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PAPER

Potent enantioselective inhibition of DNA-dependent protein kinase (DNA-PK) by atropisomeric chromenone derivatives†

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Substitution at the 7-position of the chromen-4-one pharmacophore of 8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholino-4*H*-chromen-4-one NU7441, a potent and selective DNA-dependent protein kinase (DNA-PK) inhibitor, with allyl, *n*-propyl or methyl enabled the resolution by chiral HPLC of atropisomers. Biological evaluation against DNA-PK of each pair of atropisomers showed a marked difference in potency, with biological activity residing exclusively in the laevorotatory enantiomer.

Introduction

Arguably, the most cytotoxic of all DNA lesions are DNA double-strand breaks (DSBs), the principal cytotoxic lesions produced by IR and radiomimetic chemicals, and which are also generated when the DNA replication apparatus encounters other DNA lesions, such as DNA single-strand breaks (SSBs). It is now well established that the two major mechanisms involved in DSB repair are largely distinct and complementary pathways, namely homologous recombination (HR) and non-homologous end-joining (NHEJ).[1,2] DNA-dependent protein kinase (DNA-PK), a member of the phosphatidylinositol (PI[a]) 3-kinase related kinase (PIKK) family, is a multi-component serine/threonine protein kinase that plays a key role in NHEJ of the repair of mammalian DNA DSBs.[3,4] Interestingly, human cell lines with defects in DNA-PK function are hypersensitive to agents that elicit DNA DSBs.[5,6] Therefore, by impeding DNA DSB repair, selective DNA-PK inhibitors have potential application as radio- and chemo-potentiators in the treatment of cancer.[7–11]

Using a homology model of the ATP-binding site of DNA-PK, derived from the crystal structure of PI3Kγ,[12] we have identified potent DNA-PK inhibitors with defined structure–activity relationships (SARs).[13–18] Notably, the incorporation of a dibenzothiophen-4-yl substituent at the 8-position of 2-morpholino-4*H*-chromen-4-one conferred excellent inhibitory activity against DNA-PK, as exemplified by NU7441 (**1**, IC_{50} = 28 nM).[19] With a view to optimising the biological and pharmaceutical properties of **1**, both the core chromenone scaffold and the dibenzothiophen-4-yl moiety have been systematically modified. Importantly, our interest in substituted dibenzothiophenes arose from the preparation of the highly potent DNA-PK inhibitor KU-0060648 (**2**; IC_{50} = 5 nM).[20] More recently, alkylation at the 3-position of the dibenzothiophen-4-yl group of **1** has provided valuable SAR information that has enabled further refinement of the homology model (Fig. 1).[21] Thus, two possible poses were identified for the interaction of **1** with the ATP-binding domain of DNA-PK: conformation (a) positions the chromenone and dibenzothiophene rings in an orthogonal relationship, with the alternative 'in plane' pose (b) being energetically less favorable.

The introduction of an allyl (**3**), *n*-propyl (**4**) or methyl (**5**) substituent at the dibenzothiophene 3-position generated stable pairs of atropisomers due to restricted rotation between the chromen-4-one and dibenzothiophene rings. Interestingly, the differential DNA-PK inhibitory activity between the two atropisomers gave an indication of the interaction of this class of inhibitors within the ATP-binding domain of DNA-PK, albeit with a loss of potency compared with the parent compound **1**. Thus, the homology model predicts that atropisomer **5** may only adopt the energetically preferred orthogonal conformation [Fig. 1, (c)], with the methyl substituent being accommodated within a narrow hydrophobic pocket in the ATP-binding pocket.

During the past decade, increasing interest has been given to enantioselective binding of chiral drugs with their biological targets and the implication for both pharmacological activity and toxicity.[22–29] In light of this, we decided to explore further the configuration of the biphenyl junction between the

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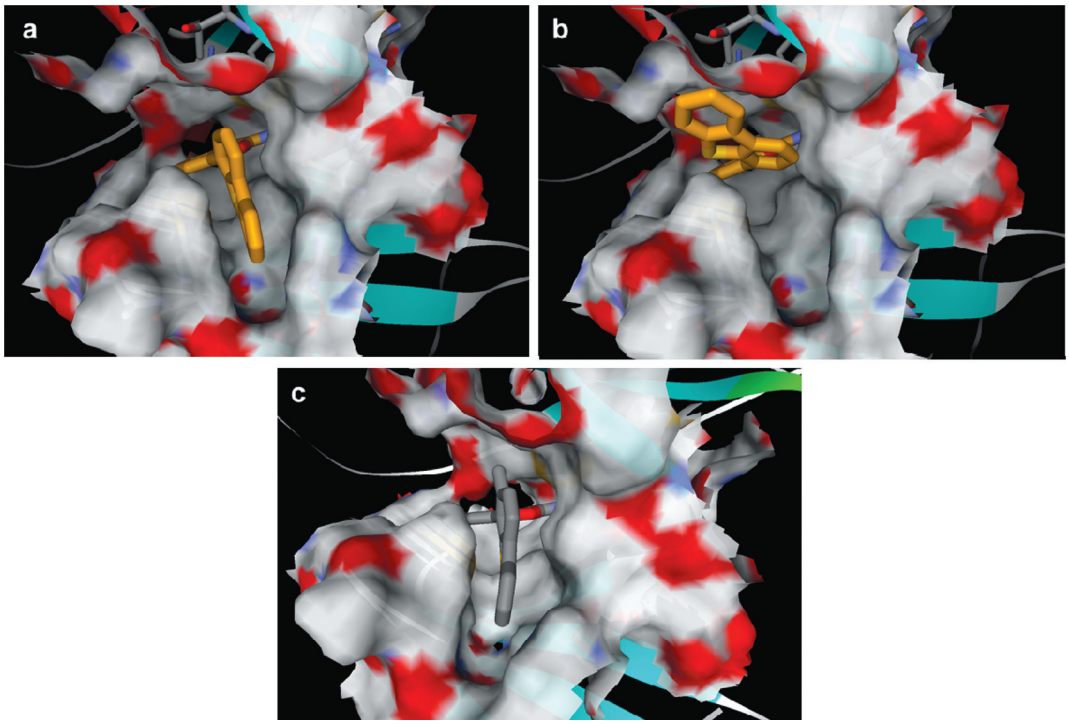


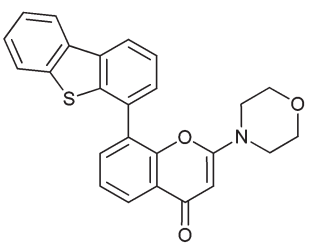
Fig. 1 Homology model of the ATP-binding site of the DNA-dependent protein kinase (DNA-PK) used to guide inhibitor design. The 3D model was constructed on the basis of the known X-ray crystal structure of PI3Kγ from the RCSB protein data bank (PDB ID: 1E7V) as a template, and with the DNA-PK sequence from Swiss-Port (ID: PRKDC_DICDI) using Prime in the Maestro molecular modelling program (licensed from Schrödinger, LGG). NU7441 (**1**) is represented in (a) an orthogonal, and (b) 'in plane' pose. (c) Representation of **5** in the orthogonal pose within the ATP-binding domain.

chromen-4-one and dibenzothiophene rings and studied the effect, upon biological activity, of alkylation at the 7-position of the chromenone core (**6–8**). Accordingly, the homology model suggested that substitution on the chromenone rather than on the dibenzothiophene ring would be less detrimental to the interaction of the inhibitor with the ATP-binding pocket of DNA-PK. As well as the prospect of refining the homology model further, the synthesis of these DNA-PK inhibitors offered the opportunity to further probe this region of the ATP-binding domain of the enzyme.

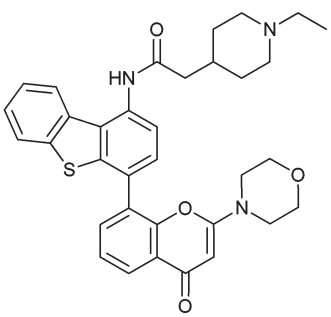
Results and discussion

Synthesis of 7-substituted dibenzothiophenylchromen-4-ones

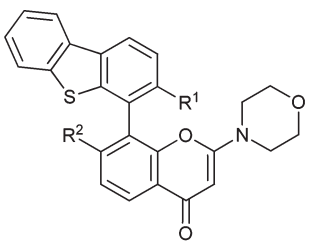
To introduce substituents at the chromen-4-one 7-position, we used a similar approach to that recently reported.[21] Alkylation of phenol **9** with allyl bromide, followed by a Claisen rearrangement furnished the 7-allylchromen-4-one derivative **11** (Scheme 1).[30] Subsequent catalytic hydrogenation of **11** followed by triflation gave the *n*-propyl intermediate **12** in 60%



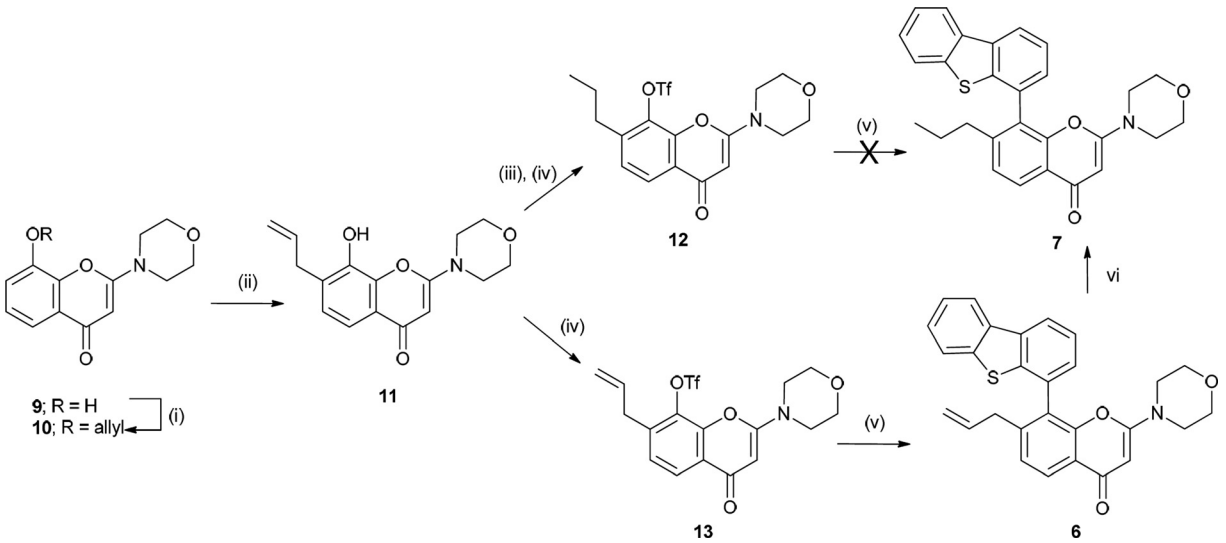
1; NU7441



2; KU-0060648



3; R^1 = allyl, R^2 = H
4; R^1 = *n*-propyl, R^2 = H
5; R^1 = methyl, R^2 = H
6; R^1 = H, R^2 = allyl
7; R^1 = H, R^2 = *n*-propyl
8; R^1 = H, R^2 = methyl



Scheme 1 *Reagents and conditions*: (i) allylbromide, K_2CO_3, CH_3CN, reflux, 2.5 h, 95%; (ii) DMF, 160 °C, 18 h, 95%; (iii) H_2, Pd/C, MeOH, r.t., 85%; (iv) $PhNTf_2$, Et_3N, THF, reflux, 4 h, then r.t., 16 h, 70% for **12** and 80% for **13**; (v) dibenzo[*b*,*d*]thiophen-4-ylboronic acid, $Pd(PPh_3)_4$ (5 mol%), K_2CO_3, 1,4-dioxane, reflux, 18 h, 65%; (vi) H_2, Pd/C, MeOH, r.t., 97%.

overall yield, while direct triflation of **11** afforded the corresponding allyl analogue **13** in 80% yield. Suzuki–Miyaura cross-coupling of the chromenone **13** with dibenzo[*b*,*d*]-thiophen-4-ylboronic acid gave the 7-substituted analogue of NU7441 (**6**). Further catalytic hydrogenation of **6** yielded the corresponding *n*-propyl derivative **7**.

Introduction of a 7-methyl substituent on the chromenone core was attempted *via* directed *ortho*-metallation (D*o*M),[31–34] but without any success. We therefore undertook the synthesis of the chromenone scaffold, and introduced the methyl group as early as possible in this multi-step approach (Scheme 2). Regioselective bromination of the methyl 2,3-dihydroxybenzoate **15** followed by methylation of the hydroxyl groups afforded the bromide key intermediate **17**.[35] Subsequent palladium-mediated Suzuki–Miyaura cross-coupling using trimethylboroxine gave the desired methyl derivative **18** in excellent 91% yield. The next steps of the synthesis followed the synthetic route we previously published, involving judicious protection and Rh-mediated deprotection of the hydroxyl with allyl groups.[36] The resulting 8-hydroxy-7-methyl-2-morpholino-4*H*-chromen-4-one **25** was converted into the corresponding triflate, and cross-coupled with dibenzo[*b*,*d*]thiophen-4-ylboronic acid assisted by microwave irradiation. The desired methyl derivative **8** was successfully isolated in 96% yield.

Atropisomer resolution by chiral HPLC

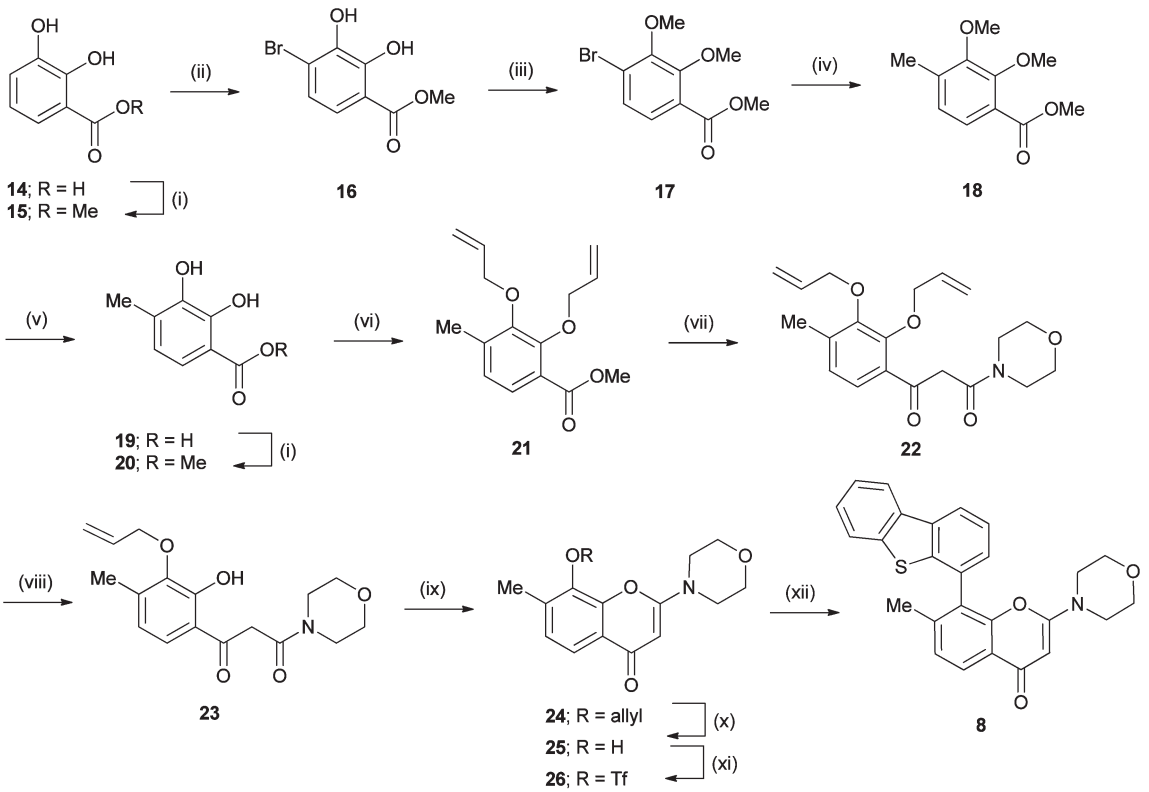
Separation of atropisomers of chromenones **6–8** was achieved by analytical chiral HPLC, where two distinct peaks were observed. Acting as a control, NU7441 gave only a single peak under these conditions because the lack of a chromenone substituent lowers the barrier to rotation about the chromenone–dibenzothiophene σ-bond (Fig. 2). The excellent separation subsequently achieved by semi-preparative chiral HPLC enabled the clear-cut resolution of each pair of atropisomers of **6–8**. Optical activities of the members of each pair were established by polarimetry, with the values confirming the resolution of the (−) and (+) stereoisomers (Table 1). The atropisomers proved remarkably stable to thermal racemisation. Thus, only chemical decomposition occurred after heating atropisomer **6-(+)** in mesitylene up to 170 °C for 10 h, with no evidence of racemisation by chiral HPLC analysis.

Biological evaluation

DNA-PK inhibitory activity was determined for the racemates **6–8**, together with each of the corresponding pairs of separate atropisomers and the results are summarised in Table 1. The introduction of an allyl (**6**) or *n*-propyl (**7**) side chain at the 7-position of the chromen-4-one resulted in an approximately 9- and 3-fold reduction in potency of the racemic compounds, respectively, compared with **1**. Importantly, substitution with a methyl group at the chromenone 7-position was tolerated, with racemic **8** showing a 7-fold improvement in potency compared with the parent compound **1**. A comparison of the DNA-PK inhibitory activity of each enantiomeric pair of chromenones **6–8** revealed that biological activity resided exclusively in the (−)-atropisomer ('eutomer') in each case, with the antipodal (+)-atropisomer ('distomer') proving to be inactive at 100 μM. In the present study, the identification of resolvable atropisomers, and the observation that only the (−)-enantiomer exhibits activity against DNA-PK, has important implications for refining the homology model.

Conclusions

By impeding DNA DSB repair, DNA-PK inhibitors have considerable therapeutic potential as chemo- and radio-potentiating agents in the therapy of cancer. As a prominent member of the PIKK family of atypical serine–threonine kinases, DNA-PK is,



Scheme 2 *Reagents and conditions*: (i) conc. H_2SO_4, MeOH, reflux, 18 h, 97% for **15** and 91% for **20**; (ii) Br_2, *t*-butylamine, DCM, toluene, −78 °C, 2 h to r.t., 35%; (iii) MeI, K_2CO_3, acetone, reflux, 2 h, 90%; (iv) trimethylboroxine, $PdCl_2$(dppf)·DCM, Cs_2CO_3, 1,4-dioxane, MW, 120 °C, 2 h, 91%; (v) Me_3SiI, DCM, reflux, 24 h, 88%; (vi) allyl bromide, Cs_2CO_3, THF, reflux, 15 h, 84%; (vii) LDA, acetylmorpholine, THF, −10 °C, 1.5 h, then r.t., 1 h, 91%; (viii) Bu_4NI, $TiCl_4$, DCM, −78 °C, 30 min, then −78 °C to 0 °C, 1 h, 99%; (ix) Tf_2O, DCM, 0 °C to r.t., 20 h, 51%; (x) $RhCl(PPh_3)_3$, DABCO, EtOH, reflux, 2 h, 85%; (xi) $PhNTf_2$, Cs_2CO_3, THF, MW, 100 °C, 20 min, 90%; (xii) dibenzo[*b*,*d*]thiophen-4-ylboronic acid, $PdCl_2$(d-*t*-bpf), Cs_2CO_3, 1,4-dioxane, MW, 80 °C, 30 min, 96%.

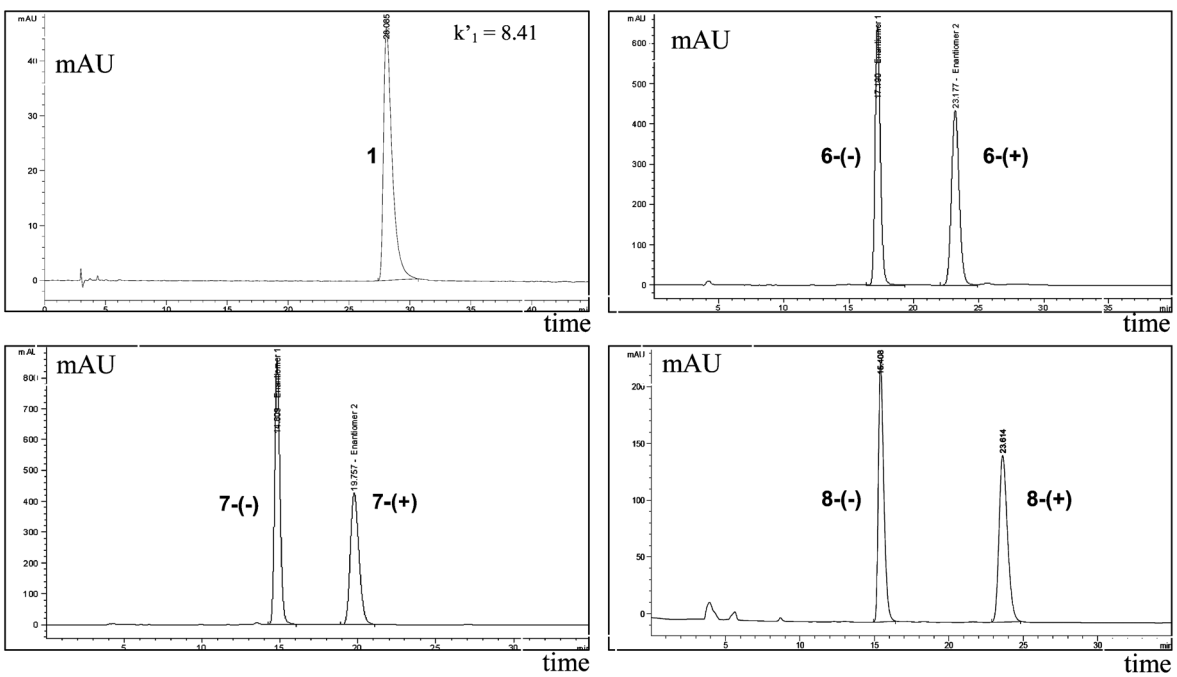
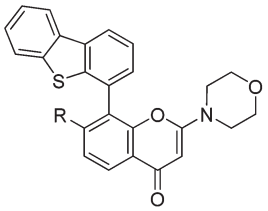


Fig. 2 Resolution of racemates **6**, **7** and **8** by chiral HPLC. Conditions used for compound **6**: Chiralpak IA, 250 × 10 mm, 5 μm, mobile phase: *tert*-butyl methyl ether–ethanol (80 : 20); **7**: Chiralpak IA, 250 × 10 mm, 5 μm, mobile phase: *tert*-butyl methyl ether–ethanol (75 : 25); **8**: Chiralpak AD-H, 250 × 10 mm, 5 μm, mobile phase: hexane–ethanol (75 : 25).

Table 1 Inhibition of DNA-PK by 7-substituted chromen-4-one derivatives (**6–8**)



R	Compound number	DNA-PK inhibition[a] (IC_{50}/μM)	Specific rotation
H	NU7441	0.028	0
Allyl	6	0.249[b] ± 0.011	0
Allyl	6-(−)	0.125[b] ± 0.005	$[\alpha_D]^{27.7} = -218$
Allyl	6-(+)	>10[b]	$[\alpha_D]^{27.8} = +218$
n-Propyl	7	0.066 ± 0.010	0
n-Propyl	7-(−)	0.060 ± 0.005	$[\alpha_D]^{27.9} = -202$
n-Propyl	7-(+)	>10	$[\alpha_D]^{28.0} = +202$
Me	8	0.005 ± 0.003	0
Me	8-(−)	0.002 ± 0.001	$[\alpha_D]^{21.2} = -254$
Me	8-(+)	7	$[\alpha_D]^{27.5} = +254$

[a] DNA-PK inhibitory activity was determined as described in ref. 37. [b] DNA-PK inhibitory activity was determined as described in ref. 17.

in principle, amenable to the development of highly kinase-selective ATP-competitive inhibitors, owing to the low sequence homology of the ATP-binding domain with other protein kinases.[38] Nevertheless, troublesome off-target kinase-inhibitory activity associated with currently available small-molecule DNA-PK inhibitors, including **2**, continues to represent an obstacle to preclinical development. As such, there is a requirement for inhibitors that combine good pharmaceutical properties with high potency and selectivity for DNA-PK over related kinases, most notably members of the PI 3-kinase family. In this paper, we report the results of ongoing studies designed to improve the selectivity of chromenone-based inhibitors through substitution on the core chromen-4-one. The introduction of alkyl substituents at the chromenone 7-position has enabled the resolution of relatively stable atropisomers, which exhibit differential DNA-PK inhibitory activity and show potency comparable to, and in one case (methyl substitution, compound **8**) superior to, the parent compound **1**. Studies are in progress to elucidate the absolute configuration of the biologically active (−)-atropisomers, prior to conducting further studies with the DNA-PK homology model. The possibility of introducing water-solubilising substituents on the dibenzothiophene ring of atropisomeric DNA-PK inhibitors, analogously to that achieved with **2**, is also under consideration.

Experimental

Materials and methods

Solvents were purchased as anhydrous. Reactions needing microwave irradiation were carried out in an Initiator™ Sixty Biotage apparatus. Chiral HPLC analysis was performed on an Agilent 1200 HPLC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a binary pump, an autosampler, a column oven and a diode array detector and controlled by Agilent Chemstation software. Analyses were performed isocratically using Daicel (Chiral Technologies Europe, Illkirch, France) columns. Conditions used for compound **6**: Chiralpak IA 250 × 4.6 mm, 5 μm, with a mobile phase consisting of *tert*-butyl methyl ether–ethanol (80 : 20) at a flow rate of 1.0 mL min^{-1} with detection at 254 nm; conditions used for compound **7**: Chiralpak IA 250 × 4.6 mm, 5 μm, with a mobile phase consisting of *tert*-butyl methyl ether–ethanol (75 : 25) at a flow rate of 1.0 mL min^{-1} with detection at 254 nm; conditions used for compound **8**: Chiralpak AD-H 250 × 4.6 mm, 5 μm with a mobile phase consisting of hexane–ethanol (75 : 25) at a flow rate of 1.0 mL min^{-1} with detection at 254 nm. Semi-preparative chiral resolution was carried out using a Varian (Varian Inc., Walnut Creek, CA, USA) ProStar HPLC system equipped with 2 ProStar 210 solvent delivery modules, a ProStar 320 UV-Vis detector and a ProStar 701 fraction collector and controlled by a Varian Star Chromatography Workstation. Separations were performed using Daicel columns. Conditions used for compound **6**: Chiralpak IA, 250 × 10 mm, 5 μm, with a mobile phase consisting of *tert*-butyl methyl ether–ethanol (80 : 20) at a flow rate of 3.8 mL min^{-1} with detection at 254 nm; conditions used for compound **7**: Chiralpak IA, 250 × 10 mm, 5 μm, with a mobile phase consisting of *tert*-butyl methyl ether–ethanol (75 : 25) at a flow rate of 3.8 mL min^{-1} with detection at 254 nm; conditions used for compound **8**: Chiralpak AD-H, 250 × 10 mm, 5 μm, with a mobile phase consisting of hexane–ethanol (75 : 25) at a flow rate of 3.8 mL min^{-1} with detection at 254 nm. Petrol refers to petroleum ether (bp 40–60 °C, reagent grade, Aldrich). NMR spectra were recorded on a Bruker Spectrospin AC 300E spectrometer (^{1}H 300 MHz or ^{13}C 75 MHz) or a Bruker Avance III 500 spectrometer (^{1}H 500 MHz or ^{13}C 125 MHz). IR spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR. Optical rotations were measured on a PolAAR3001 instrument. LC-MS was carried out on a Micromass Platform LC system operating in positive and negative ion electrospray mode (**6**, **7**), employing a 20 × 4.6 mm, Waters SymmetryShield RP18, a 5 μm column and a 3.5 min gradient elution of 0.1% formic acid and acetonitrile (5–95%) running at a flow rate of 3 mL min^{-1} or a Waters Acquity SQD operating in positive and negative ion electrospray mode (**8**), employing a 50 × 2.1 mm, Waters Acquity UPLC BEH C18, 1.7 μm column and a 1.5 min gradient elution of 0.1% formic acid and acetonitrile (5–95%) running at a flow rate of 0.6 mL min^{-1}. HRMS were measured using a Finnigan MAT 95 XP or a Finnigan MAT 900 XLT by the EPSRC National Mass Spectrometry Service Centre (Swansea).

8-Hydroxy-2-morpholino-4*H*-chromen-4-one (9). A solution of 2-morpholino-4-oxo-4*H*-chromen-8-yl trifluoromethanesulfonate (2 g, 5.3 mmol) and 2 M NaOH (26 mL) in methanol (10 mL) and 1,4-dioxane (20 mL) was stirred at room temperature overnight. The solvent was removed from the reaction mixture *in vacuo*. The resulting crude solid was purified by medium pressure column chromatography (EtOAc–MeOH 9 : 1), followed by recrystallisation from MeOH, yielding the title compound as a white crystalline solid (1.01 g, 78%): R_f = 0.36

(EtOAc–MeOH 9 : 1); mp: 240–242 °C; IR (cm^{-1}) 2951, 2866, 1638, 1575, 1448, 1410, 1350, 1243, 1114, 1028; λ_{max} (EtOH)/nm 303; ^{1}H NMR (300 MHz, MeOD-d_4) δ 3.62 (4H, t, J = 4.4 Hz, CH_2–morpholine), 3.73 (4H, t, J = 4.4 Hz, CH_2–morpholine), 5.85 (1H, s, H-3), 7.24–7.27 (2H, m, H–Ar), 7.36 (1H, dd, J = 2.2 and 7.0 Hz, H–Ar); ^{13}C NMR (75 MHz, MeOD-d_4) δ 45.9 (CH_2–*N*–morpholine), 67.1 (CH_2–*O*–morpholine), 87.1 (C-3), 115.6 (C-6), 119.9 (C-8), 124.3 (C-5), 126.1 (C-7), 145.9 (C-10), 148.8 (C-9), 164.4 (C-2), 180.0 (C-4); MS(ES+) m/z = 248.1 $[M + H]^+$; HRMS calcd for $C_{13}H_{14}NO_4$ $[M + H]^+$ 248.0923, found 248.0917.

8-Allyloxy-2-morpholino-4*H*-chromen-4-one (10). To a solution of 8-hydroxy-2-morpholino-4*H*-chromen-4-one (0.467 g, 1.89 mmol) in acetonitrile (20 mL) containing suspended potassium carbonate (0.522 g, 3.78 mmol) was added dropwise allyl bromide (0.33 mL, 3.78 mmol). The mixture was heated at reflux for 2.5 h, cooled and filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by medium pressure column chromatography (EtOAc–MeOH 9 : 1) yielding the title compound as a pale yellow solid (0.506 g, 95%): R_f = 0.55 (EtOAc–MeOH 9 : 1); IR (cm^{-1}) 2951, 2866, 1638, 1575, 1448, 1410, 1350, 1243, 1114, 1028; λ_{max} (EtOH)/nm 235; ^{1}H NMR (500 MHz, MeOD-d_4) δ 3.64 (4H, t, J = 5.1 Hz, CH_2–morpholine), 3.83 (4H, t, J = 5.1 Hz, CH_2–morpholine), 4.72–4.73 (2H, m, CH_2–CH=CH_2), 5.32 (1H, dd, J = 1.6 and 10.6 Hz, CH_2–CH=CH_2*cis*), 5.47 (1H, dd, J = 1.6 and 17.4 Hz, CH_2–CH=CH_2*trans*), 5.61 (1H, s, H-3), 6.13 (1H, ddt, J = 5.1, 10.6 and 17.4 Hz, CH_2–C*H*=CH_2), 7.32–7.33 (2H, m, H–Ar), 7.59–7.62 (1H, m, H–Ar); ^{13}C NMR (75 MHz, MeOD-d_4) δ 46.4 (CH_2–*N*–morpholine), 67.5 (CH_2–*O*–morpholine), 71.7 (CH_2–CH=CH_2), 87.7 (C-3), 117.6 (C–Ar–H), 118.0 (C–Ar–H), 118.4 (CH_2–CH=CH_2), 125.0 (C-5), 126.2 (C–Ar–H), 134.7 (CH_2–CH=CH_2), 145.9 (C-10), 148.8 (C-9), 164.8 (C-2), 179.8 (C-4); MS(ES+) m/z = 288.1 $[M + H]^+$; HRMS calcd for $C_{16}H_{18}NO_4$ $[M + H]^+$ 288.1236, found 288.1230.

7-Allyl-8-hydroxy-2-morpholino-4*H*-chromen-4-one (11). A solution of 8-allyloxy-2-morpholino-4*H*-chromen-4-one (0.443 g, 1.54 mmol) in DMF (10 mL) was heated at 160 °C overnight. The solvent was then removed *in vacuo*. Purification by medium pressure column chromatography (EtOAc–MeOH 9 : 1) followed by recrystallisation from MeOH–petrol 1 : 1 yielded the title compound as a white solid (0.420 g, 95%): R_f = 0.50 (EtOAc–MeOH 9 : 1); IR (cm^{-1}) 2917, 2859, 1605, 1548, 1418, 1359, 1245, 1191, 1113, 1030; λ_{max} (EtOH)/nm 260; ^{1}H NMR (500 MHz, MeOD-d_4) δ 3.52 (2H, d, J = 6.5 Hz, CH_2–CH=CH_2), 3.66–3.68 (4H, m, CH_2–morpholine), 3.82 (4H, t, J = 4.9 Hz, CH_2–morpholine), 5.04–5.09 (2H, m, CH_2–CH=CH_2), 5.56 (1H, s, H-3), 5.97–6.05 (1H, m, CH_2–C*H*=CH_2), 7.14 (1H, d, J = 8.2 Hz, H–Ar), 7.47 (1H, d, J = 8.2 Hz, H–Ar); ^{13}C NMR (125 MHz, MeOD-d_4) δ 35.2 (CH_2–CH=CH_2), 46.1 (CH_2–*N*–morpholine), 67.1 (CH_2–*O*–morpholine), 87.1 (C-3), 116.3 (C-6), 118.0 (CH_2–CH=CH_2), 124.4 (C-5), 127.1 (C-7), 134.2 (CH_2–CH=CH_2), 137.2 (C-8), 145.2 (C-10), 148.3 (C-9), 164.5 (C-2), 179.7 (C-4); MS(ES+) m/z = 288.1 $[M + H]^+$; HRMS calcd for $C_{16}H_{18}NO_4$ $[M + H]^+$ 288.1236, found 288.1230.

2-Morpholino-4-oxo-7-propyl-4*H*-chromen-8-yl trifluoromethanesulfonate (12). To an ice bath cooled solution of 7-allyl-8-hydroxy-2-morpholino-4*H*-chromen-4-one (0.157 g, 0.547 mmol) in methanol (35 mL) was added Pd/C (10%, 0.048 g). The reaction mixture was stirred at room temperature for 16 h under H_2 atmosphere. The reaction mixture was filtered over a pad of celite and concentrated *in vacuo*, recrystallisation from methanol yielded 8-hydroxy-2-morpholino-7-propyl-4*H*-chromen-4-one as an off-white solid (0.134 g, 85%). A solution of 8-hydroxy-2-morpholino-7-propyl-4*H*-chromen-4-one intermediate (0.064 g, 0.219 mmol), triethylamine (0.1 mL, 0.658 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (0.117 g, 0.329 mmol) in THF (12 mL) was heated at reflux for 4 h. The mixture was subsequently stirred at room temperature for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) yielding the title compound as a pale brown crystalline solid (0.065 g, 70%): R_f = 0.47 (EtOAc–MeOH 95 : 5); mp: 115–116 °C; IR (cm^{-1}) 2924, 2853, 1597, 1550, 1449, 1409, 1253, 1211, 1109, 1012, 979, 875, 802; λ_{max} (EtOH)/nm 311, 213; ^{1}H NMR (500 MHz, MeOD-d_4) δ 1.00 (3H, t, J = 7.5 Hz, CH_2–CH_2–CH_3) 1.72 (2H, sextet, J = 7.5 Hz, CH_2–CH_2–CH_3), 2.80 (2H, t, J = 7.4 Hz, CH_2–CH_2–CH_3), 3.68 (4H, t, J = 4.0 Hz, CH_2–morpholine), 3.82 (4H, t, J = 4.0 Hz, CH_2–morpholine), 5.63 (1H, s, H-3), 7.46 (1H, d, J = 8.1 Hz, H–Ar), 8.01 (1H, d, J = 8.1 Hz, H–Ar); ^{13}C NMR (125 MHz, MeOD-d_4) δ 14.0 (CH_2–CH_2–*C*H_3), 24.3 (CH_2–*C*H_2–CH_3), 32.9 (*C*H_2–CH_2–CH_3), 46.5 (CH_2–*N*–morpholine), 67.0 (CH_2–*O*–morpholine), 87.6 (C-3), 121.8 (C-5), 124.6 (C-6), 126.1 (C-7), 135.7 (C-8), 141.9 (C-9), 147.3 (C-10), 164.1 (C-2), 177.5 (C-4); MS(ES+) m/z = 422.2 $[M + H]^+$; HRMS calcd for $C_{17}H_{19}F_3NO_6S$ $[M + H]^+$ 422.0885, found 422.0874.

7-Allyl-2-morpholino-4-oxo-4*H*-chromen-8-yl trifluoromethanesulfonate (13). A solution of 7-allyl-8-hydroxy-2-morpholino-4*H*-chromen-4-one (0.300 g, 1.05 mmol), triethylamine (0.53 mL, 3.80 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (1.36 g, 3.80 mmol) in THF (10 mL) was heated at reflux for 4 h. The mixture was subsequently stirred at room temperature for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) yielding the title compound as a white crystalline solid (0.349 g, 80%): R_f = 0.65 (EtOAc–MeOH 95 : 5); IR (cm^{-1}) 3067, 2948, 2865, 1601, 1550, 1415, 1202, 1134, 1110; λ_{max} (EtOH)/nm 314; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54 (2H, d, J = 6.6 Hz, CH_2–CH=CH_2), 3.58 (4H, t, J = 4.9 Hz, CH_2–morpholine), 3.83 (4H, t, J = 4.9 Hz, CH_2–morpholine), 5.16 (1H, dd, J = 1.4 and 17.0 Hz, CH_2–CH=CH_2*trans*), 5.22 (1H, dd, J = 1.3 and 10.0 Hz, CH_2–CH=CH_2*cis*), 5.55 (1H, s, H-3), 5.85–5.93 (1H, m, CH_2–C*H*=CH_2), 7.30 (1H, d, J = 8.3 Hz, H–Ar), 8.09 (1H, d, J = 8.3 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.8 (*C*H_2–CH=CH_2), 45.3 (CH_2–*N*–morpholine), 66.0 (CH_2–*O*–morpholine), 87.6 (C-3), 118.53 (CH_2–CH=*C*H_2), 118.56 (1C, q, J = 320 Hz, OSO_2CF_3), 123.4 (C-5), 125.1 (C-6), 126.4 (C-7),

133.6 (CH_2–*C*H═CH_2), 134.2 (C-9), 137.5 (C-8), 146.1 (C-10), 162.3 (C-2), 175.5 (C-4); MS(ES+) *m*/*z* = 420.2 $[M + H]^+$; HRMS calcd for $C_{17}H_{17}F_3NO_6S$ $[M + H]^+$ 420.0729, found 420.0720.

7-Allyl-8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholino-4*H*-chromen-4-one (6). Potassium carbonate (0.100 g, 0.715 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) were sequentially added to a degassed solution of 7-allyl-2-morpholino-4-oxo-4*H*-chromen-8-yl trifluoromethanesulfonate (0.100 g, 0.238 mmol), dibenzo-[*b*,*d*]thiophen-4-ylboronic acid (0.109 g, 0.477 mmol) in anhydrous 1,4-dioxane (5 mL). The reaction mixture was heated at reflux for 18 h. Upon cooling, the mixture was filtered through a pad of celite and the organic solvent removed *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) to yield the title compound as an off-white solid (0.070 g, 65%): R_f = 0.38 (EtOAc–MeOH 95 : 5); mp: 204–205 °C; IR (cm^{-1}) 2951, 2919, 2848, 1620, 1584, 1555, 1410, 1381, 1350, 1227, 1107; λ_{max} (EtOH)/nm 236, 313; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85–2.95 (4H, m, CH_2–morpholine), 3.22–3.36 (2H, m, C*H*$_2$–CH═CH_2), 3.38–3.90 (4H, m, CH_2–morpholine), 4.88 (1H, dd, *J* = 1.5 and 19.0 Hz, CH_2–CH═C*H*$_2$*trans*), 4.97 (1H, dd, *J* = 1.4 and 10.0 Hz, CH_2–CH═C*H*$_2$*cis*), 5.50 (1H, s, H-3), 5.76–5.85 (1H, m, CH_2–C*H*═CH_2), 7.37 (1H, dd, *J* = 1.0 and 7.3 Hz, H–Ar), 7.41 (1H, d, *J* = 8.2 Hz), 7.46–7.52 (2H, m, H–Ar), 7.58 (1H, dd, *J* = 7.4 and 7.5 Hz, H–Ar), 7.79 (1H, d, *J* = 7.0 Hz, H–Ar), 8.20–8.23 (3H, m, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.8 (*C*H_2–CH═CH_2), 44.5 (CH_2–*N*–morpholine), 65.8 (CH_2–*O*–morpholine), 86.8 (C-3), 117.0 (CH_2–CH═*C*H_2), 121.3 (C–Ar), 121.4 (C–Ar), 122.0 (C–Ar), 123.9 (C–Ar), 124.8 (C–Ar), 124.9 (C–Ar), 125.6 (C–Ar), 126.4 (C–Ar), 127.3 (C–Ar), 127.5 (C–Ar), 128.2 (C–Ar), 130.0 (C–Ar), 135.6 (C–Ar), 135.9 (C–Ar), 136.2 (CH_2–*C*H═CH_2), 139.4 (C–Ar), 140.7 (C–Ar), 144.0 (C–Ar), 151.3 (C-10), 162.3 (C-2), 177.1 (C-4); MS (ES+) *m*/*z* = 454.3 $[M + H]^+$; HRMS calcd for $C_{28}H_{24}NO_3S$ $[M + H]^+$ 454.1471, found 454.1474.

8-(Dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholino-7-propyl-4*H*-chromen-4-one (7). To an ice bath cooled solution of 7-allyl-8-(dibenzo[*b*,*d*]thiophen-4-yl)-2-morpholino-4*H*-chromen-4-one (0.038 g, 0.084 mmol) in methanol (15 mL) was added Pd/C (10%, 0.019 g). The reaction mixture was stirred at room temperature for 18 h under H_2 atmosphere. The reaction mixture was filtered over a pad of celite and concentrated *in vacuo*, recrystallisation from MeOH gave the title compound as a white crystalline solid (0.037 g, 97%); R_f = 0.63 (EtOAc–MeOH 95 : 5); mp 219–220 °C; IR (cm^{-1}) 3066, 2950, 2922, 2862, 1624, 1587, 155, 1411, 1387, 1298, 1246, 1109; λ_{max} (EtOH)/nm 235, 311; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (3H, t, *J* = 7.4 Hz, CH_2–CH_2–C*H*$_3$), 1.48 (2H, sextet, *J* = 7.5 Hz, CH_2–C*H*$_2$–CH_3), 2.46 (1H, dt, *J* = 7.5 and 13.7 Hz, C*H*$_2$–CH_2–CH_3), 2.61 (1H, dt, *J* = 7.5 and 13.7 Hz, C*H*$_2$–CH_2–CH_3), 2.80–2.91 (4H, m, CH_2–morpholine), 3.31–3.39 (4H, m, CH_2–morpholine), 5.45 (1H, s, H-3), 7.37 (1H, dd, *J* = 1.0 and 7.3 Hz, H–Ar), 7.0 (1H, d, *J* = 8.2 Hz, H–Ar), 7.43–7.50 (2H, m, H–Ar), 7.56 (1H, dd, *J* = 7.5 and 7.6 Hz, H–Ar), 7.75–7.79 (1H, m, H–Ar), 8.15–8.22 (3H, m, H–Ar); ^{13}C (125 MHz, $CDCl_3$) δ 14.1 (CH_2–CH_2–*C*H_3), 24.4 (CH_2–*C*H_2–CH_3), 35.6 (*C*H_2–CH_2–CH_3), 44.5 (CH_2–*N*–morpholine), 65.8 (CH_2–*O*–morpholine), 86.8 (C-3), 121.0 (C–Ar), 121.3 (C–Ar), 122.0 (C–Ar), 123.1 (C–Ar), 124.8 (C–Ar), 124.9 (C–Ar), 125.5 (C–Ar), 126.3 (C–Ar), 127.3 (C–Ar), 127.4 (C–Ar), 128.3 (C–Ar), 130.5 (C–Ar), 135.7 (C–Ar), 135.9 (C–Ar), 139.5 (C–Ar), 140.9 (C–Ar), 146.8 (C–Ar), 151.3 (C–Ar), 162.4 (C-2), 177.4 (C-4); MS(ES+) *m*/*z* = 455.6 $[M + H]^+$; HRMS calcd for $C_{28}H_{26}NO_3S$ $[M + H]^+$ 456.1628 found 456.1626.

2,3-Dihydroxymethylbenzoate (15). To a solution of the 2,3-dihydroxybenzoic acid (1 g, 6.5 mmol) in MeOH (10 mL) at 0–5 °C was added dropwise conc. sulfuric acid (0.7 mL). The reaction mixture was heated to reflux and stirred for 18 h. The solvent was removed from the reaction mixture *in vacuo*, diluted with EtOAc and a saturated aqueous solution of $NaHCO_3$ was added until effervescing ceased. The aqueous layer was extracted into EtOAc, the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product that was purified by medium pressure column chromatography (petrol–EtOAc 9 : 1) to yield the title compound as beige crystals (1.06 g, 97%): R_f = 0.24 (petrol–EtOAc 9 : 1); mp: 81–83 °C (lit. 81 °C);[39] IR (cm^{-1}) 3456, 2152, 1669, 1458, 1433, 1311, 1260, 1191, 1147, 1005, 907, 834, 753, 718; λ_{max} (EtOH)/nm 249, 321; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (3H, s, $COOCH_3$), 5.65 (1H, s, OH), 6.72 (1H, dd, *J* = 7.9, 8.0 Hz, H–Ar), 7.04 (1H, d, *J* = 7.9 Hz, H–Ar), 7.28 (1H, d, *J* = 8.0 Hz, H–Ar), 10.82 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.6 (OCH_3), 112.5 (C-1), 119.4 (C-5), 119.9 (C-4), 120.7 (C-6), 145.2 (C-3), 149.0 (C-2), 170.9 (C═O); MS (ES+) *m*/*z* = 169.1 $[M + H]^+$; HRMS calcd for $C_8H_9O_4$ $[M + H]^+$ 169.0495, found 169.0491.

2,3-Dihydroxy-4-bromo methylbenzoate (16). Bromine (1.1 mL, 21.4 mmol) was added dropwise to a solution of *tert*-butylamine (3.7 mL, 35.7 mmol) in toluene (36 mL) and DCM (6 mL) at −60 °C. The reaction mixture was cooled to −78 °C and 2,3-dihydroxymethylbenzoate (3.0 g, 17.8 mmol) in DCM (15 mL) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 30 min and then warmed to room temperature slowly. The reaction mixture was diluted with EtOAc (50 mL) and washed with 1 M HCl (2 × 50 mL). The aqueous phase was extracted into EtOAc and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (petrol–EtOAc 9 : 1) yielding the title compound as a white solid (1.55 g, 35%): R_f = 0.26 (petrol–EtOAc 9 : 1); mp: 76–78 °C; IR (cm^{-1}) 3383, 3154, 2921, 2852, 1661, 1605, 1442, 1309, 1184, 1151, 1125, 1003, 872, 799, 761, 727; λ_{max} (EtOH)/nm 215, 259, 317; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (3H, s, $COOCH_3$), 5.96 (1H, s, OH), 6.97 (1H, d, *J* = 8.7 Hz, H–Ar), 7.19 (1H, d, *J* = 8.7 Hz, H–Ar), 11.03 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.8 (OCH_3), 111.6 (C-1), 114.6 (C-4), 120.8 (C-6), 123.0 (C-5), 142.9 (C-3), 149.3 (C-2), 170.5 (C═O); MS (ES+) *m*/*z* = 247.1, 249.1 (100%) $[M + H]^+$, 215.0, 217.0 (50%); HRMS calcd for $C_8H_8BrO_4$ (^{79}Br) $[M + H]^+$ 246.9600, found 246.9604.

2,3-Dimethoxy-4-bromo methylbenzoate (17). A mixture of 2,3-dihydroxy-4-bromo methylbenzoate (2.2 g, 9.0 mmol), potassium carbonate (3.7 g, 27.0 mmol), methyl iodide (5.6 mL,

90.0 mmol) and acetone (50 mL) was heated at reflux for 2.5 h, cooled to room temperature, a saturated aqueous solution of $NaHCO_3$ (30 mL) was introduced and the reaction mixture stirred for 10 min. The reaction mixture was extracted into EtOAc, the organic phase was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (petrol–EtOAc 9 : 1) yielding the title compound as a colourless oil (2.2 g, 90%): R_f = 0.37 (petrol–EtOAc 9 : 1); IR (cm^{-1}) 2942, 1729, 1576, 1457, 1398, 1285, 1236, 1139, 1027, 1003, 881, 852, 784, 748; λ_{max} (EtOH)/nm 210, 240; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (3H, s, OCH_3), 3.84 (3H, s, $COOCH_3$), 3.88 (3H, s, OCH_3), 7.27 (1H, d, J = 8.5 Hz, H–Ar), 7.34 (1H, d, J = 8.5 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.3 ($COO\mathit{C}H_3$), 60.8 (OCH_3), 61.8 (OCH_3), 122.6 (C-4), 125.5 (C-1), 126.6 (C-6), 127.8 (C-5), 151.7 (C-3), 154.3 (C-2), 165.7 (C═O); MS (ES+) m/z = 243.1, 245.1 (100%) $[M - 2Me]^+$, 275.1, 277.1 (20%) $[M + H]^+$; HRMS calcd for $C_{10}H_{12}{}^{79}BrO_4$ $[M + H]^+$ 274.9913, found 274.9919.

2,3-Dimethoxy-4-methyl methylbenzoate (18). $PdCl_2$(dppf)·DCM (0.3 g, 5 mol%) was added to a degassed solution of 2,3-dimethoxy-4-bromo methylbenzoate (2.1 g, 7.5 mmol), trimethyl boroxine (1.4 mL, 9.7 mmol) and caesium carbonate (3.4 g, 10.5 mmol) in 1,4-dioxane (10 mL). The mixture was heated under microwave irradiation at 120 °C for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with a saturated aqueous solution of NH_4Cl (50 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed *in vacuo* to give the crude product that was purified by medium pressure column chromatography (petrol–EtOAc 9 : 1) to yield the title compound as a colourless oil (1.4 g, 91%): R_f = 0.35 (petrol–EtOAc 9 : 1); IR (cm^{-1}) 2943, 1727, 1604, 1462, 1402, 1260, 1204, 1133, 1064, 1023, 998, 924, 875, 791, 756, 684; λ_{max} (EtOH)/nm 207, 240; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 3.83 (3H, s, $COOCH_3$), 3.84 (3H, s, OCH_3), 6.87 (1H, d, J = 8.5 Hz, H–Ar), 7.37 (1H, d, J = 8.5 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2 (CH_3), 52.0 ($COO\mathit{C}H_3$), 60.3 (OCH_3), 61.4 (OCH_3), 123.6 (C-1), 125.5 (C-5), 125.7 (C-6), 137.5 (C-4) 153.3 (C-3), 153.4 (C-2), 166.4 (C═O); MS (ES+) m/z = 179.2 (100%) $[M - 2Me]^+$, 199.1 (70%); HRMS calcd for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.0965, found 211.0964.

2,3-Dihydroxy-4-methylbenzoic acid (19). Iodotrimethylsilane (4.2 mL, 30.9 mmol) was added dropwise to a solution of 2,3-dimethoxy-4-methyl methylbenzoate (1.0 g, 5.2 mmol) in DCM (10 mL) and the reaction mixture heated at reflux for 23 h. In parallel, three reactions were completed, the reaction mixtures were cooled and to each reaction mixture MeOH (5 mL) was added to destroy the excess silane. The three reaction mixtures were combined and the organic solvent was removed *in vacuo*. The crude product was diluted with EtOAc (50 mL) and extracted with 1 M NaOH (15 mL). The resulting aqueous phase was acidified with 1 M HCl to pH 2 and extracted into EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*, the title compound was isolated as a brown solid (2.3 g, 88%) and was used without further purification: R_f = 0.20 (Si-C18, H_2O–MeOH 0.1% formic acid 1 : 1); mp: 195–197 °C; IR (cm^{-1}) 3514, 2598, 1624, 1457, 1387, 1305, 1266, 1232, 1157, 1045, 967, 861, 765, 734; λ_{max} (EtOH)/nm 211, 249, 308; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (3H, s, CH_3), 6.43 (1H, d, J = 8.1 Hz, H–Ar), 7.05 (1H, d, J = 8.1 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1 (CH_3), 113.1 (C-1), 121.6 (C-5), 126.0 (C-6), 139.7 (C-4), 147.4 (C-3), 156.4 (C-2), 173.7 (C═O); MS (ES+) m/z = 169.2 $[M + H]^+$; HRMS calcd for $C_8H_9O_4$ $[M + H]^+$ 169.0495, found 169.0491.

2,3-Dihydroxy-4-methyl methylbenzoate (20). To a solution of the 2,3-dihydroxy-4-methylbenzoic acid (0.320 g, 0.19 mmol) in MeOH (20 mL) at 0–5 °C was added dropwise conc. sulfuric acid (0.25 mL). The reaction mixture was heated to reflux and stirred for 18 h. The solvent was removed from the reaction mixture *in vacuo*, diluted with EtOAc and a saturated aqueous solution of $NaHCO_3$ was added until effervescing ceased. The aqueous layer was extracted into EtOAc, the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product that was purified by medium pressure column chromatography (petrol–EtOAc 9 : 1) to yield the title compound as an off-white solid (0.314 g, 91%): R_f = 0.27 (petrol–EtOAc 9 : 1); mp: 41–43 °C; IR (cm^{-1}) 3482, 2967, 2922, 1668, 1433, 1305, 1248, 1197, 1156, 1049, 995, 943, 902, 766, 735, 703; λ_{max} (EtOH)/nm 210, 251, 312; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 5.63 (1H, s, OH), 6.59 (1H, d, J = 8.2 Hz, H–Ar), 7.19 (1H, d, J = 8.2 Hz, H–Ar), 10.78 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4 (CH_3), 52.6 (OCH_3), 120.5 (C-6), 121.1 (C-5), 123.8 (C-1), 130.6 (C-4), 142.5 (C-3), 148.4 (C-2), 172.2 (C═O); MS (ES+) m/z = 183.2 $[M + H]^+$; HRMS calcd for $C_9H_{11}O_4$ $[M + H]^+$ 183.0652, found 183.0647.

2,3-Diallyloxy-4-methyl methylbenzoate (21). A mixture of 2,3-dihydroxy-4-methyl methylbenzoate (0.314 g, 1.72 mmol), allyl bromide (0.60 mL, 0.70 mmol) and caesium carbonate (1.45 g, 4.46 mmol) in THF (10 mL) was heated at reflux for 15 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (15 mL) and washed with water (10 mL). The aqueous phase was re-extracted with EtOAc (2 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (petrol–EtOAc 9 : 1) to give the title compound as a colourless oil (0.379 g, 84%): R_f = 0.30 (petrol–EtOAc, 9 : 1); IR (cm^{-1}) 1949, 1728, 1603, 1414, 1261, 1197, 1135, 1059, 986, 923, 829, 787, 756, 710; λ_{max} (EtOH)/nm 210, 239, 285; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.44 (2H, d, J = 3.5 Hz, $C\mathit{H}_2$–CH═CH_2), 4.49 (2H, d, J = 5.9 Hz, $C\mathit{H}_2$–CH═CH_2), 5.17 (2H, dd, J = 1.5 and 10.2 Hz, CH_2–CH═$C\mathit{H}_2$*cis*) 5.30 (2H, dd, J = 1.5 and 17.1, Hz, CH_2–CH═$C\mathit{H}_2$*trans*), 5.97–6.10 (2H, m, CH_2–$C\mathit{H}$═CH_2), 6.88 (1H, d, J = 8.0 Hz, H–Ar), 7.39 (1H, d, J = 8.0 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6 (CH_3), 52.1 ($COO\mathit{C}H_3$), 73.8 ($\mathit{C}H_2$CH═CH_2), 75.0 ($\mathit{C}H_2$CH═CH_2), 117.8 (CH_2CH═$\mathit{C}H_2$), 117.9 (CH_2CH═$\mathit{C}H_2$), 124.0 (C-1), 125.7 ($CH_2\mathit{C}$H═CH_2), 125.8 ($CH_2\mathit{C}$H═CH_2), 134.0 (2C, C-2 and C-3), 137.8 (C-4), 151.3 (C-3), 152.1 (C-2), 166.5 (C═O); MS (ES+) m/z = 263.2 $[M + H]^+$; HRMS calcd for $C_{15}H_{19}O_4$ $[M + H]^+$ 263.1278, found 263.1280.

1-(2,3-Bis(allyloxy)-4-methylphenyl)-3-morpholinopropane-1,3-dione (22). To a solution of diisopropylamine (0.80 mL, 5.7 mmol) in THF (20 mL) at −78 °C was added dropwise *n*BuLi (2.5 M in hexanes, 2.28 mL, 5.7 mmol), the reaction mixture was warmed to 0 °C and stirred for 20 min. The reaction mix was cooled to −10 °C, acetyl morpholine (0.44 mL, 3.8 mmol) was added dropwise and stirring was continued at −10 °C for 90 min. To the reaction mixture was added dropwise 2,3-diallyloxy-4-methyl methylbenzoate (0.500 g, 1.9 mmol) in THF (5 mL) and stirring continued at room temperature for 1 h. The reaction mixture was diluted with water, acidified to pH 1 with a 1 M HCl and extracted with DCM (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (DCM–MeOH 95 : 5) to give the title compound as a colourless oil (0.690 g, quant.): R_f = 0.46 (DCM–MeOH 95 : 5); IR (cm^{-1}) 2965, 2923, 2856, 2358, 1621, 1413, 1232; λ_{max} (EtOH)/nm 260, 300; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (2.1H, s, CH_3), 2.29 (2.4H, s, CH_3), 2.30 (3H, s, CH_3), 3.48–3.70 (20H, m, CH_2–morpholine), 4.14 (2H, s, C(O)CH_2C(O)), 4.35 (1.4H, d, J = 5.6 Hz, CH_2–CH=CH_2), 4.47 (2H, d, J = 5.7 Hz, CH_2–CH=CH_2), 4.49–4.51 (3.2H, m, CH_2–CH=CH_2), 4.63 (2H, d, J = 5.7 Hz, CH_2–CH=CH_2), 4.67 (1.4H, d, J = 5.6 Hz, CH_2–CH=CH_2), 5.21–5.28 (4.9H, m, CH_2–CH=CH_2), 5.34–5.46 (5.1H, m, CH_2–CH=CH_2), 6.02–6.17 (5H, m, CH_2–C*H*=CH_2), 6.26 (0.8H, s, enolic CH), 6.28 (0.7H, s, enolic CH), 6.91 (0.7H, d, J = 8.1 Hz, H–Ar), 6.98 (1.8H, d, J = 8.0 Hz, H–Ar), 7.35 (0.7H, d, J = 8.1 Hz, H–Ar), 7.40 (1H, d, J = 8.0 Hz, H–Ar), 7.48 (0.8H, d, J = 8.0 Hz, H–Ar), 15.1 (0.7H, s, enolic OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 16.6, 16.7, 41.6, 41.9, 42.0, 42.2, 46.8, 46.9, 47.0, 49.5, 66.7, 66.8, 66.9, 66.96, 66.99, 67.0, 73.2, 73.3, 73.8, 73.9, 74.0, 74.3, 74.7, 88.3, 117.2, 117.4, 117.7, 117.8, 118.1, 118.4, 123.8, 124.9, 125.7, 126.2, 126.3, 127.4, 131.0, 132.4, 133.8, 134.1, 134.2, 134.5, 135.7, 137.1, 139.0, 148.1, 150.3, 150.57, 150.59, 151.0, 151.5, 166.4, 169.2, 170.6, 194.9; MS (ES+) m/z = 360.1 $[M + H]^+$; HRMS calcd for $C_{20}H_{26}NO_5$ $[M + H]^+$ 360.1805, found 360.1803.

1-(3-(Allyloxy)-2-hydroxy-4-methylphenyl)-3-morpholinopropane-1,3-dione (23). To a solution of tetrabutylammonium iodide (0.257 g, 0.70 mmol) in DCM (2 mL) at −78 °C was added titanium(IV) chloride (1 M in DCM, 0.70 mL, 0.70 mmol) dropwise over 30 min, and the mixture was stirred for an additional 10 min. 1-(2,3-Bis(allyloxy)-4-methylphenyl)-3-morpholinopropane-1,3-dione (0.119 g, 0.33 mmol) in DCM (2 mL) was added dropwise to give a dark brown solution, which was stirred for 50 min at −78 °C and then allowed to warm to 0 °C over 1 h. The mixture was poured into a saturated aqueous solution of Rochelle's salt (10 mL) and extracted into DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (DCM–MeOH 95 : 5) to give the title compound as a brown oil (0.105 g, 99%): R_f = 0.43 (DCM–MeOH 95 : 5); IR (cm^{-1}) 2965, 2924, 2859, 2358, 1628, 1413, 1337, 1226; λ_{max} (EtOH)/nm 272, 338; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (3H, s, CH_3), 3.46 (2H, t, J = 4.8 Hz, CH_2–morpholine), 3.60–3.64 (6H, m, CH_2–morpholine), 4.05 (2H, s, C(O)CH_2C(O)), 4.51 (2H, d, J = 5.9 Hz, CH_2–CH=CH_2), 5.18 (1H, dd, J = 1.3 and 10.3 Hz, CH_2–CH=CH_2*cis*), 5.32 (1H, dd, J = 1.3 and 17.2 Hz, CH_2–CH=CH_2*trans*), 6.04 (1H, ddt, J = 5.9, 10.3 and 17.2 Hz CH_2–C*H*=CH_2), 6.67 (1H, d, J = 8.3 Hz, H–Ar), 7.41 (1H, d, J = 8.3 Hz, H–Ar), 12.1 (1H, br s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0 (CH_3), 42.3 (CH_2–*N*–morpholine), 45.2 (C(O)-CH_2C(O)), 46.9 (CH_2–*N*–morpholine), 66.5 (CH_2–*O*–morpholine), 66.6 (CH_2–*O*–morpholine), 73.2 (CH_2CH=CH_2), 117.8 (CH_2CH=CH_2), 118.4 (C-1), 120.9 (C-5), 125.2 (C-6), 134.0 (CH_2CH=CH_2), 141.1 (C-4), 145.4 (C-3), 156.2 (C-2), 164.9 (C=O), 199.4 (C=O); MS (ES+) m/z = 320.1 $[M + H]^+$; HRMS calcd for $C_{17}H_{22}NO_5$ $[M + H]^+$ 320.1492, found 320.1493.

8-(Allyloxy)-7-methyl-2-morpholino-4*H*-chromen-4-one (24). To a solution of 1-(2-hydroxy-3-allyloxy-4-methylphenyl)-3-morpholinopropane-1,3-dione (0.497 g, 1.56 mmol) in DCM (15 mL) at 0 °C was added dropwise trifluoromethanesulfonic anhydride (0.65 mL, 3.89 mmol). The reaction mixture was warmed to room temperature and stirred for 7 h. MeOH (10 mL) was added to the reaction mixture which was stirred for 1 h. The solvent was removed *in vacuo* and sodium bicarbonate solution (30 mL) was added to the residue, which was extracted into DCM. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) to give the title compound as an off-white solid (0.238 g, 51%): R_f = 0.38 (EtOAc–MeOH 95 : 5); mp: 123–125 °C; IR (cm^{-1}) 2979, 2942, 2866, 2362, 1646, 1608, 1558, 1397, 1236; λ_{max} (EtOH)/nm 304, 236, 225; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (3H, s, CH_3), 3.51–3.53 (4H, m, CH_2–morpholine) 3.82–3.84 (4H, m, CH_2–morpholine), 4.50 (2H, d, J = 5.6 Hz, CH_2–CH=CH_2), 5.29 (1H, dd, J = 1.3 and 10.4 Hz, CH_2–CH=CH_2*cis*), 5.41 (1H, dd, J = 1.3 and 17.2 Hz, CH_2–CH=CH_2*trans*), 5.47 (1H, s, H-3), 6.03 (1H, ddt, J = 5.6, 10.4 and 17.2 Hz, CH_2–C*H*=CH_2), 7.15 (1H, d, J = 8.3 Hz, H–Ar), 7.79 (1H, d, J = 8.3 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6 (CH_3), 44.9 (CH_2–*N*–morpholine), 66.1 (CH_2–*O*–morpholine), 74.5 (CH_2CH=CH_2), 87.3 (C-3), 118.2 (CH_2CH=CH_2), 120.3 (C-7), 122.6 (C-5), 126.9 (C-6), 133.6 (CH_2CH=CH_2), 136.4 (C-10), 144.5 (C-9), 147.6 (C-8), 162.2 (C-2), 177.9 (C-4); MS (ES+) m/z = 302.0 $[M + H]^+$; HRMS calcd for $C_{17}H_{20}NO_4$ $[M + H]^+$ 302.1387, found 302.1390.

8-Hydroxy-7-methyl-2-morpholino-4*H*-chromen-4-one (25). To a mixture of 2-morpholin-4-yl-7-methyl-8-allyloxychromen-4-one (30 mg, 0.10 mmol) in degassed ethanol (4 mL) was added $RhCl(PPh_3)_3$ (6.4 mg, 0.007 mmol) and DABCO (1.1 mg, 0.010 mmol). The mixture was heated at reflux for 2 h, filtered through a pad of celite and the solvent was removed *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) to give the title compound as a white solid (0.022 g, 85%): R_f = 0.19 (EtOAc–MeOH 95 : 5); mp: 296 °C decomp.; IR (cm^{-1}) 2972, 2916, 2857, 1610, 1550, 1423, 1403, 1349; λ_{max} (EtOH)/nm 303, 239; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (3H, s, CH_3), 3.57 (4H, t, J = 4.9 Hz, CH_2–morpholine), 3.73 (4H, t, J = 4.9 Hz, CH_2–morpholine), 5.44 (1H, s, H-3), 7.11 (1H, d, J = 7.9 Hz, H–Ar), 7.30 (1H, d, J = 7.9 Hz, H–Ar), 9.38 (1H, s, OH); ^{13}C NMR

(125 MHz, DMSO-d_6) δ 16.3 (CH_3), 44.5 (CH_2–*N*–morpholine), 65.4 (CH_2–*O*–morpholine), 86.0 (C-3), 114.2 (C-7), 121.6 (C-5), 126.2 (C-6), 129.4 (C-8), 142.5 (C-9), 143.0 (C-10), 162.1 (C-2), 175.6 (C-4); MS (ES+) *m*/*z* = 262.0 $[M + H]^+$; HRMS calcd for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.1074, found 262.1077.

7-Methyl-2-morpholino-4-oxo-4*H*-chromen-8-yl trifluoromethanesulfonate (26). 8-Hydroxy-7-methyl-2-morpholino-4*H*-chromen-4-one (0.140 g, 0.54 mmol), *N*-phenyl-bis(trifluoromethanesulfonimide) (0.383 g, 1.07 mmol) and caesium carbonate (0.245 g, 0.75 mmol) were suspended in THF (15 mL). The mixture was heated under microwave irradiation at 100 °C for 20 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (50 mL) and water (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) to give the title compound as a white solid (0.190 g, 90%): R_f = 0.39 (EtOAc–MeOH 95 : 5); mp: 193–195 °C; IR (cm^{-1}) 2869, 2362, 2161, 1610, 1595, 1552, 1400, 1361; λ_{max} (EtOH)/nm 311, 215; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (3H, s, CH_3), 3.56–3.58 (4H, m, CH_2–morpholine), 3.82–3.84 (4H, m, CH_2–morpholine), 5.49 (1H, s, H-3), 7.26 (1H, d, *J* = 8.0 Hz, H–Ar), 8.04 (1H, d, *J* = 8.0 Hz, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7 (CH_3), 45.3 (CH_2–*N*–morpholine), 66.1 (CH_2–*O*–morpholine), 87.6 (C-3), 118.6 (1C, q, *J* = 318 Hz, OSO_2CF_3), 123.2 (C-5), 125.0 (C-6), 127.4 (C-7), 134.9 (C-9), 135.7 (C-8), 146.3 (C-10), 162.3 (C-2), 175.6 (C-4); MS (ES+) *m*/*z* 394.0 $[M + H]^+$; HRMS calcd for $C_{15}H_{15}F_3NO_6S$ $[M + H]^+$ 394.0567, found 394.0569.

8-(Dibenzo[*b*,*d*]thiophen-4-yl)-7-methyl-2-morpholino-4*H*-chromen-4-one (8). 2 M Sodium carbonate (0.55 mL, 1.1 mmol) and $Pd(PPh_3)_4$ (0.032 g, 0.027 mmol) were sequentially added to a degassed solution of 7-methyl-2-morpholino-4-oxo-4*H*-chromen-8-yl trifluoromethanesulfonate (0.216 g, 0.55 mmol), dibenzo[*b*,*d*]thiophen-4-ylboronic acid (0.250 g, 1.1 mmol) in 1,4-dioxane (15 mL). The mixture was heated under microwave irradiation at 150 °C for 50 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (50 mL) and water (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by medium pressure column chromatography (EtOAc–MeOH 95 : 5) to yield the title compound as a white solid (0.225 g, 96%): R_f = 0.44 (EtOAc–MeOH 95 : 5); mp: 237–239 °C; IR (cm^{-1}) 2914, 2869, 2161, 1733, 1616, 1589, 1557, 1404, 1246; λ_{max} (EtOH)/nm 311, 287, 233; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (3H, s, CH_3), 2.86–2.95 (4H, m, CH_2–morpholine), 3.40–3.43 (4H, m, CH_2–morpholine), 5.42 (1H, s, H-3), 7.36 (1H, dd, *J* = 1.0 and 7.3 Hz, H–Ar), 7.37 (1H, d, *J* = 8.1 Hz, H–Ar), 7.46–7.52 (2H, m, H–Ar), 7.59 (1H, t, *J* = 7.6 Hz, H–Ar), 7.78–7.80 (1H, m, H–Ar), 8.17 (1H, d, *J* = 8.1 Hz, H–Ar), 8.21–8.23 (2H, m, H–Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1 (CH_3), 44.5 (CH_2–*N*–morpholine), 65.8 (CH_2–*O*–morpholine), 86.8 (C-3), 121.23 (C–Ar), 121.24 (C–Ar), 122.0 (C–Ar), 123.0 (C–Ar), 124.8 (C–Ar), 124.9 (C–Ar), 125.4 (C–Ar), 127.0 (C–Ar), 127.3 (C–Ar), 127.5 (C–Ar), 128.0 (C–Ar), 130.5 (C–Ar), 135.7 (C–Ar), 136.0 (C–Ar), 139.5 (C–Ar), 140.4 (C–Ar), 142.2 (C–Ar), 151.3 (C–Ar), 162.3 (C-2), 177.4 (C-4); MS (ES+) *m*/*z* 428.3 $[M + H]^+$; HRMS calcd for $C_{26}H_{22}NO_3S$ $[M + H]^+$ 428.1315, found 428.1313.

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