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Iodine-catalyzed stepwise [4+2] cycloaddition of phenothiazine- and ferrocene-containing Schiff bases with DHP promoted by microwave irradiation

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ABSTRACT

On simultaneous effect of iodine-catalysis and microwave irradiation Schiff bases deactivated by electron-donating *C*-phenothiazinyl- and ferrocenyl-substituents, respectively, underwent formal inverse electron demand aza-Diels–Alder (DA) cycloaddition with 3,4-dihydro-2*H*-pyrane (DHP) employed as donor component. Depending on the substitution pattern of the *N*-phenyl group the reactions of phenothiazine-containing imines afforded 2*H*-pyrano[3,2-*c*]quinolines or 3-(3-hydroxypropyl)quinolines. Irrespective of the electronic properties of the *N*-phenyl substituent the less reactive ferrocene-based imines were directly converted into quinoline products. The intermediate iodoiminium ions were analysed by B3LYP/DGZVP calculations suggesting stepwise mode for the cycloaddition process. In one case the regioselectivity of the second step of cycloaddition was also interpreted by DFT analysis of the alternative rotamers of the primarily formed DHP adduct.

1. Introduction

Phenothiazine and quinoline are two heterocyclic cores responsible for diverse biological activities as well as physical and chemical properties of their derivatives. Investigations related to new synthetic methods and properties of such heterocyclic compounds appear interesting for both fundamental research and industrial applications. Phenothiazine is present as a major pharmacophore in many types of drugs, pesticides and compounds with analytical applications (redox indicators and reagents in spectrophotometric determinations), high temperature antioxidants for lubricants and dyes.[1] Quinoline and tetrahydroquinoline derivatives are often encountered in both natural and synthetic products displaying valuable biological activity.[2] On the other hand, during the last decades ferrocene-containing heterocycles have also attracted remarkable attention due to their wide range of promising biological activity and application even in therapy.[3] The common feature of both phenothiazine and ferrocene units is their low reduction potential allowing the generation of reactive radical cations under physiological conditions actually responsible for the observed activity.[4,5] In the light of these aspects we have focused our attention on phenothiazinyl- and ferrocenyl-substituted quinolines having in mind the synthetic combination of the beneficial properties of the biologically promising molecular motifs to obtain novel model compounds for an ongoing biological assay. Here we present the microwave-assisted synthesis of new phenothiazinyl- and ferrocenyl-Schiff bases incorporating an imine group of decreased electrophilicity and their microwave-assisted formal aza-Diels–Alder (DA) cycloaddition with 3,4-dihydro-2*H*-pyrane (DHP) conducted in the presence of catalytic amount of iodine to obtain a series of novel hexahydro-2*H*-pyrano[3,2-*c*]quinolines. To our best knowledge the combination of microwave irradiation and iodine catalysis was used for the first time to promote the envisaged cycloadditions of our substrates with decreased reactivity, although a variety of conditions have also been reported for related cyclisations of *N*-aryl imines: (i) iodine-catalyzed multistep reactions of imines and enolizable aldehydes taking place by aza-Henry reaction followed by ring closure and dehydrogenation led to the formation of 2-arylquinolines[6] and 2-ferrocenylquinolines;[7] (ii) hexahydro-2*H*-pyrano[3,2-*c*]quinoline- and furo[3,2-*c*]quinoline-derivatives were prepared by inverse electron demand aza-DA addition reactions of *N*-aryl imines and DHP and 2,3-dihydrofurane, respectively, catalyzed by Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$, $ZrCl_4$, $AlCl_3$, $InCl_3$, $NbCl_5$, $FeCl_3$, $LiBF_4$, salen-AlCl, $Yb(OTf)_3$, $Sc(OTf)_3$, $Sm(OTf)_3$),[8] as well as phosphomolybdic acid,[9a] tungstophosphoric acid,[9b] cerium(IV)-ammonium-nitrate,[9c] proline-triflate[9d] and iodine;[10] (iii) hexahydro-2*H*-pyrano[3,2-*c*]quinolines were also resulted in short reaction times from TFA-catalyzed aza-DA cycloaddition of in situ generated imines and DHP conducted under controlled microwave conditions.[11]

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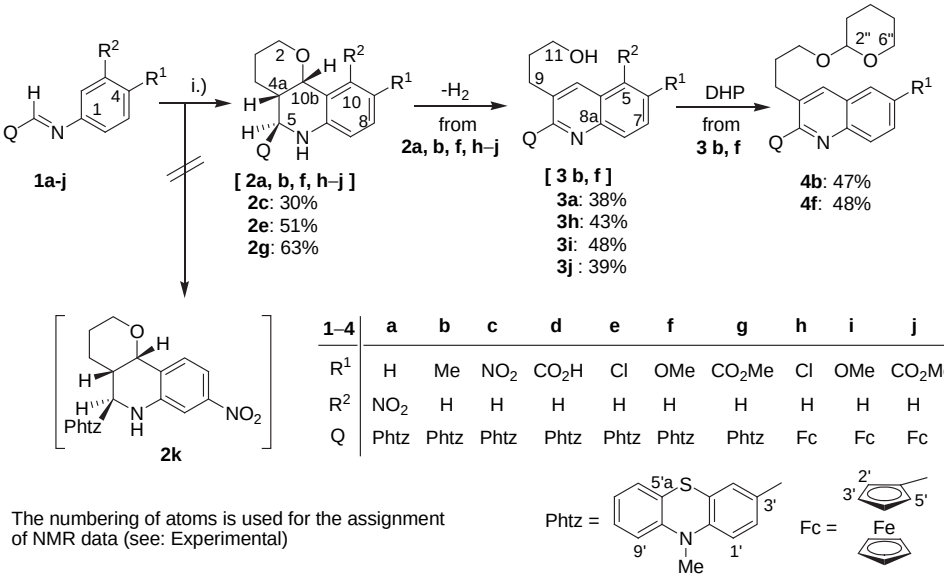
2. Results and discussion

2.1. Synthesis of precursor Schiff bases

Phenothiazinyl- and ferrocenyl-Schiff bases **1a**–**j** (Scheme 1) were obtained in excellent yields in 5 h by the microwave-assisted condensation of the corresponding carbaldehydes and anilines using MeCN as solvent (see Experimental). Schiff bases **1a**–**f** have also been conventionally prepared by heating several hours under reflux the solution of 3-formyl-10-methylphenothiazine and the corresponding aromatic amine.[12] Ferrocenyl Schiff bases **1h**,**i** have previously been prepared under solvent-free conditions.[13] The condensation of formylferrocene was also attempted with 3- and 4-nitroanilines using conventional heating and microwave irradiation but no imine products were obtained by either methods.

isolated as they underwent facile dehydrogenation followed by the fission of the pyrane ring leading to 3-(3-hydroxypropyl)quinolines **3b**,**f**, which finally reacted with the excess of DHP to give acetals **4b**,**f** (Scheme 1). It is noteworthy that despite of the presence of nitro group expected to decrease the tendency of dehydrogenation the reaction of imine **1a** afforded quinoline **3a** as the only isolable product. This reactivity can probably be ascribed to the repulsive interaction of O1 and the adjacent 10-nitro group in **2a** promoting the opening of the pyrane ring presumably followed by facile dehydrogenation of the resulted 1,2-dihydroquinoline intermediate. It is also of interest that neither 8-nitropyranoquinoline **2k** nor the corresponding 7-nitroquinolines of types **3** and **4** could be isolated from the reaction mixture. Under microwave irradiation the iodine-mediated transformations of ferrocenyl-Schiff bases **1h**–**j** with DHP conducted in MeCN (Scheme 1) afforded 2-ferrocenyl-3-(3-



i.) DHP, MeCN, I_2 (1 mol%), MW, 80°C, 0.5 h for **1a**–**g** and 1 h for **1h**–**j**.

Scheme 1. Microwave-assisted [4+2] cycloadditions of phenothiazinyl- and ferrocenyl-Schiff bases with DHP catalyzed by iodine.

2.2. Transformations of Schiff bases with DHP under MW irradiation

The prepared Schiff bases **1a**–**j** containing highly electron-donating phenothiazinyl- or ferrocenyl groups were tested as acceptor components under the conditions of inverse electron demand aza-DA cycloaddition reactions. In the presence of catalysts TFA, $BF_3 \cdot OEt_2$, $AlCl_3$ and $FeCl_3$, which have been applied successfully to analogous reactions of *N*-aryl imines neither microwave irradiation nor thermal conditions proved to be efficient enough to achieve cycloaddition of DHP with these imines containing electron-donating *C*-aryl groups. To our delight, when iodine was used as catalyst, microwave-assisted cyclisation of **1a**–**j** followed by substituent-dependent transformations could be performed in acetonitrile (Scheme 1). Since these reactions of the employed sensitive substrates were accompanied by uncontrolled decompositions, possibly including e.g., polymerisation, the products could be isolated in mediocre yields, but no any reaction took place when carboxylic acid **1d** was used as precursor. The other interesting feature of the observed substrate-dependence is the relative stability of the primarily formed 5-(10-methylphenothiazin-3-yl)-2*H*-pyrano[3,2-*c*]quinolines **2c**,**e**,**g** with electron-withdrawing substituent in the 9-position preventing spontaneous dehydrogenation finally leading to aromatisation. When the reactions of imines **1b**,**f** with electron-donating substituents were conducted under the same conditions the primarily formed adducts **2b**,**f** could not be hydroxypropyl)-quinolines **3h**–**j** as solely isolable products irrespective of the electronic nature of the R^1-substituent referring to highly favoured dehydrogenation and subsequent fission of the pyrane ring in the primarily formed unisolable pyrano-tetrahydroquinolines **2h**–**j**. According to TLC-monitoring the completion of these conversions accompanied by the formation of tarry substances required ca. 1 h taking place significantly slower than those of the corresponding phenothiazinyl-Schiff bases **1e**–**g**.

It must be noted here that—contrary to unisolable 3-(3-hydroxypropyl)quinolines **3b**,**f**—the isolable **3a** and **3h**–**j** do not react with DHP under the employed conditions probably due to the decreased reactivity of the less accessible hydroxypropyl group sterically hindered by the rotating proximal nitro- or bulky-ferrocenyl substituent, respectively. On the other hand, since equimolar amounts of the corresponding Schiff base and DHP were used in the reactions studied, the isolated yields of **4b**,**f** (47% and 48%, respectively) suggest that the rate-limiting cycloaddition is followed by fast aromatisation affording **3b**,**f**, which readily add to the unreacted DHP present in the reaction mixture.

2.3. Structure-determination of compounds 2c,e,g, 3a, h–j and 4b,f

The spectroscopic data listed in the Experimental section are consistent with the structures of the novel quinoline derivatives, only the following remarks are necessary. In angular tricycles **2c**,**e**,**g**

the presence of cis-fused six-membered rings and the pseudoequatorial position of the phenothiazinyl group in the 5-position follow from the coupling pattern of H5-, H4a- and H10b signals with small values of vicinal coupling constants (2.1–2.5 Hz) measured for the proton pair H4a/H10b and large coupling constants between protons H4a and H5 (10.7–11.0 Hz). Accordingly, irradiating the pseudoaxial H5 proton besides H2′- and H4′-protons on the phenothiazinyl group the equatorial H4 and the axial H3 protons gave NOE responses in keeping with the *cis* anellation of the pyrane- and tetra-hydroquinoline rings. In **2c**,**e**,**g**, **3h**–**j** and **4b**,**f** the position of the R^1 group is reflected by the coupling pattern of the three protons attached to the condensed benzene ring with a broadening or a minimal split (1.5–2.5 Hz) of H10- or H5-signals. In the ^{1}H–^{13}C-HMBC spectra of **3a**,**h**–**j** and **4b**,**f** the protons of the CH_2 group directly bonded to the aromatic ring give cross peaks with the C2–C4 atoms supporting the vicinal position of the Q-substituent and the hydroxypropyl- or pyranyloxypropyl-group.

Due to the presence of the adjacent 5-nitro group in the *peri* position the signal of the H4 proton incorporated in a six-membered chelate-like structure is significantly downfield-shifted (8.90 ppm) in the ^{1}H NMR spectrum of **3a**, while the same signal of **3h**–**j** and **4b**,**f** appears in the range of 7.71–7.89 ppm.

In **4b**,**f** the 2″-alkoxy group is in an axial position on the saturated pyrane ring as evidenced by the coupling constants (J=4.3 and 2.7 Hz) of the signal from the equatorial H2″ proton.

2.4. Structure-reactivity relationships observed for the reactions of the Schiff bases

In order to disclose the characteristic substituent-dependence experimentally observed for cycloadditions and subsequent aromatisation of the quinoline moiety comparative DFT calculations[14] were carried out on appropriately selected models at the B3LYP level of theory[15] using a DGZVP basis set.[16] We concentrated on the structure and reactivity of the activated intermediates formed by iodination of the precursor imines, and compared the characteristics of iodine- and proton-activation by DFT analysis performed on iodoiminium ion **1g**/**A**, zwitterion **1d**/**B** as well as on simplified iodoiminium- and protoiminium-ions **1l**–**n**/**A** and **1l**–**n**/**B**, respectively (Fig. 1, Scheme 2, for calculated data and further details, see Supplementary data).

As it was found for **1g**/**A** the population analysis of **1l**–**n**/**A** revealed the participation of LUMO+1 in the primary interaction with DHP. The highest LUMO concentration can be found on the iodine centre as spectacularly represented by the visualized orbitals of **1m**,**n**/**A** (Fig. 2) suggesting an equilibrium formation of DHP-epiiodonium ion **5** (Scheme 2), which may decrease the rate of the cycloaddition process. On the other hand, pointing to the efficiency of iodine-activation in the actual addition step, the energy difference between the LUMO of a protonated imine and the LUMO+1 of its iodinated analogue is relatively small (0.22 eV–0.28 eV) and the atomic charge on the imino carbon is slightly more positive in each investigated iodoiminium ion type **1**/**A** than that in its protonated counterpart type **1**/**B**, although the relatively low values of chemical hardness (η) obtained for both types of ions (see: Supplementary data) show pronounced orbital control[17] in their transformations.

The influence of the *C*-aryl substituent on the reactivity of iodoiminium ions towards DHP was studied on the simplified models **1l**–**n**/**A**. The electron chemical potential and the energy level of LUMO+1 of phenyl-substituted **1l**/**A** are significantly lower than those of **1m**,**n**/**A** with electron-donating Q-groups obviously decreasing the tendency to undergo electrophilic addition to DHP, the first step of cycloaddition process of type **1**/**A**→**6**→**7** (Scheme 2). In keeping with our proposed mechanism Overman and Wolfe postulated that in situ generated *N*-amidinyliminium ions and polysubstituted styrenes undergo stepwise cycloaddition affording diastereomeric dihydropyrimidines.[18]

In contrast to the experimental findings comparison of reactivity indices μ and $\Sigma c^2_{\mathrm{LUMO+1}}$ and atomic charges calculated for **1m**/**A** and **1n**/**A** (Table S1) would lead to a conclusion that the ferrocene-containing iodoiminium ion is more reactive than the phenothiazinyl-substituted ion. The experimentally observed decreased reactivity of ferrocenylimines (reaction time: 1 h) relative to that of phenothiazinyl analogues (reaction time: 0.5 h) can be attributed to the unfavourable energetics of the addition step with DHP as demonstrated on model reactions **1l**–**n**/**A** → **6l**–**n** by means of B3LYP/DGZVP method (Scheme 2). The order of calculated energies seems to correlate with the electron-donating ability of the Q-substituents and the experimental observations pointing to the significantly decreased reactivity of **1n**/**A** stabilized by the highly electron-donating ferrocenyl group (ΔE=25.53 kcal/mol). This stabilization is probably associated with the bonding overlap

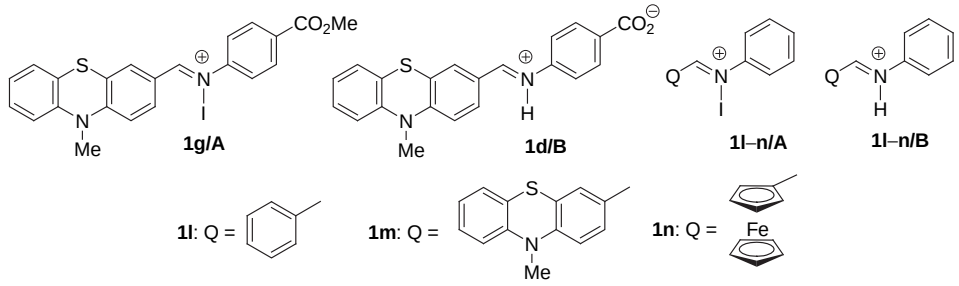
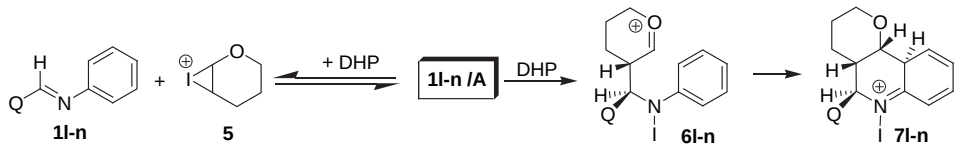


Fig. 1. Model iodoiminium- and protoiminium-ions analyzed by B3LYP/DGZVP calculations.



for **1l**–**n**/**A** + DHP ⟶ **6l**–**n**: ΔE(**l**) = + 5.58 kcal/mol; ΔE(**m**) = + 13.30 kcal/mol; ΔE(**n**) = + 25.53 kcal/mol

Desigantion of **l-n** by substituent Q: see on Figure 1

Scheme 2. Proposed mechanism of iodine-catalyzed cycloaddition reactions of activated model imines **1l**–**n**/**A** and the energetics of the first step calculated by B3LYP/DGZVP method.

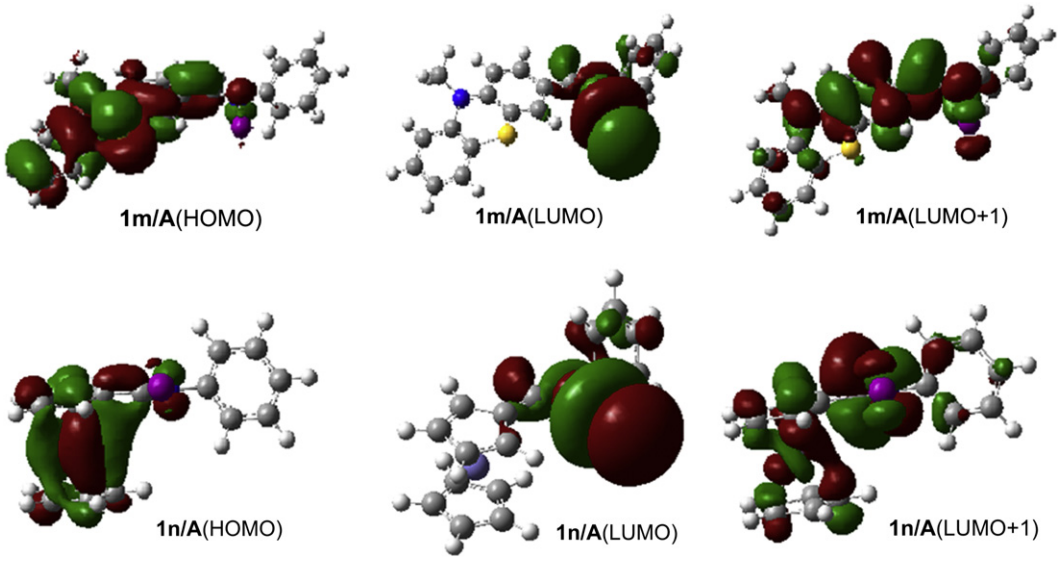


Fig. 2. Contour plot of frontier MO's of iodoiminium ions **1m**/**A** and **1n**/**A**.

between the iron centre and the imino carbon atom[19] as clearly discernible on the contour plot of the HOMO shown in Fig. 2. The DHP-mediated cycloaddition of *N*-3-nitrophenylimine **1a** affording selectively **3a** was interpreted via DFT analysis of the simplified rotamer models of the primarily formed DHP-adduct (**8**/**I** and **8**/**II**: Fig. 3) carried out at B3LYP/DGZVP level of theory. In agreement with the experimentally observed regioselectivity **8**/**I** proved to be more stable by 4.15 kcal/mol than **8**/**II**. This relative stability can at least partially be due to a much stronger π-stacking interaction between the nitrophenyl group and the pyrane-1-ium moiety in **8**/**I** than in **8**/**II** as suggested by the distances between the interacting atoms in the optimized structures (d[2–2′]=2.701 Å in **8**/**I**; d [6–2′]=3.820 Å in **8**/**II**). This view gains spectacular support from the contour plot of HOMO calculated for **8**/**I**, which clearly indicates electron delocalization associated with partial bonding between C2 and C2′ atoms, while the HOMO of the less stable **8**/**II** is concentrated on the *C*-phenyl group (Fig. 3).

anellated pyranoquinolines could not be detected by ^{1}H NMR in the crude reaction mixtures even in traces. On the other hand (4a*R**,5*S**,10b*R**) was established as relative configuration for each isolated pyrano[3,2-*c*]quinoline. These compounds were resulted from the cyclisation of adducts (e.g., types **6** and **8**), which are sterically less crowded than their less stable diastereomers [e.g., **9**, Δ*E* (**9**–**8**/**I**)=7.55 kcal/mol: Fig. 3], the potential precursors of pyrano [3,2-*c*]quinolines with relative configuration (4a*R**,5*R**,10b*R**). Consequently, it seems that the formation of the tricyclic products with relative configuration (4a*R**,5*S**,10b*R**) can probably be ascribed to the slow, thermodynamically controlled diastereoselective addition of DHP to the iminium ions containing electron rich *C*-aryl substituents. It is also worth to point out that a significant π-stacking interaction was also detected in **9** as evidenced by the C2–C2′ distance (d[2–2′]=2.430 Å) and the calculated HOMO showing electron density between these interacting atoms (Fig. 3). Accordingly, the analogous DHP-mediated transformations of more

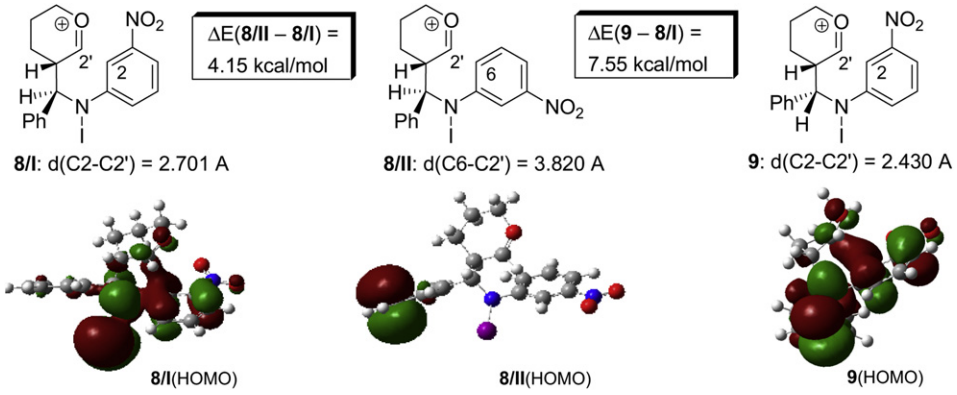
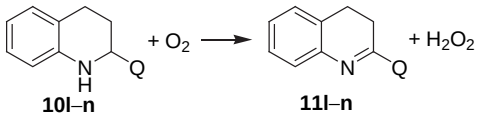


Fig. 3. Non-bonding distances of the interacting atoms, relative stability and contour plot of HOMO's calculated for rotamer models **8**/**I** and **8**/**II** and diastereomeric adduct **9** by B3LYP/DGZVP method.

The π-stacking interaction must also control the stereochemical outcome of the cyclisation steps type **6** → **7** (Scheme 2) yielding products incorporating *cis* fused pyrane- and quinoline-rings. By means of further DFT modelling of adduct **8** we could not find any local minimum representing such a conformation predisposed for cylisation leading to trans anellated rings. The validity of this 'negative result' can obviously be extended to DHP-adducts with other aryl substituents in keeping with the fact that the presence of *trans* reactive imines without highly electron-donating *C*-aryl substituents generally afford mixtures of diastereomeric pyrano[3,2-*c*] quinolines with relative configurations (4a*R**,5*S**,10b*R**) and (4a*R**,5*R**,10b*R**), respectively.[8–10]

A further issue of substituent-dependent reactivity to be discussed here is that—contrary to isolable 5-(10-methylphenothiazin-3-yl)-2*H*-pyrano[3,2-*c*]quinolines **2e**,**g**—their unisolable ferrocenyl-analogues **2h**,**j** with the same electron-withdrawing substituents in the

9-position undergo aromatisation involving dehydrogenation and subsequent fission of the pyrane ring (Scheme 1). This spectacular difference in stability can be attributed to the enhanced stability of the ferrocenylimine moiety formed in the primary dehydrogenation step. This view was supported by the energetics of hypothetical oxygen-mediated transformations of tetrahydroisoquinolines **10l–n** into **11l–n** (Scheme 3) obtained by B3LYP/DGZVP calculations.



10l–n **11l–n**

Desigantion of **l-n** by substituent Q: see on Figure 1

ΔE(**l**) = – 47.33 kcal/mol; ΔE(**m**) = – 48.11 kcal/mol; ΔE(**n**) = – 51.88 kcal/mol

Scheme 3. Calculated energetics of hypothetical oxygen-mediated dehydrogenation of models **10l–n**.

3. Conclusion

Our novel method based on simultaneous application of microwave irradiation and iodine-catalysis to a formal hetero DA reaction of DHP and imines with decreased electrophilic character provides an easy access to hexahydro-2*H*-pyrano[3,2-*c*]quinolines- and 3-(3-hydroxypropyl)quinolines with phenothiazinyl- and ferrocenyl-substituents of potential biological interest. The results of high-level DFT analysis carried out on the intermediate iodoiminium ions, highlighting a multistep mechanism and characteristic substituent-dependence in the cycloaddition process and subsequent aromatisation, allow the prediction of reliable structure –reactivity relationships, which must be taken into account to set up procedures for related cycloadditions.

4. Experimental

4.1. General

Melting points were obtained with an Electrothermal 1A 9200 digital melting point apparatus. IR spectra were recorded in liquid film with an FT-IR Bruker Vector 22 spectrometer. The UV spectra were recorded with an UV–vis Perkin–Elmer Lambda 35 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at rt, on a Bruker DRX-500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, respectively, with the deuterium signal of the solvent as the lock and TMS as internal standard. The assignments of ^{1}H- and ^{13}C-signals were based on DEPT, 2D-COSY, 2D-HSQC, 2D-HMBC and DNOE experiments.

All calculations were carried out with the Gaussian 03 suite of programs.[20] On request the optimized structures are available from the authors.

The reaction mixtures were irradiated in a CEM Discover LabMate microwave reactor. Purification of compounds **2e**, **3a** and **4b**,**f** was performed by semi preparative HPLC instrument Agilent 1200. The reactions were monitored by analytical TLC carried out on precoated plates (silica gel 60, F_{254}) and visualized by UV light. Phenothiazinyl Schiff bases **1a–f** and ferrocenyl Schiff bases **1h**,**i** were prepared according to described procedures (cf. Refs. 12,13, respectively).

4.2. General procedures for synthesis of Schiff bases 1g and 1j

Method A: 3-Formyl-10-methyl-10*H*-phenothiazine/for-mylferrocene (2.0 mmol) and methyl-4-aminobenzoate (0.302 g, 2.0 mmol) were refluxed in EtOH (10 mL) under nitrogen (reaction time: 5 h for **1g** and 8 h for **1j**). After cooling the reaction mixture the precipitated product was filtered off. Analytical sample was recrystallized from ethanol.

Method B: 3-Formyl-10-methyl-10*H*-phenothiazine/for-mylferrocene (2.0 mmol) and methyl-4-aminobenzoate (0.302 g, 2.0 mmol) were dissolved in MeCN (4 mL) in a 10 mL microwave reaction vessel. The reaction mixture was subjected to microwave irradiation using power level of 100 W at 80 °C for 30 min. After cooling the precipitated product was filtered off. Analytical sample was recrystallized from ethanol.

*4.2.1. Methyl 4-[(10-methyl-10H-phenothiazin-3-yl)methyl-eneamino]benzoate (**1g**).* Yellow powder; yield: 0.696 g, 93% (by method A), 0.674 g, 90% (by method B); mp 190–192 °C; ν_{max} 2977, 2894, 1707 cm^{-1}, 1437, 1330, 1079 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} cm^{-1}) 273 (55,881), 386 (897) nm; ^{1}H NMR δ 8.21(1H, s, C*H*=N), 7.98 (2H, br d, *J*=8.3 Hz, H3,5), 7.62 (1H, d, *J*=1.6 Hz, H4′), 7.56 (1H, dd, *J*=8.3 and 1.6 Hz, H2′), 7.13–7.10 (3H, overlapping br d and t, *J*=8.3 and 7.8 Hz, H2,6 and H8′), 6.89 (1H, t, *J*=7.8 Hz, H7′), 6.76 and 6.75 (2H, overlapping d's, *J*=8.4 and 8.2 Hz, H1′ and H9′), 3.84 (3H, s, CO_2CH_3), 3.34 (3H, s, NCH_3); ^{13}C NMR δ 167.3 (CO_2CH_3), 160.5, (*C*H=N), 156.7 (C1), 149.3 (C10′a), 145.0 (C9′a), 135.0 (C3′), 131.3 (C3,5), 130.8 (C4), 129.7 (C2′), 128.0 (C4′), 127.7 (C8′), 127.5 (C6′), 124.2 (C4′a), 123.6 (C7′), 123.2 (C5′a), 121.2 (C2,6), 114.9 (C9′), 114.3 (C1′), 52.4 (CO_2CH_3), 36.1 (NCH_3). Anal. Calcd for $C_{22}H_{18}N_2O_2S$ (374.46) C, 70.57; H, 4.85; N, 7.48; S, 8.56. Found: C, 70.73; H, 4.90; N, 7.38; S, 8.50%. The analytical and spectroscopic data of the samples obtained by the two methods are identical within experimental error.

*4.2.2. Methyl 4-(ferrocenylmethyleneamino)benzoate (**1j**).* Orange powder; yield: 0.590 g, 85% (by method A), 0.576 g, 83% (by method B); mp 146–148 °C; ν_{max} 2990, 2842, 1620, 1435, 2956 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} cm^{-1}) 271 (227,300); 468 (1421) nm; ^{1}H NMR δ 8.21(1H, s, C*H*=N), 7.97 (2H, br d, *J*=8.3 Hz, H3), 7.10 (2H, br d, *J*=8.3 Hz, H2), 4.77 (2H, br s, H2′,5′), 4.48 (2H, br s, H3′,4′), 4.20 (5H, s, Cp ring, Fc), 3.85 (3H, s, CO_2CH_3); ^{13}C NMR δ 167.3 (CO_2CH_3), 163.6, (*C*H=N), 156.9 (C1), 131.4 (C3,5), 127.2 (C4), 121.0 (C2,6), 80.1 (C1′), 72.5 (C3′,4′), 70.1 (C2′,5′), 52.5 (CO_2CH_3). Anal. Calcd for $C_{19}H_{17}FeNO_2$ (347.19) C, 65.73; H, 4.94; N, 4.03. Found: C, 65.88; H, 4.78; N, 3.98%. The analytical and spectroscopic data of the samples obtained by the two methods are identical within experimental error.

4.3. General procedure for iodine-catalyzed cycloadditions assisted by microwave irradiation

To a solution of the corresponding Schiff base **1a–j** (2.85 mmol) and 3,4-dihydro-2*H*-pyran (0.24 g, 2.85 mmol) in 4 mL of MeCN was added iodine (7.2 mg, 0.0285 mmol). The resulting mixture was subjected to irradiation in microwave reactor using power level of 100W at 80 °C (reaction time: 0.5 h for **1a–g**; 1 h for **1h–j**). Water (15 mL) was added to the reaction mixture then the mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried on anhydrous sodium sulfate and then filtered. The solvent was removed in vacuo and the residue was purified by column chromatography on silica using CH_2Cl_2/MeOH (80/1) as eluent to afford **2c**,**e**,**g**, **3a**,**h–j** and **4b**,**f**. After the reaction of **1d** no formation of any product was detected by TLC. Further purification of **2e**, **3a** and **4b**,**f** were performed by HPLC equipped with column Luna® C_8 (2), 150×10 mm, 5 μm, 00F-4249-N0, Phenomenex; mobile phase:

water-MeCN (25/75 v/v%); solvent for the samples: MeOH/MeCN (25/75 v/v%); column temperature: 50 ± 1 °C; ELSD detector temperature: 50 ± 1 °C; flow rate: 2 mL/min; injected volume: 100 μL; run time: 30 min. Under these conditions the following retention times (min) were measured for the appropriate substrates, products and reference compounds: ≈12 (**1a**,**b**,**e**,**f**,); ≈17 (**2e** and **3a**); ≈23 (**4b**); ≈19 (**4f**); ≈11 (10-methylphenothiazine); ≈8 (10-methyl-3-formylphenothiazine).

4.3.1. (4aR,5S*,10bR*)-5-(10-Methyl-10H-phenothiazin-3-yl)-9-nitro-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (**2c**).* Dark yellow powder; yield: 0.381 g, 30%; mp 106–109 °C; ν_{max} 3376, 2932, 1546, 1464, 1331, 1256, 1083 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 258 (58,982), 379 (8145) nm; ^1H NMR δ 8.17 (1H, d, *J*=2.0 Hz, H10), 7.99 (1H, dd, *J*=9.0, 2.0 Hz, H8), 7.19 (1H, br t, *J*=7.9 Hz, H8′), 7.17–7.11 (3H, m, H2′, H4′, H6′), 6.95 (1H, br t, *J*=7.9 Hz, H7′), 6.84 (1H, br d, *J*=7.9 Hz, H9′), 6.80 (1H, d, *J*=8.3 Hz, H1′), 6.45 (1H, d, *J*=9.0 Hz, H7), 4.74 (1H, br s, NH), 4.69 (1H, d, *J*=10.9 Hz, H5), 4.41 (1H, d, *J*=2.1 Hz, H10b), 4.10 (1H, br d, *J*=11.5 Hz, $H2_{eq}$), 3.73 (1H, dt, *J*=11.2, 2.1 Hz, $H2_{ax}$), 3.39 (3H, s, N*C*H_3), 2.02 (1H, m, H4a), 1.82 (1H, qat, *J*=11.2, 2.1 Hz, $H3_{ax}$), 1.70 (1H, tt, *J*=11.2, 2.1 Hz, $H4_{ax}$), 1.55 (1H, br d, *J*=11.2 Hz, $H4_{eq}$), 1.40 (1H, br d, *J*=11.2 Hz, $H3_{eq}$); ^{13}C NMR δ 150.2 (C6a), 146.5 (C10′a), 145.9 (C9′a), 138.4 (C9), 135.1 (C3′), 128.4 (C10), 128.1 (C8′), 127.6, 127.3, 126.5 (C2′, C4′, C6′), 126.3 (C8), 124.9 (C4′a), 123.3 (C7′), 123.2 (C5′a), 119.8 (C10a), 114.6 (C9′), 114.5 (C1′), 113.5 (C7), 74.2 (C10b), 69.2 (C2), 54.4 (C5), 38.5 (C4a), 35.8 (NCH_3), 24.1 (C4), 22.1 (C3). Anal. Calcd for $C_{25}H_{23}N_3O_3S$ (445.53) C, 67.40; H, 5.20; N, 9.43; S, 7.20. Found: C, 67.21; H, 5.28; N, 9.57; S, 7.26%.

4.3.2. (4aR,5S*,10bR*)-10-Chloro-5-(10-methyl-10H-phenothiazin-3-yl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (**2e**).* Yellowish-white powder; yield: 0.632 g, 51%; mp 73–76 °C; ν_{max} 3360, 2937, 1465, 12,581,074 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 229 (28,940), 259 (39,754) nm; ^1H NMR δ 7.20–7.12 (5H, m, H10, H2′, H4′, H6′, H8′), 7.02 (1H, dd, *J*=8.7, 2.4 Hz, H8), 6.93 (1H, t, *J*=7.8 Hz, H7′), 6.82 (1H, d, *J*=7.9 Hz, H9′), 6.78 (1H, d, *J*=8.5 Hz, H1′), 6.41 (1H, d, *J*=8.7 Hz, H7), 3.98 (1H, br s, NH), 4.57 (1H, d, *J*=11.2 Hz, H5), 4.30 (1H, d, *J*=2.7 Hz, H10b), 4.08 (1H, br d, *J*=11.1 Hz, $H2_{eq}$), 3.70 (1H, dt, *J*=11.3, 2.1 Hz, $H2_{ax}$), 3.38 (3H, s, N*C*H_3), 2.00 (1H, m, H4a), 1.79 (1H, qat, *J*=12.2, 2.6 Hz, $H3_{ax}$), 1.64 (1H, tt, *J*=12.1, 2.2 Hz, $H4_{ax}$), 1.51 (1H, br d, *J*=12.7 Hz, $H4_{eq}$), 1.34 (1H, br d, *J*=12.2 Hz, $H3_{eq}$); ^{13}C NMR δ 146.2 (C10′a), 145.9 (C9′a), 144.2 (C6a), 136.3 (C3′), 130.9 (C10), 129.7 (C8), 128.0, 127.6, 127.4, 126.6 (C2′, C4′, C6′, C8′), 124.6 (C4′a), 124.2 (C9), 123.5 (C5′a), 123.0 (C7′), 120.7 (C10a), 114.5 (C9′), 114.4 (C1′), 115.7 (C7), 74.5 (C10b), 69.1 (C2), 54.4 (C5), 39.0 (C4a), 35.8 (NCH_3), 24.4 (C4), 22.4 (C3). Anal. Calcd for $C_{25}H_{23}ClN_2OS$ (434.98) C, 69.03; H, 5.33; Cl, 8.15; N, 6.44; S, 7.37. Found: C, 68.91; H, 5.25; Cl, 8.24; N, 6.31; S, 7.30%.

4.3.3. Methyl-(4aR,5S*,10bR*)-5-(10-methyl-10H-phenothiazin-3-yl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline-9-carboxylate (**2g**).* Yellowish-white powder 0.823 g, 63%; mp 95–98 °C; ν_{max} 3374, 2954, 2857, 1692, 1464, 1437, 1332, 1079 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 275 (175,105) nm; ^1H NMR δ 7.96 (1H, d, *J*=2.0 Hz, H10), 7.78 (1H, dd, *J*=8.7, 2.0 Hz, H8), 7.20 (1H, t, *J*=7.9 Hz, H8′), 7.18–7.11 (3H, m, H2′, H4′, H6′), 6.93 (1H, br t, *J*=7.9 Hz, H7′), 6.84 (1H, br d, *J*=7.9 Hz, H9′), 6.81 (1H, d, *J*=8.5 Hz, H1′), 6.48 (1H, d, *J*=8.7 Hz, H7), 4.79 (1H, br s, NH), 4.67 (1H, d, *J*=10.9 Hz, H5), 4.40 (1H, d, *J*=2.4 Hz, H10b), 4.08 (1H, br d, *J*=11.3 Hz, $H2_{eq}$), 3.85 (3H, s, CO_2CH_3), 3.71 (1H, dt, *J*=11.3, 2.1 Hz, $H2_{ax}$), 3.40 (3H, s, N*C*H_3), 1.98 (1H, m, H4a), 1.81 (1H, qat, *J*=11.3, 2.4 Hz, $H3_{ax}$), 1.70 (1H, tt, *J*=11.2, 2.4 Hz, $H4_{ax}$), 1.53 (1H, br d, *J*=11.3 Hz, $H4_{eq}$), 1.39 (1H, br d, *J*=11.3 Hz, $H3_{eq}$); ^{13}C NMR δ 167. 6 (CO_2CH_3), 149.0 (C6a), 146.1 (C10′a), 146.0 (C9′a), 136.1 (C3′), 133.9 (C10), 131.8 (C8), 128.1 (C8′), 127.6, 127.4, 126.5 (C2′, C4′, C6′), 124.6 (C4′a), 123.4 (C5′a), 123.1 (C7′), 119.1 (C9), 118.9 (C10a), 114.6 (C9′), 114.5 (C1′), 113.7 (C7), 74.7 (C10b), 69.1 (C2), 54.3 (C5), 52.0 (CO_2CH_3), 38.8 (C4a), 35.8 (NCH_3), 24.3 (C4), 22.3 (C3). Anal. Calcd for $C_{27}H_{26}N_2O_3S$ (458.57) C, 70.72; H, 5.71; N, 6.11; S, 6.99. Found: C, 70.79; H, 5.62; N, 6.27; S, 7.04%.

*4.3.4. 3-[(3-Hydroxypropyl)-5-nitroquinoline-2-yl)-10-methyl-10H-phenothiazine (**3a**).* Light-brown powder, 0.480 g, 38%; mp 85–88 °C; ν_{max} 3214, 2963, 2876, 1539, 1474, 1331, 1291, 1055 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 269 (174,466) nm; ^1H NMR δ 8.90 (1H, s, H4), 8.43 (1H, d, *J*=7.9 Hz, H8), 8.34 (1H, d, *J*=7.9 Hz, H6), 7.73 (1H, t, *J*=7.9 Hz, H7), 7.42 (1H, br d, *J*=8.3 Hz, H2′), 7.39 (1H, br s, H4′), 7.19 (1H, br t, *J*=7.9 Hz, H8′), 7.15 (1H, d, *J*=7.9 Hz, H6′), 6.96 (1H, br t, *J*=7.9 Hz, H7′), 6.91 (1H, br d, *J*=7.9 Hz, H9′), 6.85 (1H, d, *J*=8.3 Hz, H1′), 3.61 (2H, t, *J*=6.8 Hz, H11), 3.43 (3H, s, N*C*H_3), 3.00 (2H, t, *J*=6.8 Hz, H9), 1.94 (1H, br s, O*H*), 1.84 (2H, qi, *J*=6.8 Hz, H10); ^{13}C NMR δ 161. 0 (C2), 149.0 (C5), 147.5 (C10′a), 146.4 (C9′a), 145.4 (C8a), 136.4 (C8), 134.3 (C3), 132.4 (C4), 128.6 (C2′), 128.0 (C8′), 127.7 (C6′), 127.3 (C7), 127.0 (C4′), 125.8 (C4a), 125.4 (C3′), 125.0 (C4′a), 124.7 (C6), 124.1 (C5′a), 123.3 (C7′), 114.7 (C9′), 114.3 (C1′), 62.2 (C11), 35.9 (NCH_3), 33.6 (C10). Anal. Calcd for $C_{25}H_{21}N_3O_3S$ (443.52) C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.84; H, 4.61; N, 9.57; S, 7.19%.

*4.3.5. 6-Chloro-2-ferrocenyl-3-(3-hydroxypropyl)quinoline (**3h**).* Dark red powder, 0.500 g, 43%; mp 98–100 °C; ν_{max}. 3234, 2954, 2927, 2854, 1285, 1057 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 273 (473,989), 380 (3864) nm; ^1H NMR δ 7.91 (1H, d, *J*=8.0 Hz, H8), 7.71 (1H, s, H4), 7.61 (1H, br s, H5), 7.48 (1H, br d, *J*=8.0 Hz, H7), 4.97 (2H, br s, H2′,5′), 4.39 (2H, br s, H3′,4′), 4.05 (5H, s, Cp ring, Fc), 3.71 (2H, t, *J*=6.8 Hz, H11), 3.16 (2H, t, *J*=6.8 Hz, H9), 1.94 (1H, br s, O*H*), 1.89 (2H, qi, *J*=6.8 Hz, H10); ^{13}C NMR δ 159.3 (C2), 145.3 (C8a), 135.7 (C4), 134.4 (C3), 131.6 (C6), 130.5 (C7), 129.5 (C8), 128.1 (C4a), 85.3 (C1′), 70.9 (C3′,4′), 70.3 (C2′,5′), 70.3 (Cp ring, Fc), 62.5 (C11), 34.2 (C10), 29.9 (C9). Anal. Calcd for $C_{22}H_{20}ClFeNO$ (405.70) C, 65.13; H, 4.97; Cl, 8.74; N, 3.45. Found: C, 65.09; H, 5.08; Cl, 8.67; N, 3.55%.

*4.3.6. 5-Ferrocenyl-3-(3-hydroxypropyl)-6-methoxyquinoline (**3i**).* Dark red powder, 0.553 g, 48%; mp 137–138 °C; ν_{max} 2989, 2930, 2823, 1272, 1033 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 274 (542,360) nm; ^1H NMR δ 7.90 (1H, d, *J*=8.2 Hz, H8), 7.72 (1H, s, H4), 7.22 (1H, br d, *J*=8.2 Hz, H7), 6.92 (1H, br s, H5), 4.92 (2H, br s, H2′,5′), 4.34 (2H, br s, H3′,4′), 4.06 (5H, s, Cp ring, Fc), 3.85 (3H, s, O*C*H_3), 3.71 (2H, t, *J*=6.8 Hz, H11), 3.14 (2H, t, *J*=6.8 Hz, H9), 1.96 (1H, br s, O*H*), 1.90 (2H, qi, *J*=6.8 Hz, H10); ^{13}C NMR δ 157.8 (C2), 155.9 (C6), 143.0 (C8a), 134.9 (C3), 134.0 (C4), 130.7 (C4a), 130.2 (C8), 122.0 (C7), 107.3 (C5), 86.0 (C1′), 70.6 (C3′,4′), 69.8 (C2′,5′), 70.0 (Cp ring, Fc), 62.6 (C11), 56.0 (OCH_3), 34.2 (C10), 29.7 (C9). Anal. Calcd for $C_{23}H_{23}FeNO_2$ (401.28) C, 68.84; H, 5.78; N, 3.49. Found: C, 68.79; H, 5.68; N, 3.60%.

*4.3.7. Methyl-5-ferrocenyl-3-(3-hydroxypropyl)quinoline-6-carboxylate (**3j**).* Red powder, 0.476 g, 39%; mp 54–57 °C; ν_{max} 3139, 2998, 2935, 2832, 1721, 1291, 1038 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 273 (489,344) nm; ^1H NMR δ 8.40 (1H, br s, H5), 8.12 (1H,br d, *J*=7.4 Hz, H7), 7.97 (1H, d, *J*=7.4 Hz, H8), 7.88 (1H, s, H4), 5.01 (2H, br s, H2′,5′), 4.41 (2H, br s, H3′,4′), 4.07 (5H, s, Cp ring, Fc), 3.90 (3H, s, CO_2CH_3), 3.73 (2H, t, *J*=6.8 Hz, H11), 3.17 (2H, t, *J*=6.8 Hz, H9), 1.92 (2H, qi, *J*=6.8 Hz, H10); ^{13}C NMR δ 167.4 (CO_2CH_3), 161.6 (C2), 148.8 (C8a), 136.9 (C4), 134.6 (C3), 130.5 (C5), 129.3 (C8), 128.6 (C7), 127.3 (C4a), 126.3 (C6), 85.1 (C1′), 71.2 (C3′,4′), 70.7 (C2′,5′), 70.3 (Cp ring, Fc), 62.5 (C11), 52.7 (CO_2CH_3), 34.0 (C10), 29.8 (C9). Anal. Calcd for $C_{24}H_{23}FeNO_3$ (429.29) C, 67.15; H, 5.40; N, 3.26. Found: C, 67.33; H, 5.61; N, 3.34%.

*4.3.8. 3-{6-Methyl-3-[3-(tetrahydro-2H-pyran2yloxy)-propyl]quinolin-2-yl}-10-methyl-10H-phenothiazine (**4b**).* Yellow oil, 0.665 g, 47%; ν_{max} 2955, 2983, 1463, 1392, 1331, 1256, 1175 cm^{-1}; $\lambda(\epsilon$ in L mol^{-1} $cm^{-1})$ 270 (229,712) nm; ^1H NMR δ 7.95 (1H, d, *J*=8.5 Hz,

H8), 7.72 (1H, s, H4), 7.32–7.29 (2H, overlapping br d and br s, J=8.4, H2′ and H4′), 7.46 (1H, br s, H5), 7.42 (1H, br d, J=8.5 Hz, H7), 7.10 (1H, br t, J=7.7 Hz, H8′), 7.07 (1H, br d, J=7.7, Hz, H6′), 6.86 (1H, br t, J=7.7 Hz, H7′), 6.81 (1H, d, J=8.7 Hz, H1′), 6.76 (1H, br d, J=8.4 Hz, H1′), 4.39 (1H, dd, J=4.4, 2.7 Hz, H2″), 3.69 (1H, m, H6″$_{ax}$), 3.61 (1H, m, H11A), 3.34 (3H, s, NCH_3), 3.33–3.26 (2H, m, H6″$_{eq}$ and H11B), 2.89–2.75 (2H, m, H9), 2.46 (3H, s, CH_3),1.78 (2H, qi, J=7.4 Hz, H10), 1.65 (1H, m, H4″$_{ax}$), 1.55–1.36 (5H, H3″$_{ax}$, H3″$_{eq}$, H4″$_{eq}$, H5″$_{ax}$ H5″$_{eq}$); ^{13}C NMR δ 158.9 (C2), 146.2 (C10′a), 145.9 (C9′a), 145.4 (C8a), 136.7 (C6), 135.4 (C3′), 136.0 (C4), 133.7 (C3), 129.1 (C8), 128.1 (C4a), 128.6 (C2′), 128.1 (C4′), 127.9 (C8′), 127.6 (C6′), 123.9 (C4′a), 123.7 (C5′a), 123.0 (C7′), 131.7 (C7), 114.5 (C9′), 114.1 (C1′), 126.1 (C5), 99.1 (C2″), 66.9 (C11), 62.7 (C6″), 35.8 (NCH_3), 31.2 (C3″), 31.0 (C10), 30.0 (C9), 25.9 (C5″), 22.0 (CH_3), 19.9 (C4″). Anal. Calcd for $C_{31}H_{32}N_2O_2S$ (496.66) C, 74.97; H, 6.49; N, 5.64; S, 6.46. Found: C, 75.08; H, 6.41; N, 5.59; S, 6.55%.

*4.3.9. 3-{6-Methoxy-3-[3-(tetrahydro-2H-pyran2yloxy)-propyl]quinolin-2-yl}-10-methyl-10H-phenothiazine (**4f**).* Light-yellow powder, 0.702 g, 48%; mp 48–52 °C; ν_{max} 2960, 2870, 1468, 1383, 1258, 1226, 1166 cm^{-1}; λ(ϵ in L mol^{-1} cm^{-1}) 229 (36,656); 261 (46,009); 333 (9064) nm; ^{1}H NMR δ 7.92 (1H, d, J=9.0 Hz, H8), 7.87 (1H, s, H4), 7.30 (1H, dd, J=9.0, 1.7 Hz, H2′), 7.26 (1H, br s, H4′), 7.22 (1H, dd, J=9.0, 2.9 Hz, H7), 7.11 (1H, td, J=7.7, 1.8 Hz, H8′), 7.07 (1H, dd, J=7.7, 1.8 Hz, H6′), 6.97 (1H, d, J=2.9 Hz, H5), 6.87 (1H, br t, J=7.7 Hz, H7′), 6.81 (1H, d, J=8.7 Hz, H1′), 6.77 (1H, br d, J=7.7 Hz, H1′), 4.39 (1H, dd, J=4.4, 2.7 Hz, H2″), 3.86 (3H, s, OCH_3), 3.69 (1H, m, H6″$_{ax}$), 3.61 (1H, m, H11A), 3.36 (3H, s, NCH_3), 3.32–3.27 (2H, m, H6″$_{eq}$ and H11B), 2.89–2.75 (2H, m, H9), 1.77 (2H, qi, J=7.4 Hz, H10), 1.65 (1H, m, H4″$_{ax}$), 1.53–1.36 (5H, H3″$_{ax}$, H3″$_{eq}$, H4″$_{eq}$, H5″$_{ax}$ H5″$_{eq}$); ^{13}C NMR δ 158.2 (C6), 157.6 (C2), 146.0 (two coalesced lines, C9′a and C10′a), 143.1 (C8a), 135.7 (C3′), 135.2 (C4), 134.0 (C3), 131.2 (C8), 128.9 (C4a), 128.6 (C2′), 128.2 (C4′), 127.7 (C8′), 127.5 (C6′), 123.9 (C4′a), 123.7 (C5′a), 122.9 (C7′), 122.0 (C7), 114.5 (C9′), 114.1 (C1′), 104.8 (C5), 99.1 (C2″), 67.0 (C11), 62.8 (C6″), 55.9 (OCH_3), 35.8 (NCH_3), 31.2 (C3″), 31.0 (C10), 30.1 (C9), 25.9 (C5″), 19.9 (C4″). Anal. Calcd for $C_{31}H_{32}N_2O_3S$ (512.66) C, 72.63; H, 6.29; N, 5.46; S, 6.25. Found: C, 72.78; H, 6.34; N, 5.54; S, 6.22%.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.10.046.

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