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# Development of Cholinesterase Inhibitors using 1-Benzyl Piperidin-4-yl ($\alpha$)-Lipoic Amide Molecules

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A series of hybrid molecules between ($\alpha$)-lipoic acid (ALA) and 4-amino-1-benzyl piperidines were synthesized and their *in vitro* cholinesterase (acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)) inhibitory activities were evaluated. Even though the parent compounds did not exhibit any inhibitory activity against cholinesterase (ChE) with the exception of compound **14** ($IC_{50}$ = 255.26 ± 4.41 against BuChE), all hybrid molecules demonstrated BuChE inhibitory activity. Some hybrid compounds also displayed AChE inhibitory activity. Specifically, compound **17** was shown to be an effective inhibitor against both AChE ($IC_{50}$ = 1.75 ± 0.30 μM) and BuChE ($IC_{50}$ = 5.61 ± 1.25 μM) comparable to galantamine ($IC_{50}$ = 1.7 ± 0.9 μM against AChE and $IC_{50}$ = 9.4 ± 2.5 μM against BuChE). Inhibition kinetic studies using compound **17** indicated a mixed inhibition type for AChE and a noncompetitive inhibition type for BuChE. Its binding affinity ($K_i$) values to AChE and BuChE were 3.8 ± 0.005 μM and 7.0 ± 0.04 μM, respectively.

**Key Words :** Molecular hybridization, ($\alpha$)-Lipoic acid, 4-Amino-1-benzyl piperidines, Cholinesterase inhibitors

## 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 knocked out 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]

Since the active site of ChEs contains the binding site for the cationic choline moiety, we have tried to design the target molecules to efficiently bind the cationic choline binding site. In previous papers,[8,9] we reported that the cationic 2-(piperazin-1-yl)ethanol linker (linker 2)[8] demonstrated better inhibitory activity against BuChE than the neutral 2-(2-aminoethoxy)ethanol linker (linker-1)[10] and that the benzyl piperazine hybrid molecules also showed inhibitory activity against ChEs.[9] Since the piperazine moiety of 2-(piperazin-1-yl)ethanol linker and the benzyl piperazine hybrid molecules might influence inhibitory activity against ChEs, we have sought to investigate the inhibitory effect on ChEs of hybrid compounds containing 4-amino piperazine moiety as another cationic moiety. In the present study, we have reported the synthesis of the series of hybrid compounds containing 4-amino piperidine moiety and the evaluation of their *in vitro* inhibitory activities against ChEs.

## Results and Discussions

The parent structures (ALA and compounds containing 4-amino piperidine moiety) involved in this work are shown in Figure 1. 4-Amino-1-benzyl piperidine (**4**) and its derivatives (**5-16**) substituted at the *ortho* (except methoxy), *meta*, or *para* position with chlorine, nitrile, methoxy, or methyl were selected as the compounds containing 4-amino piperidine moiety.

The functional group selection at the *ortho*, *meta*, and *para* positions of benzene was considered to cover all of the quadrants for SAR analysis parameters (Craig plot) such as hydrophobicity ($\pi$) for the x-axis value and electronic effect ($\sigma$) for the y-axis value (Table 1).[11]

Benzyl piperidines (**4-16**) have been synthesized through coupling between 4-*N*-Boc-aminopiperidine (**1**) and a corresponding benzyl chloride or bromide. The deprotection of the Boc group with TFA resulted in the 4-amino-1-benzyl piperidine-TFA salts (Scheme 1). Compound **13** was synthesized by a reductive amination between Boc-aminopiperidine (**1**) and piperonyl aldehyde and then followed by a deprotection reaction with TFA. The hybrid compounds (**17-**

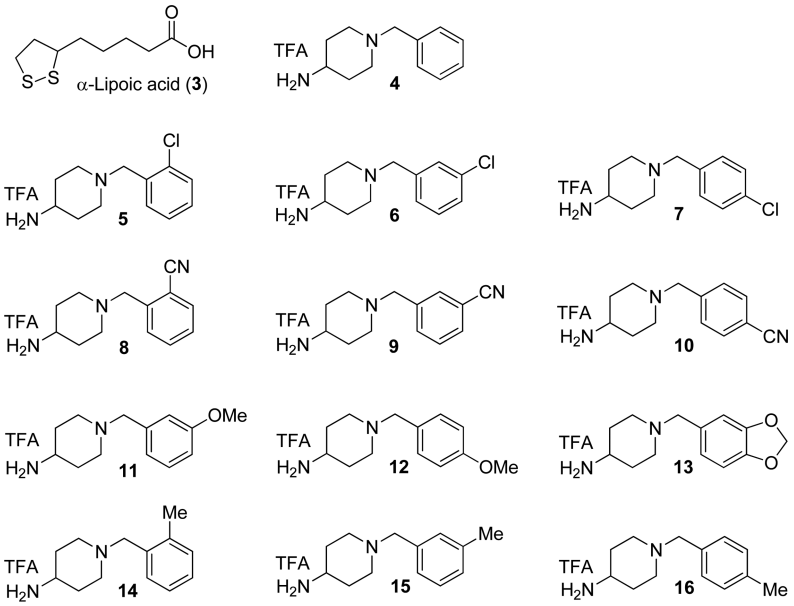



**Figure 1.** The structures of parent molecules utilized in this work.

**Table 1.** Aromatic substituent constants for the SAR analysis and their Craig plot ($\pi$ *vs* $\sigma$ plot) coverage[11]

| Substitution group | Craig plot coverage ($\pi$, $\sigma$) | $\pi$ | $\sigma_m$ | $\sigma_p$ |
|---|---|---|---|---|
| -H | Origin (0, 0) | 0 | 0 | 0 |
| -Cl | 1st quadrant ($+\pi$, $+\sigma$) | 0.71 | 0.37 | 0.23 |
| -CN | 2nd quadrant ($-\pi$, $+\sigma$)] | -0.57 | 0.56 | 0.66 |
| -OMe* | 3rd quadrant ($-\pi$, $-\sigma$) | -0.02 | 0.12 | -0.27 |
| -Me | 4th quadrant ($+\pi$, $-\sigma$) | 0.56 | -0.07 | -0.17 |

*Only $\sigma_p$ for the 3rd quadrant ($\sigma_m$ located in the 2nd quadrant)

**29**) were synthesized by a coupling reaction between 4-amino-1-benzyl piperidine TFA salts and NHS-activated ALA (Scheme 1) in the presence of TEA. ALA-4-amino-1-benzyl piperidine derivatives synthesized for this work are listed in Figure 2.

The inhibitory results ($IC_{50}$ value) against AChE and BuChE with ALA, 4-amino-1-benzyl piperidines, and hybridized compounds are shown in Table 2.

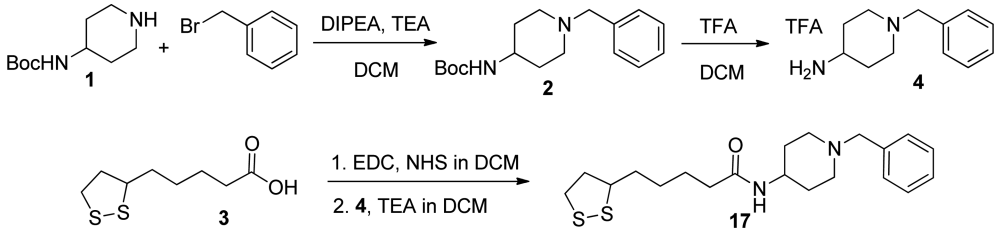
The parent benzyl piperazines did not demonstrate any inhibitory activity for ChEs ($IC_{50}$ value > 600 uM, except **14** against BuChE), but all hybrids (**17-29**) showed inhibitory activity against BuChE. Some hybrid compounds (**17**, **20-22**, & **25-29**) exhibited inhibitory activity for both ChEs.

Compound **17** is revealed as the best inhibitor against both ChEs ($IC_{50}$ = 1.75 ± 0.30 μM against AChE and $IC_{50}$ = 5.61 ± 1.25 μM against BuChE) among the hybrid compounds and its inhibitory activities are almost the same as or more effective than those of galantamine ($IC_{50}$ = 1.7 ± 0.9 μM against AChE and $IC_{50}$ = 9.4 ± 2.5 μM against BuChE) (Table 2). Since compound **17** is the most active inhibitor among the hybrid compounds (**17-29**), it appears that there are few substitution effects at the *ortho*, *meta*, and *para* positions such as hydrophobicity ($\pi$) and the electronic effect ($\sigma$) for the SAR analysis to decrease the $IC_{50}$ values.[11] But the substitution group and position might effect on the inhibitory selectivity.

Within the same substitution group, *ortho* and *meta* substitution usually showed a better inhibitory effect against BuChE than did *para* substitution (Figure 3).

The inhibitory selectivity against BuChE than AChE may depend on the substitution position and the substitution group. The substitution groups such as –Cl and –CN (**18-23**) located in the 1st quadrant ($+\pi$, $+\sigma$) and the 2nd quadrant ($-\pi$, $+\sigma$) on the Craig plot showed great inhibitory selectivity against BuChE than AChE. But methoxy and methyl substitution compounds (**25-29**) located in the 3rd quadrant ($-\pi$, $-\sigma$) and the 4th quadrant ($+\pi$, $-\sigma$) on the Craig plot demonstrated less inhibitory selectivity than –Cl and –CN substitution compounds (**18-23**).

The methoxy group acted as an electron withdrawing




**Scheme 1.** Synthesis of *N*-(1-benzylpiperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (**17**).

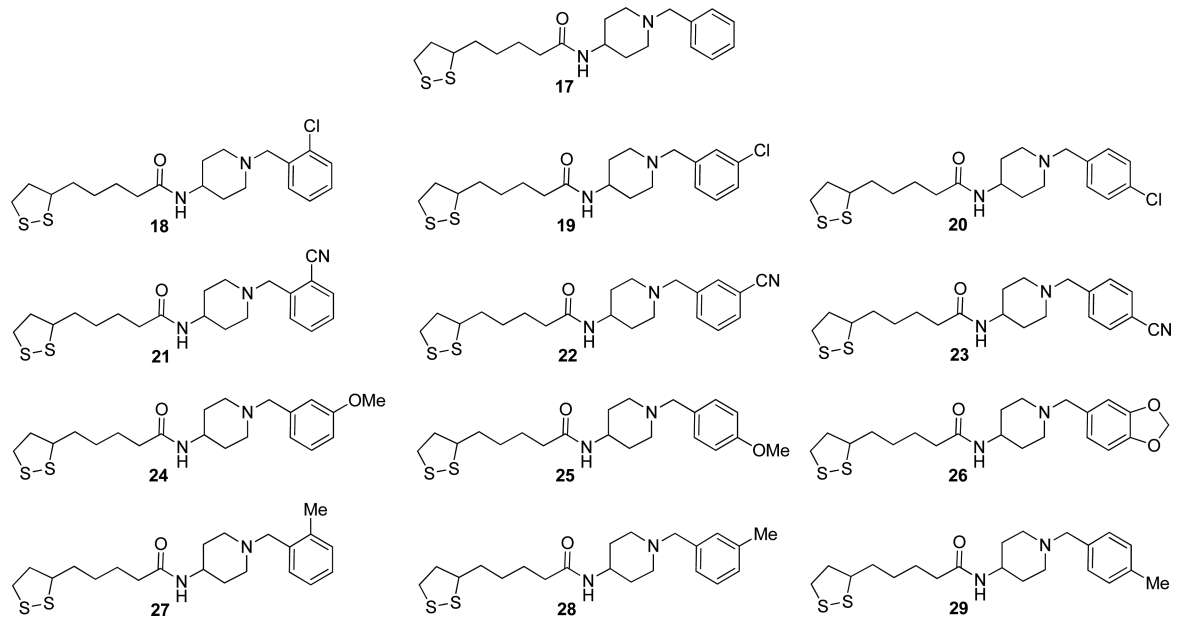



**Figure 2.** The structures of ALA-piperidine derivatives synthesized in this work.

**Table 2.** $IC_{50}$ values for ALA and ALA-benzyl piperazine derivatives for ChE inhibition[a]

| Sample | Parent compounds | | Sample | Hybrid compounds | |
|---|---|---|---|---|---|
| | AChE inh. $IC_{50}$ (μM) | BuChE inh. $IC_{50}$ (μM) | | AChE inh. $IC_{50}$ (μM) | BuChE inh. $IC_{50}$ (μM) |
| **3** | > 950 | > 950 | **17** | 1.75 ± 0.30 | 5.61 ± 1.25 |
| **4** | > 650 | > 650 | **18** | > 450 | 13.02 ± 0.96 |
| **5** | > 600 | > 600 | **19** | > 450 | 17.31 ± 0.61 |
| **6** | > 600 | > 600 | **20** | 137.3 ± 0.90 | 21.80 ± 1.20 |
| **7** | > 600 | > 600 | **21** | 193.35 ± 39.74 | 51.67 ± 0.57 |
| **8** | > 600 | > 600 | **22** | 115.84 ± 0.28 | 66.07 ± 0.28 |
| **9** | > 600 | > 600 | **23** | > 450 | 69.18 ± 0.84 |
| **10** | > 600 | > 600 | **24** | > 450 | 5.95 ± 1.34 |
| **11** | > 600 | > 600 | **25** | 26.10 ± 0.61 | 34.2 ± 1.80 |
| **12** | > 600 | > 600 | **26** | 67.13 ± 0.36 | 37.30 ± 0.94 |
| **13** | > 600 | > 600 | **27** | 18.94 ± 0.55 | 21.73 ± 0.30 |
| **14** | > 650 | 255.26 ± 4.41 | **28** | 11.66 ± 0.56 | 13.14 ± 0.45 |
| **15** | > 650 | > 650 | **29** | 62.46 ± 2.36 | 27.47 ± 0.69 |
| **16** | > 650 | > 650 | **Gal**[b] | 1.7 ± 0.9 | 9.4 ± 2.5 |

[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. [b]Galantamine-HBr was used as a positive control for the measurement of ChEs inhibitory activity.

group ($+\sigma$) under the *meta* substitution rather than in its normal function as an electron donating group ($-\sigma$). Compound **24** ($-\pi$, $+\sigma$) had a similar $IC_{50}$ value ($IC_{50}$ = 5.95 ± 1.34 μM) to that of compound **17** against BuChE, but it showed a great selectivity against BuChE than AChE ($IC_{50}$ > 450 μM). The $\pi$ value (-0.02) and $\sigma_m$ value (0.12) of methoxy group are similar as those of hydrogen, but its size is larger than that of hydrogen. The larger size of –OMe than that of hydrogen may give rise to its increased selectivity against BuChE. Also, from the selectivity analysis of -Cl, -CN, and -OMe (*meta*) substitution compounds (**18**-**24**), the positive electronic value ($+\sigma$) appears to be an important factor for increasing the inhibitory selectivity against BuChE than AChE. Therefore, the electronic effect ($\sigma$) of the substitution group may be a more important parameter than hydrophobicity ($\pi$) for a result of increased selectivity against BuChE over AChE.

Kinetic studies for AChE and BuChE at different concentrations of **17** were carried out to explore the inhibitory mechanism. Even though there are mismatches at the 2 μM plot for AChE and at the 8 μM plot for BuChE in the Lineweaver-Burk plots, it appears to be a mixed inhibition type for AChE and a noncompetitive inhibition type for BuChE (Figure 4). Its binding affinity ($K_i$) values to AChE

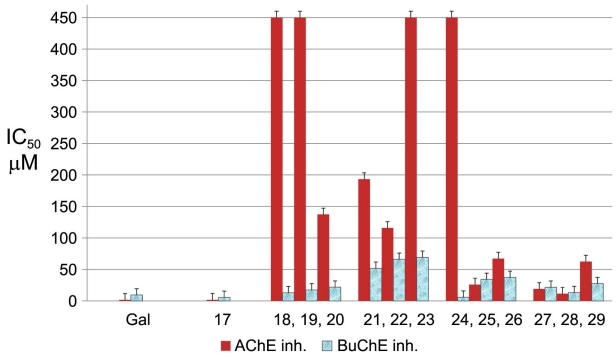



**Figure 3.** $IC_{50}$ values for galantamine and hybrid compounds (**17-29**).

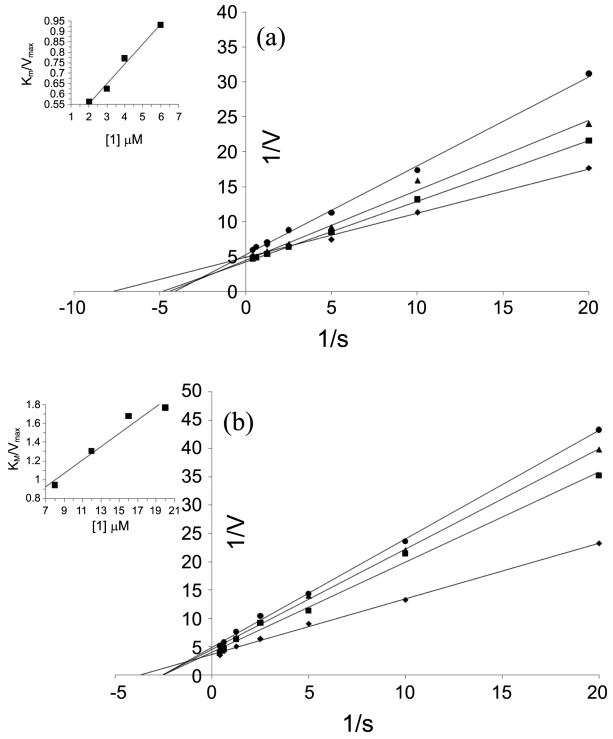



**Figure 4.** Lineweaver-Burk plot using compound **17** for the inhibitory kinetic study against ChEs. (a) for AChE (● = 6 μM, ▲ = 4 μM, ■ = 3 μM, ◆ = 2 μM). (b) BuChE (● = 20 μM, ▲ = 16 μM, ■ = 12 μM, ◆ = 8 μM). The inset is a plot of [I] *vs.* $K_M/V_{max}$.

and BuChE are 3.8 ± 0.005 μM and 7.0 ± 0.04 μM, respectively.

## Conclusions

Thirteen hybrid compounds (**17-29**) were synthesized to investigate the effectiveness of 4-amino piperidine moiety for ChE inhibitory activity. They acted as an effective inhibitor against BuChE, and some derivatives (compounds **17**, **20-22**, & **25-29**) additionally demonstrated inhibitory activity against AChE. Substitution at the *ortho*, *meta*, and *para* positions exhibited decreased inhibitory activity against ChEs compared with the unsubstituted compound **17**. Therefore, hydrophobicity (p) and the electronic substituent effect (s) do not appear to be important parameters for decreasing the $IC_{50}$ value, but the electronic substituent effect (s) does appear to be an important factor for increasing selectivity against BuChE than AChE. Since compound **17** is an inhibitor against both ChEs and compound **24** is a selective inhibitor for BuChE, further investigations will be carried out to evaluate their activity for 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, TFA, benzyl chlorides, benzyl bromides, 4-(*N*-Boc-amino)piperidine, and cholinesterases [acetylcholinesterase (electric eel, cat. C2888) and butyryl-cholinesterase (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.[12] 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 **17**. Addition of a solution of NHS (1.12 g, 9.7 mmol) and EDC (1.86 g, 9.7 mmol) in 30mL DMC to ALA (1 g, 4.85 mmol) solution in 20 mL DCM resulted in ALA-NHS. A mixture of 1-benzylpiperidin-4-amine (**4**, 110 mg, 0.39 mmol) and TEA (0.23 mL, 1.65 mmol) in 5 mL DCM was added to a solution of ALA-NHS (110 mg, 0.33 mmol) in 3 mL DCM. The reaction mixture was stirring for 5 h at room temperature. The reaction mixture was quenched by adding 10 mL $H_2O$ and then was extracted with DCM (10 mL × 3 times). The organic layer was dried over anhydrous $MgSO_4$ and then was concentrated under vacuum. Hybrid compounds were isolated by silica gel column chromatography (DCM: MeOH (15:1, v/v)).

***N*-(1-Benzylpiperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (17).** Compound **17** (100 mg, 80% yield) was obtained by using 1-benzyl piperidin-4-amine (**4**, 110 mg, 0.39

mmol) and TEA (0.23 mL, 1.65 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.43 (m, 4H), 1.62 (m, 4H), 1.85 (m, 3H), 2.04 (t, *J* = 10 Hz, 2H), 2.1 (t, *J* = 7.2 Hz, 2H), 2.41 (m, 1H), 2.75 (d, *J* = 12.4 Hz, 2H), 3.09 (m, 2H), 3.44 (s, 2H), 3.51 (m, 1H), 3.75 (m, 1H), 5.28 (d, *J* = 7.2 Hz, 1H), 7.18-7.28 (Ar, 5H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.4, 52.2(2C), 56.3, 62.9, 126.9, 128.1(2C), 129(2C), 138.2, 171.8, ESI-MS: *m/z* $[M+H]^+$ 379.2 (calcd. 378.59).

***N*-(1-(2-Chlorobenzyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (18).** Compound **18** (246 mg, 90% yield) was obtained by using 1-(2-chlorobenzyl)piperidin-4-amine (**5**, 275 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 4H), 1.62 (m, 4H), 1.86 (m, 3H), 2.11 (t, *J* = 7.6 Hz, 2H), 2.18 (dt, *J* = 11.2 Hz, *J* = 2 Hz, 2H), 2.41 (m, 1H), 2.77 (d, *J* = 11.2 Hz, 2H), 3.09 (m, 2H), 3.51 (m, 1H), 3.54 (s, 2H), 3.77 (m, 1H), 5.28 (d, *J* = 8 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.3(2C), 34.5, 36.6, 38.4, 40.1, 46.3, 52.2(2C), 56.3, 59.2, 126.5, 128, 129.3, 130.4, 134.2, 136.1, 171.8 ESI-MS: *m/z* $[M]^+$ 413.2 (calcd. 413.04).

***N*-(1-(3-Chlorobenzyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (19).** Compound **19** (244 mg, 90% yield) was obtained by using 1-(3-chlorobenzyl)piperidin-4-amine (**6**, 277 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 4H), 1.62 (m, 4H), 1.85 (m, 3H), 2.05 (t, *J* = 11.6 Hz, 2H), 2.11 (t, *J* = 7.6 Hz, 2H), 2.42 (m, 1H), 2.73 (d, *J* = 12 Hz, 2H), 3.09 (m, 2H), 3.4 (s, 2H), 3.51 (m, 1H), 3.75 (m, 1H), 5.3 (d, *J* = 7.6 Hz, 1H), 7.13-7.18 (Ar, 3H), 7.28 (s, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.3, 52.2(2C), 56.3, 62.3, 126.9, 127.1, 128.8, 129.4, 134.1, 140.7, 171.8 ESI-MS: *m/z* $[M]^+$ 413.2 (calcd 413.04).

***N*-(1-(4-Chlorobenzyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (20).** Compound **20** (51 mg, 76% yield) was obtained by using 1-(4-chlorobenzyl)piperidin-4-amine (**7**, 53 mg, 0.16 mmol) and TEA (0.11 mL, 0.82 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 4H), 1.72 (m, 4H), 1.92 (m, 3H), 2.12 (t, *J* = 10.8 Hz, 2H), 2.17 (t, *J* = 7.2 Hz, 2H), 2.49 (m, 1H), 2.78 (d, *J* = 10.8 Hz, 2H), 3.18 (m, 2H), 3.46 (s, 2H), 3.58 (m, 1H), 3.82 (m, 1H), 5.28 (d, *J* = 7.2 Hz, 1H), 7.23-7.29 (Ar, 4H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.3, 52.2(2C), 56.3, 62.1, 128.3(2C), 130.2(2C), 132.6, 136.9, 171.8 ESI-MS: *m/z* $[M]^+$ 413.2 (calcd, 413.04).

***N*-(1-(2-Cyanobenzyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (21).** Compound **21** (221 mg, 83% yield) was obtained by using 2-((4-aminopiperidin-1-yl)methyl)-benzonitrile (**8**, 267 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 4H), 1.62 (m, 4H), 1.83 (m, 3H), 2.1 (t, *J* = 7.6 Hz, 2H), 2.2 (dt, *J* = 11.2 Hz, *J* = 2.4 Hz, 2H), 2.41 (m, 1H), 2.75 (d, *J* = 12.4 Hz, 2H), 3.09 (m, 2H), 3.52 (m, 1H), 3.62 (s, 2H), 3.77 (m, 1H), 5.29 (d, *J* = 7.6 Hz, 1H), 7.29 (dt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.49 (dt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.59 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.1(2C), 34.5, 36.5, 38.4, 40.1, 46.2, 52(2C), 56.3, 60.4, 112.9, 117.7, 127.4, 129.8, 132.4, 132.9, 142.7, 171.9 ESI-MS: *m/z* $[M+H]^+$ 404.2 (calcd. 403.6).

***N*-(1-(3-Cyanobenzyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (22).** Compound **22** (161 mg, 61% yield) was obtained by using 3-((4-aminopiperidin-1-yl)methyl)-benzonitrile (**9**, 265 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 4H), 1.62 (m, 4H), 1.82 (m, 3H), 2.06 (t, *J* = 12 Hz, 2H), 2.12 (dt, *J* = 7.2 Hz, *J* = 2 Hz, 2H), 2.41 (m, 1H), 2.71 (d, *J* = 11.6 Hz, 2H), 3.09 (m, 2H), 3.44 (s, 2H), 3.51 (m, 1H), 3.75 (m, 1H), 5.35 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 8 Hz, 1H), 7.49 (d, *J* = 8 Hz, 2H), 7.6 (s, 1H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.3, 52.3(2C), 56.3, 61.9, 112.3, 118.9, 128.9, 130.6, 132.2, 133.1, 140.3, 171.9 ESI-MS: *m/z* $[M+H]^+$ 404.1 (calcd. 403.6).

***N*-(1-(4-Cyanobenzyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (23).** Compound **23** (210 mg, 79% yield) was obtained by using 4-((4-aminopiperidin-1-yl)methyl)-benzonitrile (**10**, 270 mg, 0.86 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 4H), 1.62 (m, 4H), 1.85 (m, 3H), 2.07 (t, *J* = 11.2 Hz, 2H), 2.1 (t, *J* = 6.8 Hz, 2, 2H), 2.41 (m, 1H), 2.71 (d, *J* = 11.6 Hz, 2H), 3.08 (m, 2H), 3.47 (s, 2H), 3.49 (m, 1H), 3.74 (m, 1H), 5.33 (d, *J* = 8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.3, 52.3(2C), 56.3, 62.3, 110.7, 118.9, 129.3 (2C), 132(2C), 144.4, 171.9 ESI-MS: *m/z* $[M+H]^+$ 404.1 (calcd. 403.6).

**5-(1,2-Dithiolan-3-yl)-*N*-(1-(3-methoxybenzyl)piperidin-4-yl)pentanamide (24).** The product **24** (210 mg, 78% yield) was obtained by 1-(3-methoxybenzyl)piperidin-4-amine (**11**, 271 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.43 (m, 4H), 1.67 (m, 4H), 1.91 (m, 3H), 2.11 (t, *J* = 12 Hz, 2H), 2.2 (t, *J* = 7.2 Hz, 2H), 2.44 (m, 1H), 2.8 (d, *J* = 11.6 Hz, 2H), 3.14 (m, 2H), 3.46 (s, 2H), 3.56 (m, 1H), 3.79 (m, 1H), 3.8 (s, 3H), 5.33 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, *J* = 2.4 Hz, 1H), 6.87-6.89 (3H), 7.22 (t, *J* = 8.0 Hz, 1H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.3(2C), 34.5, 36.6, 38.4, 40.1, 46.4, 52.2(2C), 55.1, 56.3, 62.9, 112.3, 114.5, 121.3, 129.1, 140, 159.5, 171.8 ESI-MS: *m/z* $[M+H]^+$ 409.2 (calcd. 408.62).

**5-(1,2-Dithiolan-3-yl)-*N*-(1-(4-methoxybenzyl)piperidin-4-yl)pentanamide (25).** The product **25** (72 mg, 78% yield) was obtained by 1-(4-methoxybenzyl)piperidin-4-amine (**12**, 79 mg, 0.24 mmol) and TEA (0.16 mL, 1.13 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.4 (m, 4H), 1.61 (m, 4H), 1.83 (m, 3H), 2.04 (t, *J* = 11.2 Hz, 2H), 2.09 (t, *J* = 7.2 Hz, 2H), 2.4 (m, 1H), 2.74 (d, *J* = 12 Hz, 2H), 3.09 (m, 2H), 3.38 (s, 2H), 3.5 (m, 1H), 3.74 (s, 3H), 3.74 (m, 1H), 5.32 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.4, 52(2C), 55.1, 56.3, 62.3,

113.5(2C), 130.0, 130.2(2C), 158.6, 171.8 ESI-MS: *m/z* $[M+H]^+$ 409.3 (calcd. 408.62).

***N*-(1-(Benzo[d][1,3]dioxol-5-ylmethyl)piperidin-4-yl)-5-(1,2-dithiolan-3-yl)pentanamide (26).** The product **26** (112 mg, 81% yield) was obtained by 1-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-4-amine (**13**, 130 mg, 0.39 mmol) and TEA (0.23 mL, 1.67 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.43 (m, 4H), 1.62 (m, 4H), 1.85 (m, 3H), 2.04 (t, *J* = 10 Hz, 2H), 2.08 (t, *J* = 7.6 Hz, 2H), 2.41 (m, 1H), 2.74 (d, *J* = 11.6 Hz, 2H), 3.09 (m, 2H), 3.35 (s, 2H), 3.52 (m, 1H), 3.75 (m, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 5.89 (s, 2H), 6.68 (s, 2H), 6.79 (s, 1H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.4, 52.0(2C), 56.3, 62.6, 100.8, 107.7, 109.2, 122, 132.2, 146.4, 147.5, 171.9 ESI-MS: *m/z* $[M+H]^+$ 423.2 (calcd. 422.6).

**5-(1,2-Dithiolan-3-yl)-*N*-(1-(2-methylbenzyl)piperidin-4-yl)pentanamide (27).** The product **27** (217 mg, 84% yield) was obtained by 1-(2-methylbenzyl)piperidin-4-amine (**14**, 259 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 4H), 1.64 (m, 4H), 1.86 (m, 3H), 2.11 (t, *J* = 10.4 Hz, 2H), 2.18 (t, *J* = 6.8 Hz, 2, 2H), 2.3 (s, 3H), 2.41 (m, 1H), 2.73 (d, *J* = 12 Hz, 2H), 3.09 (m, 2H), 3.38 (s, 2H), 3.52 (m, 1H), 3.76 (m, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 7.07-7.20 (Ar, 4H) $^{13}$C NMR ($CDCl_3$, 100 MHz) 19.1, 25.3, 28.7, 32.4(2C), 34.5, 36.6, 38.4, 40.1, 46.5, 52.3(2C), 56.3, 60.7, 125.4, 126.9, 129.6, 130.1, 136.6, 137.3, 171.8 ESI-MS: *m/z* $[M+H]^+$ 393.2 (calcd. 392.62).

**5-(1,2-Dithiolan-3-yl)-*N*-(1-(3-methylbenzyl)piperidin-4-yl)pentanamide (28).** The product **28** (215 mg, 83% yield) was obtained by 1-(3-methylbenzyl)piperidin-4-amine (**15**, 256 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 4H), 1.63 (m, 4H), 1.84 (m, 3H), 2.05 (t, *J* = 11.6 Hz, 2H), 2.14 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 2.39 (m, 1H), 2.75 (d, *J* = 11.6 Hz, 2H), 3.11 (m, 2H), 3.4 (s, 2H), 3.51 (m, 1H), 3.74 (m, 1H), 5.3 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 21.3, 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.4, 52.2(2C), 56.3, 63, 126.1, 127.7, 128, 129.7, 137.7, 138.1, 171.8 ESI-MS: *m/z* $[M+H]^+$ 393.2 (calcd. 392.62).

**5-(1,2-Dithiolan-3-yl)-*N*-(1-(4-methylbenzyl)piperidin-4-yl)pentanamide (29).** The product **29** (203 mg, 79% yield) was obtained by 1-(4-methylbenzyl)piperidin-4-amine (**16**, 258 mg, 0.85 mmol) and TEA (0.5 mL, 3.29 mmol).

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.44 (m, 4H), 1.64 (m, 4H), 1.86 (m, 3H), 2.05 (t, *J* = 11.6 Hz, 2H), 2.11 (t, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 2.42 (m, 1H), 2.74 (d, *J* = 12 Hz, 2H), 3.11 (m, 2H), 3.4 (s, 2H), 3.51 (m, 1H), 3.75 (m, 1H), 5.29 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 21, 25.3, 28.7, 32.2(2C), 34.5, 36.5, 38.4, 40.1, 46.5, 52.1(2C), 56.3, 62.7, 128.8(2C), 129(2C), 135.1, 136.5, 171.8 ESI-MS: *m/z* $[M+H]^+$ 393.2 (calcd. 392.62).

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