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Development of Cholinesterase Inhibitors Using (*a*)-Lipoic Acid-benzyl Piperazine Hybrid Molecules

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A series of hybrid molecules between (α)-lipoic acid (ALA) and benzyl piperazines were synthesized and their *in vitro* cholinesterase [acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)] inhibitory activities were evaluated. Even though the parent compounds did not show any inhibitory activity against cholinesterase (ChE), all hybrid molecules showed BuChE inhibitory activity. Some hybrid compounds also displayed AChE inhibitory activity. Specifically, ALA-1-(3-methylbenzyl)piperazine (**15**) was shown to be an effective inhibitor of both BuChE (IC_{50} = 2.3 ± 0.7 μM) and AChE (IC_{50} = 30.31 ± 0.64 μM). An inhibition kinetic study using compound **15** indicated a mixed inhibition type. Its binding affinity (K_i) value to BuChE is 2.91 ± 0.15 μM.

Key Words : Molecular hybridization, (α)-Lipoic acid, Benzyl piperazines, Butyrylcholinesterase inhibitor

Introduction

Two types of ChE, AChE (EC 3.1.1.7) and BuChE (EC 3.1.1.8), exist within the nervous system. AChE is primarily associated with cholinergic neurons while BuChE is associated with supporting glial cells in the human brain and specific cholinergic nerve tracts.[1] AChE and BuChE both play important roles in the regulation of acetylcholine (ACh) levels and may also have an important role in the development and progression of Alzheimer's disease (AD).[2] Until recently, the relative contribution of BuChE in the regulation of ACh levels had been largely ignored. However, there are growing evidences that BuChE may be one of the important enzymes involved in AD as AChE activity is decreased but BuChE activity is increased by 40-90% in cases of AD.[3] Also, BuChE activity predominates in cognition and behavior regions of the brain.[4] Selective BuChE inhibition by cymserine analogs resulted in increased ACh levels in the brains of rodents,[5] but BuChE knockout mice and silent mutants in humans have not exhibited any physiological disadvantage from this.[6] Therefore, development of BuChE inhibitors may be a promising strategy for treating AD.[7]

The active site of ChEs contains the binding site for the cationic choline moiety. In a previous paper (*Bull. Korean Chem. Soc.*, **2013**, *34*, 1025),[8] the hybrid molecules between α-lipoic acid (ALA) and polyphenols (PPs) connected with the cationic 2-(piperazin-1-yl)ethanol linker (linker 2) demonstrated better inhibitory activity against BuChE than with the neutral 2-(2-aminoethoxy)ethanol linker (linker-1).[9] The piperazine moiety of 2-(piperazin-1-yl)ethanol linker may form a piperazinium at the physiological pH. The piperazinium might strongly bind to the cationic choline binding site within BuChE and resulted in lowering the IC_{50} values of ALA-derivatives.[8] In this study, we further investigated the effect of piperazine moiety on ChEs inhibitory activity. A series of hybrid compounds connected between ALA and benzyl piperazines were synthesized and their *in vitro* inhibitory activities against ChEs were evaluated.

Results and Discussions

The structures of parent molecules (ALA and benzyl piperazine compounds) involved in this work are shown in Figure 1.

ALA-1-(3-methylbenzyl)piperazine (**15**) was synthesized by the activation/coupling reaction (Scheme 1). ALA was initially activated with EDC/NHS in dichloromethane (DMC). NHS-activated ALA was reacted with 1-(3-methylbenzyl)-piperazine, resulting in compound **15** (79% isolated yield).

ALA-benzyl piperazine derivatives synthesized by the same method are listed in Figure 2.

The inhibitory results (IC_{50} value) against AChE and BuChE with ALA, benzyl piperazines, and ALA-piperazine hybridized compounds are shown in Table 1. Benzyl piperazine derivatives substituted at *ortho*-, *meta*-, or *para*-position with methyl, fluorine, and chlorine were used to synthesize the hybrid compounds. The parent benzyl piperazines did not demonstrate any inhibitory activity for ChEs, but some ALA-benzyl piperazine derivatives (**15**, **17**, and **18**) showed inhibitory activity against both ChEs and generally showed better inhibitory activity against BuChE compared with AChE (8-111 fold). The others only showed inhibitory activity against BuChE. The IC_{50} values of **14** and **15** for BuChE inhibition decreased to 4.5 ± 2.1 and 2.3 ± 0.7 μM, respectively.

In the case of methyl and fluorine substitution (**14-19**), *ortho*- (**14** & **17**) and *meta*-substituted compounds (**15** & **18**) were a better inhibitor against BuChE compared with *para*-substituted compounds (**16** & **19**). With methyl substitution (**14**, **15**, and **16**), *ortho*- (**14**) or *para*-substituted compounds

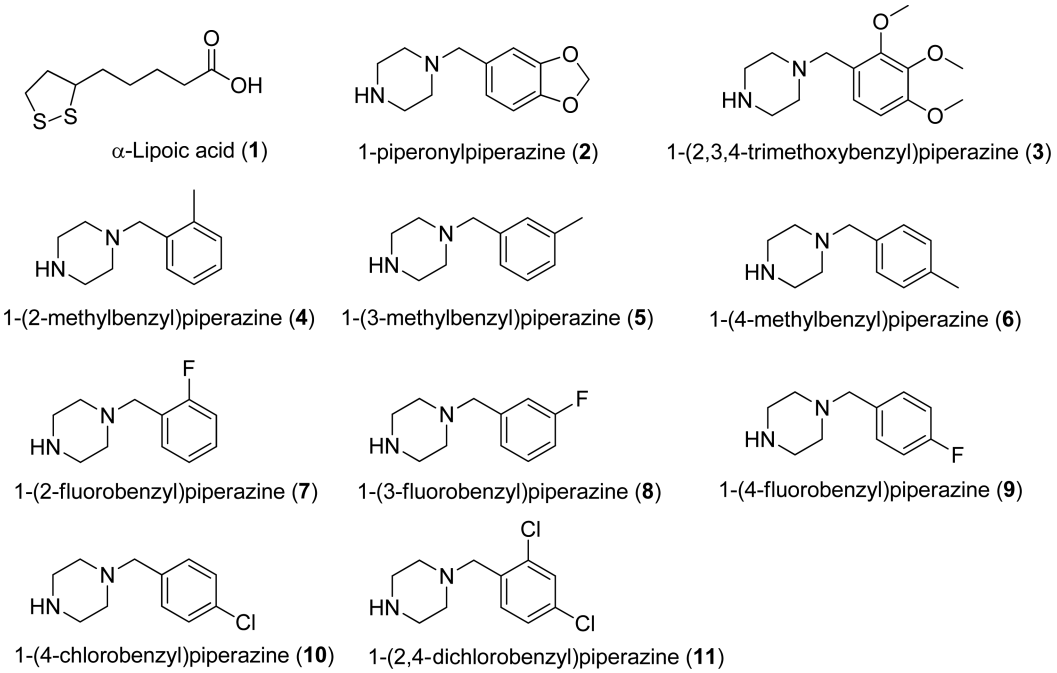
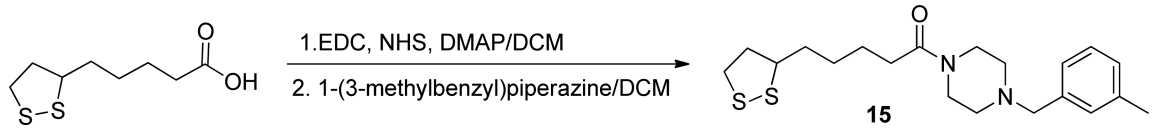


Figure 1. The structures of parent molecules utilized in this work.



Scheme 1. Synthesis of 5-(1,2-dithiolan-3-yl)-1-(4-(3-methylbenzyl)piperazin-1-yl)pentan-1-one (**15**).

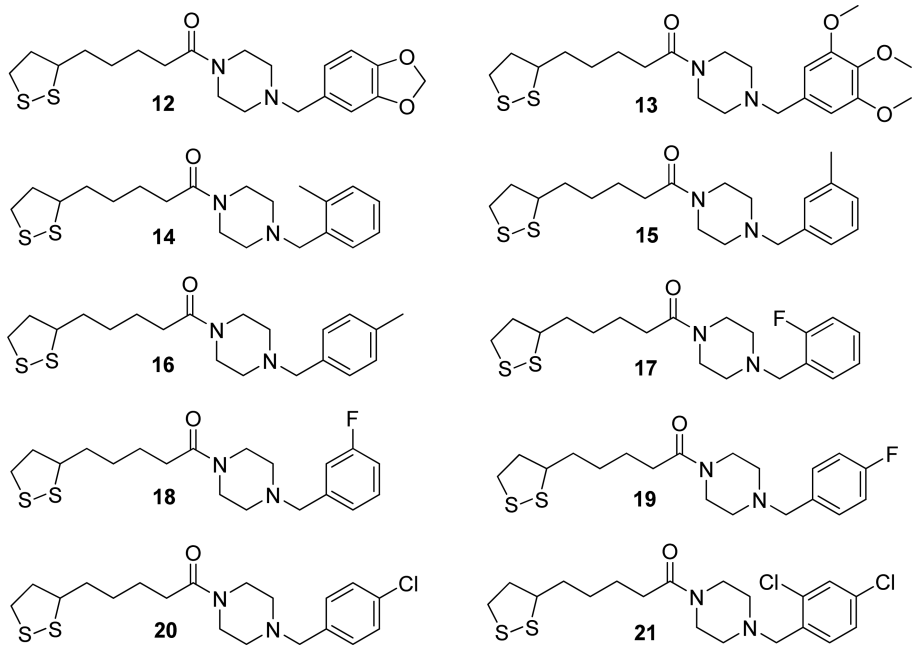


Figure 2. The structures of ALA-piperazine derivatives synthesized in this work.

(**16**) showed only BuChE inhibitory activity but *meta*-substituted compounds (**15**) inhibited both ChEs (IC_{50} = 30.3 ± 0.6 for AChE and 2.3 ± 0.7 μM for BuChE). With fluorine substitution (**17**, **18**, and **19**), compounds **17** (*ortho*) and **18** (*meta*) inhibited both ChEs but *para*-substituted compounds (**19**) inhibited only BuChE.

Table 1. IC_{50} values for ALA and ALA-benzyl piperazine derivatives for ChE inhibition[a]

Samples	AChE inhibition IC_{50} (μM)	BuChE inhibition IC_{50} (μM)	Selectivity (AChE/BuChE)
1	> 950	> 950	
2	> 900	> 900	
3	> 750	> 750	
4	> 1050	> 1050	
5	> 1050	> 1050	
6	> 1050	> 1050	
7	> 1000	> 1000	
8	> 1000	> 1000	
9	> 1000	> 1000	
10	> 900	> 900	
11	> 800	> 800	
12	> 450	18.0 ± 4.7	> 25
13	> 400	5.1 ± 1.1	> 78
14	> 500	4.5 ± 2.1	> 111
15	30.3 ± 0.6	2.3 ± 0.7	13
16	> 500	17.6 ± 3.1	> 28
17	88.3 ± 11.6	4.0 ± 0.43	22
18	73.3 ± 51.5	9.1 ± 2.4	8
19	> 500	32.7 ± 19.8	> 15
20	> 500	8.7 ± 1.6	> 57
21	> 450	4.5 ± 28.3	> 100
Galantamine	1.7 ± 0.9	9.4 ± 2.5	0.18

[a]AChE (from electric eel) and BuChE (from horse serum) were used. IC_{50} values represent the concentration of inhibitors that is required to decrease enzyme activity by 50% and are calculated by using the mean of measurements, performed in triplicate.

Comparing methyl *versus* fluorine substitution at *ortho*-position (**14** *vs*. **17**), there is no significantly different IC_{50} value. But methyl substitution exhibited better inhibitory effect against BuChE than fluorine substitution at *meta*- (**15** *vs.* **18**) and *para*-position (**16** *vs.* **19**). Since hybrid compounds having *para*-substitution, such as **12**, **13**, **16**, **19**, **20**, and **21**, showed only BuChE inhibitory activity, *para*-substitution may give some influence to BuChE selectivity over AChE.

Kinetic studies at different concentrations of **15** were carried out to explore the inhibition mechanism. The Lineweaver-Burk plot shows that it is a mixed-type inhibition (Figure 3). The K_i value of **15** for BuChE is 2.91 ± 0.15 μM.

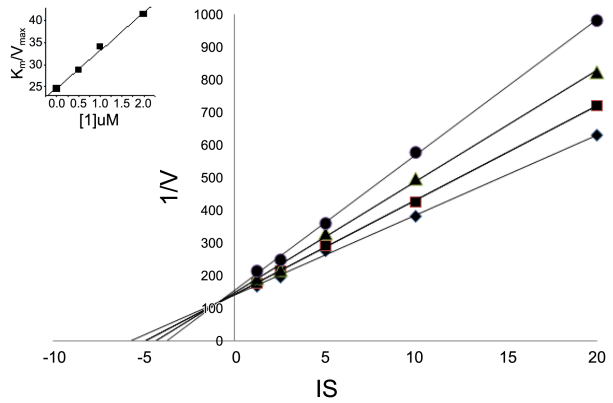


Figure 3. Lineweaver-Burk plot using **15** for the inhibitory kinetic study against BuChE (● = 2 μM, ▲ = 1 μM, ■ = 0.5 μM, ◆ = 0 μM). The inset is a plot of [I] *vs*. K_M/V_{max}.

Conclusions

Ten hybrid compounds (**12-21**) were synthesized to investigate the effectiveness of piperazine derivatives in improving inhibitory activity against ChEs. All ALA-benzyl piperazine derivatives showed inhibitory activity against BuChE, and some derivatives such as **15**, **17**, and **18** showed inhibitory activity against both ChEs. Substitution at *ortho*- or *meta*-position exhibited increased inhibitory activity against BuChE compared with *para*-position substitution. There was a selectivity for BuChE over AChE resulted from *ortho*-, *meta*-, and *para*-substitution. Substitution at *ortho*- or *meta*-position with methyl or fluorine inhibited all ChEs except for **14**, but substitution at *para*-position resulted in only inhibition of BuChE.

From the inhibitory activity comparison between *para*-substitution groups (**16**, **19**, & **20**), compound **20** (-Cl) was the best inhibitor among the three compounds. Since chlorine has a larger hydrophobicity parameter (π) and Hammett electronic substituent constant (σ_p) value than the methyl and fluorine group in the QSAR parameter,[10] further QSAR analysis needs to determine the relationship between the activity and substitution group. The inhibitors for selective BuChE or both ChEs may have more beneficial effects than those for AChE. Further investigations will be carried out to evaluate their activity against AD.

Experimental

General Methods. ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on a Varian Mercury 400 (400 MHz). Melting points were determined on SMP3. Mass spectrum was taken by using in Agilent G1956B. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040-0.063 mm). Analytical thin layer chromatography (TLC) was performed using pre-coated TLC plates with silica Gel 60 F254 (E. Merck). All of the synthetic reactions were carried out under argon atmosphere with dry solvent, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use and dichloromethane (DCM) was dried from calcium hydride. All chemicals were reagent grade unless otherwise specified. (α)-Lipoic acid, NHS, EDC, benzyl piperazines, and cholinesterases [acetylcholinesterase (electric eel, cat. C2888) and butyrylcholinesterase (from horse serum, cat. C-7512)] were purchased from Sigma-Aldrich Chemical Co. and used without purification.

Cholinesterase Assay. ChE-catalyzed hydrolysis of the thiocholine esters was monitored by following production of the anion of thiocholine at 412 nm by the Ellman's coupled assay.[11] Assays were conducted on HP8452A or HP8453A diode array UV-visible spectrophotometers and the cell compartments were thermostated by circulating water or Peltier

temperature controller. Acetylthiocholine (ATCh) and butyrylthiocholine (BuTCh) were used as substrates for AChE and BuChE, respectively.

Synthesis. General procedures: The following procedure is a brief synthetic procedure for the synthesis of compound **12**. ALA-NHS was prepared by addition of NHS (1.12 g, 9.7 mmol), EDC (1.86 g, 9.7 mmol) in DMC 30 mL to ALA (1.0 g, 4.85 mmol) in DCM. To ALA-NHS (410 mg, 1.36 mmol) in DCM (10 mL), 1-piperonylpiperazine (**2**, 200 mg, 0.91 mmol) in DCM was added. The reaction mixture was stirring for 5 h at rt. The reaction mixture was quenched by adding 10 mL H_2O and then was extracted with ether (10 mL × three times). The organic layer was dried over anh. $MgSO_4$ and then was concentrated under vacuum. The product **12** (330 mg, 89% yield) was isolated by silica gel column chromatography (MC:MeOH = 15:1).

1-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-5-(1,2-dithiolan-3-yl)pentan-1-one (12). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.61 (m, 4H), 1.86 (m, 1H), 2.25 (t, *J* = 7.6 Hz, 2H), 2.41 (m, 1H), 2.64 (br-s, 4H), 3.09 (m, 2H), 3.5 (m, 1H), 3.63 (br-s, 2H), 3.68 (s, 2H), 3.76 (br-s, 2H), 3.76 (br-s, 2H), 5.9 (s, 2H), 6.71 (d, *J* = 8 Hz, 1H), 6.80 (d, *J* = 8 Hz, 1H), 6.94 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 28.9, 32.7, 34.6, 38.4, 39.9, 51.7(2C), 52.1(2C) 56.3, 61.7, 101.2(2C), 108.2, 110.2, 123.7, 147.9, 148.0, 171.0 ESI-MS: *m/z* $[M+H]^+$ 409.2 (calcd 408.5).

5-(1,2-Dithiolan-3-yl)-1-(4-(3,4,5-trimethoxybenzyl)piperazin-1-yl)pentan-1-one (13). The product **13** (140 mg, 81% yield) was obtained by using 1-(2,3,4-trimethoxybenzyl)-piperazine (**3**, 100 mg, 0.38 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.68 (m, 5H), 1.92 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.44 (m, 4H), 2.47 (m, 1H), 3.15 (m, 2H), 3.44 (t, *J* = 4.8 Hz, 2H), 3.48 (s, 2H), 3.48 (s, 2H), 3.56 (m, 1H), 3.58 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.3, 33.2, 33.20, 35.0, 39.0, 40.4, 41.9, 45.9, 52.8, 53.3, 56.2, 56.7, 61.0, 61.4, 107.2, 123.5, 125.3, 142.5, 153.3, 153.9, 170.9 ESI-MS: *m/z* $[M+H]^+$ 455.3 (calcd 454.6).

5-(1,2-Dithiolan-3-yl)-1-(4-(2-methylbenzyl)piperazin-1-yl)pentan-1-oneacrylate (14). The product **14** (230 mg, 60% yield) was obtained by using 1-(2-methylbenzyl)piperazine (**4**, 0.28 mL, 1.49 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.65 (m, 5H), 1.91 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 3H), 2.42 (t, *J* = 5.2 Hz, 4H), 2.47 (m, 1H), 3.15 (m, 2H), 3.42 (m, 2H), 3.47 (s, 2H), 3.58 (m, 1H), 3.60 (m, 2H), 7.12-7.26 (m, 5H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 25.2, 29.3, 33.2, 34.9, 38.7, 40.5, 41.9, 45.9, 53.1, 53.4, 56.7, 60.9, 125.7, 127.5, 130.1, 130.5, 136.2, 137.8, 171.5 ESI-MS: *m/z* $[M+H]^+$ 379.2 (calcd 378.59).

5-(1,2-Dithiolan-3-yl)-1-(4-(3-methylbenzyl)piperazin-1-yl)pentan-1-one (15). The product **15** (130 mg, 34% yield) was obtained by using 1-(3-methylbenzyl)piperazine (**5**, 0.28 mL, 1.49 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.67 (m, 5H), 1.91 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.35 (s, 3H), 2.43 (br-s, 4H), 2.47 (m, 1H), 3.15 (m, 2H), 3.42 (br-s, 2H), 3.47 (s, 2H), 3.56 (m, 1H), 3.63 (br-s, 2H), 7.07-7.13 (m, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 25.2, 29.3, 29.9, 33.2, 34.9, 38.7, 40.4, 41.7, 45.7, 52.9, 53.3, 56.6, 63.1, 126.5, 128.3, 128.4, 130.1, 138.1(2C), 171.7 ESI-MS: *m/z* $[M+H]^+$ 379.2 (calcd 378.59).

5-(1,2-Dithiolan-3-yl)-1-(4-(4-methylbenzyl)piperazin-1-yl)pentan-1-one (16). The product **16** (1.07 g, 85% yield) was obtained by using 1-(4-methylbenzyl)piperazine (**6**, 1.28 g, 6.60 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.65 (m, 5H), 1.90 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 2.41 (m, 4H), 2.47 (m, 1H), 3.15 (m, 2H), 3.44 (t, *J* = 5.2 Hz, 2H), 3.46 (s, 2H), 3.58 (m, 1H), 3.61 (t, *J* = 5.2 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.9, 29.0, 32.9, 34.7, 38.4, 40.1, 41.5, 45.5, 52.7, 53.0, 56.3, 62.5, 128.9(2C), 129.0(2C), 134.4, 136.8, 171.1 ESI-MS: *m/z* $[M+H]^+$ 379.2 (calcd: 378.59).

5-(1,2-Dithiolan-3-yl)-1-(4-(2-fluorobenzyl)piperazin-1-yl)pentan-1-one (17). The product **17** (190 mg, 75% yield) was obtained by using 1-(2-fluorobenzyl)piperazine (**7**, 0.11 mL, 0.66 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.66 (m, 4H), 1.90 (m, 1H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.44 (m, 5H), 3.15 (m, 2H), 3.45 (t, *J* = 5.2 Hz, 2H), 3.56 (m, 1H), 3.59 (s, 2H), 3.60 (t, *J* = 5.2 Hz, 2H), 7.03 (t, *J* = 9.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.26 (q, *J* = 9.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 29.0, 32.8, 34.6, 38.4, 40.1, 41.4, 45.4, 52.4, 52.8, 55.0, 56.3, 115.2 (d, *J* = 22.1 Hz), 123.9, 124 (d, *J* = 86.8 Hz), 128.9, 131.4, 161.5 (d, *J* = 244.8 Hz), 171.0 ESI-MS: *m/z* $[M+H]^+$ 383.2 (calcd 382.56).

5-(1,2-Dithiolan-3-yl)-1-(4-(3-fluorobenzyl)piperazin-1-yl)pentan-1-one (18). The product **18** (420 mg, 54% yield) was obtained by using 1-(3-fluorobenzyl)piperazine (**8**, 0.47 mL, 2.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.59 (m, 4H), 1.92 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.41 (m, 4H), 2.48 (m, 1H), 3.13 (m, 2H), 3.45 (br-s, 2H), 3.50 (s, 2H), 3.60 (m, 1H), 3.62 (br-s, 2), 6.94 (t, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 14.4 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 6.4 Hz, 1H), 7.28 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.2, 33.1, 34.9, 38.7, 40.4, 41.7, 45.7, 52.9, 53.3, 56.6, 62.3, 114.2 (d, *J* = 20.5 Hz), 115.7 (d, *J* = 21.2 Hz), 124.6 (d, *J* = 2.2 Hz), 129.9 (d, *J* = 8.1 Hz), 140.7 (d, *J* = 6.6 Hz), 163.2 (d, *J* = 250 Hz), 171.2 ESI-MS: *m/z* $[M+H]^+$ 383.2 (calcd 382.56).

5-(1,2-Dithiolan-3-yl)-1-(4-(4-fluorobenzyl)piperazin-1-yl)pentan-1-one (19). The product **19** (230 mg, 93% yield) was obtained by using 1-(4-fluorobenzyl)piperazine (**9**, 194 mg, 0.99 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 2H), 1.65 (m, 4H), 1.88 (m, 1H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.40 (m, 4H), 2.48 (m, 1H), 3.11 (m, 2H), 3.45 (br, 4H), 3.59 (br, 3H), 6.98 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.2, 33.1, 34. 9, 38.6, 40.4, 41.7, 45.7, 52.8, 53.2, 56.6, 62.1, 115.2 (2C, d, *J* = 20.5 Hz), 130.7 (2C, d, *J* = 7.4 Hz), 133.5 (d, *J* = 3.0 Hz), 162.1 (d, *J* = 243.2 Hz), 171.3

ESI-MS: *m/z* $[M+H]^+$ 383.2 (calcd 382.56).

1-(4-(4-Chlorobenzyl)piperazin-1-yl)-5-(1,2-dithiolan-3-yl)pentan-1-one (20). The product **20** (220 mg, 84% yield) was obtained by using 1-(4-chlorobenzyl)piperazine (**10**, 0.2 mL, 0.99 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.59 (m, 4H), 1.82 (m, 1H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.32 (q, *J* = 4.8 Hz, 4H), 2.39 (m, 1H), 30.6 (m, 2H), 3.36 (t, *J* = 5.2 Hz, 2H), 3.39 (s, 2H), 3.47 (m, 1H), 3.52 (t, *J* = 5.2 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.3, 33.2, 33.3, 34.9, 38.7, 38.7, 40.5, 41.7, 45.7, 52.9, 53.3, 56.7, 62.3, 128.7(2C), 130.6(2C), 133.2, 136.4, 171.4 ESI-MS: *m/z* $[M+H]^+$ 400.2 (calcd 399.01).

1-(4-(2,4-Dichlorobenzyl)piperazin-1-yl)-5-(1,2-dithiolan-3-yl)pentan-1-one (21). The product **21** (200 mg, 99% yield) was obtained by using 1-(2,4-Dichlorobenzyl)piperazine (**11**, 0.13 mL, 0.66 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 2H), 1.65 (m, 4H), 1.89 (m, 1H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.45 (br-s, 4H), 3.11 (br-s, 2H), 3.58 (s, 2H), 3.62 (br-s, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.3, 33.1, 34.9, 38.7, 40.4, 41.7, 45.7, 52.9, 53.3, 56.6, 58.7, 127.2, 129.4, 131.6, 133.5, 134.2, 135.1, 171.3 ESI-MS: *m/z* $[M+H]^+$ 434.2 (calcd 433.46).

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