Effects of Conformational Restriction of 2-Amino-3-benzoylthiophenes on A₁ Adenosine Receptor Modulation

Luigi Aurelio,[†,‖] Celine Valant,[‡,‖] Bernard L. Flynn,[†] Patrick M. Sexton,[‡] Jonathan M. White,[§] Arthur Christopoulos,*,[‡] and Peter J. Scammells*,[†]

[†]*Medicinal Chemistry and Drug Action, and* [‡]*Drug Discovery Biology and Department of Pharmacology, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville VIC 3052, Australia, and* [§]*School of Chemistry and the Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, VIC 3010, Australia.* [‖]*These authors contributed equally to this work.*

2-Amino-3-benzoylthiophenes (2A3BTs) have been widely reported to act as allosteric enhancers (AEs) at the A₁ adenosine receptor (A₁AR). Herein we describe the synthesis of a series of 1-aminoindeno[1,2-*c*]-thiophen-8-ones and a series of (2-aminoindeno[2,1-*b*]thiophen-3-yl)(phenyl)methanones as conformationally rigid analogues of the 2A3BTs. These compounds were screened using a functional assay of A₁AR-mediated phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) in intact Chinese hamster ovary (CHO) cells to identify both potential agonistic effects as well as the ability to allosterically modulate the activity of the orthosteric agonist, N^6-(*R*-phenylisopropyl)adenosine (R-PIA). All of the 1-aminoindeno[1,2-*c*]thiophen-8-ones (**14a−c** and **17a−f**) proved either to be inactive or behaved as antagonists in the functional assay. However, the (2-aminoindeno[2,1-*b*]thiophen-3-yl)(phenyl)methanones with *para*-chloro substitution (compounds **25b**, **25d**, and **25f**) did significantly augment the R-PIA response, indicating a positive allosteric effect.

Introduction

The A₁AR is one of four subtypes of G protein-coupled receptor (GPCR[a]) that mediate many of the actions of the purine nucleoside, adenosine, via coupling to multiple intracellular pathways, including the inhibition of adenylate cyclase and the phosphorylation ERK1/2.[1,2] It is well documented that there are numerous therapeutic applications for selective adenosine receptor ligands, particularly in the treatment of cardiovascular, inflammatory, and neurodegenerative diseases.[3] To date, a number of adenosine ligands have been reported as potent and relatively selective orthosteric agonists,[4] yet they have not been pursued as therapeutic agents due to the associated side effects of nondiscriminately activating multiple adenosine receptor subtypes and/or their tendency to cause receptor desensitization upon prolonged use. An alternative approach toward selective A₁AR activation that has been pursued is one of allosteric modulation; ligands that can bind to the A₁AR at an allosteric site and augment the action of endogenous adenosine are highly desirable because they can theoretically achieve high selectivity via receptor subtype-, tissue-, and event-specific mechanisms.[5]

Bruns et al.[6,7] discovered that 2A3BTs, typified by the benchmark compound, PD 81,723 (**1**) (Figure 1), acted as A₁AR-selective AEs, although higher concentrations of
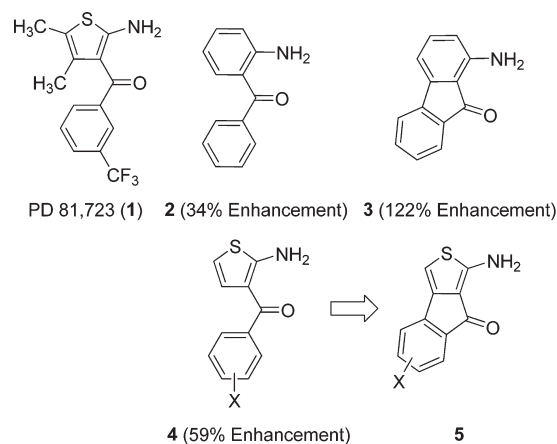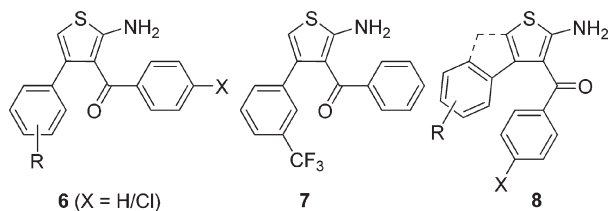

Figure 1. 2A3BT allosteric enhancers reported by Bruns and co-workers.[6,7]

these compounds led to subsequent inhibition of receptor responsiveness.[7] In that study, the 2-amino and 3-keto groups were revealed as important functionalities and that their omission or derivatization resulted in loss of activity. Interestingly, the replacement of the thiophene with a benzene ring retained activity, with 2-aminobenzophenone **2** showing a little over half the degree of enhancement compared to the 2-amino-3-benzoylthiophene (general structure **4**, X = H) at 100 μM when assayed using a radioligand dissociation kinetic paradigm.[7] This activity was improved by conformationally constraining the 2-aminobenzophenone **2**, and therefore 1-amino-fluoren-9-one **3** was approximately three times as active as 2-aminobenzophenone **2** at 100 μM. Collectively, these results implied that a planar conformation of the aromatic rings of

*To whom correspondence should be addressed. For A.C.: phone, +61 (0)3 9903 9067; E-mail, Arthur.Christopoulos@monash.edu. For P.J.S.: phone, +61 (0)3 9903 9542; fax, 61 3 9903 9582; E-mail, Peter.Scammells@monash.edu.

[a] Abbreviations: AE, allosteric enhancer; AR, adenosine receptor; CHO, Chinese hamster ovary; 2A3BT, 2-amino-3-benzoylthiophene; GPCR, G protein-coupled receptor; ERK1/2, extracellular signal-regulated kinases 1 and 2; DMEM, Dulbecco's Modified Eagle Medium; FBS, fetal bovine serum; R-PIA, N^6-(*R*-phenylisopropyl)adenosine.

Figure 2. 4-Phenyl substituted 2A3BT allosteric enhancers and proposed conformationally restricted analogues.

the 2-aminobenzophenone **2** was preferred. Therefore, one aim of the current study was to synthesize and evaluate a corresponding series of conformationally restricted 2A3BTs (Figure 1, general structure **5**) to determine if fixing the thiophene and benzoyl group in a planar conformation imparts similar improvements in AE activity.

More recently, we also found that certain 4-phenyl substituents on the 2-amino-3-benzoylthiophene scaffold promoted allosteric activity (Figure 2, general structure **6**), with compound **7** producing a strong functional potentiation of orthosteric agonist activity in an assay of A_1AR-mediated ERK1/2 phosphorylation.[8] Thus, a second aim of the current study was to assess the activity of conformationally restricted analogues of **7** in which the 4-phenyl group is effectively locked in a coplanar conformation relative to the thiophene ring via the incorporation of a methylene tether to the 5-position (Figure 2, general structure **8**).

Results and Discussion

Chemistry. To the best of our knowledge, there is only one reference describing the synthesis of 1-amino-8*H*-indeno-[1,2-*c*]thiophen-8-one, in a patent by Moorman et al., for the treatment of neuropathic pain.[9] The synthetic route utilized in that patent was also adopted by us in the synthesis of our analogues, with slight modification (Scheme 1). The synthesis began with the 3-ethoxycarbonyl thiophenes **10**, which were synthesized by the classical two-step procedure,

first forming the Knoevenagel intermediate and then cyclizing with elemental sulfur in the presence of base.[9] We found that forming the Knoevenagel intermediate under Lewis acid-mediated condensation with titanium(IV) chloride[10] provided near-quantitative yields of olefin (not shown). The olefin was then cyclized to the thiophene **10** at room temperature in high yield, which was then treated with phthalic anhydride to protect the 2-amino group. Phthalimide was considered to be a feasible protecting group for the synthesis of the 1-amino-8*H*-indeno[1,2-*c*]thiophen-8-one analogues for several reasons. First, the phthalimide is not entirely removed in the saponification step and, although it is ring-opened in this step, it is subsequently ring-closed during the chlorination step. Second, both valences of the 2-amino group are removed and associated complications with the cyclization step are eliminated. Third, phthalimide tolerates the acidic condition of the Friedel−Crafts acylation. The crucial step in the synthesis involved the cyclization of the intermediate acid chloride of **12** and has been shown to be a poor-to-moderate yielding step, as was also the case in our hands.[9] We found that replacement of thionyl chloride with oxalyl chloride and the use of a catalytic amount of DMF to form the corresponding acid chloride provided quantitative yields of indenothiophenes **13** after the Friedel−Crafts acylation. The phthalimide was removed by hydrazinolysis to afford the initial conformationally restricted targets **14a−c**. Compounds **14a** and **14b** were elaborated further toward the corresponding 5-aryl substituted derivatives. This initially involved acetyl protection of the 2-amino group since the phthalimide created problems in the subsequent Suzuki cross-coupling reactions due to ring-opening under the basic conditions. The acetylated derivatives **15a** and **15b** were subsequently brominated with NBS/AcOH but were found to be quite sluggish in the Suzuki cross-coupling reactions. Alternatively, iodination of **15a** and **15b** with $AgNO_3/I_2$[11] provided the corresponding iodides **16a** and **16b**. The iodide **16a** was far superior to the bromide in cross-coupling reactions, which were quantitatively converted within 30 min.
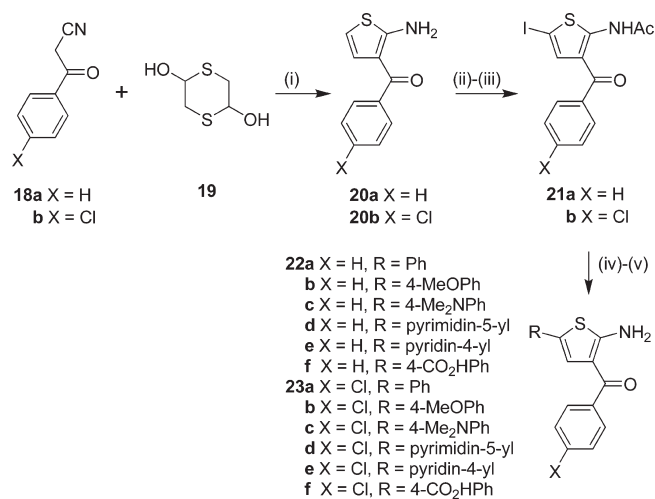
Scheme 1[a]
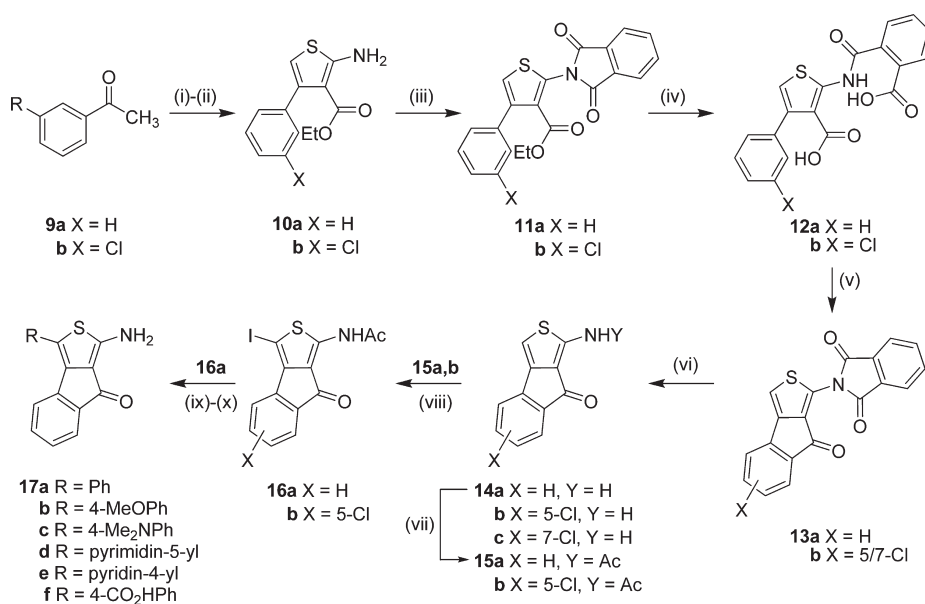
[a](i) TiCl4, pyridine, EtOCOCH2CN; (ii) S8, Et2NH, THF; (iii) phthalic anhydride, AcOH reflux; (iv) NaOH, H2O, EtOH; (v) Cl(CO)2Cl, CH2Cl2, cat. DMF then AlCl3, CH2Cl2 reflux; (vi) N2H4, DMF/dioxane; (vii) Ac2O, AcOH reflux; (viii) I2, AgNO3, DMSO/CH3CN; (ix) cat Pd[PPh3]2Cl2, 2M K3PO4, DMF, boronic acid; (x) NaOH, EtOH MW.

Several attempts to remove the acetyl group by classical methods such as basic, acidic, and nucleophilic conditions proved unfruitful due to the insolubility of these derivatives. Ultimately, a suspension of the intermediates in absolute

Scheme 2[a]

[a] (i) Et$_2$NH, EtOH; (ii) Ac$_2$O, reflux; (iii) I$_2$, AgNO$_3$, CH$_3$CN, DMF; (iv) cat. Pd[PPh$_3$]$_2$Cl$_2$, 2M K$_3$PO$_4$, DMF, boronic acid; (v) NaOH, EtOH, H$_2$O.

Scheme 3[a]
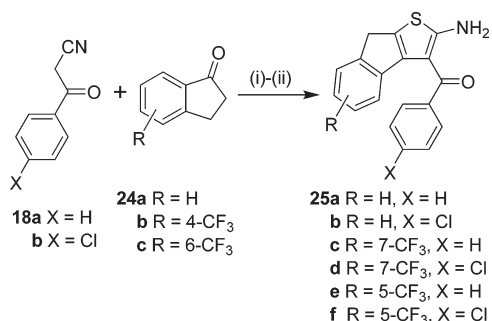
[a] (i) TiCl$_4$, pyridine; (ii) S$_8$, Et$_2$NH, THF, or (i) β-ala, PhCO$_2$H 110−120 °C; (ii) S$_8$, morpholine, EtOH.

ethanol and sodium hydroxide pellets and microwave irradiation removed the acetyl group. This method was advantageous since, after the reaction, the final compounds **17a−f** were soluble in the ethanolic sodium hydroxide mixture. By filtering this mixture, the insoluble impurities were removed and the 1-aminoindenothiophen-8-ones **17a−f** were recovered by acidifying with acetic acid. These compounds were triturated with boiling ethanol and in most cases provided final compounds **17a−f** in a pure state; otherwise, recrystallization from DMF or DMF/MeOH provided pure compound. In the case of cross-coupled products of **16b**, removal of the acetyl group resulted in intractable mixtures. Even replacement of the acetyl group with Boc protection resulted in mixtures when removed under the acidic conditions. This result was not further investigated, and the pursuit of compounds of this type was abandoned.

The corresponding "unconstrained" thiophenes, which possess a 3-benzoyl group and no substituent in the 4-position, were prepared using the approach outlined in Scheme 2. Briefly, this involved use of the Gewald synthesis to construct the 2A3BT **20a** and **20b**,[12] which we subsequently acetyl protected and iodinated under standard conditions to afford the corresponding 5-iodothiophenes **21a** and **21b**. Aryl substituents were subsequently incorporated in the 5-position via Suzuki coupling with the appropriate boronic acid. These substituents were identical to those employed previously in the corresponding conformationally restricted series (compounds **17a−f**). Finally, a base mediated cleavage of the acetyl protecting group afforded the desired target compounds **22a−f** and **23a−f**.

The final series of compounds, in which the 4-phenyl is effectively locked in a coplanar conformation relative to the thiophene ring, were prepared as described in Scheme 3. Once again, a Gewald synthesis was used to prepare the thiophene ring. This involved a reaction of a benzoylnitrile **18** with an appropriately substituted indanone **24**. Although these reactions were very low yielding, sufficient quantities of the desired product could be isolated for pharmacological evaluation in one step.

An X-ray structure of the (2-aminoindeno[2,1-b]thiophen-3-yl)(phenyl)methanone **25c** was obtained (Figure 3). This structure highlights the expected planar nature of the molecule and also supports Bruns' original suggestion[7] that a
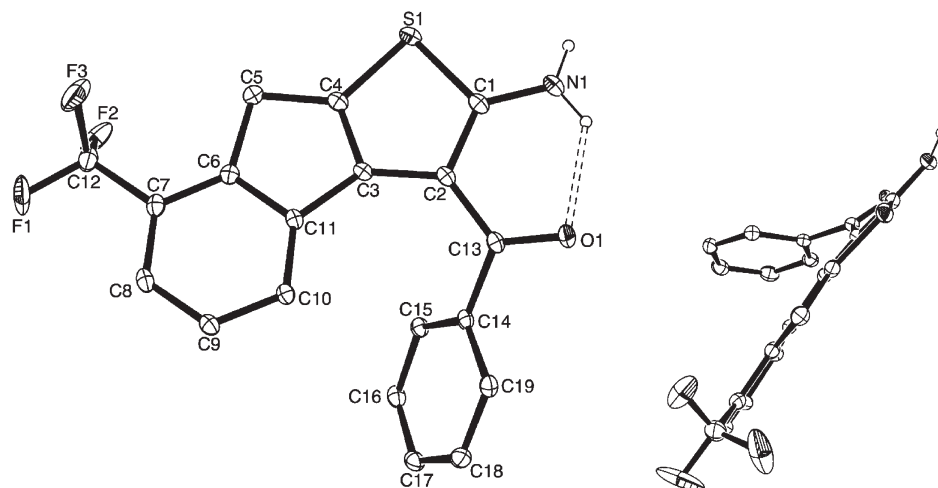
Figure 3. Ortep diagrams of the X-ray crystal structure of (2-amino-7-(trifluoromethyl)-8H-indeno[2,1-b]thiophen-3-yl)(phenyl)methanone (**25c**).
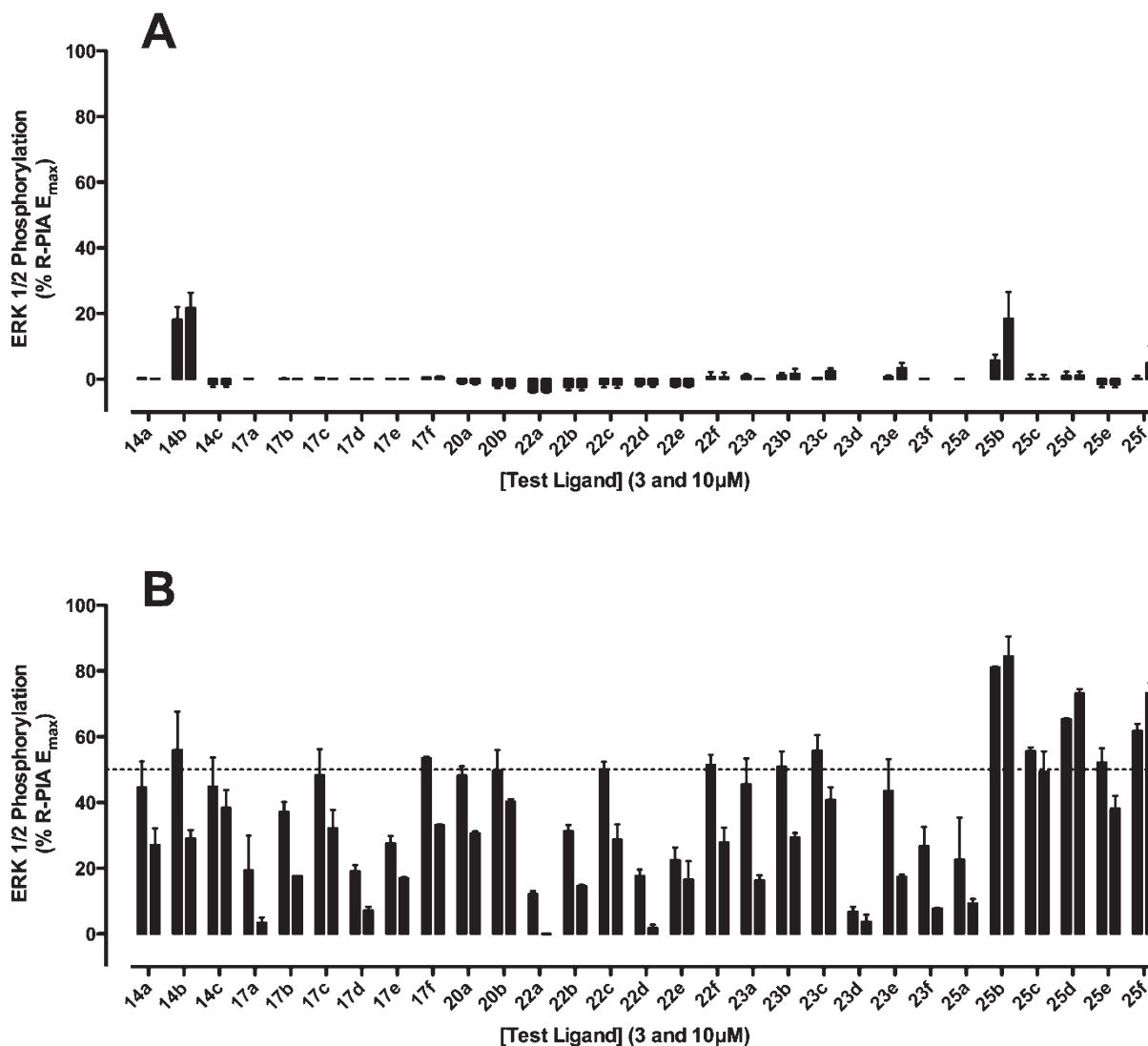
Figure 4. Effect of two different concentrations (3 μM, left bar; 10 μM, right bar) of test ligands on A_1AR-mediated stimulation of ERK1/2 phosphorylation in intact CHO FlpIn cells, in the absence (A) or in the presence (B) of an EC_{50} concentration (0.3 nM) of R-PIA (determined on the same day as each assay); dashed line denotes 50% response level. 0% is defined as basal ERK1/2 phosphorylation in the absence of R-PIA, whereas 100% is defined as the maximal response to a saturating concentration (100 nM) of R-PIA. Data represent the mean ± standard deviation of two experiments conducted in triplicate.

hydrogen bond between the 2-amino group and the ketone may create an additional ring coplanar with the thiophene ring. The "resonance-enhanced" intramolecular hydrogen bond is characterized by the parameters; N1−H 0.87 Å, N1−H···O1 130.1°, and N1···O1 2.682(2) Å, the second hydrogen of the amino group also forms an intermolecular, hydrogen bond with O1; N1−H 0.88 Å, N1−H···O1(−x+3/2, y−1/2, −z+1/2) 151.5°, N1···O1(−x+3/2, y−1/2, −z+1/2) 2.800 Å. Delocalization of the amino group lone pair onto the ketone carbonyl, which is enhanced due to the intramolecular hydrogen bond between O1 and N1, is clearly apparent from inspection of the relevant bond distances; thus the C13−O1 bond distance 1.248(2) Å is significantly longer than a typical ketone C=O distance of 1.20 Å, the C13−C2 bond distance 1.433(2) Å has partial double-bond character, the C1−C2 distance 1.410(2) Å is significantly longer than the second thiophene double bond (C3−C4), which is 1.359(2) Å, and the C1−N1 distance 1.359(2) Å has some double-bond character. There is significant twisting of the phenyl group defined by atoms C14−C19 from coplanarity with the carbonyl group, a dihedral angle C2−C13−C14−C15 42.9(2)° which minimizes steric interactions with the indane ring.

Biological Activity. To assess the biological activity of the compounds, we utilized a functional assay of A_1AR-mediated phosphorylation of ERK1/2 in intact CHO cells.[8] For each compound, two concentrations (3 and 10 μM) were initially tested alone (Figure 4A), to assess potential for direct agonist effects, and against an EC_{50} concentration of the orthosteric agonist, R-PIA (Figure 4B), to assess the potential for enhancement or inhibition of orthosteric agonist-mediated function. With the exception of **14b** and **25b** (each yielding approximately 20% of the maximum R-PIA response; Figure 4A), none of the compounds displayed any substantial ability to activate the receptor on their own, as evidenced by the fact that compound-mediated phosphorylation of ERK1/2 was within ±5% of the maximum response mediated by R-PIA. When tested in the presence of an EC_{50} concentration of R-PIA, a number of the compounds were found to be inactive in modulating the response of the orthosteric agonist when

Table 1. Effect of Test Compounds on A_1AR-Mediated Stimulation of ERK1/2 Phosphorylation in Intact CHO FlpIn Cells in the Presence of an EC_{50} Concentration of R-PIA[a]

Structure	No.	R	X	Activity[§] 3 μM	Activity[§] 10 μM
(R–thiophene–NH₂ / X–indenone core)	14a	H	H	45 ± 8	27 ± 5
	14b	H	5-Cl	56 ± 11	29 ± 3
	14c	H	7-Cl	45 ± 9	38 ± 4
	17a	Ph	H	19 ± 10	3 ± 2
	17b	4-MeOPh	H	37 ± 3	18 ± 1
	17c	4-Me₂NPh	H	48 ± 8	32 ± 5
	17d	pyrimidin-5-yl	H	19 ± 2	7 ± 1
	17e	pyridine-4-yl	H	28 ± 2	17 ± 1
	17f	4-HO₂CPh	H	19 ± 2	7 ± 1
(R–thiophene–NH₂ benzoyl core)	20a	H	H	48 ± 3	30 ± 1
	20b	H	Cl	50 ± 6	40 ± 1
	22a	Ph	H	12 ± 1	1 ± 1
	22b	4-MeOPh	H	31 ± 2	14 ± 1
	22c	4-Me₂NPh	H	50 ± 2	29 ± 5
	22d	pyrimidin-5-yl	H	18 ± 2	2 ± 1
	22e	pyridine-4-yl	H	23 ± 4	17 ± 6
	22f	4-HO₂CPh	H	51 ± 3	27 ± 5
	23a	Ph	Cl	46 ± 8	16 ± 2
	23b	4-MeOPh	Cl	51 ± 5	29 ± 1
	23c	4-Me₂NPh	Cl	56 ± 5	41 ± 4
	23d	pyrimidin-5-yl	Cl	7 ± 2	4 ± 2
	23e	pyridine-4-yl	Cl	44 ± 10	17 ± 1
	23f	4-HO₂CPh	Cl	27 ± 6	29 ± 1
(R–indeno-thiophene–NH₂ / X core)	25a	H	H	23 ± 13	9 ± 1
	25b	H	Cl	81 ± 1	84 ± 6
	25c	7-CF₃	H	56 ± 1	49 ± 6
	25d	7-CF₃	Cl	65 ± 1	73 ± 1
	25e	5-CF₃	H	52 ± 4	38 ± 4
	25f	5-CF₃	Cl	62 ± 2	73 ± 3

[a]§Effect of two different concentrations (3 and 10 μM) of the test compound on A_1AR-mediated stimulation of ERK1/2 phosphorylation in intact CHO FlpIn cells, in the presence of an EC_{50} concentration (0.3 nM) of R-PIA (determined on the same day as each assay). Data represent the mean ± standard deviation of two experiments conducted in triplicate. 0% is defined as basal ERK1/2 phosphorylation in the absence of R-PIA, whereas 100% is defined as the maximal response to a saturating concentration (100 nM) of R-PIA

utilized at 3 μM; this is evidenced in Table 1 by those compounds whose standard deviation includes 50% (the response mediated by R-PIA alone). With the exception of **25c**, all compounds displayed some activity (either inhibitory or enhancing) when tested at 10 μM (Table 1; Figure 4B). For compounds, **17a**, **17b**, **17d**, **17e**, **22a**, **22d**, **22e**, **23f**, and **25a**, inhibition of orthosteric agonist-mediated ERK1/2 phosphorylation was noted in the presence of both tested concentrations, whereas potentiation of the R-PIA-mediated response was noted with **25b**, **25d**, and **25f** (Figure 4; Table 1).

To further assess this finding, we constructed complete R-PIA concentration−response curves in the absence or presence of increasing concentrations four of the compounds that appeared to have the most striking effects, i.e., **17d**, **22a**, **23d**, and **25b**. As shown in Figure 5, the inhibitory effect of **17d**, **22a**, or **23d** on R-PIA-mediated ERK1/2 phosphorylation was consistent with simple competitive (orthosteric) antagonism, and application of a competitive model of interaction yielded the following pA_2 values: **17d**, 6.19 ± 0.06; **22a**, 6.68 ± 10; **23d**, 6.84 ± 0.08 ($n = 3$). In contrast, **25b** behaved as expected of an allosteric enhancer, yielding a concentration-dependent increase in the potency of the orthosteric agonist. Application of an operational model of allosterism[5] to the data yielded a pK_B estimate of the affinity of the compound for the allosteric site of 6.01 ± 0.16, and an estimate of the positive cooperativity of the interaction of $\log \alpha\beta = 0.44 \pm 0.07$ (i.e., $\alpha\beta = 2.7$); $n = 3$.

Conclusions

The major finding of this study was that, in general, conformational restriction in which the 3-benzoyl group of 2A3BTs is tethered to the 4-position (general structure **5**), locking the benzoyl and thiophene ring in a planar conformation, does not lead to improved allosteric potentiation of agonist function at the A_1AR. All of the 1-aminoindeno[1,2-*c*]thiophen-8-ones (**14a−c** and **17a−f**) that we prepared as conformationally restricted analogues of the corresponding 2A3BTs proved either to be inactive or behaved as antagonists in a functional assay of A_1AR-mediated phosphorylation of ERK1/2 in intact CHO cells. Even the corresponding 2A3BTs (**20a−b**, **22a−f**, and **23a−f**) appeared to exhibit this behavior. Given that compounds **20a** and **22a** were previously reported to be allosteric enhancers based on their ability to slow the dissociation of [³H] N^6-cyclohexyladenosine at 100 μM concentrations,[7] our findings suggest that the ability of an allosteric ligand to stabilize a pre-equilibrated agonist-receptor-G protein complex in membrane preparations is not necessarily predictive of a positive allosteric effect in whole cell functional assays.

In contrast, conformational restriction in which a 4-phenyl substituent is effectively constrained in a planar conformation relative to the thiophene ring via a methylene tether to the 5-position (general structure **8**) gave mixed results. Three members of the (2-aminoindeno[2,1-*b*]thiophen-3-yl)(phenyl)-methanone series (compounds **25b**, **25d**, and **25f**) did significantly augment the R-PIA response, indicating a positive allosteric effect. Given that the other three members of this series (compounds **25a**, **25c**, and **25e**) did not show any evidence of allosteric activity and that the only difference between the two subsets of compounds was the absence or presence of a *para*-chloro substituent, this result highlights the delicate balance between allosteric enhancement and antagonism (or lack of activity) in terms of A_1AR modulator structure−activity relationships. The presence of the *para*-chloro would not be expected to have a major influence on the conformation of **25b**, **25d**, and **25f**, and its marked effect on allosteric activity presumably results from favorable interactions with the allosteric binding site. Nonetheless, evaluation of the effects of (2-amino-8*H*-indeno[2,1-*b*]thiophen-3-yl)(4-chlorophenyl)methanone (**25b**) as a positive allosteric modulator of R-PIA revealed that the affinity of this modulator and its cooperativity with the agonist was comparable with the best of the 4-phenyl substituted 2A3BTs that we reported recently.[8] For instance, in that series, (2-amino-4-(3-(trifluoromethyl)phenyl)thiophen-3-yl)(phenyl)methanone (**7**, Figure 2) had an estimated pK_B of 6.37 ± 0.16 and $\log \alpha\beta$ of 0.38 ± 0.07 (i.e., $\alpha\beta = 2.4$-fold positive cooperativity) for the stimulation of ERK1/2 phosphorylation.

In summary, we have found that certain 2A3BTs, previously thought to be allosteric enhancers, as well as the corresponding conformationally restricted (1-aminoindeno[1,2-*c*]-thiophen-8-one) derivatives are either inactive or behave as orthosteric antagonists in a functional assay of A_1AR-mediated phosphorylation of ERK1/2. This highlights the value of conducting functional assays rather than relying solely on bindings assays when evaluating novel allosteric ligands of the A_1AR. In addition, we have identified a new class of A_1AR allosteric enhancer with a indeno[2,1-*b*]thiophene heterocyclic core.

Experimental Section

Chemistry. Melting points were determined with an electrothermal melting point apparatus and are uncorrected. All ¹H
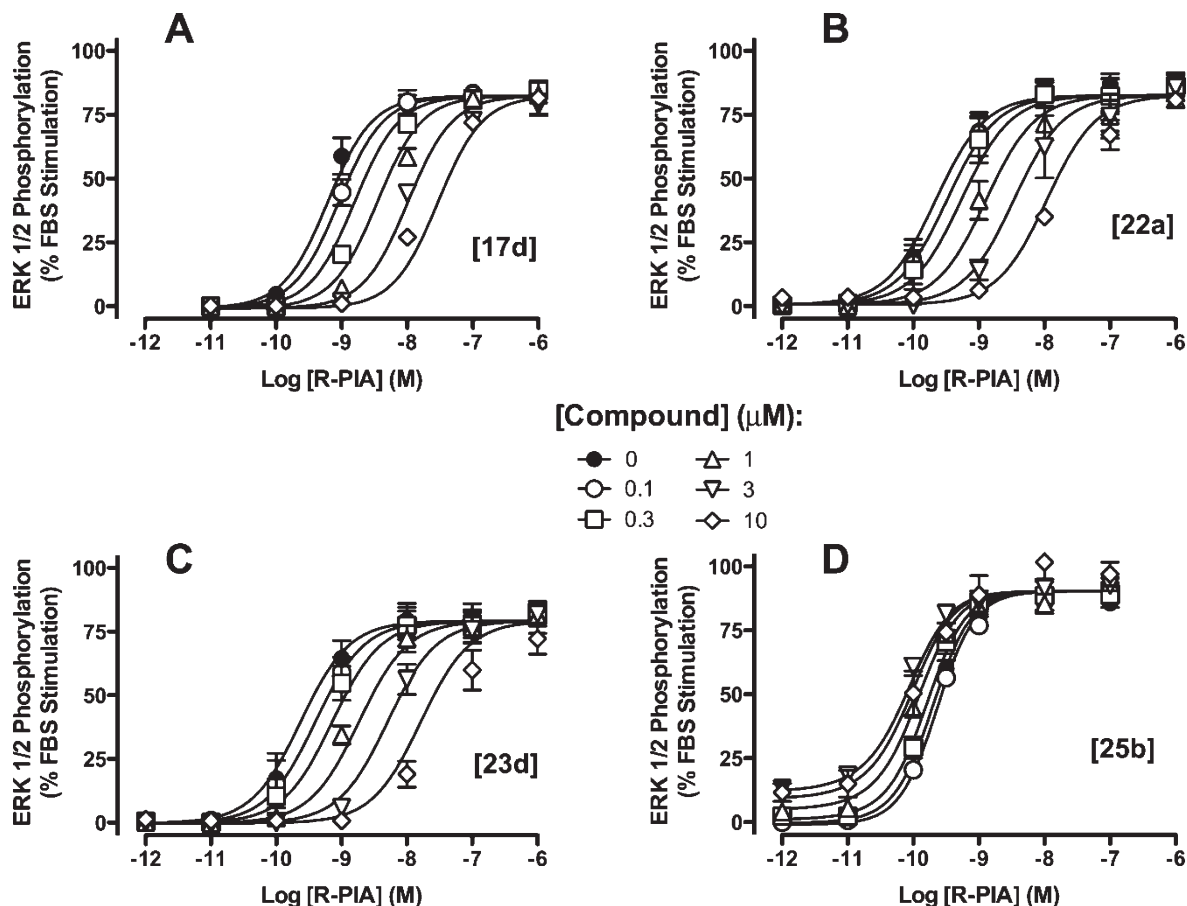
Figure 5. R-PIA mediated stimulation of ERK1/2 phosphorylation in the absence or presence of the indicated concentrations of test compounds in intact CHO FlpIn A_1AR cells. Data points represent the mean $\pm$ SEM of three experiments conducted in triplicate. Curves drawn through the points represent the best global fit of a competitive (A−C) or allosteric (D) model of ligand−receptor interaction.

NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300.13 MHz, unless stated otherwise, or on a Varian Unity Inova 600 spectrometer at 599.8 MHz. All ^{13}C NMR spectra were recorded on a Varian Unity Inova 600 spectrometer at 150.8 MHz, unless stated otherwise, or on a Bruker Avance DPX 300 spectrometer at 75.4 MHz. Unless stated otherwise, samples were dissolved in $CDCl_3$. Thin-layer chromatography was conducted on 0.2 mm plates using Merck silica gel 60 F_{254}. Column chromatography was achieved using Merck silica gel 60 (particle size 0.063−0.200 μm, 70−230 mesh). High resolution mass spectra (HR-ESI) were obtained on a Waters LCT Premier XE (TOF) using electrospray ionization. Compound purity was analyzed via LCMS (Agilent 1200 series LC coupled directly to a photodiode array detector and an Agilent 6120 Quadrupole MS) using a Phenomenex column (Luna 5 μm C8, 50 mm $\times$ 4.60 mm ID). All compounds were of > 95% purity.

General Procedure for the Synthesis of 10a,b.[13] The appropriate acetophenone **9a** or **9b** (50.24 mmol) and ethyl cyanoacetate (6.42 mL, 60.29 mmol) were dissolved in dry CH_2Cl_2 (200 mL) and cooled to 0 °C in an ice bath. Neat $TiCl_4$ (11.02 mL, 100.48 mmol) was added dropwise. After completion of the addition, the mixture was stirred for 0.5 h and then dry pyridine (3.40 mL) was added dropwise. The ice bath was subsequently removed, and the mixture was stirred at room temperature for 1 h. A further aliquot of dry pyridine (10 mL) was added dropwise and the mixture was allowed to stir overnight. The mixture was poured into 3 M HCl (200 mL) and the organic layer separated. The aqueous layer was further extracted with CH_2Cl_2 (2 × 50 mL), and the combined organics were washed with water and finally brine, dried ($MgSO_4$),

filtered, and concentrated to a viscous amber oil. The oil is dissolved in THF (40 mL) and elemental sulfur (2.0 g, 62.38 mmol) was added followed by Et_2NH (10 mL) dropwise, and the solution was stirred at room temperature for 2 h. The mixture was diluted with ether (200 mL) and washed with water (2 × 100 mL) and finally with brine. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo.

Ethyl 2-Amino-4-phenylthiophene-3-carboxylate (10a).[13] Yield 97%. ^{1}H NMR δ 7.30 (bs, 5H, ArH), 6.08 (s, 1H, H5), 5.46 (bs, 2H, NH_2), 4.05 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 0.94 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3).

Ethyl 2-Amino-4-(3-chlorophenyl)thiophene-3-carboxylate (10b).[13] Yield 93%. ^{1}H NMR δ 7.30−7.16 (m, 4H, ArH), 6.21 (bs, 2H, NH_2), 6.06 (s, 1H, H5), 4.06 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 0.98 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3).

General Procedure for the Synthesis of 12a,b. To the appropriate thiophene **10a** or **10b** (30.86 mmol) in glacial acetic acid (120 mL) was added phthalic anhydride (5.48 g, 37.03 mmol), and the mixture was refluxed for 3 h. The mixture was concentrated to a solid and stirred in petroleum ether (150 mL) for 0.5 h. The solid was filtered on a Buchner funnel/flask and washed with two portions of petroleum ether and dried (quantitative recovery). The crude phthalimide **11a** or **11b** was suspended in EtOH (120 mL) and water (120 mL) and NaOH pellets (175 mmol) was added. The heterogeneous mixture was heated to approximately 90 °C on an oil bath for 3−4 h (monitored by TLC), allowed to cool to room temperature, and diluted with water (200 mL). The mixture was washed with diethyl ether, and the aqueous layer was separated and cooled on an ice bath. HCl (6M) was added dropwise with stirring to the cooled mixture until pH $\approx$ 2 was obtained. A precipitate formed

and was collected on a Buchner funnel/flask and washed with copious amounts of water.

2-(2-Carboxybenzamido)-4-phenylthiophene-3-carboxylic Acid (12a). Yield 87%; mp 196 °C dec. ^{1}H NMR (DMSO-d_6) δ 13.13 (bs, 2H, 2 × CO$_2$H), 11.64 (bs, 1H, NH), 7.93−7.90 (m, 1H, phthalyl), 7.76−7.65 (m, 3H, phthalyl), 7.38−7.30 (m, 5H, ArH), 6.94 (s, 1H, H5). ^{13}C NMR (DMSO-d_6) δ 167.8, 167.3, 166.1, 149.2, 140.1, 137.7, 136.3, 132.6, 131.3, 131.2, 130.4, 129.4, 128.1, 127.9, 127.4, 116.2, 113.1.

2-(2-Carboxybenzamido)-4-(3-chlorophenyl)thiophene-3-carboxylic Acid (12b). Yield 85%; mp 192 °C dec. ^{1}H NMR (DMSO-d_6) δ 13.18 (bs, 2H, 2 × CO$_2$H), 11.68 (bs, 1H, NH), 7.94−7.92 (m, 1H, phthalyl), 7.75−7.67 (m, 3H, phthalyl), 7.40−7.31 (m, 4H, ArH), 7.03 (s, 1H, H5). ^{13}C NMR (DMSO-d_6) δ 167.5, 166.6, 165.8, 149.0, 139.4, 138.0, 135.9, 132.3, 132.2, 131.0, 130.7, 130.0, 129.4, 128.8, 127.9, 127.7, 127.0, 116.6, 112.6.

General Procedure for the Synthesis of 13a,b. The bis-carboxylic acid **12a** or **12b** (22.41 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL) under an atmosphere of N$_2$ and DMF (200 μL) was added. Neat oxalyl chloride (18.96 mL, 224.10 mmol) was subsequently added dropwise [CAUTION: vigorous gas evolution occurs!] over a period of an hour. The resultant mixture was stirred overnight. The volatiles were evaporated and the residue was redissolved in CH$_2$Cl$_2$ (160 mL) [NOTE: all operations performed under an inert atmosphere]. The two neck flask was fitted with reflux condenser, and AlCl$_3$ (17.93 g, 134.46 mmol) was added and the mixture was refluxed for 2 h. The mixture was allowed to cool to room temperature and then slowly poured with stirring into a mixture of 3 M HCl (200 mL), crushed ice (400−600 g), and CH$_2$Cl$_2$ (300 mL). The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic extracts were washed with water, saturated bicarbonate, and finally with brine, dried (MgSO$_4$), filtered, and concentrated to provide a solid.

2-(8-Oxo-8H-indeno[1,2-c]thiophen-1-yl)isoindoline-1,3-dione (13a). Yield 90%; mp 225−229 °C. ^{1}H NMR (DMSO-d_6) δ 8.06−8.02 (m, 2H, phthalyl), 7.99−7.95 (m, 2H, phthalyl), 7.77 (s, 1H, H3), 7.73 (d, J = 7.5 Hz, 1H, ArH), 7.63 (t, J = 7.5 Hz, 2H, ArH), 7.58 (d, J = 7.5 Hz, 2H, ArH), 7.37 (t, J = 7.5 Hz, 2H, ArH). ^{13}C NMR (DMSO-d_6) δ 183.7, 164.9, 143.2, 140.9, 140.6, 135.8, 135.6, 134.6, 132.1, 131.7, 129.2, 125.0, 124.6, 122.2, 117.7.

2-(5-Chloro-8-oxo-8H-indeno[1,2-c]thiophen-1-yl)isoindoline-1,3-dione and 2-(7-chloro-8-oxo-8H-indeno[1,2-c]thiophen-1-yl)-isoindoline-1,3-dione (13b). Yield 81% of a mixture of isomers in an approximate 7:3 ratio of the 5-chloro to 7-chloro and used in the next step without purification.

General Procedure for the Synthesis of 14a−c. The phthalimide **13a** or **13b** (12.07 mmol) was suspended in DMF:dioxane (1:1, 20 mL) at room temperature. After the dropwise addition of hydrazine hydrate (1 mL), all of the solids had dissolved. The reaction mixture was stirred for 1 h, diluted with ether (100 mL), and stirred for a further 10 min. The mixture was filtered through Celite, and the organics were washed thoroughly with water, then brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel eluting with 30% ethyl acetate/petroleum ether to yield the desired product (**14a−c**) as a solid. A small portion of each were recrystallized from MeOH for analytical purposes. Compounds **14a** and **14b** were subsequently refluxed for 10 min in a mixture of Ac$_2$O:AcOH (1:1, 10 mL). The mixture was concentrated and triturated with ether. The resultant solid was collected by suction filtration and washed with ether to provide a yellow solid **15a** and **15b**.

1-Amino-8H-indeno[1,2-c]thiophen-8-one (14a). Yield 73%, mp 128−130 °C. ^{1}H NMR (DMSO-d_6) δ 7.66 (bs, 2H, NH$_2$), 7.55−7.44 (m, 3H, ArH), 7.31−7.26 (m, 1H, ArH), 6.60 (s, 1H, H3). ^{13}C NMR (DMSO-d_6) δ 183.1, 158.8, 143.2, 142.0, 139.1, 132.8, 128.1, 123.3, 121.5, 114.8, 103.0. LCMS R_f (min) = 6.58. HR-ESI calcd for C$_{11}$H$_8$NOS$^+$ (M + H) 202.0321, found 202.0318.

1-Amino-5-chloro-8H-indeno[1,2-c]thiophen-8-one (14b). Yield 55%; mp 194−196 °C. ^{1}H NMR (DMSO-d_6) δ 7.82 (bs, 2H, NH$_2$), 7.70 (m, 1H, aromatic), 7.51−7.48 (m, 1H, aromatic), 7.33−7.31 (m, 1H, aromatic), 6.72 (s, 1H, 3H-aromatic). ^{13}C NMR (DMSO-d_6) δ 181.2, 158.7, 141.2, 140.1, 140.0, 137.0, 127.5, 124.4, 121.3, 114.1, 104.3. LCMS R_f (min) = 7.10. HR-ESI calcd for C$_{11}$H$_7$ClNOS$^+$ (M + H) 235.9931, found 235.9940.

1-Amino-7-chloro-8H-indeno[1,2-c]thiophen-8-one (14c). Yield 22%; mp 262 °C dec. ^{1}H NMR (DMSO-d_6) δ 7.79 (bs, 2H, NH$_2$), 7.54−7.52 (m, 1H, ArH), 7.47−7.42 (m, 1H, ArH), 7.27−7.24 (m, 1H, aromatic), 6.70 (s, 1H, 3H-aromatic). ^{13}C NMR (DMSO-d_6) δ 180.0, 158.8, 140.8, 139.7, 137.0, 133.5, 129.7, 129.2, 120.0, 114.4, 103.5. LCMS R_f (min) = 6.82. HR-ESI calcd for C$_{11}$H$_7$ClNOS$^+$ (M + H) 235.9931, found 235.9942.

N-(8-Oxo-8H-indeno[1,2-c]thiophen-1-yl)acetamide (15a). Yield 85%; mp 212−214 °C. ^{1}H NMR (DMSO-d_6) δ 11.42 (bs, 1H, NH), 7.63−7.53 (m, 3H, ArH), 7.35−7.30 (m, 1H, ArH), 7.13 (s, 1H, H3), 2.25 (s, 3H, Ac). ^{13}C NMR (DMSO-d_6) δ 184.4, 169.6, 142.8, 141.2, 140.6, 140.5, 134.5, 128.6, 124.3, 122.1, 121.9, 110.6, 23.1.

N-(5-Chloro-8-oxo-8H-indeno[1,2-c]thiophen-1-yl)acetamide (15b). Yield 75%; mp 298−300 °C. ^{1}H NMR (DMSO-d_6) δ 11.53 (bs, 1H, NH), 7.76 (m, 1H, ArH), 7.58−7.55 (m, 1H, ArH), 7.36−7.33 (m, 1H, ArH), 7.21 (s, 1H, H3), 2.25 (s, 3H, Ac). ^{13}C NMR (DMSO-d_6) δ 183.0, 169.7, 143.2, 142.1, 139.8, 139.3, 139.2, 128.4, 125.9, 122.3, 121.9, 112.2, 23.0.

General Procedure for the Synthesis of 16a,b. Acetamide **15d** or **15e** (20.55 mmol) was dissolved in DMSO (100 mL) and CH$_3$CN (400 mL). To the mixture was added I$_2$ (5.74 g, 22.61 mmol) and stirred until all solids had dissolved. AgNO$_3$ (4.19 g, 24.67 mmol) was added, and a precipitate immediately formed with concomitant decolouration of the solution. After stirring for 1 h, the mixture was filtered through Celite and the Celite pad washed with ethyl acetate (500 mL). The organic mixture was washed with water (×5), then brine, dried (MgSO$_4$), filtered, and concentrated to a solid. This material was triturated with ether, collected by suction filtration, and washed with diethyl ether to afford **16a** and **16b**, as bright-yellow solids.

N-(3-Iodo-8-oxo-8H-indeno[1,2-c]thiophen-1-yl)acetamide (16a). Yield 71%; mp 250 °C dec. ^{1}H NMR (DMSO-d_6) δ 11.73 (bs, 1H, NH), 7.97 (d, J = 7.2 Hz, 1H, ArH), 7.67−7.61 (m, 2H, ArH), 7.40 (t, J = 7.5 Hz, 1H, ArH), 2.26 (s, 3H, Ac). ^{13}C NMR (DMSO-d_6) δ 182.9, 170.1, 146.3, 143.5, 141.1, 140.2, 134.4, 129.2, 124.7, 123.2, 119.7, 64.7, 22.8.

N-(5-Chloro-3-iodo-8-oxo-8H-indeno[1,2-c]thiophen-1-yl)acetamide (16b). Yield 86%; mp 275−278 °C. ^{1}H NMR (DMSO-d_6) δ 11.89 (bs, 1H, NH), 7.90 (d, J = 1.5 Hz, 1H, ArH), 7.64 (d, J = 8.1 Hz, 1H, ArH), 7.47 (dd, J = 1.8 Hz, 8.1 Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 180.8, 169.6, 146.0, 141.5, 141.1, 139.1, 138.3, 128.4, 125.7, 122.5, 118.7, 66.2, 22.3.

General Procedure for the Synthesis of 17a−f. The iodide **16a** (650 mg, 1.76 mmol) in DMF (11 mL, degassed) was added 2 M K$_3$PO$_4$ (3.25 mL, degassed) and the appropriate boronic acid (3.52 mmol) followed by Pd[PPh$_3$]$_2$Cl$_2$ (124 mg, 10 mol %). After heating for 10−15 min at 75−80 °C under an atmosphere of N$_2$, a precipitate formed. The mixture was stirred for a further 30−45 min at 75−80 °C. The mixture was then diluted with water (30 mL), and the precipitate was collected by suction filtration. This solid was washed with water (50 mL) and diethyl ether (50 mL) to provide quantitative yields of crude cross-coupled products. The crude cross-coupled product was suspended in EtOH (12 mL) and NaOH (4 pellets ≈ 800 mg) was added and the mixture was capped in a sealed vessel and heated (microwave) at 150 °C for 20 min. The cooled solution was filtered to remove insoluble material, concentrated to a residue that was dissolved in water (50 mL), and acidified with AcOH until no more precipitate formed. The solid was collected on a Buchner funnel/flask and washed with water (100 mL), dried, and then suspended in EtOH (5 mL) and refluxed for 10 min. The cooled mixture was

collected by suction filtration and washed with EtOH and then ether. If required, the resultant solid was recrystallized from DMF or DMF/MeOH.

1-Amino-3-phenyl-8*H*-indeno[1,2-*c*]thiophen-8-one (17a). Yield 40%; mp 224−226 °C dec. ^{1}H NMR (DMSO-d_6) δ 7.86 (bs, 2H, NH$_2$), 7.60−7.47 (m, 5H, ArH), 7.44−7.38 (m, 3H, ArH), 7.33−7.29 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 182.4, 157.8, 142.8, 138.3, 135.6, 132.7, 132.4, 129.1, 128.1, 128.0, 127.9, 123.1, 120.9, 120.3, 115.9. LCMS R_f (min) = 7.59. HR-ESI calcd for C$_{17}$H$_{12}$NOS$^+$ (M + H) 278.0634, found 278.0647.

1-Amino-3-(4-methoxyphenyl)-8*H*-indeno[1,2-*c*]thiophen-8-one (17b). Yield 27%; mp 215−218 °C. ^{1}H NMR δ 7.68 (d, J = 7.5 Hz, 1H, ArH), 7.53 (d, J = 8.4 Hz, 3H, ArH), 7.33 (t, J = 7.4 Hz, 1H, ArH), 7.25 (t, J = 6.9 Hz, 1H, ArH), 6.99 (d, J = 8.4 Hz, 1H, ArH), 5.52 (bs, 2H, NH$_2$), 3.88 (s, 3H, OMe). ^{13}C NMR (DMSO-d_6) δ 182.3, 159.2, 157.5, 142.8, 138.4, 134.6, 132.3, 129.3, 127.7, 124.8, 123.1, 120.7, 120.5, 115.7, 114.5, 55.3. LCMS R_f (min) = 7.63. HR-ESI calcd for C$_{18}$H$_{14}$NO$_2$S$^+$ (M + H) 308.0740, found 308.0736.

1-Amino-3-(4-(dimethylamino)phenyl)-8*H*-indeno[1,2-*c*]thiophen-8-one (17c). Yield 56%; mp 241 °C dec. ^{1}H NMR (DMSO-d_6) δ 7.71 (bs, 2H, NH$_2$), 7.54 (d, J = 7.5 Hz, 2H, ArH), 7.43−7.38 (m, 3H, ArH), 7.27 (t, J = 7.5 Hz, 1H, ArH), 6.82 (d, J = 9.0 Hz, 2H, ArH), 2.97 (s, 6H, NMe$_2$). ^{13}C NMR (DMSO-d_6) δ 182.6, 157.7, 150.5, 143.2, 139.1, 133.6, 132.6, 129.1, 127.8, 123.5, 122.6, 121.2, 120.2, 116.3, 112.4, 40.3. LCMS R_f (min) = 7.63. HR-ESI calcd for C$_{19}$H$_{17}$N$_2$OS$^+$ (M + H) 321.1056, found 321.1059.

1-Amino-3-(pyrimidin-5-yl)-8*H*-indeno[1,2-*c*]thiophen-8-one (17d). Yield 46%; mp 294 °C dec. ^{1}H NMR (DMSO-d_6) δ 9.20 (s, 1H, ArH), 9.04 (s, 2H, ArH), 7.99 (bs, 2H, NH$_2$), 7.59−7.56 (m, 1H, ArH), 7.48−7.33 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6) δ 182.8, 159.1, 157.7, 155.9, 143.1, 139.4, 138.2, 133.2, 129.1, 128.1, 123.7, 121.1, 116.5, 112.1. LCMS R_f (min) = 6.78. HR-ESI calcd for C$_{15}$H$_8$N$_3$OS$^-$ (M − H) 278.0394, found 278.0392.

1-Amino-3-(pyridin-4-yl)-8*H*-indeno[1,2-*c*]thiophen-8-one (17e). Yield 59%; mp 272 °C dec. ^{1}H NMR (DMSO-d_6) δ 8.67−864 (m, 2H, ArH), 7.99 (bs, 2H, NH$_2$), 7.67−7.64 (m, 1H, ArH), 7.60−7.55 (m, 3H, ArH), 7.51−7.42 (m, 1H, ArH), 7.40−7.34 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 182.9, 158.7, 150.8, 143.1, 140.7, 139.0, 138.2, 133.1, 129.1, 123.7, 122.3, 121.9, 117.2, 116.8. LCMS R_f (min) = 5.87. HR-ESI calcd for C$_{16}$H$_{11}$N$_2$OS$^+$ (M + H) 279.0587, found 279.0598.

4-(1-Amino-8-oxo-8*H*-indeno[1,2-c]thiophen-3-yl)benzoic Acid (17f). Yield 53%; mp 318 °C dec. ^{1}H NMR (DMSO-d_6) δ 13.01 (bs, 1H, CO$_2$H), 8.05 (d, J = 8.1 Hz, 2H, ArH), 7.92 (bs, 2H, NH$_2$), 7.71 (d, J = 8.1 Hz, 2H, ArH), 7.62−7.56 (m, 2H, ArH), 7.45 (t, J = 7.4 Hz, 1H, ArH), 7.35 (t, J = 7.4 Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 182.9, 167.3, 158.5, 143.2, 138.5, 133.0, 130.6, 130.5, 130.2, 128.8, 128.2, 127.6, 123.6, 121.7, 119.4, 116.6. LCMS R_f (min) = 7.15. HR-ESI calcd for C$_{18}$H$_{12}$NO$_3$S$^+$ (M + H) 322.0532, found 322.0543.

General Procedure Synthesis of 20a−b.[12] The appropriate nitrile **18a** or **18b** (34.45 mmol), 2,5-dihydroxy-1,4-dithiane **19** (2.62 g, 17.22 mmol), and diethylamine (3.58 mL) were suspended in EtOH (14 mL) and stirred at 50 °C for several hours, during which time a solid precipitated. The mixture was diluted with EtOH (∼5 mL) and chilled on an ice bath with stirring (∼0.5 h). The fine yellow powder was filtered using a Buchner funnel/flask and washed with ice-cold EtOH until a pale-yellow filtrate was obtained. The solid was left to dry overnight, providing **20a** and **20b** that were used in the next step without further purification. A small portion of each were recrystallized from MeOH.

(2-Aminothiophen-3-yl)(phenyl)methanone (20a).[12] Yield 64%; mp 144−146 °C. ^{1}H NMR δ 7.68−7.66 (m, 2H, ArH), 7.51−7.42 (m, 3H, ArH), 6.96 (bs, 2H, NH$_2$), 6.88 (d, J = 5.7 Hz, 1H, H4), 6.13 (d, J = 5.4 Hz, 1H, H5). ^{13}C NMR δ 191.3, 166.4, 140.8, 130.8, 128.2 (×2), 127.7, 115.0, 106.1. LCMS R_f (min) = 6.68. HR-ESI calcd for C$_{11}$H$_{10}$NOS$^+$ (M + H) 204.0478, found 204.0485.

(2-Aminothiophen-3-yl)(4-chlorophenyl)methanone (20b).[12] Yield 68%; mp 168−170 °C. ^{1}H NMR (599.8 MHz) δ 7.62 (d, J = 7.2 Hz, 1H, ArH), 7.42 (d, J = 7.2 Hz, 1H, ArH), 6.98 (bs, 2H, NH$_2$), 6.83 (d, J = 4.8 Hz, 1H, H4), 6.14 (d, J = 4.8 Hz, 1H, H5). ^{13}C NMR δ 189.8, 166.5, 139.1, 136.9, 129.6, 128.4, 127.3, 114.8, 106.4. LCMS R_f (min) = 7.12. HR-ESI calcd for C$_{11}$H$_9$ClNOS$^+$ (M + H) 238.0088, found 238.0091.

General Procedure for the Synthesis of 21a and 21b. The appropriate thiophene **20a** or **20b** (12.62 mmol) was refluxed for 10 min in acetic anhydride (15 mL). The cooled mixture was quenched with bicarbonate solution and extracted with diethyl ether. The ether layer was dried (MgSO$_4$), filtered, and concentrated to a solid that was dissolved in CH$_3$CN (50 mL) and DMF (50 mL). Iodine (3.52 g, 13.88 mmol) was added, and the mixture was stirred until it had dissolved. Neat AgNO$_3$ (2.57 g, 15.14 mmol) was added, and the iodine color dissapeared after 1 min with precipitation of AgI. After stirring a further 20 min, the mixture was diluted with EtOAc (∼100 mL) and filtered through Celite. The mixture was washed with dilute Na$_2$S$_2$O$_3$ and then H$_2$O (×4) and finally brine, dried (MgSO$_4$), filtered, and concentrated to a solid. The products were recrystallized from MeOH (**21a**) and *i*PrOH (**21b**).

N-(3-Benzoyl-5-iodothiophen-2-yl)acetamide (21a). Yield 71%; mp 162−164 °C. ^{1}H NMR δ 12.06 (bs, 1H, NH), 7.69−7.67 (m, 2H, ArH), 7.61−7.48 (m, 3H, ArH), 6.96 (s, 1H, H4), 2.24 (s, 3H, Ac). ^{13}C NMR δ 191.5, 168.1, 155.2, 139.4, 135.1, 132.1, 128.6 (×2), 121.7, 66.1, 23.4.

N-(3-(4-Chlorobenzoyl)-5-iodothiophen-2-yl)acetamide (21b). Yield 84%; mp 175−177 °C. ^{1}H NMR δ 11.99 (bs, 1H, NH), 7.64 (d, J = 8.7 Hz, 2H, ArH), 7.49 (d, J = 8.7 Hz, 2H, ArH), 7.23 (s, 1H, 4H-aromatic), 2.24 (s, 3H, Ac). ^{13}C NMR δ 190.0, 168.1, 155.4, 138.4, 137.6, 134.6, 130.0, 128.9, 121.4, 66.4, 23.4.

General Procedure for the Synthesis of 22a−f and 23a−f. The appropriate iodide **21a** or **21b** (1.23 mmol) in DMF (7.7 mL, degassed) was added 2 M K$_3$PO$_4$ (2.28 mL, degassed) and the appropriate boronic acid (2.46 mmol) followed by Pd[PPh$_3$]$_2$Cl$_2$ (10 mol %, 87 mg) and heated with stirring on an oil bath at 75−80 °C in an N$_2$ atmosphere for 1 h. The mixture was diluted with ether and washed with water (×4) then brine, dried (MgSO$_4$), filtered, and evaporated to dryness. The crude cross-coupled product was suspended in EtOH (15 mL), dioxane (10 mL), and water (5 mL) and NaOH (250 mg, 6.25 mmol) was added and the mixture was stirred on an oil bath at 30−35 °C for 1−3 h (monitored by TLC). The cooled solution was diluted with water, and if a solid formed, it was filtered on a Buchner funnel/flask, otherwise it was extracted with diethyl ether. The crude hydrolyzed compounds were chromatographed on silica gel (10−50% EtOAc/petroleum ether) and then recrystallized from MeOH. For compounds **22f** and **23f**, after completion of the hydrolysis, the mixture was diluted with water (∼100 mL) and acidified to pH 3 (2 M HCl). The resultant solid was collected by suction filtration and washed with plenty of water before being recrystallized from MeOH.

(2-Amino-5-phenylthiophen-3-yl)(phenyl)methanone (22a). Yield 66%; mp 159−161 °C. ^{1}H NMR δ 7.73−7.71 (m, 2H, ArH), 7.55−7.45 (m, 3H, ArH), 7.41−7.38 (m, 2H, ArH), 7.34−7.29 (m, 2H, ArH), 7.23−7.18 (m, 1H, ArH), 7.12 (s, 1H, H4), 7.08 (bs, 2H, NH$_2$). ^{13}C NMR δ 191.3, 166.2, 140.8, 133.8, 130.9, 128.9, 128.3, 128.2, 126.8, 124.8, 123.9, 122.8, 116.0. LCMS R_f (min) = 7.69. HR-ESI calcd for C$_{17}$H$_{14}$NOS$^+$ (M + H) 280.0791, found 280.0800.

(2-Amino-5-(4-methoxyphenyl)thiophen-3-yl)(phenyl)methanone (22b). Yield 66%; mp 158−160 °C. ^{1}H NMR δ 7.73−7.70 (m, 2H, ArH), 7.54−7.45 (m, 3H, ArH), 7.32 (d, J = 7.5 Hz, 2H, ArH), 7.03 (bs, 2H, NH$_2$), 6.97 (s, 1H, H4), 6.86 (d, J = 7.5 Hz, 2H, ArH), 3.81 (s, 3H, OMe). ^{13}C NMR δ 191.2, 165.6, 158.7, 140.9, 130.8, 128.3, 128.1, 126.6, 126.2, 124.0, 121.4, 116.0, 114.3, 55.4. LCMS R_f (min) = 7.58. HR-ESI calcd for C$_{18}$H$_{16}$NO$_2$S$^+$ (M + H) 310.0896, found 310.0909.

(2-Amino-5-(4-(dimethylamino)phenyl)thiophen-3-yl)(phenyl)-methanone (22c). Yield 42%; mp 206−208 °C. ^{1}H NMR δ 7.73−7.72 (m, 2H, ArH), 7.51−7.46 (m, 3H, ArH), 7.28−726 (m, 2H, ArH), 6.98 (bs, 2H, NH$_2$), 6.91 (s, 1H, H4), 6.88 (d, J = 7.8 Hz, 2H, ArH), 2.96 (s, 6H, NMe$_2$). ^{13}C NMR δ 191.1, 165.2, 149.6, 141.0, 130.7, 128.2 (×2), 126.0, 125.0, 122.3, 120.0, 116.0, 112.7, 40.5. LCMS R_f (min) = 7.18. HR-ESI calcd for C$_{19}$H$_{19}$N$_2$OS$^+$ (M + H) 323.1213, found 323.1216.

(2-Amino-5-(pyrimidin-5-yl)thiophen-3-yl)(phenyl)methanone (22d). Yield 15%; mp 150−152 °C dec. ^{1}H NMR δ 9.03 (s, 1H, ArH), 8.74 (s, 2H, ArH), 7.71−7.70 (m, 2H, ArH), 7.56−7.50 (m, 3H, ArH), 7.26 (s, 1H, H4), 7.20 (bs, 2H, NH$_2$). ^{13}C NMR δ 191.3, 166.8, 156.2, 152.2 (×2), 140.3, 131.2, 128.5, 128.1, 125.9, 116.1, 115.5. LCMS R_f (min) = 6.82. HR-ESI calcd for C$_{15}$H$_{12}$N$_3$OS$^+$ (M + H) 282.0696, found 282.0696.

(2-Amino-5-(pyridin-4-yl)thiophen-3-yl)(phenyl)methanone (22e). Yield 42%; mp 218−220 °C dec. ^{1}H NMR δ 8.49 (s, 2H, ArH), 7.71−7.70 (m, 2H, ArH), 7.56−7.50 (m, 3H, ArH), 7.37 (s, 1H, H4), 7.34 (bs, 2H, NH$_2$), 7.23 (m, 2H, ArH). ^{13}C NMR δ 190.5, 168.0, 149.7, 141.1, 140.5, 130.6, 128.1, 127.7, 126.0, 119.2, 118.2, 114.9. LCMS R_f (min) = 5.27. HR-ESI calcd for C$_{16}$H$_{13}$N$_2$OS$^+$ (M + H) 281.0743, found 281.0754.

4-(5-Amino-4-benzoylthiophen-2-yl)benzoic acid (22f). Yield 37%; mp 284−286 °C. ^{1}H NMR (DMSO-d_6) δ 12.83 (bs, 1H, CO$_2$H), 7.86 (d, J = 8.4 Hz, 2H, ArH), 7.67−7.65 (m, 2H, ArH), 7.56−7.52 (m, 5H, ArH and NH$_2$), 7.30 (s, 1H, H4). ^{13}C NMR δ 189.5, 167.5, 167.0, 140.6, 137.8, 130.8, 130.1, 128.4, 128.0, 127.9, 124.6, 123.9, 120.5, 114.3. LCMS R_f (min) = 7.15. HR-ESI calcd for C$_{18}$H$_{14}$NO$_3$S$^+$ (M + H) 324.0689, found 324.0688.

(2-Amino-5-phenylthiophen-3-yl)(4-chlorophenyl)methanone (23a). Yield 37%; mp 168−170 °C. ^{1}H NMR δ 7.67 (d, J = 7.2 Hz, 2H, ArH), 7.45 (d, J = 7.2 Hz, 2H, ArH), 7.41−7.30 (m, 4H, ArH), 7.25−7.20 (m, 1H, ArH), 7.07 (bs, 2H, NH$_2$), 7.06 (s, 1H, H4). ^{13}C NMR δ 189.8, 166.2, 139.1, 137.0, 133.6, 129.6, 128.9, 128.6, 126.9, 124.8, 124.3, 122.3, 115.8. LCMS R_f (min) = 8.05. HR-ESI calcd for C$_{17}$H$_{13}$ClNOS$^+$ (M + H) 314.0401, found 314.0409.

(2-Amino-5-(4-methoxyphenyl)thiophen-3-yl)(4-chlorophenyl)-methanone (23b). Yield 58%; mp 139−141 °C dec. ^{1}H NMR δ 7.66 (d, J = 7.5 Hz, 2H, ArH), 7.45 (d, J = 7.5 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 2H, ArH), 7.03 (bs, 2H, NH$_2$), 6.91 (s, 1H, H4), 6.87 (d, J = 8.1 Hz, 2H, ArH), 3.81 (s, 3H, OMe). ^{13}C NMR (150.8 MHz) δ 189.7, 165.9, 158.8, 139.2, 136.9, 129.6, 128.5, 126.4, 126.2, 124.3, 120.9, 115.7, 114.3, 55.4. LCMS R_f (min) = 7.92. HR-ESI calcd for C$_{18}$H$_{15}$ClNO$_2$S$^+$ (M + H) 344.0507, found 344.0493.

(2-Amino-5-(4-(dimethylamino)phenyl)thiophen-3-yl)(4-chloro-phenyl)methanone (23c). Yield 35%; mp 170−172 °C dec. ^{1}H NMR δ 7.67 (d, J = 8.4 Hz, 2H, ArH), 7.44 (d, J = 8.1 Hz, 2H, ArH), 7.27 (d, J = 8.2 Hz, 2H, ArH), 7.00 (bs, 2H, NH$_2$), 6.85 (s, 1H, H4), 6.68 (d, J = 8.7 Hz, 2H, ArH), 2.96 (s, 6H, NMe$_2$). ^{13}C NMR δ 189.6, 165.7, 149.7, 139.4, 136.9, 129.8, 128.6, 126.1, 125.4, 122.2, 119.5, 115.8, 112.8, 40.6. LCMS R_f (min) = 7.65. HR-ESI calcd for C$_{19}$H$_{18}$ClN$_2$OS$^+$ (M + H) 357.0823, found 357.0840.

(2-Amino-5-(pyrimidin-5-yl)thiophen-3-yl)(4-chlorophenyl)-methanone (23d). Yield 18%; mp 229−231 °C dec. ^{1}H NMR δ 9.04 (s, 1H, ArH), 8.75 (s, 2H, ArH), 7.66 (d, J = 7.5 Hz, 2H, ArH), 7.48 (d, J = 7.2 Hz, 2H, ArH), 7.26 (s, 1H, H4), 7.20 (bs, 2H, NH$_2$). ^{13}C NMR δ 188.7, 168.2, 155.6, 151.7 (×2), 138.9, 136.4, 129.3, 128.3, 125.0, 114.7, 114.5. LCMS R_f (min) = 7.13. HR-ESI calcd for C$_{15}$H$_{11}$ClN$_3$OS$^+$ (M + H) 316.0306, found 316.0313.

(2-Amino-5-(pyridin-4-yl)thiophen-3-yl)(4-chlorophenyl)methan-one (23e). Yield 37%; mp 262−264 °C dec. ^{1}H NMR (DMSO-d_6) δ 8.77 (bs, 2H, NH$_2$), 8.43 (d, J = 4.8 Hz, 2H, ArH), 7.69 (d, J = 7.2 Hz, 2H, ArH), 7.58 (d, J = 7.5 Hz, 2H, ArH), 7.50 (s, 1H, H4), 7.42 (d, J = 4.8 Hz, 2H, ArH). ^{13}C NMR (DMSO-d_6) δ 188.1, 167.9, 149.8, 140.6, 139.0, 135.6, 129.9, 128.5, 126.2, 118.7, 118.3, 114.1. LCMS R_f (min) = 5.67. HR-ESI calcd for C$_{16}$H$_{12}$ClN$_2$OS$^+$ (M + H) 315.0353, found 315.0366.

4-(5-Amino-4-(4-chlorobenzoyl)thiophen-2-yl)benzoic Acid (23f). Yield 50%; mp 274−276 °C dec. ^{1}H NMR (DMSO-d_6) δ 12.88 (bs, 1H, CO$_2$H), 8.72 (bs, 2H, NH$_2$), 7.86 (d, J = 7.8 Hz, 2H, ArH), 7.69 (d, J = 8.1 Hz, 2H, ArH), 7.58 (d, J = 7.5 Hz, 2H, ArH), 7.56 (d, J = 7.5 Hz, 2H, ArH), 7.33 (s, 1H, H4). ^{13}C NMR δ 188.1, 167.8, 167.0, 139.2 137.8, 135.5, 130.1, 129.9, 128.5, 128.1, 124.5, 124.0, 120.8, 114.2. LCMS R_f (min) = 7.39. HR-ESI calcd for C$_{18}$H$_{13}$ClNO$_3$S$^+$ (M + H) 358.0299, found 358.0316.

General Procedure for the Synthesis of 25a,b. 1-Indanone **24a** (200 mg, 1.51 mmol) and the appropriate nitrile **18a** or **18b** (1.51 mmol) were dissolved in dry CH$_2$Cl$_2$ (10 mL) and cooled to 0 °C in an ice bath. Neat TiCl$_4$ (166 μL, 1.51 mmol) was added dropwise, and the mixture was stirred for 0.5 h. Dry pyridine (111 μL) was added dropwise, and the mixture was warmed to room temperature and stirred for 1 h. A further aliquot of dry pyridine (308 μL) was added dropwise, and stirring was continued overnight. The mixture was poured into 3 M HCl (20 mL) and the organic layer separated. The aqueous layer was further extracted with CH$_2$Cl$_2$ (2 × 10 mL), and the combined organics were washed with water and brine before being dried (MgSO$_4$), filtered, and concentrated to a viscous amber oil. The oil was dissolved in THF (3 mL) and elemental sulfur (53 mg, 1.66 mmol) and Et$_2$NH (400 μL) were added. The reaction was stirred at ∼60 °C for 2 h. The deep blue−purple mixture was concentrated to a residue and then chromatographed on silica gel (10% EtOAc/petroleum ether) to afford **25a,b** as solids that were recrystallized from *i*PrOH.

(2-Amino-8H-indeno[2,1-b]thiophen-3-yl)(phenyl)methanone (25a). Yield 9%; mp 183−185 °C. ^{1}H NMR δ 7.74−7.71 (m, 2H, ArH), 7.55−7.50 (m, 1H, ArH), 7.43−7.34 (m, 3H, ArH), 7.02−6.97 (m, 1H, ArH), 6.77 (t, J = 7.5 Hz, 1H, ArH), 6.58 (bs, 2H, NH$_2$), 5.67 (d, J = 7.8 Hz, 1H, ArH), 3.69 (s, 2H, CH$_2$). ^{13}C NMR (DMSO-d_6) δ 191.9, 168.5, 146.1, 142.2, 141.5, 139.7, 131.8, 129.1, 128.7, 126.3, 126.0, 124.0, 123.8, 121.3, 111.0, 34.6. LCMS R_f (min) = 7.38. HR-ESI calcd for C$_{18}$H$_{14}$NOS$^+$ (M + H) 292.0791, found 292.0803.

(2-Amino-8H-indeno[2,1-b]thiophen-3-yl)(4-chlorophenyl)methan-one (25b). Yield 18%; mp 198−200 °C. ^{1}H NMR δ 7.69 (d, J = 7.8 Hz, 2H, ArH), 7.39−7.37 (m, 3H, ArH), 7.03 (t, J = 7.4 Hz, 1H, ArH), 6.86 (t, J = 7.5 Hz, 1H, ArH), 6.59 (bs, 2H, NH$_2$), 5.80 (d, J = 7.8 Hz, 1H, ArH), 3.70 (s, 2H, CH$_2$). ^{13}C NMR (DMSO-d_6) δ 190.3, 168.8, 146.2, 141.9, 139.7, 139.5, 138.0, 130.7, 128.9, 126.6, 126.1, 124.1, 124.0, 121.2, 110.6, 34.6. LCMS R_f (min) = 7.74. HR-ESI calcd for C$_{18}$H$_{13}$ClNOS$^+$ (M + H) 326.0401, found 326.0403.

General Procedure for the Synthesis of 25c−f. Indanone **24b** and **24c** (500 mg, 2.50 mmol), the appropriate nitrile **18a** or **18b** (3.25 mmol), benzoic acid (305 mg, 2.50 mmol), and β-alanine (45 mg, 20 mol %) was heated at 110−120 °C for 3−6 h (monitored by TLC). The reaction was then cooled to ∼60 °C and EtOH (1 mL) was added, followed by morpholine (655 μL, 7.49 mmol) and elemental sulfur (120 mg, 3.75 mmol). The mixture was stirred at this temperature for 3 h and then cooled to room temperature, diluted with ether, and washed with water. The organic layer was dried (MgSO$_4$), filtered, and concentrated to a residue that was chromatographed on silica gel (CH$_2$Cl$_2$), providing **25c−f** as solids. Recrystallization (**25c,d** from ether/pet. ether and **25e,f** from MeOH) afforded the pure products.

(2-Amino-7-(trifluoromethyl)-8H-indeno[2,1-b]thiophen-3-yl)-(phenyl)methanone (25c). Yield 21%; mp 188−190 °C. ^{1}H NMR δ 7.71 (d, J = 7.5 Hz, 2H, ArH), 7.54 (t, J = 7.2 Hz, 1H, ArH), 7.41 (t, J = 7.2 Hz, 2H, ArH), 7.23 (d, J = 8.1 Hz, 1H, ArH), 6.88 (t, J = 7.8 Hz, 1H, ArH), 6.63 (bs, 2H, NH$_2$), 5.83 (d, J = 7.8 Hz, 1H, ArH), 3.89 (s, 2H, CH$_2$). ^{13}C NMR (DMSO-d_6) δ 191.6, 168.9, 143.4, 141.4, 141.1, 141.0, 131.9, 129.0, 128.8, 127.4, 126.5, 126.0 (q, J = 31.9 Hz), 124.5 (q, J = 273.0 Hz), 124.3, 120.5 (q, J = 4.5 Hz), 110.5, 33.8. LCMS R_f (min) = 8.09. HR-ESI calcd for C$_{19}$H$_{13}$F$_3$NOS$^+$ (M + H) 360.0664, found 360.0664.

(2-Amino-7-(trifluoromethyl)-8H-indeno[2,1-b]thiophen-3-yl)-(4-chlorophenyl)methanone (25d). Yield 17%; mp 152−154 °C

dec. ^{1}H NMR δ 7.67 (d, J = 7.8 Hz, 2H, ArH), 7.39 (d, J = 7.5 Hz, 2H, ArH), 7.28−7.26 (m, 1H, ArH), 6.97 (t, J = 8.1 Hz, 1H, ArH), 6.63 (bs, 2H, NH$_2$), 5.96 (d, J = 7.8 Hz, 1H, ArH), 3.90 (s, 2H, CH$_2$). ^{13}C NMR (DMSO-d_6) δ 190.0, 169.0, 143.4, 140.9, 140.7, 139.6, 138.2, 130.6, 129.1, 127.7, 126.7, 126.3 (q, J = 28.2 Hz), 124.5 (q, J = 273.3 Hz), 124.2, 120.7 (q, J = 4.5 Hz), 110.2, 33.8. LCMS R_f (min) = 8.56. HR-ESI calcd for C$_{19}$H$_{12}$ClF$_3$NOS$^+$ (M + H) 394.0275, found 394.0280.

(2-Amino-5-(trifluoromethyl)-8H-indeno[2,1-b]thiophen-3-yl)-(phenyl)methanone (25e). Yield 1%; mp 202−207 °C dec. ^{1}H NMR δ 7.68 (d, J = 7.8 Hz, 2H, ArH), 7.56 (t, J = 7.4 Hz, 1H, ArH), 7.44−7.39 (m, 3H, ArH), 7.26−7.24 (m, 1H, ArH), 6.71 (bs, 2H, NH$_2$), 5.78 (s, 1H, ArH), 3.74 (s, 2H, CH$_2$). LCMS R_f (min) = 7.74. HR-ESI calcd for C$_{19}$H$_{13}$F$_3$NOS$^+$ (M + H) 360.0664, found 360.0666.

(2-Amino-5-(trifluoromethyl)-8H-indeno[2,1-b]thiophen-3-yl)-(4-chlorophenyl)methanone (25f). Yield 1%; mp 202−204 °C dec. ^{1}H NMR δ 7.63 (d, J = 8.4 Hz, 2H, ArH), 7.45−7.39 (m, 3H, ArH), 7.30−7.26 (m, 1H, ArH), 6.74 (bs, 2H, NH$_2$), 5.85 (s, 1H, ArH), 3.75 (s, 2H, CH$_2$). LCMS R_f (min) = 7.99. HR-ESI calcd for C$_{19}$H$_{12}$ClF$_3$NOS$^+$ (M + H) 394.0275, found 394.0274.

Crystallography. Intensity data for **25c** were collected on an Oxford Diffraction Sapphire CCD diffractometer using Cu Kα radiation (graphite crystal monochromator λ = 1.54184). The temperature during data collection was maintained at 130.0(1) using an Oxford cooling device. The structures were solved by direct methods and difference Fourier synthesis. Thermal ellipsoid plots were generated using the program ORTEP-3[14] integrated within the WINGX[15] suite of programs.

Crystal Data for 25c. C$_{19}$H$_{12}$F$_3$NOS, M = 359.36, T = 130.0(1) K, λ = 1.54184, monoclinic, space group $P2(1)/n$, a = 14.0649(3), b = 8.2172(2), c = 15.1871(3) Å, β = 112.070(2)∞, V = 1626.62(6) Å^3, Z = 4, D_c = 1.467 mg M^{-3} μ(Cu Kα) 2.129 mm^{-1}, $F(000)$ = 736, crystal size 0.5 × mm 0.4 mm × 0.16 mm. 5996 reflections measured, 3173 independent reflections (R_{int} = 0.014) the final R was 0.0387 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1112 (all data).

A$_1$AR-Mediated ERK 1/2 Phosphorylation. CHO FlpIn cells, stably transfected with the human A$_1$AR (FlpIn-CHO A$_1$ cells), were grown to 90% confluence and maintained in Dulbecco's Modified Eagle Medium (DMEM) containing 20 mM HEPES, 5% fetal bovine serum (FBS), and 200 μG/mL of hygromycin at 37 °C in a humidified incubator containing 5% CO$_2$:95% O$_2$. Cells were then harvested by trypsinization followed by centrifugation (300g, 5 min). Cells were then seeded into 96-well plates at a density of 50000 cells/well. After 4 h, the cells were washed twice with phosphate-buffered saline (PBS) and then maintained in DMEM containing 20 mM HEPES for at least 4 h. Prior to agonist stimulation, cells were pretreated for 30 min with 1 U/mL adenosine deaminase (ADA) and then for 30 min with test compound (3 or 10 μM for initial screens; more detailed concentration−response analyses for compounds **17d**, **22a**, **23d**, and **25b**) at 37 °C. R-PIA (0.3 nM) was then added and stimulation allowed to proceed for 5 min before the reaction was terminated by the removal of media and the addition of 100 μL of *SureFire* lysis buffer to each well. The plate was then agitated for 1−2 min. A 4:1 v/v dilution of lysate:*SureFire* activation buffer was made in a total volume of 50 μL. A 1:100:120 v/v dilution of AlphaScreen beads:activated lysate mixture:*SureFire* reaction buffer in a 11 μL total volume was then transferred to a white opaque 384-well Proxiplate in diminished light. This plate was then incubated in the dark at 37 °C for 1.5 h, after which time the fluorescence signal was measured by a Fusion-α plate reader (PerkinElmer) using standard AlphaScreen settings. Two-point screening data were normalized to the percent of the maximum response attained to R-PIA, with 0% representing basal ERK1/2 phosphorylation in the absence of R-PIA and 100% representing the maximal response attained at a saturating concentration of R-PIA (100 nM). For the full concentration−response curves, the data were expressed as a percentage of the ERK1/2 phosphorylation mediated after a 6 min exposure to DMEM containing 3% FBS.

Supporting Information Available: LC-MS analysis of compounds **14a−c**, **17a−f**, **20a−b**, **22a−f**, **23a−f**, and **25a−f**. Crystallographic data for **25c** have been deposited with the Cambridge Crystallographic Data Centre (CCDC code 790719). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) May, L. T.; Avlani, V. A.; Sexton, P. M.; Christopoulos, A. Allosteric Modulation of G Protein-Coupled Receptors. *Curr. Pharm. Des.* **2004**, *10*, 2003–2013.

(2) Schulte, G.; Fredholm, B. B. Signalling from Adenosine Receptors to Mitogen-Activated Protein Kinases. *Cell. Signalling* **2003**, *15*, 813–827.

(3) Jacobson, K. A.; Gao, Z.-G. Adenosine Receptors as Therapeutic Targets. *Nature Rev. Drug Discovery* **2006**, *5*, 247–264.

(4) Hutchinson, S. A.; Scammells, P. J. A$_1$ Adenosine Receptor Agonists: Medicinal Chemistry and Therapeutic Potential. *Curr. Pharm. Des.* **2004**, *10*, 2021–2039.

(5) May, L. T.; Leach, K.; Sexton, P. M.; Christopoulos, A. Allosteric Modulation of G Protein Coupled Receptors. *Annu. Rev. Pharmacol. Toxicol.* **2007**, *47*, 1–51.

(6) Bruns, R. F.; Fergus, J. H. Allosteric Enhancement of Adenosine A$_1$ Receptor Binding and Function by 2-Amino-3-benzoylthiophenes. *Mol. Pharmacol.* **1990**, *38*, 939–949.

(7) Bruns, R. F.; Fergus, J. H.; Coughenour, L. L.; Courtland, G. G.; Pugsley, T. A.; Dodd, J. H.; Tinney, F. J. Structure−activity Relationships for Enhancement of Adenosine A$_1$ Receptor Binding by 2-Amino-3-benzoylthiophenes. *Mol. Pharmacol.* **1990**, *38*, 950–958.

(8) Aurelio, L.; Valant, C.; Flynn, B. L.; Sexton, P. M.; A. Christopoulos, A.; Scammells, P. J. Allosteric Modulators of the Adenosine A$_1$ Receptor: Synthesis and Pharmacological Evaluation of 4-Substituted 2-Amino-3-benzoylthiophenes. *J. Med. Chem.* **2009**, *52*, 4543–4547.

(9) Moorman, A. R; Romagnoli, R; Baraldi, P. G. Preparation of Fused Thiophenes for the Treatment of Neuropathic Pain. PCT Int. Appl. WO02083083, 2002.

(10) Lehnert., W. Knoevenagel Kondensationen mit TiCL$_4$/Base−III. Umsetzungen von Ketonen und α-Halogenketonen mit Malonester. *Tetrahedron* **1973**, *29*, 635–638.

(11) Stephens, C. E; Felder, T. M; Sowell, J. W, Sr.; Andrei, G; Balzarini, J; Snoeck, R; Clercq, D. E. Synthesis and Antiviral/Antitumor Evaluation of 2-amino- and 2-Carboximido-3-arylsulfonylthiophenes and Related Compounds as a New Class of Diarylsulfones. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 1123–1132.

(12) Tranberg, C. E.; Zickgraf, A.; Giunta, B. N.; Lutjens, H.; Figler, H.; Murphree, L. J.; Falke, R.; Fleischer, H.; Linden, J.; Scammells, P. J.; Olsson, R. A. 2-Amino-3-aroyl-4,5-alkylthiophenes: Agonist Allosteric Enhancers at Human A$_1$ Adenosine Receptors. *J. Med. Chem.* **2002**, *45*, 382–389.

(13) Tormyshev, V. M.; Trukhin, D. V.; Rogozhnikova, O. U.; Mikhalina, T. V.; Troitskaya, T. I.; Flinn, A. Aryl Alkyl Ketones in a One-Pot Gewald Synthesis of 2-Aminothiophenes. *Synlett* **2006**, 2559–2564.

(14) Farrugia, L. J. ORTEP-3 for windows—a version of ORTEP-III with a graphical user interface (GUI). *J. Appl. Crystallogr.* **1997**, *30*, 565.

(15) Farrugia, L. J. WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr.* **1999**, *32*, 837–338.