Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 690–702

Sequential palladium-catalysed C- and N-arylation reactions as a practical and general protocol for the synthesis of the first series of oxcarbazepine analogues

Mónica Carril, Raul SanMartin,* Esther Domínguez* and Imanol Tellitu

Kimika Organikoa II Saila, Zientzia eta Teknologia Fakultatea, Euskal Herriko Unibertsitatea, PO Box 644, 48080 Bilbao, Spain

Received 11 September 2006; revised 31 October 2006; accepted 1 November 2006
Available online 28 November 2006

Abstract—The first series of oxcarbazepine analogues, starting from readily-available materials and through a high-yielding five-step sequence based on palladium catalysis, is reported. The so-obtained compounds incorporate not only a variety of substituents in both of the aryl rings comprising the framework of an oxcarbazepine, but also involve the more challenging palladium-catalysed coupling of a number of heteroaromatic substrates. The addition of small amounts of water in some of the metal-catalysed processes showed a beneficial effect, highly increasing the selectivity of such reactions.

1. Introduction

Oxcarbazepine (Trileptal®) has become the most widely prescribed drug for the treatment of epilepsy, due to its anticonvulsant properties and improved side-effect profile compared to the previously employed antiepileptic agent carbamazepine (Tegretol®) (Fig. 1).[1] The efficacy of oxcarbazepine (OXC) in the treatment of psychosomatic diseases,[2] trigeminal neuralgia,[2] Parkinsonian syndromes[3] and AIDS-related neural disorders[4] is, in addition to its analgesic properties, well-established. More recently, OXC has additionally proved effective in the treatment of refractory bipolar and schizoaffective disorders.[5]

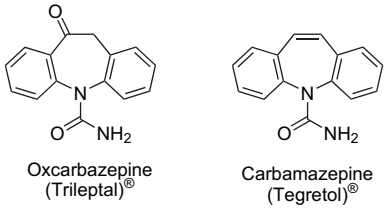


Figure 1.

Due to its aforementioned appealing properties, a number of routes leading to OXC has been described in the literature. Most of them are based on transformations in the iminostilbene or iminodibenzyl rings obtained through a sequence of drastic oxidation and reduction reactions from *o*-nitrotoluene. Since these harsh reaction conditions may only be achieved using specialised production equipment, they are inadequate and economically disadvantageous for industrial manufacturing purposes.[6]

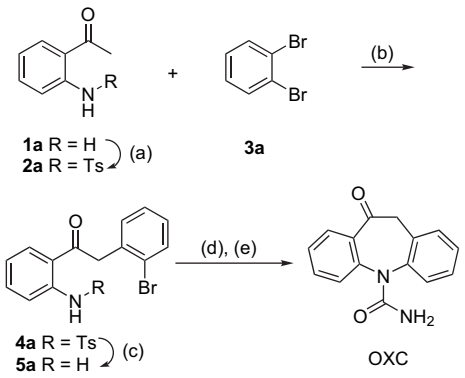
Thus, Novartis Pharma has recently designed two valuable protocols that provide access to OXC, employing either remote metallation[7] or Friedel–Crafts acylation[8] as key steps in the construction of the tricyclic skeleton of OXC. Whereas the scale-up process for the latter protocol has been successfully achieved,[6,9] this is still limited for the former due to the excess of LDA–TMEDA required.[7] Nevertheless, none of these synthetic routes to OXC has led to the formation of analogues, presumably because of the scope of the reaction conditions employed or the limited availability of the required starting materials.

In this context, we have recently reported a straightforward and high-yielding synthesis of OXC through a sequence of palladium-catalysed C- and N-arylation reactions,[10] that were performed in inter- and intramolecular fashions, respectively, and starting from commercially available 2′-aminoacetophenone **1a** and 1,2-dibromobenzene **3a** (Scheme 1).[11]

Given that this approach employs simple protocols, affordable palladium-catalysts, standard carbonate and phosphate-type bases and water as a co-solvent, its application to the synthesis of a range of OXC analogues was envisaged (Scheme 2). Furthermore, the lack of a general and an

Keywords: Oxcarbazepine; Analogues; Palladium; Cross-coupling.
* Corresponding authors. Tel.: +34946015435; fax: +34946012748 (R.S.); tel.: +34946012577; fax: +34946012748 (E.D.); e-mail addresses: raul.sanmartin@ehu.es; esther.dominguez@ehu.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.11.003



Scheme 1. Synthesis of OXC. Reagents and conditions: (a) TsCl, Py, CH_2Cl_2, rt; (b) $Pd(OAc)_2$, Xantphos, Cs_2CO_3, PhMe, H_2O; (c) H_2SO_4, rt; (d) $Pd(OAc)_2$, BINAP, K_3PO_4, PhMe, H_2O and (e) $ClSO_2NCO$.

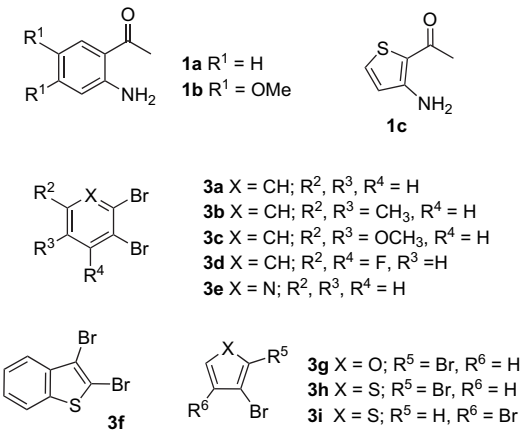
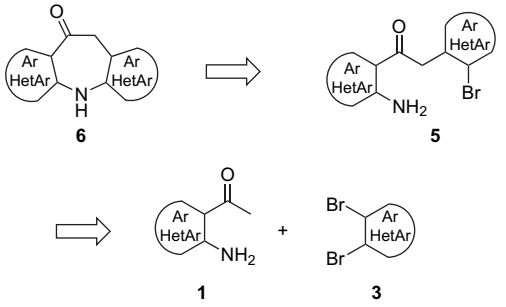


Figure 2. Starting materials **1** and **3**.

efficient entry to such analogues, that could potentially exhibit therapeutic activity, was particularly attractive. Herein, we present the synthesis of a series of OXC analogues obtained by varying not only the substituents located on the two aryl rings of the parent pharmaceutical, but also by incorporating suitably substituted heteroaryls into the tricyclic skeleton of OXC, as depicted below (Scheme 2). Indeed, the random modification of the structure of known drugs, for instance by introducing different substitution patterns, is a promising and respected strategy for the discovery of new antiepileptic drugs, thus far more successful than the rational-design of new molecules.[1b]



Scheme 2. Retrosynthetic proposal.

2. Results and discussion

2.1. Synthesis of diarylethanones 4

The first key step of the retrosynthetic route displayed above, consists of a palladium-catalysed arylation reaction of an aryl ketone enolate with an *o*-dibromoarene. In order to obtain a family of OXC analogues, a range of commercially available starting materials was chosen (Fig. 2), including not only aryl derivatives **1a**, **1b** and **3a–d**, but also the structurally-diverse heteroarenes **1c** and **3e–i**.

In order to selectively achieve the desired C-arylation reaction avoiding competitive N-arylation processes, substrates **1a–c** were first transformed into the corresponding sulfonamide derivatives **2a–c**. Each of these sulfonamides was subsequently reacted with dibromoarenes **3a–d** using our conditions previously reported for the palladium-catalysed α-arylation reaction, or modified forms thereof (Table 1).

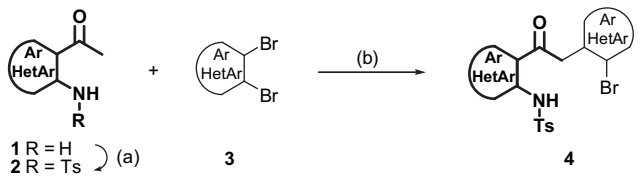
The proposed methodology proved to be suitable for the coupling of phenyl derivatives **2a**, **2b** and **3a–d** rendering the corresponding deoxybenzoins **4a–h** in good to excellent yields (Table 1, entries 1–8). As it happened for the synthesis of OXC, the addition of small amounts of water clearly improved the selectivity of the reactions tested, diminishing the impact of side-reactions.[12]

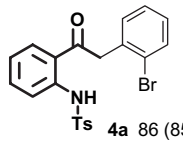
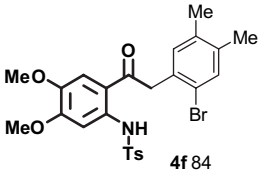
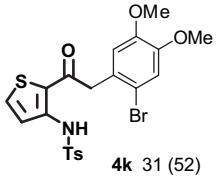
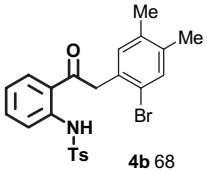
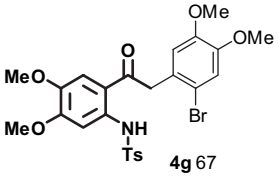
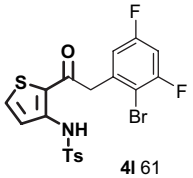
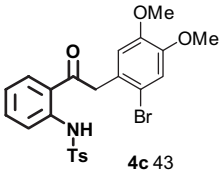
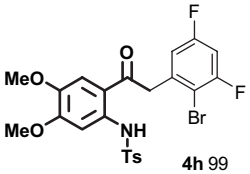
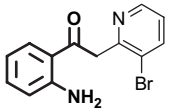
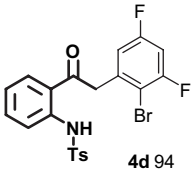
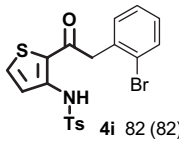
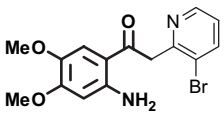
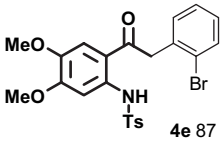
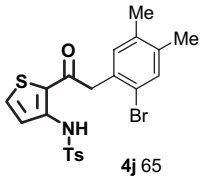
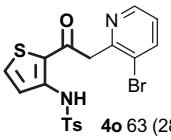
It should be mentioned that the coupling reaction between sulfonamide **2a** and the dimethoxylated dibromide **3c** was disfavoured, presumably because of the greater electron density present in the aryl ring of the electrophilic counterpart (Table 1, entry 3). Further evidence for this postulate was obtained by performing the coupling reaction with the electron-deficient, fluorinated dibromoarene **3d**. In this case, the product was furnished in 94% yield, as it could be predicted taking into account its more electrophilic nature compared to the rest of the dibromoarenes **3a–c** (Table 1, entry 4). Interestingly, when the reaction between the dibromoarenes **3b** and **3c** and the methoxy-substituted sulfonamide **2b** was performed, an increase in the yield was observed (relative to that in which the simple sulfonamide **2a** was used) (Table 1, entries 6 and 7). This suggests that the methoxy substituents in the ketone coupling partner conversely have a beneficial effect on the reaction outcome (**4f** 84% vs **4b** 68% or **4g** 67% vs **4c** 43%).

Of the heteroarene substrates, thiophene derivative **2c** initially failed to react with dibromoarenes **3a–e** under the conditions employed above and was especially challenging to arylate. Furthermore, application of the experimental conditions reported for the only similar C-arylation example found in the literature resulted in no conversion of any of the substrates.[13] Fortunately, by means of slight modifications to our procedure[14] the desired products **4i–l** were obtained in moderate to good yields (Table 1, entries 9–12), apparently overcoming the tendency of the sulfur atom to bind to the palladium and hinder the reaction progress.[15]

Following with the use of heteroarene substrates, it was observed that the 2,3-dibromopyridine **3e** successfully

Table 1. Synthesis of diarylethanones **4**



Entry	4[a]	Entry	4[a]	Entry	4[a]
1	 **4a** 86 (85)	6	 **4f** 84	11[d,e]	 **4k** 31 (52)
2	 **4b** 68	7	 **4g** 67	12[e,f]	 **4l** 61
3	 **4c** 43	8	 **4h** 99	13[g]	 **5m** 78
4	 **4d** 94	9[c,d,e]	 **4i** 82 (82)	14[g]	 **5n** 71
5[b]	 **4e** 87	10[d,e]	 **4j** 65	15[c,d,e]	 **4o** 63 (28)

Reagents and conditions: (a) TsCl, Py, CH_2Cl_2, rt and (b) 1 equiv **2**, 2.4 equiv **3**, 4.4% $Pd(OAc)_2$, 8.5% Xantphos, 1.4 equiv Cs_2CO_3, PhMe, H_2O, 120 °C, 47–72 h.

[a] Isolated yields calculated on the basis of the percentage conversion (assumed to be 100% unless otherwise indicated in parentheses) of substrates **2**.

[b] [**2b**]:[**3a**]=1:3.7.

[c] [**2c**]:[**3a**]=1:1.6.

[d] [Pd]:[Xantphos]=0.045:0.096.

[e] K_3PO_4 (2.65 equiv) was used as base, 1,4-dioxane as solvent and the reaction was performed in a sealed tube for 4 days.

[f] [**2c**]:[**3d**]:[Pd]:[Xantphos]=1.5:1:0.04:0.083.

[g] (i) 1.2 equiv **2**, 1 equiv **3e**, 4.3% $Pd(OAc)_2$, 8% Xantphos, 2.3 equiv K_3PO_4, PhMe, 130 °C, 24 h and (ii) H_2SO_4, 60 °C, 25 min.

participated in the palladium-catalysed α-arylation reactions of substrates **2a**, **2b**, although the purification of the so-obtained diarylethanones **4m** and ,**4n** was not easily accomplished. For this reason they were directly transformed into the corresponding free amine derivatives **5m** and **5n** in good overall yield (Table 1, entries 13 and 14). When ketone **2c** was employed instead, the interesting diheteroaryl product **4o** was obtained in 63% yield, together with a substantial amount of unreacted ketone **2c** (Table 1, entry 15), despite several unsuccessful attempts to increase the conversion of the starting materials. Since such C-arylated product **4o** could not be obtained in synthetically useful quantities it was not considered for the subsequent steps in the scheduled sequence.

However, when the original reaction conditions and modified ones were applied to the reactions in which ketone **2a** and the 1,2-dibromoheteroarenes **3f–i** were involved, the results obtained were rather disappointing. For instance, the furan derivative **3g** systematically decomposed under every set of reaction conditions tested, whereas the thiophene derivative **3h** remained largely unreacted,[16] even though a number of examples featuring palladium-catalysed arylation reactions of 2-bromothiophene derivatives can be found in the literature.[17] However, when the benzothiophene **3f** or the 3,4-dibromothiophene **3i** was used, the corresponding diarylethanones bearing a second thiophene unit were obtained in 25% yield or trace amounts, respectively.[18] Unfortunately, all attempts to avoid these side-reactions were unsuccessful.[19]

The protocol described thus far has proved to be a useful tool, delivering a diverse array of up to 15 diarylethanones **4a–o**, which may be regarded as potential precursors of OXC analogues. In addition, this methodology, slightly modified, has allowed us to perform several examples of the palladium-catalysed α-arylation reaction employing different heteroarene substrates, field much less explored than other related palladium-catalysed arylation reactions.[20]

2.2. Syntheses of dibenzoazepinones 6 and OXC analogues 7

On the basis of our previous work depicted in Scheme 1,[11] we first carried out the deprotection of the amine moiety in substrates **4** in order to accomplish the second and final key step of the sequence, i.e. the intramolecular palladium-catalysed N-arylation reaction to render the target tricyclic framework. The removal of the protective tosyl group was performed by stirring intermediates **4** in concentrated sulfuric acid for several minutes to afford, in almost quantitative yield, the corresponding free amine derivatives **5a–n** (Table 2). Then, the reaction conditions previously employed for the palladium-catalysed cyclisation step in the synthesis of azepinone **6a** from amine **5a**,[11] were subsequently tested for the rest of primary amines **5b–n**, as shown in Table 2.

In general, the non-heteroaromatic substrates **5a–h** smoothly underwent cyclisation to deliver the corresponding azepinone derivatives **6a–h** in good to excellent yields (Table 2, entries 1–8), although it was sometimes necessary to slightly modify the original protocol to allow certain substrates to react until complete conversion. Once again, the presence of water played an important role, as for the synthesis of the corresponding diarylethanones.[12] Surprisingly, the electron-rich aryl bromide moiety of substrates **5c** and **5g** favoured nucleophilic attack of the amine moiety (in contrast to previously observed difficulties in the formation of the corresponding deoxybenzoins **4c** and **4g**).

In the case of the heteroaromatic substrates, the aforementioned procedure worked extremely well for the thiophene substrates **5i–l** (Table 2, entries 9–12), with the exception of **5k** (Table 2, entry 11), which cyclised to form target **6k** in a modest yield. In contrast, the pyridine derivatives **5m** and **5n**, did not render the desired azepinones (Table 2, entries 13 and 14), although a range of different experimental conditions was tested on both substrates.[21]

By employing the methodology developed by our research group for the synthesis of OXC, a range of 12 tricyclic compounds was successfully prepared, each of which could, in principle, be directly transformed into OXC analogues through a simple carbamoylation reaction (Scheme 1). Indeed, by applying the improved carbamoylation conditions reported in the recently patented synthesis of OXC from azepine **6a**,[22] it was possible to increase our previously reported yield for this transformation up to 95%. Consequently, the same carbamoylation procedure without further optimisation was applied to the selected substrates **6b**, **6d** and **6g–j** furnishing the corresponding OXC analogues **7b**, **7d** and **7g–j** in modest to excellent yields. The pharmaceutical activity of each of these analogues is currently being investigated and will be reported elsewhere.

3. Conclusion

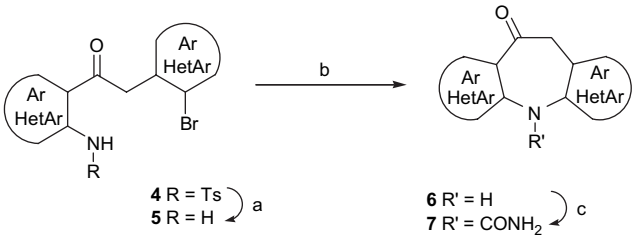
In summary, we have shown that the methodology previously designed by our research group for the synthesis of OXC may be conveniently applied (albeit with slight modifications) to the synthesis of a number of azepinone derivatives in good to excellent yields, several of which have been subjected to simple carbamoylation to afford the first family of analogues of this important pharmaceutical. The facile and high-yielding procedures involving simple catalyst and reagent systems, together with the readily-available starting materials, not only lend this methodology to the synthesis of a wide variety of OXC analogues, otherwise unattainable via existing methodologies,[23] but also presents a significant contribution to the scope of palladium-catalysed C- and N-arylation chemistry involving the more challenging heteroaromatic substrates, especially regarding the palladium-catalysed α-arylation of ketone enolates.

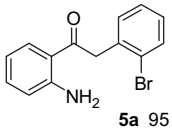
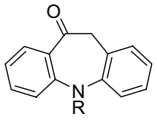
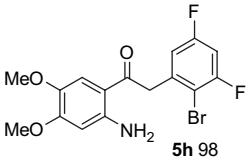
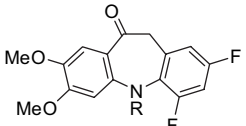
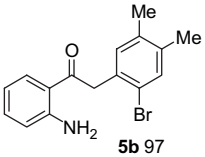
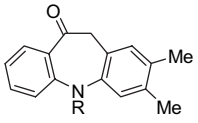
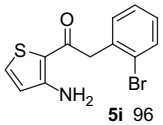
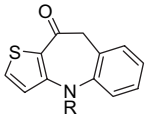
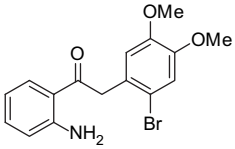
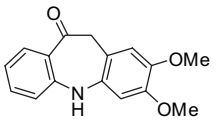
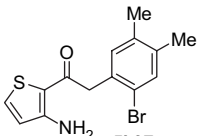
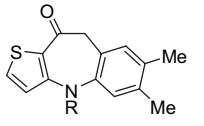
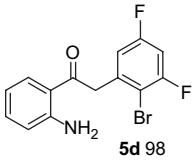
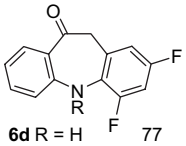
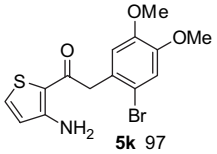
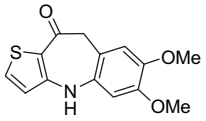
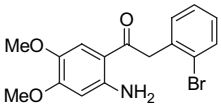
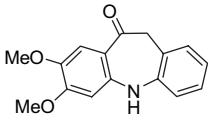
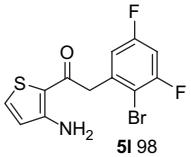
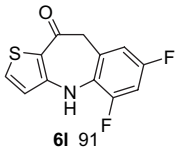
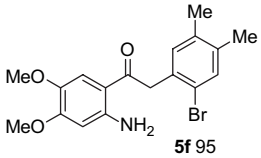
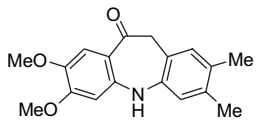
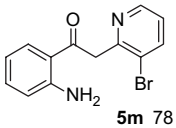
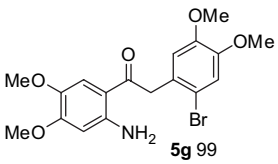
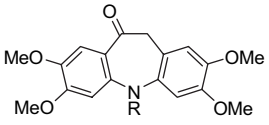
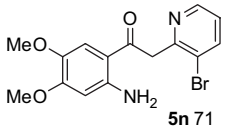
4. Experimental section

4.1. General remarks

All reagents and solvents were purchased and used without further purification. Redistilled water was employed for the palladium-catalysed reactions when indicated. ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ solution in a Bruker AC-250, AC-300 and AC-500. Chemical shifts are reported in parts per million downfield (δ) from Me_4Si. Coupling constants (J) are expressed in hertz (Hz). IR spectra were recorded on a Perkin–Elmer 1600 FT infrared spectrophotometer and only noteworthy absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). Drying of organic extracts after work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. HRMS were measured using a Waters GCT Mass Spectrometer. Except for the protection and deprotection steps, the rest of reactions were carried out under argon.

Table 2. Syntheses of azepinones **6** and OXC analogues **7**



Entry	5	6/7[a]	Entry	5	6/7[a]
1	 **5a** 95	 **6a** R = H 91 **OXC** R = $CONH_2$ 95	8	 **5h** 98	 **6h** R = H 87 **7h** R = $CONH_2$ 50
2	 **5b** 97	 **6b** R = H 81 **7b** R = $CONH_2$ 80 (95)	9[e]	 **5i** 96	 **6i** R = H 85 **7i** R = $CONH_2$ 80 (80)
3[b]	 **5c** 93	 **6c** 80	10[e]	 **5j** 97	 **6j** R = H 71 **7j** R = $CONH_2$ 89 (94)
4[c,d]	 **5d** 98	 **6d** R = H 77 **7d** R = $CONH_2$ 65	11[e]	 **5k** 97	 **6k** 47
5	 **5e** 98	 **6e** 84	12[c]	 **5l** 98	 **6l** 91
6	 **5f** 95	 **6f** 89	13[f]	 **5m** 78	NR
7	 **5g** 99	 **6g** R = H 80 **7g** R = $CONH_2$ 83 (93)	14[f]	 **5n** 71	NR

Reagents and conditions: (a) H_2SO_4, rt; (b) 4.9% $Pd(OAc)_2$, 7.9% BINAP, 2 equiv K_3PO_4, PhMe, H_2O, 130 °C, 4.5–6 h and (c) (i) $ClSO_2NCO$, CH_2Cl_2, 0 °C and (ii) AcOH, H_2O, 0 °C→rt.

[a] Isolated yields calculated on the basis of the percentage conversion (assumed to be 100% unless otherwise indicated in brackets).

[b] Cyclisation performed over 24 h.

[c] Cyclisation performed in a sealed tube, using 1,4-dioxane as solvent.

[d] Cyclisation performed over 21 h.

[e] H_2O was not added as a co-solvent.

[f] NR=no reaction.

4.2. Typical procedure for the synthesis of substrates 2a–c

4.2.1. 1-[2-*N*-(4-Methylbenzenesulfonamido)phenyl]-ethanone (2a).[11] *Typical procedure*: A solution of 2′-amino-acetophenone **1a** (3 g, 21.75 mmol), *p*-toluenesulfonyl chloride (12 g, 61.77 mmol) and pyridine (8 ml, 98.12 mmol) in CH_2Cl_2 (200 ml) was stirred overnight. The reaction mixture was washed twice with a saturated aqueous solution of $CuSO_4$ and once with water. The organic layer was dried and concentrated in vacuo and the resulting residue was purified by crystallisation from ethyl acetate to yield sulfonamide **2a** (6.03 g, 96%).

4.2.2. 1-[4,5-Dimethoxy-2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (2b). The typical procedure was followed employing **1b** (500 mg, 2.51 mmol) to afford compound **2b** (804.7 mg, 92%) as a yellow solid, mp 158–159 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.46 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 7.10 (1H, s), 7.17 (2H, d, J=7.92), 7.25 (1H, s), 7.64 (2H, d, J=8.32), 11.53 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.4, 27.9, 56.1 (CH_3), 102.5, 113.2, 115.1, 127.1, 129.5 (CH), 136.0, 136.2, 143.8, 144.1, 154.2, 200.4 (C); IR (film, cm^{-1}) 2955.3, 2850.5, 1637.4; EIMS (*m*/*z*, %) 349 (M, 5), 194 (22), 166 (100); HRMS calcd for $C_{17}H_{19}NO_5S$, 349.0984; found, 349.0988.

4.2.3. 1-[3-*N*-(4-Methylbenzenesulfonamido)-2-thienyl]-ethanone (2c). The typical procedure was followed employing **1c** (402.4 mg, 2.76 mmol) to afford compound **2c** (812.3 mg, 99%) as a white solid, mp 144–146 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 2.37 (3H, s), 7.22 (2H, d, J=7.93), 7.37 (1H, d, J=5.55), 7.40 (1H, d, J=5.55), 7.72 (2H, d, J=8.32), 10.68 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.5 (CH_3), 119.2 (C), 120.4, 126.8, 129.7, 132.2 (CH), 136.3, 143.3, 144.1, 192.8 (C); IR (film, cm^{-1}) 3108.1, 2920.1, 1625.8; EIMS (*m*/*z*, %) 295 (M, 63), 155 (60), 140 (82), 126 (92), 112 (92), 98 (53), 91 (100), 83 (32); HRMS calcd for $C_{13}H_{13}NO_3S_2$, 295.0337; found, 295.0337.

4.3. Typical procedure for the synthesis of 1,2-diaryl-ethanones 4a–h

4.3.1. 2-(2-Bromophenyl)-1-[2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4a).[11] A solution of sulfonamide **2a** (150 mg, 0.52 mmol), 1,2-dibromobenzene **3a** (0.15 ml, 1.25 mmol), $Pd(OAc)_2$ (5.3 mg, 0.023 mmol), Xantphos (26.5 mg, 0.044 mmol), Cs_2CO_3 (243.6 mg, 0.74 mmol), toluene (2.6 ml) and water (0.5 ml) was heated at 120 °C. After 48 h the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and concentrated in vacuo. The crude product was then purified by flash chromatography (CH_2Cl_2) to give starting material **2a** (22.1 mg) and deoxybenzoin **4a** (167.8 mg, 86%) as translucent prisms.

4.3.2. 2-(2-Bromo-4,5-dimethylphenyl)-1-[2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4b). The typical procedure was followed employing **2a** (310 mg, 1.08 mmol) and **3b** (702 mg, 2.58 mmol) to afford compound **4b** (346.6 mg, 68%) as a white solid, mp 182–184 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.22 (3H, s), 2.25 (3H, s), 2.36 (3H, s), 4.34 (2H, s), 6.94 (1H, s), 7.10 (1H, t, J=7.53), 7.21 (2H, d, J=8.33), 7.38 (1H, s), 7.48 (1H, t, J=7.53), 7.74 (1H, d, J=8.32), 7.98 (1H, d, J=7.93, H_{arom}), 11.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.2, 21.5 (CH_3), 46.1 (CH_2), 118.9 (CH), 121.5, 121.6 (C), 122.6, 127.2, 129.6, 131.0, 132.7, 133.4, 135.0 (CH), 136.2, 136.5, 137.9, 140.3, 143.7, 200.8 (C); IR (film, cm^{-1}) 3119.9, 2920.1, 1655.0; EIMS (*m*/*z*, %) 274 (13), 111 (18), 97 (31), 85 (39), 83 (32), 57 (100); HRMS calcd for $C_{23}H_{22}BrNO_3S$, 471.0504; found, 471.0507.

4.3.3. 2-(2-Bromo-4,5-dimethoxyphenyl)-1-[2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4c). The typical procedure was followed employing **2a** (401 mg, 1.39 mmol) and **3c** (1005 mg, 3.33 mmol) to afford compound **4c** (301.9 mg, 43%) as a brown solid, mp 165–166 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 4.33 (2H, s), 6.69 (1H, s), 7.05 (1H, s), 7.09 (1H, dd, J=1.18, 7.93), 7.19 (2H, d, J=7.92), 7.46 (1H, dt, J=1.19, 7.14), 7.72 (2H, d, J=8.33), 7.97 (1H, dd, J=1.19, 7.92), 11.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 46.2 (CH_2), 56.0, 56.1 (CH_3), 114.0 (CH), 114.9 (C), 115.4, 118.8 (CH), 121.4 (C), 122.5 (CH), 125.9 (C), 127.2, 129.6, 131.1, 135.0 (CH), 136.5, 140.3, 143.8, 148.4, 148.9, 200.7 (C); IR (film, cm^{-1}) 3123.5, 2943.6, 2850.5, 1655.0; EIMS (*m*/*z*, %) 505 (M+2, 3), 503 (M, 4), 319 (18), 317 (19), 274 (100), 209 (23), 119 (24), 91 (43); HRMS calcd for $C_{23}H_{22}BrNO_5S$, 503.0402; found, 503.0407.

4.3.4. 2-(2-Bromo-4,6-difluorophenyl)-1-[2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4d). The typical procedure was followed employing **2a** (152 mg, 0.53 mmol) and **3d** (359.3 mg, 1.33 mmol) to afford compound **4d** (238.2 mg, 94%) as a white solid, mp 147–149 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 4.41 (2H, s), 6.72–6.77 (1H, m), 6.89 (1H, td, J=2.77, 8.32), 7.12 (1H, t, J=7.53), 7.22 (2H, d, J=7.93), 7.51 (1H, td, J=1.58, 7.13), 7.69–7.78 (3H, m), 7.92 (1H, dd, J=1.19, 8.32), 11.14 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 46.3 (CH_2), 104.1 (t, J=25.47, CH), 106.9 (d, J=16.15, C), 114.3 (dd, J=3.59, 23.3), 119.5 (CH), 121.4 (C), 122.8, 127.3, 129.7, 130.9, 135.5 (CH), 136.5, 137.7 (d, J=8.97), 140.5, 143.9, 159.4 (dd, J=12.56, 247.73), 161.6 (dd, J=10.77, 249.52), 199.0 (C); IR (film, cm^{-1}) 3083.8, 1654.6; EIMS (*m*/*z*, %) 481 (M+2, 4), 479 (M, 3), 274 (100), 210 (88), 182 (12); HRMS calcd for $C_{21}H_{16}BrF_2NO_3S$, 479.0002; found, 479.0006.

4.3.5. 2-(2-Bromophenyl)-1-[4,5-dimethoxy-2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4e). The typical procedure was followed employing **2b** (249.8 mg, 0.72 mmol) and **3a** (0.33 ml, 2.65 mmol) to afford compound **4e** (314.8 mg, 87%) as a pale yellow solid, mp 147–149 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 3.81 (3H, s), 3.89 (3H, s), 4.28 (2H, s), 7.05 (1H, d, J=7.14), 7.09–7.25 (5H, m), 7.30 (1H, s), 7.55 (1H, d, J=7.53), 7.63 (1H, d, J=7.93), 11.43 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 46.6 (CH_2), 56.0, 56.1 (CH_3), 102.7, 112.4 (CH), 114.3, 124.6 (C), 124.6, 127.0, 127.5, 128.8, 129.5, 131.2, 132.6 (CH), 134.5, 136.2, 136.4, 143.7, 144.1, 154.3, 198.7 (C); IR (film, cm^{-1}) 3085.3, 2943.6, 2850.5, 1637.5;

EIMS (*m*/*z*, %) 505 (M+2, 3), 503 (M, 4), 334 (100), 269 (12); HRMS calcd for $C_{23}H_{22}BrNO_5S$, 503.0402; found, 503.0387.

4.3.6. 2-(2-Bromo-4,5-dimethylphenyl)-1-[4,5-dimethoxy-2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4f). The typical procedure was followed employing **2b** (149.5 mg, 0.43 mmol) and **3b** (285 mg, 1.03 mmol) to afford compound **4f** (191.1 mg, 84%) as a pale yellow solid, mp 144–146 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.16 (3H, s), 2.21 (3H, s), 2.35 (3H, s), 3.82 (3H, s), 3.91 (3H, s), 4.22 (3H, s), 6.89 (1H, s), 7.18 (2H, d, *J*=8.32), 7.23 (1H, s), 7.32 (1H, s), 7.34 (1H, s), 7.66 (2H, d, *J*=8.32), 11.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.2, 21.5 (CH_3), 46.1 (CH_2), 56.1, 56.2 (CH_3), 102.5, 112.6 (CH), 114.3, 121.2 (C), 127.1, 129.5 (CH), 131.4 (C), 132.2, 133.3 (CH), 136.3, 136.3, 136.6, 137.9, 143.7, 144.1, 154.3, 199.1 (C); IR (film, cm^{-1}) 3010.1, 2931.0, 2850.5, 1637.0; EIMS (*m*/*z*, %) 533 (M+2, 1), 531 (M, 1), 334 (100); HRMS calcd for $C_{25}H_{26}BrNO_5S$, 531.0715; found, 531.0719.

4.3.7. 2-(2-Bromo-4,5-dimethoxyphenyl)-1-[4,5-dimethoxy-2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4g). The typical procedure was followed employing **2b** (249.4 mg, 0.72 mmol) and **3c** (518 mg, 1.72 mmol) to afford compound **4g** (270 mg, 67%) as a pale yellow solid, mp 180–181 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.35 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 4.23 (2H, s), 6.69 (1H, s), 7.03 (1H, s), 7.18 (2H, d, *J*=7.93), 7.25 (1H, s), 7.31 (1H, s), 7.67 (2H, d, *J*=8.33), 11.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 46.2 (CH_2), 56.0, 56.1, 56.2, 56.3 (CH_3), 102.3, 112.6, 113.4, 114.1 (CH), 114.6 (C), 115.3 (CH), 126.2 (C), 127.2, 129.6 (CH), 136.5, 136.8, 143.8, 144.1, 148.5, 148.8, 154.5, 199.0 (C); IR (film, cm^{-1}) 3010.1, 2931.0, 2850.5, 1637.0; EIMS (*m*/*z*, %) 334 (100); HRMS calcd for $C_{25}H_{26}BrNO_7S$, 563.0613; found, 563.0614.

4.3.8. 2-(2-Bromo-4,6-difluorophenyl)-1-[4,5-dimethoxy-2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone (4h). The typical procedure was followed employing **2b** (252.6 mg, 0.72 mmol) and **3d** (462 mg, 1.72 mmol) to afford compound **4h** (388.7 mg, 99%) as a yellow solid, mp 163–164 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.35 (3H, s), 3.84 (3H, s), 3.91 (3H, s), 4.31 (2H, s), 6.67–6.71 (1H, m), 6.84 (1H, dt, *J*=2.77, 8.33), 7.17–7.19 (3H, m), 7.32 (1H, s), 7.62 (2H, d, *J*=7.93), 11.28 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 46.1 (CH_2), 56.2, 56.3 (CH_3), 102.8, 103.9 (t, *J*=26.03, CH), 106.7 (dd, *J*=3.59, 21.54, C), 112.2, 113.9 (dd, *J*=3.59, 23.34, CH), 114.1 (C), 127.1, 129.6 (CH), 136.2, 136.7, 138.0 (d, *J*=10.77), 143.9, 144.4, 154.8, 159.3 (dd, *J*=12.57, 247.73), 161.5 (dd, *J*=12.57, 249.37), 197.3 (C); IR (film, cm^{-1}) 3084.6, 2955.3, 2850.5, 1608.0; EIMS (*m*/*z*, %) 541 (M+2, 17), 539 (M, 19), 334 (100), 269 (15); HRMS calcd for $C_{23}H_{20}BrF_2NO_5S$, 539.0214; found, 539.0216.

4.4. Typical procedure for the synthesis of 1-thiophene-2-arylethanones 4i–l,o

4.4.1. 2-(2-Bromophenyl)-1-[3-*N*-(4-methylbenzenesulfonamido)-2-thienyl]ethanone (4i). A solution of sulfonamide **2c** (151.3 mg, 0.51 mmol), 1,2-dibromobenzene **3a** (0.1 ml, 0.8 mmol), $Pd(OAc)_2$ (5.3 mg, 0.023 mmol), Xantphos (29.5 mg, 0.049 mmol), K_3PO_4 (298 mg, 1.36 mmol) and 1,4-dioxane (2.5 ml) was heated at 130 °C in a sealed tube. After 4 days the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and concentrated in vacuo. The crude product was then purified by flash chromatography (CH_2Cl_2) to give starting material **2c** (26.5 mg) and compound **4i** (156.3 mg, 82%) as a yellow solid, mp 124–126 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 4.18 (2H, s), 7.15–7.33 (5H, m), 7.46 (2H, s), 7.58 (1H, d, *J*=8.32), 7.73 (1H, d, *J*=7.93), 10.62 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 47.8 (CH_2), 118.6 (C), 120.7 (CH), 125.1 (C), 127.0, 127.6, 129.2, 129.8, 131.8, 132.5, 132.8 (CH), 133.9, 136.5, 144.1, 144.4, 191.6 (C); IR (film, cm^{-1}) 3108.1, 2920.1, 1631.5; EIMS (*m*/*z*, %) 451 (M+2, 82), 449 (M, 81), 370 (33), 280 (99), 215 (100), 186 (94), 171 (60), 169 (65), 125 (94), 97 (50); HRMS calcd for $C_{19}H_{16}BrNO_3S_2$, 448.9755; found, 448.9756.

4.4.2. 2-(2-Bromo-4,5-dimethylphenyl)-1-[3-*N*-(4-methylbenzenesulfonamido)-2-thienyl]ethanone (4j). The typical procedure was followed employing **2c** (175.2 mg, 0.59 mmol) and **3b** (388 mg, 1.43 mmol) to afford compound **4j** (184.5 mg, 65%) as a white solid, mp 191–192 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.19 (3H, s), 2.22 (3H, s), 2.38 (3H, s), 4.10 (2H, s), 6.98 (1H, s), 7.23 (2H, d, *J*=8.32), 7.34 (1H, s), 7.44 (2H, s), 7.73 (2H, d, *J*=8.32), 10.67 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.2, 21.5 (CH_3), 47.3 (CH_2), 118.6 (C), 120.6 (CH), 121.5 (C), 126.9, 129.7 (CH), 130.7 (C), 132.5, 132.7, 133.3 (CH), 136.1, 136.4, 138.0, 144.1, 144.2, 192.0 (C); IR (film, cm^{-1}) 3108.1, 2908.3, 1625.6; EIMS (*m*/*z*, %) 479 (M+2, 6), 477 (M, 5), 398 (88), 280 (100), 215 (98), 199 (28), 125 (58), 91 (93); HRMS calcd for $C_{21}H_{20}BrNO_3S_2$, 477.0068; found, 477.0070.

4.4.3. 2-(2-Bromo-4,5-dimethoxyphenyl)-1-[3-*N*-(4-methylbenzenesulfonamido)-2-thienyl]ethanone (4k). The typical procedure was followed employing **2c** (269.7 mg, 0.91 mmol) and **3c** (666.5 mg, 2.19 mmol) to afford starting material **2c** (129 mg) and compound **4k** (75 mg, 31%) as a pale yellow solid, mp 154–155 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 4.11 (2H, s), 6.74 (1H, s), 7.04 (1H, s), 7.24 (2H, d, *J*=8.71), 7.45 (1H, s), 7.74 (2H, d, *J*=7.93), 10.67 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 47.5 (CH_2), 56.0, 56.1 (CH_3), 114.1, 115.4 (CH), 118.4 (C), 120.6 (CH), 125.6 (C), 127.0, 127.3, 129.8 (CH), 132.6, 136.5, 144.1, 144.5, 148.4, 148.9, 191.9 (C); IR (film, cm^{-1}) 3302.5, 2920.1, 2850.5, 1625.6; EIMS (*m*/*z*, %) 511 (M+2, 4), 509 (M, 4), 430 (57), 280 (100), 275 (96), 231 (21), 215 (80), 91 (77); HRMS calcd for $C_{21}H_{20}BrNO_5S_2$, 508.9966; found, 508.9963.

4.4.4. 2-(2-Bromo-4,6-difluorophenyl)-1-[3-*N*-(4-methylbenzenesulfonamido)-2-thienyl]ethanone (4l). The typical procedure was followed employing **2c** (150.5 mg, 0.51 mmol) and **3d** (95 mg, 0.35 mmol) to afford compound **4l** (102.6 mg, 61%) as a yellow solid, mp 144–146 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 4.19 (2H, s), 6.79–6.91 (2H, m), 7.25 (2H, d, *J*=8.33), 7.46 (1H, d, *J*=5.55), 7.49 (1H, d, *J*=5.55), 7.73 (2H, d, *J*=8.32),

10.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 47.2 (CH_2), 104.1 (t, J=26.92, CH), 106.9 (dd, J=3.59, 21.54, C), 114.4 (dd, J=3.59, 23.33, CH), 118.3 (C), 120.9, 126.9, 129.8, 132.9 (CH), 136.4, 137.2 (d, J=8.98), 144.3, 144.7, 159.3 (dd, J=12.56, 249.52), 161.5 (dd, J=12.56, 249.52), 190.2 (C); IR (film, cm^{-1}) 3302.5, 2920.1, 1625.6; EIMS (*m*/*z*, %) 487 (M+2, 33), 485 (M, 33), 280 (100), 251 (27), 222 (33), 215 (92), 125 (71), 91 (90); HRMS calcd for $C_{19}H_{14}BrF_2NO_3S_2$, 484.9567; found, 484.9552.

4.4.5. 2-(3-Bromo-2-pyridinyl)-1-[3-*N*-(4-methylbenzenesulfonamido)-2-thienyl]ethanone (4o). The typical procedure was followed employing **2c** (52.9 mg, 0.18 mmol) and **3e** (67.7 mg, 0.43 mmol) to afford starting material **2c** (76.7 mg) and compound **4o** (14 mg, 63%) as a yellow solid, mp 68–70 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s), 4.45 (2H, s), 7.13 (1H, dd, J=4.77, 7.95), 7.24 (2H, d, J=8.35), 7.45 (1H, d, J=5.56), 7.46 (1H, d, J=5.55), 7.73 (2H, d, J=8.35), 7.89 (1H, dd, J=1.19, 8.15), 8.50 (1H, dd, J=1.19, 4.57), 10.60 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_3), 49.6 (CH_2), 119.9 (C), 120.7, 123.8 (CH), 124.9 (C), 127.0, 129.8, 132.7 (CH), 136.5 (C), 140.4 (CH), 144.2, 144.4 (C), 147.9 (CH), 153.6, 190.6 (C); IR (film, cm^{-1}) 3300.5, 2920.1, 1625.6; EIMS (*m*/*z*, %) 452 (M+2, 3), 450 (M, 3), 297 (56), 295 (56), 269 (45), 267 (46), 216 (100), 187 (84), 91 (66); HRMS calcd for $C_{18}H_{15}N_2O_3S_2Br$, 449.9712; found, 449.9707.

4.5. Typical procedure for the synthesis of 1,2-diarylethanones 5m and 5n

4.5.1. 1-(2-Aminophenyl)-2-(3-bromo-2-pyridinyl)ethanone (5m). A solution of sulfonamide **2a** (251 mg, 0.87 mmol), 2,3-dibromopyridine **3e** (166 mg, 0.7 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), Xantphos (33.4 mg, 0.056 mmol), K_3PO_4 (350 mg, 1.61 mmol) and toluene (3.8 ml) was heated at 130 °C. After 24 h the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and concentrated in vacuo. The crude product was partially purified by flash chromatography (4% Et_2O/CH_2Cl_2) and then treated with concentrated sulfuric acid (5 ml) at 60 °C for 25 min to afford compound **5m** (159 mg, 78% over two steps) as a yellow solid, mp 124–126 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 4.71 (2H, s), 6.26 (2H, br s), 6.64–6.70 (2H, m), 7.07–7.12 (1H, m), 7.25–7.31 (1H, m), 7.80–7.90 (2H, m), 8.52 (1H, d, J=4.76); ^{13}C NMR ($CDCl_3$) δ 48.4 (CH_2), 115.8, 117.3 (CH), 122.5 (C), 123.2, 131.1, 134.5, 140.1, 147.9 (CH), 150.6 (C), 155.5, 197.6 (C); IR (film, cm^{-1}) 3459.8, 3342.3, 3048.5, 1642.8; EIMS (*m*/*z*, %) 292 (M+2, 20), 290 (M, 22), 211 (72), 120 (100), 92 (77); HRMS calcd for $C_{13}H_{11}BrN_2O$, 290.0055; found, 290.0065.

4.5.2. 1-(2-Amino-4,5-dimethoxyphenyl)-2-(3-bromo-2-pyridinyl)ethanone (5n). The typical procedure was followed employing **2b** (304 mg, 0.86 mmol) and **3e** (168.8 mg, 0.71 mmol) to afford compound **5n** (176.9 mg, 71% over two steps) as a brown solid, mp 111–112 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.74 (3H, s), 3.75 (3H, s), 4.54 (2H, s), 6.04 (1H, s), 6.30 (1H, br s), 7.00 (1H, dd, J=4.76, 7.92), 7.10 (1H, s), 7.79 (1H, d, J=7.92), 8.42 (1H, d, J=3.56); ^{13}C NMR ($CDCl_3$) δ 48.2 (CH_2), 55.5, 56.4 (CH_3), 98.9 (CH), 109.1 (C), 112.5 (CH), 122.1 (C), 123.0 (CH), 139.7 (C), 139.9, 147.6 (CH), 148.1, 155.2, 155.4, 194.8 (C); IR (film, cm^{-1}) 3448.9, 3331.4, 2931.8, 2850.5, 1631.5; EIMS (*m*/*z*, %) 352 (M+2, 87), 350 (M, 91), 336 (21), 334 (21), 271 (90), 180 (100), 152 (90), 94 (57); HRMS calcd for $C_{15}H_{15}BrN_2O_3$, 350.0266; found, 350.0276.

4.6. Typical procedure for the synthesis of substrates 5a–l

4.6.1. 1-(2-Aminophenyl)-2-(2-bromophenyl)ethanone (5a).[11] A solution of deoxybenzoin **4a** (1.19 g, 2.68 mmol) in 20 ml of concentrated sulfuric acid was stirred at room temperature in an open vessel for 10 min (until complete solution of the substrate is visually observed). The reaction mixture was then poured onto an ice-water mixture. The resulting solution was allowed to reach room temperature and then was extracted with dichloromethane. The organic layer was dried and the solvent was removed in vacuo to give amine **5a** (736 mg, 95%).

4.6.2. 1-(2-Aminophenyl)-2-(2-bromo-4,5-dimethylphenyl)ethanone (5b). The typical procedure was followed employing **4b** (178.9 mg, 0.38 mmol) to afford compound **5b** (116.8 mg, 97%) as a yellow solid, mp 100–101 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.21 (3H, s), 2.24 (3H, s), 4.38 (2H, s), 6.11 (2H, br s), 6.65–6.73 (2H, m), 7.01 (1H, s), 7.29 (1H, t, J=7.14), 7.39 (1H, s), 7.89 (1H, d, J=7.93); ^{13}C NMR ($CDCl_3$) δ 19.0, 19.2 (CH_3), 45.6 (CH_2), 115.7, 117.3 (CH), 121.7 (C), 131.0, 132.4, 132.6 (CH), 133.2 (C), 134.4 (CH), 135.9, 137.3, 150.5, 198.7 (C); IR (film, cm^{-1}) 3460.7, 3343.2, 2920.0, 1649.1; EIMS (*m*/*z*, %) 319 (M+2, 44), 317 (M, 49), 238 (98), 121 (100), 92 (99); HRMS calcd for $C_{16}H_{16}BrNO$, 317.0415; found, 317.0412.

4.6.3. 1-(2-Aminophenyl)-2-(2-bromo-4,5-dimethoxyphenyl)ethanone (5c). The typical procedure was followed employing **4c** (301.9 mg, 0.59 mmol) to afford compound **5c** (194.2 mg, 93%) as a yellow solid, mp 120–122 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 3.86 (3H, s), 4.36 (2H, s), 6.28 (2H, br s), 6.64–6.70 (2H, m), 6.73 (1H, s), 7.06 (1H, s), 7.28 (1H, dt, J=1.19, 7.53), 7.86 (1H, d, J=7.93); ^{13}C NMR ($CDCl_3$) δ 5.8 (CH_2), 55.9, 56.0 (CH_3), 113.9 (CH), 115.0 (C), 115.3, 115.7, 117.3 (CH), 127.3 (C), 130.9, 134.5 (CH), 148.2, 148.4, 150.5, 198.6 (C); IR (film, cm^{-1}) 3460.7, 3343.2, 2931.8, 2850.5, 1608.0; EIMS (*m*/*z*, %) 351 (M+2, 23), 349 (M, 26), 270 (99), 229 (21), 121 (100), 92 (97); HRMS calcd for $C_{16}H_{16}BrNO_3$, 349.0314; found, 349.0324.

4.6.4. 1-(2-Aminophenyl)-2-(2-bromo-4,6-difluorophenyl)-ethanone (5d). The typical procedure was followed employing **4d** (360.3 mg, 0.75 mmol) to afford compound **5d** (240.2 mg, 98%) as an orange solid, mp 130–132 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 4.46 (2H, s), 6.17 (2H, br s), 6.65–6.73 (2H, m), 6.82–6.89 (2H, m), 7.31 (1H, dt, J=1.19, 8.32), 7.81 (1H, d, J=7.53); ^{13}C NMR ($CDCl_3$) δ 45.7 (CH_2), 55.8, 56.7 (CH_3), 99.2, 103.5 (t, J=25.13, CH), 106.8 (dd, J=3.59, 21.54), 109.1 (C), 112.4, 114.0 (dd, J=3.59, 23.34, CH), 139.4 (d, J=8.98), 140.3, 148.4, 155.8, 159.2 (dd, J=12.57, 247.73), 161.5 (dd, J=12.57,

247.73), 194.7 (C); IR (film, cm^{-1}) 3472.4, 3343.2, 3084.0, 1649.1; EIMS (*m/z*, %) 327 (M+2, 6), 325 (M, 6), 214 (12), 120 (100), 92 (27); HRMS calcd for $C_{16}H_{14}BrF_2NO_3$, 324.9914; found, 324.9923.

4.6.5. 1-(2-Amino-4,5-dimethoxyphenyl)-2-(2-bromophenyl)ethanone (5e). The typical procedure was followed employing **4e** (208.8 mg, 0.41 mmol) to afford compound **5e** (141.8 mg, 98%) as a brown solid, mp 109–110 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.82 (3H, s), 4.33 (2H, s), 7.07–7.13 (1H, m), 7.16 (1H, s), 7.23 (1H, s), 7.24 (1H, d, J=7.53), 7.57 (1H, d, J=7.53); ^{13}C NMR ($CDCl_3$) δ 46.2 (CH_2), 55.6, 56.5 (CH_3), 99.1 (CH), 109.3 (C), 112.6 (CH), 124.8 (C), 127.4, 128.4, 131.3, 132.5 (CH), 135.8, 139.9, 148.1, 155.3, 196.1 (C); IR (film, cm^{-1}) 3448.9, 3331.4, 2931.8, 2850.0, 1631.5; EIMS (*m/z*, %) 351 (M+2, 96), 349 (M, 98), 180 (100), 152 (96), 137 (13), 125 (25), 94 (46); HRMS calcd for $C_{16}H_{16}BrNO_3$, 349.0314; found, 349.0311.

4.6.6. 1-(2-Amino-4,5-dimethoxyphenyl)-2-(2-bromo-4,5-dimethylphenyl)ethanone (5f). The typical procedure was followed employing **4f** (177.8 mg, 0.33 mmol) to afford compound **5f** (120 mg, 95%) as a pale yellow solid, mp 146–148 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.15 (3H, s), 2.18 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 4.26 (2H, s), 6.05 (2H, br s), 6.10 (1H, s), 7.00 (1H, s), 7.18 (1H, s), 7.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.9, 19.1 (CH_3), 45.7 (CH_2), 55.6, 56.6 (CH_3), 99.2 (CH), 109.5 (C), 112.7 (CH), 121.3 (C), 132.2 (CH), 132.6 (C), 133.1 (CH), 136.0, 137.2, 139.9, 147.8, 155.2, 196.6 (C); IR (film, cm^{-1}) 3448.9, 3319.7, 2931.0, 2850.5, 1631.5; EIMS (*m/z*, %) 379 (M+2, 88), 377 (M, 93), 180 (100), 152 (84), 125 (28), 94 (31); HRMS calcd for $C_{18}H_{20}BrNO_3$, 377.0627; found, 377.0619.

4.6.7. 1-(2-Amino-4,5-dimethoxyphenyl)-2-(2-bromo-4,5-dimethoxyphenyl)ethanone (5g). The typical procedure was followed employing **4g** (268 mg, 0.48 mmol) to afford compound **5g** (193 mg, 99%) as a brown solid, mp 170–171 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.79 (3H, s), 3.82 (9H, s), 4.25 (2H, s), 6.08 (1H, s), 6.29 (2H, s), 6.75 (1H, s), 7.03 (1H, s), 7.18 (1H, s); ^{13}C NMR ($CDCl_3$) δ 45.8 (CH_2), 55.7, 55.8, 56.0, 56.6 (CH_3), 99.1 (CH), 109.3 (C), 112.6, 113.5 (CH), 114.6 (C), 115.2 (CH), 127.6, 140.0, 148.2, 148.3, 148.4, 155.4, 196.5 (C); IR (film, cm^{-1}) 3448.9, 3319.7, 2931.8, 2850.5, 1631.5; EIMS (*m/z*, %) 411 (M+2, 50), 409 (M, 50), 330 (45), 180 (100), 152 (71), 125 (39), 111 (15), 97 (32); HRMS calcd for $C_{18}H_{20}BrNO_5$, 409.0525; found, 409.0521.

4.6.8. 1-(2-Amino-4,5-dimethoxyphenyl)-2-(2-bromo-4,6-difluorophenyl)ethanone (5h). The typical procedure was followed employing **4h** (209.2 mg, 0.39 mmol) to afford compound **5h** (146.8 mg, 98%) as a yellow solid, mp 155–157 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.83 (3H, s), 3.86 (3H, s), 4.35 (2H, s), 6.10 (1H, s), 6.20 (2H, br s), 6.78–6.87 (2H, m), 7.11 (1H, s); ^{13}C NMR ($CDCl_3$) δ 45.7 (CH_2), 55.8, 56.7 (CH_3), 99.2, 103.5 (t, J=25.13, CH), 106.8 (dd, J=3.59, 21.54), 109.1 (C), 112.4, 114.0 (dd, J=3.59, 23.34, CH), 139.4 (d, J=8.98), 140.3, 148.4, 155.8, 159.2 (dd, J=12.57, 247.73), 161.5 (dd, J=12.57, 247.73), 194.7 (C); IR (film, cm^{-1}) 3448.9, 3331.4, 2931.8, 2850.5, 1631.0; EIMS (*m/z*, %) 387 (M+2, 68), 385 (M, 74), 180 (100), 152 (80), 125 (38), 94 (45); HRMS calcd for $C_{16}H_{14}BrF_2NO_3$, 385.0125; found, 385.0118.

4.6.9. 1-(3-Amino-2-thienyl)-2-(2-bromophenyl)ethanone (5i). The typical procedure was followed employing **4i** (259.3 mg, 0.58 mmol) to afford compound **5i** (162.9 mg, 96%) as an orange solid, mp 146–148 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 4.18 (2H, s), 5.82 (2H, br s), 6.54 (1H, d, J=5.15), 7.11–7.17 (1H, m), 7.28–7.32 (3H, m), 7.58 (1H, d, J=7.93); ^{13}C NMR ($CDCl_3$) δ 47.4 (CH_2), 110.7 (C), 119.9 (CH), 125.2 (C), 127.4, 128.6, 131.8, 132.2, 132.6 (CH), 135.2, 154.9, 189.7 (C); IR (film, cm^{-1}) 3425.4, 3307.9, 3096.4, 1602.1; EIMS (*m/z*, %) 297 (M+2, 24), 295 (M, 25), 216 (79), 126 (100), 89 (22); HRMS calcd for $C_{12}H_{10}BrNOS$, 294.9666; found, 294.9682.

4.6.10. 1-(3-Amino-2-thienyl)-2-(2-bromo-4,5-dimethylphenyl)ethanone (5j). The typical procedure was followed employing **4j** (317.1 mg, 0.66 mmol) to afford compound **5j** (209 mg, 97%) as a brown solid, mp 113–114 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.18 (3H, s), 2.21 (3H, s), 4.09 (2H, s), 6.18 (2H, br s), 6.54 (1H, d, J=4.36), 7.05 (1H, s), 7.29 (1H, d, J=5.15), 7.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.0, 19.1 (CH_3), 46.8 (CH_2), 111.2 (C), 120.0 (CH), 121.6, 132.0, 132.1, 132.7, 133.2 (CH), 135.9, 137.4, 154.3, 190.1 (C); IR (film, cm^{-1}) 3437.2, 3319.7, 2920.1, 1596.3; EIMS (*m/z*, %) 322 (30), 244 (79), 126 (100), 98 (19); HRMS calcd for $C_{14}H_{14}BrNOS$, 322.9979; found, 322.9992.

4.6.11. 1-(3-Amino-2-thienyl)-2-(2-bromo-4,5-dimethoxyphenyl)ethanone (5k). The typical procedure was followed employing **4k** (74.2 mg, 0.15 mmol) to afford compound **5k** (50.4 mg, 97%) as a brown solid, mp 126–128 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.84 (3H, s), 3.85 (3H, s), 4.09 (2H, s), 6.12 (2H, br s), 6.53 (1H, d, J=5.55), 6.80 (1H, s), 7.04 (1H, s), 7.30 (1H, d, J=5.16); ^{13}C NMR ($CDCl_3$) δ 46.9 (CH_2), 55.9, 56.0 (CH_3), 110.6 (C), 114.1, 115.3, 119.8 (CH), 126.9, 129.8 (C), 132.3 (CH), 148.2, 148.5, 155.0, 190.0 (C); IR (film, cm^{-1}) 3448.1, 3330.5, 2919.2, 2850.3, 1595.8; EIMS (*m/z*, %) 276 (77), 219 (28), 126 (100); HRMS calcd for $C_{14}H_{14}BrNO_3S$, 354.9878; found, 354.9861.

4.6.12. 1-(3-Amino-2-thienyl)-2-(2-bromo-4,6-difluorophenyl)ethanone (5l). The typical procedure was followed employing **4l** (78.1 mg, 0.16 mmol) to afford compound **5l** (52 mg, 98%) as an orange solid, mp 103–104 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 4.18 (2H, s), 6.21 (2H, br s), 6.56 (1H, d, J=5.15), 6.80–6.92 (2H, m), 7.34 (1H, d, J=5.16); ^{13}C NMR ($CDCl_3$) δ 46.8 (CH_2), 103.6 (t, J=26.03, CH), 106.9 (dd, J=3.59, 21.54), 110.4 (C), 114.3 (dd, J=3.59, 23.34), 119.9, 132.7 (CH), 138.7 (d, J=8.97), 155.3, 159.3 (dd, J=12.57, 247.73), 161.5 (dd, J=12.57, 247.73), 188.3 (C); IR (film, cm^{-1}) 3448.9, 3331.4, 3084.6, 2920.1, 1590.4; EIMS (*m/z*, %) 322 (25), 126 (39), 83 (100); HRMS calcd for $C_{12}H_8BrF_2NOS$, 330.9478; found, 330.9471.

4.7. Typical procedure for the synthesis of dibenzoazepinones 6a–h

4.7.1. 10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-10-one (6a).[11] A solution of amine **5a** (100.6 mg, 0.35 mmol), $Pd(OAc)_2$

(4 mg, 0.017 mmol), BINAP (17.4 mg, 0.027 mmol), previously ground K_3PO_4 (150 mg, 0.68 mmol), toluene (3.5 ml) and water (1.5 ml) was heated at 130 °C. After 5 h the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and concentrated in vacuo. The crude product was then purified by flash chromatography (5% Et_2O/CH_2Cl_2) to give compound **6a** (66 mg, 91%) as yellow needles.

4.7.2. 10,11-Dihydro-5*H*-2,3-dimethyldibenzo[*b*,*f*]azepin-10-one (6b). The typical procedure was followed starting from **5b** (95 mg, 0.29 mmol) to afford compound **6b** (57.1 mg, 81%) as a yellow solid, mp 180–182 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.21 (6H, s), 3.75 (2H, s), 6.75 (1H, br s), 6.84 (1H, s), 6.90 (1H, dt, J=0.79, 7.13), 7.01 (1H, d, J=8.32), 7.04 (1H, s), 7.38 (1H, dt, J=1.58, 7.54), 8.02 (1H, dd, J=1.58, 8.32); ^{13}C NMR ($CDCl_3$) δ 18.9, 19.4 (CH_3), 48.7 (CH_2), 118.8, 119.0, 119.9 (CH), 121.1, 123.9, 130.4 (C), 130.5, 133.3 (CH), 135.9, 139.1, 146.7, 189.9 (C); IR (film, cm^{-1}) 3307.9, 1643.3; EIMS (*m*/*z*, %) 237 (99), 222 (100), 208 (44), 194 (47); HRMS calcd for $C_{16}H_{15}NO$, 237.1154; found, 237.1156.

4.7.3. 10,11-Dihydro-5*H*-2,3-dimethoxydibenzo[*b*,*f*]azepin-10-one (6c). The typical procedure was followed starting from **5c** (165 mg, 0.47 mmol) to afford compound **6c** (101.6 mg, 80%) as an orange solid, mp 172–174 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.70 (2H, s), 3.74 (3H, s), 3.81 (3H, s), 6.61 (1H, s), 6.74 (1H, s), 6.88 (1H, t, J=8.01), 6.98 (1H, s), 7.04 (1H, d, J=8.22), 7.37 (1H, t, J=7.61), 8.00 (1H, d, J=8.01); ^{13}C NMR ($CDCl_3$) δ 48.5 (CH_2), 55.8, 56.1 (CH_3), 102.9, 111.8 (CH), 115.4 (C), 118.8, 118.9 (CH), 123.6 (C), 130.3, 133.2 (CH), 134.8, 146.7, 146.8, 148.1, 189.3 (C); IR (film, cm^{-1}) 3331.4, 2815.3, 1649.1; EIMS (*m*/*z*, %) 269 (M, 13), 254 (63), 226 (100); HRMS calcd for $C_{16}H_{15}NO_3$, 269.1052; found, 269.1052.

4.7.4. 10,11-Dihydro-5*H*-1,3-difluorodibenzo[*b*,*f*]azepin-10-one (6d). The typical procedure was followed starting from **5d** (64.3 mg, 0.19 mmol), but by using 1,4-dioxane instead of toluene and the reaction was performed in a sealed tube to afford compound **6d** (34.6 mg, 77%) as a yellow solid, mp 166–167 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.86 (2H, s), 6.65 (1H, br s), 6.78–6.86 (2H, m), 6.98 (1H, t, J=7.53), 7.09 (1H, d, J=8.32), 7.45 (1H, dt, J=1.59, 8.72), 8.03 (1H, dd, J=1.19, 7.93); ^{13}C NMR ($CDCl_3$) δ 49.1 (CH_2), 102.4 (dd, J=26.81, 26.86), 111.4 (dd, J=3.81, 22.69), 119.6, 120.2 (CH), 124.5, 126.6 (dd, J=3.38, 12.10), 127.5 (d, J=11.40, C), 130.6, 133.9 (CH), 145.9, 152.8 (dd, J=12.68, 245.19), 158.9 (dd, J=11.92, 245.89), 188.3 (C); IR (film, cm^{-1}) 3307.9, 1655.0; EIMS (*m*/*z*, %) 245 (M, 95), 216 (100), 196 (17), 169 (18); HRMS calcd for $C_{14}H_9F_2NO$, 245.0652; found, 245.0654.

4.7.5. 10,11-Dihydro-5*H*-7,8-dimethoxydibenzo[*b*,*f*]azepin-10-one (6e). The typical procedure was followed starting from **5e** (101.6 mg, 0.29 mmol) to afford compound **6e** (65.7 mg, 84%) as a yellow solid, mp 188–190 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.78 (2H, s), 3.79 (6H, s), 6.55 (1H, s), 7.06–7.23 (5H, m), 7.48 (1H, s); ^{13}C NMR ($CDCl_3$) δ 48.9 (CH_2), 55.8, 55.9 (CH_3), 101.5, 110.4 (CH), 116.3 (C), 118.7 (CH), 123.9 (C), 124.5, 127.3, 129.5 (CH), 141.9, 142.9, 143.3, 154.0, 188.9 (C); IR (film, cm^{-1}) 3296.2, 2815.0, 1608.0; EIMS (*m*/*z*, %) 269 (M, 49), 254 (62), 226 (100), 198 (45); HRMS calcd for $C_{16}H_{15}NO_3$, 269.1052; found, 269.1052.

4.7.6. 10,11-Dihydro-5*H*-2,3-dimethyl-7,8-dimethoxydibenzo[*b*,*f*]azepin-10-one (6f). The typical procedure was followed starting from **5f** (91.5 mg, 0.24 mmol) to afford compound **6f** (64.1 mg, 89%) as a yellow solid, mp 166–168 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 2.16 (6H, s), 3.72 (2H, s), 3.79 (3H, s), 3.82 (3H, s), 6.51 (1H, s), 6.84 (1H, s), 6.96 (1H, s), 6.99 (1H, s), 7.48 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.8, 19.4 (CH_3), 48.5 (CH_2), 55.8, 55.9 (CH_3), 101.3, 110.5 (CH), 116.2 (C), 119.7 (CH), 121.2 (C), 130.3 (CH), 132.9, 135.7, 139.7, 142.8, 143.5, 153.9, 189.2 (C); IR (film, cm^{-1}) 3319.7, 2943.6, 2820.0, 1608.0; EIMS (*m*/*z*, %) 297 (M, 100), 282 (96), 252 (15), 211 (14), 97 (15); HRMS calcd for $C_{18}H_{19}NO_3$, 297.1365; found, 297.1354.

4.7.7. 10,11-Dihydro-5*H*-2,3,7,8-tetramethoxydibenzo-[*b*,*f*]azepin-10-one (6g). The typical procedure was followed starting from **5g** (184.7 mg, 0.45 mmol) to afford compound **6g** (118 mg, 80%) as a yellow solid, mp >300 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.68 (2H, s), 3.76 (3H, s), 3.82 (6H, s), 3.86 (3H, s), 6.47 (1H, s), 6.59 (1H, s), 6.72 (1H, s), 6.74 (1H, s), 7.46 (1H, s); ^{13}C NMR ($CDCl_3$) δ 48.3 (CH_2), 55.9, 56.0, 56.1 (CH_3), 101.2, 102.9, 110.6, 111.8 (CH), 115.8, 116.1, 135.4, 142.9, 143.3, 146.7, 147.9, 153.9, 188.5 (C); IR (film, cm^{-1}) 3343.2, 2943.6, 2815.3, 1608.0; EIMS (*m*/*z*, %) 329 (97), 314 (100), 286 (21), 97 (16); HRMS calcd for $C_{18}H_{19}NO_5$, 329.1263; found, 329.1259.

4.7.8. 10,11-Dihydro-5*H*-1,3-difluoro-7,8-dimethoxydibenzo[*b*,*f*]azepin-10-one (6h). The typical procedure was followed starting from **5h** (98.5 mg, 0.26 mmol) to afford compound **6h** (67.6 mg, 87%) as a yellow solid, mp>300 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s), 3.87 (3H, s), 3.96 (2H, s), 6.50 (1H, s), 6.77–6.84 (2H, m), 7.48 (1H, s); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 48.4 (CH_2), 55.7 (CH_3), 101.7, 101.9 (dd, J=2.75, 23.83), 110.1, 110.6 (dd, J=3.67, 22.91, CH), 116.1, 126.8 (dd, J=3.67, 11.91), 127.8 (d, J=8.25), 143.2, 143.3, 152.8 (dd, J=11.91, 245.60), 154.4, 158.6 (dd, J=11.92, 245.61), 188.0 (C); IR (film, cm^{-1}) 3331.4, 2955.3, 2815.0, 1608.0; EIMS (*m*/*z*, %) 305 (M, 97), 290 (100), 262 (36), 234 (19), 219 (24), 214 (18), 203 (21), 190 (42); HRMS calcd for $C_{16}H_{13}F_2NO_3$, 305.0863; found, 305.0857.

4.7.9. 9,10-Dihydro-4*H*-thieno[3,2,*b*][*f*]benzazepin-10-one (6i). The typical procedure was followed without the addition of water starting from **5i** (41.5 mg, 0.14 mmol) to afford compound **6i** (25.7 mg, 85%) as a brown solid, mp 181–182 °C (Et_2O) (lit.[23] 195 °C). ^{1}H NMR ($CDCl_3$) δ 3.76 (2H, s), 6.84 (1H, d, J=5.15), 7.05 (1H, d, J=7.53), 7.12–7.29 (3H, m), 7.35 (1H, br s), 7.49 (1H, d, J=5.16); ^{13}C NMR ($CDCl_3$) δ 48.5 (CH_2), 118.6, 121.4 (CH), 122.5 (C), 124.8, 127.5, 130.9, 133.3 (CH), 141.3, 149.6, 185.3 (C); IR (film, cm^{-1}) 3284.4, 3084.6, 1602.1; EIMS (*m*/*z*, %) 215 (M, 62), 187 (23), 186 (100), 115 (23); HRMS calcd for $C_{12}H_9NOS$, 215.0405; found, 215.0396.

4.7.10. 9,10-Dihydro-4*H*-6,7-dimethylthieno[3,2,*b*][*f*]-benzazepin-10-one (6j). The typical procedure was followed without the addition of water starting from **5j** (209 mg, 0.65 mmol) to afford compound **6j** (111 mg, 71%) as a yellow solid, mp>300 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 2.22 (6H, s), 3.68 (2H, s), 6.79 (1H, d, J=5.15), 6.82 (1H, s), 7.02 (1H, s), 7.13 (1H, br s), 7.46 (1H, d, J=5.15); ^{13}C NMR ($CDCl_3$) δ 18.9, 19.4 (CH_3), 47.9 (CH_2), 119.6 (CH), 119.8, 120.3 (C), 121.2, 131.7, 133.0 (CH), 133.3, 135.9, 139.0, 149.6, 185.5 (C); IR (film, cm^{-1}) 3260.9, 2955.3, 1602.1; EIMS (*m*/*z*, %) 243 (M, 100), 228 (88), 214 (44), 199 (18); HRMS calcd for $C_{14}H_{13}NOS$, 243.0718; found, 243.0712.

4.7.11. 9,10-Dihydro-4*H*-6,7-dimethoxythieno[3,2,*b*]-[*f*]benzazepin-10-one (6k). The typical procedure was followed without the addition of water starting from **5k** (31.9 mg, 0.09 mmol) to afford compound **6k** (11.5 mg, 47%) as an orange solid, mp 190–191 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.65 (2H, s), 3.84 (3H, s), 3.85 (3H, s), 6.57 (1H, s), 6.74 (1H, s), 6.80 (1H, d, J=5.16), 7.12 (1H, br s), 7.47 (1H, d, J=5.15); ^{13}C NMR ($CDCl_3$) δ 47.8 (CH_2), 56.0, 56.2 (CH_3), 102.7, 113.0 (CH), 114.2 (C), 121.0 (CH), 133.0, 134.6, 146.7, 148.1, 149.6, 185.1 (C); IR (film, cm^{-1}) 3272.6, 2920.1, 2815.0, 1602.1; EIMS (*m*/*z*, %) 275 (M, 100), 260 (90), 232 (34), 189 (13), 83 (21); HRMS calcd for $C_{14}H_{13}NO_3S$, 275.0616; found, 275.0630.

4.7.12. 9,10-Dihydro-4*H*-6,8-difluorothieno[3,2,*b*][*f*]benz-azepin-10-one (6l). The typical procedure was followed but without the addition of water, using 1,4-dioxane instead of toluene and the reaction was performed in a sealed tube starting from **5l** (29.1 mg, 0.09 mmol) to afford compound **6l** (19.9 mg, 91%) as an orange solid, mp 220–221 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.78 (2H, s), 6.81–6.87 (3H, m), 7.16 (1H, br s), 7.54 (1H, d, J=5.15); ^{13}C NMR ($CDCl_3$) δ 48.3 (CH_2), 100.0 (C), 102.3 (dd, J=26.86, 26.90), 112.4 (dd, J=3.72, 22.65), 121.5 (CH), 126.1 (d, J=11.12), 126.5 (dd, J=3.48, 12.09, C), 133.8 (CH), 148.7, 152.4 (dd, J=12.64, 244.51), 158.8 (dd, J=12.08, 245.87), 183.6 (C); IR (film, cm^{-1}) 3249.1, 2908.3, 1619.8; EIMS (*m*/*z*, %) 251 (M, 92), 222 (100), 202 (52), 158 (47); HRMS calcd for $C_{12}H_7F_2NOS$, 251.0216; found, 251.0213.

4.8. Experimental data for oxcarbazepine analogues 7

4.8.1. 10,11-Dihydro-5-aminocarbonyl-5*H*-2,3-dimethyl-dibenzo[*b*,*f*]azepin-10-one (7b). The patented procedure for the carbamoylation[22] was followed starting from **6b** (66.8 mg, 0.28 mmol) to give unreacted starting material **6b** (3.5 mg) and compound **7b** (60.1 mg, 80%) as an orange solid, mp 216–218 °C (acetone). ^1H NMR ($CDCl_3$) δ 2.26 (6H, s), 3.78 (1H, d, J=14.11), 4.39 (1H, d, J=13.84), 5.08 (2H, br s), 7.17 (1H, s), 7.27 (1H, s), 7.34 (1H, dt, J=0.59, 7.35), 7.57 (1H, dt, J=1.59, 8.15), 7.66 (1H, d, J=7.95), 8.10 (1H, dd, J=1.20, 7.95); ^{13}C NMR ($CDCl_3$) δ 19.4, 19.5 (CH_3), 48.5 (CH_2), 127.1, 128.4, 128.9 (CH), 129.9 (C), 130.6 (CH), 130.9 (C), 131.2, 133.8 (CH), 137.2, 138.1, 138.9, 140.0, 156.0, 192.1 (C); IR (film, cm^{-1}) 3489.1, 3350.2, 2920.1, 1672.6, 1590.4; EIMS (*m*/*z*, %) 280 (M, 33), 237 (76), 222 (100), 208 (81), 194 (36); HRMS calcd for $C_{17}H_{16}N_2O_2$, 280.1212; found, 280.1210.

4.8.2. 10,11-Dihydro-5-aminocarbonyl-5*H*-1,3-difluoro-dibenzo[*b*,*f*]azepin-10-one (7d). The same procedure was followed starting from **6d** (36 mg, 0.15 mmol) to give compound **7d** (25.2 mg, 65%) as a pale yellow solid, mp 194–196 °C (acetone). ^1H NMR ($CDCl_3$) δ 3.86 (1H, d, J=14.58), 4.43 (1H, d, J=14.58), 4.95 (2H, br s), 6.84 (1H, dt, J=2.43, 8.79), 6.90 (1H, d, J=7.67), 7.42 (1H, t, J=7.57), 7.62–7.68 (2H, m), 8.12 (1H, dd, J=0.93, 7.95); ^{13}C NMR ($CDCl_3$) δ 49.0 (CH_2), 104.0 (t, J=23.83), 112.3 (dd, J=2.75, 22.91, CH), 125.3 (dd, J=3.66, 14.00, C), 128.2 (CH), 128.6 (C), 130.1, 131.2, 134.6 (CH), 137.6 (d, J=9.17), 142.2, 154.9, 158.7 (dd, J=13.29, 255.69), 162.1 (dd, J=11.50, 252.93), 190.8 (C); IR (film, cm^{-1}) 3459.8, 3331.4, 2920.1, 1678.5, 1596.3; EIMS (*m*/*z*, %) 288 (M, 5), 245 (55), 216 (100), 196 (21), 169 (16); HRMS calcd for $C_{15}H_{10}F_2N_2O_2$, 288.0710; found, 288.0711.

4.8.3. 10,11-Dihydro-5-aminocarbonyl-5*H*-2,3,7,8-tetra-methoxydibenzo[*b*,*f*]azepin-10-one (7g). The same procedure was followed starting from **6g** (64.2 mg, 0.19 mmol) to give unreacted starting material **6g** (4.7 mg) and compound **7g** (55.5 mg, 83%) as an orange solid, mp 214–216 °C (acetone). ^1H NMR ($CDCl_3$) δ 3.67 (1H, d, J=14.21), 3.85 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.97 (3H, s), 4.33 (1H, d, J=14.02), 5.06 (2H, br s), 6.83 (1H, s), 6.96 (1H, s), 7.08 (1H, s), 7.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ 48.2 (CH_2), 56.1, 56.2, 56.3, 56.32 (CH_3), 110.6, 111.1, 111.2, 112.2 (CH), 122.9, 126.6, 134.1, 138.3, 148.0, 148.5, 149.4, 153.2, 156.3, 191.1 (C); IR (film, cm^{-1}) 3452.6, 3332.6, 1660.9, 1596.3; EIMS (*m*/*z*, %) 372 (M, 18), 328 (53), 314 (53), 286 (100), 227 (21); HRMS calcd for $C_{19}H_{20}N_2O_6$, 372.1321; found, 372.1320.

4.8.4. 10,11-Dihydro-5-aminocarbonyl-5*H*-1,3-difluoro-7,8-dimethoxydibenzo[*b*,*f*]azepin-10-one (7h). The same procedure was followed starting from **6h** (57.5 mg, 0.19 mmol) to give compound **7h** (33 mg, 50%) as a pale yellow solid, mp 228–230 °C (Et_2O). ^1H NMR ($CDCl_3$) δ 3.79 (1H, d, J=14.51), 3.89 (3H, s), 3.98 (3H, s), 4.36 (1H, d, J=14.51), 5.23 (2H, br s), 6.79–6.83 (1H, m), 6.88 (1H, d, J=7.55); ^{13}C NMR ($CDCl_3$) δ 40.8 (CH_2), 56.2, 56.5 (CH_3), 103.7 (dd, J=23.83, 25.66), 110.7, 111.5, 112.2 (d, J=23.82, CH), 123.0, 125.5 (d, J=11.92), 137.1, 138.2 (d, J=4.58), 148.7, 153.8, 155.2, 158.5 (dd, J=12.05, 256.60), 161.9 (dd, J=11.91, 252.03), 189.9 (C); IR (film, cm^{-1}) 3460.4, 3332.9, 2920.1, 1666.8, 1596.3; EIMS (*m*/*z*, %) 348 (M, 15), 305 (82), 290 (100), 262 (67), 234 (50), 214 (43); HRMS calcd for $C_{17}H_{14}F_2N_2O_4$, 348.0922; found, 348.0922.

4.8.5. 9,10-Dihydro-4-aminocarbonyl-4*H*-thieno[3,2,*b*]-[*f*]benzazepin-10-one (7i). The same procedure was followed starting from **6i** (61.2 mg, 0.28 mmol) to give unreacted starting material **6i** (12.4 mg) and compound **7i** (46.9 mg, 80%) as a pale yellow solid, mp 224–225 °C (acetone). ^1H NMR ($CDCl_3$) δ 3.78 (1H, d, J=13.71), 4.28 (1H, d, J=13.71), 4.99 (2H, br s), 7.34–7.35 (2H, m), 7.40–7.42 (1H, m), 7.48 (1H, d, J=5.16), 7.49–7.51 (1H, m), 7.58 (1H, d, J=5.37); ^{13}C NMR ($CDCl_3$) δ 48.1 (CH_2), 127.5, 127.8, 128.3, 129.2, 130.8 (CH), 131.6 (C), 131.9 (CH), 133.9, 140.8, 145.6, 154.7, 186.5 (C); IR (film, cm^{-1}) 3478.3, 3354.9, 1655.0, 1597.5; EIMS (*m*/*z*, %) 258 (M, 81), 216 (100), 186 (91), 182 (27), 169 (19), 154 (47), 128

(55), 115 (54); HRMS calcd for $C_{13}H_{10}N_2O_2S$, 258.0463; found, 258.0468.

4.8.6. 9,10-Dihydro-4-aminocarbonyl-4*H*-6,7-dimethylthieno[3,2,*b*][*f*]benzazepin-10-one (7j). The same procedure was followed starting from **6j** (58.9 mg, 0.24 mmol) to give unreacted starting material **6j** (3.5 mg) and compound **7j** (58 mg, 89%) as a brown solid, mp 246–247 °C (acetone). ^{1}H NMR ($CDCl_3$) δ 2.25 (6H, s), 3.68 (1H, d, J=13.51), 4.21 (1H, d, J=13.51), 4.97 (2H, br s), 7.15 (1H, s), 7.26 (1H, s), 7.46 (1H, d, J=5.36), 7.55 (1H, d, J=5.16); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.5 (CH_3), 47.6 (CH_2), 127.8, 128.1 (CH), 130.9 (C), 131.6, 131.7 (CH), 136.9, 138.0, 138.5, 145.9, 154.8, 186.9 (C); IR (film, cm^{-1}) 3459.8, 3320.1, 2920.0, 1655.0, 1596.7; EIMS (*m*/*z*, %) 286 (21), 243 (95), 228 (100), 214 (45), 199 (24); HRMS calcd for $C_{15}H_{14}N_2O_2S$, 286.0776; found, 286.0773.

Acknowledgements

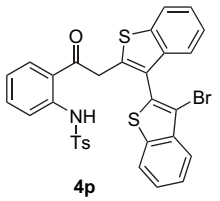
This research was supported by the University of the Basque Country (Project UPV 41.310-13656) and the Spanish Ministry of Education and Science (MEC CTQ2004-03706/BQU). M.C. also thanks the Ministry of Education and Science (MEC) for a predoctoral scholarship.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.003.

References and notes

1. (a) Shorvon, S. *Seizure* **2000**, *9*, 75; (b) Schmidt, D.; Elger, C. E. *Epilepsy Behav.* **2004**, *5*, 627; (c) Bang, L. M.; Goa, K. L. *CNS Drugs* **2004**, *18*, 57.
2. Schindler, W. (Ciba Geigy Corp., USA) U.S. Patent 3,642,775, 1972; *Chem. Abstr.* **1970**, *73*, 109711.
3. Stutzmann, J.-M.; Miquet, J.-M.; Meunier, M.; Louvel, E.; Dubedat, P.; Doble, A.; Bordier, F.; Boireau, A. (Rhone Poulenc Rorer, S. A., France) U.S. Patent 5,658,900, 1997; *Chem. Abstr.* **1994**, *121*, 141723.
4. Bousseau, A.; Doble, A.; Louvel, E. (Rhone Poulenc Rorer, S. A., France) WO 9420110, 1994; *Chem. Abstr.* **1994**, *121*, 272184.
5. (a) Pratoomsi, W.; Yatham, L. N.; Sohn, C.-H.; Solomons, K.; Lam, R. W. *Bipolar Disord.* **2005**, *7*, 37; (b) Hellewell, J. S. E. *J. Affect. Disord.* **2002**, *72*, S23; (c) Leweke, F. M.; Gerth, C. W.; Koethe, D.; Faulhaber, J.; Klosterkötter, J. *Am. J. Psychiatry* **2004**, *161*, 1130.
6. Fuenfschilling, P. C.; Zaugg, W.; Beutler, U.; Kauffmann, D.; Lohse, O.; Mutz, J.-P.; Onken, U.; Reber, J. L.; Shenton, D. *Org. Process Res. Dev.* **2005**, *9*, 272.
7. Lohse, O.; Beutler, U.; Fünfschilling, P.; Furet, P.; France, J.; Kauffmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385.
8. Kauffmann, D.; Fünfschilling, P.; Beutler, U.; Hoehn, P.; Lohse, O.; Zaugg, W. *Tetrahedron Lett.* **2004**, *45*, 5275.
9. Fünfschilling, P.; Kauffmann, D.; Lohse, O.; Beutler, U.; Zaugg, W. (Novartis AG, Switzerland) WO 01/56992 A2, 2001; *Chem. Abstr.* **2001**, *135*, 166785.
10. For some reviews on palladium N- and C-arylation reactions, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.
11. Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2005**, *7*, 4787.
12. After the optimisation of the synthetic route to OXC, we found in the literature an interesting study on the effect of the addition of small amounts of water in the palladium-catalysed amidation reactions. As in our case, the role of water was especially determining when the base was cesium carbonate and the solvents were either toluene or 1,4-dioxane. See: Dallas, A. S.; Gothelf, K. V. *J. Org. Chem.* **2005**, *70*, 3321.
13. The only related example reported in the literature was developed by Hartwig's research group and involves the palladium-catalysed α-arylation of 2-acetylthiophene with bromobenzene, rendering the corresponding product in 68% yield. See: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.
14. For a selection of the reaction conditions employed in the optimisation of this step, see the Supplementary data of this paper.
15. The tendency of the sulfur atom to strongly coordinate with palladium is well-established. It is anticipated that poisoning the catalyst in this manner will inhibit the reaction progress and therefore account for the long reaction times required for these transformations. See: (a) Mowery, D. L.; Graboski, M. S.; Ohno, T. R.; McCormick, R. L. *Appl. Catal., B* **1999**, *21*, 157; (b) Luo, T.; Vohs, J. M.; Gorte, R. J. *J. Catal.* **2002**, *210*, 397.
16. For additional information on the reaction conditions employed, see the Supplementary data of this paper.
17. For an excellent review on the use of polyhalogenated heterocycles in different cross-couplings reactions, and a rational explanation of the electronic behaviour of each of the carbons bearing an halogen, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
18. This homocoupling reaction presumably occurs on the already-formed diarylethanone product, rather than prior to the α-arylation process, because no bithiophene derivatives were detected in the crude reaction mixtures. The structure of the product **4p**, obtained from reaction of benzothiophene **3f** with substrate **2a**, is depicted below and was determined by ^{1}H NMR, LRMS and HRMS analyses. For more details on the reaction conditions employed, see the Supplementary data of this paper.

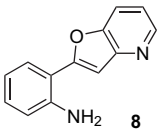


4p

19. The tendency of thiophene derivatives to undergo homocoupling reactions has been previously reported in the literature. See: (a) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276; (b) Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284.
20. The reported examples for the α-arylation of heteroaromatic ketones often require the use of the more active triflates as

the arylating agents to succeed. See: Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577.

21. In order to accomplish such cyclisation step, a whole range of reaction conditions and ligands was tested, including biphenyl-type ligands such as the one recently reported in: Wagner, F. F.; Comins, D. L. *Org. Lett.* **2006**, *8*, 3552. In many cases the substrate remained unreacted or rendered fully-aromatised compounds that were impossible to identify, with the exception of one example in which the benzofuran **8** (depicted below) was isolated and characterised by ^{1}H and ^{13}C NMR and GC–MS analyses. For more details, see the Supplementary data.



8

22. Che, D.; Corelli-Rennie, N.; Guntoori, B. R.; Faught, J. (Apotex Pharmachem, USA) U.S. Patent 20,050,282,797, 2005; *Chem. Abstr.* **2005**, *144*, 69748.
23. Guillaume, J.; Nédélec, L.; Cariou, M.; Allais, A. *Heterocycles* **1981**, *15*, 1227.