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Selective hydroboration of dieneamines. Formation of hydroxyalkylphenothiazines as MDR modulators

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ABSTRACT

N-dienylphenothiazines synthesized from tetrazolo[1,5-*a*]pyridinium salts by treatment with phenothiazine were subjected to catalytic hydrogenation to yield *N*-butylphenothiazines, whereas transformation of these dienes with borane dimethyl sulfide ($BH_3 \times Me_2S$) resulted in selective hydroboration of one double bond and full reduction of the other double bond to give 2-hydroxybutylphenothiazines. Position of the hydroxyl group was supported by NMR spectroscopy and verified by X-ray analysis. Comparison of MDR modulatory activity of the new derivatives revealed that the hydroxybutyl compounds are promising candidates for development of novel MDR inhibitors.

1. Introduction

Multidrug resistance (MDR) modulatory activity of large number of *N*-substituted phenothiazines is well known from the literature for a long time.[1,2] Some representative derivatives with such biological activity are shown in Figure 1. Some other related heterocyclic derivatives also exhibited valuable biological activities and proved to be inhibitors of mitotic kinesin Eg5 and trigger apoptosis,[3] potential antimicrobial agents,[1,4–6] antitumor agents,[7] antitubercolotic compounds,[8] potential chemotherapeutic agents,[9] antioxidants.[10]

Elaborated syntheses of these compounds include basically two strategies: (a) alkylation of the phenothiazine ring-nitrogen atom[8,13] followed by functionalization of the alkyl chain, and (b) ring closure of the appropriately functionalized alkyl-diphenylamine by sulfur to yield the phenothiazine ring.[14] Comparison of activities of some recently synthesized *N*-alkylphenothiazines[15] revealed that the optimal length of the alkyl chain is four.[16]

The chemotherapy to treat cancer often fails mainly due to tumor resistance that may be either an intrinsic feature of the specific cancer type or may be acquired during the course of initial chemotherapy. A limited intratumoral drug disposition due to the overexpression of multispecific ATP-binding cassette transporters (ABC transporters) of cancer cells is widely regarded as the main molecular mechanism of MDR. The majority of clinically important cases of MDR seems to be the result of overexpression of three ABC transporters: P-glycoprotein (P-gp, ABCB1), multidrug resistance-associated protein 1 (MRP1, ABCC1), and breast cancer resistance protein (BCRP, ABCG2).[17] An attractive approach to overcoming MDR is the inhibition of the pumping action of these transporters.[18] Hundreds of compounds able to inhibit P-glycoprotein or MRP1 have been identified. Their structural diversity is almost as wide as the diversity of substrates recognized by MDR transporters. The ability of phenothiazine derivatives to increase the accumulation of cytotoxic drugs in resistant cancer cells was discovered as early as 1982. Numerous studies have been performed in order to identify structural features important for phenothiazines to constitute good MDR reversing agents.[19]

2. Results and discussion

Recognition of a new access to *N*-dienylphenothiazines (**2**) by utilization of the ring opening reaction of tetrazolo[1,5-*a*]pyridinium salts (**1**) by phenothiazine as a nucleophile[20–22] prompted us to explore the synthetic possibility to variously substituted novel phenothiazines and to test their biological effectiveness in the area (Scheme 1).

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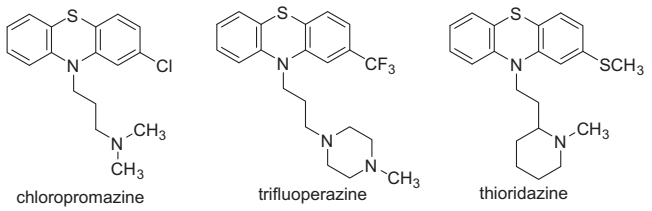


Figure 1. N-substituted phenothiazines as established MDR modulators: chloropromazine[11], trifluoperazine[12], and thioridazine.[13]

For comparative purposes the tetrazolopyridinium salts (**1**) were also reacted with carbazole to provide the analogous dienylcarbazoles (**3**). In both groups of dienes (**2** and **3**) the double bond attached to the tetrazole ring had, in majority, *cis* configuration, and *trans* isomers were observed in special cases only.[23]

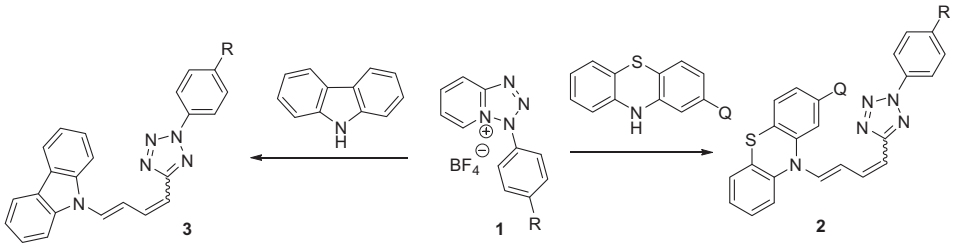
Since the known biologically active compounds contained a saturated alkyl chain at the ring-nitrogen atom of the heterocycles, reduction of the obtained diene was envisaged. A specific structural advantage of these target products is the length of the alkyl chain (4 carbon atoms) which was found to be optimal in a recent study.[16] This synthetic plan would represent an unprecedented approach to *N*-alkylphenothiazines. As catalytic hydrogenation of *N*-ethenylphenothiazine, in spite of the presence of the sulfur atom, has been carried out successfully[24] to yield the *N*-ethyl compound, catalytic hydrogenation of the dienylphenothiazines (**2**) and dienylcarbazoles (**3**) was tried first.

Both dienes (**2** and **3**) underwent saturation with catalytic hydrogenation at room temperature (Scheme 2). As expected—due to the presence of the sulfur atom—the yields strongly varied (10–99%) in case of reduction of **2**. Furthermore, the bromo and chloro atoms at the phenyl substituent (i.e. with **2b** and **2f**) also underwent hydrogenation simultaneously with reduction of the diene moiety and, thus, both of these dienes resulted in formation of unsubstituted phenyl rings (**4a** and **4e**, respectively). In contrast to reduction of **2**, hydrogenation of the dienylcarbazoles (**3**) was carried out in good yields (52–98%). Also in this case, the bromo and chloro atoms at the phenyl substituent were substituted by hydrogen atom and, thus, both **3a** and **3b** gave the same phenyltetrazolylcarbazole **5a**.

Because of the low yields experienced in some cases and the non-desired dehalogenation at the phenyl group, elaboration of another reduction method seemed necessary and, thus, reduction with borane was decided. In this respect we have shown recently[20] that treatment of *N*-dienylphenothiazines (**2**) with borane dimethyl sulfide ($BH_3 \times Me_2S$) in abs. THF resulted in formation of tetrazolo[5,1-*f*][1,2]azaborinin (**7**) as a new heterocyclic ring system (Scheme 3). As the reaction was interpreted by intermediate formation of the 2-butylborane **6**, modification of the reaction conditions seemed to provide a possibility for formation of fully reduced and boron-free products.

Thus, when the reaction of **2** with $BH_3 \times Me_2S$ in THF was warmed up to room temperature, methanol was added and the reaction mixture was stirred at room temperature in the presence of air for prolonged time. A new spot appeared on the TLC of the reaction mixture and spectral analysis of this new component revealed formation of 4-(2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)butan-2-ol (**8b**) in poor yield. As this compound was obviously result of a hydroboration reaction we had to assume that an oxidative reaction step took place on the effect of the areal oxygen. Therefore we have repeated this conversion with addition of hydrogen peroxide and found that the butanol derivative **8** was formed as main product in acceptable yield (Scheme 4). In order to check whether the earlier isolated azaborinin compound **7** is an intermediate in the pathway leading to **8**, two azaborinin derivatives (**7i** and **7j**) were prepared according to the published procedure[20], and these compounds were then subjected to oxidation by hydrogen peroxide in methanol. As a result, **8h** and **8i** have been obtained in good yields, which supported the intermediacy of **7** in the course of the hydroboration reaction.

Furthermore, thorough analysis of the reaction mixture obtained with the synthesis of **8i** revealed the presence of two



entry	R
a	Br
b	Cl
c	OMe
d	Me

3

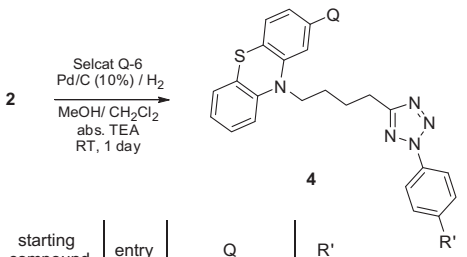
entry	R
a	Br
b	Cl
c	OMe
d	Me
e	F

1

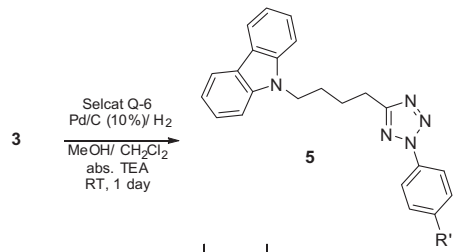
entry	Q	R
a	H	Br
b	H	Cl
c	H	OMe
d	H	Me
e	H	F
f	CF_3	Br
g	CF_3	OMe
h	2-methyl-1,3-dioxolane	OMe
i	Cl	Br
j	Cl	OMe

2

Scheme 1. Ring opening of tetrazolo[1,5-*a*]pyridinium salts (**1**) by phenothiazine and carbazole to dienylphenothiazines (**2**) and dienylcarbazoles (**3**), respectively.



starting compound	entry	Q	R'
2a, 2b	**a**	H	H
2c	**b**	H	OMe
2d	**c**	H	Me
2e	**d**	H	F
2f	**e**	CF_3	H
2g	**f**	CF_3	OMe
2h	**g**	2-methyl-1,3-dioxolane	OMe



starting compound	entry	R'
3a, 3b	**a**	H
3c	**b**	OMe
3d	**c**	Me

Scheme 2. Catalytic hydrogenation of dienylphenothiazines (**2**) and dienylcarbazoles (**3**).

additional compounds as side-products: the sulfoxide derivative **9** was formed in 25% yield, whereas the dihydroxy compound **10** was also detected in traces (6%). NMR spectra of these compounds reveal that both have been formed as diastereomeric mixtures. Formation of these minor products is clearly result of the subsequent oxidation steps.

Even if our recent study[20] on the borazine ring system showed that the boron atom attached to position 2 of the butyl chain and, consequently, introduction of the hydroxyl group can be expected at this position, a firm determination of the structure of **8** seemed of interest. To this end, NMR structure elucidation and X-ray analysis have been carried out.

The assignment of ^{1}H, ^{13}C, ^{15}N resonances for compounds **8i**, **9** and **10** followed the regular procedure: collection and analysis of 1D (^{1}H, ^{13}C, selective 1D-TOCSY, selective 1D-NOESY) and through-bond correlation (^{1}H–^{13}C gHSQC, ^{1}H–^{13}C gHMBC, ^{1}H–^{15}N gHMBC) data. The exact position of OH groups was determined from HMBC measurements. The OH–C2 and OH–C3 crosspeaks in the gHMBC spectra of **8i** and **9** suggested location of the OH substituent at C2 carbon. A further OH group could be identified at C4 carbon in compound **10**, according to the OH–C4 and OH–C3 cross peaks in the corresponding HMBC spectrum.

The compound 4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)butan-2-ol (**8a**), which crystallizes in the triclinic crystal system in the centrosymmetric *P*-1 space group, was subjected to structural analysis. The structure was determined by single crystal X-ray diffraction using a Rigaku R-Axis Rapid diffractometer with MoKα radiation at room temperature (Table 1, Supplementary data). It is an ordered structure, there is one molecule of **8a** in the asymmetric unit (Fig. 2). The unit cell contains no residual solvent accessible void. The packing coefficient is 67.3%.

The bond lengths around the heteroatoms in the molecule are listed in Table 2 (Supplementary data). The angles of the aromatic rings according to the assignment in Figure 2 are A-B: 6.50(12)°, C-D: 46.24(13)°, A–C: 20.50(12)°, A–D: 66.66(11)°, B–C: 14.40(13)° and B–D: 60.64(13)°. The conformation of the molecule is stabilized by weak intramolecular interactions, one C–H···O, and four C–H···N hydrogen bond occurs (Table 3, Fig. 5, Supplementary data). The intramolecular distance of the B and C ring centroids is 3.946(2) Å.

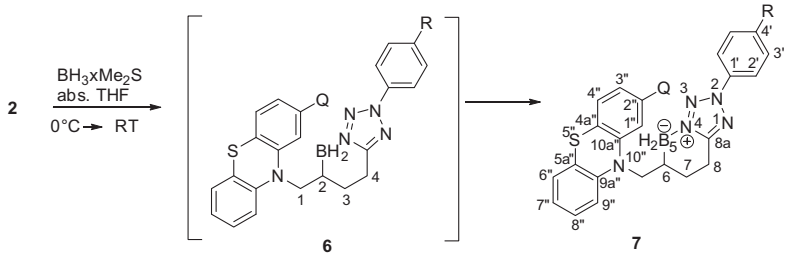
Hydroboration of butadienes has only sparingly been studied earlier, most of these results were born in laboratory of H. C. Brown. Thus, an early paper reported that some butadienes yield 1,3- and 1,4-diols[26], monohydroboration of cyclic butadienes gave allylic and homoallylic products.[27] In some special cases monohydroboration was experienced with retention of one of the double bonds.[28] To the best of our knowledge, hydroboration of a 1,3-diene to a saturated 2-butanol has not yet been reported in the literature.

The observed selectivity, that is, formation of the 2-butanol derivative **8** is obviously due to the presence of the electron releasing tertiary amine moiety provided by the nitrogen atom of the phenothiazine ring. Product of the other possible hydroboration (4-butanol) was not detected, only butan-2,4-diol (**10**) was found in traces as result of an excessive oxidation.

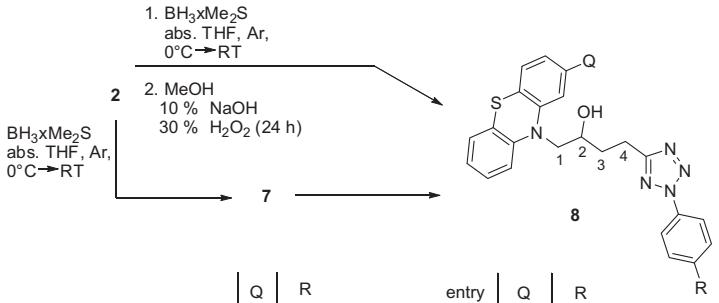
The hydroboration reaction of dienylphenothiazines proved to be a general approach to *N*-phenothiazinylbutan-2-ols and, thus, a great variety of variously substituted products (**8a**–**i**) have been synthesized in good to excellent yields (Scheme 4).

Two further synthetic modifications have been carried out in order to extend the structural variation of the new alkylphenothiazines and alkylcarbazoles:

(a) The above discussed hydroboration reaction was successfully applied also for one of the dienylcarbazoles (**3c**). Transforma-

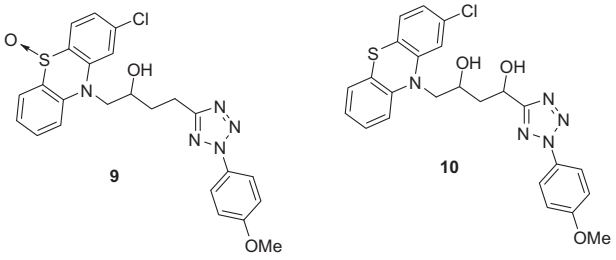


Scheme 3. Formation of tetrazolo[5,1-*f*][1,2]azaborinin (**7**) from dienylphenothiazines (**2**).



	Q	R
7i	Cl	Br
7j	Cl	OMe

entry	Q	R
a	H	Br
b	H	Cl
c	H	OMe
d	H	Me
e	H	F
f	CF_3	Br
g	CF_3	OMe
h	Cl	Br
i	Cl	OMe



Scheme 4. Hydroboration reaction of dienylphenothiazines.

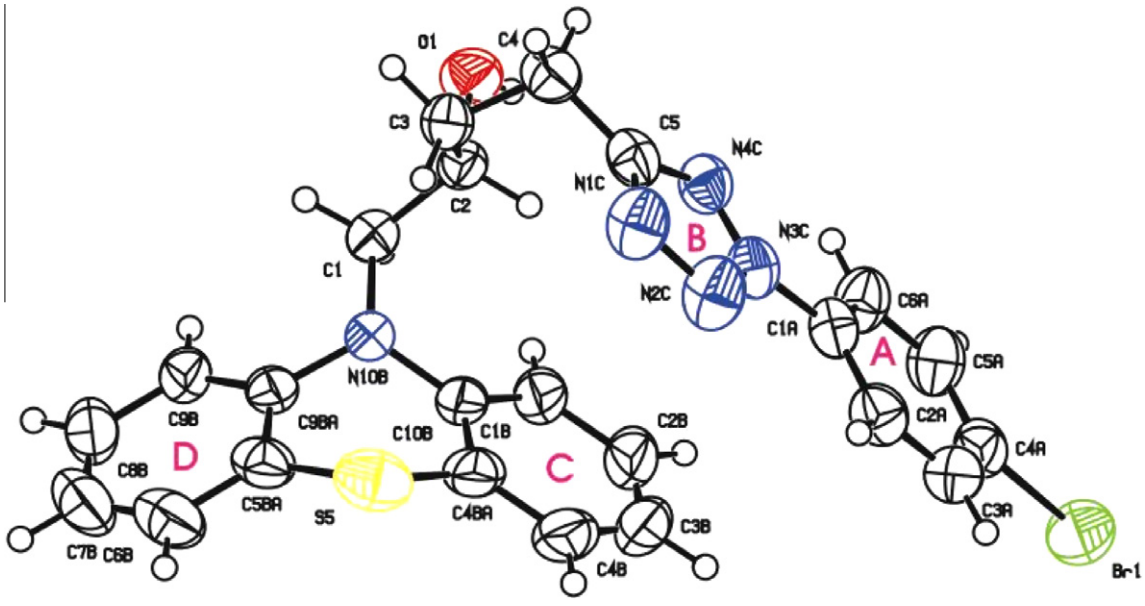
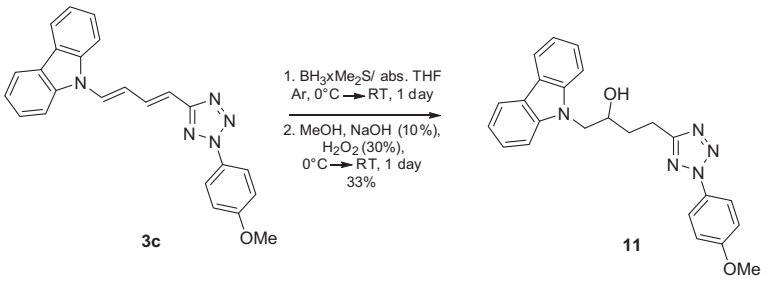


Figure 2. The ORTEP diagram of **8a** at 50% probability level with atomic labels and ring assignment.[25]

tion of this compound with $BH_3 \times Me_2S$ gave the carbazole-containing 2-butanol (**11**) in modest yield (33%) (Scheme 5).

(b) As the new alkylphenothiazines and alkylcarbazoles discussed here contained a tetrazolylbutyl chain whereas in most of



Scheme 5. Hydroboration of dienylcarbazole (**3c**).

the earlier established MDR inhibitory compounds (Fig. 1) a propyl chain attached to the ring-nitrogen atom of the heterocycle, synthesis of a tetrazolylpropylphenothiazine seemed also of interest. This has been realized as shown in Scheme 6.

The tetrazolylacrolein derivative **12** described by us recently[29,30] served proper starting compound for this purpose: its reaction with phenothiazine and NBS gave the acylphenothiazine **13** which, under the hydroboration reaction underwent reduction. Most interestingly, in this case the full reduction of the propanone chain occurred and the product (**14**) did not contain any OH group in the alkyl chain.

3. Biological evaluation. Determination of P-gp inhibitor potency of compounds

Rhodamin 123 (RH 123) accumulation studies were performed to characterize the effect of some selected compounds (**2c, 4b, 8c, 11, 14**) on P-gp dependent transport activity in primary rat hepatocyte cultures.

RH 123, a lipophilic cation, a typical P-gp substrate is a subject to a P-gp dependent extrusion through the plasma membrane. Due to its fluorescence, dye levels can easily be measured in cell extracts and accumulation can be observed in intact cells. RH 123 accumulation in cells and efflux from cells is often used to measure P-gp dependent transport activity. High intracellular steady state accumulation of the dye is interpreted of low P-gp activity, and vice versa. Accordingly, inhibition of P-gp enzymes results in a decreased efflux of the dye, subsequently in an increased accumulation level. Verapamil, a known P-gp inhibitor was used as a positive control.[31]

Cells were loaded with 5 μM RH 123 for 30 min, than incubated in the absence (control, with 0.1% DMSO) or presence of modulators for 3 h. Data represent mean values ±S.D. of three experiments performed in triplicate. Dye accumulation in control cells set to 100%.

Results are summarized in Fig. 6. At first, all compounds were applied at 100 μM concentration. Then, if a derivative at 100 μM increased RH 123 accumulation more than twofold of the control, the concentration dependence of the inhibition was also measured. **8c** proved to be the most effective P-gp inhibitor among the compounds measured. It increased the intracellular RH 123 concentration in a concentration dependent manner; however, did not reach the efficacy of verapamil. The other compounds did not show significant P-gp inhibitory potential, though some difference could have been observed.

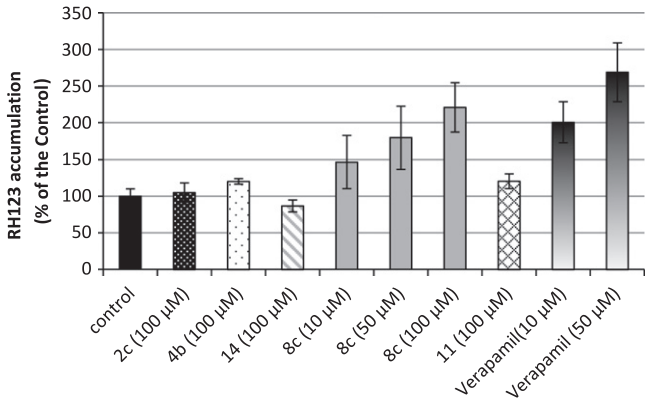
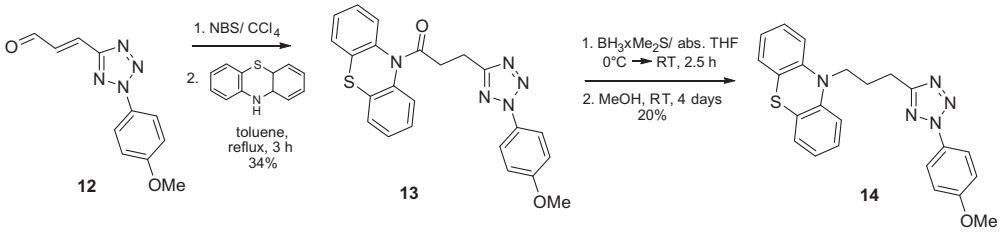


Figure 6. Modulation of intracellular RH 123 accumulation in primary rat hepatocytes cultured for 4 days.

2c and **14** did not increase the intracellular RH 123 accumulation at all and, moreover, in the presence of **14** a slight decrease was observed. **4b** slightly enhanced the dye concentration, not more than by 20% of the control, even at 100 μM. The inhibitory potential of the compounds measured showed the following order: **14** < **2c** < **4b** < **11** < **8c** < verapamil. The presence of the 2-butanol chain seemed to be essential in regard to the P-gp modulator potency of the new alkylphenothiazines. The lack of the OH group (**4b**) significantly decreased the rate of inhibition, while substitution of 2-butanol chain with an unsaturated dienyl (**2c**) or with a shorter propyl chain (**14**) resulted in the complete loss of activity. Probably, the phenothiazine part of the molecule also takes part in the interaction with P-gp, as the carbazole derivative (**11**) showed much less inhibitory potential.

4. Conclusions

As a result of our findings, a new convenient synthetic pathway to a large variety of *N*-alkyl and hydroxyalkylphenothiazines and



Scheme 6. Synthetic pathway to a *N*-tetrazolylpropylphenothiazine derivative.

related carbazoles has been elaborated by utilization of the observed selective hydroboration of the parent dienophenothiazines. Comparison of the biological tests revealed that the presence of the hydroxyl group is significantly increases the MDR inhibitory property of these compounds and, thus, can be regarded as a valuable area for discovery of clinically useful new MDR modulators. Further structural modifications of these derivatives as well as biological evaluation is in progress.

5. Experimental part

5.1. General methods

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR experiments were carried out on 300 MHz (for ^{1}H), 400 MHz (for ^{1}H) and 600 MHz (for ^{1}H) Varian NMR SYSTEM spectrometers by using 5 mm direct detection ^{15}N–^{31}P/{^{1}H–^{19}F} probes equipped with Z pulse field gradient. Measurements were performed at +25 °C in $CDCl_3$ or DMSO. ^{1}H and ^{13}C NMR spectra are referenced to residual solvent signals. ^{15}N shifts are referenced to CH_3NO_2 (90% in $CDCl_3$) chemical shift standard. The elemental analysis has been carried out with an Elementar Vario EL III apparatus (at the Analytical Laboratory for Organic Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, H-1025 Budapest, Pusztaszeri út 59). 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). All the chemicals and solvents were used as supplied.

5.2. Single crystal data, data collection and structure refinement for 8a

Crystal data for **8a**: $C_{23}H_{20}BrN_5OS$, Fwt.: 494.41, Colorless, column, size: 0.50 × 0.25 × 0.13 mm, triclinic, space group *P*-1, a = 6.3137(13) Å, b = 11.196(3) Å, c = 15.972(4) Å, α = 90.96(1)°, β = 97.645(9)°, γ = 103.294(9)°, V = 1087.7(4) Å^3, Z = 2, $F(000)$ = 504, D_x = 1.510 mg/m^3, μ = 2.012 mm^{-1}.

A crystal of **8a** was mounted on a loop. Cell parameters were determined by least-squares using 6535 ($3.105° \leqslant \theta \leqslant 35.582°$) reflections. Intensity data were collected on an R-Axis Rapid diffractometer (graphite monochromator Mo-$K\alpha$ radiation, λ = 0.71073 Å) at 293(2) K in the range $3.11° \leqslant \theta \leqslant 27.48°$. A total of 48448 reflections were collected of which 4983 were unique [R(int) = 0.0324, $R(\sigma)$ = 0.0170]; intensities of 3734 reflections were greater than $2\sigma(I)$. Completeness to θ = 0.999. Empirical absorption correction was applied to the data (the minimum and maximum transmission factors were 0.4329 and 0.7800).

The structure was solved by direct methods.[32] Neutral atomic scattering factors are taken from the International Tables for X-ray Crystallography.[33] Anisotropic full-matrix least-squares refinement[32,34] on F^2 for all non-hydrogen atoms yielded $R1$ = 0.0387 and $wR2$ = 0.0877 for 1332 [$I > 2\sigma(I)$] and $R1$ = 0.0573 and $wR2$ = 0.0953 for all (4983) intensity data, (number of parameters = 283, goodness-of-fit = 1.045, the maximum and mean shift/esd is 0.001 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.339 and −0.360e.Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2)+(0.0401P)^2 + 0.4050P]$, where $P = (F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to. Crystallographic data for the above crystal structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 862636.

5.3. Method for determination of P-gp inhibitor properties

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.[35] 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 M 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. 1 h after plating, and every day thereafter the medium was changed to Williams Medium E supplemented with glucagon, insulin, gentamicin, dexamethasone, Na_2SeO_3. RH 123 accumulation experiments were performed at 4 days after plating. Cells were preloaded with 5 αM RH 123 in Williams' Medium E for 30 min and then washed three times with ice cold Hanks Balaced Salt Solution (HBSS) and incubated with RH 123 free Williams' Medium E complemented with the inhibitors or the vehicle as control (0.1% DMSO), respectively for 3 h. Subsequently, cells were washed with ice cold HBSS and the cells were lysed with 0.5% of Triton X100/HBSS. The intracellular RH 123 concentration was measured fluorimetrically at 519/538 nm.

5.3.1. General procedure for preparation of tetrazolyldienylphenothiazines (2a–j)

To a mixture of sodium hydride suspension (60%, 0.26 g, 6.67 mmol) and phenothiazine derivative in abs. THF (50 cm^3) was added the appropriate 3-aryltetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1**) in portions over 20 min, and the mixture was stirred at room temperature for 2 days. After evaporation of the reaction mixture, the residue was dissolved in a 1:1 mixture of EtOAc:water (50 cm^3) and the solid product was filtered off. The aqueous mother liquor was extracted with EtOAc (thrice) and the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The combined organic solvent was evaporated, the residue was washed with diethyl ether then it was recrystallized from ethyl acetate – unless otherwise stated - to give the product.

5.3.2. 10-((1*E*,3*Z*)-4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (2a)

This compound was obtained from 3-(4-bromophenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1a**, 2.00 g, 5.51 mmol) and phenothiazine (1.21 g, 6.06 mmol) as yellow crystals, 1.98 g (76%).[14]

5.3.3. 10-((1*E*,3*Z*)-4-(2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (2b)

This compound was obtained from 3-(4-chlorophenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1b**, 1.75 g, 5.51 mmol) and phenothiazine (1.21 g, 6.06 mmol) as yellow crystals, 1.91 g (81%).[14]

5.3.4. 10-((1*E*,3*Z*)-4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (2c)

This compound was obtained from 3-(4-methoxyphenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1c**, 1.73 g, 5.51 mmol) and phenothiazine (1.21 g, 6.06 mmol) as yellow-brown crystals, 1.73 g (74%).[14]

5.3.5. 10-((1*E*,3*Z*)-4-(2-(*p*-Tolyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (2d)

This compound was obtained from 3-(*p*-tolyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1d**, 1.64 g, 5.51 mmol) and phenothiazine (1.21 g, 6.06 mmol) to give yellow crystals, 1.83 g (81%).[14]

5.3.6. 10-((1*E*,3*Z*)-4-(2-(4-Fluorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (2e)

This compound was obtained from 3-(4-fluoro)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1e**, 1.64 g, 5.51 mmol) and phenothiazine (1.21 g, 6.06 mmol). Recrystallization from acetonitrile gave yellow crystals, 1.30 g (57%); mp 175–177 °C; (Found: C, 66.45; H, 3.57; N, 16.56; $C_{23}H_{16}FN_5S$ requires C, 66.81; H, 3.90; N, 16.94%); ν_{max} (KBr)/cm^{-1}: 3089, 3063, 1623, 1512 and 995; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 6.19 (1H, d, J = 11.1 Hz), 6.63 (1H, dd, J = 11.4, 11.1 Hz), 7.15–7.23 (5H, m), 7.30–7.36 (4H, m), 7.54 (2H, m), 7.66 (1H, dd, J = 13.2, 11.4 Hz), 8.01 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 103.5, 105.8, 116.4 (d, $^2J_{C,F}$ = 21 Hz), 121.4 (d, $^3J_{C,F}$ = 9 Hz), 122.4 (2C), 125.5 (2C), 127.4 (2C), 128.1 (2C), 130.5 (2C), 133.1, 136.6, 141.1, 141.5 (2C), 162.7 (d, $^1J_{C,F}$ = 248 Hz), 164.8; *m/z* (EI) [M+H]$^+$: 414.20 ($C_{23}H_{16}FN_5S$ requires 413.11).

5.3.7. 10-((1*E*,3*Z*)-4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(trifluoromethyl)-10*H*-phenothiazine (2f)

This compound was obtained from 3-(4-bromophenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1a**, 2.00 g, 5.51 mmol) and 2-(trifluoromethyl)-10*H*-phenothiazine (1.62 g, 6.06 mmol) as yellow crystals, 2.27 g (76%); mp 175–180 °C; (Found: C, 53.44; H, 2.84; N, 12.57; $C_{24}H_{15}BrF_3N_5S$ requires C, 53.15; H, 2.79; N, 12.91%); ν_{max} (KBr)/cm^{-1}: 3374, 2361, 1623, 1585 and 994; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 6.24 (1H, d, J = 11.4 Hz), 6.40 (1H, t, J = 11.4 Hz), 7.15–7.43 (6H, m), 7.56–7.72 (5H, m), 7.90 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 104.4, 106.9, 118.7 (q, $^3J_{C,F}$ = 4 Hz), 121.0 (2C), 122.1 (q, $^3J_{C,F}$ = 4 Hz), 122.7, 123.0, 124.5 (q, $^1J_{C,F}$ = 270 Hz), 126.0, 127.8, 128.3, 128.4, 129.5 (q, $^2J_{C,F}$ = 30 Hz), 132.6 (2C), 135.2, 135.7, 135.8, 136.1, 140.3, 140.6, 142.2, 164.6; *m/z* (EI) [M+H]$^+$: 542.00 ($C_{24}H_{15}BrF_3N_5S$ requires 541.02).

5.3.8. 10-((1*E*,3*Z*)-4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(trifluoromethyl)-10*H*-phenothiazine (2g)

This compound was obtained from 3-(4-methoxyphenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1c**, 1.73 g, 5.51 mmol) and 2-(trifluoromethyl)-10*H*-phenothiazine (1.62 g, 6.06 mmol) as yellow crystals, 1.06 g (39%).[16]

5.3.9. 10-((1*E*,3*Z*)-4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(2-methyl-1,3-dioxolan-2-yl)-10*H*-phenothiazine (2h)

This compound was obtained from 3-(4-methoxyphenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1c**, 2.00 g, 6.61 mmol) and 2-(2-methyl-1,3-dioxolan-2-yl)-10*H*-phenothiazine (2.00 g, 7.00 mmol) as yellow crystals, 2.97 g (91%); mp 200–203 °C; (Found: C, 65.44; H, 4.99; N, 13.46; $C_{28}H_{25}N_5O_3S$ requires C, 65.74; H, 4.93; N, 13.69%); ν_{max} (KBr)/cm^{-1}: 3092, 2993, 1622, 1514 and 1033; ^{1}H NMR (300 MHz; $CDCl_3$-DMSO; Me_4Si) δ (ppm): 1.64 (3H, s), 3.79–4.02 (7H, m), 6.15 (1H, d, J = 10.8 Hz), 6.65 (1H, dd, J = 11.4, 10.8 Hz), 7.00 (2H, m), 7.17–7.68 (9H, m), 7.91 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$-DMSO; Me_4Si) δ (ppm): 27.9, 56.2, 64.7 (2C), 103.9, 105.6, 108.4, 110.0, 115.4 (2C), 119.7, 121.6, 121.9, 123.1, 126.3, 128.3 (2C), 128.5, 129.3, 130.0, 130.3, 137.3, 141.4, 141.9, 144.4, 160.7, 164.7; *m/z* (EI) [M+H]$^+$: 512.40 ($C_{28}H_{25}N_5O_3S$ requires 511.17).

5.3.10. 10-((1*E*,3*Z*)-4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-chloro-10*H*-phenothiazine (2i)

This compound was obtained from 3-(4-bromophenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1a**, 2.00 g, 5.51 mmol) and 2-chlorophenothiazine (1.42 g, 6.07 mmol) as yellow crystals, 1.54 g (55%); mp 179–181 °C; (Found: C, 54.29; H, 2.97; N, 13.76; $C_{23}H_{15}BrClN_5S$ requires C, 54.10; H, 3.00; N, 13.39%); ν_{max} (KBr)/cm^{-1}: 3087, 2921, 1620, 1583 and 995; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 6.23 (1H, d, J = 11.4 Hz), 6.62 (1H, t, J = 11.4 Hz), 7.14–7.26 (5H, m), 7.32–7.38 (2H, m), 7.50–7.58 (2H, m), 7.62–7.66 (2H, m), 7.93–7.96 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 104.1, 106.6, 121.0 (2C), 122.3, 122.6, 123.3, 125.7, 125.8, 127.6, 128.2, 128.8, 129.1, 130.2, 132.7 (2C), 133.3, 135.7, 136.3, 140.5, 141.2, 142.5, 164.6; *m/z* (EI) [M+H]$^+$: 510.10 ($C_{23}H_{15}BrClN_5S$ requires 508.82).

5.3.11. 2-Chloro-10-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (2j)

This compound was obtained from 3-(4-methoxyphenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1c**, 2.00 g, 6.35 mmol) and 2-chlorophenothiazine (1.64 g, 7.00 mmol) as yellow-brown crystals, 1.69 g (59%).[16]

5.3.12. General procedure for preparation of tetrazolyldienyl-carbazoles (3a–d)

To a mixture of sodium hydride suspension (60%, 0.26 g, 6.67 mmol) and carbazole (1.01 g, 6.06 mmol) in abs. THF (50 cm^3) was added the appropriate 3-aryltetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1**, 5.5 mmol) in portions over 20 min, and the mixture was stirred at room temperature for 2 days. After evaporation of reaction mixture the residue was dissolved in a 1:1 mixture of EtOAc:water (50 cm^3), the solid product was filtered off and washed thrice with diethyl ether. The products were isolated after recrystallization from the given solvent.

5.3.13. 9-((1*E*,3*Z*)-4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (3a)

This compound was obtained from 3-(4-bromophenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetra-fluoroborate (**1a**, 2.00 g, 5.5 mmol). Recrystallization from dimethyl formamide/ hexane gave yellow crystals, 1.5 g (62%); mp 201–206 °C; (Found: C, 62.18; H, 3.16; N, 15.81; $C_{23}H_{16}BrN_5$ requires C, 62.46; H, 3.65; N, 15.83%); ν_{max} (KBr)/cm^{-1}: 3351, 3045, 1635, 1497 and 995; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 6.54 (1H, d, J = 11.4 Hz, H4), 6.87 (1H, dd, J = 11.7, 11.4 Hz, H3), 7.37 (2H, m, H3″ + H6″), 7.53 (2H, m, H2″ + H7″), 7.65–7.74 (3H, m, H1 + H3′ + H5′), 7.92 (2H, d, J = 8.1 Hz, H4″ + H5″), 8.08–8.14 (4H, m, H2′ + H6′ + H1″ + H8″), 8.35 (1H, dd, J = 14.1, 11.7 Hz, H2); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 110.7 (C2), 111.1 (C1″ + C8″), 114.0 (C4), 120.4 (C3″ + C6″), 121.0 (C4″ + C5″), 121.7 (C2′ + C6′), 123.4 (C4′), 124.9 (C4a″ + C5a″), 126.6 (C2″ + C7″), 130.9 (C3), 132.9 (C3′ + C5′), 135.5 (C1), 135.8 (C1′), 139.1 (C8a″ + C9a″), 164.5 ($C_{tetrazole}$); *m/z* (EI) [M+H]$^+$: 442.20 ($C_{23}H_{16}BrN_5$ requires 441.06).

5.3.14. 9-((1*E*,3*Z*)-4-(2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (3b)

This compound was obtained from 3-(4-chlorophenyl)-3*H*-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1b**, 1.75 g, 5.5 mmol). Recrystallization from dimethyl formamide/MeOH gave yellow crystals, 1.34 g (61%); mp 198–203 °C; (Found: C, 69.28; H, 3.67; N, 17.59; $C_{23}H_{16}ClN_5$ requires C, 69.43; H, 4.05; N, 17.60%); ν_{max} (KBr)/cm^{-1}: 3045, 1635, 1498, 1454 and 997; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 6.55 (1H, d, J = 11.1 Hz), 6.87 (1H, dd, J = 12.0, 11.1 Hz), 7.37 (2H, t, J = 8.1 Hz), 7.51–7.59 (4H, m), 7.68 (1H, d, J = 14.1 Hz), 7.92 (2H, d, J = 8.1 Hz), 8.08–8.11 (2H, m), 8.18–8.21 (2H, m), 8.35 (1H, dd, J = 14.1, 11.1 Hz); ^{13}C NMR

(75 MHz; $CDCl_3$) δ (ppm): 110.7 (2C), 111.1, 114.0, 114.4, 120.3 (2C), 120.7 (2C), 121.1 (2C), 124.0, 126.2 (2C), 130.0 (2C), 131.3, 135.5, 135.6, 139.2, 140.5 (2C), 164.0; *m/z* (EI) $[M+H]^+$: 398.10 ($C_{23}H_{16}ClN_5$ requires 397.11).

5.3.15. 9-((1*E*,3*Z*)-4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (3c)

This compound was obtained from 3-(4-methoxyphenyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1c**, 1.73 g, 5.5 mmol). Recrystallization from dimethyl formamide/MeOH gave yellow crystals, 1.37 g (63%); mp 183–186 °C; (Found: C, 73.22; H, 4.50; N, 17.81; $C_{24}H_{19}N_5O$ requires C, 73.27; H, 4.87; N, 17.80%); ν_{max} (KBr)/cm^{-1}: 3325, 1639, 1514, 1453 and 999; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 3.88 (3H, s), 6.52 (1H, d, J = 11.4 Hz), 6.80 (1H, t, J = 11.4 Hz), 7.05 (2H, d, J = 7.5 Hz), 7.34 (2H, t, J = 7.5 Hz), 7.51 (2H, t, J = 7.5 Hz), 7.62 (1H, d, J = 14.1 Hz), 7.90 (2H, d, J = 7.5 Hz), 8.05–8.15 (4H, m), 8.33 (1H, dd, J = 14.1, 11.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 55.7, 110.0, 111.1 (2C), 114.1, 114.7 (2C), 120.3 (2C), 121.2 (2C), 121.6 (2C), 124.8 (2C), 126.6 (2C), 130.4, 130.5, 134.8, 139.1 (2C), 160.4, 164.0; *m/z* (EI) $[M+H]^+$: 394.30 ($C_{24}H_{19}N_5O$ requires 393.16).

5.3.16. 9-((1*E*,3*Z*)-4-(2-(*p*-Tolyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (3d)

This compound was obtained from 3-(*p*-tolyl)-tetrazolo[1,5-*a*]pyridin-4-ium tetrafluoroborate (**1d**, 1.64 g, 5.5 mmol). Recrystallization from dimethyl formamide/MeOH gave yellow crystals, 1.30 g (63%); mp 190–195 °C; (Found: C, 76.28; H, 4.86; N, 18.59; $C_{24}H_{19}N_5$ requires C, 76.37; H, 5.07; N, 18.55%); ν_{max} (KBr)/cm^{-1}: 3043, 1638, 1494, 1453 and 1000; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.45 (3H, s), 6.52 (1H, d, J = 11.4 Hz), 6.80 (1H, t, J = 11.4 Hz), 7.25–7.36 (4H, m), 7.51 (2H, t, J = 8.4 Hz), 7.60 (1H, d, J = 14.1 Hz), 7.90 (2H, d, J = 8.4 Hz), 8.04–8.10 (4H, m), 8.32 (1H, dd, J = 14.1, 11.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.6, 111.5, 111.6 (2C), 114.4, 119.9 (2C), 120.7 (2C), 122.0 (2 C), 125.2 (2C), 127.0 (2C), 130.6 (2 C), 130.9, 135.0, 135.3, 139.6 (2C), 140.2, 164.5; *m/z* (EI) $[M+H]^+$: 378.30 ($C_{24}H_{19}N_5$ requires 377.16).

5.3.17. General procedure for preparation of *N*-tetrazolylbutyl-phenothiazines (4a–g)

A mixture of the appropriate dienylphenothiazine (**2**, 1 mmol), Pd/C Selcat Q-6 (10%, 0.30 g) and abs. triethylamine (0.28 cm^3, 2 mmol) in MeOH (10 cm^3)/CH_2Cl_2 (2 cm^3) was hydrogenated (1 atm, under atmospheric pressure) at room temperature until the absorption of hydrogen ceased (1 day). After the Pd/C catalyst was filtered off, the solvent was removed in *vacuo*. The residue was diluted with water, pH was adjusted to 8 by 10% $NaHCO_3$ solution. The product was extracted with dichloromethane (thrice). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was triturated with diethyl ether and few drops of hexane, then the resulting crystals were collected by filtration.

5.3.18. 10-(4-(2-Phenyl-2*H*-tetrazol-5-yl)butyl)-10*H*-phenothiazine (4a)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-pheno-thiazine (**2a**, 0.47 g, 1 mmol) to give a crystalline product 0.04 g (10%) which became liquid (brown oil) at room temperature; (Found: C, 69.01; H, 5.01; N, 17.35; $C_{23}H_{21}N_5S$ requires C, 69.15; H, 5.30; N, 17.53%); ν_{max} (liquid film)/cm^{-1}: 2785, 2770, 1506, 1454 and 760; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.95–2.02 (4H, m), 3.02 (2H, t, J = 6.8 Hz), 3.93 (2H, t, J = 6.6 Hz), 6.85–6.92 (4H, m), 7.11–7.15 (4H, m), 7.44–7.56 (3H, m), 8.08 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.3, 25.5, 26.4, 47.0, 115.7 (2C), 120.0 (2C), 122.7 (2C), 125.5 (2C), 127.4 (2C), 127.7 (2C), 129.7, 129.8 (2C), 137.1, 145.5 (2C), 166.9; *m/z* (EI) $[M+H]^+$: 400.20 ($C_{23}H_{21}N_5S$ requires 399.15).

The same product (**4a**) was also obtained by the following transformations: hydrogenation of 10-((1*E*,3*Z*)-4-(2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2b**): 0.08 g (43%).

5.3.19. 10-(4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)butyl)-10*H*-phenothiazine (4b)

This compound was obtained by hydrogenation of 10-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2c**, 0.43 g, 1 mmol) to give the product as beige crystals, 0.28 g (65%); mp 82–86 °C; (Found: C, 67.07; H, 5.04; N, 16.32; $C_{24}H_{23}N_5OS$ requires C, 67.11; H, 5.40; N, 16.30%); ν_{max} (KBr)/cm^{-1}: 2945, 1512, 1455, 1254 and 999; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.87–2.09 (4H, m), 2.99 (2H, t, J = 6.6 Hz), 3.88 (3H, s), 3.93 (2H, t, J = 6.0 Hz), 6.84–6.92 (4H, m), 7.00–7.04 (2H, m), 7.07–7.18 (4H, m), 7.98 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.1, 25.3, 26.2, 46.8, 55.7, 114.6 (2C), 115.4 (2C), 121.3 (2C), 122.4 (2C), 125.2 (2C), 127.2 (2C), 127.5 (2C), 130.5, 145.2 (2C), 160.4, 166.4; *m/z* (EI) $[M+H]^+$: 430.20 ($C_{24}H_{23}N_5OS$ requires 429.16).

5.3.20. 10-(4-(2-(*p*-Tolyl)-2*H*-tetrazol-5-yl)butyl)-10*H*-phenothiazine (4c)

This compound was obtained by hydrogenation of 10-((1*E*,3*Z*)-4-(2-(*p*-tolyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2d,** 0.20 g, 0.5 mmol) to give the product as beige crystals, 0.04 g (20%); mp 71–75 °C; (Found: C, 69.41; H, 5.74; N, 16.86; $C_{24}H_{23}N_5S$ requires C, 69.71; H, 5.61; N, 16.94%); ν_{max} (KBr)/cm^{-1}: 3394, 2877, 1515, 1455 and 1006; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.93–2.05 (4H, m), 2.43 (3H, s), 3.00 (2H, t, J = 7.0 Hz), 3.92 (2H, t, J = 6.6 Hz), 6.84–6.91 (4H, m), 7.10–7.15 (4H, m), 7.32 (2H, m), 7.94 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.3, 25.2, 25.5, 26.4, 47.0, 115.6 (2C), 119.8 (2C), 122.6 (2C), 125.4 (2C), 127.3, 127.6 (2C), 130.2 (2C), 131.8, 139.8 (2C), 145.4 (2C), 166.6; *m/z* (EI) $[M+H]^+$: 414.30 ($C_{24}H_{23}N_5S$ requires 413.17).

5.3.21. 10-(4-(2-(4-Fluorophenyl)-2*H*-tetrazol-5-yl)butyl)-10*H*-phenothiazine (4d)

This compound was obtained by hydrogenation of 10-((1*E*,3*Z*)-4-(2-(4-fluorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2e**, 0.41 g, 1 mmol) to give the product as beige crystals, 0.24 g (57%) which became liquid above room temperature; (Found: C, 66.16; H, 4.84; N, 16.79; $C_{23}H_{20}FN_5S$ requires C, 66.17; H, 4.83; N, 16.77%); ν_{max} (liquid film)/cm^{-1}: 2941, 2863, 1514, 1460 and 1236; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.92–2.03 (4H, m), 3.00 (2H, t, J = 6.9 Hz), 3.93 (2H, t, J = 6.6 Hz), 6.84–6.92 (4H, m), 7.11–7.26 (6H, m), 8.05 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.2, 25.4, 26.3, 47.0, 115.6 (2C), 116.7 (2C, d, $^2J_{C,F}$ = 23 Hz), 121.9 (2C, d, $^3J_{C,F}$ = 2 Hz), 122.6 (2C), 125.4 (2C), 127.3 (2C), 127.7 (2C), 133.5, 145.4 (2C), 163.0 (d, $^1J_{C,F}$ = 249 Hz), 167.0; *m/z* (EI) $[M+H]^+$: 418.30 ($C_{23}H_{20}FN_5S$ requires 417.14).

5.3.22. 10-(4-(2-Phenyl-2*H*-tetrazol-5-yl)butyl)-2-(trifluoromethyl)-10*H*-phenothiazine (4e)

This compound was obtained by hydrogenation of 10-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(trifluoromethyl)-10*H*-phenothiazine (**2f**, 0.54 g, 0.99 mmol) to give the product as beige crystal, 0.07 g (15%); mp 81–83 °C; (Found: C, 61.72; H, 4.55; N, 14.68; $C_{24}H_{20}F_3N_5S$ requires C, 61.66; H, 4.31; N, 14.98%); ν_{max} (KBr)/cm^{-1}: 2938, 2872, 1599, 1467 and 998; ^1H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.95–2.02 (4H, m), 3.02 (2H, t, J = 6.9 Hz), 3.96 (2H, t, J = 6.6 Hz), 6.86–6.96

(2H, m), 7.02 (1H, s), 7.11–7.21 (4H, m), 7.44–7.56 (3H, m), 8.06 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.0, 25.2, 26.0, 47.0, 111.8, 115.8, 119.1, 119.7 (2C), 123.1, 124.4, 124.5 (q, $^1J_{C,F}$ = 270 Hz), 127.5 (2C), 127.6, 129.4, 129.6, 130.2, 131.0 (q, $^2J_{C,F}$ = 32 Hz), 134.4, 136.8, 144.3, 145.7, 166.5; *m/z* (EI) $[M+H]^+$: 468.40 ($C_{24}H_{20}F_3N_5S$ requires 467.14).

5.3.23. 10-(4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)butyl)-2-(trifluoromethyl)-10*H*-phenothiazine (4f)

This compound was obtained by hydrogenatiom of 10-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(trifluoromethyl)-10*H*-phenothiazine (**2g**, 0.49 g, 1.0 mmol) to give the product as brown crystals, 0.49 g (99%) which became liquid at room temperature; (Found: C, 59.99; H, 4.16; N, 13.98; $C_{25}H_{22}F_3N_5OS$ requires C, 60.35; H, 4.46; N, 14.08%); ν_{max} (liquid film)/cm^{-1}: 3064, 2940, 1598, 1423 and 1000; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.91–2.04 (4H, m), 2.99 (2H, t, *J* = 5.7 Hz), 3.88 (3H, s), 3.95 (2H, t, *J* = 6.6 Hz), 6.86–6.97 (2H, m), 7.00–7.03 (3H, m), 7.10–7.20 (4H, m), 7.96 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 24.9, 25.1, 25.9, 47.0, 55.6, 111.7, 114.5 (2C), 115.8, 119.1, 121.2 (2C), 123.1, 124.2, 124.5 (q, $^1J_{C,F}$ = 270 Hz), 127.4, 127.5 (2C), 130.1, 130.3, 131.0 (q, $^2J_{C,F}$ = 32 Hz), 144.2, 145.6, 160.3, 166.2; *m/z* (EI) $[M+H]^+$: 498.40 ($C_{25}H_{22}F_3N_5OS$ requires 497.15).

5.3.24. 10-(4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)butyl)-2-(2-methyl-1,3-dioxolan-2-yl)-10*H*-phenothiazine (4g)

This compound was obtained by hydrogenation of 10-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(2-methyl-1,3-dioxolan-2-yl)-10*H*-phenothiazine (**2h**, 0.4 g, 0.78 mmol) to give the product as beige crystals, 0.21 g (53%); mp 93–94 °C; (Found: C, 65.39; H, 5.79; N, 13.31; $C_{28}H_{29}N_5O_3S$ requires C, 65.22; H, 5.67; N, 13.58%); ν_{max} (KBr)/cm^{-1}: 2953, 1513, 1254, 1038 and 832; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.61 (3H, s), 1.93–2.06 (4H, m), 2.99 (2H, t, *J* = 6.8 Hz), 3.73 (2H, t, *J* = 7.0 Hz), 3.88 (3H, s), 3.93–4.03 (4H, m), 6.86–7.15 (9H, m), 7.97 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.3, 25.6, 26.5, 27.8, 47.0, 55.9, 64.6 (2C), 108.9, 112.8, 114.8 (2C), 115.8, 119.7, 121.5 (2C), 122.7, 125.1, 125.4, 127.4 (2C), 127.8, 130.7, 143.0, 145.4 (2C), 160.6, 166.6; *m/z* (EI) $[M+H]^+$: 516.50 ($C_{28}H_{29}N_5O_3S$ requires 515.20).

5.3.25. General procedure for preparation of tetrazolylbutyl-carbazoles (5a–c)

A suspension of the appropriate dienylcarbazole (**3**, 1 mmol), Pd/C Selcat Q-6 (10%, 0.30 g) and abs. triethylamine (0.14 cm^3, 1 mmol) in a mixture of MeOH (10 cm^3) and CH_2Cl_2 (2 cm^3) was hydrogenated (1 atm, under atmospheric pressure) at room temperature until the absorption of hydrogen ceased (1 day). After the catalyst was filtered off, washed with dichloromethane, the solvent was dried over anhydrous Na_2SO_4 and evaporated. The residue was dissolved in hot ethanol and a few drops of water was added, whereupon colorless crystals were separated.

5.3.26. 9-(4-(2-Phenyl-2*H*-tetrazol-5-yl)butyl)-9*H*-carbazole (5a)

This compound was prepared from 9-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (**3a**, 0.22 g, 0.5 mmol), to give 0.18 g (98%) of product; mp 94–95 °C; (Found: C, 74.83; H, 5.58; N, 19.29; $C_{23}H_{21}N_5$ requires C, 75.18; H, 5.76; N, 19.06%); ν_{max} (KBr)/cm^{-1}: 2942, 1597, 1484, 1233 and 747; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.95–2.02 (4H, m), 3.01 (2H, t, *J* = 7.1 Hz), 4.37 (2H, t, *J* = 6.4 Hz), 7.19–7.22 (2H, m), 7.39–7.55 (7H, m), 8.03–8.10 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.3, 25.9, 28.5, 42.9, 108.8 (2C), 119.1 (2C), 120.0 (2C), 120.6 (2C), 123.1 (2C), 125.9 (2C), 129.7, 129.8 (2C), 137.1, 140.6 (2C), 166.6; *m/z* (EI) $[M+H]^+$: 368.20 ($C_{23}H_{21}N_5$ requires 367.18).

The same product (**5a**, 0.15 g, 80%) was obtained by hydrogenation of 9-((1*E*,3*Z*)-4-(2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (**3b**).

5.3.27. 9-(4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)butyl)-9*H*-carbazole (5b)

This compound was obtained by hydrogenation of 9-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (**3c**, 0.39 g, 1 mmol) to give the product, 0.23 g (57%); mp 100–103 °C; (Found: C, 72.36; H, 5.85; N, 17.77; $C_{24}H_{23}N_5O$ requires C, 72.52; H, 5.83; N, 17.62%); ν_{max} (KBr)/cm^{-1}: 2956, 1514, 1463, 1256 and 752; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.90–2.05 (4H, m), 2.99 (2H, t, *J* = 7.2 Hz), 3.87 (3H, s), 4.37 (2H, t, *J* = 6.6 Hz), 7.00 (2H, m), 7.19–7.25 (2H, m), 7.40–7.47 (4H, m), 7.96 (2H, m), 8.08–8.10 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 25.3, 25.9, 28.5, 42.9, 55.9, 108.8 (2C), 114.8 (2C), 119.0 (2C), 120.4 (2C), 121.3 (2C), 122.9 (2C), 125.6 (2C), 130.7, 140.4, 160.4, 166.2; *m/z* (EI) $[M+H]^+$: 398.20 ($C_{24}H_{23}N_5O$ requires 397.19).

5.3.28. 9-(4-(2-(*p*-Tolyl)-2*H*-tetrazol-5-yl)butyl)-9*H*-carbazole (5c)

This compound was obtained by hydrogenation of 9-((1*E*,3*Z*)-4-(2-(*p*-tolyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (**3d**, 0.38 g, 1 mmol) to give the product, 0.20 g (52%); mp 89–93 °C; (Found: C, 75.36; H, 6.03; N, 18.57; $C_{24}H_{23}N_5$ requires C, 75.56; H, 6.08; N, 18.36%); ν_{max} (KBr)/cm^{-1}: 2929, 1515, 1469, 1232 and 818; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.95–2.05 (4H, m), 2.44 (3H, s), 3.02 (2H, t, *J* = 7.1 Hz), 4.38 (2H, t, *J* = 6.6 Hz), 7.21–7.49 (8H, m), 7.94 (2H, m), 8.09–8.12 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.4, 25.3, 25.9, 28.5, 42.9, 108.8 (2C), 119.1 (2C), 119.9 (2C), 120.6 (2C), 123.1 (2C), 125.9 (2C), 130.3 (2C), 134.9, 140.0, 140.6 (2C), 166.5; *m/z* (EI) $[M+H]^+$: 382.30 ($C_{24}H_{23}N_5$ requires 381.20).

5.3.29. General procedure for preparation of azaborinines (7i–j)

In an inert atmosphere at 0 °C, $BH_3 \times Me_2S$ (1.2 cm^3, 12 mmol) was added to the suspension of the appropriate dienylphenothiazine (3 mmol) and abs. THF (30 cm^3). After injection of $BH_3 \times Me_2S$, the mixture was stirred from 0 °C to room temperature for 1 day. During this time, the starting suspension turned to be a clear solution. This mixture was cooled to 0 °C and the excess of $BH_3 \times Me_2S$ was quenched with cold water (30 cm^3). Then the reaction mixture was made alkaline with Na_2CO_3 (10% aqueous,) and extracted with 3 × 25 cm^3 dichloromethane. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure at room temperature. The residue was purified with flash chromatography on silica gel (gradient from hexane:CH_2Cl_2 = 2:1). The solid product was recrystallized from hexane and diethyl ether. The crystals were collected by filtration.

5.3.30. 2-(4-Bromophenyl)-6-((2-chloro-10*H*-phenothiazin-10-yl)methyl)-5,6,7,8-tetrahydro-2*H*-tetrazolo[5,1-*f*][1,2]azaborinin-4-ium-5-uide (7i)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-chloro-10*H*-phenothiazine (**2i**, 1.53 g, 3 mmol) to give yellow crystals, 0.27 g (18%); mp 149–151 °C; (Found: C, 52.27; H, 3.89; N, 12.99; $C_{23}H_{20}BBrClN_5S$ requires C, 52.65; H, 3.84; N, 13.35%); ν_{max} (KBr)/cm^{-1}: 3432, 2922, 2369, 1453 and 1109; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.64–1.70 (2H, m), 2.29–3.12 (5H, m), 3.64–4.06 (2H, m), 6.85–7.51 (7H, m), 7.75 (2H, m), 8.00 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.8, 22.5, 25.2, 52.1, 116.7, 116.9, 121.8 (2C), 122.1, 122.7, 124.0, 125.3, 126.2, 127.5, 127.6, 128.0, 133.4, 133.6 (2C), 134.8, 145.7, 147.8, 162.5; *m/z* (EI) $[M+Na]^+$: 546.40 ($C_{23}H_{20}BBrClN_5S$ requires 524.67).

5.3.31. 6-((2-Chloro-10*H*-phenothiazin-10-yl)methyl)-2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-2*H*-tetrazolo[5,1-*f*][1,2]azaborinin-4-ium-5-uide (7j)

This compound was obtained from 2-chloro-10-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2j**, 1.38 g, 3 mmol) to give white crystals, 0.63 g (46%); mp 153–157 °C; (Found: C, 60.20; H, 4.93; N, 14.81; $C_{24}H_{23}BClN_5OS$ requires C, 60.58; H, 4.87; N, 14.72%); ν_{max} (KBr)/cm^{-1}: 3337, 2920, 2339, 1454 and 1109; ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 1.64 (1H, m, H7y), 1.71 (1H, m, H6), 2.27 (1H, m, H7x), 2.40 (1H, br s, H5y), 2.75 (1H, br s, H5x), 2.79 (1H, ddd, J = 17.7, 10.0, 5.6 Hz, H8y) 3.05 (1H, ddd, J = 17.7, 5.0, 4.9 Hz, H8x), 3.67 (1H, dd, J = 14.2, 11.1 Hz, Hy), 4.07 (1H, dd, J = 14.2, 3.1 Hz, Hx), 6.84 (1H, dd, J = 8.2, 2.0 Hz, H3″), 6.90 (1H, td, J = 7.4, 1.8 Hz, H7″), 6.93 (1H, d, J = 2.0 Hz, H1″), 6.97 (1H, dd, J = 7.4, 1.8 Hz, H9″), 7.01 (1H, d, J = 8.2 Hz, H4″), 7.04 (2H, m, H3′ + H5′), 7.12 (1H, dd, J = 7.4, 1.5 Hz, H6″), 7.14 (1H, td, J = 7.4, 1.5 Hz, H8″), 8.01 (2H, m, H2′ + H6′); ^{13}C NMR (100 MHz; $CDCl_3$) δ (ppm): 21.6 (C6), 22.1 (C8), 25.1 (C7), 51.9 (C), 55.8 (OCH_3), 115.0 (C3′ + C5′), 116.5 (C1″), 116.7 (C9″), 121.7 (C3″), 121.8 (C2′ + C6′), 122.4 (C7″), 123.8 (C4a″), 125.0 (C5a″), 127.3 (C8″), 127.4 (C6″), 127.8 (C4″), 129.0 (C1′), 133.2 (C2″), 145.6 (C9a″), 147.6 (C10a''), 161.6 (C4′), 161.9 (C8a); m/z (EI) [M+Na]$^+$: 498.50 ($C_{24}H_{23}BClN_5OS$ requires 475.14).

5.3.32. General procedure for preparation of tetrazolylbutan-2-olphenothiazines (8a–i)

To a solution of the appropriate dienylphenothiazine (**2**, 4 mmol) in abs. THF (40 cm^3) 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 cm^3, 16 mmol) dropwise by injection. After addition, the resulting yellow suspension was allowed to warm up to room temperature and maintained at this temperature for prologued 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 cm^3), 10% aqueous NaOH (2 cm^3) and H_2O_2 (30% aqueous solution, 2 cm^3). This mixture was then stirred at room temperature for 1 more day. The solution was then poured onto ice cold water, acidified with 10% aqueous HCl and extracted with dichloromethane (3 × 30 cm^3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using the eluent CH_2Cl_2 then hexane:EtOAc = 2:1. The crude product (foam) was triturated with diethyl ether, the mixture was cooled whereupon crystals deposited. The product was collected by filtration.

5.3.33. 4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)butan-2-ol (8a)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2a**, 1.90 g, 4.0 mmol) to give white crystals, 1.7 g (84%); mp 103–105 °C; (Found: C, 55.93; H, 3.75; N, 13.99; $C_{23}H_{20}BrN_5OS$ requires C, 55.87; H, 4.08; N, 14.17%); ν_{max} (KBr)/cm^{-1}: 3399, 1457, 1001, 825 and 754; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.64 (1H, br s), 2.06 (1H, m), 2.23 (1H, m), 3.18 (2H, m), 3.94 (1H, m), 4.06 (1H, m), 4.17 (1H, m), 6.92–6.98 (4H, m), 7.13–7.26 (4H, m), 7.67–7.70 (2H, m), 7.97 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.9, 32.1, 53.8, 66.4, 116.1 (2C), 121.2 (2C), 123.2 (2C), 126.8 (2C), 127.4 (2C), 127.8 (2C), 132.3, 132.8 (2C), 135.8, 145.3 (2C), 166.9; m/z (EI) [M+H]$^+$: 494.20 ($C_{23}H_{20}BrN_5OS$ requires 493.06).

5.3.34. 4-(2-(4-Chlorophenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)butan-2-ol (8b)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2b,** 0.86 g, 2.0 mmol) to give white crystals, 0.66 g (73%); mp 95–100 °C; (Found: C, 61.16; H, 4.17; N, 15.53; $C_{23}H_{20}ClN_5OS$ requires C, 61.39; H, 4.48; N, 15.56%); ν_{max} (KBr)/cm^{-1}: 3230, 2890, 1456, 1097 and 755; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.05 (1H, m), 2.13 (1H, br s), 2.21 (1H, m), 3.19 (2H, m), 3.94 (1H, m), 4.06 (1H, m), 4.17 (1H, m), 6.92–6.98 (4H, m), 7.13–7.21 (4H, m), 7.52 (2H, m), 8.03 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.9, 32.1, 53.8, 66.4, 116.1 (2C), 120.9 (2C), 123.2 (2C), 126.7 (2C), 127.4 (2C), 127.8 (2C), 129.8 (2C), 135.3, 135.4, 145.3 (2C), 166.8; m/z (EI) [M+H]$^+$: 450.30 ($C_{23}H_{20}ClN_5OS$ requires 449.11).

5.3.35. 4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)butan-2-ol (8c)

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)-10*H*-phenothiazine (**2c,** 1.28 g, 3 mmol). White crystals, 0.89 g (67%); mp 104–107 °C; (Found: C, 64.69; H, 5.23; N, 15.60; $C_{24}H_{23}N_5O_2S$ requires C, 64.70; H, 5.20; N, 15.72%); ν_{max} (KBr)/cm^{-1}: 3382, 1516, 1460, 1266 and 746; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.06 (1H, m), 2.20 (1H, m), 2.53 (1H, br s), 3.15 (2H, m), 3.84–4.19 (6H, m), 6.91–7.04 (6H, m), 7.12–7.21 (4H, m), 7.98 (2H, m,); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 22.2, 32.5, 53.8, 56.0, 66.8, 114.9 (2C), 116.4 (2 C), 121.6 (2C), 123.4 (2C), 127.0 (2C), 127.7 (2C), 128.1 (2C), 130.7, 145.6 (2C), 160.7, 166.7; m/z (EI) [M+H]$^+$: 446.30 ($C_{24}H_{23}N_5O_2S$ requires 445.16).

5.3.36. 1-(10*H*-Phenothiazin-10-yl)-4-(2-(*p*-tolyl)-2*H*-tetrazol-5-yl)-butan-2-ol (8d)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(*p*-tolyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2d**, 0.60 g, 1.47 mmol). White crystals, 0.34 g (54%); mp 110–115 °C; (Found: C, 67.00; H, 5.34; N, 16.48; $C_{24}H_{23}N_5OS$ requires C, 67.11; H, 5.40; N, 16.30%); ν_{max} (KBr)/cm^{-1}: 3394, 1514, 1455, 1097 and 747; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.75 (1H, br s), 2.06 (1H, m), 2.23 (1H, m), 2.44 (3H, s), 3.16 (2H, m), 3.92 (1H, m), 4.06 (1H, m), 4.18 (1H, m), 6.90–6.99 (4H, m), 7.13–7.21 (4H, m), 7.32–7.34 (2H, m), 7.95 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.2, 21.9, 32.2, 53.7, 66.5, 116.1 (2C), 119.7 (2C), 123.2 (2C), 126.8 (2C), 127.4 (2C), 127.8 (2C), 130.1 (2C), 134.7, 139.8, 145.3 (2C), 166.4; m/z (EI) [M+H]$^+$: 430.20 ($C_{24}H_{23}N_5OS$ requires 429.16).

5.3.37. 4-(2-(4-Fluorophenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)butan-2-ol (8e)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-fluorophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2e,** 0.6 g, 1.45 mmol). Brown crystals, 0.49 g (78%); mp 59–61 °C; (Found: C, 63.51; H, 4.61; N, 15.95; $C_{23}H_{20}FN_5OS$ requires C, 63.72; H, 4.65; N, 16.16%); ν_{max} (KBr)/cm^{-1}: 3250, 1514, 1454, 1219 and 749; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.74 (1H, br s), 2.06 (1H, m), 2.21 (1H, m), 3.16 (2H, m), 3.78–4.24 (3H, m), 6.80–7.07 (3H, m), 7.08–7.26 (7H, m), 8.07 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.9, 32.1, 53.8, 66.4, 116.1 (2C), 116.6 (2C, d, $^2J_{C,F}$ = 23 Hz), 121.7 (2C, d, $^3J_{C,F}$ = 8 Hz), 123.2 (2C), 126.8 (2C), 127.4 (2C), 127.8 (2C), 145.3 (2C), 162.9 (d, $^1J_{C,F}$ = 249 Hz), 166.8; m/z (EI) [M+H]$^+$: 434.40 ($C_{23}H_{20}FN_5OS$ requires 433.14).

5.3.38. 4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)-1-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)butan-2-ol (8f)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(trifluoromethyl)-10*H*-phenothiazine (**2f**, 0.54 g, 1 mmol). White crystals, 0.23 g (41%); mp 139–141 °C; (Found: C, 51.07; H, 3.37; N, 12.25; $C_{24}H_{19}BrF_3N_5OS$ requires C, 51.25; H, 3.41; N, 12.45%); ν_{max} (KBr)/cm^{-1}: 3364, 2937, 1501, 1331 and 1119; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.07 (1H, m), 2.23 (2H, m), 2.66 (1H,

s), 3.18 (2H, m), 3.96 (1H, m), 4.06–4.16 (2H, m), 6.93–7.28 (7H, m), 7.65–7.68 (2H, m), 7.95 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.8, 32.0, 54.0, 66.3, 112.9, 116.7, 120.0, 121.4 (2C), 123.6, 124.1, 124.5 (q, $^{1}J_{C,F}$ = 270 Hz), 125.9, 128.0, 128.1, 128.2, 130.1 (q, $^{2}J_{C,F}$ = 32 Hz), 131.6, 133.0 (2C), 135.9, 144.5, 146.2, 166.9; *m/z* (EI) $[M+H]^+$: 562.30 ($C_{24}H_{19}BrF_3N_5OS$ requires 561.04).

5.3.39. 4-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)-1-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)butan-2-ol (8g)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-methoxy-phenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-(trifluoromethyl)-10*H*-phenothiazine (**2g**, 0.50 g, 1 mmol). White crystals, 0.084 g (16%); mp 126–128 °C; (Found: C, 58.27; H, 4.38; N, 13.63; $C_{25}H_{22}F_3N_5O_2S$ requires C, 58.47; H, 4.32; N, 13.64%); ν_{max} (KBr)/cm^{-1}: 3366, 2938, 1517, 1333 and 1120; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.07 (1H, m), 2.23 (1H, m), 2.70 (1H, br s), 3.16 (2H, m), 3.88 (3H, s), 3.97 (1H, m), 4.06–4.17 (2H, m), 6.94–7.04 (4H, m), 7.11 (1H, s), 7.14–7.20 (3H, m), 7.25 (1H, d, *J* = 7.8 Hz), 7.97 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 22.0, 32.4, 54.2, 55.9, 66.7, 112.9, 114.8 (2C), 116.7, 120.0, 121.5 (2C), 124.0, 124.5 (q, $^{1}J_{C,F}$ = 270 Hz), 125.8, 128.0, 128.1, 128.2, 130.1 (q, $^{2}J_{C,F}$ = 32 Hz), 133.5, 131.6, 144.5, 146.2, 160.6, 166.5; *m/z* (EI) $[M+H]^+$: 514.40 ($C_{25}H_{22}F_3N_5O_2S$ requires 513.14).

5.3.40. 4-(2-(4-Bromophenyl)-2*H*-tetrazol-5-yl)-1-(2-chloro-10*H*-phenothiazin-10-yl)butan-2-ol (8h)

This compound was obtained from 10-((1*E*,3*Z*)-4-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-2-chloro-10*H*-phenothiazine (**2i**, 0.51 g, 1 mmol) to give white crystals, 0.21 g (40%); mp 101–103 °C; (Found: C, 52.14; H, 3.58; N, 13.28; $C_{23}H_{19}BrClN_5OS$ requires C; 52.24; H, 3.62; N, 13.24%); ν_{max} (KBr)/cm^{-1}: 3341, 2926, 1567, 1456 and 999; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.08 (1H, m), 2.21 (1H, m), 2.55 (1H, d, *J* = 1.8 Hz), 3.10–3.28 (2H, m), 3.91 (1H, m), 4.02 (1H, m), 4.17 (1H, m), 6.90–7.00 (4H, m), 7.08–7.20 (3H, m), 7.66–7.69 (2H, m), 7.96–7.99 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.9, 32.2, 54.0, 66.5, 116.5, 116.7, 121.3 (2C), 123.2, 123.5, 123.8, 125.2, 126.5, 127.7, 128.0, 128.4, 133.0 (2C), 133.6, 135.9, 144.7, 146.8, 166.9; *m/z* (EI) $[M+H]^+$: 530.30 ($C_{23}H_{19}BrClN_5OS$ requires 528.85).

5.3.41. 1-(2-Chloro-10*H*-phenothiazin-10-yl)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)butan-2-ol (8i), 2-chloro-10-(2-hydroxy-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)butyl)-10*H*-phenothiazine 5-oxide (9), and 4-(2-chloro-10*H*-phenothiazin-10-yl)-1-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)butane-1,3-diol (10)

A dried, round-bottomed flask, equipped with a side arm, was cooled to 0 °C under a stream of argon. In the flask 2-chloro-10-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-10*H*-phenothiazine (**2j**, 1.84 g, 4.0 mmol) was dissolved in abs. THF (80 cm^3) and $BH_3 \times Me_2S$ (1.6 cm^3, 16 mmol) added dropwise to the solution using injection. After addition the resulting yellow suspension was allowed to warm to room temperature. After the completion of the reaction (1 day, monitored by TLC), the reaction mixture was cooled to 0 °C with an ice bath, and quenched with methanol (40 cm^3), NaOH (10% aqueous, 4 cm^3) and H_2O_2 (30% aqueous, 2 cm^3) were added. This mixture was allowed to stir at room temperature for 1 day.

The solution was then poured onto ice cold water (60 cm^3), acidified with 10% aqueous HCl and extracted with 3 × 50 cm^3 dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using the eluent CH_2Cl_2 then hexane:EtOAc = 2:1. The crude product (foam) was triturated with diethyl ether, cooled and the main product *1-(2-chloro-10H-phenothiazin-10-yl)-4-(2-(4-methoxyphenyl)-2H-tetrazol-5-yl)butan-2-ol* (**8i**, 1.25 g, 65%) as white crystal was collected by filtration; mp 100–102 °C; (Found: C, 60.05; H, 4.62; N, 14.51; $C_{24}H_{22}ClN_5O_2S$ requires C, 60.06; H, 4.62; N, 14.59%); ν_{max} (KBr)/cm^{-1}: 3393, 2963, 1518, 1456 and 1254; ^{1}H NMR (600 MHz; DMSO) δ (ppm): 1.80 (1H, dddd, *J* = 13.6, 9.3, 8.1, 5.1 Hz, H3y), 2.13 (1H, dddd, *J* = 13.6, 9.1, 8.2, 2.6 Hz, H3x), 2.96 (1H, ddd, *J* = 15.2, 8.2, 8.1 Hz, H4y), 3.06 (1H, ddd, *J* = 15.2, 9.1, 5.1 Hz, H4x), 3.84 (3H, s, OCH_3), 3.85 (1H, m, H1y), 3.94 (1H, m, H2), 3.95 (1H, m, H1x), 5.07 (1H, br s, OH), 6.94 (1H, m, H3″), 6.95 (1H, m, H7″), 7.07 (1H, m, H9″), 7.10 (1H, m, H4″), 7.11 (1H, H8″), 7.13 (1H, m, H1″), 7.15 (2H, m, H3′ + H5′), 7.18 (1H, m, H6″), 7.87 (2H, m, H2′ + H6′); ^{13}C NMR (150 MHz; DMSO) δ (ppm): 21.0 (C4), 32.9 (C3), 53.0 (C1), 55.6 (OCH_3), 65.3 (C2), 114.9 (C3′ + C5′), 116.1 (C1″), 116.5 (C9″), 121.2 (C2′ + C6′), 122.2 (C7″), 123.0 (C5a″), 123.8 (C4a″), 127.2 (C8″), 127.7 (C6″), 128.1 (C4″), 129.6 (C1′), 132.4 (C2″), 144.4 (C9a″), 146.5 (C10a″), 160.1 (C4′), 166.4 ($C_{tetrazole}$); ^{15}N NMR (60 MHz; DMSO) δ (ppm): −285.2 (N10″), −92.0 ($N2_{tetrazole}$), −87.1 ($N1_{tetrazole}$), and −47.9 ($N4_{tetrazole}$); *m/z* (EI) $[M+H]^+$: 480.30 ($C_{24}H_{22}ClN_5O_2S$ requires 479.12).

Column chromatography of the mother liquor resulted in separation of two more products. Thus, first the fractions of the less polar component were collected, evaporated and the obtained solid was recrystallized from dichloromethane to yield *4-(2-chloro-10H-phenothiazin-10-yl)-1-(2-(4-methoxyphenyl)-2H-tetrazol-5-yl)-butane-1,3-diol* (**10**, 0.10 g, 6%) as white crystals were collected by filtration; mp 152–156 °C; (Found: C, 58.13; H, 4.23; N, 13.75; $C_{24}H_{22}ClN_5O_3S$ requires C, 58.12; H, 4.47; N, 14.12%); ν_{max} (KBr)/cm^{-1}: 3312, 2954, 1516, 1456 and 1257; the obtained diastereomeric pair is present in 0.6/*0.4* ratio according to NMR spectra (assignments of the minor component are in italics): ^{1}H NMR (600 MHz; DMSO) δ (ppm): *1.82 (0.4H, ddd, J = 13.8, 9.8, 3.0 Hz, H3y),* 1.98 (0.6H, ddd, *J* = 12.9, 9.6, 5.4 Hz, H3y), *2.22 (0.4H, ddd, J= 13.8, 10.3, 2.5 Hz, H3x),* 2.37 (0.6H, ddd, *J* = 12.9, 9.3, 3.0 Hz, H3y), 3.77 (0.6H, m, H2), 3.85 (3H, s, OCH_3), 3.86 (1H, m, H1y), 3.91 (1H, m, H1x), *4.20 (0.4H, m, H2),* 5.00 (1H, br s, OH), 5.15 (0.6H, m, H4), *5.16 (0.4H, m, H4), 5.74 (0.4H, br s, OH),* 5.81 (0.6H, br s, OH), 6.90 (0.6, m, H3″), 6.91 (0.6H, m, H7″), *6.97 (0.4H, m, H3″), 6.98 (0.4H, m, H7″),* 7.00 (0.6H, m, H9″), 7.03 (0.6H, m, H1″), 7.06 (0.6H, m, H4″), 7.08 (0.6H, m, H8″), *7.09 (0.4H, m, H9″),* 7.11 (0.6H, m, H6″), *7.14 (0.4H, m, H4″), 7.14 (0.4H, m, H1″), 7.16 (0.4H, m, H8″),* 7.18 (1.2H, m, H3′ + H5′), *7.19 (0.8H, m, H3′ + H5′), 7.21 (0.4H, m, H6″),* 7.85 (1.2H, m, H2′ + H6′), 7.96 (0.8H, m, H2′ + H6′); ^{13}C NMR (150 MHz; DMSO) δ (ppm): 41.3 (C3), *41.4 (C3), 53.0 (C1),* 53.4 (C1), 55.7 (OCH_3), *61.3 (C4),* 62.3 (C4), *62.9 (C2),* 63.5 (C2), 115.0 (C3′ + C5′), *115.1 (C3′ + C5′),* 116.0 (C1″), *116.1 (C1″),* 116.4 (C9″), *116.5 (C9″),* 121.2 (C2′ + C6′), *121.4 (C2′ + C6′),* 122.0 (C7″), *122.1 (C7″),* 122.9 (C3″), *123.0 (C3″),* 123.1 (C5a″), 123.7 (C4a″), 127.1 (C8″), *127.3 (C8″),* 127.5 (C6″), *127.7 (C6″),* 128.0 (C4″), *128.1 (C4″), 129.5 (C1′),* 129.6 (C1′), 132.2 (C2″), *132.4 (C2″), 144.3 (C9a″),* 144.5 (C9a″), *146.4 (C10a″),* 146.6 (C10a″), 160.2 (C4′), 168.5 ($C_{tetrazole}$), *169.5 ($C_{tetrazole}$);* ^{15}N NMR (60 MHz; DMSO) δ (ppm): −285.3 (N10″), −92.0 ($N2_{tetrazole}$), −85.3, and −48.0 ($N1_{tetrazole}$ + $N4_{tetrazole}$); *m/z* (EI) $[M+Na]^+$: 518.30 ($C_{24}H_{22}ClN_5O_3S$ requires 495.11).

Continued chromatography and collection of the more polar fractions, evaporation, and recrystallization of the crude product from ethanol gave *2-chloro-10-(2-hydroxy-4-(2-(4-methoxy-phenyl)-2H-tetrazol-5-yl)butyl)-10H-phenothiazine 5-oxide* (**9**, 0.45 g, 25%) as white crystals were collected by filtration; mp 140–145 °C; (Found: C, 58.10; H, 4.27; N, 13.82; $C_{24}H_{22}ClN_5O_3S$ requires C, 58.12; H, 4.47; N, 14.12%); ν_{max} (KBr)/cm^{-1}: 3377, 2941, 1581, 1515 and 1461; the obtained two diastereomers are present in 0.6/*0.4* ratio according to NMR spectra (assignments of the minor component are in italics): ^{1}H NMR (600 MHz; DMSO) δ (ppm): 1.87 (1H, m, H3y), 2.08 (1H, m, H3x), 2.99 (1H, m, H4y), 3.09

(1H, m, H4x), 3.83 (3H, s, OCH_3), 4.03 (0.6H, m, H2), *4.11 (0.4H, m, H2),* 4.41 (0.6H, d, *J* = 15.1 Hz, H1y), *4.43 (0.4H, d, J = 15.1 Hz, H1y),* 4.50 (0.6H, d, *J* = 15.1 Hz, H1x), *4.51 (0.4H, d, J = 15.1 Hz, H1x),* 4.88 (0.6H, d, *J* = 4.8 Hz, OH), *5.00 (0.4H, d, J = 4.8 Hz, OH),* 7.15 (2H, m, H3′ + H5′), 7.30 (1H, m, H3″), 7.31 (1H, m, H7″), 7.66 (0.6H, m, H8″), *7.68 (0.4H, m, H8″), 7.74 (0.4H, d, J = 8.3 Hz, H9″),* 7.84 (0.6H, d, *J* = 1.3 Hz, H1″), 7.91 (2H, m, H2′ + H6′), 7.92 (0.6H, d, *J* = 8.3 Hz, H9″), 7.94 (1H, m, H6″), 7.95 (1H, m, H4″), *8.09 (0.4 H, d, J = 1.3 Hz, H1″)*; ^{13}C NMR (150 MHz; DMSO) δ (ppm): 21.0 (C4), 31.9 (C3), 53.1 (C1), 55.6 (OCH_3), 66.6 (C2), *67.0 (C2),* 114.8 (C3′ + C5′), 117.3 (C1″), *117.5 (C9″), 118.0 (C1″),* 118.3 (C9″), 121.0 (C2′ + C6′), 121.6 (C3″), 122.0 (C2″), 122.3 (C7″), 126.1 (C5a″), 129.6 (C1′), 130.0 (C6″), 131.7 (C4″), *132.5 (C8″),* 132.7 (C8″), 137.1 (C4a″), 138.0 (C9a″), 139.9 (C10a″), 160.0 (C4′), 166.2 ($C_{tetrazole}$); ^{15}N NMR (60 MHz; DMSO) δ (ppm): −277.5 (N10″), *−276.5 (N10″),* −92.0 ($N2_{tetrazole}$), −86.0, and −47.8 ($N1_{tetrazole}$ + $N4_{tetrazole}$); *m/z* (EI) $[M+H]^+$: 496.30 ($C_{24}H_{22}ClN_5O_3S$ requires 495.11).

5.3.42. 1-(9*H*-Carbazol-9-yl)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)butan-2-ol (11)

To a solution of 9-((1*E*,3*Z*)-4-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)buta-1,3-dien-1-yl)-9*H*-carbazole (**3c,** 0.38 g, 0.96 mmol) in abs. dichloromethane (25 cm^3) in a dried, round-bottomed flask equipped with a side arm cooled to 0 °C in an argon atmosphere was added $BH_3 \times Me_2S$ (0.4 cm^3, 4 mmol) dropwise by using injection. After addition, the resulting yellow suspension was allowed to warm up to room temperature and maintained at this temperature. 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 (25 cm^3), 10% aqueous NaOH solution (2 cm^3) and 30% aqueous H_2O_2 (3 cm^3). This mixture was then stirred at room temperature for 1 more day. The solution was then poured onto ice cold water, acidified with 10% aqueous HCl and extracted with dichloromethane (3 × 20 cm^3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using the eluent CH_2Cl_2 then hexane:EtOAc = 2:1. The crude product (foam) was triturated with diethyl ether, cooled and the product was collected by filtration as white crystals, 0.14 g (33%); mp 137–142 °C; (Found: C, 69.33; H, 5.59; N, 16.77; $C_{24}H_{23}N_5O_2$ requires C, 69.72; H, 5.61; N, 16.94%); ν_{max} (KBr)/cm^{-1}: 3326, 2931, 1514, 1257 and 755; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.16 (2H, m), 2.36 (1H, d, *J* = 3.6 Hz), 3.18 (2H, m), 3.87 (3H, s), 4.31–4.39 (3H, m), 7.02 (2H, m), 7.20–7.25 (2H, m), 7.41–7.49 (4H, m), 7.95 (2H, m), 8.08 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 21.8, 32.5, 49.7, 55.6, 70.0, 109.0 (2C), 114.6 (2C), 119.2 (2C), 120.3 (2C), 121.3 (2C), 123.0 (2C), 125.8 (2C), 130.6, 140.8 (2C), 160.4, 166.3; *m/z* (EI) $[M+H]^+$: 414.20 ($C_{24}H_{23}N_5O_2$ requires 413.19).

5.3.43. (*E*)-3-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)prop-2-en-1-one (13)

To the solution of (*E*)-3-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)acrylaldehyde (**12**, 0.50 g, 2.17 mmol), *N*-bromo-succimide (0.42 g, 2.39 mmol) and CCl_4 (10 cm^3) was added phenotiazine (0.91 g, 4.56 mmol) dissolved in toluene (10 cm^3) and the mixture was stirring at 110 °C for 3 h. After evaporation of the reaction mixture, the residue was dissolved in dichloromethane (15 cm^3). The organic phase was extracted with water (twice), the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was washed with diethyl ether (thrice). It was recrystallized from acetonitrile and the product (0.32 g, 34%) was filtered off as yellow crystal; mp 199–204 °C; (Found: C, 64.69; H, 3.96; N, 16.09; $C_{23}H_{17}N_5O_2S$ requires C, 64.62; H, 4.01; N, 16.38%); ν_{max} (KBr)/cm^{-1}: 3061, 2983, 1677, 1515 and 1022; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 3.88 (3H, s), 7.03 (2H, m), 7.27–7.64 (9H, m), 7.89–8.02 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 55.9, 115.0 (2C), 121.7 (2C), 126.5, 127.2 (2C), 127.3 (2C), 127.4 (2C), 128.2 (2C), 128.3, 130.3 (2C), 132.9, 138.4 (2C), 161.0, 162.5, 163.4; *m/z* (EI) $[M+H]^+$: 428.30 ($C_{23}H_{17}N_5O_2S$ requires 427.11).

5.3.44. 10-(3-(2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl)propyl)-10*H*-phenothiazine (14)

To the green suspension of (*E*)-3-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)-1-(10*H*-phenothiazin-10-yl)prop-2-en-1-one (**13**, 0.21 g, 0.49 mmol) in abs. THF (5 cm^3) was added $BH_3 \times Me_2S$ (0.2 cm^3, 0.16 g, 2.06 mmol) slowly at 0 °C. The color of reaction mixture changed to yellow, and gas evolution was observed. The mixture was allowed to warm to room temperature and strirred for 2.5 h. After evapration of the mixture, MeOH (10 cm^3) was added to the residue at room temperature, intensive gas evolution was observed, then this mixture was stirred for 4 days. The crude product was purified by column chromatography using the eluent CH_2Cl_2:hexane = 2:1 to give beige crystals, 0.04 g (20%); mp 112–114 °C; (Found: C, 66.25; H, 5.12; N, 16.78; $C_{23}H_{21}N_5OS$ requires C, 66.48; H, 5.09; N, 16.85%); ν_{max} (KBr)/cm^{-1}: 3063, 2949, 1513, 1459 and 1251; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 2.30–2.42 (2H, m), 3.11 (2H, t, *J* = 7.4 Hz), 3.87 (3H, s), 4.04 (2H, t, *J* = 6.6 Hz), 6.88–7.19 (9H, m), 7.93 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm): 23.2, 25.3, 46.6, 56.0, 114.9 (2C), 115.9 (2C), 121.6 (2C), 122.9 (2C), 125.8 (2C), 127.6 (2C), 127.9 (2C), 130.8, 145.5 (2C), 160.7, 166.4; *m/z* (EI) $[M+H]^+$: 416.20 ($C_{23}H_{21}N_5OS$ requires 415.15).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.05.065.

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