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Developing the Scope of O→C Aryl Migrations: Exploring Amide Substrates as Potential Precursors for Asymmetric Reactions

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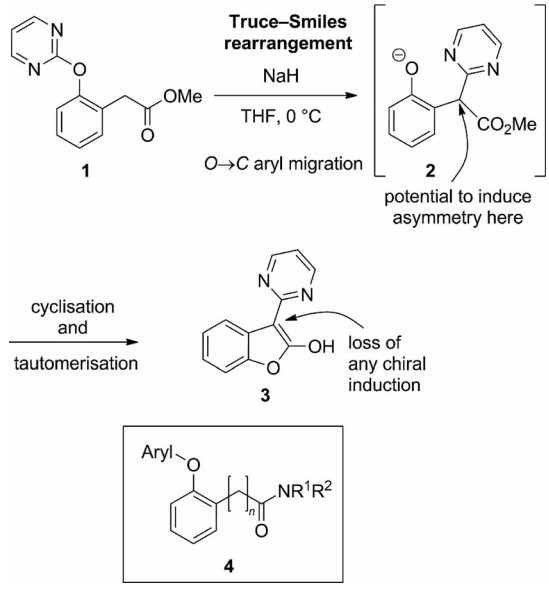
A new and mild method for the production of diastereomerically enriched α-aryl carbonyl compounds has been achieved. Although only modest diastereoselectivies are observed, they demonstrate the potential of the method for further optimisation. It also appears that reactions that proceed through a five-membered spirocyclic transition state rearrange, whereas those proceeding through a six-membered transition state do not, but stop at the diaryl ether stage.

Introduction

α-Arylated carbonyl compounds are commonly occurring motifs in synthetic intermediates and biologically interesting molecules, and they arise in a number of important therapeutic areas, such as: antiarrhythmics; antimuscarinics; phosphodiesterase inhibitors; and cannabinoid receptor ligands.[1] Despite their importance however, the synthesis of such compounds is still synthetically challenging.[2] Consequently, they remain of great interest to both academia and the pharmaceutical industry, especially if methods can be developed to prepare this motif under mild reaction conditions and in enantiomerically pure form.

Such requirements inspired us to consider whether the Truce–Smiles rearrangement[3] could be developed to meet these needs, especially because wide-ranging substrates have recently been successful in this rearrangement reaction under relatively mild conditions,[4–7] but also because such a mild, scalable method, amenable to asymmetric induction, has yet to be developed.

Erickson and McKennon demonstrated that, under typical rearrangement conditions [NaH, tetrahydrofuran (THF), $T \geq 0$ °C], ester precursors (e.g. **1**) rearrange through intramolecular nucleophilic attack of the enolate onto the electrophilic proximal diaryl ether to generate an α-aryl compound, but the products readily cyclise, followed by tautomerisation in certain cases, giving achiral products (e.g. **3**); so even if asymmetry was induced in the reaction (i.e. in **2**), it would be lost upon cyclisation and isomerisation to **3**, Scheme 1.[8] Moreover, owing to the facile C–O bond rotation in esters, chiral auxiliaries cannot be incorporated to develop a simple asymmetric variant.



Scheme 1. The Truce–Smiles rearrangement reaction on ester substrates and amide analogues (**4**) studied herein.

To the best of our knowledge, amide enolates (i.e. generated from **4**, n = 1 or 2, Scheme 1) have not been studied as precursors in the Truce–Smiles rearrangement, and because such compounds can be rendered enantiomerically pure, through auxiliary formation, aided by the associated restricted C–N bond rotation,[9–11] it was speculated that the scope of such O→C aryl migrations could be further developed and extended, first to achiral amide substrates to determine their potential, followed by further advances to exploit them as precursors for new asymmetric reactions based on this rearrangement. Furthermore, because cyclisation is not as likely with amide substrates, loss of any induced stereochemistry should be minimal through this mechanism.

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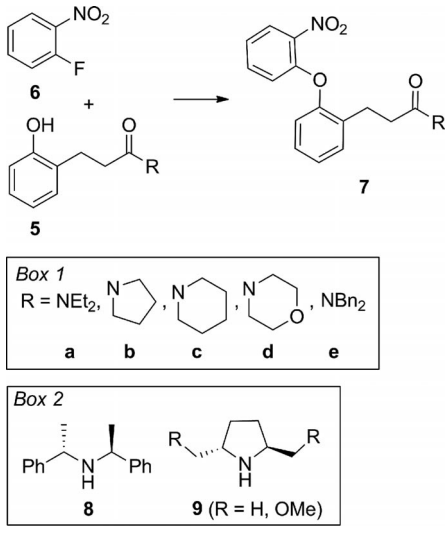
Results and Discussion

Based on previous work,[12] this study began by examining rearrangement precursors, which it was anticipated would proceed through a six-membered transition state, with the potential to make the rearrangement asymmetric by incorporating enantiomerically pure amides into the reaction, e.g. with (–)-bis[(*S*)-1-phenylethyl]amine (**8**), (2*R*,5*R*)-(–)-*trans*-2,5-dimethylpyrrolidine (**9**, R = H) or (2*S*,5*S*)-(+)-2,5-bis(methoxymethyl)pyrrolidine (**9**, R = OMe) (Scheme 2, see Box 2),[13] thus generating enantiopure rearrangement precursors. Table 1 outlines the preliminary results obtained with achiral amides as test cases.



Scheme 2. Attempted Truce–Smiles rearrangement reactions with propanamide substrates (**5a–5e**,[10] see Box 1); see Table 1 for the reaction conditions. Box 2 shows three commercially available amines with which to potentially make the reaction asymmetric.

Table 1. Reaction of propanamide substrates **5** with **6**.[a]

Entry	Rearrangement precursor	Product	Yield [%] [b]
1	**5a**	**7a**	90
2	**5b**	**7b**	92
3	**5c**	**7c**	87
4	**5d**	**7d**	90
5	**5e**	**7e**	92

[a] *Reaction conditions*: **5** (1.0 equiv.), **6** (1.05 equiv.), K_2CO_3 (2.5 equiv.), DMSO (0.1 M), 60 °C, 24 h. [b] Isolated yields.

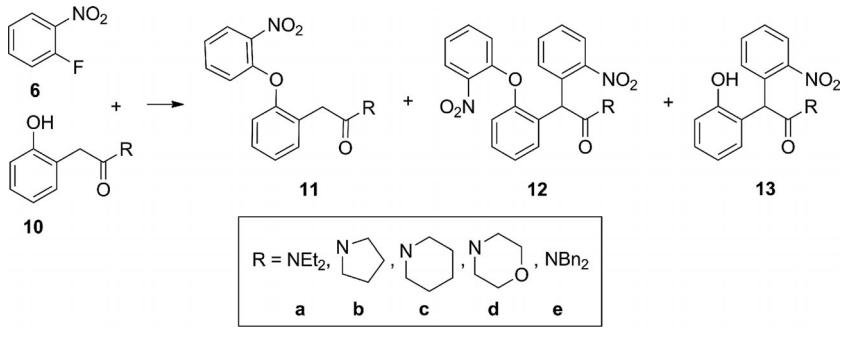
As can be seen, no rearrangement reaction occurred with precursors based on propanamide structures, Table 1; only diaryl ether products **7a–7e** were isolated. Even when the reaction temperature was increased to 100 °C (results not shown), no rearrangement was observed at all, with either pyrrolidyl derivative **5b** or dibenzyl derivative **5e**; only diaryl ethers **7b** and **7e** were isolated, again in quantitative yields. Similarly, leaving the reactions for 3 days at room temperature resulted in the same products being formed.

Such reactions proceed through a spirocyclic intermediate,[14] wherein the Meisenheimer complex is stabilised by the presence of the electron-withdrawing nitro group at the ortho position. However, despite precedent for 4-,[5] 5-,[6–8,15–19] and 6-membered[4,20,21] transition states in this type of rearrangement, the rearranged products have not been observed with compounds based on propanamide structures (**5**) in our hands. In addition, trying to force the reaction conditions to rearrange pure, isolated diaryl ethers **7b** and **7e**, met with failure, despite varying the solvent [dimethyl sulfoxide (DMSO), dimethylformamide (DMF), THF and CH_2Cl_2], base (K_2CO_3, CsOH, NaH, NaOMe) and temperature (room temp. to 100 °C).

Based on these results, under the assumption that the rearrangement reaction was failing because of the relatively high pK_a of the α-protons of amide **7**, either when formed in situ or from isolated material, attention was turned to acetamide-based substrates **10** (Scheme 3), wherein the α-protons of the amide are also benzylic and should therefore more readily be abstracted to form the desired amide enolate with K_2CO_3 prior to its intramolecular attack onto proximal diaryl ether **11**, formed in situ.

Table 2 demonstrates that, as with the propanamide derivatives, diaryl ether **11** is still the major isolated product. Nevertheless, with acetamide derivatives **10**, desired rearranged diaryl ether **12** and rearranged-only **13** products are also produced in modest yields. The amide enolate is evidently more easily formed in this case, rendering the rearrangement more likely to occur, this time through a five-membered cyclic transition-state (Scheme 4).

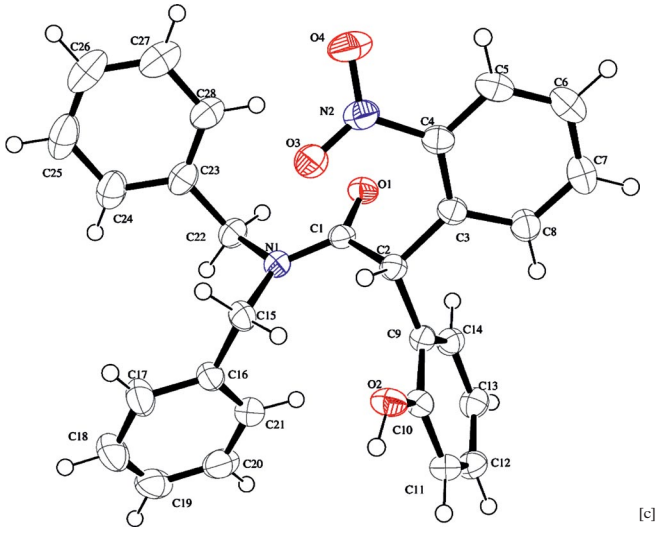
Although all starting material **10** was consumed in these reactions, a mixture of the three possible products was usually formed (Table 2) with only 1.05 equiv. of **6**. As must be the case here, diaryl ether **11** rearranges intramolecularly to **13** faster than **6** reacts intermolecularly with **10**. As such, **13** and **10** exist together during the reaction; reaction of **10**



Scheme 3. Truce–Smiles rearrangement reaction with acetamide substrates **10a–10e**[10]. See Table 2 for the reaction conditions.

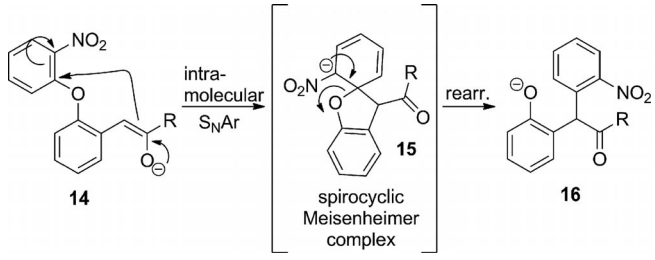
Table 2. Reaction of acetamide substrates **10** with **6**.[a]

Entry	Rearrangement precursor	Product	Yield [%][b]
1		**11a**	68
2	**10a**	**12a**	21
3		**13a**	10
4		**11b**	61
5	**10b**	**12b**	0
6		**13b**	33
7		**11c**	54
8	**10c**	**12c**	24
9		**13c**	21
10		**11d**	45
11	**10d**	**12d**	6
12		**13d**	45
13		**11e**	40
14	**10e**	**12e**	23
15		**13e**	37



[c]

[a] *Reaction conditions:* **6** (1.05 equiv.), **10** (1.0 equiv.), K_2CO_3 (2.5 equiv.), DMSO (0.1 M), 60 °C, 24 h. [b] Isolated yields. [c] X-ray crystal structure of **13e**.[22,23]



Scheme 4. Proposed mechanism for the successful rearrangement reaction through a five-membered transition state and intermediate.

ultimately giving **11** and/or **13**, and reaction of **13** giving **12**. It was also demonstrated that isolated diaryl ethers (i.e. **11**), rearrange cleanly to **13** under standard rearrangement conditions (K_2CO_3, DMSO) in good yield (50% isolated yield, 100% based on recovered starting material). Additionally, attempts at reaction optimisation show that the rearrangement reaction of **11** to **13** proceeds in other solvents (CH_2Cl_2, DMF, PhMe and THF), and with alternative bases (CsOH, NaH and NaOMe) as well, although such reactions were only studied by crude NMR, unlike the reaction/rearrangement of **10** to **11/12/13** that only works in polar aprotic solvents such as DMSO and DMF. In order to facilitate the future development of an asymmetric variant, attempts were made to force the reaction by increasing the molar equivalents of 1-fluoro-2-nitrobenzene (**6**), increasing the reaction temperature and changing base in the expectation that the complete formation of rearranged products **12** or **13** would occur (Table 3).

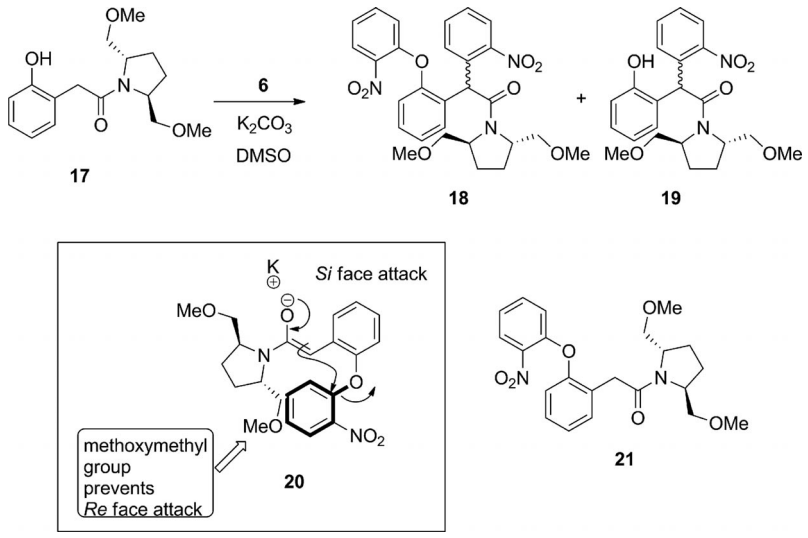
Table 3. Optimisation of the reaction between **10b** and **6**.[a]

Entry	**6** (equiv.)	Base (equiv.)	Temp. [°C]	Product ratio[b] **11b**	**12b**	**13b**
1	2.0	K_2CO_3 (2.5)	25	80	20	0
2	2.0	K_2CO_3 (2.5)	60	58	42	0
3	2.0	K_2CO_3 (2.5)	100	49	51	0
4	2.0	NaH (2.5)	60	40	55	5
5	5.0	K_2CO_3 (2.5)	25	97	3	0
6	5.0	K_2CO_3 (2.5)	60	70	30	0
7	5.0	K_2CO_3 (2.5)	100	62	38	0
8	5.0	NaH (2.5)	60	71	29	0
9	10.0	K_2CO_3 (2.5)	25	100	0	0
10	10.0	K_2CO_3 (2.5)	60	100	0	0
11	10.0	K_2CO_3 (2.5)	100	100	0	0
12	10.0	NaH (2.5)	60	54	46	0

[a] *Reaction conditions:* All reactions were carried out with **10b** (1.0 equiv.), in DMSO (0.1 M) for 24 h. [b] Ratios based integration of diagnostic signals with ^{1}H NMR spectroscopy relating to the newly generated C*H* of rearranged products **12b** and **13b**, and the CH_2 of diaryl ether **11b**.

Unexpectedly, when the number of molar equivalents of **6** was increased from 2.0 to 5.0 and to 10.0 equiv. the amount of diaryl ether **11b** also increased, at all temperatures studied (25, 60 and 100 °C), rather than an increase in the ratio of rearranged products **12b** and **13b**, as was expected. It seems as though increasing the equivalents of the electrophile halted the reaction at the diaryl ether **11b** stage. One possible explanation for this occurrence could be the stabilisation of the electron-rich enolate of diaryl ether **11b** formed during the first stage of the reaction, by certain counterions, rendering it unable to react further.

Based on the assumption that the stability of the enolate appeared to be affected by the presence of excess **6**, the effects of a stronger base and alternative counterion were examined; Table 3 outlines the results of replacing K_2CO_3 with NaH. As can be seen, increasing the number of equivalents of **6** with NaH as base, at 60 °C, results in an irreversible deprotonation, leading to an increase in the amount of rearranged diaryl ether **12b** formed relative to **11b**, which peaks with 10 equiv., in which an increase in the total rearranged products increased from zero (with K_2CO_3) to 46% (with NaH). Possibly, the smaller counterion (Na^+) and irreversible deprotonation enables the formation of a tighter ion pair thus favouring the rearrangement, whereas the more dissociated ion pair with K^+ is stabilised by the excess electrophile.



Scheme 5. Reaction between enantiomerically pure amide **17** and **6**, showing the diastereoisomeric rearranged products produced. Compound **20** outlines a suggested mechanism through which the partial diastereoselectivity was achieved.

To test the reaction conditions, and ascertain the level of asymmetry induced during the rearrangement, enantiomerically pure substrate **17** was prepared from the reaction of (2*S*,5*S*)-(+)-2,5-bis(methoxymethyl)pyrrolidine (**9**, R = OMe) with 2-coumaranone at reflux temperatures in toluene;[10] the product was isolated in excellent yield (99%). Subjecting **17** to typical rearrangement reaction conditions [**6** (1.05 equiv.), K_2CO_3 (2.5 equiv.), DMSO (0.1 M), room temp., 24 h] resulted in diastereoisomeric mixtures of rearranged products **18** (10%) and **19** (45%; Scheme 5).

There is a diagnostic ^{1}H NMR spectroscopic signal for the C*H* proton for amides **12a**–**12e** and **13a**–**13e**, in which, for all cases with compound **12**, the newly formed C*H* resonates furthest downfield at values greater than 6.0 ppm (presumably the result of an additional electron-deficient ring in these structures), whereas four out of the five amides incorporating the structure of compound **13**, resonate at upfield values of less than 6.0 ppm, such that their average values can be summarised as 6.29 ± 0.15 (for **12a**–**12e**, in which the error is ±standard deviation) and 5.77 ± 0.42 (for **13a**–**13e** see the Exp. Section). As such, this diagnostic feature enabled us to both determine the identity of rearranged products **18** and/or **19** formed in the asymmetric reaction, and determine the diastereoisomeric ratios obtained for each [i.e. (*S*,*S*,*S*)-**18**:(*R*,*S*,*S*)-**18** and (*S*,*S*,*S*)-**19**:(*R*,*S*,*S*)-**19**]. Figure 1 outlines the diagnostic section of the ^{1}H NMR spectrum of the crude reaction mixture from the reaction shown in Scheme 5.

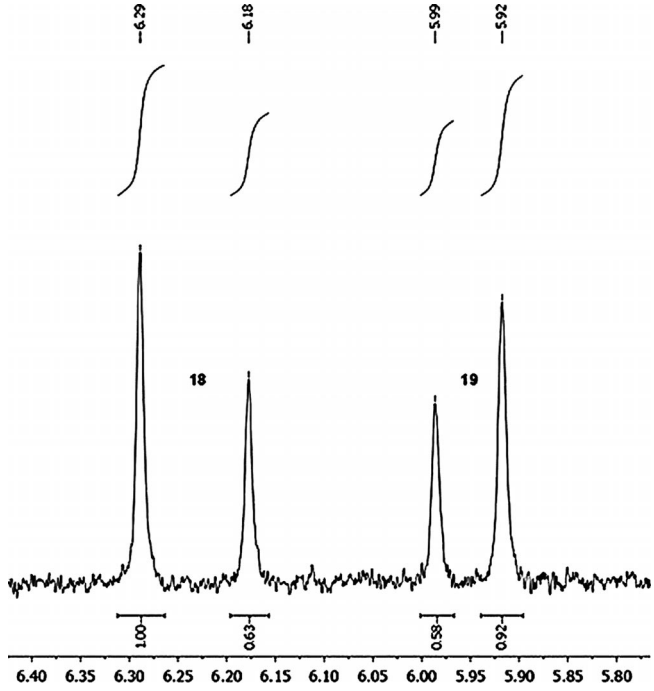


Figure 1. Diagnostic section of the ^{1}H NMR spectrum of the diastereoisomers of **18** (6.29 and 6.18 ppm) and **19** (5.99 and 5.92 ppm) as determined from the C*H* signal of the α-proton to the amide.

By using these diagnostic signals it can be calculated that the presence of the enantiopure auxiliary resulted in rearranged products with a *dr* = 1.6:1 (**18**) and *dr* = 1:1.6 (**19**). Furthermore, when the rearrangement reaction was carried out on the chiral analogue of **17** possessing chiral auxiliary *trans*-dimethylpyrrolidine (**9**, R = H), the ratios were *dr* = 1.7:1 and *dr* = 1:1.9, respectively, for the analogous products. Although these diastereoisomeric ratios are relatively low, they are not optimised, and therefore potential may exist in this mild method for generating enantioenriched chiral centres with chiral auxiliaries through an aryl-migration rearrangement reaction. Moreover, it is also possible that the *dr* induced during the reaction is actually higher than that observed in the crude ^{1}H NMR spectrum because the rearranged products are prone to racemisation owing to the increased acidity of the C*H* proton on migration of the aromatic ring [pK_a of phenol: ca. 18.0 (DMSO) and pK_a of 1,1-diphenylcarbonyls: ≥18.75

(DMSO)];[24] in an effort to ascertain whether the *dr* observed was kinetic or thermodynamic, a rearrangement reaction of isolated **21** was performed in which aliquots were taken and quenched every hour, and an NMR analysis performed. The results indicated an initial *dr* of 1:1 (after 1 h), which changed to 1.35:1 (after 4 h), and then surprisingly swapped to 1:1.54 (after 5 h), a ratio that did not change further over the course of the reaction (7 h). Moreover, attempts to optimise the *dr* were attempted by subjecting **21** to a range of rearrangement conditions [solvent (DMSO, DMF, THF, PhMe, $CHCl_3$ and CH_2Cl_2), base (K_2CO_3, CsOH, NaH, NaOMe)], but the same (thermodynamic) ratio of about 1:1.6 was obtained in all cases. These results prompted us to propose that the rearrangement is not as simple as first presumed, but that the known role of the product and starting phenols (i.e. **17** and **19**) to act as enantiopure Brønsted acids (as has been shown in the asymmetric protonation of amide enolates),[10] may be playing a part; an effect that needs further investigation.

This proposed limitation of in situ epimerisation could potentially be mitigated through the preparation of quaternary centres. To this end, diaryl ether **21** was α-acylated with methyl chloroformate prior to its attempted rearrangement reaction, upon which, if successful, a non-epimerisable quaternary carbon centre would be formed. Surprisingly, a diastereoisomeric ratio of 11:1 (83% *de*) was achieved in the 1,3-dicarbonyl product, indicating that the chiral auxiliary is capable of inducing diastereoselectivity in these substrates. Unfortunately, attempts to produce a quaternary carbon centre through aryl migration of this 1,3-dicarbonyl compound, under standard rearrangement conditions, resulted in failure, possibly owing to competing ester hydrolysis consuming base, or the newly introduced group imparting increased steric hindrance that cannot be overcome. Nevertheless, that a major diastereoisomer of the 1,3-dicarbonyl had indeed been produced was confirmed when, subject to the rearrangement reaction conditions, it was shown to epimerise to 54% *de* by crude NMR spectroscopy.

Conclusions

In preliminary efforts to produce an asymmetric Truce–Smiles rearrangement reaction – a new and potentially mild method to produce enantiomerically enriched α-aryl carbonyl compounds – we have demonstrated modest success in the application of the rearrangement reaction to new amide substrates. It has also been demonstrated that amide precursors that proceed through a five-membered spirocyclic transition state rearrange, whereas those proceeding through a six-membered transition state do not, but stop at the diaryl ether stage. Optimisation of the rearrangement reaction conditions and chiral amine auxiliary continue, the results of which will be reported in due course.

Experimental Section

General Information: Commercially available reagents were used as received without purification. Analytical thin layer chromatography (TLC) was performed with plastic-backed TLC plates coated with silica G/UV_{254}, in a variety of solvents. The plates were visualised by UV light (254 nm), *p*-anisaldehyde solution or $KMnO_4$ solution. Flash column chromatography was conducted with Davisil silica 60 Å (40–63 μm) under bellows pressure. Low-resolution mass spectra were recorded with a Thermo FinniganLCQ Advantage MAX with electron spray ionisation (ESI), and high-resolution mass spectra were recorded by the EPSRC National Mass Spectrometry Service, UK. ^1H and ^{13}C NMR spectra were recorded with a BrukerAvanceDPX 300 (300 MHz) or a Bruker 400 (400 MHz) spectrometer. All chemical shifts (δ) are quoted relative to a calibration reference of the residual protic solvent; C*H*Cl_3 (δ_H = 7.26, s) or [D_6]DMSO (δ_H = 2.50, pent) was used as the internal standard in ^1H NMR spectra, and ^{13}C NMR shifts were referenced with *C*DCl_3 (δ_C = 77.16, t) or [D_6]DMSO (δ_H = 39.5, m) with broad band decoupling. Melting points were measured on a Stuart® SMP10 melting point apparatus. $[\alpha]_D$ was measured with JASCO P-2000 polarimeter and IR spectra were recorded with a NICOLET iS10 instrument.

Procedure for the Synthesis of 2-Coumaranone: To a solution of 2-hydroxyphenyl acetic acid (5 g, 32.9 mmol) in toluene (70 mL) was added *p*-toluenesulfonic acid (0.62 g, 3.28 mmol). The resulting solution was stirred at 110 °C under Dean–Stark conditions for 6 h, after which it was cooled, washed with satd. aq. $NaHCO_3$ (3 × 30 mL), brine (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with distilled water (30 mL), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo to afford 2-coumaranone (4.23 g, 96%) as yellow crystals. R_f (30% EtOAc in petroleum ether): 0.76, m.p. 51–53 °C (EtOAc/petroleum ether) [(ref.[25] m.p. 49–51 °C) (toluene)]. IR (neat): $\tilde{\nu}_{max}$ = 1794 (C=O stretching), 1051 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 3.77 (s, 2 H), 7.12–7.21 (m, 2 H), 7.29–7.36 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 33.13 (CH_2), 110.91, 123.16, 124.22, 124.76 (CH), 129.01, 154.81, 174.24 (C) ppm. MS (APCI): *m*/*z* (%) = 134 (100) $[M + H]^+$.

General Procedure for the Synthesis of Amides 5 and 10: To a solution of 2-coumaranone (1 equiv.) in toluene (0.1 M) was added the amine (1.5 equiv.). The resulting solution was stirred at 110 °C for 4–6 h, after which it was cooled, acidified (1 M HCl to pH ≈ 1–2), and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with distilled water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo to afford the pure amide directly or after flash column chromatography.

***N*,*N*-Diethyl-3-(2-hydroxyphenyl)propionamide (5a):**[26] The solvent was evaporated in vacuo to afford the title compound as a pale yellow solid (100%). R_f (30% EtOAc in petroleum ether): 0.41, m.p. 128–130 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1613 (C=O stretching), 3175 (OH stretching), 1071 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.08 (t, *J* = 4.5 Hz, 3 H), 1.11 (t, *J* = 4.5 Hz, 3 H), 2.71 (t, *J* = 6.0 Hz, 2 H), 2.94 (t, *J* = 6.0 Hz, 2 H), 3.26 (q, *J* = 9.0 Hz, 2 H), 3.36 (q, *J* = 9.0 Hz, 2 H), 6.81 (td, *J* = 3.0, *J* = 9.0 Hz, 1 H), 6.91 (dd, *J* = 3.0, *J* = 9.0 Hz, 1 H), 7.04 (dd, *J* = 1.0, *J* = 8.0 Hz, 1 H), 7.11 (td, *J* = 1.0, *J* = 8.0 Hz, 1 H), 9.76 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 13.02, 13.88 (CH_3), 24.90, 35.04, 40.95, 42.09 (CH_2), 118.13, 120.08, 128.05, 128.48 (CH), 130.70, 155.69, 173.13 (C) ppm. MS (APCI): *m*/*z* (%) = 222 (100) $[M + H]^+$.

Pyrrolidyl-2-(2-hydroxyphenyl)propanamide (5b): After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as colourless crystals (100%). R_f (50% EtOAc in petroleum ether): 0.51, m.p. 151–153 °C (EtOAc/toluene). IR (neat):

$\tilde{\nu}_{max}$ = 1622 (C=O stretching), 1039 (C–N stretching), 3283 (OH stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.78–1.98 (m, 4 H), 2.66 (t, J = 6.0 Hz, 2 H), 2.94 (t, J = 6.0 Hz, 2 H), 3.33 (t, J = 7.5 Hz, 2 H), 3.45 (t, J = 6.0 Hz, 2 H), 6.82 (t, J = 6.0 Hz, 1 H), 6.92 (dd, J = 1.0, J = 8.0 Hz, 1 H), 7.04–7.12 (m, 2 H), 9.90 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.40, 24.44, 26.05, 36.74, 46.31, 46.66 (CH_2), 118.32, 120.12, 128.09, 128.62 (CH), 130.73, 155.70, 172.42 (C) ppm. MS (APCI): m/z (%) = 220 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{13}H_{17}NO_2$ $[M + H]^+$ 220.1332; found 220.1332.

3-(2-Hydroxyphenyl)-1-(1-piperidyl)propan-1-one (5c): Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as colourless crystals (78%). R_f (30% EtOAc in petroleum ether): 0.46, m.p. 130–132 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1619 (C=O stretching), 3278 (OH stretching), 1013 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.55–1.62 (m, 6 H), 2.71 (t, J = 4.5 Hz, 2 H), 2.94 (t, J = 4.5 Hz, 2 H), 3.34 (t, J = 4.5 Hz, 2 H), 3.55 (t, J = 4.5 Hz, 2 H), 6.82 (t, J = 6.0 Hz, 1 H), 6.91 (d, J = 9.0 Hz, 1 H), 7.5 (d, J = 9.0 Hz, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 9.87 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.39, 24.82, 25.51, 26.21, 35.25, 43.39, 46.45, (CH_2), 118.14, 120.12, 128.06 (CH), 128.55 (C), 130.77 (CH), 155.69, 172.00 (C) ppm. MS (APCI): m/z (%) = 234 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{14}H_{19}NO_2$ $[M + H]^+$ 234.1489; found 234.1489.

3-(2-Hydroxyphenyl)-1-morpholinopropan-1-one (5d): Flash column chromatography (SiO_2; 20% EtOAc in petroleum ether) afforded the title compound as a colourless solid (82%). R_f (30% EtOAc in petroleum ether): 0.29, m.p. 129–131 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1618 (C=O stretching), 2974 (OH stretching), 1035 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 2.71 (t, J = 6.0 Hz, 2 H), 2.96 (t, J = 6.0 Hz, 2 H), 3.42 (t, J = 6.0 Hz, 2 H), 3.62 (m, 6 H), 6.84 (t, J = 5.5 Hz, 1 H), 6.92 (d, J = 9.0 Hz, 1 H), 7.05 (d, J = 9.0 Hz, 1 H), 7.13 (td, J = 1.0, J = 8.0 Hz, 1 H), 9.43 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.59, 35.11, 42.48, 45.73, 66.34, 66.76 (CH_2), 118.11, 120.34, 128.14 (CH), 128.21 (C), 130.76 (CH), 155.45, 172.64 (C) ppm. MS (APCI): m/z (%) = 236 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{13}H_{17}NO_3$ $[M + H]^+$ 236.1283; found 236.1283.

***N*,*N*-Dibenzyl-3-(2-hydroxyphenyl)propanamide (5e):** After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as a colourless solid (92%). R_f (10% EtOAc in toluene): 0.63, m.p. 148–150 °C (EtOAc/toluene). IR (neat): $\tilde{\nu}_{max}$ = 1613 (C=O stretching), 3181 (O–H stretching), 1142 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 2.82 (t, J = 6.0 Hz, 2 H), 3.01 (t, J = 6.0 Hz, 2 H), 4.41 (s, 2 H), 4.58 (s, 2 H), 6.82 (td, J = 1.0, J = 8.0 Hz, 1 H), 6.96–7.01 (m, 4 H), 7.13–7.20 (m, 3 H), 7.27–7.30 (m, 6 H), 9.31 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 25.00, 35.11, 48.98, 49.97 (CH_2), 118.19, 120.40, 126.37, 127.78, 127.90 (CH), 128.10 (C), 128.15, 128.50, 128.82, 129.17, 130.75 (CH), 135.48, 136.63, 155.37, 174.99 (C) ppm. MS (APCI): m/z (%) = 346 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{23}H_{23}NO_2$ $[M + H]^+$ 346.1802; found 346.1807.

***N*,*N*-Diethyl-2-(2-hydroxyphenyl)acetamide (10a):** Flash column chromatography (SiO_2; 15% EtOAc in petroleum ether) afforded the title compound as an off-white solid (96%). R_f (30% EtOAc in petroleum ether): 0.54, m.p. 88–90 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1618 (C=O stretching), 3173 (OH stretching), 1090 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.13 (t, J = 7.5 Hz, 3 H), 1.29 (t, J = 6.0 Hz, 3 H), 3.39 (q, J = 6.0 Hz, 2 H), 3.50 (q, J = 7.5 Hz, 2 H), 3.71 (s, 2 H), 6.82 (td, J = 1.5, J = 8.0 Hz, 1 H), 6.97–7.04 (m, 2 H), 7.19 (td, J = 3.0, J = 9.0 Hz, 1 H), 10.47 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 13.05, 14.94 (CH_3), 37.06, 41.47, 43.67 (CH_2), 118.41, 119.97 (CH), 121.31 (C), 129.15, 130.54 (CH), 157.43, 172.83 (C) ppm. MS (APCI): m/z (%) = 208 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{12}H_{17}NO_2$ $[M + H]^+$ 208.1332; found 208.1332.

2-(2-Hydroxyphenyl)-1-(pyrrolidin-1-yl)ethanone (10b): After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as colourless crystals (89%). R_f (20% EtOAc in toluene): 0.42, m.p. 120–122 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1610 (C=O stretching), 2959 (OH stretching), 1094 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.89 (pent, J = 6.0 Hz, 2 H), 2.01 (pent, J = 6.0 Hz, 2 H), 3.48 (t, J = 7.5 Hz, 2 H), 3.68 (t, J = 6.0 Hz, 2 H), 3.70 (s, 2 H), 6.81 (td, J = 1.0, J = 8.0 Hz, 1 H), 6.99 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.03 (dd, J = 1.0, J = 8.0 Hz, 1 H), 7.19 (td, J = 1.0, J = 8.0 Hz, 1 H), 10.37 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.53, 26.12, 39.03, 46.34, 47.77 (CH_2), 118.44, 119.99, 121.06, 129.17 (CH), 130.56, 157.35, 171.60 (C) ppm. MS (APCI): m/z (%) = 206 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{12}H_{15}NO_2$ $[M + H]^+$ 206.1176; found 206.1176.

2-(2-Hydroxyphenyl)-1-(piperidin-1-yl)ethanone (10c): Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as a yellow crystals (98%). R_f (30% EtOAc in petroleum ether): 0.48, m.p. 107–109 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1616 (C=O stretching), 3166 (OH stretching), 1039 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.52–1.63 (m, 6 H), 3.55 (t, J = 6.0 Hz, 2 H), 3.61 (t, J = 6.0 Hz, 2 H), 3.73 (s, 2 H), 6.81 (t, J = 7.5 Hz, 1 H), 6.95 (d, J = 9.0 Hz, 1 H), 7.03 (d, J = 9.0 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 9.87 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.25, 25.36, 26.52, 36.41, 43.45, 48.16, (CH_2), 117.99, 120.03 (CH), 121.11 (C), 128.91, 130.18 (CH), 157.03, 171.17 (C) ppm. MS (APCI): m/z (%) = 220 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{13}H_{17}NO_2$ $[M + H]^+$ 220.1332; found 220.1331.

2-(2-Hydroxyphenyl)-1-morpholinoethanone (10d): Flash column chromatography (SiO_2; 50% EtOAc in petroleum ether) afforded the title compound as a lemon-yellow crystalline solid (81%). R_f (30% EtOAc in petroleum ether): 0.34, m.p. 123–125 °C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1615 (C=O stretching), 2931 (OH stretching), 1092 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 3.65–3.68 (m, 8 H), 3.74 (s, 2 H), 6.83 (td, J = 1.5, J = 8.0 Hz, 1 H), 6.99 (t, J = 6.0 Hz, 2 H), 7.19 (td, J = 1.5, J = 8.0 Hz, 1 H), 9.56 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 36.31, 42.59, 47.29, 66.51, 66.65 (CH_2), 118.32, 120.36 (CH), 120.62 (C), 129.9, 130.17 (CH), 165.95, 171.71 (C) ppm. MS (APCI): m/z (%) = 222 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{12}H_{15}NO_3$ $[M + H]^+$ 222.1125; found 222.1125.

***N*,*N*-Dibenzyl-2-(2-hydroxyphenyl)acetamide (10e):** After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as yellow crystals (91%). R_f (20% EtOAc in petroleum ether): 0.66, m.p. 139–141 °C (toluene). IR (neat): $\tilde{\nu}_{max}$ = 1613 (C=O stretching), 3064 (O–H stretching), 1477 (C–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 3.81 (s, 2 H), 4.63 (s, 2 H), 4.64 (s, 2 H), 6.68–6.76 (m, 2 H), 7.02 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.14–7.21 (m, 5 H), 7.26–7.41 (m, 6 H), 10.07 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 37.18, 49.33, 51.26, (CH_2), 118.33, 120.14 (CH), 120.99 (C), 126.52, 127.91, 128.15, 128.42, 128.90, 129.23, 129.28, 130.70 (CH), 135.70, 136.28, 157.06, 174.45 (C) ppm. MS (APCI): m/z (%) = 332 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{22}H_{21}$ NO_2 $[M + H]^+$ 332.1651; found 332.1645.

General Procedure for the Rearrangement Reactions: To a solution of the amide (**5a**–**5e**, **10a**–**10e**) (1 equiv.) in dimethyl sulfoxide (0.1 M) was added potassium carbonate (2.5 equiv.) and the resulting solution was stirred at room temperature for 30 min. 1-Fluoro-2-nitrobenzene (1.05 equiv.) was added and the reaction stirred for 24 h at 60 °C. After being stirred, the mixture was acidified with hydrochloric acid solution (1 M, 30 mL). The product was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were washed with distilled water (2 × 20 mL), brine (10 mL), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo to afford the crude residue which was purified by flash column chromatography.

***N*,*N*-Diethyl-2-[2-(2-nitrophenoxy)phenyl]propanamide (7a):** After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as a yellow oil (90%). IR (neat): $\tilde{\nu}_{max}$ = 1631 (C=O stretching), 1098 (C–O stretching), 1524, 1349 (N–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 0.95–1.01 (m, 6 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 2.87 (t, *J* = 7.5 Hz, 2 H), 3.15 (q, *J* = 7.5 Hz, 2 H), 3.24 (q, *J* = 7.5 Hz, 2 H), 6.79 (t, *J* = 7.5 Hz, 2 H), 7.02–7.15 (m, 3 H), 7.27 (d, *J* = 6.0 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 12.92, 14.01 (CH_3), 26.69, 33.14, 39.96, 41.75 (CH_2), 118.72, 119.05, 122.54, 125.13, 125.74, 127.89, 131.46 (CH), 132.93 (C), 134.29 (CH), 140.33, 150.74, 152.95, 171.08 (C) ppm. MS (APCI): *m*/*z* (%) = 343 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{19}H_{22}NO_2$ $[M + H]^+$ 343.1652; found 343.1646.

3-[2-(2-Nitrophenoxy)phenyl]-1-(pyrrolidin-1-yl)propan-1-one (7b): Flash column chromatography (SiO_2; 100% petroleum ether) afforded the title compound as a yellow oil (92%). R_f (30% EtOAc in petroleum ether): 0.32. IR (neat): $\tilde{\nu}_{max}$ = 1604 (C=O stretching), 1039 (C–N stretching), 1100 (C–O stretching), 1523, 1344 (N–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.80 (tt, *J* = 6.0 Hz, 2 H), 1.88 (tt, *J* = 6.0 Hz, 2 H), 2.65 (t, *J* = 9.0 Hz, 2 H), 2.95 (t, *J* = 7.5 Hz, 2 H), 3.34 (t, *J* = 7.5 Hz, 2 H), 3.42 (t, *J* = 6.0 Hz, 2 H), 6.90 (dd, *J* = 3.0, *J* = 6.0 Hz, 1 H), 6.90 (dd, *J* = 3.0, *J* = 6.0 Hz, 1 H), 7.15 (td, *J* = 1.5, *J* = 8.0 Hz, 2 H), 7.12–7.20 (dd, *J* = 1.5, *J* = 8.0 Hz, 1 H), 7.38 (dd, *J* = 1.5, *J* = 8.0 Hz, 1 H), 7.46 (td, *J* = 1.5, *J* = 8.0 Hz, 1 H), 7.97 (dd, *J* = *J* = 1.5, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.52, 26.20, 26.49, 35.02, 45.74, 46.56 (CH_2), 118.81, 119.52, 122.65, 125.49, 126.06, 128.14, 131.81, 133.40 (CH), 134.48, 140.58, 151.16, 153.13, 170.84 (C) ppm. MS (APCI): *m*/*z* (%) = 341 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{19}H_{22}N_2O_4$ $[M + H]^+$ 341.1496; found 341.1503.

2-[2-(2-Nitrophenoxy)phenyl]-1-(1-piperidyl)propanone (7c): After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as a yellow oil (87%). R_f (30% EtOAc in petroleum ether): 0.36. IR (neat): $\tilde{\nu}_{max}$ = 1631 (C=O stretching), 1098 (C–O stretching), 1583, 1348 (N–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.55–1.67 (m, 6 H), 2.77 (t, *J* = 7.5 Hz, 2 H), 3.01 (t, *J* = 7.5 Hz, 2 H), 3.42 (t, *J* = 6.0 Hz, 2 H), 3.60 (t, *J* = 6.0 Hz, 2 H), 6.79 (d, *J* = 6.0 Hz, 2 H), 7.22–7.34 (m, 3 H), 7.45 (d, *J* = 6.0 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 8.04 (d, *J* = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.39, 25.44, 26.18, 26.76, 33.32, 42.52, 46.42 (CH_2), 118.63, 119.17, 122.53, 125.22, 125.77, 127.94, 131.42 (CH), 132.93 (C), 134.29 (CH), 140.32, 150.75, 152.89, 170.24 (C) ppm. MS (APCI): *m*/*z* (%) = 355 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{20}H_{22}N_2O_4$ $[M + H]^+$ 355.1652; found 355.1646.

2-[2-(2-Nitrophenoxy)phenyl]-1-(1-morpholino)propanone (7d): Flash column chromatography (SiO_2; 50% petroleum ether) afforded the title compound as a yellow oil (90%). R_f (30% EtOAc in petroleum ether): 0.36. IR (neat): $\tilde{\nu}_{max}$ = 1639 (C=O stretching), 1023 (C–O stretching), 1582, 1349 (N–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 2.72 (t, *J* = 7.5 Hz, 2 H), 2.94 (t, *J* = 7.5 Hz, 2 H), 3.42 (t, *J* = 7.5 Hz, 2 H), 3.53 (t, *J* = 7.5 Hz, 2 H), 3.61 (t, *J* = 7.5 Hz, 4 H), 6.89 (dd, *J* = 1.5, *J* = 8.0 Hz, 2 H), 7.15–7.28 (m, 3 H), 7.36 (dd, *J* = 1.5, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.97 (dd, *J* = 1.5, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 26.72, 32.75, 41.73, 45.73, 66.36, 66.58 (CH_2), 118.69, 118.96, 122.66, 125.15, 125.75, 128.06, 131.50 (CH), 132.37 (C), 134.31 (CH), 140.35, 150.45, 152.90, 170.71, (C) ppm. MS (APCI): *m*/*z* (%) = 357 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{19}H_{20}N_2O_5$ $[M + H]^+$ 357.1445; found 357.1444.

3-[2-(2-Nitrophenoxy)phenyl]-*N*,*N*-dibenzylpropanamide (7e): After aqueous work-up the solvent was evaporated in vacuo to afford the title compound as a yellow oil (100%). R_f (10% EtOAc in toluene): 0.46. IR (neat): $\tilde{\nu}_{max}$ = 1644 (C=O stretching), 1101 (C–O stretching), 1524, 1347 (N–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 2.82 (t, *J* = 7.5 Hz, 2 H), 3.06 (t, *J* = 7.5 Hz, 2 H), 4.42 (s, 2 H), 4.57 (s, 2 H), 6.78 (dd, *J* = 1.0, *J* = 9.0 Hz, 1 H), 6.82 (dd, *J* = 1.0, *J* = 9.0 Hz, 1 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 7.11–7.15 (m, 4 H), 7.20 (dd, *J* = 1.5, *J* = 9.0 Hz, 1 H), 7.23–7.31 (m, 6 H), 7.34–7.39 (m, 2 H), 7.91 (dd, *J* = 1.5, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 26.95, 33.43, 48.23, 49.90 (CH_2), 119.05, 119.33, 122.74, 125.37, 125.04, 126.51, 127.42, 127.54, 128.19, 128.27, 128.68, 128.94, 131.83, 132.93 (CH), 134.41, 136.52, 137.38, 140.63, 150.98, 153.31, 172.92 (C) ppm. MS (APCI): *m*/*z* (%) = 467 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{29}H_{26}N_2O_4$ $[M + H]^+$ 467.1965; found 467.1973.

***N*,*N*-Diethyl-2-[2-(2-nitrophenoxy)phenyl]acetamide (11a):** Flash column chromatography (SiO_2; 100% EtOAc in toluene) afforded the title compound as a yellow oil (74%). R_f (50% EtOAc in toluene): 0.73. IR (neat): $\tilde{\nu}_{max}$ = 1638 (C=O stretching), 1098 (C–O stretching), 1526, 1368 (N–O stretching) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 0.97 (t, *J* = 7.5 Hz, 3 H), 1.09 (t, *J* = 7.5 Hz, 3 H), 3.52 (m, 4 H), 3.71 (s, 2 H), 6.90–6.98 (m, 2 H), 7.15–7.29 (m, 3 H), 7.39–7.48 (m, 2 H), 7.90 (dd, *J* = 1.5, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 12.74, 14.02 (CH_3), 34.25, 40.31, 42.33 (CH_2), 119.12, 119.34, 123.60, 125.11, 125.39 (CH), 127.90 (C), 128.33, 131.49, 134.21 (CH), 140.44, 150.60, 152.73, 169.37 (C) ppm. MS (APCI): *m*/*z* (%) = 329 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{18}H_{20}N_2O_4$ $[M + H]^+$ 329.1496; found 329.1495.

{2-{2-(Diethylamino)-1-[2-(2-nitrophenoxy)phenyl]-2-oxoethyl}phenyl}azinic Acid (12a): Flash column chromatography (SiO_2; 15% EtOAc in toluene) afforded the title compound as a lemon-yellow solid (21%). R_f (50% EtOAc in toluene): 0.82, m.p. 124–126 °C (EtOAc in toluene). IR (neat): $\tilde{\nu}_{max}$ = 1639 (C=O stretching), 1091 (C–O stretching), 1520, 1346 (N–O stretching) cm^{-1}. ^1H NMR (CDCl3, 300 MHz): δ_H = 1.12 (t, *J* = 7.5 Hz, 3 H), 1.17 (t, *J* = 7.5 Hz, 3 H), 3.24–3.57 (m, 4 H), 6.27 (s, 1 H), 6.63 (d, *J* = 9.0 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.24–7.37 (m, 5 H), 7.44–7.52 (m, 2 H), 7.86 (d, *J* = 9.0 Hz, 1 H), 7.95 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 12.69, 13.66 (CH_3), 40.73, 42.45 (CH_2), 44.44, 118.49, 120.08, 123.65, 124.63, 125.08, 126.04, 127.74, 129.33, 129.51, 130.59, 132.30, 132.74 (CH), 134.16, 134.40, 140.88, 148.93, 149.93, 153.08, 169.43 (C) ppm. MS (APCI): *m*/*z* (%) = 450 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{24}H_{23}N_3O_6$ $[M + H]^+$ 450.1654; found 450.1660.

{2-[2-(Diethylamino)-1-(2-hydroxyphenyl)-2-oxoethyl]phenyl}azinic Acid (13a): Flash column chromatography (SiO_2; 15% EtOAc in toluene) afforded the title compound as a yellow solid (10%). R_f (50% EtOAc in toluene): 0.62, m.p. 161–163 °C (EtOAc in toluene). IR (neat): $\tilde{\nu}_{max}$ = 1616 (C=O stretching), 1590, 1376 (N–O stretching) cm^{-1}. ^1H NMR ([D$_6$]DMSO, 300 MHz): δ_H = 0.09–0.17 (m, 6

H), 2.22–2.47 (m, 4 H), 5.09 (s, 1 H), 5.99–6.08 (m, 3 H), 6.15 (d, J = 6.0 Hz, 1 H), 6.33 (t, J = 7.5 Hz, 1 H), 6.61 (t, J = 7.5 Hz, 1 H), 6.71 (t, J = 7.5 Hz, 1 H), 7.09 (d, J = 9.0 Hz, 1 H), 8.96 (s, 1 H) ppm. ^{13}C N: δ = MR ([D$_6$]DMSO, 75 MHz): 12.30, 13.08 (CH_3), 39.38, 41.09 (CH_2), 43.40, 115.22, 119.28 (CH), 123.42, 123.81 (C), 127.43, 128.49, 128.74, 131.18, 132.47, 134.57 (CH), 149.00, 154.29, 169.04 (C) ppm. MS (APCI): m/z (%) = 329 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{18}H_{20}N_2O_4$ [M + H]$^+$ 329.1496; found 329.1497.

2-[2-(2-Nitrophenoxy)phenyl]-1-(pyrrolidin-1-yl)ethanone (11b): Flash column chromatography (SiO_2; 100% petroleum ether) afforded the title compound as yellow oil (90%). R_f (30% EtOAc in petroleum ether): 0.39. IR (neat): $\tilde{\nu}_{max}$ = 1636 (C=O stretching), 1247 (C–N stretching), 1098 (C–O stretching), 1522, 1345 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.69–1.92 (m, 4 H), 3.31 (t, J = 6.0 Hz, 2 H), 3.43 (t, J = 7.5 Hz, 2 H), 3.67 (s, 2 H), 6.90 (dd, J = 1.5, J = 8.0 Hz, 1 H), 6.95 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.13–7.26 (m, 3 H), 7.41 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.45 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.92 (dd, J = 1.5, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.43, 26.15, 35.89, 45.93, 46.89 (CH_2), 119.49, 119.56, 122.68, 125.41, 125.51 (CH), 127.84 (C), 128.60, 132.01, 134.35 (CH), 140.64, 150.92, 153.09, 168.74 (C) ppm. MS (APCI): m/z (%) = 327 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{18}H_{18}N_2O_4$ [M + H]$^+$ 327.1339; found 327.1343.

2-[2-(2-Nitrophenoxy)phenyl]-2-(2-nitrophenyl)-1-(pyrrolidin-1-yl)ethanone (12b): Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a yellow solid (19%). R_f (30% EtOAc in toluene): 0.46, m.p. 160–162 °C (EtOAc in toluene). IR (neat): $\tilde{\nu}_{max}$ = 1638 (C=O stretching), 1187 (C–O stretching), 1234 (C–N stretching),1518, 1341 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.77–1.95 (m, 4 H), 3.18–3.25 (m, 1 H), 3.35–3.44 (m, 1 H), 3.49–3.55 (m, 1 H), 3.58–3.66 (m, 2 H), 6.08 (s, 1 H), 6.55 (dd, J = 1.0, J = 8.0 Hz, 1 H), 6.80 (dd, J = 1.0, J = 8.0 Hz, 1 H), 7.06 (td, J = 1.0, J = 8.0 Hz, 1 H), 7.14–7.29 (m, 5 H), 7.39–7.46 (m, 2 H), 7.77 (d, J = 8.0 Hz, 1 H) 7.84 (dd, J = 1.0, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.45, 26.81 (CH_2), 45.88 (CH), 46.31, 46.46 (CH_2), 118.63, 119.80, 123.47, 124.63, 125.21, 125.95, 127.81, 129.07, 129.43, 130.53, 132.23, 132.91 (CH), 133.91, 134.10, 140.74, 148.99, 149.46, 153.27, 168.53 (C) ppm. MS (APCI): m/z (%) = 448 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{24}H_{21}N_3O_6$ [M + H]$^+$ 448.1503; found 448.1495.

2-(2-Hydroxyphenyl)-2-(2-nitrophenyl)-1-(pyrrolidin-1-yl)ethanone (13b): Flash column chromatography (SiO_2; 16% EtOAc in toluene) afforded the title compound as a colourless solid (33%). R_f (30% EtOAc in toluene): 0.67, m.p. 189–191 °C (EtOAc in toluene). IR (neat): $\tilde{\nu}_{max}$ = 1615 (C=O stretching), 1584, 1345 (N–O stretching), 2951 (H–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.81–1.97 (m, 3 H), 2.03–2.10 (m,1 H), 3.38–3.62 (m, 3 H), 3.87–3.94 (m, 1 H), 5.64 (s, 1 H), 6.92–6.99 (m, 2 H), 7.15 (t, J = 7.5 Hz, 2 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.40–7.50 (m, 2 H), 7.99 (d, J = 7.5 Hz, 1 H), 8.74 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.44, 26.14, 25.87, 25.90 (CH_2), 46.68, 119.04 (CH), 120.27 (C), 120.67, 125.22 (CH), 120.27 (C), 128.40, 130.36, 131.21, 132.20, 133.44 (CH), 132.39, 148.88, 157.25, 170.60 (C) ppm. MS (APCI): m/z (%) = 327 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{18}H_{18}N_2O_4$ [M + H]$^+$ 327.1339; found 327.1343.

2-[2-(2-Nitrophenoxy)phenyl]-1-(1-piperidyl)ethanone (11c): Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a lemon-yellow solid (54%). R_f (50% EtOAc in toluene): 0.55, m.p. 74–76 °C (EtOAc in toluene). IR (neat): $\tilde{\nu}_{max}$ = 1642 (C=O stretching), 1068 (C–O stretching), 1584, 1350 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.48–1.57 (m, 4 H), 1.65–1.7 (m, 2 H), 3.52 (t, J = 6.0 Hz, 2 H), 3.61 (t, J = 6.0 Hz, 2 H), 3.86 (s, 2 H), 7.03 (t, J = 9.0 Hz, 2 H), 7.29 (d, J = 6.0 Hz, 1 H), 7.34–7.41 (m, 2 H), 7.53–7.62 (m, 2 H), 8.04 (dd, J = 1.5, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.37, 25.45, 26.16, 34.24, 42.88, 46.99 (CH_2), 119.28, 119.35, 122.72, 125.23, 125.52, 128.40, 131.31, 134.25 (CH), 127.70, 140.55, 150.65, 152.55, 168.54 (C) ppm. MS (APCI): m/z (%) = 341 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{19}H_{20}N_2O_4$ [M + H]$^+$ 341.1496; found 341.1498.

2-[2-(2-Nitrophenoxy)phenyl]-2-(2-nitrophenyl)-1-(1-piperidyl)ethanone (12c): Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a lemon-yellow oil (24%). R_f (50% EtOAc in toluene): 0.63. IR (neat): $\tilde{\nu}_{max}$ = 1639 (C=O stretching), 1094 (C–O stretching), 1521, 1346 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.48–1.60 (m, 6 H), 3.29–3.36 (m, 1 H), 3.51–3.57 (m, 2 H), 3.68–3.74 (m, 1 H), 6.32 (s, 1 H), 6.60 (d, J = 9.0 Hz, 1 H), 6.88 (d, J = 9.0 Hz, 1 H), 7.09–7.37 (m, 6 H), 7.47 (t, J = 6.0 Hz, 2 H), 7.85 (d, J = 9.0 Hz, 1 H), 7.90 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 24.55, 25.67, 25.86, 43.42, 47.03 (CH_2), 44.32, 118.68, 119.89, 123.57, 124.65, 125.08, 125.95, 127.67 (CH), 128.84 (C), 129.51, 130.86, 132.11, 132.80, 134.08 (CH), 134.55, 140.69, 148.70, 149.26, 152.82, 168.49 (C) ppm. MS (APCI): m/z (%) = 462 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{25}H_{23}N_3O_6$ [M + H]$^+$ 462.1660; found 462.1654.

2-(2-Hydroxyphenyl)-2-(2-nitrophenyl)-1-(1-piperidyl)ethanone (13c): Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a colourless solid (21%). R_f (50% EtOAc in toluene): 0.81, m.p. 177–179 °C. IR (neat): $\tilde{\nu}_{max}$ = 1618 (C=O stretching), 1596, 1352 (N–O stretching), 3177 (H–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.44–1.75 (m, 6 H), 3.44–3.51 (m, 1 H), 3.56–3.65 (m, 3 H), 5.96 (s, 1 H), 6.88–6.92 (m, 2 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.17 (d, J = 7.5 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 8.00 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]-DMSO, 75 MHz): δ_C = 24.45, 25.64, 25.73, 43.86, 47.51 (CH_2), 49.45, 118.16, 120.70 (CH), 121.39 (C), 125.06, 128.08, 129.99, 131.46, 131.51, 133.30, (CH), 133.62, 148.82, 156.24, 170.32 (C) ppm. MS (APCI): m/z (%) = 341 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{19}H_{20}N_2O_4$ [M + H]$^+$ 341.1496; found 341.1499.

2-[2-(2-Nitrophenoxy)phenyl]-1-morpholinoethanone (11d): Flash column chromatography (SiO_2; 40% EtOAc in toluene) afforded the title compound as a lemon-yellow oil (45%). R_f (50% EtOAc in toluene): 0.37. IR (neat): $\tilde{\nu}_{max}$ = 1642 (C=O stretching), 1068 (C–O stretching), 1584, 1350 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 3.47–352 (m, 8 H), 3.71 (s, 2 H), 6.89 (m, 2 H), 7.12–7.18 (m, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.38–7.47 (m, 2 H), 7.89 (d, J = 9.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ_C = 34.09, 42.25, 46.37, 66.64, 66.79 (CH_2), 119.27, 119.53, 123.05, 125.44, 125.74 (CH), 127.09 (C), 128.79, 131.46, 134.41 (CH), 140.75, 150.55, 152.62, 169.20, (C) ppm. MS (APCI): m/z (%) = 343 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{18}H_{18}N_2O_5$ [M + H]$^+$ 343.1288; found 343.1288.

2-[2-(2-Nitrophenoxy)phenyl]-1-morpholino-2-(2-nitrophenyl)ethanone (12d): Flash column chromatography (SiO_2; 30% EtOAc in toluene) afforded the title compound as a sticky orange oil (6%). R_f (50% EtOAc in toluene): 0.48. IR (neat): $\tilde{\nu}_{max}$ = 1645 (C=O stretching), 1111 (C–O stretching), 1522, 1347 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 3.35–3.45 (m, 2 H), 3.62–3.79 (m, 6 H), 6.31 (s, 1 H), 6.61 (d, J = 8.0 Hz, 1 H), 6.85

(d, J = 8.0 Hz, 1 H), 7.11–7.18 (m, 2 H), 7.23–7.37 (m, 4 H), 7.45–7.50 (m, 2 H), 7.90 (t, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 42.82 (CH_2), 44.44 (CH), 46.47, 66.59, 66.95 (CH_2), 118.38, 120.41, 123.97, 124.93, 125.18, 126.18, 127.98, 129.85, 130.89, 132.02, 133.06, 134.16 (CH), 134.40, 140.88, 148.93, 149.93, 153.08, 169.43 (C) ppm. MS (APCI): m/z (%) = 464 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{24}H_{22}N_3O_7$ [M + H]$^+$ 464.1452; found 464.1455.

2-(2-Hydroxyphenyl)-1-morpholino-2-(2-nitrophenyl)ethanone (13d): Flash column chromatography (SiO_2; 10% EtOAc in toluene) afforded the title compound as a yellow solid (45%). R_f (50% EtOAc in toluene): 0.22, m.p. 157–159 °C. IR (neat): $\tilde{\nu}_{max}$ = 1619 (C=O stretching), 1112 (C–O stretching), 1515, 1343 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 3.08–3.18 (m, 2 H), 3.35–3.57 (m, 6 H), 5.99 (s, 1 H), 6.88–6.92 (m, 3 H), 7.04 (d, J = 6.0 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.99 (d, J = 9.0 Hz, 1 H), 9.86 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ_C = 41.95, 45.55, 65.30, 65.88 (CH_2), 43.39, 115.42, 119.41 (CH), 122.50 (C), 124.08, 127.63, 128.83, 128.98, 131.06, 132.83, (CH), 134.50, 148.73, 154.15, 168.78 (C) ppm. MS (APCI): m/z (%) = 343 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{18}H_{18}N_2O_5$ [M + H]$^+$ 343.1289; found 343.1288.

2-[2-(2-Nitrophenoxy)phenyl]-*N*,*N*-dibenzylacetamide (11e): Flash column chromatography (SiO_2; 10% EtOAc in petroleum ether) afforded the title compound as a yellow oil (40%). R_f (30% EtOAc in petroleum ether): 0.49. IR (neat): $\tilde{\nu}_{max}$ = 1644 (C=O stretching), 1079 (C–O stretching), 1523, 1349 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 3.90 (s, 2 H), 4.55 (s, 2 H), 4.59 (s, 2 H), 6.88 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.07 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.12–7.15 (m, 3 H), 7.18–7.36 (m, 10 H), 7.45 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.50 (dd, J = 1.5, J = 8.0 Hz, 1 H), 7.97 (dd, J = 1.5, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 34.80, 48.65, 50.38 (CH_2), 118.83, 120.41, 123.04, 125.08, 125.67, 126.53, 127.41, 127.64, 128.34, 128.61, 128.76, 128.98, 131.99, 134.46 (CH), 136.43, 137.29, 141.00, 150.76, 153.65, 171.19 (C) ppm. MS (APCI): m/z (%) = 453 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{28}H_{24}N_2O_4$ [M + H]$^+$ 453.1809; found 453.1810.

2-[2-(2-Nitrophenoxy)phenyl]-*N*,*N*-dibenzyl-2-(2-nitrophenyl)acetamide (12e): Flash column chromatography (SiO_2; 20% EtOAc in petroleum ether) afforded the title compound as orange crystals (54%). R_f (30% EtOAc in petroleum ether): 0.44, m.p. 170–172 °C (EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1647 (C=O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 4.39 (d, J = 15.0 Hz, 1 H, $H_{A/B}$), 4.52 (d, J = 15.0 Hz, 1 H, $H_{C/D}$), 4.64 (d, J = 15.0 Hz, 1 H, $H_{D/C}$), 4.88 (d, J = 15.0 Hz, 1 H, $H_{B/A}$), 6.45 (dd, J = 3.0, J = 9.0 Hz, 1 H), 6.51 (s, 1 H), 6.75 (dd, J = 1.0, J = 8.0 Hz, 1 H), 6.94–6.98 (m, 2 H), 7.11 (td, J = 3.0, J = 9.0 Hz, 1 H), 7.16–7.38 (m, 13 H), 7.50 (d, J = 6.0 Hz, 2 H), 7.88 (dt, J = 3.0, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 44.27 (CH), 48.44 50.68 (CH_2), 118.59, 120.21 123.65, 124.84, 124.93, 125.95, 127.45, 127.48, 127.96, 128.59, 128.65, 128.74, 129.63, 130.95, 132.33, 132.95, 134.10 (CH), 135.73, 136.91, 140.96, 148.89, 149.29, 153.25, 171.08 (C) ppm. MS (APCI): m/z (%) = 574 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{34}H_{27}N_3O_6$ [M + H]$^+$ 574.1973; found 574.1963.

***N*,*N*-Dibenzyl-2-(2-hydroxyphenyl)-2-(2-nitrophenyl)acetamide (13e):** Flash column chromatography (SiO_2; 25% EtOAc in petroleum ether) afforded the title compound as a colourless solid (37%). R_f (30% EtOAc in petroleum ether): 0.60, m.p. 195–197 °C (EtOAc in petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1618 (C=O stretching), 1599, 1344 (N–O stretching), 3267 (H–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 4.21 (d, J = 15.0 Hz, 1 H, $H_{A/B}$), 4.53 (d, J = 15.0 Hz, 1 H, $H_{C/D}$), 4.73 (d, J = 15.0 Hz, 1 H, $H_{D/C}$), 4.88 (d, J = 15.0 Hz, 1 H, $H_{B/A}$), 6.15 (s, 1 H), 6.82 (t, J = 7.5 Hz, 1 H), 6.94 (m, 3 H), 7.01 (d, J = 6.0 Hz, 1 H), 7.14 (m, 2 H), 7.24–7.31 (m, 4 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.53 (t, J = 7.5 Hz, 1 H), 7.79 (s, 1 H), 8.01 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 48.35 (CH_2), 49.36 (CH), 50.90 (CH_2), 118.21, 121.00 (CH), 121.51, 125.20, 127.63, 127.69, 127.88, 128.35, 128.68, 128.86, 130.19, 131.48 (CH), 131.82 (C), 133.00 (CH), 133.31, 135.17, 136.30, 148.97, 155.85, 172.98 (C) ppm. MS (APCI): m/z (%) = 451 (100) [M – H]$^+$. HRMS (FAB): calcd. for $C_{28}H_{24}N_2O_4$ [M + H]$^+$ 453.1809; found 453.1805.

1-[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]-2-(2-hydroxyphenyl)ethanone (17): Flash column chromatography (SiO_2; 60% EtOAc in petroleum ether) to afford the title compound as yellow sticky oil (99%). R_f (30% EtOAc in petroleum ether): 0.42. $[\alpha]_{589}$ = –53.43 (ethanol, c = 0.46 g/100 mL). IR (neat): $\tilde{\nu}_{max}$ = 1618 (C=O stretching), 2929 (OH stretching), 1040 (C–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.88–2.01 (m, 3 H), 2.12–2.21 (m, 1 H), 2.25–3.54 [m, 10 H includes 2× (s, 3 H) at 3.24 and 3.37], 3.73 (d, J = 14.0 Hz, 1 H, $H_{A/B}$), 3.82 (d, J = 14.0 Hz, 1 H, $H_{B/A}$), 4.20–4.27 (m, 2 H), 6.81 (t, J = 6.0 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.03 (d, J = 7.0 Hz, 1 H), 7.18 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 25.81, 27.54, 39.53 (CH_2), 57.69, (CH), 59.15 (CH_3), 59.41 (CH), 71.29, 74.79 (CH_2), 118.49, 119.95 (CH), 121.62 (C), 129.18, 130.08 (CH), 157.23, 173.46 (C) ppm. MS (APCI): m/z (%) = 294 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{16}H_{23}NO_4$ [M + H]$^+$ 294.1700; found 294.1702.

1-[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]-2-[2-(2-nitrophenoxy)phenyl]-2-(2-nitrophenyl)ethanone (18): Flash column chromatography (SiO_2; 35% EtOAc in petroleum ether) to afford the title compound as a lemon-yellow sticky oil (10%). R_f (60% EtOAc in petroleum ether): 0.65. $[\alpha]_{589}$ = –62.85 (ethanol, c = 0.24 g/100 mL). IR (neat): $\tilde{\nu}_{max}$ = 1639 (C=O stretching), 1109 (C–O stretching), 1524, 1348 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 0.75–0.79 (m, 1 H), 1.73–1.92 (m, 8 H), 2.83 (s, 3 H), 2.95–3.09 [m, 5 H, includes (s, 3 H) at 3.09], 3.18 (s, 3 H), 3.21–3.27 [m, 6 H, includes (s, 3 H) at 3.23], 3.36 (dd, J = 9.0 Hz, 1 H), 3.52 (td, J = 6.0, J = 9.0 Hz, 3 H), 3.71–3.73 (m, 1 H), 4.08–4.15 (m, 1 H), 4.16–4.20 (m, 2 H), 6.07 (s, 1 H), 6.18 (s, 1 H), 6.48 (d, J = 8.0 Hz, 1 H), 6.75 (t, J = 9.0 Hz, 3 H), 7.00–7.40 (m, 15 H), 7.65 (d, J = 9.0 Hz, 1 H), 7.81 (dd, J = 1.0, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 2 = 5.49, 25.58, 27.48, 27.73 (CH_2), 45.61, 46.20, 57.82, 57.89 (CH_3), 58.59, 58.75, 58.81, 58.90 (CH), 70.60, 70.71, 73.76,73.79 (CH_2), 117.97, 118.88, 119.76, 120.72, 123.32, 123.82, 124.51, 124.68, 124.75, 125.04, 125.81, 127.78, 128.01, 129.10, 129.25 (CH), 129.42 (C), 130.20, 130.40 (CH), 130.66 (C), 132.15,132.57, 132.80, 132.89 (CH), 133.74, 133.94 (C), 134.09, 134.27 (CH), 140.85, 141.39, 149.05, 149.36, 149.62, 152.98, 153.75, 168.92, 169.50 (C) ppm. MS (APCI): m/z (%) = 536 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{28}H_{29}N_3O_8$ [M + H]$^+$ 536.2027; found 536.2015.

1-[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]-2-(2-hydroxyphenyl)-2-(2-nitrophenyl)ethanone (19): Flash column chromatography (SiO_2; 35% EtOAc in petroleum ether) to afford the title compound as a yellow solid (45%). R_f (60% EtOAc in petroleum ether): 0.73, m.p. 126–128 °C (EtOAc in petroleum ether). $[\alpha]_{589}$ = –75.76 (ethanol, c = 0.5 g/100 mL). IR (neat): $\tilde{\nu}_{max}$ = 1620 (C=O stretching), 1113 (C–O stretching), 1524, 1356 (N–O stretching), 3243 (O–H stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 0.62–0.66 (m, 1 H), 1.58–1.63 (m, 4 H), 1.69–1.76 (m, 2 H), 1.92–1.98 (m, 1 H), 2.78 (s, 3 H), 2.93 (d, J = 3.0 Hz, 1 H), 2.99 (s, 3

H), 3.02 (s, 3 H), 3.08 (s, 3 H), 3.13 (d, J = 9.0 Hz, 1 H), 3.22 (t, J = 9.0 Hz, 1 H), 3.39 (td, J = 2.0, J = 9.0 Hz, 2 H), 3.51–3.59 (m, 2 H), 3.99–4.06 (m, 2 H), 5.73 (s, 1 H), 5.81 (s, 1 H), 6.43 (d, J = 7.5 Hz, 1 H), 6.60–6.63 (m, 2 H), 6.85 (d, J = 7.5 Hz, 1 H), 6.88 (m, 3 H), 6.95–7.12 (m, 5 H), 7.60 (d, J = 7.5 Hz, 1 H), 7.66 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 25.23, 27.04, 27.30 (CH_2), 46.90, 47.33, 57.21, 57.68 (CH_3), 58.06, 58.26, 58.47, 58.57 (CH), 70.26, 70.40, 73.11 (CH_2), 116.01, 116.19, 119.77, 119.95 (CH), 122.86, 122.95 (C), 124.29, 124.32, 127.43, 127.68, 129.14,129.24, 129.42, 129.82, 131.68, 131.84, 132.66, 132.75 (CH), 133.85, 133.94, 148.86, 149.12, 154.75, 154.85, 171.02, 171.25 (C) ppm. MS (APCI): m/z (%) = 415 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{22}H_{26}N_2O_6$ $[M + H]^+$ 415.1864; found 415.1861.

1-[(2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl]-2-(2-hydroxyphenyl)ethanone: Flash column chromatography (SiO_2; 5% EtOAc in toluene) afforded the title compound as a colourless solid (73%). R_f (20% EtOAc in toluene): 0.56, m.p. 142–144 °C (EtOAc in toluene). $[\alpha]_{589}$ = –69.8 (ethanol, c = 0.2 g/100 mL). IR (neat): $\tilde{\nu}_{max}$ = 1560 (C=O stretching), 2965 (OH stretching), 1035 (C–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.15 (d, J = 6.0 Hz, 3 H), 1.31 (d, J = 6.0 Hz, 3 H), 1.57–1.61 (m, 1 H), 1.66–1.71 (m, 1 H), 2.07–2.29 (m, 2 H), 3.67 (d, J = 15.0 Hz, 1 H, $H_{A/B}$), 3.73 (d, J = 15.0 Hz, 1 H, $H_{B/A}$), 4.21–4.28 (m, 2 H), 6.80 (t, J = 7.5 Hz, 1 H), 6.97–7.03 (m, 2 H), 7.17 (t, J = 7.5 Hz, 1 H), 11.01 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 19.02, 22.56 (CH_3), 29.20, 30.84, 39.32 (CH_2), 53.99, 55.04 (CH), 118.54, 119.77 (CH), 121.62 (C), 129.14, 130.73 (CH), 157.55, 172.18 (C) ppm. MS (APCI): m/z (%) = 234 (100) $[M + H]^+$.

1-[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]-2-[2-(2-nitrophenoxy)phenyl]ethanone (21): Flash column chromatography (SiO_2; 40% EtOAc in petroleum ether) to afford the title compound as lemon-yellow sticky oil (45%). R_f (60% EtOAc in petroleum ether): 0.50. IR (neat): $\tilde{\nu}_{max}$ = 1639 (C=O stretching), 1107 (C–O stretching), 1583, 1350 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.83–1.98 (m, 4 H), 2.97 (t, J = 6.0 Hz, 1 H), 3.18 (s, 3 H), 3.20–3.41 [m, 6 H, includes (s, 3 H) at 3.29], 3.64 (d, J = 15.0 Hz, 1 H, $H_{A/B}$), 3.94 (d, J = 15.0 Hz, 1 H, $H_{B/A}$), 4.08–4.14 (m, 2 H), 6.89 (d, J = 8.0 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 1 H), 7.15–7.26 (m, 3 H), 7.37 (dd, J = 1.0, J = 8.0 Hz, 1 H), 7.46 (td, J = 1.0, J = 8.0 Hz, 1 H), 7.90 (dd, J = 1.0, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 25.34, 27.09, 36.54 (CH_2), 57.07, 57.93 (CH_3), 58.79, 59.09 (CH), 70.88, 74.20 (CH_2), 119.109, 119.67, 122.71, 125.21, 125.49 (CH), 128.18 (C), 128.52, 132.21, 134.26 (CH), 140.84, 150.82, 153.21, 169.80 (C) ppm. MS (APCI): m/z (%) = 415 (100) $[M + H]^+$. HRMS (FAB): calcd. for $C_{22}H_{26}N_2O_6$ $[M + H]^+$ 415.1864; found 415.1861.

Methyl 3-[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]-2-[2-(2-nitrophenoxy)phenyl]-3-oxopropanoate: Flash column chromatography (SiO_2; 36% EtOAc in petroleum ether) to afford the title compound as a lemon-yellow powder (57%). R_f (60% EtOAc in petroleum ether): 0.63, m.p. 191–193°C (EtOAc/petroleum ether). IR (neat): $\tilde{\nu}_{max}$ = 1766 (C=O stretching, ester), 1646 (C=O stretching), 1113 (C–O stretching), 1521, 1340 (N–O stretching) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 1.87–2.08 (m, 3 H), 2.13–2.25 (m, 1 H), 2.94–3.00 [m, 5 H, includes (s, 3 H) at 2.94], 3.25–3.32 [m, 4 H, includes (s, 3 H) at 3.28], 3.61–3.76 [m, 4 H, includes (s, 3 H) at 3.65], 4.22–4.28 (m, 1 H), 4.31–4.35 (m, 1 H), 5.97 (s, 1 H), 6.19 (s, 1 H), 7.17 (d, J = 7.83 Hz, 1 H), 7.24 (d, J = 9.0 Hz, 1 H), 7.30 (d, J = 9.0 Hz, 1 H), 7.37 (t, J = 9.0 Hz, 2 H), 7.48 (d, J = 9.0 Hz, 1 H), 7.53 (d, J = 9.0 Hz, 1 H), 7.90 (d, J = 9.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C = 25.47, 27.76 (CH_2), 45.58, 55.55, 58.21 (CH_3), 58.30, 58.63, 58.88 (CH), 70.58, 73.80, (CH_2), 122.71, 124.23, 126.57, 128.06, 129.11, 130.05 (CH), 131.12 (C), 133.18, 133.26 (CH), 133.96, 148.73, 153.30, 168.55 (C) ppm. MS (APCI): m/z (%) = 471 $[M – H]^+$, (40), 457 (100) $[M – CH_3]^+$.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

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