

6-Aryl-8*H*-indeno[1,2-*d*]thiazol-2-ylamines: A₁ Adenosine Receptor Agonist Allosteric Enhancers Having Improved Potency

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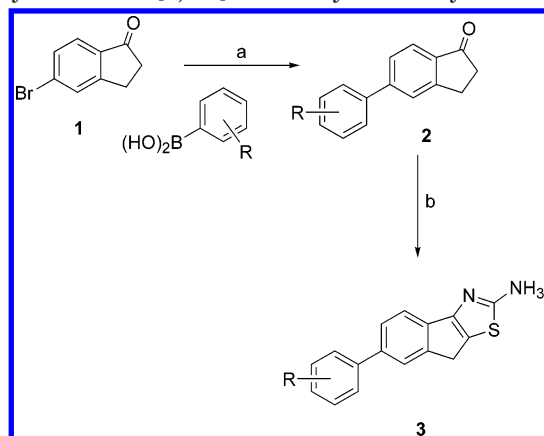
Allosteric enhancers (AEs) of the A₁ adenosine receptor (A₁AR) have potential as drugs for treating neurological, cardiovascular, and renal diseases. This report describes the synthesis and evaluation of a series of 6-aryl-8*H*-indeno[1,2-*d*]thiazol-2-ylamines that exhibited AE activity at the A₁AR. Palladium-mediated condensation of arylboronic acids with 5-bromoindan-1-one generated arylindanones **2a–aj** for iodine-catalyzed condensation with thiourea, generating 2-aminothiazolium salts **3a–aj**. Binding studies using membranes from cells stably expressing human A₁ARs, A_{2A}ARs, or A₃ARs evaluated AE activity and receptor subtype selectivity. The EC₅₀ of the AE activities of compounds **3m–o**, **3x**, and **3ae** were 2.2, 1.5, 0.9, 1.0, and 3.0 μM, respectively, substantially lower than that of the well characterized 2-amino-3-arylthiophene (PD 81,723), >10 μM. The new compounds also have substantially higher maximal AE activity. These compounds had no AE activity at the A_{2A}AR and only minimal activity at the A₃AR.

Introduction

Adenosine activates the A₁ adenosine receptor (A₁AR) in many organs, notably the central nervous system, where it exerts neuromodulatory activity,¹ in the heart, where it exerts negative chronotropic, dromotropic, and atrial inotropic actions,² and in the kidney, where it participates in tubuloglomerular feedback.³ Although potent and highly selective A₁AR agonists have been known for nearly 20 years, none is available for clinical use perhaps because conventional agonists have significant cardiac and renal effects and are poorly accessible to the central nervous system.

All tissues of the body release adenosine constantly, but because cellular uptake and incorporation into the adenylate pool is very efficient,⁴ adenosine concentrations are usually below the level that activates adenosine receptors. However, metabolic stress, especially hypoxia, increases adenosine and adenine nucleotide release and simultaneously inhibits adenosine kinase,⁵ thereby raising the local adenosine concentration. A₁AR agonist allosteric enhancers amplify the action of adenosine by stabilizing the activated agonist–receptor–G protein ternary complex^{6,7} that forms when local adenosine concentrations increase. Accordingly, they act predominantly at sites and at times of elevated endogenous adenosine levels. In other words, their action is site- and event-specific and therefore less likely to cause side effects by indiscriminately activating A₁ARs throughout the body.

Scheme 1. Synthesis of 6-Aryl-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide^a



^a Reagents and conditions: (a) Pd(OAc)₂, K₂CO₃, Bu₄NBr, H₂O, 70–80 °C; (b) I₂, thiourea, DMF, or EtOH, heating.

The 2-amino-3-arylthiophene allosteric enhancers discovered by Bruns and his colleagues^{8,9} have been shown to enhance adenosine actions in heart and thus could be antiarrhythmic,^{10–12} to potentiate ischemic preconditioning¹³ and thus could be cardioprotective, and to mitigate allodynia¹⁴ and thus apparently are accessible to the central nervous system and could be useful in managing chronic pain. Despite such evidence of potential as drugs, these agents have drawbacks. They are aromatic amines and so have carcinogenic risk. More importantly, they are unstable, undergoing oxidation in DMSO in vitro and perhaps rapid metabolism in vivo.¹⁵

We recently reported that 2-aminothiazole derivatives have A₁AR allosteric enhancer activity.¹⁶ Here, we

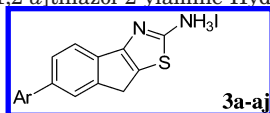
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Table 1. Biological Evaluation of 6-Aryl-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide Salts **3a–aj**

compd	Ar	AE score (%) at 50 μM^a			max AE score (%) ^b	EC ₅₀ @ A ₁ antagonist ^b (μM)	
		A ₁	A _{2a}	A ₃		A ₁	
3a	H	8.2 $\pm$ 1.5	0.0	1.6	ND	>10	ND
3b	2-CH ₃	36.6 $\pm$ 1.2	0.0	0.0	ND	>10	34.4
3c	3-CH ₃	59.2 $\pm$ 2.7	2.0	11.4	ND	>10	ND
3d	2-F	4.9 $\pm$ 1.0	0.0	3.6	ND	>10	13.2
3e	3-F	42.8 $\pm$ 1.8	0.0	3.6	ND	>10	ND
3f	4-F	54.4 $\pm$ 2.1	0.0	11.8	ND	>10	ND
3g	2-Cl	36.7 $\pm$ 1.5	0.0	0.0	ND	>10	ND
3h	3-Cl	22.7 $\pm$ 1.8	0.0	1.0	ND	>10	ND
3i	3-OH	10.0 $\pm$ 1.8	0.0	1.0	ND	>10	36.7
3j	4-OH	4.0 $\pm$ 1.5	0.0	1.0	ND	>10	36.7
3k	2-OCH ₃	38.0 $\pm$ 2.2	0.0	1.0	ND	>10	43.5
3l	3-OCH ₃	64.0 $\pm$ 4.7	0.0	1.8	ND	>10	19.3
3m	4-OCH ₃	87.0 $\pm$ 2.0	0.0	18.0	90.2	2.2	13.0
3n	4-OPh	83.0 $\pm$ 2.6	0.0	3.4	86.7	1.5	8.8
3o	4- <i>N,N</i> -(CH ₃) ₂	81.0 $\pm$ 7.6	3.4	24.8	81.8	0.9	12.5
3p	2-NO ₂	40.1 $\pm$ 2.1	0.0	0.0	49.7	6.3	8.3
3q	3-NO ₂	13.0 $\pm$ 2.9	0.0	0.0	ND	>10	8.3
3r	2-CF ₃	50.1 $\pm$ 1.0	0.0	6.6	57.0	5.1	ND
3s	3-CF ₃	15.8 $\pm$ 1.9	0.0	0.0	ND	>10	ND
3t	4-CF ₃	8.9 $\pm$ 1.1	0.0	0.0	ND	>10	ND
3u	2,5-(CH ₃) ₂	47.7 $\pm$ 1.6	0.0	0.0	51.0	7.3	ND
3v	3,4-(CH ₃) ₂	52.0 $\pm$ 1.1	0.0	0.0	ND	>10	30.1
3w	3,5-(CH ₃) ₂	10.5 $\pm$ 1.0	0.0	0.0	ND	>10	8.7
3x	3,4-(OCH ₃) ₂	82.0 $\pm$ 10.6	0.2	10.1	82.7	1.0	19.2
3y	2,4-(OCH ₃) ₂	73.0 $\pm$ 2.8	0.0	1.9	ND	>10	16.0
3z	3,4,5-(OCH ₃) ₃	23.3 $\pm$ 2.4	0.0	0.8	ND	>10	11.8
3aa	2,3,4-(OCH ₃) ₂	64.5 $\pm$ 2.6	0.3	0.0	ND	>10	18.0
3ab	3,4-OCH ₂ O–	82.0 $\pm$ 7.5	0.0	2.9	91	6.8	11.6
3ac	3,4-Cl ₂	45.3 $\pm$ 4.6	0.0	0.0	22.6	ND	8.0
3ad	3,5-Cl ₂	44.0 $\pm$ 2.3	0.0	0.0	19.3	ND	10.0
3ae	2,3-C ₄ H ₄	61.2 $\pm$ 3.5	0.0	4.2	65.6	3.0	13.0
3af	3,4-C ₄ H ₄	38.6 $\pm$ 3.2	0.0	4.5	ND	>10	4.2
3ag	6-Ome-3,4-C ₄ H ₄	24.4 $\pm$ 3.9	0.0	0.0	ND	>10	ND
3ah	2-thiophenyl	32.0 $\pm$ 2.6	0.0	1.8	ND	>10	11.4
3ai	3-thiophenyl	68.8 $\pm$ 5.7	0.0	3.8	ND	>10	18.2
3aj	2-benzofuranyl	51.0 $\pm$ 2.8	0.8	11.9	ND	>10	ND
	PD 81,723	20.0 $\pm$ 2.2	0.0	5.0	ND	>10	ND

^a AE score activity at a single dose of 50 μM from two to three experiments, $\pm$ SEM when $N = 3$. ^b Curve fitting was used to calculate maximal AE activity and EC₅₀ values only for compounds with EC₅₀ < 10 μM . Parameters are calculated from two to three dose–response curves. ND = not determined because EC₅₀ > 10 μM .

describe the synthesis and allosteric enhancer activities of new 6-arylindeno[1,2-*d*]thiazoles; some are active at the low micromolar to submicromolar range.

Chemistry

Scheme 1 details the two-step synthesis of the target compounds. The palladium-catalyzed coupling¹⁷ of aryl-boronic acids with 5-bromo-1-indanone, **1**, generated 5-arylidene-1-ones **2a–aj** in yields between 62% and 84%. They reacted with thiourea¹⁸ to afford target compounds **3a–aj** as the powdery hydroiodide salts in yields between 62% and 85%.

Results and Discussion

Table 1 summarizes the results of in vitro assays for agonist allosteric enhancer activity at the A₁AR, A_{2A}-AR, and A₃AR. For the assessment of A₁AR enhancer activity, we used a previously described activity score^{7,19} ranging from 0% to 100% that reflects the ability of a compound to retard the dissociation of the agonist–receptor–G protein complex. We used curve fitting (Figure 1) to calculate the EC₅₀ and maximal score of

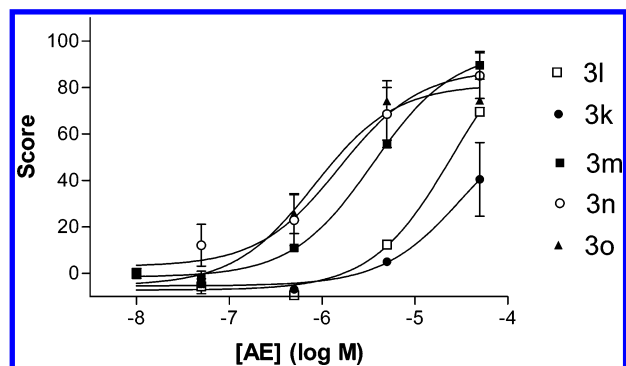


Figure 1. Concentration dependence of AE activity at the A₁-AR of selected 2-aminothiazolium salts.

compounds with EC₅₀ < 10 μM . For compounds with EC₅₀ > 10 μM we could not accurately calculate the maximum response, so we report the score at 50 μM , the maximum concentration used. Compounds **3m–o**, **3x**, and **3ab** had maximal scores greater than 80% and EC₅₀ less than 10 μM . Additionally, compounds **3p**, **3r**, **3u**, and **3ae** had modest efficacy scores, 40–58%, but EC₅₀ values between 3 and 7 μM . As a basis for

Table 2. Comparison of AE Activities of Selected 6-Aryl-8H-indeno[1,2-d]thiazol-2-ylamines at Rat and Human A₁ARs

compd	activity score (%) @ 50 μ M ^a	
	human	rat
3m	72.0 $\pm$ 1.3	32.3 $\pm$ 4.2
3n	46.2 $\pm$ 7.7	19.8 $\pm$ 2.0
3o	67.9 $\pm$ 2.7	31.7 $\pm$ 2.6
3x	83.9 $\pm$ 2.8	39.1 $\pm$ 6.2
3ab	90.7 $\pm$ 4.0	48.8 $\pm$ 2.9

^a Data are the mean values of duplicate assays.**Table 3.** Inhibition of Agonist Equilibrium Binding Selected 6-Aryl-8H-indeno[1,2-d]thiazol-2-ylamines at Human A₁AR and A₃AR

compd	inhibition of agonist binding by 10 μ M AE (%) ^a	
	hA ₁ AR	hA ₃ AR
3m	25.2 $\pm$ 3.2	37.6 $\pm$ 0.9
3n	27.6 $\pm$ 4.3	28.2 $\pm$ 2.7
3o	23.1 $\pm$ 2.9	38.6 $\pm$ 6.2
3x	18.8 $\pm$ 4.1	45.0 $\pm$ 2.9
3ab	10.5 $\pm$ 3.3	22.5 $\pm$ 1.5

^a Data are the mean values of duplicate assays.

comparison, 50 μ M 2-amino-3-arylthiophene (PD 81, 723) has an allosteric enhancer (AE) score of 20 and an EC₅₀ greater than 10 μ M. AE activity at the A_{2A}AR was negligible, but compounds **3c**, **3f**, **3m**, **3o**, **3x**, and **3aj** had modest activity at the A₃AR, their scores ranging between 10% and 25%. Such a result might reflect a similar, though obviously not identical, allosteric site in the hA₁ and hA₃ receptors, which show substantial homology in their amino acid sequences.²⁰

In addition to their allosteric enhancing activity, some of the 2-amino-3-arylthiophenes are competitive antagonists. Since allosteric enhancers do not influence antagonist binding to receptor, antagonist activity can be measured independently of enhancer activity by using antagonist radioligands. All the title compounds had weak antagonist activity, inhibiting the binding of the A₁AR antagonist [³H]8-cyclopentyl-1,3-dipropyl-xanthine from 4% to 44%. There was no correlation between allosteric enhancer and competitive antagonist activities.

Pharmacological studies frequently use the rat, so we examined the AE and antagonist activities of **3m-o**, **3x**, and **3ab** at the rA₁AR. Table 2 summarizes the results, which show that each was less active at the rat than at the human receptor.

Because some aminothiophenes are A₃AR antagonists,²¹ the characterization of **3m-o**, **3x**, and **3ab** included assessment of A₃AR antagonist activity. Since none of the aminothiazoles increased equilibrium binding of [¹²⁵I]ABA (ABA is N⁶-3-aminobenzyl)adenosine) to the A₃AR, antagonist activity could be estimated on the basis of the potency of these compounds to compete for equilibrium [¹²⁵I]ABA binding.⁸ At 10 μ M, these compounds inhibited radioligand binding to a greater extent at the A₃AR than at the A₁AR (Table 3), but in all cases the inhibition was less than 50%.

Because the instability of the 5-alkyl-2-aminothiophenes and the possibility that C-8 of these indenothiazoles might also be a site of oxidation, we examined their stability, finding them stable in DMSO solutions for 2–3 months, as evidenced by unchanged ¹H NMR spectra and consistent AE activity.

The results of this study and our previous report¹⁶ indicate that 2-aminothiazole hydroiodide salts are active as AEs. However, a recent report²² indicates that free bases of 2-aminothiazoles prepared by base treatment of hydroiodide salts and purification by silica gel column chromatography are inactive. Using the same method of purification, we confirmed that free bases of compounds **3l**, **3m**, and **3o** in fresh solutions are weakly active as AEs. However, the AE activity in solutions of these compounds in DMF, DMSO, or acetonitrile increases after 4 h and increases further to a constant activity equivalent to that of the hydroiodine salts after 12 h. When free bases **3l** and **3m** are dissolved in deuterated solvents such as DMSO-*d*₆, DMF-*d*₄, and acetonitrile-*d*₃ and monitored for several hours, no apparent change in ¹H NMR was observed along with the increase in AE activity. The reason for this increase in AE activity of the free bases over time is under investigation.

Although the panel of aminothiazoles characterized to date does not provide detailed information about structure–activity rules, a few trends are evident. Electron-donating phenyl substituents, especially in the para position, supported activity (compounds **3m-o**, **3x**, and **3ab**), and conversely, electron-withdrawing substituents tended to reduce activity. A large aryl substituent (compounds **3ae-ag**, **3aj**) neither promoted nor diminished AE activity.

There is some evidence that the 2-aminoindenothiazoles and the 2-amino-3-arylthiophenes might have similar docking modes in the allosteric site. Whereas the AE activity of the 2-aminothiophenes depended on both the 2-amino and the 3-aryl groups, these aminothiazoles lack a substituent that corresponds to the aryl group. However, superimposing the two heterocycles suggests that the thiazole nitrogen could serve as a surrogate for the aryl carbonyl, acting, for example, as a hydrogen-bond acceptor. The aryl group of the 2-amino-3-arylthiophenes can occupy a position near, but not overlapping, the benzene moiety of the indenothiazole (Figure 2). Finally, Bruns has suggested⁹ that the AE activity of a 2-amino-3-arylthiophene is due to the planarity of the molecule, conferred by a hydrogen bond between the 2-amino and the aryl carbonyl groups. By analogy with another 6:5:6 tricyclic, 9H-fluorene, a planar molecule,²³ these indeno[1,2-d]thiazoles are probably also planar, which would support the Bruns model.

Conclusion

In conclusion, we report the preparation and evaluation of new 6-arylindenothiazoles for their allosteric enhancer activity at the human A₁ adenosine receptor. Several of the new compounds were more potent A₁AR agonist enhancers than known 2-aminothiophenes and some of the aminothiazoles reported previously. Unlike the 2-aminothiophenes, these 2-aminoindenothiazoles in DMSO do not appear to be susceptible to oxidation. However, both the aminothiazoles, and the aminothiophenes, are aromatic, so future work must assess their carcinogenic potential.

Experimental Section

5-Bromoindanone was from Acros Organics, and palladium acetate was from Strem Chemicals. Other reagents and chemicals were of the highest purity offered by Aldrich, Acros

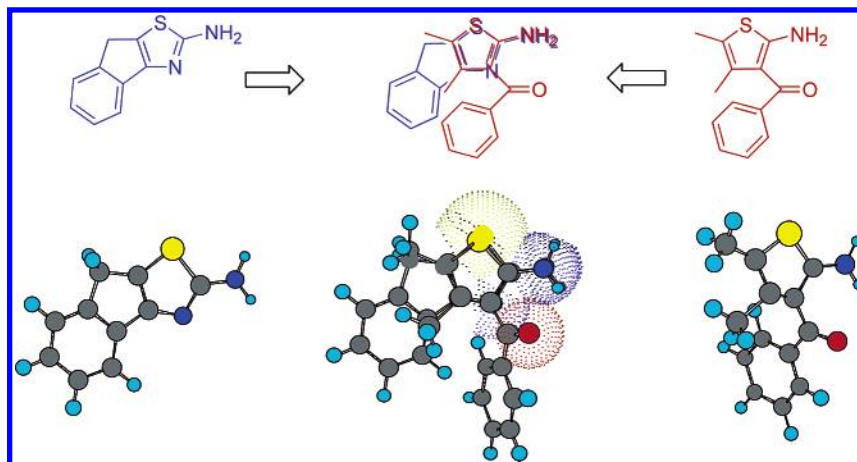


Figure 2. Superimposition of a 2-aminoindeno[1,2-*d*]thiazole (left, blue) on a 2-amino-3-benzoylthiophene (right, red). Also shown is chem3D MM2 minimized overlay of models with electron density map. Note the proximity of the thiazole N and the benzoyl carbonyl and the phenyl moieties of the indene and the benzoyl groups.

Organics, or Lancaster and were used without further purification. Suzuki coupling reactions were carried out in freshly deoxygenated, deionized water continuously bubbled with nitrogen. ^1H NMR spectra were recorded on Varian Unity 300 MHz spectrometer. ^{13}C NMR was recorded on either a General Electric GN 300 or a Varian Unity 300 spectrometer working at 75 MHz. The chemical shifts are reported as ppm. ^{13}C NMR data were proton-decoupled. Sample purity and mass spectral analyses for new 6-aryllindanone derivatives were performed on an HP GCD plus GC-MS system. A Finnigan Matt TSQ 7000 spectrometer provided electron spray ionization mass spectra. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Atlantic Microlab Inc., Norcross, GA, performed the elemental analyses on some of the target compounds, while other samples were analyzed in house on a Perkin-Elmer series II 2400 CHNS analyzer, which agreed within $\pm 0.4\%$ of the calculated composition. In other instances, high-resolution MS and HPLC in two systems evaluated the identity and purity of the compounds.

General Procedure for Suzuki Coupling: Synthesis of 5-Aryllindan-1-ones (2a–aj). A mixture of 5-bromoindan-1-one (1.0 mmol), the appropriate arylboronic acid (1.1 mmol), tetrabutylammonium bromide (1.0 mmol), and K_2CO_3 (8–10 mmol) was suspended in freshly nitrogen-purged deionized water (3.0 mL) and purged with nitrogen for an additional 20 min. $\text{Pd}(\text{OAc})_2$ (2.5 mg, 0.01 mmol, ~ 1 mol %) was added, and the resulting suspension was stirred with heating for 2–3 h on an oil bath at 70°C . After the solution had cooled to room temperature it was diluted with water (10 mL) and extracted twice with CH_2Cl_2 (15 mL). The combined extracts were washed once with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to yield crude residue. Purification of residue consisted of chromatography on silica, eluting with a gradient of ethyl acetate–hexane that began with 10% and ended with 30% ethyl acetate. Evaporation of fractions containing product gave the 5-aryllindan-1-one as a solid.

5-Phenyl-2,3-dihydroindene-1-one (2a). Mp $104\text{--}5^\circ\text{C}$. ^1H NMR (CDCl_3): δ 2.75 (t, $J = 6.4$ Hz, 2H, CH_2), 3.21 (t, $J = 6.4$ Hz, 2H, CH_2), 7.25–7.51 (m, 3H, ArH), 7.61 (d, $J = 8.0$ Hz, 1H, ArH), 7.64 (dd, $J = 8.4$ Hz, 2H, ArH), 7.68 (s, 1H, ArH), 7.83 (d, $J = 8.1$ Hz, 1H, ArH).

5-(2-Methylphenyl)-2,3-dihydroindene-1-one (2b). Yield 84%, mp 87°C . ^1H NMR (CDCl_3): δ 2.28 (s, 3H, CH_3), 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 6.6$ Hz, 2H, CH_2), 7.21–7.35 (m, 5H, ArH), 7.42 (s, 1H, ArH), 7.80 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 20.3, 25.8, 36.4, 123.3, 125.8, 127.2, 127.9, 128.7, 129.4, 130.4, 135.0, 135.6, 140.9, 148.7, 155.2, 206.6. MS (ESI) m/z : 222 (M^+).

5-(3-Methylphenyl)-2,3-dihydroindene-1-one (2c). Yield 79%, mp 92°C . ^1H NMR (CDCl_3): δ 2.44 (s, 3H, CH_3), 2.74 (m, $J = 6.6$ Hz, 2H, CH_2), 3.20 (t, $J = 6.6$ Hz, 2H, CH_2), 7.23

(d, $J = 7.5$ Hz, 1H, ArH), 7.36 (t, $J = 7.2$ Hz, 1H, ArH), 7.43 (d, $J = 6.9$ Hz, 1H, ArH), 7.60 (d, $J = 7.8$ Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.81 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 21.4, 25.8, 36.4, 123.9, 124.5, 1125.0, 126.7, 128.1, 128.8, 129.0, 135.8, 138.5, 140.1, 147.8, 155.7, 206.5. MS (ESI) m/z : 222 (M^+).

5-(2-Fluorophenyl)-2,3-dihydroindene-1-one (2d). Yield 68%, mp 90°C . ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 5.7$ Hz, 2H, CH_2), 7.16 (dd, $J = 1.2, 8.1$ Hz, 1H, ArH), 7.24 (dd, $J = 7.5, 8.1$ Hz, 1H, ArH), 7.35 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.50 (d, $J = 8.1$ Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.82 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.4, 116.1 and 116.4 (d), 123.6, 125.8, 124.5, 127.2, 128.4, 130.0 and 129.9 (d), 130.6, 136.2, 142.2, 155.2, 157.9, 161.1, 206.5. MS (ESI) m/z : 226 (M^+).

5-(3-Fluorophenyl)-2,3-dihydroindene-1-one (2e). Yield 71%, mp $114\text{--}5^\circ\text{C}$. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.18 (t, $J = 5.7$ Hz, 2H, CH_2), 7.08 (m, 1H, ArH), 7.30 (dt, $J = 2.4, 9.9$ Hz, 1H, ArH), 7.36–7.46 (m, 2H, ArH), 7.55 (dd, $J = 1.5, 8.1$ Hz, 1H, ArH), 7.64 (d, $J = 1.5$ Hz, 1H, ArH), 7.80 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 114.1 and 114.4 (d), 114.9 and 115.2 (d), 123.0, 124.1, 125.1, 126.6, 130.4 and 130.3 (d), 136.3, 142.3, 146.1, 155.8, 161.4 and 164.7 (d), 206.3. MS (ESI) m/z : 226 (M^+).

5-(4-Fluorophenyl)-2,3-dihydroindene-1-one (2f). Yield 65%, mp $93\text{--}4^\circ\text{C}$. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 5.7$ Hz, 2H, CH_2), 7.17 (t, $J = 8.1$ Hz, 2H, ArH), 7.53–7.69 (m, 4H, ArH), 7.81 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.3, 115.6 and 115.9 (d), 123.9, 124.8, 126.4, 129.0 and 129.3 (d), 135.8, 136.1, 146.4, 155.8, 161.2 and 164.5 (d), 206.3. MS (ESI) m/z : 226 (M^+).

5-(2-Chlorophenyl)-2,3-dihydroindene-1-one (2g). Yield 72%, mp 76°C . ^1H NMR (CDCl_3): δ 2.72 (m, $J = 6.6$ Hz, 2H, CH_2), 3.18 (t, $J = 6.0$ Hz, 2H, CH_2), 7.29–7.40 (m, 3H, ArH), 7.42 (dd, $J = 0.9, 7.8$ Hz, 1H, ArH), 7.48 (m, 1H, ArH), 7.52 (brs, 1H, ArH), 7.79 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.3, 123.2, 126.9, 127.5, 128.9, 129.1, 130.0, 131.0, 132.1, 136.1, 139.5, 145.7, 154.9, 206.4. MS (ESI) m/z : 242, 244 (M^+).

5-(3-Chlorophenyl)-2,3-dihydroindene-1-one (2h). Yield 74%, mp 111°C . ^1H NMR (CDCl_3): δ 2.72 (m, $J = 6.6$ Hz, 2H, CH_2), 3.17 (t, $J = 5.7$ Hz, 2H, CH_2), 7.32–7.38 (m, 2H, ArH), 7.47 (dt, $J = 2.1, 6.3$, 1H, ArH), 7.53 (dd, $J = 0.9, 8.1$ Hz, 1H, ArH), 7.57 (t, $J = 2.1$ Hz, 1H, ArH), 7.62 (brs, 1H, ArH), 7.79 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.4, 124.0, 125.1, 125.5, 126.5, 127.4, 128.1, 130.1, 134.7, 136.3, 141.9, 145.9, 155.7, 206.3. MS (ESI) m/z : 242, 244 (M^+).

5-(3-Hydroxyphenyl)-2,3-dihydroindene-1-one (2i). Yield 74%, mp $185\text{--}6^\circ\text{C}$. ^1H NMR (CDCl_3): δ 2.75 (m, 2H, CH_2), 3.19 (t, $J = 5.7$ Hz, 2H, CH_2), 6.91 (dd, $J = 2.4, 8.1$ Hz, 1H, ArH), 7.12 (t, $J = 1.8$ Hz, 1H, ArH), 7.18 (d, $J = 7.5$ Hz, 1H, ArH), 7.34 (t, $J = 7.8$ Hz, 1H, ArH), 7.56 (dd, $J = 0.9, 8.1$ Hz,

1H, ArH), 7.65 (s, 1H, ArH), 7.81 (d, $J = 7.8$ Hz, 1H, ArH). MS (ESI) m/z : 224 (M^+).

5-(4-Hydroxyphenyl)-2,3-dihydroindene-1-one (2j). Yield 70%, mp 212–3 °C. ^1H NMR ($\text{CDCl}_3 + \text{DMSO}-d_6$): δ 2.57 (m, 2H, CH_2), 3.04 (t, $J = 5.7$ Hz, 2H, CH_2), 6.82 (dd, $J = 1.8$, 8.4 Hz, 2H, ArH), 7.35 (dd, $J = 2.1$, 8.4 Hz, 2H, ArH), 7.41 (dd, $J = 1.8$, 8.4 Hz, 2H, ArH), 7.48 (d, $J = 1.8$ Hz, 1H, ArH), 7.61 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR ($\text{CDCl}_3 + \text{DMSO}-d_6$): δ 25.0, 35.7, 115.3 $\times$ 2, 122.9, 123.4, 125.1, 127.7 $\times$ 2, 134.2, 146.7, 155.2, 157.3, 205.6. MS (ESI) m/z : 224 (M^+).

5-(2-Methoxyphenyl)-2,3-dihydroindene-1-one (2k). Yield 69%, mp 114–5 °C. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 6.6$ Hz, 2H, CH_2), 3.83 (s, 3H, OCH₃), 6.95 (ddd, $J = 0.9$, 1.8, 8.1 Hz, 1H, ArH), 7.15 (t, $J = 1.8$, 8.1 Hz, 1H, ArH), 7.20 (ddd, $J = 0.9$, 1.5, 8.1 Hz, 1H, ArH), 7.39 (t, $J = 7.5$ Hz, 1H, ArH), 7.59 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.67 (d, $J = 1.5$ Hz, 1H, ArH), 7.82 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 55.5, 111.2, 120.8, 123.1, 127.5, 129.1, 129.5, 129.6, 130.7, 135.6, 145.3, 155.0, 156.3, 206.7. MS (ESI) m/z : 238 (M^+).

5-(3-Methoxyphenyl)-2,3-dihydroindene-1-one (2l). Yield 72%, mp 103–4 °C. ^1H NMR (CDCl_3): δ 2.74 (m, $J = 6.6$ Hz, 2H, CH_2), 3.20 (t, $J = 6.6$ Hz, 2H, CH_2), 3.88 (s, 3H, OCH₃), 6.95 (ddd, $J = 0.9$, 1.8, 8.1 Hz, 1H, ArH), 7.15 (t, $J = 1.8$, 8.1 Hz, 1H, ArH), 7.20 (ddd, $J = 0.9$, 1.5, 8.1 Hz, 1H, ArH), 7.39 (t, $J = 7.5$ Hz, 1H, ArH), 7.59 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.67 (d, $J = 1.5$ Hz, 1H, ArH), 7.82 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 55.3, 113.1, 113.6, 119.9, 124.0, 125.1, 126.7, 129.9, 136.0, 141.6, 147.5, 155.7, 159.9, 206.5. MS (ESI) m/z : 238 (M^+).

5-(4-Methoxyphenyl)-2,3-dihydroindene-1-one (2m). Yield 76%, mp 154–5 °C. ^1H NMR (CDCl_3): δ 2.73 (m, 2H, CH_2), 3.18 (t, $J = 5.7$ Hz, 2H, CH_2), 3.86 (s, 3H, OCH₃), 7.01 (d, $J = 8.7$ Hz, 2H, ArH), 7.56 (brd, $J = 8.4$ Hz, 1H, ArH), 7.58 (d, $J = 8.7$ Hz, 2H, ArH), 7.63 (s, 1H, ArH), 7.80 (d, $J = 8.4$ Hz, 1H, ArH). Partial ^{13}C NMR (CDCl_3): δ 25.8, 36.5, 55.3, 114.3 $\times$ 2, 124.0, 126.2, 128.6 $\times$ 2, 135.4, 146.7, 155.2, 157.3, 206.1. MS (ESI) m/z : 238 (M^+).

5-(4-Phenoxyphenyl)-2,3-dihydroindene-1-one (2n). Yield 80%, mp 142–3 °C. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 6.6$ Hz, 2H, CH_2), 7.06–7.13 (m, 4H, ArH), 7.16 (d, $J = 8.7$ Hz, 1H, ArH), 7.35–7.41 (m, 2H, ArH), 7.56–7.63 (m, 3H, ArH), 7.65 (brs, 1H, ArH), 7.81 (d, $J = 8.1$ Hz, 1H, ArH). MS (ESI) m/z : 300 (M^+).

5-(4-*N,N*-Dimethylaminophenyl)-2,3-dihydroindene-1-one (2o). Yield 64%, mp 217–8 °C. ^1H NMR (CDCl_3): δ 2.71 (m, $J = 6.6$ Hz, 2H, CH_2), 3.02 (s, 6H, N-CH₃ $\times$ 2), 3.16 (t, $J = 6.3$ Hz, 2H, CH_2), 6.81 (d, $J = 8.4$ Hz, 2H, ArH), 7.55 (dd, $J = 1.8$, 7.8 Hz, 1H, ArH), 7.57 (d, $J = 8.4$ Hz, 2H, ArH), 7.63 (dd, $J = 0.6$, 8.1 Hz, 1H, ArH), 7.77 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.5, 114.0, 115.0, 117.8, 123.9, 125.0, 126.7, 129.8, 135.9, 141.3, 146.8, 147.9, 155.7, 206.6. MS (ESI) m/z : 251 (M^+).

5-(2-Nitrophenyl)-2,3-dihydroindene-1-one (2p). Yield 68%, mp 124 °C. ^1H NMR (CDCl_3): δ 2.71 (m, $J = 6.0$ Hz, 2H, CH_2), 3.16 (t, $J = 6.0$ Hz, 2H, CH_2), 7.28 (dd, $J = 1.2$, 7.5 Hz, 1H, ArH), 7.41 (d, $J = 2.1$ Hz, 1H, ArH), 7.43 (d, $J = 7.8$ Hz, 1H, ArH), 7.54 (dt, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.65 (dt, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.77 (d, $J = 8.1$ Hz, 1H, ArH), 7.92 (dd, $J = 1.2$, 8.1 Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.6, 36.2, 123.8, 124.3, 126.4, 127.3, 128.9, 131.6, 132.6, 135.6, 136.6, 143.9, 148.7, 155.3, 206.2. MS (ESI) m/z : 253 (M^+).

5-(3-Nitrophenyl)-2,3-dihydroindene-1-one (2q). Yield 79%, mp 147 °C. ^1H NMR (CDCl_3): δ 2.77 (m, $J = 6.0$ Hz, 2H, CH_2), 3.24 (t, $J = 6.0$ Hz, 2H, CH_2), 7.63 (ddd, $J = 4\text{H}$, ArH), 7.68 (d, $J = 8.1$ Hz, 1H, ArH), 7.73 (d, $J = 0.6$ Hz, 1H, ArH), 7.87 (d, $J = 8.1$ Hz, 1H, ArH), 7.96 (ddd, $J = 1.2$, 1.8, 7.5 Hz, 1H, ArH), 8.27 (ddd, $J = 1.2$, 3.6, 8.1 Hz, 1H, ArH), 8.49 (t, $J = 1.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 122.3, 122.9, 124.4, 125.4, 126.7, 129.9, 133.3, 136.9, 141.9, 144.8, 148.7, 155.9, 206.2. MS (ESI) m/z : 253 (M^+).

5-(2-Trifluoromethylphenyl)-2,3-dihydroindene-1-one (2r). Yield 70%, mp 112 °C. ^1H NMR (CDCl_3): δ 2.75 (m, $J = 5.7$ Hz, 2H, CH_2), 3.19 (t, $J = 5.7$ Hz, 2H, CH_2), 7.32 (d, $J = 7.5$ Hz, 2H, ArH), 7.43 (s, 1H, ArH), 7.51 (t, $J = 7.5$

Hz, 1H, ArH), 7.59 (t, $J = 7.2$ Hz, 1H, ArH), 7.77 (d, $J = 7.5$ Hz, 1H, ArH), 7.78 (d, $J = 7.5$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.6, 36.3, 122.9, 126.0, 127.1, 127.9, 128.4, 131.4, 136.3, 140.2, 146.2, 154.6, 206.4. MS (ESI) m/z : 253 (M^+).

5-(3-Trifluoromethylphenyl)-2,3-dihydroindene-1-one (2s). Yield 75%, mp 120 °C. ^1H NMR (CDCl_3): δ 2.70 (m, $J = 5.7$ Hz, 2H, CH_2), 3.17 (t, $J = 5.7$ Hz, 2H, CH_2), 7.55 (t, $J = 7.8$ Hz, 2H, ArH), 7.63 (d, $J = 8.4$ Hz, 1H, ArH), 7.64 (brs, 1H, ArH), 7.77 (t, $J = 8.1$ Hz, 2H, ArH), 7.84 (d, $J = 1.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.3, 124.0, 124.7, 125.1, 126.5, 129.3, 130.6, 136.4, 140.8, 145.7, 155.8, 206.2. MS (ESI) m/z : 253 (M^+).

5-(4-Trifluoromethylphenyl)-2,3-dihydroindene-1-one (2t). Yield 74%, mp 118 °C. ^1H NMR (CDCl_3): δ 2.76 (m, $J = 6.6$ Hz, 2H, CH_2), 3.22 (t, $J = 5.7$ Hz, 2H, CH_2), 7.60 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.68 (d, $J = 1.5$ Hz, ArH), 7.73 (brs, 4H, ArH), 7.85 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 124.2 $\times$ 2, 125.4, 125.8, 126.8, 127.7 $\times$ 2, 130.0, 136.6, 143.7, 146.0, 155.8, 206.2. MS (ESI) m/z : 253 (M^+).

5-(2,5-Dimethylphenyl)-2,3-dihydroindene-1-one (2u). Yield 84%, mp 114 °C. ^1H NMR (CDCl_3): δ 2.23 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.74 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 6.3$ Hz, 2H, CH_2), 7.05 (s, 1H, ArH), 7.12 (dd, $J = 1.5$, 9.0 Hz, 1H, ArH), 7.19 (d, $J = 7.8$ Hz, 1H, ArH), 7.33 (dd, $J = 1.2$, 7.8 Hz, 1H, ArH), 7.41 (d, $J = 1.2$ Hz, 1H, ArH), 7.89 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 19.8, 20.8, 25.7, 36.3, 123.2, 127.2, 128.5, 128.7, 130.1, 130.4, 131.8, 135.3, 135.5, 140.7, 148.8, 155.1, 206.6. MS (ESI) m/z : 236 (M^+).

5-(3,4-Dimethylphenyl)-2,3-dihydroindene-1-one (2v). Yield 81%, mp 111 °C. ^1H NMR (CDCl_3): δ 2.23 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.75 (m, 2H, CH_2), 3.19 (t, $J = 6.0$ Hz, 2H, CH_2), 7.05 (s, 1H, ArH), 7.12 (d, $J = 8.4$ Hz, 2H, ArH), 7.19 (d, $J = 7.8$ Hz, 1H, ArH), 7.33 (d, $J = 7.8$ Hz, 1H, ArH), 7.42 (s, 1H, ArH), 7.79 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 19.8, 21.3, 25.7, 36.3, 123.2, 126.7, 128.5, 128.7, 130.1, 130.4, 131.8, 135.3, 135.5, 140.7, 148.8, 155.1, 206.6. MS (ESI) m/z : 236 (M^+).

5-(3,5-Dimethylphenyl)-2,3-dihydroindene-1-one (2w). Yield 84%, mp 107–8 °C. ^1H NMR (CDCl_3): δ 2.40 (s, 6H, CH₃ $\times$ 2), 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.19 (t, $J = 6.3$ Hz, 2H, CH_2), 7.06 (s, 1H, ArH), 7.24 (d, $J = 1.8$ Hz, 2H, ArH), 7.58 (dd, $J = 1.6$, 7.8 Hz, 1H, ArH), 7.66 (d, $J = 1.6$ Hz, 1H, ArH), 7.80 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 21.3, 25.8, 36.4, 123.8, 125.0, 125.2 $\times$ 2, 126.7, 129.9, 135.7, 138.4 $\times$ 2, 140.0, 147.9, 155.7, 206.6. MS (ESI) m/z : 236 (M^+).

5-(3,4-Dimethoxyphenyl)-2,3-dihydroindene-1-one (2x). Yield 75%, mp 175 °C. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.0$ Hz, 2H, CH_2), 3.19 (t, $J = 6.6$ Hz, 2H, CH_2), 3.94 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 6.97 (d, $J = 8.4$ Hz, 1H, ArH), 7.14 (d, $J = 2.1$ Hz, 1H, ArH), 7.21 (dd, $J = 2.1$, 8.4 Hz, 1H, ArH), 7.57 (brd, $J = 7.8$ Hz, 1H, ArH), 7.64 (d, $J = 0.6$ Hz, 1H, ArH), 7.80 (d, $J = 7.8$ Hz, 1H, ArH). MS (ESI) m/z : 236 (M^+).

5-(2,3-Dimethoxyphenyl)-2,3-dihydroindene-1-one (2y). Yield 68%, mp 129 °C. ^1H NMR (CDCl_3): δ 2.71 (m, $J = 6.0$ Hz, 2H, CH_2), 3.17 (t, $J = 6.0$ Hz, 2H, CH_2), 3.81 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.57 (brs, 1H, ArH), 6.59 (dd, $J = 2.4$, 7.5 Hz, 1H, ArH), 7.26 (d, $J = 7.4$ Hz, 1H, ArH), 7.51 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.58 (brs, 1H, ArH), 7.76 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.4, 55.4, 55.5, 98.9, 104.7, 122.4, 123.0, 127.2, 128.9, 131.3, 135.1, 145.1, 155.1, 157.4, 160.6, 206.7. MS (ESI) m/z : 236 (M^+).

5-(3,4,5-Trimethoxyphenyl)-2,3-dihydroindene-1-one (2z). Yield 76%, mp 161 °C. ^1H NMR (CDCl_3): δ 2.75 (m, $J = 6.0$ Hz, 2H, CH_2), 3.21 (t, $J = 6.3$ Hz, 2H, CH_2), 3.91 (s, 3H, OMe), 3.94 (s, 6H, OMe $\times$ 2), 6.81 (s, 2H, ArH), 7.57 (d, $J = 8.7$ Hz, 1H, ArH), 7.63 (brs, 1H, ArH), 7.81 (d, $J = 8.4$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 56.1, 60.8, 104.5, 123.7, 124.8, 126.4, 135.6, 135.7, 138.1, 147.4, 153.3, 155.6, 206.1. MS (ESI) m/z : 298 (M^+).

5-(2,3,4-Trimethoxyphenyl)-2,3-dihydroindene-1-one (2aa). Yield 72%, mp 158–9 °C. ^1H NMR (CDCl_3): δ 2.71 (m, $J = 6.0$ Hz, 2H, CH_2), 3.17 (t, $J = 5.7$ Hz, 2H, CH_2), 3.68 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.92 (s, 6H, OMe), 6.75 (d, $J = 8.4$ Hz, 1H, ArH), 7.05 (d, $J = 8.7$ Hz, 1H, ArH), 7.50 (dd, $J =$

1.2, 8.4 Hz, 1H, ArH), 7.59 (brs, 1H, ArH), 7.76 (d, $J = 7.8$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.6, 36.2, 55.8, 60.8, 60.9, 107.3, 123.0, 124.7, 126.9, 128.4, 135.2, 142.3, 144.7, 151.2, 153.6, 155.0, 206.5. MS (ESI) m/z : 298 (M^+).

5-(3,4-Methylenedioxyphenyl)-2,3-dihydroindene-1-one (2ab). Yield 74%, mp 171–2 °C. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.18 (t, $J = 6.0$ Hz, 2H, CH_2), 6.02 (s, 2H, OCH_2O), 6.90 (dd, $J = 1.5, 7.5$ Hz, 1H, ArH), 7.10 (brs, 1H, ArH), 7.12 (dd, $J = 1.8, 7.8$ Hz, 1H, ArH), 7.52 (brd, $J = 8.1$ Hz, 1H, ArH), 7.59 (brs, 1H, ArH), 7.78 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 101.3, 107.7, 108.7, 121.2, 124.0, 124.6, 126.4, 134.4, 135.6, 147.3, 147.9, 148.3, 155.8, 206.4. MS (ESI) m/z : 298 (M^+).

5-(3,4-Dichlorophenyl)-2,3-dihydroindene-1-one (2ac). Yield 62%, mp 151 °C. ^1H NMR (CDCl_3): δ 2.75 (m, $J = 6.0$ Hz, 2H, CH_2), 3.21 (t, $J = 6.3$ Hz, 2H, CH_2), 7.45 (dd, $J = 2.4, 8.4$ Hz, 1H, ArH), 7.54 (d, $J = 8.1$ Hz, 1H, ArH), 7.63 (d, $J = 0.9$ Hz, 1H, ArH), 7.72 (d, $J = 2.4$ Hz, 1H, ArH), 7.83 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 124.3, 125.0, 126.4, 126.6, 129.2, 130.8, 132.5, 133.1, 136.6, 140.1, 144.9, 155.8, 206.3. MS (ESI) m/z : 276, 278, 280 (M^+).

5-(3,5-Dichlorophenyl)-2,3-dihydroindene-1-one (2ad). Yield 64%, mp 170 °C. ^1H NMR (CDCl_3): δ 2.75 (m, $J = 6.0$ Hz, 2H, CH_2), 3.21 (t, $J = 6.3$ Hz, 2H, CH_2), 7.40 (dd, $J = 1.8, 2.1$ Hz, 1H, ArH), 7.50 (m, 2H, ArH), 7.55 (d, $J = 8.1$ Hz, 1H, ArH), 7.64 (d, $J = 0.6$ Hz, 1H, ArH), 7.83 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 23.7, 36.3, 124.2, 125.1, 125.8, 126.5, 128.0, 135.4, 143.0, 144.5, 155.7, 206.7. MS (ESI) m/z : 276, 278, 280 (M^+).

5-(Naphth-1-yl)-2,3-dihydroindene-1-one (2ae). Yield 68%, mp 155 °C. ^1H NMR (CDCl_3): δ 2.78 (m, 2H, CH_2), 3.24 (t, $J = 5.7$ Hz, 2H, CH_2), 7.42–7.56 (m, 5H, ArH), 7.60 (brs, 1H, ArH), 7.82–7.95 (m, 4H, ArH). ^{13}C NMR (CDCl_3): δ 25.6, 36.2, 123.0, 124.9, 125.1, 125.6, 126.0, 126.6, 127.8, 129.1, 130.7, 133.3, 135.6, 138.7, 147.0, 154.9, 206.0. MS (ESI) m/z : 258 (M^+).

5-(Naphth-2-yl)-2,3-dihydroindene-1-one (2af). Yield 72%, mp 168 °C. ^1H NMR (CDCl_3): δ 2.77 (m, 2H, CH_2), 3.24 (t, $J = 6.6$ Hz, 2H, CH_2), 7.50–7.65 (m, 2H, ArH), 7.60–7.80 (m, 2H, ArH), 7.81 (d, $J = 0.6$ Hz, 1H, ArH), 7.85–7.94 (m, 3H, ArH), 7.96 (d, $J = 8.4$ Hz, 1H, ArH), 8.10 (d, $J = 1.5$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.9, 36.5, 123.9, 125.1, 126.4, 126.8, 127.5, 128.2, 128.5, 132.8, 133.3, 135.8, 137.2, 147.3, 155.7, 206.4. MS (ESI) m/z : 258 (M^+).

5-(6-Methoxynaphth-2-yl)-2,3-dihydroindene-1-one (2ag). Yield 72%, mp not determined. ^1H NMR (CDCl_3): δ 2.76 (m, 2H, CH_2), 3.22 (t, $J = 6.6$ Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3), 7.16–7.25 (m, 2H, ArH), 7.55–7.86 (m, 6H, ArH), 8.03 (s, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.8, 36.4, 55.2, 105.5, 119.4, 124.0, 124.9, 125.7, 126.3, 126.6, 127.4, 128.9, 129.8, 134.2, 135.1, 147.5, 155.9, 158.1, 206.6. MS (ESI) m/z : 288 (M^+).

5-(Thiophen-2-yl)-2,3-dihydroindene-1-one (2ah). Yield 68%, mp 111 °C. ^1H NMR (CDCl_3): δ 2.72 (m, $J = 6.6$ Hz, 2H, CH_2), 3.17 (t, $J = 6.6$ Hz, 2H, CH_2), 7.12 (dd, $J = 3.6, 5.1$ Hz, 1H, ArH), 7.38 (dd, $J = 0.9, 5.1$ Hz, 1H, ArH), 7.45 (dd, $J = 0.9, 3.6$ Hz, 1H, ArH), 7.63 (dd, $J = 1.5, 8.17$ Hz, 1H, ArH), 7.69 (m, 1H, ArH), 7.75 (d, $J = 8.1$ Hz, 1H, ArH). MS (ESI) m/z : 214 (M^+).

5-(Thiophen-3-yl)-2,3-dihydroindene-1-one (2ai). Yield 65%, mp 154 °C. ^1H NMR (CDCl_3): δ 2.73 (m, $J = 6.6$ Hz, 2H, CH_2), 3.18 (t, $J = 5.7$ Hz, 2H, CH_2), 7.44 (brd, $J = 2.1$ Hz, 2H, ArH), 7.59 (t, $J = 2.1$ Hz, 1H, ArH), 7.68 (brs, 1H, ArH), 7.78 (d, $J = 8.1$ Hz, 1H, ArH). ^{13}C NMR (CDCl_3): δ 25.7, 36.4, 122.3, 124.0, 124.1, 125.8, 126.2, 126.7, 135.7, 141.2, 141.7, 155.9, 206.3. MS (ESI) m/z : 214 (M^+).

5-(Benzofuran-2-yl)-2,3-dihydroindene-1-one (2aj). Yield 72%, mp not determined. ^1H NMR (CDCl_3): δ 2.74 (m, $J = 6.6$ Hz, 2H, CH_2), 3.18 (t, $J = 6.0$ Hz, 2H, CH_2), 7.18 (s, 1H, ArH), 7.23–7.29 (m, 2H, ArH), 7.34 (dt, $J = 1.5, 8.4$ Hz, 1H, ArH), 7.54 (brd, $J = 8.4$ Hz, 1H, ArH), 7.62 (brd, $J = 7.8$ Hz, 1H, ArH), 7.83 (ABd, $J = 8.1$ Hz, 2H, ArH), 7.98 (s, 1H, ArH). MS (ESI) m/z : 248 (M^+).

6-Phenyl-8H-indeno[1,2-d]thiazol-2-ylamine (3a–aj). General Method B. A mixture of **2a–aj** (1 mmol), thiourea

(152 mg, 2 mmol), and iodine (279 mg, 1.1 mg-at.) in 2 mL of absolute ethanol was heated for 3 h in an open vessel in a 105 °C oil bath. The alcohol was evaporated; more ethanol (2 mL) was added, and the mixture was taken to dryness. The dark residue was washed with ether (5 mL $\times$ 3), and the washings were discarded. The residue was dissolved in hot water (~3 mL) with vigorous stirring; solid product separated on cooling to room temperature. The solid was filtered and washed with warm water and finally with ether (~5 $\times$ 2 mL). The solid was vacuum-dried. Occasionally, obtaining an analytical sample required reprecipitation from hot water.

6-(Phenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3a). Yield 89%. Anal. ($\text{C}_{16}\text{H}_{13}\text{IN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 3.85 (s, 2H, CH_2), 7.35 (dt, $J = 1.2, 7.2$ Hz, 1H, ArH), 7.46 (t, $J = 8.1$ Hz, 2H, ArH), 7.60 (d, $J = 8.1$ Hz, 2H, ArH), 7.65–7.70 (m, 3H, ArH), 7.85 (brs, 1H, ArH), 8.80 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 33.9, 118.5, 122.5, 123.4, 125.6, 126.6 $\times$ 2, 127.4, 129.0 $\times$ 2, 132.5, 137.5, 140.0, 143.8, 146.2, 173.9. MS (ESI) m/z : 264 (M^+).

6-(2-Methylphenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3b). Yield 84%. Anal. ($\text{C}_{17}\text{H}_{15}\text{IN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 2.23 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 7.19–7.32 (m, 4H, ArH), 7.34 (d, $J = 7.8$ Hz, 1H, ArH), 7.52 (s, 1H, ArH), 7.61 (d, $J = 7.8$ Hz, 1H, ArH), 9.00 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 20.2, 33.9, 117.8 br, 122.4, 125.8, 125.9, 127.7 br, 129.5 br, 130.3 br, 130.5 br, 132.0, 134.8, 138.7, 141.2, 143.8, 145.4, 174.0. MS (ESI) m/z : 278 (M^+).

6-(3-Methylphenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3c). Yield 79%. Anal. ($\text{C}_{17}\text{H}_{15}\text{IN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 2.35 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 7.14 (d, $J = 7.5$ Hz, 1H, ArH), 7.29 (t, $J = 7.5$ Hz, 1H, ArH), 7.46 (d, $J = 7.8$ Hz, 1H, ArH), 7.49 (s, 1H, ArH), 7.62 (d, $J = 8.1$ Hz, 1H, ArH), 7.66 (d, $J = 9.0$ Hz, 1H, ArH), 7.83 (s, 1H, ArH), 9.26 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 21.1, 34.1, 118.5, 122.3, 123.4, 123.7, 125.5, 127.3, 128.0, 128.8, 132.0, 137.7, 138.0, 139.8, 142.7, 146.1, 173.9. MS (ESI) m/z : 278 (M^+).

6-(2-Fluorophenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3d). Yield 68%. Anal. ($\text{C}_{16}\text{H}_{12}\text{FIN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 3.87 (s, 2H, CH_2), 7.25–7.34 (m, 2H, ArH), 7.37–7.44 (m, 1H, ArH), 7.54 (t, $J = 7.8$ Hz, 2H, ArH), 7.65 (d, $J = 8.1$ Hz, 1H, ArH), 7.73 (s, 1H, ArH), 9.00 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 21.1 $\times$ 2, 34.1, 118.5, 122.3, 123.5, 124.5 $\times$ 2, 125.5, 132.0, 137.9, 138.0 $\times$ 2, 139.9, 143.0, 146.1, 174.0. MS (ESI) m/z : 282 (M^+).

6-(3-Fluorophenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3e). Yield 71%. Anal. ($\text{C}_{16}\text{H}_{12}\text{FIN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 3.86 (s, 2H, CH_2), 7.17 (tt, $J = 1.5, 8.1$ Hz, 1H, ArH), 7.45–7.56 (m, 3H, ArH), 7.62 (d, $J = 8.1$ Hz, 1H, ArH), 7.72 (dd, $J = 1.8, 8.1$ Hz, 1H, ArH), 7.90 (s, 1H, ArH), 9.00 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 34.1, 113.0 and 113.3, 113.8 and 114.1, 118.5, 122.6, 122.9, 123.4, 125.7, 130.7 and 130.8, 132.7, 135.9, 142.3, 143.0, 146.1, 161.0 and 164.2, 173.8. MS (ESI) m/z : 282 (M^+).

6-(4-Fluorophenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3f). Yield 65%. Anal. ($\text{C}_{16}\text{H}_{12}\text{FIN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 3.84 (s, 2H, CH_2), 7.17 (t, $J = 8.7$ Hz, 1H, ArH), 7.59 (d, $J = 7.8$ Hz, 1H, ArH), 7.65 (d, $J = 7.8$ Hz, 1H, ArH), 7.70–7.75 (m, 2H, ArH), 7.81 (s, 1H, ArH), 8.80 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 33.4, 115.4, 115.7, 118.1, 122.7, 123.2, 125.3, 128.4, 128.9, 129.0, 133.3, 136.0, 136.5, 146.1, 163.2, 173.6. MS (ESI) m/z : 282 (M^+). HRMS calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{FS}$, exact mass 283.070 52; found m/z , 283.070 82.

6-(2-Chlorophenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3g). Yield 65%. Anal. ($\text{C}_{16}\text{H}_{12}\text{ClIN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 3.85 (s, 2H, CH_2), 7.35–7.46 (m, 4H, ArH), 7.57 (dt, $J = 1.8, 7.8$ Hz, 1H, ArH), 7.61 (brs, 1H, ArH), 7.63 (d, $J = 7.5$ Hz, 1H, ArH), 9.00 (brs, NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): δ 34.1, 117.9, 122.9, 125.9, 127.5, 128.2, 129.2, 129.8, 131.3, 131.5, 132.3, 136.1, 139.6, 142.5, 145.2, 173.9. MS (ESI) m/z : 298, 300 (M^+).

6-(3-Chlorophenyl)-8H-indeno[1,2-d]thiazol-2-ylamine Hydroiodide (3h). Yield 67%. Anal. ($\text{C}_{16}\text{H}_{12}\text{ClIN}_2\text{S}$) C, H, N. ^1H NMR ($\text{DMSO}-d_6$): δ 3.86 (s, 2H, CH_2), 7.40 (brd, $J = 7.8$ Hz, 1H, ArH), 7.49 (dd, $J = 7.5, 8.1$ Hz, 1H, ArH),

7.63 (d, $J = 8.1$ Hz, 1H, ArH), 7.67 (dt, $J = 7.8$ Hz, 1H, ArH), 7.70–7.76 (m, 2H, ArH), 7.91 (brs, 1H, ArH), 9.00 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.1, 118.5, 122.9, 123.5, 125.2, 125.7, 126.3, 127.1, 130.7, 132.7, 133.7, 135.8, 142.0, 142.8, 146.1, 173.9. MS (ESI) m/z : 298, 300 (M^+).

6-(3-Hydroxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3i). Yield 74%. Anal. (C₁₆H₁₃IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.86 (s, 2H, CH₂), 6.75 (dd, $J = 2.1$, 8.1 Hz, 1H, ArH), 7.04 (d, $J = 2.1$ Hz, 1H, ArH), 7.09 (d, $J = 7.5$ Hz, 1H, ArH), 7.25 (t, $J = 8.1$ Hz, 1H, ArH), 7.61 (s, 2H, ArH), 7.78 (s, 1H, ArH), 9.00 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.1, 113.4, 114.4, 117.5, 118.5, 122.3, 123.4, 125.5, 130.0, 132.0, 137.8, 141.4, 142.5, 146.1, 157.8, 173.9. MS (ESI) m/z : 280 (M^+).

6-(4-Hydroxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3j). Yield 71%. Anal. (C₁₆H₁₃IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.82 (s, 2H, CH₂), 6.84 (d, $J = 8.4$ Hz, 2H, ArH), 7.51 (d, $J = 8.4$ Hz, 2H, ArH), 7.55 (m, 2H, ArH), 7.75 (s, 1H, ArH), 9.00 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 33.8, 115.7 $\times$ 2, 118.3, 121.8, 122.7, 124.6, 126.9, 127.7 $\times$ 2, 130.7, 131.7, 137.6, 146.1, 157.0, 173.8. MS (ESI) m/z : 280 (M^+).

6-(2-Methoxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3k). Yield 75%. Anal. (C₁₇H₁₅IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.76 (s, 3H, OCH₃), 3.82 (s, 2H, CH₂), 7.02 (t, $J = 7.5$ Hz, 1H, ArH), 7.11 (d, $J = 7.5$ Hz, 1H, ArH), 7.29 (dd, $J = 1.5$, 7.5 Hz, 1H, ArH), 7.32 (dd, $J = 7.2$, 8.1 Hz, 1H, ArH), 7.45 (dd, $J = 1.5$, 8.1 Hz, 1H, ArH), 7.57 (d, $J = 8.1$ Hz, 1H, ArH), 7.63 (brs, 1H, ArH), 9.00 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 33.9, 55.5, 111.7, 117.7, 120.8, 122.1, 126.0, 128.0, 128.9, 129.6, 130.4, 131.6, 135.7, 143.1, 145.0, 156.1, 173.9. MS (ESI) m/z : 294 (M^+).

6-(3-Methoxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3l). Yield 74%. Anal. (C₁₇H₁₅IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.82 (s, 3H, OCH₃), 3.86 (s, 2H, CH₂), 6.92 (dt, $J = 1.8$, 8.1 Hz, 1H, ArH), 7.21 (t, $J = 1.5$ Hz, 1H, ArH), 7.25 (dd, $J = 0.9$, 7.8 Hz, 1H, ArH), 7.37 (t, $J = 7.8$ Hz, 1H, ArH), 7.61 (d, $J = 8.1$ Hz, 1H, ArH), 7.69 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.87 (brs, 1H, ArH), 9.00 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 34.1, 55.1, 112.0, 113.0, 118.4, 118.9, 122.5, 123.5, 125.7, 130.0, 132.3, 137.5, 141.4, 142.9, 146.1, 159.7, 173.9. MS (ESI) m/z : 294 (M^+).

6-(4-Methoxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3m). Yield 72%. Anal. (C₁₇H₁₅IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.78 (s, 3H, OCH₃), 3.85 (s, 2H, CH₂), 7.02 (dd, $J = 2.1$, 6.9 Hz, 2H, ArH), 7.60–7.65 (m, 4H, ArH), 7.81 (brs, 1H, ArH), 9.00 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.0, 55.2, 114.3, 114.4 $\times$ 2, 118.4, 121.9, 122.9, 124.9, 127.7 $\times$ 2, 131.5, 132.2, 137.3, 146.1, 158.8, 173.9. MS (ESI) m/z : 294 (M^+).

6-(4-Phenoxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3n). Yield 81%. Anal. (C₂₂H₁₇IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.85 (s, 2H, CH₂), 7.04–7.10 (m, 4H, ArH), 7.16 (dt, $J = 0.9$, 7.2 Hz, 1H, ArH), 7.38–7.45 (m, 2H, ArH), 7.58–7.75 (m, 4H, ArH), 7.84 (s, 1H, ArH), 8.99 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.1, 118.5, 118.8 $\times$ 2, 118.9 $\times$ 2, 122.3, 123.2, 123.7, 125.3, 128.2 $\times$ 2, 130.1 $\times$ 2, 131.9, 135.0, 136.9, 142.8, 146.2, 156.3, 173.9. MS (ESI) m/z : 356 (M^+).

6-(4-*N,N*-Dimethylaminophenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3o). Yield 75%. ¹H NMR (DMSO-*d*₆): δ 3.08 (s, 6H, NMe₂), 3.86 (s, 2H, CH₂), 7.24 (brd, 2H, ArH), 7.67 (Abd, $J = 7.5$ Hz, 2H, ArH), 7.72 (d, $J = 8.4$ Hz, 2H, ArH), 7.86 (s, 1H, ArH), 9.05 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.2, 43.9 $\times$ 2, 118.4, 118.6 $\times$ 2, 122.4, 123.2, 125.3, 127.8 $\times$ 3, 131.9, 136.6, 142.4, 144.7, 146.2, 174.0. HRMS calcd for C₁₈H₁₇N₃S, exact mass 307.114 32; found m/z , 307.121 76.

6-(2-Nitrophenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3p). Yield 79%. Anal. (C₁₆H₁₂IN₃O₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.78 (s, 2H, CH₂), 7.27 (dd, $J = 1.5$, 7.5 Hz, 1H, ArH), 7.49 (d, $J = 1.5$ Hz, 1H, ArH), 7.50 (d, $J = 8.1$ Hz, 1H, ArH), 7.58 (dd, $J = 0.9$, 7.5 Hz, 1H, ArH), 7.61 (dt, $J = 1.2$, 7.8 Hz, 1H, ArH), 7.76 (dt, $J = 1.5$, 7.5 Hz, 1H, ArH), 7.97 (dd, $J = 1.2$, 7.8 Hz, 1H, ArH). ¹³C NMR (DMSO-

*d*₆): δ 33.1, 117.9, 123.8, 124.1, 124.3, 126.6, 128.6, 131.8, 132.8, 133.3, 135.1, 145.9, 148.9, 173.5. MS (ESI) m/z : 309 (M^+).

6-(3-Nitrophenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3q). Yield 71%. Anal. (C₁₆H₁₂IN₃O₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.88 (s, 2H, CH₂), 7.66 (d, $J = 8.1$ Hz, 1H, ArH), 7.75 (d, $J = 8.1$ Hz, 1H, ArH), 7.81 (dd, $J = 1.8$, 8.1 Hz, 1H, ArH), 8.00 (s, 1H, ArH), 8.19 (dt, $J = 2.4$, 8.4 Hz, 2H, ArH), 8.46 (t, $J = 1.8$, 1H, ArH), 8.98 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.1, 118.6, 120.9, 122.0, 123.5, 123.6, 126.0, 130.5, 133.1, 133.4, 134.9, 141.5, 143.3, 146.3, 148.4, 174.0. MS (ESI) m/z : 309 (M^+).

6-(2-Trifluoromethylphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3r). Yield 81%. Anal. (C₁₇H₁₂F₃IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.82 (s, 2H, CH₂), 7.29 (d, $J = 8.1$ Hz, 1H, ArH), 7.42 (d, $J = 7.5$ Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.57 (d, $J = 7.8$ Hz, 1H, ArH), 7.62 (d, $J = 7.8$ Hz, 1H, ArH), 7.72 (t, $J = 7.5$ Hz, 1H, ArH), 7.83 (d, $J = 7.2$ Hz, 1H, ArH). Partial ¹³C NMR (DMSO-*d*₆): δ 33.6, 117.4, 123.0, 125.3, 126.1, 127.5, 128.0, 132.2, 133.4, 136.3, 140.6, 145.0, 173.8. MS (ESI) m/z : 309 (M^+).

6-(3-Trifluoromethylphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3s). Yield 79%. Anal. (C₁₇H₁₂F₃IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.87 (s, 2H, CH₂), 7.63 (d, $J = 8.1$ Hz, 2H, ArH), 7.71 (m, 2H, ArH), 7.77 (dd, $J = 1.5$, 8.1 Hz, 2H, ArH), 7.96 (s, 1H, ArH), 7.99 (s, 1H, ArH), 8.02 (t, $J = 5.1$ Hz, 1H, ArH), 8.90 (brs, 3H, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.1, 118.6, 123.0, 123.2, 123.7, 123.9, 125.9, 129.5, 130.1, 130.6, 133.0, 135.7, 141.0, 143.2, 146.3, 174.0. MS (ESI) m/z : 332 (M^+).

6-(4-Trifluoromethylphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3t). Yield 74%. Anal. (C₁₇H₁₂F₃IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.85 (s, 2H, CH₂), 7.61 (d, $J = 8.1$ Hz, 2H, ArH), 7.74 (dd, $J = 1.8$, 7.8 Hz, 1H, ArH), 7.80 (d, $J = 8.4$ Hz, 2H, ArH), 7.91 (d, $J = 8.1$ Hz, 2H, ArH), 7.92 (d, $J = 1.2$ Hz, 1H, ArH), 8.50 (s, NH₃). Partial ¹³C NMR (DMSO-*d*₆): δ 33.6, 118.4, 123.5, 125.7, 125.9, 127.3 $\times$ 2, 134.4, 135.3, 144.1, 146.3, 173.7. MS (ESI) m/z : 332 (M^+).

6-(2,5-Dimethylphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3u). Yield 72%. Anal. (C₁₈H₁₇IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 2.18 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 3.84 (s, 2H, CH₂), 7.02 (s, 1H, ArH), 7.07 (d, $J = 7.8$ Hz, 1H, ArH), 7.17 (d, $J = 7.8$ Hz, 1H, ArH), 7.31 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.51 (s, 1H, ArH), 7.61 (d, $J = 8.1$ Hz, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 19.8, 20.5, 34.0, 117.9, 122.2, 125.8, 127.9, 128.0, 130.2, 130.3, 131.5, 134.8, 138.9, 140.9, 142.7, 145.3, 174.0. MS (ESI) m/z : 292 (M^+).

6-(3,4-Dimethylphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3v). Yield 81%. Anal. (C₁₈H₁₇IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 2.17 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 3.82 (s, 2H, CH₂), 7.01 (brs, 1H, ArH), 7.06 (d, $J = 7.5$ Hz, 1H, ArH), 7.17 (d, $J = 7.8$ Hz, 1H, ArH), 7.31 (dd, $J = 1.2$, 7.8 Hz, 1H, ArH), 7.49 (s, 1H, ArH), 7.59 (d, $J = 7.5$ Hz, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 19.8, 20.6, 34.0, 117.9, 122.3, 125.8, 127.8, 128.0, 130.2, 130.4, 131.6, 131.8, 134.9, 138.9, 140.9, 143.5, 145.4, 174.0. MS (ESI) m/z : 292 (M^+).

6-(3,5-Dimethylphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3w). Yield 84%. Anal. (C₁₈H₁₇IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 2.31 (s, 6H, CH₃ $\times$ 2), 3.84 (s, 2H, CH₂), 6.97 (brs, 1H, ArH), 7.28 (brs, 2H, ArH), 7.59 (d, $J = 8.1$ Hz, 1H, ArH), 7.64 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 7.82 (s, $J = 7.5$ Hz, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 21.1 $\times$ 2, 34.1, 118.5, 122.3, 123.5, 124.5 $\times$ 2, 125.5, 128.9, 132.0, 137.9, 138.0 $\times$ 2, 139.9, 143.0, 146.1, 174.0. MS (ESI) m/z : 292 (M^+).

6-(3,4-Dimethoxyphenyl)-8*H*-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3x). Yield 68%. Anal. (C₁₈H₁₇IN₂O₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.78 (s, 3H, OCH₃), 3.84 (s, 5H, CH₂ and CH₃), 7.03 (d, $J = 8.1$ Hz, 1H, ArH), 7.21 (dd, $J = 1.8$, 8.1 Hz, 1H, ArH), 7.24 (s, 1H, ArH), 7.58 (d, $J = 7.8$ Hz, 1H, ArH), 7.66 (dd, $J = 1.5$, 8.1 Hz, 1H, ArH), 7.8d (s, 1H, ArH), 9.00 (brs, NH₃). ¹³C NMR (DMSO-*d*₆): δ 34.1, 55.6 $\times$ 2, 110.2, 112.1, 118.4, 118.7, 122.0, 123.1, 125.1, 131.5, 132.6, 137.6, 143.0, 146.1, 148.4, 149.0, 173.9. MS (ESI) m/z : 324 (M^+).

6-(2,4-Dimethoxyphenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3y). Yield 68%. Anal. (C₁₈H₁₇IN₂O₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.76 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.81 (s, 2H, CH₂), 6.61 (dd, *J* = 1.8, 8.1 Hz, 1H, ArH), 6.66 (s, 1H, ArH), 7.23 (d, *J* = 8.1, 1H, ArH), 7.42 (dd, *J* = 1.5, 7.8 Hz, 1H, ArH), 7.55 (d, *J* = 7.8, 1H, ArH), 7.60 (s, 1H, ArH), 9.00 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 33.9, 55.3, 55.6, 98.9, 105.3, 117.6, 121.7, 122.2, 125.9, 127.8, 130.9, 131.1, 135.7, 143.1, 145.0, 157.1, 160.0, 173.9. MS (ESI) *m/z*: 324 (M⁺).

6-(3,4,5-Trimethoxyphenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3z). Yield 64%. Anal. (C₁₉H₁₉IN₂O₃S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.69 (s, 3H, OCH₃), 3.86 (brs, 8H, OCH₃ × 2, CH₂), 6.95 (s, 2H, ArH), 7.25 (brs, NH₂), 7.61 (d, *J* = 7.8 Hz, 1H, ArH), 7.72 (dd, *J* = 1.5, 7.8 Hz, 1H, ArH), 7.91 (s, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 34.0, 56.0 × 2, 60.1, 104.0 × 2, 118.3, 122.3, 123.5, 125.6, 132.1, 135.7, 137.0, 137.7, 143.3, 146.0, 153.2 × 2, 173.9. MS (ESI) *m/z*: 354 (M⁺).

6-(2,3,4-Trimethoxyphenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3aa). Yield 72%. Anal. (C₁₉H₁₉IN₂O₃S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.58 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.83 (s, 2H, CH₂), 6.89 (d, *J* = 8.1 Hz, 1H, ArH), 7.06 (d, *J* = 8.1 Hz, 1H, ArH), 7.45 (dd, *J* = 1.5, 7.8, 1H, ArH), 7.58 (d, *J* = 7.8 Hz, 1H, ArH), 7.62 (s, 1H, ArH), 9.00 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 34.0, 55.9, 60.4, 60.7, 108.2, 117.9, 122.0, 124.6, 125.6, 127.4, 127.6, 131.1, 135.4, 142.0, 142.8, 145.2, 150.8, 152.9, 173.9. MS (ESI) *m/z*: 354 (M⁺).

6-(3,4-Methylenedioxyphenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ab). Yield 65%. Anal. (C₁₇H₁₃IN₂O₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.84 (s, 2H, CH₂), 6.05 (s, 2H, OCH₂O), 6.99 (d, *J* = 8.1, 1H, ArH), 7.17 (dd, *J* = 1.8, 8.1 Hz, 1H, ArH), 7.26 (d, *J* = 1.8 Hz, 1H, ArH), 7.60 (dd, *J* = 1.5, 7.8 Hz, 2H, ArH), 7.80 (s, 1H, ArH), 9.10 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 34.1, 101.1, 107.0, 108.6, 118.4, 120.2, 122.0, 123.2, 125.2, 131.5, 134.1, 137.4, 142.5, 146.0, 146.7, 147.9, 173.9. MS (ESI) *m/z*: 308 (M⁺).

6-(3,4-Dichlorophenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ac). Yield 62%. Anal. (C₁₆H₁₁Cl₂IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.85 (s, 2H, CH₂), 7.62 (d, *J* = 7.8 Hz, 1H, ArH), 7.69 (dd, *J* = 1.8, 7.8 Hz, 1H, ArH), 7.91 (d, *J* = 0.9 Hz, 1H, ArH), 7.94 (t, *J* = 1.2, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 34.2, 118.5, 123.1, 123.4, 125.7, 126.6, 128.2, 129.9, 130.9, 131.6, 132.8, 134.7, 140.4, 142.5, 146.1, 173.9. MS (ESI) *m/z*: 332, 334, 336 (M⁺).

6-(3,5-Dichlorophenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ad). Yield 65%. Anal. (C₁₆H₁₁Cl₂IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.85 (s, 2H, CH₂), 7.57 (t, *J* = 2.1 Hz, 1H, ArH), 7.61 (d, *J* = 7.5 Hz, 1H, ArH), 7.71–7.78 (m, 3H, ArH), 7.94 (brs, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 34.1, 118.5, 123.4, 123.6, 125.1 × 2, 125.9, 126.5, 133.2, 134.3, 134.6 × 2, 142.7, 143.3, 146.1, 173.9. MS (ESI) *m/z*: 332, 334, 336 (M⁺).

6-(Naphth-1-yl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ae). Yield 67%. Anal. (C₂₀H₁₅IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.89 (s, 2H, CH₂), 7.45 (dd, *J* = 1.5, 7.5, 1H, ArH), 7.49 (s, 1H, ArH), 7.52 (dd, *J* = 1.8, 3.0 Hz, 1H, ArH), 7.55 (m, 1H, ArH), 7.58 (d, *J* = 7.2, 1H, ArH), 7.64 (s, 1H, ArH), 7.69 (d, *J* = 7.5 Hz, 1H, ArH), 7.81 (d, *J* = 8.1 Hz, 1H, ArH), 7.94 (d, *J* = 8.1 Hz, 1H, ArH), 7.99 (d, *J* = 7.8 Hz, 1H, ArH), 9.01 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 34.1, 118.1, 122.6, 125.2, 125.5, 126.4, 126.5, 127.0, 127.6, 128.4, 128.7, 130.8, 132.1, 133.4, 137.4, 139.3, 142.8, 145.6, 174.0. MS (ESI) *m/z*: 344 (M⁺).

6-(Naphth-2-yl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3af). Yield 79%. Anal. (C₂₀H₁₅IN₂S) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.90 (s, 2H, CH₂), 7.45–7.59 (m, 3H, ArH), 7.69 (d, *J* = 8.1 Hz, 1H, ArH), 7.86 (dd, *J* = 7.5 Hz, 2H, ArH), 7.93 (d, *J* = 8.4 Hz, 1H, ArH), 7.95–8.02 (m, 2H, ArH), 8.24 (s, 1H, ArH), 9.20 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 33.9, 118.4, 122.5, 123.5, 124.8, 125.0, 125.7, 125.9, 126.3, 127.3, 128.0, 128.3, 132.0, 132.2, 133.2, 137.1, 133.2, 143.0, 146.1, 173.8. MS (ESI) *m/z*: 344 (M⁺).

6-(6-Methoxynaphth-2-yl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ag). Yield 71%. ¹H NMR (DMSO-*d*₆): δ 3.88 (s, 2H, CH₂), 7.19 (dd, *J* = 2.4, 8.7 Hz, 1H, ArH), 7.34 (d, *J* = 2.4 Hz, 1H, ArH), 7.62 (d, *J* = 8.4 Hz, 1H, ArH), 7.78–7.92 (m, 4H, ArH), 7.98 (s, 1H, ArH), 8.17 (s, 1H, ArH). ¹³C NMR (DMSO-*d*₆): δ 33.9, 55.2, 105.7, 118.5, 118.9, 122.4, 123.3, 124.9, 125.3, 125.5, 127.3, 128.7, 129.6, 132.4, 133.4, 134.9, 137.3, 144.3, 146.2, 157.4, 173.8. HRMS calcd for C₂₁H₁₇N₂OS, exact mass 345.106 16; found *m/z*, 345.105 71.

6-(Thiophen-2-yl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ah). Yield 74%. Anal. (C₁₄H₁₁IN₂S₂) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.85 (s, 2H, CH₂), 7.56–7.61 (m, 2H, ArH), 7.65 (dd, *J* = 3.0, 4.8 Hz, 1H, ArH), 7.74 (dd, *J* = 1.2, 7.8 Hz, 1H, ArH), 7.69 (dd, *J* = 1.5, 7.8 Hz, 1H, ArH), 7.89 (dd, *J* = 1.5, 6.0 Hz, 1H, ArH), 7.93 (brs, 1H, ArH), 9.04 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 34.0, 118.4, 120.8, 122.1, 122.8, 124.9, 126.1, 127.2, 131.7, 132.6, 141.2, 143.0, 146.1, 173.9. MS (ESI) *m/z*: 270 (M⁺). HRMS calcd for C₁₄H₁₁N₂OS₂, exact mass 271.036 36; found *m/z*, 271.036 87.

6-(3-Thiophenyl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3ai). Yield 68%. Anal. (C₁₄H₁₁IN₂S₂) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.84 (s, 2H, CH₂), 7.56–7.61 (m, 2H, ArH), 7.65 (dd, *J* = 3.0, 4.8 Hz, 1H, ArH), 7.74 (dd, *J* = 1.2, 7.8 Hz, 1H, ArH), 7.69 (dd, *J* = 1.5, 7.8 Hz, 1H, ArH), 7.89 (dd, *J* = 1.5, 6.0 Hz, 1H, ArH), 7.93 (brs, 1H, ArH), 9.04 (brs, NH₂). ¹³C NMR (DMSO-*d*₆): δ 34.0, 118.4, 120.8, 122.2, 122.8, 124.9, 126.1, 127.2, 131.9, 132.6, 141.2, 143.4, 146.1, 173.9. MS (ESI) *m/z*: 270 (M⁺).

6-(Benzofuran-2-yl)-8H-indeno[1,2-*d*]thiazol-2-ylamine Hydroiodide (3aj). Yield 63%. Anal. (C₁₈H₁₃IN₂OS) C, H, N. ¹H NMR (DMSO-*d*₆): δ 3.88 (s, 2H, CH₂), 7.21–7.31 (m, 2H, ArH), 7.40 (s, 1H, ArH), 7.58 (d, *J* = 7.8 Hz, 1H, ArH), 7.61–7.70 (m, 1H, ArH), 7.92 (d, *J* = 7.8 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 9.05 (brs, NH₂). ¹³C NMR (CDCl₃): δ 34.1, 101.9, 111.0, 118.6, 121.1, 121.2, 123.2, 123.5, 123.7, 124.5, 126.9, 128.9, 133.4, 143.3, 146.1, 154.1, 155.2, 173.9. MS (ESI) *m/z*: 304 (M⁺).

Assay of AE Activity. Stock solutions of **3a–aj** were in DMSO. Binding assays employed membranes from CHO-K1 cells stably expressing the hA₁AR or from HEK 293 cells expressing the hA_{2A}AR or hA₃AR. Agonist radioligands were [¹²⁵I]ABA (ABA is N⁶-3-aminobenzyladenosine) for the A₁AR and the A₃AR and [¹²⁵I]N⁶-[2(4-aminophenyl)ethyladenosine] for the A_{2A}AR. The assay of AE activity consisted of three phases: (1) formation of the agonist–A₁AR–G protein ternary complex, (2) stabilization of that complex by the AE, and (3) dissociation of the complex by adding a combination of an A₁AR antagonist to compete with agonist at the orthosteric site and GTPγS to accelerate dissociation by displacing GDP from the G protein. The assay employed membranes from CHO-K1 cells stably expressing the hA₁AR. For agonist binding to equilibrium, the incubation mixture consisted of 10 mM HEPES, pH 7.2, containing 0.5 mM MgCl₂, 1 U/mL adenosine deaminase, 0.5 nM [¹²⁵I]ABA, and 10 μg of membrane protein (*B*_{max} ≈ 4 pmol/mg protein) in a final volume of 100 μL. After 90 min at room temperature, the addition of 50 μL of a 0.3 mM solution of a candidate AE (50 μM final) initiated stabilization of the ternary complex. Five minutes later, the addition of 50 μL of a solution of 400 μM 8-cyclopentyltheophylline and 200 μM GTPγS initiated the dissociation of the ternary complex. After 10 min for dissociation, filtering through a 96-well multiscreen Millipore filter plate, washing, drying, and counting ¹²⁵I activity allowed measurement of the residual bound radioligand. The percentage of specifically bound agonist remaining after 10 min of dissociation served as a score of AE activity, as calculated by the formula

$$\text{AE activity (\%)} = 100 \times \frac{B - B_0}{B_{\text{eq}} - B_0}$$

where *B* is the residual binding (cpm) bound at the end of 10 min of dissociation in the presence of an AE, *B*₀ is the residual binding (cpm) at the end of 10 min of dissociation in

the absence of an AE, and B_{eq} is the cpm bound at the end of 90 min of equilibration. A score of 0% indicates the lack of AE activity, and a score of 100% indicates no dissociation of the ternary complex in <10 min, the maximal possible allosteric effect. To initiate dissociation from the A_{2A} or A_3 receptors, 100 μ M ZM241385 or BW-1433, respectively, was added along with GTP γ S. Table 1 reports the mean and standard error of two to three separate assays, each in triplicate.

EC₅₀ of Allosteric Enhancer Activity. These assays differed from the screening assays only in that the concentration of candidate AE varied over a range of 10 nM to 50 μ M. The analysis program (Graph Pad) estimated EC₅₀, the concentration producing half-maximum AE activity from data on the activity score and AE concentration. Table 1 reports the mean and standard error of two to three separate assays, each in triplicate.

Assay of A₁AR Antagonist Activity. Assays of antagonism of equilibrium binding by allosteric enhancers used membranes from CHO-K1 cells expressing the hA₁AR. Assays, in triplicate, consisted of mixing 50 μ L aliquots of membrane suspensions (15 μ g of protein) in 10 mM HEPES, pH 7.4, containing 1 mM EDTA, 1 U/mL adenosine deaminase, and 4 nM [³H]CPX with 50 μ L of either 200 μ M enhancer dissolved in HEPES buffer containing 10% methyl sulfoxide or, as controls, HEPES containing 10% DMSO. Additional aliquots of membrane suspension mixed with 50 μ L of 200 μ M NECA in HEPES–10% DMSO served for measurements of unspecific binding. Incubation for 3 h at room temperature established binding equilibrium. Filtration through Whatman GF/C membranes separated free and bound radioligand. The membranes were washed three times and dried, and ³H activity was measured by liquid scintillation spectrometry. Inhibition was expressed as the percentage of control specific binding. Table 1 reports the mean $\pm$ standard error of two to three separate assays, each in triplicate.

Assay of A₁AR and A₃AR Antagonist Activity by Competition for Radioligand Binding. The assays for antagonism of the allosteric enhancers rely on competition for equilibrium radioligand binding and used membranes from CHO-K1 cells expressing hA₁AR or from HEK293 cells expressing hA₃AR. The membranes were resuspended at 0.5 mg/mL in 10 mM HEPES, pH 7.4, containing 1 mM EDTA, 1 U/mL adenosine deaminase, 5 mM MgCl₂, and 2 nM [³H]CPX (for A₁ receptors) or 0.5 nM [¹²⁵I]ABA (for A₃ receptors). Fifty-microliter aliquots of membrane solution (in triplicate) were added to 50 μ L of HEPES buffer containing 20 μ M allosteric enhancer, vehicle (DMSO), or 100 μ M NECA to define nonspecific binding. Incubation for 3 h at room temperature established equilibrium binding. Filtering through a 96-well multiscreen Millipore filter plate, washing, drying, and counting ¹²⁵I activity allowed measurement of the residual bound radioligand separated by filtration. Inhibition was expressed as the percentage of control specific binding.

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Supporting Information Available: Elemental analysis in table form. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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