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Influence of thiazole regioisomerism on second-order nonlinear optical chromophores

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Dedicated to Dra. Nuria Gallego-Planas for her friendship, enthusiasm, support and inspiration while she was with us

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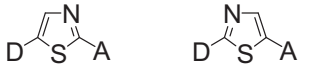
ABSTRACT

Two series of matched and mismatched donor–thiazole–acceptor chromophores have been synthesized to disclose the role that the orientation of the thiazole ring plays on their second-order nonlinear optical (NLO) properties. Whereas previous theoretical studies predict that the matched systems show markedly higher NLO responses, our experimental results do not parallel this trend, showing differences between regioisomers much lower than those predicted.

1. Introduction

Second-order nonlinear optical (NLO) materials based on donor–π-spacer–acceptor (D–π–A) chromophores have been developed for the last two decades in both academia and industry.[1] Among the traditional π-spacers, polyenes allow for efficient intramolecular charge transfer (ICT) from donor to acceptor, but they impart low thermal and chemical stabilities, whereas the reverse situation is found for aryl-type spacers.

The required balance between stability and charge delocalization was not reached until the replacement of aryl rings with the more easily delocalizable heteroaromatic rings was explored later on.[2,3] In this way, and taking into account the low aromatic delocalization energy (ADE) of thiazole (25 kcal/mol) with respect to that of benzene (36 kcal/mol),[4] considerable interest has been focused on D–π–A chromophores bearing a thiazole spacer, for which, due to its unsymmetrical nature, two regioisomers should be considered. They are usually referred to as showing the *matched* orientation (when the electron-poor 2-position of the thiazole is linked to the acceptor and the electron-rich 5-position to the donor) or the *mismatched* one (in the opposite situation).



Breitung et al.[3] first, and other authors later on,[2c,5,6] carried out theoretical calculations showing that the regioisomerism of thiazole-containing chromophores significantly modulates the first hyperpolarizability (β), with considerably better second-order NLO properties being predicted for the matched derivatives. Unfortunately, most thiazole-containing NLO chromophores hitherto described are mismatched compounds[7,47] and only a few matched derivatives bearing either aromatic,[8–11] or quinoidal thiazoles[12–17] have been reported.

Consequently, the effect of thiazole regioisomerism on second-order NLO properties has been scantly studied experimentally. As far as we know, there are only four pairs of analogous matched/mismatched thiazole derivatives for which their second-order NLO properties have been compared[9,10,18] and the matched derivatives show only slightly enhanced β values, at variance with previous theoretical studies.

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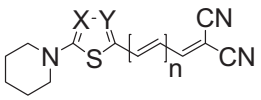
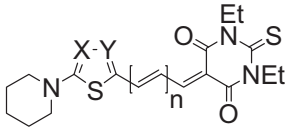
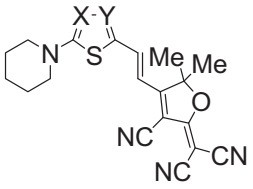
To get a better understanding of the role that the orientation of thiazole plays on the experimental second-order NLO properties of D–thiazole–A chromophores, in this paper we describe the synthesis, characterization and study of a series of comparable matched/mismatched thiazole derivatives **1**–**10**, bearing different donor and acceptor groups. Experimental NLO measurements are compared to the results of theoretical calculations.



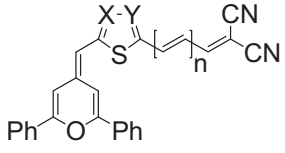
1a-b; 2a-b



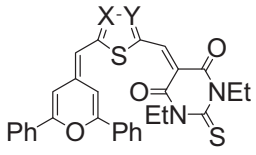
3a-b; 4a-b



5,6



7a-b; 8a-b



9,10

a: n = 0; **b**: n = 1

1,3,5,7,9: X=CH,Y=N; matched chromophores

2,4,6,8,10: X=N,Y=CH; mismatched chromophores

2. Results and discussion

2.1. Synthesis

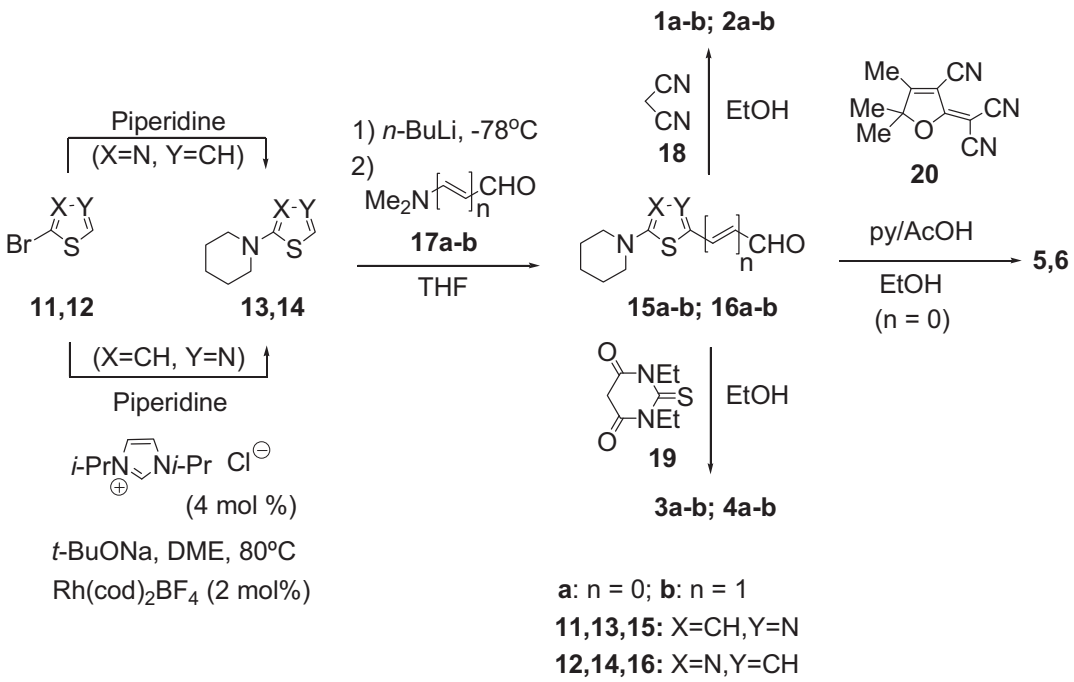
Compounds **1**–**6**, with a piperidine moiety as a donor were prepared through a three-step synthesis, as shown in Scheme 1. Mismatched aldehyde **16a**[19] was prepared by lithiation of **14**[20] followed by reaction with DMF (**17a**).[21] An analogous reaction using (*E*)-3-dimethylaminoacrylaldehyde (**17b**) gave the new aldehyde **16b**. Unlike **14**, 5-piperidinothiazole **13** has not been previously reported. This compound cannot be prepared by nucleophilic aromatic substitution of 5-bromothiazole with piperidine,[22] but, to our delight, a Rh-catalyzed version of this reaction[23] gave **13** in excellent yield. Matched aldehydes **15a**,**b** were prepared analogously to **16a**,**b**, but starting from **13**.

Finally, the Knoevenagel reactions between aldehydes **15**, **16** and acceptors, **19** and **20**[24] yielded the new D–π–A piperidine derivatives, **1**–**6**. To the best of our knowledge, compounds **1**, **3** and **5** are the first examples of 5-piperidinothiazole-based chromophores.

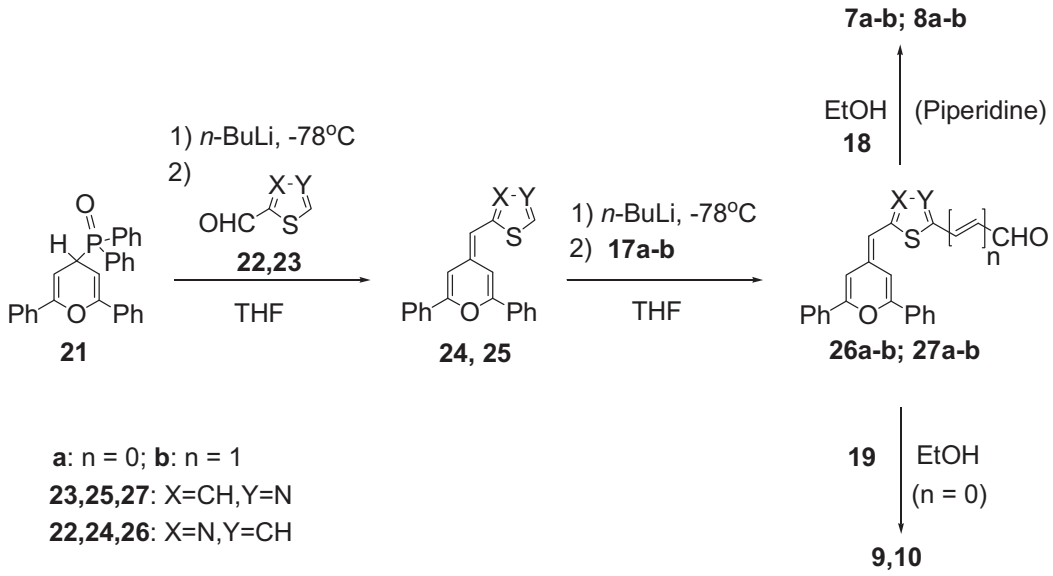
Concerning compounds **7**–**10**, with a 4*H*-pyranylidene moiety as a donor, their synthesis is shown in Scheme 2. Thus, the Horner reaction of (2,6-diphenyl-4*H*-pyran-4-yl)diphenylphosphine oxide (**21**)[25] with the commercially available thiazolecarbaldehydes (**22**, **23**) yielded the desired precursors **24** and **25**, which, by lithiation and reaction with **17a** or **17b** afforded the corresponding aldehydes bearing a matched (**27a**,**b**) or a mismatched (**26a**,**b**) thiazole ring. The Knoevenagel reaction of these aldehydes with acceptors **18** and **19** afforded the desired D–π–A compounds **7**–**10**. To the best of our knowledge, there is only a previous report[16] in the literature on compounds bearing a 4*H*-pyranylidene unit and a thiazole ring in their structure.

2.2. X-ray diffraction: crystal structures of 4a and 6

Single crystals of **4a** were grown from a $CHCl_3$ solution at room temperature (Fig. 1).



Scheme 1. Synthesis of chromophores **1**–**6**.



Scheme 2. Synthesis of chromophores **7**–**10**.

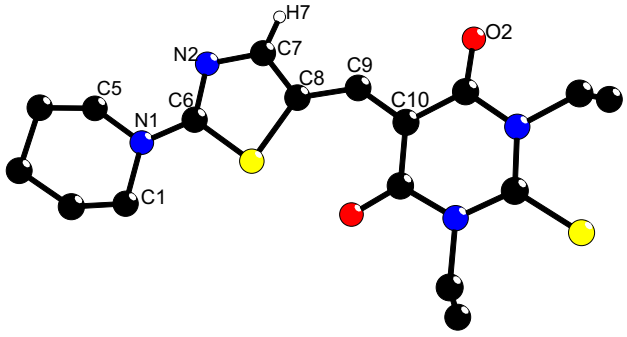


Fig. 1. Molecular structure of **4a**.

Compound **4a** crystallizes in the triclinic space group *P*−1. The neighbouring chromophores are linked by a nonclassical C7−H7···O2 hydrogen bonding interaction (geometric parameters for intermolecular contact: *D*−H 0.93 Å, H···*A* 2.37 Å, *D*···*A* 3.216(4) Å, *D*−H···*A* 151.8°; symmetry code: 1−*x*, 1−*y*, 1−*z*; see Fig. S69, in Supplementary data), that has already been found in other thiazole systems.[26]

The π-system is essentially planar, as expected for highly conjugated structures. In fact, the angle between the mean planes of the thiazole and the acceptor rings is 1.8°. There is evidence for opening out of the bond angle in the methine bridge to accommodate the planar structure, with the angle C10−C9−C8 of 135.5° being particularly large for a trigonal centre (bigger distortions have been found for related compounds containing a phenyl ring instead of the thiazole unit).[27]

Moreover, it can be seen that the thiazole-exocyclic C8−C9 bond has an s-trans conformation, like that found in related 2-aminothiazole-5-carbaldehydes.[28]

Bond lengths reveal intramolecular charge transfer from the donor to the acceptor. Thus, N1−C6 and N2−C7 bonds are shorter than the corresponding bonds in 2-aminothiazole derivatives lacking a powerful electron-withdrawing group in 5-,[29] whereas an accompanying lengthening of the N2−C6 and C7−C8 bonds in **4a** is also observed. An additional evidence of the charge delocalization along the chromophore is the sp^2 hybridization of the piperidine nitrogen (geometrical angles of 122.6° for C5−N1−C6, 122.5° for C1−N1−C6 and 114.7° for C1−N1−C5).

Moreover, the fact that the C8−C9 bond is shorter (1.390 Å) than the corresponding bond in a related compound with a phenyl ring instead of thiazole (1.430 Å),[27] is consistent with the increase in electronic delocalization when using five-membered heteroaromatic rings instead of phenyl.[2a,b,3,7a,8,47] As an additional confirmation for the ICT, the difference between the C8−C9 and the C9=C10 bond lengths is 0.014 Å, and although **4a** contains only a single methine unit, this value can be approximated as the bond length alternation (*BLA*) along the spacer (defined as the difference between the average carbon−carbon single and double bond lengths).[30] Given that for cyanines *BLA* ~0 Å, **4a** is close to the cyanine limit in the solid state.

Single crystals of compound **6** were obtained by slow diffusion of hexane into a concentrated solution of the chromophore in $CH_2Cl_2/CHCl_3$ at room temperature. Compound **6** crystallizes in the monoclinic space group *P*21/*n*, and some of the main features of its structure are similar to those of **4a**. The *BLA* value for **6** is 0.050 Å, close to the optimal one.[31] A complete description of the crystal structure is reported in the Supplementary data.

2.3. ^{1}H NMR studies

The structures of the chromophores were analyzed by ^{1}H NMR spectroscopy. This technique affords valuable information about both the geometry and the ground-state polarization of the studied molecules. Concerning the stereochemistry, $^3J_{HH}$ coupling constant analysis of the polyenic derivatives (**1b**–**4b**, **7b**, **8b**) and **5**, **6** indicates an all-trans geometry along the spacer, with $^3J_{HH}$ values ranging from 14.1 Hz to 15.8 Hz for the −CH=CH− bonds and from 10.8 to 12.5 Hz for the =CH−CH=bonds (compound **1b** was obtained as an *E*/*Z* mixture (80:20)). Selective ge-1D NOESY experiments were carried out in order to determine the conformations adopted in solution by our D−thiazole−A systems (see discussion in Supplementary data).

^{1}H NMR data also provide valuable information about the ground-state polarization of the studied chromophores, through the use of $^3J_{HH}$ and Δ*J* values, since Δ*J*, defined as the difference between the averaged $^3J_{HH}$ values of the double and single bonds along the polymethine chain[32] ranges from 0 Hz in cyanines to ca. 6 Hz in polyenes.[33] Comparison of the $^3J_{HH}$ values of compounds **1b** and **2b** (Fig. 2), reveals that the presence of a matched thiazole gives rise to a less polarized/more alternated structure than that of

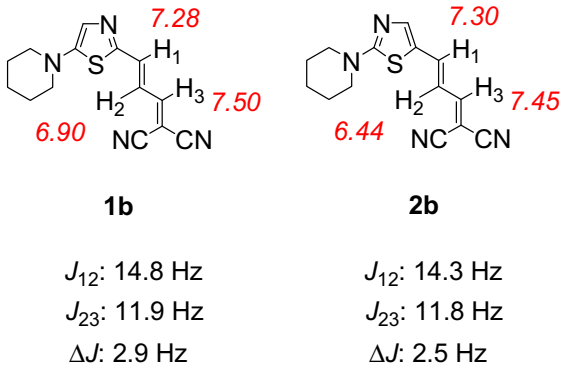


Fig. 2. δ (ppm), $^3J_{HH}$ and ΔJ values (in CD_2Cl_2) for compounds **1b** ((*E*)-isomer) and **2b**.

a mismatched analogue as judged by the higher ΔJ values shown by the former. This trend in *J* values is in agreement with that found in other thiazole regioisomers recently studied.[10] Furthermore, the chemical shifts of the H atoms along the spacer (Fig. 2) show the typical oscillatory behaviour[33a,34] of a merocyanine-like chromophore. The increased shielding of H2 in **2b** when compared to **1b**, also points to an increased electron density on the π-conjugated bridge in **2b**, and consequently to a more polarized structure.

ΔJ values for **3b** (2.3 Hz) and **4b** (1.6 Hz) also reveal less alternated structures for thiobarbiturates than for the dicyanomethylene derivatives, according to the higher acceptor ability of the former. When different donors are compared, the pyranylidene derivatives show higher ΔJ values (ΔJ for **7b**: 3.9 Hz; ΔJ for **8b**: 2.8 Hz), than the piperidino analogues, thus suggesting a lower ICT for the pyranylidene-containing chromophores. The shift of the polyenic spacer protons of **7b**, **8b** to lower fields respect to **1b**, **2b** confirms this feature.

The proaromatic character of the pyranylidene donor has been previously established,[16,35] and it is known that the protons of the pyranylidene ring undergo downfield shifts as the pyrylium character of the ring increases.[36] For the herein reported compounds (Table S1, Supplementary data), the chemical shifts of the pyranylidene ring protons increase on shortening the polyenic spacer, thus demonstrating that the contribution of the aromatic pyrylium form is higher for the shorter derivatives, in agreement with other D–π–A systems with a 4*H*-pyran-4-ylidene unit previously described.[35]

2.4. Electrochemistry

The redox properties of compounds **1**–**10** were investigated by cyclic voltammetry (CV) (Table 1). All the NLO chromophores show irreversible redox processes except for **2a** and **6**, that exhibit reversible oxidation–reduction properties in positive scans.

For compounds **1**–**4** and **7**–**8**, lengthening the spacer gives rise to a decrease of E_{ox} and $|E_{red}|$ values, thus pointing to a decrease in the interaction between the donor and acceptor end groups.

Moreover, for a given donor and spacer length, when changing the acceptor from dicyanomethylene to the thiobarbiturate group there is a shift of the $|E_{red}|$ values towards less cathodic potentials, pointing to the superior acceptor ability of the thiobarbiturate group when compared to dicyanomethylene. ^{1}H NMR and UV–vis also support the comparatively weaker electron-withdrawing effect of the dicyanomethylene group. On the other hand, there is a shift of the E_{ox} values towards less anodic potentials when passing from dicyanomethylene to thiobarbiturate derivatives.

In comparison, all the matched thiazole-based NLO chromophores exhibit lower reduction/oxidation potentials than their mismatched isomers, in agreement with previous results.[9–11]

Table 1
Electrochemical[a] and UV–vis data

Compd	E_{ox}	E_{red}	λ_{max}[b] (CH_2Cl_2) (log ε)	λ_{max}[b] (DMF) (log ε)
1a	+1.25	−1.12	481 (4.82)	488 (4.67)
2a	+1.44[c]	−1.36	428 (4.69)	428 (4.69)
1b	+0.95	−0.97	529 (4.48)	536 (4.52)
2b	+1.15	−1.12	488 (4.66)	487 (4.65)
3a	+1.13	−1.00	506 (sh), 534 (4.89)	511 (sh), 538 (4.85)
4a	+1.31	−1.16	486 (4.94)	487 (4.98)
3b	+0.92	−0.75	611 (4.73)	629[d]
4b	+1.06	−0.90	564 (4.94)	516 (sh), 568 (4.95)
5	+0.97	−0.68	617 (4.49)	642 (4.66)
6	+1.17[e]	−0.83	535 (4.80), 568 (4.86)	532 (sh), 569 (4.80)
7a	+0.90	−0. 87	603 (4.66)	592 (4.56)
8a	+0.90	−1.01	546 (4.73), 576 (sh)	544 (4.70)
7b	+0.74	−0.80	614 (4.58)	600 (4.59)
8b	+0.81	−0.94	569 (4.72)	559 (4.74)
9	+0.80	−0.71	672 (4.69)	633 (4.49)
10	+0.85	−0.83	584 (sh), 618 (4.64)	608 (4.55)

[a] In volts, 10^{-3} M in CH_2Cl_2 versus Ag/AgCl (KCl 3 M), glassy carbon working electrode, Pt counter electrode, 20 °C, 0.1 M Bu_4NPF_6 100 mV s^{-1} scan rate. Ferrocene internal reference $E^{1/2}$=+0.46 V.
[b] In nm.
[c] $E_{ox}^{1/2}$(ΔE_p=0.16 V).
[d] ε cannot be determined due to its decomposition.
[e] $E_{ox}^{1/2}$ (ΔE_p=0.15 V).

2.5. UV–vis spectroscopy

All compounds show strong intramolecular charge transfer transitions in the visible region (Table 1) (see spectra in Supplementary data). For systems **1**–**4**, λ_{max} values increase on lengthening the spacer showing vinylene shifts between 50 and 80 nm (both in CH_2Cl_2 and DMF) pointing to weakly alternated structures, whereas for **7**–**8**, the increase in λ_{max} values is remarkably low (around 10–20 nm), possibly due to their less polarized structures, as disclosed by ^{1}H NMR data.

λ_{max} values also allow a broad comparison of the electron-withdrawing abilities of the different acceptor groups (TCF>thiobarbiturate>dicyanomethylene).

The orientation of thiazole has a significant effect on the electronic absorption properties of the chromophores.[9–11,18] Thus, the presence of a matched thiazole causes a significant red shift of λ_{max} (e.g., 48 nm for **3a**/**4a** and 57 nm for **7a**/**8a**, both in CH_2Cl_2), in agreement with the electrochemical measurements.

In general, larger molar extinction coefficients ε are found for the mismatched derivatives, contrary to the few experimental examples of matched/mismatched pairs reported in the literature.[9–11] This trend parallels that of the calculated oscillator strengths *f* reported for other thiazole D–π–A compounds.[37,38]

Most of the compounds show an almost negligible solvatochromism from CH_2Cl_2 to DMF ($\Delta\lambda$ values ranging from −14 to 7 nm, except for **5** that shows $\Delta\lambda$=25 nm and **9**, $\Delta\lambda$=−39 nm; on the energy scale these shifts range from +0.05 to −0.04 eV and values for **5** and **9** are −0.08 eV and +0.11 eV, respectively), thus suggesting a cyanine-like character for these compounds. For instance, the $\Delta\lambda$ value of compound **4a** (1 nm) is in line with its very low *BLA* value obtained from X-ray data, indicating that its structure is close to cyanine limit both in the solid state and in solution. It is interesting to note that when comparing dioxane and CH_2Cl_2, compounds **7**–**8** exhibit positive solvatochromism (λ_{max} (nm) in dioxane: **7a**: 544; **7b**: 586; **8a**: 530; **8b**: 550). This variety of solvatochromic behaviour has already been reported for other D–π–A systems,[39] including thiazole derivatives.[10]

2.6. Calculated structures

In order to gain insight into the ground-state electronic structures of the studied chromophores their gas phase structures were

calculated using the Hartree–Fock (HF) model. Given the number of possible conformational isomers, and in order to simplify the following discussion, we have chosen for push–pull systems **1**–**10** the geometries shown in Fig. 3, and from now on, calculated data used in the text will refer to these conformations, which may not necessarily represent the lowest-energy conformation of each chromophore, but mimic the ones observed by X-ray studies for **4a** and **6**.

2.7. Nonlinear optical properties

The second-order nonlinear optical properties of compounds **1**–**9** were measured by electric field-induced second harmonic generation (EFISH) in CH_2Cl_2 at 1907 nm (Table 3). The corresponding static (zero-frequency) $\mu\beta_0$ values determined using the two-level model[40] are also gathered in Table 3 (for the sake of

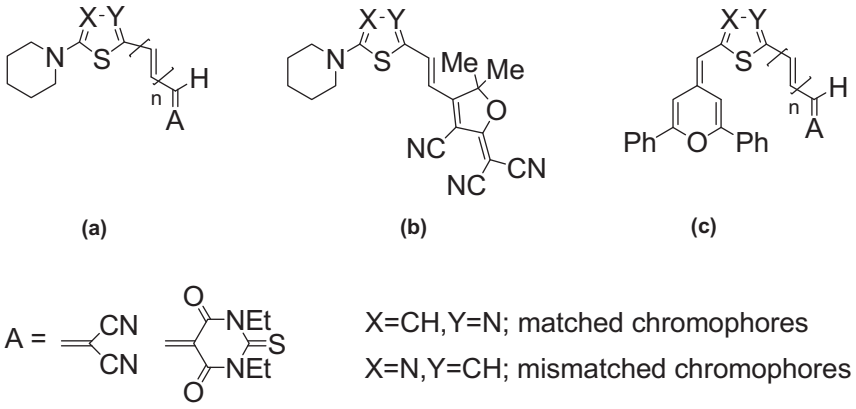


Fig. 3. Geometries used for the calculations: (a) for **1**–**4**; (b) for **5**–**6**; (c) for **7**–**10**.

Calculated *BLA* values (along the acyclic spacer connecting the thiazole moiety to the acceptor group) on gas phase HF/6-31G* geometries for compounds **1b**, **2b**, **3a**, **4a**, **5**, **6** (chosen as model compounds) are collected in Table 2.

Table 2
Calculated *BLA* values along the spacer for selected compounds

Compd	*BLA* (Å)	Compd	*BLA* (Å)
1b	0.111	**2b**	0.093
3a	0.080	**4a**	0.046
3b	0.101	**4b**	0.082
5	0.116	**6**	0.095

Inspection of data reveals that *BLA* is reduced in the chromophores with mismatched thiazoles compared to that of the corresponding matched species. This is consistent with the results obtained for other thiazole D–π–A systems[10,37] and with our NMR studies, showing that the introduction of a matched thiazole results in a more alternated structure.

Moreover, when dicyanomethylene and thiobarbiturate derivatives are compared, *BLA* values decrease in the order **1b**, **2b**>**3b**, **4b**, suggesting that the thiobarbiturate group is a stronger acceptor, in agreement with NMR and UV–vis data and CV measurements. Besides, it can be seen that on lengthening the π-spacer *BLA* increases (**3a**, **4a**<**3b**, **4b**) confirming that longer derivatives (**3b**, **4b**) are less polarized.

Finally, as exemplified by pyranylidene derivatives **7a**, **8a**, **9**, **10** Mulliken charges (Fig. 4) show that the negative charge is concentrated on the acceptor,[11,12,15,16] and the positive charge is spread over the donor and the π-spacer, whereas the thiazole moiety remains almost neutral. Moreover, the mismatched derivatives are more polarized than their matched analogues, thus confirming the ^{1}H NMR and *BLA* results.

For piperidine derivatives **1**–**6**, the same trends are observed (see Fig. S74 in Supplementary data), although more negative charges are concentrated on the acceptor end of these compounds (e.g., **1a**: −0.30/**7a**: −0.27; **3a**: −0.35/**9**: −0.30); this higher degree of polarization for the piperidine derivatives is in agreement with ^{1}H NMR results and UV–vis data.

comparison, Disperse Red 1, a common benchmark for organic NLO chromophores, gives a $\mu\beta_0$ value of $\sim 480\times10^{-48}$ esu in the same experimental conditions).

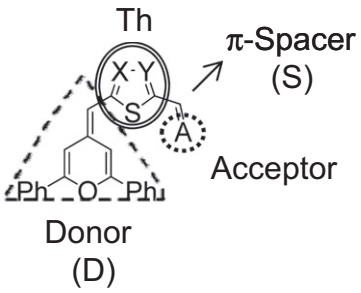
As it has been previously observed for other NLO-chromophores studied, thiobarbituric derivatives (**3b**, **4b**, **9**) show $\mu\beta$ values higher than those of their dicyanomethylene analogues (**1b**, **2b**, **7a**) (the comparison between **1a**–**2a** and **3a**–**4a**, respectively constitutes an exception). Moreover, comparison of compounds **a** and **b** reveals that lengthening the polyenic chain by a single vinylene unit gives rise to an important increase in the NLO responses.

Regarding the influence of a matched/mismatched thiazole on the NLO properties of the studied chromophores (Fig. 5; red bars), the largest experimental difference between a matched/mismatched pair is found for compounds **1a**/**2a** (factor of 1.8), whereas for compounds **3**–**4**, this value is close to 1.35 and for the rest of the measured systems, there is an almost negligible difference between the $\mu\beta_0$ values of the matched and the mismatched derivatives. Therefore the experimental results do not conform with the previous theoretically-derived trends.[2c,3,5,6] In fact, the reported experimental increase in the NLO properties when passing from a mismatched D–π–A derivative to a matched analogue[9,10,18] is not that considerable, since the values of the experimental ratio (β_0 matched/β_0 mismatched) are around 1.1–1.2, in agreement with our own data.

In order to gain a deeper understanding of the structure-properties relationship in our chromophores, $\mu\beta_0$ values were also calculated theoretically. Although it has been reported that most Quantum-chemistry methods predict successfully trends in hyperpolarizabilities,[41] DFT methods often give rise to highly overestimated values.[42] Therefore we have chosen the coupled perturbed Hartree–Fock (CPHF) method with the aim to obtain more reliable calculated β values. The calculations were performed using the HF/6-31G* model chemistry on the geometries described in Section 2.6. These values, together with the calculated ground-state dipole moments (μ) are collected in Table 3.

The calculated $\mu\beta_0$ values show essentially the same trends that the experimental results in terms of the effects of the acceptor and the length of the polyenic chain.

Concerning the influence of a matched/mismatched thiazole on the calculated NLO properties (Fig. 5; blue bars), it should be noted



Compd	D	Th	S	A
7a	+0.14	−0.07	+0.20	−0.27
8a	+0.19	−0.05	+0.20	−0.34
9	+0.13	−0.03	+0.20	−0.30
10	+0.18	+0.01	+0.19	−0.38

Fig. 4. Mulliken atomic charges on various molecular domains for compounds **7a**, **8a**, **9**, **10**.

Table 3
Experimental and CPHF-calculated[a] NLO properties

Compd	Experimental		Calculated	
	$\mu\beta^{b,c}$	$\mu\beta_0{}^{c,d}$	$\mu\beta_0{}^{c,e}$	$\mu^{e,f}$
1a	300	210	303	9.78
2a	160	120	169	9.78
1b	780	500	488	9.76
2b	620	430	452	10.52
3a	200	125	367	8.73
4a	140	95	158	8.86
3b	1220	640	662	8.84
4b	780	460	526	9.28
5	1400	730	920	17.20
6	1300	765	837	16.34
7a	1200	650	399	8.11
8a	1000	620	262	8.06
7b	2200	1150	522	8.16
8b	1990	1170	447	8.42
9	2000	880	445	6.48
10	[g]	[g]	287	6.88

[a] Calculations using the HF/6-31G* model for the structures shown in Fig. 3.
[b] $\mu\beta$ values determined in CH_2Cl_2 at 1907 nm; experimental accuracy: ±15%, except for **7a**,**9** (±20%).
[c] In 10^{-48} esu.
[d] Experimental $\mu\beta_0$ values calculated using the two-level model.
[e] CPHF/6-31G* on HF/6-31G* geometries optimized.
[f] In Debye.
[g] Not determined due to its low solubility.

that most of the $\mu\beta_0$ enhancement on passing from the mismatched to the matched systems is due to the hyperpolarizability contribution, since the change in μ values is comparatively small.[43] As it can be seen in Fig. 5 our calculated $\mu\beta_0$ values based on HF optimized geometries reproduce quite well the experimental results, with a very close parallelism, being compounds **3a**/**4a** an exception.

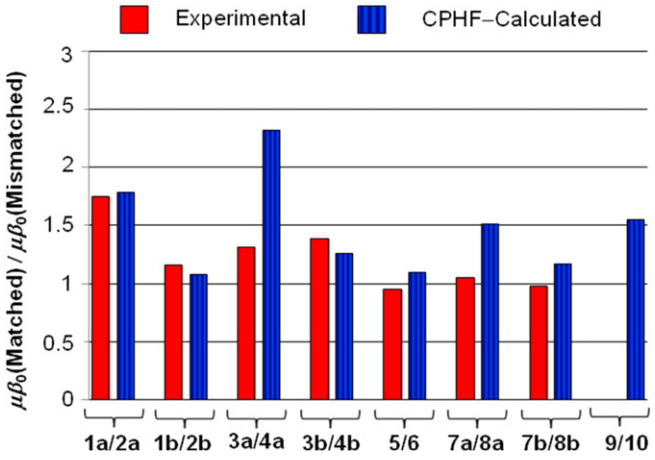


Fig. 5. Experimental (■) and CPHF-calculated (■) $\mu\beta_0$ (matched)/$\mu\beta_0$ (mismatched) ratio.

Thus, when a considerable number of pairs of matched/mismatched chromophores have been studied it can be seen that previous theoretical studies carried out on semiempirical[2c,3] or B3LYP geometries,[5] with semiempirical[3] (ZINDO) or Density Functional Theory (DFT) methods[2c,5] (B3LYP, LDA, PW86P86 functionals) for β_0 calculations do not reproduce the experimental results. Matched chromophores do not always show markedly higher second-NLO responses than its mismatched isomers. Nevertheless, our theoretical CPHF calculations carried out on HF geometries parallel the experimental data.

Taking all data into account, our experimental and calculated results show that the role played by the orientation of the thiazole ring is less relevant than the character of the end groups for tuning the second-order NLO responses of D–thiazole–A compounds.[5] Moreover, this behaviour is also observed in other D–thiazole–A compounds where the donor and the thiazole spacer are not directly linked, but connected through aromatic rings, as demonstrated by their low experimental β_0 matched/β_0 mismatched ratio (ca. 1.1).[9,10,18]

3. Conclusions

The influence of thiazole regioisomerism on second-order NLO properties has been experimentally studied by synthesizing and comparing the NLO responses of eight new pairs of analogous matched/mismatched D–thiazole–A systems.

Mismatched derivatives show more polarized structures than their matched analogues, as shown by ^{1}H NMR spectra, calculated *BLA* values and Mulliken charges. On the other hand, CV and UV–vis spectra show lower gaps for the matched chromophores.

Whereas previous theoretical results show that the matched derivatives have much higher calculated $\mu\beta_0$ values than their mismatched analogues, experimental NLO measurements of regioisomers **1**–**10** show that, in general, there are only small differences between the NLO responses of the matched and the mismatched derivatives. Our theoretical CPHF calculations parallel this trend.

This indicates that the influence of the orientation of the thiazole ring in D–thiazole–A compounds on second-order NLO properties has been overestimated by previous theoretical calculations and that this orientation is less relevant than the character of the donor and acceptor groups for tuning the second-order nonlinearities.

4. Experimental

4.1. General experimental methods

Compounds **11**, **12**, **17a**,**b**, **18**, **19**, **22** and **23** are commercially available and were used without further purification. THF was

refluxed with sodium and benzophenone and freshly distilled prior to use.

Infrared measurements were carried out in Nujol mulls using a Perkin–Elmer FTIR 1600 spectrometer. Melting points were obtained on a Gallenkamp apparatus and are uncorrected. Elemental analysis was performed with a Perkin–Elmer 240C microanalyzer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX300 or a Bruker AV400 at 300 or 400 MHz and 75 or 100 MHz, respectively; δ values are given in parts per million (relative to TMS) and J values in hertz. ^{1}H–^{1}H COSY experiments were recorded at 400 MHz in order to establish peaks assignment and spatial relationships. Selective ge-1D NOESY experiments (mixing time: 1.1–3.7 s; selective 180 pulse: 20–40 ms) were recorded at 300 MHz for compounds **5**, **6**, **7a**, **8a**, in order to determine the conformations adopted in solution. Electrospray mass spectra were recorded on a Bruker Q-ToF spectrometer; accurate mass measurements were achieved using sodium formate as external reference. Electronic spectra were recorded with a UV–vis UNICAM UV4 spectrophotometer. Cyclic voltammetry measurements were performed with a μ-Autolab ECO-Chemie potentiostat, using a glassy carbon working electrode, Pt counter electrode, and Ag/AgCl reference electrode. The experiments were carried out under argon, in CH_2Cl_2, with Bu_4NPF_6 as supporting electrolyte (0.1 mol L^{-1}); scan can rate was 100 mV s^{-1}.

4.2. X-ray diffraction

X-ray data collection were carried out on an Xcalibur, Sapphire 3 diffractometer equipped with a graphite monochromator (Mo Kα radiation, λ=0.71073 Å). The diffraction frames were integrated and corrected for absorption using the CrysAlis RED package.[44] The structures were solved by direct methods.[45] All refinements were carried out using SHELXL-97[46] against the F^2 data using full-matrix least squares methods. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed at idealized positions and assigned isotropic displacement parameters 1.2 times the U_{iso} value of the corresponding bonding partner (1.5 times for methyl hydrogen atoms).

A complete description of the crystal structures is reported in the Supplementary data.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 875491 (**4a**) and 875490 (**6**). Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

4.3. NLO measurements

Electric field-induced second harmonic generation (EFISH) measurements have been performed using as the fundamental radiation the 1.9 μm output of a H_2 Raman shifter pumped by a Q-switched Nd/YAG laser. This laser operates at 1064 nm, with a repetition rate of 10 Hz and pulse width of 8 ns. A computer controlled NLO spectrometer completes the SHG experimental set-up. The 1.9 μm incident light is split in two beams. The less intense one is directed to a *N*-(4-nitrophenyl)-(L)-prolinol (NPP) powder sample whose SH signal is used as a reference in order to reduce the effects of laser fluctuations. The other beam is passed through a linear polarizer and focused into the EFISH wedge shaped liquid cell. Voltage pulses of 5 kV and 3 μs are applied across the cell (2 mm gap between the electrodes) synchronously with the laser pulses. The harmonic signals from both the EFISH cell and the NPP reference are measured with two photomultipliers. Interference filters are used to remove the residual excitation light beyond the sample and the reference.

The molecular $\mu\beta$ values have been determined in dichloromethane for all compounds. As a rule, three solutions of concentration in the range (5×10^{-3}M–4×10^{-4} M) were measured. $\mu\beta_0$ values were extrapolated using a two-level dispersion model.[40a] Under the same experimental conditions $\mu\beta_0$ deduced for DR1 was 480×10^{-48} esu, quite close to the value reported in the same solvent by Dirk et al.[47]

4.4. Computational procedures

All theoretical calculations were performed by using the Gaussian 09[48] program. The molecular geometries were optimized using the HF functional and the 6-31G*[49] basis set. Molecular hyperpolarizabilities at zero frequency were calculated by the Coupled Perturbed Hartree–Fock method (CPHF).

4.5. Synthesis and characterization

Compounds **14**,[20] **16a**,[19,21] **20**[24] and **21**[25] were prepared as previously described.

*4.5.1. 5-(Piperidin-1-yl)thiazole (**13**).* 5-Bromothiazole (1.55 g, 9.0 mmol), piperidine (2.7 mL, 27.0 mmol), sodium *tert*-butoxide (1.78 g, 18.0 mmol), $Rh(cod)_2BF_4$ (73 mg, 2.0 mol %), 1,3-diisopropylimidazolium chloride (70 mg, 4.0 mol %) and 1,2-dimethoxyethane (9 mL) were mixed under argon atmosphere. The reaction mixture was vigorously stirred at 80 °C overnight, then it was cooled down to room temperature and diluted with AcOEt. The crude reaction was filtered through a pad of silica gel, the organic solvents were evaporated and the residue was purified by flash chromatography on silica gel using as eluent CH_2Cl_2/AcOEt 10:0.5, then 10:1, to afford a slightly yellow oil (1.40 g; 92%). Found: C 57.49, H 6.92, N 16.48. $C_8H_{12}N_2S$ requires C 57.11, H 7.19, N 16.65%. IR (Nujol, cm^{-1}): 1651 (C=N), 1558 (C=C), 1539 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.01 (s, 1H), 3.15–3.05 (m, 4H), 1.75–1.68 (m, 4H), 1.60–1.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 140.5, 122.3, 53.5, 25.1, 23.5. HRMS (ESI^+): found 169.0789 $[M+H]^+$. $C_8H_{13}N_2S$ requires 169.0794.

*4.5.2. Compounds **15a**,**b** and **16b**. General procedure*. A solution of the corresponding (piperidin-1-yl)thiazole **13**, **14** (353 mg, 2.1 mmol) in anhydrous THF (15 mL) was cooled down to −78 °C under argon atmosphere, and *n*-BuLi (1.6 M in hexanes, 1.6 mL, 2.5 mmol) was added dropwise. After stirring for 1 h, DMF (**17a**) (for **15a**) or (*E*)-3-dimethylaminoacrylaldehyde (**17b**) (for **15b**, **16b**) (3.2 mmol) was added dropwise and the reaction medium was slowly warmed to 0 °C. Water (10 mL) was added for quenching the reaction, and the aqueous layer was then extracted with AcOEt (3×10 mL). The organic layer was washed with H_2O (10 mL) and dried over $MgSO_4$. Solvent was evaporated.

*4.5.2.1. 5-(Piperidin-1-yl)thiazol-2-carbaldehyde (**15a**).* The product was used without further purification. Yield: brown oil (387 mg; 94%). Found: C 54.78, H 5.98, N 14.51. $C_9H_{12}N_2OS$ requires C 55.08, H 6.16, N 14.27%. IR (Nujol, cm^{-1}): 1653 (C=O), 1507 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (s, 1H), 7.15 (s, 1H), 3.35–3.28 (m, 4H), 1.75–1.57 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.3, 163.0, 148.6, 123.7, 51.9, 24.7, 23.2. HRMS (ESI^+): found 219.0571 $[M+Na]^+$. $C_9H_{12}N_2NaOS$ requires 219.0563.

*4.5.2.2. (E)-3-(5-(Piperidin-1-yl)thiazol-2-yl)acrylaldehyde (**15b**).* The product was dissolved in ether and cooled down to 0 °C. The precipitate was filtered and washed with cold ether. Yield: brown solid (135 mg; 29%). Found: C 59.70, H 6.58, N 12.49. $C_{11}H_{14}N_2OS$ requires C 59.43, H 6.35, N 12.60%. Mp 95–106 °C. IR (Nujol, cm^{-1}): 1663 (C=O), 1603 (C=N), 1508 (C=

C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, J=7.7 Hz, 1H), 7.47 (d, J=15.7 Hz, 1H), 7.07 (s, 1H), 6.43 (dd, J=15.7 Hz, J'=7.7 Hz, 1H), 3.30–3.25 (m, 4H), 1.78–1.70 (m, 4H), 1.69–1.60 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 192.5, 159.9, 146.7, 144.7, 126.3, 123.3, 52.5, 24.9, 23.4. HRMS (ESI$^+$): found 223.0891 [M+H]$^+$. $C_{11}H_{15}N_2OS$ requires 223.0900; found 245.0703 [M+Na]$^+$. $C_{11}H_{14}N_2NaOS$ requires 245.0719.

*4.5.2.3. (E)-3-(2-(Piperidin-1-yl)thiazol-5-yl)acrylaldehyde (**16b**).* The product was purified by flash chromatography (silica gel) using as eluent first hexane/AcOEt (1:1), then hexane/AcOEt (3:4). Yield: brown solid (248 mg; 53%). Found: C 59.10, H 6.11, N 12.86. $C_{11}H_{14}N_2OS$ requires C 59.43, H 6.35, N 12.60%. Mp 107–109 °C. IR (Nujol, cm^{-1}): 1650 (C=O), 1601 (C=N). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 9.39 (d, J=7.8 Hz, 1H), 6.00 (dd, J=15.0 Hz, J'=7.8 Hz, 1H), 7.38 (d, J=15.0 Hz, 1H), 7.37 (s, 1H), 3.52–3.44 (m, 4H), 1.63–1.55 (m, 6H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 192.5, 173.8, 149.0, 143.3, 124.4, 123.6, 50.2, 25.7, 24.5. HRMS (ESI$^+$): found 223.0896 [M+H]$^+$. $C_{11}H_{15}N_2OS$ requires 223.0900; found 245.0718 [M+Na]$^+$. $C_{11}H_{14}N_2NaOS$ requires 245.0719.

*4.5.3. Compounds **1a**,**b** and **2a**,**b**. General procedure.* The corresponding aldehyde (**15a**,**b**, **16a**,**b**) (0.33 mmol) and malononitrile (**18**) (26 mg, 0.40 mmol) were dissolved in EtOH (8 mL) under argon atmosphere (for **2a**, piperidine (1 drop) was added additionally) and the reaction mixture was refluxed during 1–4 h (TLC monitoring). Then, it was cooled down to 0 °C and after the addition of hexane, the resulting precipitate was filtered and washed with cold hexane. For compound **1b** a further purification by recrystallization from CH_2Cl_2/isopropyl alcohol was needed.

*4.5.3.1. 2-((5-(Piperidin-1-yl)thiazol-2-yl)methylene)malononitrile (**1a**).* Reaction time: 1 h 30 min. Yield: orange solid (45 mg; 56%). Found: C 59.08, H 4.67, N 22.99. $C_{12}H_{12}N_4S$ requires C 58.99, H 4.95, N 22.93%. Mp 128–129 °C. IR (Nujol, cm^{-1}): 2213 (C≡N), 1579 (C=C). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.69 (s, 1H), 7,34 (s, 1H), 3.53–3.45 (m, 4H), 1.82–1.65 (m, 6H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 165.0, 149.9, 140.1, 126.2, 115.9, 115.2, 70.5, 53.3, 25.5, 23.8. HRMS (ESI$^+$): found 245.0851 [M+H]$^+$. $C_{12}H_{13}N_4S$ requires 245.0855; found 267.0678 [M+Na]$^+$. $C_{12}H_{12}N_4NaS$ requires 267.0675.

*4.5.3.2. 2-(3-(5-(Piperidin-1-yl)thiazol-2-yl)allylidene)malononitrile (**1b**).* Reaction time: 4 h. Yield: purple solid as an *E*/*Z* mixture (80:20 ratio) (41 mg; 47%). Found: C 62.45, H 5.43, N 20.54. $C_{14}H_{14}N_4S$ requires C 62.20, H 5.22, N 20.72%. Mp 139–141 °C. IR (Nujol, cm^{-1}): 2216 (C≡N), 1574 (C=C), 1554 (C=C). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 9.08 (dd, J=12.2 Hz, J'=0.6 Hz, 1H, (*Z*)-isomer), 7.50 (dd, J=11.9 Hz, J'=0.5 Hz, 1H, (*E*)-isomer), 7.28 (dd, J=14.8 Hz, J'=0.5 Hz, 1H, (*E*)-isomer), 7.18 (s, 1H, (*Z*)-isomer), 7.15 (s, 1H, (*E*)-isomer), 6.90 (dd, J=14.8 Hz, J'=11.9 Hz, 1H, (*E*)-isomer), 6.74 (dd, J=11.0 Hz, J'=0.6 Hz, 1H, (*Z*)-isomer), 6.46 (dd, J=12.2 Hz, J'=11.0 Hz, 1H, (*Z*)-isomer), 3.39–3.27 (m, 8H, (*E*)+(*Z*)-isomers), 1.79–1.61 (m, 12H, (*E*)+(*Z*)-isomers). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 161.9, 159.2, 158.1, 145.8, 142.2, 134.6, 125.6, 125.3, 120.0, 119.1, 115.1, 113.1, 78.7, 52.9, 25.4, 23.8. HRMS (ESI$^+$): found 271.1011 [M+H]$^+$. $C_{14}H_{15}N_4S$ requires 271.1012; found 293.0831 [M+Na]$^+$. $C_{14}H_{14}N_4NaS$ requires 293.0831.

*4.5.3.3. 2-((2-(Piperidin-1-yl)thiazol-5-yl)methylene)malononitrile (**2a**).* Reaction time: 1 h. Yield: yellow solid (47 mg; 59%). Found: C 58.77, H 4.73, N 23.09. $C_{12}H_{12}N_4S$ requires C 58.99, H 4.95, N 22.93%. Mp 177–179 °C. IR (Nujol, cm^{-1}): 2218 (C≡N), 1585 (C=C), 1549 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.60 (s, 1H), 3.78–3.64 (m, 4H), 1.80–1.68 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 157.6, 148.5, 120.6, 115.3, 114.6, 68.7, 50.4, 25.2, 23.7. HRMS (ESI$^+$): found 245.0846 [M+H]$^+$. $C_{12}H_{13}N_4S$ requires 245.0855; found 267.0658 [M+Na]$^+$. $C_{12}H_{12}N_4NaS$ requires 267.0675.

*4.5.3.4. (E)-2-(3-(2-(Piperidin-1-yl)thiazol-5-yl)allylidene)malononitrile (**2b**).* Reaction time: 4 h. Yield: red solid (70 mg; 78%). Found: C 62.43, H 4.95, N 20.89. $C_{14}H_{14}N_4S$ requires C 62.20, H 5.22, N 20.72. Mp 177–182 °C. IR (Nujol, cm^{-1}): 2221 (C≡N), 1599 (C=N), 1584 (C=C), 1543 (C=C). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.54 (s, 1H), 7.45 (d, J=11.8 Hz, 1H), 7.30 (d, J=14.3 Hz, 1H), 6.44 (dd, J=14.3 Hz, J'=11.8 Hz, 1H), 3.68–3.57 (m, 4H), 1.77–1.65 (m, 6H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 174.5, 160.0, 152.6, 141.3, 124.7, 117.9, 115.5, 113.5, 76.0, 50.5, 25.7, 24.4. HRMS (ESI$^+$): found 271.1012 [M+H]$^+$. $C_{14}H_{15}N_4S$ requires 271.1012; found 293.0819 [M+Na]$^+$. $C_{14}H_{14}N_4NaS$ requires 293.0831.

*4.5.4. 1,3-Diethyl-5-((5-(piperidin-1-yl)thiazol-2-yl)methylene)-2-thioxo-dihydropyrimidine-4,6-dione (**3a**).* 5-(Piperidin-1-yl)thiazole-2-carbaldehyde (**15a**) (49 mg, 0.25 mmol) and 1,3-diethyl-2-thiobarbituric acid (**19**) (48 mg, 0.24 mmol) were dissolved in EtOH (5 mL) under argon atmosphere. The reaction mixture was stirred for 90 min at room temperature and then it was cooled down to 0 °C. The resulting precipitate was filtered and washed with cold EtOH. The solid was dissolved in AcOEt, washed first with a saturated solution of K_2CO_3 (2×2 mL) and then with water (2 mL). The organic layer was dried over $MgSO_4$, and the solvent evaporated to afford a pink pure solid (11 mg; 11%). Found: C53.68, H 5.65, N 14.98. $C_{17}H_{22}N_4O_2S_2$ requires C 53.94, H 5.86, N 14.80%. Mp 190 °C (dec). IR (Nujol, cm^{-1}): 1645 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.66 (s, 1H), 4.65–4.52 (m, 4H), 3.66–3.56 (m, 4H), 1.86–1.70 (m, 6H), 1.38–1.25 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 168.2, 161.1, 160.5, 148.4, 142.2, 130.3, 105.1, 52.3, 43.7, 42.8, 25.2, 23.3, 12.5, 12.3. HRMS (ESI$^+$): found 379.1243 [M+H]$^+$. $C_{17}H_{23}N_4O_2S_2$ requires 379.1257; found 401.1063 [M+Na]$^+$. $C_{17}H_{22}N_4NaO_2S_2$ requires 401.1076.

*4.5.5. (E)-1,3-Diethyl-5-(3-(5-(piperidin-1-yl)thiazol-2-yl)allylidene)-2-thioxo-dihydropyrimidine-4,6-dione (**3b**).* (*E*)-3-(5-(Piperidin-1-yl)-thiazol-2-yl)acrylaldehyde (**15b**) (222 mg, 1.0 mmol) and 1,3-diethyl-2-thiobarbituric acid (**19**) (180 mg, 0.9 mmol) were dissolved in EtOH (3 mL) under argon atmosphere and the mixture was stirred at room temperature for 1 h. Then it was cooled down to 0 °C and the resulting precipitate was filtered and washed with hexane/EtOH (7:3) to afford a dark green solid (39 mg; 60%). Found: C 56.69, H 5.85, N 13.96. $C_{19}H_{24}N_4O_2S_2$ requires C 56.41, H 5.98, N 13.85%. Mp 179 °C (dec). IR (Nujol, cm^{-1}): 1659 (C=O), 1560 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, J=14.7 Hz, J'=12.4 Hz, 1H), 8.15 (d, J=12.4 Hz, 1H), 7.53 (d, J=14.7 Hz, 1H), 7.19 (s, 1H), 4.60–4.51 (m, 4H), 3.42–3.37 (m, 4H), 1.80–1.73 (m, 4H), 1.72–1.66 (m, 2H), 1.34–1.22 (m, 6H). ^{13}C NMR was not registered due to decomposition of the product during the experiment ($CDCl_3$ and CD_2Cl_2). HRMS (ESI$^+$): found 405.1412 [M+H]$^+$. $C_{19}H_{25}N_4O_2S_2$ requires 405.1413; found 427.1231 [M+Na]$^+$. $C_{19}H_{24}N_4NaO_2S_2$ requires 427.1233.

*4.5.6. Compounds **4a**,**b**. General procedure.* 1,3-Diethyl-2-thiobarbituric acid (**19**) (180 mg, 0.9 mmol) and the corresponding aldehyde (**16a**,**b**) (1.0 mmol) were dissolved in EtOH (7 mL) under argon atmosphere. The reaction mixture was refluxed for 5–30 min (TLC monitoring), then cooled down to 0 °C. The resulting precipitate was filtered and washed.

*4.5.6.1. 1,3-Diethyl-5-((2-(piperidin-1-yl)thiazol-5-yl)methylene)-2-thioxo-dihydropyrimidine-4,6-dione (**4a**).* Solvent used for washing: cold EtOH. Yield: orange solid (191 mg; 56%). Found: C 54.19, H 5.58, N 14.59. $C_{17}H_{22}N_4O_2S_2$ requires C 53.94, H 5.86, N 14.80%. Mp 240–241 °C. IR (Nujol, cm^{-1}): 1647 (C=O), 1633 (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.10 (s, 1H), 4.60–4.52 (m, 4H), 3.90–3.66 (m, 4H), 1.78–1.72 (m, 6H), 1.34–1.27 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.1, 178.7, 166.0, 161.3, 160.5, 147.4, 124.1, 103.8, 43.6, 42.7, 25.4, 23.8, 12.5, 12.3. HRMS (ESI$^+$): found 379.1267 [M+H]$^+$. $C_{17}H_{23}N_4O_2S_2$ requires 379.1257; found 401.1063 [M+Na]$^+$. $C_{17}H_{22}N_4NaO_2S_2$ requires 401.1076.

*4.5.6.2. (E)-1,3-Diethyl-5-(3-(2-(piperidin-1-yl)thiazol-5-yl)allylidene)-2-thioxo-dihydropyrimidine-4,6-dione (**4b**).* Solvent used for washing: hexane. Yield: purple solid (326 mg; 81%). Found: C 56.63, H 5.76, N 13.71. $C_{19}H_{24}N_4O_2S_2$ requires C 56.41, H 5.98, N 13.85%. Mp 216 °C (dec). IR (Nujol, cm^{-1}): 1656 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J=12.5 Hz, 1H), 7.90 (dd, J=14.1 Hz, J'=12.5 Hz, 1H), 7.62 (s, 1H), 7.51 (d, J=14.1 Hz, 1H), 4.57–4.49 (m, 4H), 3.68–3.61 (m, 4H), 1.76–1.68 (m, 6H), 1.32–1.25 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 174.4, 161.0, 160.1, 158.3, 152.9, 146.4, 126.5, 121.9, 110.4, 50.1, 43.5, 42.9, 25.2, 23.8, 12.4, 12.3. HRMS (ESI$^+$): found 405.1425 [M+H]$^+$. $C_{19}H_{25}N_4O_2S_2$ requires 405.1413; found 427.1239 [M+Na]$^+$. $C_{19}H_{24}N_4NaO_2S_2$ requires 427.1233.

*4.5.7. (E)-2-(3-Cyano-5,5-dimethyl-4-(2-(5-(piperidin-1-yl)thiazol-2-yl)vinyl)furan-2-ylidene)malononitrile (**5**).* 5-(Piperidin-1-yl)thiazole-2-carbaldehyde (**15a**) (56 mg, 0.29 mmol) and acceptor TCF (**20**) (57 mg, 0.29 mmol) were dissolved in EtOH (7 mL) under argon atmosphere. A mixture of pyridine (218 μL) and acetic acid (105 μL) was added and the reaction mixture was stirred for 24 h (TLC monitoring) at room temperature. Then, another portion of pyridine/acetic acid was added and the reaction was stirred for 24 further hours. Then it was cooled down to 0 °C and the resulting precipitate was filtered, washed with EtOH and Et_2O and finally purified by recrystallization from CH_2Cl_2/hexane to afford a purple solid (24 mg; 22%). Found: C 63.74, H 4.84, N 18.32. $C_{20}H_{19}N_5OS$ requires C 63.64, H 5.07, N 18.55%. Mp 234 °C (dec). IR (Nujol, cm^{-1}): 2223 (C≡N), 1567 (C=C), 1523 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J=15.8 Hz, 1H), 7.24 (s, 1H), 6.69 (d, J=15.8 Hz, 1H), 3.47–3.42 (m, 4H), 1.83–1.68 (m, 12H). ^{13}C NMR was not registered due to its low solubility. HRMS (ESI$^+$): found 378.1377 [M+H]$^+$. $C_{20}H_{20}N_5OS$ requires 378.1383; found 400.1199 [M+Na]$^+$. $C_{20}H_{19}N_5NaOS$ requires 400.1203.

*4.5.8. (E)-2-(3-Cyano-5,5-dimethyl-4-(2-(2-(piperidin-1-yl)thiazol-5-yl)vinyl)furan-2-ylidene)malononitrile (**6**).* 2-(Piperidin-1-yl)thiazole-5-carbaldehyde (**16a**) (121 mg, 0.62 mmol) and acceptor TCF (**20**) (113 mg, 0.57 mmol) were dissolved in EtOH (10 mL) under argon atmosphere. A mixture of pyridine (436 μL) and acetic acid (210 μL) was added and the reaction mixture was refluxed for 20 h (TLC monitoring), then another portion of pyridine/acetic acid was added and the reaction was refluxed for 4 further hours. It was cooled down to 0 °C and the resulting precipitate was filtered and washed with pentane to afford a light blue solid (147 mg; 68%). Found: C 63.73, H 4.79, N 18.61. $C_{20}H_{19}N_5OS$ requires C 63.64, H 5.07, N 18.55%. Mp >300 °C. IR (Nujol, cm^{-1}): 2223 (C≡N), 1571 (C=C), 1540 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J=15.2 Hz, 1H), 7.69 (s, 1H), 6.09 (d, J=15.2 Hz, 1H), 3.75–3.65 (m, 4H), 1.78–1.73 (m, 6H), 1.73–1.69 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 175.3, 174.5, 155.5, 139.0, 126.0, 113.3, 112.7, 112.2, 109.3, 97.3, 51.0, 26.9, 25.8, 24.3. HRMS (ESI$^+$): found 378.1401 [M+H]$^+$. $C_{20}H_{20}N_5OS$ requires 378.1383; found 400.1211 [M+Na]$^+$. $C_{20}H_{19}N_5NaOS$ requires 400.1203.

*4.5.9. Compounds **24** and **25**. General procedure.* A solution of (2,6-diphenyl-4*H*-pyran-4-yl)diphenylphosphine oxide (**21**) (2.0 g, 4.6 mmol) in anhydrous THF (45 mL) was cooled down to −78 °C, and *n*-BuLi (1.6 M in hexanes, 2.9 mL, 4.6 mmol) was added dropwise under argon atmosphere. After stirring for 25–30 min, a solution of the corresponding thiazole carbaldehyde **22**, **23** (520 mg, 4.6 mmol) dissolved in anhydrous THF (5 mL) was added and the reaction medium was slowly warmed to room temperature overnight. A saturated solution of NH_4Cl (15 mL) was added and the mixture was stirred for 5 min. THF was evaporated and AcOEt was added to the aqueous phase. The resulting precipitate was filtered and washed with H_2O and cold AcOEt. For compound **25** a further purification by recrystallization from CH_2Cl_2/EtOH was needed.

*4.5.9.1. 2-((2,6-Diphenyl-4H-pyran-4-yliden)methyl)thiazole (**24**).* Yield: dark yellow solid (1.27 g; 85%). Found: C 76.74, H 4.38, N 4.36. $C_{21}H_{15}NOS$ requires C 76.57, H 4.59, N 4.25%. Mp 148–150 °C. IR (Nujol, cm^{-1}): 1651 (C=N), 1583 (C=C, Ar), 1559 (C=C, Ar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J=1.8 Hz, J'=0.6 Hz, 1H), 7.92–7.89 (m, 2H), 7.82–7.78 (m, 3H), 7.52–7.40 (m, 6H), 7.11 (d, J=3.3 Hz, 1H), 6.49 (d, J=1.8 Hz, J'=0.3 Hz, 1H), 6.09 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 154.3, 152.7, 143.2, 133.1, 133.0, 132.8, 129.6, 129.4, 128.6, 128.5, 125.2, 124.6, 115.2, 107.5, 104.7, 103.9. HRMS (ESI$^+$): found 330.0952 [M+H]$^+$. $C_{21}H_{16}NOS$ requires 330.0947.

*4.5.9.2. 5-((2,6-Diphenyl-4H-pyran-4-yliden)methyl)thiazole (**25**).* Yield: yellow solid (983 mg; 65%). Found: C 76.69, H 4.47, N 4.47. $C_{21}H_{15}NOS$ requires C 76.57, H 4.59, N 4.25%. Mp 174–178 °C. IR (Nujol, cm^{-1}): 3056 (=CH), 1656 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65–8.63 (m, 1H), 7.85–7.74 (m, 5H), 7.51–7.40 (m, 6H), 6.98 (dd, J=2.0 Hz, J'=0.7 Hz, 1H), 6.45 (dd, J=2.0 Hz, J'=0.4 Hz, 1H), 6.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 151.4, 149.3, 140.7, 136.1, 133.0, 132.8, 130.2, 129.7, 129.3, 128.7, 128.6, 125.0, 124.5, 107.9, 102.8, 102.0. HRMS (ESI$^+$): found 330.0942 [M+H]$^+$. $C_{21}H_{16}NOS$ requires 330.0947.

*4.5.10. Compounds **26a**,**b** and **27a**,**b**. General procedure.* A solution of **24** or **25** (329 mg, 1.0 mmol) in anhydrous THF (15 mL) was cooled down to −78 °C under argon atmosphere, and *n*-BuLi (1.6 M in hexanes, 0.75 mL, 1.2 mmol) was added dropwise. The mixture was stirred for 1 h. The corresponding electrophile **17a**,**b** (1.5 mmol) was added and stirring was continued for a further hour at −78 °C, then the reaction medium was slowly warmed to 0 °C. Water (20 mL) was added for quenching the reaction and then the crude mixture was warmed to room temperature. Hexane was added, the resulting precipitate was filtered, washed with cold hexane and dried. For **27b**, THF was evaporated, the aqueous layer was extracted with AcOEt (3×10 mL) and the combined organic phases were first washed with H_2O (2×15 mL) and then dried over $MgSO_4$. Solvent was evaporated and the crude was purified by flash chromatography on silica gel using CH_2Cl_2/AcOEt (9.5:0.5) as eluent.

*4.5.10.1. 2-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl)thiazol-5-carbaldehyde (**26a**).* Yield: red solid (340 mg; 95%). Found: C 74.08, H 4.05, N 4.17. $C_{22}H_{15}NO_2S$ requires C 73.93, H 4.23, N 3.92%. Mp 249–252 °C. IR (Nujol, cm^{-1}): 1650 (C=O), 1641 (C=N), 1576 (C=C), 1554 (C=C, Ar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.39 (dd, J=1.8 Hz, J'=0.4 Hz, 1H), 8.33 (s, 1H), 7.96–7.91 (m, 2H), 7.84–7.81 (m, 2H), 7.56–7.48 (m, 6H), 6.62 (d, J=1.8 Hz), 6.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.5, 174.4, 171.1, 156.5, 155.0, 153.7, 138.5, 132.5, 132.2, 130.4, 130.2, 128.9, 128.9, 125.6, 125.1, 108.1, 104.7, 104.5. HRMS (ESI$^+$): found 358.0892 [M+H]$^+$. $C_{22}H_{16}NO_2S$ requires 358.0896.

*4.5.10.2. (E)-3-(2-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl)thiazol-5-yl)acrylaldehyde (**26b**).* Yield: red solid (316 mg; 83%). Found: C 75.39, H 4.29, N 3.85. $C_{24}H_{17}NO_2S$ requires C 75.17, H 4.47, N 3.65%. Mp 231–233 °C. IR (Nujol, cm^{-1}): 1660 (C=O), 1646 (C=N), 1604 (C=N), 1578 (C=C, Ar), 1543 (C=C, Ar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (d, J=7.7 Hz, 1H), 8.32 (d, J=1.7 Hz, 1H), 7.96 (s, 1H),

7.94–7.90 (m, 2H), 7.84–7.80 (m, 2H), 7.60 (d, *J*=15.3 Hz, 1H), 7.55–7.46 (m, 6H), 6.58 (d, *J*=1.7 Hz, 1H), 6.35 (dd, *J*=15.3 Hz, *J′*=7.7 Hz, 1H), 6.06 (s, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 192.7, 171.0, 156.4, 154.9, 149.9, 142.0, 137.4, 133.2, 132.9, 131.4, 130.8, 130.6, 129.4, 129.4, 128.5, 126.0, 125.5, 108.4, 105.1, 104.8. HRMS (ESI^+): found 384.1046 $[M+H]^+$. $C_{24}H_{18}NO_2S$ requires 384.1053.

*4.5.10.3. 5-((2,6-Diphenyl-4H-pyran-4-yliden)methyl)thiazol-2-carbaldehyde (**27a**).* Yield: maroon solid (309 mg; 87%). Found: C 74.21, H 4.10, N 4.03. $C_{22}H_{15}NO_2S$ requires C 73.93, H 4.23, N 3.92%. Mp 239–243 °C (dec). IR (Nujol, cm^{-1}): 1661 (C=O), 1649 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.92 (s, 1H), 7.90–7.85 (m, 2H), 7.83–7.77 (m, 2H), 7.58–7.44 (m, 6H), 7.11 (d, *J*=1.9 Hz, 1H), 6.58 (d, *J*=1.9 Hz, 1H), 6.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.4, 160.0, 155.7, 153.2, 145.1, 143.7, 134.5, 132.3, 132.2, 130.5, 130.0, 129.0, 128.9, 125.4, 124.8, 108.5, 102.9, 102.5. HRMS (ESI^+): found 358.0862 $[M+H]^+$. $C_{22}H_{16}NO_2S$ requires 358.0896; found 380.0722 $[M+Na]^+$. $C_{22}H_{15}NNaO_2S$ requires 380.0716.

*4.5.10.4. (E)-3-(5-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl) thiazol-2-yl)acrylaldehyde (**27b**).* Yield: red solid (143 mg; 37%). Found: C 75.38, H 4.38, N 3.84. $C_{24}H_{17}NO_2S$ requires C 75.17, H 4.47, N 3.65%. Mp 158–162 °C. IR (Nujol, cm^{-1}): 1674 (C=O), 1653 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (d, *J*=7.7 Hz, 1H), 7.88–7.83 (m, 2H), 7.83 (s, 1H), 7.81–7.75 (m, 2H), 7.63 (d, *J*=15.8 Hz, 1H), 7.58–7.43 (m, 6H), 7.03 (d, *J*=1.5 Hz, 1H), 6.81 (dd, *J*=15.8 Hz, *J′*=7.7 Hz, 1H), 6.53 (d, *J*=1.5 Hz, 1H), 6.14 (s, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 192.9, 158.7, 155.3, 152.9, 144.0, 143.6, 141.7, 133.1, 133.0, 132.8, 130.7, 130.2, 130.0, 129.4, 129.3, 125.7, 125.2, 108.8, 103.9, 102.8. HRMS (ESI^+): found 384.1048 $[M+H]^+$. $C_{24}H_{18}NO_2S$ requires 384.1053.

*4.5.11. Compounds **7a**,**b** and **8a**,**b**. General procedure*. The corresponding aldehydes **26a**,**b**, **27a**,**b** (0.21 mmol) were dissolved in EtOH (10 mL) under argon atmosphere and malononitrile (**18**) (16 mg, 0.25 mmol) was added (piperidine (2 drops) was added for the synthesis of **7a** and **8a**). The reaction mixture was refluxed for 1–6 h (TLC monitoring), then it was cooled down to room temperature. In the case of **7a**, after cooling, the precipitate was isolated by filtration, washed with cold EtOH and dried. For **7b**, **8a**,**b**, the solvent was evaporated and the crude was purified by flash chromatography (silica gel) using CH_2Cl_2 as eluent.

*4.5.11.1. 2-((5-((2,6-Diphenyl-4H-pyran-4-yliden)methyl)thiazol-2-yl)methylene)malononitrile (**7a**).* Reaction time: 1 h. Yield: dark green solid (48 mg; 58%). Found: C 74.21, H 3.94, N 10.12. $C_{25}H_{15}N_3OS$ requires C 74.05, H 3.73, N 10.36%. Mp 248–252 °C (dec). IR (Nujol, cm^{-1}): 2218 (C≡N), 1651 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.91–7.89 (m, 3H), 7.83–7.80 (m, 2H), 7.54–7.49 (m, 6H), 7.22 (d, *J*=1.8 Hz, 1H), 6.67 (d, *J*=1.8 Hz, 1H), 6.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 154.4, 151.5, 148.7, 147.4, 144.8, 136.7, 131.9, 131.8, 130.9, 130.4, 129.1, 129.0, 125.4, 125.0, 114.4, 113.8, 108.9, 103.2, 103.0. HRMS (ESI^+): found 406.1012 $[M+H]^+$. $C_{25}H_{16}N_3OS$ requires 406.1009.

*4.5.11.2. (E)-2-(3-(5-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl) thiazol-2-yl)allylidene)malononitrile (**7b**).* Reaction time: 3 h. Yield: dark green solid (25 mg, 28%). Found: C 75.33, H 4.10, N 9.57. $C_{27}H_{17}N_3OS$ requires C 75.15, H 3.97, N 9.74%. Mp 249–251 °C. IR (Nujol, cm^{-1}): 2218 (C≡N), 1654 (C=N), 1581 (C=C, Ar), 1546 (C=C, Ar). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.94–7.90 (m, 2H), 7.86 (d, *J*=0.6 Hz, 1H), 7.47–7.45 (m, 2H), 7.59 (d, *J*=10.8 Hz, 1H), 7.57–7.45 (m, 6H), 7.43 (d, *J*=14.8 Hz, 1H), 7.36 (dd, *J*=14.8 Hz, *J′*=10.8 Hz, 1H), 7.08 (dd, *J*=2.0 Hz, *J′*=0.6 Hz, 1H), 6.64 (dd, *J*=2.0 Hz, *J′*=0.2 Hz, 1H), 6.24 (s, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 158.9, 157.9, 156.2, 153.6, 145.4, 143.6, 140.8, 134.1, 133.0, 132.8, 130.9, 130.4, 129.5, 129.4, 125.9, 125.3, 123.8, 109.2, 104.3, 103.2, 82.6. HRMS (ESI^+): found 432.1160 $[M+H]^+$. $C_{27}H_{18}N_3OS$ requires 432.1165.

*4.5.11.3. 2-((2-((2,6-Diphenyl-4H-pyran-4-yliden)methyl)thiazol-5-yl)methylene)malononitrile (**8a**).* Reaction time: 6 h. Yield: dark violet solid (29 mg; 37%). Found: C 74.27, H 3.55, N 10.22. $C_{25}H_{15}N_3OS$ requires C 74.05, H 3.73, N 10.36%. Mp 262–265 °C. IR (Nujol, cm^{-1}): 2214 (C≡N), 1651 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J*=1.7 Hz, 1H), 8.19 (s, 1H), 7.95–7.93 (m, 2H), 7.86–7.84 (m, 2H), 7.80 (s, 1H), 7.56–7.50 (m, 6H), 6.70 (d, *J*=1.7 Hz, 1H), 6.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 157.6, 156.8, 156.3, 148.2, 141.0, 132.2, 131.9, 130.8, 130.7, 129.1, 129.0, 127.0, 125.8, 125.3, 114.7, 113.9, 108.6, 105.7, 103.9, 74.6. HRMS (ESI^+): found 406.0993 $[M+H]^+$. $C_{25}H_{16}N_3OS$ requires 406.1009.

*4.5.11.4. (E)-5-(3-(2-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl) thiazol-5-yl)allylidene)malononitrile (**8b**).* Reaction time: 1 h 30 min. Yield: dark green solid (34 mg; 38%). Found: C 75.28, H 3.85, N 9.86. $C_{27}H_{17}N_3OS$ requires C 75.15, H 3.97, N 9.74%. Mp 229–230 °C. IR (Nujol, cm^{-1}): 2217 (C≡N), 1648 (C=N), 1540 (C=C, Ar). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.47 (d, *J*=1.4 Hz, 1H), 7.99 (s, 1H), 7.98–7.90 (m, 2H), 7.88–7.81 (m, 2H), 7.57–7.48 (m, 7H), 7.43 (d, *J*=14.5 Hz, 1H), 6.77 (dd, *J*=14.5 Hz, *J′*=11.7 Hz, 1H), 6.66 (d, *J*=1.4 Hz, 1H), 6.10 (s, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 172.4, 159.6, 157.0, 155.6, 152.3, 140.1, 138.8, 133.1, 132.8, 132.1, 131.0, 130.8, 129.5, 129.4, 126.1, 125.6, 122.2, 114.9, 113.0, 108.7, 105.6, 104.9, 79.8. HRMS (ESI^+): found 432.1185 $[M+H]^+$. $C_{27}H_{18}N_3OS$ requires 432.1165.

*4.5.12. Compounds **9** and **10**. General procedure*. 1,3-Diethyl-2-thiobarbituric acid (**19**) (56 mg, 0.28 mmol) and the corresponding aldehydes **27a**, **26a** (100 mg, 0.28 mmol) were dissolved in EtOH (3 mL) under argon atmosphere. The reaction mixture was refluxed for 15–25 min (TLC monitoring) and then it was cooled down to 0 °C. Hexane was added and the resulting solid was filtered and washed.

*4.5.12.1. 5-((5-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl)thiazol-2-yl)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6-dione (**9**).* Solvent for washing: first hexane, then CH_2Cl_2/MeOH. Yield: green solid (74 mg; 48%). Found: C 66.94, H 4.46, N 7.90. $C_{30}H_{25}N_3O_3S_2$ requires C 66.77, H 4.67, N 7.79%. Mp 254–255 °C. IR (Nujol, cm^{-1}): 1651 (C=O), 1529 (C=C, Ar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.21 (s, 1H), 8.02–7.97 (m, 2H), 7.86–7.81 (m, 2H), 7.57–7.48 (m, 7H), 6.71 (d, *J*=1.9 Hz, 1H), 6.29 (s, 1H), 4.67 (q, *J*=6.9 Hz, 2H), 4.61 (q, *J*=6.9 Hz, 2H), 1.41 (t, *J*=6.9 Hz, 3H), 1.34 (t, *J*=6.9 Hz, 3H). ^{13}C NMR was not registered due to its low solubility. HRMS (ESI^+): found 540.1378 $[M+H]^+$. $C_{30}H_{26}N_3O_3S_2$ requires 540.1410.

*4.5.12.2. 5-((2-((2,6-Diphenyl-4H-pyran-4-ylidene)methyl)thiazol-5-yl)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6-dione (**10**).* Solvent for washing: first EtOH, then CH_2Cl_2/hexane. Yield: purple solid (125 mg; 84%). Found: C 66.54, H 4.86, N 7.98. $C_{30}H_{25}N_3O_3S_2$ requires C 66.77, H 4.67, N 7.79%. Mp 310–311 °C. IR (Nujol, cm^{-1}): 1646 (C=O), 1530 (C=C, Ar). ^{1}H NMR (300 MHz, $CDCl_3$, 320 K): δ 8.74 (s, 1H), 8.65 (s, 1H), 8.50 (s, 1H), 8.04–7.82 (m, 4H), 7.63–7.49 (m, 6H), 6.73 (s, 1H), 6.22 (s, 1H), 4.72–4.55 (m, 4H), 1.43–1.30 (m, 6H). ^{13}C NMR was not registered due to its low solubility. HRMS (ESI^+): found 540.1385 $[M+H]^+$. $C_{30}H_{26}N_3O_3S_2$ requires 540.1410.

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Supplementary data

NMR and UV–vis spectra of new compounds, X-ray crystallographic data and diagrams of the crystal structures of **4a** and **6**, computed energies and Cartesian coordinates of optimized HF/6-31G* geometries can be found. Supplementary data associated with this article can be found in online version at http://dx.doi.org/10.1016/j.tet.2012.05.123.

References and notes

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