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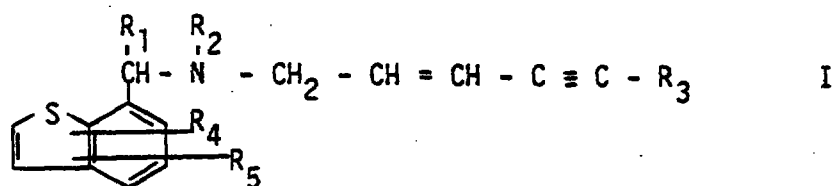
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Benzothienylallylamines Processes for their Production and their Use as Pharmaceuticals

The invention concerns benzothienylallylamines processes for their production and their use as pharmaceuticals.

5 More particularly the invention concerns compounds of formula I



wherein

- R_1 represents hydrogen or methyl,
 R_2 represents methyl or ethyl,
 R_3 represents tertiary alkyl or an alkenyl group; and
10 R_4 and R_5 represent, independently of each other, hydrogen, halogen, hydroxy, lower alkynyl, cyano, formyl, lower-alkoxy, lower alkylcarbonyl, lower alkyl which is unsubstituted or bears one or more substituents selected from halogen, cyano, hydroxy, lower alkylthio and lower alkoxy; or lower alkenyl
15 which is unsubstituted or bears one or more substituents selected from halogen and cyano,
in free base form or in the form of an acid addition salt.

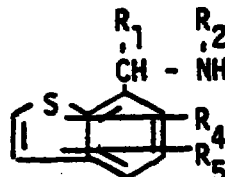
EP Publication No. 0,024,587 discloses a wide range of aromatic allylamines without specifically disclosing compounds of the type
20 comprising the present invention. It has now been found that in tests such as hereinafter described the compounds of the present invention not only exhibit high activity against dermatophytes but also a

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surprisingly high activity against candida spp. not possessed to the same degree by the compounds of EP0 024587.

The compounds of the invention can be prepared e.g. by

a) reacting a compound of formula II

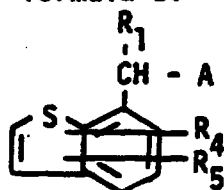


5 with a compound of formula III



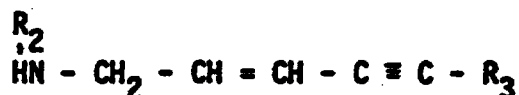
or

b) reacting a compound of formula IV



IV

with a compound of formula V



V.

whereby in the formulae II, III, IV and V

10 R_1 , R_2 , R_3 , R_4 and R_5 are as defined under formula I and
A represents a leaving group,

and recovering the compound thus obtained in free base form or in the form of an acid addition salt.

Processes a) and b) can be carried out in conventional manner, for
15 example in a solvent, inert under the reaction conditions, such as
a lower alcohol, e.g. ethanol, optionally in mixture with water; an
aromatic hydrocarbon such as benzene or toluene; a cyclic ether, such

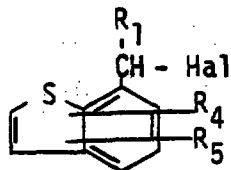
as dioxane; or a carboxylic acid dialkylamide such as dimethylformamide and at reaction temperatures of between room temperature (which is preferred) and the boiling point of the reaction mixture. Leaving group A can for example be halogen e.g. chlorine or bromine or an organic sulphonyloxy group having 1 to 10 carbon atoms, e.g. alkarylsulphonyloxy such as tosyloxy or alkylsulphonyloxy such as mesyloxy. The reaction is conveniently carried out, when appropriate, in the presence of an acid binding agent, e.g. an alkali or alkaline earth metal hydroxide or carbonate such as sodium or potassium carbonate.

The compounds of formula I may be converted in conventional manner into their acid addition salts and vice versa.

The compounds of the formula I and their intermediates can be obtained in the form of isomeric mixtures of the various cis/trans isomers which can be separated according to established methods.

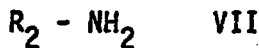
"Lower" as employed herein refers to any lower alkyl radical present as or in a substituent being straight or branched-chained and having 1 to 4 carbon atoms, especially 1 or 2 carbon atoms; alkynyl or alkenyl groups can be straight or branch-chained and have preferably 2 to 6 carbon atoms especially 2 to 4 as ring substituents or 3 or 4 (alkenyl) as R_3 , examples are vinyl and ethynyl as ring substituents and allyl (preferably β -allyl) as R_3 . Tertiary alkyl groups as R_3 contain preferably 4 to 10 especially 4 to 6 carbon atoms e.g. t.-butyl. Halogen represents fluorine, chlorine or bromine preferably chlorine or bromine.

The starting materials of formula II are in part new and can be prepared in conventional manner e.g. by reacting a compound of formula VI



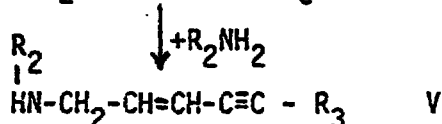
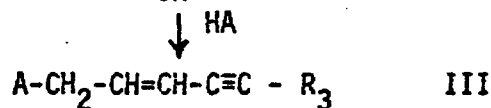
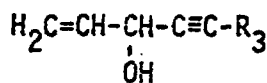
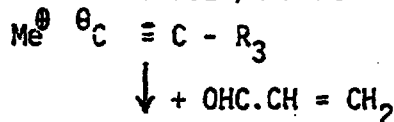
VI

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This process can be performed analogously to processes a) and b) described above.

The starting materials of formulae III and V are in part new and can be prepared in conventional manner, e.g. according to the following scheme.



(R_1 , R_2 , R_3 and A as defined above $Me^{\oplus}$ = metalcation).

10 Reaction conditions are those conventionally employed in such reactions whereby the various intermediates can, where appropriate, be reacted further without isolation. Where isolation takes place it is carried out in conventional manner.

The remaining starting materials and intermediate compounds are 15 either known or can be prepared according to known methods.

The compounds of formula I exhibit chemotherapeutic activity. In

particular, they exhibit antimycotic activity, as indicated in vitro in various families and types of mycetes, including Trichophyton spp.,

Aspergillus spp., Microsporum spp., Sporotrix schenckii and especially Candida spp., at concentrations of, for example 0.1 to

5 25 ug/ml, and in vivo in the experimental skin mycosis model in guinea pigs. The test substance is administered daily for 7 days beginning 24 hours after the infection either on local application by rubbing the test substance (taken up in polyethylene glycol) on the skin surface, or perorally or sub-cutaneously, the test substance
10 being administered as a suspension. The Candida activity is shown in vivo employing conventional intravaginal/intrauterine- or disseminated-infection models on mice or rats. The activity is shown on local application at concentrations of for example 0.01 to 0.5%. The oral activity is shown in vivo in the guinea-pig-trichophytosis
15 at dosages of, for example, 2 to 70 mg/kg.

The compounds are therefore indicated for use as chemotherapeutic agents, in particular, as anti-mycotic agents.

An indicated daily dose is from about 70-2000 mg administered e.g. in unit dosage forms containing from about 17.5 to 1000 mg
20 two to four times daily or in sustained release form. The active substance can also be administered topically.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts. Such salt forms exhibit the same order of activity as the free base forms. Suitable such salt forms are e.g. hydrochloride, hydrogen fumarate
5 or naphthalene-1,5-disulphonate.

The invention therefore also concerns a method of treating diseases or infections caused by mycetes which comprises administering to a subject in need of such treatment an effective amount of a compound of formula I or a chemotherapeutically acceptable acid
10 addition salt thereof as well as compounds of formula I or chemotherapeutically acceptable acid addition salts thereof for use as chemotherapeutic agents especially as anti-mycotics.

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other
15 excipients and administered e.g. orally in such forms as tablets or capsules. The compounds may alternatively be administered topically (in such conventional forms as ointments or creams), parenterally or intravenously. The concentrations of the active substance will, of course, vary depending on the compound employed, the treatment
20 desired and the nature of the form etc. In general, however, satisfactory results are obtained e.g. in topical application forms at concentrations of from 0.05 to 5, in particular 0.1 to 1 wt.%.
C

Such compositions also form part of the invention.

Preferred meanings for the substituents are as follows:

- 25 R_1 = hydrogen
 R_2 = methyl
 R_3 = a) C_{4-10} alkyl
b) C_{4-6} alkyl
c) t.butyl or t.-pentyl, especially t.butyl
30 d) C_{3-6} alkenyl
e) allyl, especially β -allyl
 R_4, R_5 = hydrogen, or

- a) C_{1-4} alkyl
- b) C_{1-2} alkyl, especially methyl
- c) halogen, especially chlorine
- d) C_{1-4} haloalkyl, especially CF_3
- e) C_{2-5} alkylcarbonyl, especially acetyl,
- f) C_{1-4} hydroxyalkyl, especially $-CH_2OH$
- g) cyano
- h) C_{1-4} alkylthio or -alkoxy e.g. methylthio or methoxy
- i) formyl
- j) C_{2-4} alkenyl (e.g. vinyl) optionally halogen substituted
- k) C_{2-4} alkynyl e.g. ethynyl

whereby one of R_4 and R_5 is preferably hydrogen.

Substituents present as R_4 and/or R_5 are preferably in the thienyl ring i.e. at position 2 and/or 3.

Compounds in which the double bond adjacent to the nitrogen has the trans (E) configuration are preferred.

A particular compound group is that of formula I wherein R_5 represents hydrogen and R_4 hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy.

A particularly preferred single compound is:

(E)-N-(3-chloro-7-benzo[b]thienylmethyl)-N-methyl-6,6-dimethyl-hept-2-en-4-ynamine.

The following examples illustrate the invention whereby temperatures are given in degrees centigrade.

Example 1

5 N-(7-benzo[b]thienylmethyl)-N-methyl-6,6-dimethyl-hept-2-en-4-ynamine in (E)- and (Z)-form (compounds 1a) and 1b) respectively; process a))

12 g of 1-bromo-6,6-dimethyl-hept-2-en-4-yne are added dropwise to a mixture of 10.5 g N-(7-benzo[b]thienylmethyl)methylamine, 10 8.2 g of potassium carbonate and 100 ml of dimethylformamide and stirred overnight. The reaction mixture is filtered and the solvent removed under vacuum. The residue is partitioned between ether and saturated aq. NaHCO_3 and the organic phase dried, concentrated in a rotary evaporator and chromatographed over silica gel (eluant : 15 toluene/ethylacetate = 4/1). This yields first the (E)- and then the (Z)-isomer as oils. M.p. of the (E)-hydrochloride = 148-158°.

Example 2

N-(3-chloro-7-benzo[b]thienylmethyl)-N-methyl-6,6-dimethyl-hept-2-en-4-ynamine in (E)- and (Z)-form (compounds 2a) and 2b) respectively; process b)).

690 mg of N-(6,6-dimethyl-hept-2-en-4-ynyl)methylamine dissolved 20 in dimethylformamide are added dropwise to 1.4 g of 7-bromomethyl-3-chloro-benzo[b]thiophene and 480 mg of NaCO_3 in 40 ml of dimethylformamide and stirred overnight. The reaction mixture is concentrated under vacuum and the residue taken up in ether/water. The organic phase is washed with saturated NaHCO_3 , dried and concentrated by 25 evaporation. The residue is chromatographed over silica gel (eluant : toluene/ethylacetate = 95/5) to yield first the (E)- and then the (Z)-

isomer as oils. M.p. of the (E)-hydrochloride = 180-184°.

The following compounds of the formula I can be obtained analogously to examples 1 and 2 or as otherwise described hereinbefore. ($R_1 = H$; $R_2 = CH_3$).

Compd. No.	R_3	R_4	R_5	Position of R_3 -bearing side chain	Configuration	Physical data
3 a)	$\begin{matrix} C_2H_5 \\ \\ -C(CH_3)_2 \end{matrix}$	H	H	7	E	oil m.p. ¹⁾ = 128-131°
b)					Z	oil
4 a)	$-C(CH_3)_3$	3-Br	H	7	E	m.p. 51-57°: m.p. ¹⁾ = 168-174°
b)					Z	oil
5 a)	"	4-Br	H	7	E	m.p. 55-58°
6 a)	"	2-Cl	H	7	E	m.p. 67-70°
b)					Z	oil
7	"	3-F	H	7	E	oil m.p. ¹⁾ = 150-170°
8 a)	"	3-CF ₃	H	7	E	oil m.p. ¹⁾ = 175-188°
b)	"				Z	oil

Compd. No.	R ₃	R ₄	R ₅	Position of R ₃ -bearing side chain	Configuration	Physical data
9	-C(CH ₃) ₃	2-F	H	7	E	oil m.p. ¹⁾ = 141-151°
10 a)	"	3-COCH ₃	H	7	E	m.p. 101-107°
b)	"	"	"	"	Z	oil
11 a)	"	3-CH ₃	H	7	E	oil m.p. ¹⁾ = 185-187°
b)	"	"	"	"	Z	oil
12 a)	$\begin{array}{c} -C=CH_2 \\ \\ CH_3 \end{array}$	H	H	7	Z	oil m.p. ¹⁾ = 134-143°
b)	"	"	"	"	Z	oil
13	-C(CH ₃) ₃	3-CH ₂ OH	H	7	E	oil
14	"	3-CHO	H	7	E	oil
15 a)	"	2-Cl	3-Cl	7	E	m.p. 82°
b)	"	"	"	"	Z	oil
16 a)	"	3-CN	H	7	E	oil m.p. ¹⁾ = 188-192°
b)	"	"	"	"	Z	oil
17	"	2-SCH ₃	3-Br	7	E	m.p. 45-50°
18	"	2-SCH ₃	H	7	E	oil
19	"	3-CH=C(Br) ₂	H	7	E	oil m.p. ¹⁾ = 118-125°
20	"	3-C≡CH	H	7	E	oil
21	"	3-COOCH ₃	H	7	E	oil
22	"	3-CH=CH ₂	H	7	E	oil
23	"	3-CH=CHCN	H	7	E	oil
24	"	2-Br	3-CN	7	E	oil
25	"	3-CH ₂ CN	H	7	E	oil
26	"	3-CH ₂ OCH ₃	H	7	E	oil

1) = melting point of hydrochloride

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NMR-Spectra (δ , CDCl_3 , TMS-Standard):

- 1 a) E 7,7 (dd, $J = 7$ u. 2Hz, 1H); 7,2-7,5 (m, 4H); 6,16 (dt, $J = 16$ u. $2 \times 6,5$ Hz, 1H); 5,66 (dt, $J = 16$ u. 2×1 Hz, 1H); 3,74 (s, 2H); 3,10 (dd, $J = 6,5$ u. 1Hz, 2H); 2,2 (s, 3H); 1,22 (s, 9H).
- b) Z 7,7 (dd, $J = 7$ u. 2Hz, 1H); 7,15-7,45 (m, 4H); 6,04 (dt, $J = 11$ u. 2×7 Hz, 1H); 5,6 (dt, $J = 11$ u. 2×1 Hz, 1H); 3,78 (s, 2H); 3,34 (dd, $J = 7$ u. 1Hz, 2H); 2,24 (s, 3H); 1,24 (s, 9H).
- 2 a) E 7,78 (dd, $J = 7$ u. 2Hz, 1H); 7,25-7,5 (m, 3H); 6,16 (dt, $J = 16$ u. 2×6 Hz, 1H); 5,65 (dt, $J = 16$ und 2×1 Hz, 1H); 3,76 (s, 2H); 3,10 (dd, $J = 6$ u. 1Hz, 2H); 2,20 (s, 3H); 1,22 (s, 9H).
- b) Z 7,78 (dd, $J = 7$ u. 2Hz, 1H); 7,2-7,5 (m, 3H); 6,05 (dt, $J = 11$ u. $2 \times 6,5$ Hz, 1H); 5,63 (dt, $J = 11$ u. 2×1 Hz, 1H); 3,8 (s, 2H); 3,33 (dd, $J = 6,5$ u. 1Hz, 1H); 2,24 (s, 3H); 1,24 (s, 9H).

- 3 c) E 7,78 (dd, J = 7 u. 2Hz, 1H); 7,25-7,5 (m, 4H); 6,20 (dt, J = 16 u. 2x6,4Hz, 1H); 5,70 (dt, J = 16 u. 2x1Hz, 1H); 3,77 (s, 2H); 3,12 (dd, J = 6,4 u. 1Hz, 2H); 2,22 (s, 3H); 1,3-1,6 (m, 2H); 1,18 (s, 6H); 0,98 (ps.t, 3H).
- d) Z 7,88 (dd, J = 6,5 u. 2,5Hz, 1H); 7,2-7,5 (m, 4H); 6,1 (dt, J = 11 u. 2x7Hz, 1H); 5,65 (dt, J = 11 u. 2x1Hz, 1H); 3,8 (s, 2H); 3,35 (dd, J = 7 u. 1Hz, 1H); 2,26 (s, 3H); 1,3-1,7 (m, 2H); 1,2 (s, 6H); 1,0 (ps.t, 3H).
- 4 a) E 7,77 (dd, J = 7 u. 2Hz, 1H); 7,2-7,55 (m, 3H); 6,18 (dt, J = 16 u. 2x6,5Hz, 1H); 5,66 (dt, J = 16 u. 2x1Hz, 1H); 3,8 (s, 2H); 3,1 (dd, J = 6,5 u. 1Hz, 2H); 2,22 (s, 3H); 1,24 (s, 9H).
- b) Z 7,88 (dd, J = 7 u. 2Hz, 1H); 7,2-7,55 (m, 3H); 6,05 (dt, J = 11 u. 2x6Hz, 1H); 5,64 (dt, J = 11 u. 2x1Hz, 1H); 3,8 (s, 2H); 3,3 (dd, J = 6 u. 1Hz, 2H); 2,24 (s, 3H); 1,24 (s, 9H).

- 5 a) E 7,25-7,6 (m, 4H); 7,22 (dt, J = 16 u. 2x7Hz, 1H); 6,70 (dt, J = 16 u. 2x1Hz, 1H); 3,96 (s, 2H); 3,17 (dd, J = 7 u. 1Hz, 2H); 2,25 (s, 3H); 1,24 (s, 9H).
- 6 a) E 7,58 (dd, J = 7 u. 2Hz, 1H); 7,1-7,4 (m, 3H); 6,20 (dt, J = 16 u. 2x7Hz, 1H); 6,65 (dt, J = 16 u. 1Hz, 1H); 3,68 (s, 2H); 3,08 (dd, J = 7 u. 1Hz, 2H); 2,20 (s, 3H); 1,22 (s, 9H).
- b) Z 7,58 (dd, J = 7 u. 2Hz, 1H); 7,1-7,4 (m, 3H); 6,08 (dt, J = 11 u. 2x7Hz, 1H); 5,64 (dt, J = 11 u. 2x1Hz, 1H); 3,72 (s, 2H); 3,34 (dd, J = 7 u. 1Hz, 2H); 2,24 (s, 3H); 1,24 (s, 9H).
- 7 a) E 7,70 (dd, J=7.5 u. 2.0 Hz, 1H); 7,38 (t, J=7.5 Hz, 1H); 7,28 (dd, J=7.5 u. 2.0 Hz, 1H); 6,84 (d, J=2.5 Hz, 1H); 6,19 (dt, J=16 u. 2x6.5 Hz, 1H); 5,68 (dt, J=16 u. 2x1.5 Hz, 1H); 3,76 (s, 2H); 3,10 (dd, J=6.5 u. 1.5 Hz, 2H); 2,21 (s, 3H); 1,22 (s, 9H).

- 8 a) E 7.90 (s, 1H); 7.86 (1H); 7.42 (t, J=7.5 Hz, 1H); 7.25 (1H); 6.16 (dt, J=16 u. 2x6.5 Hz, 1H); 5.65 (d, J=16 u. 2x1.5 Hz, 1H); 3.78 (s, 2H); 3.10 (dd, J= 6.5 u. 1.5 Hz, 2H); 2.22 (s, 3H); 1.24 (s, 9H).
- b) Z 7.89 (s, 1H); 7.86 (1H); 7.42 (t, 2x7.5 Hz, 1H); 7.30 (1H); 6.04 (dt, J=11 u. 2x7 Hz, 1H); 5.64 (dt, J=11 u. 2x1.2 Hz, 1H); 3.80 (s, 2H); 3.33 (dd, J=6.5 u. 1.5 Hz, 2H); 2.24 (s, 3H); 1.24 (s, 9H).
- 9 E 7.52 (dd, J=7.5 u. 2.0 Hz, 1H); 7.28 (t, J=7.5 Hz, 1H); 7.12 (dd, J= 7.5 u. 2.0 Hz, 1H); 6.69 (d, J=3.0 Hz, 1H); 6.18 (dt, J=16 u. 2x6.5 Hz, 1H); 5.68 (dt, J=16 u. 1.5 Hz, 1H); 3.68 (s, 2H); 3.10 (dd, J=6.5 u. 1.5 Hz, 2H); 2.21 (s, 3H); 1.23 (s, 9H).

- 10 a) E 8.72 (dd, J=7.5 u. 2.0 Hz, 1H); 8.30 (s, 1H); 7.45 (t, J=7.5 Hz, 1H); 7.27 (m, 1H); 6.18 (dt, J=16 u. 2x6.5 Hz, 1H); 5.68 (dt, J=16 u. 2x1.5 Hz, 1H); 3.78 (s, 2H); 3.11 (dd, J=6.5 u. 1.5 Hz, 2H); 2.64 (s, COCH_3); 2.21 (s, 3H); 1.24 (s, 9H).
- b) Z 8.72 (dd, J=7.5 u. 2.0 Hz, 1H); 8.30 (s, 1H); 7.46 (t, J=7.5 Hz, 1H); 7.30 (m, 1H); 6.06 (dt, J=11 u. 2x7 Hz, 1H); 5.66 (dt, J=11 u. 1.2 Hz, 1H); 3.82 (s, 2H); 3.35 (dd, J=6.5 u. 1.5 Hz, 2H); 2.65 (s, COCH_3); 2.24 (s, 3H); 1.25 (s, 9H).
- 11 a) E 7.68 (dd, J=7.5 u. 2.0 Hz, 1H); 7.40 (t, J=7.5 Hz, 1H); 7.30 (m, 1H); 7.10 (qua, J=1 Hz, 1H); 6.20 (dt, J=16 u. 2x6.5 Hz, 1H); 5.70 (dt, J=16 u. 2x1.5 Hz, 1H); 3.78 (s, 2H); 3.12 (dd, J=6.5 u. 1.5 Hz, 2H); 2.46 (d, J=1 Hz, 3H); 2.24 (s, 3H); 1.25 (s, 9H).
- b) Z 7.68 (dd, J=7.5 u. 2.0 Hz, 1H); 7.40 (t, J=7.5 Hz, 1H); 7.30 (m, 1H); 7.10 (qua, J=1 Hz, 1H); 6.09 (dt, J=11 u. 2x7 Hz, 1H); 5.66 (dt, J=11 u. 2x1.2 Hz, 1H); 3.81 (s, 2H); 3.36 (dd, J=6.5 u. 1.5 Hz, 2H); 2.47 (d, J=1 Hz, 3H); 2.28 (s, 3H); 1.27 (s, 9H).
- 12 a) E 7.75 (dd, J=7.5 u. 2.0 Hz, 1H); 7.2-7.5 (m, 4H); 6.30 (dt, J=16 u. 2x6.5 Hz, 1H); 5.81 (dt, J=16 u. 2x1.5 Hz, 1H); 5.2-5.4 (m, 2H); 3.77 (s, 2H); 3.14 (dd, J=6.5 u. 1.5 Hz, 2H); 2.23 (s, 3H); 1.90 (m, 3H).

- b) Z 7.75 (m, 1H); 7.2-7.5 (m, 4H); 6.19 (dt, J=11 u. 2x7 Hz, 1H); 5.75 (dt, J=11 u. 2x1.5 Hz, 1H); 5.2-5.4 (m, 2H); 3.81 (s, 2H); 3.37 (dd, J=6.5 u. 1.5 Hz, 2H); 2.28 (s, 3H); 1.93 (m, 3H).
- 13 E 7.80 (dd, J=7.5 u. 2.0 Hz, 1H); 7.38 (t, J=7.5 Hz, 1H); 7.41 (s, 1H); 7.30 (m, 1H); 6.18 (dt, J=16 u. 2x6.5 Hz, 1H); 5.68 (dt, J=16 u. 2x1.5 Hz, 1H); 4.95 (d, J=1 Hz, 1H); 3.77 (s, 2H); 3.10 (dd, J=6.5 u. 1.5 Hz, 2H); 2.23 (s, 3H); 1.24 (s, 9H).
- 14 E 10.17 (s, 1H); 8.66 (dd, J=7.5 u. 2.0 Hz, 1H); 8.35 (s, 1H); 7.47 (t, J=7.5 Hz, 1H); 7.30 (m, 1H); 6.18 (dt, J=16 u. 2x6.5 Hz, 1H); 5.70 (dt, J=16 u. 2x1.5 Hz, 1H); 3.80 (s, 2H); 3.12 (dd, J=6.5 u. 1.5 Hz, 2H); 2.23 (s, 3H); 1.25 (s, 9H).
- 15 a) E 7.68 (dd, J=7.5 u. 2 Hz, 1H); 7.4 (t, J=7.5 Hz, 1H); 7.15-7.35 (m, 1H); 6.20 (dt, J=16 u. 2x6.5 Hz, 1H); 5.65 (dt, J=16 u. 2x1.5 Hz, 1H); 3.75 (s, 2H); 3.10 (dd, J=6.5 u. 1.5 Hz, 2H); 2.20 (s, 3H); 1.22 (s, 9H).
- b) Z 7.68 (dd, J=7.5 u. 2 Hz, 1H); 7.4 (t, J=7.5 Hz, 1H); 7.15-7.3 (m, 1H); 6.08 (dt, J=11 u. 2x6.5 Hz, 1H); 5.65 (dt, J=11 u. 2x1.5 Hz, 1H); 3.78 (s, 2H); 3.34 (dd, J=6.5 u. 1.5 Hz, 2H); 2.24 (s, 3H); 1.24 (s, 9H).
- 16 a) E 8.18 (s, 1H); 7.95 (dd, J=7.5 u. 2 Hz, 1H); 7.5 (t, J=7.5 Hz, 1H); 7.25-7.4 (m, 1H); 6.2 (dt, J=16 u. 2x6.5 Hz, 1H); 5.70 (dt, J=16 u. 2x1.5 Hz, 1H); 3.82 (s, 2H); 3.14 (dd, J=6.5 u. 1.5 Hz, 2H); 2.22 (s, 3H); 1.24 (s, 9H).

- b) Z 8.18 (s, 1H); 7.96 (dd, J=7.5 u. 1.5 Hz, 2H); 7.52 (t, J=7.5 Hz, 1H); 6.08 (dt, J=11 u. 2x6.5 Hz, 1H); 5.68 (dt, J=11 u. 2x1.5 Hz, 1H); 3.86 (s, 2H); 3.36 (dd, J=6.5 u. 1.5 Hz, 2H); 2.26 (s, 3H); 1.26 (s, 9H).
- 17 E 7.62 (dd, J=7.5 u. 2 Hz, 1H); 7.35 (t, J=7.5 Hz, 1H); 7.18 (dd, J=7.5 u. 2 Hz, 1H); 6.15 (dt, J=16 u. 2x6.5 Hz, 1H); 5.67 (dt, J=16 u. 2x1.5 Hz, 1H); 3.74 (s, 2H); 3.10 (dd, J=6.5 u. 1.5 Hz, 2H); 2.64 (s, 3H); 2.22 (s, 3H); 1.24 (s, 9H).
- 18 E 7.55 (dd, J=7.5 u. 2 Hz, 1H); 7.26 (t, J=7.5 Hz, 1H); 7.19 (s, 1H); 7.13 (dd, J=7.5 u. 2 Hz, 1H); 6.16 (dt, J=16 u. 2x6.5 Hz, 1H); 5.67 (dt, J=16 u. 2x1.5 Hz, 1H); 3.69 (s, 2H); 3.10 (dd, J=6.5 u. 1.5 Hz, 2H); 2.61 (s, 3H); 2.21 (s, 3H); 1.24 (s, 9H).
- 19 E 8.1 (d, J=1.5 Hz, 1H); 7.7 (d, J=1.5 Hz, 1H); 7.68 (dd, J=7.5 u. 2 Hz, 1H); 7.4 (t, J=7.5 Hz, 1H); 7.2-7.4 (m, 1H); 6.2 (dt, J=16 u. 2x6.5 Hz, 1H); 5.58 (dt, J=16 u. 2x1.5 Hz, 1H); 3.78 (s, 2H); 3.10 (dd, J=6.5 u. 1.5 Hz, 2H); 2.2 (s, 3H); 1.22 (s, 9H).
- 20 E 7.9 (dd, J=7.5 u. 2 Hz, 1H); 7.74 (s, 1H); 7.4 (d, J=7.5 Hz, 1H); 7.3 (dd, J= 7.5 u. 2 Hz, 1H); 6.18 (dt, J=16 u. 2x6.5 Hz, 1H); 5.68 (dt, J=16 u. 2x1.5 Hz, 1H); 3.78 (s, 2H); 3.3 (s, 1H); 3.1 (dd, J=7.5 u. 1.5 Hz, 2H); 2.22 (s, 3H); 1.24 (s, 9H);

- 21 E 8.55 (dd, $J = 7.5$ u. 2 Hz, 1H); 8.42 (s, 1H);
7.45 (t, $J = 7.5$ Hz, 1H); 7.3 (m, 1H); 6.18
(dt, $J = 16$ u. 2 x 6.5 Hz, 1H); 5.66 (dt, $J =$
16 u. 2 x 1.5 Hz, 1H); 3.95 (s, 3H); 3.78 (s,
2H); 3.1 (dd, $J = 6.5$ u. 1.5 Hz, 2H); 2.2 (s,
3H); 1.22 (s, 9H).
- 22 E 7.86 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.2-7.7 (m, 3H);
7.02 (ddd, $J = 18, 12$ u. 1 Hz, 1H); 6.2 (dt, $J =$
16 u. 2 x 6.5 Hz, 1H); 5.8 (dd, $J = 18$ u. 1.5 Hz,
1H); 5.65 (dt, $J = 16$ u. 2 x 1.5 Hz, 1H); 5.38 (dd,
 $J = 12$ u. 1.5 Hz, 1H); 3.78 (s, 2H); 3.1 (dd, $J =$
6.5 u. 1.5 Hz, 2H); 2.22 (s, 3H); 1.22 (s, 9H).
- 23 E 7.84 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.80 (s, 1H);
7.7 (d, $J = 16$ Hz, 1H); 7.45 (t, $J = 7.5$ Hz, 1H);
7.34 (m, 1H); 6.18 (dt, $J = 16$ u. 2 x 6.5 Hz, 1H);
5.94 (d, $J = 16$ Hz); 5.68 (dt, $J = 16$ u. 2 x 1.5 Hz,
1H); 3.78 (s, 2H); 3.1 (dd, $J = 6.5$ u. 1.5 Hz, 2H);
2.2 (s, 3H); 1.22 (s, 9H).
- 24 E 7.76 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.42 (t, $J = 7.5$ Hz,
1H); 7.24 (dd, $J = 7$ u. 2 Hz, 1H); 6.16 (dt, $J = 16$ u.
2 x 6.5 Hz, 1H); 5.64 (dt, $J = 16$ u. 2 x 1.5 Hz, 1H);
3.74 (s, 2H); 3.12 (dd, $J = 6.5$ u. 1.5 Hz, 2H); 2.2
(s, 3H); 1.22 (s, 9H).

- 25 E 7.64 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.5 (s, 1H); 7.42 (t, $J = 7.5$ Hz, 1H); 7.32 (m, 1H); 6.2 (dt, $J = 16$ u. 2 x 6.5 Hz, 1H); 5.68 (dt, $J = 16$ u. 2 x 1.5 Hz, 1H); 3.9 (d, $J = 1$ Hz, 2H); 3.78 (s, 2H); 3.1 (dd, $J = 6.5$ Hz, 2H); 2.2 (s, 3H); 1.22 (s, 3H).
- 26 E 7.8 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.7 (s, 1H); 7.4 (t, $J = 7.5$ Hz, 1H); 7.3 (m, 1H); 6.2 (dt, $J = 16$ u. 2 x 6.5 Hz, 1H); 5.7 (dt, $J = 16$ u. 2 x 1.5 Hz, 1H); 4.72 (d, $J = 1$ Hz, 2H); 3.78 (s, 2H); 3.42 (s, 3H); 3.1 (dd, $J = 6.5$ Hz, u. 1.5 Hz, 2H); 2.22 (s, 3H); 1.25 (s, 9H).

The required starting materials can be prepared for example as follows:

A) 7-Bromomethylbenzo[b]thiophene

7 g of 7-methylbenzo[b]thiophene, 8.5 g of N-bromosuccinimide and 5 a spatula tip of α, α' -azoisobutyronitrile are refluxed together for 6 hours in 50 ml of carbon tetrachloride. The resulting mixture is cooled, filtered and concentrated by evaporation. The resulting raw title compound can be directly employed in the next step.
M.p. when isolated = 57° (isopropanol)

The following compounds may be prepared analogously:

- 3-Bromo-7-bromomethylbenzo[b]thiophene
- 4-Bromo-7-bromomethylbenzo[b]thiophene
- 7-Bromomethyl-2-chlorobenzo[b]thiophene
- 5 7-Bromomethyl-3-chlorobenzo[b]thiophene, M.p. = 75-79°(ethanol)
- 7-Bromomethyl-3-fluorobenzo[b]thiophene, oil

- 7-Bromomethyl-3-trifluoromethylbenzo[b]thiophene
- 7-Bromomethyl-2-fluorobenzo[b]thiophene
- 4-Bromomethyl-2-chlorobenzo[b]thiophene

- 10 7-Bromomethyl-3-cyanobenzo[b]thiophene
- 7-Bromomethyl-2,3-dichlorobenzo[b]thiophene
- 7-Bromomethyl-3-(2,2-dibromovinyl)benzo[b]thiophene
- 3-Ethynyl-7-bromomethylbenzo[b]thiophene

each of which may be employed directly in the next step.

15 B) N-(7-Benzo[b]thienylmethyl)methanamine

7-Bromomethylbenzo[b]thiophene is dissolved in dichloromethane added to 40 ml of a 33% solution of methylamine in ethanol and allowed to stand overnight. The resulting mixture is concentrated and the residue taken up in dichloromethane and extracted with 2N HCl. The

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aqueous phase is made strongly basic with NaOH and shaken with dichloromethane. The organic phase is dried with potassium carbonate, concentrated by evaporation and the residue vacuum distilled to produce the title product as an oil. B.p. = 103°/1.3 mbar.

- 5 The following compounds may be prepared analogously:

N-(3-Chloro-7-benzo[b]thienylmethyl)methylamine:

B.p. = 130-132°/1.3 Pascal, M.p. (hydrochloride) = 250-255°.

N-(3-Benzo[b]thienylmethyl)methylamine:

B.p. = 90-94°/1.3 Pascal.

- 10 N-(3-Cyano-7-benzo[b]thienylmethyl)methylamine:

M.p. (hydrochloride) = 280-285°.

N-(6,6-dimethyl-hept-2-en-4-ynyl)methylamine (Z,E-mixture):

Following chromatography on silica gel (toluene/ethylacetate =

- 15 4/1). NMR: 5.3-6.3 (m, 2H); [3.4(d, J=6H) + 3.16 (d, J=6Hz), 2H]; 2.38 (s, 3H); 1.46 (s, 1H); 1.21 (s, 9H).

N-(3-Bromo-7-benzo[b]thienylmethyl)methylamine:

M.p. (hydrochloride) = 260-262°.

C) 3-Bromo-7-methylbenzo[b]thiophene

- 25 g of 7-methylbenzo[b]thiophene are dissolved in chloroform and
20 27 g of bromine added at room temperature with stirring. After one hour the mixture is poured onto water and the organic phase separated, washed, dried and concentrated under vacuum. The title compound (contaminated with ca. 10% of 4-bromo-7-methylbenzo[b]thiophene) is obtained as an oil following vacuum distillation at 92-98°/2.6 mbar.

- 25 D) 2-Chloro-7-methylbenzo[b]thiophene

2 g of 7-methylbenzo[b]thiophene are dissolved in abs. ether, 8.4 ml of an 1.6M solution of butyllithium in hexane added dropwise at -10° and the resulting mixture stirred for one hour at 0° to -5°.

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1 g of gaseous chlorine is then added at -30° and, after removal of the cool bath, the mixture warmed to room temperature. After ca. one hour the mixture is repeatedly washed with water, dried and concentrated on a rotary evaporator.

5 The resulting title compound is reacted directly further.

2-Bromo-3-cyano-7-methyl-benzo[b]thiophene

NMR: of the former 7.76 (dd, $J = 7.5$ u. 2Hz, 1H); 7.46 (t, $J = 7.5$ Hz, 1H); 7.26 (dd, $J = 7.5$ u. 2 Hz, 1H); 2.54 (s, 3H).

E) 2,3-Dichloro-7-methylbenzo[b]thiophene

10 20 g of 7-methylbenzo[b]thiophene are dissolved in carbon tetrachloride and saturated with gaseous chlorine at room temperature. After 2 hours the excess chlorine is removed, the mixture concentrated on a rotary evaporator and the residue taken up in dichloromethane, washed with saturated aqueous NaHCO_3 , dried and concentrated on a
15 rotary evaporator. The title compound is obtained, following crystallisation from methanol, as colourless crystals. M.p. = $48-50^{\circ}$.

2,3-Dichloro-4-methylbenzo[b]thiophene may be prepared analogously.

F) 3-Chloro-7-methylbenzo[b]thiophene

10 g of 2,3-Dichloro-7-methylbenzo[b]thiophene are dissolved in
20 200 ml ether and 28.8 ml of a 1.6M solution of butyllithium in hexane added dropwise at 0° . After one hour the mixture is poured into dilute aqueous HCl, the organic phase separated, washed, dried and concentrated on a rotary evaporator. The raw title product thus obtained is reacted directed further (B.p. = $60-62^{\circ}/0.13$ Pascal).

25 3-Chloro-4-methylbenzo[b]thiophene may be prepared analogously.

G) 3-Fluoro-7-methylbenzo[b]thiophene

50 ml of a 1.6M solution of butyllithium in abs. ether are added dropwise at -78° to a solution of 18.1 g of 3-bromo-7-methylbenzo[b]-

thiophene in abs. ether. After 20 Minutes 9g of perchlorylfluoride are introduced under inert gas and with stirring whereby the reaction temperature is maintained below -60° . The resulting mixture is stirred for 30 minutes at -78° and then slowly warmed to 0° , mixed with water and the organic phase separated, washed, dried and concentrated under vacuum. The residue is chromatographed over silica gel (eluant : hexane) to obtain the title compound as an oil.

H) 7-Methyl-3-trifluoromethylbenzo[b]thiophene

A mixture of 2 g of 3-bromo-7-methylbenzo[b]thiophene, 4.8 g of CF_3COONa , 3 g CuI and 20 ml of 1-methylpyrrolidone are vigorously stirred and heated at 160° . After a short while evolution of gas commences. Stirring is continued for one hour at 160° and a further hour at 180° . After cooling the reaction mixture is poured into water, extracted with ether/hexane (1/1) and the organic phase washed, dried and concentrated under vacuum. The raw product is chromatographed over silica gel (eluant : n-hexane) and the title compound obtained as a colourless oil.

I) 2-Fluoro-7-methylbenzo[b]thiophene

To a solution of 7 g of 7-methylbenzo[b]thiophene in abs. tetrahydrofuran are added dropwise at -78° , 30 ml of a 1.6M solution of n-butyllithium in hexane. After 20 minutes 5.5 g of perchloryl fluoride are introduced whereby the reaction temperature is maintained below -60° . After 30 minutes at -78° the temperature is slowly raised to 0° . The mixture is then mixed with water and the organic phase separated, washed, dried and concentrated under vacuum. The residue is chromatographed (eluant : n-hexane) to obtain the title compound as an oil.

J) 3-Acetyl-7-methylbenzo[b]thiophene

420 mg of borontrifluoride-etherate are added to a mixture of 2 g of 7-methylbenzo[b]thiophene and 1.4 ml acethanhydride at 50° and the mixture warmed to 60° for 80 minutes. The resulting mixture is poured onto ice, extracted with ether and the organic phase washed,

dried and concentrated on a rotary evaporator. The residue is chromatographed on silica gel (eluant : n-hexane) to obtain the title compound, contaminated with the 2-acetyl isomer, as an oil for direct further reaction.

5 K) N-(3-Methyl-7-benzo[b]thienylmethyl)methylamine

a) N-(t.-butoxycarbonyl)-N-(3-cyano-7-benzo[b]thienylmethyl)methylamine

3.6 g of N-(3-cyano-7-benzo[b]thienylmethyl)methylamine and 3.9 g of di-t-butyl dicarbonate are stirred in dichloromethane for 10 one hour at room temperature. The solution is concentrated under vacuum and the resulting title compound directly further reacted. $R_f=0.9$ (in chloroform/ethanol = 95/5).

NMR: 8.15 (s, 1H); 7.9 (d, 1H); 7.2-7.7 (m, 2H); 4.75 (s, 2H); 2.8 (s, 3H); 1.5 (s, 9H).

15 b) N-(t.-butoxycarbonyl)-N-(3-formyl-7-benzo[b]thienylmethyl)methylamine

1.44 g of N-(t.-butoxycarbonyl)-N-(3-cyano-7-benzo[b]thienylmethyl)methylamine are taken up in abs. ether and 4 ml of a 1.2M solution of diisobutylaluminum hydride in toluene added dropwise at 0°. 20 Stirring is continued for one hour at room temperature and the mixture then poured into ice-cooled 2N acetic acid and extracted with ether and the organic phase washed neutral, dried and concentrated under vacuum. The oily title compound is directly further reacted.

25 NMR: 10.1 (s, 1H, CHO); 8.6 (dd, 1H); 8.35 (s, 1H); 7.2-7.7 (m, 2H); 4.8 (s, 2H); 2.8 (s, 3H); 1.55 (s, 9H);

3-Formyl-7-methylbenzo[b]thiophene: M.p. = 55-60° may be prepared analogously.

NMR: 10.0 (s, 1H); 8.4 (d, 1H); 8.2 (s, 1H); 7.1-7.7 (m, 2H); 2.55 (s, 3H).

c) N-(t.-butoxycarbonyl)-N-(3-methyl-7-benzo[b]thienylmethyl)methylamine

5.1 g of N-(t.-butoxycarbonyl)-N-(3-formyl-7-benzo[b]thienylmethyl)-methylamine and 12 ml of hydrazinehydrate (85 %) are warmed at 160° for 10 minutes in 40 ml of diethylglycol, cooled, 3.17 g of pulverized potassium hydroxide added and the mixture heated for one hour at 170°. Following cooling the reaction mixture is poured onto ice and extracted with ether and the organic phase washed, dried and concentrated under vacuum to give the title compound which is directly further reacted.

NMR: 7.2-7.8 (m, 4H); 4.7 (s, 2H); 2.8 (s, 3H); 2.4 (s, 3H); 1.5 (s, 9H).

d) N-(3-methyl-7-benzo[b]thienylmethyl)methylamine

4g of N-(t.-butoxycarbonyl)-N-(3-methyl-7-benzo[b]thienylmethyl)-methylamine are stirred for half an hour at 0° in 15 ml of trifluoroacetic acid. The mixture is then poured onto ice, made alkaline with NaOH and extracted with ether and the organic phase washed, dried and concentrated under vacuum. The title substance is directly further reacted. $R_f=0.15$ (in chloroform/ethanol = 95/5).

20 N-(3-Vinyl-7-benzo[b]thienylmethyl)-methylamine : oil
N-(3-hydroxymethyl-7-benzo[b]thienylmethyl)methylamine: oil
N-(3-Formyl-7-benzo[b]thienylmethyl)methylamine: oil
may be prepared analogously.

L) 1-Bromo-6-methyl-2,6-heptadien-4-yne

25 a) 6-Methyl-1,6-heptadien-4-yn-3-ol

10 g Isopropenylacetylene are taken up in abs. tetrahydrofuran and under an inert gas 94.5 ml of 1.6M solution of n-butyllithium in hexane added dropwise at -20°. The mixture is then cooled to -78° and 8.5 g of acrolein added dropwise. The reaction mixture is warmed

to room temperature, poured into saturated aqueous NH_4Cl and repeatedly extracted with ether. The organic phase is washed, dried and concentrated in vacuum. An oil is obtained.

5 NMR: 6.02 (ddd, $J=17, 10$ u. 5.5 Hz, 1H); 5.0 (m, 1H); 5.2-5.55 (m, 2H); 1.9 (dd, $J=1.4$ u. 1 Hz, 3H).

b) 1-Bromo-6-methyl-2,6-heptadien-4-yne

An alcoholic solution of 6-methyl-1,6-heptadien-4-yn-3-ol is added dropwise to 40 ml of fuming HBr and the mixture stirred for 1.5 hours at room temperature. The reaction mixture is poured onto 10 ice and extracted with hexane. The organic phase is repeatedly washed with aqueous NaCl, dried and concentrated on a rotary evaporator. The oily reaction product consists (according to NMR) of a 3 : 1 mixture of (E)- and (Z)-1-bromo-6-methyl-2,6-heptadien-4-yne and is directly employed for further reaction.

15 NMR: (pure E-isomer): 6.28 (dt, $J=15.5$ u. 2x7 Hz, 1H); 5.85 (d, $J=15.5$ Hz, 1H); 4.0 (dd, $J=7$ u. 0.7 Hz, 2H); 5.2-5.4 (m, 2H); 1.90 (dd, $J=1$ u. 1.4 Hz, 1H).

M) N-(t.-butoxycarbonyl)-N-(3-hydroxymethyl-7-benzo[b]thienyl-methyl)methylamine

20 600 mg of N-(t.-butoxycarbonyl)-N-(3-formyl-7-benzo[b]thienyl-methyl)methylamine are dissolved in ethanol, reacted with 100 mg NaBH_4 and stirred for 2 hours at room temperature. The reaction mixture is concentrated, the residue partitioned between ether and water and the organic phase washed, dried and concentrated on a 25 rotary evaporator. The oily title compound is directly further reacted. 3-Hydroxymethyl-7-methyl-benzo[b]thiophene may be prepared analogously.

N) 3-Cyano-7-methylbenzo[b]thiophene

30 3 g of 3-bromo-7-methylbenzo[b]thiophene and 1.1 g CuCN are dissolved in dry pyridine and heated at 220° in an autoclave

for 12 hours. The mixture is cooled, concentrated, the residue partitioned between dichloromethane and dilute HCl and the organic phase washed, dried and concentrated. Chromatography of the residue over silica gel (toluene) yields the title compound as pale-yellow crystals. M.p. = 82-84°.

O) N-(2-methylthio-3-bromo-7-benzo[b]thienylmethyl)methylamine

To a solution of 2.55 g of N-(3-bromo-7-benzo[b]thienylmethyl)-methylamine in abs. ether are added dropwise under inert gas at -70° 13.8 ml (2 equivalents) of a 15% solution of n-butyllithium in 10 n-hexane. 1.9 ml of dimethyldisulfide are then added slowly at -70° and the reaction mixture gradually warmed to room temperature. It is then poured into ice-cooled 2N HCl, shaken and the acid phase separated, made alkaline with NaOH and extracted with ether. The ether phase is dried, concentrated under vacuum and the oil thus 15 obtained directly further reacted.

NMR: 7.2-7.7 (m, 3H); 4.0(s, 2H); 2.6 (s, 3H); 2.45 (s, 3H); 1.5 (br, N-H).

P) N-(2-methylthio-7-benzo[b]thienylmethyl)methylamine

To a solution of 0.3 g of N-(2-methylthio-3-bromo-7-benzo[b]- 20 thienylmethyl)methylamine in abs. ether are added dropwise under inert gas at -70°, 1.4 ml of a 15% solution of n-butyllithium in n-hexane and stirring continued at -70° for half an hour. The mixture is then poured into ice-cooled 2N HCl, shaken and the acidic phase separated, made alkaline with NaOH and extracted with 25 ether. The ether phase is dried, concentrated in vacuum and the resulting oil directly further reacted.

Q) 3-(2,2-Dibromovinyl)-7-methylbenzo[b]thiophene

1.04 g of Zn dust and 4.17 g of triphenylphosphine are taken up in dichloromethane and 5.27 of tetrabromomethane dissolved in dichloromethane added dropwise under inert gas and with cooling.

- 5 Following stirring for 24 hours at room temperature 1.4 g of 3-formyl-7-methylbenzo[b]thiophene dissolved in dichloromethane are added dropwise with ice-cooling and stirring continued overnight at room temperature. Pentane is added and the precipitated Ph_3PO filtered off. Evaporation of the filtrate under vacuum yields a
10 residue which is chromatographed over silica gel to yield the title compound, M.p. = 75-78°.

R) 3-Ethynyl-7-methylbenzo[b]thiophene

0.6 g of 3-(dibromovinyl)-7-methylbenzo[b]thiophene are dissolved in abs. tetrahydrofuran and 3.38 ml of a 15% solution of *n*-butyl-
15 lithium in *n*-hexane are added dropwise under inert gas and at -78°. Stirring is continued for one hour at -78° and the mixture subsequently warmed to room temperature, poured into saturated aq. NaHCO_3 and extracted with ether. The organic phase is washed, dried, concentrated and directly further reacted.

- 20 NMR: 7.85 (dd, $J=7$ u. 2 Hz, 1H); 7.70 (s, 1H); 7.40 (t, $J=7$ Hz, 1H); 7.20 (dd, $J=7$ and 2 Hz, 1H); 3.28 (s, 1H); 2.58 (s, 3H).

S) N-(*t*.-Butoxycarbonyl)-N-(3-vinyl-7-benzo[b]thienylmethyl)-methylamine

- 0.7 ml of a 15% solution of *n*-butyllithium in hexane are added
25 dropwise under inert gas to a suspension of 0.43 g of methyltriphenylphosphonium bromide in abs. tetrahydrofuran and the mixture stirred for 1 hour at room temperature. A solution of 0.37 g N-(*t*.-butoxycarbonyl)-N-(3-formyl-7-benzo[b]thienylmethyl)methylamine in tetrahydrofuran is then added dropwise and the resulting mixture refluxed

for 20 hours. The reaction mixture is poured onto ice, repeatedly extracted with ether and the organic phase washed, dried, concentrated and chromatographed over silica-gel (eluant : toluene/glacial acetic acid = 9 : 1) to give the title compound as an oil.

5 NMR: 7.88 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.5 (s, 1H);
7.44 (t, $J = 7.5$ Hz, 1H); 7.25 (dd, $J = 7.5$ u.
~1 Hz, 1H); 7.02 (ddd, $J = 18, 12$ u. ~1 Hz, 1H);
5.82 (dd, $J = 18$ u. ~1.5 Hz, 1H); 5.4 (dd, $J =$
12 u. 1.5 Hz, 1H); 4.72 (s, 2H); 2.8 (s, 3H);
10 1.5 (s, 9H).

3-(2-Cyanovinyl)-7-methyl-benzo[b]thiophene may be prepared analogously.

NMR: 7.80 (s, 1H); 7.76 (dd, $J = 7.5$ u. 2 Hz, 1H); 7.68
(d, $J = 16$ Hz, 1H); 7.46 (t, $J = 7.5$ Hz, 1H); 7.26
15 (m, 1H); 5.96 (d, $J = 16$ Hz, 1H); 2.6 (s, 3H).

T) 3-Cyanomethyl-7-methyl-benzo[b]thiophene

290 mg of 3-hydroxymethyl-7-methyl-benzo[b]thiophene are dissolved in ether, 0.6 ml SOCl_2 added and the mixture stirred for 2 hours at room temperature. The reaction mixture is poured onto ice
20 and the organic phase washed neutral, dried and concentrated under vacuum. The crude 3-chloromethyl-7-methyl-benzothiophene thus obtained is dissolved in acetone, mixed with an aqueous solution of 170 mg of KCN and refluxed for 18 hours. The reaction mixture is concentrated, the residue partitioned between water and ether and
25 the organic phase washed, dried, concentrated and chromatographed over silica-gel (eluant : toluene) to yield the title product as an oil.

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NMR: 6.7-7.6 (m, 4H); 3.6 (br, 2H); 2.5 (s, 3H).

U) 3-Methoxymethyl-7-methyl-benzo[b]thiophene

400 mg of 3-hydroxymethyl-7-methyl-benzo[b]thiophene are dissolved in tetrahydrofuran, mixed with 82 mg of NaH (80%) and
5 after addition of 48 mg of methyl iodide heated for half an hour at 50°C. The reaction mixture is mixed with water, repeatedly extracted and the organic phase washed, dried and concentrated on a rotary evaporator. The residue is chromatographed over silica-gel (eluant : toluene/glacial acetic acid = 95 : 5) to yield the title
10 compound as an oil.

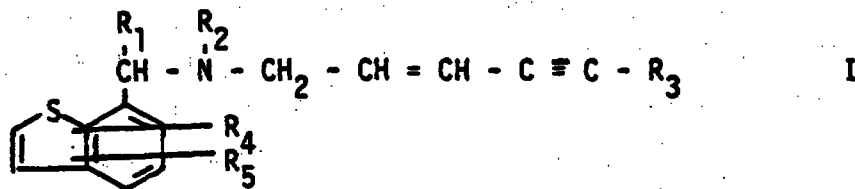
NMR: 7.2-7.9 (m, 4H); 4.75 (s, 2H); 3.5 (s, 3H); 2.66 (s, 3H).

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Claims

1. Compounds of formula I



wherein

- R₁ represents hydrogen or methyl,
- R₂ represents methyl or ethyl,
- R₃ represents tertiary alkyl or an alkenyl group; and
- R₄ and R₅ represent, independently of each other, hydrogen, halogen, hydroxy, lower alkynyl, cyano, formyl, lower alkoxy, lower alkoxy carbonyl, lower alkyl carbonyl, lower alkyl which is unsubstituted or bears one or more substituents selected from halogen, cyano, hydroxy, lower alkylthio and lower alkoxy; or lower alkenyl which is unsubstituted or bears one or more substituents selected from halogen and cyano

in free base form or in the form of an acid addition salt.

2. A compound as claimed in Claim 1, wherein R₄ and/or R₅ are in the 2- and/or 3-position.

3. (E)-N-(3-chloro-7-benzo[b]thienylmethyl)-N-methyl-6,6-dimethylhept-2-en-4-ynamine in free base form or in the form of an acid addition salt.

4. A compound according to Claim 1 or 2 wherein R₅ represents hydrogen and R₄ represents hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy.



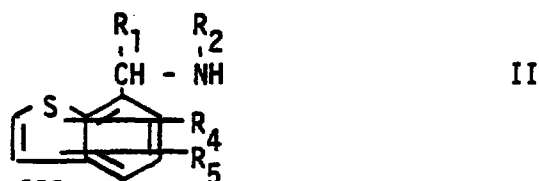
5. A chemotherapeutical composition comprising a compound as claimed in Claim 1 in free base form or in the form of a chemotherapeutically acceptable acid addition salt together with a chemotherapeutically acceptable diluent or carrier.

6. A compound of formula I as claimed in Claim 1 in free base form or in the form of a chemotherapeutically acceptable acid addition salt for use as a chemotherapeutical agent.

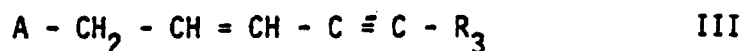
7. A compound of formula I as claimed in Claim 1 in free base form or in the form of a chemotherapeutically acceptable acid addition salt for use as an anti-mycotic.

8. A process for preparing a compound as claimed in Claim 1 in free base form or in the form of an acid addition salt which comprises

a) reacting a compound of formula II

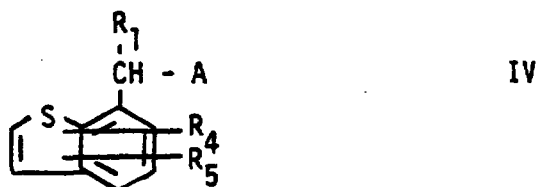


with a compound of formula III



or

b) reacting a compound of formula IV

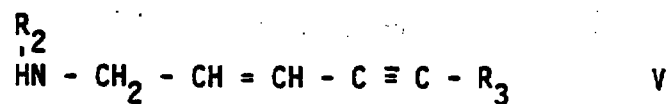


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with a compound of formula V



whereby in the formulae II, III, IV and V

R_1 , R_2 , R_3 , R_4 and R_5 are as defined under formula I and

A represents a leaving group,

and recovering the compound thus obtained in free base form or in the form of an acid addition salt.
