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(54) Title: NOVEL AMINE-BORANE COMPOUNDS AND USES THEREOF

(57) Abstract: Novel families of amine-borane compounds, including fluorinated aminoboranes, novel bis-aminoboranes and aminoboranes having saturated and unsaturated ling alkyl chains are provided. Processes of preparing, pharmaceutical compositions and methods utilizing these novel compounds are also provided. Radiolabeled aminoboranes and uses thereof in radioimaging (e.g., PET) and radiotherapy are further provided.



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NOVEL AMINE-BORANE COMPOUNDS AND USES THEREOF

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to novel amine-borane compounds and to uses thereof in a variety of therapeutic and diagnostic applications.

In the past few decades, amine-borane compounds have been considered as highly sought synthetic targets. Amine-borane compounds exhibit high similarity to organic compounds mainly due to the atomic radii and the characteristics of the B-N bond, which resemble those of carbon-carbon bonds. Thus, for example, a $\text{H}_2\text{B}-\text{NH}_2$ bond resembles a $\text{H}_2\text{C}=\text{CH}_2$ double bond, while a $\text{H}_3\text{B}\leftarrow\text{NH}_3$ bond resembles a $\text{H}_3\text{C}-\text{CH}_3$ single bond.

Amine-borane compounds such as, for example, α -aminoboronic acids, amine-carboxyboranes, amine-cyanoboranes, and related compounds are therefore isoelectronic and isostructural analogs of many biologically active compounds such as amino acids, neurotransmitters, nucleosides, and nucleic acids and hence can mimic the biological activity of such compounds in the body. Doing so, these boron compounds may act as inhibitors, antagonists and otherwise effectors of many biological systems and hence have been widely recognized as highly potential therapeutic agents.

For example, α -amino alkylboronic acids are analogs of α -amino acids which may act as inhibitors of enzymes involved in amino acid and peptide metabolism. α -Amino alkylboronic acids, in which the carboxyl group of the corresponding amino acids is replaced by a boronic acid function, constitute a unique class of amino acid mimics from which a number of potent enzyme inhibitors were synthesized. The inhibitory activity of such compounds mainly stems from the fact that the tetrahedral adduct of electrophilic boronic acid is a good mimic of the putative tetrahedral transition state or intermediate encountered in the enzymatic hydrolysis or formation of peptides. Since the peptide hydrolysis and formation invariably involves the tetrahedral high energy species in the course of the reaction, these amino acid mimics serve as a general key element for inhibitors of a broad spectrum of proteases and peptide ligases.

Additional amine-boranes and compounds having a bis-borane, and mainly cyano and carboxy borane derivatives of these families are disclosed in U.S. Patent

Nos. 4,301,129, 4,312,989, 4,368,194, 4,550,186, 4,647,555, 4,658,051, 4,740,504, 4,774,354, 4,855,493, 4,977,268, 5,280,119 and 5,312,816 and in Hall, I.H. *et al.*, *J. Pharm. Sci.* **1980**, 69(9), 1025.; Sood, C.K. *et al.*, *J. Pharm. Sci.* **1991**, 80(12), 1133; Dembitsky, V.M., *et al.*, *Tetrahedron* **2003**, 59, 579; E. Shalom *et al.*, *Organometallics*. **2004**, 23, 4396-4399; Berdy, J., *Handbook of Antibiotic Compounds. Part IV*, CRC, **1980**; Fink, K. *et al.*, *Science*, **1948**, 108, 358-9; Hunt, S., *Methods Enzymol.* **1984**, 107, 413-438; Jimenez, E. C. *et al.*, *Biochemistry* **1997**, 36, 984-989; Takroui *et al.*, *Organometallics*, **2004**, 23(11), 2817-2820; and Gyoei, B. *et al.*, *Inorganic Chemistry*, **1998**, 37(20), 5131-5141.

The first amine-cyanoboranes and amine-carboxyboranes which stood-out as pharmacologically promising compounds in the early 1980's [1] were adducts of tertiary low-alkyl ammonium salts, typically trimethylammonium chloride, and sodium cyanoborane. Further derivatization of this basic form afforded amines-boranes with aromatic, heterocyclic and silyl substituents on the amine, substitutions of the boron by low-alkyls and bromine, and esters of amine-carboxyboranes [2].

Model studies had shown that these compounds have potent anticancer activity [3, 4-8], antihyperlipodemic activity [9, 11], anti-obesity activity [9], antiosteoporotic activity [9, 12], anti-inflammatory activity [9, 1, 13], hypolipidemic activity [5, 14], anti-neoplastic activity [15, 16] and other promising biological activities [17], yet their exact mechanism of action is still not fully understood.

For example, amine-cyanoboranes and amine-carboxyborane with varying alkyl chain lengths [7], derivatives and metal complexes [4] thereof were examined in various *in vitro* and *in vivo* experiments [9, 18], and shown to be effective anti-neoplastic and cytotoxic agents with selective activity against single-cell and solid tumors derived from murine and human leukemias, lymphomas, sarcomas, and carcinomas. These agents inhibited DNA and RNA synthesis in preference to protein synthesis in L1210 lymphoid leukemia cells, possibly targeting inosine-monophosphate dehydrogenase. Similar effects on phosphoribosyl-pyrophosphate amido transferase, orotidine-monophosphate decarboxylase, and both nucleoside and nucleotide kinases were also observed, as well as deoxyribonucleotide pool levels reduction in the cells and DNA strand scission.

In experiments conducted with rodents, amine carboxyboranes and amine-cyanoboranes were found to act as potent hypolipidemic agents, lowering both serum cholesterol and triglyceride concentrations, in addition to lowering cholesterol content of very low-density lipoprotein and low-density lipoprotein (LDL) and elevating high-density lipoprotein (HDL) cholesterol concentrations [19]. De novo regulatory enzymes involved in lipid synthesis (e.g., hypocholesterolemic 3-hydroxy-3-methyl-CoA reductase, acyl-CoA cholesterol acyltransferase and sn-glycerol-3-phosphate acyltransferase) were also found to be inhibited by these compounds. Concurrently, these compounds modulated LDL and HDL receptor binding, internalization, and degradation, so that less cholesterol was delivered to the plaques and more was broken down from esters and conducted to the liver for biliary excretion. Tissue lipids in the aorta wall of the rat were reduced and fewer atherosclerotic morphology lesions were present in quail aortas after treatment with the agents. Cholesterol resorption from the rat intestine was reduced in the presence of these compounds. Genetic hyperlipidemic mice demonstrated the same types of reduction after treatment with these compounds. The amine-borane compounds effectively lowered lipids in tissue based on the inhibition of regulatory enzymes in pigs.

The amine-boranes were further found to act as effective anti-inflammatory agents against septic shock, induced edema, pleurisy, and chronic arthritis at 2.5 to 8 mg/kg. Lysosomal and proteolytic enzyme activities were also inhibited. More significantly, the amine-borane compounds were found to exhibit dual inhibitory activity of prostaglandin cyclooxygenase and 5'-lipoxygenase. These compounds also affected cytokine release and white cell migration. Subsequent studies showed that the amine-boranes were potent anti-osteoporotic agents reducing calcium resorption as well as increasing calcium and proline incorporation into mouse pup calvaria and rat UMR-106 collagen [9].

In another study, acyclic amine-carboxyboranes were shown to be more efficacious anti-inflammatory agents and in reducing local pain in mice than indomethacin, pentoxifylline, and phenylbutazone, while on the other hand the heterocyclic amine derivatives as well as amine-carbamoylboranes, amine-carboalkoxyboranes, and amine-cyanoboranes were generally less efficacious. These amine-borane compounds were also pharmaceutically active in rat induced

with edema, rat induced with chronic arthritis, and in pleurisy screens [15, 20]. For example, trimethylamine-carbomethoxyborane, $\text{Me}_3\text{NBH}_2\text{CO}_2\text{Me}$, was found to be an effective hypolipidemic amine-borane in rodents and to exhibit a safe therapeutic index, making it a promising therapeutic agent [21].

Furthermore, amine-carboxyboranes and amine-cyanoboranes were shown to act in synergy with tumor necrosis factor alpha ($\text{TNF}\alpha$) in cytotoxicity and inhibition of DNA synthesis in selected types of cancer cells. The synergistic effect was found to be dependent on the presence of a high affinity $\text{TNF}\alpha$ receptor on the membrane of the cells. This event correlated with increased DNA protein linked breaks, DNA fragmentation and cell death [8].

Apart from having an evident direct therapeutic value, boron containing compounds, and especially compounds which can interact with biological systems, can be used as radiotherapy agents in Neutron Capture Therapy (NCT). NCT is a form of treatment that requires the infusion of an element such as boron or gadolinium and exposure of the patient to a neutron beam from a nuclear reactor. At the present time there are two therapeutic targets, glioblastoma, a highly malignant tumor whose treatment is not satisfactory, and malignant melanoma. Boron Neutron Capture Therapy (BNCT) achieves the selective irradiation and destruction of malignant tumor cells by using boronated compounds having the ^{10}B isotope incorporated therein.

The analogous structure of amine-boranes to naturally occurring biological compounds, make them ideal candidates for designing highly specific ligands of high affinity to a variety of biological targets and systems, rendering these compounds valuable tools for nuclear medicinal and research procedures, apart of being ideal candidates for drug discovery and development. Yet, hitherto, radiolabeled amine-boranes that can be used as radiopharmaceutical compounds have not been taught.

While the presently known amine-boranes compounds have shown to be useful therapeutic agents, these compounds are still far from having an acceptable pharmaceutical profile, eligible for use in humans and animals. These compounds suffer from low affinity to their intended target, and therefore require administration of relatively high doses. The non-specificity and high dosage of the presently

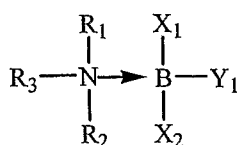
known amine-borane compounds are typically associated with adverse effects and toxicity.

There is thus a widely recognized need for, and it would be highly advantageous to have novel amine-borane compounds devoid of the above limitations.

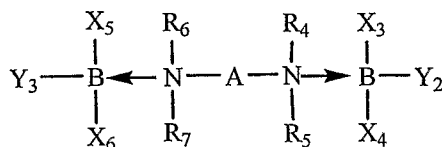
SUMMARY OF THE INVENTION

The present inventors have now designed and successfully prepared and practiced novel classes of amine-borane compounds.

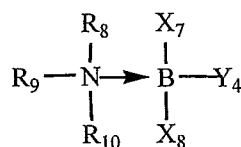
Thus, according to one aspect of the present invention there is provided a compound having a general formula selected from the group consisting of Formula I, II and III:



Formula I



Formula II



Formula III

or a pharmaceutically acceptable salt thereof,

wherein:

Y_1 - Y_4 are each independently selected from the group consisting of a cyano group ($-\text{C}\equiv\text{N}$), a $-\text{C}(=\text{O})\text{Ra}$ group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X_1 - X_8 are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, and aryl, provided that:

at least one of X_1 and X_2 in Formula I is fluorine;

R₁-R₁₀ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl and aryl or, alternatively, two of R₁-R₃, R₄ and R₅, R₆ and R₇ and/or R₈-R₁₀ form a carbocyclic ring, provided that:

one or more of R₈-R₁₀ in Formula III is a saturated alkyl having at least 11 carbon atoms; one or more of R₈-R₁₀ in Formula III is an unsaturated alkyl having 5-20 carbon atoms; and/or one or more of R₈-R₁₀ in Formula III comprises at least one fluorine; and

A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms.

According to further features in preferred embodiments of the invention described below, when the compound comprises fluorine, the fluorine is selected from the group consisting of a non-radioactive fluorine and a radioactive fluorine. Preferably, the radioactive fluorine is fluorine-18 [¹⁸F].

According to still further features in the described preferred embodiments the compound has the general Formula I, wherein Y₁ is preferably a cyano group - (C≡N) or a -C(=O)Ra group and Ra is preferably selected from the group consisting of hydroxy and alkoxy (e.g., methoxy or ethoxy).

According to still further features in the described preferred embodiments X₁ is fluorine and X₂ is selected from the group consisting of hydrogen, fluorine, bromine and iodine. Preferably X₁ is fluorine and X₂ is bromine.

According to still further features in the described preferred embodiments each of R₁-R₃ is alkyl, preferably selected from the group consisting of methyl, ethyl and n-butyl.

According to still further features in the described preferred embodiments at least one of R₁-R₃ is a C₅-C₂₀ alkyl. The alkyl can be a saturated alkyl or an unsaturated alkyl.

According to still further features in the described preferred embodiments non-limiting examples of compounds having Formula I include dimethyl-undecyl-amine cyanofluoroborane, trimethyl-amine cyanofluoroborane, ethyl-dimethyl-amine cyanofluoroborane, butyl-dimethyl-amine cyanofluoroborane, trimethyl-amine carboxyfluoroborane methyl ester, trimethyl-amine carboxyfluoroborane ethyl ester, ethyl-dimethyl-amine carboxyfluoroborane methyl ester, butyl-dimethyl-amine carboxyfluoroborane methyl ester, trimethyl-amine

cyanodifluoroborane, trimethyl-amine carboxydifluoroborane methyl ester, trimethyl-amine carboxydifluoroborane ethyl ester, trimethyl-amine cyanofluorobromoborane, trimethyl-amine carboxyfluorobromoborane ethyl ester, dimethyl-undecyl-amine cyanofluoroborane and triethyl-amine carboxydifluoroborane.

According to still further features in the described preferred embodiments the compound has the general Formula II. Preferably each of Y_2 and Y_3 is a cyano group ($-C\equiv N$). Optionally, each of Y_2 and Y_3 is a $-C(=O)R_a$ group, R_a is selected from the group consisting of hydroxy and alkoxy.

According to still further features in the described preferred embodiments each of X_3 , X_4 , X_5 and X_6 is independently selected from the group consisting of hydrogen, fluorine, bromine and iodine. Preferably one or more of X_3 , X_4 , X_5 and X_6 is bromine.

According to still further features in the described preferred embodiments each of R_4 - R_7 is alkyl (e.g., methyl).

According to still further features in the described preferred embodiments A is a saturated, non-substituted hydrocarbon. Preferably, the hydrocarbon has from 8 to 14 carbon atoms.

According to still further features in the described preferred embodiments non-limiting examples of compounds having Formula II include N,N,N',N' -tetramethyl-decane-1,10-diamine bis-cyanoborane, N,N,N',N' -tetramethyl-decane-1,10-diamine bis-cyanobromoborane, N,N,N',N' -tetramethyl-decane-1,10-diamine bis-cyanodibromoborane, N,N,N',N' -tetramethyl-decane-1,10-diamine bis-carboxyboranes, N,N,N',N' -tetramethyl-dodecane-1,12-diamine bis-cyanoborane and N,N,N',N' -tetramethyl-tetradecane-1,14-diamine bis-cyanoborane.

According to still further features in the described preferred embodiments the compound has the general Formula III.

According to still further features in the described preferred embodiments one or more of R_8 - R_{10} is a saturated alkyl having 11-17 carbon atoms or one or more of R_8 - R_{10} is an unsaturated alkyl having 5-20 carbon atoms.

According to still further features in the described preferred embodiments at least one of R_8 - R_{10} is an unsaturated alkyl.

According to still further features in the described preferred embodiments at least one of R_8 - R_{10} comprises a hydroxy, whereas the hydroxy is at position β to the amine nitrogen.

According to still further features in the described preferred embodiments at least one of R_8 - R_{10} comprises a fluorine, whereas the fluorine is at position β to the amine nitrogen.

According to still further features in the described preferred embodiments Y_1 is selected from the group consisting of a cyano group $-(C\equiv N)$ and a $-C(=O)Ra$ group, as described hereinabove.

According to still further features in the described preferred embodiments each of X_7 and X_8 is independently selected from the group consisting of hydrogen, fluorine, bromine and iodine. Preferably one or more of X_7 and X_8 is bromine.

According to still further features in the described preferred embodiments non-limiting examples of compounds having Formula III include dimethyl-undecyl-amine cyanoborane, dimethyl-undecyl-amine cyanobromoborane, dimethyl-undecyl-amine cyanodibromoborane, dodecyl-dimethyl-amine cyanoborane, 1-dimethylamino-2-methyl-octan-2-ol cyanoborane, dimethyl-nonyl-amine cyanoborane, dimethyl-tridecyl-amine cyanoborane, dimethyl-pentadecyl-amine cyanoborane, heptadecyl-dimethyl-amine cyanoborane, 1-dimethylamino-dodecan-2-ol cyanoborane, 1-dimethylamino-undecan-2-ol cyanoborane, dimethyl-undecyl-amine cyanofluorobromoborane, dimethyl-undecyl-amine cyanofluoroborane, hex-5-enyl-dimethyl-amine cyanoborane and (2-fluoro-nonyl)-dimethyl-amine cyanoborane.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising, as an active ingredient, any of the novel compounds described herein and a pharmaceutically acceptable carrier.

According to still another aspect of the present invention there is provided a method of treating a medical condition associated with a pathogenic microorganism, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds described herein.

According to yet another aspect of the present invention there is provided a use of the novel compounds described herein in the treatment of a medical condition associated with a pathogenic microorganism.

According to an additional aspect of the present invention there is provided a use of the novel compounds described herein for the preparation of a medicament.

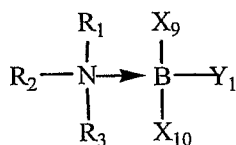
The medicament can be, for example, for the treatment of a medical condition associated with a pathogenic microorganism.

The medical condition can be, for example, a bacterial infection, a protozoan infection, a fungal infection, malaria and leishmaniasis.

Preferably the method of treatment and uses described herein are directed at pathogenic microorganism which are drug-resistant to conventional antimicrobial drugs and agents.

According to a further aspect of the present invention there is provided a process of preparing the compound having the general Formula I, the process comprising:

reacting a compound having the general Formula IV:



Formula IV

or a pharmaceutically acceptable salt thereof,

wherein:

Y_1 is selected from the group consisting of a cyano group $-(C\equiv N)$, a $-C(=O)$ group, amine and alkyl, whereas R_a is hydrogen, halo, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol, and amine;

X_9 and X_{10} are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, aryl, provided that at least one of X_1 and X_2 is bromine; and

R_1 - R_3 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R_1 - R_3 form a carbocyclic ring,

with a fluorinating agent, thereby obtaining the compound having general Formula I.

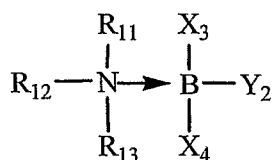
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The fluorinating agent is preferably selected from the group consisting of silver fluoride and a mixture of triethylamine and trihydrofluoride.

The reacting is preferably performed in the presence of a non-polar organic solvent and optionally and preferably comprises sonication of the reaction mixture.

5 According to still a further aspect of the present invention there is provided a process of preparing a compound having the general Formula II, the process comprising:

reacting a compound having the general Formula V:



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Formula V

or a pharmaceutically acceptable salt thereof,

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wherein:

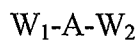
Y_2 is selected from the group consisting of a cyano group $-(C\equiv N)$, a $-C(=O)$ Ra group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

20 X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl; and

R_{11} - R_{13} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R_{11} - R_{13} form a carbocyclic ring, provided that at least one of R_{11} - R_{13} in Formula V is methyl,

with a compound having the general Formula VI:

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Formula VI

wherein:

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A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms; and

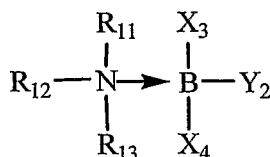
W_1 and W_2 are each independently a functional group,

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in the presence of n-alkyl lithium, thereby obtaining the compound having general Formula II.

According to yet a further aspect of the present invention there is provided a process of preparing a compound having Formula III, wherein at least one of R₈-R₁₀ is a saturated alkyl having 11-17 carbon atoms or an unsaturated alkyl having 5-2-

reacting a compound having the general Formula V:



Formula V

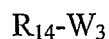
or a pharmaceutically acceptable salt thereof,
wherein:

Y₂ is selected from the group consisting of a cyano group -(C≡N), a -C(=O) group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X₃ and X₄ are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl; and

R₁₁-R₁₃ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R₁₁-R₁₃ form a carbocyclic ring, provided that at least one of R₁₁-R₁₃ in Formula V is methyl,

with a compound having the general Formula VII:



Formula VII

wherein:

R₁₄ is selected from the group consisting of saturated alkyl having at least 10 carbon atoms or an unsaturated alkyl having at least 5 carbon atoms; and

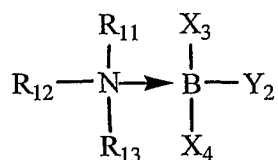
W₃ is a functional group,

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in the presence of n-alkyl lithium, thereby obtaining the compound having general Formula III.

According to another aspect of the present invention there is provided a process of preparing a compound having Formula III, wherein at least of R₈-R₁₀ comprises a fluorine, the process comprising:

reacting a compound having the general Formula V:



Formula V

or a pharmaceutically acceptable salt thereof,

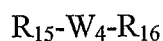
wherein:

Y₂ is selected from the group consisting of a cyano group -(C≡N), a -C(=O) Ra group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X₃ and X₄ are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl; and

R₁₁-R₁₃ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R₁₁-R₁₃ form a carbocyclic ring, provided that at least one of R₁₁-R₁₃ in Formula V is methyl,

with a compound having the general Formula VIII:



Formula VIII

wherein:

W₄ is a carboxy (C=O) group;

R₁₅ is selected from the group consisting of alkyl, cycloalkyl, and aryl; and

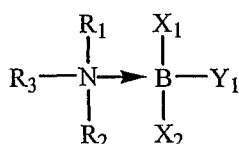
R₁₆ is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl,

in the presence of n-alkyl lithium, to thereby obtaining a compound having the general Formula III, wherein at least one of R₈-R₁₀ comprises a hydroxy or alkoxy; and

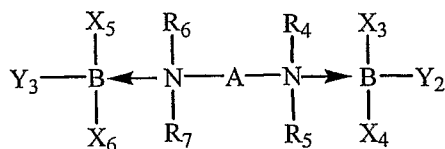
converting the hydroxy or the alkoxy to the fluorine.

Preferably, the converting comprises reacting the compound having the general Formula III and at least of R₈-R₁₀ being a hydroxy or alkoxy, with a fluorinating agent. Exemplary fluorinating agents include triflic anhydride, 2,6-lutidine and cesium fluoride (CsF). Optionally, the fluorinating agent comprises a radioactive fluorine, and most preferably fluorine-18 [¹⁸F].

According to an additional aspect of the present invention there is provided a radiolabeled compound having the general Formula X or XI:



Formula X



Formula XI

or a pharmaceutically acceptable salt thereof,

wherein:

Y₁-Y₃ are each independently selected from the group consisting of a cyano group (-C≡N), a -C(=O) R_a group, amine and alkyl, whereas R_a is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X₁-X₆ are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl,

R₁-R₇ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R₁-R₃, R₄ and R₅ and/or R₆ and R₇ form a carbocyclic ring, and

A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms,

whereas at least one of X₁-X₆, R₁-R₇ and A comprises a radioactive atom and/or at least boron atom is a radioactive boron atom.

According to further features in preferred embodiments of the invention described below, the radioactive atom is selected from the group consisting of radioactive fluorine, radioactive carbon, radioactive bromine and radioactive iodine.

According to still further features in the described preferred embodiments at least one of X_1 - X_6 is the radioactive atom.

Preferably the radioactive atom is radioactive fluorine, and more preferably the radioactive fluorine is fluorine-18 [^{18}F].

According to still further features in the described preferred embodiments at least one of R_1 - R_7 comprises the radioactive atom.

According to still further features in the described preferred embodiments the radioactive atom is a radioactive carbon.

According to still further features in the described preferred embodiments the radioactive atom is a selected from the group consisting of as radioactive fluorine, a radioactive bromine and a radioactive iodine. Preferably, such a radioactive atom is at position β to the amine nitrogen.

According to still further features in the described preferred embodiments the compound has the general Formula X.

According to still further features in the described preferred embodiments at least one of X_1 and X_2 is the radioactive atom.

According to still further features in the described preferred embodiments at least one of R_1 - R_3 comprises a radioactive atom.

According to still further features in the described preferred embodiments the radioactive atom is a radioactive carbon.

According to still further features in the described preferred embodiments at least one of R_1 - R_3 is an alkyl substituted by a radioactive atom.

According to still further features in the described preferred embodiments the radioactive atom is a selected from the group consisting of a radioactive fluorine, a radioactive bromine and a radioactive iodine. Such a radioactive atom is preferably at position β to the amine nitrogen.

According to still further features in the described preferred embodiments at least one of R_1 - R_3 is an alkyl.

According to still further features in the described preferred embodiments each of R_1 - R_3 is alkyl.

According to still further features in the described preferred embodiments the alkyl is selected from the group consisting of methyl, ethyl and n-butyl.

According to still further features in the described preferred embodiments at least one of R_1 - R_3 is a C_5 - C_{20} alkyl.

5 According to still further features in the described preferred embodiments the alkyl is selected from the group consisting of a saturated alkyl and an unsaturated alkyl.

According to still further features in the described preferred embodiments Y_1 is selected from the group consisting of a cyano group $-(C\equiv N)$ and a $-C(=O)Ra$ group.

10 According to still further features in the described preferred embodiments Ra is selected from the group consisting of hydroxy and alkoxy.

According to still further features in the described preferred embodiments Y_1 is selected from the group consisting of a cyano group $-(C\equiv N)$ and a $-C(=O)Ra$ group, wherein Ra is selected from the group consisting of hydroxy and alkoxy (e.g., methoxy and ethoxy).

15 According to still an additional aspect of the present invention there is provided a pharmaceutical composition comprising, as an active ingredient, any of the radiolabeled compounds described herein and a pharmaceutically acceptable carrier.

20 According to yet an additional aspect of the present invention there is provided a use of the radiolabeled compounds presented herein in radioimaging (e.g., positron emitting tomography (PET), Computed Tomography (CT), PET/CT and Single Photon Emission Tomography (SPECT)) and/or radiotherapy. In a preferred embodiment, the radiolabeled compounds are designed suitable for use in a radioimaging technique such as positron emitting tomography.

25 According to yet an additional aspect of the present invention there is provided a use of the radiolabeled compounds presented herein in the preparation of a diagnostic agent.

30 According to yet an additional aspect of the present invention there is provided a method of radioimaging which includes administering to a patient the radiolabeled compound(s) presented herein in or the composition presented herein

and employing a radioimaging technique for monitoring a distribution of the radiolabeled compound within the body or within a portion thereof.

According to features in the described preferred embodiments the radioimaging technique is selected from the group consisting of Positron Emission
5 Tomography (PET), Computed Tomography (CT), PET/CT and Single Photon Emission Tomography (SPECT).

The present invention successfully addresses the shortcomings of the presently known configurations by providing novel classes of amine-borane compounds which possess unique and novel features that render these compounds
10 superior to other amine-borane compounds known in the art and further enable to efficiently produce radiolabeled amine-borane compounds.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent
15 to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

20 The term "comprising" means that other steps and ingredients that do not affect the final result can be added. This term encompasses the terms "consisting of" and "consisting essentially of".

The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional
25 ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method.

As used herein, the singular form "a," "an," and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds,
30 including mixtures thereof.

Throughout this disclosure, various aspects of this invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an

inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases “ranging/ranges between” a first indicate number and a second indicate number and “ranging/ranges from” a first indicate number “to” a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 presents a plot showing the antilishmenial effect of Compound **K-I** as determined by a dose-response assay against the *Leishmania donovani* strain;

FIG. 2 presents a plot showing the antimalarial effect of Compound **K-I** as determined by a dose-response assay against the *Plasmodium falciparum* strain;

FIG. 3 presents a schematic illustration of a semiautomatic radiolabeling synthesis system designed to safely and efficiently prepare ^{18}F -labeled amine-borane compounds according to the present embodiments;

FIG. 4 presents a schematic illustration of a 25 ml platinum dish designed for and utilized in the semiautomatic radiolabeling synthesis of ^{18}F -labeled amine-borane compounds according to the present embodiments; and

FIG. 5 presents a series of PET-images obtained for normal, female Sprague-Dawley rats (250-300 grams each) which were injected with an exemplary ^{18}F -radiolabeled amine-borane compound according to the present embodiments, Compound [^{18}F]K-I₄ (4.5 mCi/ml), clearly showing the uptake of the ^{18}F -radiolabeled amine-borane compound into the bones of the tested rats.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of novel families of amine-borane compounds, which can be beneficially used in the treatment of a variety of medical conditions and other applications. The present invention is further of novel, radiolabeled amine-borane compounds, which can be used in radioimaging and/or radiotherapy.

As discussed hereinabove, amine-boranes are promising compounds which have a great potential as therapeutic agents, mostly due to their similarity to biologically occurring molecules, such as amino acids, neurotransmitters, nucleosides, and nucleic acids. Amine-boranes are isoelectronic and isostructural analogs of such biomolecules and hence are capable of mimicking the biological activity thereof in the body. However, the use of the presently known amine-boranes as therapeutic agents is oftentimes limited by poor efficacy and inferior pharmacokinetic profile.

In a search for novel amine-borane compounds, the present inventors have designed and successfully prepared and practiced novel families of amine-borane compounds. The present inventors have uncovered that by altering the chemical structure of amine-borane compounds and adding functionalities thereto, a spectrum of active, efficacious and non-toxic therapeutic agents are obtained.

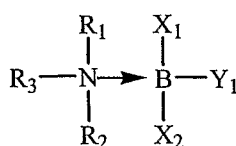
As used herein, the phrase "amine-borane compounds", which is also referred to herein interchangeably as "aminoboranes", describes any compound that includes at least one boron atom that is substituted by one or more amine group(s), as is defined hereinunder.

While conceiving the present invention, it was envisioned that since halogenated biologically occurring molecules, in particular naturally occurring

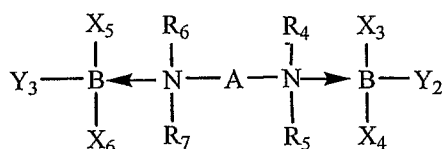
organofluoride compounds, are metabolically active substances and are hence very intriguing, particularly in medicinal chemistry, fluorinated amine-borane compounds may provide an improved class of aminoborane compounds, which can be further utilized in radioimaging applications. It was further hypothesized that the activity and pharmacokinetic profile of amine-borane compounds can be improved by incorporating therein an elongated hydrocarbon chain (e.g., a long alkyl).

While reducing the present invention to practice, as is demonstrated in the Examples section that follows, the present inventors have successfully prepared novel families of amine cyanoboranes and amine carboxyboranes, as well as amine bis-boranes, primarily fluorinated and/or including a long hydrocarbon chain.

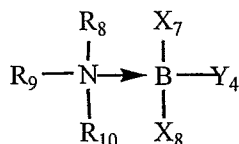
The present invention therefore provides amine-borane compounds and/or a pharmaceutically acceptable salt thereof, having the general Formula I, II or III:



Formula I



Formula II



Formula III

or a pharmaceutically acceptable salt thereof, wherein:

each of Y₁-Y₄ is independently a cyano group (-C≡N), a -C(=O)Ra group, amine or alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

each of X₁-X₈ is independently hydrogen, alkyl, halogen, cycloalkyl, aryl, whereby one or more of X₁ and X₂ in Formula I is fluorine;

each of R₁-R₁₀ is independently hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R₁-R₃, R₄ and R₅, R₆ and R₇ and/or R₈-R₁₀ form a carbocyclic ring, whereby one or more of R₈-R₁₀ in Formula III is a saturated alkyl having at

least 11 carbon atoms, one or more of R₈-R₁₀ in Formula III is an unsaturated alkyl having 5-20 carbon atoms and/or one or more of R₈-R₁₀ in Formula III is substituted by fluorine; and

A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms.

As used herein, the term "halogen", which is also referred to herein as "halo" describes a radical of fluorine, chlorine, bromine or iodine.

As used herein, the term "hydroxy" describes an -OH group.

The term "alkoxy" describes a -OR group, where R is alkyl or cycloalkyl, as these terms are defined herein.

The term "thiohydroxy" or "thiol" refers to a -SH group.

The term "thioalkoxy" describes a -SR group, where R is alkyl or cycloalkyl.

The term "aryloxy" describes both an -O-aryl and an -O-heteroaryl group, as defined herein.

The term "thioaryloxy" describes both a -S-aryl and a -S-heteroaryl group, as defined herein.

As used herein, the term "amine" describes a -NR'R" group where each of R' and R" is independently hydrogen, alkyl, cycloalkyl or aryl, as these terms are defined herein.

As used herein, the term "alkyl" describes an aliphatic, and unsaturated (alkenyl and alkynyl) hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms. Whenever a numerical range; e.g., "1-20", is stated herein, it implies that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. The alkyl can be substituted or unsubstituted. the alkyl can further be saturated or unsaturated. This term therefore encompasses alkenyl and alkynyl.

The term "alkenyl" describes an unsaturated alkyl having at least two carbon atoms and at least one carbon-carbon double bond.

The term "alkynyl" an unsaturated alkyl having at least two carbon atoms and at least one carbon-carbon triple bond.

The term "cycloalkyl" describes an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group where one or more of the rings does not have a completely conjugated pi-electron system.

The term "aryl" describes an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system.

The compounds disclosed herein, represented by Formulae I, II and III, possess unique and novel features, as discussed hereinbelow.

In preferred embodiments of the present invention, the novel families of aminoboranes disclosed herein include cyano amino boranes and carboxy amino boranes.

Thus, in each of Formulae I, II and III above, Y_1 is a cyano group ($-C\equiv N$) being attached to the boron atom, or a carboxy group, $-C(=O)Ra$, being attached to the boron atom.

The Ra group may be a hydrogen, defining the $-C(=O)Ra$ group as an aldehyde; an alkoxy or aryloxy group, defining the $-C(=O)Ra$ group as an ester; a halo, defining the $-C(=O)Ra$ group as an acyl halide; a hydroxyl, defining the $-C(=O)Ra$ group as a carboxylic acid; a thiohydroxy (thiol), defining the $-C(=O)Ra$ group as a thiocarboxylic acid; a thioalkoxy or thioaryloxy, defining the $-C(=O)Ra$ group as a thioester; and an amine, defining the $-C(=O)Ra$ group as an amide. Preferably Ra is a hydroxyl or alkoxy, and preferably the alkoxy is methoxy group or ethoxy group.

In additional preferred embodiments of the present invention, the other two substituents on the boron atom, denoted as X_1 - X_8 in Formulae I, II and III, are hydrogen or halogen, preferably bromine or fluorine.

In still additional preferred embodiments of the present invention, at least one of X_1 - X_8 is fluorine.

While reducing the present invention to practice, the present inventors have surprisingly uncovered that the presence of a fluorine atom in aminoborane compounds imparts to the compounds unique and novel features.

The improved activity of fluorinated aminoboranes is discussed below and is demonstrated in the Examples section that follows, where the activity of various structurally diverse aminoboranes was tested against various microorganisms.

These studies, as well as the beneficial effect of the incorporation of a fluorine atom, are further discussed in detail in U.S. Provisional Patent Application No. 60/716,082, filed September 13, 2005, and in a PCT International Patent Application, by the present assignee, having Attorney Docket No. 32561 and
5 entitled "use of amine-borane compounds as anti-microbial agents", which is co-filed on the same date as the instant application, both being incorporated herein as if fully set forth herein.

In particular preferred embodiments of the present invention, the amine-borane compound has the general Formula I above, and one or both of X_1 and X_2
10 is/are fluorine. Such compounds represent a novel class of aminoboranes.

Preferred compounds having general Formula I and one or more fluorine substituents on the boron atom are those in which at least one and preferably all of R_1 , R_2 and R_3 in Formula I, is a saturated or unsaturated low alkyl. Representative examples include compounds in which each of R_1 , R_2 and R_3 is a low alkyl such as
15 methyl, ethyl and n-butyl.

Additionally preferred compounds in this class are those in which one or more of R_1 , R_2 and R_3 is a saturated and unsaturated high alkyl group having from 5 to 20 carbons.

As is demonstrated in the Examples section that follows, the present
20 inventors have designed and successfully prepared and practiced several exemplary members of this class of compounds. These include, for example, dimethyl-undecyl-amine cyanofluoroborane, trimethyl-amine cyanofluoroborane, ethyl-dimethyl-amine cyanofluoroborane, butyl-dimethyl-amine cyanofluoroborane, trimethyl-amine carboxyfluoroborane methyl ester, trimethyl-amine
25 carboxyfluoroborane ethyl ester, ethyl-dimethyl-amine carboxyfluoroborane methyl ester, butyl-dimethyl-amine carboxyfluoroborane methyl ester, trimethyl-amine cyanodifluoroborane, trimethyl-amine carboxydifluoroborane methyl ester, trimethyl-amine carboxydifluoroborane ethyl ester, trimethyl-amine cyanofluorobromoborane, trimethyl-amine carboxyfluorobromoborane ethyl ester,
30 dimethyl-undecyl-amine cyanofluoroborane and triethyl-amine carboxydifluoroborane.

While further reducing the present invention to practice, the present inventors have uncovered that the incorporation of a long N-alkyl chain to amine-

borane compounds further improves the activity thereof. The present inventors have conducted a structure-activity relation studies and have uncovered that the length of such an alkyl chain strongly affects the activity of the compounds. Therefore, the preferred chain length for one or more of R_1 - R_3 or R_8 - R_{10} the compounds having the general Formulae I and III, according to the present invention, and particularly to one or more of R_8 - R_{10} in Formula III, is between eleven and fifteen carbon-long chain, and more preferred is a fifteen long (C_{15}) chain, as demonstrated for Compound **K-R** (see, Table 2 hereinbelow).

While further reducing the present invention to practice, it was found that the presence of an unsaturated $C=C$ double bond in an alkyl substitution in one or more of R_1 - R_{10} in Formulae I, II and III and particularly in one or more of R_8 - R_{10} in Formula III, preferably at the terminal position of the unsaturated alkyl group, dramatically enhanced the biologic activity of the amine-borane compound. This finding is demonstrated in the Examples section that follows in Example 2 as presented for Compound **K-D** and Compound **K-V**. Therefore one or more of R_8 - R_{10} in Formula III is preferably an unsaturated alkyl group having 5-20 carbon atoms.

While further reducing the present invention to practice, the present inventors have prepared and tested the efficacy of a number of the above-described diamine bis-cyanoboranes belonging to Formula II, as presented hereinbelow in the Examples section that follows. In general, the efficacy results for these compounds indicated that the compounds having a longer N-alkyl-N chain exhibited higher bioactivity activity. Therefore, the preferred length of A in Formula II (the N-alkyl-N chain), according to the present invention, is a fourteen carbon-long chain (C_{14}), as demonstrated for Compound **K-N** (see, Table 2 hereinbelow).

Thus, according to additional preferred embodiments of the present invention, the amine-borane compound has the general Formula II. Such amine-borane compounds constitutes another class of novel compounds which have a bis-amine-borane functionality, namely, have two amine-borane functionalities, each of which is defined similarly to the amine-borane functionality described hereinabove, whereby the moiety linking these functionalities is a hydrocarbon chain being at least 5 carbons in length.

As is demonstrated in the Examples section that follows, the present inventors have designed and successfully prepared several exemplary members of this class of compounds. These include, for example, N,N,N',N'-tetramethyl-decane-1,10-diamine bis-cyanoborane, N,N,N',N'-tetramethyl-decane-1,10-diamine
 5 bis-cyanobromoborane, N,N,N',N'-tetramethyl-decane-1,10-diamine bis-cyanodibromoborane, N,N,N',N'-tetramethyl-decane-1,10-diamine bis-carboxyboranes, N,N,N',N'-tetramethyl-dodecane-1,12-diamine bis-cyanoborane and N,N,N',N'-tetramethyl-tetradecane-1,14-diamine bis-cyanoborane.

According to still additional preferred embodiments of the present
 10 invention, the amine-borane compounds have the general Formula III. Such compounds constitutes a novel class of compounds which have a unique and novel feature being primarily the saturated and unsaturated high alkyl group having from 5 to 20 carbons at one or more of R₈-R₁₀, and secondarily may have a substituent at position β to the amine nitrogen on one or more of R₈-R₁₀.

15 Preferably, the substituent at position β to the amine nitrogen is a hydroxyl or a fluorine; the latter constitutes a unique and novel feature of this group of amine-borane compounds.

The present inventors have designed and successfully prepared several exemplary members of this class of compounds, including, for example, dimethyl-
 20 undecyl-amine cyanoborane, dimethyl-undecyl-amine cyanobromoborane, dimethyl-undecyl-amine cyanodibromoborane, dodecyl-dimethyl-amine cyanoborane, 1-dimethylamino-2-methyl-octan-2-ol cyanoborane, dimethyl-nonyl-amine cyanoborane, dimethyl-tridecyl-amine cyanoborane, dimethyl-pentadecyl-amine cyanoborane, heptadecyl-dimethyl-amine cyanoborane, 1-dimethylamino-
 25 dodecan-2-ol cyanoborane, 1-dimethylamino-undecan-2-ol cyanoborane, dimethyl-undecyl-amine cyanofluorobromoborane, dimethyl-undecyl-amine cyanofluoroborane, hex-5-enyl-dimethyl-amine cyanoborane and (2-fluoro-nonyl)-dimethyl-amine cyanoborane.

While further conceiving the present invention, it was envisioned that these
 30 novel fluorinated amine-borane compounds, which may possess similar or improved activities as compared with their non-fluorinated counterparts, will offer the possibility of introducing a detectible isotope thereto in the form of ¹⁸F (fluorine-18), thus rendering novel radiolabeled amine-borane compounds.

Therefore, as is further detailed hereinbelow, according to an embodiment of the present invention, an ^{18}F isotope can replace any or all of the fluorine atoms in each and every one of the compounds having the Formulae I, II and III, as described hereinabove.

5 While further reducing the present invention to practice, a series of structurally diverse amine-borane compounds according to the present invention were prepared and assayed for antimicrobial activity, as demonstrated in the Examples section that follows. These assays have clearly shown that the compounds presented herein exhibit exceptional and selective antimicrobial
10 activity, mostly in a dose-dependent manner, as compared to amine-borane compounds taught in the art and to conventionally used antifungal agents and drugs.

The compounds according to the present invention were tested for antifungal activity against pathogenic and antibiotic-resistant strains. A number of relationships were observed according to their structural type. The following
15 modifications in the structure significantly enhanced the activity: (i) the N-alkyl chain length in alkyl dimethylamine cyanoboranes and diamine bis-cyanoboranes, (ii) halogenation, (iii) the incorporation of the C=C double bond at the end of the N-alkyl chain, and (iv) the conversion of the amine cyanoborane to the amine carboxyborane. However, no significant enhancement of activity was observed
20 with other modifications in the structure, such as addition of a hydroxyl group, an aromatic group, an unsaturated cyclic group, and a silyl group. As presented in details in the Examples section that follows, in Example 2, the most active compounds were dimethylundecylamine cyanoborane ($\text{C}_{11}\text{H}_{23}\text{N}(\text{CH}_3)_2\text{BH}_2\text{CN}$) Compound **K-I**, with MIC values for the most important human pathogenic fungi
25 ranging from 16.25 to 32.5 μmol per liter, and its dibromo derivative, dimethylundecylamine dibromocyanoborane ($\text{C}_{11}\text{H}_{23}\text{N}(\text{CH}_3)_2\text{BBr}_2\text{CN}$) Compound **K-I₂**, in which the MIC values ranged from 10.05 to 79 μmol per liter. These compounds possess considerable activity against fungal strains which are resistant to fluconazole. Anti-leishmanial and anti-malarial, as well as reduced toxicity was
30 also observed with these compounds.

Particularly the amine-borane compounds presented herein were found highly effective against several highly virulent fungi such as *Aspergillus fumigatus*.

More particularly the compounds of the present invention were shown to have high antifungal antimicrobial active against drug-resistant fungi strains, such as the highly malicious *Candida glabrata* and *Candida krusei* which are known to be resistant to fluconazole, a conventional and widely used antifungal drug, as demonstrated in the Examples section that follows.

Candida glabrata, *Candida krusei* and *Aspergillus fumigatus* have been recognized as highly pernicious pathogens, and are considered as the one of the most frequent fatal factor among the ever increasing population of immunocompromised individuals. Recent studies have shown *Candida glabrata* and *Candida krusei* to be highly opportunistic pathogens of the urogenital tract, and of the bloodstream (Candidemia) which is especially prevalent in HIV positive people, and the elderly.

Resistance of microorganism to antimicrobial agents is the ability of a microorganism to withstand the antimicrobial effects of any given agents (antibiotics). The antimicrobial action of any given agent is putting an environmental pressure on the target (and also non-targeted) microorganisms. The microorganisms which have a mutation that will allow it to survive will live on to reproduce. These newly evolved strain(s) will then pass this trait to their offspring, which will constitute a fully resistant generation. Resistance can develop naturally via natural selection through random mutation and programmed evolution governed by low-fidelity polymerases which can cause a higher rate of random mutations in the microorganism genetic code. Once such a gene is generated, the microorganism may also transfer the genetic information in a horizontal fashion, namely between individuals, via plasmid exchange, hence resistance is a consequence of evolution via natural selection or programmed evolution.

It has been demonstrated that habitude of antimicrobial agents usage greatly affects the number of resistant organisms which develop. For example, overuse of broad-spectrum antibiotics of low specificity, such as second- and third-generation cephalosporins and fungicides such as fluconazole, greatly accelerated the development of methicillin or fluconazole resistance, even in organisms that have never been exposed to the selective pressure of methicillin or fluconazole *per se*. Other factors contributing to the ever growing emergence of resistance to antimicrobials include incorrect diagnosis, unnecessary prescriptions, improper use

of antimicrobials by patients, and the use of antimicrobials in livestock food as additives for growth promotion.

Thus, according to another aspect of the present invention, there is provided a method of treating a medical condition associated with a pathogenic microorganism. The method is effected by administering to a subject in need thereof a therapeutically effective amount of an amine-borane compound according to the present embodiments.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "preventing" includes barring an organism from acquiring a condition in the first place.

As used herein, the terms "treating" and "treatment" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

As used herein, the phrase "therapeutically effective amount" describes an amount of the compound being administered which will relieve to some extent one or more of the symptoms of the condition being treated.

According to embodiments of this aspect of the present invention, the medical condition associated with a pathogenic microorganisms include bacterial infections, protozoan infections and a fungal infection, and preferably the medical conditions wherein use of the amine-borane of the present invention is beneficial are malaria and leishmaniasis, as demonstrated and exemplified in the Examples section that follows.

As used herein, the phrase "pathogenic microorganism" describes any microorganism which can cause a disease or infection in a higher organism, such as any animals grown for commercial or recreational purposes, fish, poultry, insects (e.g., bees) and mammals. In particular, the pathogenic microorganisms maybe those which cause diseases and adverse effects in humans. The pathogenic

microorganism may belong to any family of organisms such as, but not limited to, prokaryotic organisms, eubacterium, archaebacterium, eukaryotic organisms, yeast, fungi, algae, protozoa, and other parasites.

As used herein the term "associated" in the context of the present invention means that at least one adverse manifestation of the medical condition is caused by a pathogenic microorganism. The phrase "medical condition associated with a pathogenic microorganism" therefore encompasses medical conditions of which the microorganism may be the primary cause of the medical condition or a secondary effect of the main medical condition(s).

Medical conditions associated with a pathogenic microorganism include infections, infestation, contaminations and transmissions by or of pathogenic microorganisms such as those described herein. In general, a disease causing infection is the invasion into the tissues of a plant or an animal by pathogenic microorganisms. The invasion of body tissues by parasitic worms and other higher pathogenic organisms such as lice is oftentimes referred to as infestation.

According to a preferred embodiment of this aspect of the present invention, the pathogenic microorganism is a drug-resistant pathogenic microorganism, as discussed hereinabove.

Acute toxicity assays were conducted for an exemplary compound according to the present invention using rats as an animal model. As demonstrated in the Examples section that follows, the amine-borane compounds presented herein have been shown to be non-toxic at the effective concentration range thereof and higher.

In any of the above aspects of the present invention, the amine-borane compounds of the present invention can be utilized either *per se* or, preferably, as a part of a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier.

Thus, according to additional aspects of the present invention, there are provided pharmaceutical compositions, which are identified for use in the treatment of any of the medical conditions listed above, and which comprise one or more amine-borane compounds and a pharmaceutically acceptable carrier.

In addition there is provided a use of the compounds presented herein in the preparation of a medicament. The medicament can be used to treat any of the

conditions known in the art to be treatable by amine-borane as discussed hereinabove, and particularly those associated with pathogenic microorganisms.

As used herein a "pharmaceutical composition" refers to a preparation of amine-borane compounds, with other chemical components such as pharmaceutically acceptable and suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

Hereinafter, the term "pharmaceutically acceptable carrier" refers to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound. Examples, without limitations, of carriers are: propylene glycol, saline, emulsions and mixtures of organic solvents with water, as well as solid (e.g., powdered) and gaseous carriers.

As used herein, the term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered.

Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the silver-coated enzymes into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

The pharmaceutical composition may be formulated for administration in either one or more of routes depending on whether local or systemic treatment or administration is of choice, and on the area to be treated. Administration may be done topically (including ophtalmically, vaginally, rectally, intranasally), orally, by
5 inhalation, or parenterally, for example by intravenous drip or intraperitoneal, subcutaneous, intramuscular or intravenous injection.

Formulations for topical administration may include but are not limited to lotions, ointments, gels, creams, suppositories, drops, liquids, sprays and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners
10 and the like may be necessary or desirable.

Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, sachets, capsules or tablets. Thickeners, diluents, flavorings, dispersing aids, emulsifiers or binders may be desirable.

15 Formulations for parenteral administration may include, but are not limited to, sterile solutions which may also contain buffers, diluents and other suitable additives. Slow release compositions are envisaged for treatment.

The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of
20 administration, the judgment of the prescribing physician, etc.

Compositions of the present invention may, if desired, be presented in a pack or dispenser device, such as an FDA (the U.S. Food and Drug Administration) approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such
25 as, but not limited to a blister pack or a pressurized container (for inhalation). The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval
30 by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a silver-coated enzyme of the invention

formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition or diagnosis, as is detailed hereinabove.

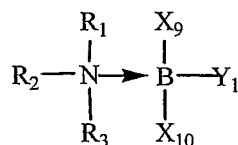
Thus, according to an embodiment of the present invention, depending on the selected amine-borane compound, the pharmaceutical compositions of the present invention are packaged in a packaging material and identified in print, in or on the packaging material, for use in the treatment of a medical condition associated with a pathogenic microorganism, as is defined hereinabove.

The present invention further encompasses processes of preparing any of the compounds disclosed herein, as is described hereinbelow and is further detailed in the Examples section that follows.

Hence, according to another aspect of the present invention there is provided a process of preparing the compounds having the general Formula I presented above. The process is generally effected by providing a corresponding brominated aminoborane, having one or more bromines on the boron, and converting either one or both bromines into fluorines, via reaction with a fluorinating agent. While some of the brominated starting materials are known, some have been specifically designed for use in the context of the present invention. In general, brominated amine-borane compounds are prepared using known procedures, as indicated in the Examples section that follows.

The process according to this aspect of the present invention is therefore effected by:

reacting, with a fluorinating agent, a brominated compound having the general Formula IV:



Formula IV

or a pharmaceutically acceptable salt thereof, wherein Y_1 is a cyano group, a $-\text{C}(=\text{O})\text{Ra}$ group, amine or alkyl, whereas Ra is as defined hereinabove; each of X_9 and X_{10} is hydrogen, alkyl, halogen, cycloalkyl, or aryl, provided that at least one

of X_9 and X_{10} is bromine; and each of R_1 - R_3 are as defined hereinabove for Formula I.

Basically, this process takes advantage of a trait of the bromo substituent on the boron atom to act as a good leaving group, and be replaced by a fluorine. The bromo substituent is more prone to such a substitution reaction than, for example, a hydrogen or an alkyl substituent, hence the same process can be utilized to replace a single bromo or two bromo substituents on the boron atom. Thus the process of preparing this group of compounds is essentially a bromo-to-fluoro exchange process.

Thus, in one particular, the starting compound can be a compound having Formula IV, wherein one of X_9 and X_{10} is bromine. This compound can be obtained by reacting a non-halogenated amine-borane compound with 1 equivalent of a brominating agent, and is then reacted with a fluorinating agent, to provide the desired compounds having Formula I. Alternatively, the starting can be a compound having Formula IV, wherein both X_9 and X_{10} are bromine. This compound can be obtained by reacting a non-halogenated amine-borane compound with 2 equivalents of a brominating agent, and is then reacted with a fluorinating agent, to provide the desired compound having Formula I.

This bromo-to-fluoro exchange process can be effected by using any fluorinating agent(s) as these are known to a person skilled in the art. Representative examples of fluorinating agents that have been shown suitable for use in the context of the present invention include, without limitation, silver fluoride and a mixture of triethylamine and trihydrofluoride.

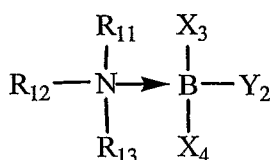
According to preferred embodiments, the process according to this aspect of the present invention is performed in an organic solvent and preferably in a non-polar organic solvent such as toluene or benzene. In order to accelerate the reaction, the process is preferably performed while subjecting the reaction mixture to sonication.

As described hereinabove, the compounds described herein can comprise a fluorine which is either radioactive or non-radioactive. Compounds having general Formula I and a radioactive fluorine can be readily prepared using the process described herein, by performing the fluorination reaction with a fluorinating agent that comprises a radioactive fluorine (e.g., a ^{18}F isotope). Exemplary fluorinating

agents in this respect include, for example, $K^{18}F$, $H^{18}F$ and $Ag^{18}F$. The preparation and use of the ^{18}F -radiolabeled amine-borane compounds presented herein is further discussed hereinbelow.

According to another aspect of the present invention, there is provided a process of preparing the amine bis-borane compounds having the general Formula II presented above. The process, according to this aspect of the present invention, is effected by:

reacting a compound having the general Formula V:



Formula V

or a pharmaceutically acceptable salt thereof, wherein Y_2 is as defined hereinabove; X_3 and X_4 are as defined hereinabove; and R_{11} - R_{13} are each independently hydrogen, alkyl, cycloalkyl or aryl or, alternatively, two of R_{11} - R_{13} form a carbocyclic ring, provided that at least one of R_{11} - R_{13} in Formula V is methyl,

with a compound having the general Formula VI:



Formula VI

wherein:

A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms; and W_1 and W_2 are each independently a functional group;

in the presence of n-alkyl lithium..

As used herein, the phrase "functional group" describes a chemical group that enables the occurrence of a chemical reaction that typically leads to a bond formation. The bond, according to the present invention, is preferably a covalent bond. Chemical reactions that lead to a bond formation include, for example,

nucleophilic and electrophilic substitutions, nucleophilic and electrophilic addition reactions, addition-elimination reactions, cycloaddition reactions, rearrangement reactions and any other known organic reactions that involve a functional group.

Herein, the functional group is preferably a leaving group. As used herein, the phrase "leaving group" describes a labile group that readily undergoes detachment from an organic molecule during a chemical reaction, while the detachment is facilitated by the relative stability of the leaving atom thereafter. Typically, any group that is the conjugate base of a strong acid can act as a leaving group. Preferably, the leaving group is a halo, and most preferably it is bromo.

Thus, according to preferred embodiments of the process according to this aspect of the present invention, the n-alkyl lithium acts as a strong base, which converts the methyl substituting the amine in the starting compound into an anion.

In one particular, two equivalents of such an anion react with a compound having Formula VI, replacing the functional leaving groups W_1 and W_2 , to thereby form the bis-borane compound. Alternatively, the same process can be performed in steps, so as to allow the sequential attachment of two different units of the starting amine-borane (having Formula V) to the hydrocarbon moiety in the compound having Formula VI. Thus, for example, a compound having Formula VI can have a protected or inactivated functional group at one end. An activated (ionized) amine-borane compound reacts with the functional end of the compound of Formula VI and thereafter the inactivated functional group is activated, so as to react with another activated amine-borane, so as to form the amine bis-borane compound having Formula II.

Each of the amine-borane compounds used in this process as a starting material, having Formula V above, can be either prepared by known methods or can be one of the novel compounds disclosed herein.

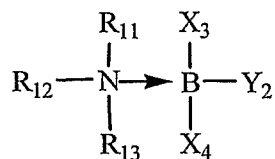
As the above process is basically an alkylating process for one or more of the substituents on the amine, a similar process can be effected to prepare novel amine-borane compounds having a high alkyl substituent.

Hence, according to yet another aspect of the present invention, there is provided a process of preparing the compound having the general Formula III presented above, wherein at least of R_8 - R_{10} is a saturated alkyl having 11-17 carbon

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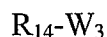
atoms or an unsaturated alkyl having 5-20 carbon atoms. The process, according to this aspect of the present invention, is effected by:

reacting a compound having the general Formula V:



Formula V

or a pharmaceutically acceptable salt thereof, wherein Y_2 is as defined hereinabove; X_3 and X_4 are as defined hereinabove; and R_{11} - R_{13} are as defined hereinabove, provided that at least one of R_{11} - R_{13} in Formula V is methyl, with a compound having the general Formula VII:



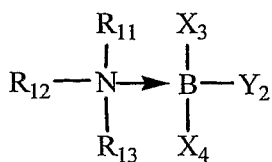
Formula VII

wherein R_{14} is selected from the group consisting of saturated alkyl having at least 10 carbon atoms or an unsaturated alkyl having at least 4 carbon atoms; and W_3 is a functional group, as this term is defined hereinabove, in the presence of n-alkyl lithium.

The methodology used in this process is similar to that described above with respect to the preparation of compounds having the general Formula II. Such a methodology can be practiced with both saturated and unsaturated high alkyls.

According to yet another aspect of the present invention, there is provided a process of preparing the compound having the general Formula III presented above, wherein at least of R_8 - R_{10} includes an hydroxy, alkoxy or fluorine. The process according to this aspect of the present invention is effected by:

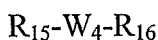
reacting a compound having the general Formula V:



Formula V

or a pharmaceutically acceptable salt thereof, wherein Y_2 is as defined hereinabove; X_3 and X_4 are as defined hereinabove; and R_{11} - R_{13} are as defined hereinabove,

5 with a compound having the general Formula VIII:



Formula VIII

10 wherein W_4 is a carboxy ($C=O$) group; R_{15} is selected from the group consisting of alkyl, cycloalkyl, and aryl; and R_{16} is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl, as these terms are defined hereinabove,

15 in the presence of n-alkyl lithium, so as to obtain a compound having general Formula III, wherein at least one of R_8 - R_{10} comprises a hydroxy or alkoxy.

The methodology used in this process is similar to that described above with respect to compounds having general Formula II or III. However, when an activated compound having Formula V is reacted with a compound having a carboxy group, as in Formula VIII, the product resulting from the addition reaction
20 has an hydroxy or alkoxy functionality, depending on the chemistry of the reacting compound (having Formula VIII).

In a preferred embodiment of this aspect of the present invention, in the compound having Formula V, at least one of R_8 - R_{10} is methyl, such that upon reacting with a compound having Formula VIII, a hydroxy or alkoxy groups at
25 position β to the amine are obtained.

The introduction of a hydroxyl or alkoxy group into the amine-borane compounds may alter the aqueous solubility of these compounds and may be used to change and improve their bioavailability in physiological condition.

30 The formation of a hydroxy or an alkoxy group β to the amine nitrogen also opens the path incorporation of a fluorine, either radioactive or non-radioactive, within the amine-borane compound, by substitution of the alkoxy or hydroxy groups.

Thus, the process according to this aspect of the present invention is further effected by converting the hydroxy or alkoxy substituent to fluorine. Such a conversion is preferably effected by reacting the compound having the hydroxy or alkoxy substituents with a fluorinating agent.

5 A representative example of a fluorinating agent that is suitable for use in this context of the present invention comprises a mixture of triflic anhydride and 2,6-lutidine, used to activate the hydroxy or alkoxy groups, followed by cesium fluoride (CsF).

10 As mentioned above, the introduction of a radioactive isotope of fluorine into the amine-borane compounds of the present invention would produce a radiolabeled compounds which can be used in a variety of application such as, for example, nuclear medicine, imaging and diagnostics.

Biologically active compounds which contain one or more fluorine atoms are commonly used in medical imaging techniques such as, for example, positron emission tomography (PET). Typically, a fluorine atom in these compounds is replaced with the positron emitting radioactive isotope fluorine-18 to produce ^{18}F -radiolabeled compound. After injection into a patient, a PET scanner can form images of the distribution of ^{18}F -labeled compound in the body. The images can be assessed by a radiologist to provide diagnoses of various medical conditions and investigate the tissues which absorb a given radiolabeled compound.

20 PET is a nuclear imaging modality which allows for the four-dimensional, quantitative determination of the distribution of radioactivity within the human body. This imaging modality allows performing accurate measurements of radioactivity concentrations in small volume compartments *in vivo*, as well as the ability to follow the kinetics of the radiolabeled biomarker.

According to the present invention, amine-borane compounds containing one or more ^{18}F atoms can be prepared by similar synthetic routes as presented above for non-radiolabeled compounds, by using a ^{18}F -radiolabeled starting material, or, preferably, employ a step which will substitute one or more non-radioactive atom(s) with radioactive atoms during, or at the end, of the synthesis.

30 Preferably the compounds of the present invention can be radiolabeled with radioactive halogens such as ^{18}F ($t_{1/2}$ 1.83 hours), ^{123}I ($t_{1/2}$ 13 hours), ^{125}I ($t_{1/2}$ 60 days), ^{131}I ($t_{1/2}$ 8 days), ^{77}Br ($t_{1/2}$ 2.4 days) and the likes.

According to the present invention, amine-borane compounds containing one or more ^{18}F atoms may be used effectively in radioimaging, for example, in diagnosis of many medical conditions, as the required biomarker in radioimaging techniques such as positron emission tomography (PET). Used as labeled bioprobes with high affinity and selectivity for a microorganism, specific receptor, enzyme or membrane, the radiolabeled amine-borane compounds might accumulate in those organs and tissues where the targeted microorganism, protein or membrane component is expressed. Scanning such radiolabeled amine-borane compounds can therefore provide an accurate distribution of these microorganisms, proteins or membrane components within the living human body.

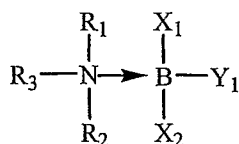
An exemplary ^{18}F -radiolabeled amine-borane compound according to the present invention, Compound $[^{18}\text{F}]\text{K-I}_4$, was prepared and characterized, as demonstrated in the Examples section that follows.

The efficacy of Compound $[^{18}\text{F}]\text{K-I}_4$ as a radiolabeled amine-borane compound was demonstrated in a PET radioimaging experiment in rats, as presented in the Examples section that follows.

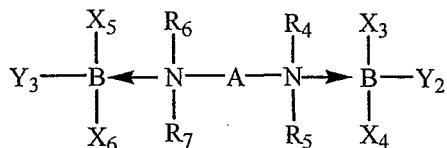
Therefore, according to an embodiment of the present invention the above process wherein the hydroxy or alkoxy groups are exchanged with a fluoro, use a fluorinating agent which includes a radioactive ^{18}F , *e.g.*, Cs^{18}F or X^{18}F .

While the incorporation of a radioactive fluorine isotope has been described above, similarly, other radioactive isotopes can be incorporated in the amine-borane compounds disclosed herein, using radiolabeling reagents and techniques known in the art. These include, for example various isotopes of iodine, bromine, boron and carbon.

Thus, according to the present invention there is provided a radiolabeled compound having the general Formulae:



Formula X



Formula XI

or a pharmaceutically acceptable salt thereof, wherein Y_1 - Y_3 are as defined hereinabove; X_1 - X_6 are as defined hereinabove, R_1 - R_7 are as defined hereinabove, and A is as defined hereinabove,

5 whereas at least one of X_1 - X_6 , R_1 - R_7 and/or A comprises a radioactive atom, or, alternatively, the boron is a radioactive boron.

The radioactive atom can be, for example, boron-10 (^{10}B), carbon-11 (^{11}C), fluorine-18 (^{18}F), bromine-76 (^{76}Br), bromine-77 (^{77}Br), iodine-123 (^{123}I), iodine-124 (^{124}I) and iodine-131 (^{131}I).

10 As used herein, the phrase "radiolabeled compound" or "radioactive atom" (type specified or not) refer to a compound that comprises one or more radioactive atoms or to a radioactive atom with a specific radioactivity above that of background level for that atom. It is well known, in this respect, that naturally occurring elements are present in the form of varying isotopes, some of which are
15 radioactive isotopes. The radioactivity of the naturally occurring elements is a result of the natural distribution of these isotopes, and is commonly referred to as a background radioactive level. However, there are known methods of enriching a certain element with isotopes that are radioactive. The result of such enrichment is a population of atoms characterized by higher radioactivity than a natural
20 population of that atom, and thus the specific radioactivity thereof is above the background level.

Thus, the radiolabeled compounds of the present invention have a specific radioactivity that is higher than the corresponding non-labeled compounds, and can therefore be used as agents for radioimaging and radiotherapy.

25 The term "radioactive", as used herein with respect to an atom or a derivatizing group, refers to an atom or a derivatizing group that comprise a radioactive atom and therefore the specific radioactivity thereof is above the background level.

Radiolabeled compounds having one or more of the above radioactive
30 atoms, can be used in a variety of applications, depending on the radioactive atom present in the compounds.

Thus, for example, compounds having a fluorine-18, carbon-11, bromine-76 and/or iodine-124 atom can be beneficially used as biomarkers in radioimaging such as PET, as discussed in detail hereinabove.

Compounds having a iodine-123 can be used in radioimaging such as
5 SPECT (single photon emission computed tomography).

Compounds having a bromine-77, boron-10, iodine-124 and/or iodine-131 can be used as radiopharmaceuticals in radiotherapy.

The various chemical features of the radiolabeled compounds according to the present embodiments are similar to those described regarding the non-labeled
10 novel compounds presented hereinabove.

The present invention therefore also encompasses pharmaceutical compositions, uses and methods of treatment, as these are defined hereinabove, utilizing the radiolabeled compounds of the present invention discussed and presented herein.

15

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated
20 hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the
25 above descriptions, illustrate the invention in a non limiting fashion.

EXAMPLE 1

CHEMICAL SYNTHESSES

Materials and methods:

30 All reactions were carried out under nitrogen atmosphere. The solvents were dried by conventional methods and were distilled before use. All other chemicals were obtained from Sigma-Aldrich and were used as received without any further purification.

The following amine-boranes were prepared according to published procedures: (2-hydroxy-2-phenyl-ethyl)-dimethyl-amine cyanoborane (K-B) [22], ethyl-dimethyl-amine cyanoborane (K-C) [22], but-3-enyl-dimethyl-amine cyanoborane (K-D) [22], trimethyl-amine cyanodibromoborane (K-E) [Takrouri *et al.*, *J. Organometallic Chem.*, 2005, **690**, 4150; Györi *et al.*, *Inorg. Chim. Acta*, 1994, **218**, 21], trimethyl-amine cyanoborane (K-F) [Wisian-Neilson *et al.*, *Inorg. Chem.* **1978**, *17*, 2327], butyl-dimethyl-amine cyanoborane (K-G) [22], pentyl-dimethyl-amine cyanoborane (K-H) [22] and dimethyl-trimethylsilanylmethyl-amine cyanoborane (K-K) [22].

Sonication was performed, for example, on an Astrason® 50/60Hz 1.2Amps sonicator.

¹H, ¹¹B, ¹³C and ¹⁹F NMR spectra were recorded in a CDCl₃ or a D₂O solution on a Varian Unity Spectrometer (300, 96, 75, 282 MHz) using Me₄Si as an internal standard.

LC-MS analyses were performed on a Finnigan LCQDUO Thermo Quad, with electron spray detector.

Infrared spectra for solid samples were measured in KBr disks or NaCl cells on a Bruker Vector 22 FT-IR spectrophotometer.

Elemental analyses were performed using the Perkin-Elmer 2400 series II Analyzer, using a combustion method to convert the sample elements to simple gases. Determination of halogens was performed using the oxygen-flask method (Schoniger application) for the decomposition of organic samples and then potentiometric titration by the Metrohm 686 Titroprocessor

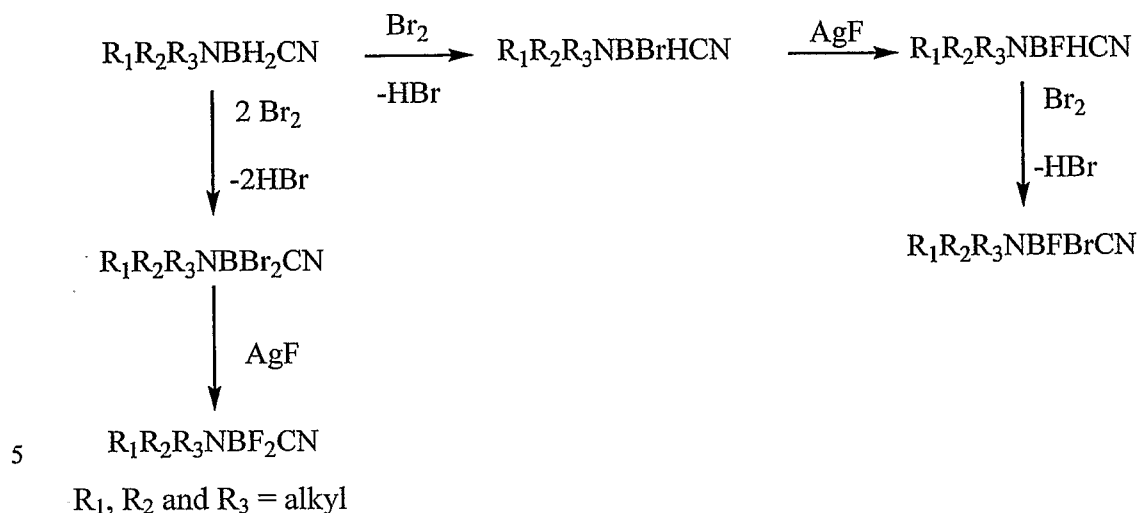
The melting point of the solid samples was measured on a Fisher Scientific melting point apparatus.

Preparation of amine fluorocyanoboranes from bromocyanoboranes – General Procedure:

Synthesis of amine fluorocyanoboranes (R₁R₂R₃NBHFCN, R₁R₂R₃NBF₂CN and R₁R₂R₃NBFBrCN) wherein R₁, R₂ and R₃ are each an alkyl, is carried out by reacting the corresponding amine bromocyanoboranes (R₁R₂R₃NBHBrCN and R₁R₂R₃NBBBr₂CN) with Silver fluoride (AgF) according to a method developed by

the present inventors and described in Shalom *et al.*, *Organometallics* (2004), 23(11), 4396-4399 (see, Scheme 1 below).

Scheme 1



Briefly, amine cyanobromoborane and cyanodibromoborane are prepared as described in the art [Gyoeri, Bela *et al.*, *Inorganic Chemistry* (1998), 37(20), 5131-5141; *Synthesis* (1995), (2), 191-4; and *J. Organometallic Chem.* (1994), 484(1-2), 225-31].

Silver fluoride (AgF, 5-15 equivalents) is added to dry benzene or toluene, and the obtained amine cyanobromoborane or amine cyanodibromoborane ($\text{R}_1\text{R}_2\text{R}_3\text{NBHBrCN}$ or $\text{R}_1\text{R}_2\text{R}_3\text{NBBr}_2\text{CN}$, 1 equivalent), dissolved in dry benzene or toluene is added dropwise under nitrogen to the silver solution while the mixture is subjected to sonication and stirring for 5 to 15 hours. The reaction mixture is thereafter filtered to remove excess AgF and the solvent is evaporated under reduced pressure to thereby obtain the amine cyanofluoroborane or amine cyanodifluoroborane.

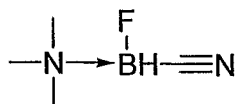
The amine cyanofluorobromoborane is prepared by brominating the corresponding amine cyanodifluoroborane with bromine (1.1 equivalents) to thereby obtain mixed halocyanoborane, namely amine cyanofluorobromoborane.

Alternatively, the bromine to fluorine exchange is carried out by dissolving the corresponding amine cyanobromoborane or amine cyanodibromoborane in toluene. Triethylamine trihydrofluoride ($\text{Et}_3\text{N}/3\text{HF}$, 3.3 equivalents) is added

thereafter and the reaction mixture is refluxed for 24 hours. The solvent is thereafter evaporated under reduced pressure and the corresponding amine cyanofluoroborane, amine cyanofluorobromoborane or amine cyanodifluoroborane are obtained and isolated.

Using this general procedure, the following novel fluorinated amine-boranes were prepared:

Trimethyl-amine cyanofluoroborane (Compound 1):



Trimethyl-amine cyanobromoborane (1 mmol, 1 equivalent) was dissolved in 2 ml of dry benzene. Silver fluoride (AgF, 99 % pure, 5 equivalents) was suspended in 5 ml of dry benzene and added to the reaction mixture, and thereafter sonicated for 5 hours. The solution was then filtered and the solvent was removed from the filtrate under reduced pressure.

Compound **1** was obtained as colorless crystals at 65 % yield.

Melting point: 53 °C.

¹H NMR (CDCl₃): δ = 2.69 (s, 9H), 3.60 (s, 3H).

¹³C {¹H} NMR (CDCl₃): δ = 1.23, 48.68 (BC cannot be detected).

¹¹B NMR (CDCl₃): δ = -2.30 (dd *J*_{B-H} = 64 Hz *J*_{B-F} = 64 Hz).

¹⁹F NMR (CDCl₃): δ = -27.1 (qd *J*_{F-B} = 61 Hz, *J*_{F-H} = 18 Hz).

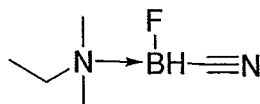
LC-MS: 115.33

IR (Kerosene, cm⁻¹): (2971 cm⁻¹) C-H, (2219cm⁻¹) C≡N, (1455cm⁻¹) C-N, (1104) B-F, (2413) B-H stretching vibrations.

Elemental analysis for C₄H₁₀BFN₂: Calculated - C, 41.44; H, 8.69; N, 24.16,

F, 16.39; Measured - C, 40.21; H, 8.55; N, 23.51; F, 16.41.

Ethyl-dimethylamine cyanofluoroborane (Compound 2):



Compound **2** was prepared from the corresponding ethyl-dimethyl-amine cyanobromoborane as described for Compound **1** hereinabove.

44

Compound **2** was obtained as a yellow oil at 63 % yield.

^1H NMR (CDCl_3): $\delta = 1.28$ (t, 3H, $J = 7.2$ Hz), 2.66 (s, 6H), 3.21 (q, 2H, $J = 7.2$ Hz).

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 8.64, 47.1, 56.69$, (BC cannot be detected).

5 ^{11}B NMR (CDCl_3): $\delta = -2.42$ (dd $J_{\text{B-H}}$, $J_{\text{B-F}} = 64$ Hz).

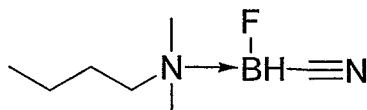
^{19}F NMR (CDCl_3): $\delta = -25.9$ (qd $J_{\text{F-B}} = 39$ Hz, $J_{\text{F-H}} = 15$ Hz).

LC-MS: 129.91

IR (Kerosene, cm^{-1}): (2959cm^{-1}) C-H, (2234cm^{-1}) $\text{C}\equiv\text{N}$, (1455cm^{-1}) C-N, (1040) B-F, (2452) B-H stretching vibrations.

10 Elemental analysis for $\text{C}_5\text{H}_{12}\text{BFN}_2$: Calculated - C, 46.21; H, 9.31; N, 21.55, F, 14.62; Measured - 46.83; H, 9.20; N, 21.32; F, 14.62.

Butyldimethylamine cyanofluoroborane (Compound 3):



15

Compound **3** was prepared from the corresponding butyl-dimethyl-amine cyanobromoborane as described for Compound **1** hereinabove.

Compound **3** was obtained as a brown oil at 66 % yield.

20 ^1H NMR (CDCl_3): $\delta = 0.97$ (t, 3H, $J = 5.4$ Hz), 1.32 (m, 2H, $J = 7.2$ Hz), 1.65 (m, 2H, $J = 3.9$ Hz), 2.61 (s, 6H), 2.87 (t, 2H, $J = 3.6$ Hz).

^{11}B NMR (CDCl_3): $\delta = -2.45$ (dd $J_{\text{B-H}}$, $J_{\text{B-F}} = 42$ Hz).

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 13.95, 20.50, 24.5, 45.02, 59.68, 128.57$ (BC cannot be detected).

^{19}F NMR (CDCl_3): $\delta = -25.5$ (qd $J_{\text{F-B}} = 40$ Hz, $J_{\text{F-H}} = 16$ Hz).

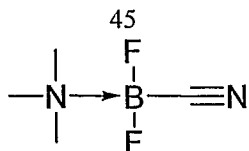
25 LC-MS: 158.11

IR (Kerosene, cm^{-1}): (2962cm^{-1}) C-H, (2218cm^{-1}) $\text{C}\equiv\text{N}$, (1455cm^{-1}) C-N, (1110) B-F, (2418) B-H stretching vibrations.

Elemental analysis for $\text{C}_7\text{H}_{16}\text{BF}_2\text{N}_2$: Calculated - C, 53.20; H, 10.21; N, 17.73, F, 12.02; Measured - C, 53.46; H, 10.36; N, 18.11; F, 12.26.

30

Trimethylamine cyanodifluoroborane (Compound 8):



Trimethyl-amine cyanodibromoborane (1 mmol, 1 equivalent) was dissolved in 2 ml of dry benzene. Silver fluoride (AgF, 99 % pure, 5 equivalents) was suspended in 5 ml of dry benzene and added to the reaction mixture, and thereafter sonicated for 10 hours. The solution was then filtered and the solvent was removed from the filtrate under reduced pressure.

Compound **8** was obtained as a solid at 67 % yield.

Melting point: 48 °C.

^1H NMR (CDCl_3): $\delta = 2.69$ (s, 9H).

^{13}C { ^1H } NMR (CDCl_3): $\delta = 42.92$ (BC cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -2.86$ (t $J = 38.4$ Hz).

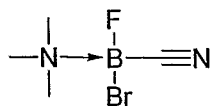
^{19}F NMR (CDCl_3): $\delta = -159.75$ (q $J = 36.6$ Hz).

LC-MS : 134.11.

IR (KBr, cm^{-1}): (2955- 2971 cm^{-1}) C-H, (2219-2260 cm^{-1}) $\text{C}\equiv\text{N}$, (1455-1493 cm^{-1}) C-N, (1104-1193) B-F, (2413-2473).

Elemental analysis for $\text{C}_4\text{H}_9\text{BF}_2\text{N}_2$: Calculated - C, 35.87; H, 6.77; N, 20.92, F, 28.37; Measured - C, 36.02; H, 6.58; N, 21.16; F, 28.35.

Trimethylamine cyanofluorobromoborane (Compound 11):



Trimethyl amine cyanofluoroborane (Compound **1**, 0.5 mmol, 1 equivalent) was dissolved in 2 ml of distilled water and cooled to 0 °C. Bromine (0.51 mmol) was dissolved in 5 ml distilled water and was added dropwise to solution containing the amine-borane. The reaction mixture was allowed to stir at 0 °C for 4 hours. The produced precipitate was thereafter filtrated, and recrystallized from hot water.

Compound **11** was obtained as a brown oil at 65 % yield.

^1H NMR (CDCl_3): $\delta = 2.69$ (s, 9H), 3.60 (s, 3H).

^{13}C { ^1H } NMR (CDCl_3): $\delta = 1.23, 48.68$ (BC cannot be detected).

46

^{11}B NMR (CDCl_3): $\delta = -2.30$ (q $J = 64$ Hz).

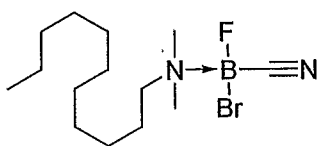
^{19}F NMR (CDCl_3): $\delta = -27.1$ (q $J = 61$ Hz).

LC-MS: 193.91.

IR (KBr, cm^{-1}): 2954 (C-H) stretching vibrations, 1681 (C=O), 1460 (C-H) bending vibrations, 1204 (C-O), 450 (B-N).

Elemental analysis for $\text{C}_4\text{H}_{10}\text{BFN}_2$: Calculated - C, 41.44; H, 8.69; N, 24.16, F, 16.39; Measured - C, 24.56; H, 4.56; ; N, 14.38; Br, 40.91; F, 9.75.

Dimethyl-undecyl-amine cyanofluorobromoborane (Compound **K-I₃**) was similarly prepared.

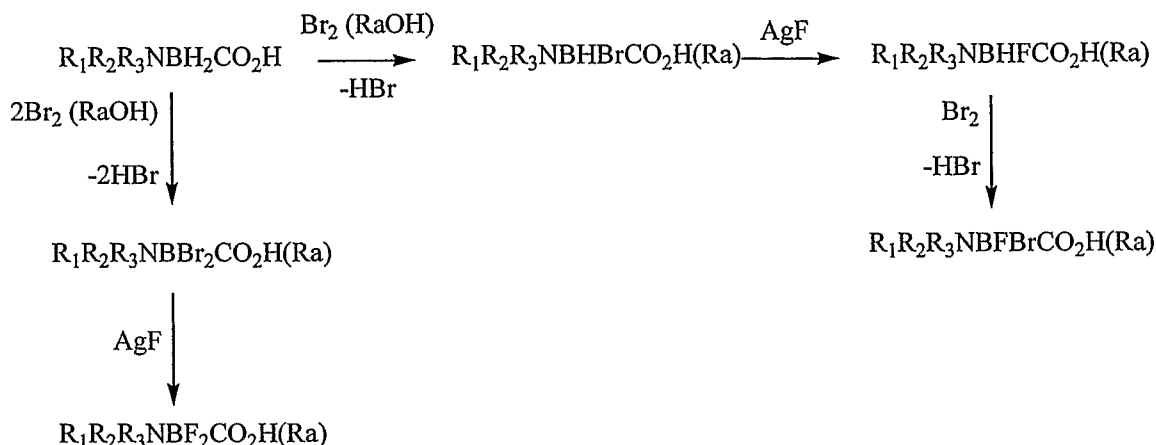


Compound **K-I₃**

Preparation of amine fluorocarboxyboranes and esters thereof from bromocarboxyboranes – General Procedure:

Synthesis of amine fluorocarboxyboranes and esters thereof ($\text{R}_1\text{R}_2\text{R}_3\text{NBHFCO}_2\text{H}$, $\text{R}_1\text{R}_2\text{R}_3\text{NBF}_2\text{CO}_2\text{H}$, $\text{R}_1\text{R}_2\text{R}_3\text{NBFBrCO}_2\text{H}$, $\text{R}_1\text{R}_2\text{R}_3\text{NBHFCO}_2\text{Ra}$, $\text{R}_1\text{R}_2\text{R}_3\text{NBF}_2\text{CO}_2\text{Ra}$ and $\text{R}_1\text{R}_2\text{R}_3\text{NBFBrCO}_2\text{Ra}$) wherein R_1 , R_2 and R_3 are each an alkyl and Ra is e.g. alkyl, alkenyl and aryl, is carried out by reacting the corresponding amine bromocarboxyboranes, dibromocarboxyboranes or the corresponding amine bromocarboxyborane or dibromocarboxyboranes esters ($\text{R}_1\text{R}_2\text{R}_3\text{NBHBrCO}_2\text{H}$, $\text{R}_1\text{R}_2\text{R}_3\text{NBBBr}_2\text{CO}_2\text{H}$, $\text{R}_1\text{R}_2\text{R}_3\text{NBHBrCO}_2\text{Ra}$ and $\text{R}_1\text{R}_2\text{R}_3\text{NBBBr}_2\text{CO}_2\text{Ra}$) with AgF according to a method developed by the present inventors and described in Shalom *et al.*, *Organometallics* (2004), 23(11), 4396-4399 (see, Scheme 2 below).

47

Scheme 2

R_1, R_2 and R_3 = alkyl

5 Ra = e.g. alkyl, alkenyl and aryl

Briefly, amine carboxybromoborane, amine carboxydibromoborane and alkyl esters thereof are prepared as described in the art [Shalom et al., Organometallics 2004, 23, 4396-4399; Gyoeri, Bela *et al.*, *Inorganic Chemistry* 10 (1998), 37(20), 5131-5141; *Synthesis* (1995), (2), 191-4; and *J. Organometallic Chem.* (1994), 484(1-2), 225-31].

Silver fluoride (AgF, 5-15 equivalents) is added to dry benzene or toluene, and the obtained amine carboxybromoborane, amine carboxydibromoborane or esters thereof ($R_1R_2R_3NBHBrCOOH/R_4$ or $R_1R_2R_3NBBR_2COOH/R_4$, 1 equivalent), 15 dissolved in dry benzene or toluene is added dropwise under nitrogen to the reaction mixture while the mixture is subjected to sonication and stirring for 5 to 15 hours. The reaction mixture is thereafter filtered to remove excess AgF and the solvent is evaporated under reduced pressure to thereby obtain the amine carboxyfluoroborane, the amine carboxydifluoroborane or the esters thereof.

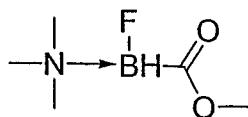
20 The amine carboxyfluorobromoborane is prepared by brominating the corresponding amine carboxyfluoroborane with bromine (1.1 equivalents) to thereby obtain mixed halocarboxyborane, namely amine carboxyfluorobromoborane.

Alternatively, the bromine to fluorine exchange is carried out by dissolving the corresponding amine carboxybromoborane or amine carboxydibromoborane and 25 the corresponding esters thereof in toluene. Triethylamine trihydrofluoride ($Et_3N/3HF$, 3.3 equivalents) is added and the reaction mixture is refluxed for 24

hours. The solvent is thereafter evaporated under reduced pressure and the corresponding amine carboxyfluoroborane or amine carboxydifluoroborane and the corresponding esters thereof are obtained and isolated.

Using this general procedure the following novel compounds were prepared:

Trimethylamine carboxyfluoroborane methyl ester (Compound 4):



Compound 4 was prepared from the corresponding trimethyl-amine carboxybromoborane methyl ester as described for Compound 1 hereinabove.

Compound 4 was obtained as a yellow oil at 69 % yield.

^1H NMR (CDCl_3): δ = 2.66 (s, 9H), 3.58 (s, 3H).

^{13}C { ^1H } NMR (CDCl_3): δ = 1.23, 48.68, 128.55 (BC cannot be detected).

^{11}B NMR (CDCl_3): δ = 0.26 (dd $J_{\text{B-H}}$, $J_{\text{B-F}}$ = 44 Hz).

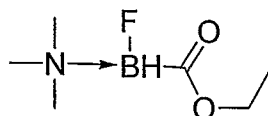
^{19}F NMR (CDCl_3): δ = -27.3 (qd $J_{\text{F-B}}$ = 52 Hz, $J_{\text{F-H}}$ = 21 Hz).

LC-MS: 149.03.

IR (Kerosene, cm^{-1}): (2955cm^{-1}) C-H, (1696cm^{-1}) C=O, (1455cm^{-1}) C-N, (1030) B-F, (2473) B-H stretching vibrations.

Elemental analysis for $\text{C}_5\text{H}_{13}\text{BFNO}_2$: Calculated - C, 40.31; H, 8.80; N, 9.40, F, 12.75; Measured - C, 40.43; H, 9.02; N, 9.57; F, 12.73.

Trimethylamine carboxyfluoroborane ethyl ester (Compound 5):



Compound 5 was prepared from the corresponding trimethyl-amine carboxybromoborane ethyl ester as described for Compound 1 hereinabove.

Compound 5 was obtained as a yellow oil at 65 % yield.

^1H NMR (CDCl_3): δ = 1.24 (t, 3H, J = 7.2 Hz), 2.67 (s, 9H), 4.08 (q, 2H, J = 6.9 Hz).

^{13}C { ^1H } NMR (CDCl_3): δ = 14.85, 48.69, 57.02, (BC cannot be detected).

49

^{11}B NMR (CDCl_3): $\delta = 0.29$ (dd $J_{\text{B-H}}$, $J_{\text{B-F}} = 38$ Hz).

^{19}F NMR (CDCl_3): $\delta = -26.98$ (qd $J_{\text{F-B}} = 46$, Hz $J_{\text{F-H}} = 20$ Hz).

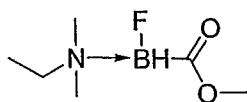
LC-MS: 163.12.

IR (Kerosene, cm^{-1}): (2960cm^{-1}) C-H, (1702cm^{-1}) C=O, (1205cm^{-1}) C-O,
5 (1493 cm^{-1}) C-N, (1098) B-F, (2473) B-H stretching vibrations.

Elemental analysis for $\text{C}_6\text{H}_{15}\text{BFNO}_2$: Calculated - C, 44.21; H, 9.28; N, 8.59, F, 11.66; Measured - C, 44.13; H, 8.98; N, 8.57; F, 11.62.

Ethyl-dimethylamine carboxyfluoroborane methyl ester (Compound 6):

10



Compound **6** was prepared from the corresponding ethyl-dimethyl-amine carboxyfluoroborane methyl ester as described for Compound **1** hereinabove.

Compound **6** was obtained as a yellow oil at 69 % yield.

15

^1H NMR (CDCl_3): $\delta = 1.21$ (t, 3H, $J = 7.2$ Hz), 2.59 (s, 6H), 2.97 (q, 2H, $J = 7.5$ Hz), 3.58 (s, 3H).

^{13}C { ^1H } NMR (CDCl_3): $\delta = 16.47$, 47.75, 52.19, 62.13 (BC cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -0.23$ (dd $J_{\text{B-H}}$, $J_{\text{B-F}} = 76$ Hz).

20

^{19}F NMR (CDCl_3): $\delta = -27.7$ (qd $J_{\text{F-B}} = 46$ Hz, $J_{\text{F-H}} = 20$ Hz).

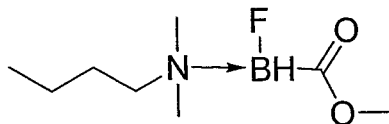
LC-MS: 163.12.

IR (Kerosene, cm^{-1}): (2960cm^{-1}) C-H, (1702cm^{-1}) C=O, (1204cm^{-1}) C-O, (1493 cm^{-1}) C-N, (1098) B-F, (2475) B-H stretching vibrations.

Elemental analysis for $\text{C}_6\text{H}_{15}\text{BFNO}_2$: Calculated - C, 44.21; H, 9.28; N, 8.59, F, 11.66; Measured - C, 44.37; H, 9.56; N, 8.72; F, 11.62.

25

Butyl-dimethylamine carboxyfluoroborane methyl ester (Compound 7):



Compound 7 was prepared from the corresponding butyl-dimethyl-amine carboxyfluoroborane methyl ester as described for Compound 1 hereinabove.

Compound 7 was obtained as a brown oil at 59 % yield.

^1H NMR (CDCl_3): $\delta = 0.97$ (t, 3H, $J = 5.4$ Hz), 1.32 (m, 2H, $J = 7.2$ Hz),
 5 1.65 (m, 2H, $J = 3.9$ Hz), 2.61 (s, 6H), 2.87 (t, 2H, $J = 3.6$ Hz).

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 13.95, 20.50, 24.5, 45.02, 59.68, 128.57$ (BC cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -2.45$ (dd $J_{B-H}, J_{B-F} = 42$ Hz).

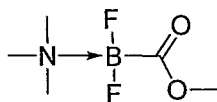
^{19}F NMR (CDCl_3): $\delta = -25.5$ (qd $J_{F-B} = 40$ Hz, $J_{F-H} = 17$ Hz).

10 LC-MS: 191.03.

IR (Kerosene, cm^{-1}): (2957cm^{-1}) C-H, (1698cm^{-1}) C=O, (1248cm^{-1}) C-O, (1495cm^{-1}) C-N, (1131) B-F, (2475) B-H stretching vibrations.

Elemental analysis for $\text{C}_7\text{H}_{16}\text{BF}_2\text{N}_2$: Calculated - C, 53.20; H, 10.21; N, 17.73, F, 12.02; Measured - C, 53.46; H, 10.26; N, 18.11; F, 12.06.

15 ***Trimethylamine carboxydifluoroborane methyl ester (Compound 9):***



Compound 9 was prepared from the corresponding trimethyl-amine
 20 carboxydibromoborane methyl ester as described for Compound 8 hereinabove.

Compound 9 was obtained as a solid at 70 % yield.

Melting point: 66 °C.

^1H NMR (CDCl_3): $\delta = 2.69$ (s, 9H), 3.62 (s, 3H).

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 47.34, 49.05$, (BC cannot be detected).

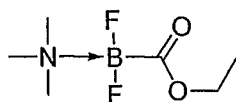
25 ^{11}B NMR (CDCl_3): $\delta = -1.47$ (t, $J = 54.91$ Hz).

^{19}F NMR (CDCl_3): $\delta = -167.63$ (q $J = 54.7$ Hz).

LC-MS: 166.9.

IR (KBr, cm^{-1}): (2960cm^{-1}) C-H, (1702cm^{-1}) C=O, (1204cm^{-1}) C-O, (1493cm^{-1}) C-N, (1098) B-F, (2475).

30 Elemental analysis for $\text{C}_5\text{H}_{12}\text{BF}_2\text{NO}_2$: Calculated - C, 35.97; H, 7.24; N, 8.39, F; 22.76; Measured - C, 35.82; H, 7.21; N, 8.42; F; 22.84.

Trimethylamine carboxydifluoroborane ethyl ester (Compound 10):

Compound **10** was prepared from the corresponding trimethyl-amine carboxydibromoborane ethyl ester as described for Compound **8** hereinabove.

Compound **10** was obtained as a yellow oil at 66 % yield.

^1H NMR (CDCl_3): $\delta = 1.26$ (t, 3H, $J = 6.9$ Hz), 2.69 (s, 9H), 4.12 (q, 2H, $J = 7.2$ Hz).

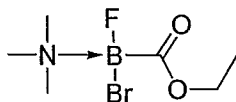
^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 16.57, 47.34, 53.05$, (BC cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -1.64$ (t $J = 66.2$ Hz).

^{19}F NMR (CDCl_3): $\delta = -167.75$ (q $J = 48.8$ Hz).

IR (Kerosene, cm^{-1}): (2957cm^{-1}) C-H, (1703cm^{-1}) C=O, (1204cm^{-1}) C-O, (1493cm^{-1}) C-N, (1098) B-F, (2475).

Elemental analysis for $\text{C}_6\text{H}_{14}\text{BF}_2\text{NO}_2$: Calculated - C, 39.82; H, 7.80; N, 7.74, F, 20.99; Measured - C, 40.03; H, 7.99; N, 7.86; F, 20.71.

Trimethylamine carboxyfluorobromoborane ethyl ester (Compound 12):

Compound **12** was prepared from the corresponding trimethyl-amine carboxyfluoroborane ethyl ester (Compound **5**) as described for Compound **11** hereinabove.

Compound **12** was obtained as a brown oil at 57 % yield.

^1H NMR (CDCl_3): $\delta = 1.27$ (t, 3H, $J = 6.3$ Hz), 2.93 (s, 9H), 4.16 (q, 2H, $J = 6.2$ Hz).

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 14.85, 46.69, 58.02$, (BC cannot be detected).

^{11}B NMR (CDCl_3): $\delta = 2.92$ (q $J = 38.4$ Hz).

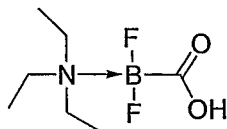
^{19}F NMR (CDCl_3): $\delta = -120.77$ (q $J = 91.3$ Hz).

52

IR (Kerosene, cm^{-1}): (2971 cm^{-1}) C-H, (1493 cm^{-1}) C-N, (1705) C=O, (607 cm^{-1}) B-Br, (1193) B-F.

Elemental analysis for $\text{C}_6\text{H}_{14}\text{BBrFNO}_2$: Calculated - C, 29.79; H, 5.83; N, 5.79, Br, 33.03; F, 7.85; Measured - C, 28.85; H, 6.02; N, 5.82, Br, 32.93, F, 7.87.

5 ***Triethylamine carboxydifluoroborane (Compound 13):***



Compound **13** was prepared from the corresponding triethyl-amine
10 carboxydibromoborane ethyl ester as described for Compound **8** hereinabove

Compound **13** was obtained as a colorless oil at 62 % yield.

^1H NMR (CDCl_3): δ = 1.08 (t, 3H, J - 7.5 Hz), 2.89 (q, 2H, J - 5.4 Hz).

^{13}C { ^1H } NMR (CDCl_3): δ = 12, 48.05, (BC cannot be detected).

^{11}B NMR (CDCl_3): δ = -1.05 (t, J - 54.91 Hz).

15 ^{19}F NMR (CDCl_3): δ = -130.51 (q, J - 54.7 Hz).

LC-MS: 195.33.

IR (Kerosene, cm^{-1}): (2959 cm^{-1}) C-H, (1703 cm^{-1}) C=O, (1200 cm^{-1}) C-O, (1490 cm^{-1}) C-N, (1100) B-F.

Elemental analysis for $\text{C}_7\text{H}_{16}\text{BF}_2\text{NO}_2$: Calculated - C, 43.11; H, 8.27; F, 19.48; N, 7.18; Measured - C, 42.95; H, 8.37; F, 19.66; N, 7.27
20

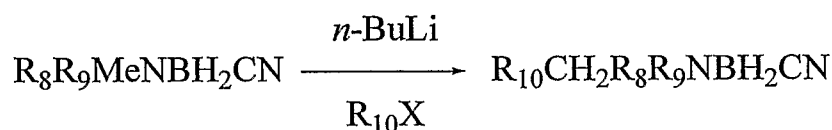
Preparation of amine cyanoboranes having a long alkyl chain attached to the amine moiety – General Procedure:

Synthesis of amine cyanoboranes ($\text{R}_8\text{R}_9\text{R}_{10}\text{CH}_2\text{NBH}_2\text{CN}$) wherein R_{10} is a
25 high alkyl (long chain alkyl), is carried out according to a method developed by the present inventors and described in Takrouri *et al.*, *Organometallics* (2004), 23(11), 2817-2820 (see, Scheme 3 below). The corresponding starting amine cyanobromoborane and amine cyanodibromoborane are prepared as described in the art [Takrouri *et al.*, *J. Organometallic Chem.*, 690 (2005) 4150–4158; Shalom *et al.*,
30 *Organometallics* 2004, 23, 4396-4399; Gyoeri *et al.*, *Inorganic Chemistry* (1998),

37(20), 5131-5141; *Synthesis* (1995), (2), 191-4; and *J. Organometallic Chem.* (1994), 484(1-2), 225-31].

Scheme 3

5



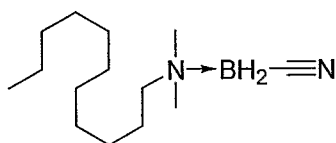
R_8, R_9 and R_{10} = alkyl

X = Cl, Br or I

10

Using this general procedure, the following compounds were prepared:

Dimethylundecylamine cyanoborane (Compound K-I):



15

Compound **K-I** was obtained as white solid at 87 % yield (0.207 gram).

^1H NMR (CDCl_3): δ = 0.86 (t, 3H, J - 7.2 Hz), 1.25 (broad s, 14H), 1.66 (hept, 2H, J - 3.6), 1.83 (pent, 2H, J - 7.2), 2.63 (s, 6H), 2.84 (t, 2H, J - 5.0), (HB cannot be detected).

20

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): δ = 14.34, 22.89, 23.49, 27.13, 29.44, 29.52, 29.65, 32.09, 45.18, 46.97, 50.03, 63.84, (CB cannot be detected).

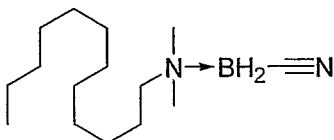
^{11}B NMR (CDCl_3): δ = -16.67 (t, $J_{\text{B-H}}$ - 97.1 Hz).

IR (KBr, cm^{-1}): 2919 (B-H), 2852 (C-H), 2358 ($\text{C}\equiv\text{N}$), 1469 (C-N), 440 (BN).

25

Elemental analysis for $\text{C}_{14}\text{H}_{31}\text{BN}_2$: Calculated - C, 70.59; H, 13.12; N, 11.76; Measured - C, 70.52; H, 13.11; N, 11.75.

Dodecyldimethylamine cyanoborane (Compound K-L):



Compound K-L was obtained as yellow oil, 87 % (0.219 grams) yield.

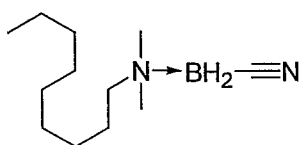
^1H NMR (CDCl_3): δ = 0.84 (t, 3H, J = 7.2 Hz), 1.22 (broad s, 16H), 1.64 (hept, 2H, J = 3.6), 1.80 (pent, 2H, J = 7.2), 2.60 (s, 6H), 2.80 (t, 2H, J = 5.0), (HB cannot be detected).

5 $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 14.30, 22.87, 23.47, 27.11, 28.36, 28.96, 29.41, 29.64, 29.68, 29.77, 32.09, 33.03, 34.22, 50.00, 63.78, (CB cannot be detected).

^{11}B NMR (CDCl_3): δ = -14.80 (t, $J_{\text{B-H}}$ = 102.6 Hz). IR (KBr, cm^{-1}): 2921 (B-H), 2854 (C-H), 2361 ($\text{C}\equiv\text{N}$), 1541 (C-N), 440 (B-N).

Dimethylnonylamine cyanoborane (Compound K-P):

10



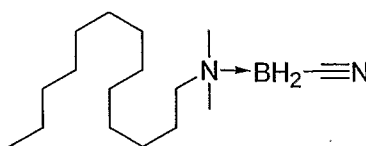
Compound K-P was obtained as white solid, 84 % (0.177 gram) yield.

15 ^1H NMR (CDCl_3): δ = 0.86 (t, 3H, J = 7.2 Hz), 1.29 (broad s, 10H), 1.63 (hept, 2H, J = 3.6), 1.80 (pent, 2H, J = 7.2), 2.65 (s, 6H), 2.83 (t, 2H, J = 5.0), (HB cannot be detected).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 14.13, 22.81, 23.23, 27.13, 29.44, 29.65, 32.09, 45.18, 50.03, 63.84, (CB cannot be detected).

20 ^{11}B NMR (CDCl_3): δ = -16.01 (t, $J_{\text{B-H}}$ = 97.1 Hz). IR (KBr, cm^{-1}): 2920 (B-H), 2850 (C-H), 2358 ($\text{C}\equiv\text{N}$), 1469 (C-N), 432 (B-N).

Dimethyltridecylamine cyanoborane (Compound K-Q):



25

Compound K-Q was obtained as white solid, 84 % (0.224 gram) yield.

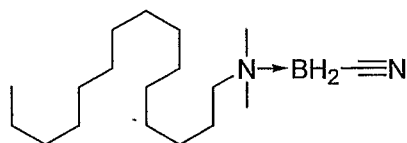
^1H NMR (CDCl_3): δ = 0.87 (t, 3H, J = 7.2 Hz), 1.25 (broad s, 16H), 1.41 (m, 2H), 1.65 (hept, 2H, J = 3.6), 1.84 (pent, 2H, J = 7.2), 2.63 (s, 6H), 2.84 (t, 2H, J = 3.9), (HB cannot be detected).

55

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 14.35, 22.91, 23.49, 27.14, 28.40, 29.00, 29.57, 29.67, 29.84, 32.13, 33.06, 34.31, 50.02, 64.00$, (CB cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -15.55$ (t, $J_{\text{B-H}} = 106.3$ Hz). IR (KBr, cm^{-1}): 2921 (B-H), 2852 (C-H), 2345 ($\text{C}\equiv\text{N}$), 1542 (C-N), 440 (B-N).

5 ***Dimethylpentadecylamine cyanoborane (Compound K-R):***



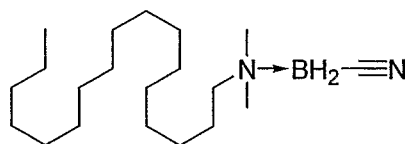
Compound K-R was obtained as white solid, 86 % (0.253 gram) yield.

10 ^1H NMR (CDCl_3): $\delta = 0.87$ (t, 3H, $J = 7.2$ Hz), 1.25 (broad s, 20H), 1.41 (m, 2H), 1.66 (hept, 2H, $J = 3.6$), 1.84 (pent, 2H, $J = 7.2$), 2.63 (s, 6H), 2.84 (t, 2H, $J = 3.6$), (HB cannot be detected).

15 $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 14.35, 22.92, 23.50, 27.16, 28.41, 29.01, 29.60, 29.68, 29.78, 29.89, 32.16, 33.08, 34.27, 47.04, 50.02, 63.84$, (CB cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -15.89$ (t, $J_{\text{B-H}} = 106.3$ Hz). IR (KBr, cm^{-1}): 2919 (B-H), 2852 (C-H), 2346 ($\text{C}\equiv\text{N}$), 1538 (C-N), 440 (B-N).

Dimethylheptadecylamine cyanoborane (Compound K-S):



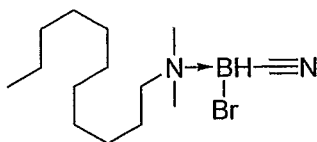
20

Compound K-S was obtained as white solid, 83 % (0.268 gram) yield.

25 ^1H NMR (CDCl_3): $\delta = 0.88$ (t, 3H, $J = 7.2$ Hz), 1.25 (broad s, 24H), 1.41 (m, 2H), 1.65 (m, 2H), 1.85 (pent, 2H, $J = 7.2$), 2.64 (s, 6H), 2.85 (t, 2H, $J = 4.2$), (HB cannot be detected).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 14.36, 22.93, 28.42, 29.01, 29.60, 29.91, 33.16, 33.07, 34.33, 48.25, 52.10, 62.95$, (CB cannot be detected).

^{11}B NMR (CDCl_3): $\delta = -16.04$ (t, $J_{\text{B-H}} = 106.3$ Hz). IR (KBr, cm^{-1}): 2921 (B-H), 2852 (C-H), 2344 ($\text{C}\equiv\text{N}$), 1542 (C-N), 433 (B-N).

Dimethylundecylamine cyanobromoborane (Compound K-I₁):

5 Compound **K-I₁** was obtained as brown oil, at 80 % yield (0.254 grams).

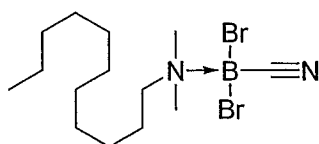
¹H NMR (CDCl₃): δ = 0.83 (t, 3H, *J* - 7.2 Hz), 1.22 (broad s, 14H), 1.65 (hept, 2H, *J* - 3.6), 1.81 (pent, 2H, *J* - 7.2), 2.77 (s, 6H), 2.94 (t, 2H, *J* - 6.9), (HB cannot be detected).

¹³C {¹H} NMR (CDCl₃): δ = 14.35, 22.89, 22.90, 27.00, 29.38, 29.51,
10 29.61, 32.09, 43.61, 45.24, 47.60, 47.70, 61.98, (CB cannot be detected).

¹¹B NMR (CDCl₃): δ = -10.95 (d, *J* - 177.7 Hz).

IR (KBr, cm⁻¹): 2919 (B-H), 2854 (C-H), 2358 (C≡N), 1469 (C-N), 442 (B-N).

Elemental analysis for C₁₄H₃₀BBrN₂: Calculated - C, 53.02; H, 9.54; Br, 25.20; N, 8.83; Measured - C, 53.05; H, 9.51; Br, 25.22; N, 8.80.
15

Dimethylundecylamine cyanodibromoborane (Compound K-I₂):

20 Compound **K-I₂** was obtained as brown oil, at a 82 % yield (0.324 gram).

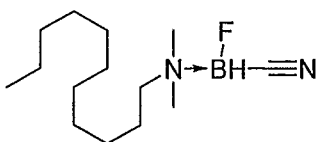
¹H NMR (CDCl₃): δ = 0.85 (t, 3H, *J* - 7.2 Hz), 1.30 (broad s, 14H), 1.68 (hept, 2H, *J* - 3.6), 1.82 (pent, 2H, *J* - 7.2), 2.94 (s, 6H), 3.38 (t, 2H, *J* - 6.9), (HB cannot be detected).

¹³C {¹H} NMR (CDCl₃): δ = 14.35, 22.89, 26.98, 29.37, 29.42, 29.50,
25 29.66, 29.73, 32.08, 46.01, 47.71, 61.98, (CB cannot be detected).

¹¹B NMR (CDCl₃): δ = -9.36 (s).

IR (KBr, cm⁻¹): 2854 (C-H), 2362 (C≡N), 1409 (C-N), 435 (B-N).

Elemental analysis for C₁₄H₂₉BBr₂N₂: Calculated - C, 42.46; H, 7.38; Br, 40.35; N, 7.07; Measured - C, 42.42; H, 7.35; Br, 40.37; N, 7.10.

Dimethyl-undecyl-amine cyanofluoroborane (Compound K-I₄):**Compound K-I₄**

5

Dimethyl-undecyl-amine cyanofluoroborane (Compound K-I₄) was prepared by dissolving Compound K-I₁ (1 mmol, see synthesis hereinabove) in 2 ml of dry benzene. Silver (I) fluoride 99 % (5 equivalents) was suspended in 5 ml of dry benzene and added to the reaction mixture which was sonicated for 5 hours.

10 Thereafter, the solvent was filtered and removed under high vacuum.

Compound K-I₄ was obtained as a brown oil at 66 % yield.

¹H NMR (CDCl₃): δ = 0.86 (t, 3H, *J* - 6.9 Hz), 1.25 (broad s, 16H), 1.4 (broad s, 2H) 2.78 (s, 6H), 3.39 (t, 2H, *J* - 6.9 Hz).

¹³C {¹H} NMR (CDCl₃): δ = 14.07, 22.63, 26.72, 29.33, 29.4, 31.82, 47.4, 15 61.71, (BC cannot be detected).

¹¹B NMR (CDCl₃): δ = -2.08 (dd, *J*_{B-H} - 75.2, *J*_{B-F} - 64.0 Hz).

¹⁹F NMR (CDCl₃): δ = -25.09 (qd, *J*_{F-B} - 40 Hz, *J*_{F-H} - 16 Hz).

IR (neat, cm⁻¹): 2924 (C-H), 2209 (C_≡N), 1455 (C-N), 1074 (B-F), 2491 (B-H) stretching vibrations.

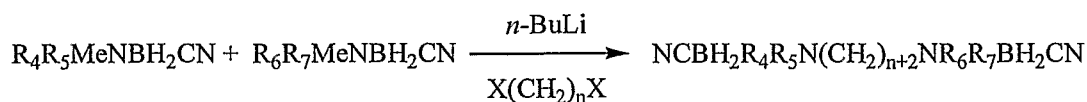
20 Elemental analysis for C₁₃H₂₈BFN₂: Calculated -C, 64.47; H, 11.65; N, 4.46, F, 7.84; Measured - C, 64.21; H, 11.68; N, 4.49, F, 7.86.

Preparation of amine bis-cyanoboranes – General Procedure:

Synthesis of amine bis-cyanoboranes (NCBH₂R₄R₅N(CH₂)_{n+2}NR₆R₇BH₂CN), wherein n ranges from 1 to 20, is carried out as illustrated in Scheme 4 below according to the procedure described in Takrouri *et al.*, *Organometallics* (2004), 23(11), 2817-2820. The corresponding starting amine cyano/carboxybromoborane, amine cyano/carboxydibromoborane and alkyl esters thereof are prepared as described in the art [Takrouri *et al.*, *J. Organometallic Chem.*, 690 (2005) 4150–4158; Gyoeri, Bela *et al.*, *Inorganic* 30

Chemistry (1998), 37(20), 5131-5141; *Synthesis* (1995), (2), 191-4; and *J. Organometallic Chem.* (1994), 484(1-2), 225-31].

Scheme 4



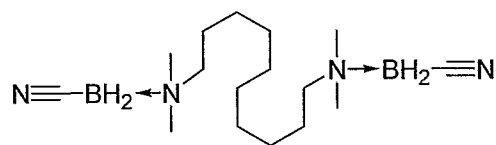
$R_4, R_5, R_6,$ and R_7 = alkyl;

X = Cl, Br or I; and

n = 1-20

Using this general procedure, the following novel compounds were prepared:

***N,N,N',N'*-tetramethyldecane-1,10-diamine bis-cyanoborane (Compound K-J):**



Compound **K-J** was obtained as white solid, at a 90 % yield (0.276 gram).

1H NMR ($CDCl_3$): δ = 1.29 (broad s, 8H), 1.66 (m, 4H), 1.84 (m, 4H), 2.63 (s, 12H), 2.84 (t, 4H, J - 3.9 Hz), (HB cannot be detected).

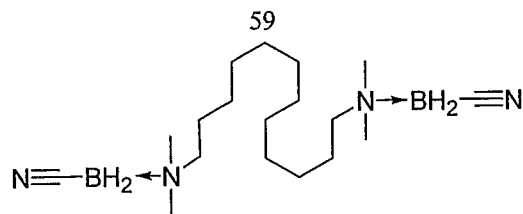
^{13}C { 1H } NMR ($CDCl_3$): δ = 23.47, 27.04, 29.27, 29.40, 50.15, 63.78, (CB cannot be detected).

^{11}B NMR ($CDCl_3$): δ = -16.67 (t, J_{B-H} 101.1 Hz).

IR (KBr, cm^{-1}): 2923 (B-H), 2854 (C-H), 2332 (C≡N), 1542 (C-N), 433 (B-N).

Elemental analysis for $C_{16}H_{36}B_2N_4$: Calculated - C, 62.78; H, 11.85; N, 18.30; Measured - C, 62.73; H, 11.88; N, 18.33.

***N,N,N',N'*-tetramethyldodecane-1,12-diamine bis-cyanoborane (Compound K-M):**



Compound K-M was obtained as yellow solid, 88 % (0.294 gram) yield.

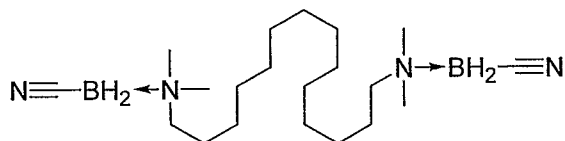
^1H NMR (CDCl_3): δ = 1.27 (broad s, 12H), 1.66 (m, 4H), 1.98 (m, 4H), 2.63 (s, 12H), 2.85 (t, 4H, J = 3.9 Hz), (HB cannot be detected).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 23.45, 27.06, 29.33, 29.53, 29.86, 50.07, 63.77, (CB cannot be detected).

^{11}B NMR (CDCl_3): δ = -15.53 (t, $J_{\text{B-H}}$ = 106.3 Hz).

IR (KBr, cm^{-1}): 2921 (B-H), 2852 (C-H), 2362 ($\text{C}\equiv\text{N}$), 1542 (C-N), 440 (B-N).

N,N,N',N'-tetramethyltetradecane-1,14-diamine *bis-cyanoborane*
(Compound K-N):



Compound K-N was obtained as white solid, 87 % (0.315 g) yield.

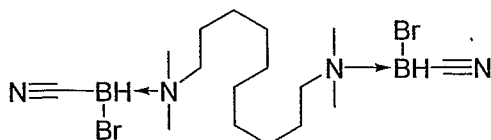
^1H NMR (CDCl_3): δ = 1.22 (broad s, 16H), 1.62 (m, 4H), 1.81 (m, 4H), 2.60 (s, 12H), 2.80 (m, 4H), (HB cannot be detected).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 23.49, 27.11, 28.96, 29.62, 33.03, 34.34, 50.07, 63.82, (CB cannot be detected).

^{11}B NMR (CDCl_3): δ = -14.86 (t, $J_{\text{B-H}}$ = 112.3 Hz).

IR (KBr, cm^{-1}): 2920 (B-H), 2853 (C-H), 2334 ($\text{C}\equiv\text{N}$), 1542 (C-N), 440 (B-N).

N,N,N',N'-tetramethyldecane-1,10-diamine *bis-cyanobromoborane*
(Compound K-J₁):



60

Compound **K-J₁** was obtained as brown oil at 82 % yield (0.380 gram).

¹H NMR (CDCl₃): δ = 1.30 (broad s, 8H), 1.68 (m, 4H), 1.86 (m, 4H), 2.78 (s, 12H), 3.05 (m, 4H), (HB cannot be detected).

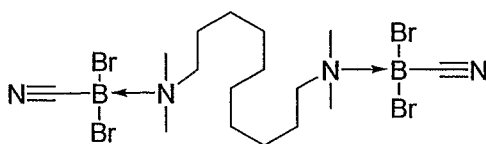
¹³C {¹H} NMR (CDCl₃): δ = 22.91, 26.89, 29.17, 29.32, 50.84 61.98, (CB cannot be detected).

¹¹B NMR (CDCl₃): δ = -11.38 (d, *J*_{B-H} = 113.7 Hz).

IR (neat, cm⁻¹): 2927 (B-H), 2856 (C-H), 2341 (C≡N), 1542 (C-N), 440 (B-N).

Elemental analysis for C₁₆H₃₄B₂Br₂N₄: Calculated - C, 41.43; H, 7.39; Br, 34.45; N, 12.08; Measured - C, 41.45; H, 7.41; Br, 34.43; N, 12.12.

N,N,N',N'-tetramethyldecane-1,10-diamine *bis*-cyanodibromoborane
(Compound **K-J₂**):



Compound **K-J₂** was obtained as brown oil at 83 % yield (0.516 gram).

¹H NMR (CDCl₃): δ = 1.31 (broad s, 8H), 1.70 (m, 4H), 1.88 (m, 4H), 2.95 (s, 12H), 3.38 (m, 4H), (HB cannot be detected).

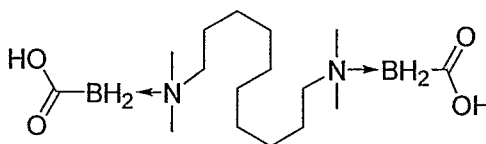
¹³C {¹H} NMR (CDCl₃): δ = 22.90, 26.88, 29.17, 29.31, 50.82, 61.97, (CB cannot be detected).

¹¹B NMR (CDCl₃): δ = -9.38 (s).

IR (neat, cm⁻¹): 2856 (C-H), 2362 (C≡N), 1542 (C-N), 440 (B-N).

Elemental analysis for C₁₆H₃₂B₂Br₄N₄: Calculated - C, 30.91; H, 5.19; Br, 51.41; N, 9.01; Measured - C, 30.88; H, 5.22; Br, 51.39; N, 9.05.

N,N,N',N'-tetramethyldecane-1,10-diamine *bis*-carboxyborane (Compound **K-J₃**):



Compound **K-J₃** was obtained as white oil at 78 % yield (0.268 gram).

61

^1H NMR (CDCl_3): δ = 1.26 (broad s, 8H), 1.61 (m, 4H), 1.83 (pent, 4H, J - 6.9 Hz), 2.66 (s, 12H), 2.91 (t, 4H, J - 4.2 Hz), (HB cannot be detected).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 23.27, 29.31, 32.91, 34.35, 52.36, 62.78, (CB cannot be detected).

5 ^{11}B NMR (CDCl_3): δ = -8.96 (broad s).

IR (KBr, cm^{-1}): 3450 (B-O), 2960 (B-H), 2716 (C-H), 2371 ($\text{C}\equiv\text{N}$), 1459 (C-N), 433 (B-N).

Elemental analysis for $\text{C}_{16}\text{H}_{38}\text{B}_2\text{N}_2\text{O}_4$: Calculated - C, 55.85; H, 11.13; N, 8.14; Measured - C, 55.79; H, 11.17; N, 8.21.

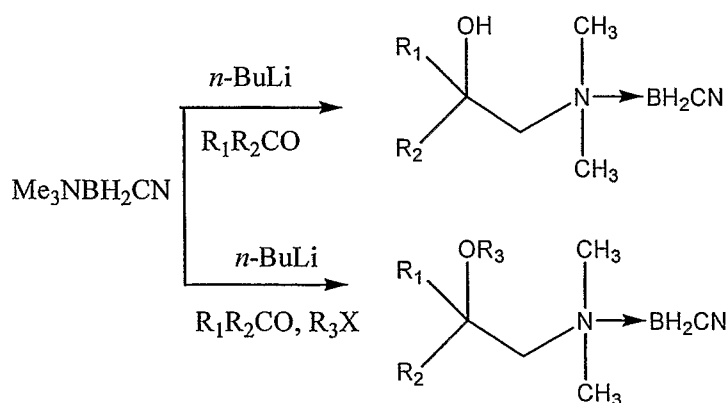
10

Preparation of β -hydroxyamine cyanoboranes and β -alkoxyamine cyanoboranes – General Procedure:

Synthesis of β -hydroxyamine cyanoboranes and β -alkoxyamine cyanoboranes, with the intention of altering the aqueous solubility of these amine cyanoborane derivatives, is carried out using either long chain aldehydes or ketones according to a method developed by the present inventors and described in Takrouri *et al.*, *Organometallics* (2004), 23(11), 2817-2820 (see, Scheme 5 below).

Scheme 5

20



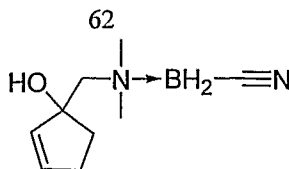
R_1 , R_2 and R_3 = alkyl; and

X = Cl, Br or I

25

Using this general procedure, the following compounds were prepared:

1-dimethylaminomethyl-cyclopent-2-enol cyanoborane (Compound K-A):



Compound K-A was obtained as yellowish solid at 80 % yield (0.144 gram).

^1H NMR (CDCl_3): δ = 2.00 (m, 2H), 2.15 (m, 2H), 2.87 (s, 3H), 2.89 (s, 3H), 3.14 (s, 1H), 3.16 (s, 1H), 5.78 (m, 1H), 6.01 (m, 1H), (HB cannot be detected).

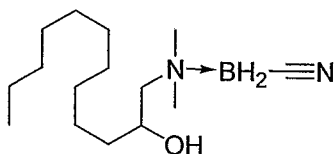
$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 26.29, 33.03, 54.57, 67.82, 77.60, 129.51, 140.04, (CB cannot be detected).

^{11}B NMR (CDCl_3): δ = -14.861 (t, JB-H) 106.3 Hz).

IR (KBr, cm^{-1}): 3450 (B-O), 2920 (B-H), 2853 (C-H), 2334 ($\text{C}\equiv\text{N}$), 1542 (C-N), 440 (B-N).

Elemental analysis for $\text{C}_9\text{H}_{17}\text{BN}_2\text{O}$: Calculated - C, 60.04; H, 9.52; N, 15.56; Measured - C, 59.99; H, 9.31; N, 15.51.

1-dimethylamino-dodecan-2-ol cyanoborane (Compound K-T):



Compound K-T was obtained as yellow oil, 85 % (0.228 gram) yield.

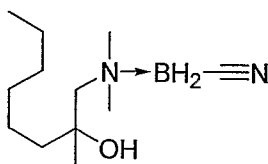
^1H NMR (CDCl_3): δ = 0.80 (t, 3H, J = 7.2 Hz), 1.18 (broad s, 14H), 1.45 (m, 4H), 2.67 (s, 3H), 2.72 (s, 3H), 2.85 (m, 2H), 4.07 (m, 1H), (HB cannot be detected).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ = 14.26, 22.83, 25.33, 29.49, 29.76, 31.05, 32.06, 36.84, 43.60, 49.30, 52.49, 52.89, 68.59, (CB cannot be detected).

^{11}B NMR (CDCl_3): δ = -14.87 (t, $J_{\text{B-H}}$ = 102.7 Hz).

IR (KBr, cm^{-1}): 2920 (B-H), 2854 (C-H), 2360 ($\text{C}\equiv\text{N}$), 1464 (C-N), 430 (B-N).

1-dimethylamino-2-methyl-octan-2-ol cyanoborane (Compound K-O):



63

Compound **K-J** was obtained as white solid, at 85 % yield (0.192 gram).

^1H NMR (CDCl_3): δ 0.81 (m, 7H), 1.12 (pent, 2H, J - 6.0 Hz), 1.51 (m, 4H), 2.09 (s, 1H), 2.10 (s, 1H), 2.38 (td, 3H, J_t - 12 Hz, J_d - 6.0 Hz), 2.68 (s, 3H), 2.69 (s, 3H), (HB cannot be detected).

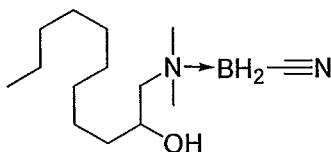
^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): δ 14.24, 22.67, 22.82, 31.78, 32.03, 43.61, 45.73, 48.58, 53.01, (CB cannot be detected).

^{11}B NMR (CDCl_3): δ -12.46 (t, $J_{\text{B-H}}$ 104.4 Hz).

IR (neat, cm^{-1}): 3447 (O-H), 2930 (B-H), 2958 (C-H), 2361 ($\text{C}\equiv\text{N}$), 1461 (C-N), 433 (B-N).

Elemental analysis for $\text{C}_{12}\text{H}_{27}\text{BN}_2\text{O}$: Calculated - C, 63.73; H, 12.03; N, 12.39; Measured - C, 63.71; H, 12.01; N, 12.35.

1-Dimethylamino-undecan-2-ol cyanoborane (Compound K-U):



Compound **K-U** was obtained as yellow oil, 84 % (0.214 gram) yield.

^1H NMR (CDCl_3): δ = 0.86 (t, 3H, J = 6.3 Hz), 1.25 (broad s, 14H), 1.43 (m, 2H), 2.75 (s, 3H), 2.78 (s, 3H), 2.89 (m, 2H), 4.18 (m, 1H), (HB cannot be detected).

^{13}C $\{^1\text{H}\}$ NMR (CDCl_3): δ = 14.33, 22.89, 25.35, 29.54, 29.73, 29.79, 32.11, 36.87, 43.61, 45.17, 46.99, 53.01, (CB cannot be detected).

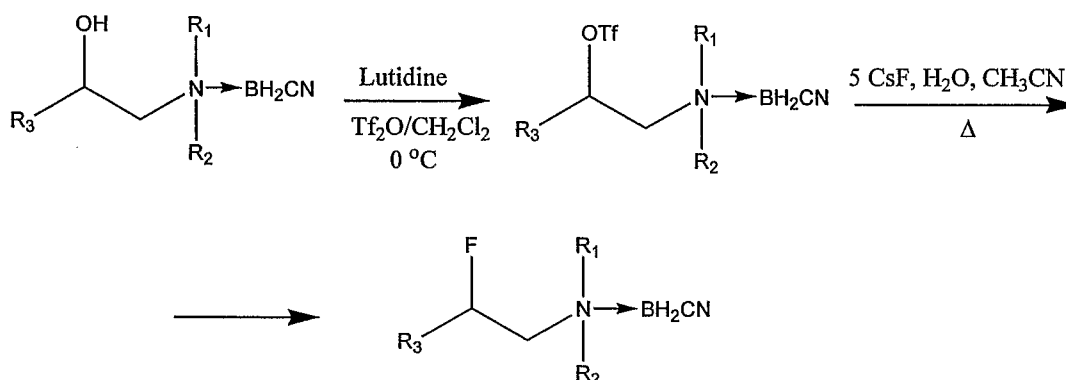
^{11}B NMR (CDCl_3): δ = -16.67 (t, $J_{\text{B-H}}$ = 97.1 Hz).

IR (neat, cm^{-1}): 3447 (O-H), 2926 (B-H), 2954 (C-H), 2334 ($\text{C}\equiv\text{N}$), 1543 (C-N), 443 (B-N).

Preparation of β -fluoroamine cyanoboranes and β -fluoroamine carboxyboranes – General Procedure:

Synthesis of β -fluoroalkylamine cyanoboranes is carried out using a β -hydroxy amine cyanoborane described hereinabove (see, Scheme 6 below). A β -hydroxy amine cyanoborane is treated with triflic anhydride and 2,6-lutidine at

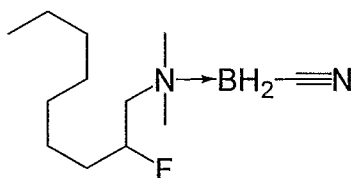
0 °C for 1 hour. The reaction mixture is then extracted to give the crude β -OTf amine cyanoborane. Without additional purification β -OTf amine cyanoborane is reacted with 5 equivalents of cesium fluoride (CsF) and 90 μ l of water in 3 ml acetonitrile, and the reaction mixture is refluxed for 20 minutes at 100 °C, followed by extraction with ether.

Scheme 6

R₁, R₂ and R₃ = alkyl

Using this general procedure, the following compound was prepared:

(2-fluoro-nonyl)-dimethyl-amine cyanoborane (Compound 14):



¹H-NMR (CDCl₃): δ = 2.22 (s, 3H), 2.24 (s, 3H).

¹⁹F-NMR (CDCl₃): δ = -74.31 (s).

Preparation of amine cyanoboranes having an unsaturated alkyl chain attached to the amine moiety – General Procedure:

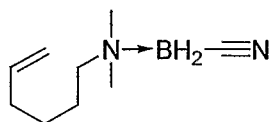
The presence of an unsaturated C=C bond in one or more of the alkyl *N*-substitutions was found to have a significant effect on the efficacy of the compounds presented herein, as presented in Example 2 that follows below.

Synthesis of amine cyanoboranes ($R_1R_2R_3CH_2NBH_2CN$) wherein R_3 is an alkyl having an unsaturated C=C bond at it end is carried out according to a method developed by the present inventors and described in Takrouri *et al.*, *Organometallics* (2004), 23(11), 2817-2820 (see, Scheme 3 above). The corresponding starting
 5 amine cyanobromoborane and amine cyanodibromoborane are prepared as described in the art [Takrouri *et al.*, *J. Organometallic Chem.*, 690 (2005) 4150-4158; Shalom *et al.*, *Organometallics* 2004, 23, 4396-4399; Gyoeri *et al.*, *Inorganic Chemistry* (1998), 37(20), 5131-5141; *Synthesis* (1995), (2), 191-4; and *J. Organometallic Chem.* (1994), 484(1-2), 225-31].

10

Using this general procedure, the following compounds were prepared:

Hex-5-enyl-dimethyl-amine cyanoborane (Compound K-V):



15

Compound **K-V** was obtained as yellow oil at 87 % yield (0.144 gram).

1H NMR ($CDCl_3$): δ = 1.39 (pent, 2H, J - 7.5 Hz), 1.68 (m, 2H), 2.10 (q, 2H, J - 7.0 Hz), 2.85 (t, 3H, J - 4.5 Hz), 5.00 (td, 2H, J_d - 0.6 Hz, J_t - 9.0 Hz), 5.74 (m, 1H), (BH cannot be detected).

20

^{13}C $\{^1H\}$ NMR ($CDCl_3$): δ = 22.79, 26.22, 33.34, 50.07, 63.54, 115.72, 137.82, (CB cannot be detected).

^{11}B NMR ($CDCl_3$): δ = -15.87 (t, J_{B-H} - 104.5 Hz).

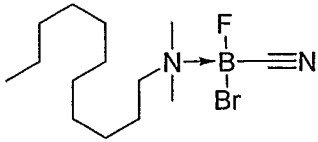
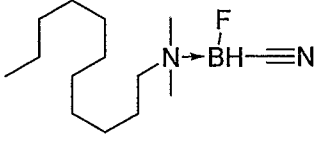
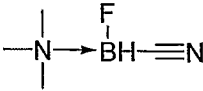
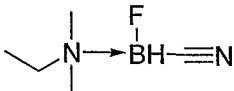
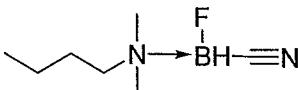
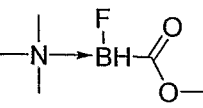
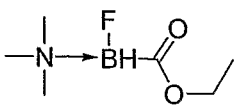
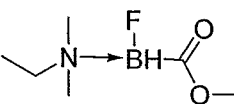
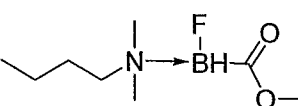
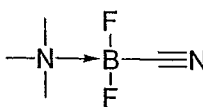
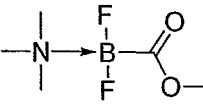
IR (neat, cm^{-1}): 2909 (B-H), 2360 ($C\equiv N$), 1645 ($C=C$), 1470 (C-N), 443 (B-N).

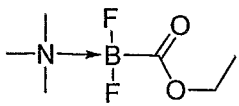
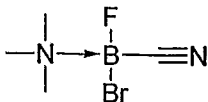
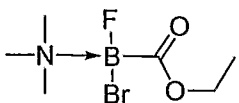
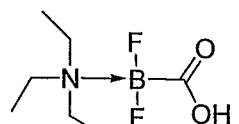
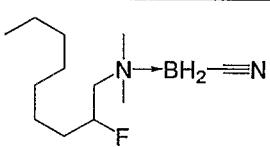
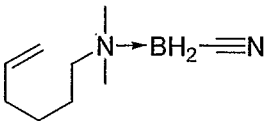
25

Elemental analysis for $C_9H_{19}BN_2$: C, 65.09; H, 11.53; N, 16.87; Measured - C, 65.13; H, 11.47; N, 16.90.

Table 1 below presents the novel amine fluoroboranes prepared using the procedures described above.

Table 1

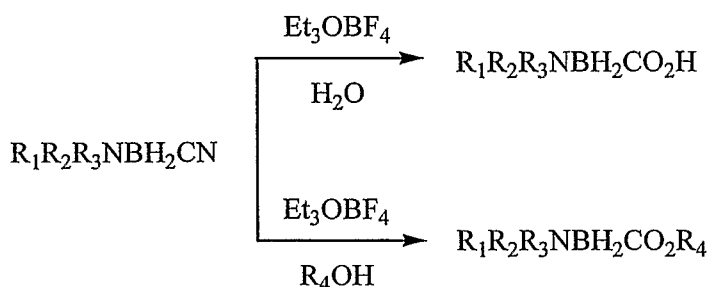
Compound	Name	Structure
K-I ₃	dimethyl-undecyl-amine cyanofluorobromoborane	
K-I ₄	dimethyl-undecyl-amine cyanofluoroborane	
1	trimethyl-amine cyanofluoroborane	
2	ethyl-dimethyl-amine cyanofluoroborane	
3	butyl-dimethyl-amine cyanofluoroborane	
4	trimethyl-amine carboxyfluoroborane methyl ester	
5	trimethyl-amine carboxyfluoroborane ethyl ester	
6	ethyl-dimethyl-amine carboxyfluoroborane methyl ester	
7	butyl-dimethyl-amine carboxyfluoroborane methyl ester	
8	trimethyl-amine cyanodifluoroborane	
9	trimethyl-amine carboxydifluoroborane methyl ester	

10	trimethyl-amine carboxydifluoroborane ethyl ester	
11	trimethyl-amine cyanofluorobromoborane	
12	trimethyl-amine carboxyfluorobromoborane ethyl ester	
13	triethyl-amine carboxydifluoroborane	
14	(2-fluoro-nonyl)-dimethyl- amine cyanoborane	
K-V	hex-5-enyl-dimethyl-amine cyanoborane	

Preparation of amine carboxyboranes and esters thereof – General Procedure:

- 5 Synthesis of amine carboxyboranes [17] and amine carboxyboranes esters [23-26] ($R_1R_2R_3NBH_2CO_2H$ and $R_1R_2R_3NBH_2CO_2Ra$) wherein R_1 , R_2 and R_3 are each an alkyl and Ra is alkyl, alkenyl, aryl and the likes, is carried out according to published procedures, for example as illustrated in Scheme 7 below, by hydrolysis of the corresponding $R_1R_2R_3NMe_2BH_2CN$ obtained as described hereinabove.

68

Scheme 7

R₁, R₂ and R₃ = alkyl; and

5 Ra = e.g. alkyl, alkenyl and aryl

EXAMPLE 2**ANTIFUNGAL ACTIVITY**

10 **Antifungal activity assays:**

Antifungal activity of the amine-borane compounds was determined using *in vitro* susceptibility tests by microbroth dilution method, as detailed below.

Several yeast strains were used for susceptibility testing, namely *Candida albicans* CBS 562 (a reference type strain of the main common cause of yeast
 15 infection in humans; Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands) and two clinical isolates, 607, and 615; *Candida glabrata* 4210; *Candida glabrata* 4475, a yeast strain is known to be a resistant to azoles; *Candida glabrata* 566, 572, 578, 646, and 648 and *Candida krusei* 603 and 638; *Candida glabrata* 4681; *Candida glabrata* 4787; *Saprolegnia parasitica* T1, a water mould
 20 which causes a severe disease in tropical fish – *Saprolegniasis* and massive economical damages, with no effective treatment to date as well as the mold *Aspergillus fumigatus* ATCC 64026 (a reference strain; The American Type Culture Collection, Manassas, VA), a mould which is the main cause of mould infection in immunocompromised host also a main cause of fungal infection in fowl. In
 25 addition, all isolates were obtained from disseminated candidemia patients from Hadassah-Hebrew University Medical Center (Isolate numbers refer to an internal index).

The *in vitro* susceptibility of the tested strains to each of the tested compounds was determined by the broth micro dilution method according to

National Committee for Clinical Laboratory Standards for yeasts (NCCLS/CLSI) recommendations for yeasts (M27-A241) [10] and for filamentous fungi (M-38A42) [27]. Briefly, 2-fold serial dilutions of drugs from stock solutions were prepared in an RPMI-1640 broth medium (Sigma, St. Louis, MO.) buffered to a final pH of 7.0
5 with 0.165 M morpholinepropanesulfonic acid (MOPS; Sigma) and 1M NaOH, and sterilized by filtration and inoculated with 10^4 cells per ml. A stock solution of 10 mg/ml was prepared in dimethyl sulfoxide (DMSO, Sigma) for the various amine cyanoborane compounds and for two conventional anti-fungal agents (CAF), amphotericin B (referred to herein as CAF1) and fluconazole (referred to herein as
10 CAF2), which were used as controls. The final drug concentrations in the test ranged from 1024 mg/L to 4 mg/L in a final volume of 0.1 ml.

The minimum fungicidal concentration (MFC) was established as the lowest concentration of drug producing negative subcultures, after plating 20 μ l of each clear well after 72 hours incubation at 35 °C on drug-free SDA plate.

15 Specifically, fungal inocula were prepared from 24-hours (for *Candida sp.*) or 72 hours (for *A. fumigatus*) cultures on SDA plates (Difco, Detroit, MI). The inocula were harvested by harvesting a single colony of yeast into a sterile saline tube. Mold cultures were suspended in plates with sterile saline containing a 0.05 % (v/v) Tween-20 (Difco) suspension and pipeted into sterile tubes and allowed to
20 rest for 30 minutes for the debris to sink down. The supernatant was then transferred to a fresh tube. Both yeast and mold were diluted into RPMI-1640 broth medium to yield a final inoculum concentration of 2×10^3 yeast per ml for *Candida* and 2×10^4 spores per ml for *Aspergillus*, as measured by counting the initial suspension with a hemacytometer. The micro dilution wells, which contained 0.1
25 ml of the serially diluted drug, were inoculated with 0.1 ml of the resulting suspension. The final inoculum concentration after dilution with the drug suspension was 10^3 - 10^4 cells per ml. Two wells containing the drug-free medium and inoculum were used as controls. The inoculated plates were incubated at 35 °C for 24 hour (for *Candida sp.*) or 72 hours (for *A. fumigatus*). The growth in each
30 well was then visually estimated. The MICs were determined visually, and were defined as the lowest drug concentration at which there was complete absence of growth (MIC-0).

The results of the antifungal activity of amine-borane compounds are presented in Table 2 below, wherein the MIC values of various compounds against various fungi are given in $\mu\text{mol/liter}$ or mg/liter .

Column A of Table 2 presents the antifungal activity against *Candida albicans* CBS 562;

Column B of Table 2 presents the antifungal activity against *Candida albicans* 607;

Column C of Table 2 presents the antifungal activity against *Candida albicans* 615;

Column D of Table 2 presents the antifungal activity against *Candida glabrata* 4210;

Column E of Table 2 presents the antifungal activity against *Candida glabrata* 4475 (resistant to azoles);

Column F of Table 2 presents the antifungal activity against *Candida glabrata* 4681;

Column G of Table 2 presents the antifungal activity against *Candida glabrata* 4787;

Column H of Table 2 presents the antifungal activity against *Saprolegnia parasitica* T1; and

Column I of Table 2 presents the antifungal activity against *Aspergillus fumigatus* 64026.

As can be seen in Table 2, amine cyanoboranes with diverse structures exhibited considerable antifungal activity. Particularly significant activity was demonstrated with amine cyanoborane compounds such as, for example, Compounds K-I, K-I₂ and K-N (see, entries 9, 11 and 20 respectively in Table 2 below).

Structure Activity Relationship (SAR) studies:

A number of relationships were observed regarding the effect of the structure of the amine cyanoboranes and carboxyboranes and their derivatives, according to the present invention, on the antifungal activity thereof.

Effect of length of the N-alkyl chain in alkyl dimethylamine cyanoboranes (see, R₈-R₁₀ in Formula III above):

Compound **K-F**, Compound **K-C**, Compound **K-G**, Compound **K-H**, Compound **K-P**, Compound **K-L**, Compound **K-Q**, and Compound **K-R** (see, 5 corresponding entries 6, 5, 7, 8, 22, 18, 23 and 24 in Table 2), have the general structure of R_nNMe₂-BH₂C≡N, with varying lengths of the N-alkyl chain (n) in the R=(CH₂)_n group.

As can be seen in Table 2, compounds having a longer N-alkyl chain exhibited higher antifungal activity. The optimized chain length was for Compound 10 **K-R** (C₁₅ in the N-alkyl group). The chain length was restricted to this length because attempts to use longer chain lengths resulted in solubility problems, as in Compound **K-S**, which has a C₁₇ in the N-alkyl group.

Effect of length of the N-alkyl-N chain in diamine bis-cyanoboranes for the diamine cyanoboranes (see, A in Formula II above):

15 Compounds **K-J**, **K-M**, and **K-N** (see, corresponding entries 13, 19 and 20 in Table 2), have the general structure N≡CBH₂Me₂N-(CH₂)_n-NMe₂-BH₂C≡N, with varying N-alkyl-N chain length (n).

As can further be seen in Table 2, compounds having a longer N-alkyl-N chain exhibited higher antifungal activity, until a limit of insolubility is reached. 20 The optimized chain length is exhibited in Compound **K-N** (C₁₄ in the N-alkyl group) as attempts to form compounds with longer chain lengths (C₁₆ and above, data not shown) resulted in solubility problems.

Effect of halogenating (see, X₁-X₈ in Formulae I, II and III above):

As can be seen in Table 2, bromination of the compounds of the present 25 invention generally enhances the antifungal activity. The bromination of Compound **K-F** to give the dibromo derivative Compound **K-E** enhanced the activity against *C. albicans* CBS 562 from 5100 to 1970 μmol/liter. Also, the bromination of Compound **K-J** to the monobromo derivative Compound **K-J₁** and the dibromo derivative Compound **K-J₂** enhanced the activity against *C. albicans* 30 CBS 562 from 408 μmol/liter for Compound **K-J** to 140 and 104 μmol/liter for Compound **K-J₁** and Compound **K-J₂**, respectively, whereas the bromination or the fluorination of Compound **K-I** to give Compound **K-I₁**, Compound **K-I₂**, and Compound **K-I₄** had no such effect.

Effect of an unsaturated alkyl chain in alkyl dimethylamine cyanoboranes (see, R_8 - R_{10} in Formula III above):

As can further be seen in Table 2, the presence of unsaturated C=C double bond in the alkyl group dramatically enhanced the activity as seen in Compound K-G and Compound K-D, where the MIC value against *C. albicans* CBS 562 was reduced from 3570 to 470 $\mu\text{mol/L}$ in the presence of a C=C double bond at the end of the alkyl group. For Compound K-H and Compound K-V, the effect on activity with increased N-alkyl chain length was even greater, taking into account the difference of one methylene (CH_2) unit.

Effect of conversion of the amine cyanoborane to the amine carboxyborane derivative:

As can be seen in Table 2 below the antifungal activity against *C. albicans* CBS 562 was enhanced from 408 $\mu\text{mol/L}$ for Compound K-J (see, entry 13 in Table 2) to 188 $\mu\text{mol/L}$ for its carboxyborane derivative Compound K-J₃ (see, entry 16 in Table 2).

Effect of other modifications:

As can further be seen in Table 2, other structural modifications of amine cyanoboranes, such as, for example, addition of a hydroxyl group in one of R_8 - R_{10} in General Formula III as in Compound K-O, Compound K-U, Compound K-T, Compound K-A and Compound K-R, an aromatic group in one of R_8 - R_{10} as in Compound K-B, an unsaturated cyclic group as in Compound K-A, and a silyl group as in Compound K-K, did not result in significant enhancement in the antifungal activity of the compounds.

As can further be seen in Table 2, the amine cyanoboranes and derivatives thereof possess activity against *Candida glabrata* 4475, known to be resistant to azoles (see, column 6 in Table 2 below).

As can be concluded from Table 2 below, the presently most promising compound is dimethyl-undecyl-amine cyanoborane (Compound K-I) which was also tested against moulds, typically more resistant to antifungal agents, and exhibited dramatic activity against both *Saprolegnia* and *Aspergillus*. Furthermore, Compounds K-I, K-I₁ and K-I₃ showed little activity against *Rhizopus oryzae* with MIC of 63 $\mu\text{g/ml}$.

Comparisons of antifungal activity to that of conventional antifungal agents against resistant strains:

The novel amine-boranes described herein were further tested for their activity against fungal strains which are known to be resistant to conventional anti-fungal drugs, using the protocol described hereinabove.

Table 3 below summarizes the results of the anti-fungal assays conducted for the presently leading amine cyanoborane Compounds **K-I** and **K-I₂**, as they are reflected by the MIC values of Compounds **K-I** and **K-I₂** against various fungal strains and particularly fungal strains that are resistant to fluconazole namely *Candida glabrata* 566, *Candida glabrata* 572, *Candida glabrata* 578, *Candida glabrata* 646, *Candida glabrata* 648, *Candida krusei* 603 and *Candida krusei* 638, given in $\mu\text{mol/L}$ or $\mu\text{g/ml}$ and compared to two conventional anti-fungal agents amphotericin B (CAF1) and fluconazole CAF2).

As can be seen in Table 3, Compound **K-I** is highly active against all the tested fungi. As can further be seen in Table 3, isolates of *C. glabrata*, which generate considerably high fluconazole MICs, and isolates of *C. krusei*, which are known as intrinsically resistant to fluconazole, were highly susceptible to the lead Compound **K-I** and its dibromo derivative Compound **K-I₂**, exhibiting much lower MIC values than those obtained with fluconazole. These results strongly suggest that these compounds can become potent antifungal agents, particularly in cases where conventional drugs are involved with development of resistance.

Table 3

Fungal Strain	MIC ($\mu\text{mol/L}$)			
	K-I	K-I ₂	CAF1	CAF2
<i>Candida glabrata</i> 566	32.5	20.2	0.13	26.1
<i>Candida glabrata</i> 572	32.5	40.4	1.07	>836
<i>Candida glabrata</i> 578	32.5	40.4	2.14	>836
<i>Candida glabrata</i> 646	32.5	20.2	0.41	52.2
<i>Candida glabrata</i> 648	32.5	20.2	0.82	26.1
<i>Candida krusei</i> 603	16.25	10.05	4.32	104.5 ^a
<i>Candida krusei</i> 638	16.25	10.05	4.32	104.5 ^a
<i>Candida albicans</i> 563	2-4 ^b			
<i>Cryptococcus neoformans</i> H-99	0.4 ^b			
<i>Cryptococcus neoformans</i> B-3501	0.8 ^b			
<i>Saprolegnia parasitica</i> T-1	2-4 ^b			
<i>Saprolegnia parasitica</i> CBS 540.67	2-4 ^b			

^a *Candida krusei* is intrinsically resistant to fluconazole;

^b Values given in $\mu\text{g/ml}$.

5

EXAMPLE 3

ANTILISHEMANIAN ACTIVITY

Compound **K-I**, an exemplary amine-borane compound according to the present embodiments was further tested for anti-lishmenial activity (against *Leishmania*, a parasitic flagellated protozoan which causes diseases in animals and humans). To this end, various strains of leishmania were grown under optimal conditions, either in Schneiders or in RPMI 1640 medium (Bet-Haemek, Israel), containing 20 % fetal calf serum. Some strains were isolated from humans infected with *L. tropica*, *L. major* and *L. infantum*. Some strains, including *L. donovani*, were received from the World Health Organization Leishmania Strain Bank which

15

is located in the Kuvim Centre, in the Hebrew University of Jerusalem. These strains depict CL and VL leishmaniasis. Promastigotes and axenic amastigotes were grown as published [28].

The *in vitro* antileishmanial effect of Compound **K-I** was determined on promastigotes (the flagellate stage of the *Leishmania* parasites). Parasites, after 3 or 4 days of growth, were washed and resuspended in fresh medium containing fetal calf serum to a concentration of 15×10^4 promastigotes in 200 μ l and distributed into flat bottom wells. The plates were incubated at 28 °C in a wet chamber in an atmosphere of 5 % CO₂, 5 % O₂, and 90 % N₂. After 24 hours, 0.5 μ Ci of [³H]thymidine was added to each well, the parasites were incubated for additional 24 hours, and then harvested on glass-microfiber filters. Radioactivity was measured in a liquid scintillation counter. Each treatment was performed in triplicate; the results are expressed as percent growth inhibition. $[(100 - \text{cpm of wells with drug}) / \text{cpm of untreated wells}] \times 100$ (cpm stands for counts per minute), representing the MIC value in μ g/ml [Golenser, J. *et al.*, 1999, *Antimicrob. Agents Chemother.*, 43:2209-2214].

The *in vitro* antileishmanial effect of Compound **K-I** was further tested on amastigotes (an intracytoplasmic, nonflagellated form of the *Leishmania* parasites). Peritoneal macrophages were obtained from 10-week-old to 12-week-old outbred mice previously stimulated for 4 or 5 days with 3 % thioglycolate. The macrophages were distributed into 8-well slides to 2.5×10^5 cells in 300 μ l per well and incubated at 37 °C and 5 % CO₂ for 3 hours in order to allow for cell adhesion. The supernatant was discarded, and promastigotes (8×10^5 to 10×10^5 per well) were added. After incubation overnight, fresh medium containing Compound **K-I** was added for an additional 24 to 48 hours. At the end of this period, the wells were washed, fixed with methanol, and stained with Giemsa (CAS No.: 51811-82-6). Each treatment was done in duplicate wells; 100 macrophages in each well and the number of amastigotes they contained were counted, representing the MIC value in μ g/ml.

The antileishmanial effect of Compound **K-I** was determined as described above. As can be seen in Figure 1, the measured radioactivity which is indicative of the live parasite diminishes rapidly as a dose of the amine-borane increases, indicating a strong antileishmanial effect. The results of the antileishmanial effect

assay are presented in Table 4 below, wherein the concentration of the amine-borane is given in $\mu\text{g/ml}$ versus the counts per minute recorded for the parasite sample.

5

Table 4

$\mu\text{g/ml}$	cpm
0	8699
3.6	8003
11	7898
33	537
100	138

EXAMPLE 4**ANTI-MALARIAL ACTIVITY**

10 Cultures of *P. falciparum* were grown in human erythrocytes by standard methods under a low-oxygen atmosphere. The culture medium was RPMI 1640, supplemented with 40 mM HEPES, 25 mg/liter gentamicin sulfate, 10 mM D-glucose, 2 mM glutamine and 8 % heat-inactivated plasma.

15 *P. falciparum* growth was assessed by measuring the incorporation of the radiolabeled nucleic acid precursor [^3H]hypoxanthine according to the method described in Desjardins, R.E. *et al.*, 1979, *Antimicrob. Agents Chemother.*, 16: 710–718.

The antimalarial effect of Compound **K-I**, an exemplary amine-borane compound of the present invention was determined as described above. Compound
20 **K-I** was dissolved in DMSO and eleven samples of concentrations ranging from 0.5 to 100 $\mu\text{g/ml}$ (final concentrations) were distributed in duplicate in 96-well culture plates and dried in a laminar flow hood. The *in vitro* response of the parasite was determined by the isotopic microtest developed by Desjardins *et al.*. Infected erythrocytes were suspended in the complete RPMI 1640 medium with 10 % fetal
25 bovine serum at a 1.0-2.5 % hematocrit media. The suspension (200 μl) was

distributed into each well. Parasitemia was adjusted to 0.6 % by adding fresh uninfected erythrocytes if the initial parasitemia was ≥ 1 %. Parasite growth was assessed after incubation at 37 °C for 24 hours by adding ^3H -hypoxanthine. The cells were incubated for further 15 hours, and then collected by filtration on glass fiber filters and radioactivity was counted. The mean values for parasite control uptake and non-parasitized erythrocyte control uptake of $[\text{G-}^3\text{H}]\text{hypoxanthine}$ were calculated from the disintegrations per minute. The IC_{50} was determined by non-linear regression fitting of the data using the Sigmaplot computer program.

As can be seen in Figure 2, the measured radioactivity which is indicative of the live parasite diminishes rapidly as a dose of the amine-borane increases, indicating a strong antimalarial effect. The results of the antimalarial effect assay are presented in Table 5 below, wherein the concentration of the amine-borane is given in $\mu\text{g/ml}$ versus the counts per minute recorded for the parasite sample.

Table 5

$\mu\text{g/ml}$	cpm
0	3500
0.3	3491
1	3335
3	2836
9	959
26.8	33
80.6	13

EXAMPLE 5

TOXICITY STUDIES

Acute toxicity studies in vivo:

The acute toxicity of the novel compounds described herein was determined according to the method described by Falk *et al.* [29]. Briefly, male ICR mice

weighing about 30 grams were injected through the tail vein with various doses of exemplary amine-borane compounds as presented herein and Fungizone (amphotericin B deoxycholate micellar formulation, Bristol-Myers-Squibb, Dublin, Ireland) as control. Each dosage form (Fungizone 0.1 mg/ml; and exemplary
5 amine-borane compounds 1-2 mg/ml in saline) was administered intravenously as single bolus injections (0.12 ml) of the same dose every 10 minutes to a group of three mice until death was observed. The survival of mice that received the maximal tolerated dose (MTD) was monitored for 8 days.

To study the safety of the compounds of the present invention, the MTD that
10 did not kill ICR mice within the 8 days of the experimental period was determined for two exemplary compounds, namely Compound **K-I** and Compound **K-I₂**, using Fungizone as a control. The average calculated MTD for both compounds were 121.9 and 73.1 $\mu\text{mol/kg}$, respectively. The MTD for Fungizone was 2.6 $\mu\text{mol/kg}$. No changes in clinical signs, body weights, and the gross necropsy (on
15 day 8) of mice that received these dosages were observed. These MTD values were well above that of the in vitro MIC values obtained with Compound **K-I** (see, Table 2), and the ratio between the MTD and MIC values are comparable to those obtained with amphotericin B, indicating reduced toxicity and therapeutic potential.

20 **EXAMPLE 6**

RADIOSYNTHESSES

The introduction of a halogen atom during the preparation of the compounds described herein enables to provide radiolabeled aminoboranes and thus harness their biologic activity in a variety of analytical, diagnostic and therapeutic
25 applications which are based on the use of radiolabeled biologically active compounds.

Most practically, the compounds of the present invention can be radiolabeled with radioactive halogens such as ^{18}F ($t_{1/2}$ 1.83 hours), ^{123}I ($t_{1/2}$ 13 hours), ^{125}I ($t_{1/2}$ 60 days) ^{131}I ($t_{1/2}$ 8 days), ^{77}Br ($t_{1/2}$ 2.4 days) and the likes.

30 Handling radioactive materials should be restricted or avoided so as to minimize the exposure of personnel to significant levels of radioactivity. In order to exercise this precaution, radiosyntheses are oftentimes practiced in a fully or semiautomatic procedures. To this end, the present inventors have designed a

system for performing such semiautomatic procedure for affording a ^{18}F -radiolabeled amine-borane, as is detailed hereinbelow.

Semiautomatic synthesis of ^{18}F -radiolabeled amine-borane compounds – General Procedure:

5 The radiosynthesis of a ^{18}F -radiolabeled amine-borane is performed using a novel semiautomatic synthesis system designed to suit the reaction conditions, as is schematically illustrated in Figure 3 and is further detailed hereinbelow.

10 The radiosynthesis is performed in three steps. In the first step, the fluorinating reagent Ag^{18}F is prepared in a platinum dish. Thereafter the precursor, namely a brominated amine-borane according to the present invention, such as, for example, Compounds **K-E**, **K-I₁**, **K-I₂**, **K-I₃**, **K-J₁**, and **K-J₂**, is added under sonication. The obtained [^{18}F] product is thereafter transferred to another vial, the solvent is removed, and the product is re-dissolved in a physiologic solution (saline).

15 The setup and flow diagram of semiautomated radio-synthesis system **10** is presented in Figure 3. The semiautomated radiosynthesis of [^{18}F] labeled amine cyanoboranes is carried out using a modified module which is inserted inside a hot cell (see, Figure 3). All the reaction steps are handled using manipulator arms. Platinum is the element of choice for reaction vessel since platinum can resist both
20 HF and high temperatures. Sonication is necessary for the nucleophilic substitution to occur in the fluorination reaction. Since benzene (the reaction solvent) can dissolve plastic stopcocks, special clips are added to hold the silicon crochets (Degania Silicon Ltd.) from the outside in order to prevent contact of benzene with the plastic stopcocks. Prior to the start of synthesis, Ag_2CO_3 is loaded into platinum
25 reaction vessel **11** that is thereafter closed using a rubber septum (Sigma-Aldrich). Solutions containing the appropriate reagents are loaded into glass vials type 1 (Bunderglass) which are sealed with silicon rubber septa. Precursor vial **12**, intermediate vial **14** and platinum reaction vessel **11** are all equipped with an inlet line for nitrogen gas to pressurize the vial, and silicon line (Degania Silicon Ltd.)
30 outlets for delivery of precursor vial **12** contents to platinum reaction vessel **11** and platinum reaction vessel **11** contents to intermediate vial **14**.

 The 7 ml precursor vial **12** is fitted with silicon rubber stopper (ABX). The 12 ml intermediate vial **14** is fitted with latex rubber stopper (West). Product vial

16 is a 25 ml glass vial (Mallinckrodt) which is used to collect the product. The 25 ml platinum reaction vessel 11 is designed to be hermetically sealed with an O-ring and latex septum in order to withstand the high pressure caused by nitrogen (see, Figure 4).

5 *Semiautomatic synthesis of [¹⁸F]dimethyl-undecyl-amine cyanofluoroborane (Compound [¹⁸F]K-I₄):*

The radiosynthesis of [¹⁸F]dimethyl-undecyl-amine cyanofluoroborane (Compound [¹⁸F]K-I₄), an exemplary amine-borane according to the present invention, was performed using semiautomated radiosynthesis system 10 (see, Figure 3) as presented hereinabove.

Materials and Methods:

Dimethyl-undecyl-amine cyanobromoborane (Compound K-I₁) was synthesized as described hereinabove.

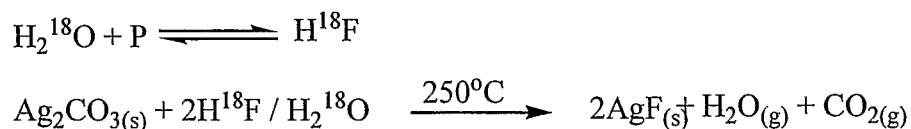
H₂¹⁸O was purchased from Rotem laboratories.

15 H¹⁸F was produced using an IBA cyclotron at 10/5 MeV.

Sonication was performed with an (Astrason[®] 50/60Hz, 1.2 amps).

One hundred mCi of H¹⁸F were dissolved in 1.1 ml of H₂¹⁸O and added to platinum reaction vessel 11 containing 15 mg of Ag₂CO₃. The reaction mixture was thereafter heated to 250 °C to obtain the desired radioactive fluorinating reagent, Ag¹⁸F (see, Scheme 8 below).

Scheme 8



25 [¹⁸F]Dimethyl-undecyl-amine cyanofluoroborane (Compound [¹⁸F]K-I₄) started was prepared by first adding 100 mCi of H¹⁸F dissolved in 1.1 ml of H₂¹⁸O to platinum reaction vessel 11 to dissolve the Ag₂CO₃. Immediately thereafter, the reaction mixture was heated to 250 °C for less then 5 minutes to afford the desired Ag¹⁸F as a precipitate. Platinum reaction vessel 11 was transferred to ultrasonic bath 18, and cooled for 3 minutes. Thereafter, 0.15 mg of dimethyl-undecyl-amine cyanobromoborane (Compound K-I₁) dissolved in 4 ml of dry benzene was added

to platinum reaction vessel **11** and ultrasonic bath **18** was operated for 50 minutes, which was found to be the optimized time in order to complete the chemical conversion as determined by sampling the reaction on TLC (silica gel F₂₅₄). The product was then transferred and filtered through stainless steel filter **20** containing
5 a 0.22 μm Teflon membrane. The nitrogen pressure was set at 1.1 Bar and controlled by a 0.4 liter per minute flow rate into intermediate vial **14**. Intermediate vial **14** was thereafter transferred to heater **22** and the benzene was vaporized at 110 °C for 15 minutes while being vented with nitrogen. Thereafter the vial was sampled once and injected in a GC to verify that no benzene was present.
10 Intermediate vial **14** was then cooled with external air for 3 minutes. Thereafter the product was dissolved in saline (0.9 % NaCl in water) by inserting syringe **24** containing 5 ml saline and injecting the saline into intermediate vial **14** using a needle that reached to the bottom of the vial, and the entire content of the vial was retracted back into syringe **24**. 4-Way stopcock **26** was turned on to transfer the
15 final product into product vial **16** via a 0.22 μm filter as AgF is a solid and does not pass through the 0.22 μm filter.

The final [¹⁸F] labeled dimethyl-undecyl-amine cyanofluoroborane was subjected to a number of quality control measures including assessment of radiochemical purity, γ -detector and pH measurements. Silica TLC tests were
20 performed to assess the radiochemical purity. TLC of the product on silica plates with 100 % methanol demonstrated a single radioactive peak with an R_f of 0.23 which was identical to the R_f of the non-radioactive dimethyl-undecyl-amine cyanofluoroborane. The ¹⁸F was detected with Wallac Wizard γ -counter with sodium iodide detector and showed 511 KeV. The tested pH of the radioactive
25 [¹⁸F] labeled product solution in saline was 6.3.

The chemical purity was evaluated using radiometric TLC. The radiochemical purity was 100 %. T_{1/2} of ¹⁸F was tested according to the ¹⁸F specification. TLC was performed utilizing Merck silica gel F₂₅₄ plates with a mobile phase of 100 % methanol and analyzed with radiometric detection. The R_f
30 of the radio-labeled product was compared with the observed R_f of the non-radioactive form. The pH was determined using pH test papers in the range 3.8-5.5 and 6.0-8.1. The ¹⁸F was detected with Wallac Wizard γ -counter with sodium iodide detector.

A 22 % radiochemical yield was obtained in product vial 16 at the end of synthesis with specific radioactivity of 455 mCi/mg. The saline solution of the final product (4.5 mCi/ml) was then shielded to prevent irradiation.

5 The final product was tested on TLC (silica gel 60 F₂₅₄) after 10 hours and found stable.

EXAMPLE 7

PET IMAGING

Positron emission tomography (PET) imaging using Compound [¹⁸F]K-I₄:

10 The exemplary [¹⁸F] labeled amine fluorocyanoborane according to the present embodiments, Compound [¹⁸F]K-I₄, was injected into normal rats, and was monitored by a PET/CT Philips camera. The images detected the bio-distribution and showed an uptake in the rat's bones.

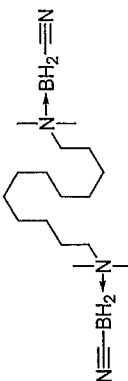
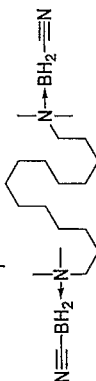
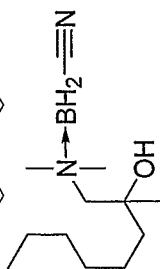
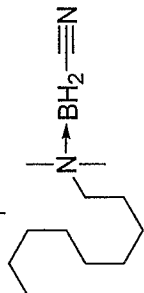
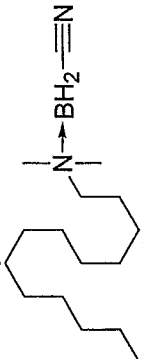
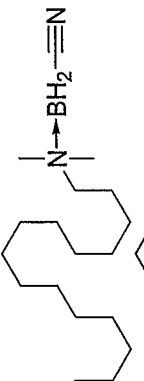
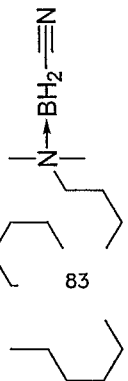
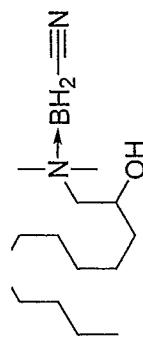
15 Four normal, female Sprague-Dawley rats (250-300 grams each) were injected via the tail vein with 50 µCi of Compound [¹⁸F]K-I₄ solution in saline (4.5 mCi/ml). Fifteen minutes after injection, the rats were anesthetized with 45 mg Ketamine and 24 mg Acepromazin, and after 30 minutes each rat was imaged for 15 minutes.

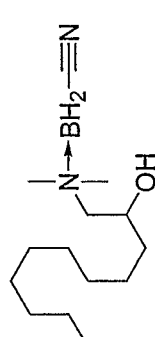
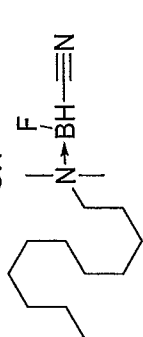
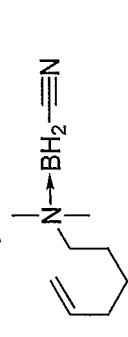
20 Figure 5 presents the PET-images obtained, and clearly show uptake of the radiolabeled amine-borane compound into the bones of the tested rats, demonstrating that [¹⁸F] labeling of the amine-borane compounds of the present invention can be practically used as a diagnostic tool and further shed light on their mode of action in the body.

Table 2

No.	Code	Name	Structure	A	B	C	D	E	F	G	H	I
1	K-A	1-dimethylaminomethyl-cyclopent-2-enol cyanoborane		1388	2776	2776	500 °	>500°				
2	K-B	(2-hydroxy-2-phenylethyl)-dimethylamine cyanoborane		245	>245	>2450	>500°	>500°				
3	K-C	ethyl-dimethylamine cyanoborane		4460	4460	4460	500 °	500 °				
4	K-D	but-3-enyl-dimethylamine cyanoborane		470	3620	>3620	500°	500°				>3620
5	K-E	trimethylamine cyanodibromoborane		1970	>1970	>1970	500 °	>500°				
6	K-F	trimethylamine cyanoborane		5100	>5100	>5100						>5100
7	K-G	butyl-dimethylamine cyanoborane		3570	>3570	>3570						>3570
8	K-H	pentyl-dimethylamine cyanoborane		810	3240	3240						3240
9	K-I	dimethyl-undecylamine cyanoborane		32.5	32.5	32.5	7.8 °	15.6 °			1-3	32.5

10	K-I ₁	dimethyl-undecyl-amine cyanobromoborane		49	49	7.8°	7.8°	7.8°	15.6	131
11	K-I ₂	dimethyl-undecyl-amine cyanodibromoborane		39	39	15.6°	32°	32°	32	79
12	K-I ₃	dimethyl-undecyl-amine cyanofluorobromoborane		7.8						
13	K-J	N,N,N',N'-tetramethyl- decane-1,10-diamine cyanoborane		408	408	32°	65°	65°	817	817
14	K-J ₁	N,N,N',N'-tetramethyl- decane-1,10-diamine bis- cyanobromoborane		140	140	65°	65°	65°	65	65
15	K-J ₂	N,N,N',N'-tetramethyl- decane-1,10-diamine bis- cyanodibromoborane		104	104	65°	65°	65°	65	65
16	K-J ₃	N,N,N',N'-tetramethyl- decane-1,10-diamine bis- carboxyborane		188	188	65°	31.2°	65°	65	65
17	K-K	dimethyl- trimethylsilyl-amine cyanoborane		2940	2940				2940	2940
18	K-L	dodecyl-dimethyl-amine cyanoborane		61	61	65°	15.6°	7.8°	32	32

19	K-M	N,N,N',N'-tetramethyl- dodecane-1,12-diamine bis-cyanoborane		96	194	46	>250°	>250°	125°	250	
20	K-N	N,N,N',N'-tetramethyl- tetradecane-1,14-diamine bis-cyanoborane		43	43	43	7.8°	15.6°			86
21	K-O	1-dimethylamino-2- methyl-octan-2-ol cyanoborane		2210	1100	1100	>250°	>250°			
22	K-P	dimethyl-nonyl-amine cyanoborane		150	150	300					300
23	K-Q	dimethyl-tridecyl-amine cyanoborane		58	58	117					58
24	K-R	dimethyl-pentadecyl- amine cyanoborane		53	53	106					53
25	K-S	heptadecyl-dimethyl- amine cyanoborane		83							
26	K-T	1-dimethylamino- dodecan-2-ol cyanoborane									

27	K-U	1-dimethylamino-undecan-2-ol cyanoborane		492	492	983	492	492
28	K-L ₄	dimethyl-1-undecyl-amine cyanofluoroborane		129	64	64	64	64
29	K-V	hex-5-enyl-dimethyl-amine cyanoborane		94	94	94	94	94
30	CAF1	Amphotericin B		0.5	0.54	0.27	0.27	0.27
31	CAF2	Fluconazole		>208	1.6	1.6	1.6	1.6

^c Values given in µg per liter.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be
5 provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all
10 such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein
15 by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

REFERENCES CITED BY NUMERALS*(Other references are cited in the text)*

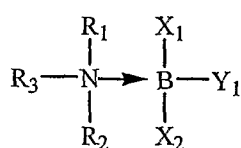
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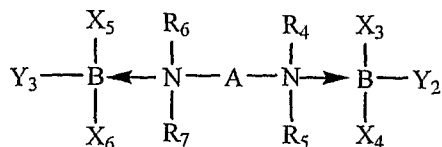
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WHAT IS CLAIMED IS:

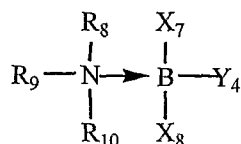
1. A compound having a general formula selected from the group consisting of Formula I, II and III:



Formula I



Formula II



Formula III

or a pharmaceutically acceptable salt thereof,

wherein:

A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms;

Y₁-Y₄ are each independently selected from the group consisting of a cyano group (-C≡N), a -C(=O)Ra group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X₁-X₈ are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, and aryl, provided that at least one of X₁ and X₂ in Formula I is fluorine; and

R₁-R₁₀ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl and aryl or, alternatively, two of R₁-R₃, R₄ and R₅ R₆ and R₇ and/or R₈-R₁₀ form a carbocyclic ring, provided that:

at least one of R₈-R₁₀ in Formula III is a saturated alkyl having at least 11 carbon atoms;

at least one of R₈-R₁₀ in Formula III is an unsaturated alkyl having 5-20 carbon atoms; and/or

at least one of R₈-R₁₀ in Formula III comprises at least one fluorine.

2. The compound of claim 1, wherein when the compound comprises fluorine, said fluorine is selected from the group consisting of a non-radioactive fluorine and a radioactive fluorine
3. The compound of any of claims 1 and 2, having the general Formula I.
4. The compound of claim 3, wherein Y₁ is selected from the group consisting of a cyano group -(C≡N) and a -C(=O)Ra group.
5. The compound of claim 3, wherein X₁ is fluorine and X₂ is selected from the group consisting of hydrogen, fluorine, bromine and iodine.
6. The compound of any of claims 3-5, wherein X₁ is fluorine and X₂ is bromine.
7. The compound of any of claims 3-5, wherein each of R₁-R₃ is alkyl.
8. The compound of any of claims 3-5, wherein at least one of R₁-R₃ is a C₅-C₂₀ alkyl.
9. The compound of any of claims 7 and 8, wherein said alkyl is selected from the group consisting of a saturated alkyl and an unsaturated alkyl.
10. The compound of claim 3, being selected from the group consisting of dimethyl-undecyl-amine cyanofluorobromoborane, trimethyl-amine cyanofluoroborane, ethyl-dimethyl-amine cyanofluoroborane, butyl-dimethyl-amine cyanofluoroborane, trimethyl-amine carboxyfluoroborane methyl ester, trimethyl-amine carboxyfluoroborane ethyl ester, ethyl-dimethyl-amine carboxyfluoroborane methyl ester, butyl-dimethyl-amine carboxyfluoroborane methyl ester, trimethyl-amine cyanodifluoroborane, trimethyl-amine carboxydifluoroborane methyl ester, trimethyl-amine carboxydifluoroborane ethyl ester, dimethyl-undecyl-amine

cyanofluoroborane, trimethyl-amine cyanofluorobromoborane, trimethyl-amine carboxyfluorobromoborane ethyl ester and triethyl-amine carboxydifluoroborane.

11. The compound of any of claims 1 and 2, having the general Formula II.

12. The compound of claim 11, wherein each of X_3 , X_4 , X_5 and X_6 is independently selected from the group consisting of hydrogen, fluorine, bromine and iodine.

13. The compound of claim 11, wherein at least one of X_3 , X_4 , X_5 and X_6 is bromine.

14. The compound of any of claims 11-13, wherein A is a saturated, non-substituted hydrocarbon.

15. The compound of claim 14, wherein said hydrocarbon has from 8 to 14 carbon atoms.

16. The compound of claim 11, being selected from the group consisting of N,N,N',N'-tetramethyl-decane-1,10-diamine bis-cyanoborane, N,N,N',N'-tetramethyl-decane-1,10-diamine bis-cyanobromoborane, N,N,N',N'-tetramethyl-decane-1,10-diamine bis-cyanodibromoborane, N,N,N',N'-tetramethyl-decane-1,10-diamine bis-carboxyboranes, N,N,N',N'-tetramethyl-dodecane-1,12-diamine bis-cyanoborane and N,N,N',N'-tetramethyl-tetradecane-1,14-diamine bis-cyanoborane.

17. The compound of any of claims 1 and 2, having the general Formula III.

18. The compound of claim 17, wherein at least one of R_8 - R_{10} is a saturated alkyl having 11-15 carbon atoms.

19. The compound of claim 17, wherein at least one of R₈-R₁₀ is an unsaturated alkyl having 5-20 carbon atoms.

20. The compound of claim 17, wherein at least one of R₈-R₁₀ comprises a hydroxy, whereas said hydroxy is at position β to the amine nitrogen.

21. The compound of claim 17, wherein at least one of R₈-R₁₀ comprises a fluorine, whereas said fluorine is at position β to the amine nitrogen.

22. The compound of any of claims 17-21, wherein each of X₇ and X₈ is independently selected from the group consisting of hydrogen, fluorine, bromine and iodine.

23. The compound of any of claims 17-21, wherein at least one of X₇ and X₈ is bromine.

24. The compound of claim 17, being selected from the group consisting of dimethyl-undecyl-amine cyanoborane, dimethyl-undecyl-amine cyanobromoborane, dimethyl-undecyl-amine cyanodibromoborane, dodecyl-dimethyl-amine cyanoborane, 1-dimethylamino-2-methyl-octan-2-ol cyanoborane, dimethyl-nonyl-amine cyanoborane, dimethyl-tridecyl-amine cyanoborane, dimethyl-pentadecyl-amine cyanoborane, heptadecyl-dimethyl-amine cyanoborane, 1-dimethylamino-dodecan-2-ol cyanoborane, 1-dimethylamino-undecan-2-ol cyanoborane, dimethyl-undecyl-amine cyanofluorobromoborane, dimethyl-undecyl-amine cyanofluoroborane, hex-5-enyl-dimethyl-amine cyanoborane and (2-fluoro-nonyl)-dimethyl-amine cyanoborane.

25. A pharmaceutical composition comprising, as an active ingredient, the compound of any of claims 1-24 and a pharmaceutically acceptable carrier.

26. A method of treating a medical condition associated with a pathogenic microorganism, the method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any of claims 1-24.

27. Use of the compound of any of claims 1-24 in the treatment of a medical condition associated with a pathogenic microorganism.

28. Use of the compound of any of claims 1-24 as a medicament.

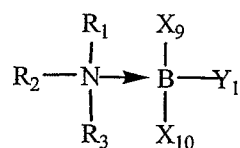
29. The use of claim 28, wherein said medicament is for the treatment of a medical condition associated with a pathogenic microorganism.

30. The method or use of any of claims 26-28, wherein said medical condition is selected from the group consisting of a bacterial infection, a protozoan infection, a fungal infection, malaria and leishmaniasis.

31. The method or use of any of claims 26-30, wherein said pathogenic microorganism is a drug-resistant microorganism.

32. A process of preparing the compound of claim 3, the process comprising:

reacting a compound having the general Formula IV:



Formula IV

or a pharmaceutically acceptable salt thereof,

wherein:

Y_1 is selected from the group consisting of a cyano group $-(\text{C}\equiv\text{N})$, a $-\text{C}(=\text{O})$ group, amine and alkyl, whereas R_a is hydrogen, halo, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol, and amine;

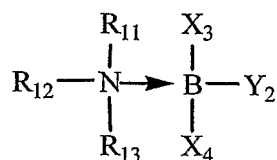
X_9 and X_{10} are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, aryl, provided that at least one of X_9 and X_{10} is bromine; and

R_1 - R_3 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R_1 - R_3 form a carbocyclic ring,

with a fluorinating agent, thereby obtaining the compound having general Formula I.

33. A process of preparing the compound of claim 11, the process comprising:

reacting a compound having the general Formula V:



Formula V

or a pharmaceutically acceptable salt thereof,

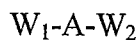
wherein:

Y_2 is selected from the group consisting of a cyano group $-(C\equiv N)$, a $-C(=O)$ group, amine and alkyl, whereas R_a is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl; and

R_{11} - R_{13} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R_{11} - R_{13} form a carbocyclic ring, provided that at least one of R_{11} - R_{13} in Formula V is methyl,

with a compound having the general Formula VI:



Formula VI

wherein:

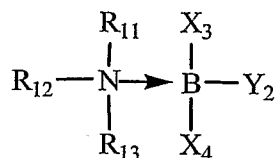
A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms; and

W_1 and W_2 are each independently a functional group,

in the presence of n-alkyl lithium, thereby obtaining the compound having general Formula II.

34. A process of preparing the compound of claim 17, wherein at least of R₈-R₁₀ is a saturated alkyl having 11-17 carbon atoms or an unsaturated alkyl having 5-20 carbon atoms, the process comprising:

reacting a compound having the general Formula V:



Formula V

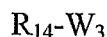
or a pharmaceutically acceptable salt thereof,
wherein:

Y₂ is selected from the group consisting of a cyano group -(C≡N), a -C(=O)Ra group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X₃ and X₄ are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl; and

R₁₁-R₁₃ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R₁₁-R₁₃ form a carbocyclic ring, provided that at least one of R₁₁-R₁₃ in Formula V is methyl,

with a compound having the general Formula VII:



Formula VII

wherein:

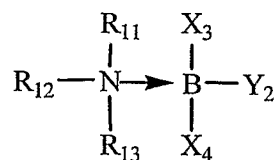
R₁₄ is selected from the group consisting of saturated alkyl having at least 10 carbon atoms or an unsaturated alkyl having at least 4 carbon atoms; and

W₃ is a functional group,

in the presence of n-alkyl lithium, thereby obtaining the compound having general Formula III.

35. A process of preparing the compound of claim 17, wherein at least of R_8 - R_{10} comprises a fluorine, the process comprising:

reacting a compound having the general Formula V:



Formula V

or a pharmaceutically acceptable salt thereof,

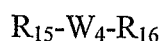
wherein:

Y_2 is selected from the group consisting of a cyano group $-(C\equiv N)$, a $-C(=O)$ group, amine and alkyl, whereas R_a is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl; and

R_{11} - R_{13} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R_{11} - R_{13} form a carbocyclic ring, provided that at least one of R_{11} - R_{13} in Formula V is methyl,

with a compound having the general Formula VIII:



Formula VIII

wherein:

W_4 is a carboxy $(C=O)$ group;

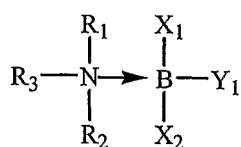
R_{15} is selected from the group consisting of alkyl, cycloalkyl, and aryl; and

R_{16} is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl,

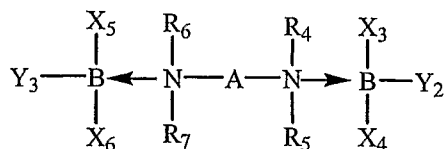
in the presence of n-alkyl lithium, to thereby obtaining a compound having said general Formula III, wherein at least one of R₈-R₁₀ comprises a hydroxy or alkoxy; and

converting said hydroxy or said alkoxy to said fluorine.

36. A radiolabeled compound having the general Formula X or XI:



Formula X



Formula XI

or a pharmaceutically acceptable salt thereof,

wherein:

Y₁-Y₃ are each independently selected from the group consisting of a cyano group (-C≡N), a -C(=O)Ra group, amine and alkyl, whereas Ra is hydrogen, halogen, hydroxy, alkoxy, thiohydroxy, thioalkoxy, aryloxy, thioaryloxy, thiol and amine;

X₁-X₆ are each independently selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl and aryl,

R₁-R₇ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl or, alternatively, two of R₁-R₃, R₄ and R₅ and/or R₆ and R₇ form a carbocyclic ring, and

A is a substituted or non-substituted, saturated or non-saturated hydrocarbon having from 5 to 20 carbon atoms,

whereas at least one of X₁-X₆, R₁-R₇ and A comprises a radioactive atom and/or at least one boron atom is a radioactive boron atom.

37. The radiolabeled compound of claim 36, wherein said radioactive atom is selected from the group consisting of radioactive fluorine, radioactive carbon, radioactive bromine and radioactive iodine.

38. The radiolabeled compound of claim 37, wherein said radioactive atom is at position β to the amine nitrogen.

39. The radiolabeled compound of claim 36, having the general Formula X.

40. The compound of claim 36, wherein at least one of X_1 and X_2 is said radioactive atom.

41. The radiolabeled compound of claim 39, wherein at least one of R_1 - R_3 is an alkyl substituted by a radioactive atom.

42. The radiolabeled compound of claim 41, wherein said radioactive atom is at position β to the amine nitrogen.

43. A pharmaceutical composition comprising, as an active ingredient, the radiolabeled compound of any of claims 36-42 and a pharmaceutically acceptable carrier.

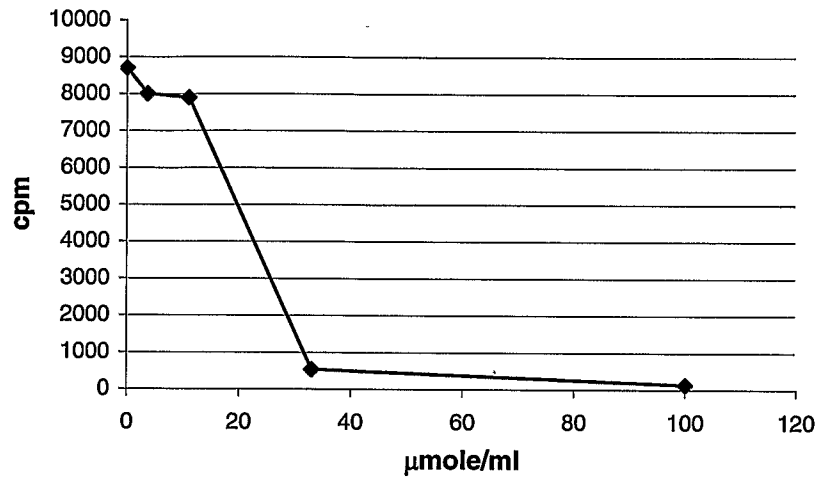
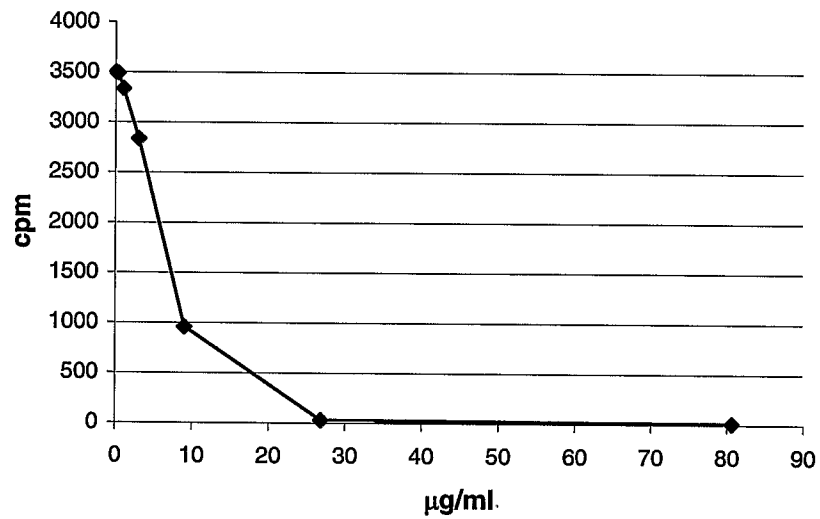
44. Use of the radiolabeled compound of any of claims 36-42 or of the composition of claim 43 in radioimaging and/or radiotherapy.

45. The use of claim 44, wherein said radioimaging comprises positron emitting tomography (PET), Computed Tomography (CT), PET/CT and Single Photon Emission Tomography (SPECT).

46. Use of the radiolabeled compound of any of claims 36-42 in the preparation of a diagnostic agent.

47. A method of radioimaging comprising administering to a patient the radiolabeled compound of any of claims 36-42 or the composition of claim 43; and employing a radioimaging technique for monitoring a distribution of said radiolabeled compound within the body or within a portion thereof.

48. The method of claim 47, wherein said radioimaging technique is selected from the group consisting of Positron Emission Tomography (PET), Computed Tomography (CT), PET/CT and Single Photon Emission Tomography (SPECT).

Figure 1**Figure 2**

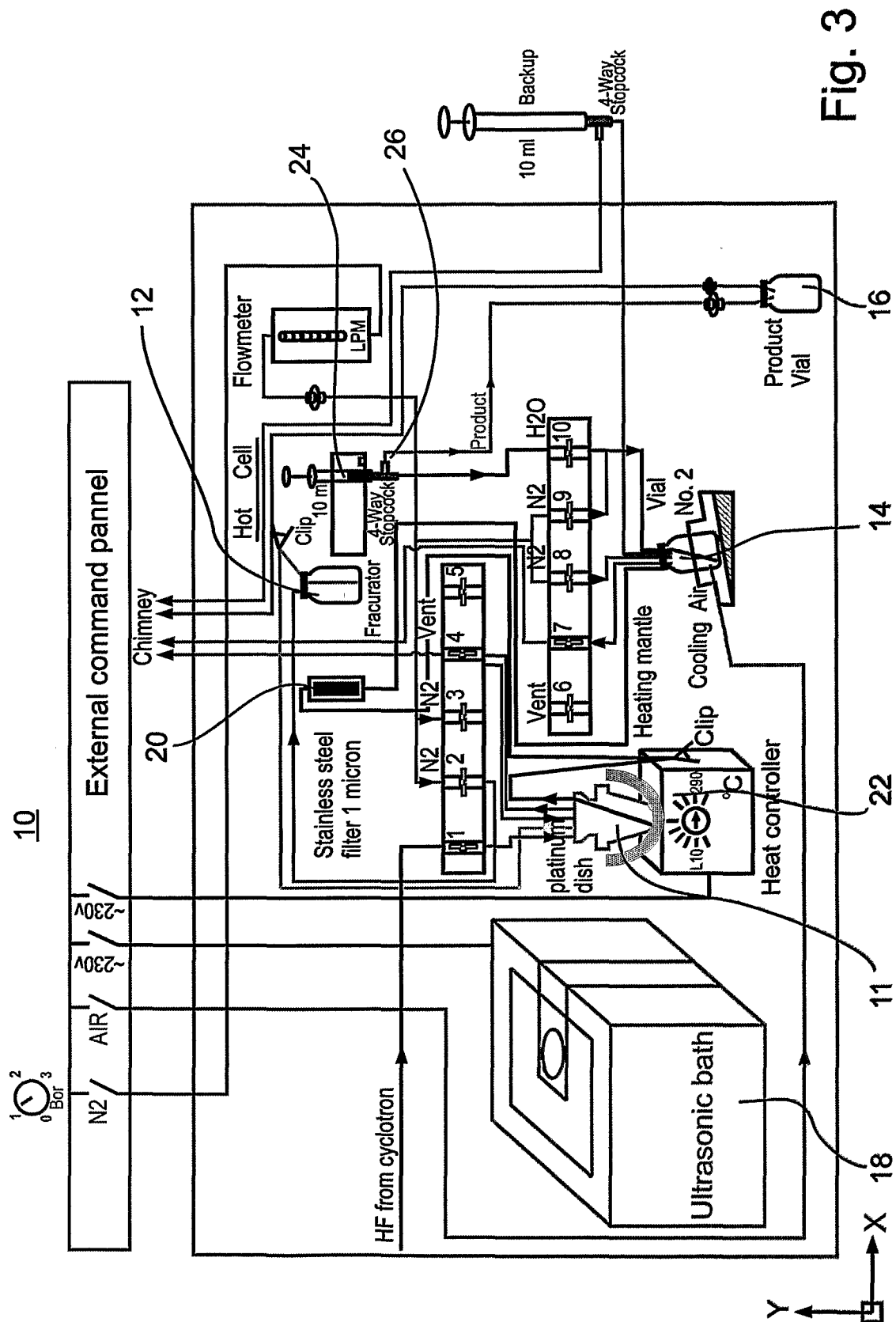


Figure 4

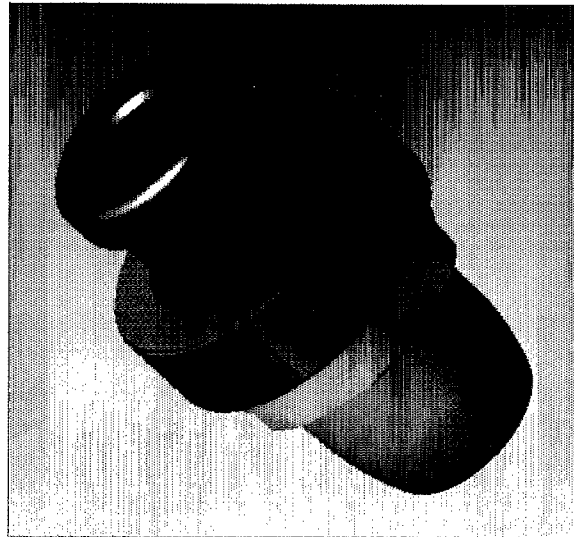


Figure 5

