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Synthesis and pharmacological investigation of new *N*-hydroxyalkyl-2-aminophenothiazines exhibiting marked MDR inhibitory effect

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ABSTRACT

Novel *N*-hydroxyalkyl-2-aminophenothiazines implying a tetrazole moiety at the alkyl chain have been synthesized by hydroboration–oxidation of dienes followed by Buchwald–Hartwig cross-coupling reaction. Also, some sulfoxide and sulfone derivatives have been prepared by selective oxidations. MDR inhibition studies on rat hepatocyte cell culture revealed that some derivatives exhibit marked biological efficacy exceeding that of the standard verapamil (e.g., **3h**, **4h**, **16**). Selected derivatives were subjected to chemical resolution to provide both enantiomers which were shown of similar activity on P-gp interaction measurements. The new compounds exhibited no toxicity.

1. Introduction

Multidrug resistance (MDR) is a major clinical obstacle in the treatment of several cancers including hematological malignancies and solid tumors. The ATP-binding cassette transporter P-glycoprotein (P-gp, ABCB1), is one molecule that is involved in drug resistance.[1] Cancer cells can escape from the toxic effect of drugs mainly due to the highly expressed membrane transporters that pump drugs out of cells.[2] To overcome P-gp mediated MDR, modulators, so called P-gp inhibitors, can be used to block efflux pump activity. P-gp inhibitors can be used in combination with anticancer drugs to enhance the effectiveness of chemotherapy against resistant tumor cells. On the other hand, P-gp is presented in normal tissues, thus non-selective blockage of P-gp can cause undesired side effects. Therefore, it is important to deliver P-gp inhibitor only to the tumor cells (along with anticancer drug) and limit its distribution in the body. Much effort has been devoted to developing P-gp inhibitors to modulate MDR. However, none of the inhibitors on the market have been successful. Three generations of inhibitors have been developed in order to reverse MDR. First-generation inhibitors including verapamil, and cyclosporine A were limited by unacceptable toxicity.[3] Second-generation agents such as dexverapamil, PSC833 had better tolerability but displayed unwanted pharmacokinetic interactions. Third-generation inhibitors can specifically and potently inhibit P-gp function, several of them have been tested in controlled clinical trials, but no satisfactory results have been obtained.[4] For almost three decades, research has been conducted to overcome MDR through pharmacological inhibition of ABC transporters with limited clinical success. Therefore it is still urgent to develop some new agents to overcome MDR.[5]

During the recent years, investigation of inhibition of multidrug resistance (MDR) attracted an increased interest world-wide.[6] Among the effective compounds that proved to inhibit resistance, some phenothiazine derivatives were found of high activity.[7] With some of the most important such compounds involving chloropromazine,[8] trifluoperazine,[9] thioridazine,[10] two common structural features of these compounds should be pointed out: (i) presence of an alkyl chain attached to the nitrogen atom of the phenothiazine ring; (ii) presence of an amino moiety in most of the derivatives.

Earlier, we described a novel synthetic approach to *N*-dienylphenothiazines[11] and, quite recently, reduction of these compounds to *N*-butyl and *N*-hydroxybutyl derivatives[12] has been reported. Even if the MDR inhibitory efficacy of these new compounds proved to be only moderate, further functionalization of these derivatives seemed promising in order to discover new potent MDR inhibitors among the newly synthesized phenothiazine derivatives.

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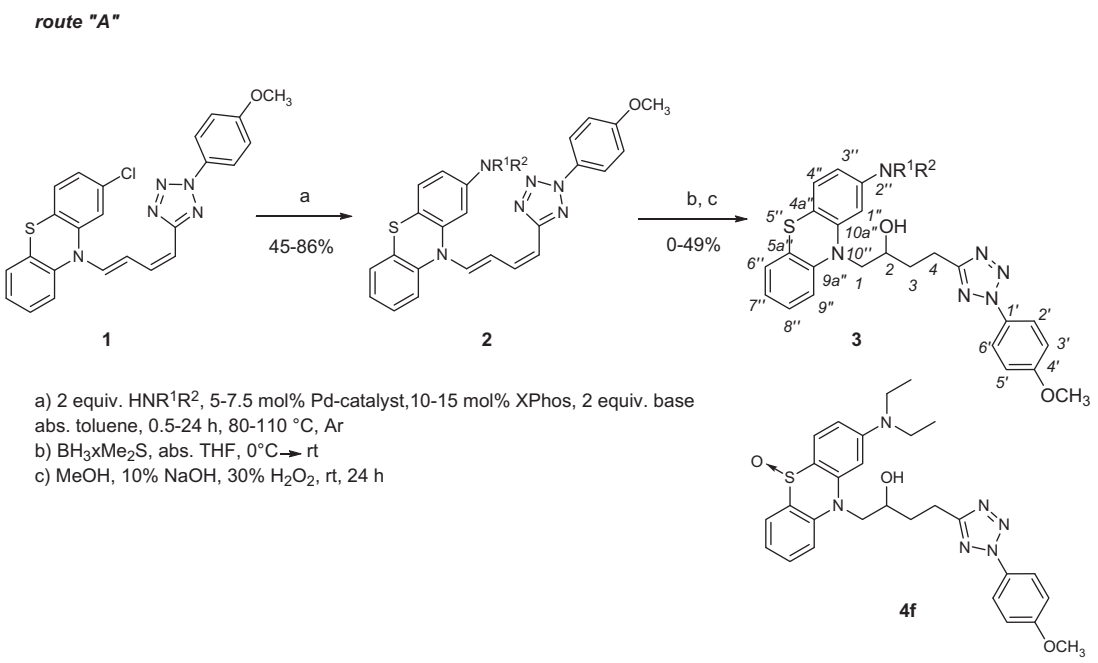


Scheme 1. Synthetic *route* '*A*' to *N*-(2-hydroxybutyl)-2-aminophenothiazines (**3**).

2. Results and discussion

2.1. Synthesis

In this paper we report on a well executable synthetic protocol to *N*-tetrazolylbutylphenothiazines bearing various amino functions in position 2 of the tricyclic ring as well as on biological evaluation of the new derivatives.

Two of our recent findings provided proper starting point in order to perform the above planned transformations: (a) the successful reduction of phenothiazinyldienes to the related butyl compounds by borane[12] and, (b) the convenient introduction of amino groups into the desired position of phenothiazine by Buchwald–Hartwig cross-coupling reaction of the commercially available 2-chlorophenothiazine.[13a]

By utilization of these structural conversions, the synthetic strategy *route* '*A*' starting from the easily accessible dienylphenothiazine (**1**) shown in Scheme 1 seemed straightforward, that is, Buchwald–Hartwig amination to **2** followed hydroboration–oxidation to give the saturated monohydroxy product (**3**). As pharmacological measurements indicated that, concerning the MDR modulatory activity, those compounds bearing a 4-methoxyphenyl group on the N2 atom of the tetrazole ring are superior and, thus, all further chemical transformations have been carried out with such methoxy compounds (cf. Table 2 later in this publication).

Scheme 1 reveals these transformations proceeded in medium to low yield only and, in some cases, decomposition was experienced and no product could be isolated (Table 1). It is interesting to note that in one case: with the diethylamino derivative **2f**, the expected product **3f** was found as a minor component of the reaction mixture, whereas a sulfoxide (**4f**) was formed in majority (67%). A specific NMR spectral feature of this product is appearance of two sets of signals due to the presence of two chiral centers (i.e., the secondary alcohol and sulfoxide moeties).

The above findings prompted us to apply another synthetic strategy and, thus, *route* '*B*' was decided next (Scheme 2). This route involved the hydroboration–oxidation of the diene (**1**) to the hydroxybutyl derivative (**5**) as described in our recent publication,[12] followed by protection of the OH group (formation of **6** by benzylation). Also, an alternative *route* '*C*' was applied by reacting **5** with *tert*-butyldiphenylchlorosilane (^{t}BuPh$_2$SiCl) to give the

Table 1
Used primary/secondary amines and acid amides in the synthesis of *N*-(2-hydroxybutyl)-2-aminophenothiazines (**3**) via *route A* (Scheme 1)

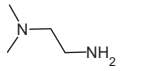
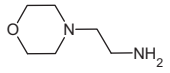
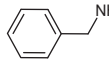
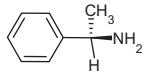
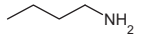
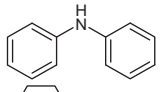
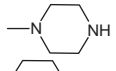
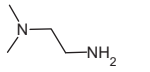
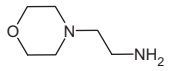
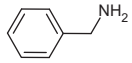
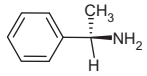
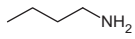
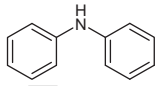
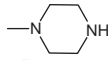
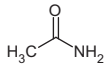
Compound **3**	HNR^1R^2	Yield %
a		–
b		26
c		30
d		46
e		–
f		23
g		49
h		33
i		49
j		44
k		–
l		–
m		–

Table 2
Comparison of yields obtained via *routes* '*B*' and '*C*' depicted in Scheme 2

Entry	HNR^1R^2	*Route* '*B*'		*Route* '*C*'	
		Buchwald–Hartwig amination **7** (%)	Debenzylation **3** (%)	Buchwald–Hartwig amination **9** (%)	Desilylation **3** (%)
a		–	–	84	91
b		–	–	93	84
c		67	Quant.	–	–
d		64	–	–	–
e		–	–	57	49
f		–	–	57	86
g		–	–	–	–
h		–	–	91	87
i		99	33	73	64
j		–	–	–	–
k		80	62	–	–
l		29	–	64	Quant.
m		–	–	44	96

O-protected 2-chlorophenothiazine compound **8**. Formation of the benzyloxy and *tert*-butyldiphenylsilyloxy compounds (**6** and **8**) was accomplished according to analogous procedures described in the literature.[14,15]

Both O-protected compounds (**6** and **8**) were subjected to Buchwald–Hartwig amination to give the amines **7** and **9**, respectively. In contrast to the poor yields experienced in *route* '*A*' with the transformation **1** → **3** (Scheme 1), the cross-coupling amination of **6** and **8** was found to proceed in good to excellent yields (44–93%) in most cases: $Pd_2(dba)_3$ or $Pd(OAc)_2$ were used as the Pd-catalysts in the presence of NaO^tBu, Cs_2CO_3 or K_2CO_3 as a base, the ligand was XPhos in every case, whereas toluene or 1,4-dioxane were used as a solvent.

The amino components involved primary amines (**a**–**e**), secondary amines (**f**–**k**), and two amides (**l**, **m**) as specified in Scheme 1.

Finally, deprotection of **7** and **9** by acidic treatment and reaction with TBAF, respectively, by using literature procedures[16] yielded the free hydroxy group containing products (**3a**–**m**). Table 2 summarizes all 2-aminophenothiazines prepared by *route* '*B*' or '*C*'. Inspection of this table reveals that the best yields were obtained with *route* '*C*'.

The aforementioned finding with formation of a sulfoxide (**4f**) in course of the hydroboration–oxidation reaction directed our attention to a deeper study on synthetic possibilities to such compounds. Inspection of the pertinent literature revealed that relatively few data on phenothiazine-sulfoxides exist. Thus, oxidation to phenothiazinyl sulfoxides,[17–19] and sulfones[20,21] has been reported. Also, selective procedures to sulfoxides and sulfones have been described.[22]

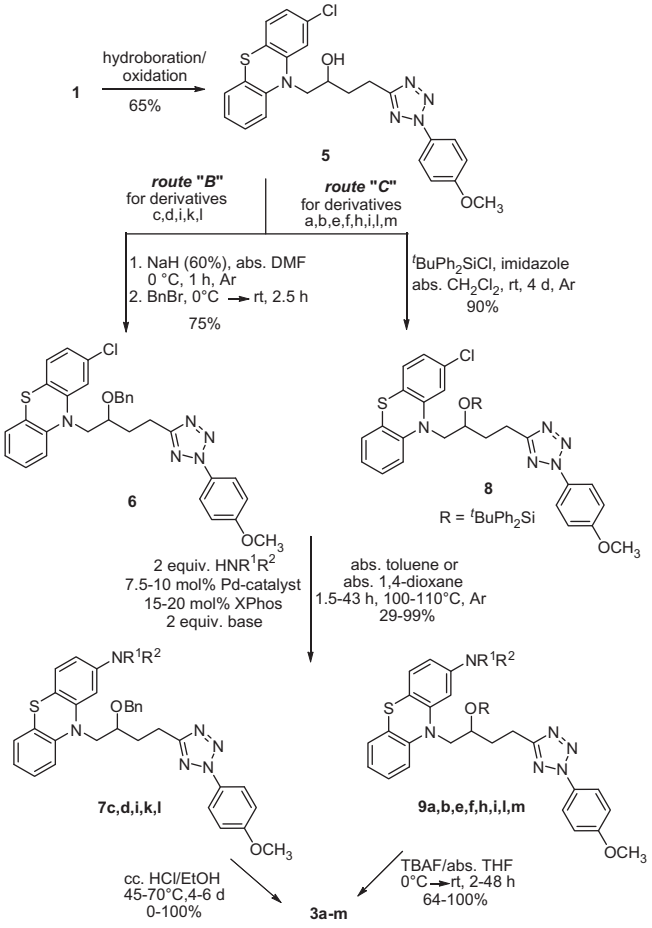
In order to prepare a series of amine-containing sulfoxides (e.g., **4f**) the chloro compound **5** was first oxidized by *m*-CPBA to the 2-chlorosulfoxide **10**[22] (Scheme 3) and, then this compound was subjected to Buchwald–Hartwig cross-coupling reaction with three selected secondary amines to give **4h**,**i**. Most interestingly, reaction of **10** with diethylamine resulted in dehalogenation to yield the 2-unsubstituted compound **11**. The structures of **4h**,**i** involve two chirality centers (i.e., the secondary alcohol function and the novel of the sulfoxide moiety) and, accordingly, in the ^1H NMR spectra two sets of resonances corresponding to the two diastereomers appeared. Attempts for further oxidation of these sulfoxides, unfortunately, failed and prologued oxidation of **4h** resulted in formation of an *N*-oxide (**12**) rather than the expected sulfone.

In order to circumvent this problem, the silylated 2-chloro compound **8** was oxidized to a sulfoxide (**13**) and, then, a further oxidation of **13** by *m*-CPBA under more forced conditions yielded the O-protected 2-chlorophenothiazine sulfones (**14**). Subsequent Buchwald–Hartwig amination with secondary amines to **15f**,**h**,**i** and the cleavage of protecting group provided the desired 2-aminophenothiazinyl sulfones (**16f**,**h**,**i**) in high yields.

As revealed by the biological assays as discussed below, **3h** proved to be one of the most active MDR inhibitor (exceeding the efficacy of that of verapamil). As the above discussed synthesis provided this compound as a racemic mixture, separation of the enantiomeric pairs was decided. Among the several possible resolution strategies, application of the semiequivalent method was decided.[23] To this end, **5** was first functionalized by reaction of the hydroxy group with maleic acid anhydride to give semiacid (**17**). A solution of this compound in ethyl acetate was treated with

a half equivalent of *S*-(−)-phenylethylamine in order to obtain a mixture of diastereomeric salts. The (−)-diastereomeric salt (**18**) precipitated from the mixture, whereas the dissolved (−)-diastereomeric salt and the (+)-monoester (**19**) remained in the solution. The crystalline **18** was filtered off and, after several recrystallizations, it was hydrolyzed to the (−)-monoester ((−)-**17**). Saponification of (−)-**17** with sodium hydroxide solution under reflux afforded the optically pure (−)-hydroxy compound ((−)-**5**) with excellent enantiomeric purity (ee 99.9%). Similar work-up of the solution containing mainly **19** via formation of (+)-monoester (+)-**17** resulted in isolation of the (+)-enantiomer of **5** with lower optical purity (ee 74–98%) (Scheme 4).

The obtained optically pure (−)-**5** and (+)-**5** were suitable starting materials for preparation of those amines (*i.e.*, (**3f**,**h**,**i**) that seemed to be promising lead candidates on the basis of biological evaluations (see below section). To this end, *route* '*C*' was applied. Accordingly, (−)-**5** and (+)-**5** were silylated to (−)-**8** and (+)-**8**, Buchwald–Hartwig amination yielded the O-protected amines (−)-**9f**,**h**,**i**- and (+)-**9f**,**h**,**i** and, finally, deprotection afforded the desired (−)-**3f**,**h**,**i** and (+)-**3f**,**h**,**i** (Scheme 5).



Scheme 2. Synthetic *route* '*B*' and '*C*' to *N*-(2-hydroxybutyl)-2-aminophenothiazines (**3**).

2.2. P-gp interaction studies

The above discussed set of *N*-substituted phenothiazine derivatives was tested for P-gp inhibitor activity in primaty rat hepatocyte culture. The rate of rhodamine 123 (RH123) accumulation was studied in the presence of these molecules and of verapamil, a commonly used P-gp inhibitor. All compounds were studied at 10 μM concentration, and data are expressed as % of the inhibition by verapamil.

Table 3 demonstrates the inhibitor activity of three pairs of derivatives having hydrogen, chloro atoms, and trifluoromethyl group on position 2 of the phenothiazine ring, whereas substituents on the phenyl ring attaching to N2 of the tetrazol involved chloro, methoxy, and ethoxycarbonyl groups (**1**, **20a**–**d**). These data reveal that molecules containing 4-methoxyphenyltetrazole moiety were found to be most effective, irrespective of the substituents on position 2 of the phenothiazine ring even if the rate of inhibition was considerably influenced by substituents on the latter position.

A further variety of *N*-2-hydroxybutylphenothiazine compounds, all containing a 4-methoxyphenyl group on the tetrazole ring and differently substituted amino groups on position 2 of phenothiazine is shown in Table 4. P-gp inhibitor capacity of some of these derivatives (**3f**, **3h**, **3m**) was comparable to that of verapamil.

As revealed by the above data, the 2-butanol part of phenothiazine derivatives **3** was essential for a potent P-gp inhibition. This part of the molecule contains a chirality center. As chirality of many compounds has an impact on their protein binding, we have investigated whether the use of stereoisomers of the most potent derivatives alters their inhibitor property. For this purpose, products of resolution of two derivatives (**3h**,**i**) each isolated as pure enantiomers ((+)-**3h**, (−)-**3h**, (+)-**3i**, (−)-**3i**) have been selected and their activity has been compared with that of the related racemic form as well as with verapamil. As shown in Figure 1 there was no significant difference in RH123 accumulation in the presence of either the racemic or any of the stereoisomer derivatives of these compounds.

Oxidation of the sulfur atom of the phenothiazine ring further improved the inhibitor potency of the molecules (Table 5). Two of these derivatives (**4h**, **16h**) proved to be significantly better P-gp inhibitors than verapamil.

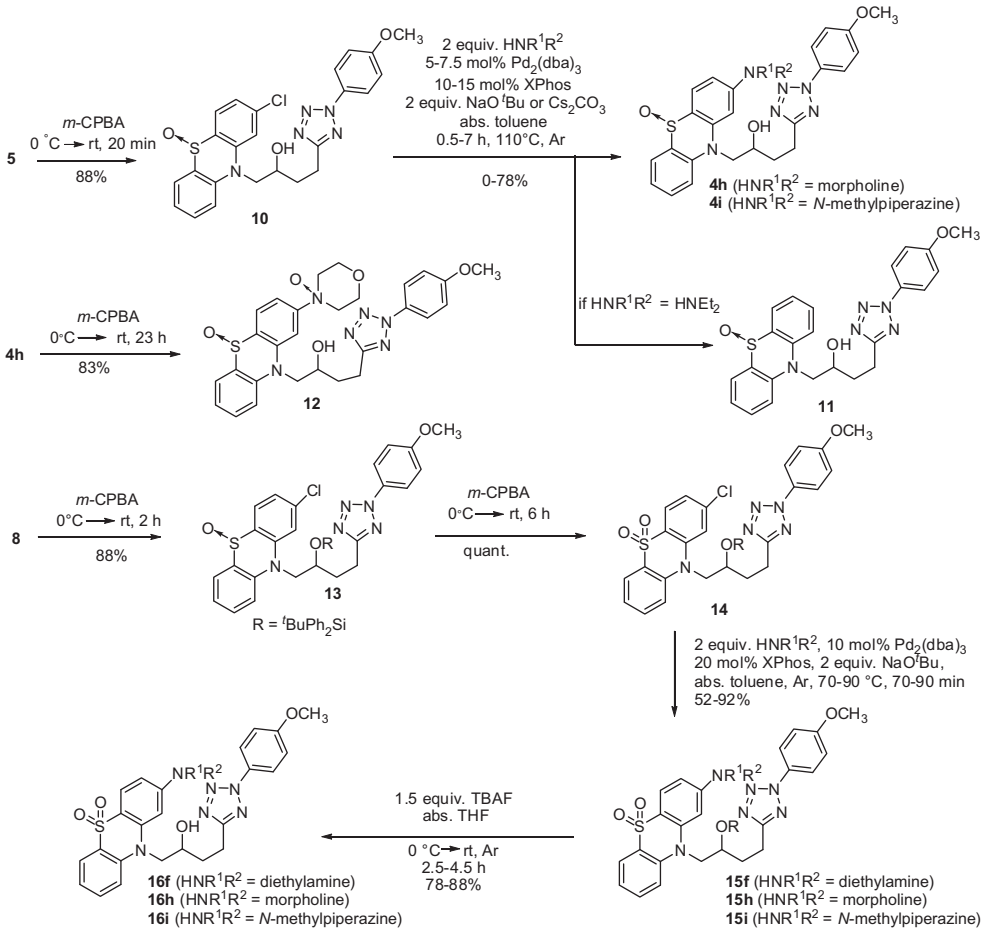
The concentration dependence concerning P-gp interactions of the most potent compounds was compared to that of verapamil. No significant difference was found between the effect of **3f**, **3h** and verapamil up to 50 μM (Fig. 2). In order to gain a more precise relationship between the inhibitor capacity and molecular structure of the derivatives, their influence at a lower (up to 10 mM) concentration range was also studied. No remarkable difference between the actions of this set of compounds was observed; the rate of inhibition was comparable to that of verapamil. In case of sulfoxide derivative (**4f**) obtained first as an unexpected product of hydroboration–oxidation, a slight, but significant increase in P-gp inhibition could be observed (Fig. 3).

This latter finding directed our attention to the study of the effect of oxidation of the sulfur atom in the phenothiazine ring as shown in Figure 4. The number of oxygen atoms attached to the sulfur atom had an impact on the interaction potential of the molecule. Compared to **3h**, one additional oxygen atom (i.e., the sulfoxide **4h**) slightly, but significantly, and a second oxygen atom (i.e., the sulfone **16h**) considerably increased the accumulation of RH123.

2.3. Cytotoxicity assays

MTT assay was used to assess cell viability, cytotoxicity. These assays were performed with the most potent P-gp inhibitor compounds (**3h**, **3f**, **3b**, **4h**, **16h**). The viability of the hepatocytes as shown in Figure 5 did not change, so the observed decrease of the P-gp activity was not due to cytotoxic effects in the presence of any of these derivatives.

Hepatocytes were treated for 3 h with 10 μM of **3h**, **3f**, **3b**, **4h**, **16h** or the vehicle (control), respectively. Data are shown as % of the control.



Scheme 3. Synthetic routes to preparation of sulfoxide and sulfone derivatives.

3. Conclusion

Hydroboration–oxidation of dienylphenothiazines and Buchwald–Hartwig cross-coupling reaction of 2-chloro derivatives allowed the synthesis a set of new *N*-2-hydroxybutylphenothia zines and their sulfoxides and sulfone derivatives. The structure of these compounds has been systematically modified at those positions that have been shown to have an impact on the rate of P-gp inhibitor activity of the molecule. The extent of inhibition by the most potent derivatives slightly exceeded that of verapamil, a well-known P-gp inhibitor. A high variety of efficacy was observed as a function of the quality of substituents on position 2 of the phenothiazine and the phenyltetrazole moiety. The *N*-2-hydroxybutyl chain proved to be essential for the interaction with P-gp. The sulfone derivative **16h** exhibited the highest efficacy. MTT assays revealed that the new MDR inhibitory compounds are not toxic.

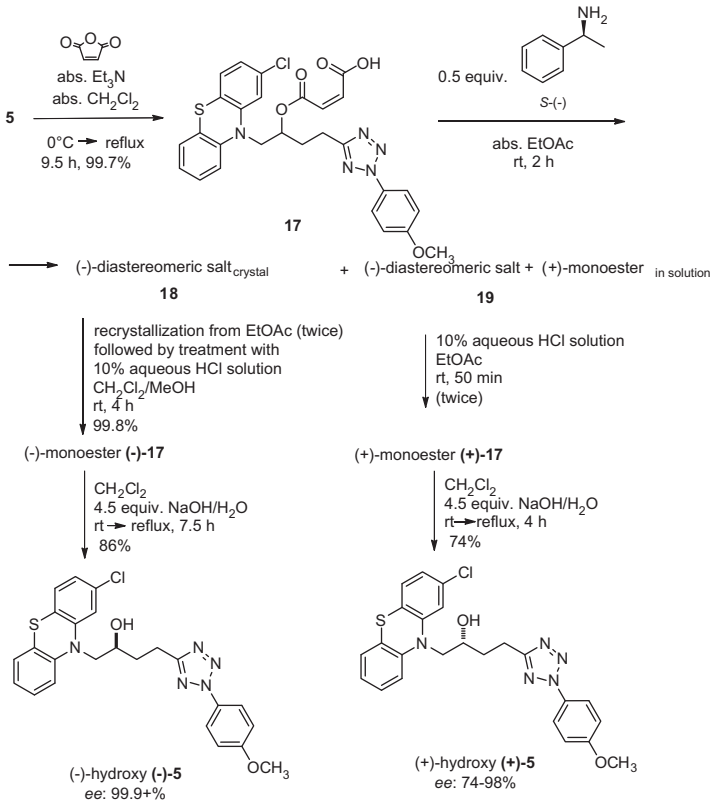
4. Experimental section

4.1. Cytotoxicity assays

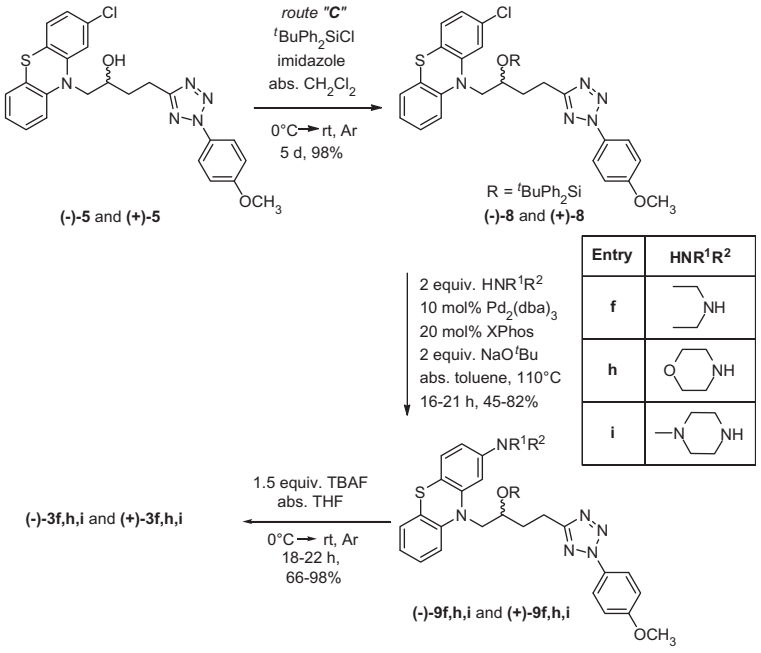
MTT is added directly to the culture medium and is reduced by metabolically active cells to insoluble purple formazan dye crystals. The absorbance of the sample is read directly in the wells at an optimal wavelength of 570 nm. The amount of formazan produced is in direct proportion to the viability of the cells. After treatment with the compounds indicated at 10 μM, or with the vehicle (control) for 3 h, hepatocytes were washed and incubated with 1 mg/mL MTT for 2 h. Then the cells were lysed with 1 mL of DMSO and the absorbance was measured at 570 nm using a microplate reader. Data are shown as % of the control.

4.2. Method for determination of P-gp inhibitor properties

P-gp interaction of the phenothiazine derivatives was studied in a conventional monolayer culture of primary rat hepatocytes. Hepatocytes were prepared from male Wistar rats (200–250 g) (Charles River, Budapest) by two-step, in situ liver collagenase perfusion according to the method of Seglen.[24] Cell viability (>90%) was determined by trypan blue exclusion. All procedures were approved by the Institutional Animal Care and Use Committee. Hepatocytes were plated at a density of 1.9×10^5 cells/cm^2 in 24-well plates precoated with rat tail collagen in Williams Medium E containing 5% of fetal calf serum, 100 nM insulin, 0.1 mg/mL gentamicin, 30 nM Na_2SeO_3, and 0.1 μM dexamethasone. Calf serum was present for the first 24 h then omitted. Cells were maintained at 37 °C in a humidified atmosphere of 95% air–5% CO_2. In 1 h after plating, and every day thereafter, the medium was changed to Williams Medium E supplemented with insulin, gentamicin, dexamethasone, Na_2SeO_3. The RH123 accumulation assay was performed as described previously,[12] briefly, at 4 days after plating cells were washed and preloaded with 5 μM RH123 in Williams' Medium E for 30 min. Then the hepatocytes were washed three times with an ice cold Hanks Balaced Salt Solution (HBSS) and incubated with RH123 free Williams' Medium E containing the



Scheme 4. Resolution of racemic **5** to enantiomers.



Scheme 5. Synthesis of (−)-**3f**,**h**,**i** and (+)-**3f**,**h**,**i** derivatives applying *route* '*C*.

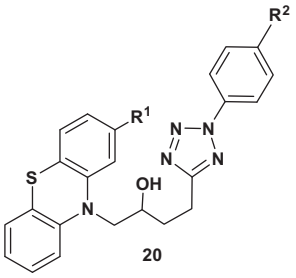
phenothiazine derivatives, verapamil at different concentrations, or the vehicle as control (0.1% DMSO), respectively for 3 h. Subsequently, the cells were washed with ice cold HBSS and were lysed with 0.5% of Triton X100/HBSS. The intracellular RH123 concentration was measured fluorimetrically at 519/538 nm.

The results are expressed as mean ± SD for all experiments. Triplicate experiments of three independent hepatocyte isolations were run, and four wells were used for each set of conditions. Statistical analysis was performed using the Student's *t*-test.

4.3. Chemistry

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet

Table 3
Comparison of the effects of R1 and R2 of derivatives **1**, **20a–e** on the RH123 accumulation



20

R^1	R^2	Compound	Inhibition of RH123 efflux (% of the effect of 10 μM verapamil)
H	Cl	**20a**[7]	<25
H	OCH_3	**20b**[7]	25<; <75
Cl	Cl	**20c**[7]	<25
Cl	OCH_3	**1**	25<; <75
CF_3	OCH_3	**20d**[7]	25<; <75
CF_3	COOEt	**20e**	<25

Table 4
Comparison of inhibition of RH123 accumulation by of *N*-hydroxyalkyl-2-aminophenothiazines **3a–m**

Compound	Inhibition of RH123 efflux (% of the effect of 10 μM verapamil)
3a	>75
3b	>75[a]
3c	25<; <75
3d	25<; <75
3e	25<; <75
3f	≈100[a]
3g	<25
3h	≈100[a]
3i	>75[a]
3j	<25
3k	25<; <75
3l	>75
3m	≈100

[a] Highest activity, concentration-dependence was also studied, see Figures 2–4.

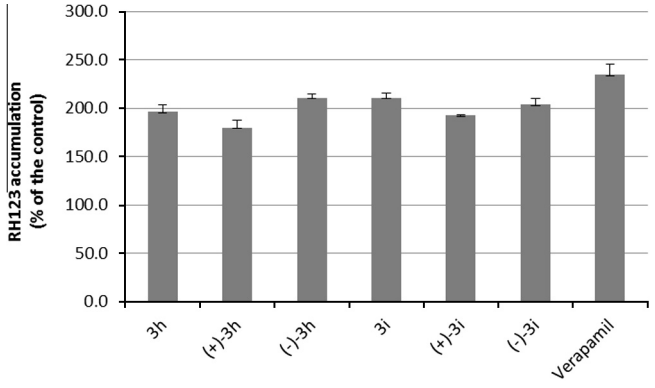


Figure 1. Comparison of P-gp interaction activity of racemic phenothiazines and their stereoisomer counterparts.

Table 5
Comparison of inhibition of RH123 accumulation by sulfoxide and sulfone derivatives of 2-aminopheno-thiazines **11**, **10**, **4f**,**h**,**i**, **16f**,**h**,**i**

Compound	Inhibition of RH123 efflux (% of the effect of 10 μM verapamil)
11	>75
10	>75
4f	>75
4h	>100[a]
4i	25<; <75
16f	>75
16h	>100[a]
16i	>75

[a] Highest activity, concentration-dependence was also studied, see Figures 2–4.

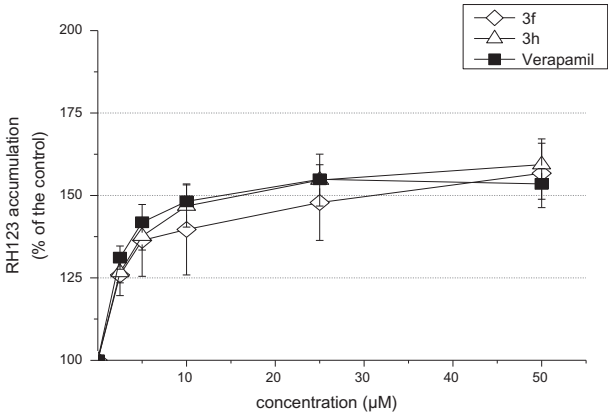


Figure 2. Comparison of RH123 accumulation in the presence of **3f**, **3h**, and verapamil.

Avatar 320 FT-IR spectrometer. NMR experiments were carried out on 300 MHz (for ^1H) and 400 MHz (for ^1H) Varian NMR SYSTEM spectrometers by using 5 mm Z gradient auto tunable probes. Measurements were performed at +25 °C in $CDCl_3$ or DMSO-d_6. ^1H and ^{13}C NMR spectra are referenced to residual solvent signals. For the complete ^1H, ^{13}C assignments standard 1D and homo and hetero-correlation 2D measurements were performed. The elemental analysis has been carried out with an Elementar Vario EL III apparatus (at the Analytical Laboratory for Organic Chemistry, Institute of Organic Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Pusztaszeri út 59, H-1025 Budapest, Hungary). The exact mass measurements were performed using a Q-TOF Premier mass spectrometer (Waters Corporation, 34 Maple St, Milford, MA, USA) in positive electrospray mode. Enantiomeric purities of the compounds were determined by chiral HPLC method. The chiral separation was performed with a system composed of a Jasco PU-980 pump, a Rheodyne 7125 injector (20 μl loop), a Jasco MD 2010 Plus UV/Vis photodiode-array detector (at 260 nm) and a ChromPass chromatographic software. Successful separation of compounds **3f**, **3h**, **3i**, **5** (–OH derivatives) and the protected –Cl (**8**) was performed on a Chiralpak AD column

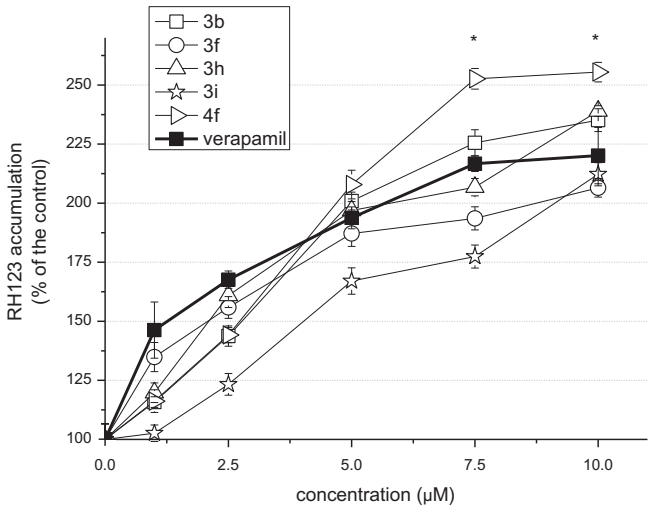


Figure 3. Comparison of RH123 accumulation in the presence of **3b**, **3f**, **3i**, **3h**, **4h**, and verapamil.

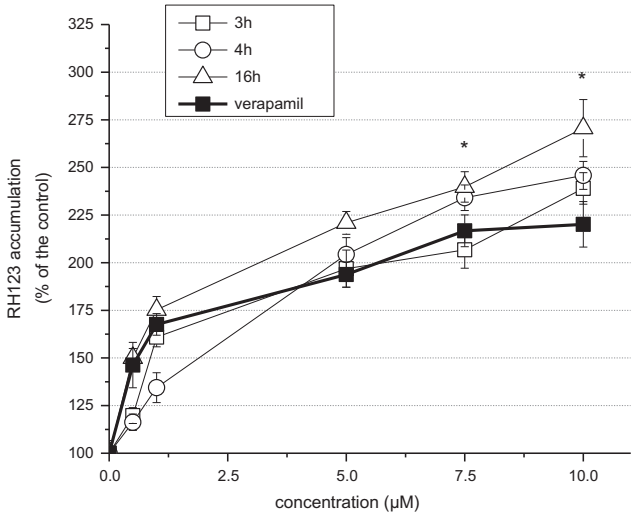


Figure 4. Comparison of RH123 accumulation in the presence of **3h**, **4h**, **16h**, and verapamil.

(250 × 4.6 mm I.D. Daicel Chemical Ind., Tokyo, Japan). The mobile phase was 70% *n*-hexane, 30% 2-propanol with 0.1% diethylamine and 98% *n*-hexane, 2% 2-propanol with 0.1% diethylamine for **8**, the flow rate was 1 mL/min. The basic protected compounds (**9f**, **9h**, **9i**) were analysed on a LUX-Amylose-2 column (250 × 4.6 mm I.D. Phenomenex Inc., USA). The mobile phase was 75% *n*-hexane, 25% 2-propanol with 0.1% diethylamine, the flow rate was 1 mL/min. Optical rotation values were determined on AA-10R and JASCO P-2000 polarimeters, (λ = 589 nm). Chromatographic separations were carried out on silica gel (60 H, Merck). Reactions were monitored with Merck silica gel 60 F254, TLC plates (0.25 mm thickness). $BH_3 \times Me_2S$ (borane–dimethyl sulfide complex) >90% in dimethyl sulfide was purchased from Sigma–Aldrich. All the chemicals and solvents were used as supplied.

4.3.1. General procedure for the synthesis of 1-(2-amino-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (3) derivatives by hydroboration–oxidation of dienes 2. *Route 'A'*

To a solution of the appropriate 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-10*H*-phenothiazin-2-amine (**2**, 4 mmol) in abs THF (40 mL) in a dried, round-bottomed flask equipped with a side arm and cooled to 0 °C in an argon atmosphere was added $BH_3 \times Me_2S$ (1.6 mL, 16 mmol) dropwise by injection. After addition, the resulting yellow suspension was allowed to warm up to rt and maintained at this temperature for prolongued time. After the completion of the reation (1 day, monitored by TLC), the reaction mixture was cooled to 0 °C with an ice bath, and treated with methanol (30 mL), 10% aqueous NaOH (2 mL) and H_2O_2 (30% aqueous solution, 2 mL). This mixture was then stirred at rt for 1 day. The solution was then poured onto ice cold water, neutralized with 10% aqueous HCl and extracted with dichloromethane (3 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel using the eluent dichloromethane then *n*-hexane:ethyl acetate = 2:1. The crude product (foam) was triturated with diethyl ether, the mixture was cooled whereupon a solid product deposited. The product was collected by filtration.

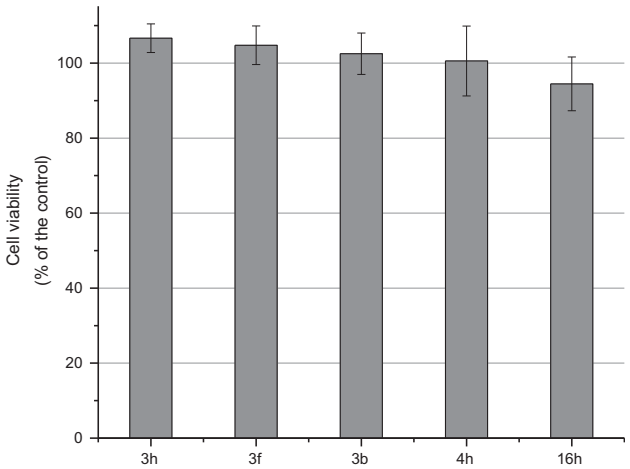


Figure 5. Results of the viability (MTT) assays.

4.3.2. General procedure for preparation of 1-(2-amino-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol derivatives (3a–k) as well as the related amides (3l,m) by debenzylation of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazin-2-amine/amide derivatives (7). *Route 'B'*

To the clear solution of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazin-2-amine/amide (**7**, 0.08 mmol) in ethanol (1.2 mL) was added concd HCl (1.2 mL) dropwise, very slowly and the reaction mixture was refluxed for 4–6 days. The mixture was concentrated under reduced pressure. The residue was dissolved in water (2 mL), neutralized with concd $NaHCO_3$ solution and extracted with dichloromethane (3 × 3 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 then 1:1 to give the final product as a solid.

4.3.3. General procedure for preparation of 1-(2-amino-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol derivatives (3a–k) as well as the related amides (3l,m) by desilylation of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine/amide derivatives (9). *Route 'C'*

To the solution 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine/amide (**9**, 0.14 mmol) in anhydrous THF (1 mL) in a dried,

round-bottomed flask equipped with a side arm and cooled to 0 °C in an argon atmosphere was added the solution of TBAF (0.20 mmol) in abs THF (1 mL). After 48 h, the reaction mixture was allowed to warm up to rt and the reaction the mixture was evaporated. The residue was purified by column chromatography on silica gel using the eluent chloroform:methanol = 50:1, then 20:1 to give the product.

4.3.4. 1-(2-{[2-(Dimethylamino)ethyl]amino}-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (3a)

According to *route* '*C*', this compound was obtained from *N*′-[10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-yl]-*N*,*N*-dimethylethane-1,2-diamine (**9a**, 0.11 g) as a beige amorphous solid, 76 mg (91%); mp 56–58 °C; (found: C, 63.01; H, 6.18; N, 18.38; $C_{28}H_{33}N_7O_2S$ requires C, 63.25; H, 6.26; N, 18.44); *m*/*z* (EI) $[M+H]^+$: 532.20 ($C_{28}H_{33}N_7O_2S$ requires 531.24); ν_{max} (KBr)/cm^{-1}: 3368, 2930, 1601, 1516 and 1464; δ_H (300 MHz, $CDCl_3$) 2.05 (1H, m), 2.21 (1H, m), 2.24 (6H, s), 2.47 (1H, m), 2.54 (2H, t, *J* = 7.8 Hz), 3.09–3.22 (4H, m), 3.85 (3H, s), 3.87 (1H, m), 4.07 (1H, m), 4.18 (1H, m), 4.25 (1H, m), 6.25–6.27 (2H, m), 6.89–7.19 (7H, m), 7.97 (2H, m); δ_C (75 MHz, $CDCl_3$) 21.9, 32.2, 41.1, 45.1 (2C), 53.8, 55.6, 57.8, 66.5, 101.9, 107.8, 113.0, 114.6 (2C), 116.1, 121.3 (2C), 122.8, 126.9, 127.6, 128.0, 128.2, 130.4, 145.5, 146.7, 148.6, 160.4, 166.5.

4.3.5. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-{2-[(2-morpholin-4-ylethyl)amino]-10*H*-phenothiazin-10-yl}butan-2-ol (3b)

According to *route* '*A*', this compound was obtained from 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-*N*-(2-morpholin-4-ylethyl)-10*H*-phenothiazin-2-amine (**2b**, 2.22 g) as yellow amorphous solid, 0.6 g (26%).

According to *route* '*C*', this compound was obtained from 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*-(2-morpholin-4-ylethyl)-10*H*-phenothiazin-2-amine (**9b**, 0.12 g) as yellow amorphous solid, 85 mg (84%); mp 65–68 °C; (found: C, 63.19; H, 6.06; N, 16.90; $C_{30}H_{35}N_7O_3S$ requires C, 62.81; H, 6.15; N, 17.09); *m*/*z* (EI) $[M+H]^+$: 574.10 ($C_{30}H_{35}N_7O_3S$ requires 573.25); ν_{max} (KBr)/cm^{-1}: 3374, 2933, 1601, 1515 and 1464; δ_H (300 MHz, $CDCl_3$) 2.03 (1H, m), 2.20 (1H, m), 2.34–2.43 (4H, m), 2.58 (2H, t, *J* = 5.9 Hz), 2.85 (1H, br s), 3.07–3.19 (4H, m), 3.68 (4H, t, *J* = 4.3 Hz), 3.86 (3H, s), 3.88 (1H, m), 4.04 (1H, m), 4.20 (1H, m), 4.22 (1H, m), 6.24–6.26 (2H, m), 6.89–7.02 (5H, m), 7.13 (2H, m), 7.95 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.1, 32.5, 40.3, 53.5 (2C), 54.0, 55.9, 57.2, 66.7, 67.1 (2C), 102.1, 108.1, 113.5, 114.9 (2C), 116.4, 121.6 (2C), 123.1, 127.2, 127.9, 128.2, 128.5, 135.0, 145.7, 147.0, 148.8, 160.6, 166.7.

4.3.6. 1-[2-(Benzylamino)-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (3c)

According to *route* '*A*', this compound was obtained from *N*-benzyl-10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-10*H*-phenothiazin-2-amine (**2c**, 2.10 g) as a brown oil, 0.65 g (30%).

According to *route* '*B*', this compound was obtained from *N*-benzyl-10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]-butyl}-10*H*-phenothiazin-2-amine (**7c**, 0.05 g, 0.08 mmol) as a brown oil, 42 mg (quant.); (found: C, 67.42; H, 5.83; N, 15.06; $C_{31}H_{30}N_6O_2S$ requires C, 67.61; H, 5.49; N, 15.26); HRMS calcd for $C_{31}H_{30}N_6O_2S$ 550.2151 found: 550.2151; *m*/*z*: 534 (87%), 506 (22), 464 (6), 385 (98), 352 (26), 330 (9), 303 (100), 267 (13), 213 (28), 185 (63), 160 (15), 123 (49) and 91 (74); ν_{max} (film)/cm^{-1}: 3381, 2928, 1600, 1515 and 1257; δ_H (300 MHz, $CDCl_3$) 1.97 (1H, m), 2.11 (1H, m), 2.66 (1H, br s), 3.06–3.17 (2H, m), 3.78 (1H, dd, *J* = 13.0, 9.0 Hz), 3.87 (3H, s), 3.95 (1H, dd, *J* = 13.0, 3.2 Hz), 4.07 (1H, m), 4.15 (1H, br s), 4.29 (2H, s), 6.22–6.29 (2H, m), 6.87–7.03 (5H, m), 7.09–7.19 (2H, m), 7.26–7.36 (5H, m), 7.96 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.1, 32.3, 48.6, 54.0, 55.9, 66.6, 102.1, 108.3, 113.7, 114.8 (2C), 116.3, 121.5 (2C), 123.1, 127.2, 127.5 (2C), 127.8, 128.1, 128.5, 128.9 (2C), 130.7, 139.4, 145.9, 146.6, 148.4 (2C), 160.6, 166.7.

4.3.7. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-{[(1*R*)-1-phenylethyl]amino}-10*H*-phenothiazin-10-yl)butan-2-ol (3d)

According to *route* '*A*', this compound was obtained from 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-*N*-[(1*R*)-1-phenylethyl]-10*H*-phenothiazin-2-amine (**2d**, 2.19 g) as beige amorphous solid, 1.04 g (46%); mixture of two diastereomers; mp 63–68 °C; (found: C, 68.15; H, 6.05; N, 14.65; $C_{32}H_{32}N_6O_2S$ requires C, 68.06; H, 5.71; N, 14.88); *m*/*z* (EI) $[M+H]^+$: 565.30 ($C_{32}H_{32}N_6O_2S$ requires 564.23); ν_{max} (KBr)/cm^{-1}: 3374, 2924, 1600, 1515 and 1466; δ_H (400 MHz, DMSO-d_6) 1.38 [1.37] (3H, d, *J* = 6.5 Hz, CH_3), 1.70 (1H, m, H3y), 2.00 [2.09] (1H, m, H3x), 2.88 (1H, m, H4y), 3.00 (1H, m, H4x), 3.66 (1H, m, H1y), 3.80 (1H, m, H1x), 3.83 [3.90] (1H, m, H2), 3.85 (3H, s, OCH_3), 4.43 [4.46] (1H, qd, *J* = 6.5, 6.2 Hz, NH–C*H*), 4.91 [4.95] (1H, d, *J* = 5.8 Hz, OH), 6.09 [6.12] (1H, dd, *J* = 8.6, 2.0 Hz, H3″), 6.19 [6.21] (1H, d, *J* = 6.2 Hz, NH), 6.27 (1H, d, *J* = 2.0 Hz, H1″), 6.71 (1H, d, *J* = 8.6 Hz, H4″), 6.86 (1H, dd, *J* = 7.8, 7.5 Hz, H7″), 7.00 (1H, d, *J* = 7.8 Hz, H9″), 7.05 (1H, d, *J* = 7.8 Hz, H6″), 7.11 (1H, dd, *J* = 7.8, 7.5 Hz, H8″), 7.15 (1H, m, H4‴), 7.16 (2H, m, H3′ + H5′), 7.27 (2H, m, H3‴ + H5‴), 7.35 (2H, m, H2‴ + H6‴), 7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 21.0 (C4), 24.5 [24.6] (CH_3), 33.0 (C3), 52.2 [52.1] (HN–CH), 52.7 (C1), 55.6 (OCH_3), 65.4 [65.3] (C2), 101.7 [101.5] (C1″), 107.4 [107.6] (C3″), 108.8 (C4a″), 115.0 (C3′ + C5′), 115.9 (C9″), 121.3 (C2′ + C6′), 122.0 (C7″), 125.6 (C5a″), 125.8 (C2‴ + C6‴), 126.4 (C4‴), 126.9 (C6″ + C8″), 127.3 (C4″), 128.3 (C3‴ + C5‴), 129.6 (C1′), 145.3 (C9a″), 146.0 (C1‴), 146.1 (C10a″), 148.1 (C2″), 160.1 (C4′), 166.5 ($C_{tetrazole}$).

4.3.8. 1-[2-(Butylamino)-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (3e)

According to *route* '*C*', this compound was obtained from *N*-butyl-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine (**9e**, 95 mg) as amorphous solid, 32 mg (49%); mp 114–115 °C; (found: C, 65.01; H, 6.39; N, 15.93; $C_{28}H_{32}N_6O_2S$ requires C, 65.09; H, 6.24; N, 16.27); *m*/*z* (EI) $[M+H]^+$: 517.50 ($C_{28}H_{32}N_6O_2S$ requires 516.23); ν_{max} (KBr)/cm^{-1}: 3403, 2956, 1601, 1517 and 1466; δ_H (300 MHz, $CDCl_3$) 0.94 (3H, t, *J* = 7.2 Hz), 1.36 (2H, m), 1.56 (2H, m), 2.13 (1H, m), 2.20 (1H, m), 2.86 (1H, br s), 3.02–3.26 (5H, m), 3.81 (1H, m), 3.84 (3H, s), 4.04 (1H, dd, *J* = 13.2, 3.0 Hz), 4.19 (1H, m), 6.22–6.24 (2H, m), 6.89–7.19 (7H, m), 7.97 (2H, m); δ_C (75 MHz, $CDCl_3$) 13.9, 20.2, 21.9, 31.5, 32.2, 43.8, 53.7, 55.6, 66.4, 101.7, 107.6, 112.8, 114.6 (2C), 116.1, 121.3 (2C), 122.8, 126.9, 127.6, 128.0, 128.2, 130.4, 145.5, 146.6, 148.7, 160.4, 166.4.

4.3.9. 1-[2-(Diethylamino)-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (3f)

According to *route* '*A*', this compound was obtained from *N*,*N*-diethyl-10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-10*H*-phenothiazin-2-amine (**2f**, 2.0 g) as white amorphous solid, 0.48 g (23%).

According to *route* '*C*', this compound was obtained from 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine (**9f**, 0.11 g, 0.14 mmol) as white amorphous solid, 0.14 g (86%); mp 51–53 °C; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention times: 9.5 min, 22.1 min; (found: C, 65.01; H, 6.23; N, 15.90; $C_{28}H_{32}N_6O_2S$ requires C, 65.09; H, 6.24;

N, 16.27); *m*/*z* (EI) $[M+H]^+$: 517.50 ($C_{28}H_{32}N_6O_2S$ requires 516.23); ν_{max} (KBr)/cm^{-1}: 2967, 2929, 1598, 1516 and 1467; δ_H (400 MHz, DMSO-d_6) 1.03 (6H, t, *J* = 7.1 Hz, $N(CH_2)_2(CH_3)_2$), 1.76 (1H, dddd, *J* = 13.5, 9.3, 8.2, 5.4 Hz, H3y), 2.12 (1H, m, H3x), 2.94 (1H, ddd, *J* = 15.3, 8.2, 7.4 Hz, H4y), 3.03 (1H, ddd, *J* = 15.3, 9.1, 5.4 Hz, H4x), 3.28 (4H, q, *J* = 7.1 Hz, $N(CH_2)_2(CH_3)_2$), 3.79 (1H, m, H1y), 3.83 (3H, s, OCH_3), 3.96 (1H, m, H1x), 4.00 (1H, m, H2), 5.02 (1H, d, *J* = 5.4 Hz, OH), 6.27 (1H, m, H3″), 6.29 (1H, m, H1″), 6.86 (1H, d, *J* = 8.0 Hz, H4″), 6.88 (1H, t, *J* = 7.5 Hz, H7″), 7.05 (1H, d, *J* = 7.5 Hz, H9″), 7.10 (1H, d, *J* = 7.5 Hz, H6″), 7.14 (1H, m, H8″), 7.16 (2H, m, H3′ + H5′), 7.88 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 12.4 ($N(CH_2)_2(CH_3)_2$, 2C), 21.0 (C4), 33.1 (C3), 43.8 ($N(CH_2)_2(CH_3)_2$, 2C), 53.0 (C1), 55.6 (OCH_3), 65.6 (C2), 100.5 (C1″), 106.5 (C3″), 108.5 (C4a″), 114.9 (C3′ + C5′), 116.1 (C9″), 121.3 (C2′ + C6′), 122.1 (C7″), 125.8 (C5a″), 126.9 (C6″ + C8″), 127.6 (C4″), 129.6 (C1′), 145.4 (C9a″), 146.4 (C10a″), 147.5 (C2″), 160.0 (C4′), 166.4 ($C_{tetrazole}$).

4.3.10. 1-[2-(Diphenylamino)-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (3g)

According to *route* '*A*', this compound was obtained from 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-*N*,*N*-diphenyl-10*H*-phenothiazin-2-amine (**2g**, 2.38 g) as beige amorphous solid, 1.20 g (49%); mp 70–74 °C, (found: C, 70.51; H, 5.37; N, 13.55; $C_{36}H_{32}N_6O_2S$ requires C, 70.57; H, 5.26; N, 13.72); HRMS calcd for $C_{36}H_{32}N_6O_2S$ 612.2307 found: 612.2289; *m*/*z*: 612 (23%), 584 (62), 569 (3), 488 (7), 463 (42), 436 (2), 408 (2), 379 (100), 365 (42), 347 (28), 332 (19), 304 (5), 292 (9), 269 (14), 255 (12), 239 (5), 225 (9), 210 (13), 186 (6), 167 (12), 136 (4), 122 (38), 108 (22), 91 (15), 77 (23), 63 (5) and 51 (9); ν_{max} (KBr)/cm^{-1}: 2929, 1580, 1516, 1456 and 1256; δ_H (400 MHz, DMSO-d_6) 1.69 (1H, m), 2.00 (1H, m), 2.88 (1H, m), 2.98 (1H, m), 3.61 (1H, dd, *J* = 13.5, 6.2 Hz), 3.74 (1H, dd, *J* = 13.5, 5.6 Hz), 3.83 (1H, m), 3.84 (3H, s), 4.94 (1H, d, *J* = 5.7 Hz), 6.53–6.56 (2H, m), 6.93–7.03 (9H, m), 7.14–7.26 (8H, m), 7.89 (2H, m); δ_C (100 MHz, DMSO-d_6) 21.0, 32.9, 52.9, 55.6, 65.3, 112.0, 115.0 (2C), 116.3, 118.0, 118.2, 121.2 (2C), 122.6 (2C), 122.9, 123.6 (4C), 124.5, 127.1, 127.4, 127.8, 129.4 (4C), 129.6, 145.0, 146.0, 147.0 (2C), 147.1, 160.1, 166.4.

4.3.11. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-morpholin-4-yl-10*H*-phenothiazin-10-yl)butan-2-ol (3h)

According to *route* '*A*', this compound was obtained from 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-2-morpholin-4-yl-10*H*-phenothiazine (**2h**, 2.05 g, 0.49 mmol) as white crystals, 0.70 g (33%).

According to *route* '*C*', this compound was obtained from 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine (**9h**, 0.11 g) as white crystals, 0.14 g (87%); mp 64–68 °C; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention times: 11.8 min, 17.4 min; (found: C, 63.37; H, 5.80; N, 15.48; $C_{28}H_{30}N_6O_3S$ requires C, 63.38; H, 5.70; N, 15.84); *m*/*z* (EI) $[M+H]^+$: 531.40 ($C_{28}H_{30}N_6O_3S$ requires 530.21); ν_{max} (KBr)/cm^{-1}: 3307, 2959, 1596, 1516 and 1466; δ_H (300 MHz, $CDCl_3$) 2.06 (1H, m), 2.21 (1H, m), 2.77 (1H, br s), 3.09–3.18 (6H, m), 3.83–4.19 (6H, m), 3.89 (3H, s), 3.95 (1H, br s), 6.45–6.58 (2H, m), 6.91–7.20 (7H, m), 7.97 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.0, 32.4, 49.9 (2C), 54.2, 55.9, 66.6, 67.0 (2C), 105.1, 111.2, 114.9 (2C), 116.5, 117.2, 121.5 (2C), 123.3, 127.4, 127.7, 127.9, 128.3, 130.6, 145.6, 146.7, 151.7, 160.6, 166.6.

4.3.12. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-[2-(4-methylpiperazin-1-yl)-10*H*-phenothiazin-10-yl]butan-2-ol (3i)

According to *route* '*A*', this compound was obtained from 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine (**2i**, 2.01 g) as a brown oil, 1.06 g (49%).

According to *route* '*B*', this compound was obtained from 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine (**7i**, 0.32 g, 0.50 mmol) as a brown oil, 0.09 g (33%).

According to *route* '*C*', this compound was obtained from 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine (**9i**, 51 mg) as a brown oil, 47 mg (64%); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention times: 17.3, 23.8 min; (found: C, 64.06; H, 6.18; N, 17.91; $C_{29}H_{33}N_7O_2S$ requires C, 64.06; H, 6.12; N, 18.03); HRMS calcd for $C_{29}H_{33}N_7O_2S$ 543.2416 found: 543.2434; *m*/*z*: 543 (54%), 515 (70), 464 (26), 394 (47), 310 (83), 239 (29), 207 (38), 167 (18), 108 (56) and 70 (87); ν_{max} (film)/cm^{-1}: 2966, 2843, 1594, 1514 and 1257; δ_H (300 MHz, $CDCl_3$) 2.06 (1H, m), 2.26 (1H, m), 2.34 (3H, s), 2.54 (4H, t, *J* = 5.1 Hz), 2.80 (1H, br s), 3.10–3.24 (6H, m), 3.87 (1H, m), 3.88 (3H, s), 4.07 (1H, dd, *J* = 13.5, 3.6 Hz), 4.20 (1H, m), 6.52–6.56 (2H, m), 6.90–7.20 (7H, m), 7.98 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.1, 32.4, 46.3, 49.6 (2C), 54.2, 55.2 (2C), 55.9, 66.7, 105.4, 111.5, 114.9 (2C), 116.5, 116.7, 121.6 (2C), 123.2, 127.3, 127.9, 128.0, 128.2, 130.9, 145.6, 146.7, 151.8, 160.6, 166.6.

4.3.13. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-piperidin-1-yl-10*H*-phenothiazin-10-yl)butan-2-ol (3j)

According to *route* '*A*', this compound was obtained from 10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-2-piperidin-1-yl-10*H*-phenothiazin (**2j**, 2.0 g) as beige amorphous solid, 0.91 g (44%); mp 63–67 °C; (found: C, 65.81; H, 6.31; N, 15.50; $C_{29}H_{32}N_6O_2S$ requires C, 65.88; H, 6.10; N, 15.90); HRMS calcd for $C_{29}H_{32}N_6O_2S$ 528.2307 found: 528.2314; *m*/*z*: 528 (79%), 500 (50), 485 (2), 379 (22), 346 (17), 307 (4), 295 (100), 281 (95), 263 (29), 225 (11), 205 (16), 179 (5), 137 (4), 122 (30), 106 (11), 92 (4), 80 (10) and 65 (4); ν_{max} (KBr)/cm^{-1}: 2931, 1595, 1516, 1464 and 1256; δ_H (300 MHz, $CDCl_3$) 1.56 (2H, m), 1.68 (4H, m), 2.05 (1H, m), 2.24 (1H, m), 2.78 (1H, br s), 3.06–3.25 (6H, m), 3.84 (1H, m), 3.86 (3H, s), 4.04–4.21 (2H, m), 6.52–6.57 (2H, m), 6.93–7.20 (7H, m), 7.99 (2H, m); δ_C (75 MHz, $CDCl_3$) 21.9, 24.9, 25.8 (2C), 32.2, 51.0 (2C), 53.8, 55.6, 66.4, 105.6, 111.8, 114.6 (2C), 115.8, 116.2, 121.3 (2C), 122.9, 127.0, 127.7, 127.8, 127.9, 132.0, 145.4, 146.3, 152.5, 160.4, 166.4.

4.3.14. 4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-pyrrolidin-1-yl-10*H*-phenothiazin-10-yl)butan-2-ol (3k)

According to *route* '*B*', this compound was obtained from 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-pyrrolidin-1-yl-10*H*-phenothiazine (**7k**, 50 mg) as brown amorphous solid, 26 mg (62%); mp 154–157 °C; (found: C, 64.99; H, 6.01; N, 15.93; $C_{28}H_{30}N_6O_2S$ requires C, 65.35; H, 5.88; N, 16.33), *m*/*z* (EI) $[M+Na]^+$: 536.30 ($C_{28}H_{30}N_6O_2S$ requires 514.64); ν_{max} (KBr)/cm^{-1}: 3345, 2852, 1598, 1515 and 1257; δ_H (300 MHz, $CDCl_3$) 1.96–2.09 (5H, m), 2.21 (1H, m), 2.85 (1H, br s), 3.13–3.22 (6H, m), 3.88 (3H, s), 3.91 (1H, m), 4.09 (1H, dd, *J* = 13.5, 3.3 Hz), 4.23 (1H, m), 6.14–6.21 (2H, m), 6.89–7.29 (7H, m), 7.98 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.1, 25.6 (2C), 32.4, 48.0 (2C), 54.1, 55.9, 66.7, 100.8, 107.3, 111.4, 114.8 (2C), 116.4, 121.5 (2C), 123.0, 127.1, 127.8, 128.3, 128.5, 130.7, 145.9, 146.9, 148.3, 160.6, 166.7.

4.3.15. *N*-(10-{2-Hydroxy-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazin-2-yl)formamide (3l) (*E*/*Z* isomers)

According to *route* '*C*', this compound was obtained from *N*-[10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-yl]formamide (**9l**, 0.10 g, 0.14 mmol) as grey amorphous solid, 0.06 g (99%); mp 75–78 °C;

(found: C, 61.16; H, 4.61; N, 17.02; $C_{25}H_{24}N_6O_3S$ requires C, 61.46; H, 4.95; N, 17.20); *m*/*z* (EI) $[M+H]^+$: 489.20 ($C_{25}H_{24}N_6O_3S$ requires 488.16); ν_{max} (KBr)/cm^{-1}: 3266, 1685, 1591, 1515 and 1461; δ_H (300 MHz, $CDCl_3$) 2.07 (1H, m), 2.21 (1H, m), 2.84 (1H, br s), 3.16 (2H, m), 3.86 (3H, s), 3.88 (1H, m), 4.07 (1H, m), 4.17 (1H, m), 6.67 [6.70] (1H, s), 6.91–7.58 (9H, m), 7.96 (2H, m), 8.33 [8.64] (1H, d, *J* = 1.1, [*J* = 11.0] Hz); δ_C (75 MHz, $CDCl_3$) 22.1, 32.5, 54.1, 55.9, 66.6, 108.7 [108.0], 114.6 [113.4], 114.9 (2C), 116.4, 116.5, 121.5 (2C), 123.5, 123.8, 127.7, 127.8, 128.0, 128.7, 136.9, 145.3 [145.0], 146.0 [146.9], 159.1, 162.3 [160.7], 166.6 [166.4].

4.3.16. *N*-(10-{2-Hydroxy-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazin-2-yl)acetamide (3m)

According to *route* '*C*', this compound was obtained from *N*-[10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-yl]acetamide (**9m**, 0.10 g, 0.14 mmol) as grey amorphous solid, 65 mg (96%); mp 99–100 °C; (found: C, 62.04; H, 4.99; N, 16.56; $C_{26}H_{26}N_6O_3S$ requires C, 62.13; H, 5.21; N, 16.72); *m*/*z* (EI) $[M+H]^+$: 503.30 ($C_{26}H_{26}N_6O_3S$ requires 502.18); ν_{max}(KBr)/cm^{-1}: 3306, 2934, 1666, 1515 and 1462; δ_H (400 MHz, DMSO-d_6) 1.77 (1H, dddd, *J* = 14.1, 9.0, 8.4, 5.4 Hz, H3y), 2.00 (3H, s, CH_3), 2.12 (1H, m, H3x), 2.94 (1H, ddd, *J* = 14.8, 8.4, 7.4 Hz, H4y), 3.05 (1H, ddd, *J* = 14.8, 8.4, 5.4 Hz, H4x), 3.77 (1H, dd, *J* = 13.6, 6.5 Hz, H1y), 3.84 (3H, s, OCH_3), 3.92 (1H, dd, *J* = 13.6, 5.8 Hz, H1x), 4.00 (1H, m, H2), 5.04 (1H, d, *J* = 5.5 Hz, OH), 6.92 (1H, m, H7″), 7.03 (1H, d, *J* = 8.0 Hz, H4″), 7.08 (1H, d, *J* = 8.1 Hz, H9″), 7.12 (1H, dd, *J* = 7.8, 1.3 Hz, H6″), 7.15–7.16 (4H, m, H3′ + H5′ + H3″ + H8″), 7.40 (1H, d, *J* = 1.3 Hz, H1″), 7.87 (2H, m, H2′ + H6′), 9.90 (1H, s, NH); δ_C (100 MHz, DMSO-d_6) 20.9 (C4), 23.9 (O=C–CH_3), 33.0 (C3), 52.9 (C1), 55.6 (OCH_3), 65.3 (C2), 107.1 (C1″), 113.2 (C3″), 115.0 (C3′ + C5′), 116.2 (C9″), 117.6 (C2″), 121.3 (C2′ + C6′), 122.6 (C7″), 124.6 (C5a″), 127.0 (C6″), 127.1 (C4″), 127.3 (C8″), 129.6 (C1′), 139.2 (C4a″), 144.9 (C9a″), 145.5 (C10a″), 160.0 (C4′), 166.4 ($C_{tetrazole}$), 168.3 (O=C–CH_3).

4.3.17. 1-[2-(Diethylamino)-5-oxido-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (4f)

This compound was obtained from the hydroboration–oxidation of *N*,*N*-diethyl-10-{(1*E*,3*Z*)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]buta-1,3-dien-1-yl}-10*H*-phenothiazin-2-amine[13a] (**2f**, 0.21 g, 0.42 mmol) as yellow amorphous solid; 0.15 g (67%); the mixture of two diastereomers; mp 76–80 °C; (found: C, 63.01; H, 5.90; N, 15.66; $C_{28}H_{32}N_6O_3S$ requires C, 63.14; H, 6.06; N, 15.78); *m*/*z* (EI) $[M-N_2]^+$: 504.00 ($C_{28}H_{32}N_6O_3S$ requires 532.23); ν_{max} (KBr)/cm^{-1}: 3301, 2968, 1590, 1516 and 1466; δ_H (400 MHz, DMSO-d_6) 1.12 (6H, m, $N(CH_2)_2(CH_3)_2$), 1.84 (1H, m, H3y), 2.06 (1H, m, H3x), 2.98 (1H, m, H4y), 3.03 (1H, m, H4x), 3.43 (4H, m, $N(CH_2)_2(CH_3)_2$), 3.86 (3H, s, OCH_3), 4.07 (1H, m, H2), 4.30 (1H, m, H1y), 4.44 (1H, m, H1x), 5.00 (1H, br s, OH), 6.58 (1H, m, H3″), 6.89 [6.56] (1H, m, H1″), 7.16 (2H, m, H3′ + H5′), 7.19 (1H, m, H9″), 7.57 (1H, m, H7″), 7.60 (1H, m, H8″), 7.61 [7.87] (1H, m, H4″), 7.81 (1H, m, H6″), 7.93 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 12.3 ($N(CH_2)_2(CH_3)_2$, 2C), 21.1 (C4), 32.3 (C3), 44.0 ($N(CH_2)_2(CH_3)_2$, 2C), 54.4 [54.3] (C1), 55.6 (OCH_3), 67.4 [67.2] (C2), 98.9 [97.9] (C1″), 106.3 [106.4] (C3″), 113.1 [113.0] (C4a″), 115.0 (C3′ + C5′), 117.8 [118.6] (C4″), 121.2 (C9″), 121.3 (C2′ + C6′), 126.6 [126.8] (C5a″), 129.6 (C6″), 129.7 (C1′), 131.7 (C7″), 131.8 (C8″), 140.0 [139.0] (C9a″), 141.7 [140.7] (C10a″), 150.7 (C2″), 160.1 (C4′), 166.4 ($C_{tetrazole}$).

4.3.18. General procedure for preparation of 1-(2-amino)-5-oxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol derivatives (4 and 11)

A round-bottomed flask was charged with Pd-catalyst: $Pd_2(dba)_3$ or $Pd(OAc)_2$ (5–7.5 mol %), ligand: XPhos (10–15 mol %), 1-(2-chloro-5-oxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol[12] (**10**), secondary amine, base: NaO^{t}Bu or Cs_2CO_3, and dry toluene (5 mL). The flask was flushed with argon for 5 min. The resulting mixture was heated under reflux with magnetic stirring for 0.5–7 h. After cooling down to rt the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 2:1 and 1:1 and the crude product was recrystallized from methanol to give the final product as yellow-white crystals.

4.3.19. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-morpholin-4-yl-5-oxido-10*H*-phenothiazin-10-yl)butan-2-ol (4h)

This compound was obtained from the reaction of 1-(2-chloro-5-oxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (**10**, 0.30 g, 0.61 mmol), $Pd_2(dba)_3$ (0.03 g, 0.03 mmol, 5 mol %), XPhos (0.03 g, 0.06 mmol, 10 mol %), NaO^{t}Bu (0.12 g, 1.21 mmol), and morpholine (0.11 mL, 1.21 mmol). The reaction time was 0.5 h. After recrystallization, the white-yellow crystals were collected by filtration, 0.26 g (78%); mp 88–90 °C; (found: C, 61.15; H, 5.64; N, 14.99; $C_{28}H_{30}N_6O_4S$ requires C, 61.52; H, 5.53; N, 15.37); *m*/*z* (EI) $[M+H]^+$: 547.40 ($C_{28}H_{30}N_6O_4S$ requires 546.20); ν_{max} (KBr)/cm^{-1}: 3274, 2926, 1589, 1516 and 1256; δ_H (400 MHz, DMSO-d_6) 1.86 (1H, m, H3y), 2.06 (1H, m, H3x), 2.97 (1H, m, H4y), 3.06 (1H, m, H4x), 3.29 (4H, m, N–$(CH_2)_2$), 3.74 (4H, m, O–$(CH_2)_2$), 3.84 (3H, s, OCH_3), 4.05 (1H, m, H2), 4.34 (1H, m, H1y), 4.48 (1H, m, H1x), 5.17 (1H, br s, OH), 6.89 (1H, m, H3″), 6.97 [7.25] (1H, m, H1″), 7.16 (2H, m, H3′ + H5′), 7.22 (1H, m, H7″), 7.58 [7.61] (1H, m, H8″), 7.70 (1H, m, H4″), 7.85 (1H, m, H6″), 7.86 [7.65] (1H, m, H9″), 7.92 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 21.0 (C4), 32.0 (C3), 47.4 (N–$(CH_2)_2$, 2C), 54.0 [54.2] (C1), 55.6 (OCH_3), 65.9 (O–$(CH_2)_2$, 2C), 67.2 [67.3] (C2), 102.0 [102.7] (C1″), 109.1 [109.3] (C3″), 115.0 (C3′ + C5′), 116.5 (C4a″), 118.5 [118.0] (C9″), 121.3 (C2′ + C6′), 121.5 (C7″), 127.2 (C5a″), 129.6 (C1′), 129.8 (C6″), 131.1 (C4″), 132.1 [132.3] (C8″), 138.8 (C9a″), 140.4 (C10a″), 154.2 (C2″), 160.1 (C4′), 166.4 ($C_{tetrazole}$).

The same product was isolated from the reaction of 4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)-1-(2-morpholino-10*H*-phenothiazin-10-yl)butan-2-ol (**3h**, 0.04 g, 0.08 mmol) and *m*-CPBA (0.02 g, 0.11 mmol) in abs dichloromethane (1 mL) to give white-yellow crystals, 0.04 g (98%).

4.3.20. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-[2-(4-methylpiperazin-1-yl)-5-oxido-10*H*-phenothiazin-10-yl]butan-2-ol (4i)

This compound was obtained from the reaction of $Pd(OAc)_2$ (0.01 g, 0.05 mmol, 7.5 mol %), XPhos (0.04 g, 0.09 mmol, 15 mol %), NaO^{t}Bu (0.12 g, 1.21 mmol), 1-(2-chloro-5-oxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]-butan-2-ol (**10**, 0.30 g, 0.61 mmol) and *N*-methylpiperazine (0.14 mL, 1.21 mmol). The reaction time was 0.5 h. After recrystallization, the white-yellow crystals were collected by filtration, 73 mg (22%); mp 211–214 °C; (found: C, 62.20; H, 5.69; N, 17.21; $C_{29}H_{33}N_7O_3S$ requires C, 62.23; H, 5.94; N, 17.52); *m*/*z* (EI) $[M+H]^+$: 560.20 ($C_{29}H_{33}N_7O_3S$ requires 559.24); ν_{max} (KBr)/cm^{-1}: 3285, 2950, 1589, 1516 and 1255; δ_H (400 MHz, DMSO-d_6) 1.85 (1H, m, H3y), 2.04 (1H, m, H3x), 2.22 (3H, s, CH_3), 2.42 (4H, m, H_3C–N–$(CH_2)_2$), 3.00 (1H, ddd, *J* = 15.4, 8.6, 7.6 Hz, H4y), 3.06 (1H, ddd, *J* = 15.4, 9.4. 5.4 Hz, H4x), 3.34 (4H, m, N–$(CH_2)_2$), 3.85 (3H, s, OCH_3), 4.03 (1H, m, H2), 4.36 (1H, dd, *J* = 14.4, 8.2 Hz, H1y), 4.44 (1H, dd, *J* = 14.4, 3.5 Hz, H1x), 4.86 (1H, d, *J* = 3.5 Hz, OH), 6.86 (1H, dd, *J* = 8.5, 1.3 Hz, H3″), 6.94 (1H, d, *J* = 1.3 Hz, H1″), 7.18 (2H, m, H3′ + H5′), 7.22 (1H, dd, *J* = 7.9, 7.1 Hz, H7″), 7.59 (1H, ddd, *J* = 8.4, 7.1, 1.4 Hz, H8″), 7.67 (1H, d, *J* = 8.5 Hz, H4″), 7.85 (1H, dd, *J* = 7.9, 1.4, H6″), 7.86 (1H, d, *J* = 8.4 Hz, H9″),

7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 21.0 (C4), 32.0 (C3), 45.7 (CH_3), 47.1 (N–(CH_2)$_2$, 2C), 54.0 (C1), 54.3 (H_3C–N–(CH_2)$_2$, 2C), 55.6 (OCH_3), 67.2 (C2), 102.0 (C1″), 109.3 (C3″), 115.0 (C3′ + C5′), 116.0 (C4a″), 118.6 (C9″), 121.3 (C2′ + C6′), 121.6 (C7″), 127.2 (C5a″), 129.6 (C1′), 129.7 (C6″), 131.1 (C4″), 132.0 (C8″), 138.8 (C9a″), 141.3 (C10a″), 154.0 (C2″), 160.1 (C4′), 166.4 ($C_{tetrazole}$).

4.3.21. 1-(2-Chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (5)

This compound was synthesized according to the literature procedure.[12]

4.3.22. 10-{2-(Benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (6)

To a solution of 1-(2-chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (**5**, 0.30 g, 0.63 mmol) in abs DMF (5 mL) in a dried, round-bottomed flask equipped with a side arm and cooled to 0 °C in an argon atmosphere was added sodium hydride (60%, 0.30 g, 7.65 mmol). The reaction mixture became a suspension. To this suspension was added benzyl bromide (0.66 mL, 5.63 mmol) dropwise and the starting suspension turned to a clear solution. This mixture was then stirred at rt for 2.5 h, then the solvent was removed in vacuo. The residue was dissolved in water (20 mL), and was neutralized by saturated NH_4Cl solution. After extraction with dichloromethane (3 × 10 mL), the combined organic phase was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 4:1. The crude product was recrystallized from *n*-hexane and the white crystals were collected by filtration, 0.27 g (75%); mp 114–116 °C; (found: C, 65.22; H, 4.89; N, 12.11; $C_{31}H_{28}ClN_5O_2S$ requires C, 65.31; H, 4.95; N, 12.28); ν_{max} (KBr)/cm^{-1}: 3410, 2960, 1515, 1454 and 1252; δ_H (300 MHz, $CDCl_3$) 2.11 (1H, m), 2.54 (1H, m), 3.02–3.11 (2H, m), 3.85 (3H, s), 3.92 (1H, m), 4.07 (2H, m), 4.58 (1H, d, *J* = 11.1 Hz), 4.67 (1H, d, *J* = 11.1 Hz), 6.79–7.30 (14H, m), 7.90 (2H, m); δ_C (75 MHz, $CDCl_3$) 22.4, 31.2, 51.8, 55.8, 72.9, 73.8, 114.7 (2C), 116.2, 116.3, 121.4 (2C), 122.7, 123.4, 124.5, 125.7, 127.6, 127.9 (2C), 128.3 (2C), 128.5, 129.3, 130.5, 130.8, 133.6, 138.3, 144.7, 146.8, 160.5, 166.4.

4.3.23. General procedure for preparation of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazine-2-amine/amide derivatives (7) applying Buchwald–Hartwig cross-coupling reaction

A round-bottomed flask was charged with Pd-catalyst: $Pd_2(dba)_3$ (7.5 mol %), ligand: XPhos (15 mol %), 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (**6**), the appropriate amine/amide, base: NaO^{t}Bu or K_2CO_3, and dry toluene (5 mL). The flask was flushed with argon for 5 min. The resulting mixture was heated under reflux with magnetic stirring for 1.5–43 h. After cooling down to rt the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 2:1 and 1:1 to give the final product.

4.3.24. *N*-Benzyl-10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazin-2-amine (7c)

This compound was obtained from the reaction of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (**6**, 0.30 g, 0.52 mmol) and benzylamine (0.11 mL, 1.00 mmol) to give the product as brown amorphous solid, 0.25 g (67%). The reaction time was 1.5 h; mp 40–45 °C; (found: C, 71.28; H, 5.70; N, 13.05; $C_{38}H_{36}N_6O_2S$ requires C, 71.22; H, 5.66; N, 13.11); HRMS calcd for $C_{38}H_{36}N_6O_2S$ 640.2620 found: 640.2592; *m*/*z*: 640 (2%), 612 (14), 491 (75), 458 (2), 401 (5), 342 (2), 317 (75), 226 (25), 186 (27), 123 (27) and 91 (100); ν_{max} (KBr)/cm^{-1}: 2927, 2853, 1515, 1453 and 1256; δ_H (400 MHz, DMSO-d_6) 1.90 (1H, m, H3y), 2.13 (1H, m, H3x), 2.90 (1H, m, H4y), 2.98 (1H, m, H4x), 3.85 (3H, s, OCH_3), 3.88 (1H, m, H1y), 3.90 (1H, m, H2), 4.05 (1H, m, H1x), 4.25 (2H, m, NH–CH_2), 4.43 (1H, d, *J* = 12.0 Hz, O–CH1y), 4.67 (1H, d, *J* = 12.0 Hz, O–CH1x), 6.25–6.28 (2H, m, H3″ + NH), 6.37 (1H, d, *J* = 2.1 Hz, H1″), 6.83 (1H, d, *J* = 8.2 Hz, H4″), 6.90 (1H, dd, *J* = 7.8, 7.4 Hz, H7″), 7.05 (1H, d, *J* = 8.3 Hz, H9″), 7.10–7.25 (10H, m, H3′ + H5′ + H6″ + H8″ + H4‴ + H2⁗ + H3⁗ + H4⁗ + H5⁗ + H6⁗), 7.28 (2H, m, H3‴ + H5‴), 7.33 (2H, m, H2‴ + H6‴), 7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 20.7 (C4), 30.5 (C3), 46.5 (NH–CH_2), 50.7 (C1), 55.6 (OCH_3), 71.3 (O–CH_2), 73.3 (C2), 101.1 (C1″), 107.2 (C3″), 109.1 (C4a″), 115.0 (C3′ + C5′), 116.2 (C9″), 121.3 (C2′ + C6′), 122.2 (C7″), 126.0 (C5a″), 126.6 (C4‴), 127.0 (C8″), 127.1 (C2‴ + C6‴), 127.3 (C4″), 127.6 (C6″ + C4⁗), 127.8 (C2⁗ + C6⁗), 128.0 (C3⁗ + C5⁗), 128.2 (C3‴ + C5‴), 129.6 (C1′), 138.5 (C1⁗), 140.0 (C1‴), 145.4 (C10a″), 146.1 (C9a″), 148.9 (C2″), 160.1 (C4′), 166.2 ($C_{tetrazole}$).

4.3.25. 10-{2-(Benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-*N*-[(1*R*)-1-phenylethyl]-10*H*-phenothiazin-2-amine (7d)

This compound was obtained from the reaction of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (**6**, 0.30 g, 0.52 mmol) and (*R*)-phenylethylamine (0.13 mL, 1.04 mmol) to give the product as a brown oil; 0.22 g (64%); a mixture of two diastereomers. The reaction time was 1.5 h; (found: C, 71.67; H, 5.95; N, 12.53; $C_{39}H_{38}N_6O_2S$ requires C, 71.53; H, 5.85; N, 12.83); HRMS calcd for $C_{39}H_{38}N_6O_2S$ 654.2777 found: 654.2794; *m*/*z*: 654 (79%), 626 (21), 584 (50), 505 (40), 463 (61), 433 (16), 399 (6), 379 (88), 331 (84), 281 (60), 226 (30), 167 (26), 137 (24) and 108 (100); ν_{max} (film)/cm^{-1}: 3408, 2927, 1600, 1515 and 1454; δ_H (400 MHz, DMSO-d_6) 1.38 [1.39] (3H, d, *J* = 7.1 Hz, CH_3), 1.90 (1H, m, H3y), 2.10 (1H, m, H3x), 2.95 (2H, m, H4y + H4x), 3.83 (1H, m, H1y), 3.99 (1H, m, H1x), 3.85 (3H, s, OCH_3), 3.91 (1H, m, H2), 4.41 (1H, d, *J* = 11.5 Hz, O–CH1y), 4.45 (1H, m, HN–C*H*), 4.64 (1H, d, *J* = 11.5 Hz, O–CH1x), 6.16 (1H, dd, *J* = 8.2, 2.2 Hz, H3″), 6.21 [6.20] (1H, d, *J* = 8.5 Hz, NH), 6.29 (1H, d, *J* = 2.2 Hz, H1″), 6.76 (1H, d, *J* = 8.2 Hz, H4″), 6.89 (1H, ddd, *J* = 8.0, 7.3, 2.2 Hz, H7″), 7.02 (1H, dd, *J* = 8.6, 1.4 Hz, H9″), 7.10–7.38 (14H, m, H3′ + H5′ + H6″ + H8″ + H2‴ + H3‴ + H4‴ + H5‴ + H6‴ + H2⁗ + H3⁗ + H4⁗ + H5⁗ + H6⁗), 7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 20.6 (C4), 24.6 (CH_3), 30.4 (C3), 50.7 (C1), 52.1 (HN–CH), 55.6 (OCH_3), 71.3 (O–CH_2), 73.2 (C2), 101.6 (C1″), 107.7 (C3″), 108.9 (C4a″), 115.0 (C3′ + C5′), 116.1 (C9″), 121.3 (C2′ + C6′), 122.2 (C7″), 125.7 (C5a″), 125.8 (C2‴ + C6‴), 125.9 (C4⁗), 126.4 (C4‴), 127.0 (C8″), 127.3 (C6″), 127.4 (C4″), 127.8 (C2⁗ + C6⁗), 128.0 (C3⁗ + C5⁗), 128.3 (C3‴ + C5‴), 129.6 (C1′), 138.5 (C1⁗), 145.3 (C9a″), 145.9 (C1‴), 146.1 (C10a″), 148.1 (C2″), 160.1 (C4′), 166.2 ($C_{tetrazole}$).

4.3.26. 10-{2-(Benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine (7i)

This compound was obtained from the reaction of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (**6**, 0.20 g, 0.35 mmol) and *N*-methylpiperazine (0.08 mL, 0.70 mmol) to give the product as a brown oil, 0.44 g (99%). The reaction time was 18 h. (found: C, 68.28; H, 6.53; N, 15.20; $C_{36}H_{39}N_7O_2S$ requires C, 68.22; H, 6.20; N, 15.47); *m*/*z* (EI) $[M+H]^+$: 634.60 ($C_{36}H_{39}N_7O_2S$ requires 633.29); ν_{max} (film)/cm^{-1}: 3061, 2937, 2839 1583 and 1515; δ_H (300 MHz, $CDCl_3$) 2.11 (1H, m), 2.25 (3H, s), 2.28 (1H, m), 2.53 (4H, t, *J* = 5.1 Hz), 2.91–3.14 (6H, m), 3.88 (3H, s), 3.97 (1H, dd, *J* = 12.6, 4.8 Hz), 4.05–4.18 (2H, m), 4.60 (1H, d, *J* = 11.2 Hz), 4.78 (1H, d, *J* = 11.2 Hz), 6.48–

6.53 (2H, m), 6.80–7.26 (12H, m), 7.89–7.94 (2H, m); δ_C (75 MHz, $CDCl_3$) 21.5, 31.4, 43.2, 49.6 (2C), 52.1, 55.3 (2C), 55.9, 72.9, 74.2, 105.0, 111.2, 114.8 (2C), 116.1, 121.5 (2C), 122.8, 126.0, 127.1, 127.2, 127.8 (2C), 127.9, 128.0, 128.1 (2C), 128.2, 128.4, 138.6, 145.4, 146.9, 151.7, 160.5, 166.6.

4.3.27. 10-{2-(Benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-pyrrolidin-1-yl-10*H*-phenothiazine (7k)

This compound was obtained from the reaction of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (**6**, 0.30 g, 0.52 mmol) and pyrrolidine (0.09 mL, 1.04 mmol) to give the product as beige amorphous solid, 0.26 g (80%). The reaction time was 1.5 h; mp 43–44 °C; (found: C, 69.86; H, 6.06; N, 13.81; $C_{35}H_{36}N_6O_2S$ requires C, 69.51; H, 6.00; N, 13.90): HRMS calcd for $C_{35}H_{36}N_6O_2S$ 604.2620 found: 604.2593; *m*/*z*: 604 (59%), 535 (40), 455 (64), 422 (13), 322 (9), 281 (100), 212 (94), 180 (29), 138 (11) and 108 (69); ν_{max} (KBr)/cm^{-1}: 2838, 1599, 1515, 1459 and 1255; δ_H (300 MHz, DMSO-d_6) 1.95 (4H, t, *J* = 6.3 Hz), 2.13 (1H, m), 2.31 (1H, m), 3.08 (2H, m), 3.19 (4H, t, *J* = 6.3 Hz), 3.88 (3H, s), 4.00 (1H, m), 4.18 (2H, m), 4.60 (1H, d, *J* = 11.2 Hz), 4.80 (1H, d, *J* = 11.2 Hz), 6.10–6.18 (2H, m), 6.81–7.29 (12H, m), 7.91 (2H, m); δ_C (75 MHz, DMSO-d_6) 21.5, 25.6 (2C), 31.4, 48.0 (2C), 52.0, 55.9, 72.9, 74.3, 100.4, 106.9, 110.6, 114.8 (2C), 115.9, 121.5 (2C), 122.6, 127.0, 127.5, 127.7, 127.8, 127.9, 128.3, 128.4 (2C), 128.5 (2C), 138.7, 145.9, 146.9, 148.2, 160.5, 166.7.

4.3.28. *N*-(10-{2-(Benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-10*H*-phenothiazin-2-yl)formamide (7l) (*E*/*Z* isomers)

This compound was obtained from the reaction of 10-{2-(benzyloxy)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl}-2-chloro-10*H*-phenothiazine (**6**, 0.30 g, 0.52 mmol) and formamide (0.04 mL, 1.04 mmol) to give the product as beige amorphous solid, 87 mg (29%); the mixture of amide rotamers. The reaction time was 43 h; mp 63–67 °C; (found: C, 66.34; H, 5.49; N, 14.12; $C_{32}H_{30}N_6O_3S$ requires C, 66.42; H, 5.23; N, 14.52); *m*/*z* (EI) $[M+H]^+$: 579.30 ($C_{32}H_{30}N_6O_3S$ requires 578.21); ν_{max} (KBr)/cm^{-1}: 2930, 2855, 1694, 1591 and 1516; δ_H (400 MHz, DMSO-d_6) 1.97 (1H, m, H3y), 2.18 (1H, m, H3x), 3.00 (2H, m, H4y + H4x), 3.86 (3H, s, OCH_3), 3.98 (1H, m, H2), 3.99 (1H, m, H1y), 4.16 (1H, m, H1x), 4.52 [4.50] (1H, m, O–CHy), 4.73 [4.70] (1H, m, O–CHx), 6.95 [6.93] (1H, m, H7″), 7.08–7.30 (8H, m, H4″ + H6″ + H8″ + H2‴ + H3‴ + H4‴ + H5‴ + H6‴), 7.12 (1H, m, H9″), 7.15 (1H, m, H3″), 7.16 (2H, m, H3′ + H5′), 7.51 [7.00] (1H, s, H1″), 7.86 (2H, m, H2′ + H6′), 8.2 (8.8) (1H, d, *J* = 1.1, [*J* = 11.0] Hz, O=C–H), 10.2 (10.1) (1H, d, *J* = 1.1, [*J* = 11.0] Hz, NH); δ_C (100 MHz, DMSO-d_6) 20.7 (C4), 30.5 (C3), 50.8 (C1), 55.5 (OCH_3), 71.3 (O–CH_2), 73.4 (C2), 107.4 [105.8] (C1″), 111.8 (C4a″), 113.5 (C3″), 115.0 (C3′ + C5′), 116.4 (C9″), 119.4 (C4″), 121.2 (C2′ + C6′), 122.8 [119.4] (C7″), 127.3 (C8″ + C6″), 127.4 (C5a″), 127.5 (C4‴), 127.7 (C2‴ + C6‴), 128.0 (C3‴ + C5‴), 129.6 (C1′), 138.4 [138.1] (C1‴), 144.8 [144.7] (C9a″), 145.4 [145.2] (C10a″), 146.3 (C2″), 160.0 (C4′), 162.6 (C=O), 166.2 ($C_{tetrazole}$).

4.3.29. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (8)

A solution of 1-(2-chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (**5**, 3.50 g, 7.29 mmol) in anhydrous dichloromethane (175 mL) in a dried, round-bottomed flask equipped with a side arm and cooled to 0 °C in an argon atmosphere was treated with imidazole (1.49 g, 21.88 mmol) in small portions. *tert*-Butyldiphenylchlorosilane (7.30 mL, 28.13 mmol) was added dropwise to the mixture, which became a suspension. The resulting reaction was allowed to warm up to rt and stirred for 4 days. After completion of the reaction, the mixture was diluted with dichloromethane (175 mL) and methanol (22 mL). The clear solution was washed with water (150 mL), neutralized with saturated aqueous $NaHCO_3$, again with water (150 mL) and finally with saturated aqueous NaCl solution (150 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 6:1 and recrystallized by *n*-hexane to give white crystals, 4.71 g (90%); mp 116–118 °C; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 98:2, retention times: 12.4 min, 14.4 min; (found: C, 66.86; H, 5.45; N, 9.67; $C_{40}H_{40}ClN_5O_2SSi$ requires C, 66.88; H, 5.61; N, 9.75); ν_{max} (KBr)/cm^{-1}: 3070, 2931, 1516, 1456 and 1255; δ_H (300 MHz, $CDCl_3$) 1.09 (9H, s), 2.13 (1H, m), 2.25 (1H, m), 3.05 (2H, t, *J* = 7.8 Hz), 3.80–3.82 (2H, m), 3.86 (3H, s), 4.31 (1H, m), 6.14 (1H, m), 6.59 (1H, m), 6.80–6.83 (3H, m), 6.90–7.00 (4H, m), 7.32–7.45 (6H, m), 7.71–7.77 (4H, m), 7.87 (2H, m); δ_C (75 MHz, $CDCl_3$) 19.6, 20.7, 27.3 (3C), 32.7, 52.0, 55.9, 68.8, 114.7 (2C), 116.1, 116.3, 121.4 (2C), 122.8, 123.2, 124.5, 125.7, 127.5, 127.8, 128.0 (2C), 128.1 (2C), 128.3, 130.1, 130.2, 130.8, 133.4 (2C), 134.0, 136.1 (2C), 136.2 (2C), 144.3, 147.2, 160.4, 166.7.

4.3.30. General procedure for the preparation of the 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine/amide derivatives (9) applying Buchwald–Hartwig amination

A round-bottomed flask was charged with Pd-catalyst: $Pd_2(dba)_3$ or $Pd(OAc)_2$ (10 mol %), ligand: XPhos (20 mol %), 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**), appropriate amine/amide, base: NaO^tBu or K_2CO_3), and dry toluene or 1,4-dioxane (5 mL). The flask was flushed with argon for 5 min. The resulting mixture was heated at reflux with magnetic stirring for 4–31 h. After cooling down to rt the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 2:1 and 1:1 to give the product.

4.3.31. *N*′-[10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-yl]-*N*,*N*-dimethylethane-1,2-diamine (9a)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.20 g, 0.28 mmol) and *N*,*N*-dimethylethane-1,2-diamine (0.06 mL, 0.56 mmol) to give the product as brown amorphous solid, 0.18 g (84%). The reaction time was 4 h; mp 56–58 °C; (found: C, 68.43; H, 6.38; N, 12.53; $C_{44}H_{51}N_7O_2SSi$ requires C, 68.63; H, 6.68; N, 12.73); *m*/*z* (EI) $[M+H]^+$: 770.30 ($C_{44}H_{51}N_7O_2SSi$ requires 769.36); ν_{max} (KBr)/cm^{-1}: 3382, 2932, 1601, 1516 and 1459; δ_H (300 MHz, $CDCl_3$) 1.08 (9H, s), 2.14 (1H, m), 2.22 (1H, m), 2.23 (6H, s), 2.52 (2H, t, *J* = 5.8 Hz), 2.98–3.07 (4H, m), 3.81–3.84 (2H, m), 3.86 (3H, s), 4.10 (1H, m), 4.36 (1H, m), 5.86 (1H, d, *J* = 1.8 Hz), 6.10–6.17 (2H, m), 6.75–6.84 (3H, m), 6.97–7.03 (3H, m), 7.35–7.47 (6H, m), 7.72–7.80 (4H, m), 7.90 (2H, m); δ_C (75 MHz, $CDCl_3$) 19.6, 20.7, 27.3 (3C), 32.6, 41.4, 45.4 (2C), 51.8, 55.8, 58.2, 69.0, 101.7, 107.2, 112.5, 114.7 (2C), 115.7, 121.5 (2C), 122.4, 126.9, 127.3, 127.5, 127.9 (2C), 128.0 (2C), 128.3, 130.0, 130.1, 130.8, 133.6, 134.5, 136.2 (2C), 136.3 (2C), 145.1, 147.2, 148.8, 160.4, 166.9.

4.3.32. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*-(2-morpholin-4-ylethyl)-10*H*-phenothiazin-2-amine (9b)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.10 g, 0.14 mmol) and 2-morpholinoethanamine (0.04 mL, 0.27 mmol) to give the product

as white amorphous solid, 0.17 g (78%). The reaction time was 31 h; mp 64–67 °C; (found: C, 67.90; H, 6.98; N, 11.97; $C_{46}H_{53}N_7O_3SSi$ requires C, 68.03; H, 6.58; N, 12.07); *m*/*z* (EI) $[M+H]^+$: 812.60 ($C_{46}H_{53}N_7O_3SSi$ requires 811.37); ν_{max} (KBr)/cm^{-1}: 2957, 2855, 1601, 1516 and 1460; δ_H (300 MHz, $CDCl_3$) 1.08 (9H, s), 2.15 (1H, m), 2.25 (1H, m), 2.48 (4H, t, *J* = 3.9 Hz), 2.60 (2H, t, *J* = 5.4 Hz), 2.95–3.15 (4H, m), 3.74 (4H, t, *J* = 3.9 Hz), 3.82 (2H, m), 3.85 (3H, s), 4.10 (1H, br s), 4.36 (1H, m), 5.87 (1H, d, *J* = 1.8 Hz), 6.10–6.17 (2H, m), 6.76–6.85 (3H, m), 7.00–7.03 (3H, m), 7.33–7.47 (6H, m), 7.73–7.88 (6H, m); δ_C (75 MHz, $CDCl_3$) 19.6, 20.7, 27.3 (3C), 32.6, 40.2, 51.8, 53.6 (2C), 55.9, 57.4, 67.2 (2C), 69.0, 101.6, 107.3, 112.8, 114.7 (2C), 115.7, 121.4 (2C), 122.5, 126.9, 127.2, 127.5, 127.9 (2C), 128.0 (2C), 128.3, 130.0, 130.1, 130.8, 133.5, 134.6, 136.2 (2C), 136.3 (2C), 145.1, 147.3, 148.5, 160.4, 166.9.

4.3.33. *N*-Butyl-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine (9e)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.20 g, 0.28 mmol) and *n*-butylamine (0.06 mL, 0.56 mmol) to give the product as beige amorphous solid, 0.12 g (57%). The reaction time was 21 h; mp 46–50 °C; (found: C, 70.38; H, 6.79; N, 10.83; $C_{44}H_{50}N_6O_2SSi$ requires C, 69.99; H, 6.67; N, 11.13); *m*/*z* (EI) $[M+H]^+$: 755.40 ($C_{44}H_{50}N_6O_2SSi$ requires 754.35); ν_{max} (KBr)/cm^{-1}: 3408, 2957, 1601, 1516 and 1460; δ_H (300 MHz, $CDCl_3$) 0.97 (3H, t, *J* = 7.2 Hz), 1.08 (9H, s), 1.40 (2H, m), 1.55 (2H, m), 2.13 (1H, m), 2.23 (1H, m), 2.95–3.06 (4H, m), 3.26 (1H, br s), 3.83 (2H, m), 3,85 (3H, s), 4.35 (1H, m), 5.74 (1H, s), 6.09–6.18 (2H, m), 6.74–6.84 (3H, m), 7.00–7.03 (3H, m), 7.32–7.48 (6H, m), 7.73–7.89 (6H, m); δ_C (75 MHz, $CDCl_3$) 13.9, 19.4, 20.3, 20.5, 27.0 (3C), 31.6, 32.3, 43.7, 51.6, 55.6, 68.6, 101.4, 106.5, 112.0, 114.4 (2C), 115.4, 121.2 (2C), 122.2, 126.7, 127.0, 127.3, 127.6 (2C), 127.8 (2C), 128.0, 129.7, 129.8, 130.5, 133.2, 134.3, 136.0 (2C), 136.1 (2C), 145.0, 146.7, 148.3, 160.1, 166.6.

4.3.34. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine (9f)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 1.00 g, 1.39 mmol) and diethylamine (0.17 mL, 2.79 mmol) to give the product as white amorphous solid, 0.92 g (87%). The reaction time was 4 h; mp 56–57 °C; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention times: 9.6 min, 10.2 min; (found: C, 69.68; H, 6.68; N, 10.75; $C_{44}H_{50}N_6O_2SSi$ requires C, 69.99; H, 6.67; N, 11.13); *m*/*z* (EI) $[M+H]^+$: 755.50 ($C_{44}H_{50}N_6O_2SSi$ requires 754.35); ν_{max} (KBr)/cm^{-1}: 2964, 2856, 1598, 1516 and 1466; δ_H (300 MHz, $CDCl_3$) 1.07 (9H, s), 1.09 (6H, t, *J* = 6.9 Hz), 2.13 (1H, m), 2.27 (1H, m), 3.07 (2H, t, *J* = 7.2 Hz), 3.23 (4H, q, *J* = 6.9 Hz), 3.86 (2H, m), 3.88 (3H, s), 4.36 (1H, m), 5.91 (1H, d, *J* = 8.4 Hz), 6.06 (1H, d, *J* = 2.4 Hz), 6.23 (1H, dd, *J* = 8.4, 2.7 Hz), 6.67–6.75 (2H, m), 6.85 (1H, d, *J* = 8.7 Hz), 6.98–7.00 (3H, m), 7.32–7.45 (6H, m), 7.73–7.79 (4H, m), 7.88 (2H, m); δ_C (75 MHz, $CDCl_3$) 12.8 (2C), 19.6, 20.9, 27.2 (3C), 32.7, 44.8 (2C), 52.2, 55.9, 69.2, 100.8, 107.4, 111.0, 114.7 (2C), 115.8, 121.4 (2C), 122.3, 126.8, 127.3, 127.5, 127.9 (2C), 128.0 (2C), 128.2, 129.9, 130.1, 130.8, 133.4, 134.6, 136.1 (2C), 136.3 (2C), 144.8, 147.8, 148.2, 160.4, 166.9.

4.3.35. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine (9h)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.60 g, 0.83 mmol) and morpholine (0.15 mL, 1.67 mmol) to give the product as white amorphous solid, 0.59 g (91%). The reaction time was 18 h; mp 63–66 °C; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention times: 18.6 min, 19.5 min; (found: C, 68.98; H, 6.52; N, 10.53; $C_{44}H_{48}N_6O_3SSi$ requires C, 68.72; H, 6.29; N, 10.93); *m*/*z* (EI) $[M+H]^+$: 769.60 ($C_{44}H_{48}N_6O_3SSi$ requires 768.33); ν_{max} (KBr)/cm^{-1}: 2958, 2855, 1595, 1516 and 1461; δ_H (300 MHz, $CDCl_3$ + DMSO-d_6) 1.06 (9H, s), 2.08 (1H, m), 2.22 (1H, m), 2.92–3.03 (6H, m), 3.77 (4H, t, *J* = 4.8 Hz), 3.85 (2H, m), 3.87 (3H, s), 4.31 (1H, m), 6.09 (1H, m), 6.24 (1H, d, *J* = 2.1 Hz), 6.44 (1H, dd, *J* = 8.4, 2.1 Hz), 6.76–6.79 (2H, m), 6.89 (1H, d, *J* = 8.4 Hz), 6.96–7.05 (3H, m), 7.30–7.46 (6H, m), 7.69–7.77 (4H, m), 7.83 (2H, m); δ_C (75 MHz, $CDCl_3$ + DMSO-d_6) 12.8, 24.3, 32.0 (3C), 37.4, 54.3 (2C), 56.8, 60.7, 71.6 (2C), 73.6, 103.1, 109.4, 113.7 (2C), 114.6, 114.8, 120.3 (2C), 121.6, 125.4, 126.1, 126.5, 126.8 (2C), 126.9 (2C), 128.9, 129.1, 129.4, 132.0, 133.2, 134.9 (2C), 135.0 (2C), 143.6, 145.8, 150.5 (2C), 159.4, 165.5.

4.3.36. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine (9i)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.60 g, 0.83 mmol) and *N*-methylpiperazine (0.19 mL, 1.67 mmol) to give the product as beige amorphous solid, 0.48 g (73%). The reaction time was 18 h; mp 58–60 °C; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention times: 20.5 min, 23.5 min; (found: C, 68.79; H, 6.63; N, 12.24; $C_{45}H_{51}N_7O_2SSi$ requires C, 69.11; H, 6.57; N, 12.54); *m*/*z* (EI) $[M+H]^+$: 782.30 ($C_{45}H_{51}N_7O_2SSi$ requires 781.36); ν_{max} (KBr)/cm^{-1}: 2932, 2855, 1596, 1516 and 1461; δ_H (300 MHz, $CDCl_3$) 1.07 (9H, s), 2.11 (1H, m), 2.28 (1H, m), 2.36 (3H, s), 2.53 (4H, t, *J* = 4.8 Hz), 3.02–3.07 (6H, m), 3.83 (2H, m), 3.85 (3H, s), 4.34 (1H, m), 5.99 (1H, m), 6.27 (1H, d, *J* = 2.1 Hz), 6.44 (1H, dd, *J* = 8.4, 2.1 Hz), 6.73–6.77 (2H, m), 6.90 (1H, d, *J* = 8.4 Hz), 6.96–7.01 (3H, m), 7.31–7.45 (6H, m), 7.73–7.79 (4H, m), 7.86 (2H, m); δ_C (75 MHz, $CDCl_3$) 19.6, 20.8, 27.2 (3C), 32.7, 46.4, 49.5 (2C), 52.1, 55.3 (2C), 55.9, 69.1, 104.8, 110.8, 114.7 (2C), 115.9, 116.0, 121.5 (2C), 122.6, 126.9, 127.0, 127.6, 127.9 (2C), 128.1 (2C), 129.9, 130.2, 130.8, 133.3, 134.6, 136.1 (2C), 136.3 (2C), 144.7, 147.3, 151.6 (2C), 160.4, 166.9.

4.3.37. *N*-[10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-yl]formamide (9l) (*E*/*Z* isomers)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.20 g, 0.28 mmol) and formamide (0.02 mL, 0.56 mmol) to give the product as beige amorphous solid, 0.14 g (67%). The reaction time was 22 h; mp 68–71 °C; (found: C, 67.36; H, 5.85; N, 11.37; $C_{41}H_{42}N_6O_3SSi$ requires C, 67.74; H, 5.82; N, 11.56); *m*/*z* (EI) $[M+H]^+$: 727.50 ($C_{41}H_{42}N_6O_3SSi$ requires 726.28); ν_{max} (KBr)/cm^{-1}: 3309, 2930, 2856, 1697 and 1561; δ_H (300 MHz, DMSO-d_6) 0.95 (9H, s), 2.05 (2H, m), 2.96 (2H, m), 3.84 (3H, s), 3.94 (2H, m), 4.19 (1H, m), 6.35 [6.40] (1H, d, *J* = 8.1 Hz), 6.84–6.87 (2H, m), 7.03 (2H, m), 7.10–7.15 (3H, m), 7.29–7.40 (7H, m), 7.57–7.59 (4H, m), 7.78 (2H, m), 8.24 [8.72] (1H, d, *J* = 1.1, [*J* = 11.0] Hz, O=C–H), 10.1 [10.0] (1H, d, *J* = 1.1, [*J* = 11.0] Hz, NH); δ_C (75 MHz, DMSO-d_6) 18.8, 19.9, 26.8 (3C), 32.2, 51.5, 55.6, 68.6, 107.1, 113.5, 114.9 (2C), 115.7, 118.7, 121.1 (2C), 122.7, 124.8, 127.2 (2C), 127.3, 127.6 (2C), 127.7 (2C), 129.6, 129.7, 129.9, 132.8 (2C), 135.3 (2C), 135.4 (2C), 138.1, 143.9, 145.9, 159.6, 160.0, 165.9.

4.3.38. *N*-[10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-yl]acetamide (9m)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.20 g, 0.28 mmol) and acetamide (0.03 g, 0.56 mmol) to give the product as beige amorphous solid, 0.09 g (44%). The reaction time was 22 h; mp 73–76 °C; (found: C, 68.04; H, 5.69; N, 11.16; $C_{42}H_{44}N_6O_3SSi$ requires C, 68.08; H, 5.99; N, 11.34); *m*/*z* (EI) $[M+H]^+$: 741.70 ($C_{42}H_{44}N_6O_3SSi$ requires 740.30); ν_{max} (KBr)/cm^{-1}: 2958, 2930, 2856, 1516 and 1463; δ_H (400 MHz, DMSO-d_6) 0.97 (9H, s, ^{t}Bu), 1.90 (1H, m, H3y), 2.00 (3H, s, O=C–CH_3), 2.10 (1H, m, H3x), 2.97 (2H, m, H4y + H4x), 3.84 (3H, s, OCH_3), 3.93 (2H, m, H1y + H1x), 4.20 (1H, m, H2), 6.34 (1H, d, *J* = 6.8 Hz, H9″), 6.86–6.87 (2H, m, H7″ + H8″), 7.01 (1H, d, *J* = 8.1 Hz, H4″), 7.06 (1H, dd, *J* = 6.8, 2.0 Hz, H6″), 7.13 (1H, dd, *J* = 8.1, 2.0 Hz, H3″), 7.16 (2H, m, H3′ + H5′), 7.31 (4H, m, H3‴ + H5‴ + H3⁗ + H5⁗), 7.37 (1H, s, H1″), 7.40 (2H, m, H4‴ + H4⁗), 7.60 (4H, m, H2‴ + H6‴ + H2⁗ + H6⁗), 7.81 (2H, m, H2′ + H6′), 9.90 (1H, s, NH); δ_C (100 MHz, DMSO-d_6) 18.8 (*C*-^{t}Bu), 19.8 (C4), 23.9 (O=C–CH_3), 26.8 (^{t}Bu, 3C), 32.1 (C3), 51.4 (C1), 55.6 (OCH_3), 68.3 (C2), 106.8 (C1″), 113.3 (C3″), 114.9 (C3′ + C5′), 115.7 (C9″), 117.8 (C2″), 121.2 (C2′ + C6′), 122.7 (C7″), 124.9 (C5a″), 127.2 (C4″ + C6″ + C8″), 127.6 (C3‴ + C5‴), 127.7 (C3⁗ + C5⁗), 129.6 (C1′), 129.7 (C4‴), 129.8 (C4⁗), 132.8 (C1‴ + C1⁗), 135.4 (C2‴ + C6‴ + C2⁗ + C6⁗), 139.2 (C4a″), 143.9 (C9a″), 145.8 (C10a″), 160.0 (C4′), 165.9 ($C_{tetrazole}$), 168.2 (O=C–CH_3).

4.3.39. 1-(2-Chloro-5-oxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (10)

This compound was prepared as described in the literature.[12]

4.3.40. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(5-oxido-10*H*-phenothiazin-10-yl)butan-2-ol (11)

This compound was obtained from reaction of 1-(2-chloro-5-oxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (**10**, 0.30 g, 0.61 mmol) and diethylamine (0.12 mL, 1.21 mmol) by using the reaction conditions with preparation of derivatives **4h**,**i** (see above). The reaction time was 7 h. After column chromatography the crude product was recrystallized from ethyl acetate and white crystals were collected by filtration, 0.11 g (39%); mp 167–169 °C; (found: C, 62.25; H, 4.70; N, 14.89; $C_{24}H_{23}N_5O_3S$ requires C, 62.46; H, 5.02; N, 15.17); *m*/*z* (EI) $[M+H]^+$: 462.20 ($C_{24}H_{23}N_5O_3S$ requires 461.15); ν_{max} (KBr)/cm^{-1}: 3374, 2926, 1585, 1515 and 1462; δ_H (400 MHz, DMSO-d_6) 1.84 (1H, m, H3y), 2.06 (1H, m, H3x), 2.96 (1H, m, H4y), 3.07 (1H, m, H4x), 3.86 (3H, s, OCH_3), 4.06 (1H, m, H2), 4.42 (1H, m, H1y), 4.51 (1H, m, H1x), 5.16 (1H, br s, OH), 7.18 (2H, m, H3′ + H5′), 7.28 [7.29] (2H, m, H3″ + H7″), 7.67 [7.65] (2H, m, H2″ + H8″), 7.92 (2H, m, H2′ + H6′), 7.93 [7.76] (4H, m, H1″ + H4″ + H6″ + H9″); δ_C (100 MHz, DMSO-d_6) 21.0 (C4), 32.1 (C3), 53.3 (C1), 55.6 (OCH_3), 67.2 (C2), 115.0 (C3′ + C5′), 118.3 [117.7] (C1″ + C9″), 121.3 (C2′ + C6′), 122.0 [121.8] (C3″ + C7″), 125.3 [125.9] (C4a″ + C5a″), 129.6 (C1′), 130.1 [130.0] (C4″ + C6″), 132.5 [132.7] (C2″+ C8″), 139.2 [138.5] (C9a″ + C10a″), 160.1 (C4′), 166.4 ($C_{tetrazole}$).

4.3.41. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-[5-oxido-2-(4-oxidomorpholin-4-yl)-10*H*-phenothiazin-10-yl]butan-2-ol (12)

To a solution of 4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-morpholin-4-yl-5-oxido-10*H*-phenothiazin-10-yl)butan-2-ol (**4h**, 0.04 g, 0.07 mmol) in abs dichloromethane (1 mL) *m*-CPBA (0.02 g, 0.11 mmol)/abs dichloromethane (0.5 mL) was added dropwise at 0 °C. The clear purple reaction mixture became a white suspension. After completion of the reaction (23 h), the mixture was cooled to 0 °C, water was added and stirred for 45 min. It was made alkaline with 10% aqueous Na_2CO_3 and extracted with dichloromethane (3 × 0.5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using the eluent chloroform:methanol = 15:1, then 10:1 to give white-grey crystals, 34 mg (83%); mp 152–154 °C; (found: C, 59.80; H, 5.30; N, 14.84; $C_{28}H_{30}N_6O_5S$ requires C, 59.77; H, 5.37; N, 14.94); *m*/*z* (EI) $[M+H]^+$: 563.50 ($C_{28}H_{30}N_6O_5S$ requires 562.20); ν_{max} (KBr)/cm^{-1}: 2963, 2927, 1588, 1515 and 1260; δ_H (400 MHz, DMSO-d_6) 1.86 (1H, m, H3y), 2.08 (1H, m, H3x), 2.87 (2H, m, H3y‴ + H5y‴), 2.96 (1H, m, H4y), 3.07 (1H, m, H4x), 3.79 (2H, m, H2y‴ + H6y‴), 3.85 (3H, s, OCH_3), 4.08 (1H, m, H2), 4.14 (2H, m, H3x‴ + H5x‴), 4.44 (2H, m, H2x‴ + H6x‴), 4.47 (1H, m, H1y), 4.55 (1H, m, H1x), 5.17 (1H, d, *J* = 6.2 Hz, OH), 7.16 (2H, m, H3′ + H5′), 7.32 [7.31] (1H, m, H7″), 7.68 [7.71] (1H, m, H8″), 7.91 (2H, m, H2′ + H6′), 7.95 [7.78] (1H, m, H9″), 7.97 [8.06] (1H, m, H6″), 8.02 [8.07] (1H, m, H3″), 8.07 [7.96] (1H, m, H4″), 8.72 [8.77] (1H, m, H1″); δ_C (100 MHz, DMSO-d_6) 21.0 (C4), 32.2 (C3), 53.3 (C1), 55.6 (OCH_3), 61.7 (C2‴ + C6‴), 66.7 (C3‴ + C5‴), 66.8 (C2), 110.9 [111.2] (C1″), 114.7 [114.3] (C3″), 115.0 (C3′ + C5′), 118.3 [117.7] (C9″), 121.3 (C2′ + C6′), 122.3 [122.4] (C7″), 125.9 [125.3] (C2″), 129.6 (C1′), 129.6 [130.2] (C6″), 130.7 [129.6] (C4″), 130.8 [130.3] (C5a″), 132.7 [132.9] (C8″), 138.8 [138.4] (C9a″), 139.4 [138.9] (C10a″), 159.2 [159.1] (C4a″), 160.1 (C4′), 166.3 ($C_{tetrazole}$).

4.3.42. General procedure for the preparation of *O*-*tert*-butyldiphenylsilyl protected sulfoxide and sulfone derivatives (13, 14)

To the solution of the appropriate protected hydroxy compound (**8** or **13**, 0.56 mmol) in abs dichloromethane, *m*-CPBA (0.12 g, 0.72 mmol)/abs dichloromethane (6 mL) was added dropwise at 0 °C. The clear purple reaction mixture became a white suspension. After completion of the reaction (2–6 h), the mixture was cooled to 0 °C, water was added and stirred for 45 min. It was made alkaline with 10% aqueous Na_2CO_3 and extracted with dichloromethane (three times). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 ill. 1:1 to give white crystals.

4.3.43. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5-oxide (13)

This compound was obtained from 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**, 0.40 g) to give the product as white crystals, 0.36 g (88%); mp 64–68 °C; (found: C, 65.28; H, 5.60; N, 9.17; $C_{40}H_{40}ClN_5O_3SSi$ requires C, 65.42; H, 5.49; N, 9.54); *m*/*z* (EI) $[M+H]^+$: 734.30 ($C_{40}H_{40}ClN_5O_3SSi$ requires 733.23); ν_{max} (KBr)/cm^{-1}: 2931, 1581, 1516, 1456 and 1256; δ_H (300 MHz, $CDCl_3$) 0.93 (9H, s), 2.04 (1H, m), 2.17 (1H, m), 2.99 (2H, m), 3.88 (3H, s), 4.10–4.52 (3H, m), 6.62 (1H, m), 7.00 (2H, m), 7.07–7.45 (10H, m), 7.54–7.80 (6H, m), 7.89 (2H, m); δ_C (75 MHz, $CDCl_3$) 19.4, 20.8, 27.0 (3C), 32.5, 51.6, 55.9, 69.2, 114.7 (2C), 116.3, 116.5, 117.5, 121.5 (2C), 122.6, 122.7, 123.0, 124.5, 126.2, 128.0 (2C), 128.1 (2C), 129.5, 130.3, 130.6, 131.4, 131.9, 132.7, 133.2, 136.0 (4C), 138.8, 141.0, 160.5, 166.2.

4.3.44. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5,5-dioxide (14)

This compound was obtained from 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5-oxide (**13**, 0.42 g, 0.35 mmol) to give the product as white crystals, 0.43 g (quant.); mp 62–67 °C;

(found: C, 64.40; H, 5.47; N, 9.27; $C_{40}H_{40}ClN_5O_4SSi$ requires C, 64.02; H, 5.37; N, 9.33); *m/z* (EI) $[M+H]^+$: 750.30 ($C_{40}H_{40}ClN_5O_4SSi$ requires 749.23); ν_{max} (KBr)/cm^{-1}: 2930, 1585, 1516, 1461 and 1256; δ_H (300 MHz, $CDCl_3$) 1.00 (9H, s), 1.96 (1H, m), 2.14 (1H, m), 2.98 (2H, t, J = 7.5 Hz), 3.88 (3H, s), 4.10–4.43 (3H, m), 6.66 (1H, d, J = 8.1 Hz), 7.00 (2H, m), 7.13–7.28 (4H, m), 7.37–7.45 (6H, m), 7.68–7.71 (4H, m), 7.85–7.97 (4H, m); δ_C (75 MHz, $CDCl_3$) 19.5, 20.7, 27.1 (3C), 32.0, 51.7, 55.9, 69.1, 114.7 (2C), 117.1, 117.2, 121.5 (2C), 122.8 (2C), 123.6, 124.1, 125.2, 125.9, 128.1 (2C), 128.2 (2C), 130.3, 130.4, 130.7, 133.0, 133.2, 133.5, 136.1 (4C), 139.4, 141.0, 143.1, 160.5, 166.2.

4.3.45. General procedure for preparation of 10-(2-{[*tert*-butyl (diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-amino-10*H*-phenothiazine 5,5-dioxide derivatives (15)

A round-bottomed flask was charged with Pd-catalyst: $Pd_2(dba)_3$ (10 mol %), ligand: XPhos (20 mol %), 10-(2-{[*tert*-butyl (diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5,5-dioxide (**14**), secondary amine, base: NaO^tBu, and dry toluene (5 mL). The flask was flushed with argon for 5 min. The resulting mixture was heated under reflux with magnetic stirring for 70–90 min. After cooling down to rt the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 2:1 and 1:1 to give the final product as beige amorphous solid.

4.3.46. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine 5,5-dioxide (15f)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5,5-dioxide (**14**, 0.35 g, 0.47 mmol) and diethylamine (0.10 mL, 0.93 mmol). The reaction time was 70 min. After flash chromatography the product was isolated as beige amorphous solid, 0.11 g (58%); mp 71–75 °C; (found: C, 66.87; H, 6.42; N, 9.89; $C_{44}H_{50}N_6O_4SSi$ requires C, 67.15; H, 6.40; N, 10.68); *m/z* (EI) $[M+H]^+$: 787.70 ($C_{44}H_{50}N_6O_4SSi$ requires 786.34); ν_{max} (KBr)/cm^{-1}: 3430, 2931, 1594, 1516 and 1471; δ_H (300 MHz, $CDCl_3$) 1.00 (9H, s), 1.18 (6H, t, J = 6.9 Hz), 2.04 (1H, m), 2.16 (1H, m), 3.02 (2H, t, J = 7.5 Hz), 3.38 (4H, q, J = 6.9 Hz), 3.88 (3H, s), 4.06–4.41 (3H, m), 6.21–6.25 (2H, m), 6.45 (1H, d, J = 9.0 Hz), 6.97–7.04 (4H, m), 7.36–7.50 (6H, m), 7.72–7.74 (5H, m), 7.86–7.89 (3H, m); δ_C (75 MHz, $CDCl_3$) 12.5 (2C), 19.3, 20.6, 26.8 (3C), 31.6, 44.6 (2C), 51.2, 55.6, 69.2, 97.0, 106.4, 113.1, 114.4 (2C), 116.5, 121.4 (2C), 122.6, 123.9, 125.0, 127.0, 127.8 (2C), 128.0 (2C), 130.0, 130.1, 130.5, 131.8, 132.8, 133.9, 135.8 (2C), 136.0 (2C), 141.0, 144.5, 151.1, 160.1, 166.3.

4.3.47. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine 5,5-dioxide (15h)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5,5-dioxide (**14**, 0.20 g, 0.27 mmol) and morpholine (0.05 mL, 0.53 mmol). The reaction time was 90 min. After flash chromatography the product was isolated as beige amorphous solid, 0.20 g (92%); mp 56–60 °C; (found: C, 65.85; H, 6.09; N, 10.30; $C_{44}H_{48}N_6O_5SSi$ requires C, 65.97; H, 6.04; N, 10.49); *m/z* (EI) $[M+H]^+$: 801.50 ($C_{44}H_{48}N_6O_5SSi$ requires 800.32); ν_{max} (KBr)/cm^{-1}: 2930, 1694, 1516, 1464 and 1256; δ_H (300 MHz, $CDCl_3$) 0.98 (9H, s), 2.04 (1H, m), 2.13 (1H, m), 2.97 (2H, t, J = 7.5 Hz), 3.10–3.18 (4H, m), 3.83 (4H, m), 3.87 (3H, s), 4.09–4.43 (3H, m), 6.47–6.67 (3H, m), 6.98–7.45 (11H, m), 7.70–7.93 (7H, m); δ_C (75 MHz, $CDCl_3$) 19.5, 20.6, 27.0 (3C), 32.0, 48.2 (2C), 51.5, 55.9, 66.8 (2C), 69.2, 101.3, 109.5, 114.7 (2C), 116.8, 116.9, 121.5 (2C), 122.0, 123.1, 125.1, 126.7, 128.0 (2C), 128.2 (2C), 130.2, 130.4, 130.5, 132.4, 133.0, 134.0, 136.0 (2C), 136.2 (2C), 141.4, 144.0, 154.7, 160.5, 166.4.

4.3.48. 10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine 5,5-dioxide (15i)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine 5,5-dioxide (**14**, 0.20 g, 0.27 mmol) and *N*-methylpiperazine (0.06 mL, 0.53 mmol). The reaction time was 70 min. After flash chromatography the product was isolated as beige amorphous solid, 0.20 g (92%); mp 81–86 °C; (found: C, 66.31; H, 6.29; N, 11.94; $C_{45}H_{51}N_7O_4SSi$ requires C, 66.39; H, 6.31; N, 12.04); *m/z* (EI) $[M+H]^+$: 814.30 ($C_{45}H_{51}N_7O_4SSi$ requires 813.35); ν_{max} (KBr)/cm^{-1}: 3418, 2932, 1593, 1516 and 1456; δ_H (300 MHz, $CDCl_3$) 1.00 (9H, s), 1.98 (1H, m), 2.14 (1H, m), 2.38 (3H, s), 2.56 (4H, t, J = 4.8 Hz), 2.98 (2H, t, J = 7.2 Hz), 3.28 (4H, t, J = 4.8 Hz), 3.88 (3H, s), 4.10 (1H, m), 4.21 (1H, m), 4.41 (1H, m), 6.39 (1H, d, J = 6.9 Hz), 6.52 (1H, s), 6.66 (1H, d, J = 9.0 Hz), 6.97–7.13 (4H, m), 7.36–7.47 (6H, m), 7.71–7.79 (5H, m), 7.85–7.92 (3H, m); δ_C (75 MHz, $CDCl_3$) 19.5, 20.7, 27.1 (3C), 31.9, 46.2, 47.9 (2C), 51.4, 54.9 (2C), 55.9, 69.2, 101.4, 109.8, 114.7 (2C), 116.3, 116.9, 121.5 (2C), 122.0, 123.1, 125.0, 126.9, 128.0 (2C), 128.2 (2C), 130.2, 130.4, 130.7, 132.4, 133.0, 134.1, 136.1 (2C), 136.2 (2C), 141.3, 144.2, 154.5, 160.4, 166.4.

4.3.49. General procedure for the preparation of 1-(2-amino-5,5-dioxido-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol derivatives (16)

To the solution of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-amino-10*H*-phenothiazine 5,5-dioxide derivative (**15**, 0.22 mmol) in anhydrous THF (15 mL) in a dried, round-bottomed flask equipped with a side arm and cooled to 0 °C in an argon atmosphere was added the solution of TBAF (0.33 mmol)/abs THF (1 mL). The reaction mixture was allowed to warm up to rt. After the completion of the reaction as specified (2.5–4.5 h) the reaction mixture was evaporated. The residue was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 then 1:1 to give the product.

4.3.50. 1-[2-(Diethylamino)-5,5-dioxido-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (16f)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine 5,5-dioxide (**15f**, 0.25 g, 0.32 mmol) and TBAF (0.12 g, 0.48 mmol)/abs THF (1 mL). The reaction time was 2.5 h. After column chromatography yellow amorphous solid were isolated, 0.14 g (78%); mp 49–52 °C; (found: C, 61.13; H, 5.48; N, 14.98; $C_{28}H_{32}N_6O_4S$ requires C, 61.30; H, 5.88; N, 15.32); *m/z* (EI) $[M+H]^+$: 549.30 ($C_{28}H_{32}N_6O_4S$ requires 548.22); ν_{max} (KBr)/cm^{-1}: 2968, 2928, 1593, 1516 and 1470; δ_H (400 MHz, DMSO-d_6) 1.12 (6H, t, J = 6.9 Hz, $N(CH_2)_2(CH_3)_2$), 1.84 (1H, dddd, J = 14.2, 9.4, 9.0, 5.0 Hz, H3y), 2.07 (1H, m, H3x), 2.99 (1H, ddd, J = 15.2, 9.0, 7.1 Hz, H4y), 3.08 (1H, ddd, J = 15.2, 9.4, 5.2 Hz, H4x), 3.42 (4H, m, $N(CH_2)_2(CH_3)_2$), 3.85 (3H, s, OCH_3), 4.15 (1H, m, H2), 4.24 (1H, dd, J = 15.0, 4.8 Hz, H1y), 4.32 (1H, dd, J = 15.0, 7.3 Hz, H1x), 5.22 (1H, d, J = 5.3 Hz, OH), 6.63 (1H, m, H3″), 6.64 (1H, s, H1″), 7.16 (2H, m, H3′ + H5′), 7.25 (1H, dd, J = 7.9, 7.3 Hz, H7″), 7.62 (1H, m, H8″), 7.65 (1H, m, H4″), 7.69 (1H, d, J = 8.6 Hz, H9″), 7.87 (1H, dd, J = 7.9, 1.4 Hz, H6″), 7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 12.2 ($N(CH_2)_2(CH_3)_2$, 2C), 21.0 (C4), 32.6 (C3), 44.0 ($N(CH_2)_2(CH_3)_2$, 2C), 53.5 (C1), 55.7 (OCH_3), 66.8 (C2), 97.5 (C1″), 106.3 (C3″), 111.2 (C4a″), 115.0 (C2′ + C6′), 117.8 (C9″), 121.3 (C2′ + C6′ + C7″), 121.8 (C6″), 124.0 (C4″), 125.3 (C5a″), 129.6 (C1′), 132.5 (C8″), 141.4 (C9a″), 143.0 (C10a″), 150.8 (C2″), 160.1 (C4′), 166.4 ($C_{tetrazole}$).

4.3.51. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-morpholin-4-yl-5,5-dioxido-10*H*-phenothiazin-10-yl)butan-2-ol (16h)

This compound was obtained from the reaction of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine 5,5-dioxide (**15h**, 0.18 g, 0.22 mmol) and TBAF (0.09 g, 0.33 mmol)/abs THF (1 mL). The reaction time was 4.5 h. After column chromatography yellow amorphous solid were isolated, 0.10 g (82%); mp 71–76 °C. The air sensitive product was stored in an argon atmosphere; (found: C, 59.41; H, 5.34; N, 14.93; $C_{28}H_{30}N_6O_5S$ requires C, 59.77; H, 5.37; N, 14.94); *m*/*z* (EI) $[M+H]^+$: 563.30 ($C_{28}H_{30}N_6O_5S$ requires 562.20); ν_{max} (KBr)/cm^{-1}: 2924, 2853, 1593, 1516 and 1468; δ_H (400 MHz, DMSO-d_6) 1.81 (1H, m, H3y), 2.04 (1H, m, H3x), 2.97 (1H, m, H4y), 3.06 (1H, m, H4x), 3.30 (4H, m, N–(CH_2)$_2$), 3.74 (4H, m, O–(CH_2)$_2$), 3.84 (3H, s, OCH_3), 4.10 (1H, m, H2), 4.31 (1H, m, H1y), 4.36 (1H, m, H1x), 5.18 (1H, d, *J* = 5.3 Hz, OH), 6.92 (1H, m, H3″), 7.01 (1H, s, H1″), 7.16 (2H, m, H3′ + H5′), 7.28 (1H, m, H7″), 7.65 (1H, m, H8″), 7.71 (1H, m, H9″), 7.72 (1H, m, H4″), 7.89 (1H, m, H6″), 7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 20.9 (C4), 32.4 (C3), 47.3 (N–(CH_2)$_2$, 2C), 53.1 (C1), 55.6 (OCH_3), 65.8 (O–(CH_2)$_2$, 2C), 66.6 (C2), 101.4 (C1″), 109.1 (C3″), 114.5 (C4a″), 115.0 (C2′ + C6′), 117.9 (C9″), 121.3 (C2′ + C6′ + C6″), 121.6 (C7″), 123.6 (C5a″), 125.0 (C4″), 129.6 (C1′), 132.7 (C8″), 141.4 (C9a″), 142.8 (C10a″), 154.2 (C2″), 160.1 (C4′), 166.3 ($C_{tetrazole}$).

4.3.52. 4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-[2-(4-methylpiperazin-1-yl)-5,5-dioxido-10*H*-phenothiazin-10-yl]butan-2-ol (16i)

This compound was obtained from the reaction of 10-(2-((*tert*-butyldiphenylsilyl)oxy)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl) butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine-5,5-dioxide (**15i**, 0.20 g, 0.25 mmol) and tetrabutylammonium fluoride (0.10 g, 0.37 mmol)/abs THF (1 mL). The reaction time was 4.5 h. The crude product was purified by column chromatography on silica gel using the eluent chloroform:methanol = 15:1 then 10:1. Yellow amorphous solid were isolated, 0.13 g (88%); mp 74–80 °C. The air sensitive product was stored in an argon atmosphere; (found: C, 60.41; H, 5.70; N, 16.75; $C_{29}H_{33}N_7O_4S$ requires C, 60.50; H, 5.78; N, 17.03); *m*/*z* (EI) $[M+H]^+$: 576.20 ($C_{29}H_{33}N_7O_4S$ requires 575.23); ν_{max} (KBr)/cm^{-1}: 2937, 2842, 1593, 1516 and 1455; δ_H (400 MHz, DMSO-d_6) 1.83 (1H, m, H3y), 2.05 (1H, m, H3x), 2.21 (3H, s, H_3C–N–(CH_2)$_2$), 2.42 (4H, m, H_3C–N–(CH_2)$_2$), 2.97 (1H, m, H4y), 3.07 (1H, m, H4x), 3.33 (4H, m, H_3C–N–(CH_2)$_2$), 3.84 (3H, s, OCH_3), 4.10 (1H, m, H2), 4.30 (2H, m, H1y + H1x), 5.18 (1H, d, *J* = 5.3 Hz, OH), 6.92 (1H, m, H3″), 6.98 (1H, s, H1″), 7.16 (2H, m, H3′ + H5′), 7.28 (1H, m, H7″), 7.64 (1H, m, H8″), 7.69 (1H, m, H4″), 7.71 (1H, m, H9″), 7.88 (1H, m, H6″), 7.90 (2H, m, H2′ + H6′); δ_C (100 MHz, DMSO-d_6) 20.9 (C4), 32.4 (C3), 45.6 (N–CH_3), 47.0 (N–(CH_2)$_2$, 2C), 53.1 (C1), 54.3 (H_3C–N–(CH_2)$_2$, 2C), 55.7 (OCH_3), 66.6 (C2), 101,4 (C1″), 109.3 (C3″), 114.0 (C4a″), 115.0 (C2′ + C6′), 117.9 (C9″), 121.3 (C2′ + C6′), 121.5 (C7″), 121.9 (C6″), 123.6 (C4″), 125.1 (C5a″), 129.6 (C1′), 132.7 (C8″), 141.4 (C9a″), 142.8 (C10a″), 154.1 (C2″), 160.1 (C4′), 166.3 ($C_{tetrazole}$).

4.3.53. (2*Z*)-4-{1-[(2-Chloro-10*H*-phenothiazin-10-yl)methyl]-3-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]propoxy}-4-oxobut-2-enoic acid (17)

To a solution of racemic 1-(2-chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol (**5**, 4.15 g, 8.64 mmol) in abs dichloromethane (30 mL), abs triethylamine (2.59 mL, 18.70 mmol) was added and the mixture was stirred at rt. After 30 min, maleic anhydride (1.59 g, 16.17 mmol) was added to the mixture and it was heated up and refluxed for 9.5 h. The mixture was then cooled to rt, the pH was adjusted to acidic with 10% aqueous HCl solution. After separation, the organic phase was washed with water, dried over Na_2SO_4, filtered and concentrated. The crude product (foam) was triturated with *n*-hexane, the mixture was cooled whereupon crystals deposited. The product was filtered off to yield yellow crystals, 4.98 g (quant.); mp 56–60 °C; (found: C, 57.81; H, 3.96; N, 11.99; $C_{28}H_{24}ClN_5O_5S$ requires C, 58.18; H, 4.18; N, 12.12); *m*/*z* (EI) $[M+H]^+$: 578.30 ($C_{28}H_{24}ClN_5O_5S$ requires 577.12); ν_{max} (KBr)/cm^{-1}: 2925, 2361, 1516, 1458 and 1256; δ_H (300 MHz, $CDCl_3$) 2.29 (1H, m, H3y), 2.39 (1H, m, H3x), 3.07 (2H, t, *J* = 7.8 Hz, H4y + H4x), 3.88 (3H, s, OCH_3), 4.08 (1H, dd, *J* = 13.8, 6.6 Hz, H1y), 4.17 (1H, dd, *J* = 13.8, 6.3 Hz, H1x), 5.56 (1H, m, H2), 6.21 (1H, d, *J* = 12.9 Hz, C*H*=CH–COOH), 6.40 (1H, d, *J* = 12.9 Hz, CH=C*H*–COOH), 6.90–7.20 (10H, m, H3′ + H5′ + H1″ + H3″ + H4″ + H6″ + H7″ + H8″ + H9″ + COOH), 7.93 (2H, m, H2′ + H6′); δ_C (75 MHz, $CDCl_3$) 21.4 (C4), 29.9 (C3), 49.8 (C1), 55.9 (OCH_3), 72.6 (C2), 114.9 (C3′ + C5′), 116.4 (CH), 116.6 (CH), 121.5 (C2′ + C6′), 123.4 (CH), 124.0 (CH), 125.3 (C), 126.5 (C), 127.9 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 130.4 (C), 133.7 (C), 136.1 (CH), 144.3 (C), 146.5 (C), 160.8 (C4′), 164.7 (COO), 165.6 ($C_{tetrazole}$), 167.0 (COOH).

4.3.54. Resolution of racemic (2*Z*)-4-{1-[(2-chloro-10*H*-phenothiazin-10-yl)methyl]-3-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]propoxy}-4-oxobut-2-enoic acid (17) with *S*-(−)-phenylethylamine[23d]

4.3.54.1. Diastereomeric salt$_{crystal}$ (18). Racemic 4-((1-(2-chloro-10*H*-phenothiazin-10-yl)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)butan-2-yl)oxy)-4-oxobut-2-enoic acid (**17**, 5.72 g, 9.90 mmol) was dissolved in ethyl acetate (60 mL), and *S*-(−)-phenylethylamine (0.64 mL, 4.95 mmol) was added to the solution. The reaction mixture was stirred at rt for 2 h. Precipitation of the diastereomeric salt$_{crystal}$ (**18**) commenced in a few minutes. The precipitated diastereomer salt was collected by filtration and washed with ethyl acetate (3 × 10 mL). The white crystals were recrystallized from hot ethyl acetate and cooled slowly (recrystallization from ethyl acetate was repeated once again) to give 4-((1-(2-chloro-10*H*-phenothiazin-10-yl)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)butan-2-yl)oxy)-4-oxobut-2-enoic acid (*S*)-phenylethylamine salt **18** as white crystals, 2.49 g (75%); mp 147–150 °C; $[\alpha]_D^{25}$ − 4.90 = (*c* 0.368, methanol); (found: C, 61.51; H, 5.03; N, 11.67; $C_{36}H_{35}ClN_6O_5S$ requires C, 61.84; H, 5.05; N, 12.02); ν_{max} (KBr)/cm^{-1}: 3421, 2934, 2540, 1515 and 1460.

4.3.55. (−)-4-{1-[(2-Chloro-10*H*-phenothiazin-10-yl)methyl]-3-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]propoxy}-4-oxobut-2-enoic acid ((−)-17)

The recrystallized diastereomeric salt (**18**, 2.36 g, 3.37 mmol) was dissolved in a mixture of methanol (52 mL) and dichloromethane (15 mL) and stirred at rt. To the reaction mixture 10% aqueous HCl solution (14.13 mL) was added. After 4 h, the phases were separated and the organic phase was extracted with 10% aqueous HCl solution (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was triturated with *n*-hexane and yellow crystals were collected by filtration, 1.94 g (99.8%); $[\alpha]_D^{25}$ − 11.00 (*c* 0.310, chloroform); (found: C, 57.81; H, 3.96; N, 11.99; $C_{28}H_{24}ClN_5O_5S$ requires C, 58.18; H, 4.18; N, 12.12); ν_{max} (KBr)/cm^{-1}: 2929, 1516, 1458, 1256 and 1170.

4.3.56. (−)-1-(2-Chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol ((−)-5)

(−)-4-{1-[(2-Chloro-10*H*-phenothiazin-10-yl)methyl]-3-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]propoxy}-4-oxobut-2-enoic acid ((−)-**17**, 1.75 g, 3.02 mmol) was dissolved in dichloromethane (37 mL) at rt and the solution of NaOH (0.54 g, 13.6 mmol)/H_2O (2 mL) was added to the mixture then refluxed for 7.5 h. After cooling, water (30 mL) was added to the mixture, it was acidified with 10% aqueous HCl solution and extracted with dichloromethane (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered

and concentrated. The crude product was purified by flash chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 then 1:1. The product (foam) was triturated with diethyl ether and the mixture was cooled whereupon crystals deposited. The product, white crystals were collected by filtration, 1.25 g (86%); mp 90–92 °C; $[\alpha]_D^{25}$ −21.30 (*c* 0.282, chloroform); ee: 99.9+%; HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 15.2 min; (found: C, 59.72; H, 4.70; N, 14.30; $C_{24}H_{22}ClN_5O_2S$ requires C, 60.06; H, 4.62; N, 14.59); *m*/*z* (EI) $[M+H]^+$: 480.20 ($C_{24}H_{22}ClN_5O_2S$ requires 479.12); ν_{max} (KBr)/cm^{-1}: 3422, 2929, 1515, 1461 and 1259.

4.3.57. (+)-4-{1-[(2-Chloro-10*H*-phenothiazin-10-yl)methyl]-3-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]propoxy}-4-oxobut-2-enoic acid ((+)-17)

The mother liquor obtained after separation of crystalline **18** was evaporated to give a solid (**19**, 3.44 g) containing a mixture of the non-reacted part of **17**, that is, (+)-**17** and, additionally, traces of **18**. This mixture was dissolved in ethyl acetate (20 mL), stirred at rt and, then, 10% aqueous HCl solution (1.35 mL) was added (this amount of HCl was calculated as an excess for the assumed amount of **18** being present in the mixture **19**). After 50 min, the phases were separated and the organic phase was washed with 10% aqueous HCl solution (2 × 0.5 mL), dried over Na_2SO_4, filtered and concentrated. The crude product (foam) was triturated with *n*-hexane, yellow crystals deposited and were collected by filtration. As the mass spectrum still indicated the presence of the reagent *S*-(−)-phenylethylamine, the hydrolysis was repeated again. Yield: 3.07 g (107%, calculated for the expected amount of (+)-monoester: (+)-**17**); for the crude product: $[\alpha]_D^{25}$ +14.00 (*c* 0.470, methanol); ν_{max} (KBr)/cm^{-1}: 2931, 1516, 1458, 1256 and 1170.

4.3.58. (+)-1-(2-Chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol ((+)-5)

The (+)-monoester ((+)-**17**, 2.84 g, 4.90 mmol) was dissolved in abs dichloromethane (59 mL) at rt and the solution of NaOH (0.88 g, 22.09 mmol) in water (2.6 mL) was added to the reaction mixture. The mixture was stirred and heated up to reflux. After completion (4 h), the mixture was allowed to cool down to rt, water (40 mL) was added to the solution, acidified with 10% aqueous HCl solution and extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 then 1:1. The crude product (foam) was triturated with diethyl ether, the mixture was cooled, and the white crystals were collected by filtration (twice), total yield: 1.85 g (74%) (m_1 = 1.57 g, ee: 89% + m_2 = 0.28 g, ee: 94%); mp 90–92 °C; $[\alpha]_D^{25}$ +21.20 (*c* 0.358, chloroform (m_2)). HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 10.1 min; (found: C, 59.97; H, 4.68; N, 14.45; $C_{24}H_{22}ClN_5O_2S$ requires C, 60.06; H, 4.62; N, 14.59); *m*/*z* (EI) $[M+H]^+$: 480.20 ($C_{24}H_{22}ClN_5O_2S$ requires 479.12); ν_{max} (KBr)/cm^{-1}: 3422, 2929, 1515, 1461 and 1259.

4.3.59. General procedure for the preparation of (−)- and (+) 1-(2-amino-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol derivatives ((−)-3 and (+)-3) by desilylation of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine derivatives ((−)-9 and (+)-9)

The procedure followed the aforementioned preparation of racemic 1-(2-amino-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol derivatives (**3**) by desilylation of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine derivatives (**9**).

4.3.60. (−)-1-[2-(Diethylamino)-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol ((−)-3f)

This compound was obtained from (−)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine ((−)-**9f**, 0.20 g, 0.26 mmol). The crude product was purified by flash chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 2:1 to give white amorphous solid, 0.09 g (66%); ee: 99.6%; $[\alpha]_D^{25}$ −9.98 (*c* 0.259, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 22.1 min.

4.3.61. (−)-4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-morpholin-4-yl-10*H*-phenothiazin-10-yl)butan-2-ol ((−)-3h)

This compound was obtained from (*S*)-(−)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine ((−)-**9h**, 0.31 g, 0.40 mmol). The crude product was purified by flash chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 4:1 to give beige amorphous solid, 0.21 g (98%); ee: 99.9+%; $[\alpha]_D^{25}$ −15.24 (*c* 0.289, chloroform). HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 17.4 min.

4.3.62. (−)-4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-[2-(4-methylpiperazin-1-yl)-10*H*-phenothiazin-10-yl]butan-2-ol ((−)-3i)

This compound was obtained from (−)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine ((−)-**9i**, 0.39 g, 0.49 mmol). The crude product was purified by flash chromatography on silica gel using the eluent chloroform:methanol = 30:1, 15:1 then 10:1 to give a brown oil, 0.25 g (95%); ee: 99.8%; $[\alpha]_D^{25}$ −4.42 (*c* 0.328, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 23.8 min.

4.3.63. (+)-1-[2-(Diethylamino)-10*H*-phenothiazin-10-yl]-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol ((+)-3f)

This compound was obtained from (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine ((+)-**9f**, 0.29 g, 0.39 mmol). The crude product was purified by column chromatography on silica gel using the eluent chloroform to give a white amorphous solid, 0.18 g (88%); ee: 74%; $[\alpha]_D^{25}$ +9.32 (*c* 0.352, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 9.5 min.

4.3.64. (+)-4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(2-morpholin-4-yl-10*H*-phenothiazin-10-yl)butan-2-ol ((+)-3h)

This compound was obtained from (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine ((+)-**9h**, 0.28 g, 0.36 mmol). The crude product was purified by flash chromatography on silica gel using the eluent chloroform, then chloroform:methanol = 50:1 to give white amorphous solid, 0.16 g (84%); ee: 73.4%; $[\alpha]_D^{25}$ +9.92 (*c* 0.277, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 11.8 min.

4.3.65. (+)-4-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-1-[2-(4-methylpiperazin-1-yl)-10*H*-phenothiazin-10-yl]butan-2-ol ((+)-3i)

This compound was obtained from (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine ((+)-**9i**, 0.39 g,

0.49 mmol). The crude product was purified by column chromatography on silica gel using the eluent chloroform:methanol = 30:1, 15:1 then 10:1 to give a brown oil, 0.22 g (83%), ee: 72%; $[\alpha]_D^{25}$ + 6.21 (*c* 0.346, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 70:30, retention time: 17.3 min.

4.3.66. General procedure for the preparation of (−)- and (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((−)-8) and (+)-8)

The procedure followed the aforementioned preparation of racemic 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine (**8**).

4.3.67. (−)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((−)-8)

This compound was obtained from (−)-1-(2-chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol ((−)-**5**, 1.60 g, 3.33 mmol) as white crystals, 2.35 g (98%); ee: 99.9+%; $[\alpha]_D^{25}$ + 31.20 (*c* 0.353, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 98:2; retention time: 14.5 min; ν_{max} (KBr)/cm^{-1}: 3071, 2932, 1516, 1456 and 1255.

4.3.68. (+)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((+)-8)

This compound was obtained from (+)-1-(2-chloro-10*H*-phenothiazin-10-yl)-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butan-2-ol ((+)-**5**, 1.60 g, 3.33 mmol) as white crystals, 2.35 g (98%); ee: 74%; $[\alpha]_D^{25}$ − 22.80 (*c* 0.440, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 98:2, retention time: 12.4 min; ν_{max} (KBr)/cm^{-1}: 3070, 2958, 1516, 1456 and 1255.

4.3.69. General procedure for the preparation of 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine derivatives ((−)-9 and (+)-9)

The procedure followed the aforementioned preparation of racemic 10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-10*H*-phenothiazin-2-amine (**9**).

4.3.70. (−)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine ((−)-9f)

This compound was obtained from the reaction of (−)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((−)-**8**, 0.50 g, 0.67 mmol) and diethylamine (0.15 mL, 1.40 mmol). The crude product was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 to give brown amorphous solid, 0.24 g (45%); ee: 99.9+%; mp 64–70 °C; $[\alpha]_D^{25}$ + 7.39 (*c* 0.299, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention time: 9.6 min; ν_{max} (KBr)/cm^{-1}: 2964, 2930, 1598, 1516 and 1466.

4.3.71. (−)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine ((−)-9h)

This compound was obtained from the reaction of (−)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((−)-**8**, 0.40 g, 0.55 mmol) and morpholine (0.10 mL, 1.11 mmol). The crude product was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 4:1 to give beige amorphous solid, 0.35 g (82%); mp 72–80 °C; $[\alpha]_D^{25}$ + 11.13 (*c* 0.289, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention time: 18.6 min; ν_{max} (KBr)/cm^{-1}: 3429, 2957, 2855, 1595 and 1516.

4.3.72. (−)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine ((−)-9i)

This compound was obtained from the reaction of (−)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((−)-**8**, 0.40 g, 0.56 mmol) and *N*-methyl-piperazine (0.12 mL, 1.11 mmol). The crude product was purified by column chromatography on silica gel using the eluent chloroform:methanol = 20:1, 15:1 then 10:1 to give beige amorphous solid, 0.31 g (71%); mp 66–74 °C; $[\alpha]_D^{25}$ + 11.50 (*c* 0.264, chloroform). HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention time: 20.5 min; ν_{max} (KBr)/cm^{-1}: 2932, 2855, 1584, 1516 and 1461.

4.3.73. (+)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-*N*,*N*-diethyl-10*H*-phenothiazin-2-amine ((+)-9f)

This compound was obtained from the reaction of (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((+)-**8**, 0.50 g, 0.70 mmol) and diethylamine (0.15 mL, 1.40 mmol). The crude product was purified by column chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 2:1 to give beige amorphous solid, 0.34 g (65%); mp 65–70 °C; ee: 78%; $[\alpha]_D^{25}$ − 6.42 (*c* 0.265, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention time: 10.2 min; ν_{max} (KBr)/cm^{-1}: 2964, 2856, 1598, 1516 and 1466.

4.3.74. (+)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-morpholin-4-yl-10*H*-phenothiazine ((+)-9h)

This compound was obtained from the reaction of (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((+)-**8**, 0.40 g, 0.56 mmol) and morpholine (0.10 mL, 1.11 mmol). The crude product was purified by flash chromatography on silica gel using the eluent *n*-hexane:ethyl acetate = 4:1 to give beige amorphous solid, 0.34 g (79%); mp 78–80 °C; $[\alpha]_D^{25}$ − 11.57 (*c* 0.271, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention time: 19.5 min; ν_{max} (KBr)/cm^{-1}: 2958, 2856, 1596, 1516 and 1462.

4.3.75. (+)-10-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-(4-methylpiperazin-1-yl)-10*H*-phenothiazine ((+)-9i)

This compound was obtained from the reaction of (+)-10-(2-{[*tert*-butyl(diphenyl)silyl]oxy}-4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]butyl)-2-chloro-10*H*-phenothiazine ((+)-**8**, 0.40 g, 0.56 mmol) and *N*-methylpiperazine (0.12 mL, 1.11 mmol). The crude product was purified by column chromatography on silica gel using the eluent chloroform:methanol = 20:1, 15:1 then 10:1 to give beige amorphous solid, 0.33 g (75%); mp 65–72 °C; $[\alpha]_D^{25}$ − 7.75 (*c* 0.299, chloroform); HPLC: using the eluent *n*-hexane:2-propanol + 0.1% diethylamine = 75:25, retention time: 23.5 min; ν_{max} (KBr)/cm^{-1}: 2932, 2855, 1584, 1516 and 1461.

4.3.76. Ethyl 4-(5-{3-hydroxy-4-[2-(trifluoromethyl)-10*H*-phenothiazin-10-yl]butyl}-2*H*-tetrazol-2-yl)benzoate (20e)

To a solution of ethyl 4-(5-{(1*Z*,3*E*)-4-[2-(trifluoromethyl)-10*H*-phenothiazin-10-yl]buta-1,3-dien-1-yl}-2*H*-tetrazol-2-yl)benzoate[11] (0.56 g, 1 mmol) in abs THF (10 mL) in a dried, round-bottomed flask equipped with a side arm and cooled to 0 °C in an argon atmosphere was added $BH_3 \times Me_2S$ (0.4 mL, 4 mmol) dropwise by injection. After addition, the resulting yellow suspension was allowed to warm up to rt and maintained at this temperature for prolongued time. After the completion of the reation (1 day, monitored by TLC), the reaction mixture was evaporated, then methanol (15 mL) was given to the residue, and stirred for 3 weeks. The reaction mixture was contentrated in vacuo and purified by flash chromatography on silica gel using the eluent dichloromethane, then *n*-hexane:ethyl acetate = 2:1. The crude product (foam) was triturated with diethyl ether and few drops of *n*-hexane, the mixture was cooled whereupon crystals deposited. The product was collected by filtration as white crystals, 0.11 g (19%); mp 107–108 °C; (found: C, 58.50; H, 4.30; N, 12.84; $C_{27}H_{24}F_3N_5O_3S$ requires: C, 58.37; H, 4.35; N, 12.61); *m*/*z* (EI) $[M+H]^+$: 556.30 ($C_{27}H_{24}F_3N_5O_3S$ requires 555.16); ν_{max} (KBr)/cm^{-1}: 3394, 1720, 1425, 1272 and 1125; δ_H (300 MHz, $CDCl_3$) 1.44 (3H, t, J = 7.2 Hz), 2.08 (1H, m), 2.25 (1H, m), 2.63 (1H, br s), 3.17–3.25 (2H, m), 3.90–4.18 (3H, m), 4.43 (2H, q, J = 7.2 Hz), 6.94–7.28 (7H, m), 8.14–8.24 (4H, m); δ_C (75 MHz, $CDCl_3$) 14.3, 21.8, 28.0, 32.1, 53.9, 61.5, 66.3, 112.6, 116.4, 119.4 (2C), 119.8, 123.8, 125.6, 127.8, 127.9, 128.0, 130.0, 130.4, 131.0 (2C), 131.3; 139.5, 144.2, 145.9, 165.4, 166.9.

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