An Orally Active, Water-Soluble Neurokinin-1 Receptor Antagonist Suitable for Both Intravenous and Oral Clinical Administration

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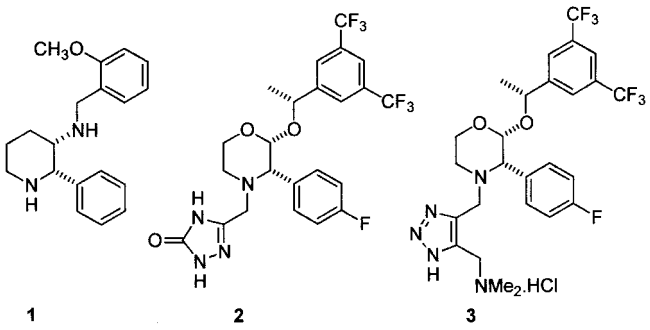
1-(5-{[(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2*H*-1,2,3-triazol-4-yl)-*N*,*N*-dimethylmethanamine hydrochloride **3** is a high affinity, orally active, h-NK_1 receptor antagonist with a long central duration of action and a solubility in water of >100 mg/mL. The construction of the 5-dimethylaminomethyl 1,2,3-triazol-4-yl unit, which incorporates the solubilizing group of **3**, was accomplished by thermal rearrangement of a propargylic azide in the presence of dimethylamine. Compound **3** is highly effective in pre-clinical tests that are relevant to clinical efficacy in emesis and depression.

Introduction

The search for potent, non-peptide antagonists of the human neurokinin-1 (h-NK_1) receptor has been a long standing objective of pharmaceutical research.[1] It has been demonstrated that **1** (CP-99,994), a selective h-NK_1 antagonist, displays anti-emetic activity against a range of emetogens, including those for which conventional therapy might fail.[2] Interest in this area has been further stimulated recently by the disclosure that blockade of central h-NK_1 receptors provides a new and distinct mechanism for antidepressant activity.[3] A recent report from these laboratories described the identification of **2** (MK-0869), a potent, orally active, morpholine acetal-based h-NK_1 antagonist.[4] Although this compound displays an excellent in vivo profile, and is a potent anti-emetic, the low aqueous solubility of **2** required development of a phosphorylated pro-drug for intravenous administration in order to allow maximum flexibility in clinical use.[5] We therefore sought to develop an alternative to **2** which retained the excellent in vivo profile, including long duration of action and excellent CNS penetration, but which would be suitable for intravenous administration in humans without the need for pro-drug modification. We hereby report that **3** fulfills these requirements.

Because the morpholine acetal core of **2** had been optimized to provide compounds with excellent duration of action, we sought to keep this portion of the molecule intact and modify the pendant heterocyclic group. Although substitution of the 3-oxo-1,2,4-triazol-5-yl moiety with a range of heterocycles was investigated, the 5-aminomethyl-substituted 1,2,3-triazol-4-yl group proved to be optimal in terms of CNS penetration and duration. We were able to construct the triazole moiety in such a way that the amine substituent was introduced at the end of the synthesis by taking advantage of a novel triazole synthesis developed by Banert.[6] This allowed a wide range of amines to be efficiently screened as potential solubilizing groups.



1 **2** **3**

Chemistry

The synthesis of the key morpholine acetal **4** has been described previously.[4] Reaction of **4** with two equivalents of 1,4-dichloro-2-butyne in the presence of K_2CO_3 afforded propargyl chloride **5** in 68% yield. The chloride could be displaced with azide at room temperature in 98% yield by treatment with sodium azide in DMSO. Warming the propargylic azide **6** in dioxane with an amine in a sealed tube provided triazoles **7**. This reaction has been shown to proceed via isomerization of the propargylic azide to an allenic azide, followed by cyclization to form a triazafulvene, and finally trapping by the amine.[6] The triazafulvene is a powerful electrophile, and a wide range of other nucleophiles (alcohols and thiols − results not shown) can be introduced at the 5-position of the triazole by application of this reaction (Scheme 1).

Pharmacology

CNS Penetration and Duration of Action. CNS penetration of NK_1 antagonists is essential for their anti-emetic and antidepressant activity in preclinical assays.[8] Central infusion of the selective NK_1 receptor agonist GR73632 in gerbils (a species with human-like NK_1 receptor pharmacology)[9] elicits a vigorous, repeti-

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Scheme 1

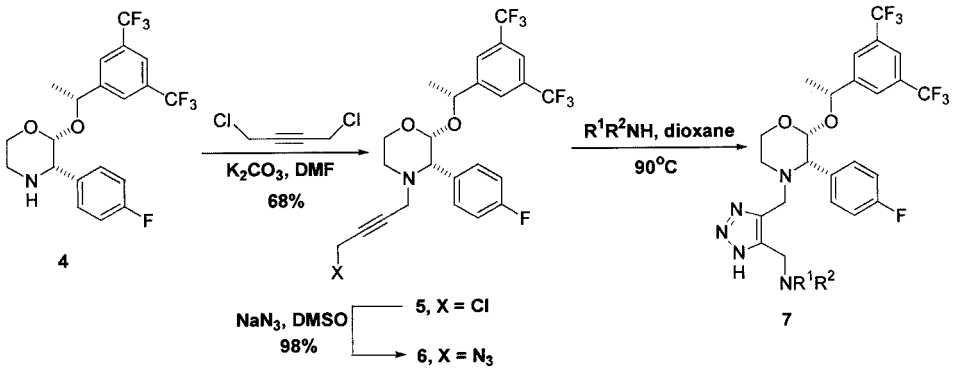

Table 1. IC_{50} for Inhibition of Binding of ^{125}I-substance P to the h-NK_1 Receptor in vitro[7] and ID_{50} for Inhibition of GR73632-induced Gerbil Foot Tapping[10] by h-NK_1 Antagonists

compound	NR^1R^2 in compound **7**	h-NK_1 IC_{50} (nM ± SD)	immediate pretreatment ID_{50} (mg/kg iv)[a]	24 h pretreatment ID_{50} (mg/kg iv)[a]
8	NH_2	0.25 ± 0.10	5.3	
9	NHMe	0.29 ± 0.15	3.1	
3	NMe_2·HCl	0.19 ± 0.08	0.2	0.3
10	N^iPr_2	0.35 ± 0.05	1.0	
11	azetidine	0.19 ± 0.02	0.4	
12	pyrrolidine	0.21 ± 0.04	0.4	
MK-0869	-	0.09 ± 0.06	0.4	0.3

[a] Test compounds were administered iv as a solution in aqueous acid followed by GR73632 challenge icv at the time indicated.

tive hindfoot tapping response, which can be blocked by brain penetrant (but not by non brain penetrant) antagonists.[10] This assay thus provides a convenient measure of CNS penetration, and can be used to give an indication of the central duration of action of antagonists by treating with test compounds prior to the agonist challenge (Table 1).

It can be seen that a range of amines (primary, secondary, and tertiary) could be introduced at the 5-position of the heterocycle without significant reduction of the h-NK_1 IC_{50}. However, potency in the gerbil foot-tapping model, which provides a measure of brain NK_1 receptor occupancy, increased in the order primary<secondary<tertiary amine. Both acyclic and cyclic tertiary amines provided compounds with excellent CNS activity, although potency in the gerbil assay decreased as the lipophilicity of the amine increased (compare **3** and **10**). Compound **3**, which had the highest potency of the compounds tested after immediate pretreatment, also had excellent duration in this test (ID_{50} 0.3 mg/kg iv following 24 h pretreatment). On the basis of this excellent duration of activity and a favorable pharmacokinetic profile in rat, dog, and Rhesus monkey, **3** was selected for further profiling.

In Vitro Pharmacology of 3. Compound **3** inhibits the binding of ^{125}I-substance P to the h-NK_1 receptor with an IC_{50} of 0.19 ± 0.08 nM.[7] The Kd calculated from these data is 119 ± 18 pM. In the presence of 1% human serum albumin, **3** inhibits binding of ^{125}I-substance P to the h-NK_1 receptor with IC_{50} of 0.5 nM, suggesting the compound has low affinity for serum proteins. The binding affinities of **3** at h-NK_2 and h-NK_3 receptors were determined by displacement of ^{125}I-neurokinin A from the h-NK_2 receptor and ^{125}I-[iodo-histidyl-methyl-Phe7] neurokinin B from the h-NK_3 receptor, all stably expressed in CHO cells.[7] Compound **3** showed excellent selectivity (>3000-fold) with respect to both h-NK_2 and h-NK_3 receptors. Further counterscreening demonstrated that **3** had >3000-fold selectivity versus 100 receptors, ion-channels, and enzymes (data not shown). Compound **3** is a stable, non-hygroscopic hydrochloride salt. The solubility of **3** in water is >100 mg/mL at room temperature.

Anti-Emetic Activity in Ferrets. In addition to inhibiting the retching and vomiting induced by cytotoxic chemotherapeutic agents such as cisplatin, the NK_1 receptor antagonist CP-99,994 has also been shown to be effective against the emesis produced by centrally acting drugs such as morphine and apomorphine[2] which is resistant to treatment with 5-HT_3 receptor antagonists.[11] This action may be of value in the control of emesis associated with the use of opiate analgesics in situations such as post-operative pain. NK_1 Receptor antagonists may thus provide broader anti-emetic protection than 5-HT_3 receptor antagonists. The effects of **3** against cisplatin-induced emesis in the ferret were therefore examined. Compound **3** (0.1−3 mg/kg iv) inhibited retching and vomiting in a dose-dependent manner over the 4 h observation period after cisplatin administration (Figure 1). The anti-emetic effect observed was significant even at the lowest dose tested (0.1 mg/kg iv) with protection being complete at doses ≥ 1 mg/kg iv. After orally dosing a solution of **3** in water, marked inhibition of retching and vomiting was observed; this was virtually complete at doses of 1 and 3 mg/kg (Figure 1). The ID_{90} (inhibitory dose giving ≥ 90% inhibition of retching) for **3** was 0.1 mg/kg intravenously and 1.0 mg/kg orally.

Inhibition of Neonatal Vocalization in Guinea Pigs. The ability of centrally acting NK_1 receptor antagonists and established antidepressant drugs to inhibit separation-induced vocalizations in guinea pig pups suggested an antidepressant-like preclinical profile of NK_1 receptor antagonists, which was subsequently confirmed in clinical trials.[3] Compound **3** caused a dose-dependent inhibition of neonatal vocalization with an ID_{50} of 0.2 mg/kg po given 4 h before maternal separation (Figure 2).

Conclusion

Compound **3** is a potent, water soluble, highly brain-penetrant h-NK_1 antagonist with a long central duration of action which is suitable for both oral and intravenous clinical administration. The amino-methyl triazole unit, which confers excellent water solubility to **3**, was

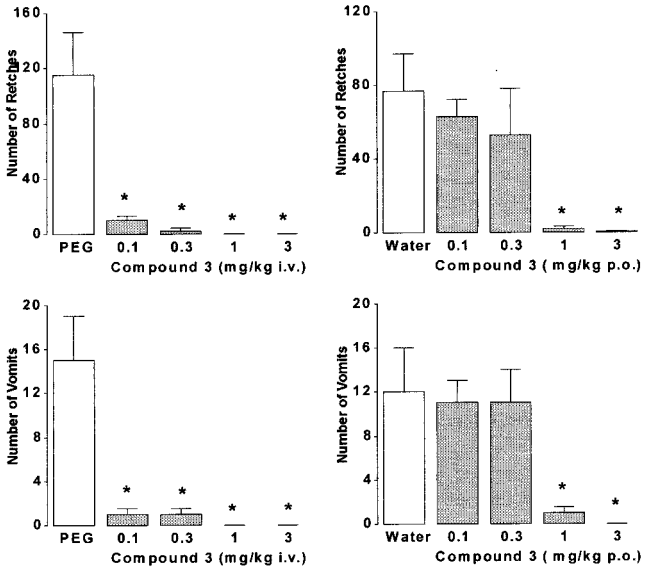

Figure 1. Effect of **3** (0.1−3 mg/kg iv and po) on the retching and vomiting response to cisplatin (10 mg/kg iv) in the ferret. Bars represent means ± SEM ($n = 4$). *p<0.05 compared with vehicle treatment, ANOVA followed by Dunnett's t-test.

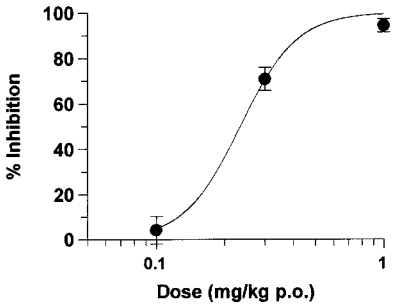

Figure 2. Effect of **3** (0.1−1 mg/kg po) on neonatal vocalization in guinea pigs. Values are means ± SEM ($n = 4$−6).

constructed using a novel triazole synthesis developed by Banert.[6] Compound **3** is highly effective in preclinical tests that are relevant to clinical efficacy in emesis and depression.

Experimental Section

Chemistry. Merck Kieselgel 60 F_{254} precoated silica plates for TLC were obtained from BDH, Poole, Dorset, U.K. Column chromatography was carried out on Fluka Kieselgel 60 0.035−0.070 mm. Infrared (IR) spectra were recorded in the range 4000−600 cm^{-1} using a Nicolet 205 FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded using Bruker (AC250, AM360, and AM400 MHz) spectrometers. Solvents are indicated in the text, and tetramethylsilane was used as the internal reference. Mass spectra were recorded using a VG Quattro mass spectrometer.

(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-4-(4-chlorobut-2-ynyl)-3-(4-fluorophenyl)morpholine, 5. A solution of *cis* (2*R*,3*S*)-2-({(1*R*)-1-[3,5 Bis-(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholine **4**[4] (5 g, 11.5 mmol) in dry *N*,*N*-dimethylformamide (20 mL) was added dropwise during 20 min to a stirred mixture of 1,4-dichloro-2-butyne (2.2 mL, 23 mmol) and K_2CO_3 (4.8 g, 34.5 mmol) in dry *N*,*N*-dimethylformamide (20 mL) maintained at 50−60 °C (bath temperature). The reaction mixture was stirred at 50−60 °C for 2 h, then cooled to 23 °C, diluted with H_2O (400 mL), and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL), and then dried ($MgSO_4$) and concentrated to leave an oil. Purification by chromatography on silica gel using hexanes−ethyl acetate (successively with 19:1, 9:1, 6:1, and 4:1, followed by 100% ethyl acetate) as eluant provided, in order of elution, **5** (4.1 g, 68%) as a clear, colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (3H, d, J = 6.6 Hz), 2.80 (1H, app. t, J = 10.8 Hz), 2.87 (1H, td, J = 3.5, 11.7 Hz), 3.22 (2H, t, J = 1.9 Hz), 3.52 (1H, d, J = 2.8 Hz), 3.68 (1H, dd, J = 1.4, 11.1 Hz), 4.00 (2H, t, J = 1.9 Hz), 4.22−4.32 (2H, m), 4.81 (1H, q, J = 6.6 Hz), 6.96 (2H, t, J = 8.7 Hz), 7.10 (2H, s), 7.31 (2H, br s), 7.56 (1H, s), m/z (CI^+) 524 (M+H, 100%); the 1,4-bis(morpholino)-2-butynyl dimer (0.45 g, 8.5%); and recovered starting material (0.65 g, 13%).

(2*R*,3*S*)-4-(4-Azidobut-2-ynyl)-2-({(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholine, 6. Sodium azide (0.562 g, 8.65 mmol) was added to a stirred solution of **5** (4.0 g, 7.67 mmol) in dry dimethyl sulfoxide (17 mL) and the reaction mixture was stirred at 23 °C for 20 h. The mixture was then partitioned between saturated aqueous NH_4Cl solution (200 mL) and ethyl acetate (80 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with H_2O (1 × 80 mL). then dried ($MgSO_4$) and concentrated (bath temp < 35 °C) to afford **6** (3.9 g, 98%) as a clear, colorless oil which was used without further purification (purification could be performed if necessary by chromatography on silica eluting with 20% ethyl acetate in petroleum ethers (bp 60−80 °C)). ^1H NMR (360 MHz, $CDCl_3$) δ 1.48 (3H, d, J = 6.6 Hz), 2.87 (1H, app t, J = 10.2 Hz), 2.98 (1H, td, J = 3.6, 11.7 Hz), 3.35 (2H, t, J = 1.9 Hz), 3.61 (1H, d, J = 2.8 Hz), 3.72 (1H, dq, J = 1.4, 10.0 Hz), 3.92 (2H, t, J = 1.9 Hz), 4.30−4.40 (2H, m), 4.89 (1H, q, J = 6.6 Hz), 7.03 (2H, t, J = 8.7 Hz), 7.17 (2H, s), 7.27 (2H, br s), 7.63 (1H, s).

1-(5-{[(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2*H*-1,2,3-triazol-4-yl)-*N*,*N*-dimethylmethanamine hydrochloride, 3. A solution of **6** (3.2 g, 6.0 mmol) in dry dioxane (15 mL) was added to dimethylamine (ca 10 mL) which had been condensed at −78 °C under N_2 in a screw-top sealed tube. The tube was sealed and allowed to warm to room temperature followed by heating at 80−90 °C (bath temperature) with stirring for 20 h. After the tube was cooled to 5 °C, it was opened, and the volatiles were removed in vacuo to leave a foam. This residue was purified by column chromatography (CH_2Cl_2/MeOH/NH_3, 95:5:0.2 then 90:10:0.2) to provide the free-base of **3** (3.0 g, 87%) as a white foam. ^1H NMR (360 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 6.6 Hz, C*H*$_3$CH), 2.23 (6H, s, (C*H*$_3$)$_2$N), 2.56 (1H, app. t, J = 11.9 Hz, NC*H*HCH$_2$O), 2.90 (1H, d, J = 11.9 Hz, NCH*H*CH$_2$O), 3.24 (1H, d, J = 13.9 Hz, O(CH$_2$)$_2$NC*H*H), 3.42 (1H, d, J = 13.7 Hz, Me$_2$NC*H*H), 3.45 (1H, d, J = 2.7 Hz, NC*H*Ar), 3.51 (1H, d, J = 13.7 Hz, Me$_2$NCH*H*), 3.61 (1H, d, J = 11.4 Hz, OC*H*H), 3.78 (1H, d, J = 13.9 Hz, O(CH$_2$)$_2$NCH*H*), 4.22 (1H, app. t, J = 11.4 Hz, OCH*H*), 4.32 (1H, d, J = 2.7 Hz, OC*H*O), 4.85 (1H, q, J = 6.6 Hz, C*H*CH$_3$), 7.05 (2H, t, J = 8.6 Hz, *H*C═C(F)═C*H*), 7.16 (2H, s, (CF$_3$)C═C*H*-C═C*H*-C(CF$_3$)), 7.47 (2H, br s, *H*C═C−C*H*═), 7.64 (1H, s, (CF$_3$)C═C*H*-C(CF$_3$)). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 24.4 (*C*H$_3$), 45.0 (2 × *C*H$_3$), 48.9 (*C*H$_2$), 52.0 (*C*H$_2$), 52.3 (*C*H$_2$), 59.5 (*C*H$_2$), 69.3 (*C*H), 72.3 (*C*H), 95.6 (O*C*HO), 115.13 (d, $^2J_{CF}$ 21.4 Hz), 123.02 (q, $^1J_{CF3}$ 272.7 Hz), 126.2, 131.0 (d, $^3J_{CF}$ 8.0 Hz), 131.586 (q, $^2J_{CF}$ 33.2 Hz), 132.93 (d, $^4J_{CF}$ 3.3 Hz), 139.94, 140.91, 145.52, 162.64 (d, $^1J_{CF}$ 247.5 Hz). m/z (CI^+) 576 (M+H). IR (film) ν 3150 (br), 1618 (w), 1520 (m), 1285 (s), 1145 (s), 1075 (s), 1035 (m), 765 (s) cm^{-1}.

HCl Salt Formation. The free base of **3** (3 g, 5.2 mmol) was dissolved in dry diethyl ether (30 mL), and HCl in MeOH (1 M solution, 5.2 mL, 5.2 mmol) was added. The solution was concentrated in vacuo to a partial foam, then redissolved in dry diethyl ether (ca. 50 mL). The product which crystallized was isolated by filtration then washed with dry diethyl ether and dried in vacuo at 60 °C to provide the HCl salt 3 (2.5 g, 79%) as a crystalline, white solid, mp 194−198 °C, $[\alpha]^{22}_D$ + 65.0 (c = 0.5, H_2O). A further batch (0.3 g) crystallized from the mother liquors on standing overnight. Anal. ($C_{26}H_{29}F_7N_5O_2$-Cl) C, H, N.

1-(5-{[(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2*H*-1,2,3-triazol-4-yl)methanamine, 8. Prepared from **6** following the procedure described for the preparation of **3** in 15% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, J=6.2 Hz, C*H*$_3$CH), 2.45 (1H, t, J = 10.4 Hz, NC*H*HCH$_2$O), 2.79 (1H, d, J = 11.4 Hz, NH*H*CH$_2$O), 3.10 (1H, d, J = 13.6 Hz, O(CH$_2$)$_2$-NC*H*H), 3.44 (1H, s, NC*H*Ar), 3.62 (1H, d, J = 10.5 Hz, OC*H*HCH$_2$N), 3.76 (1H, d, J = 13.6 Hz, O(CH$_2$)$_2$NCH*H*), 3.95 (2H, app. t, J = 15.9 Hz, C*H*$_2$NH$_2$), 4.16 (1H, t, J = 11.1 Hz, OCH*H*CH$_2$N), 4.32 (3H, m, N*H*$_2$ and OC*H*O), 4.89 (1H, q, J = 6.2 Hz, CH$_3$C*H*Ar), 7.08 (2H, t, J = 7.8 Hz, Ar*H*), 7.20 (2H, s, Ar*H*) 7.49 (2H, m Ar*H*), 7.63 (1H, s, Ar*H*). Anal. ($C_{24}H_{24}F_7N_5O_2$) C, H, N.

1-(5-{[(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2*H*-1,2,3-triazol-4-yl)-*N*-methylmethanamine, 9. Prepared from **6** following the procedure described for the preparation of **3** in 77% yield.^{1}H NMR (360 MHz, $CDCl_3$) δ 1.46 (3H, d, J = 6.6 Hz, C*H*$_3$CHAr), 2.44 (1H, td, J = 12.1 Hz and 3.5 Hz, NC*H*HCH$_2$O), 2.53 (3H, s, C*H*$_3$), 2.74 (1H, d, J = 11.6 Hz, NCH*H*CH$_2$O), 3.10 (1H, d, J = 13.5 Hz, O(CH$_2$)$_2$N*H*H), 3.4 (1H, d, J = 2.6 Hz, NC*H*Ar), 3.61 (1H, d, J = 11.7 Hz, OC*H*H), 3.76 (1H, d, J = 13.6 Hz, O(CH$_2$)$_2$NCH*H*), 3.78 (1H, d, J = 13.8 Hz, C*H*HNHMe), 3.86 (1H, d, J = 13.7 Hz, CH*H*NHMe), 4.16 (1H, t, J = 11.7 Hz, OCH*H*), 4.32 (1H, d, J = 2.6 Hz, OC*H*O), 4.89 (1H, q, J = 6.6 Hz, C*H*CH$_3$), 5.30 (1H, vbs, NH), 7.08 (2H, d, J = 8.7 Hz, ArH), 7.20 (2H, s, ArH), 7.47 (2H, m, ArH), 7.64 (1H, s, ArH). Anal. ($C_{25}H_{26}F_7N_5O_2$.0.5 H_2O) C, H, N.

1-[(5-{[(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2*H*-1,2,3-triazol-4-yl)]-*N*-isopropylpropan-2-amine, 10. Prepared from **6** following the procedure described for the preparation of **3** in 54% yield. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.00 (12H, d, J = 1.8 Hz, 2 × C*H*$_3$CHC*H*$_3$), 1.44 (3H, d, J = 6.6 Hz, C*H*$_3$CHAr), 2.64 (1H, dt, J = 3.5, 12.0 Hz, NC*H*HCH$_2$O), 2.93−3.03 (3H, m, 2 × CH$_3$C*H*CH$_3$, NCH-*H*CH$_2$O), 3.30 (1H, d, J = 14.1 Hz, O(CH$_2$)$_2$NC*H*H), 3.48 (1H, d, J = 2.8 Hz, NC*H*Ar), 3.51−3.76 (4H, m, O(CH$_2$)$_2$NCH*H*, Triaz. C*H*$_2$N, OC*H*H), 4.24 (1H, dt, J = 2.4, 11.6 Hz, OCH*H*), 4.33 (1H, d, J = 2.8 Hz, OC*H*O), 4.87 (1H, q, J = 6.5 Hz, C*H*CH$_3$), 7.02−7.07 (2H, m, Ar*H*), 7.17 (2H, s, Ar*H*), 7.47 (2H, vbs, Ar*H*), 7.63 (1H, s, Ar*H*). Anal. ($C_{30}H_{37}F_7N_5O_2Cl$) C, H, N.

(2*R*,3*S*)-4-{[5-(Azetidin-1-ylmethyl)-2*H*-1,2,3-triazol-4-yl]methyl}-2-({(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)morpholine, 11. Prepared from **6** following the procedure described for the preparation of **3** in 50% yield. ^{1}H NMR(250 MHz, $CDCl_3$) δ 1.45 (3H, d, J = 6.6 Hz, C*H*$_3$), 2.07−2.19 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.56 (1H, dt, J = 3.5, 12.0 Hz, NC*H*HCH$_2$O), 2.88 (1H, m, NCH*H*CH$_2$O), 3.18−3.45 (6H, m, C*H*$_2$CH$_2$C*H*$_2$, O(CH$_2$)$_2$NC*H*H, NC*H*Ar), 3.60−3.80 (4H, m, O(CH$_2$)$_2$NCH*H*, Triaz. C*H*$_2$N, OC*H*H), 4.17−4.25 (1H, m, OCH*H*), 4.33 (1H, d, J = 2.8 Hz, OC*H*O), 4.87 (1H, m, C*H*CH$_3$), 7.04−7.09 (2H, m, Ar*H*), 7.16 (2H, s, Ar*H*), 7.50 (2H, m, Ar*H*), 7.64 (1H, s, Ar*H*). Anal. ($C_{27}H_{28}F_7N_5O_2$·0.5H_2O) C, H, N.

(2*R*,3*S*)-2-({(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}oxy)-3-(4-fluorophenyl)-4-{[5-(pyrrolidin-1-ylmethyl)-2*H*-1,2,3-triazol-4-yl]methyl}morpholine, 12. Prepared from **6** following the procedure described for the preparation of **3** in 80% yield. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.44 (3H, d, J = 6.6 Hz, C*H*$_3$CHAr), 1.80 (4H, br s, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N), 2.51−2.60 (5H, m, NC*H*HCH$_2$O and NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 2.90 (1H, d, J = 11.7 Hz, NCH*H*CH$_2$O), 3.23 (1H, d, J = 13.9 Hz, O(CH$_2$)$_2$NC*H*H), 3.45 (1H, d, J = 2.7 Hz, NC*H*Ar), 3.58−3.63 (2H, d, J = 13.6 Hz and m, (CH$_2$)$_4$-NC*H*H and OC*H*HCH$_2$N), 3.69 (1H, d, J = 13.6 Hz, (CH$_2$)$_4$-NCH*H*), 3.79 (1H,d, J = 14.0 Hz, O(CH$_2$)$_2$NCH*H*), 4.22 (1H, td, J = 2.1 and 11.5 Hz, OCH*H*CH$_2$N), 4.30 (1H, d, J = 2.8 Hz, OC*H*O), 4.86 (1H, q, J = 6.6 Hz, CH$_3$C*H*Ar), 7.16 (2H, s, Ar*H*), 7.48 (2H, m, Ar*H*), 7.64 (1H, s, Ar*H*). Anal. ($C_{28}H_{30}F_7N_5O_2$) C, H, N.

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