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Antidermatophytic action of new 1-naphthylmethyl and benzo[*b*]thiophen-7-ylmethyl hydrazones related to inhibitors of squalene epoxidase

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Two series of hydrazone compounds related to main classes of inhibitors of fungal squalene epoxidase (SE) were designed and prepared on the hypothesis of a pharmacophoric model. The antifungal activity of the new compounds was evaluated *in vitro* against dermatophytes, moulds and yeasts. Antidermatophytic activity resulted for several hydrazones, particularly for those containing a *tert*-butylacetylenic group, supporting the hypothesis that the introduction of a hydrazone function in the model could retain the antimycotic activity.

1. Introduction

The search for new antimycotic drugs is currently focused on inhibition of squalene epoxidase (SE) [1]. The discovery of this key enzyme in the ergosterol biosynthesis pathway provided an alternative starting point for the design of non-substrate-like inhibitors and led to the identification of new classes of antimycotics: the allylamines [2–5], the benzylamines [6, 7] and the omopropargylamines [8]. A pharmacophoric model proposed by Nussbaumer et al. (Fig., A) resumes the structural features common to these classes of inhibitors [8]. In this model two lipophilic domains L1 and L2 are linked by a spacer of appropriate length, containing a polar centre (P) usually represented by a N-methyl group. In particular, studies with carbon-analogues of terbinafine showed that the nitrogen atom is not essential for the SE inhibition, but is required for penetration through the fungal cell envelope [9]: inserted in the spacer of the model, the N-methylic group appears as the bio-conducting moiety of the pharmacophoric systems L1 and L2. Moreover, recent reports demonstrated that even thiocarbamates act by inhibition of fungal SE [10]; in relation to our hypothesis, this finding suggests a variability of the spacer of the model, particularly of the chemical neighbourhoods of polar centre P.

The present study was designed in order to investigate whether antifungal action can also be attained by compounds in which a N-methyl hydrazone function is introduced in the spacer of the pharmacophore A (Fig. 1, B). Particularly, in this work we propose the 1-naphthylmethyl hydrazones **4** and the benzo[*b*]thiophen-7-ylmethyl hydrazones **11** in which the substituents on L1 and L2 domains arise from a selection of characteristic groups featuring the related classes.

2. Investigations, results and discussion

2.1. Chemistry

The synthetic approach to the final compounds was accomplished through the preliminary preparation of hydrazines **3** (Scheme 1) and **10** (Scheme 2), which were directly condensed with the suitable aldehydes to yield hydrazones **4** and **11**.

The classic N-nitrosation with nitrous acid [11] of amines **1** and **8** easily led to the N-nitrosamines **2** and **9**, which were reduced in excellent yields to the desired hydrazines with diisobutylaluminum hydride (DIBAL-H) [12]. This

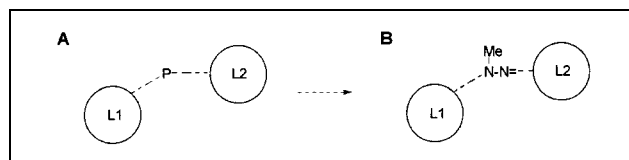
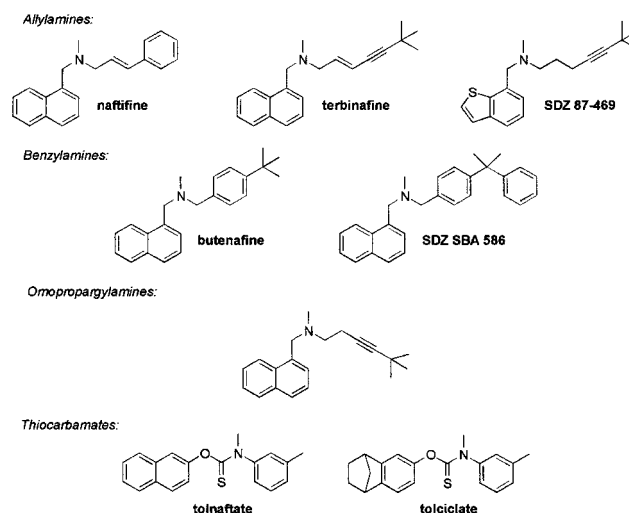


Fig.: Pharmacophoric models for inhibitors of fungal SE

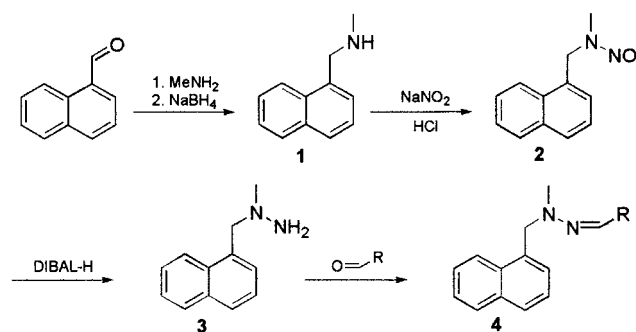
reducing agent provided a good alternative to traditional methods (zinc in acetic acid, tin in hydrochloric acid, lithium aluminium hydride) which gave poor yields.

Amine **1** was obtained by reductive amination of 1-naphthaldehyde with methylamine and sodium borohydride [13].

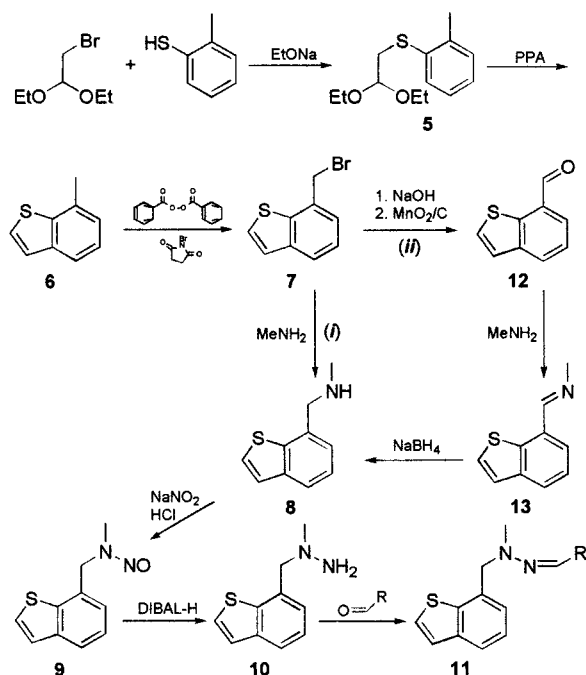
Amine **8** was successfully prepared through two alternative pathways (i, ii), using 7-bromomethyl-benzo[*b*]thiophene (**7**) as common intermediate. This was obtained from 7-methyl-benzo[*b*]thiophene (**6**), prepared in high yields by cyclization of the acetalic intermediate **5** with polyphosphoric acid in toluene, by use of a slight modification of the procedure described by Noyce and Forsyth [14]. Radical bromination of **6** with *N*-bromosuccinimide using dibenzoylperoxide as a catalyst, according to Nussbaumer et al. [5], and the following reaction (i) with excess of methylamine afforded the desired amine **8** in 60% yield. In the alternative pathway (ii), the synthesis of **8** was accomplished in 75% yield by reductive amination of aldehyde **12**, obtained according to Noyce and Forsyth from **7** (52% yield for the two steps) [14].



Scheme 1



Scheme 2



Aldehyde **14** (Scheme 3) was obtained from 2,2-diphenylpropane using the Duff reaction, in trifluoroacetic acid [7].

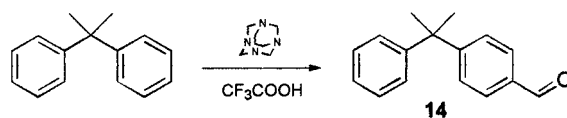
4,4-Dimethylpentynal **15** (Scheme 4) was prepared from 3,3-dimethyl-1-butene which, after conversion to the corresponding Grignard's intermediate, was formylated with dimethylformamide, as described by Kruithof et al. [15].

2.2. Mycology

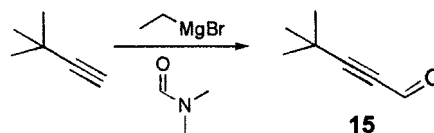
The *in vitro* antifungal activity of the novel compounds was investigated against several dermatophytes (*Trichophyton mentagrophytes*, *T. rubrum*, *Microsporum canis*, *Epidermophyton floccosum*), yeasts (*Candida albicans* and *C. parapsilosis*) and moulds (*Aspergillus fumigatus*) (Table 1). The fungal strains were clinical isolates of human or animal origin. Minimal inhibitory concentrations (MICs) were determined using Nutrient broth (Unipath, Milan, Italy) in case of dermatophytes and *A. fumigatus*, RPMI 1640 medium with L-glutamine (Difco) and Sabouraud's dextrose broth (Unipath) in case of yeasts.

The evaluation of susceptibility for dermatophytes and *A. fumigatus* was performed with the method of microculture in 96-well microtiter trays (Nunc, Copenhagen, Denmark), according to Granade and Artis [16] techniques; for yeasts, with the broth dilution method in test tubes, as described by Grove and Randall [17].

Scheme 3



Scheme 4



The compounds were dissolved in dimethylsulphoxide and serially diluted with the suitable growth media. The test concentrations ranged from 64 to 0.06 g/ml; the final fungal inoculum was approximately 10^4 CFU/ml. The growth assessment was made after 48 h of incubation at 33 °C for yeasts, after 6 days of incubation at 35 °C for dermatophytes and *A. fumigatus*. Griseofulvin was used as classical reference drug for the evaluation of the inhibitory activity against dermatophytes. The MIC was defined as the lowest substance concentration where fungal growth was macroscopically undetectable.

2.3. Biological results

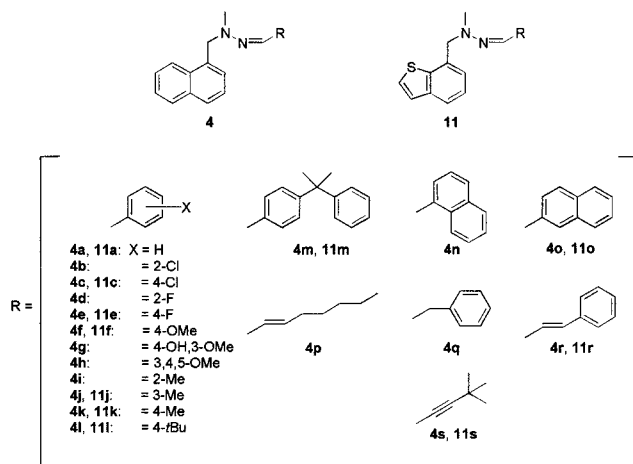
As shown in the Table, none of the tested compounds had any effect on the growth of *Candida* and *Aspergillus* species. However, several compounds showed significant anti-dermatophytic activity against tested strains.

Table: *In vitro* antimycotic activity

Gris.	MIC (µg/ml)						
	<i>M. can.</i> 0.25	<i>T. ment.</i> 4	<i>T. rub.</i> 1	<i>E. flocc.</i> 8	<i>A. fum.</i> –	<i>C. alb.</i> –	<i>C. par.</i> –
4a	64	32	1	64	>64	>64	>64
4b	64	>64	64	64	>64	>64	>64
4c	0.5	2	0.12	1	>64	>64	>64
4d	64	>64	>64	64	>64	>64	>64
4e	1	2	0.25	1	>64	>64	>64
4f	64	64	2	16	>64	>64	>64
4g	64	64	32	32	>64	>64	>64
4h	>64	>64	>64	64	>64	>64	>64
4i	64	>64	>64	64	>64	>64	>64
4j	64	64	0.12	64	>64	>64	>64
4k	0.5	2	4	0.5	>64	>64	>64
4l	64	>64	0.5	0.5	>64	>64	>64
4m	4	>64	4	0.5	>64	>64	>64
4n	>64	>64	>64	64	>64	>64	>64
4o	>64	>64	1	1	>64	>64	>64
4p	>64	>64	8	>64	>64	>64	>64
4q	>64	>64	>64	>64	>64	>64	>64
4r	0.5	>64	0.5	0.5	>64	>64	>64
4s	0.25	1	0.5	0.12	>64	>64	>64
11a	64	64	64	64	>64	>64	>64
11c	1	64	0.06	1	>64	>64	>64
11e	64	2	0.25	64	>64	>64	>64
11f	64	64	1	64	>64	>64	>64
11j	64	64	0.5	64	>64	>64	>64
11k	1	2	0.12	2	>64	>64	>64
11l	64	>64	32	64	>64	>64	>64
11m	4	>64	1	4	>64	>64	>64
11o	64	>64	1	64	>64	>64	>64
11r	0.5–32	64	0.12	2–32	>64	>64	>64
11s	0.5	0.5	0.12	0.5	>64	>64	>64

Griseofulvine (Gris.); *Microsporum canis* (*M. can.*); *Trichophyton mentagrophytes* (*T. ment.*); *Trichophyton rubrum* (*T. rubr.*); *Epidermophyton floccosum* (*E. flocc.*); *Aspergillus fumigatus* (*A. fum.*); *Candida albicans* (*C. alb.*); *Candida parapsilosis* (*C. par.*).

Among the dermatophytes, the most susceptible fungus was *T. rubrum*, easily inhibited at concentrations ranging from 0.06 to 1 µg/ml. *T. mentagrophytes* appeared to be



less sensitive; nevertheless, the efficacy of **4c**, **4e**, **4k**, **4s**, **11e**, **11k** and **11s** against *T. mentagrophytes* was superior to that of griseofulvin, with MICs ranging from 0.5 to 2 µg/ml.

Six compounds showed significant antidermatophytic effectiveness against all tested strains: the *para*-substituted benzaldehyde derivatives **4c**, **4e**, **4k** and **11k** (MICs = 0.12–4 µg/ml) and, particularly, the *tett*-butylacetylenic derivatives **4s** and **11s**, which exhibited inhibitory action higher than griseofulvin (except **11s** against *M. canis*, with 0.5 µg/ml in comparison to 0.25 µg/ml of the reference compound).

It seemed evident that in benzaldehyde derivatives the *para* substitution at the phenyl ring was essential for antidermatophytic action; this hypothesis was supported by the ineffectiveness of the unsubstituted **4a**, **11a** and **4q** and the partial activity of the cinnamyl derivatives **4r** and **11r**. Among the *para* substituents, an improvement of activity was observed with the methyl group, with small differences between the 1-naphthylmethyl compound **4k** and its benzo[b]thiophenyl analogue **11k**. Introduction of a *tett*-butyl group (**4l**, **11l**) resulted in a decrease in antifungal activities, which seemed strongly dependent on the overall lipophilicity; however, the replacement of one of the methyl groups with a phenyl ring as in **4m** and **11m** restored a partial activity, leading to consider that other factors could be involved in the final activity.

For the most part, comparable results were shown by benzo[b]thiophene analogues of naphthalene derivatives, without evident changes in biological activity. The only exception was observed with the modification of the activity profile of **11c** and **11e**, negatively affected by the differences in physicochemical properties produced by the bicyclic system replacement. Although far from the biologic potency of terbinafine or butenafine against dermatophytes, our results show that the cell-penetration is not only restricted to the N-methyl group; the introduction of the hydrazonic group in the pharmacophoric model would lead to sufficient penetration as reflected in antidermatophytic activity. For drug effectiveness, the respect of steric, electronic and structural parameters of the whole molecule seems a necessary requirement in some cases (as in *para*-substituted benzaldehyde derivatives), while, in others, parameters related to bio-functional portions (as in **4s** and **11s**) are required. Due to the presence of a hydra-

zonic function, the changes of electronic density distribution, the steric requirement and the polarity/basicity balance could be even responsible for the modification of the biological activity profile, resulting in loss of activity against yeasts and *A. fumigatus*. Further investigations are under way to assess the role of the hydrazonic group in the spacer of the model and to elucidate the mechanism of inhibition on dermatophytes.

3. Experimental

3.1. Materials and apparatus

N-methyl-*N*-(1-naphthylmethyl)amine [4], *o*-tolylthioacetaldehyde diethyl-acetal [18], 7-bromomethylbenzo[b]thiophene [5], 7-hydroxymethylbenzo[b]thiophene [14], benzo[b]thiophene-7-carboxaldehyde [14], 4-(1-methyl-1-phenylethyl)benzaldehyde [7], 4,4-dimethyl-2-pentynal [15] were prepared according to published literature.

M.p.'s were determined on a Kofler apparatus and are not corrected.

The compounds were identified by IR spectra on a Perkin Elmer 298 spectrophotometer or a FT-IR Paragon 500 of the same supplier, and ¹H- and ¹³C NMR data recorded in CDCl₃ at 200 (Varian XL 200) or 300 MHz (Varian VXR 300). Chemical shifts are given as δ units, using TMS as internal standard. The purity of the compounds was checked by GLC (HP 5790) using quartz capillaries (stationary phase HP1, internal diameter 0.2 mm, film thickness 0.11 µm) under the following operating conditions: inj. 200 °C; oven temp. from 80–100 °C to 300 °C (10 °C/min); det. 250–300 °C; pressure 10 PSI; carrier gas helium. MS were recorded on a MS Engine HP 5970A instrument. Elemental analyses (C, H, N) were measured on Perkin-Elmer Elemental Analyzer 2400 CHN instrument and were within ±0.3% of theoretical values. Analytical TLC was performed on silica gel F₂₅₄ plates (Merck) with visualisation by UV or iodine vapour. CC was performed with silica gel 60 (0.040–0.063 mm, Merck) at a pressure of 3.5 bar.

All the solvents were purified and, if requested, dehydrated before use. All reactions requiring anhydrous conditions were performed in flame-dried glassware, under nitrogen atmosphere, using gas-tight syringes.

Commercially available compounds were used without further purification. 1M DIBAL-H solution in CH₂Cl₂ was extemporarily prepared from pure DIBAL-H (Sure/PackTM metal-cylinders, Aldrich), under nitrogen atmosphere.

3.2. Synthesis of the intermediates

3.2.1. Synthesis of *N*-nitrosamines: *N*-nitrosation of secondary amines

3.2.1.1. 1-Methyl-1-(1-naphthylmethyl)-2-oxohydrazine (2)

19 g of **1** hydrochloride (91.8 mmol) were dissolved in 60 ml of H₂O and acidified with HCl 2N. The resulting solution was stirred vigorously and maintained at 70–75 °C, while 6.9 g of NaNO₂ (100 mmol) in 10 ml of H₂O were added over a period of 1 h. The reaction mixture was frequently tested and maintained barely acid to litmus by further addition of HCl 2N, if necessary. After stirring for 2 h, the mixture was partitioned between Et₂O and H₂O and the combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give 18.3 g of crude product. Purification was achieved by distillation under reduced pressure (118–120 °C, 0.01 mm Hg) which yielded **2** as yellow oil 17.9 g; yield: 97%. IR: ν = 3020, 2810, 1600, 1460–1430, 1320, 1500; MS (m/z): 200 [(M)⁺], 170 [(M)⁺–(N=O)⁺], 155 [(–CH₃)⁺], 141, 127; ¹H NMR (isomeric mixture 8/2): δ = 2.92 (s, 2.4H, CH₃ syn), 3.53 (s, 0.6H, CH₃ anti), 5.24 (s, 1.6H, CH₂ syn), 5.76 (s, 0.4H, CH₂ anti), 7.48 (m, 4H arom.), 7.86 (m, 2H, arom.), 8.09 (m, 1H, arom.). ¹³C NMR (isomeric mixture): δ = 30.49 (CH₃ of major isomer), 37.93 (CH₃ of minor isomer), 45.64 (CH₂ of minor isomer), 55.67 (CH₂ of major isomer), 123.01, 123.05 (2 CH), 125.16, 125.21 (2 CH), 126.26 (CH), 127.02 (CH), 127.71 (CH), 127.99, 129.16 (2 C), 128.79, 128.89 (2 CH), 129.64 (CH), 131.16, 131.62 (2 C), 133.90, 134.00 (2 C).

C₁₂H₁₂N₂O (200.2)

3.2.1.2. 1-(Benzo[b]thiophen-7-ylmethyl)-1-methyl-2-oxohydrazine (9)

Obtained from **8** in the same manner, yellow oil; yield: 94%, b.p. (0.01 mm Hg): 128–130 °C. IR: ν = 3060, 2920, 1450, 1330; MS (m/z): 206 [(M)⁺], 176 [(M)⁺–(N=O)⁺], 161 [(–CH₃)⁺], 147, 133; ¹H NMR (isomeric mixture 8/2): δ = 2.94 (s, 2.4H, CH₃ syn), 3.66 (s, 0.6H, CH₃ anti), 5.05 (s, 1.6H, CH₂ syn), 5.57 (s, 0.4H, CH₂ anti), 7.35 (m, 4H, arom.), 7.84 (d, J = 7.8 Hz, 1H, arom.). ¹³C NMR (isomeric mixture): δ = 30.68 (CH₃ of major isomer), 38.29 (CH₃ of minor isomer), 46.47 (CH₂ of minor isomer), 56.68 (CH₂ of major isomer), 123.55, 124.07 (2 CH), 124.29, 124.41 (2 CH), 124.50, 124.65 (2 CH), 126.27, 126.73 (2 CH), 127.58 (C), 128.51 (CH), 138.75, 138.80 (2 C), 140.30, 140.71 (2 C).

C₁₀H₁₀N₂OS (206.3)

3.2.2. Reduction of secondary *N*-nitrosamines with DIBAL-H

3.2.2.1. 1-Methyl-1-(1-naphthylmethyl)hydrazine (3)

A solution of 8.5 g of **2** (42.5 mmol) in 200 ml of anhydrous CH_2Cl_2 was treated at 0 °C under N_2 atmosphere with 193 ml of 1M DIBAL-H solution in CH_2Cl_2 , adding the reagent over a period of 30 min. After the addition was completed, the solution was heated to 40 °C and stirred for 24 h. The resulting solution was cooled with an ice-bath while 200 ml of H_2O and 20 ml of NaOH 0.1 N were gently added, until the yellow complex was destroyed in a gelatinous uncoloured suspension. The organic layer was decanted, and the aqueous phase extracted with CH_2Cl_2 . All the combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure. Purification of the remaining orange crude oil was achieved by vacuum distillation, which gave 6.5 g of **3** as pale yellow oil. Yield: 83%, b.p. (0.01 mm Hg): 85–87 °C. IR: $\nu = 3380, 3250, 3020, 1580, 1500$; MS (m/z): 186 $[(\text{M})^+]$, 169 $[(\text{M})^+-(\text{NH}_3)^+]$, 141, 127. ^1H NMR: $\delta = 2.56$ (s, 3 H, CH_3), 2.90 (broad, 2 H, D_2O exchange, NH_2), 4.02 (s, 2 H, CH_2), 7.47 (m, 4 H, arom.), 7.83 (m, 2 H, arom.), 8.27 (m, 1 H, arom.). ^{13}C NMR: $\delta = 48.95$ (CH_3), 66.45 (CH_2), 124.52 (CH), 125.07 (CH), 125.70 (CH), 126.04 (CH), 127.68 (CH), 128.36 (CH), 128.39 (CH), 132.40 (C), 133.58 (C), 133.88 (C). $\text{C}_{12}\text{H}_{14}\text{N}_2$ (186.3)

3.2.2.2. 1-(Benzo[*b*]thiophen-7-ylmethyl)-1-methylhydrazine (10)

2.33 g of **9** (11.3 mmol) dissolved in 12 ml of anhydrous CH_2Cl_2 were added at –15 °C, under N_2 atmosphere, to a stirring 1M DIBAL-H solution in CH_2Cl_2 (51 mmol), over a period of 1 h. After addition, the solution was heated to room temperature for 48 h, diluted with 60 ml of the same solvent and heated to reflux for 2 h. After cooling to –5 °C, 100 ml of 10% KOH were slowly added, until the yellow complex in solution was destroyed in an uncoloured suspension. The organic layer was decanted and the remaining aqueous suspension was extracted with CH_2Cl_2 . All the organic layers, combined and dried over anhydrous MgSO_4 , were concentrated in vacuo to obtain a crude oil, which was purified by distillation under reduced pressure.

10: pale yellow oil, 1.78 g; yield: 82%; b.p. (0.01 mm Hg): 88–90 °C. IR: $\nu = 3350, 3300, 1580, 1560$; MS (m/z): 192 $[(\text{M})^+]$, 147. ^1H NMR: $\delta = 2.61$ (s, 3 H, CH_3), 2.96 (broad, 2 H, D_2O exchange, NH_2), 3.91 (s, 2 H, CH_2), 7.35 (m, 4 H, arom.), 7.77 (d, $J = 7.4$ Hz, 1 H, arom.). ^{13}C NMR: $\delta = 48.77$ (CH_3), 67.23 (CH_2), 122.81 (CH), 123.64 (CH), 124.16 (CH), 126.69 (CH), 126.86 (CH), 132.16 (C), 139.23 (C), 140.17 (C). $\text{C}_{10}\text{H}_{12}\text{N}_2\text{S}$ (192.3)

3.2.3. Reductive amination

3.2.3.1. *N*-Methylbenzo[*b*]thiophen-7-ylmethanamine (8)

Methylamine (2 ml, 16 mmol, 8.03 M solution in EtOH) and 4 Å molecular sieve were added to a solution of **12** (0.6 g, 3.7 mmol) in 10 ml of anhydrous Et_2O and stirred overnight at room temperature. The mixture was filtered and the solvent distilled-off. The residual Schiff base **13** (0.48 g, oil, 74% yield of crude product) was used in the following reduction procedure without further purification. IR: $\nu = 3050, 2920, 2860, 1648, 1380$. MS (m/z): 175 $[(\text{M})^+]$, 159 $[-(\text{CH}_3)^+]$, 147 $[(\text{CH}_2\text{-benzothiophenyl})^+]$, 133 $[(\text{benzothiophenyl})^+]$. ^1H NMR: $\delta = 3.67$ (s, 3 H, CH_3), 7.49 (m, 4 H, arom.), 7.91 (d, $J = 7.4$ Hz, 1H), 8.57 (m, 1 H, arom.). ^{13}C NMR: $\delta = 47.92$ (CH_3), 122.94 (CH), 123.78 (CH), 125.56 (CH), 127.21 (CH), 129.81 (CH), 130.55 (C), 136.00 (C), 140.66 (C), 161.46 (CH).

0.38 g of **13** (2.2 mmol) were dissolved in 5 ml of anhydrous MeOH, treated with NaBH_4 (0.17 g, 4.5 mmol) in portions, and heated to 40 °C for 1 h. The solvent was distilled-off and the residue partitioned between H_2O and Et_2O . The organic layer was separated, dried over MgSO_4 and evaporated, to give 0.3 g of crude amine **8** (oil, 80% yield). For purification, the crude product was treated with $\text{HCl-Et}_2\text{O}$ to obtain the pure hydrochloride (white crystals, m.p. 166–167 °C from $i\text{-PrOH/Et}_2\text{O}$). Vacuum distillation (b.p. 90–92 °C, 0.01 mm Hg) of a sample of the crude product for analytical reasons yielded the title compound as pale yellow oil. IR: $\nu = 3350$ (hydrochloride: 2850–2250), 1580, 1470, 1450; MS (m/z): 177 $[(\text{M})^+]$, 147, 133. ^1H NMR: $\delta = 1.55$ (broad, 1 H, D_2O exchange, NH), 2.48 (s, 3 H, CH_3), 4.05 (s, 2 H, CH_2), 7.37 (m, 4 H, arom.), 7.74 (d, $J = 7$ Hz, 1 H, arom.). ^{13}C NMR: $\delta = 36.10$ (CH_3), 55.12 (CH_2), 122.43 (CH), 123.25 (CH), 124.11 (CH), 124.32 (CH), 126.19 (CH), 134.28 (C), 138.73 (C), 140.08 (C). $\text{C}_{10}\text{H}_{11}\text{NS}$ (177.3)

3.2.4. Direct alkylation; *N*-Methyl-benzo[*b*]thiophen-7-ylmethanamine (8)

A solution of **7** (13.2 mmol) in anhydrous EtOH (30 ml) was slowly dropped to a 33% solution of methylamine in EtOH (8.03 M, 0.112 mol), with ice-cooling. After addition, the solution was heated to room temperature for 12 h and then to 50 °C for 2 h.

After distillation of the solvent, the residual crude product was taken up in HCl 2N, washed with Et_2O , made alkaline with K_2CO_3 , and extracted again with Et_2O , to obtain 1.4 g of pure amine **8** (60% yield).

3.2.5. 7-Methylbenzo[*b*]thiophene (6)

14.7 g of **5** (61.3 mmol) in anhydrous toluene (120 ml) were heated to reflux. While stirring, polyphosphoric acid (prepared from 250 g of H_3PO_4 and 220 g of P_2O_5) maintained at 120–150 °C, was dropped over a period of 1 h. The mixture was cooled to 90 °C and the toluene layer decanted and saved. To the hot acid layer were slowly added, while vigorously stirring, 120 ml of H_2O and then further 100 ml of fresh toluene; after stirring at 90 °C to mix the layers, the toluene phase was decanted. The extraction was repeated and completed at room temperature in a separatory funnel; all the organic layers were combined, dried over MgSO_4 and concentrated under reduced pressure. The purification of the crude product was achieved by vacuum distillation (b.p.: 56–57 °C, 0.01 mm Hg) which yielded 8.32 g of **6** as uncoloured oil (92% yield).

3.3. Synthesis of hydrazones **4** and **11**: general procedure

The suitable aldehyde (0.01 mol) and hydrazine (0.01 mol) in 30–50 ml of abs. EtOH were heated to 40–50 °C on a steam bath for 30–60 min. In several cases few drops of conc. HCl were added at the start of reaction. Mostly, the hydrazones crystallized directly from the cooled alcohol solution and were collected, in good yield, by filtration. In other cases the solvent was distilled off and the product was recrystallized from different solvents (see below) or, in the case of an oil product, distilled at reduced pressure.

3.3.1. Benzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4a)

Yield: 74%; white crystals from abs. EtOH, m.p.: 68–69 °C. IR: $\nu = 3020$ cm^{-1} , 2820, 1600, 1580, 1420; MS (m/z): 274 $[(\text{M})^+]$, 170 $[(\text{CH}_3\text{N-CH}_2\text{-naphthyl})^+]$, 141 $[(\text{CH}_2\text{-naphthyl})^+]$, 127 $[(\text{naphthyl})^+]$, 115. ^1H NMR: $\delta = 2.83$ (s, 3 H, CH_3), 4.94 (s, 2 H, CH_2), 7.26 (s, 1 H, CH=N), 7.47 (m, 9 H, arom.), 7.82 (m, 2 H, arom.), 8.25 (m, 1 H, arom.). ^{13}C NMR: $\delta = 36.88$ (CH_3), 60.38 (CH_2), 124.36 (CH), 125.19 (CH), 125.53 (CH), 125.72 (2 CH), 126.10 (CH), 127.08 (CH), 128.25 (CH), 128.43 (3 CH), 128.50 (CH), 131.13 (CH), 132.09 (C), 133.45 (C), 133.93 (C), 137.14 (C). $\text{C}_{19}\text{H}_{18}\text{N}_2$ (274.4)

3.3.2. 2-Chlorobenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4b)

Yield: 74%; white crystals from EtOH/ H_2O , m.p.: 48–49 °C. IR: $\nu = 3020, 2815, 1600, 1580, 1420$; MS (m/z): 310 $[(\text{M} + 2)^+]$, 308 $[(\text{M})^+]$, 170, 169, 167, 141, 127, 115. ^1H NMR: $\delta = 2.86$ (s, 3 H, CH_3), 4.99 (s, 2 H, CH_2), 7.22 (m, 4 H, arom. + CH=N), 7.48 (m, 4 H, arom.), 7.84 (m, 2 H, arom.), 8.04 (d, $J = 7.6$ Hz, 1 H arom.), 8.25 (m, 1 H, arom.). ^{13}C NMR: $\delta = 36.59$ (CH_3), 60.64 (CH_2), 124.25 (CH), 125.21 (CH), 125.77 (CH), 125.82 (CH), 126.17 (CH), 126.74 (CH), 126.91 (CH), 127.20 (CH), 127.67 (CH), 128.39 (CH), 128.57 (CH), 129.51 (CH), 132.01 (C), 132.07 (C), 133.31 (C), 133.94 (C), 134.38 (C). $\text{C}_{19}\text{H}_{17}\text{ClN}_2$ (308.8)

3.3.3. 4-Chlorobenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4c)

Yield: 75%; white crystals from abs. EtOH, m.p.: 67–68 °C. IR: $\nu = 3030, 2820, 1600, 1580, 1410$; MS (m/z): 310 $[(\text{M} + 2)^+]$, 308 $[(\text{M})^+]$, 170, 169, 167, 141, 127, 115. ^1H NMR: $\delta = 2.83$ (s, 3 H, CH_3), 4.95 (s, 2 H, CH_2), 7.17 (s, 1 H, CH=N), 7.30 (m, 4 H, arom.), 7.47 (m, 4 H, arom.), 7.85 (m, 2 H, arom.), 8.25 (m, 1 H, arom.). ^{13}C NMR: $\delta = 37.49$ (CH_3), 61.03 (CH_2), 124.10 (CH), 125.85 (CH), 126.42 (CH), 126.79 (CH), 126.92 (CH), 127.29 (2 CH), 127.52 (CH), 128.99 (CH), 129.23 (2 CH), 130.05 (CH), 132.69 (C), 133.10 (C), 133.90 (C), 134.60 (C), 136.41 (C). $\text{C}_{19}\text{H}_{17}\text{ClN}_2$ (308.8)

3.3.4. 2-Fluorobenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4d)

Yield: 73%; white crystals from abs. EtOH, m.p.: 80–82 °C. IR: $\nu = 3030, 2860, 1600, 1580, 1420$; MS (m/z): 292 $[(\text{M})^+]$, 141, 127, 115. ^1H NMR: $\delta = 2.85$ (s, 3 H, CH_3), 4.99 (s, 2 H, CH_2), 7.19 (m, 4 H, arom. + CH=N), 7.47 (m, 4 H, arom.), 7.84 (m, 2 H, arom.), 7.99 (m, 1 H arom), 8.24 (m, 1 H, arom.). ^{13}C NMR: $\delta = 35.92$ (CH_3), 59.99 (CH_2), 114.71 (CH, d, $J_2 = 24$ Hz), 122.61 (CH, d, $J_3 = 7$ Hz), 122.67 (CH), 123.46 (CH, d, $J_4 = 4$ Hz), 123.68 (CH), 124.65 (CH, d, $J_3 = 8$ Hz), 124.79 (CH), 125.14 (CH), 125.53 (CH), 126.30 (CH), 126.62 (CH), 127.35 (C, d, $J_2 = 21$ Hz), 127.82 (CH, d, $J_3 = 10$ Hz), 131.48 (C), 132.74 (C), 133.33 (C), 159.51 (C, d, $J_1 = 255$ Hz). $\text{C}_{19}\text{H}_{17}\text{FN}_2$ (292.4)

3.3.5. 4-Fluorobenzaldehyde-1-methyl-1-(1-naphthylmethyl)hydrazone (4e)

Yield: 70%; white crystals from abs. EtOH, m.p.: 82–84 °C. IR: $\nu = 3030, 2860, 1600, 1580, 1420$; MS (m/z): 292 $[(\text{M})^+]$, 141, 127, 115. ^1H NMR: $\delta = 2.76$ (s, 3 H, CH_3), 4.92 (s, 2 H, CH_2), 7.02 (t, $J_{\text{HFO}} = 8.6$ Hz, 2 H), 7.23 (s, 1 H, CH=N), 7.51 (m, 6 H, arom.), 7.82 (m, 2 H, arom.), 8.24 (m, 1 H, arom.). ^{13}C NMR: $\delta = 36.98$ (CH_3), 60.41 (CH_2), 115.35 (2 CH, d,

$J_2 = 24$ Hz), 124.33 (CH), 124.58 (CH), 125.21 (CH), 125.76 (CH), 126.11 (CH), 126.92 (CH), 127.04 (2 CH, d, $J_3 = 7$ Hz), 128.44 (CH), 130.09 (CH), 132.09 (C), 133.36 (C), 133.40 (C), 133.96 (C), 162.17 (C, d, $J_1 = 293$ Hz).
C₁₉H₁₇FN₂ (292.4)

3.3.6. 4-Methoxybenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4f)

Yield: 71%; white crystals from abs. EtOH, m.p.: 59–60 °C. IR: $\nu = 3040$, 2960, 2840, 1610, 1590, 1450; MS (m/z): 304 [(M)⁺], 163 [(M)⁺–(CH₂-naphthyl)⁺], 148 [–(CH₃)⁺], 133 [–(CH₃)⁺], 127, 115, 92 [(C₆H₄O)⁺]. ¹H NMR: $\delta = 2.77$ (s, 3 H, CH₃), 3.78 (s, 3 H, CH₃), 4.87 (s, 2 H, CH₂), 6.87 (m, 2 H, arom.), 7.27 (s, 1 H, CH=N), 7.48 (m, 6 H, arom.), 7.81 (m, 2 H, arom.), 8.28 (m, 1 H, arom.). ¹³C NMR: $\delta = 37.16$ (CH₃), 55.25 (CH₃), 60.47 (CH₂), 119.98 (2 CH), 124.45 (CH), 125.19 (CH), 125.69 (CH), 126.04 (CH), 126.84 (2 CH), 126.95 (CH), 128.18 (CH), 128.47 (CH), 130.05 (C), 131.89 (CH), 132.12 (C), 133.63 (C), 133.91 (C), 159.16 (C).
C₂₀H₂₀N₂O (304.4)

3.3.7. 4-Hydroxy-3-methoxybenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4g)

Yield: 70%; rose crystals from abs. EtOH, m.p.: 104–105 °C. IR: $\nu = 3500$ –3200, 3020, 2840, 2820, 1610, 1590, 1420; MS (m/z): 320 [(M)⁺], 179 [(M)⁺–(CH₂-naphthyl)⁺], 164 [–(CH₃)⁺], 149 [–(CH₃)⁺], 141, 127, 115. ¹H NMR: $\delta = 2.79$ (s, 3 H, CH₃), 3.89 (s, 3 H, CH₃), 4.87 (s, 2 H, CH₂), 5.78 (broad, 1 H, OH), 6.90 (d, $J = 7.8$ Hz, 2 H, arom.), 7.25 (s, 1 H, CH=N), 7.30 (s, 1 H, arom.), 7.44 (m, 4 H, arom.), 7.80 (m, 2 H, arom.), 8.28 (m, 1 H, arom.). ¹³C NMR: $\delta = 37.43$ (CH₃), 55.87 (CH₃), 60.31 (CH₂), 106.82 (CH), 114.15 (CH), 120.16 (CH), 124.38 (CH), 125.21 (CH), 125.68 (CH), 126.02 (CH), 126.94 (CH), 128.17 (CH), 128.50 (CH), 129.83 (C), 132.10 (C), 132.38 (CH), 133.59 (C), 133.90 (C), 145.51 (C), 146.90 (C).
C₂₀H₂₀N₂O₂ (320.4)

3.3.8. 3,4,5-Trimethoxybenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4h)

Yield: 67%; white crystals from abs. EtOH, m.p.: 152–153 °C. IR: $\nu = 3020$, 2840, 1580, 1520, 1410; MS (m/z): 364 [(M)⁺], 320, 223 [(M)⁺–(CH₂-naphthyl)⁺], 193, 178, 168 [⁺C₆H₂(OCH₃)₃], 141, 127, 115. ¹H NMR: $\delta = 2.85$ (s, 3 H, CH₃), 3.85 (s, 6 H, 2 CH₃), 3.88 (s, 3 H, CH₃), 4.93 (s, 2 H, CH₂), 6.85 (s, 2 H, arom.), 7.20 (s, 1 H, CH=N), 7.47 (m, 4 H, arom.), 7.83 (m, 2 H, arom.), 8.26 (m, 1 H, arom.). ¹³C NMR: $\delta = 37.34$ (CH₃), 56.04 (2 CH₃), 60.14 (CH₃), 60.84 (CH₂), 102.60 (2 CH), 124.23 (CH), 125.19 (CH), 125.69 (CH), 126.03 (CH), 126.81 (CH), 128.16 (CH), 128.20 (CH), 131.02 (CH), 132.01 (C), 132.82 (C), 133.33 (C), 133.88 (C), 137.67 (C), 153.38 (2 C).
C₂₂H₂₄N₂O₃ (364.4)

3.3.9. 2-Methylbenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4i)

Yield: 76%; white crystals from abs. EtOH, m.p.: 78–80 °C. IR: $\nu = 3030$, 2860, 1600, 1560, 1410; MS (m/z): 288 [(M)⁺], 170, 147 [(M)⁺–(CH₂-naphthyl)⁺], 141, 127, 115. ¹H NMR: $\delta = 2.37$ (s, 3 H, CH₃), 2.83 (s, 3 H, CH₃), 4.95 (s, 2 H, CH₂), 7.17 (m, 4 H, arom. + CH=N), 7.47 (m, 4 H, arom.), 7.84 (m, 3 H, arom.), 8.28 (m, 1 H, arom.). ¹³C NMR: $\delta = 19.64$ (CH₃), 36.93 (CH₃), 60.61 (CH₂), 124.40 (CH), 125.03 (CH), 125.21 (CH), 125.75 (CH), 126.04 (CH), 126.14 (CH), 126.94 (2 CH), 128.28 (CH), 128.54 (CH), 129.67 (CH), 130.51 (CH), 132.14 (C), 133.59 (C), 133.96 (C), 134.60 (C), 134.96 (C).
C₂₀H₂₀N₂ (288.4)

3.3.10. 3-Methylbenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4j)

Yield: 72%; white crystals from abs. EtOH, m.p.: 41–43 °C. IR: $\nu = 3030$, 2840, 1600, 1580, 1450; MS (m/z): 288 [(M)⁺], 170, 147 [(M)⁺–(CH₂-naphthyl)⁺], 141, 127, 115. ¹H NMR: $\delta = 2.36$ (s, 3 H, CH₃), 2.81 (s, 3 H, CH₃), 4.93 (s, 2 H, CH₂), 7.04 (d, $J = 7.4$ Hz, 1 H, arom.), 7.24 (m, 2 H, arom. + CH=N), 7.38 (m, 6 H, arom.), 7.83 (m, 2 H, arom.), 8.27 (m, 1 H, arom.). ¹³C NMR: $\delta = 21.38$ (CH₃), 36.98 (CH₃), 60.35 (CH₂), 122.95 (CH), 124.38 (CH), 125.19 (CH), 125.72 (CH), 126.04 (2 CH), 126.85 (CH), 127.99 (CH), 128.23 (CH), 128.34 (CH), 128.50 (CH), 131.52 (CH), 132.09 (C), 133.48 (C), 133.93 (C), 137.04 (C), 137.95 (C).
C₂₀H₂₀N₂ (288.4)

3.3.11. 4-Methylbenzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4k)

Yield: 73%; white crystals from abs. EtOH, m.p.: 98–100 °C. IR: $\nu = 3030$, 2860, 1600, 1580, 1405; MS (m/z): 288 [(M)⁺], 170, 147 [(M)⁺–(CH₂-naphthyl)⁺], 141, 127, 115. ¹H NMR: $\delta = 2.34$ (s, 3 H, CH₃), 2.80 (s, 3 H, CH₃), 4.91 (s, 2 H, CH₂), 7.14 (d, $J = 7.8$ Hz, 2 H, arom.), 7.26 (s, 1 H, CH=N), 7.46 (m, 6 H, arom.), 7.81 (m, 2 H, arom.), 8.28 (m, 1 H, arom.). ¹³C NMR: $\delta = 21.22$ (CH₃), 36.10 (CH₃), 60.43 (CH₂), 124.43 (CH), 125.19 (CH), 125.54 (CH), 125.70 (CH), 126.01

(CH), 126.91 (CH), 128.21 (2 CH), 128.49 (CH), 129.16 (2 CH), 131.73 (CH), 132.12 (C), 133.59 (C), 133.92 (C), 134.40 (C), 136.95 (C).
C₂₀H₂₀N₂ (288.4)

3.3.12. 4-(tert-Butyl)benzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4l)

Yield: 69%; white crystals from abs. EtOH, m.p.: 112–113 °C. IR: $\nu = 3030$, 2840, 2210, 1670, 1600, 1570, 1410; MS (m/z): 330 [(M)⁺], 146, 141, 132, 127, 115, 57 [(tert-C₄H₉)⁺]. ¹H NMR: $\delta = 1.32$ (s, 9 H, 3 CH₃), 2.79 (s, 3 H, CH₃), 4.90 (s, 2 H, CH₂), 7.26 (s, 1 H, CH=N), 7.40 (m, 4 H, arom.), 7.52 (m, 4 H, arom.), 7.81 (m, 2 H, arom.), 8.27 (m, 1 H, arom.). ¹³C NMR: $\delta = 31.33$ (3 CH₃), 34.55 (C), 37.02 (CH₃), 60.43 (CH₂), 124.43 (CH), 125.20 (CH), 125.33 (2 CH), 125.71 (CH), 126.09 (CH), 126.36 (2 CH), 126.89 (CH), 128.21 (CH), 128.50 (CH), 131.50 (CH), 132.13 (C), 133.61 (C), 133.93 (C), 134.41 (C), 150.24 (C).
C₂₃H₂₆N₂ (330.5)

3.3.13. 4-(1-Methyl-1-phenylethyl)benzaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4m)

Yield: 63%; white crystals from abs. EtOH, m.p.: 89–91 °C. IR: $\nu = 3020$, 2960, 1580, 1560, 1460; MS (m/z): 392 [(M)⁺], 251 [(M)⁺–(CH₂-naphthyl)⁺], 207, 195 [(C₆H₄(CH₃)₂C–C₆H₅)⁺], 170, 119 [C₆H₅(CH₃)₂C⁺], 91 [(C₇H₇)⁺]. ¹H NMR: $\delta = 1.67$ (s, 6 H, 2 CH₃), 2.79 (s, 3 H, CH₃), 4.90 (s, 2 H, CH₂), 7.22 (m, 6 H, arom. + CH=N), 7.46 (m, 8 H, arom.), 7.82 (m, 2 H, arom.), 8.26 (m, 1 H, arom.). ¹³C NMR: $\delta = 30.69$ (2 CH₃), 37.04 (CH₃), 42.87 (C), 60.44 (CH₂), 124.41 (CH), 125.24 (CH), 125.57 (2 CH), 125.72 (CH), 126.11 (CH), 126.38 (CH), 126.79 (CH), 126.90 (CH), 126.98 (2 CH), 127.10 (CH), 127.72 (CH), 127.96 (CH), 128.23 (CH), 128.51 (CH), 131.31 (CH), 132.12 (C), 133.56 (C), 133.94 (C), 134.61 (C), 149.75 (C), 150.70 (C).
C₂₈H₂₈N₂ (392.5)

3.3.14. 1-Naphtaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4n)

Yield: 60%; white crystals from CH₂Cl₂/abs. EtOH, m.p.: 72–74 °C. IR: $\nu = 3040$, 3010, 1620, 1600, 1450; MS (m/z): 324 [(M)⁺], 183 [(M)⁺–(CH₂-naphthyl)⁺], 168 [–(CH₃)⁺], 153 [(N≡C-naphthyl)⁺], 141, 127, 115. ¹H NMR: $\delta = 2.92$ (s, 3 H, CH₃), 5.00 (s, 2 H, CH₂), 7.46 (m, 8 H, arom. + CH=N), 7.81 (m, 5 H, arom.), 8.30 (m, 1 H, arom.), 8.53 (m, 1 H, arom.). ¹³C NMR: $\delta = 36.98$ (CH₃), 60.59 (CH₂), 124.01 (CH), 124.24 (CH), 124.34 (CH), 125.23 (CH), 125.49 (CH), 125.60 (CH), 125.76 (CH), 125.95 (CH), 126.18 (CH), 126.96 (CH), 127.54 (CH), 128.31 (CH), 128.56 (CH), 128.59 (CH), 129.82 (CH), 130.51 (C), 132.10 (C), 132.51 (C), 133.51 (C), 133.95 (C), 134.03 (C).
C₂₃H₂₀N₂ (324.4)

3.3.15. 2-Naphtaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4o)

Yield: 71%; white crystals from CH₂Cl₂/abs. EtOH, m.p.: 105–107 °C. IR: $\nu = 3040$, 3000, 1620, 1600, 1450; MS (m/z): 324 [(M)⁺], 183 [(M)⁺–(CH₂-naphthyl)⁺], 168 [–(CH₃)⁺], 153 [(N≡C-naphthyl)⁺], 141, 127, 115. ¹H NMR: $\delta = 2.85$ (s, 3 H, CH₃), 4.97 (s, 2 H, CH₂), 7.45 (m, 8 H, arom. + CH=N), 7.82 (m, 5 H, arom.), 8.00 (m, 1 H, arom.), 8.29 (m, 1 H, arom.). ¹³C NMR: $\delta = 36.89$ (CH₃), 60.48 (CH₂), 121.43 (CH), 121.50 (CH), 122.76 (CH), 122.86 (CH), 123.61 (CH), 124.49 (CH), 124.56 (CH), 124.64 (CH), 126.21 (CH), 126.57 (CH), 126.69 (CH), 126.83 (CH), 127.01 (CH), 127.65 (CH), 127.81 (CH), 129.64 (C), 129.74 (C), 132.84 (C), 133.44 (C), 133.71 (C), 134.83 (C).
C₂₃H₂₀N₂ (324.4)

3.3.16. (E)-2-Octenal 1-methyl-1-(1-naphthylmethyl)hydrazone (4p)

Yield: 78%; yellow oil, b.p. (0.01 mm Hg): 158–160 °C. IR: $\nu = 3040$, 2960, 1600, 1580, 1450, 960; MS (m/z): 294 [(M)⁺], 153 [(M)⁺–(CH₂-naphthyl)⁺], 141, 115, 83 [(C₆H₁₁)⁺]. ¹H NMR: $\delta = 0.89$ (t, $J = 6.8$ Hz, 3 H, CH₃), 1.31 (m, 2 H, CH₂), 1.40 (m, 4 H, 2 CH₂), 2.14 (m, 2 H, CH₂), 2.66 (s, 3 H, CH₃), 4.75 (s, 2 H, CH₂), 5.79 (m, 1 H, CH), 6.30 (m, 1 H, CH), 7.07 (d, $J = 8.8$ Hz, 1 H, CH), 7.44 (m, 4 H, arom.), 7.81 (m, 2 H, arom.), 8.20 (m, 1 H, arom.). ¹³C NMR: $\delta = 15.23$ (CH₃), 22.51 (CH₂), 28.69 (CH₂), 31.24 (CH₂), 35.62 (CH₂), 38.32 (CH₃), 60.34 (CH₂), 122.74 (CH), 123.52 (CH), 124.01 (CH), 124.45 (CH), 125.31 (CH), 125.92 (CH), 126.72 (CH), 127.22 (CH), 127.54 (CH), 127.69 (CH), 129.88 (C), 133.93 (C), 137.04 (C).
C₂₀H₂₆N₂ (294.4)

3.3.17. 2-Phenylacetaldehyde 1-methyl-1-(1-naphthylmethyl)hydrazone (4q)

Yield: 88%; yellow oil, b.p. (0.01 mm Hg): 150–152 °C. IR: $\nu = 3030$, 2840, 1660, 1580, 1450; MS (m/z): 288 [(M)⁺], 147 [(M)⁺–(CH₂-naphthyl)⁺], 141, 127, 115, 91 [C₆H₅–CH₂]⁺. ¹H NMR: $\delta = 2.57$ (s, 3 H, CH₃), 3.63 (d, $J = 5.6$ Hz, 2 H, CH₂), 4.72 (s, 2 H, CH₂), 6.71 (t, $J = 5.6$ Hz, 1 H, CH=N), 7.22 (m, 5 H, arom.), 7.43 (m, 4 H, arom.), 7.79 (m, 2 H, arom.); 8.27 (m, 1 H, arom.). ¹³C NMR: $\delta = 37.52$ (CH₃), 39.62

(CH₂), 60.34 (CH₂), 124.52 (CH), 125.13 (CH), 125.32 (CH), 125.66 (CH), 125.77 (CH), 126.00 (CH), 126.27 (CH), 127.06 (CH), 128.14 (CH), 128.45 (CH), 128.81 (CH), 129.08 (CH), 132.18 (C), 133.68 (C), 133.90 (C), 135.25 (CH), 138.89 (C).
C₂₀H₂₀N₂ (288.4)

3.3.18. (E)-3-Phenyl-2-propenal 1-methyl-1-(1-naphthylmethyl)hydrazone (4r)

Yield: 64%; white crystals from abs. EtOH, m.p.: 124–126 °C. IR: ν = 3020, 2840, 1620, 1580, 1420, 960; MS (m/z): 300 [(M)⁺], 159 [(M)⁺–(CH₂-naphthyl)⁺], 141, 127, 115, 77 [(C₆H₅)⁺]. ¹H NMR: δ = 2.75 (s, 3 H, CH₃), 4.87 (s, 2 H, CH₂), 6.56 (d, J = 15.4 Hz, 1 H, CH), 7.06 (dd, J = 15.4 + 8.2 Hz, 1 H, CH), 7.12 (d, J = 8.2 Hz, 1 H, CH), 7.39 (m, 9 H, arom.), 7.81 (m, 2 H, arom.), 8.18 (m, 1 H, arom.). ¹³C NMR: δ = 36.99 (CH₃), 60.24 (CH₂), 124.18 (CH), 125.21 (CH), 125.77 (CH), 126.16 (2 CH), 126.73 (CH), 127.24 (CH), 127.50 (CH), 127.85 (CH), 128.32 (CH), 128.55 (CH), 128.60 (2 CH), 131.21 (CH), 131.98 (C), 133.20 (C), 133.81 (CH), 133.91 (C), 137.46 (C).
C₂₁H₂₀N₂ (300.4)

3.3.19. 4,4-Dimethyl-2-pentynal 1-methyl-1-(1-naphthylmethyl)hydrazone (4s)

Yield: 86%; yellow oil, b.p. (0.01 mm Hg): 153–155 °C. IR: ν = 3040, 2860, 2200, 1600, 1540; MS (m/z): 278 [(M)⁺], 221 [(M)⁺–(C₄H₉)⁺], 151 [(M)⁺–(CH₂-naphthyl)⁺], 141, 127, 115. ¹H NMR: δ = 1.29 (s, 9 H, 3CH₃), 2.69 (s, 3 H, CH₃), 4.88 (s, 2 H, CH₂), 6.40 (s, 1 H, CH=N), 7.42 (m, 4 H, arom.), 7.81 (m, 2 H, arom.), 8.12 (m, 1 H, arom.). ¹³C NMR: δ = 30.16 (C), 30.89 (3CH₃), 36.62 (CH₃), 59.99 (CH₂), 61.53 (C), 98.80 (C), 124.06 (CH), 125.15 (CH), 125.47 (CH), 125.60 (CH), 125.94 (CH), 126.53 (CH), 127.96 (CH), 128.33 (CH), 131.79 (C), 132.73 (C), 133.84 (C).
C₁₉H₂₂N₂ (278.4)

3.3.20. Benzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11a)

Yield: 85%; white crystals from abs. EtOH, m.p.: 114–115 °C. IR: ν = 3040, 2800, 1580, 1380; MS (m/z): 280 [(M)⁺], 147 [(CH₂-benzothiophenyl)⁺], 133 [(benzothiophenyl)⁺]. ¹H NMR: δ = 2.86 (s, 3 H, CH₃), 4.79 (s, 2 H, CH₂), 7.21 (m, 2 H, arom.), 7.25 (s, 1 H, CH=N), 7.33 (m, 5 H, arom.), 7.61 (m, 2 H, arom.), 7.76 (d, J = 7.5 Hz, 1 H, arom.). ¹³C NMR: δ = 37.25 (CH₃), 61.80 (CH₂), 122.85 (CH), 123.62 (CH), 123.92 (CH), 124.35 (CH), 125.68 (2 CH), 126.83 (CH), 127.23 (CH), 128.42 (2 CH), 131.99 (CH), 132.24 (C), 136.98 (C), 138.91 (C), 140.34 (C).
C₁₇H₁₆N₂S (280.4)

3.3.21. 4-Chlorobenzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11c)

Yield: 85%; white crystals from abs. EtOH, m.p.: 92–93 °C. IR: ν = 3040, 2840, 1580, 1380; MS (m/z): 316 [(M + 2)⁺], 314 [(M)⁺], 167 [(M)⁺–(CH₂-benzothiophenyl)⁺], 147, 133. ¹H NMR: δ = 2.87 (s, 3 H, CH₃), 4.79 (s, 2 H, CH₂), 7.21 (s, 1 H, CH=N), 7.27 (m, 4 H, arom.), 7.39 (m, 2 H, arom.), 7.53 (m, 2 H, arom.), 7.77 (d, J = 7.6 Hz, 1 H, arom.). ¹³C NMR: δ = 37.05 (CH₃), 61.81 (CH₂), 122.94 (CH), 123.61 (CH), 123.94 (CH), 124.34 (CH), 126.70 (2 CH), 126.84 (CH), 128.54 (2 CH), 130.14 (CH), 131.98 (C), 132.53 (C), 135.53 (C), 138.65 (C), 140.32 (C).
C₁₇H₁₅ClN₂S (314.8).

3.3.22. 4-Fluorobenzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11e)

Yield: 74%; white crystals from abs. EtOH, m.p.: 115–116 °C. IR: ν = 3040, 2800, 1600, 1380; MS (m/z): 298 [(M)⁺], 151 [(M)⁺–(CH₂-benzothiophenyl)⁺], 147, 133. ¹H NMR: δ = 2.86 (s, 3 H, CH₃), 4.77 (s, 2 H, CH₂), 7.06 (t, J_{HFO} = 8.9 Hz, 2 H), 7.26 (s, 1 H, CH=N), 7.38 (m, 4 H, arom.), 7.58 (m, 2 H, arom.), 7.79 (d, J = 7.6 Hz, 1 H, arom.). ¹³C NMR: δ = 37.29 (CH₃), 61.81 (CH₂), 115.33 (2 CH, d, J₂ = 26 Hz), 122.91 (CH), 123.64 (CH), 123.95 (CH), 124.36 (CH), 127.01 (2 CH, d, J₃ = 9 Hz), 130.87 (CH), 132.17 (C), 133.21 (C, d, J₄ = 3 Hz), 138.74 (C), 140.37 (C), 162.23 (C, d, J₁ = 294 Hz).
C₁₇H₁₅FN₂S (298.4).

3.3.23. 4-Methoxybenzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11f)

Yield: 87%; white crystals from abs. EtOH, m.p.: 100–101 °C. IR: ν = 3040, 2800, 1580, 1380; MS (m/z): 310 [(M)⁺], 163, 147, 133, 91. ¹H NMR: δ = 2.96 (s, 3 H, CH₃), 3.82 (s, 3 H, CH₃), 4.75 (s, 2 H, CH₂), 6.97 (m, 2 H, arom.), 7.26 (s, 1 H, CH=N), 7.41 (m, 4 H, arom.), 7.53 (m, 2 H, arom.), 7.78 (d, J = 7.6 Hz, 1 H, arom.). ¹³C NMR: δ = 38.36 (CH₃), 56.77 (CH₃), 61.89 (CH₂), 123.18 (CH), 123.78 (CH), 123.95 (CH), 124.12 (2 CH), 124.34 (2 CH), 126.26 (CH), 126.31 (CH), 126.79 (CH), 129.50 (C), 131.10 (C), 135.33 (C), 138.69 (C), 157.74 (C).
C₁₈H₁₈N₂OS (310.4)

3.3.24. 3-Methylbenzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11j)

Yield: 66%; white crystals from abs. EtOH, m.p.: 62–64 °C. IR: ν = 3040, 2820, 1580, 1380; MS (m/z): 294 [(M)⁺], 147, 133. ¹H NMR: δ = 2.37 (s, 3 H, CH₃), 2.87 (s, 3 H, CH₃), 4.80 (s, 2 H, CH₂), 7.06 (d, J = 7.4 Hz, 1 H, arom.), 7.23 (s, 1 H, CH=N), 7.35 (m, 7 H, arom.), 7.78 (d, J = 7.8 Hz, 1 H, arom.). ¹³C NMR: δ = 21.38 (CH₃), 37.33 (CH₃), 61.72 (CH₂), 122.81 (CH), 123.55 (CH), 123.72 (CH), 123.77 (CH), 123.91 (CH), 124.34 (CH), 126.15 (CH), 126.82 (CH), 128.13 (CH), 132.27 (C), 132.35 (CH), 136.85 (C), 137.95 (C), 138.20 (C), 140.32 (C).
C₁₈H₁₈N₂S (294.4)

3.3.25. 4-Methylbenzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11k)

Yield: 91%; white crystals from abs. EtOH, m.p.: 82–83 °C. IR: ν = 3100, 2900, 1650, 1600, 1340; MS (m/z): 294 [(M)⁺], 147. ¹H NMR: δ = 2.34 (s, 3 H, CH₃), 2.84 (s, 3 H, CH₃), 4.76 (s, 2 H, CH₂), 7.14 (d, J = 7.8 Hz, 1 H, arom.), 7.29 (s, 1 H, CH=N), 7.31 (m, 4 H, arom.), 7.47 (m, 3 H, arom.), 7.76 (d, J = 7.4 Hz, 1 H, arom.). ¹³C NMR: δ = 21.25 (CH₃), 37.37 (CH₃), 61.82 (CH₂), 122.81 (CH), 123.64 (CH), 123.92 (CH), 124.35 (CH), 125.68 (2 CH), 126.84 (CH), 129.16 (2 CH), 132.36 (C), 132.59 (CH), 134.25 (C), 137.12 (C), 138.81 (C), 140.33 (C).
C₁₈H₁₈N₂S (294.4)

3.3.26. 4-(tert-Butyl)benzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11l)

Yield: 97%; white crystals from abs. EtOH, m.p.: 103–104 °C. IR: ν = 3040, 2820, 1580, 1360; MS (m/z): 336 [(M)⁺], 189 [(M)⁺–(CH₂-benzothiophenyl)⁺], 147, 133 [(C₆H₄-tert-C₄H₉)⁺]. ¹H NMR: δ = 1.39 (s, 9 H, 3CH₃), 2.85 (s, 3 H, CH₃), 4.78 (s, 2 H, CH₂), 7.27 (d, J = 7.2 Hz, 1 H, arom.), 7.31 (s, 1 H, CH=N), 7.35 (m, 5 H, arom.), 7.50 (m, 2 H, arom.), 7.75 (d, J = 7.4 Hz, 1 H, arom.). ¹³C NMR: δ = 31.31 (3CH₃), 34.56 (C), 37.36 (CH₃), 61.78 (CH₂), 122.78 (CH), 123.60 (2 CH), 123.90 (CH), 124.33 (CH), 125.34 (2 CH), 125.45 (CH), 126.83 (C), 127.24 (CH), 132.35 (CH), 134.24 (C), 138.77 (C), 140.30 (C), 150.39 (C).
C₂₁H₂₄N₂S (336.5)

3.3.27. 4-(1-Methyl-1-phenylethyl)benzaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11m)

Yield: 70%; white crystals from abs. EtOH, m.p.: 99–100 °C. IR: ν = 3040, 2960, 1575, 1360; MS (m/z): 398 [(M)⁺], 251 [(M)⁺–(CH₂-benzothiophenyl)⁺], 206, 147, 133, 119 [(C₆H₅)–C(CH₃)₂⁺]. ¹H NMR: δ = 1.67 (s, 6 H, 2 CH₃), 2.84 (s, 3 H, CH₃), 4.76 (s, 2 H, CH₂), 7.20 (d, J = 7.4 Hz, 1 H, arom.), 7.24 (m, 5 H, arom.), 7.29 (s, 1 H, CH=N), 7.44 (m, 7 H, arom.), 7.76 (d, J = 7.4 Hz, 1 H, arom.). ¹³C NMR: δ = 30.66 (2 CH₃), 37.36 (CH₃), 42.85 (C), 61.77 (CH₂), 122.79 (CH), 123.58 (CH), 123.72 (CH), 123.77 (CH), 123.89 (CH), 124.33 (CH), 125.36 (2 CH), 125.56 (CH), 126.76 (CH), 126.83 (CH), 126.94 (2 CH), 127.95 (CH), 132.08 (CH), 132.31 (C), 134.43 (C), 138.73 (C), 140.30 (C), 149.85 (C), 150.65 (C).
C₂₆H₂₆N₂S (398.6)

3.3.28. 2-Naphthaldehyde 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11o)

Yield: 63%; white crystals from abs. EtOH, m.p.: 109–110 °C. IR: ν = 3050, 2860, 1650, 1600, 1340; MS (m/z): 330 [(M)⁺], 183 [(M)⁺–(CH₂-benzothiophenyl)⁺], 147. ¹H NMR: δ = 2.92 (s, 1 H, CH₃), 4.84 (s, 1 H, CH₂), 7.29 (m, 2 H, arom.), 7.36 (s, 1 H, CH=N), 7.42 (s, 5 H, arom.), 7.79 (m, 4 H, arom.), 7.99 (d, J = 7.2 Hz, 1 H). ¹³C NMR: δ = 37.29 (CH₃), 61.82 (CH₂), 122.89 (CH), 123.19 (CH), 123.63 (CH), 123.93 (CH), 124.37 (CH), 125.33 (CH), 125.48 (CH), 126.05 (CH), 126.83 (CH), 127.73 (CH), 127.83 (CH), 128.08 (CH), 131.93 (CH), 132.20 (C), 133.06 (C), 133.66 (C), 134.76 (C), 138.72 (C), 140.35 (C).
C₂₁H₁₈N₂S (330.5)

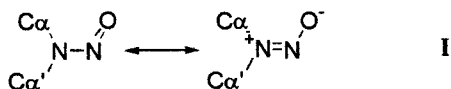
3.3.29. (E)-3-Phenyl-2-propenal 1-(benzo[b]thiophen-7-ylmethyl)-1-methylhydrazone (11r)

Yield: 91%; white crystals from abs. EtOH, m.p.: 125–126 °C. IR: ν = 3100, 2840, 1620, 1550, 1340; MS (m/z): 306 [(M)⁺], 159 [(M)⁺–(CH₂-benzothiophenyl)⁺], 147, 133. ¹H NMR: δ = 2.83 (s, 3 H, CH₃), 4.73 (s, 2 H, CH₂), 6.60 (d, J = 15.8 Hz, 1 H, CH), 7.02 (dd, J = 15.8 + 8.5 Hz, 1 H, CH), 7.21 (d, J = 8.5 Hz, 1 H, CH), 7.35 (m, 9 H, arom.), 7.77 (d, J = 7.8 Hz, 1 H, arom.). ¹³C NMR: δ = 37.32 (CH₃), 61.52 (CH₂), 122.88 (CH), 123.42 (CH), 123.88 (CH), 124.21 (CH), 126.16 (CH), 126.69 (CH), 126.84 (CH), 127.09 (CH), 127.27 (CH), 127.69 (CH), 128.55 (CH), 131.59 (CH), 131.96 (C), 134.61 (CH), 137.32 (C), 138.46 (C), 140.31 (C).
C₁₉H₁₈N₂S (306.4).

3.3.30. 4,4-Dimethyl-2-pentynal 1-(benzo[b]thiophen-7-ylmethyl)-1-methyl-hydrazone (**11s**)

Yield: 87%; yellow oil, b.p. (0.01 mm Hg): 120–122 °C. IR: ν = 3050, 2860, 2210, 1670, 1600, 1460; MS (m/z): 284 [(M)⁺], 151, 147. ¹H NMR: δ = 1.29 (s, 9H, 3 CH₃), 2.78 (s, 3H, CH₃), 4.75 (s, 2H, CH₂), 6.45 (s, 1H, CH=N), 7.35 (m, 4H, arom.), 7.77 (d, J = 7.8 Hz, 1H, arom.). ¹³C NMR: δ = 29.72 (C), 30.87 (3 CH₃), 37.23 (CH₃), 61.18 (CH₂), 61.66 (C), 98.79 (C), 122.91 (CH), 123.25 (CH), 123.90 (CH), 124.37 (CH), 124.65 (CH), 126.79 (CH), 131.59 (C), 138.27 (C), 140.33 (C). C₁₇H₂₀N₂S (284.4).

³ Contribution from the 1,3-dipolar resonance structure of **I** of the *N*-nitroso-amino group produces a planar C α C α' N–NO structure with double bond character between the two nitrogen atoms, resulting in hindered rotation around the N–N bond [19].



At room temperature the proton NMR signals due to C α and C α' are not equivalent; the notation used to distinguish the various protons is shown in **I**, each proton being referred to as *syn* or *anti* with respect to the nitroso group. The ratios of isomers were determined by integration of peak areas.

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