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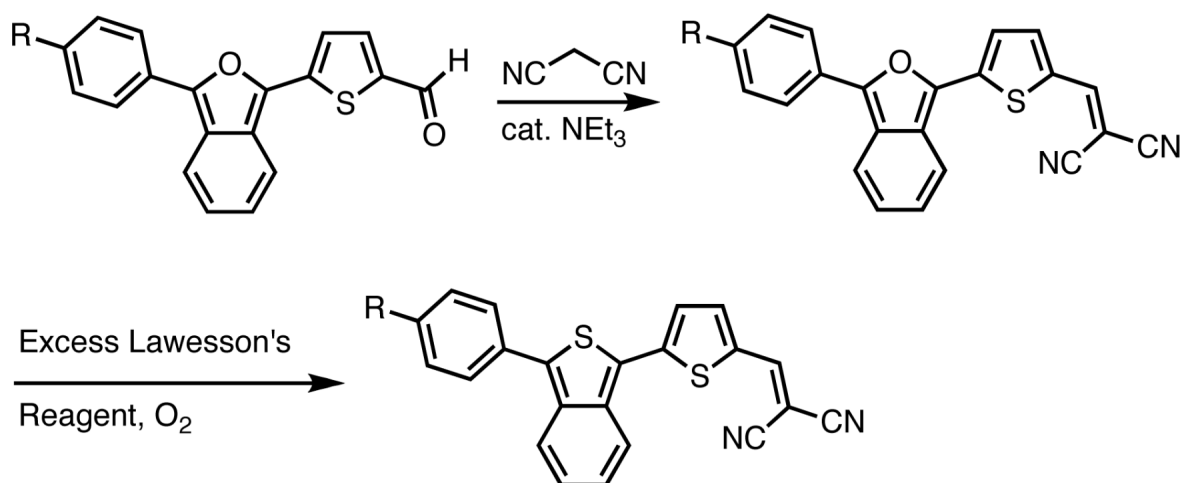
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Near-Infrared Fluorophores Containing Benzo[*c*]heterocycle Subunits

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Abstract



The syntheses and spectroscopic properties of eight new push-pull type near-infrared fluorophores that contain either isobenzofuran or isothianaphthene subunits are presented. The isobenzofuran dyes demonstrate significantly red-shifted absorption from their isothianaphthene counterparts, which is attributed to isobenzofuran's more potent pro-quinoidal character.

In vivo near-infrared (NIR) fluorescence imaging is rapidly emerging as a powerful diagnostic method.¹ In the NIR region (650–900nm) biological chromophores exhibit low absorption and autofluorescence² thus allowing photons to pass through the tissue and rendering this technique relatively non-invasive. With applications such as vascular mapping of the heart³ and brain⁴ and visualization of various pathologies including tumors⁵, atherosclerosis⁶, and β -amyloid plaques⁷, the demand for new NIR fluorescent contrast agents is ever increasing.

Our group recently reported the synthesis and *in vivo* imaging properties of NIAD-4 (**1**), NIM-1 (**2**), and NIM-2 (**3**), all donor-acceptor type dyes.^{7a,8} In the case of **2** and **3**, it was found that the incorporation of benzo[*c*]heterocycle isothianaphthene (ITN) into the conjugated bridge red-shifted both the absorption and emission substantially. Herein we explore the use of benzo[*c*]heterocycle isobenzofuran (IBF) in place of ITN as a molecular component in this class of dyes.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>

Isothianaphthene has a relatively long history as a component in functional materials, with examples in fluorophores,⁹ OLEDs,¹⁰ photovoltaics,¹¹ and low band-gap polymers, of which polyisothianaphthene (PITN)¹² is the progenitor. The smaller band-gap of these ITN containing materials over similar thiophene containing materials is a result of the increased contribution of the quinoid resonance structure (Figure 2) due to the stabilization achieved by aromatization of the benzene ring.¹³

In contrast, only a few examples¹⁴ of functional materials containing isobenzofuran are reported in the literature, presumably due its reduced stability.¹⁵ For this reason, we predicted that IBF would prove even more pro-quinoidal and that its incorporation into donor-acceptor dyes would further reduce the band-gap of these materials.

In order to test this principal, we synthesized a series of IBF and ITN dyes similar to NIAD-4 (Scheme 1). Four different electron donating (R) groups, H-, MeO-, HO-, and Me₂N-, were incorporated in order to span a range of wavelengths. Appropriately substituted aryl-lactones **5a-d** were either purchased or synthesized via acid mediated condensation¹⁶ of 2-carboxybenzaldehyde and substituted benzenes. In the case of the phenol group (R = OH), TiPS protection was employed. Initially, the IBF framework was constructed with a free 5 position on the thiophene, which was subsequently lithiated and the formylated with DMF. However, these unsubstituted intermediate compounds proved relatively difficult to isolate and purify, resulting in poor yields for the formylation.

Exploiting the acetal protected aldehydes allowed us to bypass these troublesome intermediates. Protected aldehydes **7a-d** were produced in one step by reaction of the lactones with the lithio-derivative of **6**¹⁷ followed by dehydration with acetic anhydride and deprotection with aqueous acetic acid. Knoevenagel condensation of the aldehydes with malonitrile installed the dicyanomethylene electron withdrawing group to afford dyes **8a-d** in moderate yields. Deprotection of **8d** was achieved under acidic conditions as fluoride was found to revert the dicyanovinyl group to the aldehyde.

In order to access the ITN counterparts to dyes **10a-d**, we decided to explore methods by which the IBF dyes could be converted directly. It was found that such a transformation could be accomplished with good yields, in one pot, using a 5-10 fold excess of Lawesson's reagent in the presence of air or anhydrous oxygen. The precise role of the oxygen is unknown at this time. In the case of **8c**, the dicyanovinyl group was cleaved during the reaction, presumably to a thioaldehyde, and thus treatment with excess malonitrile and base was necessary to obtain **10c**. **10d** was deprotected under acid conditions in similar manner to **8d**.

The spectroscopic properties of **8a-c**, **10a-c**, **11** and **12** are listed in Table 1. In all cases, the IBF dyes exhibited markedly red-shifted absorption from the corresponding ITN moieties, thus demonstrating the narrower band-gaps of the IBF compounds. The degree of this effect increases as the efficacy of the electron donating group increases. The degree of red-shift in the emission proved only modest, especially in the case of **8c** and **10c**, indicating that perhaps the quinoid resonance structure stabilization does not factor as heavily into the excited state energies of the these molecules.

In conclusion, we have demonstrated the greater effectiveness of isobenzofuran over isothianaphthene as a red-shifting component in donor-acceptor type dyes, and effect attributable to the great pro-quinoidal nature of IBF. Currently, these compounds are being screened as NIR contrast agents for biomedical applications, and future investigations will explore the use alternate electron withdrawing groups and the incorporation of different heterocycles into this fascinating class of compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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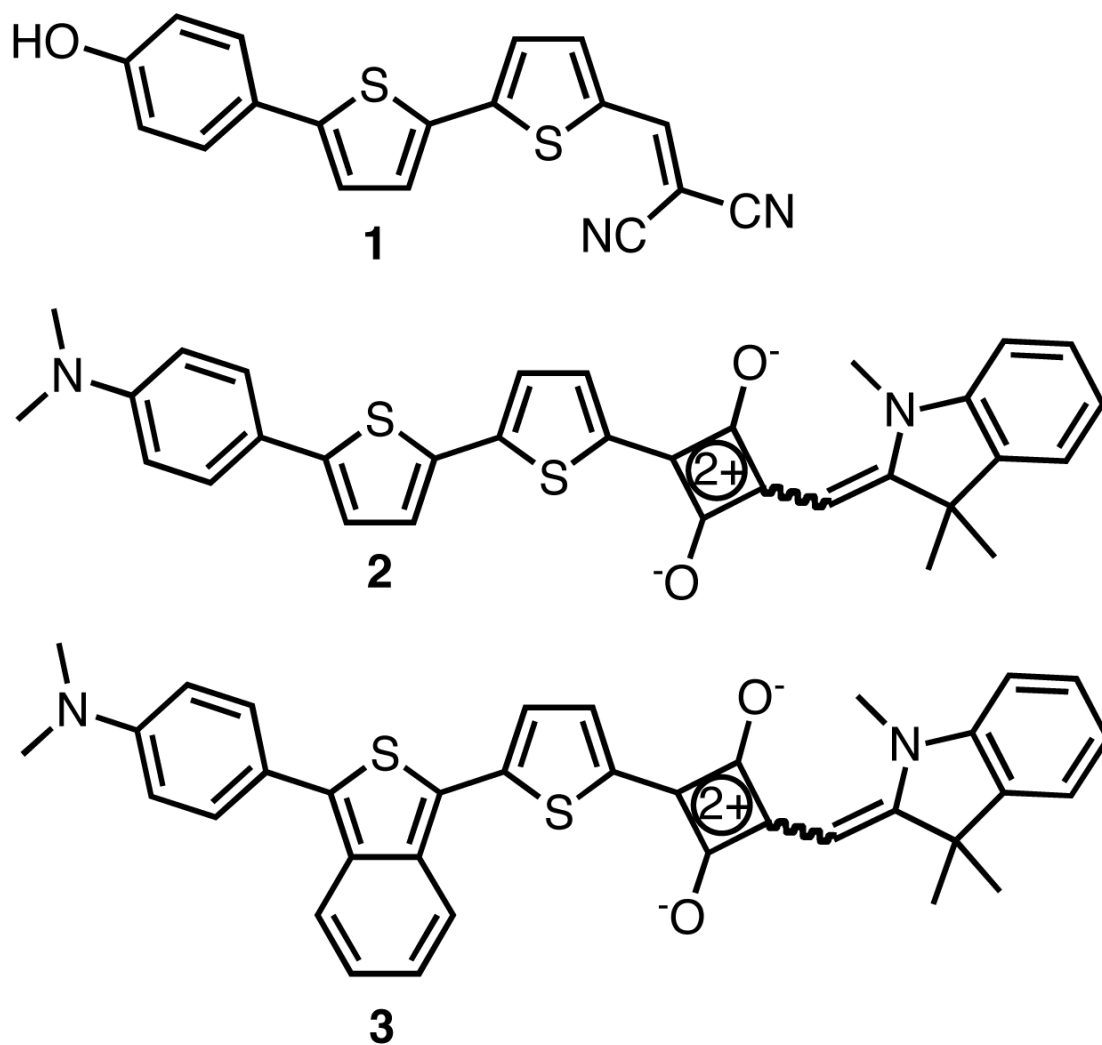


Figure 1.
Structures of NIAD-4, NIM-1, and NIM-2

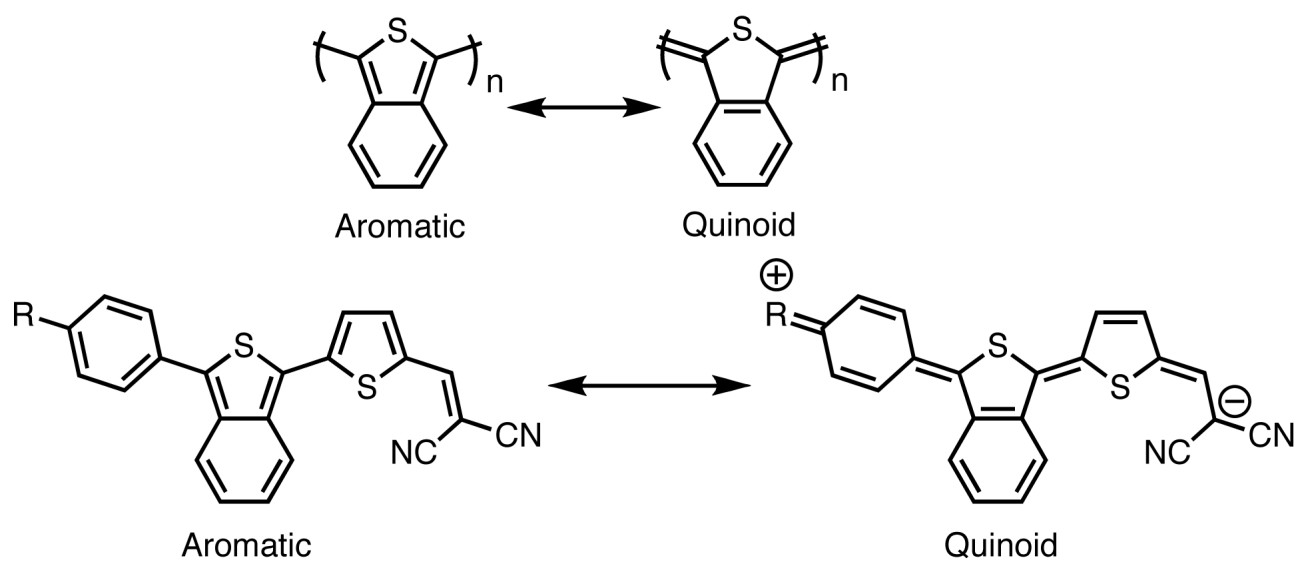
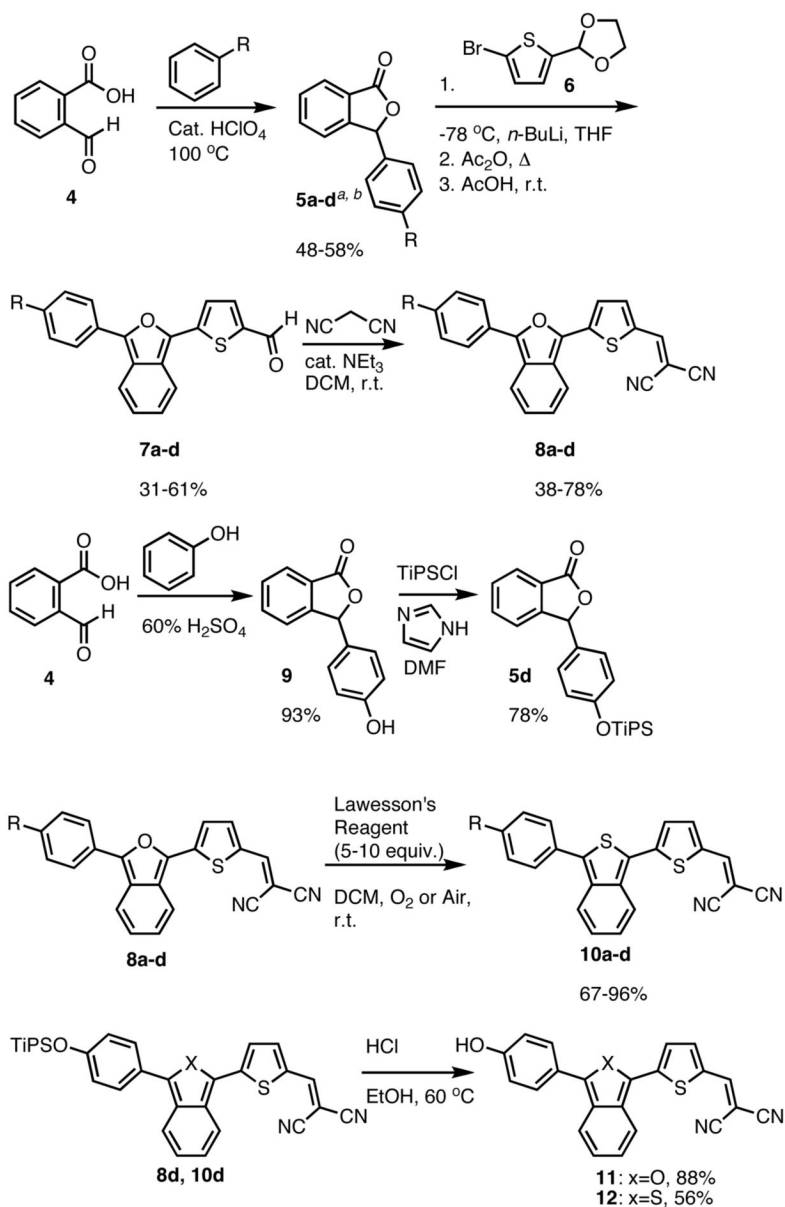
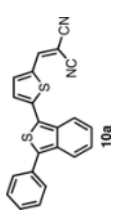


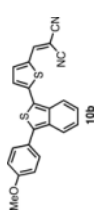
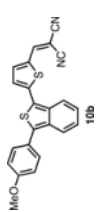
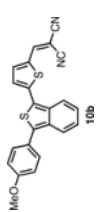
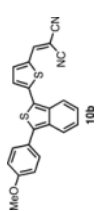
Figure 2.
The aromatic and quinoid resonance structures of PITN and ITN donor-acceptor dyes

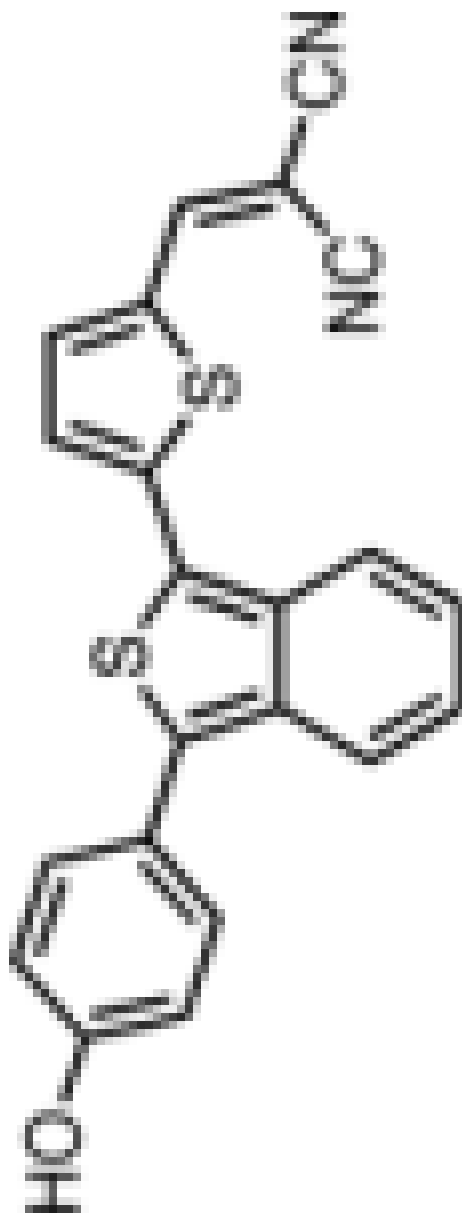


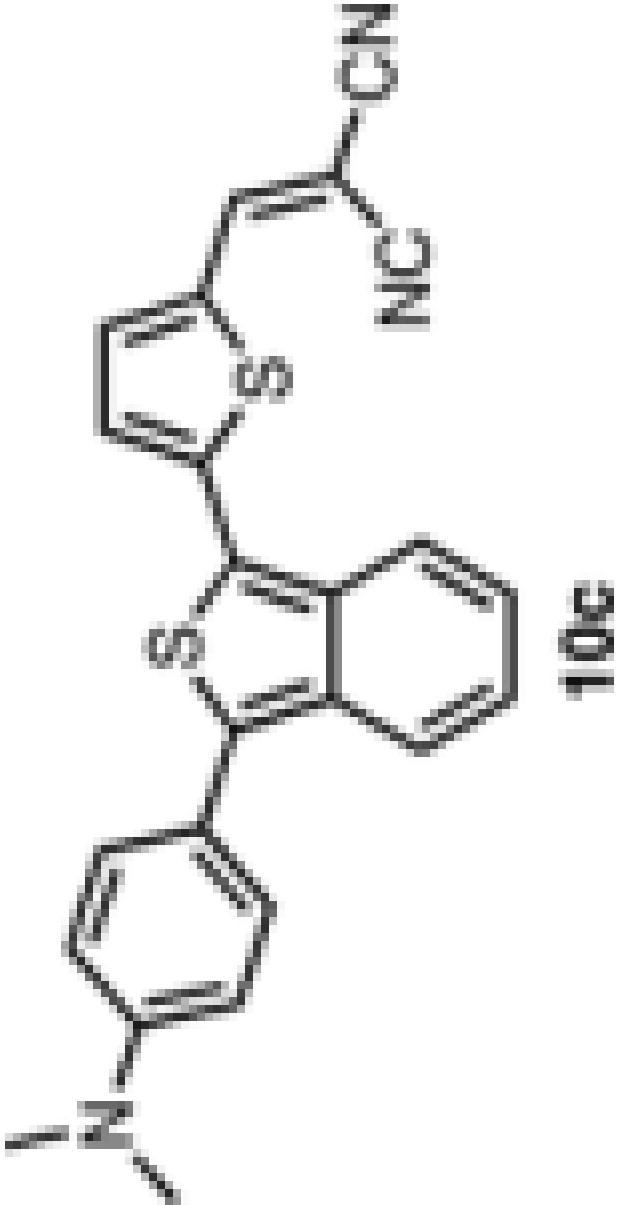
^a a: R= H-, b: R= MeO-, c: R= Me₂N-, d: R= TiPSO-. ^b **5a** is commercially available, **5d** synthesized as above.

Scheme 1.
Synthesis of IBF and ITN Dyes

em. (nm)	Φ^b	ITN Dye	λ_{max} abs. (nm)	λ_{max} em. (nm)	Φ^b
	.077 ^c		525 ^c	637 ^c	.061 ^c
	.075 ^d		544 ^d	629 ^d	.079 ^d

em. (nm)	Φ^b	ITN Dye	λ_{max} abs. (nm)	λ_{max} em. (nm)	Φ^b
.078 ^c	.046 ^c		537 ^c	672 ^c	.046 ^c
.16 ^d	.099 ^d		559 ^d	663 ^d	.099 ^d
.049 ^c	.023 ^c		545 ^c	684 ^c	.023 ^c
.12 ^d	.071 ^d		559 ^d	667 ^d	.071 ^d

**12**

em. (nm)	Φ^b	ITN Dye	λ_{max} abs. (nm)	λ_{max} em. (nm)	Φ^b
.0055 ^c			579 ^c	785 ^c	.0015 ^c
.046 ^d			604 ^d	743 ^d	.021 ^d