

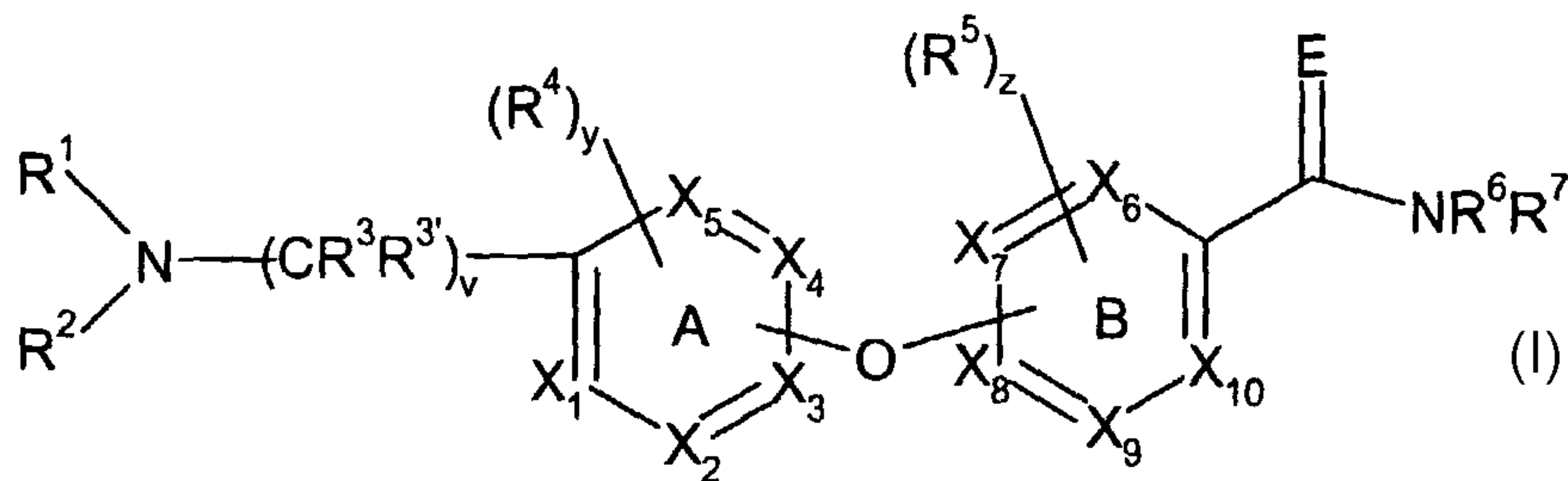


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(54) Titre : DIARYLE ETHERS UTILISES EN TANT QU'ANTAGONISTES DE RECEPTEUR OPIOIDES
 (54) Title: DIARYL ETHERS AS OPIOID RECEPTOR ANTAGONIST



(57) Abrégé/Abstract:

A compound of the formula (I) wherein the variables X_1 to X_{10} , R^1 to R^7 including R^3 , E, v, y, z, A and B are as described, or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixtures thereof, useful for the treatment, prevention or amelioration of obesity and Related Diseases is disclosed.

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- (73) Propriétaires(suite)/Owners(continued): ELI LILLY AND COMPANY, US
- (74) Agent: GOWLING LAFLEUR HENDERSON LLP

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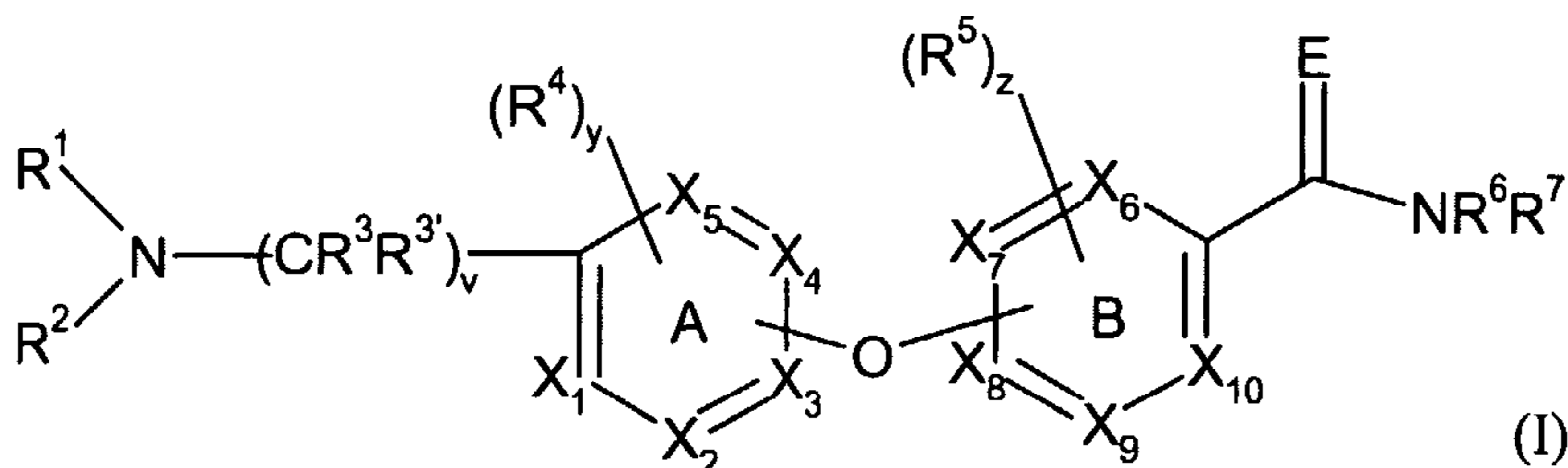
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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,

[Continued on next page]

(54) Title: DIARYL ETHERS AS OPIOID RECEPTOR ANTAGONIST



(I)

(57) Abstract: A compound of the formula (I) wherein the variables X₁ to X₁₀, R¹ to R⁷ including R^{3'}, E, v, y, z, A and B are as described, or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixtures thereof, useful for the treatment, prevention or amelioration of obesity and Related Diseases is

WO 2004/026305 A1 disclosed.

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KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ,

UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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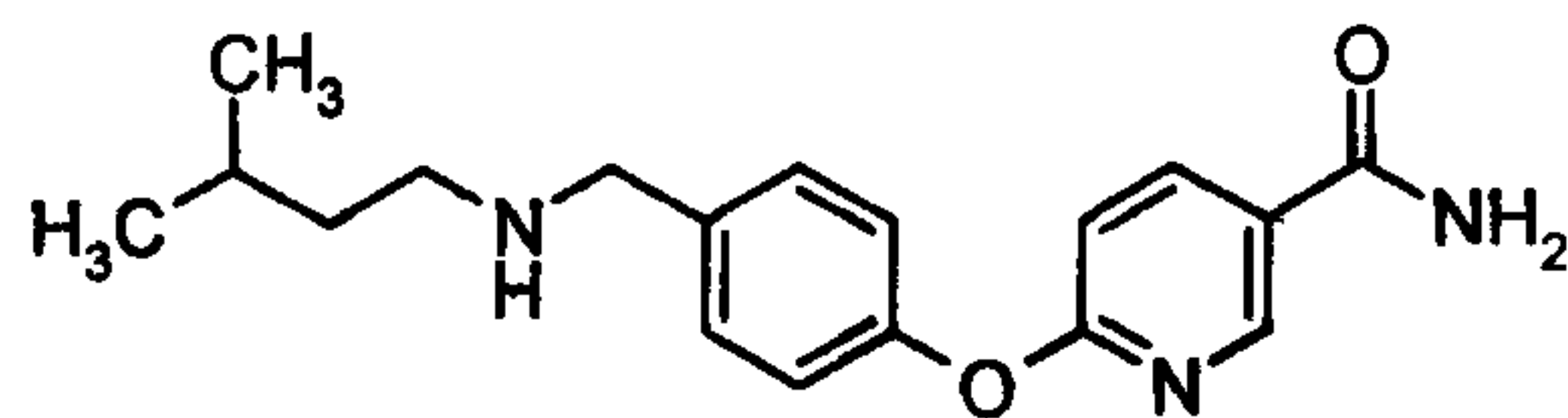
see PCT Gazette No. 20/2004 of 13 May 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

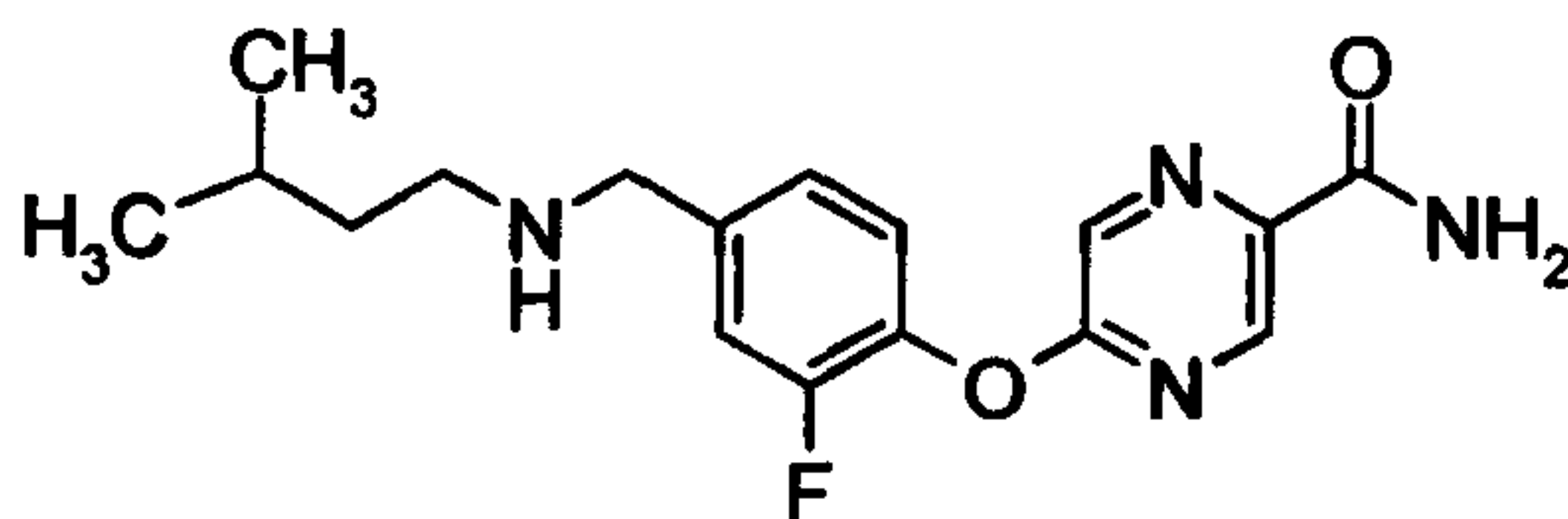
We claim:

1. A compound selected from the group consisting of:

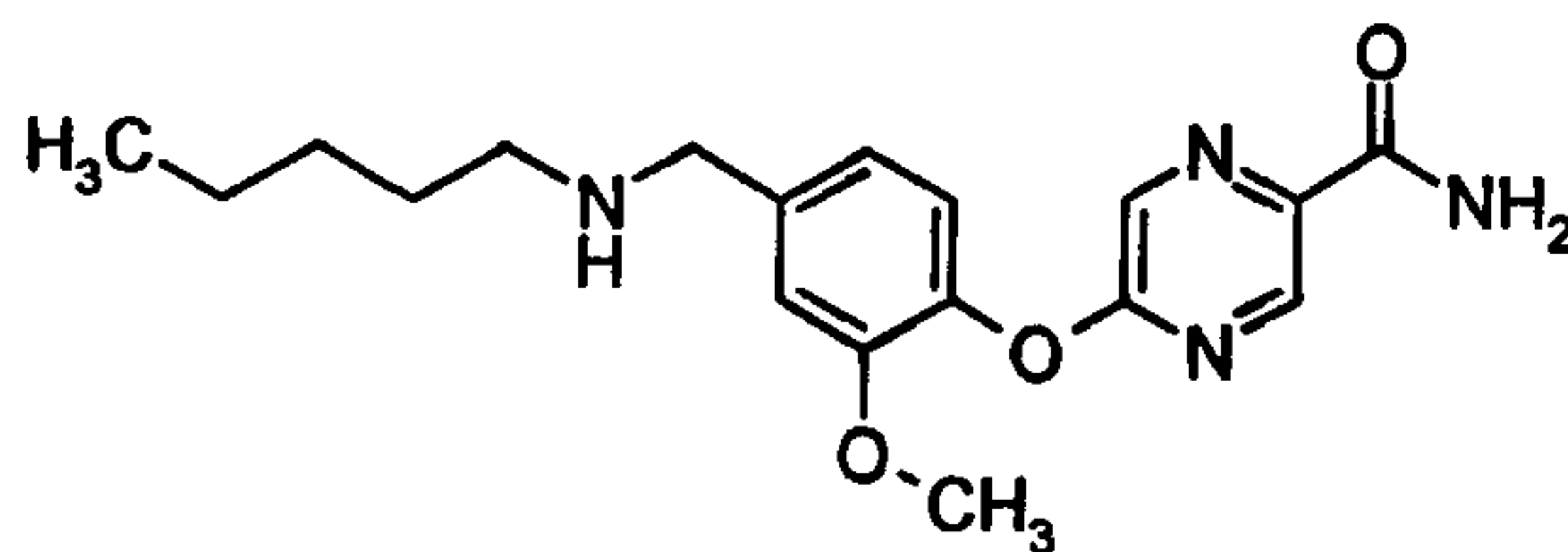
6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide



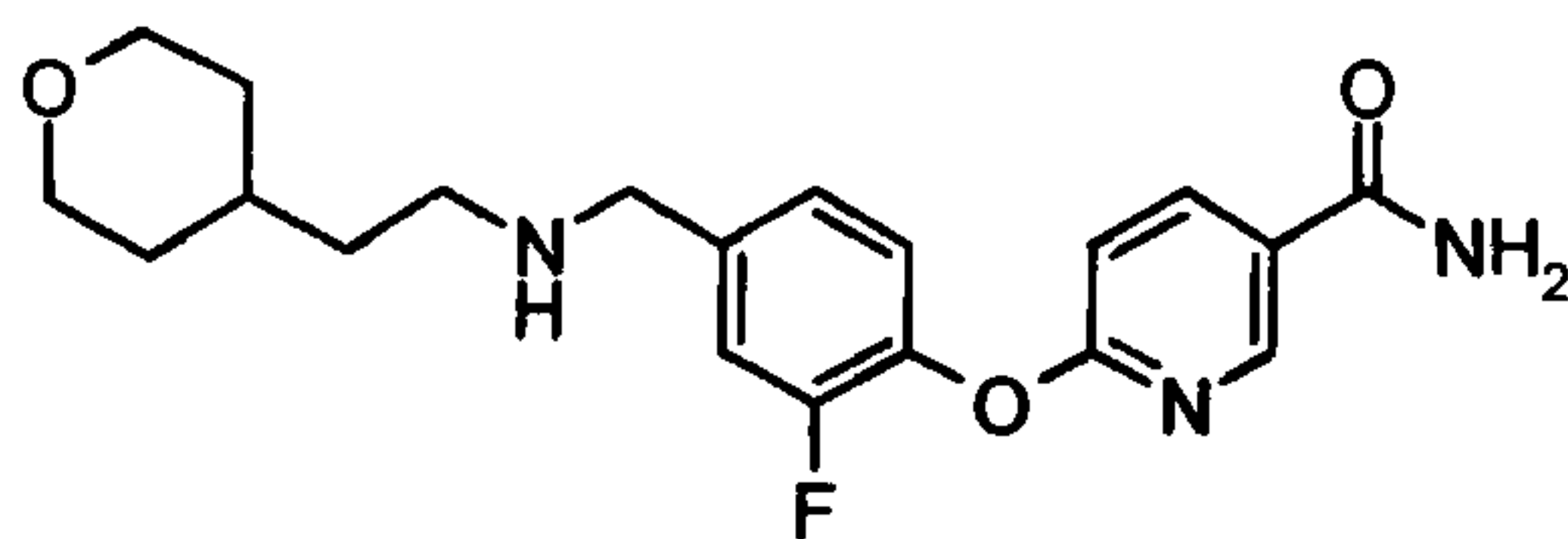
5-{2-Fluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-pyrazine-2-carboxamide



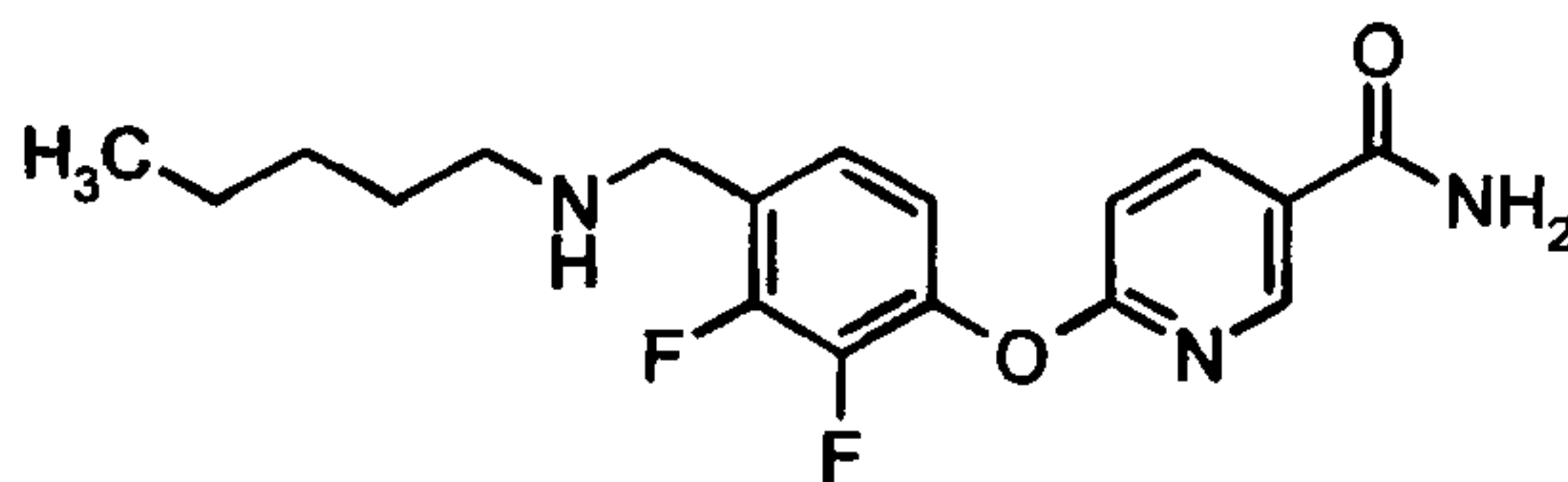
5-(2-Methoxy-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxamide



6-(2-Fluoro-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-nicotinamide

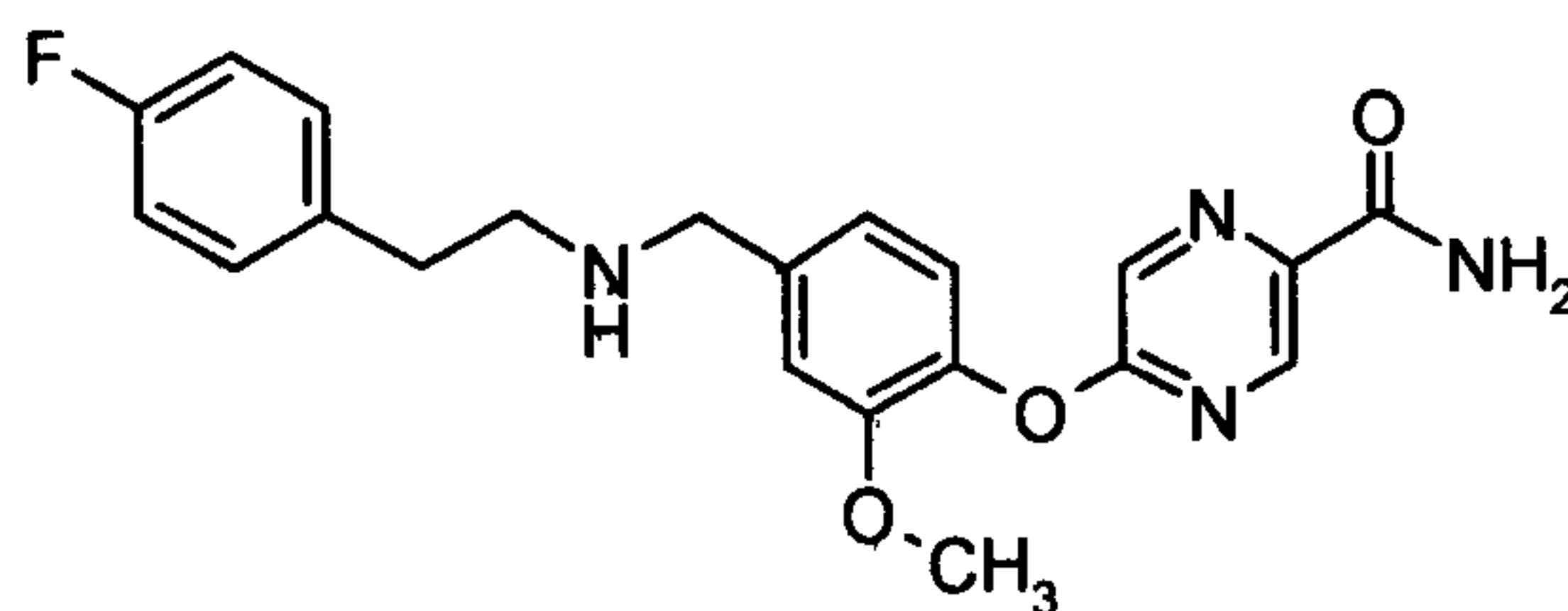


6-(2,3-Difluoro-4-pentylaminomethyl-phenoxy)-nicotinamide

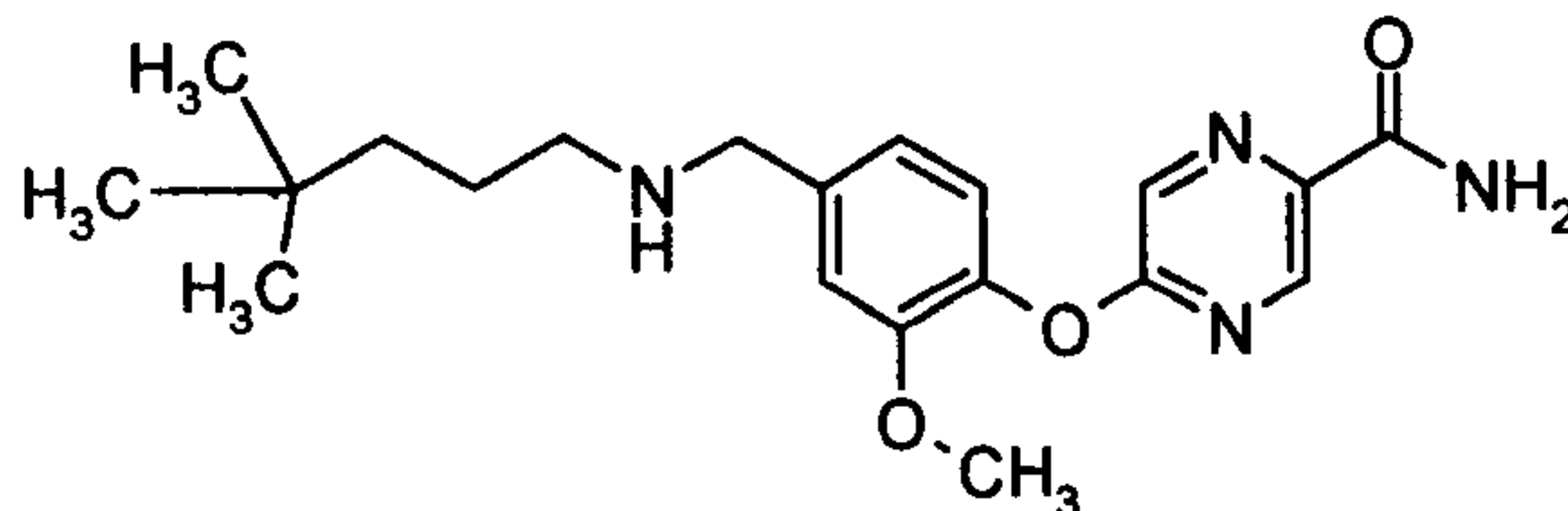


5-(4-{[2-(4-Fluoro-phenyl)-ethylamino]-methyl}-2-methoxy-phenoxy)-pyrazine-2-carboxamide

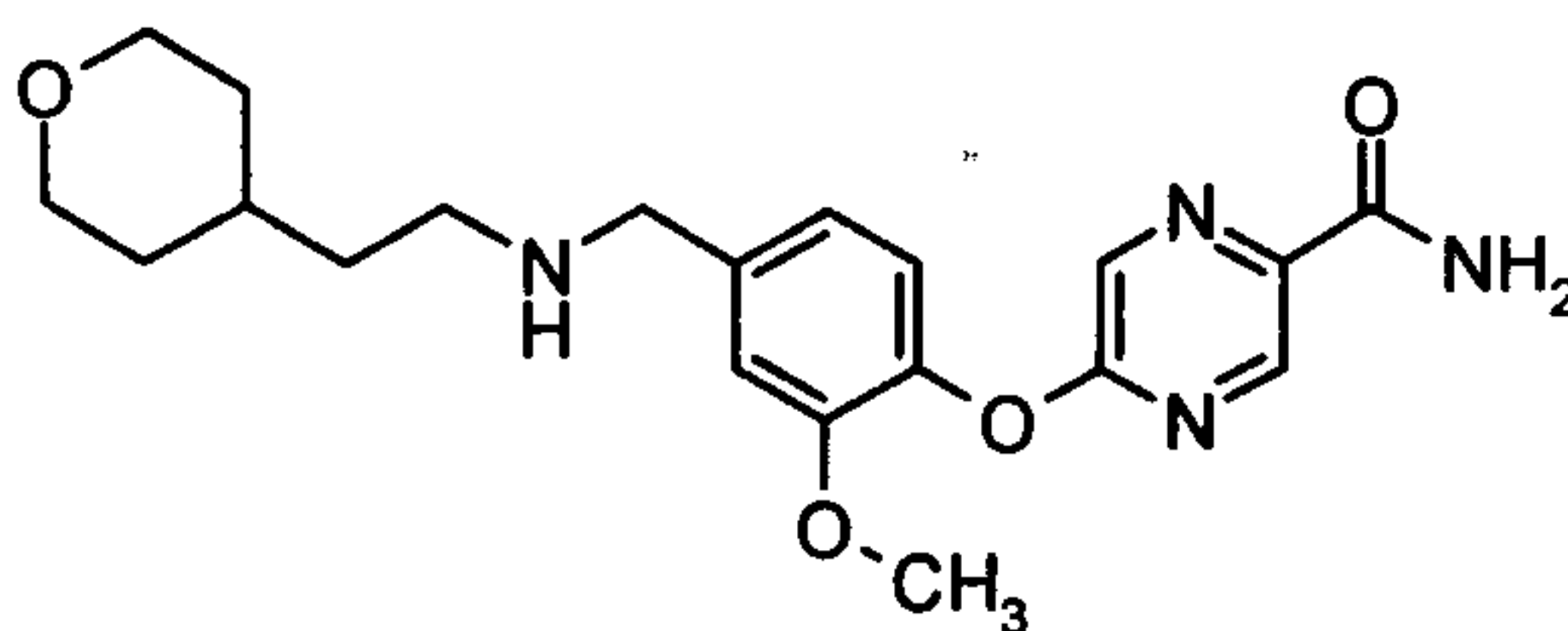
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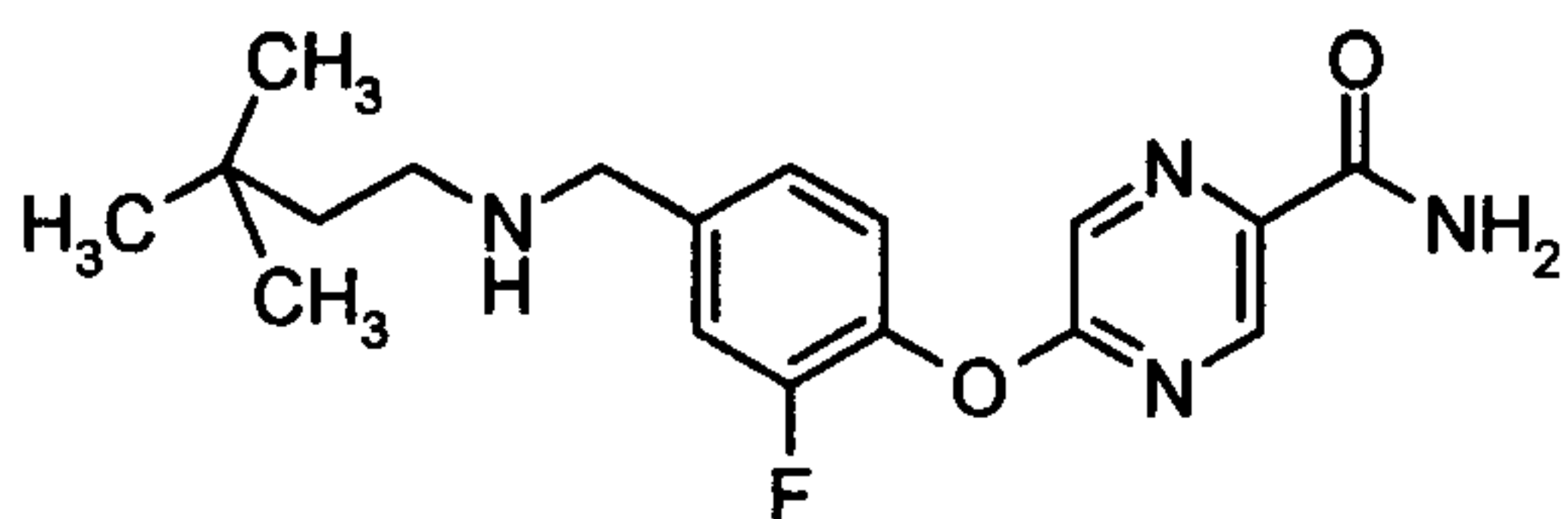
5-{4-[(4,4-Dimethyl-pentylamino)-methyl]-2-methoxy-phenoxy}-pyrazine-2-carboxamide



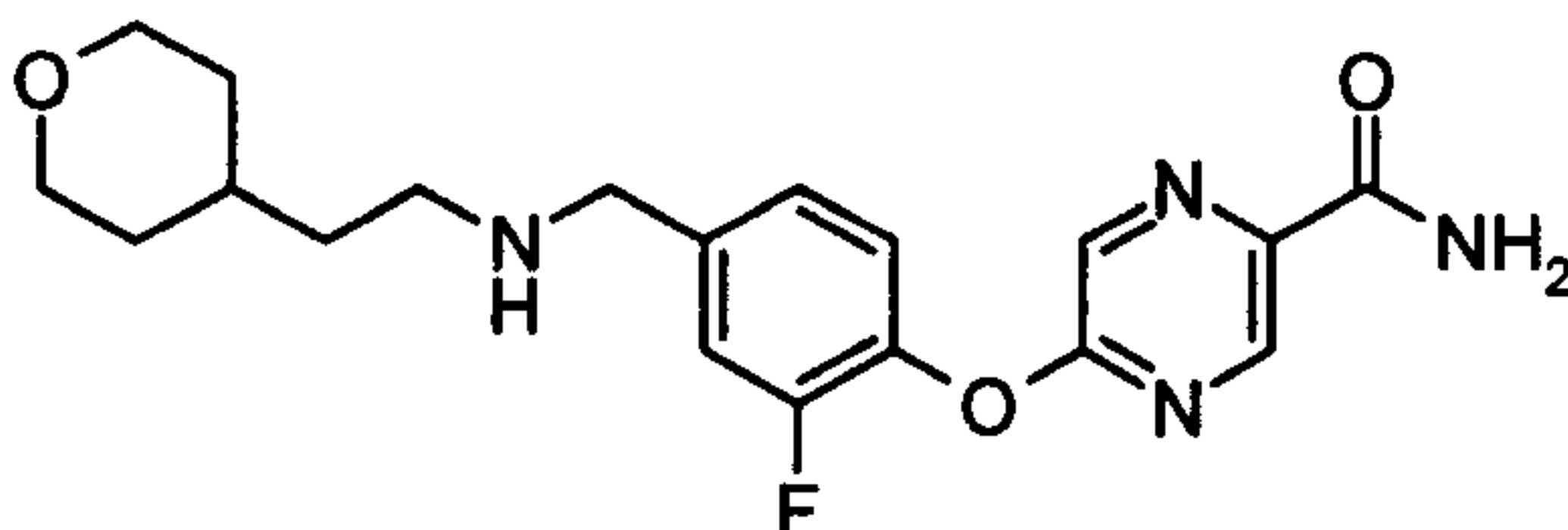
5-(2-Methoxy-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide



5-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-phenoxy}-pyrazine-2-carboxamide

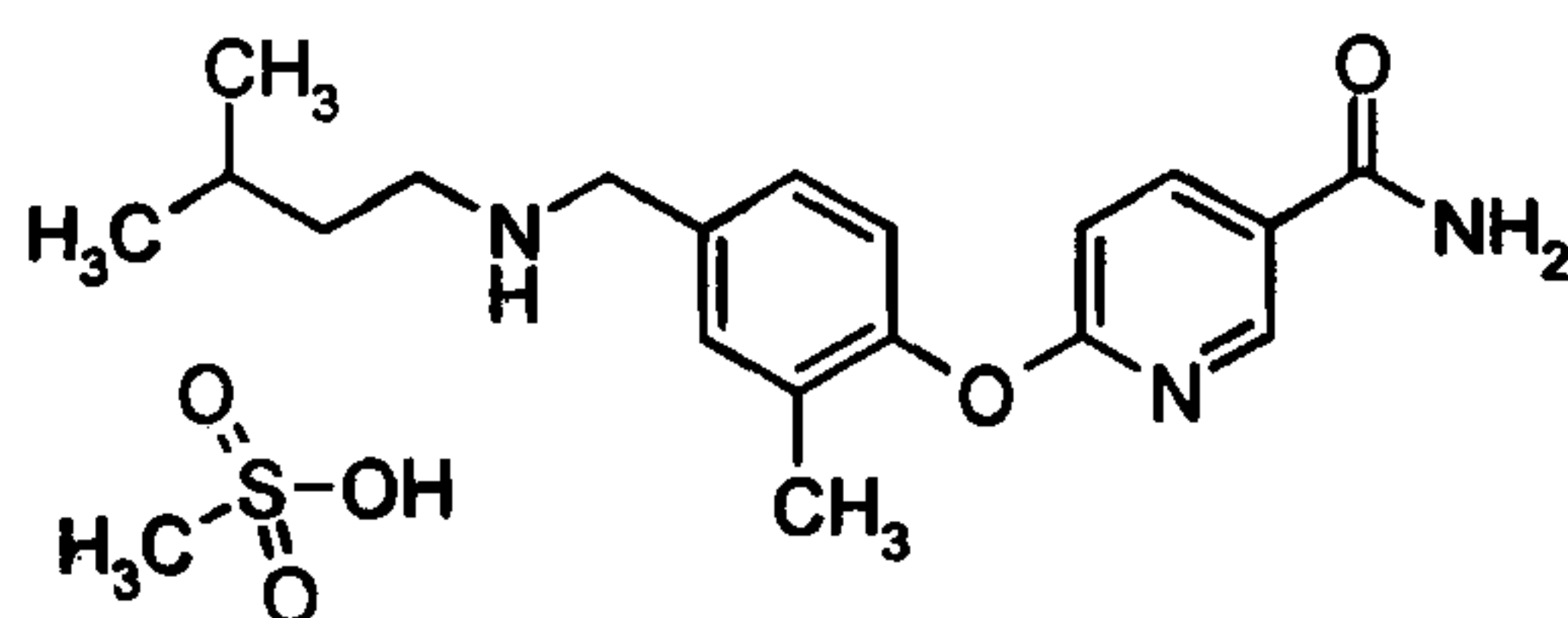


5-(2-Fluoro-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide

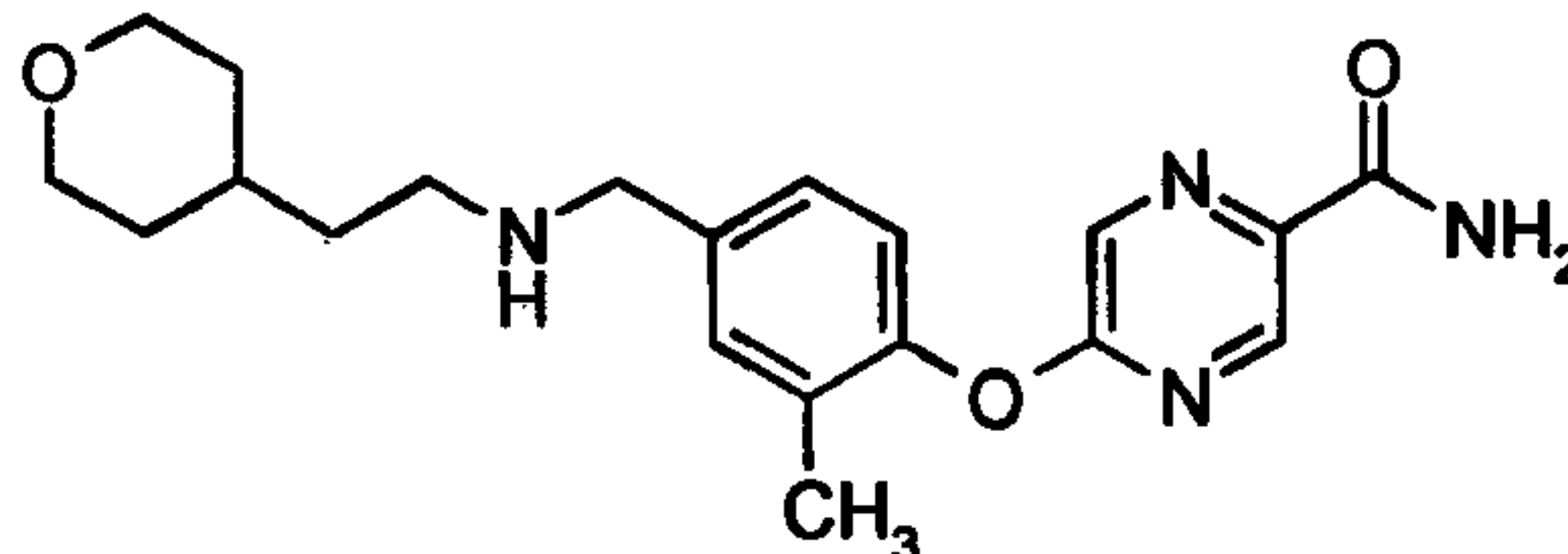


6-{2-Methyl-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide; methanesulfonic acid salt

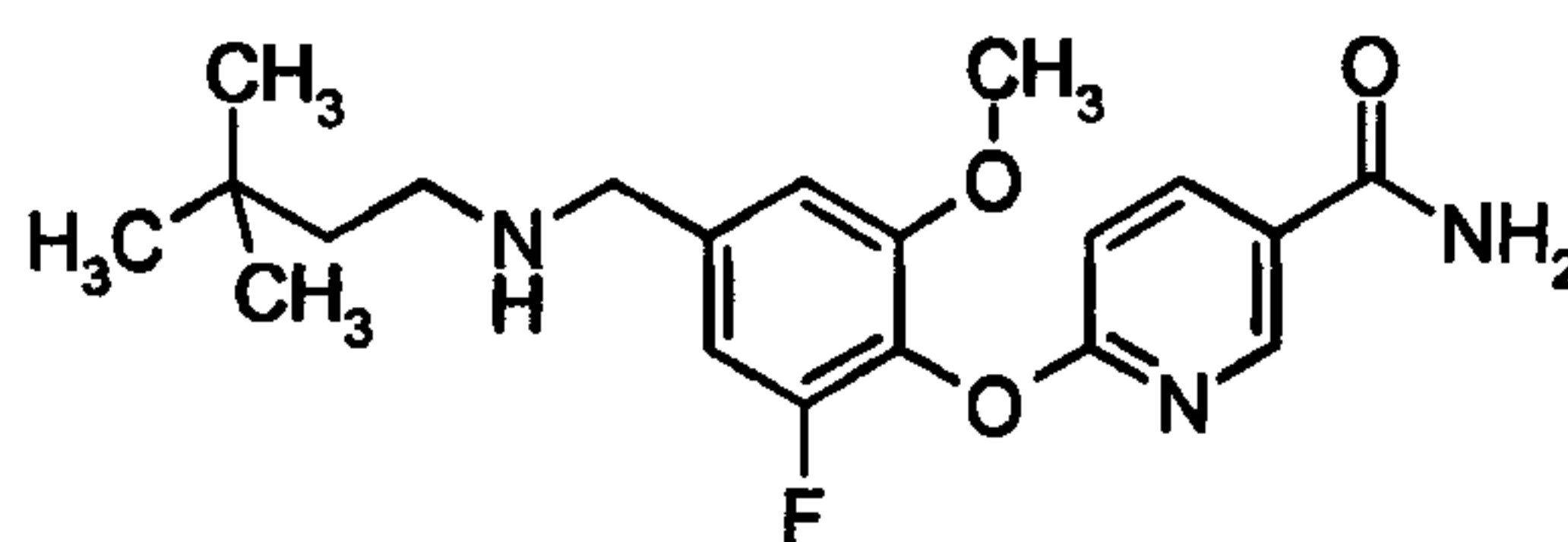
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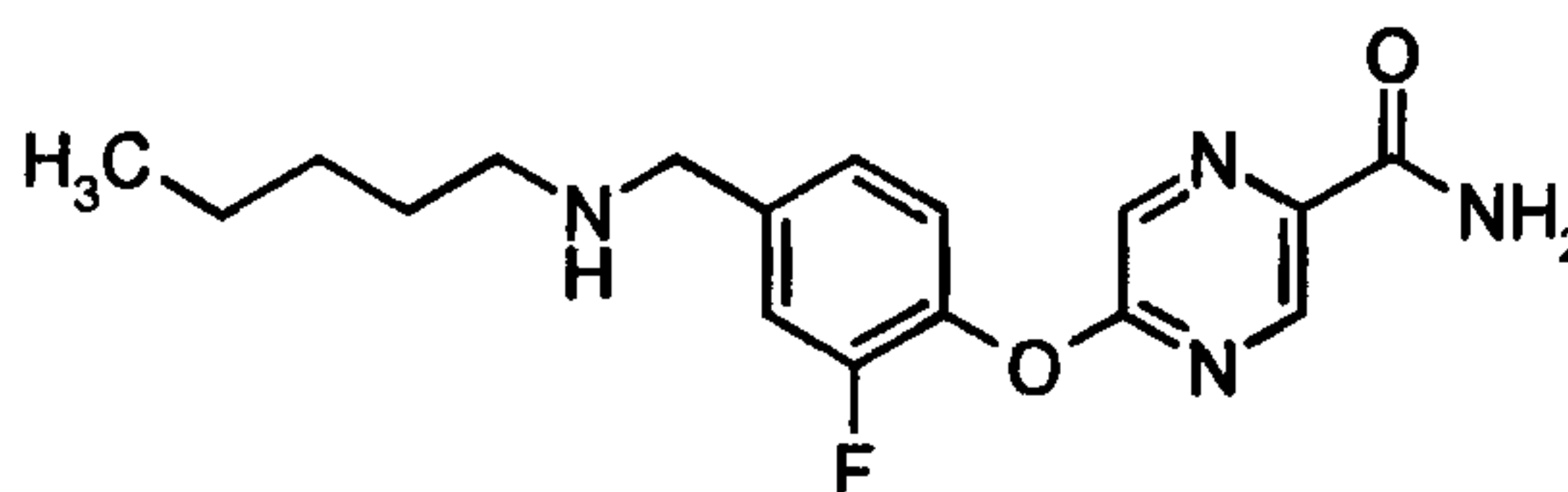
5-(2-Methyl-4-{{2-(tetrahydro-pyran-4-yl)-ethylamino}-methyl}-phenoxy)-pyrazine-2-carboxamide



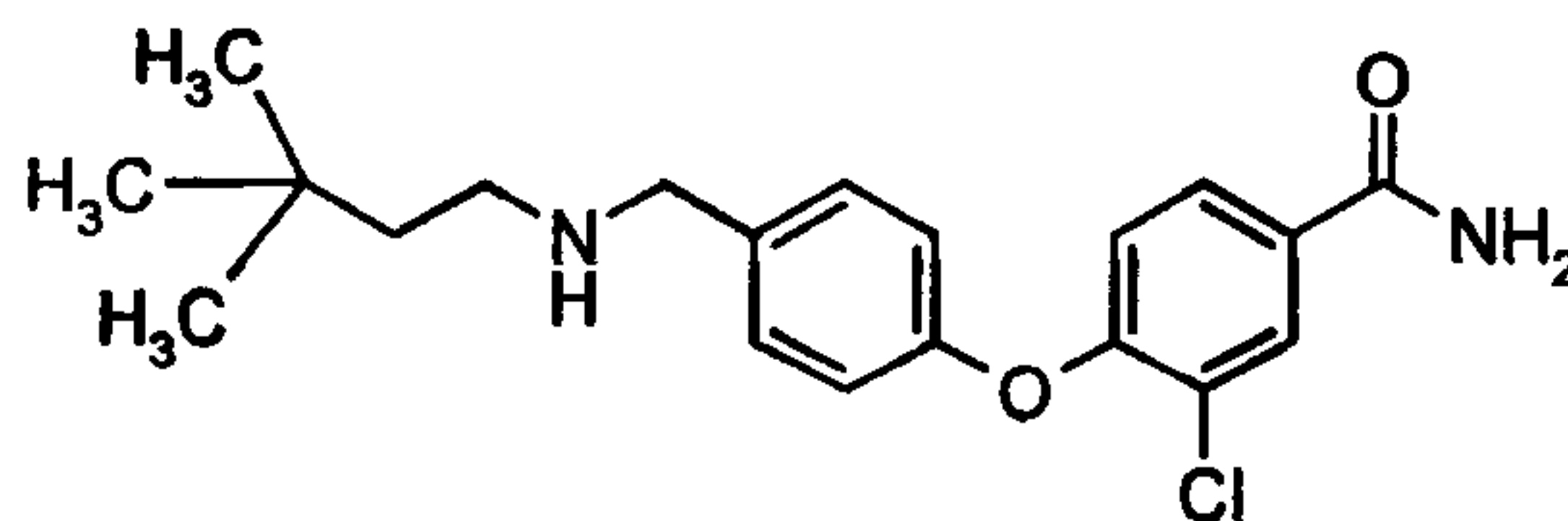
6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-6-methoxy-phenoxy}-nicotinamide



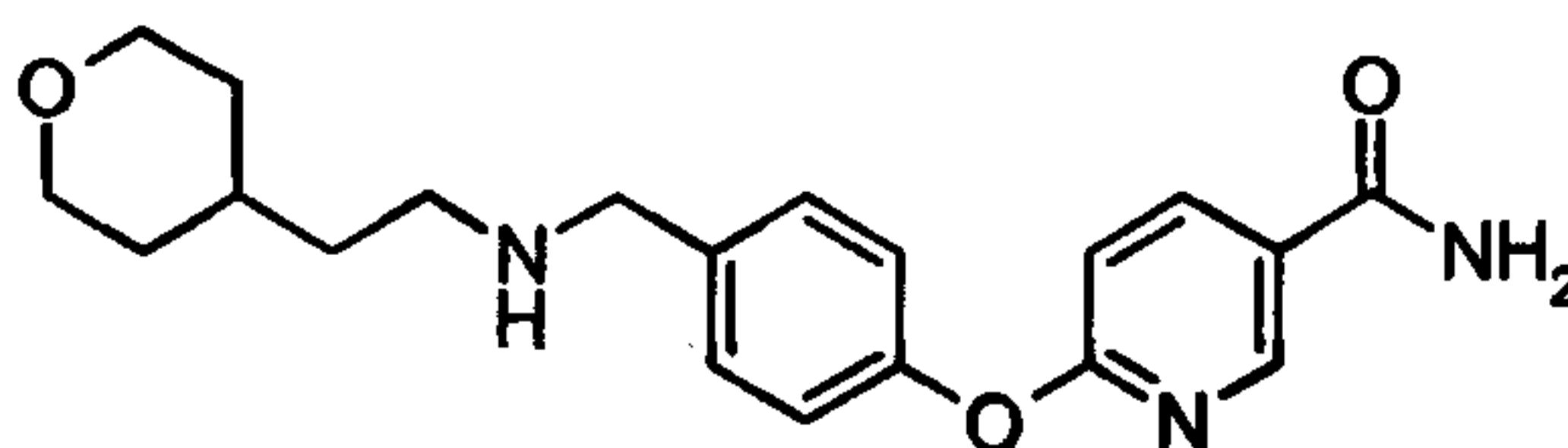
5-(2-Fluoro-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxamide



3-Chloro-4-{4-[(3,3-dimethyl-butylamino)-methyl]-phenoxy}-benzamide

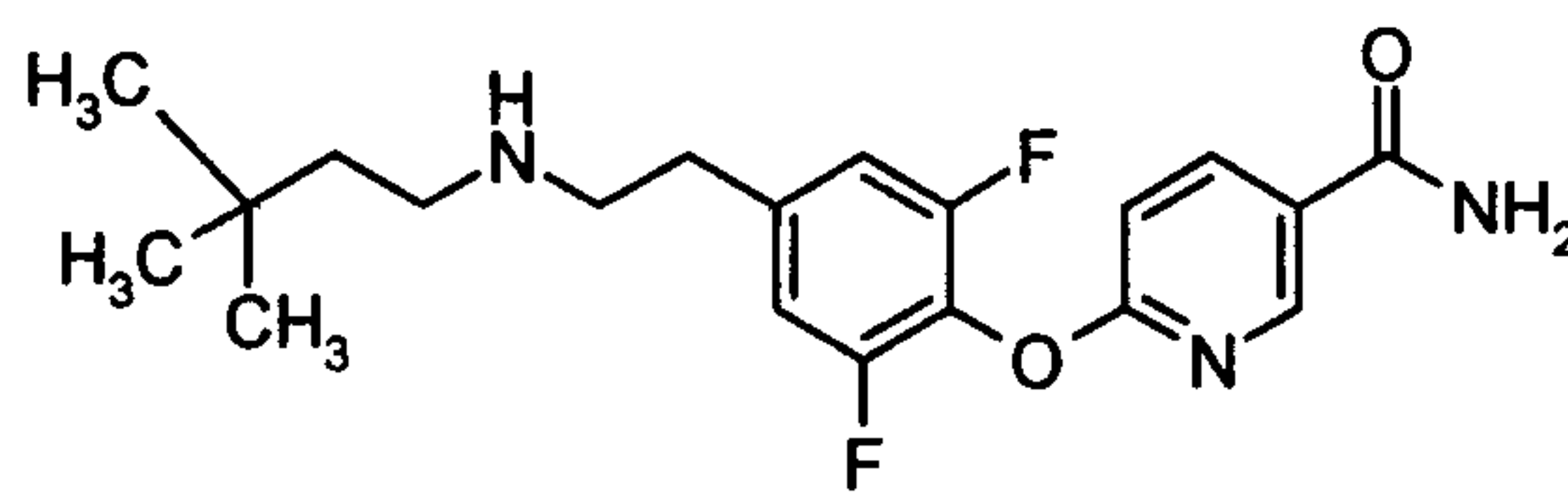


6-(4-{{2-(Tetrahydro-pyran-4-yl)-ethylamino}-methyl}-phenoxy)-nicotinamide

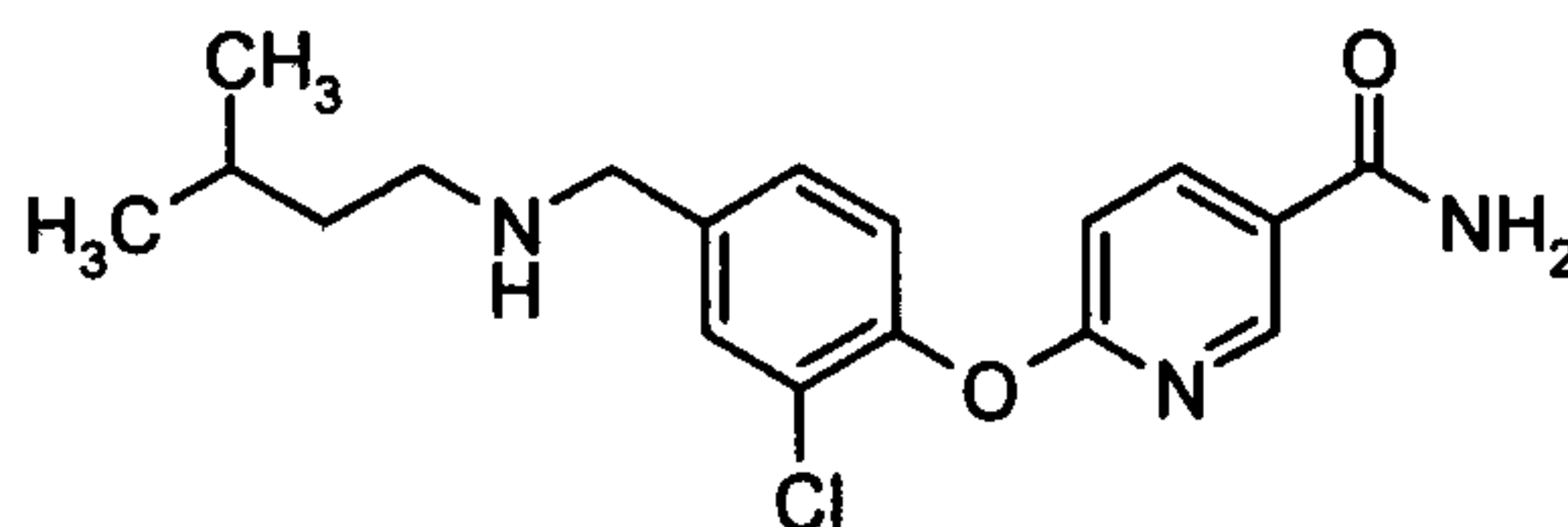


6-{4-[2-(3,3-Dimethyl-butylamino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide

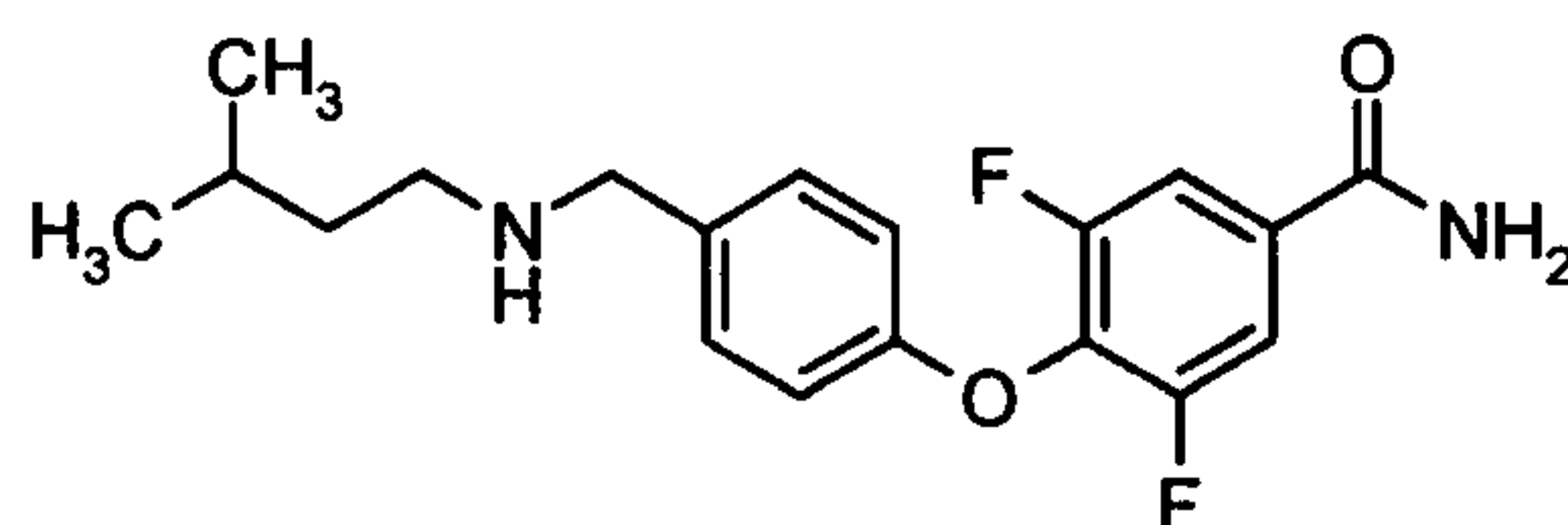
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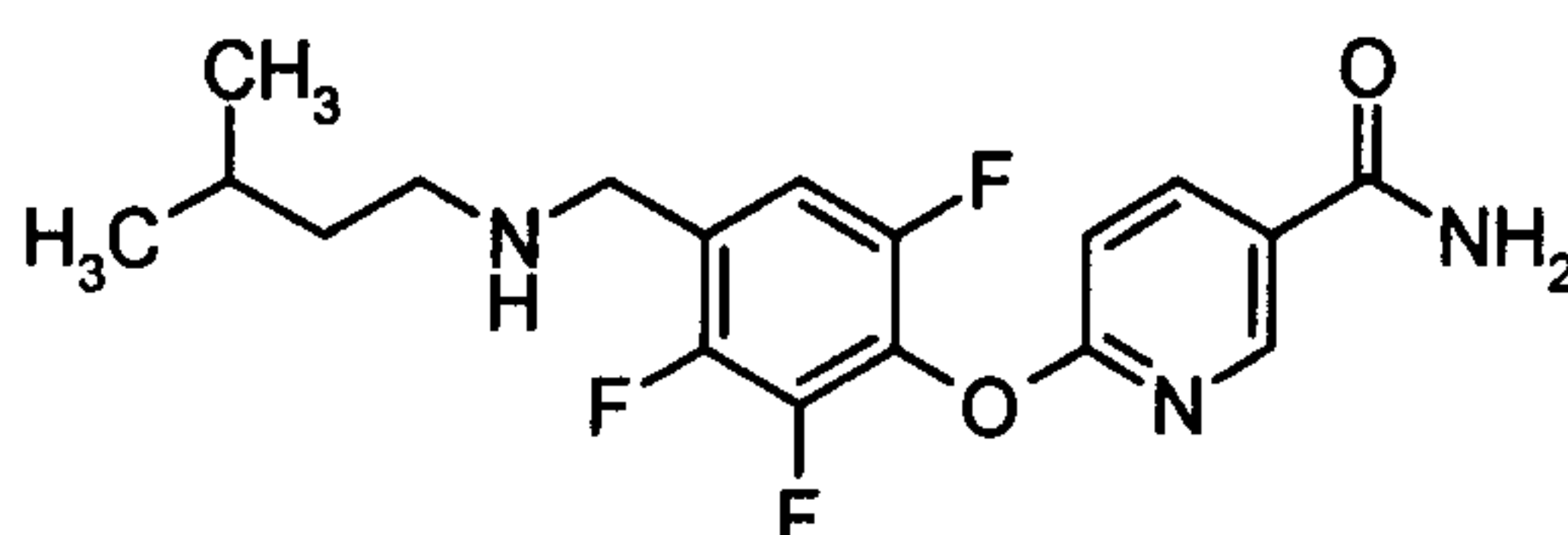
6-{2-Chloro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



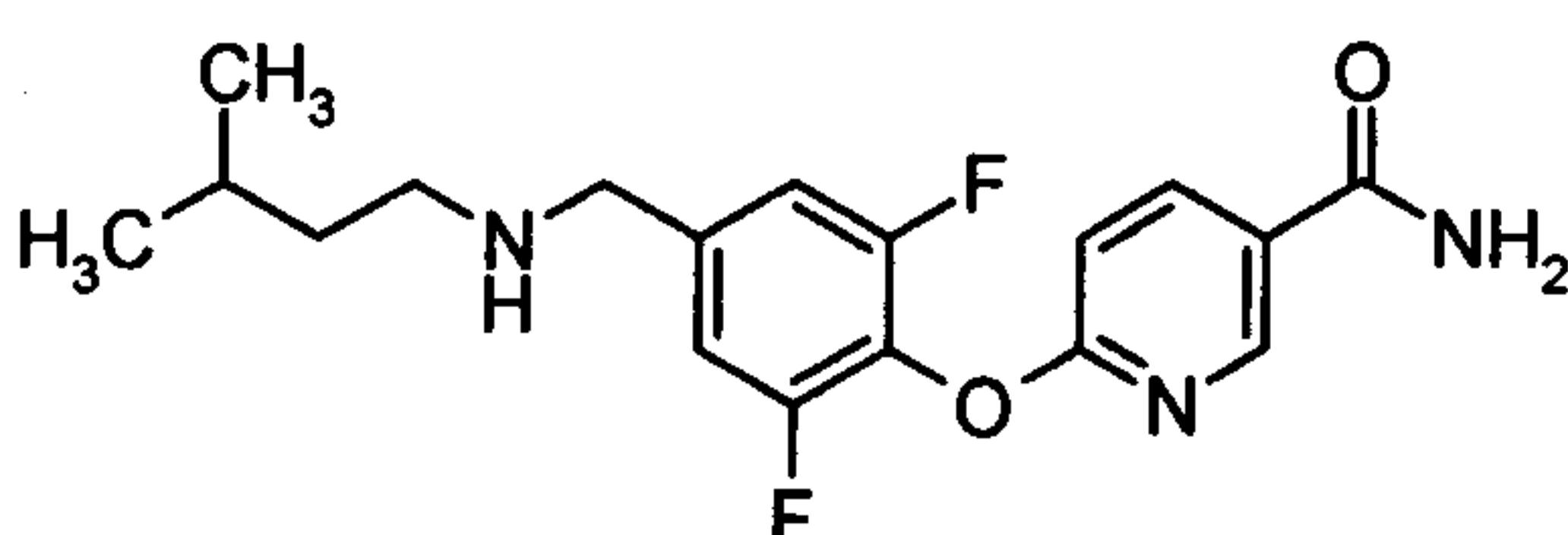
3,5-Difluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



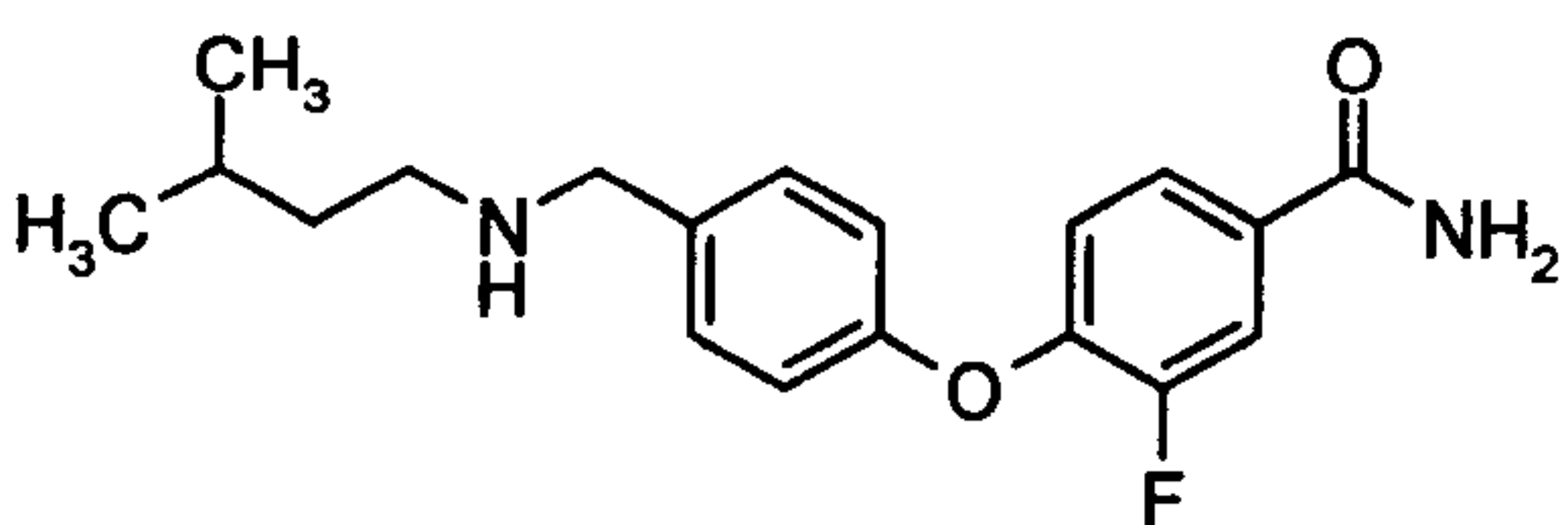
6-{2,3,6-Trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



6-{2,6-Difluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



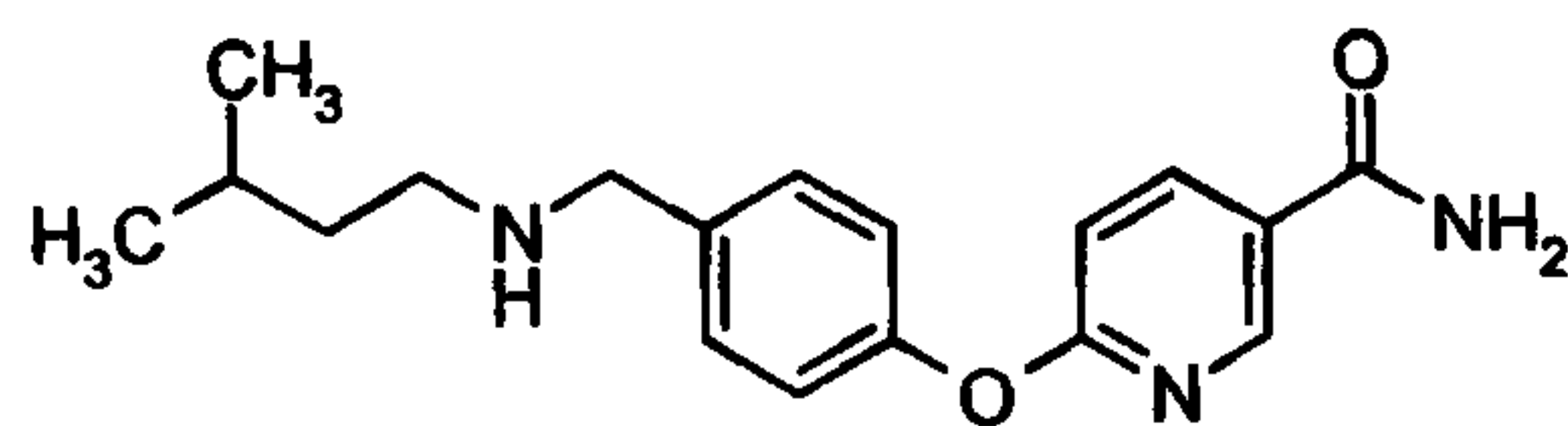
3-Fluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



and a pharmaceutically acceptable salt, or solvate thereof.

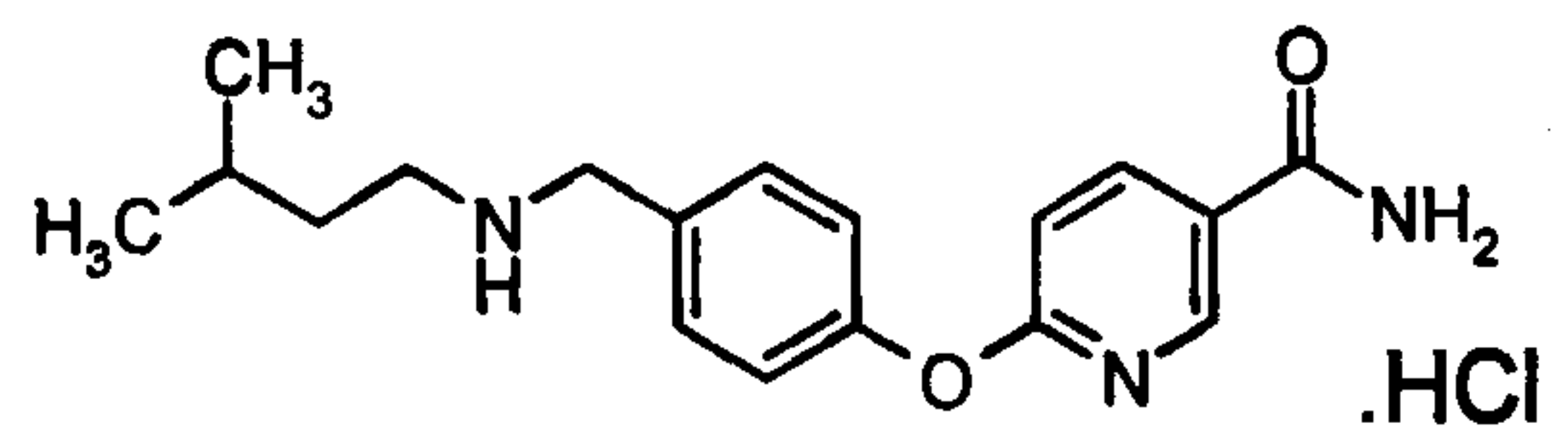
2. The compound 6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide

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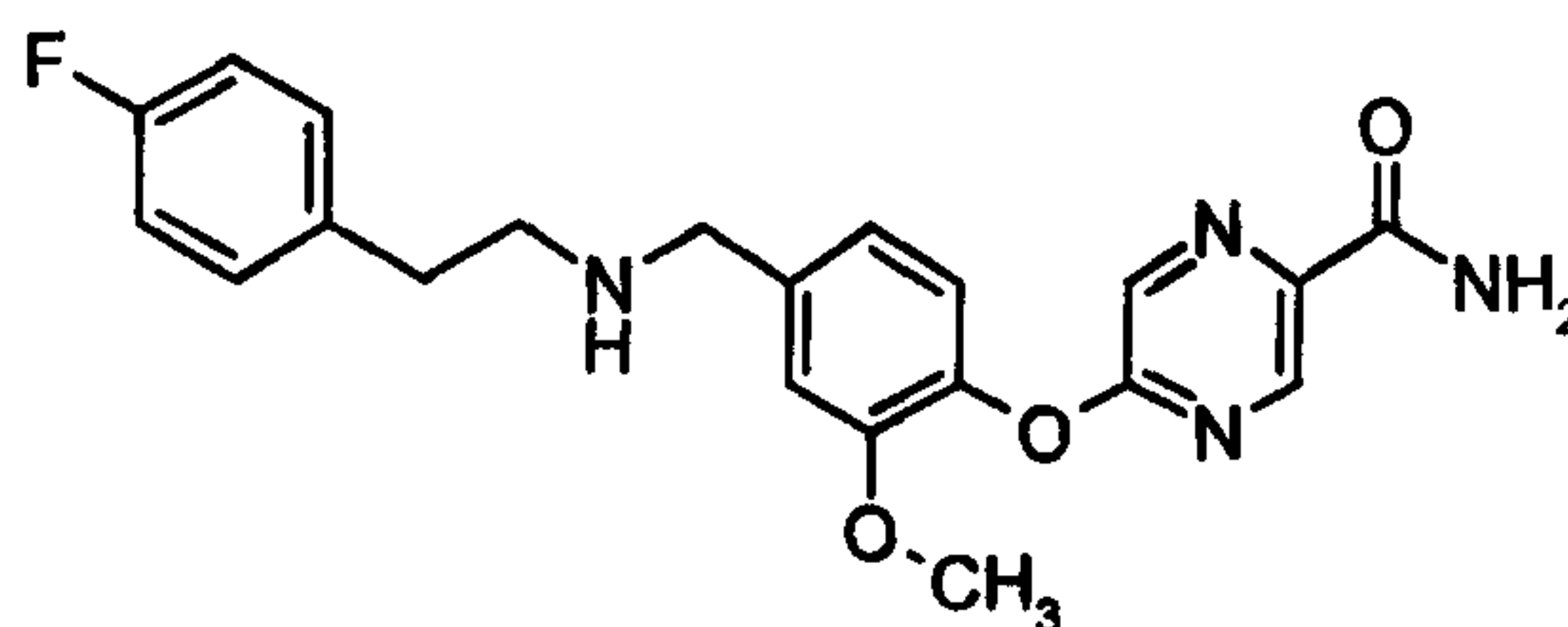


or a pharmaceutically acceptable salt, or solvate thereof.

3. The hydrochloric acid salt of the compound 6-{4-[(3-Methylbutylamino)-methyl]-phenoxy}-nicotinamide

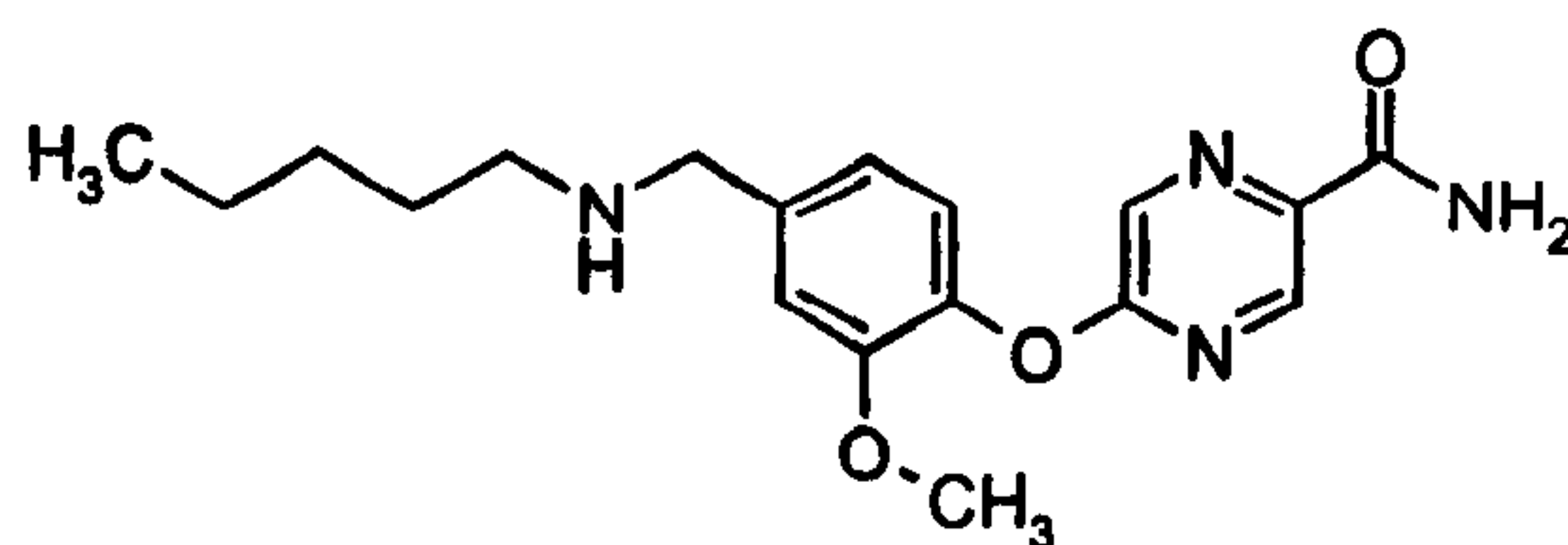


4. The compound 5-(4-{[2-(4-Fluoro-phenyl)-ethylamino]-methyl}-2-methoxy-phenoxy)-pyrazine-2-carboxamide



or a pharmaceutically acceptable salt, or solvate thereof.

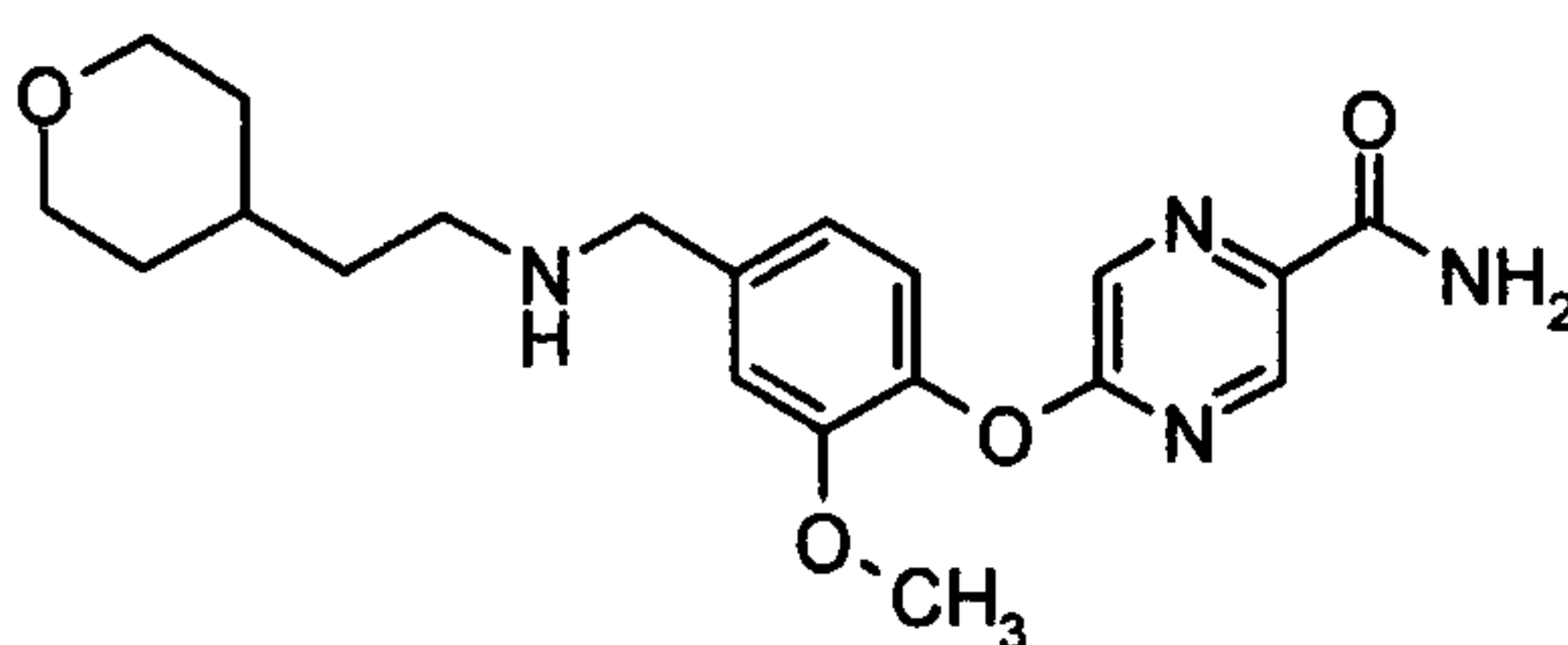
5. The compound 5-(2-Methoxy-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxylic acid amide



or a pharmaceutically acceptable salt, or solvate thereof.

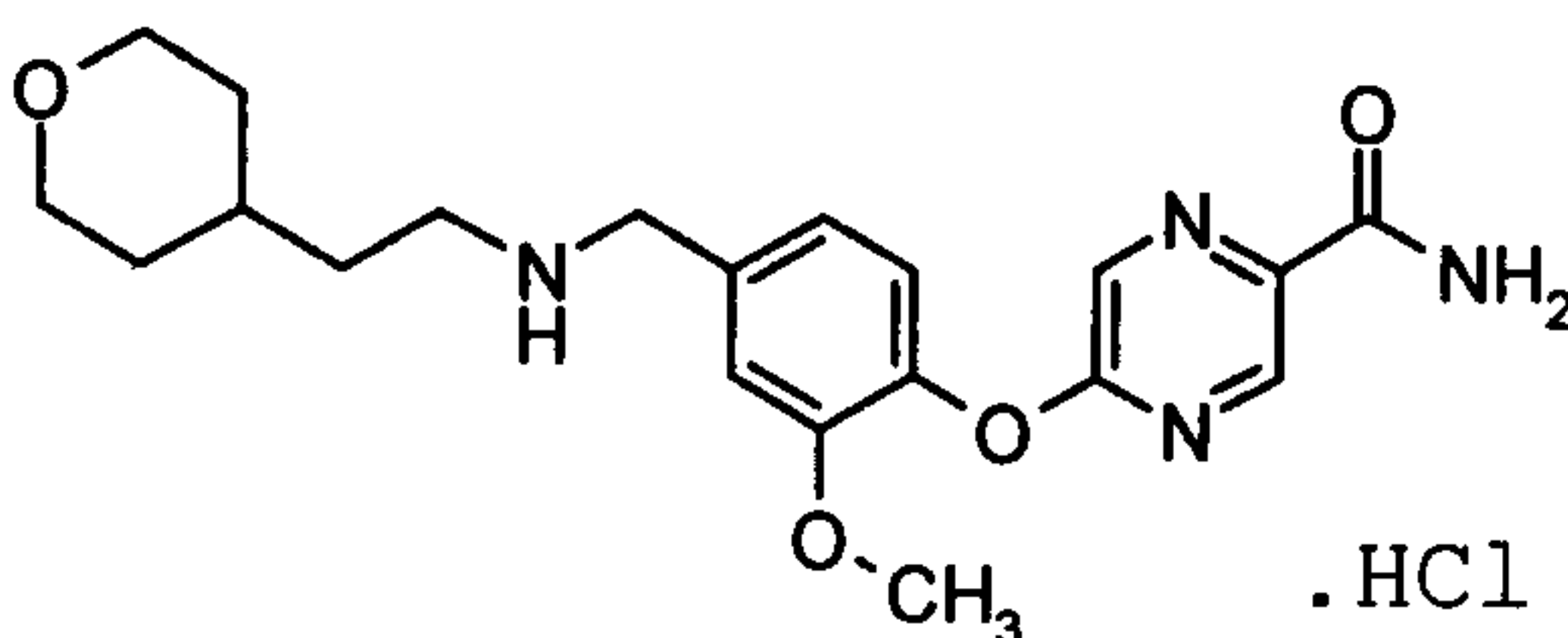
6. The compound 5-(2-Methoxy-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide

544

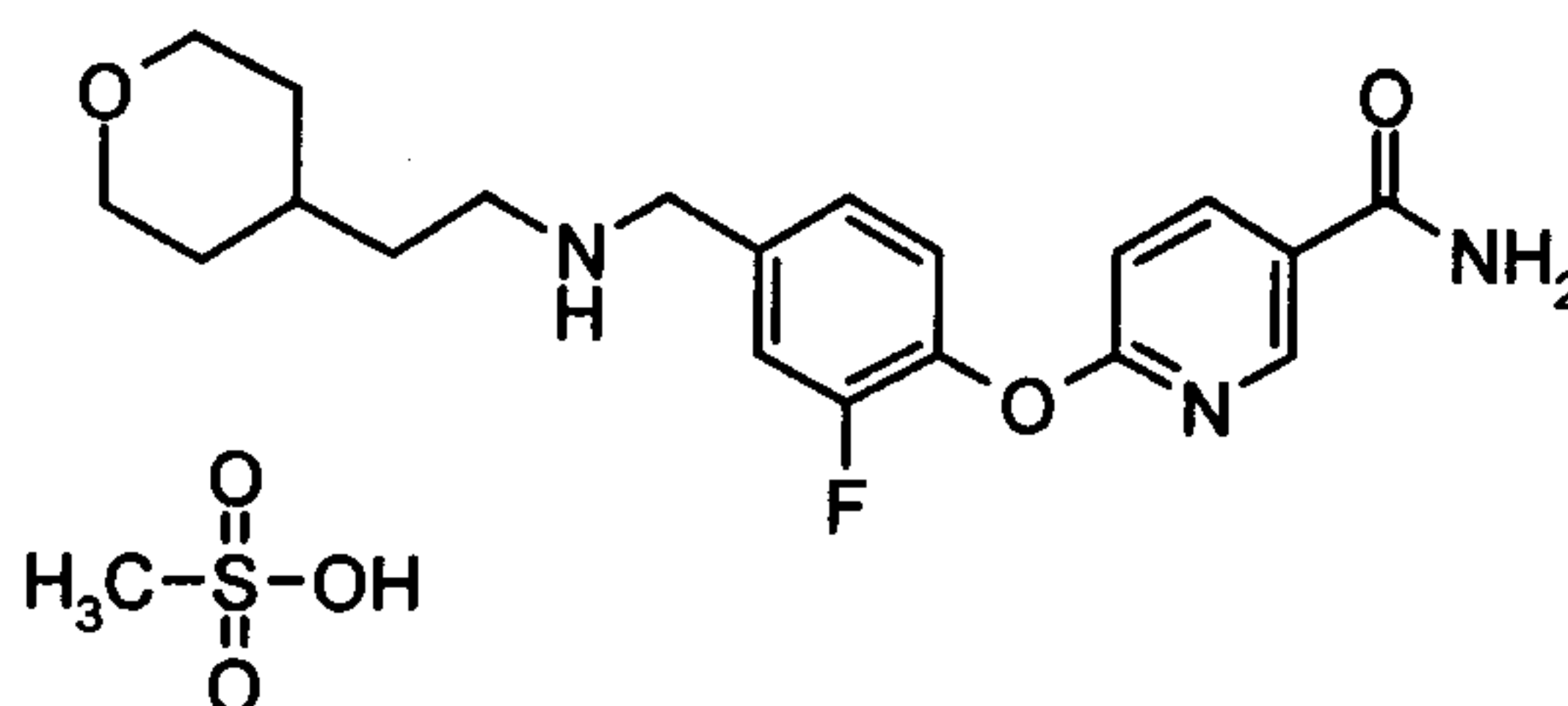


or a pharmaceutically acceptable salt, or solvate thereof.

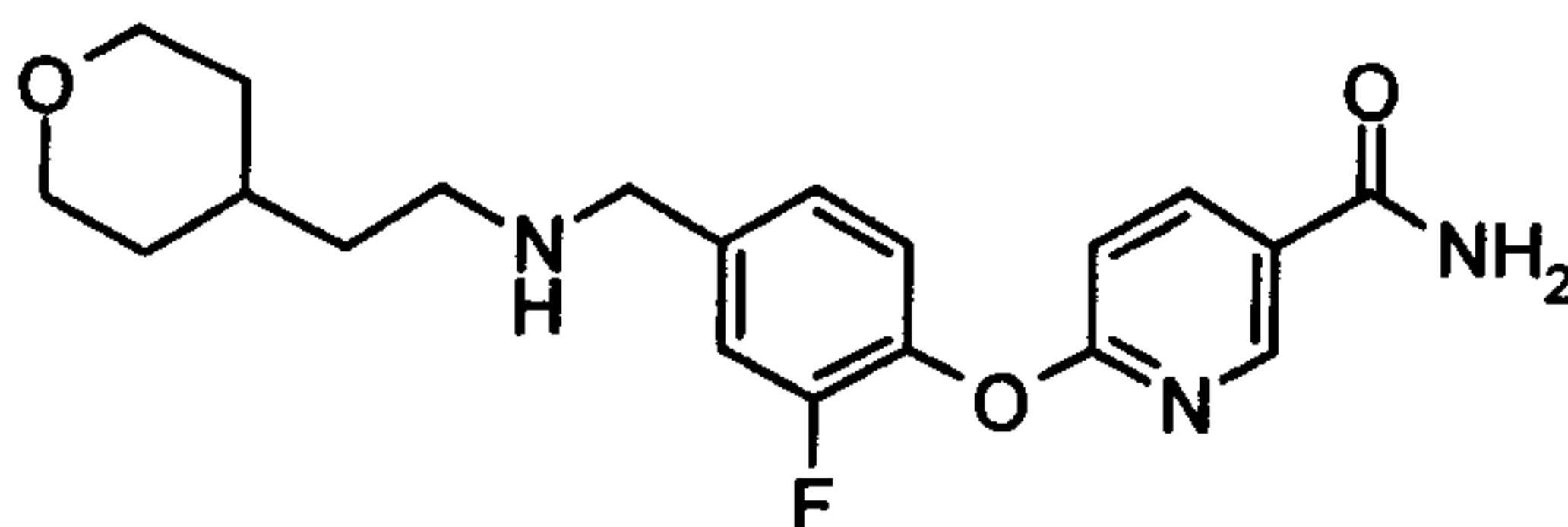
7. The compound 5-(2-Methoxy-4-([2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl)-phenoxy)-pyrazine-2-carboxamide, hydrochloric acid salt.



8. The compound 6-(2-Fluoro-4-([2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl)-phenoxy)-nicotinamide; methanesulfonic acid salt



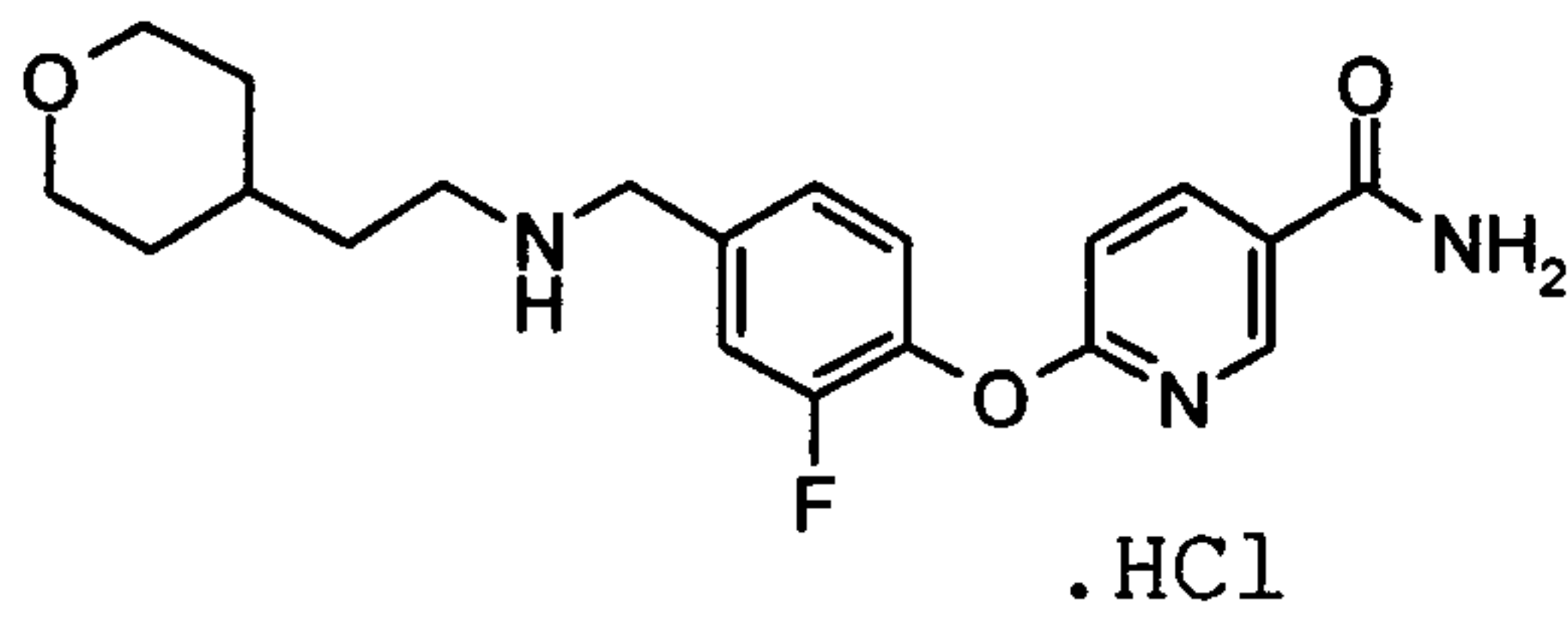
9. 6-(2-Fluoro-4-([2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl)-phenoxy)-nicotinamide



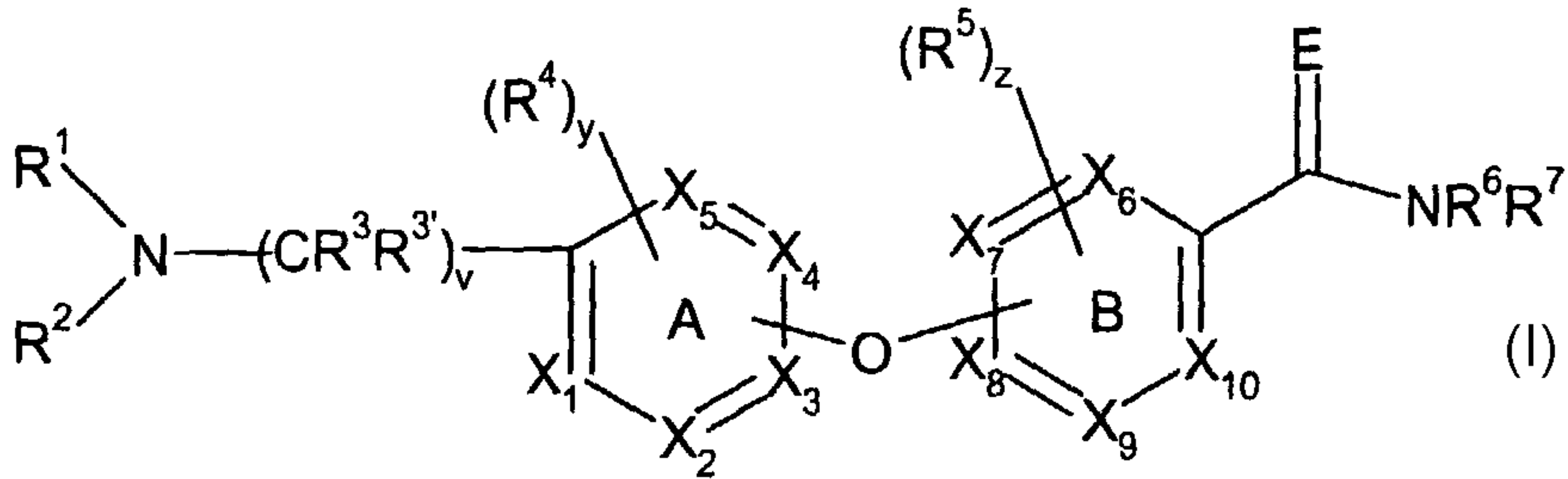
or a pharmaceutically acceptable salt, or solvate thereof.

10. 6-(2-Fluoro-4-([2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl)-phenoxy)-nicotinamide, hydrochloric acid salt.

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11. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 10 in association with a carrier, diluent and/or excipient.
12. Use of a compound according to Claim 3 or 7 or 8 or 9 or 10 for the manufacture of a medicament for treating or preventing obesity and Related Diseases.



- (51) Cl.Int./Int.Cl. (suite/continued) *C07D 213/82* (2006.01), *C07D 217/04* (2006.01), *C07D 237/24* (2006.01), *C07D 241/24* (2006.01), *C07D 307/14* (2006.01), *C07D 333/20* (2006.01), *C07D 401/06* (2006.01), *C07D 401/12* (2006.01), *C07D 401/14* (2006.01), *C07D 409/12* (2006.01), *C07D 409/14* (2006.01), *C07D 413/12* (2006.01), *C07D 417/12* (2006.01), *C07D 417/14* (2006.01)
- (72) Inventeurs(suite)/Inventors(continued): HOLLOWAY, WILLIAM GLEN, US; MATT, JAMES EDWARD JUNIOR, US; MITCH, CHARLES HOWARD, US; PEDREGAL-TERCERO, CONCEPCION, ES; QUIMBY, STEVEN JAMES, US; SIEGEL, MILES GOODMAN, US; SMITH, DANA RAE, US; STUCKY, RUSSELL DEAN, US; TAKEUCHI, KUMIKO, US; THOMAS, ELIZABETH MARIE, US; WOLFE, CHAD NOLAN, US
- (73) Propriétaires(suite)/Owners(continued): ELI LILLY AND COMPANY, US
- (74) Agent: GOWLING LAFLEUR HENDERSON LLP