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Full Paper

Synthesis and Activity of Putative Small-Molecule Inhibitors of the F-Box Protein SKP2*

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The tetrahydropyran 4-(((3-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylaniline was reported to disrupt the SCF^{SKP2} E3 ligase complex. Efficient syntheses of this tetrahydropyran derivative and analogues, including the *des*-dimethyl derivative 4-(((3-(tetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylaniline, are described. The enantiomers of the *des*-dimethyl compound were obtained using Evans' chiral auxiliaries. Structure–activity relationships for these tetrahydropyrans and analogues have been determined by measurement of growth-inhibitory activities in HeLa cells, which indicated a non-specific mechanism of action that correlates with inhibitor lipophilicity. However, preliminary data with (*R*)- and (*S*)-4-(((3-(tetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl) amino)methyl)-*N*,*N*-dimethylaniline showed enantioselective inhibition of the degradation of p27 in a cell-based assay that acts as a reporter of SKP2 activity.

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Introduction

SKP1 and SKP2 (S-phase kinase-associated proteins 1 and 2) were identified as components of a cyclin-dependent kinase 2 (CDK2)-containing complex, whose levels were found to be elevated in cancer-derived cell lines compared with their normal counterparts.[1] SKP2 has since been characterised[2,3] more extensively as a component of the SKP1-Cullin 1-F-box (SCF) E3 ubiquitin ligase, which promotes the ubiquitination of regulatory protein substrates, targeting them for degradation by the 26S proteasome.[4] Levels of $p27^{KIP1}$, a CDK inhibitor with multiple vital roles in coordinating events throughout the cell cycle, are regulated in part by ubiquitin-dependent proteolysis mediated by SCF ligases.[5–7] Decreased expression of $p27^{KIP1}$ through enhanced proteolysis mediated by elevated SKP2 expression is associated with an aggressive phenotype and poor prognosis in many cancers.[8–14] In 2010, at the outset of the project described herein, there was a single report of a small-molecule SKP2 antagonist (**1a**, Chart 1),[8] although subsequently several direct or indirect SKP2 modulators have been identified, which have greatly strengthened the case for SKP2

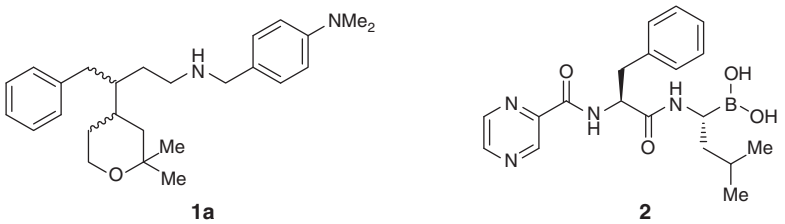
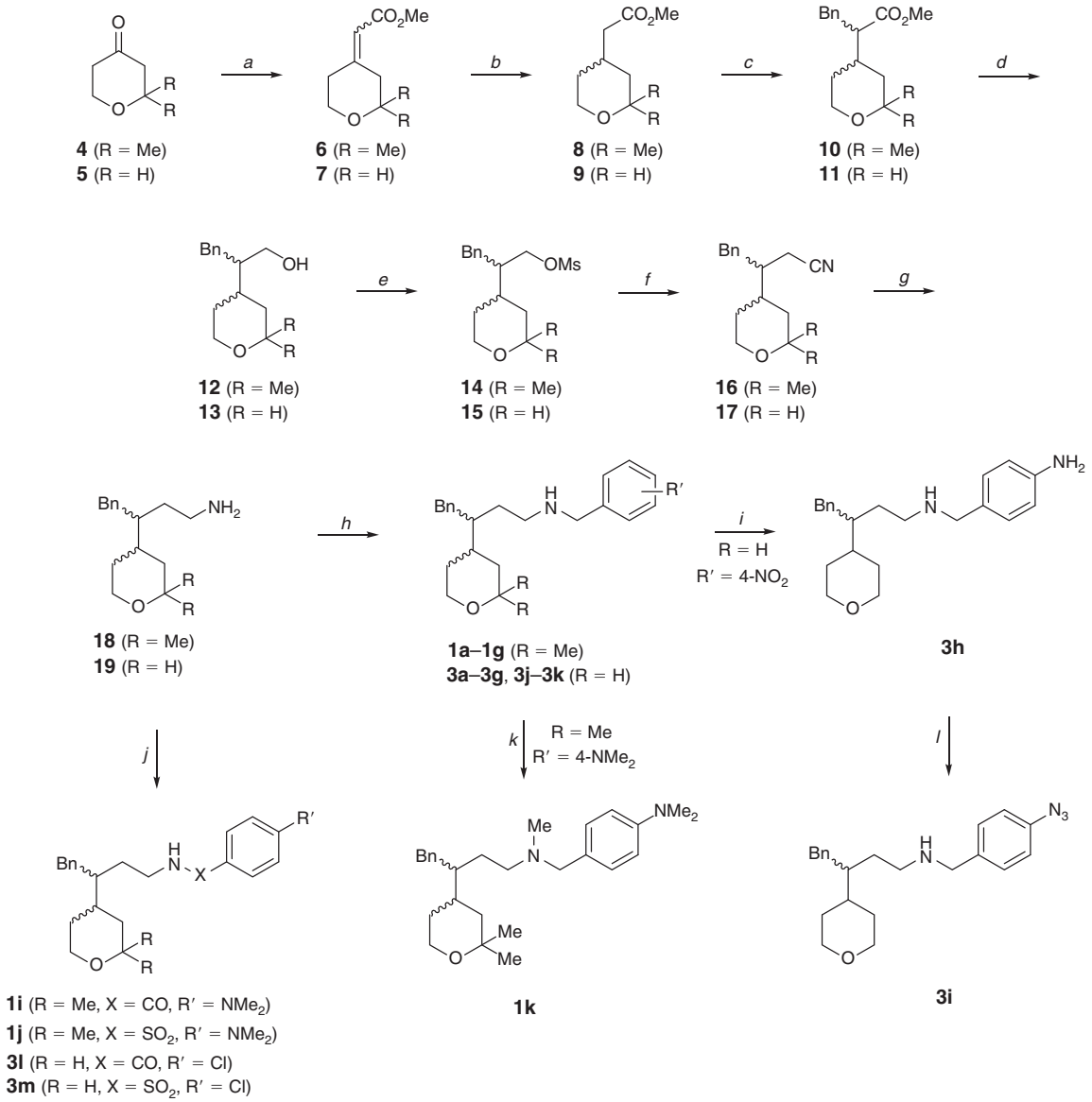


Chart 1. 4-(((3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylaniline (**1a**) and bortezomib (**2**).

*Dedicated to Sir John W. Cornforth (1917–2013), a pioneer in the application of stereochemistry for probing biological systems.

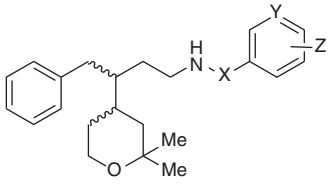


Scheme 1. (*a*) $(MeO)_2(O)PCH_2CO_2Me$, NaH, THF, 0°C–room temperature (RT), 20 h, 80–88 %; (*b*) NH_4HCO_2, 10 % Pd/C, MeOH, 0–90°C, 90 min, 90–92 %; (*c*) $^iPr_2NH$, *n*-BuLi, THF, −78°C, 1 h; BnBr, THF, 30°C, overnight, 86–89 %; (*d*) $LiAlH_4$, THF, 0°C, 2 h, 93–100 %; (*e*) MsCl, $^iPr_2NEt$, DCM, RT, 2 h, 96–97 %; (*f*) NaCN, DMF, 100°C, 7 h, 83–90 %; (*g*) $LiAlH_4$, THF, 0°C, 3 h, 73–83 %; (*h*) appropriate benzaldehyde, $MgSO_4$, DCM, RT, 4 h; $NaBH_4$, MeOH, RT, 1 h, 16–95 %; (*i*) H_2, Raney Ni, MeOH, RT, 1.01×10^5 Pa , 3 h, 99 %; (*j*) appropriate acyl or sulfonyl chloride, Et_3N or $^iPr_2NEt$, DCM, RT, 1–2 h, 63–94 %; (*k*) 37 % aq. CH_2O, 88 % aq. HCO_2H, EtOH, 40°C, 90 min, 39 %; (*l*) $NaNO_2$, 5 M HCl, 40 min, 0°C, dark; NaN_3, 0°C–RT, 3 h, dark, 75 %.

as a cancer therapeutic target.[15] Indeed, the ability of inhibitors of SKP2 to impede cancer progression[16,17] has made this protein a 'dream target in the coming age of cancer therapy'.[15] Therapeutic opportunities for SKP2 inhibition include the treatment of breast[18] and prostate cancer.[12] Targeting F-box proteins is attractive because they define E3 ligase selectivity and each SCF complex targets fewer proteins than the 26S proteasome.[17] Currently, the only marketed drug that targets the ubiquitin–proteasome system is bortezomib (Velcade, Millennium Pharmaceuticals, **2**, Chart 1), which is used to treat multiple myeloma by inhibiting the 26S proteasome,[8,19] but with several side effects.[8]

Compound **1a** (4-(((3-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylaniline) was reported to be an inhibitor of the SCF^{SKP2} complex using an in vitro reconstituted system containing the cyclin E/CDK2, SCF^{SKP2} complex and HeLa cell extract.[8] Levels of labelled p27 and its polyubiquitinated form were analysed, showing that ubiquitination was inhibited with 30 μM **1a**. Addition of an excess of SCF^{SKP2} complex restored ubiquitination in the absence of **1a** and in its presence.[8] In wild-type mouse embryonic fibroblast cells, 5 μM **1a** induced p27 levels and reduced cell viability in a dose-dependent manner, which was not observed in SKP2-deficient cells.[8] Melphalan-resistant RPMI 8226 and U266 cells exhibited similar sensitivity towards **1a** as their non-melphalan-resistant analogues and a synergistic enhancement in growth inhibition was observed on combining **1a** with **2** in RPMI 8226 cells.[8] In another study that used a structure-based approach aided by *in silico* virtual ligand screening and in vitro assays, small-molecule inhibitors were developed against the complex consisting of SKP2, p27, and the 'accessory protein' Cks1.[20]

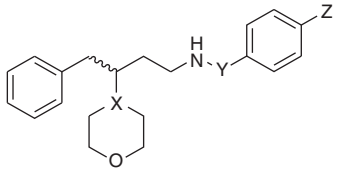
Table 1. HeLa sulforhodamine B (SRB) assay data for inhibitors 1a–1j



Compound[A]	X	Y	Z	HeLa GI_{50} [μM][B]	cLog*P*[C]
1a	CH_2	CH	4-NMe_2	16 ± 1	5.8
1b	CH_2	CH	H	17 ± 3	5.7
1c	CH_2	CH	3-NMe_2	18 ± 2	5.8
1d	CH_2	CH	4-^{i}Pr	5.8 ± 1.1	7.1
1e	CH_2	CH	4-Cl	11 ± 4	6.4
1f	CH_2	CH	4-CN	36 ± 2	5.1
1g	CH_2	CH	4-OMe	29 ± 7	5.6
1h	CH_2	N	4-NMe_2	40 ± 3	4.9
1i	CO	CH	4-NMe_2	53 ± 7	5.4
1j	SO_2	CH	4-NMe_2	35 ± 2	5.5

[A]Mixture of diastereoisomers (dr, 5 : 2).
[B]$n = 3$.
[C]Values from ChemDraw.

Table 2. HeLa sulforhodamine B (SRB) assay data for inhibitors 3a–3m and 25



Compound[A]	X	Y	Z	HeLa GI_{50} [μM][B]	cLog*P*[C]
3a	CH	CH_2	NMe_2	27 ± 4	4.8
3b	CH	CH_2	$N(CH_2)_4$	8 ± 1	4.9
3c	CH	CH_2	CF_3	16 ± 1	5.5
3d	CH	CH_2	SMe	17 ± 1	5.2
3e	CH	CH_2	Cl	18 ± 1	5.3
3f	CH	CH_2	F	45 ± 1	4.8
3g	CH	CH_2	NO_2	47 ± 5	4.4
3h	CH	CH_2	NH_2	>100	3.4
3i	CH	CH_2	N_3	17 ± 2	5.1
3j	CH	CH_2	$N(Me)CH_2CH_2OH$	33 ± 2	4.1
3k	CH	CH_2	SO_2Me	>100	3.0
3l	CH	CO	Cl	37 ± 3	4.9
3m	CH	SO_2	Cl	30 ± 1	5.1
25	N	CH_2	NMe_2	40 ± 5	4.1

[A]Racemates.
[B]$n = 3$.
[C]Values from ChemDraw.

Results and Discussion

*Synthesis of **1a**, **3a**, and Analogues*

To aid further biological studies of its mechanism of action, compound **1a** was synthesised as a mixture of diastereoisomers in overall yields up to 58 % for the eight steps (Scheme 1). The synthetic route is similar to the published methodology,[21] but gave higher overall yields. In step *b*, catalytic transfer hydrogenation was used instead of H_2(g), Pd/C and for step *d*, lithium aluminium hydride was used in place of diisobutylaluminium hydride. The diastereoisomeric ratio was 5 : 2 by ^{1}H NMR analysis (a 3 : 1 ratio was reported[21]). No information concerning the influence of chirality of the stereogenic centres in **1a** on SKP2 activity was reported. We therefore synthesised the racemic *des*-dimethyl analogue **3a** (cf. Scheme 1) with the plan to resolve *rac*-**3a** into its enantiomers, should the compound exhibit similar activity to **1a**.

Amines **18** and **19** were reacted with 4-substituted benzaldehydes to give imines that were reduced to the corresponding benzylamine analogues (**1a**–**1g** and **3a**–**3g**, **3j**, and **3k** respectively; cf. Tables 1 and 2). Amine **18** was coupled with 6-(dimethylamino)nicotinaldehyde leading to **1h**. Amines **18** and **19** were also reacted with acyl and sulfonyl chlorides, giving the corresponding amides (**1i** and **3l**) and sulfonamides (**1j** and **3m**). Methylation of the secondary amine of **1a** was accomplished using an Eschweiler–Clarke reaction to give **1k**. To synthesise azide **3i**, reductive amination of 4-nitrobenzaldehyde with amine **19** gave **3g**, which was hydrogenated to aniline **3h**. Treatment of **3h** with nitrous acid, followed by addition of sodium azide, generated **3i**.

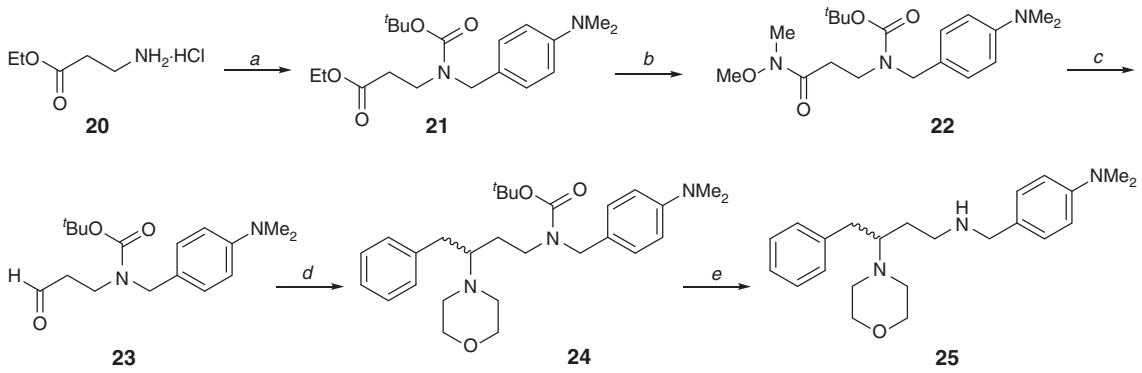
The tetrahydropyran ring of **3a** was replaced with a morpholino group (Scheme 2) employing Katritzky's protocol for the synthesis of tertiary amines.[22,23]

*Inhibition Data for **1a**, **3a**, and their Analogues*

Compounds **1a** and **3a** were assessed for their growth-inhibitory activity in a HeLa cell-based sulforhodamine B (SRB) assay (Fig. 1). Both compounds demonstrated growth-inhibitory activity, with **1a** bringing cell density below that of the pre-treatment level.

All compounds in the *gem*-dimethylpyran series (**1a**–**1j**) were active against HeLa cell growth, with **1d**, possessing a 4-isopropyl substituent, displaying superior potency to **1a**. Unsubstituted analogue **1b** and regioisomer **1c** had similar potency to **1a**, showing that the dimethylamino group was not essential for cellular activity. Replacing the 4-NMe_2 group with cyano (**1f**) or methoxy (**1g**) reduced activity by two-fold in each case. Introduction of a pyridyl ring (**1h**), as well as substituting an amide (**1i**) or sulfonamide (**1j**) for the methylene group of **1a** also reduced HeLa cell-growth inhibition. However, none of these structural changes had a significant effect on activity, although the most active compounds were also the most lipophilic (calculated log of the partition coefficient between octan-1-ol and water (clog*P*) 7.1, **1d**; 6.4, **1e**; clog*P* values for **1a**–**1c** and **1f**–**1j** were in the range 4.9–5.8). This could be due to improved cell penetration or increased hydrophobic interactions with a target protein. Methylation of the secondary amine of **1a** did not significantly affect growth-inhibitory activity, with **1k** giving a GI_{50} (concentration required to inhibit cell growth by 50 %) of 31 ± 3 μM.

In the *des*-dimethyl series **3a**–**3m**, 4-pyrrolidinyl (**3b**), 4-trifluoromethyl (**3c**), 4-methylthio (**3d**), and 4-chloro (**3e**) substituents improved HeLa cell-growth inhibitory activity relative to **3a**. Comparison of **3a** and **3e** with the corresponding *gem*-dimethyl analogues **1a** and **1e** showed that the latter had marginally superior growth-inhibitory activity. Reducing 4-nitro (**3g**) to 4-amino (**3h**) or oxidising methylthio to methylsulfone (**3k**) abolished potency. These compounds were also the least lipophilic (clog*P* 3.4, **3h**, and 3.0, **3k**, as opposed to clog*P* 4.1–5.5 for the remaining compounds). Replacing the methylene linker with an amide or sulfonamide and retaining the 4-chloro substituent (**3l** and **3m** respectively) gave compounds of similar potency to **3a**. Compound **25** was two-fold less active than **1a** but had reduced lipophilicity (clog*P* 4.1, **25**, and 5.8, **1a**)



Scheme 2. (*a*) 4-(*N*,*N*-Dimethylamino)benzaldehyde, $NaOAc{\cdot}3H_2O$, $MgSO_4$, THF, room temperature (RT), 4 h; $NaBH_4$, EtOH, RT, 1 h; Boc_2O, DCM, 0°C–RT, 1 h, 21 %; (*b*) HN(OMe)Me·HCl, $^{i}PrMgCl$, THF, 0°C, 1 h, 93 %; (*c*) $LiAlH_4$, THF, 0°C, 1 h, 72 %; (*d*) morpholine, 1*H*-benzotriazole, 3-Å molecular sieves, DCM, RT, 3 h; BnMgCl, THF, 0°C, 1 h, 61 %; (*e*) TFA, DCM, RT, 1 h, 100 %.

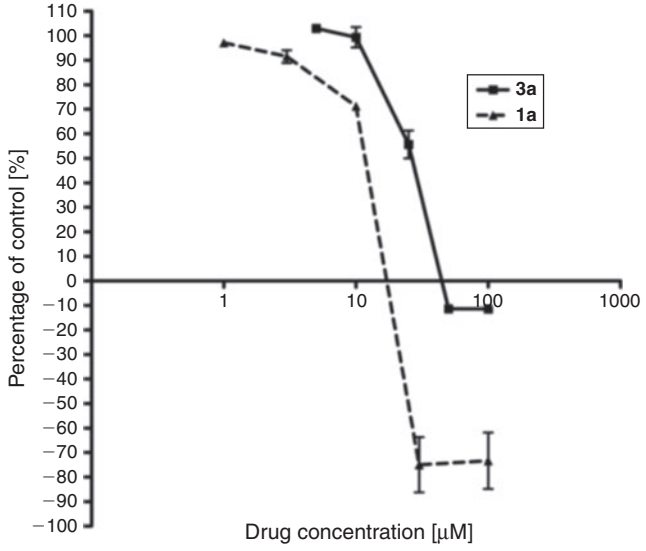
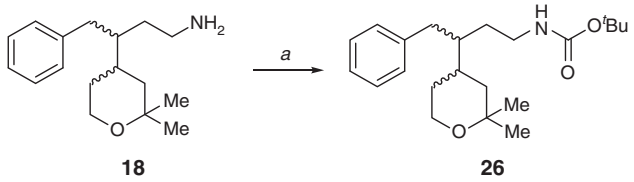


Fig. 1. Inhibition of HeLa cell growth by **1a** and **3a** measured by sulforhodamine B (SRB) assay.



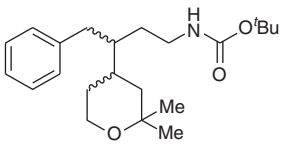
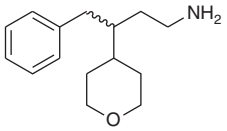
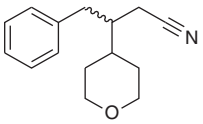
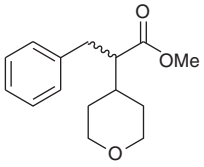
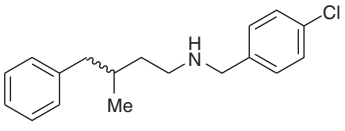
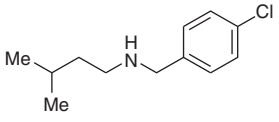
Scheme 3. (*a*) Boc_2O, DCM, 0°C–room temperature (RT), overnight, 65 %.

whereas the carbamate precursor **24** was similarly potent to **1a**, with a GI_{50} of 20 ± 4 μM.

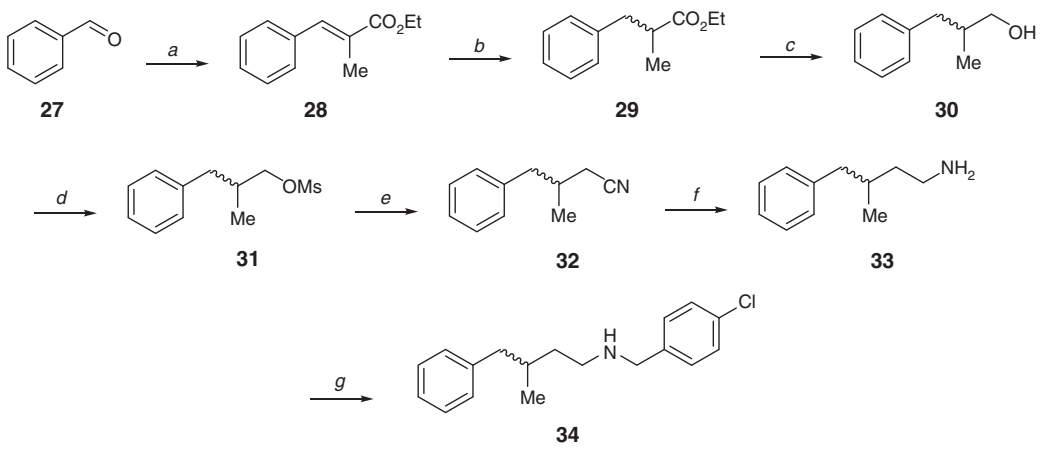
*The Minimum Pharmacophore of Compound **1a***

In the *gem*-dimethylpyran series, deletion of the dimethylamino group (cf. Table 1, **1b**) did not affect potency and indeed, substitution of the benzylamino substituent for a carbamate (**26**), synthesised by treatment of amine **18** with Boc_2O (Boc = *t*-butyloxycarbonyl) (Scheme 3), produced a similarly active species (Table 3).

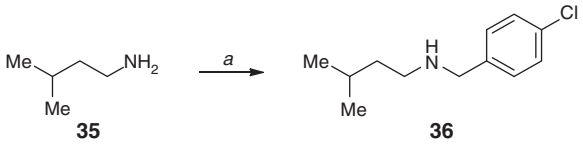
Table 3. HeLa sulforhodamine B (SRB) assay data for morpholines 24 and 25 and fragment derivatives of 1a and 3a

Compound[A]	Structure	HeLa GI_{50} [μM][B]	cLog*P*[C]
26		35 ± 2	5.2
19		>100	2.5
17		>100	2.2
11		>100	2.3
34		16 ± 1	5.6
36		>100	4.2

[A]Racemates or mixture of diastereoisomers (dr, 5 : 2).
[B]$n = 3$.
[C]Values from ChemDraw.



Scheme 4. (*a*) $(EtO)_2(O)PCH(Me)CO_2Et$, NaH, THF, 0–30°C 48 h, 33 %; (*b*) NH_4HCO_2, 10 % Pd/C, MeOH, 0–90°C, 90 min, 93 %; (*c*) $LiAlH_4$, THF, 0°C, 2 h, 87 %; (*d*) $MeSO_2Cl$, $^iPr_2NEt$, DCM, room temperature (RT), 2 h, 96 %; (*e*) NaCN, DMF, 100°C, 7 h, 81 %; (*f*) H_2, Raney Ni, 6×10^6 Pa, 70°C, 24 h, 43 %; (*g*) 4-chlorobenzaldehyde, $MgSO_4$, DCM, RT, 47 h; $NaBH_4$, MeOH, RT, 1 h, 27 %.



Scheme 5. (*a*) 4-Chlorobenzaldehyde, $MgSO_4$, DCM, room temperature (RT), 4 h; $NaBH_4$, MeOH, RT, 1 h, 48 %.

Removal of the *gem*-dimethyl group had only a minor effect on cellular potency (cf. Table 2, 3a) and deletion of the tetrahydropyran ring (**34**) also retained activity in HeLa cells (Table 3). Compound **34** was synthesised from ester **28**, obtained via Horner–Wadsworth–Emmons (HWE) olefination of benzaldehyde (**27**) with triethyl 2-phosphonopropionate (Scheme 4).

Further simplification to compound **36**, synthesised by reductive amination of 4-chlorobenzaldehyde with isopentylamine (**35**) (Scheme 5), was found to abrogate activity in HeLa cells. Several intermediates (**11**, **17**, and **19**) in the synthesis of **3a** were also evaluated and found to be inactive (Table 3).

Substitution of the tetrahydropyran ring by a methyl group (**34**) retained activity but replacement of both the pyran and phenyl ring by methyl groups (**36**) abolished potency, suggesting that the phenyl ring was important for growth inhibition. The intermediates **11**, **17**, and **19** possessed no growth-inhibitory activity, suggesting with reference to compounds **19** and **36**, that compound **34** demarcates the minimum pharmacophore.

*Synthesis of the Enantiomers of **3a***

Attempted separation of the enantiomers of **3a** by chiral HPLC was unsuccessful, necessitating the development of an enantioselective route using Evans' chiral auxiliaries.[24] Starting from pyranone **5**, HWE olefination and transfer hydrogenation yielded ester **9**. Hydrolysis with lithium hydroxide provided carboxylic acid **37**, treatment of which with pivaloyl chloride followed by (*R*)- or (*S*)-4-benzyloxazolidin-2-one gave oxazolidinones (*R*)-**38** and (*S*)-**38**, respectively (Scheme 6).

Enolate formation with lithium di-isopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) before addition of benzyl bromide gave either (*R*,*R*)-**39** or (*S*,*S*)-**39** in >98 % diastereoisomeric excess (de) (HPLC analysis). Removal of the auxiliaries using superhydride gave either (*R*)-**13** or (*S*)-**13** in 41 % yield. Mesylation, substitution with sodium cyanide, reduction with lithium aluminium hydride, and reductive amination with 4-(*N*,*N*-dimethylamino)benzaldehyde gave either (*R*)-**3a** or (*S*)-**3a** (Scheme 7).

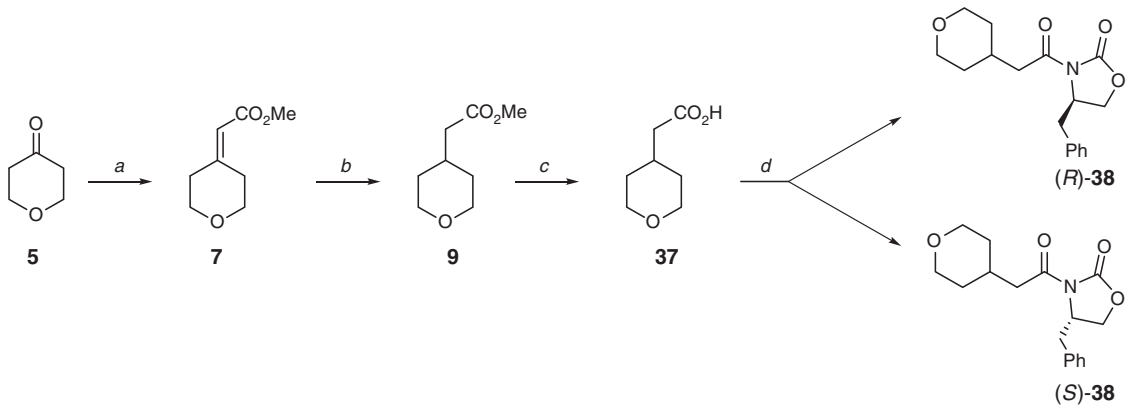
Chiral HPLC analysis of intermediates (*R*)-**19** and (*S*)-**19** confirmed that these compounds were enantiopure (>99 % enantiomeric excess (ee), see Supplementary Material Fig. A). Both enantiomers and the racemate of **3a** were equipotent in HeLa cells, suggesting a non-stereoselective mechanism of cellular toxicity (Table 4).

Effects on p27 Degradation

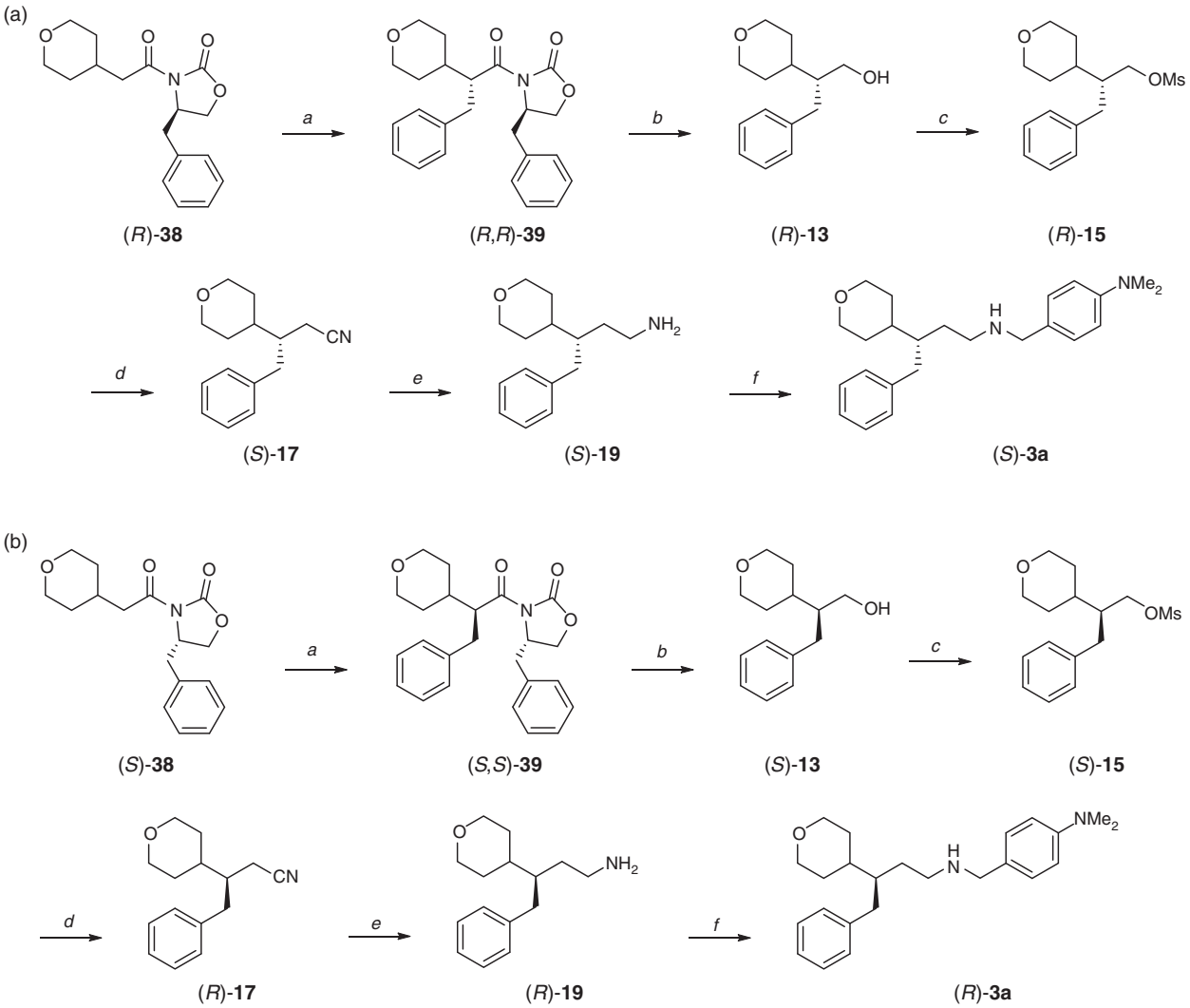
To explore whether the suppression of cell growth was related to the inhibition of p27 degradation, a HeLa cell-based assay was employed. By using a green fluorescent protein (GFP)-tagged constitutively degraded mutant of p27 as a reporter for SCF^{SKP2} activity, stabilisation of p27 was detected as an increase in green fluorescence. The percentage stabilisation of p27-GFP was calculated relative to the maximal effect of the proteasome inhibitor MG132 at 5 μM. Compounds were also re-analysed using an SRB cellular toxicity assay as the genetic manipulation used to create the HeLa-p27(T187D)-EGFP cells could have altered sensitivity, compared with the HeLa cell line (cf. Table 4). The HeLa-p27(T187D)-EGFP cell line was two-fold more sensitive to both (*S*)-**3a**- and (*R*)-**3a**-induced cellular toxicity; however, as in HeLa cells, the enantiomers were equipotent, both giving a GI_{50} of 16 μM (Table 5). Consistent with the proposed mechanism of action, (*S*)-**3a** and (*R*)-**3a** inhibited p27-GFP degradation with EC_{50} (concentration required to inhibit p27-GFP degradation by 50 %) values of 36 ± 3 and 61 ± 7 μM respectively, indicating some enantioselectivity (Table 5). However, further experiments are required to establish the relationship between cellular toxicity and inhibition of p27 degradation.

Conclusions

A modified synthesis of the first reported small-molecule inhibitor of the SCF^{SKP2} complex, **1a**, has been completed and growth-inhibitory activity has been confirmed in HeLa cells by SRB assay. Changes to the 4-(*N*,*N*-dimethylamino)benzyl substituent did not substantially affect potency. More lipophilic



Scheme 6. (*a*) $(MeO)_2(O)PCH_2CO_2Me$, NaH, THF, 0°C–room temperature (RT), 20 h, 88 %; (*b*) NH_4HCO_2, 10 % Pd/C, MeOH, 0–90°C, 90 min, 92 %; (*c*) $LiOH{\cdot}H_2O$, 50 % THF, H_2O, 60°C, 2 h, 94 %; (*d*) ^{t}BuCOCl, Et_3N, THF, 0°C, 45 min; (*R*)- or (*S*)-4-benzyloxazolidin-2-one, LiCl, THF, RT, 16 h, 66–73 %.



Scheme 7. (a) Synthesis of (*S*)-**3a**; (b) synthesis of (*R*)-**3a**; (*a*) $^i Pr_2NH$, *n*-BuLi, HMPA, THF, 0 to −78°C, 1 h; BnBr, THF, −78°C, 6 h, 79–81 %, >98 % de; (*b*) $LiBEt_3H$, Et_2O, −78°C–room temperature (RT), overnight, 41 %; (*c*) MsCl, $^i Pr_2NEt$, DCM, RT, 2 h, 96–97 %; (*d*) NaCN, DMF, 100°C, 7 h, 72–74 %; (*e*) $LiAlH_4$, THF, 0°C, 3 h, 44–47 %; (*f*) 4-(*N*,*N*-dimethylamino)benzaldehyde, $MgSO_4$, DCM, RT, 4 h; $NaBH_4$, MeOH, RT, 1 h, 16–65 %.

compounds were generally more potent, suggesting that cell permeability or hydrophobic interactions may influence the GI_{50} values obtained. Compound **3a** possessed equivalent growth-inhibitory activity as a racemate and as its separate enantiomers, which may indicate a non-specific mechanism of cellular toxicity. However, preliminary data with the enantiomers of compound **3a** demonstrated inhibition of the degradation of p27 in a cell-based assay in an enantioselective manner.

Table 4. HeLa cell-based assay inhibition data for compound 3a enantiomers
Rac-**3a** HeLa GI_{50}, 27 ± 4 μM

Compound	HeLa GI_{50} [μM][A]
(*S*)-**3a**	33 ± 4
(*R*)-**3a**	29 ± 2

[A] $n = 3$.

Table 5. HeLa-p27(T187D)-EGFP cell-based p27-GFP degradation inhibition and growth inhibition data for compound 3a enantiomers

Compound	HeLa-p27(T187D)-EGFP GI_{50} [μM][A]	HeLa-p27(T187D)-EGFP EC_{50} [μM][A]
(*S*)-**3a**	16 ± 2	36 ± 3
(*R*)-**3a**	16 ± 1	61 ± 7

[A] $n = 3$.

Experimental

Chemicals and Solvents

Chemicals were purchased from Sigma Aldrich Chemical Co., Alfa Aesar, Fluorochem, Apollo Scientific, Frontier Scientific, TCI UK, ChemBridge, and Acros Organics. Reactions were routinely performed under an atmosphere of nitrogen, employing anhydrous solvents, including dichloromethane (DCM), methanol, ethanol, DMF, diethyl ether, and THF purchased from Sigma Aldrich Chemical Co. in SureSeal bottles. Diisopropylamine (DIPA) was distilled before use over calcium hydride or potassium hydroxide, and *n*-butyllithium was titrated using a quantitative analytical solution purchased from Aldrich containing 1.0 M 2-propanol in toluene with 0.2 % 1,10-phenanthroline. Bottles of lithium aluminium hydride were purchased from Aldrich as a 2.0 M solution in anhydrous THF, and inspected by eye as being clear with little or no trace of sediment present before use. All hydrogenation reactions except transfer hydrogenations were performed in an 'H-cube' hydrogenation reactor supplied by ThalesNano Inc. using CatCarts® purchased from ThalesNano Inc.

Analytical Techniques

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) nuclear magnetic resonance (NMR) experiments were conducted on a Bruker Avance 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz, and ^{19}F at 470 MHz). Chemical shifts (δ) are quoted in parts per million (ppm), referenced to the appropriate deuterated solvent, and coupling constants (J) are quoted in hertz (Hz). The deuterated solvents used were [D]chloroform (99.8 atom-% D), [D4] methanol (99.8 atom-% D) or [D6]DMSO (99.9 atom-% D) purchased from Sigma Aldrich Chemical Co., unless otherwise specified. Multiplicities are given as: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of these and correspond to those observed in the spectrum rather than those predicted to be observed. Liquid chromatography–mass spectrometry (LC-MS) was conducted on a Waters Acquity UPLC system with photodiode array (PDA) and evaporative light scattering detection (ELSD), using an Acquity UPLC BEH C18 column measuring 1.7 μm, 2.1 × 50 mm. The mobile phase consisted of either 0.1 % v/v methanoic acid in water or 0.1 % v/v formic acid in acetonitrile. Gradients were measured over 2 min with a flow rate of 0.6 mL min^{-1} and an injection volume of 2 μL. Mass spectrometry was conducted using a Waters SQD with ESCi source in electrospray ionisation (ES) mode. Capillary voltage was 3 kV, cone voltage was 30 V, source temperature was 150°C, desolvation temperature was 450°C, desolvation gas was used at a rate of 800 L h^{-1}, and cone gas was used at a rate of 50 L h^{-1}. Analytical HPLC was used to provide an estimate of compound purity and was conducted on an Agilent 1200 HPLC system with a diode array detector (DAD) monitoring wavelengths at 210, 230, 254, 280, 310, and 340 nm. HPLC was performed on a 4.6 × 150-mm Waters XTerra RP18 5 μm column with a mobile phase consisting of either 0.1 % v/v aqueous ammonia in acetonitrile or 0.1 % v/v aqueous formic acid in acetonitrile. Gradient programs were run over 25 min (5–100 % acetonitrile) followed by column clean-up and equilibrium at a flow rate of 1.0 mL min^{-1}. An HPLC chromatogram in acidic and basic media was recorded for each compound that was screened and the lowest measured percentage purities are quoted. Chiral HPLC was used to provide an estimate of ee and was conducted on a Daicel Chiralpak AD-H 250 × 4.6 mm internal diameter, 5 μm (Chiral Technologies Europe, Illkirch, France).

Infrared spectra were recorded on a Bio-Rad FTS 3000MX Diamond ATR as a neat sample. Ultraviolet spectra were recorded in ethanol on a U-2800A spectrophotometer, using Hitachi *UV Solutions 2.0* software, in Hellma 100-QG 10-mm synthetic quartz glass cuvettes (matched pair). Optical rotations were recorded on a PolAAr 3001 automatic polarimeter from Optical Activity Ltd. High-resolution mass spectrometry (HRMS) was performed using a Finnigan MAT95 or MAT900 by the EPSRC National Mass Spectrometry Service Centre, Swansea University. Melting points were recorded on a Stuart SMP40 automatic melting point VWR® and are uncorrected.

Chromatography

Thin-layer chromatography (TLC) was conducted on Merck silica gel $60F_{254}$ and NH_2F_{254} on aluminium sheets. All sheets were dried after use and compounds visualised using short-wave (254 nm) and long-wave (365 nm) UV light and/or using an appropriate staining agent, including potassium permanganate, ninhydrin, and anisaldehyde. Column chromatography was carried out either under medium pressure using Davisil silica gel 40–63 μm 60 Å from Fisher Scientific or from Fluorochem or on a Biotage SP4 purification system using Agilent Si50 cartridges for normal-phase and Varian C18 superflash cartridges for reverse-phase. Semi-preparative HPLC was performed using an Agilent 1200 system equipped with preparative pumps, fraction collector, autosampler, and DAD, with an Agilent ChemStation data system. Samples were run on a 21.2 × 250-mm Phenomenex Luna 5-μm C8(2) column, with a mobile phase consisting of either: (A) 0.1 % v/v aqueous formic acid in acetonitrile or (B) 0.1 % v/v aqueous ammonia in acetonitrile, running at the specified flow rate.

General Procedure A

A solution of trimethyl phosphonoacetate (9.36 mmol) in THF (7 mL, 1.34 M) was added dropwise to sodium hydride (60 % in mineral oil, 9.75 mmol) suspended in THF (35 mL) at 0°C. After 40 min, the pyranone (7.80 mmol), in THF (7 mL, 1.11 M), was added dropwise and the flask was heated to 25°C. After 19 h, the mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). The precipitate was removed

by filtration and the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL) and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure B

The ester (7.06 mmol) was dissolved in methanol (7 mL, 1.0 M) and cooled to 0°C. Then 10 % Pd/C (2.12 mmol) was added, followed by methanol (55 mL). Ammonium formate (35.3 mmol) was added portion-wise and the flask was heated to 90°C. After 90 min, the mixture was cooled to room temperature and filtered through Celite. Concentration under vacuum gave the desired product, which was taken forward without further purification.

General Procedure C

Diisopropylamine (7.08 mmol) was dissolved in THF (4 mL, 1.8 M) and cooled to −78°C. *n*-Butyllithium (7.08 mmol) was added dropwise over 15 min. The flask was allowed to reach room temperature over 40 min and cooled to −78°C. The ester (6.44 mmol) was dissolved in THF (13 mL, 0.50 M) and added dropwise. The solution was stirred at −78°C for 90 min before dropwise addition of benzyl bromide (7.73 mmol) as a solution in THF (3 mL, 2.6 M), and warmed to 25°C. After 21 h, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl (10 mL) and the aqueous layers were extracted with EtOAc (10 mL). Organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure D

Lithium aluminium hydride (2.0 M in THF, 6.40 mmol) was added dropwise over 1 min to a solution of the ester (5.68 mmol) in THF (12 mL, 0.5 M) at 0°C. After 90 min, the solution was warmed to room temperature and quenched with saturated aqueous Rochelle salt (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to give the desired compound, which was taken forward without purification.

General Procedure E

Methanesulfonyl chloride (6.29 mmol) was added dropwise to a solution of the alcohol (5.72 mmol) and diisopropylethylamine (8.58 mmol) in DCM (20.5 mL) at 0°C and warmed to room temperature. After 90 min, the mixture was partitioned with distilled water (2 × 20 mL), 1 M HCl (2 × 10 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the desired compound, which was taken forward without purification.

General Procedure F

Sodium cyanide (6.06 mmol) was added to a solution of the sulfonate (5.51 mmol) in DMF (11.5 mL, 0.5 M) at room temperature and heated to 100°C. After 7 h, the mixture was cooled to room temperature and partitioned between diethyl ether (5 × 15 mL) and distilled water (10 mL). The organic layer was washed with distilled water (5 × 10 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure G

Lithium aluminium hydride (2.0 M in THF, 6.90 mmol) was added dropwise to a solution of the nitrile (4.93 mmol) in THF (24 mL, 0.20 M) at 0°C and stirred at room temperature. After 15 h, the mixture was quenched with distilled water (0.26 mL), 3 M sodium hydroxide (0.26 mL), and further distilled water (0.78 mL). The mixture was filtered through Celite, washing with DCM (20 mL), and concentrated under vacuum. The crude material was purified as indicated.

General Procedure H

The aldehyde (1.03 mmol) was added to a solution of the amine (0.86 mmol) and excess anhydrous magnesium sulfate in DCM (4.3 mL) and the mixture was stirred at room temperature. After 18 h, the reaction mixture was filtered, washing with DCM (20 mL), and concentrated under vacuum. The oil was dissolved in methanol (4.1 mL) before portion-wise addition of sodium borohydride (3.35 mmol). After 1 h, the mixture was quenched with distilled water (10 mL) and partitioned with EtOAc (2 × 20 mL). Organic fractions were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure I

The acyl or sulfonyl chloride (0.57 mmol) was added to a solution of the amine (0.34 mmol) and triethylamine or diisopropylethylamine (0.57 mmol) in DCM (2.0 mL) and stirred at room temperature. After 90 min, the mixture was partitioned with distilled water (10 mL) and DCM (3 × 10 mL). Organic layers were washed with 1 M HCl (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure J

The amine (0.78 mmol) was dissolved in methanol (15.6 mL) and hydrogenated in an H-cube hydrogen reactor at atmospheric temperature and pressure, flow rate 1 mL min^{-1}. After 3 h, the reaction mixture was concentrated under vacuum to afford the desired compound, which was taken forward without further purification.

General Procedure K

The aniline (0.30 mmol) was suspended in 5 M HCl (1.2 mL) in darkness and cooled to 0°C. Sodium nitrite (0.40 mmol) in distilled water (0.8 mL, 0.5 M) was added dropwise over 2 min. After 40 min, sodium azide (1.3 mmol) was carefully added and the mixture was stirred for 30 min, then allowed to reach room temperature. After 2 h, the mixture was diluted with distilled water (1 mL) and quenched with saturated aqueous sodium bicarbonate to pH 9. The mixture was partitioned using EtOAc (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure L

Formic acid (95 %, 0.74 mmol) was added to a solution of the amine (0.15 mmol) in ethanol (0.72 mL, 0.2 M) at 40°C and stirred for 30 min. Formaldehyde (37 %, 0.41 mmol) was added and the solution was stirred for 90 min before cooling to room temperature and quenching with 10 % sodium hydroxide (1 mL). The mixture was partitioned with DCM (3 × 10 mL) and

distilled water (10 mL). Organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure M

The aldehyde (23.4 mmol) was added to a solution of the amine hydrochloride (19.5 mmol), sodium acetate trihydrate (23.4 mmol), and excess anhydrous magnesium sulfate in THF (66 mL) and stirred at room temperature. After 24 h, the reaction mixture was filtered and concentrated under vacuum, then dissolved in ethanol (55 mL) and mixed carefully with sodium borohydride (58.5 mmol). After 30 min, the mixture was cooled to 0°C and quenched with ice-cooled distilled water (10 mL). The solution was concentrated to a small volume under vacuum and partitioned with diethyl ether (4 × 20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The oil was dissolved in DCM (50 mL), washed with saturated aqueous sodium bicarbonate (6 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. Boc_2O (14.4 mmol) was added to a solution of the oil in DCM (31.5 mL) at 0°C. After 1 h, the mixture was partitioned with distilled water (2 × 20 mL), washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure N

Isopropylmagnesium chloride (2.0 M in THF, 31.52 mmol) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (15.76 mmol) in THF (42 mL) at −20°C. After 20 min, the ester (3.94 mmol) was added and the mixture was stirred under nitrogen at −20°C. After 1 h, the mixture was quenched with saturated aqueous NH_4Cl (20 mL) and stirred at −20°C for 5 min. The mixture was partitioned between distilled water (10 mL) and diethyl ether (4 × 20 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to afford the desired compound, which was taken forward without purification.

General Procedure O

Lithium aluminium hydride (2.0 M in THF, 1.62 mmol) was added dropwise to a solution of the Weinreb amide (1.24 mmol) in THF (35 mmol) at 0°C. After 1 h, the mixture was quenched with sodium bisulfate (5.78 mmol) in distilled water (25 mL, 0.2 M) and warmed to room temperature. The mixture was partitioned with distilled water (20 mL) and EtOAc (2 × 10 mL). Organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure P

Morpholine (1.10 mmol) was added to a mixture of 1*H*-benzotriazole (1.82 mmol), the aldehyde (0.91 mmol), and 3-Å molecular sieves (600 mg) in DCM (3.8 mL) and stirred at room temperature. After 16 h, the reaction mixture was filtered and concentrated under vacuum, then partitioned with DCM (15 mL) and 2 M sodium hydroxide (2 × 10 mL), followed by distilled water (2 × 10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum, then dissolved in THF (5.5 mL) and cooled to 0°C. Benzylmagnesium chloride (2.0 M in THF, 1.82 mmol) was added dropwise and the mixture was warmed to room temperature. After 24 h, the mixture was partitioned with 2 M sodium hydroxide (2 × 10 mL) and distilled water (3 × 10 mL). The aqueous layer was extracted with diethyl ether (2 × 10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure Q

Trifluoroacetic acid (0.7 mL) was added to a solution of the carbamate (0.21 mmol) in DCM (0.7 mL, 0.3 M) and stirred at room temperature. After 1 h, the mixture was concentrated under vacuum and quenched with saturated aqueous $NaHCO_3$ (10 mL). The solution was partitioned with EtOAc (2 × 10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford the desired compound.

General Procedure R

The amine (5.53 mmol) was added to a solution of Boc_2O (6.08 mmol) in DCM (12 mL, 0.5 M) at 0°C and stirred for 5 min before warming to room temperature. After 1 h, the mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and DCM (3 × 10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure S

Lithium hydroxide monohydrate (151.7 mmol), as a solution in distilled water (79.5 mL, 1.9 M), was added to a solution of the ester (7.59 mmol) in THF (79.5 mL, 0.1 M) at room temperature in air and stirred at 60°C for 90 min. The mixture was cooled to room temperature, acidified to pH 0 with 1 M HCl and partitioned with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (20 mL) and the organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to give the desired compound, which was taken forward without purification.

General Procedure T

Triethylamine (14.84 mmol) was added to a solution of the carboxylic acid (7.42 mmol) in THF (31.0 mL, 0.2 M) at room temperature, stirred for 10 min, and then cooled to 0°C before addition of pivaloyl chloride (8.90 mmol). After 30 min at 0°C, lithium chloride (0.5 M in THF, 8.90 mmol) was added, followed by (*R*)-(+)- or (*S*)-(−)-4-benzyloxazolidin-2-one (8.90 mmol) and the mixture was stirred at room temperature for 20 h. The mixture was partitioned with EtOAc (20 mL) and 1 M HCl (3 × 20 mL) and the organic layer was washed with 1 M K_2CO_3 (3 × 20 mL). The acidic aqueous layer was extracted with EtOAc (20 mL) and the combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

General Procedure U

Lithium triethylborohydride (1.0 M in THF, 20.0 mmol) was added dropwise over 1–2 min to a solution of the oxazolidin-2-one (4.00 mmol) in diethyl ether (28 mL, 0.2 M) at −78°C and stirred overnight, allowing the mixture to reach room temperature. Saturated aqueous NH_4Cl (10 mL) was added dropwise at room temperature, followed by 3 M sodium hydroxide (20 mL),

and the layers were separated. The organic layer was washed with 3 M sodium hydroxide (10 mL) and distilled water (10 mL), and the aqueous layer was extracted with diethyl ether (10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude material was purified as indicated.

(E)- and (Z)-Methyl-2-(2,2-dimethyldihydro-2H-pyran-4-(3H)-ylidene) Acetate **6**[8,21]

General procedure A: using pyranone **4** (600 mg, 4.68 mmol) and trimethyl phosphonoacetate (0.91 mL, 1.02 g, 5.62 mmol), chromatography (silica, 20 % EtOAc/petrol) eluted **6** as a yellow oil (707 mg, 80 %, *E* : *Z* ratio 3 : 2); R_f 0.23 (silica, 5 % EtOAc/petrol). λ_{max}/nm (EtOH) 228.0. ν_{max}/cm^{-1} 2974 (C–H), 2950 (C–H), 2871 (C–H), 1715 (C=O), 1653, 1435, 1367, 1245, 1183, 1149, 1127, 1080, 1049, 1024, 847, 756. δ_H (500 MHz, $CDCl_3$) 1.21 (6H, s, *gem*-CH_3 (*E*)), 1.23 (4H, s *gem*-CH_3 (*Z*)), 2.19 (2H, s, Alk–H (*E*)), 2.25–2.27 (1.4H, m, Alk–H (*Z*)), 2.88 (1.4H, s, Alk–H (*Z*)), 2.93–2.96 (2H, m, Alk–H (*E*)), 3.69 (2H, s, CO_2CH_3 (*Z*)), 3.70 (3H, s, CO_2CH_3 (*E*)), 3.76–3.78 (2H, t, CH_2–O, (*E*), *J* 5.8), 3.80–3.82 (1.4H, t, CH_2–O, (*Z*), *J* 5.8), 5.65 (1H, s, C*H*CO_2Me, (*E*)), 5.77 (0.66H, m, C*H*CO_2Me, (*Z*)). δ_C (125 MHz, $CDCl_3$) 26.4, 26.5, 30.3, 37.2, 41.4, 48.3, 50.9, 51.0, 61.8, 62.5, 74.1, 74.3, 115.1, 115.2, 157.2, 157.4, 166.8 (2 peaks). *m*/*z* (LC-MS ESI+) 185.1 $[M + H]^+$; *m*/*z* (HRMS) 185.1170; calc. for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.1172.

Methyl 2-(Dihydro-2H-pyran-4-(3H)-ylidene) Acetate **7**

General procedure A: using pyranone **5** (1.00 g, 7.80 mmol) and trimethyl phosphonoacetate (1.52 mL, 1.70 g, 9.36 mmol), chromatography (silica, 5–50 % Et_2O/DCM) afforded **7** as a yellow oil (1.268 g, 88 %); R_f 0.75 (silica, 33 % EtOAc/hexane). λ_{max}/nm (EtOH) 225.5. ν_{max}/cm^{-1} 2953 (C–H), 2847 (C–H), 1712 (C=O), 1652, 1435, 1387, 1250, 1201, 1174, 1147, 1096, 1029, 987, 852, 683. δ_H (500 MHz, $CDCl_3$) 2.31–2.34 (2H, m, CH_2), 2.99–3.01 (2H, m, CH_2), 3.69 (3H, s, CH_3), 3.72–3.74 (2H, t, CH_2–O, *J* 5.6), 3.75–3.77 (2H, t, CH_2–O, *J* 5.5), 5.68 (1H, m, C*H*CO_2Me). δ_C (125 MHz, $CDCl_3$) 31.1, 37.5, 51.0, 68.5, 69.1, 114.1, 157.6, 166.8. *m*/*z* (LC-MS ESI+) 157.2 $[M + H]^+$.

(E)-Ethyl 2-Methyl-3-phenylacrylate **28**

General procedure A: using benzaldehyde (**27**) (0.67 mL, 700 mg, 6.60 mmol) and triethyl-2-phosphonopropionate (1.70 mL, 1.89 g, 7.92 mmol) at 40°C, chromatography (silica, 5 % EtOAc/hexane) afforded **28** as a pale yellow oil (417 mg, 33 %); R_f 0.33 (silica, 5 % EtOAc/hexane). λ_{max}/nm (EtOH) 268.0. ν_{max}/cm^{-1} 2937 (C–H), 1704 (C=O), 1635, 1447, 1366, 1248, 1200, 1110, 1032, 763, 703. δ_H (500 MHz, $CDCl_3$) 1.34–1.37 (3H, t, $CO_2CH_2CH_3$, *J* 7.2), 2.12 (3H, d, CH_3CCO_2Et, *J* 1.5), 4.26–4.30 (2H, q, $CO_2CH_2CH_3$, *J* 7.1), 7.30–7.35 (1H, m, Ar–H), 7.37–7.41 (4H, m, Ar–H), 7.69 (1H, m, CH=C). δ_C (125 MHz, $CDCl_3$) 14.1, 14.4, 60.9, 128.3, 128.4, 128.7, 129.6, 136.0, 138.7, 168.7. *m*/*z* (LC-MS ESI+) 191.2 $[M + H]^+$.

Methyl-2-(2,2-dimethyltetrahydro-2H-pyran-4-yl) Acetate **8**[8,21]

General procedure B: using ester **6** (700 mg, 3.80 mmol, *E* : *Z* ratio 3 : 2), partitioning with distilled water (10 mL) and EtOAc (2 × 10 mL), washing with brine (10 mL), drying ($MgSO_4$), filtration, and concentration under vacuum afforded **8** as a yellow oil (646 mg, 90 %); R_f 0.28 (silica, 10 % EtOAc/petrol). λ_{max}/nm (EtOH) no distinguishable peak. ν_{max}/cm^{-1} 2973 (C–H), 2926 (C–H), 2859 (C–H), 1736 (C=O), 1437, 1366, 1283, 1259, 1196, 1167, 1139, 1087, 1057, 1001, 691, 916, 856, 734. δ_H (500 MHz, $CDCl_3$) 1.09–1.14 (1H, t, CH, *J* 12.4), 1.16–1.19 (1H, m, Alk–H), 1.20 (3H, s, Alk-CH_3), 1.22 (3H, s, Alk-CH_3), 1.54–1.62 (2H, m, Alk–H), 2.16–2.21 (3H, m, C*H*CH_2CO_2Me), 3.64–3.69 (1H, td, CH_2–O, *J* 2.4 and 12.1), 3.67 (3H, s, CO_2CH_3), 3.72 (1H, qd, CH_2–O, *J* 1.6 and 5.3). δ_C (125 MHz, $CDCl_3$) 21.8, 28.6, 31.6, 32.4, 41.6, 43.1, 51.5, 61.3, 71.6, 172.9. *m*/*z* (LC-MS ESI+) molecular ion not found; *m*/*z* (HRMS) 187.1329; calc. for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.1329.

Methyl 2-(Tetrahydro-2H-pyran-4-yl) Acetate **9**

General procedure B: using ester **7** (1.30 g, 7.06 mmol), filtering through Celite, washing with EtOAc (2 × 10 mL), and concentration under vacuum afforded **9** as a yellow oil (1.212 g, 92 %); R_f spot not observed by UV or stains. λ_{max}/nm (EtOH) no distinguishable peak. ν_{max}/cm^{-1} 2920 (C–H), 2842 (C–H), 1733 (C=O), 1437, 1363, 1271, 1244, 1168, 1136, 1092, 1015, 984, 854, 814, 701. δ_H (500 MHz, $CDCl_3$) 1.28–1.37 (2H, m, CH_2), 1.60–1.64 (2H, m, CH_2), 1.96–2.05 (1H, m, CH), 2.23–2.25 (2H, d, C*H*$_2CO_2$Me, *J* 7.1), 3.36–3.41 (2H, td, CH_2–O, *J* 11.8 and 2.2), 3.66 (3H, s, CO_2CH_3), 3.91–3.94 (2H, m, CH_2–O). δ_C (125 MHz, $CDCl_3$) 32.2, 32.7, 41.2, 51.5, 67.7, 172.8. *m*/*z* (LC-MS ESI+) 159.1 $[M + H]^+$; *m*/*z* (HRMS) 159.1013; calc. for $C_8H_{15}O_3$ $[M + H]^+$ 159.1016.

Ethyl 2-Methyl-3-phenylpropanoate **29**

General procedure B: using (*E*)-ester **28** (400 mg, 2.10 mmol), partitioning with distilled water (10 mL) and EtOAc (2 × 10 mL), washing with brine (10 mL), drying ($MgSO_4$), filtration, and concentration under vacuum afforded **29** as a pale-yellow oil (375 mg, 93 %); R_f no spot seen by UV or stains. λ_{max}/nm (EtOH) 258.5. ν_{max}/cm^{-1} 2978 (C–H), 2937 (C–H), 1730 (C=O), 1454, 1376, 1283, 1251, 1163, 1117, 1029, 744, 699. δ_H (500 MHz, $CDCl_3$) 1.15–1.16 (3H, d, C*H*$_3$CHCO$_2$Et, *J* 6.8), 1.17–1.20 (3H, t, $CO_2CH_2CH_3$, *J* 7.2), 2.64–2.76 (2H, m, CH and PhC*H*$_2$), 3.00–3.04 (1H, dd, PhC*H*$_2$, *J* 6.6 and 13.0), 4.07–4.11 (2H, q, $CO_2CH_2CH_3$, *J* 7.2), 7.16–7.21 (3H, m, Ar–H), 7.26–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 14.2, 16.8, 39.8, 41.5, 60.3, 126.3, 128.3, 129.0, 139.5, 176.2. *m*/*z* (LC-MS ESI+) 193.2 $[M + H]^+$; *m*/*z* (HRMS) 193.1223; calc. for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1223.

Methyl 2-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)-3-phenylpropanoate **10**[8,21]

General procedure C: using ester **8** (640 mg, 3.44 mmol) and benzyl bromide (491 µL, 706 mg, 4.13 mmol), chromatography (silica, 5–15 % EtOAc/petrol) gave **10** as a pale-yellow solid (1.18 g, 86 %); R_f 0.30 (silica, 10 % EtOAc/petrol). Mp 56–62°C. λ_{max}/nm (EtOH) 206.0. ν_{max}/cm^{-1} 2934 (C–H), 2859 (C–H), 1732 (C=O), 1603, 1496, 1366, 1202, 1162, 1089, 1031, 960, 840, 745, 699. δ_H (500 MHz, $CDCl_3$) 1.18–1.25 (8H, m, *gem*-CH_3 and Alk–H), 1.30–1.39 (1H, m, Alk–H), 1.43–1.49 (1H, m, Alk–H), 1.68–1.72 (1H, m, Alk–H), 1.98–2.06 (1H, m, Alk–H), 2.43–2.49 (1H, m, Alk–H), 2.78–2.85 (1H, m, PhC*H*$_2$), 2.88–2.93 (1H, m, PhC*H*$_2$), 3.51–3.52 (3H, s CO_2CH_3), 3.61–3.69 (1H, m, CH_2–O), 3.72–3.80 (1H, m, CH_2–O), 7.12–7.14 (2H, d, Ar–H, *J* 7.3), 7.17–7.20 (1H, t, Ar–H, *J* 7.4), 7.24–7.27 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 21.9, 30.4, 30.5, 31.7, 31.9, 33.9, 34.1, 35.5, 41.1, 51.2, 53.9, 54.1, 61.3, 61.4, 71.6, 71.7, 126.3, 128.4, 128.7, 139.3, 174.9. *m*/*z* (LC-MS

ESI+) 277.3 $[M+H]^+$; *m/z* (HRMS) 277.1797; calc. for $C_{17}H_{25}O_3$ $[M+H]^+$ 277.1798.

Methyl 3-Phenyl-2-(tetrahydro-2H-pyran-4-yl) propanoate ***11***

General procedure C: using ester **9** (1.20 g, 6.44 mmol) and benzyl bromide (0.92 mL, 1.32 g, 7.73 mmol), chromatography (silica, 0–20 % Et_2O/hexane) afforded **11** as a pale-yellow oil (1.576 g, 89 %); R_f 0.57 (silica, 33 % EtOAc/hexane). λ_{max}/nm (EtOH) 258.5. ν_{max}/cm^{-1} 2949 (C–H), 2842 (C–H), 1730 (C=O), 1496, 1441, 1365, 1236, 1161, 1092, 1017, 985, 882, 842, 745, 699. δ_H (500 MHz, $CDCl_3$) 1.41–1.54 (3H, m, Alk–H), 1.73–1.77 (1H, m, Alk–H), 1.82–1.90 (1H, m, Alk–H), 2.51–2.56 (1H, m, Alk–H), 2.81–2.86 (1H, dd, Alk–H, *J* 10.5 and 13.5), 2.89–2.92 (1H, dd, Alk–H, *J* 5.0 and 13.6), 3.34–3.42 (2H, m, CH_2–O), 3.52 (3H, s, OMe), 3.96–4.02 (2H, m, CH_2–O), 7.13–7.14 (2H, d, Ar–H, *J* 7.3), 7.17–7.20 (1H, t, Ar–H, *J* 7.4), 7.25–7.28 (2H, t, Ar–H, *J* 7.4). δ_C (125 MHz, $CDCl_3$) 30.7, 30.9, 35.4, 37.7, 51.2, 53.7, 67.9, 126.4, 128.4, 128.7, 139.3, 174.8. *m/z* (LC-MS ESI+) 249.3 $[M+H]^+$. Analytical HPLC: 98.8 %.

*(R,R)- and (S,S)-4-Benzyl-3-(3-phenyl-2-(tetrahydropyran-4-yl)propanoyl)oxazolidin-2-one (R,R)-**39** and (S,S)-**39***

General procedure C: using (*R*)- or (*S*)-oxazolidin-2-one (*R*)-**38** (1.70 g, 5.60 mmol) or (*S*)-**38** (1.54 g, 5.08 mmol), deprotonation was achieved using DIPA (1.1 equiv.) and *n*-butyllithium (1.1 equiv.) in THF (15.5 mL) and HMPA (1.75 equiv.) before addition of benzyl bromide (4.0 equiv.). Partitioning with diethyl ether (20 mL) and 0.5 M HCl (20 mL) and washing the organic layer with 1 M HCl (3 × 10 mL) allowed the isolation of (*R*,*R*)-diastereomer (*R*,*R*)-**39** and (*S*,*S*)-diastereomer (*S*,*S*)-**39** as white solids following filtration (1.87 g, ≥96 % de, 81 %, and 1.59 g, ≥98 % de, 79 % respectively); R_f 0.14 (silica, 50 % EtOAc/petrol). Mp 153–156°C. $[\alpha]_D^{24.3}$ −38.1° (*R*,*R*) (*c* 0.10 in THF); $[\alpha]_D^{24.1}$ +29.5° (*S*,*S*) (*c* 0.10 in THF). λ_{max}/nm (EtOH) 206.2. ν_{max}/cm^{-1} 2942 (C–H), 2835 (C–H), 1758 (C=O), 1691 (C=O), 1494, 1454, 1395, 1350, 1224 (C–O), 1188, 1089, 1015, 996, 951, 868, 747, 701. δ_H (500 MHz, [D6]DMSO) 1.32–1.40 (1H, qd, OCH_2CH_2CH, *J* 4.4 and 12.4), 1.42–1.53 (2H, m, OCH_2CH_2CH), 1.67–1.69 (1H, m, OCH_2CH_2CH), 1.85–1.91 (1H, m, OCH_2CH_2CH), 2.42–2.46 (1H, dd, $PhCH_2$, *J* 7.0 and 13.6), 2.61–2.65 (1H, dd, $PhCH_2$, *J* 3.3 and 13.7), 2.88–2.98 (2H, m, $PhCH_2$), 3.23–3.31 (2H, m, O–CH_2), 3.84–3.90 (2H, m, O–CH_2), 4.01–4.04 (1H, dd, CHCO, *J* 2.5 and 8.9), 4.19–4.27 (2H, m, CH_2OCON), 4.62–4.66 (1H, CHN), 6.69–6.70 (2H, d, Ar–H, *J* 6.9), 7.11–7.25 (6H, m, Ar–H), 7.30–7.33 (2H, t, Ar–H, *J* 7.5). δ_C (125 MHz, [D6]DMSO) 29.4, 30.1, 34.1, 36.0, 37.8, 48.6, 54.1, 65.3, 67.0, 126.2, 126.7, 128.3, 128.4, 129.2, 129.3, 135.1, 139.5, 153.0, 173.8. *m/z* (LC-MS ESI+) 394.5 $[M+H]^+$; *m/z* (HRMS) 394.2014; calc. for $C_{24}H_{28}O_4N$ $[M+H]^+$ 394.2013.

2-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)-3-phenylpropan-1-ol ***12***[8,21]

General procedure D: using ester **10** (850 mg, 3.08 mmol), partitioning with EtOAc (2 × 10 mL), washing with brine (10 mL), drying ($MgSO_4$), filtering, and concentrating under vacuum afforded **12** as a yellow oil (787 mg, 93 %); R_f 0.45 (silica, 40 % EtOAc/petrol). λ_{max}/nm (EtOH) 207.0. ν_{max}/cm^{-1} 3392 (O–H), 2933 (C–H), 2845 (C–H), 1495, 1454, 1388, 1244, 1142, 1087, 1031, 921, 870, 838, 742, 699. δ_H (500 MHz, $CDCl_3$) 1.06–1.08 (1H, t, Alk–H, *J* 5.3), 1.20–1.21 (3H, s, Alk-CH_3), 1.24–1.25 (3H, s, Alk-CH_3), 1.25–1.30 (1H, m, Alk–H), 1.32–1.40 (1H, m, Alk–H), 1.56–1.65 (3H, m, Alk–H), 1.90–1.98 (1H, m, OH), 2.50–2.57 (1H, m, $PhCH_2$), 2.74–2.81 (1H, m, $PhCH_2$), 3.50–3.56 (1H, m, CH_2–OH), 3.56–3.61 (1H, m, CH_2–OH), 3.62–3.69 (1H, m, CH_2–O), 3.76–3.80 (1H, m, CH_2–O), 7.18–7.21 (3H, m, Ar–H), 7.27–7.30 (2H, t, Ar–H, *J* 7.4). δ_C (125 MHz, $CDCl_3$) 30.3, 34.3, 35.7, 47.6, 61.8, 68.4, 126.0, 128.5, 129.1, 141.0. *m/z* (LC-MS ESI+) molecular ion not found; *m/z* (HRMS) 249.1851; calc. for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.1849.

(rac)-3-Phenyl-2-(tetrahydro-2H-pyran-4-yl)propan-1-ol ***13***

General procedure D: using ester **11** (1.57 g, 5.68 mmol), partitioning with EtOAc (2 × 20 mL), washing with brine (20 mL), drying ($MgSO_4$), filtering, and concentrating under vacuum afforded **12** as a yellow oil (1.42 g, 100 %); R_f 0.33 (silica, 50 % EtOAc/hexane). λ_{max}/nm (EtOH) 259.5. ν_{max}/cm^{-1} 3427 (O–H), 2932 (C–H), 2845 (C–H), 1602, 1495, 1454, 1387, 1267, 1244, 1142, 1087, 1031, 1016, 995, 980, 921, 870, 838, 742, 699. δ_H (500 MHz, $CDCl_3$) 1.13–1.15 (1H, t, CH, *J* 5.1), 1.46–1.55 (2H, m, CH_2), 1.63–1.68 (3H, m, CH_2 and OH), 1.74–1.81 (1H, m, CH), 2.52–2.57 (1H, dd, Ph–CH_2, *J* 9.5 and 13.6), 2.76–2.80 (1H, dd, Ph–CH_2, *J* 5.1 and 13.6), 3.36–3.41 (2H, m, CH_2–O), 3.52–3.62 (2H, m, CH_2–OH), 3.99–4.02 (2H, m, CH_2–O), 7.18–7.21 (3H, m, Ar–H), 7.27–7.30 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 30.3, 30.4, 34.3, 35.7, 47.6, 61.8, 68.4, 126.0, 128.5, 129.0, 141.0. *m/z* (LC-MS ESI+) 221.3 $[M+H]^+$; *m/z* (HRMS) 221.1536; calc. for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1536.

2-Methyl-3-phenylpropan-1-ol ***30***

General procedure D: using ester **29** (440 mg, 2.47 mmol), partitioning with EtOAc (2 × 10 mL), washing with brine (10 mL), drying ($MgSO_4$), filtering, and concentrating under vacuum afforded **30** as a yellow oil (339 mg, 87 %); R_f 0.27 (silica, 20 % EtOAc/hexane). λ_{max}/nm (EtOH) 209.0. ν_{max}/cm^{-1} 3330 (O–H), 2955 (C–H), 2919 (C–H), 1495, 1453, 1030, 986, 738, 698. δ_H (500 MHz, $CDCl_3$) 0.92–0.93 (3H, d, CH_3, *J* 6.7), 1.35 (1H, s, br, OH), 1.91–2.00 (1H, m, CH), 2.41–2.45 (1H, dd, $PhCH_2$, *J* 8.0 and 13.5), 2.74–2.78 (1H, dd, $PhCH_2$, *J* 6.4 and 13.5), 3.47–3.50 (1H, dd, CH_2OH, *J* 6.0 and 10.6), 3.53–3.56 (1H, dd, CH_2OH, *J* 5.9 and 10.5), 7.17–7.21 (3H, m, Ar–H), 7.27–7.30 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 16.5, 37.8, 39.7, 67.7, 125.9, 128.3, 129.2, 140.6. *m/z* (LC-MS ESI+) 151.2 $[M+H]^+$; *m/z* (HRMS) 151.1113; calc. for $C_{10}H_{15}O$ $[M+H]^+$ 151.1117.

2-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)-3-phenylpropyl Methanesulfonate ***14***[8,21]

General procedure E: using alcohol **12** (760 mg, 3.06 mmol), partitioning with distilled water (2 × 10 mL) and 1 M HCl (2 × 10 mL), washing with brine (10 mL), drying ($MgSO_4$), filtering, and concentration under vacuum afforded **14** as a brown solid (1.01 g, 96 %); R_f 0.32 (silica, 30 % EtOAc/petrol). Mp 66–68°C. λ_{max}/nm (EtOH) 205.5. ν_{max}/cm^{-1} 3018 (C–H), 2900 (C–H), 2841 (C–H), 1602, 1468, 1345, 1248, 1173, 1089, 973, 925, 821, 747, 699. δ_H (500 MHz, $CDCl_3$) 1.20–1.21 (3H, s, Alk-CH_3), 1.24–1.27 (4H, m, Alk-CH_3 and Alk–H), 1.31–1.40 (1H, m, Alk–H), 1.60–1.69 (2H, m, Alk–H), 1.77–1.84 (1H, m, Alk–H), 1.90–1.97 (1H, m, Alk–H), 2.48–2.58 (1H, dd, $PhCH_2$, *J* 10.2 and 13.8), 2.84–2.89 (1H, dd, $PhCH_2$, *J* 4.8 and 12.3), 2.90–2.91 (3H, s, SO_2CH_3), 3.63–3.69 (1H, m, CH_2–O), 3.77–3.81 (1H, m, CH_2–O), 4.03–4.07 (1H, m, CH_2–OMs

(Ms = methanesulfonate)), 4.13–4.16 (1H, m, CH_2–OMs), 7.16–7.17 (2H, d, Ar–H, *J* 7.4), 7.21–7.23 (1H, t, Ar–H, *J* 7.4), 7.29–7.32 (2H, t, Ar–H, *J* 7.3). δ_C (125 MHz, $CDCl_3$) 30.2, 30.3, 33.9, 35.6, 37.0, 45.0, 68.1, 68.7, 126.5, 128.7, 129.0, 139.6. *m/z* (LC-MS ESI+) 299.2 $[M+H]^+$; *m/z* (HRMS) molecular ion not observed.

*3-Phenyl-2-(tetrahydro-2*H*-pyran-4-yl) propylmethanesulfonate* ***15***

General procedure E: using alcohol **13** (1.42 g, 5.72 mmol), partitioning with distilled water (2 × 20 mL) and 1 M HCl (2 × 10 mL), washing with brine (20 mL), drying ($MgSO_4$), filtering, and concentration under vacuum afforded **15** as a brown solid (1.82 g, 97 %); R_f 0.38 (silica, 50 % EtOAc/hexane). Mp 66–68°C λ_{max}/nm (EtOH) 258.5. ν_{max}/cm^{-1} 3017 (C–H), 2899 (C–H), 2841 (C–H), 1467, 1344, 1248, 1173, 1136, 1089, 974, 924, 820, 747, 699. δ_H (500 MHz, $CDCl_3$) 1.43–1.54 (2H, m, Alk–H), 1.65–1.73 (2H, m, Alk–H), 1.75–1.89 (2H, m, Alk–H), 2.51–2.56 (1H, dd, PhCH_2, *J* 9.8 and 13.8), 2.86–2.90 (1H, dd, PhCH_2, *J* 5.1 and 14.2) 2.91 (3H, s, CH_3), 3.37–3.42 (2H, m, CH_2–O), 4.01–4.03 (2H, m, CH_2–O), 4.04–4.07 (1H, dd, CH_2–OSO_2Me, *J* 4.7 and 9.9), 4.14–4.17 (1H, dd, CH_2–OSO_2Me, *J* 4.2 and 9.8), 7.16–7.18 (2H, m, Ar–H), 7.21–7.24 (1H, m, Ar–H), 7.29–7.32 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 30.2, 30.3, 33.9, 35.6, 37.0, 45.0, 68.1, 68.7, 126.5, 128.7, 129.0, 139.5. *m/z* (LC-MS ESI+) 299.3 $[M+H]^+$; *m/z* (HRMS) molecular ion not observed.

2-Methyl-3-phenylpropyl Methanesulfonate ***31***

General procedure E: using alcohol **30** (330 mg, 2.20 mmol), partitioning with distilled water (2 × 10 mL) and 1 M HCl (2 × 10 mL), washing with brine (10 mL), drying ($MgSO_4$), filtering, and concentration under vacuum afforded **31** as a brown oil (508 mg, 96 %); R_f 0.30 (silica, 20 % EtOAc/hexane). λ_{max}/nm (EtOH) no distinguishable peak. ν_{max}/cm^{-1} 3028 (C–H), 2968 (C–H), 1455, 1350, 1171, 959, 832, 740, 701. δ_H (500 MHz, $CDCl_3$) 1.00–1.01 (3H, d, CH_3, *J* 6.7), 2.16–2.25 (1H, octet, CH, *J* 6.6), 2.51–2.55 (1H, dd, $PhCH_2$, *J* 7.7 and 13.6), 2.73–2.78 (1H, dd, $PhCH_2$, *J* 6.7 and 13.6), 2.99 (3H, s, SO_2CH_3), 4.03–4.06 (1H, dd, CH_2OMs, *J* 5.9 and 9.4), 4.07–4.10 (1H, dd, CH_2OMs, *J* 5.6 and 9.5), 7.15–7.17 (2H, m, Ar–H), 7.20–7.23 (1H, m, Ar–H), 7.28–7.31 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 16.4, 35.0, 37.2, 39.2, 73.7, 126.4, 128.5, 129.1, 139.2. *m/z* (LC-MS ESI+) molecular ion peak not observed; HRMS molecular ion not observed.

*3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutanenitrile* ***16***[8,21]

General procedure F: using sulfonate **14** (1.00 g, 3.06 mmol), the mixture was partitioned with diethyl ether (10 mL) and saturated aqueous K_2CO_3 (40 mL) with brine (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the organic layer was washed with 50 % brine (6 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford **16** as a brown solid (652 mg, 83 %); R_f 0.40 (silica, 20 % EtOAc/petrol). Mp 62–64°C. λ_{max}/nm (EtOH) 207.0. ν_{max}/cm^{-1} 2945 (C–H), 2915 (C–H), 2855 (C–H), 2242 (C≡N), 1676, 1600, 1493, 1452, 1420, 1247, 1138, 1095, 1023, 984, 887, 855, 805, 748, 703. δ_H (500 MHz, $CDCl_3$) 1.21–1.27 (7H, m, Alk-CH_3 and Alk–H), 1.30–1.36 (1H, m, Alk–H), 1.58–1.65 (1H, m, CH), 1.70–1.76 (2H, m, Alk–H), 1.89–1.97 (1H, m, Alk–H), 2.16–2.22 (1H, dd, PhCH_2, *J* 5.5 and 17.1), 2.27–2.32 (1H, dd, PhCH_2, *J* 5.1 and 17.2), 2.44–2.52 (1H, dd, CH_2CN, *J* 10.6 and 13.8), 2.97–3.02 (1H, dd, CH_2CN, *J* 4.4 and 13.8), 3.66–3.72 (1H, td, CH_2–O, *J* 2.3 and 12.3), 3.79–3.83 (1H, m, CH_2–O), 7.17–7.18 (2H, d, Ar–H, *J* 7.3), 7.22–7.25 (1H, t, Ar–H, *J* 7.5), 7.30–7.33 (2H, m, Ar–H, *J* 7.2). δ_C (125 MHz, $CDCl_3$) 18.1, 30.2, 30.3, 36.4, 37.4, 42.6, 67.9, 118.5, 126.7, 128.8, 129.0, 139.1. *m/z* (LC-MS ESI+) 257.2 $[M+H]^+$; *m/z* (HRMS) molecular ion not observed.

*(*rac*)-4-Phenyl-3-(tetrahydro-2*H*-pyran-4-yl) butanenitrile* ***17***

General procedure F: using sulfonate **15** (1.80 g, 5.51 mmol), the mixture was partitioned with diethyl ether (10 mL) and saturated aqueous K_2CO_3 (40 mL) with brine (10 mL). The aqueous layer was extracted with diethyl ether (5 × 10 mL) and the organic layer was washed with distilled water (5 × 10 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford **17** as a brown solid, which could be taken forward without further purification (1.273 g, 90 %). Chromatography (silica, 10 % EtOAc/hexane) afforded **17** as a colourless oil; R_f 0.42 (silica, 33 % EtOAc/hexane). λ_{max}/nm (EtOH) 258.5. ν_{max}/cm^{-1} 2945 (C–H), 2916 (C–H), 2856 (C–H), 2242 (C≡N), 1600, 1493, 1452, 1420, 1247, 1139, 1095, 1024, 984, 887, 856, 748, 703. δ_H (500 MHz, $CDCl_3$) 1.41–1.52 (2H, quintet of doublets, Alk–H, *J* 4.6, 13.2, and 25.7), 1.66–1.69 (1H, m, Alk–H), 1.74–1.83 (3H, m, Alk–H), 2.17–2.22 (1H, dd, Alk–H, *J* 5.1 and 17.0), 2.29–2.33 (1H, dd, Alk–H, *J* 4.1 and 17.0), 2.46–2.51 (1H, dd, Alk–H, *J* 10.1 and 13.8), 2.99–3.02 (1H, dd, Alk–H, *J* 4.2 and 13.7), 3.40–3.45 (2H, m, CH_2–O), 4.02–4.06 (2H, m, CH_2–O), 7.17–7.19 (2H, m, Ar–H), 7.23–7.26 (1H, m, Ar–H), 7.31–7.34 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 18.1, 30.2, 30.3, 36.4, 37.5, 42.6, 67.9, 118.5, 126.7, 128.8, 129.0, 139.0. *m/z* (LC-MS ESI+) 230.3 $[M+H]^+$; *m/z* (HRMS) 230.1542; calc. for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1539. Analytical HPLC: 99.5 %.

*(*R*)- or (*S*)-4-Phenyl-3-(tetrahydro-2*H*-pyran-4-yl) butanenitrile (*R*)- and (*S*)-* ***17***

General procedure F: using either (*R*)- or (*S*)-mesylate (*R*)-**15** or (*S*)-**15** (569 mg, 1.91 mmol and 479 mg, 1.61 mmol respectively), chromatography (silica, 10–30 % EtOAc, hexane) afforded (*S*)- or (*R*)-**17** as colourless oils (316 mg, 72 % and 274 mg, 74 % respectively). Analytical data equivalent to (*rac*)-**17**; $[\alpha]_D^{22.1}$ −55.4° (*R*) (*c* 1.01 in EtOH), $[\alpha]_D^{22.5}$ +55.4° (*S*) (*c* 1.01 in EtOH).

3-Methyl-4-phenylbutanenitrile ***32***

General procedure F: using methanesulfonate **31** (500 mg, 2.19 mmol), the mixture was partitioned with diethyl ether (10 mL) and saturated aqueous K_2CO_3 (20 mL) with brine (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the organic layer was washed with 50 % brine (6 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford **32** as a brown oil (283 mg, 81 %); R_f 0.33 (silica, 10 % EtOAc/hexane). δ_H (500 MHz, $CDCl_3$) 1.12–1.13 (3H, d, CH_3, 6.7), 2.12–2.17 (1H, m, CH), 2.18–2.22 (1H, dd, PhCH_2, *J* 6.6 and 16.5), 2.27–2.32 (1H, dd, PhCH_2, *J* 4.9 and 16.2), 2.66–2.68 (2H, dd, CH_2CN, *J* 2.7 and 6.8), 7.16–7.18 (2H, m, Ar–H), 7.21–7.25 (1H, m, Ar–H), 7.28–7.33 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 19.5, 23.7, 32.5, 42.1, 118.7, 126.6, 128.6, 129.0, 139.0. *m/z* (LC-MS ESI+) 160.2 $[M+H]^+$; *m/z* (HRMS) 160.1119; calc. for $C_{11}H_{14}N$ $[M+H]^+$ 160.1121.

3-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)-4-phenylbutan-1-amine ***18***[8,21]

General procedure G: using nitrile **16** (1.27 g, 4.93 mmol), chromatography (silica, 0–30 % MeOH/DCM) afforded **18** as a yellow oil (1.07 g, 83 %); R_f 0.17 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 207.5. ν_{max}/cm^{-1} 3371 (N–H), 3290 (N–H), 2970 (C–H), 2927 (C–H), 2858 (C–H), 1583, 1494, 1453, 1364, 1285, 1203, 1084, 1014, 857, 737, 699. δ_H (500 MHz, $CDCl_3$) 1.15 (3H, s, CH_3), 1.22–1.25 (5H, m, CH_3 and Alk–H), 1.28–1.51 (6H, m, Alk–H), 1.53–1.60 (1H, m, Alk–H), 1.73–1.81 (1H, m, Alk–H), 2.37–2.47 (1H, dd, CH_2Ph, *J* 8.5 and 13.6), 2.57–2.67 (2H, m, CH_2CH$_2$NH$_2$), 2.70–2.74 (1H, dd, CH_2Ph, *J* 5.8 and 13.7), 3.60–3.65 (1H, td, CH_2–O, *J* 2.6 and 12.2), 3.73–3.79 (1H, m, CH_2–O), 7.13–7.15 (2H, d, Ar–H, *J* 7.3), 7.17–7.20 (1H, t, Ar–H, *J* 7.5), 7.26–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5, 29.8, 34.5, 37.4, 37.5, 40.6, 42.7, 68.5, 125.8, 128.3, 129.0, 141.5. *m/z* (LC-MS ESI+) 234.3 $[M+H]^+$; *m/z* (HRMS) 262.2164; calc. for $C_{17}H_{28}NO$ $[M+H]^+$ 262.2165.

*(*rac*)-4-Phenyl-3-(tetrahydro-2H-pyran-4-yl)butan-1-amine* ***19***

General procedure G: using nitrile **17** (100 mg, 0.435 mmol), chromatography (silica, 0–30 % MeOH/DCM) afforded **19** as a yellow oil (74 mg, 73 %); R_f 0.13 (silica, 20 % MeOH/DCM). λ_{max}/nm (EtOH) 259.5. ν_{max}/cm^{-1} 3385 (N–H), 3320 (N–H), 2929 (C–H), 2843 (C–H), 1601, 1494, 1453, 1387, 1243, 1090, 1014, 982, 841, 739, 699. δ_H (500 MHz, $CDCl_3$) 1.31–1.38 (4H, m, Alk–H), 1.44–1.64 (7H, m, Alk–H, NH_2 and H_2O), 2.41–2.46 (1H, dd, PhCH_2, *J* 7.8 and 13.6), 2.59–2.72 (3H, m, PhCH_2 and AlkCH_2NH$_2$), 3.30–3.37 (2H, m, CH_2–O), 3.97–4.02 (2H, m, CH_2–O), 7.14–7.15 (2H, m, Ar–H), 7.17–7.20 (1H, m, Ar–H), 7.26–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5, 29.8, 34.4, 37.4, 40.5, 42.7, 68.5, 125.8, 128.3, 129.0, 141.5. *m/z* (LC-MS ESI+) 234.3 $[M+H]^+$; *m/z* (HRMS) 234.1852; calc. for $C_{15}H_{23}NO$ $[M+H]^+$ 234.1852. Analytical HPLC: 93.3 %.

*(*R*)- or (*S*)-4-Phenyl-3-(tetrahydro-2H-pyran-4-yl)butan-1-amine (*R*)- and (*S*)-****19***

General procedure G: using either (*R*)- or (*S*)-nitrile (*R*)-**17** or (*S*)-**17** (264 mg, 1.15 mmol, and 316 mg, 1.38 mmol respectively), chromatography (silica, 10 % MeOH/EtOAc) afforded (*R*)- or (*S*)-**19** as yellow oils (132 mg, 47 %, and 148 mg, 44 % respectively). Analytical data equivalent to (*rac*)-**19**; $[\alpha]_D^{23.5}$ +9.6° (*R*) (*c* 1.02 in EtOH), $[\alpha]_D^{23.3}$ −9.0° (*S*) (*c* 1.03 in EtOH).

3-Methyl-4-phenylbutan-1-amine ***33***

General procedure G: using nitrile **32** (310 mg, 1.95 mmol), the crude material was partitioned with EtOAc (30 mL) and 1 M HCl (4 × 10 mL). Aqueous layers were neutralised with 2 M sodium hydroxide and partitioned with EtOAc (2 × 20 mL). Organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to give **33** as a yellow oil (145 mg, 43 %); R_f 0.10 (silica, 20 % MeOH/DCM). λ_{max}/nm (EtOH) 205.0. ν_{max}/cm^{-1} 3400 (N–H), 3282 (N–H), 2922 (C–H), 1668, 1603, 1494, 1454, 1377, 737, 699. δ_H (500 MHz, $CDCl_3$) 0.87–0.89 (3H, d, CH_3, *J* 6.7), 1.24–1.57 (4H, m, CHCH_2CH$_2$NH_2), 1.78–1.85 (1H, m, CH), 2.40–2.44 (1H, dd, PhCH_2, *J* 8.0 and 13.4), 2.59–2.63 (1H, dd, PhCH_2, *J* 6.5 and 13.4), 2.71–2.80 (2H, m, CH_2NH$_2$), 7.14–7.15 (2H, m, Ar–H), 7.16–7.19 (1H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 19.5, 32.8, 32.9, 33.2, 43.9, 125.7, 128.2, 129.2, 141.2. *m/z* (LC-MS ESI+) 164.2 $[M+H]^+$; *m/z* (HRMS) 164.1431; calc. for $C_{11}H_{18}N$ $[M+H]^+$ 164.1434.

*4-(((3-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylaniline* ***1a***[8,21]

General procedure H: using amine **18** (200 mg, 0.86 mmol) and 4-(*N,N*-dimethylamino)benzaldehyde (154 mg, 1.03 mmol), chromatography (silica, 20 % EtOAc/DCM, followed by 2 % $NH_{3(aq)}$/MeOH/DCM) afforded a yellow oil. The oil was partitioned between brine (10 mL) and DCM (3 × 10 mL), dried (Na_2SO_4), and concentrated under vacuum to give **1a** as a yellow oil (293 mg, 93 %); R_f 0.49 (silica, ~2 % $NH_{3(aq)}$/MeOH/DCM). λ_{max}/nm (EtOH) 263.0. ν_{max}/cm^{-1} 2926 (C–H), 2854 (C–H), 2801 (C–H), 1614, 1521, 1452, 1344, 1228, 1162, 1085, 946, 803, 737, 699. δ_H (500 MHz, $CDCl_3$) 1.11 (3H, s Alk-CH_3), 1.20 (3H, s Alk-CH_3), 1.22–1.29 (1H, m, Alk–H), 1.34–1.43 (2H, m, Alk–H), 1.43–1.50 (2H, m, Alk–H), 1.50–1.61 (2H, br, m, Alk–H), 1.67–1.80 (1H, m, Alk–H), 2.40 (1H, dd, Alk–H, *J* 8.3 and 13.6), 2.48–2.61 (2H, m, CH_2CH_2NH), 2.68 (1H, dd, *J* 5.4 and 13.6, Alk–H), 2.90–2.94 (6H, s, N(CH_3)$_2$), 3.56–3.63 (1H, m, Alk–H), 3.60–3.65 (2H, s, NHCH_2Ar), 3.69–3.74 (1H, m, Alk–H), 6.66–6.71 (2H, m, Ar–H), 7.09–7.15 (4H, m, Ar–H), 7.15–7.20 (1H, m, Ar–H), 7.23–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.6, 30.0, 31.9, 32.9, 33.1, 37.2, 39.5, 39.8, 40.7, 42.9, 43.0, 46.9, 53.0, 61.9, 71.8, 112.7, 125.8, 128.3, 129.1, 129.2, 141.5, 149.9. *m/z* (LC-MS ESI+) 395.2 $[M+H]^+$; *m/z* (HRMS) 395.3060; calc. for $C_{26}H_{39}N_2O$ $[M+H]^+$ 395.3057. Analytical HPLC: 95.2 %.

N-Benzyl-3-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-4-phenylbutan-1-amine ***1b***

General procedure H: using amine **18** (212 mg, 0.81 mmol) and benzaldehyde (0.10 mL, 0.10 g, 0.97 mmol), chromatography (silica, 20 % EtOAc/DCM followed by 2 % $NH_{3(aq)}$/MeOH) afforded **1b** as a yellow oil (171 mg, 60 %); R_f 0.39 (silica, 5 % $NH_{3(aq)}$/MeOH/DCM). ν_{max}/cm^{-1} 3025 (C–H), 2970 (C–H), 2927 (C–H), 2855 (C–H), 1602, 1494, 1453, 1364, 1285, 1202, 1085, 1029, 963, 909, 857, 733, 697. δ_H (500 MHz, $CDCl_3$) 1.12 (3H, s, Alk-CH_3), 1.21 (3H, s, Alk-CH_3), 1.23–1.29 (2H, m, Alk–H), 1.34–1.62 (6H, m, Alk–H), 1.70–1.79 (1H, m, NH), 2.35–2.46 (1H, dd, Alk–H, *J* 8.2 and 13.7), 2.50–2.61 (2H, m, CH_2CH_2NH), 2.63–2.73 (1H, dd, Alk–H, *J* 5.6 and 13.7), 3.58–3.63 (1H, m, Alk–H), 3.71 (2H, s, NHCH_2Ar), 3.75–3.78 (1H, m, Alk–H), 7.12 (2H, d, Ar–H, *J* 8.2), 7.16–7.19 (1H, m, Ar–H), 7.23–7.32 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.7, 30.3, 31.9, 33.0, 33.2, 37.2, 37.3, 39.5, 39.8, 42.8, 43.0, 47.4, 53.8, 61.9, 71.8, 125.8, 127.0, 128.2, 128.3, 128.4, 129.1, 141.0. *m/z* (LC-MS ESI+) 352.2 $[M+H]^+$; *m/z* (HRMS) 352.2626; calc. for $C_{24}H_{34}NO$ $[M+H]^+$ 352.2635. Analytical HPLC: 95.7 %.

*3-(((3-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylaniline* ***1c***

General procedure H: using amine **18** (100 mg, 0.38 mmol) and 3-(*N,N*-dimethylamino)benzaldehyde (69 mg, 0.46 mmol), chromatography (silica, 20 % EtOAc/DCM followed by 10 % MeOH/DCM) afforded **1c** as a yellow oil (71 mg, 53 %); R_f 0.40 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 302.5, 256.0. ν_{max}/cm^{-1} 2970 (C–H), 2927 (C–H), 2856 (C–H), 2804 (C–H), 1602, 1495, 1453, 1363, 1230, 1204, 1116, 1085, 997, 961, 857, 738, 697. δ_H (500 MHz, $CDCl_3$) 1.11–1.13 (3H, s, Alk-CH_3), 1.21–1.22 (3H, s, Alk-CH_3), 1.23–1.29 (1H, m, Alk–H), 1.35–1.61

(7H, m, Alk–H), 1.72–1.79 (1H, m, N*H*), 2.37–2.47 (1H, dd, PhCH_2–Alk, *J* 8.3 and 13.7), 2.52–2.63 (2H, m, Alk–CH_2–NH), 2.64–2.72 (1H, dd, PhCH_2–Alk, *J* 5.5 and 13.8), 2.94 (6H, s, ArN(CH_3)$_2$), 3.57–3.63 (1H, m, CH_2–O), 3.67–3.69 (2H, s, HN–CH_2–Ar), 3.71–3.78 (1H, m, CH_2–O), 6.61–6.67 (3H, m, Ar–H), 7.11–7.13 (2H, m, Ar–H), 7.16–7.19 (2H, m, Ar–H), 7.24–7.27 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.7, 30.3, 31.9, 32.9, 33.1, 37.2, 37.3, 39.4, 39.8, 40.7, 42.8, 43.0, 47.3, 47.4, 54.3, 61.9, 71.8, 111.4, 112.4, 116.5, 125.8, 128.3, 129.1, 141.5, 150.8. *m/z* (LC-MS ESI+) 395.5 $[M + H]^+$. Analytical HPLC: 95.4 %.

*3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-*N*-(4-isopropylbenzyl)-4-phenylbutan-1-amine* ***1d***[21]

General procedure H: using amine **18** (200 mg, 0.77 mmol) and 4-isopropylbenzaldehyde (0.139 mL, 0.161 g, 0.918 mmol), chromatography (silica, 20 % EtOAc/DCM followed by 5 % $NH_{3(aq)}$/MeOH/DCM) eluted **1d** as a yellow oil (47 mg, 16 %); R_f 0.37 (silica, 5 % $NH_{3(aq)}$/MeOH/DCM). ν_{max}/cm^{-1} 3026 (C–H), 2960 (C–H), 2927 (C–H), 2865 (C–H), 2818 (C–H), 1602, 1495, 1454, 1364, 1203, 1086, 818, 737, 699. δ_H (500 MHz, $CDCl_3$) 1.12 (3H, s, Alk-CH_3), 1.21–1.22 (3H, s, Alk-CH_3), 1.25 (3H, s, ArCH(CH_3)$_2$), 1.26 (3H, s, ArCH(CH_3)$_2$), 1.25–1.28 (2H, m, Alk–H), 1.36–1.62 (7H, m, Alk–H), 1.72–1.79 (1H, m, NH), 2.35–2.46 (1H, dd, Alk–H, *J* 8.5 and 13.7), 2.50–2.61 (2H, m, CH_2CH_2NH), 2.67 (1H, dd, Alk–H, *J* 5.6 and 13.6), 2.89 (1H, septet, *J* 6.9, ArC*H*(CH$_3$)$_2$)), 3.58–3.63 (1H, m, Alk–H), 3.66–3.68 (2H, s, NHCH_2Ar), 3.72–3.78 (1H, m, Alk–H), 7.11 (2H, d, Ar–H, *J* 7.4), 7.16–7.18 (5H, m, Ar–H), 7.24–7.27 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 24.0, 29.4, 29.7, 30.3, 31.9, 32.9, 33.1, 33.8, 37.2, 39.5, 39.8, 42.8, 43.0, 47.4, 53.7, 61.9, 71.8, 125.8, 126.4, 128.1, 128.3, 129.1, 137.7, 141.5, 147.6. *m/z* (LC-MS ESI+) 394.2 $[M + H]^+$; *m/z* (HRMS) 394.3091; calc. for $C_{27}H_{40}NO$ $[M + H]^+$ 394.3104. Analytical HPLC: 99.8 %.

*N-(4-Chlorobenzyl-3-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutan-1-amine* ***1e***[21]

General procedure H: using amine **18** (212 mg, 0.81 mmol) and 4-chlorobenzaldehyde (137 mg, 0.97 mmol), chromatography (silica, 20 % EtOAc/DCM followed by 5 % $NH_{3(aq)}$/MeOH/DCM) afforded **1e** as a yellow oil (80 mg, 26 %); R_f 0.34 (silica, 5 % $NH_{3(aq)}$/MeOH/DCM). ν_{max}/cm^{-1} 2970 (C–H), 2929 (C–H), 2857 (C–H), 1601, 1491, 1453, 1365, 1285, 1202, 1086, 1015, 962, 801, 738, 699. δ_H (500 MHz, $CDCl_3$) 1.13 (3H, s Alk-CH_3), 1.22 (3H, s Alk-CH_3), 1.23–1.29 (2H, m, Alk–H), 1.34–1.61 (6H, m, Alk–H), 1.73–1.80 (1H, m, NH), 2.40 (1H, dd, Alk–H, *J* 8.6 and 13.7), 2.46–2.60 (2H, m, CH_2CH_2NH), 2.68 (1H, dd, Alk–H, *J* 5.9 and 13.7), 3.58–3.64 (1H, m, Alk–H), 3.66 (2H, s, NHCH_2Ar), 3.71–3.79 (1H, m, Alk–H), 7.11 (2H, d, Ar–H, *J* 8.2), 7.17–7.20 (3H, m, Ar–H), 7.25–7.28 (4H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.7, 30.4, 31.9, 33.0, 33.3, 37.3, 39.5, 39.8, 42.8, 43.0, 47.5, 53.2, 53.4, 61.9, 71.8, 125.8, 128.3, 128.5, 129.0, 129.4, 132.6, 138.9, 141.5. *m/z* (LC-MS ESI+) 386.2 $[M + H]^+$; *m/z* (HRMS) 386.2236; calc. for $C_{24}H_{33}ClNO$ $[M + H]^+$ 386.2245. Analytical HPLC: 97.4 %.

*4-(((3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)amino)methyl)benzonitrile* ***1f***

General procedure H: using amine **18** (100 mg, 0.38 mmol) and 4-formylbenzonitrile (61 mg, 0.46 mmol), chromatography (silica, 10–50 % EtOAc/DCM) afforded **1f** as a yellow oil (82 mg, 64 %); R_f 0.17 (silica, 50 % EtOAc/DCM). λ_{max}/nm (EtOH) 279.0, 268.0. ν_{max}/cm^{-1} 2926 (C–H), 2857 (C–H), 2228 (C≡N), 1608, 1494, 1453, 1365, 1204, 1084, 1041, 857, 817, 738, 699. δ_H (500 MHz, $CDCl_3$) 1.12 (3H, s, Alk-CH_3), 1.21 (3H, s, Alk-CH_3), 1.26–1.29 (1H, m, Alk–H), 1.35–1.59 (8H, m, Alk–H), 1.73–1.80 (1H, m, NH), 2.39 (1H, dd, Alk–H, *J* 8.7 and 13.7), 2.46–2.57 (2H, m, CH_2CH_2NH), 2.70 (1H, dd, Alk–H, *J* 5.5 and 13.7), 3.61 (1H, t, Alk–H, *J* 12.1), 3.73 (2H, s, NHCH_2Ar), 3.76–3.79 (1H, m, Alk–H), 7.11 (2H, d, Ar–H, *J* 7.2), 7.16–7.19 (1H, m, Ar–H), 7.24–7.27 (2H, m, Ar–H), 7.35–7.38 (2H, m, Ar–H), 7.58 (2H, d, Ar–H, *J* 8.2). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.7, 30.5, 31.9, 33.1, 33.4, 37.4, 39.5, 39.9, 42.8, 42.9, 47.7, 53.4, 61.8, 71.8, 110.7, 119.0, 125.9, 128.3, 128.6, 129.0, 132.2, 141.4, 146.1. *m/z* (LC-MS ESI+) 377.4 $[M + H]^+$. Analytical HPLC: 95.8 %.

*3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-*N*-(4-methoxybenzyl)-4-phenylbutan-1-amine* ***1g***[21]

General procedure H: using amine **18** (100 mg, 0.38 mmol) and 4-anisaldehyde (56 µL, 62.7 mg, 0.46 mmol), chromatography (silica, 10–20 % EtOAc/DCM followed by 10 % MeOH/Et_2O) afforded **1g** as a colourless oil (69 mg, 53 %); R_f 0.39 (silica, 10 % MeOH/Et_2O). λ_{max}/nm (EtOH) 275.0. ν_{max}/cm^{-1} 2930 (C–H), 2856 (C–H), 1584, 1511, 1453, 1379, 1243, 1179, 1084, 1037, 822, 737, 699. δ_H (500 MHz, $CDCl_3$) 1.12 (3H, s, Alk-CH_3), 1.21 (3H, s, Alk-CH_3), 1.23–1.29 (1H, m, Alk–H), 1.33–1.60 (8H, m, Alk–H), 1.73–1.76 (1H, m, NH), 2.40 (1H, dd, Alk–H, *J* 8.5 and 13.7), 2.48–2.59 (2H, m, CH_2CH_2NH), 2.66 (1H, dd, Alk–H, *J* 5.7 and 13.6), 3.58–3.65 (3H, m, Alk–H and NHCH_2Ar), 3.72–3.79 (4H, m, Alk–H and OCH_3), 6.85 (2H, d, Ar–H, *J* 8.6), 7.11 (2H, d, Ar–H, *J* 7.3), 7.16–7.19 (3H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.7, 30.3, 30.4, 31.9, 32.9, 33.1, 37.2, 37.3, 39.5, 39.8, 42.9, 43.0, 47.4, 53.3, 55.3, 61.9, 71.8, 113.8, 125.8, 128.3, 129.1, 129.2, 132.5, 141.5, 158.6. *m/z* (LC-MS ESI+) 382.5 $[M + H]^+$. Analytical HPLC: 98.8 %.

*5-(((3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)amino)methyl)-*N*,*N*-dimethylpyridin-2-amine* ***1h***

General procedure H: using amine **18** (100 mg, 0.38 mmol) and 6-(*N*,*N*-dimethylamino)nicotinaldehyde (69 mg, 0.46 mmol), chromatography (silica, 5 % MeOH/Et_2O followed by 20 % MeOH/EtOAc) afforded **1h** as a dark-yellow oil (63 mg, 47 %); R_f 0.33 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 253.5. ν_{max}/cm^{-1} 2926 (C–H), 2856 (C–H), 1608, 1559, 1511, 1453, 1398, 1364, 1318, 1208, 1178, 1085, 1015, 958, 858, 806, 738, 700. δ_H (500 MHz, $CDCl_3$) 1.11–1.12 (3H, s, Alk-CH_3), 1.20–1.22 (3H, s, Alk-CH_3), 1.25–1.27 (1H, m, Alk–H), 1.34–1.59 (7H, m, Alk–H), 1.71–1.77 (1H, m, NH), 2.34–2.44 (1H, dd, PhCH_2–Alk, *J* 8.4 and 13.7), 2.46–2.58 (2H, m, AlkCH_2–NH), 2.62–2.72 (1H, dd, PhCH_2–Alk, *J* 5.3 and 13.7), 3.07 (6H, s, Ar–N(CH_3)$_2$), 3.56–3.62 (3H, m, HN–CH_2Ar and CH_2–O), 3.71–3.77 (1H, m, CH_2–O), 6.47–6.49 (1H, m, Ar–H), 7.10–7.12 (2H, m, Ar–H), 7.15–7.18 (1H, m, Ar–H), 7.24–7.27 (2H, m, Ar–H), 7.41–7.44 (1H, m, Ar–H), 8.01–8.03 (1H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.4, 29.6, 29.9, 31.9, 33.0, 33.2, 37.2, 37.3, 38.2, 39.4, 39.8, 42.8, 43.0, 46.7, 50.3, 61.8, 71.8, 105.7, 125.8, 128.3, 129.0, 129.1, 137.8, 141.3, 147.8, 158.9. *m/z* (LC-MS ESI+) 396.5 $[M + H]^+$; *m/z* (HRMS) 396.3011; calc. for $C_{26}H_{39}N_2O$ $[M + H]^+$ 396.3009. Analytical HPLC: 97.6 %.

(rac)-N,N-Dimethyl-4-(((4-phenyl-3-(tetrahydro-2H-pyran-4-yl)butyl)amino)methyl)aniline ***3a***[21]

General procedure H: using amine **19** (200 mg, 0.86 mmol) and 4-(*N*,*N*-dimethylamino)benzaldehyde (154 mg, 1.03 mmol), chromatography (silica, 20 % EtOAc/DCM followed by 2 % $NH_{3(aq)}$/MeOH) afforded **3a** as a yellow oil (299 mg, 95 %); R_f 0.54 (silica, 2 % $NH_{3(aq)}$/MeOH). λ_{max}/nm (EtOH) 302.0, 263.0. ν_{max}/cm^{-1} 3024 (C–H), 2928 (C–H), 2840 (C–H), 1614, 1521, 1443, 1342, 1228, 1091, 1014, 946, 804, 740, 699. δ_H (500 MHz, $CDCl_3$) 1.36–1.65 (9H, m, Alk–H and NH), 2.44 (1H, dd, Alk–H, *J* 7.72 and 13.7), 2.53–2.63 (2H, m, CH_2CH_2NH), 2.67 (1H, dd, Alk–H, *J* 6.2 and 13.7), 2.93 (6H, s, $N(CH_3)_2$), 3.29–3.35 (2H, m, Alk–H), 3.61 (2H, s, $NHCH_2Ar$), 3.95–4.02 (2H, m, Alk–H), 6.70 (2H, d, Ar–H, *J* 8.7) 7.10–7.15 (4H, m, Ar–H), 7.18 (1H, t, Ar–H, *J* 7.4), 7.24–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5, 29.8, 30.5, 37.3, 37.4, 40.8, 43.0, 47.4, 53.5, 68.5, 112.7, 125.8, 128.3, 128.5, 129.0, 129.1, 141.5, 149.8. *m/z* (LC-MS ESI+) 367.4 $[M+H]^+$; *m/z* (HRMS) 367.2743; calc. for $C_{24}H_{35}N_2O$ $[M+H]^+$ 367.2744. Analytical HPLC: 97.9 %.

(R)- or (S)-N,N-Dimethyl-4-(((4-phenyl-3-(tetrahydro-2H-pyran-4-yl)butyl)amino)methyl)aniline (R)- and (S)- ***3a***

General procedure H: using either (*R*)- or (*S*)-amine (*R*)-**19** or (*S*)-**19** (115 mg, 0.49 mmol, and 133 mg, 0.57 mmol respectively), chromatography (silica, 5–15 % MeOH/DCM) afforded (*R*)- or (*S*)-**3a** as yellow oils (29 mg, 16 %, and 137 mg, 65 % respectively). Analytical data equivalent to (*rac*)-**3a**; $[\alpha]_D^{26.5}$ +11.4° (*R*) (*c* 1.97 in EtOH), $[\alpha]_D^{26.5}$ −11.0° (*S*) (*c* 1.97 in EtOH).

4-Phenyl-N-(4-(pyrrolidin-1-yl)benzyl)-3-(tetrahydro-2H-pyran-4-yl)butan-1-amine ***3b***

General procedure H: using amine **19** (50 mg, 0.21 mmol) and 4-(1-pyrrolidinyl)benzaldehyde (45.6 mg, 0.26 mmol), chromatography (silica, 20 % EtOAc/DCM followed by 5–10 % MeOH/DCM) afforded **3b** as a yellow oil (392 mg, 77 %); R_f 0.35 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 262.0. ν_{max}/cm^{-1} 2930 (C–H), 2838 (C–H), 1614, 1521, 1488, 1454, 1368, 1181, 1092, 1014, 963, 802, 738, 700. δ_H (500 MHz, $CDCl_3$) 1.42–1.59 (9.5H, m, Alk–H, NH, and H_2O), 1.97–2.00 (4H, m, $(CH_2)_2$, pyrrolidino ring), 2.40–2.44 (1H, dd, $PhCH_2$, *J* 7.5 and 13.6), 2.53–2.61 (2H, m, $AlkCH_2$–NH), 2.62–2.69 (1H, dd, $PhCH_2$, *J* 5.7 and 13.6), 3.25–3.27 (4H, m, $(CH_2)_2$, pyrrolidino ring), 3.28–3.35 (2H, m, CH_2–O), 3.61 (2H, s, HN–CH_2Ar), 3.95–4.00 (2H, m, CH_2–O), 6.50–6.52 (2H, m, Ar–H), 7.11–7.13 (4H, m, Ar–H), 7.16–7.19 (1H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 25.5, 29.5, 29.7, 37.2, 37.4, 43.0, 47.7, 68.5, 111.6, 125.8, 128.3, 129.1, 129.4, 141.4, 147.3. *m/z* (LC-MS ESI+) 393.3 $[M+H]^+$; *m/z* (HRMS) 393.2901; calc. for $C_{26}H_{37}ON_2$ $[M+H]^+$ 393.2900. Analytical HPLC: 97.9 %.

4-Phenyl-3-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethyl)benzyl)butan-1-amine ***3c***

General procedure H: using amine **19** (50 mg, 0.21 mmol) and 4-(trifluoromethyl)benzaldehyde (35 µL, 44.6 mg, 0.25 mmol), chromatography (silica, 0–10 % MeOH/DCM) afforded **3c** as a yellow oil (73 mg, 85 %); R_f 0.36 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) 258.5. ν_{max}/cm^{-1} 2928 (C–H), 2843 (C–H), 1619, 1454, 1323 (sharp), 1161, 1117, 1065, 1017, 822, 739, 699. δ_H (500 MHz, $CDCl_3$) 1.37–1.63 (11.5H, Alk–H, NH, and H_2O), 2.39–2.43 (1H, dd, $PhCH_2$, *J* 8.1 and 13.6), 2.50–2.60 (2H, m, $AlkCH_2$–NH), 2.68–2.72 (1H, dd, $PhCH_2$, *J* 5.9 and 13.6), 3.29–3.36 (2H, m, CH_2–O), 3.74 (2H, s, HN–CH_2Ar), 3.96–4.01 (2H, m, CH_2–O), 7.11–7.13 (2H, d, Ar–H, *J* 7.6), 7.17–7.19 (1H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H), 7.36–7.37 (2H, d, Ar–H, *J* 8.0), 7.55–7.56 (2H, d, Ar–H, *J* 8.1). δ_C (125 MHz, $CDCl_3$) 29.5, 29.8, 30.5, 37.5, 42.9, 47.6, 53.4, 68.4, 125.2 (split), 125.9, 128.2, 128.3, 129.0, 129.3, 141.4, 144.5. *m/z* (LC-MS ESI+) 392.1 $[M+H]^+$; *m/z* (HRMS) 392.2195; calc. for $C_{23}H_{29}ONF_3$ $[M+H]^+$ 392.2196. Analytical HPLC: 95.4 %.

N-(4-(Methylthio)benzyl)-4-phenyl-3-(tetrahydro-2H-pyran-4-yl)butan-1-amine ***3d***

General procedure H: using amine **19** (100 mg, 0.43 mmol) and 4-(thiomethyl)benzaldehyde (70 µL, 80.1 mg, 0.52 mmol), chromatography (silica, 0–10 % MeOH/DCM) afforded **3d** as a yellow oil (127 mg, 77 %); R_f 0.27 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) 257.5. ν_{max}/cm^{-1} 2924 (C–H), 2838 (C–H), 1601, 1493, 1453, 1090, 1014, 800, 739, 699. δ_H (500 MHz, $CDCl_3$) 1.37–1.61 (11.5H, m, Alk–H, NH, and H_2O), 2.39–2.44 (1H, dd, $PhCH_2$, *J* 7.9 and 13.6), 2.47 (3H, s, SCH_3), 2.50–2.61 (2H, m, $AlkCH_2$–NH), 2.66–2.70 (1H, dd, $PhCH_2$, *J* 6.1 and 13.8), 3.29–3.35 (2H, m, CH_2–O), 3.65 (2H, s, HN–CH_2Ar), 3.96–4.01 (2H, m, CH_2–O), 7.11–7.13 (2H, d, Ar–H, *J* 7.1), 7.17–7.22 (5H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 16.1, 29.5, 29.7, 30.4, 37.4, 43.0, 47.4, 53.4, 68.4, 125.8, 126.9, 128.3, 128.7, 129.1, 136.8, 141.4. *m/z* (LC-MS ESI+) 370.4 $[M+H]^+$; *m/z* (HRMS) 370.2202; calc. for $C_{23}H_{32}ONS$ $[M+H]^+$ 370.2199. Analytical HPLC: 96.3 %.

N-(4-Chlorobenzyl)-4-phenyl-3-(tetrahydro-2H-pyran-4-yl)butan-1-amine ***3e***[21]

General procedure H: using amine **19** (100 mg, 0.43 mmol) and 4-chlorobenzaldehyde (74 mg, 0.52 mmol), chromatography (silica, 0–10 % MeOH/DCM) afforded **3e** as a yellow oil (116 mg, 72 %); R_f 0.38 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) 260.0. ν_{max}/cm^{-1} 2928 (C–H), 2841 (C–H), 1601, 1490, 1453, 1242, 1089, 1014, 982, 801, 739, 699. δ_H (500 MHz, $CDCl_3$) 1.36–1.61 (12H, m, Alk–H, NH, and H_2O), 2.39–2.43 (1H, dd, $PhCH_2$, *J* 7.8 and 13.8), 2.49–2.59 (2H, m, $AlkCH_2$–NH), 2.67–2.71 (1H, dd, $PhCH_2$, *J* 5.4 and 13.2), 3.29–3.36 (2H, m, CH_2–O), 3.66 (2H, s, HN–CH_2Ar), 3.96–4.01 (2H, m, CH_2–O), 7.11–7.13 (2H, d, Ar–H, *J* 7.5), 7.17–7.20 (3H, m, Ar–H), 7.25–7.28 (4H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5, 29.7, 30.5, 37.5, 43.0, 47.5, 53.2, 68.4, 125.8, 128.3, 128.5, 129.0, 129.4, 132.6, 138.9, 141.4. *m/z* (LC-MS ESI+) 358.4 $[M+H]^+$; *m/z* (HRMS) 358.1936; calc. for $C_{22}H_{29}ONCl$ $[M+H]^+$ 358.1932. Analytical HPLC: 93.8 %.

N-(4-Fluorobenzyl)-4-phenyl-3-(tetrahydro-2H-pyran-4-yl)butan-1-amine ***3f***[21]

General procedure H: using amine **19** (50 mg, 0.21 mmol) and 4-fluorobenzaldehyde (27 µL, 31.2 mg, 0.25 mmol), chromatography (silica, 0–10 % MeOH/DCM) afforded **3f** as a yellow oil (43 mg, 58 %); R_f 0.30 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) 264.0. ν_{max}/cm^{-1} 2928 (C–H), 2842 (C–H), 1602, 1508, 1454, 1387, 1219, 1091, 1014, 822, 739, 699. δ_H (500 MHz, $CDCl_3$) 1.37–1.62 (11H, m, Alk–H, NH, and H_2O), 2.39–2.44 (1H, dd, $PhCH_2$, *J* 8.0 and 13.6), 2.50–2.60 (2H, m, $AlkCH_2$–NH), 2.67–2.71 (1H, dd, $PhCH_2$, *J* 5.8 and 13.7), 3.29–3.36 (2H, m, CH_2–O), 3.66 (2H, s, HN–CH_2Ar), 3.96–4.01 (2H, m, CH_2–O), 6.97–7.00 (2H, m, Ar–H), 7.11–7.13 (2H, d, Ar–H, *J* 7.4),

7.17–7.22 (3H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5, 29.7, 30.4, 37.4, 43.0, 47.5, 53.1, 68.4, 115.1, 125.8, 128.3, 129.0, 129.6, 141.4, 160.9, 162.9. *m/z* (LC-MS ESI+) 342.1 $[M+H]^+$; *m/z* (HRMS) 342.2230; calc. for $C_{22}H_{29}ONF$ $[M+H]^+$ 342.2228. Analytical HPLC: 95.4 %.

N-*(4-Nitrobenzyl)-4-phenyl-3-(tetrahydro-2*H*-pyran-4-yl) butan-1-amine **3g***

General procedure H: using amine (**19**) (450 mg, 1.93 mmol) and 4-nitrobenzaldehyde (351 mg, 2.32 mmol), chromatography (silica, 5 % EtOAc/DCM followed by 10 % MeOH/DCM) afforded (**3g**) as a yellow gum (467 mg, 66 %); R_f 0.38 (silica, 2 % MeOH/DCM). Mp 39–45°C. λ_{max}/nm (EtOH) 266.5. ν_{max}/cm^{-1} 3409 (N–H), 2932 (C–H), 2845 (C–H), 2752 (C–H), 1605, 1519, 1454, 1344, 1090, 1014, 982, 856, 739, 698. δ_H (500 MHz, $CDCl_3$) 1.42–1.69 (8H, m, Alk–H), 1.80–1.87 (1H, m, NH), 2.28–2.33 (1H, dd, PhCH_2, *J* 9.0 and 13.8), 2.41–2.47 (1H, m, AlkCH_2–NH), 2.54–2.60 (1H, m, AlkCH_2–NH), 2.74–2.78 (1H, dd, PhCH_2, *J* 4.9 and 13.8), 3.27–3.32 (2H, m, CH_2–O), 3.89 (2H, s, HN–CH_2Ar), 3.94–3.97 (2H, m, CH_2–O), 7.08–7.10 (2H, d, Ar–H, *J* 7.0), 7.15–7.18 (1H, t, Ar–H, *J* 7.4), 7.22–7.25 (2H, m, Ar–H), 7.55–7.57 (2H, d, Ar–H, *J* 8.7), 8.16–8.18 (2H, d, Ar–H, *J* 8.8). δ_C (125 MHz, $CDCl_3$) 27.4, 29.5, 29.7, 37.5, 38.2, 42.9, 45.2, 49.7, 68.2, 124.1, 126.3, 128.6, 128.9, 130.7, 140.5, 148.2. *m/z* (LC-MS ESI+) 369.7 $[M+H]^+$; *m/z* (HRMS) 369.2175; calc. for $C_{22}H_{29}O_3N_2$ $[M+H]^+$ 369.2173. Analytical HPLC: 98.7 %.

*2-(Methyl-(4-(((4-phenyl-3-(tetrahydro-2*H*-pyran-4-yl) butyl)amino)methyl)phenyl)amino)ethanol **3j***

General procedure H: using amine **19** (100 mg, 0.43 mmol) and 4-(*N*-methyl-*N*-(2-hydroxyethyl)amino)benzaldehyde (93.2 mg, 0.52 mmol), chromatography (silica, 5–20 % MeOH/Et_2O) afforded **3j** as a yellow gum (93 mg, 55 %); R_f 0.14 (silica, 20 % MeOH/DCM). λ_{max}/nm (EtOH) 262.5. ν_{max}/cm^{-1} 3368 (br) (N–H and O–H), 2929 (C–H), 2846 (C–H), 1613, 1521, 1453, 1369, 1189, 1091, 1051, 803, 740, 700. δ_H (500 MHz, $CDCl_3$) 1.42–1.61 (9H, m, Alk–H and NH), 1.94 (1H, s, br, OH), 2.40–2.44 (1H, dd, PhCH_2, *J* 7.6 and 13.7), 2.53–2.63 (2H, m, AlkCH_2–NH), 2.65–2.69 (1H, dd, PhCH_2, *J* 5.8 and 13.7), 2.94 (3H, s, NCH_3), 3.28–3.34 (2H, m, CH_2–O), 3.43–3.45 (2H, t, MeN–CH_2, *J* 5.6), 3.61 (2H, s, HN–CH_2Ar), 3.77–3.80 (2H, t, CH_2OH, *J* 5.7), 3.95–3.99 (2H, m, CH_2–O), 6.73–6.75 (2H, m, Ar–H), 7.11–7.15 (4H, m, Ar–H), 7.17–7.20 (1H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.4, 29.7, 29.9, 37.3, 37.4, 38.9, 43.0, 47.0, 52.9, 55.6, 60.1, 68.4, 113.1, 125.9, 128.4, 129.1, 129.5, 141.4, 149.4. *m/z* (LC-MS ESI+) 397.4 $[M+H]^+$; *m/z* (HRMS) 397.2852; calc. for $C_{25}H_{37}O_2N_2$ $[M+H]^+$ 397.2850. Analytical HPLC: 96.8 %.

N-*(4-(Methylsulfonyl)benzyl)-4-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)butan-1-amine **3k***

General procedure H: using amine **19** (50 mg, 0.21 mmol) and 4-(methanesulfonyl)benzaldehyde (47.9 mg, 0.26 mmol), chromatography (silica, 17 % EtOAc/DCM followed by 20 % MeOH/DCM) afforded **3k** as a blue-green oil (63 mg, 75 %); R_f 0.22 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) no distinguishable peak. ν_{max}/cm^{-1} 2929 (C–H), 2843 (C–H), 1600, 1454, 1408, 1304, 1148, 1089, 1016, 956, 735, 701. δ_H (500 MHz, $CDCl_3$) 1.39–1.66 (10.5H, m, Alk–H, NH, and H_2O), 2.38–2.43 (1H, dd, PhCH_2, *J* 8.1 and 13.6), 2.49–2.60 (2H, m, AlkCH_2–NH), 2.69–2.73 (1H, dd, PhCH_2, *J* 5.8 and 13.7), 3.04 (3H, s, SO_2CH_3), 3.29–3.36 (2H, m, CH_2–O), 3.78 (2H, s, HN–CH_2Ar), 3.97–4.03 (2H, m, CH_2–O), 7.12–7.13 (2H, m, Ar–H), 7.17–7.20 (1H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H), 7.46–7.47 (2H, m, Ar–H), 7.86–7.89 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5, 29.7, 30.3, 37.4, 37.6, 42.9, 44.6, 47.6, 50.9, 53.0, 53.4, 68.4, 125.9, 127.5, 128.4, 128.9, 129.0, 139.2, 141.3. *m/z* (LC-MS ESI+) 402.7 $[M+H]^+$; *m/z* (HRMS) 402.2098; calc. for $C_{23}H_{32}O_3NS$ $[M+H]^+$ 402.2097. Analytical HPLC: 97.4 %.

N-*(4-Chlorobenzyl)-3-methyl-4-phenylbutan-1-amine **34***

General procedure H: using amine **33** (43 mg, 0.26 mmol) and 4-chlorobenzaldehyde (43 mg, 0.31 mmol), chromatography (silica, 5 % MeOH/DCM) afforded **34** as a yellow oil (20 mg, 27 %); R_f 0.33 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) no distinguishable peak. ν_{max}/cm^{-1} 3026 (C–H), 2918 (C–H), 1598, 1490, 1453, 1089, 1015, 803, 738, 699. δ_H (500 MHz, $CDCl_3$) 0.89–0.90 (3H, d, CH_3, *J* 6.6), 1.29–1.41 (2H, m, Alk–H and NH), 1.57–1.64 (1H, m, Alk–H), 1.79–1.89 (1H, m, Alk–H), 2.42–2.47 (1H, dd, PhCH_2, *J* 7.9 and 13.4), 2.60–2.65 (2H, m, AlkCH_2–NH), 2.68–2.73 (1H, dd, PhCH_2, *J* 5.6 and 9.4), 3.75 (2H, s, HN–CH_2Ar), 7.15–7.17 (2H, m, Ar–H), 7.19–7.22 (1H, m, Ar–H), 7.25–7.32 (6H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 19.6, 33.2, 36.8, 43.9, 47.3, 53.3, 125.8, 128.2, 128.5, 129.2, 129.5, 132.6, 138.9, 141.2. *m/z* (LC-MS ESI+) 288.3 $[M+H]^+$; *m/z* (HRMS) 288.1518; calc. for $C_{18}H_{23}NCl$ $[M+H]^+$ 288.1514. Analytical HPLC: 95.2 %.

N-*(4-Chlorobenzyl)-3-methylbutan-1-amine **36***

General procedure H: using isopentylamine (267 µL, 200 mg, 2.29 mmol) and 4-chlorobenzaldehyde (393.6 mg, 2.80 mmol), chromatography (silica, 33 % Et_2O/hexane) afforded **36** as a yellow oil (231 mg, 48 %); R_f 0.36 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) 218.0. ν_{max}/cm^{-1} 2955 (C–H), 2923 (C–H), 2869 (C–H), 2822 (C–H), 1597, 1490, 1461, 1407, 1366, 1091, 1015, 806, 745. δ_H (500 MHz, $CDCl_3$) 0.88–0.89 (6H, d, $CH(CH_3)_2$, *J* 6.6), 1.37–1.43 (3H, m, CH_2–CH_2–N*H*), 1.58–1.66 (1H, septet, C*H*$(CH_3)_2$, *J* 6.7), 2.60–2.63 (2H, m, CH_2–NH), 3.75 (2H, s, HN–CH_2Ar), 7.25–7.30 (4H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 22.7, 26.2, 39.2, 47.6, 53.4, 128.5, 129.4, 132.5, 139.0. *m/z* (LC-MS ESI+) 213.2 $[M+H]^+$; *m/z* (HRMS) 212.1202; calc. for $C_{12}H_{19}NCl$ $[M+H]^+$ 212.1201. Analytical HPLC: 98.1 %.

*4-(Dimethylamino)-*N*-(3-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)benzamide **1i***[21]

General procedure I: using amine **18** (90 mg, 0.34 mmol), triethylamine (80 µL, 0.57 mmol), and 4-(*N*,*N*-dimethylamino) benzoyl chloride (105 mg, 0.57 mmol), chromatography (18 % EtOAc/DCM) afforded **1i** as a white solid (87 mg, 63 %); R_f 0.29 (silica, 20 % EtOAc/DCM). λ_{max}/nm (EtOH) 300.0. ν_{max}/cm^{-1} 3316 (N–H), 2970 (C–H), 2928 (C–H), 2860 (C–H), 1737 (C=O), 1606, 1545, 1511, 1445, 1364, 1296, 1233, 1202, 1130, 1071, 946, 828, 737, 700. δ_H (500 MHz, $CDCl_3$) 1.17 (3H, s, Alk-CH_3), 1.23 (3H, s, Alk-CH_3), 1.28–1.30 (1H, m, Alk–H), 1.36–1.72 (7H, m, Alk–H), 1.82–1.85 (1H, m, Alk–H), 2.45 (1H, dd, Alk–H, *J* 8.9 and 13.6), 2.75 (1H, dd, Alk–H, *J* 4.9 and 13.6), 3.01 (6H, s, $N(CH_3)_2$), 3.34–3.40 (2H, m, CH_2CH_2NH), 3.58–3.67 (1H, m, Alk–H), 3.73–3.79 (1H, m, Alk–H), 5.65–5.68 (1H, m, NH), 6.64 (2H, d, Ar–H, *J* 9.0), 7.17–7.22 (3H, m, Ar–H), 7.27–7.30 (2H, t, Ar–H, *J* 7.6), 7.56 (2H, d, Ar–H, *J* 8.9). δ_C (125 MHz, $CDCl_3$) 21.9, 29.4, 29.5, 30.1, 30.2, 31.9, 33.0, 33.4, 37.1, 38.0, 39.7, 40.0, 40.1, 42.8, 42.9, 61.8, 71.8, 111.0, 121.4,

125.9, 128.2, 128.5, 129.1, 141.1, 152.4. *m/z* (LC-MS ESI+) 409.5 $[M+H]^+$; *m/z* (HRMS) 409.2851; calc. for $C_{26}H_{36}N_2O_2$ $[M+H]^+$ 409.2850. Analytical HPLC: 95.1 %.

*4-Chloro-*N*-(4-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)butyl) benzamide **3l***

General procedure I: using amine **19** (50 mg, 0.21 mmol) and 4-chlorobenzoyl chloride (54 µL, 73.7 mg, 0.42 mmol), chromatography (silica, 10 % EtOAc/DCM) afforded **3l** as a brown solid (73 mg, 94 %); R_f 0.23 (silica, 10 % EtOAc/DCM). Mp 110–112°C. λ_{max}/nm (EtOH) 235.0. ν_{max}/cm^{-1} 3304 (N–H), 2956 (C–H), 2837 (C–H), 1627 (C=O), 1595, 1530, 1484, 1271, 1145, 1093, 1015, 844, 748, 702. δ_H (500 MHz, $CDCl_3$) 1.45–1.73 (14H, Alk–H and H_2O), 2.41–2.45 (1H, dd, PhCH_2, *J* 8.9 and 13.7), 2.78–2.82 (1H, dd, PhCH_2, *J* 5.1 and 13.7), 3.34–3.40 (4H, m, CH_2–O and AlkCH_2–NH), 3.99–4.03 (2H, m, CH_2–O), 5.72 (1H, m, NH), 7.16–7.18 (2H, d, Ar–H, *J* 7.5), 7.19–7.22 (1H, m, Ar–H), 7.27–7.30 (2H, m, Ar–H), 7.37–7.38 (2H, m, Ar–H), 7.55–7.56 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.6, 29.8, 30.0, 30.9, 37.2, 37.8, 38.5, 43.0, 68.4, 126.1, 128.2, 128.6, 128.8, 129.1, 132.9, 137.6, 141.3, 166.3. *m/z* (LC-MS ESI+) 372.4 $[M+H]^+$; *m/z* (HRMS) 372.1728; calc. for $C_{22}H_{27}O_2NCl$ $[M+H]^+$ 372.1725. Analytical HPLC: 97.3 %.

*4-(Dimethylamino)-*N*-(3-(2,2dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)benzenesulfonamide **1j***

General procedure I: using amine **18** (100 mg, 0.38 mmol) and 4-(*N*,*N*-dimethylamino)benzenesulfonyl chloride (101 mg, 0.46 mmol), chromatography (silica, 0–10 % EtOAc/DCM) afforded **1j** as a white solid (134 mg, 89 %); R_f 0.57 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 278.0. ν_{max}/cm^{-1} 3268 (N–H), 2930 (C–H), 2863 (C–H), 1596, 1516, 1446, 1365 (S=O asym. stretch), 1311, 1229, 1144 (S=O sym. stretch), 1093, 1000, 944, 858, 815, 772, 737, 700. δ_H (500 MHz, $CDCl_3$) 1.10–1.11 (3H, s, Alk-CH_3), 1.14–1.20 (4H, m, Alk-CH_3 and Alk–H), 1.24–1.54 (6H, m, Alk–H), 1.64–1.69 (1H, m, Alk–H), 2.26–2.37 (1H, dd, PhCH_2, *J* 8.8 and 13.7), 2.59–2.70 (1H, dd, PhCH_2, *J* 5.5 and 13.7), 2.78–2.87 (2H, m, AlkCH_2–NH), 3.04 (6H, s, Ar–N(CH_3)$_2$), 3.52–3.58 (1H, m, CH_2–O), 3.68–3.73 (1H, m, CH_2–O), 3.99–4.05 (1H, dt, NH, *J* 6.1 and 17.0), 6.64–6.67 (2H, dd, Ar–H, *J* 2.8 and 9.0), 7.05–7.07 (2H, d, Ar–H *J* 7.3), 7.16–7.19 (1H, m, Ar–H), 7.23–7.26 (2H, m, Ar–H), 7.62–7.64 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.3, 29.5, 29.9, 30.0, 31.9, 32.8, 33.0, 36.9, 39.3, 39.7, 40.1, 41.2, 41.3, 41.9, 42.1, 61.7, 71.7, 110.9, 111.0, 125.0, 126.0, 128.4, 128.9, 129.0, 140.9, 152.8. *m/z* (LC-MS ESI+) 445.5 $[M+H]^+$; *m/z* (HRMS) 445.2519; calc. for $C_{25}H_{36}N_2O_3S$ $[M+H]^+$ 445.2519. Analytical HPLC: 96.6 %.

*4-Chloro-*N*-(4-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)butyl) benzenesulfonamide **3m***

General procedure I: using amine **19** (50 mg, 0.21 mmol) and 4-chlorobenzenesulfonyl chloride (89 mg, 0.42 mmol), chromatography (silica, 5 % EtOAc/DCM) afforded **3m** as a colourless oil (67 mg, 79 %); R_f 0.45 (silica, 10 % EtOAc/DCM). λ_{max}/nm (EtOH) 230.5. ν_{max}/cm^{-1} 3280 (N–H), 2934 (C–H), 2849 (C–H), 1586, 1328 (S=O asym. stretch), 1159 (S=O sym. stretch), 1084, 1014, 827, 751, 700. δ_H (500 MHz, $CDCl_3$) 1.30–1.56 (13.5H, Alk–H and H_2O), 2.29–2.34 (1H, dd, PhCH_2, *J* 8.6 and 13.6), 2.69–2.73 (1H, dd, PhCH_2, *J* 5.2 and 13.6), 2.79–2.88 (2H, m, AlkCH_2–NH), 3.29–3.35 (2H, m, CH_2–O), 3.96–4.00 (2H, m, CH_2–O), 4.08–4.10 (1H, m, NH), 7.06–7.08 (2H, d, Ar–H, *J* 7.1), 7.18–7.21 (1H, m, Ar–H), 7.25–7.28 (2H, m, Ar–H), 7.45–7.47 (2H, m, Ar–H), 7.69–7.70 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 29.5 (×2), 30.4, 37.2, 37.7, 41.6, 42.2, 68.3, 126.2, 128.5 (×2), 128.9, 129.4, 138.4, 139.1, 140.7. *m/z* (LC-MS ESI+) 408.3 $[M+H]^+$; *m/z* (HRMS) 408.1397; calc. for $C_{21}H_{27}O_3NClS$ $[M+H]^+$ 408.1395. Analytical HPLC: 99.2 %.

*4-(((4-Phenyl-3-(tetrahydro-2*H*-pyran-4-yl)butyl)amino) methyl)aniline **3h***

General procedure J: using amine **3g** (286 mg, 0.78 mmol) in methanol (15.6 mL), hydrogenation gave **3h** as a white solid (261 mg, 99 %); R_f 0.27 (silica, 10 % MeOH/DCM). Mp dec. λ_{max}/nm (EtOH) 248.0. ν_{max}/cm^{-1} 3320 (N–H), 2935 (C–H), 2841 (C–H), 1638, 1557, 1439, 1390, 1277, 1222, 1193, 1125, 1107, 873, 780, 738, 700. δ_H (500 MHz, $CDCl_3$) 1.46–1.66 (8H, m, Alk–H), 1.78–1.82 (1H, m, N*H*), 2.32–2.36 (1H, dd, PhCH_2–Alk, *J* 8.1 and 13.5), 2.49–2.55 (1H, m, AlkCH_2–NH), 2.58–2.64 (1H, m, AlkCH_2–NH), 2.69–2.73 (1H, dd, PhCH_2–Alk, *J* 5.4 and 13.8), 3.27–3.31 (2H, m, CH_2–O), 3.67–3.73 (4H, m, ArNH_2 and HN–CH_2Ar), 3.94–3.96 (2H, m, CH_2–O), 6.60–6.61 (2H, d, Ar–H, *J* 7.0), 7.10–7.11 (2H, d, Ar–H, *J* 7.5), 7.13–7.14 (2H, d, Ar–H, *J* 7.2), 7.17–7.19 (1H, t, Ar–H, *J* 7.3), 7.25–7.27 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 27.4, 29.5, 31.0, 37.2, 37.7, 42.9, 44.5, 50.4, 68.3, 115.1, 126.1, 128.5, 129.0, 131.0, 140.7, 146.9. *m/z* (LC-MS ESI+) 339.4 $[M+H]^+$; *m/z* (HRMS) 339.2433; calc. for $C_{22}H_{31}ON_2$ $[M+H]^+$ 339.2431. Analytical HPLC: 96.3 %.

*N-(4-Azidobenzyl)-4-phenyl-3-(tetrahydro-2*H*-pyran-4-yl) butan-1-amine **3i***

General procedure K: aniline **3h** (100 mg, 0.30 mmol), sodium nitrite (28 mg, 0.40 mmol), and sodium azide (85 mg, 1.3 mmol); chromatography (silica, 0–5 % MeOH/DCM) afforded **3i** as a yellow solid (84 mg, 75 %); R_f 0.28 (silica, 5 % MeOH/DCM). λ_{max}/nm (EtOH) 252.5. ν_{max}/cm^{-1} 2927 (C–H), 2842 (C–H), 2749 (C–H), 2103 (N=N, strong), 1604, 1507, 1454, 1281, 1124, 1091, 1013, 824, 739, 700. δ_H (500 MHz, $CDCl_3$) 1.46–1.58 (7H, m, Alk–H), 1.75 (1H, m, NH), 2.32–2.36 (1H, dd, PhCH_2, *J* 7.9 and 13.7), 2.46–2.51 (1H, m, AlkCH_2–NH), 2.55–2.61 (1H, m, AlkCH_2–NH), 2.70–2.74 (1H, dd, PhCH_2, *J* 4.8 and 13.7), 3.27–3.32 (2H, m, CH_2–O), 3.73 (2H, s, HN–CH_2Ar), 3.95–3.98 (2H, m, CH_2–O), 6.96–6.98 (2H, d, Ar–H, *J* 8.3), 7.10–7.11 (2H, d, Ar–H, *J* 7.7), 7.17–7.20 (1H, m, Ar–H), 7.24–7.27 (2H, m, Ar–H), 7.32–7.33 (2H, d, Ar–H, *J* 8.2). δ_C (125 MHz, $CDCl_3$) 28.1, 29.6 (×2), 37.3, 37.9, 42.9, 45.4, 50.7, 68.3, 119.4, 126.1, 128.5, 129.0, 130.9, 140.3, 140.8. *m/z* (LC-MS ESI+) 365.4 $[M+H]^+$; *m/z* (HRMS) 365.2338; calc. for $C_{22}H_{29}ON_4$ $[M+H]^+$ 365.2336. Analytical HPLC: 97.5 %.

*4-(((3-(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)(methyl)amino)methyl)-*N*,*N*-dimethylaniline **1k***

General procedure L: using amine **1a** (60 mg, 0.26 mmol), chromatography (silica, 0–10 % MeOH/DCM) afforded **1k** as a yellow gum (24 mg, 39 %); R_f 0.41 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 260.0. ν_{max}/cm^{-1} 2926 (C–H), 2855 (C–H), 2785 (C–H), 1614, 1521, 1453, 1345, 1229, 1185, 1162, 1084, 947, 858, 803, 737, 699. δ_H (500 MHz, $CDCl_3$) 1.07–1.11 (3H, s, pyran CH_3), 1.20–1.25 (4H, m, pyran CH_3 and Alk–H), 1.36–1.47 (5H, m, Alk–H), 1.58 (2H, m, Alk–H), 1.71 (1H, m, Alk–H), 2.10 (3H, s, N–CH_3), 2.27–2.45 (3H, m, Alk–H), 2.61–2.70 (1H, m, Alk–H), 2.93 (6H, s, N(CH_3)$_2$), 3.33 (2H, s, Alk–H),

3.55–3.60 (1H, dt, Alk–H, *J* 2.5 and 12.0), 3.70–3.76 (1H, m, Alk–H), 6.67–6.69 (2H, m, Ar–H), 7.10–7.13 (4H, m, Ar–H), 7.15–7.18 (1H, m, Ar–H), 7.24–7.27 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 29.5, 29.7, 31.9, 32.8, 37.0, 37.2, 39.4, 39.7, 40.7, 42.6, 43.0, 54.5, 61.9, 71.8, 112.5, 125.7, 128.3, 129.1, 130.2. *m/z* (LC-MS ESI+) 409.5 $[M + H]^+$; *m/z* (HRMS) 409.3212; calc. for $C_{27}H_{40}N_2O$ $[M + H]^+$ 409.3213. Analytical HPLC: 95.1 %.

*Ethyl 3-((*tert*-Butoxycarbonyl)(4-(dimethylamino)benzyl) amino)propanoate* ***21***

General procedure M: using amine hydrochloride **20** (3.00 g, 19.5 mmol), 4-(*N*,*N*-dimethylamino)benzaldehyde (3.49 g, 23.4 mmol), and Boc_2O (3.15 g, 14.4 mmol), chromatography (silica, 0–5 % EtOAc/DCM) afforded **21** as a yellow oil (1.443 g, 21 %); R_f 0.32 (silica, 20 % EtOAc/hexane). λ_{max}/nm (EtOH) 302.5, 258.5. ν_{max}/cm^{-1} 2976 (C–H), 2934 (C–H), 2805 (C–H), 1732 (C=O), 1688, 1614, 1522, 1464, 1409, 1364, 1243, 1156, 1107, 1045, 1019, 946, 885, 802, 772. δ_H (500 MHz, $CDCl_3$) 1.22–1.25 (3H, t, CH_3, *J* 7.2), 1.48 (9H, s, $C(CH_3)_3$), 2.47–2.52 (2H, m, CH_2), 2.93 (6H, s, $N(CH_3)_2$), 3.39–3.46 (2H, m, CH_2), 4.08–4.12 (2H, q, Me–CH_2–CO, *J* 7.2), 4.35 (2H, s, BocN–CH_2Ar), 6.68–6.70 (2H, m, Ar–H), 7.12 (2H, m, br, Ar–H). δ_C (125 MHz, $CDCl_3$) 14.2, 28.5, 40.7, 60.4, 79.8, 112.7, 126.1, 128.5, 129.0, 150.0. *m/z* (LC-MS ESI+) 351.4 $[M + H]^+$; *m/z* (HRMS) 351.2276; calc. for $C_{19}H_{31}N_2O_4$ $[M + H]^+$ 351.2278.

tert-*Butyl-4-(dimethylamino)benzyl-(3-(methoxy(methyl) amino)-3-oxopropyl)carbamate* ***22***

General procedure N: using ester **21** (1.38 g, 3.94 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.54 g, 15.8 mmol) and isopropylmagnesium chloride (2 M in THF, 15.76 mL, 31.52 mmol), work-up with diethyl ether (4 × 20 mL) and distilled water (10 mL) afforded **22** as a yellow oil (1.342 g, 93 %); R_f 0.33 (silica, 15 % EtOAc/DCM). λ_{max}/nm (EtOH) 302.5 and 258.5. ν_{max}/cm^{-1} 2972 (C–H), 2932 (C–H), 2800 (C–H), 1686 (C=O), 1660 (C=O), 1614, 1522, 1462, 1409, 1364, 1244, 1160, 1130, 992, 946, 886, 802, 773. δ_H (500 MHz, $CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 2.58–2.66 (2H, m, CH_2), 2.92 (6H, s, $N(CH_3)_2$), 3.15 (3H, s, NCH_3), 3.42–3.47 (2H, m, CH_2), 3.63 (3H, s, OCH_3), 4.36 (2H, s, BocN–CH_2Ar), 6.68–6.69 (2H, m, Ar–H), 7.15 (2H, m, Ar–H). *m/z* (LC-MS ESI+) 366.4 $[M + H]^+$.

tert-*Butyl-4-(dimethylamino)benzyl-(3-oxopropyl) carbamate* ***23***

General procedure O: using Weinreb amide **22** (454 mg, 1.24 mmol), chromatography (silica, 0–5 % EtOAc/DCM) afforded **23** as a colourless oil (273.6 mg, 72 %). δ_H (500 MHz, $CDCl_3$) 1.48 (9H, s, br, $C(CH_3)_3$), 2.51–2.60 (2H, m, CH_2), 2.93 (6H, s, $N(CH_3)_2$), 3.46–3.48 (2H, m, CH_2), 4.34 (2H, s, br, BocN–CH_2Ar), 6.68–6.70 (2H, m, Ar–H), 7.11 (2H, m, br, Ar–H). *m/z* (LC-MS ESI+) 307.4 $[M + H]^+$.

tert-*Butyl-4-(dimethylamino)benzyl-(3-morpholino-4-phenylbutyl)carbamate* ***24***

General procedure P: using aldehyde **23** (280 mg, 0.91 mmol), morpholine (96 µL, 96 mg, 1.10 mmol), 1*H*-benzotriazole (217 mg, 1.82 mmol), and benzylmagnesium chloride (2 M in THF, 0.91 mL, 1.82 mmol), chromatography (silica, 2–50 % EtOAc/DCM) afforded **24** as a yellow oil (253.8 mg, 61 %); R_f 0.29 (20 % EtOAc/DCM). λ_{max}/nm (EtOH) 258.5. ν_{max}/cm^{-1} 2930 (C–H), 2851 (C–H), 2810 (C–H), 1684 (C=O), 1614, 1522, 1453, 1414, 1364, 1233, 1152, 1115, 947, 880, 802, 733, 699. δ_H (500 MHz, [D6]DMSO, 130°C) 1.39 (9H, s, $C(CH_3)_3$), 1.43–1.48 (1H, m, Alk–H), 1.49–1.56 (1H, m, Alk–H), 1.60–1.66 (1H, m, Alk–H), 2.38–2.43 (1H, dd, PhCH_2, *J* 8.2 and 13.3), 2.56–2.58 (2H, m, Alk–H), 2.63–2.66 (1H, m, Alk–H), 2.91–2.94 (7H, m, $N(CH_3)_2$ and Alk–H), 3.04–3.09 (1H, m, Alk–H), 3.20–3.25 (1H, m, Alk–H), 3.52–3.59 (4H, m, $2CH_2$–O), 4.18–4.27 (2H, m, BocN–CH_2Ar), 6.69–6.71 (2H, d, Ar–H, *J* 8.6), 7.03–7.04 (2H, d, Ar–H, *J* 8.2), 7.18–7.19 (3H, m, Ar–H), 7.26–7.29 (2H, m, Alk–H). δ_C (125 MHz, [D6]DMSO, 130°C) 27.9, 28.0, 28.1, 40.2, 63.5, 66.8, 112.3, 125.6, 125.8, 128.1, 128.5, 129.1, 149.7. *m/z* (LC-MS ESI+) 468.6 $[M + H]^+$. Analytical HPLC: 93.7 %.

N,N-*Dimethyl-4-(((3-morpholino-4-phenylbutyl)amino) methyl)aniline* ***25***

General procedure Q: using carbamate **24** (100 mg, 0.21 mmol) in DCM (0.7 mL) with trifluoroacetic acid (0.7 mL), workup with saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (2 × 10 mL) afforded **25** as a brown oil (77 mg, 100 %); R_f 0.43 (silica, 10 % MeOH/DCM). λ_{max}/nm (EtOH) 263.5. ν_{max}/cm^{-1} 3418 (N–H), 2923 (C–H), 2852 (C–H), 2813 (C–H), 1677, 1614, 1526, 1454, 1354, 1197, 1168, 1113, 1065, 945, 798, 700. δ_H (500 MHz, $CDCl_3$) 1.24–1.27 (1H, m, Alk–H), 1.52–1.57 (1H, m, Alk–H), 2.02–2.09 (1H, m, Alk–H), 2.28–2.33 (1H, dd, Alk–H, *J* 10.8 and 12.9), 2.45–2.49 (2H, m, Alk–H), 2.66–2.71 (1H, m, Alk–H), 2.72–2.77 (1H, m, Alk–H), 2.92–3.01 (9H, m, $N(CH_3)_2$ and Alk–H), 3.12–3.15 (1H, m, Alk–H), 3.54–3.59 (4H, m, Alk–H), 3.66–3.68 (1H, d, Alk–H, *J* 13.1), 4.09–4.11 (1H, d, Alk–H, *J* 12.8), 6.68–6.69 (2H, d, Ar–H, *J* 8.9), 7.07–7.08 (2H, d, Ar–H, *J* 7.5), 7.18–7.23 (3H, m, Ar–H), 7.26–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 24.3, 31.0, 34.1, 40.3, 47.7, 51.1, 66.9, 69.0, 112.5, 126.5, 128.7, 129.1, 130.3, 138.9, 151.0. *m/z* (LC-MS ESI+) 368.6 $[M + H]^+$; *m/z* (HRMS) 368.2699; calc. for $C_{23}H_{34}ON_3$ $[M + H]^+$ 368.2696. Analytical HPLC: 95.4 %.

tert-*Butyl-(3-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)-4-phenylbutyl)carbamate* ***26***

General procedure R: using amine **18** (291 mg, 1.11 mmol) and Boc_2O (255 mg, 1.17 mmol) at room temperature overnight, chromatography (silica, 0–5 % EtOAc/hexane) afforded **26** as a yellow oil (243 mg, 65 %); R_f 0.25 (silica, 10 % EtOAc/DCM). λ_{max}/nm (EtOH) 259.5. ν_{max}/cm^{-1} 3338 (N–H), 2973 (C–H), 2930 (C–H), 2868 (C–H), 1698 (C=O), 1521, 1454, 1365, 1250, 1169, 1086, 739, 700. δ_H (500 MHz, $CDCl_3$) 1.15 (3H, s, Alk-CH_3), 1.22 (3H, s, Alk-CH_3), 1.23–1.39 (4H, m, Alk–H), 1.42 (9H, s, $C(CH_3)_3$), 1.47–1.53 (3H, m, Alk–H), 1.76–1.81 (1H, m, Alk–H), 2.39–2.49 (1H, m, PhCH_2), 2.63–2.75 (1H, dd, PhCH_2, *J* 5.2 and 13.5), 3.01–3.12 (2H, m, AlkCH_2–NH), 3.56–3.65 (1H, m, CH_2–O), 3.72–3.79 (1H, m, CH_2–O), 4.24–4.34 (1H, m, NH), 7.12–7.13 (2H, d, Ar–H, *J* 7.2), 7.17–7.20 (1H, Ar–H, *J* 7.3), 7.26–7.29 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 21.8, 28.4, 29.2, 29.5, 30.1, 31.9, 33.0, 37.0, 38.8, 39.3, 40.0, 42.6, 61.8, 71.8, 125.9, 128.4, 129.0, 141.2, 155.9. *m/z* (LC-MS ESI+) molecular ion not observed; *m/z* (HRMS) 362.2693; calc. for $C_{22}H_{36}O_3N$ $[M + H]^+$ 362.2690. Analytical HPLC: 99.5 %.

*2-(Tetrahydro-2*H*-pyran-4-yl)acetic Acid* ***37***

General procedure S: using ester **9** (1.20 g, 7.59 mmol) and lithium hydroxide monohydrate (6.37 g, 151.7 mmol), workup

with distilled water (20 mL) and EtOAc (2 × 20 mL) afforded **37** as a yellow solid (1.04 g, 95 %); R_f 0.26 (silica, 80 % EtOAc/petrol). Mp 56–60°C. λ_{max}/nm (EtOH) no distinguishable peak. ν_{max}/cm^{-1} 2934 (C–H), 2914 (br) (O–H), 2841 (C–H), 1703 (C=O), 1640, 1444, 1411, 1303, 1279, 1233, 1173, 1132, 1086, 1018, 981, 916, 885, 855. δ_H (500 MHz, $CDCl_3$) 1.33–1.41 (2H, qd, CH_2CH, *J* 4.3 and 12.0), 1.67–1.70 (2H, m, CH_2CH), 1.98–2.07 (1H, m, CH), 2.29–2.31 (2H, d, CH_2CO_2H, *J* 7.1), 3.39–3.44 (2H, td, CH_2–O, *J* 1.9 and 12.0), 3.95–3.98 (2H, m, CH_2–O), 10.88 (1H, s, br, CO_2H). δ_C (125 MHz, $CDCl_3$) 31.8, 32.6, 41.0, 67.7, 177.8. *m/z* (LC-MS ESI+) 143.1 $[M-H]^-$; *m/z* (HRMS) 143.0718; calc. for $C_7H_{11}O_3$ $[M-H]^-$ 143.0714.

(R)- and (S)-4-Benzyl-3-(2-(tetrahydro-2H-pyran-4-yl) acetyl)oxazolidin-2-one (R)-**38** and (S)-**38**

General procedure T: using carboxylic acid **37** (1.07 g, 7.42 mmol), triethylamine (2.07 mL, 1.50 g, 14.84 mmol), pivaloyl chloride (1.09 mL, 1.07 g, 8.90 mmol), lithium chloride (0.5 M in THF, 17.8 mL, 8.90 mmol), and (*R*)- or (*S*)-4-benzyl-2-oxazolidinone (1.58 g, 8.90 mmol), chromatography (silica, 30 % EtOAc/petrol) afforded (*R*)-enantiomer (*R*)-**38** and (*S*)-enantiomer (*S*)-**38** as white solids (1.59 g, 66 %, and 1.72 g, 73 % respectively); R_f 0.29 (silica, 30 % EtOAc/petrol). Mp 102–104°C. $[\alpha]_D^{24.5}$ −83.3° (*R*) (*c* 1.02 in EtOH), $[\alpha]_D^{24.1}$ +92.1° (*S*) (*c* 1.01 in EtOH). λ_{max}/nm (EtOH) 205.0. ν_{max}/cm^{-1} 2948 (C–H), 2912 (C–H), 2832 (C–H), 1760 (C=O), 1687 (C=O), 1395, 1354, 1279, 1211 (C–O), 1141, 1092, 1053, 984, 850, 765, 697. δ_H (500 MHz, $CDCl_3$) 1.36–1.47 (2H, m, OCH_2CH_2CH), 1.67–1.73 (2H, m, OCH_2CH_2CH), 2.11–2.20 (1H, m, C*H*CH_2CO), 2.74–2.78 (1H, dd, CH_2CO, *J* 9.7 and 13.4), 2.82–2.86 (1H, dd, PhCH_2, *J* 7.0 and 16.7), 2.92–2.97 (1H, dd, PhCH_2, *J* 6.6 and 16.7), 3.28–3.32 (1H, dd, CH_2CO, *J* 3.3 and 13.3), 3.41–3.47 (2H, m, CH_2–O), 3.95–3.98 (2H, m, CH_2–O), 4.16–4.23 (2H, m, CH_2OCON), 4.66–4.70 (1H, m, CHN), 7.20–7.22 (2H, d, Ar–H, *J* 7.0), 7.28–7.30 (1H, m, Ar–H), 7.32–7.36 (2H, m, Ar–H). δ_C (125 MHz, $CDCl_3$) 31.4, 32.8, 38.0, 42.2, 55.2, 66.3, 67.8, 67.9, 127.4, 129.0, 129.4, 135.2, 153.5, 171.8. *m/z* (LC-MS ESI+) 304.4 $[M+H]^+$; *m/z* (HRMS) 304.1546; calc. for $C_{17}H_{22}O_4N$ $[M+H]^+$ 304.1543.

(R)- or (S)-3-Phenyl-2-(tetrahydro-2H-pyran-4-yl)propan-1-ol (R)- or (S)-**40**

General procedure U: using (*R*,*R*)- or (*S*,*S*)-oxazolidin-2-one (*R*,*R*)-**39** (1.86 g, 4.73 mmol) or (*S*,*S*)-**39** (1.57 g, 4.00 mmol) and lithium triethylborohydride (1 M in THF, 5.0 equiv.), chromatography (silica, 60 % Et_2O/petrol) afforded (*R*)-enantiomer (*R*)-**40** and (*S*)-enantiomer (*S*)-**40** as yellow oils (453 mg, 41 %, and 380 mg, 41 % respectively). Analytical data equivalent to (*rac*)-**40**; $[\alpha]_D^{21.4}$ +16.1° (*R*) (*c* 0.87 in EtOH), $[\alpha]_D^{21.2}$ −16.0° (*S*) (*c* 0.84 in EtOH).

SRB Assay for Cell-Growth Inhibition

GI_{50} values were determined using the SRB assay as previously described.[25] Cells were seeded in 96-well plates 24 h before treatment with compounds at 0.01–100 μM concentration in 0.5 % (v/v – final concentration) DMSO for 72 h. Cells were then fixed in 50 % trichloroacetic acid (w/v), stained with 0.4 % SRB (w/v), and unbound dye removed with 1 % (v/v) acetic acid. Bound dye was solubilised by addition of 100 μL 10 mM Tris pH 9.5 and absorbance measured by a Microplate Reader (Model 680, Bio-Rad) at 570 nm. Data were presented as the percentage relative to DMSO-only control and GI_{50} values calculated using *Prism* software (version 6.0) based on a standard point-to-point curve with 1000 segments.

SCF-SKP2 E3 Ligase: p27 Degradation Redistribution® Assay (Thermo Scientific)

The HeLa cell-based assay was developed by Thermo Scientific (cat. no. R04–052–01) and uses Redistribution® technology to monitor the stabilisation of GFP-tagged p27. Controlled by a standard cytomegalovirus (CMV) promoter, p27-GFP is constitutively expressed and contains a T187D mutation to mimic the SKP2-targeted phosphorylated state, thereby resulting in constant degradation. Stabilisation of the p27-GFP therefore reflects reduced degradation and acts as a reporter of SKP2 activity. Cells were grown in DMEM growth medium, high glucose, without L-glutamine and sodium pyruvate (Thermo Fisher Scientific cat. no. SH30081) supplemented with 10 % (v/v) FBS (Sigma), 2 mM L-glutamine (Sigma), 1 % (v/v) penicillin-streptomycin solution (Sigma), and 0.5 mg mL^{-1} G418 (Calbiochem), and incubated at 37°C in 5 % CO_2. The assay was performed according to manufacturer's protocol. Cells were treated with inhibitors diluted in DMSO to a final concentration of 0.5 % (v/v) in the assay medium (culture medium without G418) at concentrations ranging from 0.01 to 100 μM. Cellular p27-GFP fluorescence was measured following a 24-h incubation with the compounds. Readings were taken for Hoechst staining, which reflects the cell number (355, 460 nm) and GFP (385, 520 nm) excitation and emission wavelengths respectively. Data were corrected for background fluorescence, normalised for Hoechst staining to account for any cell loss, and presented as a percentage of the fluorescence observed following treatment with the proteasome inhibitor MG132 at 5 μM, a concentration previously shown to produce maximal fluorescence. EC_{50} values were calculated using *Graphpad Prism* software (version 6.0).

Supplementary Material

Chiral HPLC results as well as selected ^{1}H and ^{13}C NMR spectra are available on the Journal's website.

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