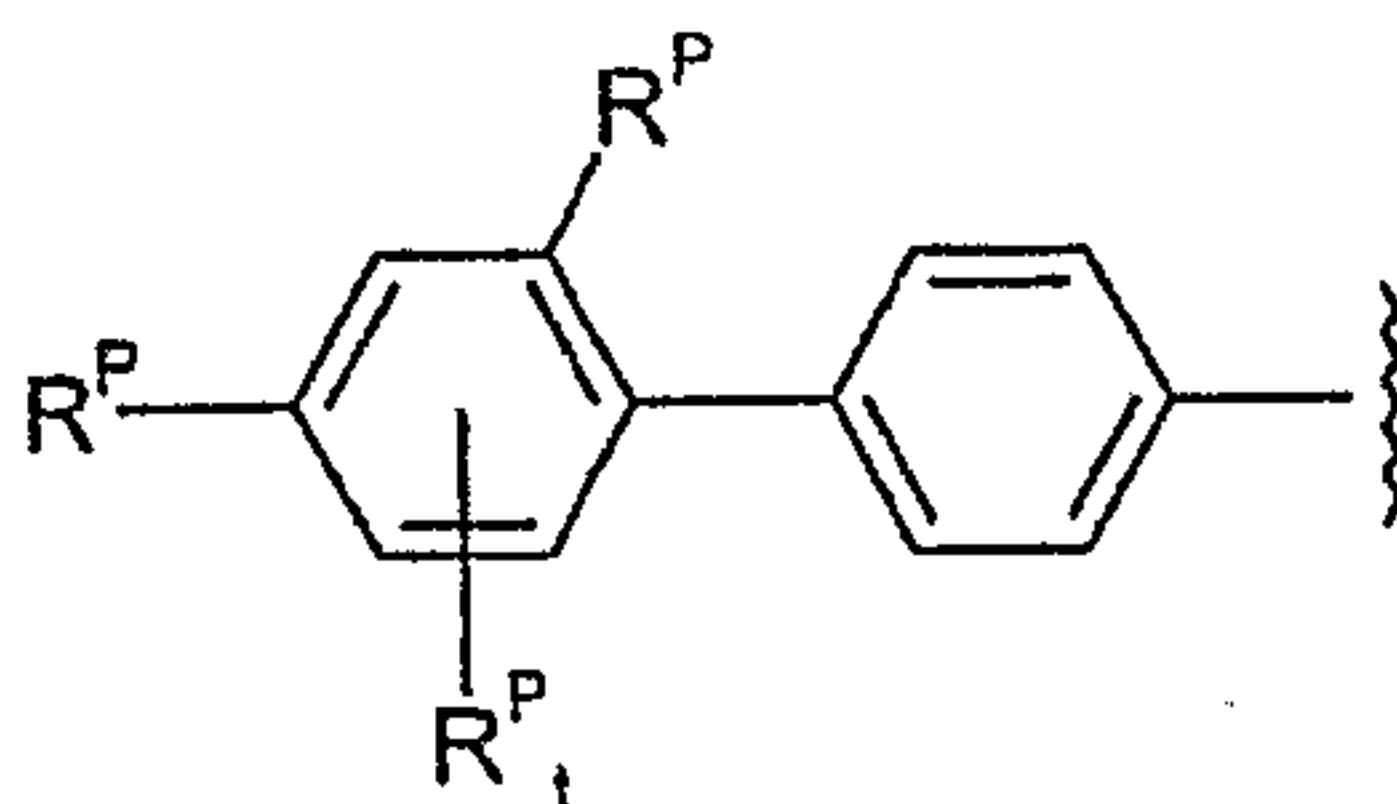
- 181 -

107. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



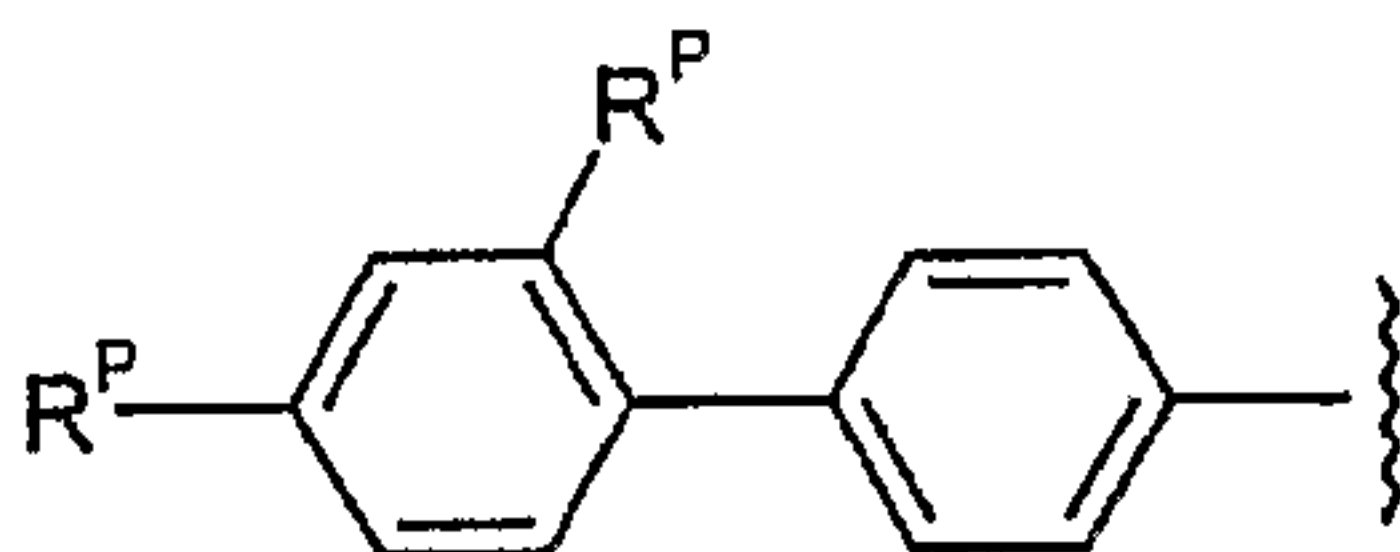
wherein R^P is independently a phenyl substituent.

108. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



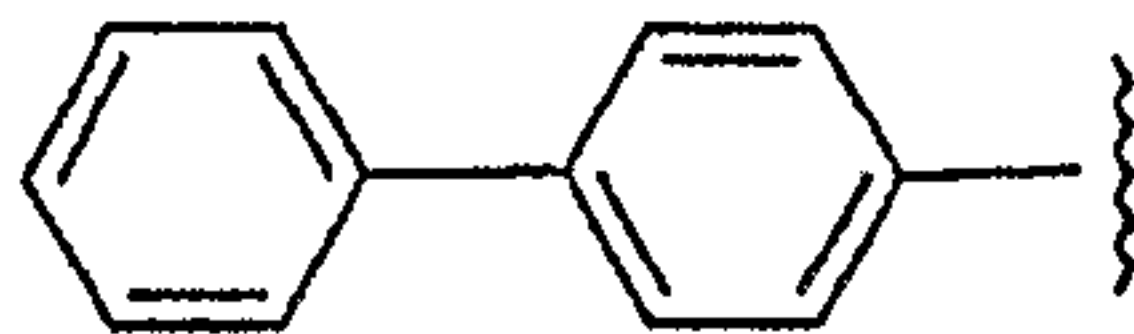
wherein each R^P is independently a phenyl substituent, and t is an integer from 0 to 3.

109. A compound according to claim 97, wherein R^{A1} is independently a substituted biphenyl-4-yl group of the following formula:



wherein each R^P is independently a phenyl substituent.

110. A compound according to claim 97, wherein R^{A1} is independently an unsubstituted biphenyl-4-yl group of the following formula:



* * *

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111. A compound according to any one of claims 97 to 109, wherein each of the phenyl substituents, R^P , is independently selected from:

C_{1-7} alkyl (optionally substituted); C_{3-20} heterocyclyl (optionally substituted); C_{5-20} aryl group (optionally substituted); halo; hydroxy; ether; acyl; carboxy; ester; acyloxy; amido; acylamido; amino; nitro; cyano; and, sulfonate.

112. A compound according to any one of claims 97 to 109, wherein each of the phenyl substituents, R^P , is independently selected from:

-Me, -Et, -iPr, -nPr, -tBu;
 -Ph;
 -F, -Cl, -Br, -I;
 -OH;
 -OMe, -OEt, -O(iPr), -O(nPr), -O(tBu), -OPh, -OBn;
 -C(=O)OH;
 -C(=O)OMe, -C(=O)OEt, -C(=O)O(tBu), -C(=O)OPh;
 -OC(C=O)Me, -OC(C=O)Et, -OC(C=O)(tBu), -OC(C=O)Ph;
 -OC(C=O)OMe, -OC(C=O)OEt, -OC(C=O)O(tBu), -OC(C=O)OPh;
 -C(=O)NH₂, -C(=O)NHMe, -C(=O)NMe₂, -C(=O)NHPh;
 -NHC(=O)Me, -NHC(=O)Et, -NHC(=O)Ph;
 -NH₂, -NHMe, -NMe₂, -NH₂Et, -NEt₂;
 -NO₂;
 -CN; and,
 -S(=O)₂OMe, -S(=O)₂OEt, -S(=O)₂OPh.

113. A compound according to any one of claims 97 to 109, wherein each of the phenyl substituents, R^P , is independently selected from: -Me, -F, -Cl, -Br, -I, -OH, -OMe, -NH₂, -NMe₂, -NO₂, and -CN.

114. A compound according to any one of claims 97 to 109, wherein each of the phenyl substituents, R^P , is independently selected from: -F, -Cl, -Br, -I, -NO₂, and -OH.

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115. A compound according to any one of claims 97 to 109, wherein each of the phenyl substituents, R^P , is independently selected from: -F, -Cl, -Br, -I.

116. A compound according to claim 97, wherein the compound is selected from the following compounds, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:

ABD-0057 (3BP);

ABD-0056 (4BP);

ABD-0055 (5BP);

ABD-0054 (6BP);

ABD-0095 (BP-4F);

ABD-0070 (Me4BP);

ABD-0072 (HO4BP);

ABD-0089 (Xy4BP);

ABD-0094 (Et4BP);

ABD-0097 (4-OMeBP);

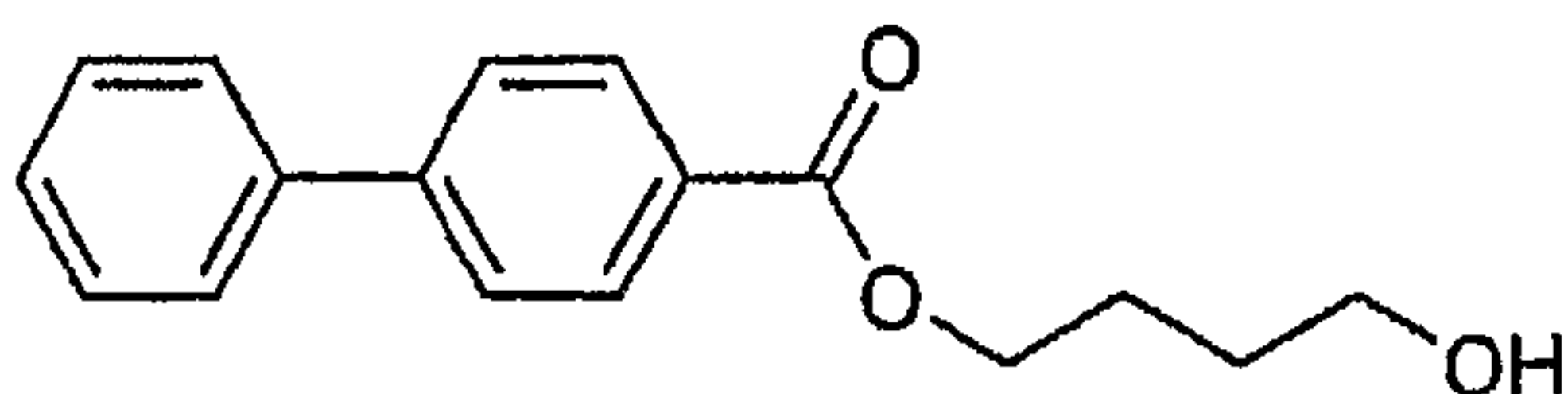
ABD-0098 (2-NO₂BP);

ABD-0099 (2-FBP);

ABD-0100 (4-FBP); and

ABD-0102 (4-BrBP).

117. A compound according to claim 97, wherein the compound is selected from the following compound, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:



ABD-0056

4BP

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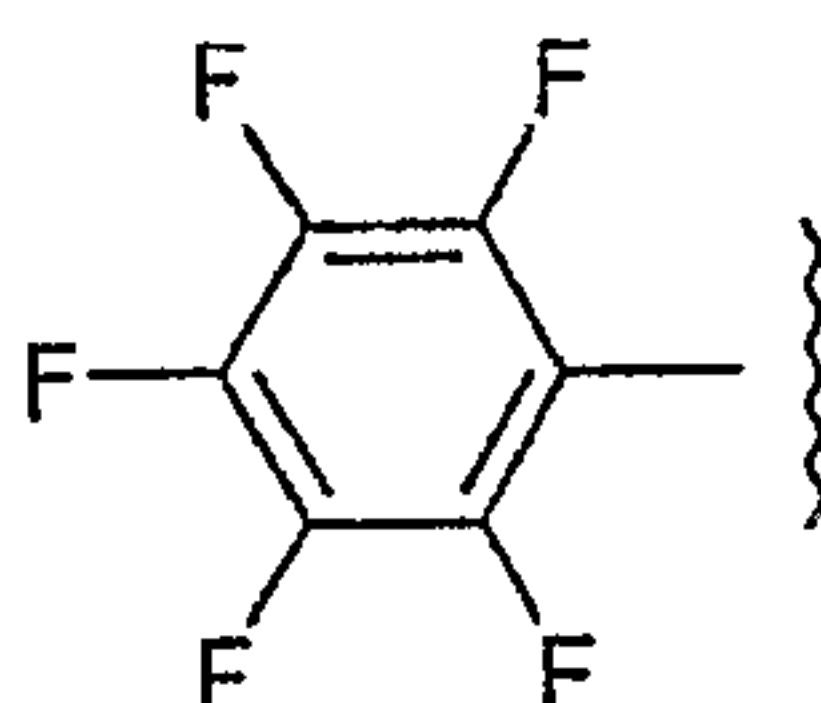
118. A compound selected from compounds of the following formula:



wherein:

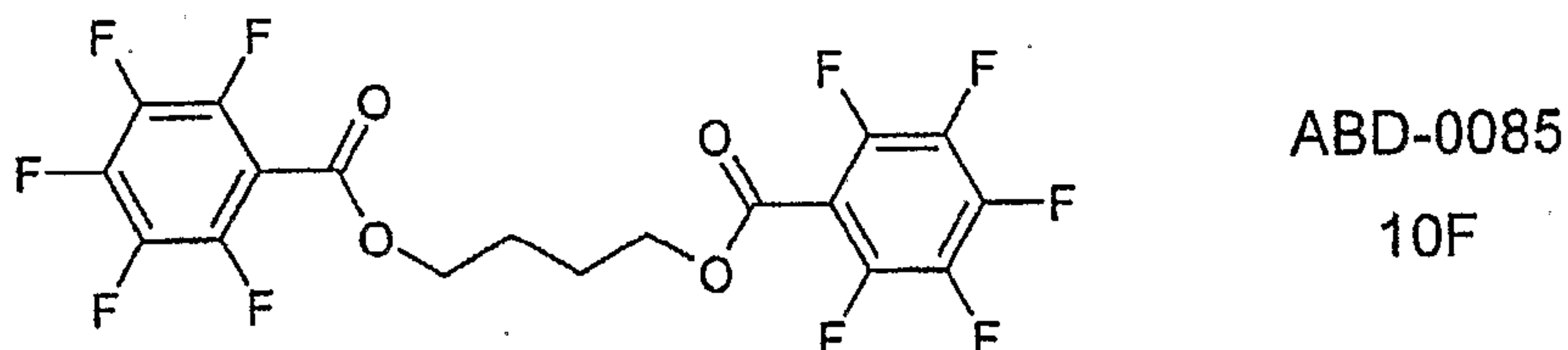
A is a C₂₋₁₀alkylene group;

each of R^{A1} and R^{A2} is:



and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

119. A compound according to claim 118, wherein the compound is selected from the following compound, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:



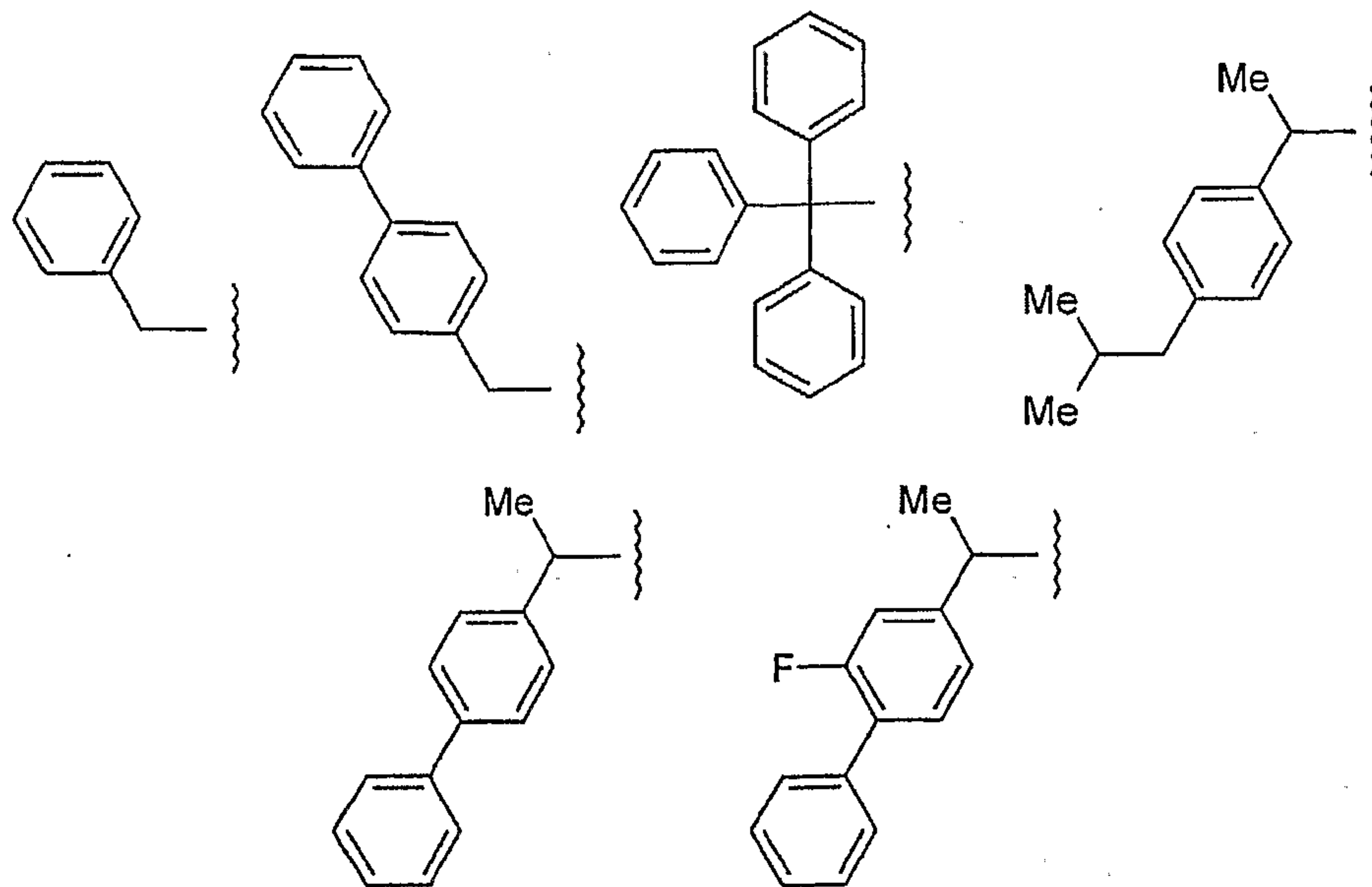
120. A compound selected from compounds of the following formula:



wherein:

A is a C₂₋₁₀alkylene group;

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R^{A1} is independently selected from:

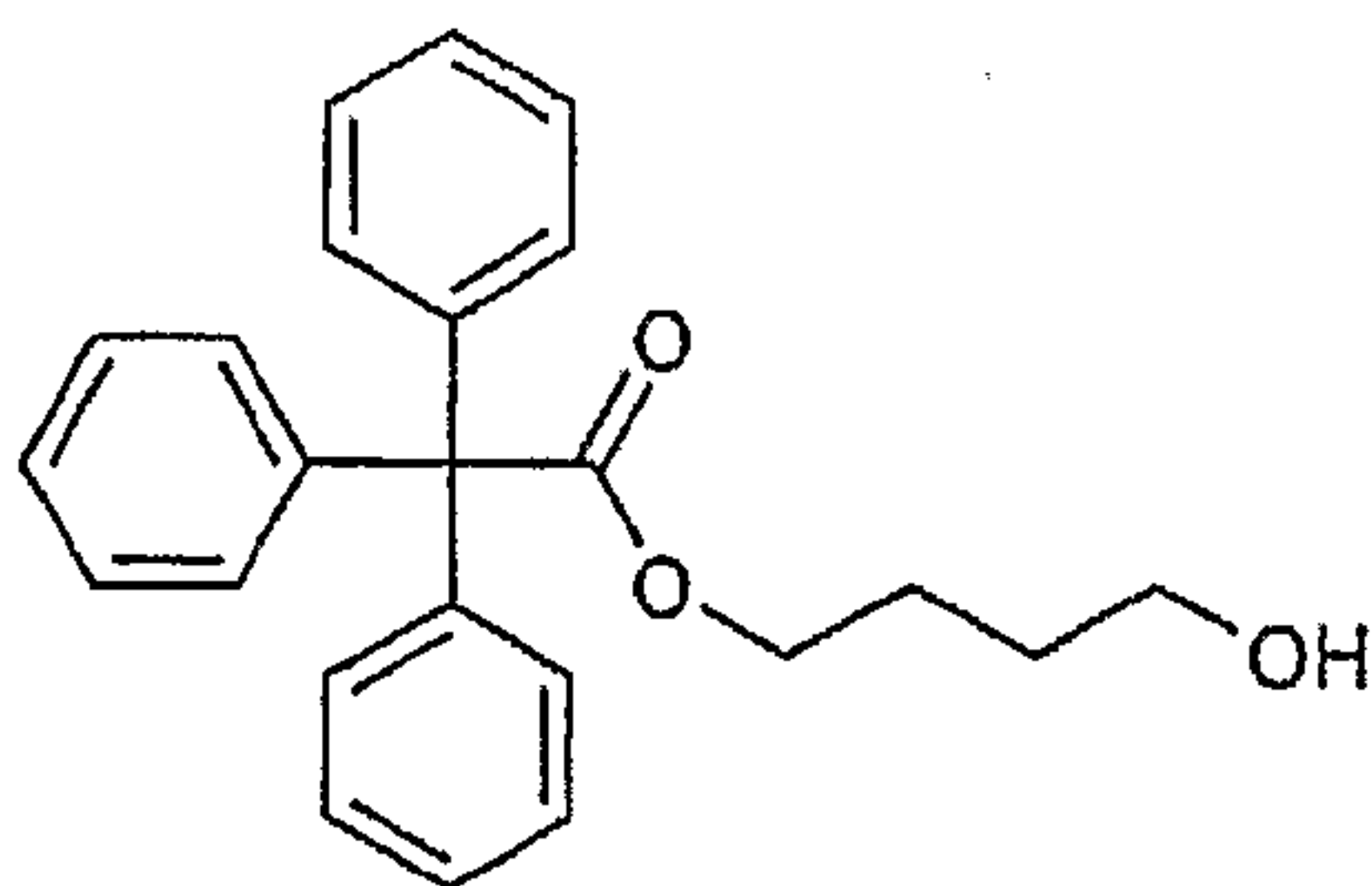
and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

121. A compound according to claim 120, wherein the compound is selected from the following compounds, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:

ABD-0014 (4P);
 ABD-0017 (6P);
 ABD-0028 (4T);
 ABD-0030 (5T);
 ABD-0031 (6T);
 ABD-0041 (3BPA);
 ABD-0042 (4BPA);
 ABD-0043 (5BPA);
 ABD-0044 (6BPA);
 ABD-0035 (BuI); and,
 ABD-0040 (BuBPA):

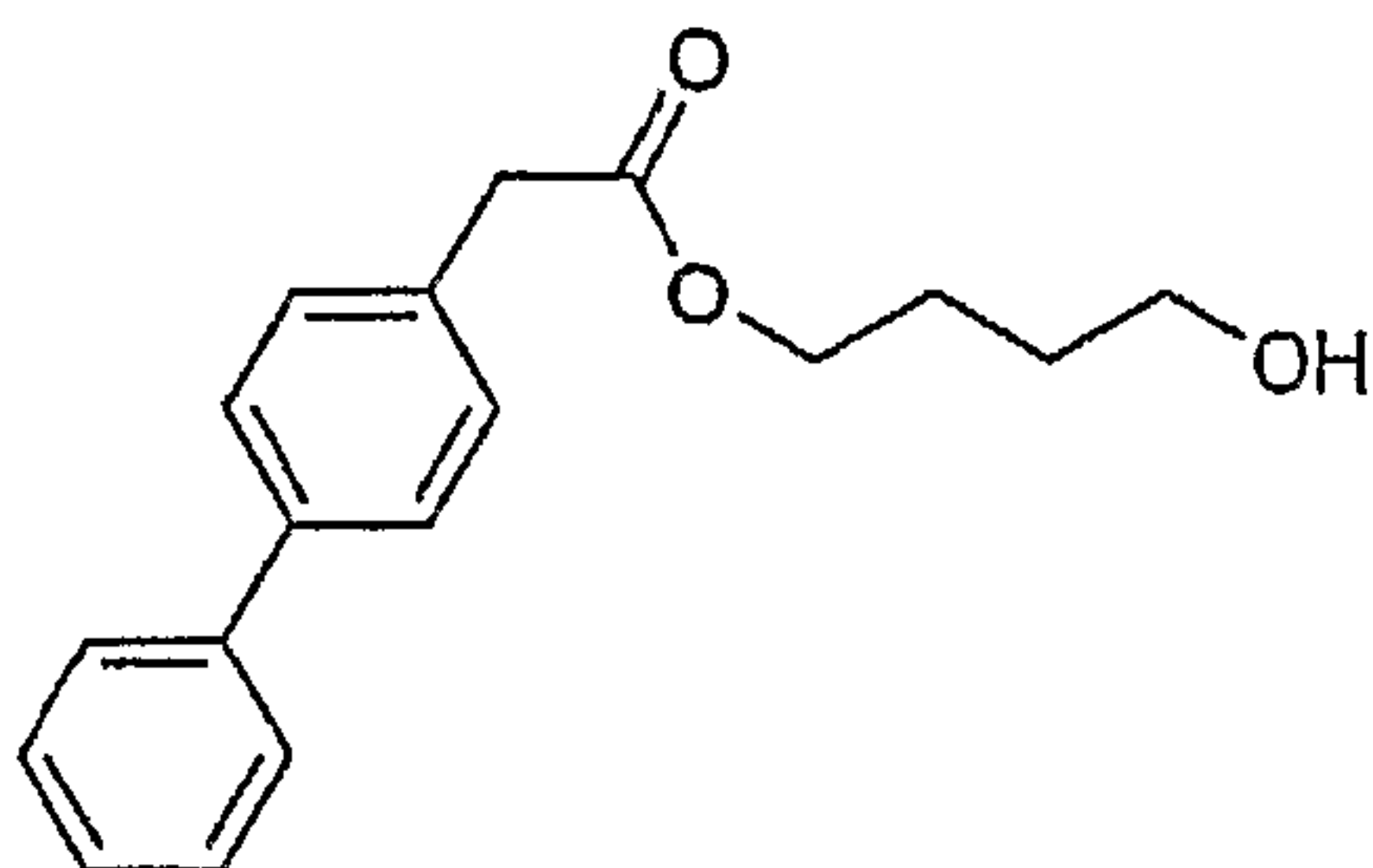
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122. A compound according to claim 120, wherein the compound is selected from the following compounds, and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof:



ABD-0028

4T



ABD-0042

4BPA

123. A composition comprising a compound as described in any one of claims 97 to 122 and a pharmaceutically acceptable carrier or diluent.

* * *

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FIGURE 1

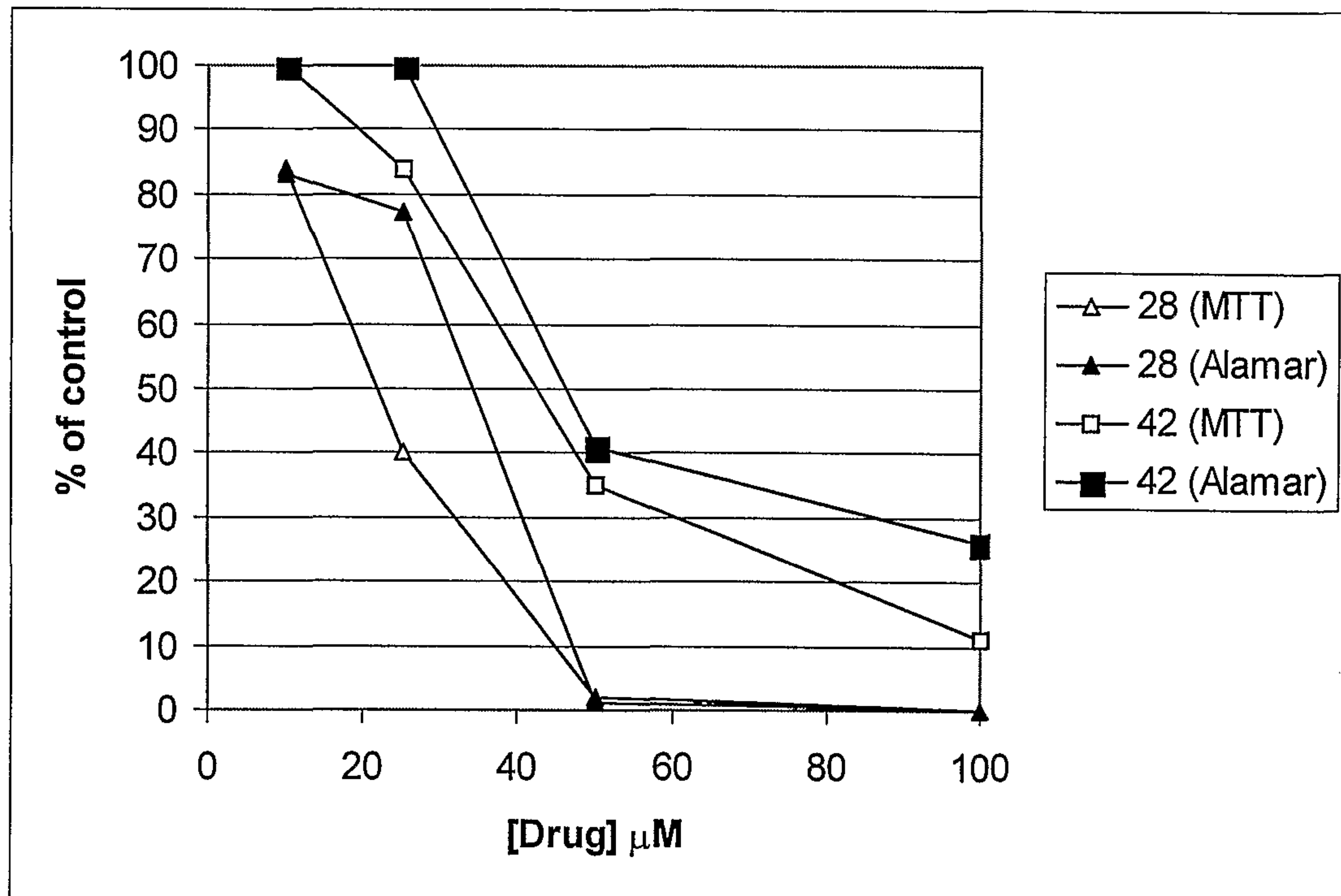
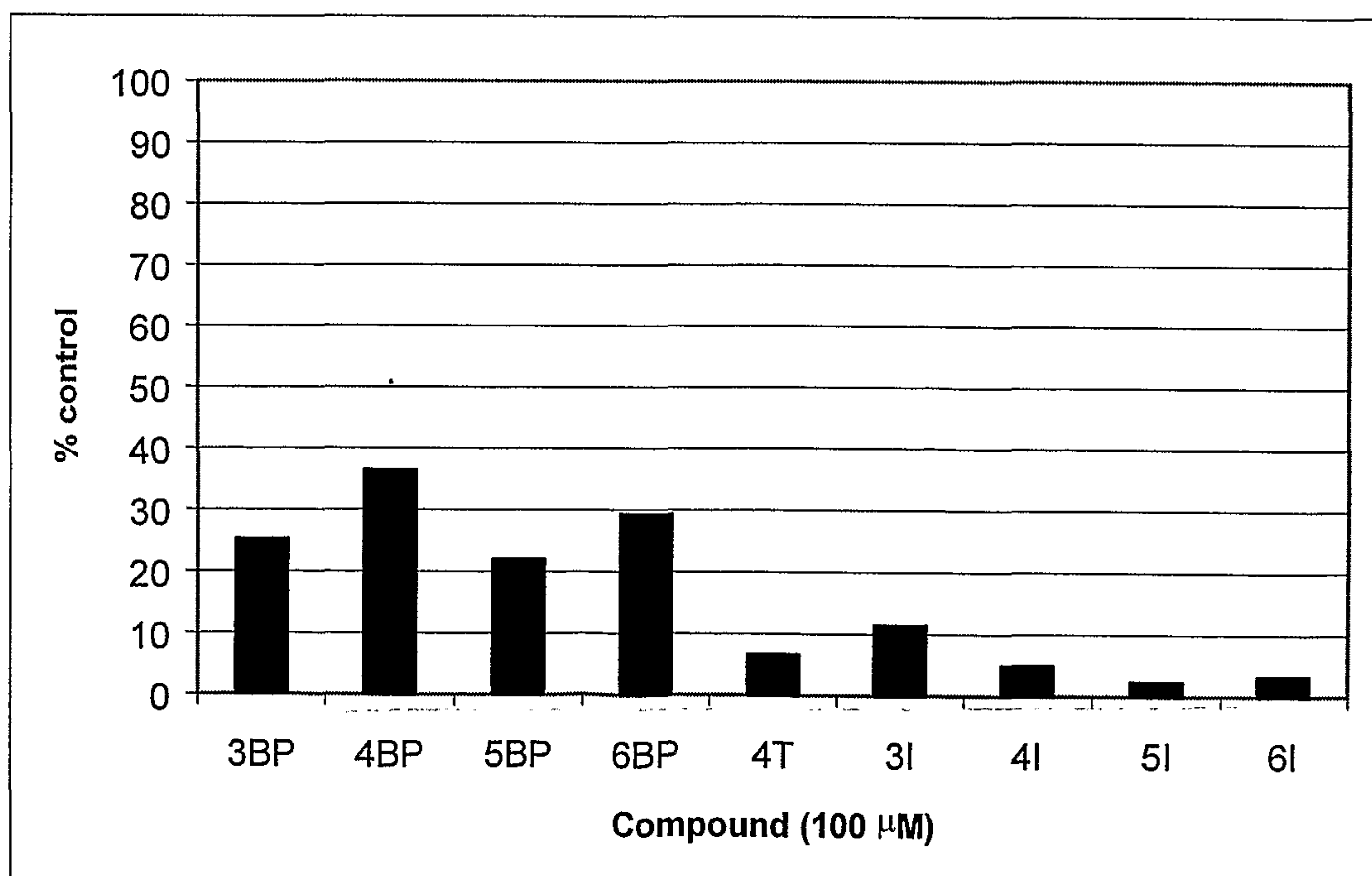


FIGURE 2



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FIGURE 3

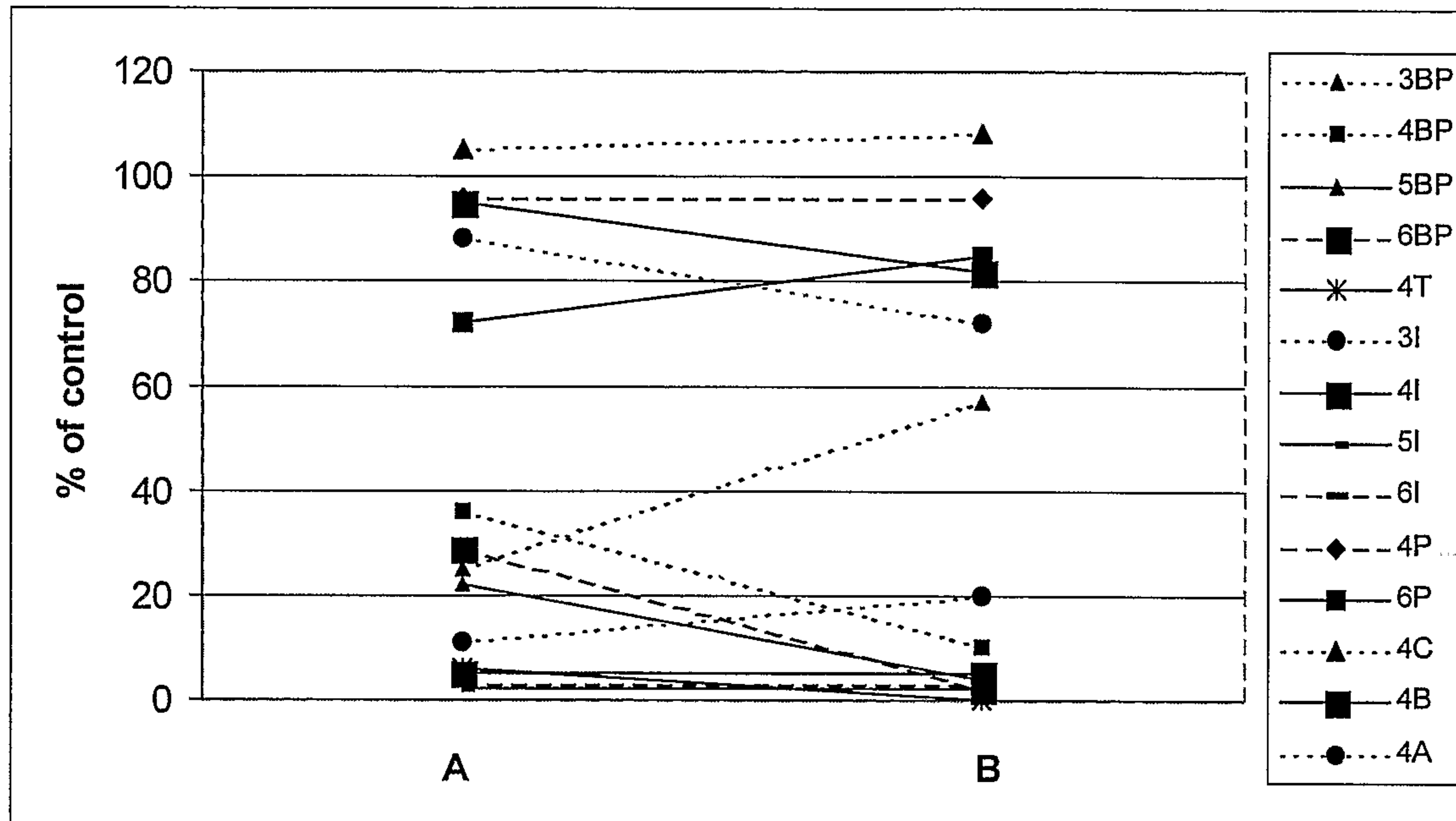
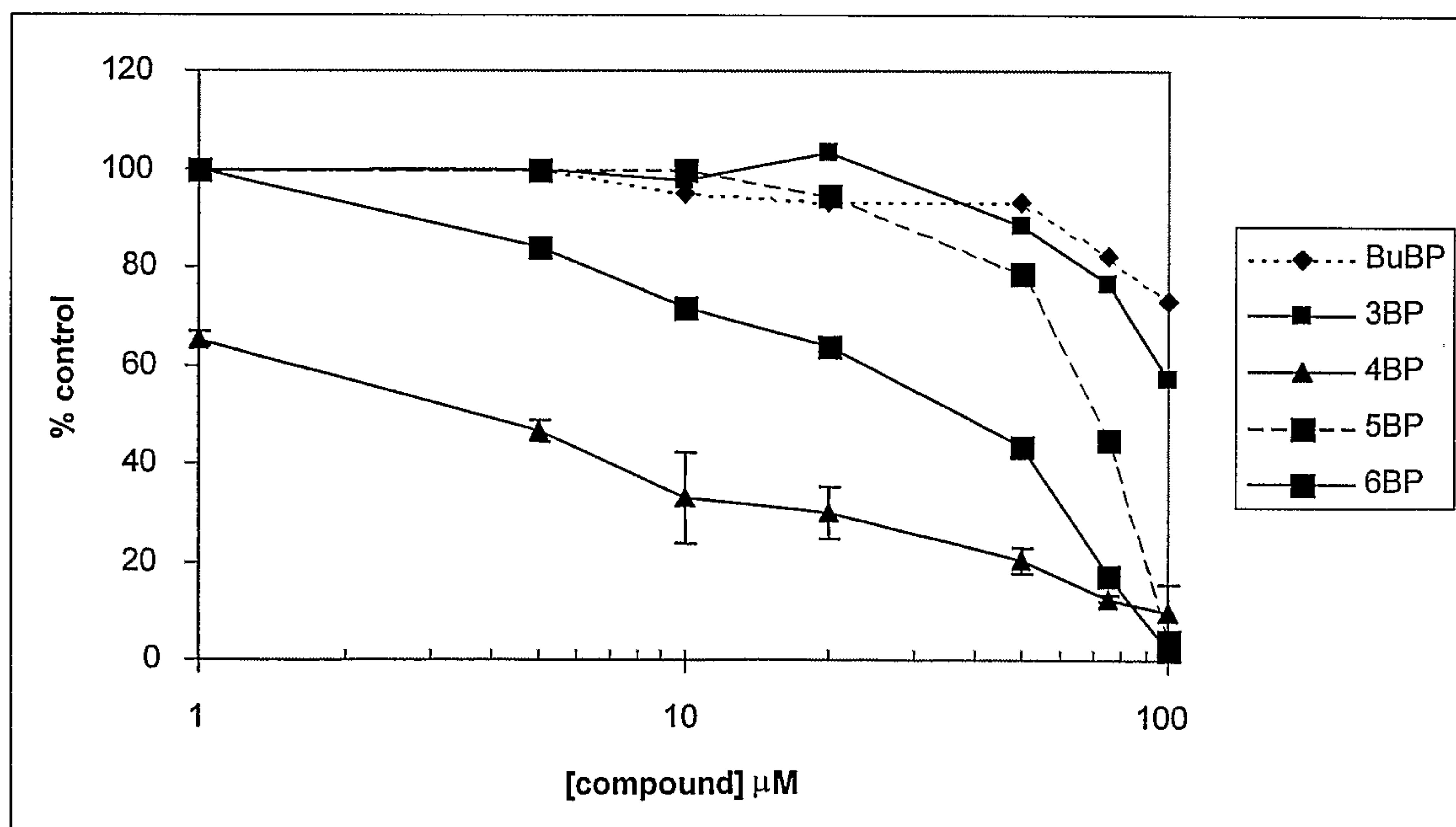


FIGURE 4



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FIGURE 5

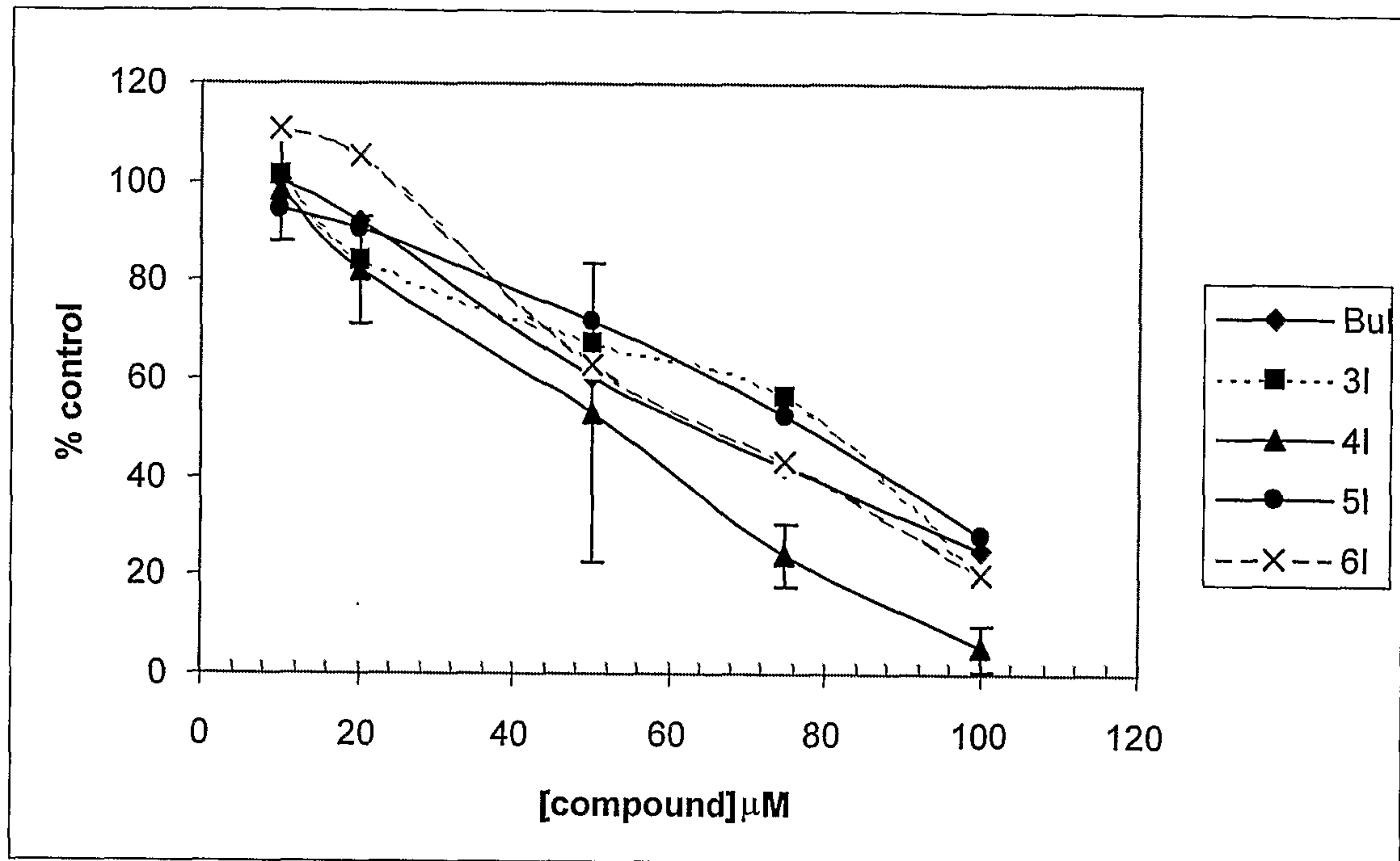
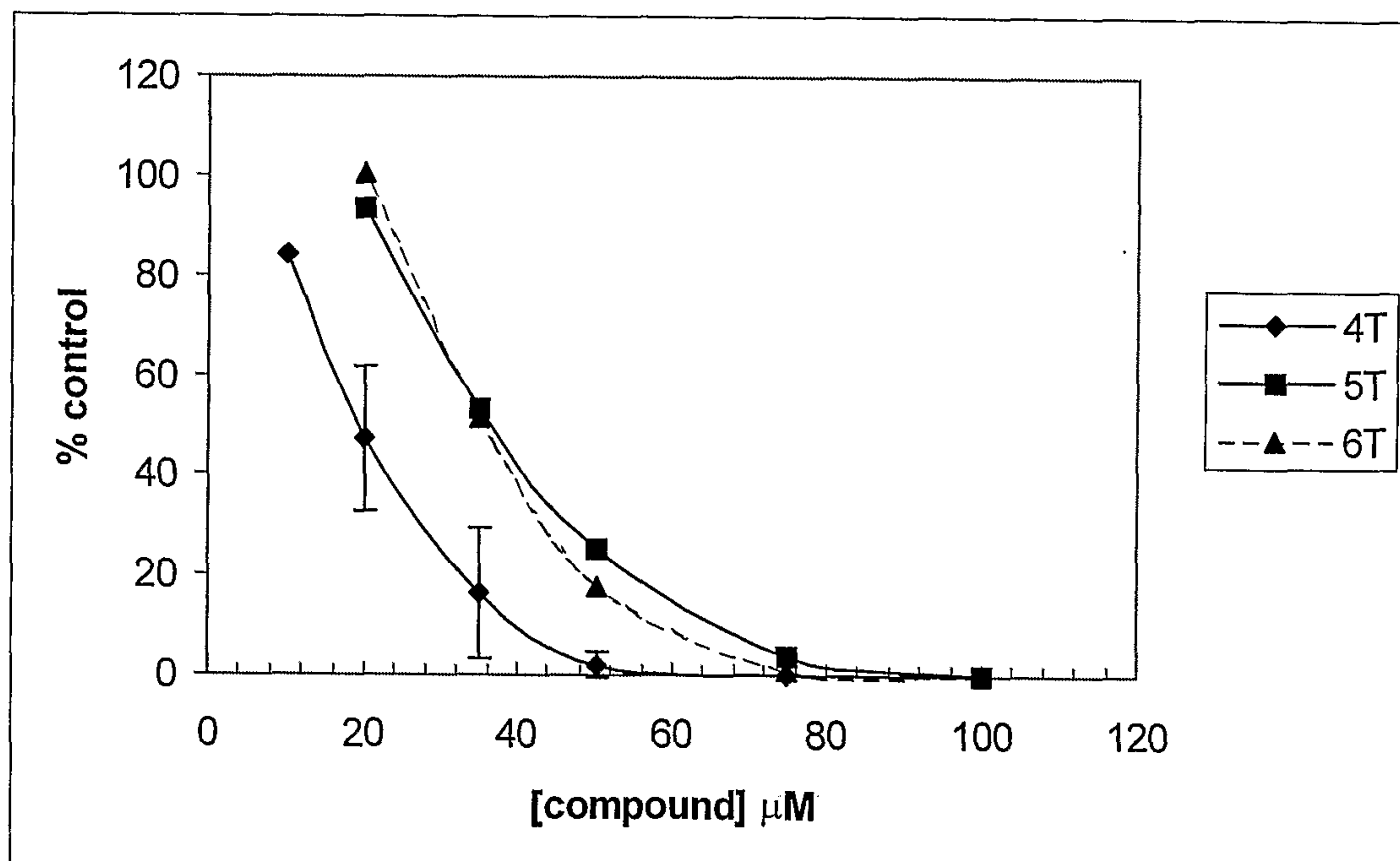


FIGURE 6



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FIGURE 7

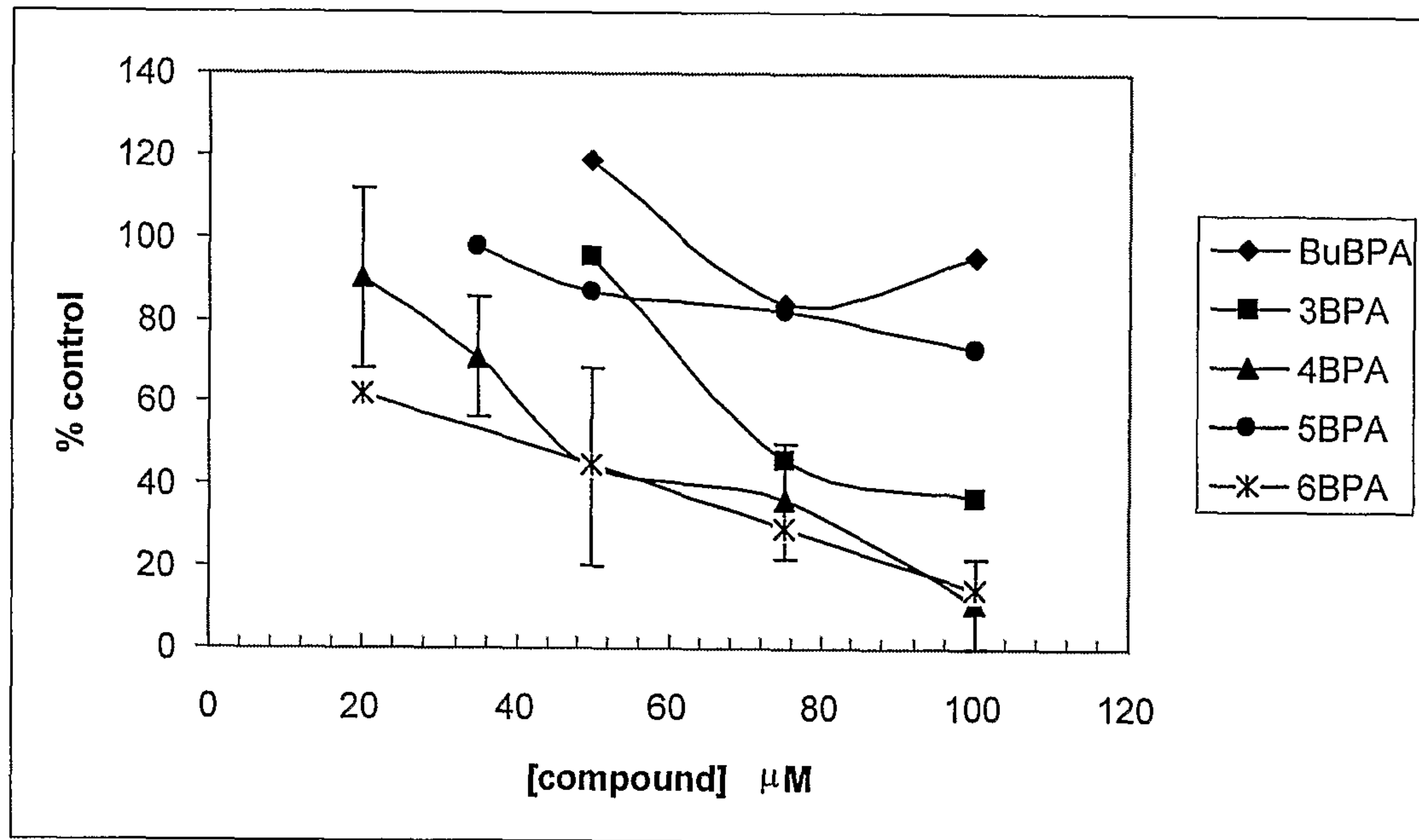
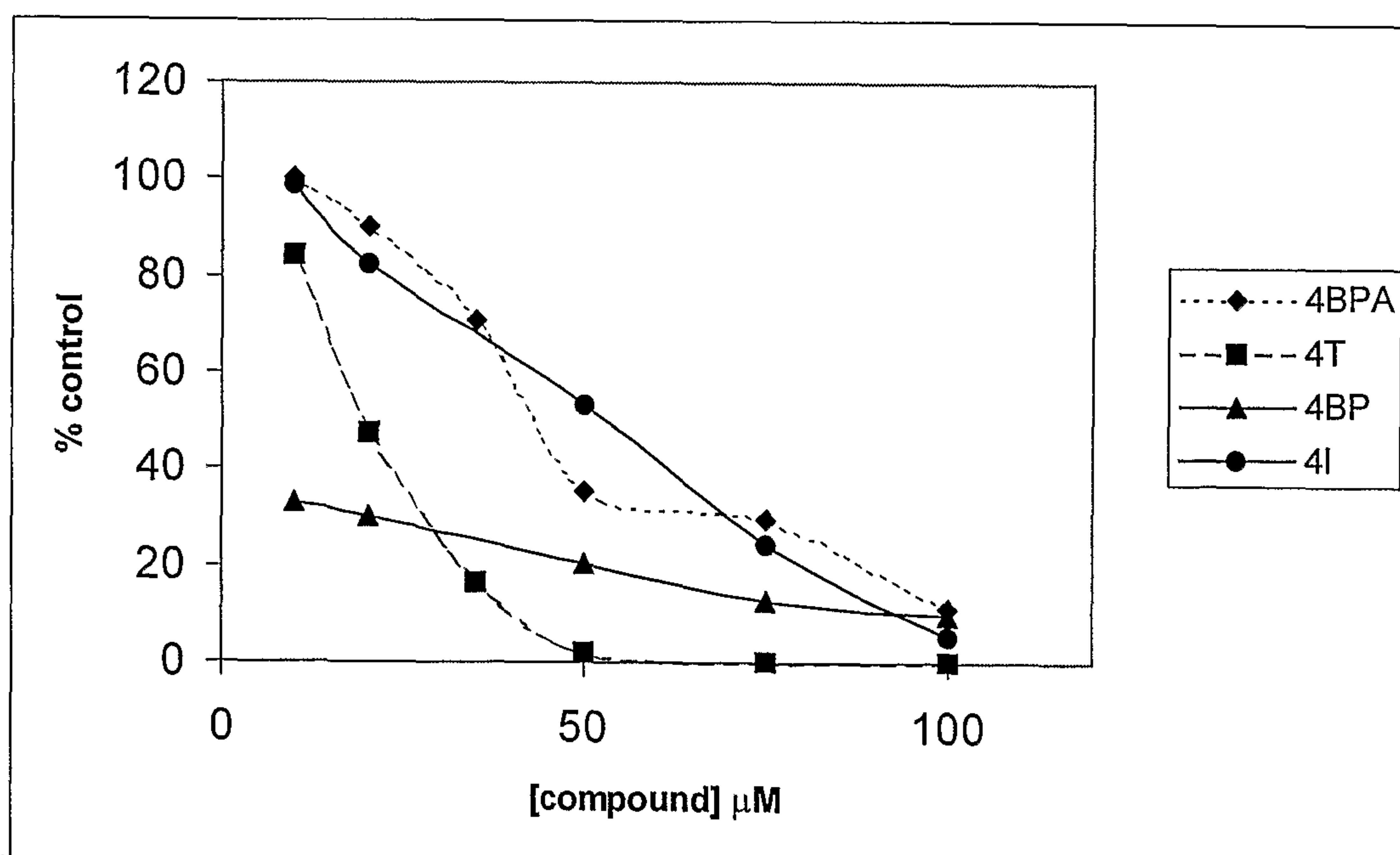


FIGURE 8



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FIGURE 9

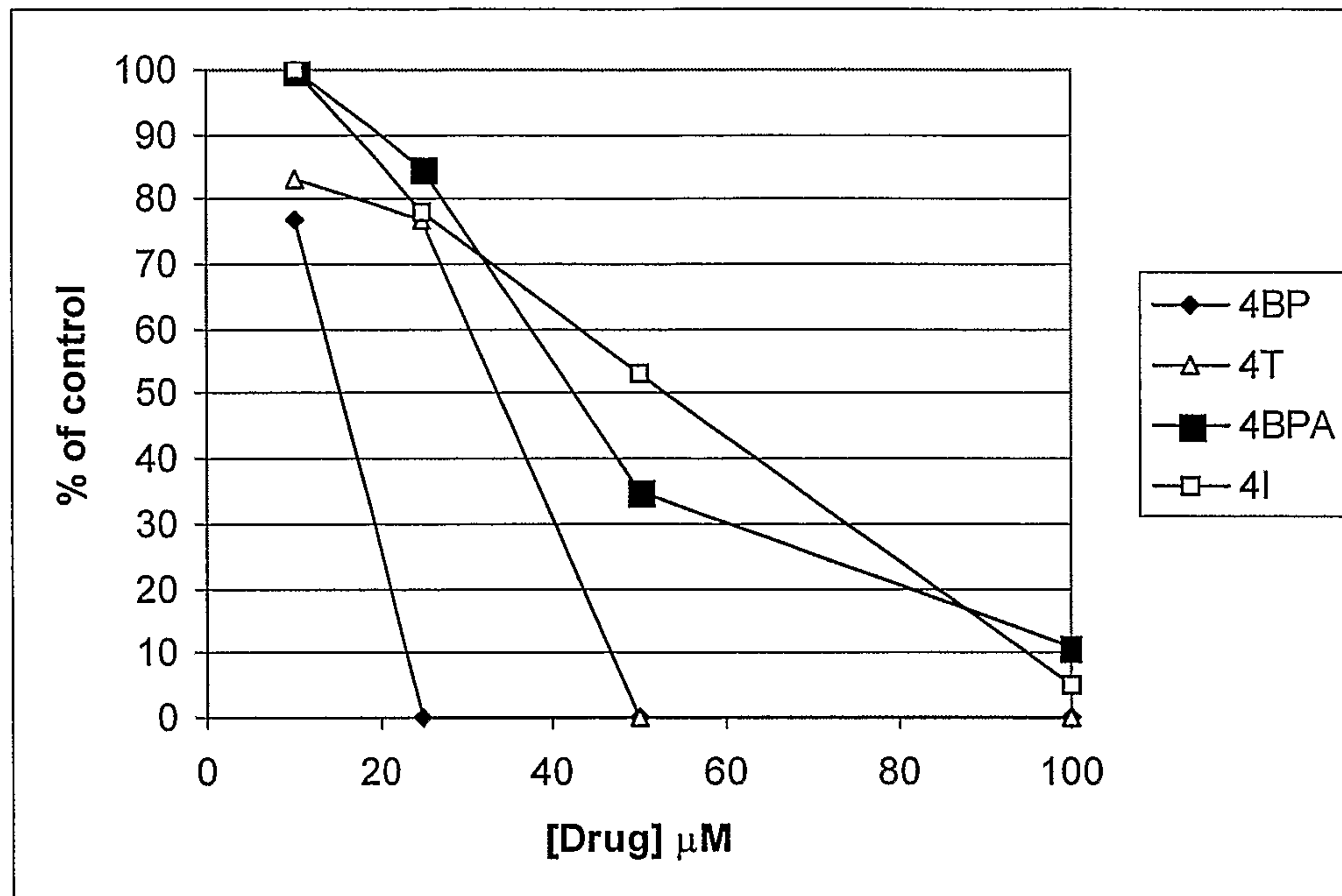
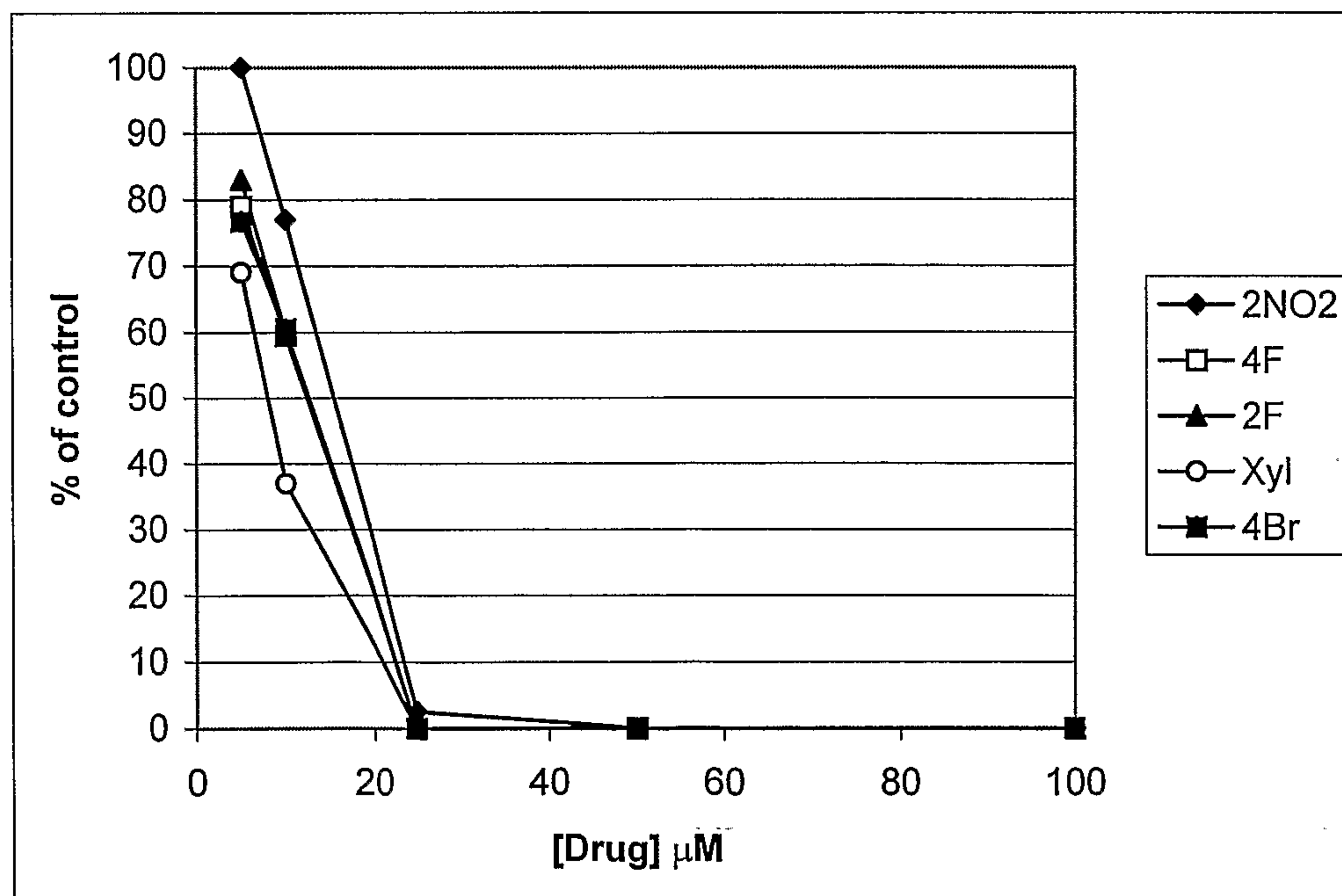


FIGURE 10



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FIGURE 11

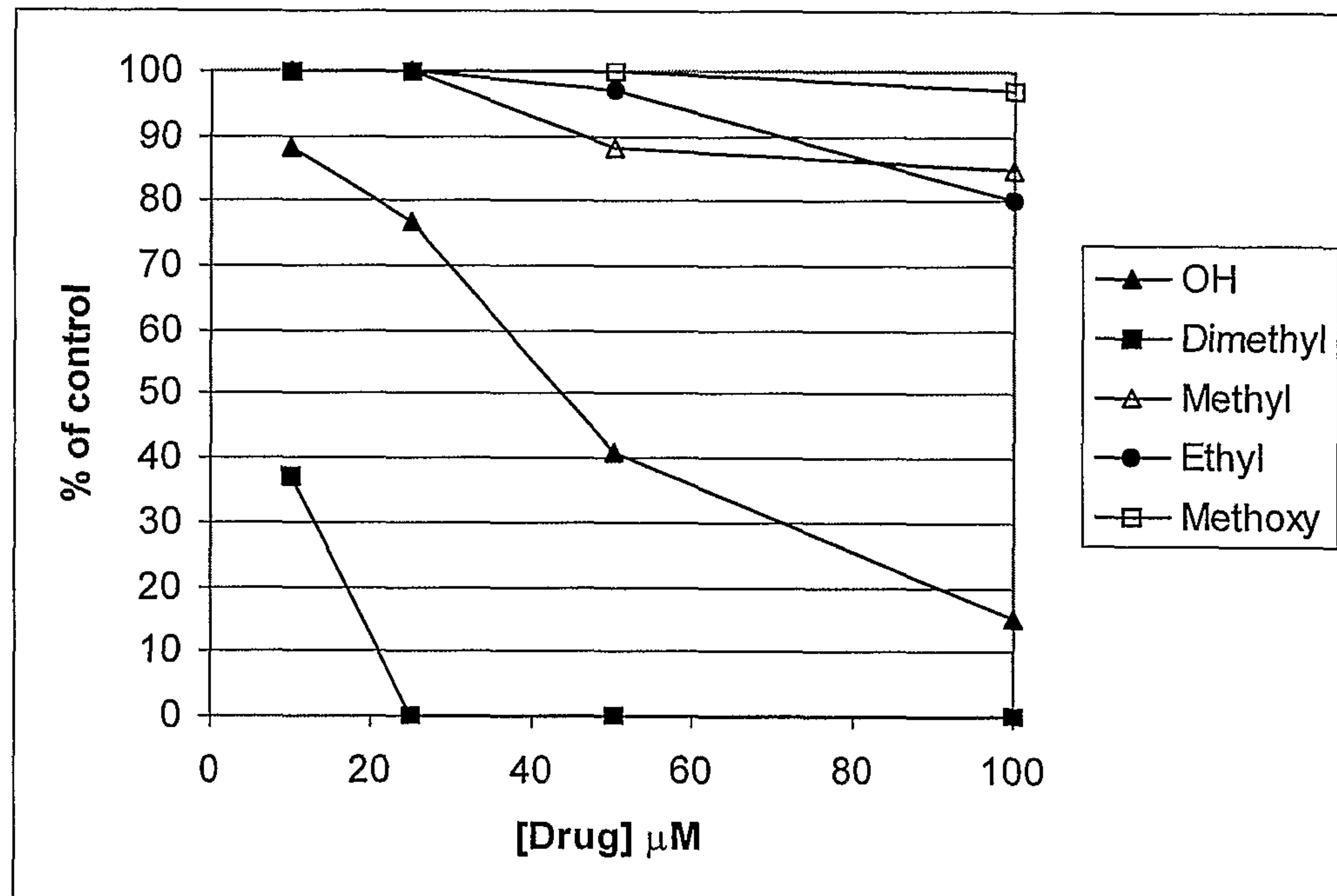
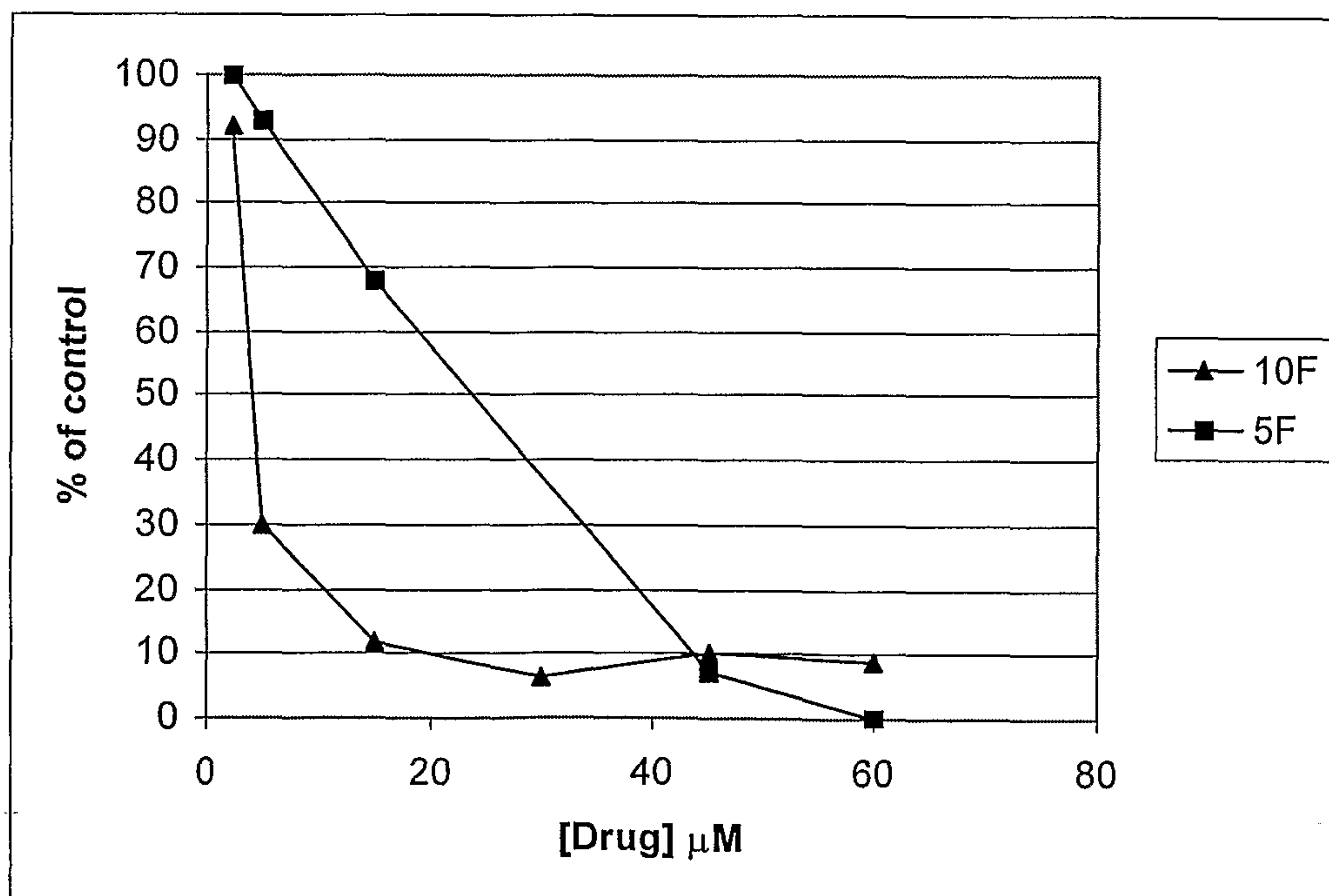


FIGURE 12



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FIGURE 13

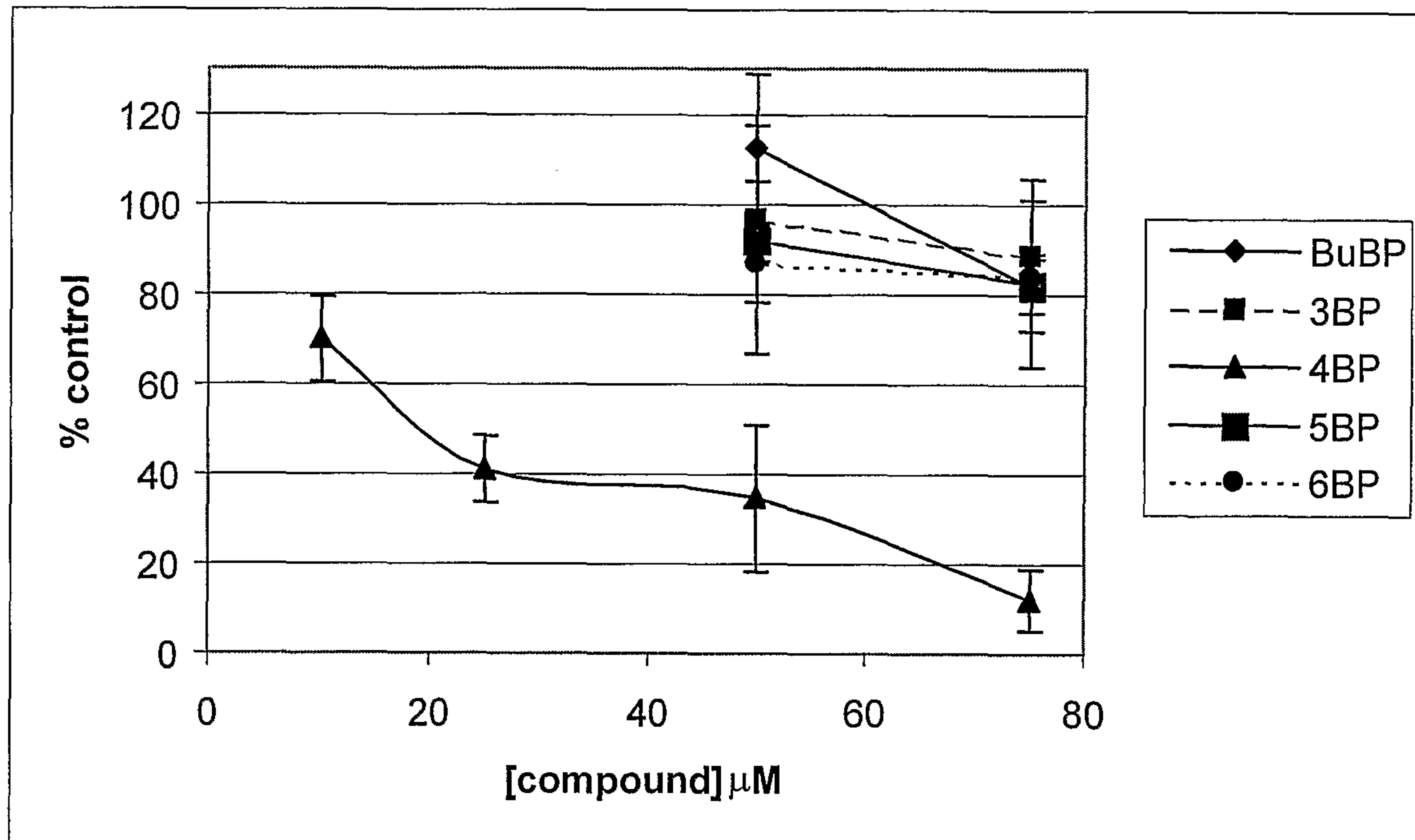
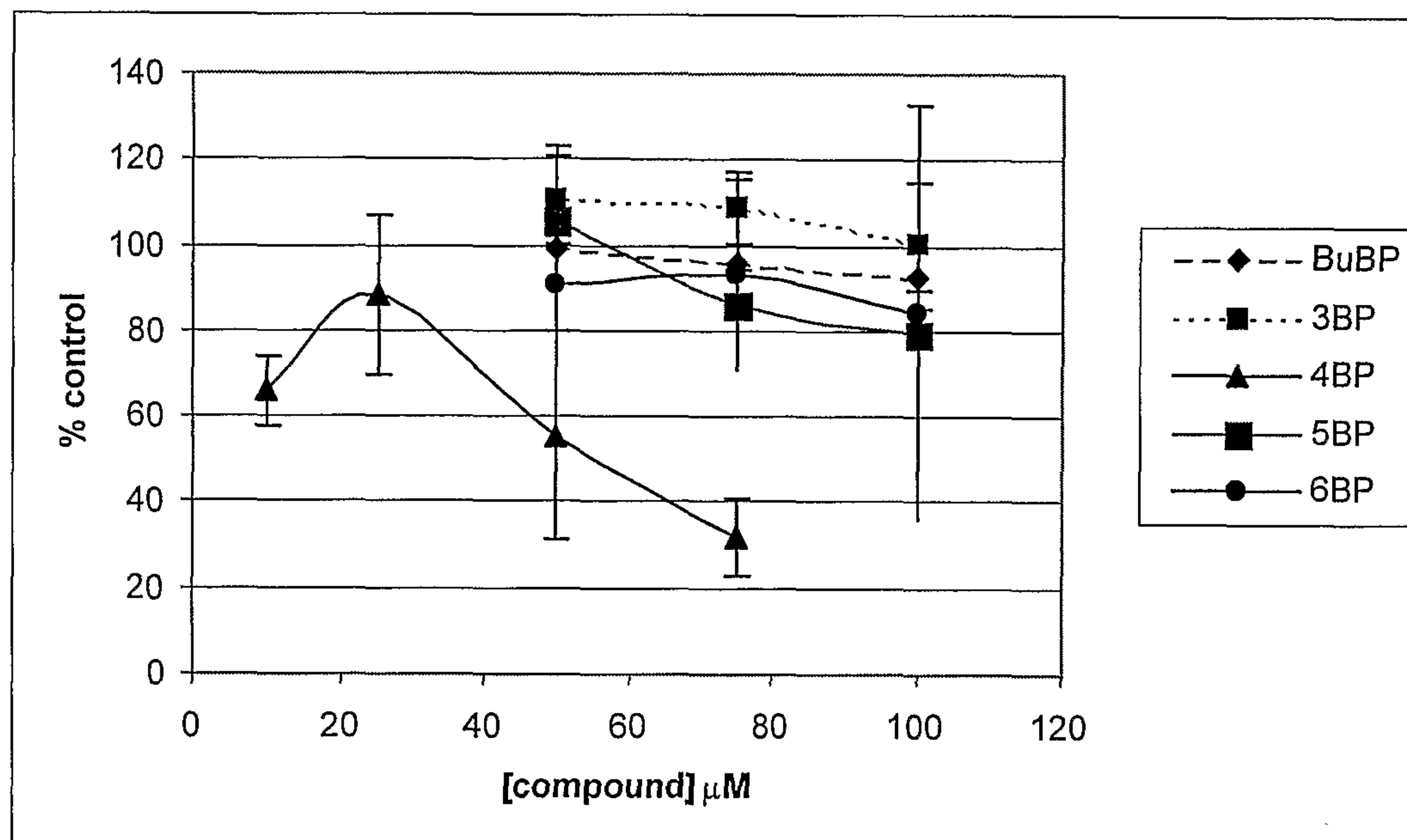


FIGURE 14



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FIGURE 15

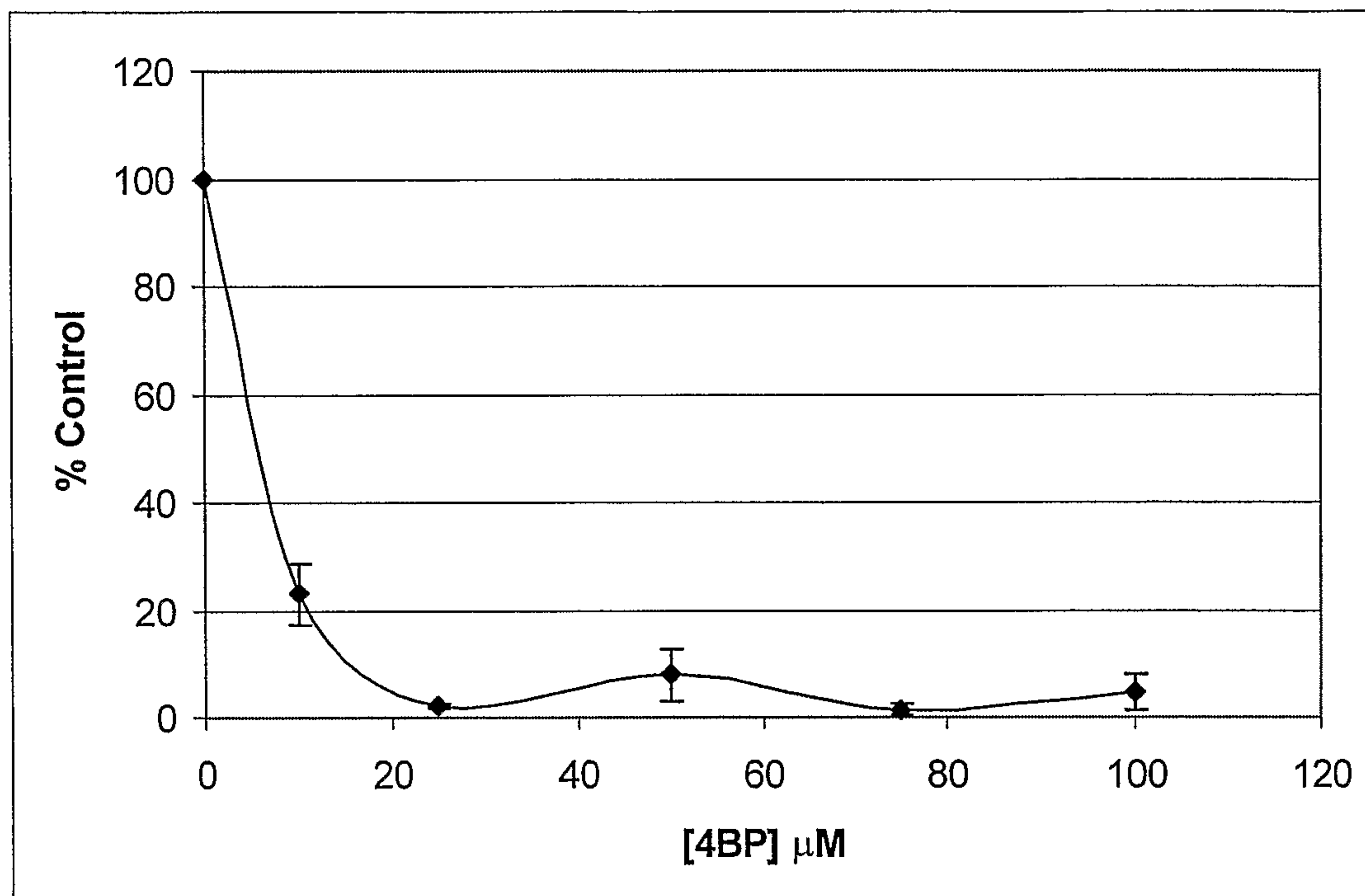
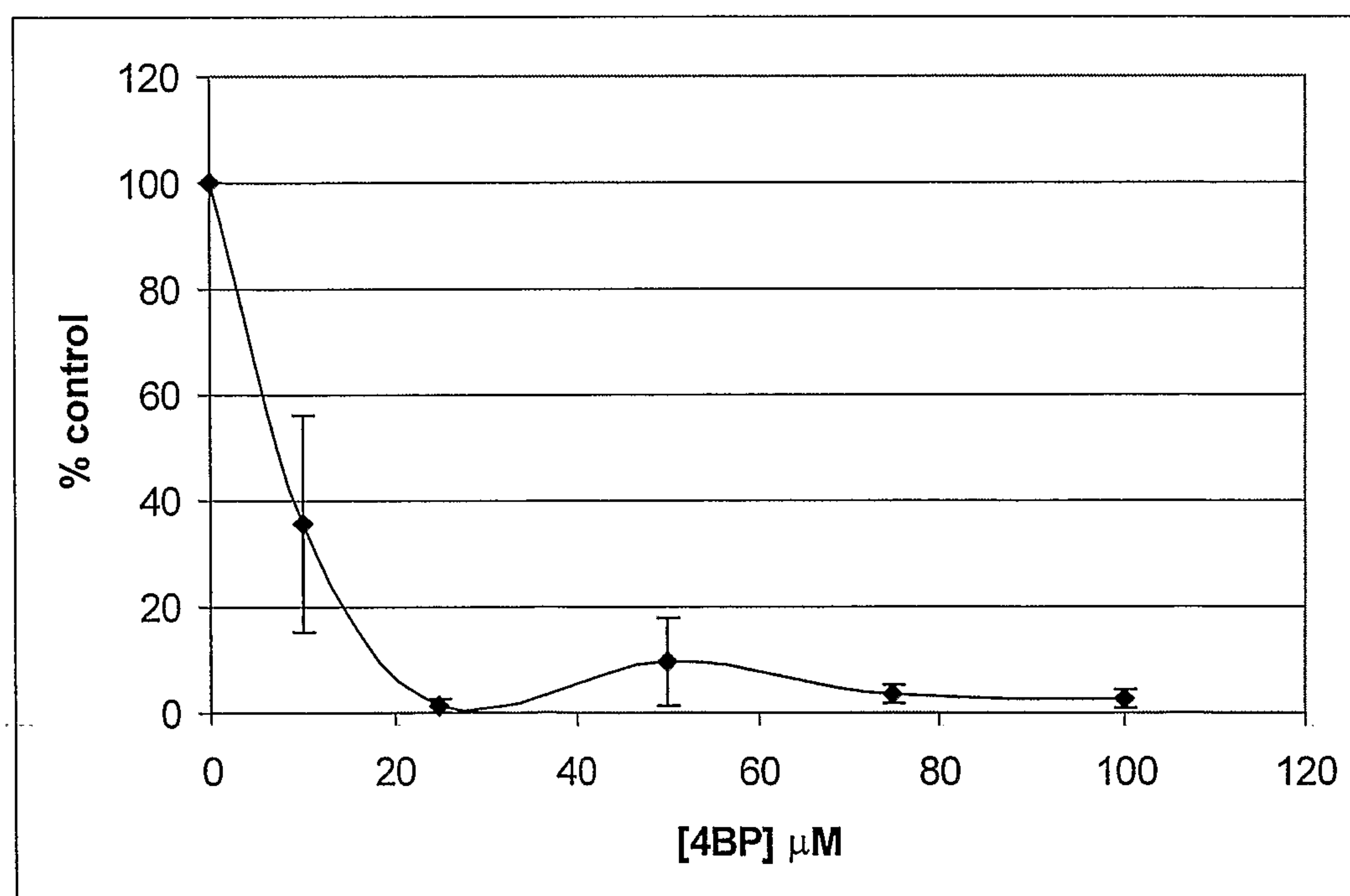


FIGURE 16



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FIGURE 17

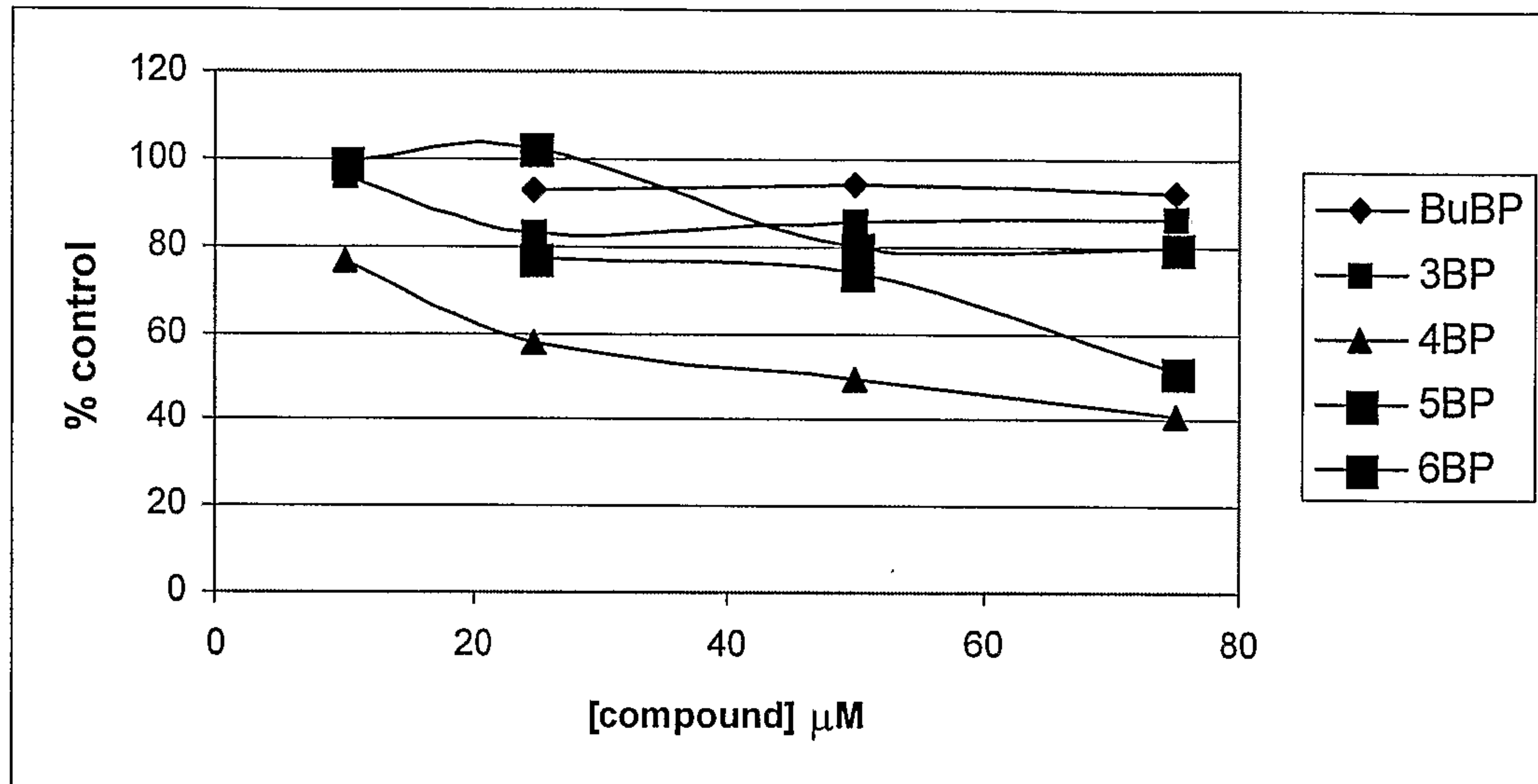
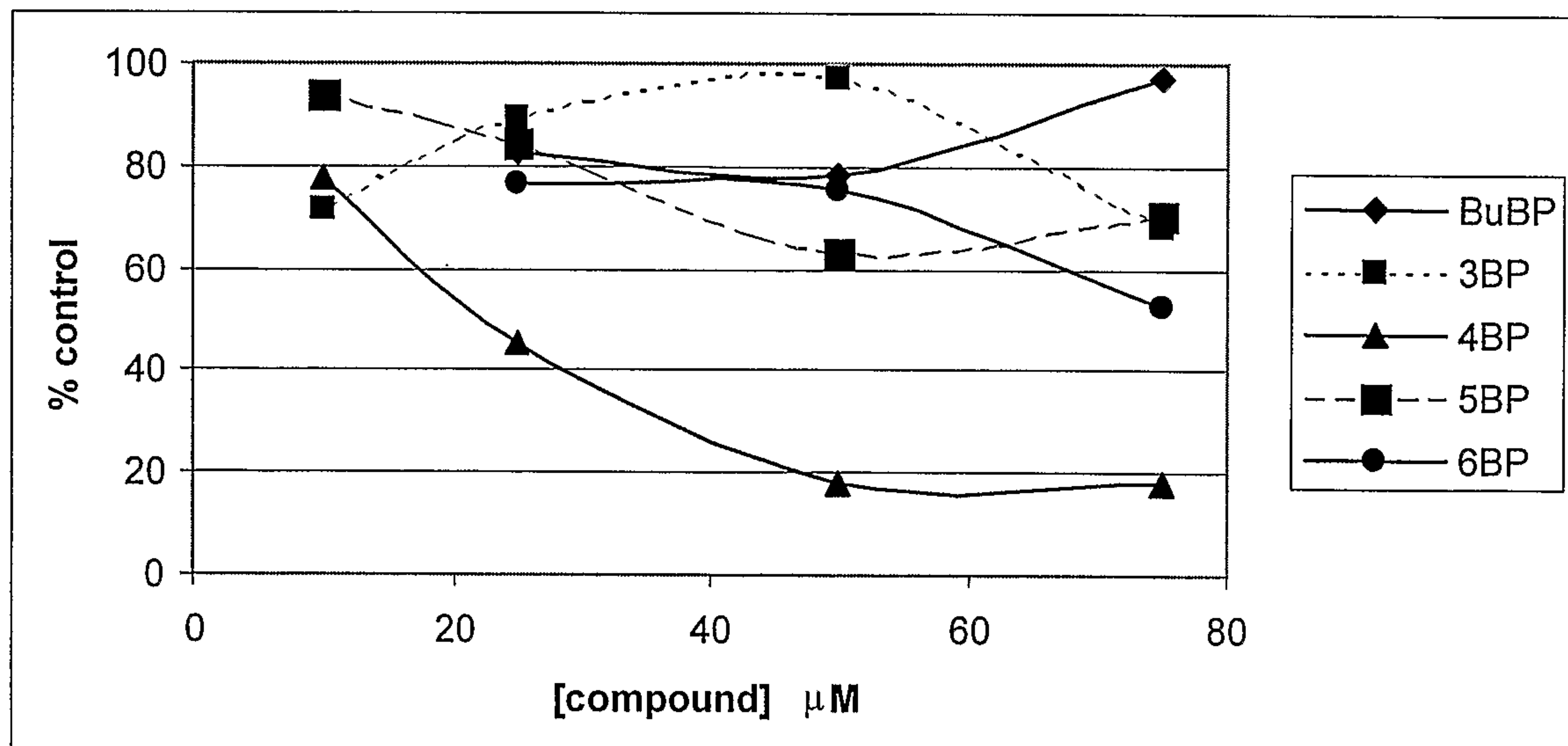


FIGURE 18



10/10**FIGURE 19**