Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Design, Synthesis and Biological Evaluation of Novel Indano- and Thiaindano-Pyrazoles with Potential Interest in Alzheimer's Disease.

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Supporting Information

Experimental part

1. General

All commercial solvents and reagents were used as-received.

The microwave reactions were performed using a Biotage Initiator Microwave oven using 2-5 mL sealed vials; temperatures were measured with an IR-sensor and reaction times given as hold times. Flash chromatography was realized on a spot 2 apparatus. Melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were recorded on KBr discs; only selected absorbances were quoted. TLC were carried out on 5x10 pre-coated plates with silica gel GF254 type 60; LC/MS (ESI) analyses were realized with a separating module using the following gradient: A (95%)/B (5%) to A (5%)/B (95%) in 5 min; this ratio was hold during 2 min before return to initial conditions in 1 min. Initial conditions were then maintained for 2 min (A: H_2O, B: CH_3CN; each containing HCOOH: 0.1%; Column: C18, flow : 0.4 mL.min^{-1}). MS detection was performed by positive or negative ESI. High Resolution Mass Spectra were performed at 40 eV by electronic impact (HREIMS) or positive or negative electrospray (HRESIMS). ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz using $CDCl_3$, *d6*-DMSO, CD_3OD or $(CD_3)_2CO$ as solvents. 2D NMR spectra and 1D NOESY experiments were recorded at 500 MHz. The apparent multiplicity is described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), m (multiplet); chemical shifts δ are reported in parts per million with the solvent resonance as the internal standard; coupling constants *J* are given in Hertz.

2. Chemistry

***2.1. N*-{(2*E*)-2-[(Dimethylamino)methylene]-5,6-dimethoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl}-2.2,2-trifluoroacetamide (2a)**

To a suspension of 10 g of **1a** (33 mmol) in toluene (150 mL) was added DMF-DMA (8.8 mL, 2 equiv). The suspension was then heated at reflux for 8 h, then cooled to room temperature and concentrated under reduced pressure. The resulting orange powder obtained was triturated in ice-cold ether and filtered, which led to **2a** as a yellow powder (11.1 g, 94%); mp > 260°C; IR (KBr) ν (cm^{-1}) 2999, 2972, 2937, 2839, 1702, 1663, 1589, 1533, 1501, 1472, 1436, 1360, 1310, 1283, 1207, 1184, 1145, 1128, 1097, 1033, 999; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.83 Hz, 1H, NH), 7.05 (s, 1H, C*H*NMe_2), 7.04 (s, 1H, Hphenyl), 7.01 (s, 1H, Hphenyl), 6.25 (1H, d, J = 8.79 Hz, C*H*NH), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.06 (6H, s, NMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 157.8 (q, J = 37.4 Hz, *C*OCF_3), 153.9, 150.2, 147.4 (2C), 141.8, 131.3, 116.2 (q, J = 287.8 Hz, CO*C*F_3), 106.4, 103.4, 103.0, 56.4, 56.0, 50.0 (2C); HREIMS [M+] *m/z* 359,1219 (calcd for $C_{16}H_{17}F_3N_2O_4$ 359,1219).

***2.2.N*-{(5*E*)-5-[(Dimethylamino)methylene]-6-oxo-5,6-dihy-dro-4*H*-cyclopenta[*b*]thien-4-yl}-2.2,2-trifluoroacetamide (2b)**

Starting from **1b** (15 g, 60.2 mmol) and DMF-DMA (16 mL, 120 mmol, 2 equiv) following the same procedure as above, **2b** was obtained as a yellow powder (17.95 g, 98%); mp 244°C; IR (KBr) ν (cm^{-1}) 3184, 1716, 1661, 1585, 1549, 1438, 1312, 1206, 1186, 1146, 1121, 987, 949, 942, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 8.03 Hz, 1H, NH), 7.65 (d, J = 4.76 Hz, 1H, Hthiophene), 7.12 (d, J = 4.76 Hz, 1H, Hthiophene), 6.78 (s, 1H, C*H*NMe_2), 6.11 (d, J = 8.03 Hz, 1H, C*H*$NHCOCF_3$), 3.00 (s, 6H, NMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 157.6 (*C*OCF_3, q, J = 38 Hz), 157.4, 147.1 (2C), 144.1, 136.2, 123.0, 115.9 (CO*C*F_3, q, J = 287 Hz, CF_3), 105.6, 47.8 (2C); HRESIMS [M+H] *m/z* 305,0569 (calcd for $C_{12}H_{11}F_3N_2O_2S$ 305,0572).

2.3. *N*-{(5*E*)-1,3-Dibromo-5-[(dimethylamino)methylene]-6-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-4-yl}-2.2,2-trifluoroacetamide (2c)

Starting from **1c** (10 g, 21.6 mmol) and DMF-DMA (5.8 mL, 43.3 mmol, 2 equiv) following the same procedure as above, **2c** was obtained as a yellow powder (10.8 g, 95%); mp > 260°C; IR (KBr) ν (cm^{-1}) 1714, 1666, 1591, 1542, 1491, 1430, 1406, 1375, 1278, 1208, 1185, 1146, 1105; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 10.02 (1H, d, J = 8.75 Hz, NH), 7.36 (1H, s, C*H*NMe$_2$), 6.09 (1H, d, J = 8.75 Hz, CHNH), 3.10 (s, 6H, NMe$_2$); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 180.8, 155.4 (d, J = 36.6 Hz, *C*OCF$_3$), 149.7, 147.6, 143.9, 115.8 (d, J = 288.5 Hz, CO*C*F$_3$), 108.0, 106.0, 104.8, 54.4, 45.5 (2C); HRESIMS [M+H] *m/z* 460,8778 (calcd for $C_{12}H_9Br_2F_3N_2O_2S$ 460,8782).

2.4. *N*-(6,7-Dimethoxy-2,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)-2.2,2-trifluoroacetamide (3a)

To a suspension of 5 g of **2a** (14 mmol) in AcOH (30 mL) was added hydrazine sulfate (2.18 g, 16.7 mmol, 1.2 equiv). The suspension was then heated at reflux for 4 h, then cooled to room temperature and concentrated under reduced pressure. The crude mixture was then triturated in water, filtered and dried under air. This led to **3a** as a yellow powder (4.34 g, 95%); mp > 260°C; IR (KBr) ν (cm^{-1}) 3271, 1702, 1550, 1486, 1386, 1284, 1212, 1187, 1156, 1034; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 12.67 (s, 1H, NHpyrazole), 10.00 (d, J = 5.8 Hz, NHCOCF$_3$), 7.66 (s, 1H, Hpyrazole), 7.18 (s, 1H, Hphenyl), 7.05 (s, 1H, Hphenyl), 5.74 (d, J = 5.8 Hz, 1H, C*H*NH), 3.83 (s, 3H, OCH$_3$), 3.76 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 157.6, 157.5 (q, J = 35.7 Hz, *C*OCF$_3$), 149.8, 148.4, 140.7, 127.2, 124.8, 123.5, 116.1 (q, J = 287.4 Hz, CO*C*F$_3$), 109.7, 103.4, 55.9 (2C), 48.0; HRESIMS [M+H] *m/z* 328.0984 (calcd for $C_{14}H_{12}F_3N_3O_3$ 328,0909).

2.5. *N*-1,4-Dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl-2.2,2-trifluoroacetamide (3b)

Starting from 5 g of **2b** (16.4 mmol) in AcOH (30 mL) and hydrazine sulfate (2.57 g, 19.7 mmol, 1.2 equiv) following the same procedure as above, a crude powder was obtained which was purified by column chromatography (SiO_2, EtOAc/cyclohexane 1/1). This led to **3b** as a white powder (4.13 g, 92%); mp > 260°C; IR (KBr) ν (cm^{-1}) 3287, 1697, 1588, 1540, 1364, 1215, 1196, 1175, 1159, 995, 819, 797; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.58 (s, 1H, Hpyrazole), 7.47 (d, J = 4.88 Hz, 1H, Hthiophene), 7.12 (d, J = 4.88 Hz, 1H, Hthiophene), 5.78 (s, 1H, C*H*NHCOCF$_3$); ^{13}C NMR (100 MHz, CD$_3$OD) δ 159.6 (*C*OCF$_3$, q, J = 37 Hz), 155.6, 154.9, 136.5, 129.9, 128.1, 125.7, 124.0, 117.5 (CO*C*F$_3$, q, J = 287 Hz), 47.8; HREIMS [M+] *m/z* 273.0184 (calcd for $C_{10}H_6F_3N_3OS$ 273,0184).

2.6. *N*-(5,7-Dibromo-2,4-dihydrothieno[3',4':4,5]cyclopenta [1,2-*c*]pyrazol-4-yl)-2.2,2-trifluoroacetamide (3c)

Starting from 5 g of **2c** (10.8 mmol) in AcOH (30 mL) and hydrazine sulfate (1.69 g, 13.0 mmol, 1.2 equiv) following the same procedure as above, a crude powder was obtained which was purified by column chromatography (SiO_2, gradient from DCM 100% to MeOH/DCM 10/90). This led to **3c** as a yellow powder (4.48 g, 96%); mp > 260°C; IR (KBr) ν (cm^{-1}) 3266, 1698, 1579, 1548, 1411, 1366, 1289, 1208, 1185, 1042, 935; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 13.11 (1H, s, NHpyrazole), 10.09 (1H, d, J = 7.79 Hz, NHCOCF$_3$), 7.82 (1H, s, Hpyrazole), 5.87 (1H, d, J = 7.79 Hz, C*H*NHCOCF$_3$); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 156.1 (q, J = 36.6 Hz, *C*OCF$_3$), 150.7 (2C), 139.0, 129.2, 124.9, 115.9 (q, J = 288.3 Hz, CO*C*F$_3$), 105.8, 97.4, 45.1; HRESIMS [M+H] *m/z* 428.84086 (calcd for $C_{10}H_6F_3N_3OS$ 428,83929).

2.7. *N*-(6,7-Dimethoxy-1-methyl-1,4-dihydroindeno[1,2-*c*] pyrazol-4-yl)-2.2,2-trifluoroacetamide (4a)

Starting from 5 g of **2a** (14 mmol) in AcOH (30 mL) and methyl-hydrazine (0.88 mL, 16.7 mmol, 1.2 equiv) following the same procedure as above, **4a** was obtained as a white powder which was pure enough for use in the next step (4.62 g, 97%); mp 229-230°C; IR (KBr) ν (cm^{-1}) 3276, 1700, 1618, 1553, 1489, 1340, 1307, 1267, 1212, 1187, 1148, 1029; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.98 (s, 1H, NH), 7.33 (s, 1H, Hpyrazole), 7.30 (s, 1H, Hphenyl), 7.08 (s, 1H, Hphenyl), 5.62 (s, 1H, C*H*NH), 4.04 (s, 3H, NCH$_3$), 3.86 (s, 3H, OCH$_3$), 3.76 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 157.3 (q, J = 37.2 Hz, *C*OCF$_3$), 149.3, 148.2, 147.9, 141.2, 132.8, 125.6, 123.8, 115.9 (q, J = 288.8 Hz, CO*C*F$_3$), 110.0, 103.6, 56.1, 55.8, 47.5, 37.3; HREIMS [M+] *m/z* 341.09994 (calcd for $C_{15}H_{14}F_3N_3O_3$ 341,09869).

***2.8.* 2,2,2-Trifluoro-*N*-(1-methyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (4b)**

Starting from 5 g of **2b** (16.4 mmol) in AcOH (30 mL) and methylhydrazine (1.06 mL, 19.7 mmol, 1.2 equiv) following the same procedure as above, a crude powder was obtained which was purified by column chromatography (SiO_2, EtOAc/cyclohexane 1/1) to give **4b** as a white powder (4.57 g, 97%); mp 228°C; IR (KBr) ν (cm^{-1}) 3276, 1700, 1548, 1447, 1365, 1227, 1205, 1188, 1167, 1153, 1007, 727, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H, Hpyrazole), 7.31 (d, J = 4.00 Hz, 1H, Hthiophene), 7.16 (d, J = 4.00 Hz, 1H, Hthiophene), 6.85 (d, J = 4.80 Hz, 1H, NH), 5.71 (d, J = 4.80 Hz, 1H, C*H*NHCOCF_3), 3.89 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (*C*OCF_3, q, J = 38 Hz), 153.6, 145.3, 134.2, 131.9, 128.1, 127.7, 123.8, 115.8 (CO*C*F_3, q, J = 288 Hz), 46.9, 37.7; HREIMS [M+] m/z 287.0326 (calcd for $C_{11}H_8F_3N_3OS$ 287,034).

***2.9.* *N*-(5,7-Dibromo-1-methyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2.2,2-trifluoroacetamide (4c)**

Starting from 5 g of **2c** (10.8 mmol) in AcOH (30 mL) and methylhydrazine (0.70 mL, 13 mmol, 1.2 equiv) following the same procedure as above, a crude powder was obtained which was purified by column chromatography (SiO_2, MeOH/DCM gradient from 0/100 to 5/95). This led to **4c** as a beige powder (4.62 g, 96%); mp 260°C; IR (KBr) ν (cm^{-1}) 3267, 1703, 1559, 1440, 1215, 1185, 1150, 1028, 941, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, Hpyrazole), 6.49 (d, J = 8.80 Hz, 1H, NH), 5.84 (d, J = 8.80 Hz, 1H, C*H*NH), 4.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1 (q, J = 18,9 Hz, *C*OCF3), 149.7, 141.8, 134.4, 134.2, 131.7, 115.7 (q, J = 288.0 Hz, CO*C*F_3), 107.7, 98.5, 44.9, 40.1; HRESIMS [M+H] m/z 443.8644 (calcd for $C_{11}H_6Br_2F_3N_3OS$ 443,8629).

***2.10.* *N*-(6,7-Dimethoxy-1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)-2.2,2-trifluoroacetamide (5a)**

Starting from 5 g of **2a** (14 mmol) in AcOH (30 mL) and phenylhydrazine (1.65 mL, 16.7 mmol, 1.2 equiv) following the same procedure as above, **5a** was obtained as a white powder which was pure enough for use in the next step (5.52 g, 98%); mp 220°C; IR (KBr) ν (cm^{-1}) 3288, 1697, 1652, 1600, 1534, 1485, 1443, 1347, 1262, 1212, 1184, 1151, 1060, 763, 697; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 10.09 (d, J =7.75 Hz, 1H, NH), 7.72 (m, 2H, Hphenyl), 7.70 (s, 1H, Hpyrazole), 7.65 (m, 2H, Hphenyl), 7.49 (m, 1H, Hphenyl), 7.14 (s, 1H, Hphenyl), 6.95 (s, 1H, Hphenyl), 5.76 (d, J = 7.75 Hz, 1H, C*H*NH), 3.78 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 157.4 (q, J = 148 Hz, *C*OCF_3), 148.9, 148.6, 146.9, 142.0, 139.3, 135.3, 129.7 (2C), 128.1, 127.9, 123.4, 122.6 (2C), 115.9 (q, J = 288 Hz, CO*C*F_3), 110.0, 103.4, 55.8, 55.5, 47.5; HRESIMS [M+H] m/z 404.1236 (calcd for $C_{20}H_{16}F_3N_3O_3$ 404.1222).

***2.11.* 2,2,2-Trifluoro-*N*-(1-phenyl-1,4-dihydrothieno [3',2': 4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (5b)**

Starting from 5 g of **2b** (16.4 mmol) in AcOH (30 mL) and phenylhydrazine (1.96 mL, 19.7 mmol, 1.2 equiv) following the same procedure as above, a crude powder was obtained which was purified by column chromatography (SiO_2, EtOAc/cyclohexane 20/80). This led to **5b** as a yellow powder (5.28 g, 92%); mp 212°C; IR (KBr) ν (cm^{-1}) 3069, 1701, 1600, 1548, 1530, 1512, 1441, 1367, 1358, 1207, 1186, 1153, 1056, 1010, 946, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.50 Hz, 2H, Hphenyl), 7.55 (s, 1H, Hpyrazole), 7.50 (t, J = 8.50 Hz, 2H, Hphenyl), 7.36 (t, J = 8.50 Hz, 1H, Hphenyl), 7.27 (d, J = 4.90 Hz, 1H, Hthiophene), 7.13 (d, J = 4.90 Hz, 1H, Hthiophene), 7.09 (d, J = 7.90 Hz, 1H, NH), 5.73 (d, J = 7.90 Hz, 1H, C*H*NHCOCF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (q, J = 37.7 Hz, *C*OCF_3), 153.9, 143.6, 139.2, 135.6, 132.5, 129.7 (2C), 129.4, 127.9, 127.4, 123.7, 120.1 (2C), 115.7 (q, J = 287.9 Hz, CO*C*F_3), 46.5; HREIMS [M+] m/z 349.0497 (calcd for $C_{16}H_{10}F_3N_3OS$ 349.0497).

***2.12.* *N*-(5,7-Dibromo-1-phenyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2.2,2-trifluoroacetamide (5c)**

Starting from 5 g of **2c** (10.8 mmol) in AcOH (30 mL) and phenylhydrazine (1.28 mL, 13 mmol, 1.2 equiv) following the same procedure as above, a crude powder was obtained which was purified by column chromatography (SiO_2, MeOH/DCM gradient from 0/100 to 5/95). This led to **5c** as a beige powder (5.21 g, 95%); mp 226°C; IR (KBr) ν (cm^{-1}) 3247, 1701, 1599, 1549, 1521, 1496, 1424, 1374, 1215, 1195, 1163, 1155, 1064, 990, 764, 721, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H, Hpyrazole), 7.52 (m, 2H, Hphenyl), 7.48 (m, 3H, Hphenyl), 6.55 (d,

J = 8.75 Hz, 1H, NH), 5.93 (d, *J* = 8.75 Hz, 1H, C*H*NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (q, *J* = 37.9 Hz, *C*OCF$_3$), 149.7, 142.0, 139.7, 135.8, 133.5, 132.5, 129.4, 129.0 (2C), 126.4 (2C), 116.8 (q, *J* = 286.4 Hz, CO*C*F3), 107.8, 100.0, 44.9; HRESIMS [M+H] *m/z* 505.8788 (calcd for $C_{16}H_8Br_2F_3N_3OS$ 505.8785).

2.13. 6,7-Dimethoxy-1,4-dihydroindeno[1,2-*c*]pyrazol-4-amine dihydrochloride (6a)

Trifluoroacetamide **3a** (2 g, 6.11 mmol) was suspended in 6 M HCl solution (15 mL) and refluxed for 2 h. The solvent was evaporated under reduced pressure and the crude powder was triturated in ice-cold EtOH, filtered, triturated in ice-cold ether and filtered again. This led to **6a** as a yellow powder (1.52 g, 82%); mp 228°C; IR (KBr) ν (cm^{-1}) 2915, 2599, 1624, 1585, 1505, 1461, 1441, 1280, 1221, 1129, 1058, 1027; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 8.90 (d, *J* = 5.2 Hz, 3H, $NH_3^+Cl^-$), 7.72 (s, 1H, Hpyrazole), 7.70 (s, 1H, Hphenyl), 7.22 (s, 1H, Hphenyl), 5.07 (q, *J* = 5.2 Hz, 1H, C*H*$NH_3^+Cl^-$), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 157.5, 150.0, 148.2, 138.0, 127.2, 126.3, 121.3, 110.9, 103.5, 55.9, 47.3, 34.2; HRESIMS [M+H] *m/z* 232.1085 (calcd for $C_{12}H_{13}N_3O_2$ 232.1086).

2.14. 1,4-Dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-amine dihydrochloride (6b)

Starting from **3b** (2 g, 7.32 mmol) and following the same procedure as above, **6b** was obtained as a white powder (1.76 g, 96%); mp > 260°C; IR (KBr) ν (cm^{-1}) 1612, 1589, 1508, 1482, 1436, 1350, 1284, 1248, 1225, 1100, 1056, 925, 755, 715; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.12 (d, *J* = 5.16 Hz, 3H, $NH_3^+Cl^-$), 7.74 (s, 1H, Hpyrazole), 7.60 (d, *J* = 4.9 Hz, 1H, Hthiophene), 7.46 (d, *J* = 4.9 Hz, 1H, Hthiophene), 5.01 (q, *J* = 5.16 Hz, 1H, C*H*NH_3Cl); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 153.0, 150.9, 136.2, 128.8, 126.2, 124.4, 124.2, 45.2; HREIMS [M+] *m/z* 177.0361 (calcd for $C_8H_7N_3S$ 177.0361).

2.15 5,7-Dibromo-1,4-dihydrothieno[3',4':4,5]cyclopenta [1, 2-*c*]pyrazol-4-amine dihydrochloride (6c)

Starting from **3c** (2 g, 4.64 mmol) and following the same procedure as above, **6c** was obtained as a beige powder (1.51 g, 80%); mp > 260°C; IR (KBr) ν (cm^{-1}) 3392, 3183, 2948, 1636, 1575, 1542, 1533, 1428, 1049, 1018, 808, 712, 609; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 13.22 (1H, s, NHpyrazole), 8.31 (3H, s, $NH_3^+Cl^-$), 7.79 (s, 1H, Hpyrazole), 5.26 (s, 1H, CH); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 150.7, 148.6, 139.0, 127.3, 126.8, 107.8, 98.4, 44.7; HREIMS [M+] *m/z* 332.8569 (calcd for $C_8H_5Br_2N_3S$ 332.85701).

2.16. 6,7-Dimethoxy-1-methyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-amine dihydrochloride (7a)

Starting from **4a** (2 g, 5.86 mmol) and following the same procedure as above, **7a** was obtained as a yellow powder (1.68 g, 90%); mp > 260°C; IR (KBr) ν (cm^{-1}) 3541, 3401, 2912, 2862, 2622, 1501, 1310, 1231, 1212, 1135, 1024; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 8.90 (d, *J* = 4.9 Hz, 3H, $NH_3^+Cl^-$), 7.74 (s, 1H, Hpyrazole), 7.44 (s, 1H, Hphenyl), 7.33 (s, 1H, Hphenyl), 4.95 (q, *J* = 4.9 Hz, 1H, C*H*$NH_3^+Cl^-$), 4.05 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 149.7, 148.3, 148.1, 138.6, 133.8, 124.0, 123.4, 111.4, 103.8, 56.2, 55.9, 46.8, 37.5; HREIMS [M+] *m/z* 245.11581 (calcd for $C_{13}H_{15}N_3O_2$ 245.11641).

2.17 1-Methyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*] pyrazol-4-amine (7b)

Starting from **4b** (2 g, 6.96 mmol) and following the same procedure as above, **7b** was obtained as a white powder (1.60 g, 87%); mp > 260°C; IR (KBr) ν (cm^{-1}) 2133, 1613, 1587, 1529, 1455, 1360, 1285, 1004, 926, 750, 708; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.06 (d, *J* = 5.36 Hz, 3H, CHN*H*$_3$Cl), 7.63 (d, *J* = 4.88 Hz, 1H, Hthiophene), 7.47 (s, 1H, CHpyrazole), 7.46 (d, *J* = 4.88 Hz, 1H, Hthiophene), 4.94 (d, *J* = 5.36 Hz, 1H, C*H*NH_3Cl), 3.91 (s, 3H, CH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 151.6, 144.5, 134.4, 131.8, 129.0, 126.2, 124.6, 45.1, 37.4; HREIMS [M+] *m/z* 191.0522 (calcd for $C_9H_9N_3S$ 191.0517).

2.18 5,7Dibromo-1-methyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-amine dihydrochloride (7c)

Starting from **4c** (2 g, 4.49 mmol) and following the same procedure as above, **7c** was obtained as a beige powder (1.59 g, 84%); mp > 260°C; IR (KBr) ν (cm^{-1}) 3435, 2861, 2703, 2612, 1592, 1559, 1508, 1444, 1361, 1174, 1078, 1017, 893, 710; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.03 (s, 3H, $NH_3^+Cl^-$), 7.69 (s, 1H, Hpyrazole), 5.23 (s, 1H,

C*H*$NH_3^+Cl^-$), 4.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 148.7, 141.1, 135.4, 134.1, 130.1, 108.2, 98.5, 43.7, 39.8; HREIMS [M+] *m/z* 346.8727 (calcd for $C_9H_7Br_2N_3S$ 346.8728).

2.19. **6,7-Dimethoxy-1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-amine dihydrochloride (8a)**

Starting from **5a** (2 g, 4.96 mmol) and following the same procedure as above, **8a** was obtained as a yellow powder (1.66 g, 88%); mp 254-255°C; IR (KBr) ν (cm^{-1}) 2921, 2600, 1596, 1491, 1455, 1317, 1266, 1216, 1114, 1058, 1082; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.06 (d, *J* = 4.9 Hz, 3H, $NH_3^+Cl^-$), 7.83 (s, 1H, Hpyrazole), 7.79 (s, 1H, Hphenyl), 7.67 (m, 4H, Hphenyl), 7.51 (m, 1H, Hphenyl), 6.96 (s, 1H, Hphenyl), 5.10 (d, *J* = 4.9 Hz, 1H, C*H*$NH_3^+Cl^-$), 3.81 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 149.2, 148.5, 147.4, 139.3, 139.1, 136.3, 129.9 (2C), 128.2, 125.9, 123.5, 122.7 (2C), 111.4, 103.5, 55.9, 55.6, 46.7; HREIMS [M+] *m/z* 307.13353 (calcd for $C_{18}H_{17}N_3O_2$ 307.13206).

2.20. **1-Phenyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*] pyrazol-4-amine dihydrochloride (8b)**

Starting from **5b** (2 g, 5.73 mmol) and following the same procedure as above, **8b** was obtained as a yellow powder (1.62 g, 87%); mp > 260°C; IR (KBr) ν (cm^{-1}) 2891, 2707, 2604, 1599, 1526, 1508, 1497, 1451, 1440, 1358, 1050, 986, 753; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 8.78 (s, 3H, NH_3), 7.79 (s, 1H, Hpyrazole), 7.73 (m, 2H), 7.69 (m, 1H), 7.65 (t, *J* = 7.70 Hz, 2H), 7.46 (m, 2H), 5.13 (s, 1H, C*H*NH_3); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 152.4, 143.1, 138.9, 136.6, 132.3, 130.2 (2C), 129.2, 128.7, 127.7, 124.6, 119.9 (2C), 45.3; HREIMS [M+] *m/z* 253.0674 (calcd for $C_{14}H_{11}N_3O_2$ 253.0674).

2.21. **5,7-Dibromo-1-phenyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-amine dihydrochloride (8c)**

Starting from **5c** (2 g, 3.94 mmol) and following the same procedure as above, **8c** was obtained as a yellow powder (1.62 g, 85%); mp 215°C; IR (KBr) ν (cm^{-1}) 3434, 2880, 1623, 1599, 1553, 1497, 763, 694; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.12 (s, 3H, $NH_3^+Cl^-$), 7.95 (s, 1H, Hpyrazole), 7.58 (m, 5H, Hphenyl), 5.31 (s, 1H, C*H*$NH_3^+Cl^-$); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 148.8, 141.4, 139.2, 137.2, 133.4, 131.2, 129.4, 129.1 (2C), 126.0 (2C), 108.5, 99.4, 43.7; HREIMS [M+] *m/z* 408.88748 (calcd for $C_{14}H_9Br_2N_3S$ 408.88831).

2.22. ***2*-Chloro-*N*-(6,7-dimethoxy-1,4-dihydroindeno[1,2-*c*] pyrazol-4-yl)acetamide (9a)**

To a suspension of **6a** (500 mg, 1.64 mmol) in DCM (10 mL) was added TEA (0.71 mL, 5.26 mmol, 3.2 equiv). After 5 min, the mixture was cooled with an ice bath and a solution of chloroacetyl chloride (144 µL, 1.80 mmol, 1.1 equiv) in DCM (10 mL) was added drop-wise. When the addition was over, the ice bath was removed and the mixture was stirred for 1 h. The solvent was then evaporated under reduced pressure and the crude powder was triturated in water, filtered and dry under air. This led to **9a** as a white powder (364 mg, 72%); mp 200-202°C; IR (KBr) ν (cm^{-1}) 2933, 1655, 1592, 1518, 1485, 1465, 1434, 1384, 1281, 1215, 1186, 1173, 1136, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H, Hpyrazole), 7.29 (s, 1H, Hphenyl), 7.08 (s, 1H, Hphenyl), 6.78 (d, *J* = 7.79 Hz, 1H, NHacetamide), 5.92 (d, *J* = 7.79 Hz, 1H, C*H*NH), 4.19 (d, *J* = 15.6 Hz, 1H, Ha), 4.14 (d, *J* = 15.6 Hz, 1H, Hb), 3.96 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 159.2, 150.3, 149.5, 141.4, 126.9, 124.8, 124.5, 109.2, 103.8, 56.4, 56.3, 48.6, 42.6; HREIMS [M+] *m/z* 307.0709 (calcd for $C_{14}H_{14}ClN_3O_3$ 307.07234).

2.23 **2-Chloro-*N*-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-ylacetamide (9b)**

Starting from **6b** (500 mg, 2.0 mmol), TEA (0.86 mL, 6.4 mmol, 3.2 equiv), chloroacetyl chloride (175 µL, 2.2 mmol, 1.1 equiv) and following the same procedure as above, a crude powder was obtained, which was further purified by column chromatography (SiO_2, gradient from MeOH/DCM 0/100 to 10/90). This led to **9b** as a beige powder (360 mg, 71%); mp 173°C; IR (KBr) ν (cm^{-1}) 2924, 1652, 1534, 1225, 1105, 996, 960, 784; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H, CHpyrazole), 7.37 (d, *J* = 4.88 Hz, 1H), 7.13 (d, *J* = 4.88 Hz, 1H), 6.80 (broad d, *J* = 7.79 Hz, 1H, NHCO), 5.82 (d, *J* = 7.79 Hz, 1H, CONHC*H*), 4.16 (d, J_{AB} = 15.4 Hz, 1H, Ha), 4.12 (d, J_{AB} = 15.4 Hz, 1H, Hb); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.8, 153.8, 135.8, 129.1, 128.1, 124.4, 122.8, 47.1, 42.5; HREIMS [M+] *m/z* 253.007 (calcd for $C_{10}H_8ClN_3OS$ 253.0077).

2.24. **2-Chloro-*N*-(5,7-dibromo-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (9c)**
Starting from **6c** (500 mg, 1.23 mmol), TEA (0.53 mL, 3.92 mmol, 3.2 equiv), chloroacetyl chloride (107 µL, 1.35 mmol, 1.1 equiv) and following the same procedure as above, a crude powder was obtained, which was further purified by column chromatography (SiO_2, gradient from MeOH/DCM 0/100 to 10/90). This led to **9c** as a beige powder (363 mg, 72%); mp 238°C; IR (KBr) ν (cm^{-1}) 3272, 2919, 2874, 1648, 1575, 1537, 1415, 1286, 1227, 1180, 1048, 1022, 985, 968, 813, 794, 612; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 8.91 (d, J = 8.50 Hz, 1H, NHCO), 7.71 (s, 1H, Hpyrazole), 5.80 (d, J = 8.50 Hz, 1H, C*H*NH), 4.08 (s, 2H, $COCH_2$); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 165.7, 151.7, 138.9, 134.1, 130.6, 125.0, 105.4, 97.1, 45.2, 42.3; HRESIMS [M+H] *m/z* 409.8383 (calcd for $C_{10}H_6Br_2ClN_3OS$ 409.8365).

2.25. **2-Chloro-*N*-(6,7-dimethoxy-1-methyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (10a)**
Starting from **7a** (500 mg, 1.57 mmol), TEA (0.68 mL, 5.03 mmol, 3.2 equiv), chloroacetyl chloride (138 µL, 1.73 mmol, 1.1 equiv) and following the same procedure as above, **10a** was obtained, without need for column chromatography, as a beige powder (369 mg, 73%); mp 238°C; IR (KBr) ν (cm^{-1}) 3258, 3073, 3010, 2939, 1655, 1551, 1522, 1488, 1341, 1307, 1267, 1222, 1207, 1128, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, Hpyrazole), 7.13 (s, 1H, Hphenyl), 6.98 (s, 1H, Hphenyl), 6.71 (d, J = 8.75 Hz, 1H, NH), 5.83 (d, J = 8.75 Hz, 1H, C*H*NH), 4.17 (s, 2H, CH_2), 4.09 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 149.7, 149.0, 148.7, 142.9, 133.5, 126.4, 124.1, 110.2, 102.7, 56.5, 56.4, 48.2, 42.6, 37.6; HREIMS [M+] *m/z* 321.08768 (calcd for $C_{15}H_6ClN_3O_3$ 321.08799).

2.26. **2-Chloro-*N*-(1-methyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (10b)**
Starting from **7b** (500 mg, 1.89 mmol), TEA (0.82 mL, 6.06 mmol, 3.2 equiv), chloroacetyl chloride (166 µL, 2.08 mmol, 1.1 equiv) and following the same procedure as above, a crude powder was obtained, which was further purified by column chromatography (SiO_2, gradient from MeOH/DCM 0/100 to 5/95). This led to **10b** as a white powder (380 mg, 75%); mp 230°C; IR (KBr) ν (cm^{-1}) 3261, 1653, 1545, 1446, 1236, 1010, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H, Hpyrazole), 7.28 (d, J = 4.9 Hz, 1H, Hthiophene), 7.14 (d, J = 4.9 Hz, 1H, Hthiophene), 6.81 (d, J = 8.0 Hz, 1H, NH), 5.73 (d, J = 8.0 Hz, 1H, C*H*NH), 4.14 (s, 2H, C*H*$_2$), 3.96 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 154.6, 145.1, 134.0, 131.5, 128.7, 127.5, 123.8, 47.0, 42.5, 37.6; HREIMS [M+] *m/z* 267.0227 (calcd for $C_{11}H_{10}ClN_3OS$ 267.0233).

2.27. **2-Chloro-*N*-(5,7-dibromo-1-methyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (10c)**
Starting from **7c** (500 mg, 1.18 mmol), TEA (0.51 mL, 3.79 mmol, 3.2 equiv), chloroacetyl chloride (104 µL, 1.30 mmol, 1.1 equiv) and following the same procedure as above, a crude powder was obtained, which was further purified by column chromatography (SiO_2, gradient from MeOH/DCM 0/100 to 10/90). This led to **10c** as a beige powder (373 mg, 74%); mp 236°C; IR (KBr) ν (cm^{-1}) 3431, 1655, 1557, 1440, 1026, 714; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 8.75 (d, J = 8.40 Hz, 1H, NH), 7.28 (s, 1H, Hpyrazole), 5.58 (d, J = 8.40 Hz, 1H, C*H*NH), 4.06 (s, 3H, CH_3), 4.00 (s, 2H, CH_2); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 165.9, 151.9, 140.6, 134.3, 134.1, 133.6, 105.9, 97.1, 44.5, 42.3, 39.7; HRESIMS [M+H] *m/z* 423.8511 (calcd for $C_{11}H_8Br_2ClN_3OS$ 423.8522).

2.28. **2-Chloro-*N*-(6,7-dimethoxy-1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (11a)**
Starting from **8a** (500 mg, 1.31 mmol), TEA (0.57 mL, 4.21 mmol, 3.2 equiv), chloroacetyl chloride (115 µL, 1.45 mmol, 1.1 equiv) and following the same procedure as above, **11a** was obtained, without need for column chromatography, as a beige powder (358 mg, 71%); mp 216°C; IR (KBr) ν (cm^{-1}) 2939, 1661, 1599, 1531, 1486, 1408, 1350, 1315, 1261, 1216, 1126, 1086, 1060, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 2H, Hphenyl), 7.65 (s, 1H, Hpyrazole), 7.57 (m, 2H, Hphenyl), 7.46 (m, 1H), 7.13 (s, 1H, Hphenyl), 6.97 (s, 1H, Hphenyl), 6.81 (d, J = 8.79 Hz, 1H, NH), 5.92 (d, J = 8.79 Hz, 1H, C*H*NH), 4.20 (s, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 149.3, 149.1, 147.8, 143.0, 139.8, 135.4, 129.4 (2C), 128.1 (2C), 124.0, 123.2 (2C), 109.7, 103.5, 56.3, 56.2, 48.1, 42.6; HREIMS [M+] *m/z* 383.10406 (calcd for $C_{20}H_{18}ClN_3O_3$ 383.10364).

2.29 **2-Chloro-*N*-(1-phenyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (11b)**

Starting from **8b** (500 mg, 1.53 mmol), TEA (0.66 mL, 4.90 mmol, 3.2 equiv), chloroacetyl chloride (134 µL, 1.69 mmol, 1.1 equiv) and following the same procedure as above, a crude powder was obtained, which was further purified by column chromatography (SiO_2, gradient from EtOAc/cyclohexane 50/50 to 100/0). This led to **11b** as a white powder (374 mg, 75%); mp 201°C; IR (KBr) ν (cm^{-1}) 3292, 2924, 1648, 1599, 1530, 1454, 1440, 1056, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H, Hphenyl), 7.65 (s, 1H, Hpyrazole), 7.56 (t, J = 8.2 Hz, 2H, Hphenyl), 7.40 (t, J = 8.2 Hz, 1H, Hphenyl), 7.29 (d, J = 4.9 Hz, 1H, Hthiophene), 7.19 (d, J = 4.9 Hz, 1H, Hthiophene), 6.82 (d, J = 7.8 Hz, 1H, NH), 5.83 (d, J = 7.8 Hz, C*H*NH), 4.18 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.0, 143.5, 139.5, 135.6, 132.4, 130.8, 129.8 (2C), 127.4, 127.3, 123.9, 120.3 (2C), 46.8, 42.5; HRESIMS [M+H] *m*/*z* 330.0474 (calcd for $C_{16}H_{12}ClN_3OS$ 330.0468).

2.30. **2-Chloro-*N*-(5,7-dibromo-1-phenyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (11c)**

Starting from **8c** (500 mg, 1.03 mmol), TEA (0.45 mL, 3.31 mmol, 3.2 equiv), chloroacetyl chloride (91 µL, 1.14 mmol, 1.1 equiv) and following the same procedure as above, a crude powder was obtained, which was further purified by column chromatography (SiO_2, gradient from MeOH/DCM 0/100 to 10/90). This led to **11c** as a beige powder (378 mg, 75%); mp 236°C; IR (KBr) ν (cm^{-1}) 3254, 1652, 1599, 1547, 1517, 1422, 1298, 1258, 1130, 1063, 1021, 996, 917, 832, 762, 696; ^{1}H NMR (400 MHz, *d6*-DMSO) δ 9.00 (d, J = 8.40 Hz, 1H, NH); 7.74 (s, 1H, Hpyrazole); 7.62 (m, 5H, Hphenyl); 5.85 (d, J = 8.40 Hz, 1H, C*H*NH); 4.18 (s, 2H, CH_2); ^{13}C NMR (100 MHz, *d6*-DMSO) δ 166.0, 152.1, 140.8, 139.4, 135.6, 135.2, 133.6, 129.1, 129.0(5) (2C), 126.0 (2C), 106.2, 98.0, 44.5, 42.3; HRESIMS [M+H] *m*/*z* 485.8661 (calcd for $C_{16}H_{10}Br_2ClN_3OS$ 485.8678).

2.31. **2-(4-Benzylpiperazin-1-yl)-*N*-(6,7-dimethoxy-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (12a)**

Chloroacetamide **9a** (100 mg, 0.32 mmol), benzylpiperazine dihydrochloride (89 mg, 0.36 mmol, 1.1 equiv) and K_2CO_3 (144 mg, 1.04 mmol, 3.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **14a** as a yellow powder (51 mg, 35%); mp 152°C; IR (KBr) ν (cm^{-1}) 2929, 2834, 1662, 1581, 1492, 1445, 1380, 1288, 1223, 1134, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H, Hpyrazole), 7.27 (m, 6H, Hphenyl), 7.04 (s, 1H, Hphenyl), 5.96 (d, J = 7.79 Hz, 1H, C*H*NH), 3.94 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2phenyl), 3.15 (d, J = 16.6 Hz, 1H, Ha), 3.10 (d, J = 16.6 Hz, 1H, Hb), 2.54 (broad m, 4H, Hpiperazine), 2.38 (broad m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 159.1, 149.9, 149.2, 142.4, 137.8, 129.1 (2C), 128.3 (2C), 127.2, 126.7, 125.5, 124.2, 108.8, 103.6, 62.8, 61.6, 56.3, 56.2, 53.5 (2C), 52.9 (2C), 47.7; HRESIMS [M+H] *m*/*z* 448.2339 (calcd for $C_{25}H_{29}N_5O_3$ 448.2349).

2.32. **2-(4-Benzylpiperazin-1-yl)-*N*-(1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (12b)**

Chloroacetamide **9b** (100 mg, 0.39 mmol), benzylpiperazine dihydrochloride (108 mg, 0.43 mmol, 1.1 equiv) and K_2CO_3 (174 mg, 1.26 mmol, 3.2 equiv) were introduced in a microwave reactor. Acetone (2.1 mL) was added, the reactor was sealed and irradiated under microwave to a temperature of 170°C for 1 h 30. After cooling to ambient temperature, the same amounts of benzylpiperazine dihydrochloride and K_2CO_3 were added and the reactor was again irradiated at 170°C for 1 h 30. After cooling to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **14b** as a yellow powder (43 mg, 28%); mp 146°C; IR (KBr) ν (cm^{-1}) 2933, 2818, 1656, 1501, 1456, 1355, 1297, 1157, 1134, 1012, 911, 736, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H, Hpyrazole), 7.25 (m, 7H, Hthiophene + 5Hphenyl + NH), 7.02 (d, J = 4.80 Hz, 1H, Hthiophene), 5.71 (d, J = 8.35 Hz, 1H, C*H*NH), 3.41 (s, 2H, CH_2CO), 3.12 (s, 2H, CH_2phenyl), 2.50 (broad m, 4H, Hpiperazine), 2.35 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 154.6, 150.9, 137.6, 135.4, 129.3, 129.2 (2C), 128.7, 128.3

(2C), 127.3 (2C), 122.7, 62.8, 61.5, 53.4 (2C), 52.8 (2C), 46.2; HRESIMS [M+H] *m/z* 394.1691 (calcd for $C_{21}H_{23}N_5OS$ 394.1702).

2.33. *N*-(5,7-Dibromo-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2-(4-benzylpiperazine) acetamide (12c)

Chloroacetamide **9c** (100 mg, 0.24 mmol), benzylpiperazine dihydrochloride (66.6 mg, 0.27 mmol, 1.1 equiv) and K_2CO_3 (107.5 mg, 0.78 mmol, 3.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **14c** as a yellow powder (30.8 mg, 23%); mp 144°C; IR (KBr) ν (cm^{-1}) 2937, 2816, 1668, 1495, 1454, 1132, 1005, 910, 733, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, Hpyrazole), 7.32 (m, 2H, Hphenyl), 7.28 (m, 2H, Hphenyl), 7.21 (m, 1H, Hphenyl), 5.81 (d, J = 8.75 Hz, 1H, C*H*NH), 3.54 (s, 2H, $COCH_2$), 3.29 (s, 2H, CH_2phenyl), 2.54 (m, 8H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 150.4, 141.7, 137.2, 134.3, 134.1, 134.0, 128.9 (2C), 128.1 (2C), 127.2, 106.3, 97.4, 63.2, 62.9, 61.1, 53.8, 52.6, 45.7, 44.1; HRESIMS [M+H] *m/z* 549.9902 (calcd for $C_{21}H_{21}Br_2N_5OS$ 549.9912).

2.34. 2-(4-Benzylpiperazin-1-yl)-*N*-(6,7-dimethoxy-1-me-thyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (13a)

Chloroacetamide **10a** (100 mg, 0.31 mmol), benzylpiperazine dihydrochloride (85.2 mg, 0.34 mmol, 1.1 equiv) and K_2CO_3 (137.4 mg, 0.99 mmol, 3.2 equiv) were refluxed in acetone (2 mL) for 36 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **15a** as a yellow powder (56 mg, 39%); mp 188°C; IR (KBr) ν (cm^{-1}) 2946, 2819, 1652, 1595, 1484, 1462, 1341, 1309, 1264, 1218, 1130, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 2H, Hpyrazole + Hphenyl), 7.24 (broad s, 4H, Hphenyl), 7.07 (s, 1H, Hphenyl), 6.94 (s, 1H, Hphenyl), 5.81 (d, J = 8.79 Hz, 1H, C*H*NH), 4.03 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2phenyl), 3.11 (s, 2H, $COCH_2$), 2.53 (broad m, 4H, Hpiperazine), 2.37 (broad m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 148.7, 148.0, 147.8, 143.1, 137.3, 132.4, 128.4 (2C), 127.6 (2C), 126.5, 126.4, 123.3, 109.1, 101.9, 62.1, 61.0, 55.7, 55.6, 52.8 (2C), 52.2 (2C), 46.7, 36.9; HRESIMS [M+H] *m/z* 462.2495 (calcd for $C_{26}H_{31}N_5O_3$ 462.2505).

2.35. 2-(4-Benzylpiperazine)-*N*-(1-methyl-1,4-dihydrothie-no[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (13b)

Chloroacetamide **10b** (100 mg, 0.37 mmol), benzylpiperazine dihydrochloride (102.3 mg, 0.41 mmol, 1.1 equiv) and K_2CO_3 (165 mg, 1.20 mmol, 3.2 equiv) were introduced in a microwave reactor. Acetone (2.1 mL) was added and the reactor was sealed and irradiated under microwave to a temperature of 170°C for 1 h 30. After cooling to ambient temperature, the same amounts of benzylpiperazine dihydrochloride and K_2CO_3 were added and the reactor was again irradiated at 170°C for 1 h 30. After cooling to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **15b** as a beige powder (47 mg, 31%); mp 130°C; IR (KBr) ν (cm^{-1}) 2940, 2821, 1674, 1601, 1488, 1452, 1431, 1155, 1138, 1054, 901, 731, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H, Hpyrazole), 7.27 (m, 7H, Hthiophene + 5Hphenyl + NH), 7.10 (d, J = 4.85 Hz, 1H, Hthiophene), 5.78 (d, J = 8.50 Hz, 1H, C*H*NH), 3.97 (s, 3H, NCH_3), 3.45 (s, 2H, CH_2CO), 3.09 (s, 2H, CH_2phenyl), 2.52 (broad m, 4H, Hpiperazine), 2.39 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 155.7, 145.1, 137.8, 133.7, 131.1, 129.6, 129.1 (2C), 128.3 (2C), 127.3, 127.2, 123.7, 62.8, 61.5, 53.5 (2C), 52.8 (2C), 46.3, 37.6; HRESIMS [M+H] *m/z* 408.1838 (calcd for $C_{22}H_{25}N_5OS$ 408.1858).

2.36. *N*-(5,7-Dibromo-1-methyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2-(4-benzyl-piperazine)acetamide (13c)

Chloroacetamide **10c** (100 mg, 0.24 mmol), benzylpiperazine dihydrochloride (64.4 mg, 0.26 mmol, 1.1 equiv) and K_2CO_3 (104 mg, 0.75 mmol, 3.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **15c** as a yellow powder (36 mg, 27%); mp 152°C; IR (KBr) ν (cm^{-1}) 2939, 2815, 1674, 1496, 1455, 1441, 1157, 1134, 1012, 911, 734, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H, Hpyrazole), 7.31 (m, 2H, Hphenyl), 7.28 (m, 3H, Hphenyl), 5.82 (d, J = 8.95 Hz, 1H, C*H*NH), 4.21 (s, 3H, NCH_3), 3.49 (s, 2H, CH_2phenyl), 3.08 (s, 2H, CH_2CO), 2.51 (m, 4H, Hpiperazine), 2.44 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 151.7, 141.4, 137.8, 134.6, 134.2 (2C), 129.1 (2C), 128.2 (2C), 127.1, 106.2, 97.6, 63.5, 62.8, 61.4, 53.9, 52.8, 45.8, 44.3, 40.0; HRESIMS [M+H] *m*/*z* 564.0048 (calcd for $C_{22}H_{23}Br_2N_5OS$ 564.0068).

2.37. 2-(4-Benzylpiperazin-1-yl)-*N*-(6,7-dimethoxy-1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (14a)

Chloroacetamide **11a** (100 mg, 0.26 mmol), benzylpiperazine dihydrochloride (71.4 mg, 0.29 mmol, 1.1 equiv) and K_2CO_3 (115 mg, 0.83 mmol, 3.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **16a** as a beige powder (56 mg, 40%); mp 164°C; IR (KBr) ν (cm^{-1}) 2937, 2821, 1644, 1486, 1350, 1261, 1215, 1134, 1060, 1014, 764, 735, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H, Hphenyl), 7.48 (s, 1H, Hpyrazole), 7.44 (m, 2H, Hphenyl), 7.39 (m, 1H, Hphenyl), 7.29 (m, 2H, Hphenyl), 7.22 (m, 2H, Hphenyl), 7.18 (m, 1H, Hphenyl), 7.09 (s, 1H, Hphenyl), 6.75 (s, 1H, Hphenyl), 6.27 (d, J = 8.40 Hz, 1H, NH), 5.79 (d, J = 8.40 Hz, 1H, C*H*NH), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.15 (s, 2H, $COCH_2$), 2.92 (s, 2H, CH_2phenyl), 2.53 (broad m, 8H, 4*CH_2piperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 149.2, 147.4, 144.1, 140.3, 138.5, 135.1, 129.2 (2C), 129.0 (2C), 128.7, 128.3 (2C), 128.0, 126.7 (2C), 123.2, 122.7 (2C), 110.2, 102.8, 63.0, 58.4, 56.1, 55.8, 53.4 (2C), 53.0 (2C), 47.7; HRESIMS [M+H] *m*/*z* 524.2640 (calcd for $C_{31}H_{33}N_5O_3$ 524.2662).

2.38. 2-(4-Benzylpiperazine)-*N*-(1-phenyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (14b)

Chloroacetamide **11b** (100 mg, 0.30 mmol), benzylpiperazine dihydrochloride (83.1 mg, 0.33 mmol, 1.1 equiv) and K_2CO_3 (134 mg, 0.97 mmol, 3.2 equiv) were introduced in a microwave reactor. Acetone (2.1 mL) was added, the reactor was sealed and irradiated under microwave to a temperature of 170°C for 1 h 30. After cooling to ambient temperature, the same amounts of benzylpiperazine dihydrochloride and K_2CO_3 were added and the reactor was again irradiated at 170°C for 1 h 30. After cooling to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **16b** as a yellow-orange powder (45.5 mg, 32%); mp 142°C; IR (KBr) ν (cm^{-1}) 2937, 2816, 1678, 1599, 1497, 1455, 1432, 1157, 1134, 1056, 1011, 910, 733, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 2H, Hphenyl), 7.48 (s, 1H, Hpyrazole), 7.39 (m, 2H, Hphenyl), 7.30 (m, 1H, Hphenyl), 7.28 (m, 2H, Hphenyl), 7.21 (m, 2H, Hphenyl), 7.18 (m, 1H, Hphenyl), 7.15 (d, J = 4.95 Hz, 1H, Hthiophene), 7.01 (d, J = 4.95 Hz, 1H, Hthiophene), 6.28 (d, J = 8.0 Hz, 1H, NH), 5.76 (d, J = 8.0 Hz, 1H, C*H*NH), 3.52 (s, 2H, $COCH_2$), 3.44 (s, 2H, CH_2phenyl), 2.54 (m, 8H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 155.9, 143.2, 139.3, 137.8, 136.1, 131.0, 129.5, 130.2 (2C), 128.9 (2C), 128.0 (2C), 126.7 (2C), 126.8, 123.2, 119.8 (2C), 63.4, 61.1, 53.1 (2C), 52.6 (2C), 46.7; HREIMS [M+] *m*/*z* 469.1936 (calcd for $C_{27}H_{27}N_5OS$ 469.1936).

2.39. *N*-(5,7-Dibromo-1-phenyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2-(4-benzylpiperazine)acetamide (14c)

Chloroacetamide **11c** (100 mg, 0.21 mmol), benzylpiperazine dihydrochloride (56.2 mg, 0.23 mmol, 1.1 equiv) and K_2CO_3 (90.7 mg, 0.66 mmol, 3.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient

temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **16c** as a yellow-orange powder (31 mg, 24%); mp 168°C; IR (KBr) ν (cm^{-1}) 2817, 1679, 1497, 1455, 1425, 1296, 1157, 1133, 1012, 912, 734, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H, Hphenyl), 7.45 (s, 1H, Hpyrazole), 7.40 (m, 2H, Hphenyl), 7.36 (m, 2H, Hphenyl), 7.29 (m, 1H, Hphenyl), 7.24 (m, 2H, Hphenyl), 7.20 (m, 1H, Hphenyl), 5.77 (d, *J* = 8.80 Hz, 1H, C*H*NH), 3.55 (s, 2H, CH_2CO), 3.27 (s, 2H, CH_2phenyl), 2.67 (m, 4H, Hpiperazine), 2.48 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.3, 141.7, 138.7, 137.4, 133.9, 133.8 (2C), 129.2 (2C), 129.0 (2C), 128.1 (2C), 127.3, 127.1, 124.1 (2C), 106.8, 97.3, 62.9, 62.6, 61.1, 54.3, 52.9, 45.5, 44.1; HRESIMS [M+H] *m/z* 626.0219 (calcd for $C_{27}H_{25}Br_2N_5OS$ 626.0225).

2.40. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-*N*-(6,7-dimeth-oxy-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (15a)

Chloroacetamide **9a** (100 mg, 0.32 mmol), *o*-fluorobenzyl-piperazine (59.3 µL, 0.36 mmol, 1.1 equiv) and K_2CO_3 (53.9 mg, 0.39 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **17a** as a yellow powder (44 mg, 29%); mp 164°C; IR (KBr) ν (cm^{-1}) 2936, 2827, 1652, 1589, 1486, 1457, 1383, 1281, 1217, 1136, 1035; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H, Hpyrazole), 7.37 (s, 1H, Hphenyl), 7.30 (t, *J* = 7.60 Hz, 1H, Hfluorophenyl), 7.23 (m, 2H, NH + Hfluorophenyl), 7.05 (m, 1H, Hfluorophenyl), 7.01 (s, 1H, Hfluorophenyl), 6.95 (s, 1H, Hphenyl), 5.78 (d, *J* = 8.70 Hz, 1H, C*H*NH), 3.98 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2-fluorophenyl), 3.15 (s, 2H, CH_2CO), 2.50 (broad m, 4H, Hpiperazine), 2.44 (broad m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 161.1 (d, *J* = 245.8 Hz, CF), 149.3, 148.5, 148.2, 143.2, 133.5, 131.7 (d, *J* = 4.62 Hz), 128.6 (d, *J* = 8.12 Hz), 127.1, 124.8 (d, *J* = 15.1 Hz), 124.2, 123.7 (d, *J* = 3.45 Hz), 115.1 (d, *J* = 22.4 Hz), 110.0, 102.2; 61.5, 56.5, 56.2, 55.1 (d, *J* = 1.60 Hz, *C*H_2-fluorophenyl), 53.4 (2C), 52.2 (2C), 47.1; HRESIMS [M+H] *m/z* 466.2244 (calcd for $C_{25}H_{28}FN_5O_3$ 466.2254).

2.41. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-*N*-(1,4-dihydro-thieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl) acetamide (15b)

Chloroacetamide **9b** (100 mg, 0.39 mmol), *o*-fluorobenzyl-piperazine (72 µL, 0.43 mmol, 1.1 equiv) and K_2CO_3 (65.4 mg, 0.47 mmol, 1.2 equiv) were introduced in a microwave reactor. Acetone (2.1 mL) was added, the reactor was sealed and irradiated under microwave to a temperature of 170°C for 1 h 30. After cooling to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **17b** as a orange powder (39 mg, 24%); mp 158°C; IR (KBr) ν (cm^{-1}) 2938, 2811, 1664, 1497, 1462, 1365, 1292, 1156, 1134, 1017, 914, 732, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H, Hpyrazole), 7.32 (m, 2H, Haromatic + NH), 7.22 (m, 2H, Haromatic), 7.06 (m, 2H, Haromatic), 7.00 (m, 1H, Haromatic), 5.84 (d, *J* = 8.30 Hz, 1H, C*H*NH), 3.54 (s, 2H, CH_2CO), 3.09 (s, 2H, CH_2phenyl), 2.53 (m, 4H, Hpiperazine), 2.44 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 161.4 (d, *J* = 246.3 Hz, CF), 154.5, 146.8, 135.4, 131.5, 129.5, 129.0 (d, *J* = 7.67 Hz), 128.6 (d, *J* = 28.4 Hz), 125.8, 123.9, 122.6, 121.7, 120.4, 115.3 (d, *J* = 22.1 Hz), 62.8, 61.5, 55.0, 53.5, 53.4, 52.6, 46.2; HRESIMS [M+H] *m/z* 412.1594 (calcd for $C_{21}H_{22}FN_5OS$ 412.1607).

2.42. *N*-(5,7-Dibromo-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2-[4-(2-fluorobenzyl) piperazine]acetamide (15c)

Chloroacetamide **9c** (100 mg, 0.24 mmol), *o*-fluorobenzyl-piperazine (44.4 µL, 0.27 mmol, 1.1 equiv) and K_2CO_3 (40.3 mg, 0.29 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 24 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by

column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **17c** as a beige powder (39 mg, 23%); mp 138°C; IR (KBr) ν (cm^{-1}) 2947, 2811, 1673, 1486, 1447, 1125, 1012, 913, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H, Hpyrazole), 7.34 (m, 1H, Hphenyl), 7.28 (m, 1H, Hphenyl), 7.14 (m, 1H, Hphenyl), 7.08 (m, 1H, Hphenyl), 5.79 (broad s, 1H, C*H*NH), 3.63 (s, 2H, $COCH_2$), 3.12 (s, 2H, CH_2phenyl), 2.60 (m, 8H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (*C*O), 161.1 (d, J = 245.9 Hz, *C*F), 151.6, 141.2, 134.8, 134.3, 134.2, 131.2 (d, J = 4.36 Hz), 128.9 (d, J = 8.15 Hz), 124.6 (d, J = 14.8 Hz), 124.0 (d, J = 3.47 Hz), 115.1 (d, J = 22.4 Hz), 106.5, 97.4, 61.2, 55.3, 53.4 (2C), 52.5 (2C), 44.1; HRESIMS [M+H] m/z 567.9798 (calcd for $C_{21}H_{21}Br_2FN_5OS$ 567.9818).

2.43. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-*N*-(6,7-dimetho-xy-1-methyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl)acetamide (16a)

Chloroacetamide **10a** (100 mg, 0.26 mmol), *o*-fluorobenzyl-piperazine (47.6 µL, 0.29 mmol, 1.1 equiv) and K_2CO_3 (43.2 mg, 0.31 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 36 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **18a** as a beige powder (49 mg, 33%); mp 176°C; IR (KBr) ν (cm^{-1}) 2940, 2825, 1663, 1587, 1489, 1455, 1342, 1305, 1267, 1224, 1135, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 1.30 Hz, 1H, Hphenyl), 7.32 (t, J = 7.55 Hz, 1H, Hfluorophenyl), 7.23 (m, 2H, NH + Hfluorophenyl), 7.10 (s, 1H, Hpyrazole), 7.08 (m, 1H, Hfluorophenyl), 7.00 (s, 1H, Hfluorophenyl), 6.98 (d, J = 1.30 Hz, 1H, Hphenyl), 5.87 (d, J = 8.75 Hz, 1H, C*H*NH), 4.09 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.52 (s, 2H, CH_2-fluorophenyl), 3.12 (s, 2H, CH_2CO), 2.54 (broad m, 4H, Hpiperazine), 2.42 (broad m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 161.4 (d, J = 246.3 Hz, CF), 149.4, 148.8, 148.5, 143.9, 133.2, 131.5 (d, J = 4.53 Hz), 128.9 (d, J = 8.18 Hz), 127.2, 124.4 (d, J = 14.6 Hz), 124.0, 123.9 (d, J = 3.52 Hz), 115.3 (d, J = 22.3 Hz), 109.9, 102.5, 61.6, 56.4, 56.3, 55.0 (d, J = 1.64 Hz, *C*H_2-fluorophenyl), 53.5 (2C), 52.6 (2C), 47.3, 37.6; HRESIMS [M+H] m/z 480.2406 (calcd for $C_{26}H_{30}FN_5O_3$ 480.2411).

2.44. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-*N*-(1-methyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (16b)

Chloroacetamide **10b** (100 mg, 0.37 mmol), *o*-fluorobenzyl-piperazine (68.2 µL, 0.41 mmol, 1.1 equiv) and K_2CO_3 (61.9 mg, 0.45 mmol, 1.2 equiv) were introduced in a microwave reactor. Acetone (2.1 mL) was added, the reactor was sealed and irradiated under microwave to a temperature of 170°C for 1 h 30. After cooling to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **18b** as a yellow powder (48 mg, 30%); mp 118°C; IR (KBr) ν (cm^{-1}) 2931, 2807, 1652, 1592, 1522, 1495, 1464, 1443, 1347, 1221, 1159, 1096, 1062, 1002, 941, 832, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H, Haromatic), 7.28 (m, 1H, Haromatic), 7.22 (m, 2H, Haromatic + NH), 7.09 (m, 2H, Haromatic), 6.99 (m, 1H, Haromatic), 5.77 (d, J = 8.40 Hz, 1H, C*H*NH), 3.95 (s, 3H, NCH_3), 3.52 (s, 2H, CH_2CO), 3.09 (s, 2H, CH_2phenyl), 2.52 (s, 4H, Hpiperazine), 2.43 (s, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 161.3 (d, J = 246.1 Hz, CF), 155.6, 145.0, 133.7, 131.5 (d, J = 4.40 Hz), 131.1, 129.5, 128.9 (d, J = 8.18 Hz), 127.3 (2C), 124.3 (d, J = 14.5 Hz), 123.9 (d, J = 3.52 Hz), 115.2 (d, J = 22.1 Hz), 61.5, 55.0, 53.4 (2C), 52.6 (2C), 46.3, 37.6; HRESIMS [M+H] m/z 426.1756 (calcd for $C_{22}H_{24}FN_5OS$ 426.1764).

2.45. *N*-(5,7-Dibromo-1-methyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2-[4-(2-fluoro-benzyl)piperazine]acetamide (16c)

Chloroacetamide **10c** (100 mg, 0.24 mmol), *o*-fluorobenzyl-piperazine (42.9 µL, 0.26 mmol, 1.1 equiv) and K_2CO_3 (39 mg, 0.28 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 36 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **18c** as a yellow powder (31.6 mg,

23%); mp 178°C; IR (KBr) ν (cm^{-1}) 2940, 2820, 1682, 1495, 1456, 1441, 1228, 1158, 1134, 1011, 911, 759, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H, Hpyrazole), 7.33 (m, 1H, Hphenyl), 7.21 (m, 1H, Hphenyl), 7.09 (m, 1H, Hphenyl), 7.00 (m, 1H, Hphenyl), 5.82 (d, *J* = 8.90 Hz, 1H, C*H*NH), 4.19 (s, 3H, NCH_3), 3.54 (s, 2H, CH_2phenyl), 3.08 (s, 2H, CH_2CO), 2.52 (m, 4H, Hpiperazine), 2.46 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (*C*O), 161.3 (d, *J* = 246.1 Hz, *C*F), 151.7, 141.3, 134.6, 134.2 (2C), 131.4 (d, *J* = 4.40 Hz), 128.8 (d, *J* = 8.24 Hz), 124.4 (d, *J* = 14.6 Hz), 123.9 (d, *J* = 3.52 Hz), 115.2 (d, *J* = 22.3 Hz), 106.2, 97.6, 61.4, 55.0 (d, *J* = 1.76 Hz, CH_2-fluorophenyl), 53.5 (2C), 52.6 (2C), 44.4, 40.0; HRESIMS [M+H] *m*/*z* 581.9959 (calcd for $C_{22}H_{22}Br_2FN_5OS$ 581.9974).

2.46. 2-[4-(2-Fuorobenzyl)piperazin-1-yl]-*N*-(6,7-dimetho-xy-1-phenyl-1,4-dihydroindeno[1,2-*c*]pyrazol-4-yl) acetamide (17a)

Chloroacetamide **11a** (100 mg, 0.26 mmol), *o*-fluorobenzyl-piperazine (47.6 µL, 0.29 mmol, 1.1 equiv) and K_2CO_3 (43.2 mg, 0.31 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 36 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **19a** as a beige powder (48 mg, 34%); mp 152°C; IR (KBr) ν (cm^{-1}) 3434, 2939, 2824, 1659, 1488, 1349, 1261, 1216, 1134, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.75 Hz, 2H, Hphenyl), 7.60 (s, 1H, Hpyrazole), 7.56 (t, *J* = 7.75 Hz, 2H, Hphenyl), 7.44 (t, *J* = 7.75 Hz, 1H, Hphenyl), 7.32 (m, 2H, NH + Hfluorophenyl), 7.21 (m, 1H, Hfluorophenyl), 7.10 (s, 1H, Hphenyl), 7.08 (t, *J* = 7.95 Hz, 1H, Hfluorophenyl), 6.99 (m, 1H, Hfluorophenyl), 6.97 (s, 1H, Hphenyl), 5.95 (d, *J* = 8.80 Hz, 1H, C*H*NH), 3.88 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.53 (s, 2H, CH_2-fluorophenyl), 3.15 (s, 2H, CH_2CO), 2.57 (broad m, 4H, Hpiperazine), 2.45 (broad m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (CO), 161.3 (d, *J* = 246.3 Hz, CF), 149.1, 149.0, 147.6, 144.1, 139.9, 135.2, 131.5 (d, *J* = 4.40 Hz), 129.4 (2C), 129.0, 128.9 (d, *J* = 8.18 Hz), 127.9, 124.4 (d, *J* = 14.6 Hz), 124.0, 123.9 (d, *J* = 3.52 Hz), 123.1 (2C), 115.3 (d, *J* = 22.3 Hz), 109.5, 103.5, 61.6, 56.3, 56.2, 55.0 (d, *J* = 1.64 Hz, CH_2-fluorophenyl), 53.5 (2C), 52.6 (2C), 47.3; HRESIMS [M+H] *m*/*z* 542.2546 (calcd for $C_{31}H_{32}FN_5O_3$ 542.2567).

2.47. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-*N*-(1-phenyl-1,4-dihydrothieno[3',2':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)acetamide (17b)

Chloroacetamide **11b** (100 mg, 0.30 mmol), *o*-fluorobenzyl-piperazine (55.4 µL, 0.33 mmol, 1.1 equiv) and K_2CO_3 (50.3 mg, 0.36 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 12 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **19b** as a yellow-orange powder (50 mg, 34%); mp 132°C; IR (KBr) ν (cm^{-1}) 2930, 2815, 1672, 1603, 1492, 1450, 1431, 1154, 1133, 1052, 1012, 908, 731, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.50 Hz, 2H, Hphenyl), 7.51 (s, 1H, Hpyrazole), 7.42 (t, *J* = 7.47 Hz, 2H, Hphenyl), 7.28 (m, 1H, Hphenyl), 7.12 (m, 1H, Hthiophene), 7.08 (d, *J* = 4.90 Hz, 1H, Hthiophene), 7.01 (m, 2H, Hphenyl), 6.92 (t, *J* = 8.70 Hz, 2H, Hphenyl), 6.63 (d, *J* = 7.95 Hz, 1H, NH), 5.72 (d, *J* = 7.95 Hz, 1H, C*H*NH), 3.47 (s, 2H, CH_2phenyl), 3.12 (s, 2H, $COCH_2$), 2.76 (t, *J* = 7.55 Hz, 2H, CH_2N), 2.38 (m, 4H, Hpiperazine), 2.33 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 161.2 (d, *J* = 246.1 Hz, CF), 156.1, 143.4, 139.5, 135.3 (2C), 131.7 (2C), 131.4, 129.7 (2C), 128.6 (d, *J* = 8.20 Hz), 127.1 (d, *J* = 4.40 Hz), 124.2 (d, *J* = 15.0 Hz), 124.0, 123.6 (d, *J* = 3.10 Hz), 120.1 (2C), 115.1 (d, *J* = 22.1 Hz), 58.7, 54.0, 53.3 (2C), 52.7 (2C), 45.8; HREIMS [M+] *m*/*z* 487.1826 (calcd for $C_{27}H_{26}FN_5OS$ 487.1842).

2.48. *N*-(5,7-Dibromo-1-phenyl-1,4-dihydrothieno[3',4':4,5]cyclopenta[1,2-*c*]pyrazol-4-yl)-2-[4-(2-fluoro-benzyl)piperazine]acetamide (17c)

Chloroacetamide **11c** (100 mg, 0.21 mmol), *o*-fluorobenzyl-piperazine (37.5 µL, 0.23 mmol, 1.1 equiv) and K_2CO_3 (34 mg, 0.25 mmol, 1.2 equiv) were refluxed in acetone (2 mL) for 24 h. After being cooled to ambient temperature, the crude mixture was filtered and the insoluble product was washed with DCM. The filtrates were combined and the solvents were evaporated under reduced pressure. The crude powder obtained was then purified by column

chromatography (Al_2O_3, gradient from MeOH/DCM 0/100 to 10/90). This led to **19c** as a yellow powder (35.7 mg, 27%); mp 162°C; IR (KBr) ν (cm^{-1}) 2943, 2825, 1668, 1489, 1452, 1437, 1233, 1162, 1131, 1015, 907, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H, Hphenyl), 7.48 (s, 1H, Hpyrazole), 7.36 (m, 1H, Hphenyl), 7.31 (m, 2H, Hphenyl) : 7.22 (m, 1H, Hphenyl), 7.17 (m, 1H, Hphenyl), 7.05 (m, 1H, Hphenyl), 7.01 (m, 1H, Hphenyl, 5.68 (broad s, 1H, C*H*NH), 3.55 (s, 2H, $COCH_2$), 3.12 (s, 2H, CH_2phenyl), 2.45 (m, 4H, Hpiperazine), 2.38 (m, 4H, Hpiperazine); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (*C*O), 161.2 (d, J = 246 Hz, *C*F), 151.9, 141.2, 140.5, 134.7, 134.5 (2C), 131.2 (d, J = 4.30 Hz), 129.1 (2C), 128.7 (d, J = 8.30 Hz), 126.2, 124.5 (d, J = 14.4 Hz), 124.1 (d, J = 3.63 Hz), 118.9 (2C), 115.3 (d, J = 22.9 Hz), 105.9, 97.6, 61.7, 55.2, 54.1 (2C), 52.5 (2C), 43.8.

3. Biology

3.1. In vitro tests of AChE and BuChE biological activity

Inhibitory capacity of compounds on AChE biological activity was evaluated through the use of the spectrometric method of Ellman. Acetyl- or butyrylthiocholine iodide and 5,5-dithiobis-(2-nitrobenzoic) acid (DTNB) were purchased from Sigma Aldrich. Lyophilized electric eel AChE (Type III, Sigma Aldrich), or BuChE from equine serum (Sigma Aldrich) was dissolved in 0.2 M phosphate buffer pH 7.4 such as to have enzyme solutions stock with 2.5 units/mL enzyme activity. AChE from human erythrocytes (buffered aqueous solution, ≥500 units/mg protein (BCA), Sigma Aldrich) was diluted in 20 mM HEPES buffer pH 8, 0.1% Triton X-100 such as to have enzyme solution with 2.5 units/mL enzyme activity. In the procedure, 100 µL of 0.3 mM DTNB dissolved in phosphate buffer pH 7.4 were added into the 96 wells plate followed by 50 µL of test compound solution and 50 µL of enzyme solution. After 5 min of preincubation, the reaction was then initiated by the injection of 50 µL of 10 mM acetyl- or butyrylthiocholine iodide solution. The hydrolysis of acetyl- or butyrylthiocholine was monitored by the formation of yellow 5-thio-2-nitrobenzoate anion as the result of the reaction of DTNB with thiocholine, released by the enzymatic hydrolysis of acetyl- or butyrylthiocholine, at a wavelength of 412 nm every minute for 10 min using a 96-well microplate plate reader (TECAN Infinite M200, Lyon, France). Test compounds were dissolved in analytical grade DMSO. Donepezil was used as reference standard.

First screening of AChE and BuChE activity was carried out at a 10^{-5} M concentration of compounds under study. For the compounds with significant inhibition (≥ 50%) after 4 min of reaction, IC_{50} values were determined graphically from 6 points inhibition curves using the Origin software.

3.2. Propidium competition assay

Propidium exhibits an increase in fluorescence on binding to AChE peripheral site, making it a useful probe for competitive ligand binding to the enzyme. Fluorescence was measured in a Tecan Infinite M200 plate reader. Measurements were carried out in 200 µl solution volume, in 96-well plates. The buffer used was 1 mM Tris/HCl, pH 8.0, 5 U eeAChE which was incubated, for 15 min at 25°C, with a 150 µL 10^{-5}M solution of the compounds or donepezil (from Tocris) as control. One micromolar propidium iodide 50 µL solution was added 10 min before fluorescence measurement. The excitation wavelength was 535 nm, and that of emission, 595 nm. Each assay was repeated, at least, three different times.

3.3. In vitro tests of AChE kinectic studies.

Kinetic studies of compounds on AChE biological activity was evaluated through the use of the spectrometric method of Ellman. Acetylthiocholine iodide, lyophilized electric eel Acetylcholinesterase (Type III, AChE electric eel) and 5,5-dithiobis-(2-nitrobenzoic) acid (DTNB) were purchased from Sigma Aldrich. AChE was dissolved in 0.2 M phosphate buffer pH 7.4 such as to have enzyme solutions stock with 0.25 units/ml AChE activity. In the procedure, 100 µL of 0.3 mM DTNB dissolved in phosphate buffer pH 7.4 were added into the 96 wells plate followed by 50 µL of test compound solution and 50 µL of enzyme solution. After 5 min of preincubation, the reaction was then initiated by the addition of 50 µL of different concentrations of acetylthiocholine iodide solution (from 0.02 to 0.2mM). The hydrolysis of acetylthiocholine was monitored by the formation of yellow 5-thio-2-nitrobenzoate anion as the result of the reaction of DTNB with thiocholine, released by the enzymatic hydrolysis of acetylthiocholine, at a wavelength of 412 nm every minute for 10 min using a 96-well microplate plate reader (TECAN Infinite M200, Lyon, France). Test compounds were dissolved in analytical grade DMSO.

The kinetic studies were performed using four concentrations of inhibitor (0-1μM).

4. X-Ray Crystallography

Single crystals of **2b** and **7a** suitable for X-ray crystallographic analysis were obtained by slow evaporation from dichloromethane and water, respectively. Data for crystal structure analysis were collected at 150 K with a Bruker–Nonius Kappa CCD area detector diffractometer with graphite–monochromatised Mo K_α radiation (λ = 0.71073 Å). The structures were solved using direct methods and refined by full-matrix least-squares analysis on F^2. Crystallographic data: Crystal size: 0.51×0.42×0.09mm. Formula $C_{12}H_{11}F_3N_2O_2S$, formula weight 304.30, crystal system monoclinic, space group $P2_1/c$, a = 6.7601(2) Å, b = 8.9249(3) Å, c = 22.5441(5) Å, α = 90°, β = 97.265(2)°, γ = 90°, V = 1349.24(7) Å^3, Z = 4, calculated density = 1.498 g/cm^3, μ = 0.277 mm^{-1}, R_{int} = 0.026, R[F^2>2σ(F^2)] = 0.047, wR(F^2) = 0.112. Crystallographic data of **7a**: the compound **7a** co-crystalised with two chlorines and two water molecule. Crystal size: 0.40×0.38×0.18mm. Formula $C_{13}H_{17}N_3O_2$, 2(Cl), 2(H_2O), formula weight 354.23, crystal system triclinic, space group P-1, a = 7.2598(2) Å, b = 10.0853(3) Å, c = 12.2011(3) Å, α = 101.010(1)°, β = 93.643(2)°, γ = 100.4820(10)°, V = 857.77(4) Å^3, Z = 2, calculated density = 1.371 g/cm^3, μ = 0.398 mm^{-1}, R_{int} = 0.025, R[F^2>2σ(F^2)] = 0.042, wR(F^2) = 0.121. Software used to solve structures: SHELXS–97. Software used to refine structures: SHELXL–97. Software used to prepare material for publication: SHELXL–97. Crystallographic data for compound **2b** CCDC899873 and **7a** CCDC899872 have been deposited at the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (+44-1223-336408; E-mail: deposit@ccdc.cam. ac.uk or http://www.ccdc.cam.ac.uk).

Figure 1: ORTEP diagram of the crystal majority conformation of **2b** (A) and the crystal structure of **7a** (B) with the thermal ellipsoid at 50% probability.