EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201600806

Link to VoR: http://dx.doi.org/10.1002/ejoc.201600806

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Synthesis, fluorescence and two-photon absorption properties of novel push-pull 5-aryl[3,2-*b*]thienothiophene derivatives

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Dedication:

Abstract: Three series of novel push-pull 5-aryl[3,2-*b*]thienothiophene derivatives functionalized with potent electron-withdrawing terminal moieties) were synthesized in moderate to excellent yields through Suzuki coupling followed by Knoevenagel condensation. These novel chromophores combine intense absorption in the near-UV down to the orange visible region in relation with a strong intramolecular charge transfer transition. By combining strong donor and acceptor, large fluorescence quantum yield are achieved as well as large two-photon absorption responses. Interestingly, due to the improved rigidity and electronic delocalization provided by the thienothiophene moiety (compared to the *bis*-thiophene one) larger one- and two-photon brightness values are achieved. As a result, several new fluorescent dyes showing enhanced brightness and tunable fluorescence (ranging from the blue to the NIR region) has been obtained which offer interesting promises for bioimaging applications.

Introduction

Organic materials displaying strong two-photon absorption (TPA)[1-3] have attracted large interest due to a variety of potential applications in photonics and optoelectronics, including three-dimensional optical data storage,[4] three-dimensional microfabrication, [5] optical limitation[6] and two-photon microscopy (TPM).[7] For microscopic imaging, in particular for *in vivo* imaging, the two-photon excitation process presents several advantages as it provides intrinsic three-dimensional resolution and improved in-depth tissue penetration.[7] Furthermore, the combination of the two-photon absorbers with efficient singlet oxygen generation offers the potential for further development of photodynamic cancer therapy (PDT) methods.[8] While much effort has been devoted to developing TPA dyes, fluorescent quantum yields are often lower than desired, while photo-bleaching can be a shortcoming for real applications. In addition to large two-photon absorption, high two-photon excited fluorescence (TPEF) cross-sections (i.e. two-photon brightness), good photostability and appreciable solubility are also required for practical applications.[1]

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Large two-photon absorption is often correlated with significant intermolecular charge transfer (ICT) processes. Hence a standard strategy for designing molecules with large TPA cross-sections is based on connecting electron rich donor entities (D) with electron deficient acceptors (A) through π-electron conjugated bridges within conjugated structures of various topologies. Different factors influence the TPA, including the conjugation length and its modulation, the molecular planarity, the dimensionality of the charge-transfer network and the donating and withdrawing abilities of the electron donor and acceptor moieties. Different structural motifs have been employed in an attempt to optimize the TPA properties including dipolar, quadrupolar, octupolar stuctures where ICT plays a major role, as well as conjugated branched or dendritic structures and macrocycles.[1-9] Although significant advances in the design of these materials have been made in recent years, there is still need for improvement, in particular when large TPA responses in the biological spectral window have to be combined with large fluorescence quantum yield, tunable fluorescence (in particular towards red and NIR-emitting fluorophores) and photostability for imaging purposes. In that perspective, a promising direction is the replacement of aromatic systems with more easily delocalizable π-excessive or π-deficient heteroaromatics which has been shown to result in an increased ICT as well as an enhanced TPA, while preserving in many cases the chemical and photochemical stability of these systems. Moreover, modification of the structure by incorporation of heterocycles into more complex π-conjugated systems allows to fine-tune the electronic and optical properties and often results in strong fluorescence emission, which is an essential prerequisite for certain TPA-based applications.[10] In this context fused thienothiophene (TT) heterocyclic systems, are expected to exhibit interesting TPA properties due to their lower resonance energy per electron when compared to thiophene as well as a their greater electronic relay role and planarity compared the bithiophene counterpart. Those features would also allow the increase of conjugation between the donor (D) and the acceptor (A), which typically results in increased NLO responses and improved thermal stability and a good transparency–nonlinearity trade-off.[11,12]

In the last 30 years, several investigators reported the synthesis and characterization of functionalized thienothiophene (TT) derivatives having in mind primarily their application in materials and medicinal chemistry due to their interesting optoelectronic properties and high thermal and chemical stabilities as well as their wide range of biological activities.[13] In materials chemistry these derivatives have found application in several areas such as nonlinear optics (NLO),[11] dye sensitized solar cells (DSSCs),[14] liquid crystals,[15] organic light emitting diodes (OLEDs),[16] organic semiconductors, field-effect transistors, conducting polymers, etc..[17] Despite their diverse

and interesting applications, the synthesis and reactivity studies of thienothiophene derivatives are less developed compared to other thiophene derivatives probably due to synthetic difficulties.[13]

In recent years we have been engaged on the synthesis of novel formyl-heterocyclic systems, (bithiophenes, oligothiophenes, aryl(bi)thiophenes, (thienyl)pyrroles)[18] through different synthetic methodologies. These heterocyclic carbaldehydes reveal to be versatile precursors for the synthesis of dicyanovinyl- and thiobarbituric acid derivatives with interesting second order nonlinear optical properties.[18a,b,f, 19] We report also the synthesis, the photophysical and TPA properties of a series of push-pull aryl-bithiophene chromophores bearing alkoxyl and *N,N*-dialkylamino electron-donating (D) groups and formyl, dicyanovinyl and 1,3-diethyl-2-thioxodihydropyrimidine-4,6-dione electron-withdrawing (A) end-groups.[18e, 20] In contrast with corresponding push-pull polyenes,[21] these chromophores bearing a phenyl-bithienyl conjugated path exhibited a significant increase in fluorescence. Additionally, some of these chromophores combine very large one and two-photon brightness as well as sizeable emission in the red/NIR region, being therefore promising biphotonic fluorescent probes for bioimaging. [20b]

Moreover, despite the large number of donor-acceptor heterocyclic systems showing TPA properties reported in the literature, the present concept of combining the 4-alkoxyl and 4-*N,N*-dialkyl groups linked to an aryl[3,2-*b*]thienothiophene bridge functionalized with dicyanovinyl and 1,3-diethyl-2-thioxodihydropyrimidine-4,6-dione strong acceptor groups has not, to the best of our knowledge, been previously communicated in the literature. Additionally, only scarce examples of thienothiophenes have been investigated for nonlinear optical applications and only as NLO-phores for second-harmonic generation.[11]

We were therefore motivated to extend our previous studies in order to explore the potential of three new series of push-pull arylthienothiophene heterocyclic systems **8-10**. Consequently, we report herein the synthesis and a detailed study of the fluorescence and TPA properties of three novel series of arylthienothiophene derivatives bearing various electron-donating (OR, NR_2) groups and electron-withdrawing (formyl, dicyanovinyl and barbiturate) end-groups (EWG) and a aryl[3,2-*b*]thienothiophene conjugated bridge.

Results and Discussion

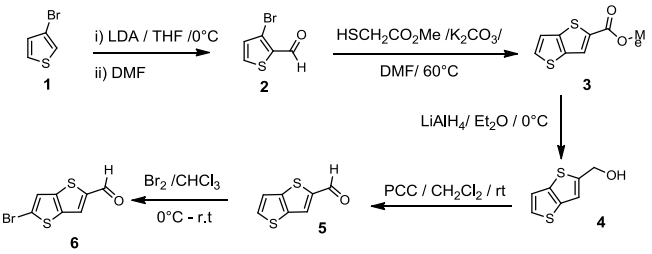
Synthesis

Due to the reasons described above we decided to focus on the synthesis and characterization of the optical and thermal properties of *p*-alkoxy and *p*-dialkylamino-substituted 5-aryl-thieno[3,2-*b*]thiophene-2-carbaldehydes **8** and the corresponding dicyanovinyl **9** and barbiturate **10** derivatives easily obtained through Knoevenagel condensation reactions.

Surprisingly, only a few works report the synthesis of 5-aryl-thieno[3,2-*b*]thiophene derivatives. A recent reference[22] described the preparation of a 2-(*p*-alkoxyphenylthieno[3,2-*b*]thiophene derivative. The synthetic method reported in this paper is especially original, based on a domino thiolation/cyclization reaction which can be applied for the synthesis of benzo[*b*]thiophenes and thieno[3,2-*b*]thiophenes as well. An earlier work report the synthesis of 2-aryl-thieno[3,2-*b*]thiophenes functionalized with acceptor groups (NO_2, CN, CO_2Me, SO_2Me) in *para* position of the phenyl ring through palladium catalysed arylation of thieno[3,2-*b*]thiophene or through intramolecular cyclisation of 2,3-disubstituted thiophenes.[23] On the other hand, the synthesis of 5-triphenylamino-substituted thieno[3,2-*b*]thiophene-2-carbaldehydes or carboxylates is more documented.[14] These compounds are generally the starting points of structurally more complex organic sensitizers designed for DSSCs application. Two different synthetic ways are generally reported, using both classical coupling reactions under mainly Suzuki, Suzuki-Miyaura and Stille conditions.[14] A firstly prepared or commercially available 2-thieno[3,2-*b*]thiophenyl-boronic acid or 2-thieno[3,2-*b*]thiophenyl-stannane can react with the suitable aryl bromide or an aryl-stannane can be coupled to 5-substituted or not 2-bromo(or iodo) thieno[3,2-*b*]thiophene. The 5-triphenylamino-thieno[3,2-*b*]thiophene can be further functionalized[14g] or deprotected[14c,h] depending on the thienothiophene derivative used.

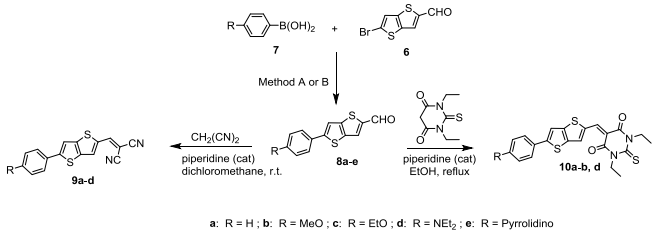
Synthesis of aldehydes 8 through Suzuki coupling

In order to prepare carbaldehydes **8** we synthesize in first place the thieno[3,2-*b*]thiophene-2-carbaldehyde precursor **5** through the combination of two synthetic methodologies described earlier by Fuller[24] and Prugh *et al*.[25] Therefore, methyl thieno[3,2-*b*]thiophene-2-carboxylate **3** was synthesized through Fuller´s method, followed by reduction of esther **3** with lithium aluminium hydride to give alcohol **4** which was reoxidized with pyridinium chlorochromate (PCC) to the thieno[3,2-*b*]thiophene-2-carboxaldehyde **5**.[25] Reaction of **5** with bromine in chloroform at 0^o till room temperature gave 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde **6** as a pale yellow solid in 88% yield (Scheme 1). The synthesis of compound **6** was only reported recently through two different methods which consists in the lithiation of 2,5-dibromothieno[3,2-*b*]thiophene followed by reaction with DMF[14b] or formylation of thieno[3,2-*b*]thiophene followed by bromination with NBS.[26] Nevertheless in both cases the characterization of compound **6** was incomplete.



Scheme 1. Synthesis of precursor **6**.

Aldehydes **8** were prepared through a Suzuki reaction of commercially available arylboronic acids **7a-e** with 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde **6**. The Suzuki cross-coupling reactions were performed under a nitrogen atmosphere through two different reaction conditions: Method A using 1,2-dimethoxyethane (DME) at 80 °C, $Pd(PPh_3)_4$ (6%), Na_2CO_3, H_2O[18e,f] or Method B using toluene at reflux, $Pd(PPh_3)_4$ (10%), K_2CO_3, H_2O, EtOH[27] (Scheme 2). In general, formyl derivatives **8** were obtained in better yields (72-84%) and shorter reactions times through Method B (Table 1).



Scheme 2. Synthesis of aldehydes **8** through Suzuki coupling and synthesis of dicyanovinyl- **9** and thiobarbituric acid thienothiophene derivatives **10** through Knoevenagel condensation of the corresponding aldehyde precursors **8** with malononitrile or thiobarbituric acid.

Table 1. Synthesis of aldehydes **8a**-**e**.

Comp.	R	Reaction time (h) Method A [a]	Yield (%) Method A	Reaction time (h) Method B [b]	Yield (%) Method B	δ_H (ppm)[c]	IR ν (cm^{-1})[d]
8a	H	24	35	1	80	9.97	1662
8b	MeO	4	50	1	72	9.94	1660
8c	EtO	4	85	1	79	9.94	1650
8d	NEt_2	4	36	2	84	9.91	1655
8e	Pyrrolidino	4	30	2	70	9.90	1657

[a] Method A: DME, $Pd(PPh_3)_4$ (6%), Na_2CO_3, H_2O / 80°.

[b] Method B: toluene, $Pd(PPh_3)_4$ (10%), K_2CO_3, H_2O, EtOH, reflux.

[c] For the CHO proton for formyl-arylthienothiophenes **8** (300 MHz, $CDCl_3$).

[d] All the spectra were recorded in nujol.

Synthesis of dicyanovinyl- 9 and thiobarbituric acid thieno[3,2-*b*]thiophene 10 derivatives through Knoevenagel condensation

Knoevenagel condensation of carbaldehydes **8** with malononitrile in dichloromethane at room temperature, or with thiobarbituric acid in acetonitrile at reflux, in the presence of a catalytical amount of piperidine, gave respectively**,** dicyanovinyl-derivatives **9** (Table 2, 49-81%) and thiobarbituric acids **10** (Table 3, 42-82%), in moderate to good yields (Scheme 2).

Table 2. Yields, ^1H NMR, IR and T_d data of dicyanovinyl-arylthienothiophene derivatives **9**.

Aldehyde **8**	R	Dicyanovinyl-arylthienothiophene **9**	Yield (%)	δ_H (ppm)[a]	IR ν (cm^{-1})[c]	T_d[d] (°C)
a	H	**a**	54	8.76	2216	366
b	MeO	**b**	49	8.72	2219	390
c	EtO	**c**	74	8.71	2221	391
d	NEt_2	**d**	81	8.63[b]	2214	412

[a] For the C*H*=$(CN)_2$ proton for dicyanovinyl-arylthienothiophenes **9** (300 MHz, DMSO-d_6).

[b] For the C*H*=$(CN)_2$ proton for dicyanovinyl-arylthienothiophenes **9** (400 MHz, DMSO-d_6).

[c] All the spectra were recorded in nujol.

[d] Decomposition temperature (T_d) measured at a heating rate of 20 ºC min^{-1} under a nitrogen atmosphere, obtained by thermogravimetric analysis (TGA).

Table 3. Yields, ^1H NMR, IR and T_d data of thiobarbituric acid thienothiophene derivatives **10**.

Aldehyde **8**	R	Thiobarbituric-arylthienothiophene **10**	Yield (%)	δ_H (ppm)[a]	IR ν (cm^{-1})[c]	T_d[d] (°C)
a	H	**a**	42	8.75	1682, 1654	333
b	MeO	**b**	74	8.74	1682, 1653	335
d	NEt_2	**d**	82	8.67[b]	1681, 1655	253

[a] For the C= C*H* proton for thiobarbituric-arylthienothiophenes **10** (400 MHz, DMSO-d_6).

[b] For the C= C*H* proton for dicyanovinyl-arylthienothiophenes **10** (300 MHz, $CDCl_3$).

[c] All the spectra were recorded in nujol.

[d] Decomposition temperature (T_d) measured at a heating rate of 20 ºC min^{-1} under a nitrogen atmosphere, obtained by thermogravimetric analysis (TGA).

The structures of novel TT derivatives **8-10** were clearly confirmed by their analytical and spectral data. The most characteristic signals in the ^{1}H NMR spectra for aldehydes **8** were those corresponding to the C*H*O protons at about 9.90-9.97 ppm. For dicyanovinyl derivatives **9a-d** as well for thiobarbituric acid derivatives **10a**, **b** and **d** a singlet at about 8.63-8.76 ppm or 8.67-8.75 ppm, respectively, were also observed corresponding to the vinylic proton of the ethylenic bridge (C=C*H*) linked to the dicyanovinyl or thiobarbituric acid acceptor moieties (Tables 1-3). The analysis of the ^{1}H NMR spectra for push-pull systems **8**-**10** showed that the chemical shifts of the C*H*O proton in compounds **8b-d** as well as the chemical shifts of protons of the ethylenic bridge (C=C*H*) linked to the acceptor moieties in derivatives **9b**-**d** and **10**, **b** and **d** exhibit signals that are shifted up-field relative to the corresponding unsubstituted derivatives **8a**, **9a** and **10a**, due to the stronger mesomeric donor effect of the alkoxy and *N,N*-dialkylamino groups substituted in *para* position of the aryl rings linked to the TT spacer. Moreover, a gradual slight up-field shift is observed with increasing donor strength.

IR spectroscopy was also used in order to identify the typical absorption bands of the carbonyl group in aldehydes **8** (1650-1662 cm^{-1}), carbonyl (1653-1655 cm^{-1}) and thiocarbonyl groups (1683-1685 cm^{-1}) in thiobarbituric compounds **10** and the nitrile groups in dicyanovinyl derivatives **9** (2214-2221 cm^{-1}).

Thermal stability studies

It is well known that a good thermal stability is critical for practical application of optical organic materials. Therefore, the thermal stability of push-pull arylthienothiophene derivatives **9-10** was determined by thermogravimetric analysis (TGA), measured at a heating rate of 20 ºC min^{-1} under a nitrogen atmosphere. The results obtained revealed the exceptional thermal stability for dicyanovinyl push-pull derivatives **9** which could be heated up to T_d = 366–412 ºC. Substitution of the dicyanovinyl acceptor group **9** by the thiobarbituric moiety **10** leads to lower decomposition temperatures (T_d= 253 – 355 ºC). These results are in agreement with earlier reports in which good to excellent thermal stabilities were communicated for other nonlinear optical thienothiophene derivatives.[11a, c, d, e]

Photophysical properties

Photophysical properties of all push-pull derivatives have been investigated in chloroform. The experimental data are gathered in Table 4.

Table 4. Photophysical and two-photon absorption properties of TT derivatives **8a-e**, **9a-d**, and **10a-d** in chloroform .

cpd	λ_{abs}^{max} [nm]	ε^{max} [$M^{-1}.cm^{-1}$]	FWHM [cm^{-1}] [a)]	λ_{em}^{max} [nm]	Stokes shift [cm^{-1}]	Φ_f [b)]	$\varepsilon^{max}\Phi_f$ [g)] [$M^{-1}.cm^{-1}$]	τ_f [h)] [ns]	$2\lambda_{abs}^{max}$ [nm]	λ_{TPA}^{max1} [nm]	$\sigma_2^{max1}\Phi_f$ [GM] [j)]	σ_2^{max1} [GM] [j)]
8a	358	$3.6\ 10^4$	$4.5\ 10^3$	413	3720	0.02 [c-e)]	$7.2\ 10^2$	0.12	716	/	/	/
8b	372	$3.5\ 10^4$	$4.5\ 10^3$	447	4510	0.58 [c)] 0.64 [d-e)]	$2.1\ 10^4$	1.26	744	750	50	82
8c	374	$3.5\ 10^4$	$4.4\ 10^3$	453	4660	0.65 [c)] 0.71 [d-e)]	$2.4\ 10^4$	1.44	748	750	60	88
8d	428	$3.9\ 10^4$	$4.2\ 10^3$	543	4950	0.87 [d-e)]	$3.4\ 10^4$	2.45	856	850	240	276
8e	428	$2.8\ 10^4$	$4.2\ 10^3$	545	5020	0.86 [d-e)]	$2.4\ 10^4$	2.44	856	850	180	209
9a	436	$5.3\ 10^4$	$3.4\ 10^3$	491	2570	0.002 [d-f)]	106	0.3	872	890	0.2	100
9b	455	$3.9\ 10^4$	$3.6\ 10^3$	531	3150	0.006 [d-f)]	234	0.2	910	940	1.4	233
9c	457	$5.1\ 10^4$	$3.6\ 10^3$	532	3080	0.007 [d] 0.006 [e-f)]	331	0.1	914	960	2.4	369
9d	534	$5.4\ 10^4$	$3.5\ 10^3$	652	3390	0.61 [e-f)]	$3.3\ 10^4$	2.2	1068	1080	510	836
10a	495	$7.2\ 10^4$	$2.8\ 10^3$	548	1950	0.003 [e-f)]	216	0.84	990	/	/	/
10b	514	$7.7\ 10^4$	$2.9\ 10^3$	579	2180	0.006 [e-f)]	462	0.13	1028	1050	2.4	400
10d	595	$7.6\ 10^4$	$3.0\ 10^3$	710	2720	0.20 [e)] *0.19* [f)]	$1.5\ 10^4$	0.78	1190	≥1160	≥150	≥750

[a)] Full width at half-maximum ; [b)] fluorescence quantum yield ; [c)] standard : quinine in 0.5M H_2SO_4 (Φ_f=0.546) ; [d)] standard : fluorescein in 0.1 M aq. NaOH (Φ_f =0.90);[e)] standard : Rhodamine 6G in EtOH (Φ_f =0.94) ; [f)] standard : cresyl violet in methanol (Φ_f =0.54) ; [g)] brightness; [h)] experimental fluorescence lifetime ; [i)] Molecular TPEF action cross section (i.e., two-photon brightness) at λ_{TPA}^{max}; [j)] Molecular TPA cross section at λ_{TPA}^{max}. 1 GM = 10^{-50} cm^4.s.photon $^{-1}$

Absorption

As shown in Table 4, all compounds show an intense absorption band in the near UV or visible region which can be ascribed to intramolecular charge transfer transition (ICT). As expected, the nature of the donor and acceptor end-groups significantly influences the position of this low-energy absorption band. Increasing the donor strength is inducing a progressive bathochromic shift as illustrated in Figure 1 for series **8a-e** and observed also for series **9a-d** and **10a-d** (see Table 4).

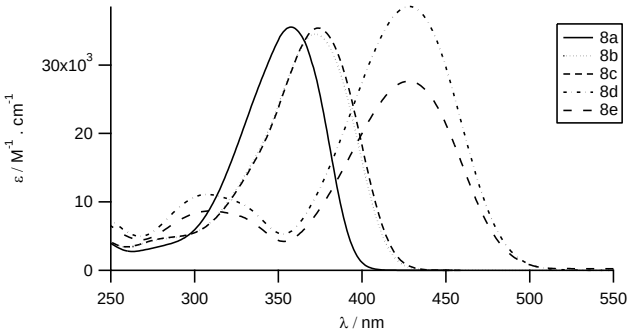


Figure 1. Absorption spectra of compounds **8a-e** in chloroform.

A marked bathochromic and hyperchromic shift as well as narrowing of the main absorption band (Table 4) is observed when increasing the electron-withdrawing strength of the acceptor as indicated by comparison of compounds **8-10d** (see Figure 2) and compounds **8-10b** (see Figure S1). These combined effects points to an increased polarization of the ground-state (in relation with larger contribution of the ICT mesomeric form in the description of the electronic structure) shifting the electronic structure towards a more "cyanine-like" structure.[28]

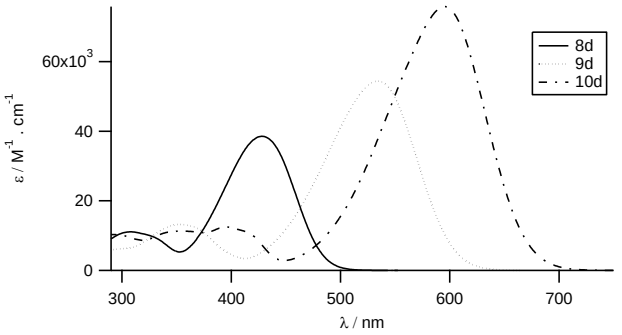


Figure 2. Absorption spectra of compounds **8-10d** in chloroform

Fluorescence

As noted from Table 4, a number of the push-pull derivatives built from a TT π-connector investigated in the present work show significant fluorescence. The fluorescence quantum yield is found to depend drastically on the nature of the acceptor and donor end-groups. Indeed all derivatives of series **8** (i.e. push-pull derivatives bearing an aldehyde as acceptor) but **8a** (lacking the presence of a donor) show significant fluorescence quantum yield. In contrast, for derivatives bearing strong acceptor end-groups (i.e. dicyano or diethylthiobarbiturate) of series **9** and **10**, only compounds **9d** and **10d** bearing the strongest donor (i.e. diakylamino) show sizeable. Such behavior was observed earlier in related homologous compounds having a thiophene or bis-thiophene unit instead of TT.[20b] This behavior can be related to the nature of the lowest-energy excited state (responsible for emission): for stronger donor and acceptor end-groups the ICT π–π* transition shifts to lower energy and the corresponding excited state is thus located below that of the n-π* transition (whose band is hidden by the more intense ICT one). In the case of compounds of series **9** and **10** having weaker donors (OMe, OEt), the n-π* transition is most probably found at slightly lower energy and thus responsible for only weak fluorescence (due to reduced transition dipole). We note that compound **9d** and **10d** show increased fluorescence quantum yield as compared to their homologues having one or two thiophene instead of a TT connecting unit (Φ_f=0.61 for **9d** instead of 0.13 and 0.34 and (Φ_f=0.20 for **10d** instead of 0.09 and 0.06). This enhanced fluorescence can be ascribed to both larger radiative rate and lower non-radiative rates. Hence the planarization induced by the TT unit induces both higher transition dipoles and increase rigidity, both responsible for improved fluorescence efficiency. As a result compound **9d** and **10d** show much larger brightness than their homologues having a thiophene or *bis*-thiophene instead of TT ($\varepsilon_{max}\Phi_f$ = 3.3 10^4 $M^{-1}.cm^{-1}$ for dye **9d** compared to 1.3 10^4 $M^{-1}.cm^{-1}$ for its *bis*-thiophene homologue[20b] and $\varepsilon_{max}\Phi_f$ = 1.5 10^4 $M^{-1}.cm^{-1}$ for the dye **10d** compared to 2.6 10^3 $M^{-1}.cm^{-1}$) while their emission maximum is located in between those of the two homologues (i.e. red-shifted compared to the homologue having one thiophene in the π-system and blue-shifted compared to that of that of the homologue having two thiophene).

The nature of the donor and acceptor end-groups also significantly influences the fluorescence spectra. In all series, increasing the strength of the donor end-groups induces a progressive red-shift of the emission spectrum as illustrated in Figure 3 for series **8a-e**. In all cases an increase of the Stokes shift value is also observed (see Table 4) indicating a more pronounced photo-induced ICT.

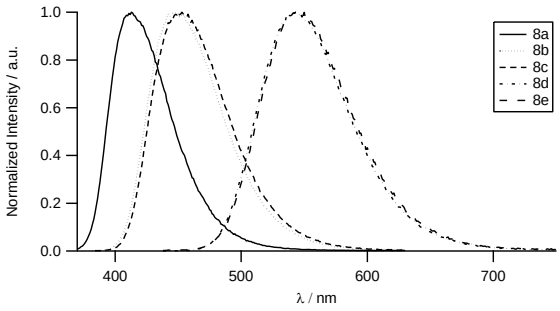


Figure 3. Emission spectra of compounds **8a-e** in chloroform

Increasing the strength of the acceptor end-group also induces a red-shift of the emission as shown in Figure 4 for series **8-10b** (and illustrated in Fig.S2 for series **8-10d**). In both cases however, we note a reduction of the Stokes shift values (Table 4). This effect concomitant with a narrowing of the ICT absorption band and red shifts of both the emission and absorption bands points to a shift of the electronic structure of the dye towards the cyanine limit (with increasing contribution of the zwitterionic mesomeric form to the description of the ground-state structure). Compound **10d** which has the larger extinction coefficient, narrowest absorption band, smallest Stokes' shift value and the most red-shifted absorption and emission (with maximum located in the NIR region) is the closest to the cyanine-dye like structure.

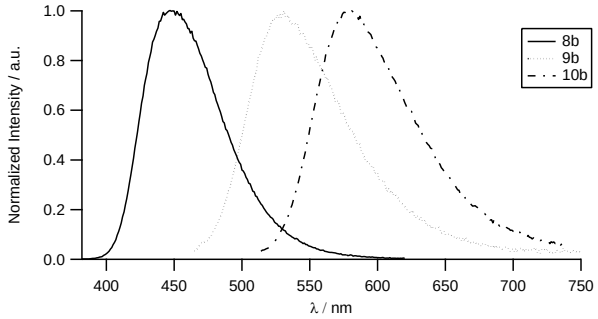


Figure 4. Emission spectra of compounds **8-10b** in chloroform

Finally, we note that whereas dye **8b-d** are either blue-(**8b-c**) or green (**8d-e**) bright emitters (with brightness values ranging between 2.1 10^4 $M^{-1}.cm^{-1}$ and 3.4 10^4 M^{-1}) dyes **9d** and **10d** are complementary bright red and NIR emitters.

Two-photon absorption

Thanks to their fluorescence properties, the TPA of most push-pull derivatives could be determined by investigating their two-photon induced fluorescence in solution. TPA spectra were obtained in the 700-1200 nm spectral range through femtosecond two-photon excited fluorescence experiments and by following the methodology described by Webb and collaborators.[28] The corresponding data are gathered in Table 4. All compounds show a broad TPA band (Figures 5-7) whose maximum is located at about twice the wavelength of the one-photon absorption (OPA) band, which indicates that the lowest excited state is both one and two-photon allowed as expected for push-pull derivatives (see Fig. S3-S5 in SI). We stress that most probably, the TPA properties of these dipolar derivatives are influenced by the solvent polarity as reported recently for other dipolar heterocyclic derivatives.[10p] Here we chose a solvent of medium polarity to conduct experiments.

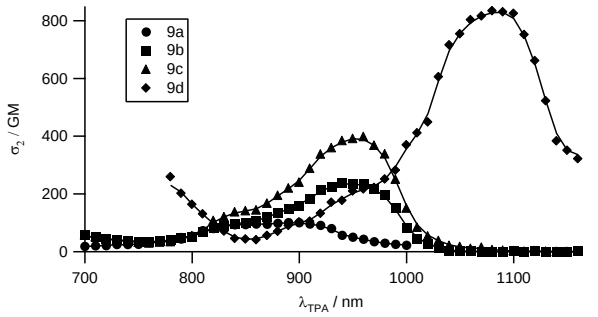


Figure 5. Two-photon absorption spectra of compounds **8a-e** in chloroform

As illustrated in Figure 5, for series **9a-d** increasing the strength of the donating end-groups induces both a red-shift of the TPA band in the NIR region and pronounced enhancement of the maximum TPA cross-section. Such effect is also observed in the case of series **8b-d** and **10b-d** (see Table 4 and SI). As the fluorescence quantum yield values also increase, the push-pull compounds bearing the strongest donating end-group (i.e., dialkylamino moiety) are found to lead to the largest two-photon brightness; respectively 240 GM for green-yellow emitter **8d**, 510 GM for red emitter **9d**, and 150 GM for NIR emitter **10d**.

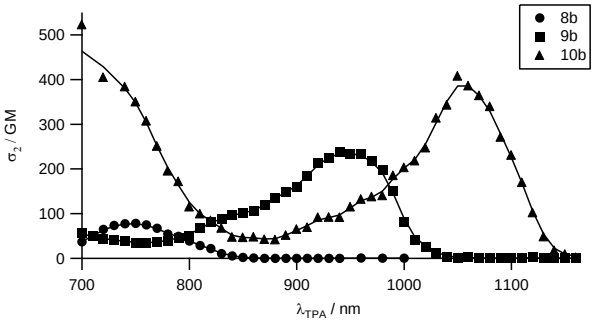


Figure 6. Two-photon absorption spectra of compounds **8-10b** in chloroform

Increasing the strength of the acceptor end-group also induces a red-shift of the TPA band as illustrated in Figure 6 for series **8-10b** and Figure 7 for series **8-10d**. In the case of the series bearing a MeO donor end-group (**8-10b**) the stronger acceptor (diethylthiobarbiturate) leads to the largest maximum TPA cross-section while in the case of the series bearing a NEt_2 donor end-group (**8-10d**), the maximum TPA cross-section is attained with the push-pull derivative bearing a dicyano acceptor (836 GM). This may be related to the electronic structure of dye **10d** which is much closer to the cyanine limit than **9d** thus leading to lower TPA response.[29] In addition, we note that in the case of the diethylthiobarbiturate acceptor, steric hindrance due to the repulsion and repulsion between the lone pairs of the sulfur of the thiophene ring and the oxygen atoms of the acceptor may cause deviation from planarity which may also influence the TPA properties.

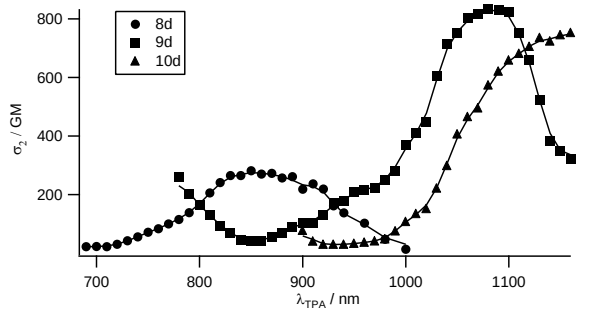


Figure 7. Two-photon absorption spectra of compounds **8-10d** in chloroform

Finally, it is of interest to compare the two-photon absorption response of the brightest two-photon dyes (i.e. **8d**, **9d** and **10d**) to that of their homologue having a bis-thiophene π-connector instead of TT π-connector in the conjugated path.[20b] The aldehyde derivative **8d** show slightly larger TPA maximum cross-section (276 GM compared to 253 GM), whereas the dicyanovinyl derivative **9d** show much larger TPA maximum cross-section (369 GM compared to 115 GM), while the thiobarbituric acid derivative **10d** show smaller response TPA maximum cross-section (750 GM compared to 1600 GM).

This trend can be interpreted by the different polarization of the derivatives bearing the different acceptor end-groups. Increasing the acceptor strength leads to increased polarization as mentioned above. Replacing the bis-thiophene π-connector by the TT π-connector also increases the polarization and shifts the electronic structure closer to the cyanine limit. This is due to the reduced aromaticity of the TT unit compared to that of the bis-thiophene (leading to lower gap *V*[29]). In addition, the planarity of the TT moiety (as compared to the free rotation of the single bond linking the two thiophene rings in the bis-thiophene π-connector) favor coupling and thus also shifts the structure closer to the cyanine limit. The narrower ICT absorption bands of the compounds **8d**, **9d** and **10d** as compared to those of their analogues having a bis-thiophene π-connector [20b] provides a clear evidence of this effect. Since there is an optimum electronic distribution (positioned in between the neutral form and the cyanine limit) which maximizes the TPA response of push-pull derivatives, the effect of increased polarization depends on the initial polarization.[29] Due the low initial polarization in aldehyde derivatives (i.e., derivatives **8**), the effect of TT is favorable as it increases the polarization and shifts the structure closer to optimum polarization. This effect is even more pronounced for the dicyanovinyl derivative which is most probably very close to the optimum polarization leading to maximum TPA response for compound **9d**. In contrast, due to the strong electron-withdrawing strength of the diethylthiobarbiturate, its electronic distribution is close to the cyanine limit (i.e. past the optimum polarization), thus leading to a decrease of the TPA response when increasing the polarization.

In any case, thanks to the much larger fluorescence quantum yield, both **8d**, **9d** and **10d** show improved two-photon brightness values as compared to their homologues having *bis*-thiophene instead of TT in the conjugated system. This demonstrates that the implemented strategy is of major interest to yield a series of bright fluorescent dyes showing tunable emission in the visible region down to the NIR region and large two-photon brightness. In particular fluorescent dye **10d** offers major promises as it can be both two-photon excited in the NIR region (close to 1.2 μm) and emits in the NIR region. As such it holds promise as novel fluorochromes for biological imaging.

Conclusions

5-Arylthieno[3,2-*b*]thiophene aldehydes **8** were synthesized through Suzuki coupling reaction of functionalized aryl boronic acids with 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde **6**. Donor-acceptor substituted thieno[3,2-*b*]thiophenes **9**-**10** have been prepared, in moderate to good yields from the formyl-substituted derivatives **8** and low cost commercially available reagents, using simple and convenient synthetic methodologies.

These new derivatives are found to show intense absorption in the near UV down to the orange visible region depending on the nature of the donor or acceptor end-groups, in relation with an strong ICT transition. Whereas all push-pull aldehydes show good fluorescence properties, only the push-pull derivatives combining a strong acceptor (i.e., dicyanonvinyl or diethylthiobarbiturate) and stronger donor (dialkylamino) show sizeable fluorescence. In addition, these derivatives are found to show both improved fluorescence quantum yield as compared to their homologues having a bis-thiophene instead of TT in the conjugated π-system as well as larger TPA response. As a result, by using the fused thiophene conjugating system, several new fluorescent dyes showing enhanced one- and two-photon brightness and tunable emission (i.e. blue, green, red and NIR) has been obtained. These dyes hold promise as new fluorescent probes for bioimaging purposes.

Experimental Section

Synthesis

Thin layer chromatography was carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F_{254}). Melting points were measured on a Gallenkamp melting point apparatus. NMR spectra were obtained on a Varian Unity Plus Spectrometer at an operating frequency of 300 MHz for ^{1}H NMR and 75.4 MHz for ^{13}C NMR or a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR using the solvent peak as internal reference at 25 ºC. All chemical shifts are given in ppm using $\delta_H Me_4Si$ = 0 ppm as reference and *J* values are given in Hz. Assignments were made by comparison of chemical shifts, peak multiplicities and *J* values and were supported by spin decoupling-double resonance and bidimensional heteronuclear HMBC and HMQC correlation techniques. IR spectra were run on a FTIR Perkin-Elmer 1600 spectrophotometer in nujol or in KBr. Elemental analyses were carried out on a Leco CHNS 932 instrument. Low and high resolution mass spectrometry analyses were performed at the "C.A.C.T.I. - Unidad de Espectrometria de Masas", at University of Vigo, Spain.

All Suzuki couplings were carried out under an argon atmosphere and all commercially available reagents and solvents were used as received.

Synthesis of 3-bromothiophene-2-carbaldehyde 2

3-Bromothiophene **1** (29.35 g, 180 mmol) was added dropwise to a stirred solution of lithium diisopropylamide (LDA) [prepared by addition of butyllithium (2.5 mol.l^{-1} in hexane; 80 mL, 200 mmol) to diisopropylamine (22.24 g, 220 mmol)] in dry tetrahydrofuran (300 mL) at 0 °C and the resulting mixture was stirred for a further 30 min at this temperature prior to addition of dimethylformamide (16.3 ml, 15.3 g, 210 mmol). The mixture was stirred during 3 hours when an excess of 20% aqueous ammonium chloride was added to it. The product was extracted with diethyl ether 3x250 mL), washed three times with water (300 mL) and dried with magnesium sulfate. Evaporation of the organic solvent gave (34.4 g, 180 mmol) of 3-bromothiophene-2-carbaldehyde **2**[24] in quantitative yield as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.13 (d, 1H, J= 5.1Hz), 7.70 (dd, 1H, J= 5.1Hz, J= 1.4Hz), 9.95 (d, 1H, J= 1.4 Hz, CHO).

Synthesis of methyl thieno[3,2-*b*]thiophene-2-carboxylate 3

3-Bromothiophene-2-carbaldehyde **2** (34.4 g, 180 mmol) was added to a stirred mixture of methyl 2-sulfanylacetate (16.1 ml, 19.10 g, 180.0 mmol), potassium carbonate (37.3 g) and *N,N*-dimethylformamide (140 ml) at room temperature and the resulting mixture was stirred during 72 h at 60°C. Then it was poured into water (600 ml) and the precipitate was

filtered to give 21.4 g of methyl thieno[3,2-*b*]thiophene-2-carboxylate **3**[24] as an yellow solid in 60% yield, mp: 95-96°. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.27 (d, 1H, J= 5.3 Hz), 7.58 (d, 1H, J= 5.3Hz), 7.99 (s, 1H).

Synthesis of 2-(hydroxymethyl)thieno[3,2-*b*]thiophene 4

A solution of methyl thieno[3,2-*b*]thiophene-2-carboxylate **3** (15 g, 75.7 mmol) in dry dimethyl ether (350 mL) was added during 2 h to a suspension of lithium aluminum hydride (5.75 g, 151.5 mmol) in dry dimetylether (200 mL) which had been cooled in an ice-water bath. After the addition was completed, the mixture was stirred at room temperature for 3 h. The reaction was worked up by cooling in an ice-water bath with successive dropwise addition of water (5.7 ml), 15% aqueous sodium hydroxide (6 mL), and water (18 mL) with vigorous stirring. Vigorous stirring was continued until the salts were well granulated. The ether solution of the product was decanted and the salts washed further with ether. The combined ether solutions were dried with $MgSO_4$ and filtered, and the solvent was evaporated under vacuum to give 11.6 g of product **4** as a white solid[25] in 90% yield. ^{1}H NMR ($CDCl_3$) δ 4.87 (s, 2H), 7.19 (s, 1H), 7.22 (d, 1H, J= 5.2 Hz), 7.34 (d, 1H, J= 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 61.0, 117.8, 119.6, 127.0, 139.2, 146.1.

Synthesis of thieno[3,2-*b*]thiophene-2-carboxaldehyde 5

A solution of 2-(hydroxymethyl)thieno[3,2-*b*]thiophene **4** (11.6 g, 68.3 mmol) in methylene chloride (160 mL) was added all at once to a stirred suspension of pyridinium chlorochromate (22.1 g, 102.4 mmol) which had been ground in a mortar and pestle and partially dissolved in methylene chloride with vigorous stirring. Stirring was continued for 2 h. Pyridinium chlorochromate (5.9 g, 27.3 mmol) was added, and the mixture was stirred vigorously for 30 min. The solution was worked up by adding dimethylether (1 L) and then filtering through a column of silica gel. The gum in the flask was washed with ether (3 x 1500 mL) and these washings were passed through the column. The solvents were evaporated under vacuum to give 8.37 g of crude dark purple crude product which was recristalised from cyclohexane to give the pure compound as a pale gray solid, mp: 51-52°C [lit.[25] 53-54]. ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 1H, J= 5.2 Hz), 7.47 (d, 1H, J= 5.2 Hz), 7.92 (s, 1H), 9.98 (s, 1H, CHO).

Synthesis of 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde 6

Thieno[3,2-*b*]thiophene-2-carboxaldehyde **5** (8.37 g, 49.8 mmol) was dissolved in 150 mL of chloroform. 4.6 g of sodium hydrogenocarbonate were added to the solution and cooled at 0°C. Bromine (2.56 mL, 8,0 g, 49.8 mmol) was added dropwise and the mixture was stirred at room temperature during 2 hours. The organic layer was extracted with 200 mL of water, and the aqueous phase was extracted (3x150 mL) with methylene chloride. The organic solutions were combined, dried with magnesium sulfate and evaporated under vacuum to leave a dark solid which was recristalised from cyclohexane to give (9.4 g, 88%) of 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde **6**[14b,26], as a gray solid mp: 142-143°C. IR (Nujol) : 1660, 1409, 1336, 1301, 1280, 1264, 1225, 1148, 1122, 990, 977, 853, 829, 807, 790, 738, 722, 694, 658, 630 cm^{-1} ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.83 (s, 1H), 9.96 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 120.9, 122.9, 128.2, 139.3, 144.5, 144.7, 183.3. MS (EI) m/z (%) : 247 (M^+ ^{81}Br, 63), 245 (M^+ ^{79}Br, 66), 219 (6), 218 (13), 217 (7), 216 (11), 139 (13), 138 (20), 95 (9), 93 (16), 81 (4), 69 (100). HRMS : m/z (EI) for $C_7H_3{}^{79}BrOS_2$ calcd: 245,8809; found: 245,8810; for $C_7H_3{}^{81}BrOS_2$ calcd: 247,8788; found 247,8790.

General procedures for Suzuki coupling

Method A:

5-Bromothieno[3,2-*b*]thiophene-2-carbaldehyde **6** (0.25 mmol, 100 mg) was coupled to boronic acids **7a-e** (0.33 mmol) in a mixture of DME (6 mL), aqueous solution of Na_2CO_3 (0.4 mL, 2 M) and $Pd(PPh_3)_4$ (6 mol%) at 80°C under nitrogen. The reactions were monitored by TLC which determined the different reaction times (4-24 h). After cooling, the mixture was filtered and ethyl acetate and a saturated solution of NaCl were added and the phases were separated. The organic phase was washed with water (3 x 10 mL) and with a solution of NaOH (10%) (1 x 10 mL). The organic phase obtained was dried using $MgSO_4$, filtered and the solvent was removed under vacuum to give the crude mixture products which were submitted to column chromatography on silica with increasing amounts of ether in light petroleum as eluent to afford the pure products **8a-e**.

Method B:

5-Bromothieno[3,2-*b*]thiophene-2-carbaldehyde **6** (0.25 mmol, 100 mg) was coupled to boronic acids **7a-e** (0.33 mmol) in a mixture of toluene (6 mL), K_2CO_3 (2,5 mmol, 0.64g, 10 eq.), ethanol (3.2 mL), 1 mL of water and $Pd(PPh_3)_4$ (10 mol%) at reflux under nitrogen. The reactions were monitored by TLC which determined the different reaction times (1-2 h). After cooling, the mixture was filtered and the solid was washed with CH_2Cl_2. The organic phase obtained was washed with water (3x10 mL), dried with $MgSO_4$ filtered and the solvent was removed under vacuum to give the crude products which were submitted to column chromatography on silica with dichloromethane as eluent to afford the coupled products **8a-e**. Recrystallization from dichloromethane/petroleum ether gave the pure compounds.

5-Phenylthieno[3,2-*b*]thiophene-2-carbaldehyde (8a): Yellow solid (Method A, 35% yield; Method B, 80% yield), m.p. 165-166°C. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.39-7.49 (m, 3H, *H*4', *H*3' and *H*5'), 7.55 (s, 1H, *H*6), 7.67-7.69 (m, 2H, *H*2'and *H*6'), 7.93 (s, 1H, *H*3), 9.97 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) : δ 115.8, 126.2 129.0, 129.2, 133.7, 138.2, 144.5, 146.7, 152.9, 181.2 ppm. IR (nujol): ū = 3094, 3059, 2851, 1662, 1625, 1513, 1498, 1259, 1021 cm^{-1}. MS (EI): m/z (%) = 245 (M^++1, 15), 244 (M^+, 100), 243 (61), 216 (14), 215 (17), 171 (33), 145 (12), 93 (17). HRMS (EI) : calcd. for $[C_{13}H_8OS_2]^+$ 244.0017 : found 244.0021.

5-(4-Methoxyphenyl)thieno[3,2-*b*]thiophene-2-carbaldehyde (8b): Yellow solid (Method A, 50% yield; Method B, 72% yield), m.p. 169-170°C. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.87 (s, 3H, OC*H*$_3$), 6.96 (d, 2H, J=6.9 Hz, *H*3' and *H*5'), 7.41 (d, 1H, J=0.6 Hz, *H*6), 7.59 (d, 2H, J=6.9 Hz, *H*2' and *H*6'), 7.88 (d, 1H, J=0.6 Hz, *H*3), 9.94 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) : δ 55.4, 114.6, 126.5, 127.6, 129.3, 137.5, 144.0, 147.0, 153.1, 160.4, 183.1 ppm. IR (nujol): ū = 3091, 3047, 2980, 2851, 1660, 1603, 1523, 1462, 1262, 1024 cm^{-1}. MS (EI): m/z (%) = 275 (M^++1, 11), 274 (M^+, 60), 259 (47), 231 (8), 203 (14), 149 (9), 137 (20), 123 (14), 121 (17), 109 (12), 95 (21), 93 (7), 81 (63), 69 (100). HRMS (EI) : calcd. for $[C_{14}H_{10}O_2S_2]$ 274.0122 : found 274.0122.

5-(4-Ethoxyphenyl)thieno[3,2-*b*]thiophene-2-carbaldehyde (8c): Yellow solid (Method A, 85% yield; Method B, 79% yield), m.p. 175-176°C. ^{1}H NMR (250 MHz, $CDCl_3$) : δ 1.37 (t, 3H, J=7.0 Hz, OCH$_2$C*H*$_3$), 4.09 (q, 2H, J=7.0 Hz, OC*H*$_2$CH$_3$), 6.95 (d, 2H, J=8.8 Hz, *H*3' and *H*5'), 7.42 (s, 1H, *H*6), 7.58 (d, 2H, J=8.8 Hz, *H*2'and *H*6'), 7.90 (s, 1H, *H*3), 9.94 (s, 1H, C*H*O) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$) : δ 14.8, 63.7, 115.1, 126.3, 127.6, 129.3, 137.5, 144.0, 147.1, 153.3, 159.8 , 183.1 ppm. IR (nujol): ū = 3091, 3050, 2978, 2850, 1650, 1605, 1523, 1469, 1259, 1044 cm^{-1}. MS (EI): m/z (%) = 289 (M^++1, 15), 288 (M^+, 98), 262 (11), 261 (22),

260 (88), 259 (100), 233 (6), 232 (14), 203 (19), 187 (11), 171 (12), 158 (9). HRMS (EI) : calcd. for $[C_{15}H_{12}O_2S_2]$ 288.0279 : found 288.0285.

5-(4-Diethylaminophenyl)thieno[3,2-*b*]thiophene-2-carbaldehyde (8d): Orange solid (Method A, 36% yield; Method B, 84% yield), m.p. 202-203°C. ^{1}H NMR (300 MHz, DMSO-d_6) : δ 1.13 (t, 6H, J=6.9 Hz, N(CH_2CH_3)$_2$), 3.40 (q, 4H, J=6.9 Hz, N(CH_2CH_3)$_2$), 6.74 (d, 2H, J=9.0 Hz, *H*3' and *H*5'), 7.52 (d, 2H, J=9.0 Hz, *H*2' and *H*6'), 7.65 (s, 1H, *H*6), 8.25 (s, 1H, *H*3), 9.91 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6) : δ 12.1, 43.4, 111.6, 112.8, 119.8, 126.8, 130.5, 135.8, 142.5, 146.3, 147.9, 153.6, 183.3 ppm. IR (nujol): $\bar{\upsilon}$ = 3089, 2892, 2803, 1655, 1602, 1552, 1430, 1355 cm^{-1}. MS (EI): m/z (%) = 316 (M$^+$+1, 7), 315 (M$^+$, 39), 300 (100), 271 (28), 243 (7), 171 (8), 150 (4). HRMS (EI) : calcd. for $[C_{17}H_{17}NOS_2]$ 315.0752 : found 315.0750.

5-(4-Pyrrolidin-1-ylphenyl)thieno[3,2-*b*]thiophene-2-carbaldehyde (8e): Orange solid (Method A, 30% yield; Method B, 70% yield), m.p. over 250°C. ^{1}H NMR (300 MHz, DMSO-d_6) : δ 1.94-1.99 (m, 4H, N(CH_2CH_2)$_2$), 3.26-3.28 (m, 4H, N(CH_2CH_2)$_2$), 6.61 (d, 2H, J=8.7 Hz, *H*3' and *H*5'), 7.55 (d, 2H, J=8.7 Hz, *H*2' and *H*6'), 7.73 (s, 1H, *H*6), 8.31 (s, 1H, *H*3), 9.90 (s, 1H, C*H*O). ^{13}C NMR (100 MHz, DMSO-d_6) : δ 24.9 (N(CH_2CH_2)$_2$), 47.3 (N(CH_2CH_2)$_2$), 112.0 (*C*6), 113.1 (*C*3' and *C*5'), 120.1 (*C*1'), 127.0 (*C*2' and *C*6'), 131.4 (*C*3), 136.0 (*C*5), 142.6 (*C*3a ou *C*6a), 146.7 (*C*6a or *C*3a), 148.2 (*C*2), 154.1 (*C*4'), 184.0 (*C*HO) ppm. IR (nujol): $\bar{\upsilon}$ = 3088 (CH-Ar), 2980 (CH-Aliph), 2803 (CH-Ald), 1657 (C=O), 1607, 1530 (C=C), 1432 (CH), 1357 (C-N) cm^{-1}. MS (EI): m/z (%) = 314 (M$^+$+1, 25), 313 (M$^+$, 100), 309 (61), 285 (5), 280 (13), 270 (9), 257 (21), 171 (14), 93 (10), 84 (5). HRMS (EI) : calcd. for $[C_{17}H_{15}NOS_2]$ 313.0595 : found 313.0599.

General procedure for the synthesis of dicyanovinyl-arylthienothiophene derivatives 9 from the corresponding formyl precursors 8 by Knoevenagel condensation with malononitrile

To a solution of malononitrile (0.08 g, 1.2 mmol) and aldehydes **8** (1.0 mmol) in dichloromethane (25 mL) was added piperidine (1 drop). The solution was stirred at room temperature during different reaction times (15 min.- 3 h), then petroleum ether (200 mL) was added and the dicyanovinyl- derivatives **9** precipitate and were filtrated. The crude compounds were submitted to silica gel column chromatography using mixtures of chloroform and light petroleum of increasing polarity. The fraction containing the purified product were collected and evaporated under vacuum. Recrystallization from dichloromethane/petroleum ether gave the pure compounds.

2-((2-Phenylthieno[3,2-*b*]thiophen-5-yl)methylene)malononitrile (9a): Orange solid (132 mg, 54%). M.p. 245-246°C. as an ^{1}H NMR (300 MHz, DMSO-d_6) : δ 7.41-7.53 (m, 3H, H3', *H*4'and *H*5'), 7.77 (d, 2H, J=6.9 Hz, *H*2'and *H*6'), 8.08 (s, 1H, *H*6), 8.27 (s, 1H, *H*3), 8.76 (s, 1 H, C*H*=C(CN)$_2$) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6) : δ 74.2, 114.0, 114.7, 117.1, 126.0, 129.5, 129.6, 133.1, 133.8, 136.4, 138.4, 148.4, 153.6 ppm. IR (nujol): $\bar{\upsilon}$ = 3020, 2948, 2216, 1606, 1509, 1413 cm^{-1}. MS (EI): m/z (%) = 293 (M$^+$, 100), 277 (32), 263 (30), 237 (31), 226 (56), 203 (11). HRMS (EI) : calcd. for $[C_{16}H_9N_2S_2]^+$ 293.0202 : found 293.0203.

2-((2-(4-Methoxyphenyl)thieno[3,2-*b*]thiophen-5-yl)methylene)malononitrile (9b): Red solid (134 mg, 49%). M.p. 212-213°C. ^{1}H NMR (300 MHz, DMSO-d_6) : δ 3.82 (s, 3 H, OCH_3), 7.06 (d, 2 H, J=8.8 Hz, *H*3' and *H*5'), 7.71 (d, 2 H, *J*=6.8 Hz, *H*2'and *H*6'), 7.95 (s, 1 H, *H*6), 8.24 (s, 1H, *H*3), 8.72 (s, 1 H, C*H*=C(CN)$_2$) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6) : δ 55.4, 73.4, 114.1, 114.8 , 115.6, 125.7, 127.6, 133.8, 135.8, 137.7, 148.9, 153.4, 160.4 ppm. IR (nujol): $\bar{\upsilon}$ = 3024, 2984, 2219, 1606, 1523, 1412, 1257, 1033 cm^{-1}. MS (EI): m/z (%) = 322 (M$^+$, 100), 298 (23), 209 (15). HRMS (EI) : calcd. for $[C_{17}H_{10}N_2OS_2]^+$ 322.0229 : found 322.0228.

2-((2-(4-Ethoxyphenyl)thieno[3,2-*b*]thiophen-5-yl)methylene)malononitrile (9c): Red solid (231 mg, 74%). M.p. 236-237°C. ^{1}H NMR (300 MHz, DMSO-d_6) : δ 1.35 (t, 3 H, J=7.2 Hz, OCH_2CH_3), 4.09 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.04 (d, 2 H, J=7.2 Hz, *H*3' and *H*5'), 7.68 (d, 2 H, *J*=7.2 Hz, *H*2'and *H*6'), 7.89 (s, 1 H, *H*6), 8.22 (s, 1 H, *H*6), 8.71 (s, 1 H, C*H*=C(CN)$_2$) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6) : δ 14.2, 63.2, 73.3, 113.8, 114.5, 115.2, 125.4, 127.3, 133.1, 135.5, 137.5, 148.6, 152.9, 159.5 ppm. IR (nujol): $\bar{\upsilon}$ = 3021, 2971, 2221, 1609, 1485, 1414, 1259, 1051, cm^{-1}. MS (EI): m/z (%) = 336 (M$^+$, 100), 274 (10), 209 (11). HRMS (EI) : calcd. for $[C_{18}H_{12}N_2OS_2]^+$ 336.0386 : found 336.0385.

2-((2-(4-(Diethylamino)phenyl)thieno[3,2-*b*]thiophen-5-yl)methylene)malononitrile (9d): Violet solid (154 mg, 49%). M.p. 220-221°C. ^{1}H NMR (400 MHz, DMSO-d_6) : δ 1.11 (t, 6H, J=7.0 Hz, N(CH_2CH_3)$_2$), 3.40 (q, 4H, J=7.0 Hz, N(CH_2CH_3)$_2$), 6.73 (d, 2H, J=8.8 Hz, *H*3' and *H*5'), 7.55 (d, 2H, J=8.8 Hz, *H*2'and *H*6'), 7.79 (s, 1H, *H*6), 8.17 (s, 1H, *H*3), 8.63 (s, 1 H, C*H*=C(CN)$_2$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) : δ 12.4, 43.8, 71.5, 111.6, 113.1, 115.2, 119.4, 127.5, 133.8, 134.8, 136.5, 148.5, 149.9, 152.9 ppm. IR (nujol): $\bar{\upsilon}$ = 3025, 2978, 2214, 1606, 1534, 1403, 1355 cm^{-1}. MS (EI): m/z (%) = 363 (M$^+$, 100), 165 (5). HRMS (EI) : calcd. for $[C_{20}H_{17}N_3S_2]^+$ 363.0858 : found 363.0855.

General procedure for the synthesis of arylthienothiophene thiobarbituric acid derivatives 10a-c from the corresponding formyl precursors 8 by Knoevenagel condensation with thiobarbituric acid

To a solution of 1,3-diethyl-2-thiobarbituric acid (80 mg, 0.38 mmol, 1.2 equiv) and aldehydes **8** (0.32 mmol, 1.0 equiv) in acetonitrile (20 mL) was added piperidine (1 drop). The solution was refluxed for 2 to 3 h, then cooled to 0°C. Compounds **8** precipitate, were filtrated, washed with 15 mL of diethyl ether and collected. Recrystallization from dichloromethane/petroleum ether gave the pure compounds.

1,3-Diethyl-dihydro-5-((2-phenylthieno[3,2-*b*]thiophen-5-yl)methylene)-2-thioxopyrimidine-4,6(1H,5H)-dione (10a): Red solid (33 mg, 42%). M.p. 227-228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) : δ 1.32-1.39 (m, 6H, N(CH_2CH_3)$_2$), 4.57-4.66 (m, 4H, N(CH_2CH_3)$_2$), 7.40-7.49 (m, 3H, *H*3', *H*'4'and *H*5'), 7.56 (s, 1H, *H*6), 7.71 (d, 2H, J=6.8 Hz, *H*2'and *H*6'), 8.08 (s, 1H, *H*3), 8.75 (s, 1 H, C=C*H*) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6) : δ 12.4, 12.5, 43.3, 44.0, 110.5, 115.8, 126.5, 129.3, 129.6, 133.6, 137.4, 139.3, 150.2, 155.2, 155.8, 159.8, 161.0, 178.6 ppm. IR (nujol): $\bar{\upsilon}$ = 3088, 1682, 1654, 1549, 1511, 1416, 1345 cm^{-1}. MS (EI): m/z (%) = 427 (M+1, 5), 391 (7), 364 (16), 339 (19), 310 (100), 279 (7), 192 (5), 153 (2). HRMS (EI) : calcd. for $[C_{21}H_{18}N_2O_2S_3 + H]^+$ 427.0603 : found 427.0602.

1,3-Diethyl-dihydro-5-((2-(4-methoxyphenyl)thieno[3,2-*b*]thiophen-5-yl)methylene)-2-thioxopyrimidine-4,6(1H,5H)-dione (10b) : Red solid (65 mg, 74%). M.p. 249-250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.33-1.37 (m, 6H, N(CH_2CH_3)$_2$), 3.88 (s, 3 H, OCH_3), 4.59-4.64 (m, 4H, N(CH_2CH_3)$_2$), 6.98 (d, 2 H, J=8.8 Hz, *H*3' and *H*5'), 7.44 (s, 1 H, *H*6), 7.66 (d, 2 H, *J*=8.8 Hz, *H*2'and *H*6'), 8.06 (s, 1H, *H*3), 8.74 (s, 1 H, C=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 12.4, 12.5, 43.2, 44.0, 55.5, 109.9, 114.7, 126.3, 127.9, 137.5, 138.6, 138.9, 150.1, 155.9, 156.3, 159.8, 160.9 161.1, 178.6 ppm. IR (nujol): $\bar{\upsilon}$ = 3089, 2978, 1682, 1653, 1606, 1479, 1416, 1330, 1262, 1063 cm^{-1}. MS (EI): m/z (%) = 457 (M+1, 6), 401 (11), 371 (100), 299 (56), 223 (12). HRMS (EI) : calcd. for $[C_{22}H_{20}N_2O_3S_3 + H]^+$ 457.0708 : found 457.0709.

1,3-Diethyl-dihydro-5-((2-(4-(diethylamino)phenyl)thieno[3,2-*b*]thiophen-5-yl)methylene)-2-thioxopyrimidine-4,6(1H,5H)-dione (10d): Green solid (83 mg, 82%). M.p. 238-239°C. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.25-1.28 (m, 6H, $N(CH_2CH_3)_2$), 1.31-1.39 (m, 6H, $N(CH_2CH_3)_2$), 3.46-3.51 (m, 4H, $N(CH_2CH_3)_2$), 4.57-4.66 (m, 4H, $N(CH_2CH_3)_2$), 6.44 (d, 2H, J=8.7 Hz, *H*3' and *H*5'), 7.66 (d, 2H, J=8.7 Hz, *H*2'and *H*6'), 8.04 (s, 1H, *H*6), 8.54 (s, 1H, *H*3), 8.67 (s, 1 H, C=C*H*) ppm. IR (nujol): υ = 3073, 2931, 1681, 1655, 1602, 1545, 1405, 1351, 1328 cm^{-1}. MS (EI): m/z (%) = 497 (M^+, 100). HRMS (EI) : calcd. for $[C_{25}H_{27}N_3O_2S_3]^+$ 497.1260 : found 497.1258. $C_{25}H_{27}N_3O_2S_3$ (497.70) : calcd. C 60.33, H 5.47, N 8.44, S 19.33; found C 60.06, H 5.58, N 8.16, S 19.23.

Photophysical study

All photophysical properties were analyzed with freshly prepared air equilibrated solutions at room temperature (293 K). UV/Vis absorption spectra were recorded using a Jasco V-570 spectrophotometer. Steady-state fluorescence measurements were performed on dilute solutions (optical density < 0.1) contained in standard 1 cm quartz cuvettes using a Horiba (FluoroLog or FluoroMax) spectrometer in photon-counting mode. Fully corrected emission spectra were obtained for each compound at $\lambda_{ex} = \lambda_{abs}^{max}$ with an optical density at $\lambda_{ex} \leq 0.1$ to minimize internal absorption. Fluorescence quantum yields were measured according to literature procedures,[30] using fluorescein in 0.1 M NaOH (Φ_f = 0.9), quinine bisulfate in 0.5 M H_2SO_4 (Φ_f = 0.546), Rhodamine 6G in EtOH (Φ_f =0.94) or cresyl violet in MeOH (Φ_f = 0.54). Fluorescence decays were measured in a time-correlated single photon counting (TCSPC) configuration, under excitation from selected nanoLED (370, 455 or 570 nm). The instrument response was determined by measuring the light scattered by a Ludox suspension. The lifetime values were obtained from the reconvolution fit analysis of the decay profiles; the quality of the fits was judged by the reduced χ2 value (χ2 <1.1). The reported lifetimes are within ±0.1 ns.

Two-photon absorption

TPA cross-sections (σ_2) were determined from the two-photon excited fluorescence (TPEF) cross sections ($\sigma_2\Phi_f$) and the fluorescence emission quantum yield (Φ_f). TPEF cross sections of 10-4 M chloroform solutions were measured relative to fluorescein in 0.01M aqueous NaOH for 715-980 nm, using the well-established method described by Xu and Webb and the appropriate solvent-related refractive index corrections.[31] The quadratic dependence of the fluorescence intensity on the excitation power was checked for each sample and all wavelengths, indicating that the measurements were carried out in intensity regimes where saturation or photodegradation did not occur.

Measurements were conducted using excitation sources delivering fs pulses. This is preferred in order to avoid excited state absorption during the pulse duration, a phenomenon which has been shown to lead to overestimated TPA cross-section values. To span the 700-980 nm range, a Nd:YLF-pumped Ti:sapphire oscillator was used generating 150 fs pulses at a 76 MHz rate. To span the 1000-1400 nm range, an OPO (PP-BBO) was added to the setup to collect and modulate the output signal of the Ti:sapphire oscillator. The excitation was focused into the cuvette through a microscope objective (10X, NA 0.25). The fluorescence was detected in epifluorescence mode via a dichroic mirror (Chroma 675dcxru) and a barrier filter (Chroma e650sp-2p) by a compact CCD spectrometer module BWTek BTC112E. Total fluorescence intensities were obtained by integrating the corrected emission. The experimental uncertainty of the action cross-section values determined by this method has been estimated to be ±10%.

Acknowledgements

MMMR thanks the Fundação para a Ciência e Tecnologia (Portugal) for financial support to the Portuguese NMR network (PTNMR, Bruker Avance III 400-Univ. Minho), FCT and FEDER (European Fund for Regional Development)-COMPETEQREN-EU for financial support to the research centre CQ/UM [PEst-C/QUI/UI0686/2013 (FCOMP-01-0124-FEDER-037302] and a PhD grant to M.C.R. Castro (SFRH/BD/78037/2011). M.B.-D. acknowledges financial support from the Conseil Régional d'Aquitaine (Chair of Excellence to M.B.-D. and fellowship to V.H.). This study has been carried out with financial support from the French State, managed by the French National Research Agency (ANR) in the frame of "the Investments for the future" Programme IdEx Bordeaux – LAPHIA (ANR-10-IDEX-03-02).

Keywords: Aldehydes • Suzuki coupling • push-pull thienothiophenes • Fluorescence •Two-photon absorption

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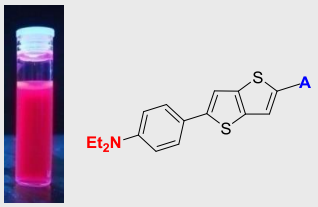
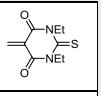


A	CHO		
λ_{em}	543 nm	652 nm	710 nm
$\sigma_2\Phi$	240 GM	510 GM	150 GM

M. Manuela M. Raposo, Cyril Herbivo, Vincent Hugues, Guillaume Clermont, M. Cidália R. Castro, Alain Comel, Mireille Blanchard-Desce**

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Synthesis, fluorescence and two-photon absorption properties of novel push-pull 5-aryl[3,2-*b*]thienothiophene derivatives

Fusion makes it better! Push-pull compounds built from a thienothiophene π-connector were synthesized. Due to improved rigidity and conjugation, derivatives having strong donor end-groups were shown to combine strong and tunable fluorescence as well as large two-photon absorption in the NIR region. These series of dyes provides a route towards bright fluorophores spanning the visible region to the NIR.