Synthesis of Trisubstituted Thiophenes Designed as Progesterone Receptor Modulator

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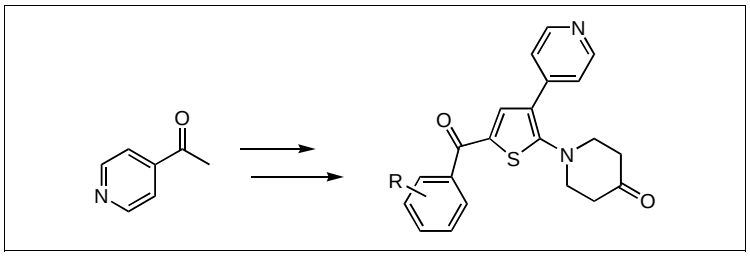

When a known 2-[4-morpholino]-3-aryl-5-substituted thiophene, which showed moderate activity as a progesterone antagonist, was superimposed with a potent steroidal progesterone antagonist Org-33628, it showed a fair alignment in most parts of the molecules. According to the molecular modelling, displacement of the morpholine oxygen atom in the thiophene derivative with a carbonyl group would provide a better alignment with the C-3 carbonyl in Org-33628. Thus, a series of novel trisubstituted thiophenes bearing a cyclic ketone moiety was synthesized. Although these compounds only showed weak activities as progesterone receptor antagonists, all target compounds are novel and are fully characterized.

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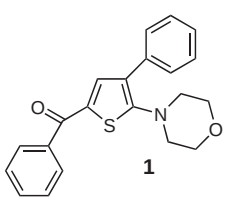
Introduction.

Progesterone plays a central role in the regulation of female reproduction [1]. Two main indications for the use of progesterone receptor modulators (PRMs) are breast cancer and fertility regulation. Compound **2**, Org-33628 [2], is a highly selective progesterone receptor modulator with respect to its anti-progestational and anti-glucocorticoidal activity. Recently, some non-steroidal compounds [3] were identified as progesterone receptor (PR) antagonists and also showed a high degree of selectivity versus the antagonistic activity on glucocorticoid receptors (GR).

In searching for non-steroidal progesterone receptor antagonists [4], we found a known tri-substituted thiophene to be weakly active in the PRM screening program (Figure 1). When compound **1** was evaluated for PR antagonist activity based on its ability to block progesterone induced alkaline phosphatase in the T47D human breast cancer cell line, it had an IC_{50} of 3200 nM.



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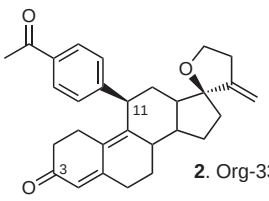


2. Org-33628

Figure 1. The structures of compound **1** and **2**.

Interestingly, when compound **1** was superimposed with compound **2**, using the automatic superimposition program FlexS [5], it showed a fair alignment in most parts of the molecules. The substituents at the 2- and 5-positions in compound **1** together with the thiophene ring spread out to mimic the steroid backbone in Org-33628, while the 3-phenyl group mimics the C-11 phenyl group in the steroid. The crystal structure of progesterone [6] complexed with PR indicates that the C-3 carbonyl forms hydrogen bonding directly or through two water molecules with Gln 725 and Arg 766. This, together with the C17-side chain carbonyl, forms the hydrogen-bonding network between progesterone and its receptor. Close examination of the aligned structures (Figure 2) provided some hints for further structure modifications. For example, displacement of the morpholine oxygen atom in the thiophene derivatives with a carbonyl group would provide better alignment with the C-3 carbonyl in Org-33628.

This modification led us to synthesize a series of the hitherto unknown tri-substituted thiophenes. We incorporated a pyridine ring in our designed structures in the hope of increasing solubility to improve the physical and chemical properties of the target molecules.

Results and Discussion.

Trisubstituted thiophenes are a common structural motif in numerous biologically relevant targets [8]. A convenient synthesis, designed to rapidly assemble this

motif, is presented in this paper. Thus, a four-step synthetic pathway to novel trisubstituted thiophenes bearing a cyclic ketone is shown in Scheme 1.

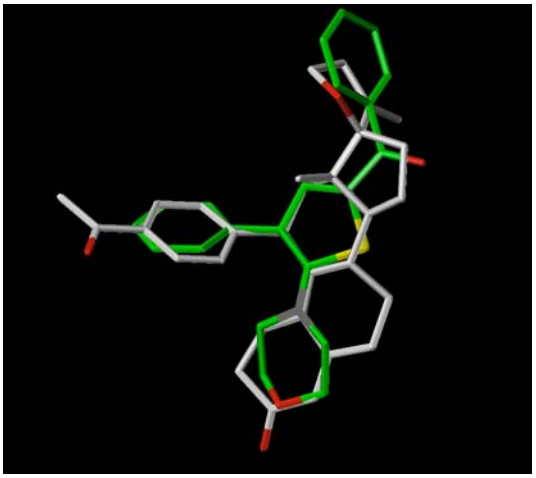
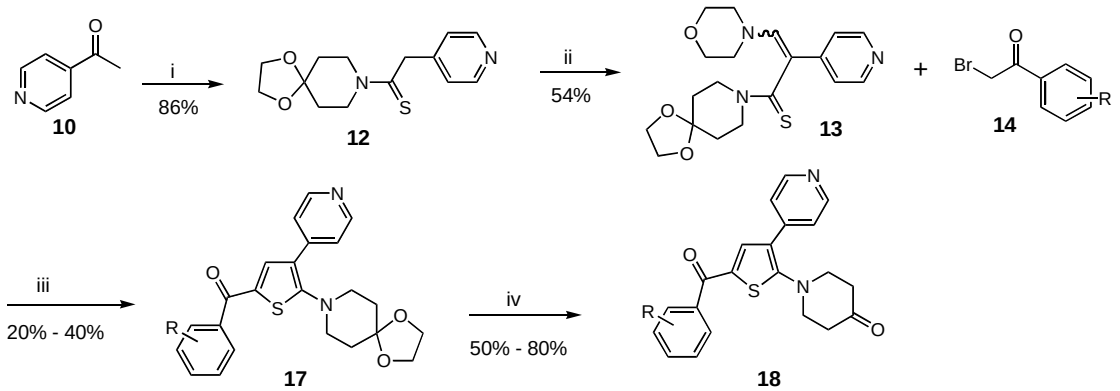


Figure 2. Compound **1** was flexibly aligned onto compound **2**, using program FlexS. Compound **1** is shown in green, Org-33628 in gray. Sulfur is shown in yellow and oxygen in red.

In order to access the substrate type designed from molecular modeling, and to make the synthetic route more amenable to a large number of compounds, we utilized the Willgerodt-Kindler (W-K) reaction [7] to generate thioacetamides **12** in one step. Thus, the ketone **10** was reacted with sulfur and the high boiling point cyclic amine **11** in the presence of a catalytic amount of acid under heat to generate the thioacetamide **12**. Although W-K reaction was discovered for a while, there are still a lot of room for detailed mechanism, as seen in reference 7a and 7c. The hallmark of the W-K reaction is its cleanliness, ease of purification, and tolerance of different functionalities. Amines can range from ammonium, primary amine bearing alkyl chain or aromatic group, secondary amine bearing dialkyl chains or diaryl groups or aryl and alkyl groups. Consistent with literature reports for similar systems, the reaction proceeds smoothly in high yield and can be carried out on multigram scale. Condensation of thioamide **12** with ethyl orthoformate followed by imine formation with morpholine gave the key intermediate 3-amino thioacrylamide **13**. By allowing **13** and **14** to react in a stoichiometric manner using a polar solvent, such as acetonitrile or methanol, a 1-benzoyl methylmercapto-substituted vinamidinium salt of the structure **15** (shown in Scheme 3) is generated. The salt **15**, can be converted *in situ* by addition of a suitable base, such as triethylamine or sodium methoxide, under reflux, into the 5-benzoyl substituted 2-aminothiophene derivative **16**. As demonstrated with a series of different β-bromo ketones **14**, this heterocyclisation reaction gives low to moderate yield (20 – 40%) of products bearing structure **17**.

A proposed mechanism for thiophene formation is shown in Scheme 2. Thus, the 3-amino thioacrylamide **13** condenses with α-bromoketone **14** to generate iminium salt **15**. Proton abstraction in compound **15** and intramolecular cyclization reaction with iminium ion provided a dihydrothiophene core **16**. Dehydroamination of compound **16** resulted in compound **17**. At this point, it is uncertain whether the reaction proceeds *via* a carbanion intermediate (E1cb, $A_{xh}D_H + D_N$) or *via* the concerted loss of a proton and the amine (E2, $A_ND_ED_N$) upon the base attack. Due to the electronegativity of carbonyl group and electron negativity of nitrogen on morpholinyl group, it is more likely that the reaction went through E1cb mechanism [9]. Due to the stoichiometric amount of HBr generated in the reaction, ketal group in compound **13** was cleaved. The resulting ketone may

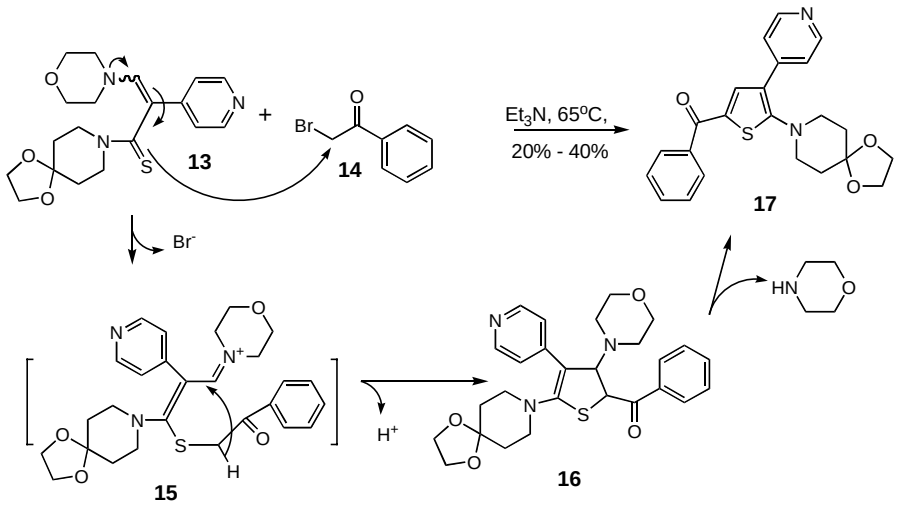
Scheme 1



i) p-TSA, S_8, 1,4-dioxa-8-aza-spiro[4.5]decane **11,** 120°C; ii) $HC(OEt)_3$, morpholine, 160°C; iii) Et_3N, 65°C, iv) p-TSA, reflux in acetone.

Synthetic route for compound **17** and **18**.

Scheme 2



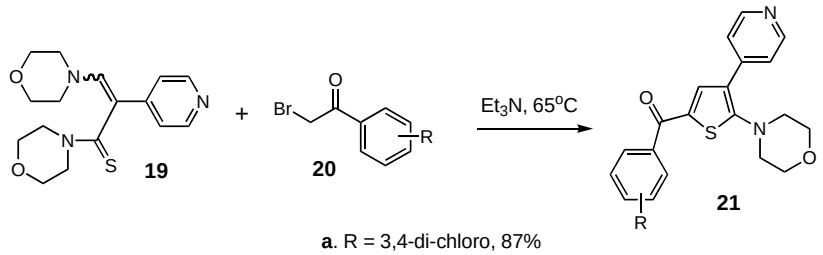
Proposed mechanism of formation of compound **17** from compound **13** and **14**.

compete with the major reaction pathway, thus leading to a decrease in yield for formation of compound **17**.

This is in consistency with our observation that the reactions of thioacrylamides without ketal functionality, such as **19**, proceed with higher yields (shown in Scheme 3), to generate thiophene **21**.

Both thiophene **17** and **18** were evaluated for PR antagonist activity based on their ability to block progesterone induced alkaline phosphatase in the human breast cancer cell line (T47D) [4c]. On the contrary to the predictions by molecular modeling, both of compound **17** and **18** showed very weak activities as progesterone

Scheme 3



Yields for compound **21**.

As shown in Scheme 2, deprotection of ketal group in compound **17** under acidic conditions afforded final product **18**. In order to maximize the coverage of the parameter space with fewest compounds, we selected various aryl substituents of β-bromo-aryl ketone **14** based on the Topliss Tree principle [10]. We also included an alkyl bromoketone for SAR purpose (see compound **18i**). The yields of compound **18** are listed in Table 1. All of the heterocyclic ketones **17** and **18** described here are new compounds. The structures were unambiguously confirmed by ^{1}HNMR, MS, elemental analysis and HRMS.

antagonists. At the present time, we do not have any explanations. From the modeling result, the modification of benzoyl group at 5-position on thiophene ring to introduce more rigidity to the molecule might be helpful.

In summary, we have prepared a series of novel trisubstituted thiophenes bearing a cyclohexyl ketone side chain. Although these compounds only showed weak activities as progesterone receptor antagonists, the molecular modelling work and the synthetic methodology are highly useful for the design and synthesis of additional substituted thiophene derivatives. Potentially, these compounds can be further derivatized, owing to their

reactive carbonyl moiety, to other pharmaceutically useful thiophenes.

Table 1

Physical and Analytical Data of Compounds **18a – 18i**

R	**Comp**	Yield (%)	Molecular Formula	**HR** Calc'd	**MS** Found		**Anal.** Calc'd	**%** Found
Ph	**18a**	63	$C_{21}H_{18}N_2O_2S$	363.1167	363.1168	C	H	N
4-F-ph	**18b**	69	$C_{21}H_{17}FN_2O_2S$	381.1073	381.1080			
4-Cl-ph	**18c**	74	$C_{21}H_{17}ClN_2O_2S$	397.0777	397.0767	63.55	4.32	7.06
						63.29	4.20	7.06
2-MeO-ph	**18d**	48	$C_{22}H_{20}N_2O_3S$	393.1273	393.1289			
3,5-di-CF_3-ph	**18e**	33	$C_{23}H_{16}F_6N_2O_2S$	499.0915	499.0914			
4-NO_2-ph	**18f**	47	$C_{21}H_{17}N_3O_4S$	408.1018	408.1024			
3-MeO-ph	**18g**	73	$C_{22}H_{20}N_2O_3S$	393.1273	393.1280			
3-Br-ph	**18h**	71	$C_{21}H_{17}ClN_2O_2S$	441.0272	441.0263	57.15	3.88	6.35
						57.48	3.93	5.97
Et	**18i**	60	$C_{17}H_{18}N_2O_2S$	315.1167	315.1171	64.94	5.77	8.91
						64.16	5.77	8.52

EXPERIMENTAL

General Information for Chemistry.

NMR spectra were obtained at 400 MHz and 300 MHz on a Bruker AVANCE300 and AVANCE400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Thin-layer chromatography was carried out using 2.5 × 7.5 –cm silica gel 60 (250 μM layer) plates with UV detection. Magnesium sulfate was employed to dry organic extracts prior to concentration by rotary evaporation. Flash chromatography was done using EM science silical gel 60 (230 - 400 mesh). Standard solvents from J. T. Baker were used as received. Anhydrous solvents from J. T. Baker or Aldrich and all other commercially available reagents were used without further purification. Microanalysis was carried out by Quantitative Technologies Inc., Whitehouse, NJ. Mass spectra were obtained on a Hewlett-Packard 5989A quadrupole mass spectrometer. Silica gel (E. Merck, 230 - 400 mesh) was used for all flash chromatography. Thin-layer chromatography was performed on Analtech silica gel GF prescored plates (250 μm). HPLC analysis was carried on Agilent 1100 Series LC/MSD equipment.

1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-pyridin-4-yl-ethanethione (**12**).

1-Pyridin-4-yl-ethanone (12.1 g, 0.10 mol), sulfur (3.36 g, 0.105 mol) and 1,4-dioxa-8-aza-spiro[4.5]decane were mixed with *p*-toluene sulfonic acid (0.50 g, 2.8 mmol) and heated to 120 °C for 3 h. The slurry was poured into MeOH (50 mL). A bright yellow solid precipitated out. This was collected by filtration and washed with another 20 mL of MeOH. The solid was dried to provide the product (24.0 g, 86.3 %). ^{1}H NMR (CD_3OD) δ 8.4 – 8.3 (m, 2H), 7.3 – 7.4 (m, 2H), 4.4 – 4.3 (m, 4H), 4.0 – 3.9 (m, 4H), 3.8 – 3.9 (m, 2H), 1.7 – 1.9 (m, 2H), 1.4 –1.5 (m, 2H); MS (m/z): 279 (MH^+).

1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-3-morpholin-4-yl-2-pyridin-4-yl-propenethione (**13**).

1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-pyridin-4-yl-ethanethione (20.0 g, 72.0 mmol), $HC(OEt)_3$ (21.3 g, 144 mol), morpholine (48.0 g, 55.0 mmol) was stirred at 125 ºC for 4 h. The solvent and excess reagent were distilled out at 100 ºC under house vacuum. The residue formed a yellow solid. After 30 min at 0 ºC, the solid was collected, washed with water (10 mL) and dried overnight under air suction to provide the product (20.0 g, 54 %). ^{1}H NMR ($CDCl_3$) δ 8.3 – 8.4 (m, 2H), 7.0 –7.1 (m, 2H), 6.40 (s, 1H), 4.6 – 4.7 (m, 1H), 4.3 – 4.4 (m, 1H), 3.8 – 4.0 (m, 4H), 3.5 – 3.7 (m, 6H), 3.50 (s, 4H), 3.2 – 3.4 (m, 2H), 2.1 – 2.2 (m, 1H), 1.7 – 1.6 (m, 2H); MS (m/z): 376 (MH^+).

[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-phenyl-methanone (**17a**).

A mixture of 1-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-morpholin-4-yl-2-pyridin-4-yl-propenethione (374.5 mg, 1.00 mmol), 2-bromo-1-(4-nitro-phenyl)-ethanone (374.5 mg, 1.00 mmol), 2-bromo-1-phenyl-ethanone (199.0 mg, 1.00 mmol), and triethylamine (0.140 mL, 1.00 mmol) in methanol (10.0 mL) was heated for 1.5 h at 65 °C. The temperature was increased to 75 °C and heated for 3 h then stirred overnight at room temperature. Water (50.0 mL) and ethyl acetate (50.0 mL) were added. The aqueous layer was extracted twice with ethyl acetate (50.0 mL). The organic extracts were washed with brine, dried, filtered, and evaporated. The crude material was purified by prep TLC eluting with 2% methanol/dichloromethane. The product was obtained as a yellow solid (114 mg, 28.0%). ^{1}H NMR ($CDCl_3$) δ 8.5 – 8.4 (m, 2H), 7.8 – 7.7 (m, 2H), 7.6 – 7.4 (m, 6H), 4.01 (s, 4H), 3.3 – 3.2 (m, 4H), 1.9 – 1.7 (m, 4H); MS (m/z): 407 (MH^+); HRMS: calc'd MH^+ for $C_{23}H_{22}N_2O_3S$ 407.1429; found 407.1436.

[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-(4-fluoro-phenyl)-methanone (**17b**).

The title product was prepared in 33% yield according to the procedure described for compound **17a** using 1-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-morpholin-4-yl-2-pyridin-4-yl-propen-

ethione and 2-bromo-1-(4-fluoro-phenyl)-ethanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.61 (dd, J = 1.5, 4.6 Hz, 2H), 7.9 – 7.8 (m, 2H), 7.6 – 7.5 (m, 3H), 7.2 – 7.1 (m, 2H), 4.0 (s, 4H), 3.23 (t, J = 5.7 Hz, 4H), 1.83 (t, J = 5.7 Hz, 4H); MS (m/z): 425 (MH^+).

(4-Chloro-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone (**17c**)

The title product was prepared in 29% yield according to the procedure described for compound **17a** using 1-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-3-morpholin-4-yl-2-pyridin-4-yl-propenethione (374.5 mg, 1.00 mmol), 2-bromo-1-(4-chloro-phenyl)-ethanone (233.0 mg, 1.00 mmol) as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 8.5 (m, 2H), 7.8 – 7.7 (m, 2H), 7.5 – 7.4 (m, 5H), 3.98 (s, 1H), 3.24 (t, J = 5.7 Hz, 4H), 1.83 (t, J = 5.8 Hz, 4H); MS (m/z): 441 (MH^+); HRMS: calc'd MH^+ for $C_{23}H_{21}ClN_2O_3S$ 441.1039; found 441.1025.

[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-(2-methoxy-phenyl)-methanone (**17d**).

The title product was prepared in 23% yield according to the procedure described for compound **17a** using 1-(2-methoxy-phenyl)-2-bromo-ethanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 8.5 (m, 2H), 7.4 – 7.3 (m, 7H), 7.0 – 6.9 (m, 2H), 3.95 (s, 4H), 3.2 – 3.1 (m, 4H), 1.9 – 1.8 (m, 4H); MS (m/z): 437 (MH^+); HRMS: calc'd MH^+ for $C_{24}H_{24}N_2O_4S$ 437.1535; found 437.1541.

(3,5-Bis-trifluoromethyl-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]-dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone (**17e**).

The title product was prepared in 18% yield according to the procedure described for compound **17a** using 1-(3,5-bis-trifluoromethyl-phenyl)-2-bromo-ethanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 7.4 (m, 7H), 3.95 (s, 4H), 3.3 – 3.2 (m, 4H), 1.9 – 1.8 (m, 4H); MS (m/z): 543 (MH^+); HRMS: calc'd MH^+ for $C_{25}H_{20}F_6N_2O_3S$ 543.1177; found 543.1157.

[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-(4-nitro-phenyl)-methanone (**17f**).

The title product was prepared in 18% yield according to the procedure described for compound **17a** using 1-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-morpholin-4-yl-2-pyridin-4-yl-propenethione (374.5 mg, 1.00 mmol), 2-bromo-1-(4-nitro-phenyl)-ethanone (244 mg, 1.00 mmol) as starting materials. ^{1}H NMR ($CDCl_3$) δ 8.61 (dd, J = 1.6, 4.5 Hz, 2H), 8.4 – 8.3 (m, 2H), 8.0 – 7.9 (m, 2H), 7.5 – 7.4 (m, 3H), 3.99 (s, 4H), 3.27 (t, J = 5.7 Hz, 4H), 1.83 (t, J = 5.7 Hz, 4H); MS (m/e): 452 (MH^+); HRMS: calc'd MH^+ for $C_{23}H_{21}N_3O_5S$ 452.1280; found 452.1286

[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-(3-methoxy-phenyl)-methanone (**17g**).

The title product was prepared in 24% yield as a yellow solid according to the procedure described for compound **17a** using 2-bromo-1-(3-methoxy-phenyl)-ethanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.7 – 8.6 (m, 2H), 7.6 – 7.1 (m, 7H), 3.95 (s, 4H), 3.3 – 3.2 (m, 4H), 1.8 – 1.6 (m, 4H); MS (m/z): 437 (MH^+); HRMS: calc'd MH^+ for $C_{24}H_{24}N_2O_4S$ 437.1535; found 437.1534.

(3-Bromo-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone (**17h**).

The title product was prepared in 25% yield according to the procedure described for compound **17a** using 1-(3,5-bis-trifluoromethyl-phenyl)-2-bromo-ethanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 8.5 (m, 2H), 7.9 – 7.3 (m, 7H), 3.94 (s, 4H), 3.3 – 3.2 (m, 4H), 1.8 – 1.7 (m, 4H); MS (m/z): 485, 487 (MH^+); HRMS: calc'd MH^+ for $C_{23}H_{21}BrN_2O_3S$ 485.0534; found 485.0514.

1-[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-1-one (**17i**).

The title product was prepared in 22% yield as a white solid according to the procedure described for compound **17a** using 1-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-morpholin-4-yl-2-pyridin-4-yl-propenethione (374.5 mg, 1.00 mmol), 1-bromo-butan-2-one (90%, 0.11 mL, 1.00 mmol) as starting material. ^{1}H NMR ($CDCl_3$) δ 8.62 (dd, J = 1.5, 4.6 Hz, 2H), 7.65 (s, 1H), 7.55 (dd, J = 1.5, 4.6 Hz, 2H), 3.97 (s, 4H), 3.17 (t, J = 5.7 Hz, 4H), 2.85 (q, J = 7.4 Hz, 2H), 1.82 (t, J = 5.7 Hz, 4H), 1.23 (t, J = 7.4 Hz, 3H); MS (m/z): 359 (MH^+); HRMS: calc'd MH^+ for $C_{19}H_{22}N_2O_3S$ 359.1429; found 359.1420.

1-(5-Benzoyl-3-pyridin-4-yl-thiophen-2-yl)-piperidin-4-one (**18a**).

A solution of [5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-phenyl-methanone (39.5 mg, 0.0970 mmol), *p*-toluenesulfonic acid monohydrate (37.0 mg, 0.194 mmol, 2 eq.), acetone (2 mL), and water (1 mL) was heated to reflux overnight. The solution was diluted with 1 *M* sodium carbonate solution and was extracted twice with ethyl acetate. The organic extracts were washed with brine, dried, filtered, and purified by column chromatography to provide the product as yellow solid (22.0 mg, 63%). ^{1}H NMR ($CDCl_3$) δ 8.6 – 8.5 (m, 2H), 7.8 – 7.4 (m, 8H), 3.5 – 3.4 (m, 4H), 2.5 – 2.4 (m, 4H). MS (m/z): 363 (MH^+), 385 (MNa^+); HRMS: calc'd MH^+ for $C_{21}H_{18}N_2O_2S$ 363.1167; found 363.1168.

1-[5-(4-Fluoro-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18b**).

The title product was prepared in 69% yield according to the procedure described for compound **18a** using [5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-(4-fluoro-phenyl)-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 7.1 (m, 9H), 3.4 – 3.3 (m, 4H), 2.6 – 2.5 (m, 4H); MS (m/z): 413 (MNa^+), 379 (MH^-); HRMS: calc'd MH^+ for $C_{21}H_{17}FN_2O_2S$ 381.1073; found 381.1080.

1-[5-(4-Chloro-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18c**).

The title product was prepared in 74% yield according to the procedure described for compound **18a** using (4-chloro-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.7 – 7.4 (m, 9H), 3.5 – 3.4 (m, 4H), 2.6 – 2.5 (m, 4H); MS (m/z): 397 (MH^+), 395 (MH^-); HRMS: calc'd MH^+ for $C_{21}H_{17}ClN_2O_2S$ 397.0777; found 397.0767.

Anal. Calc'd for $C_{21}H_{17}ClN_2O_2S$: C, 63.55; H, 4.32; N, 7.06. Found , C, 63.29; H, 4.20; N, 7.06.

1-[5-(2-Methoxy-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18d**).

The title product was prepared in 48% yield as a yellow solid according to the procedure described for compound **18a** using (2-methoxy-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-

pyridin-4-yl-thiophen-2-yl]-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 7.0 (m, 9H), 3.80 (s, 3H), 3.5 – 3.4 (m, 4H), 2.6 – 2.5 (m, 4H); MS (m/z): 393 (MH^+), 391 (MH^-); HRMS: calc'd MH^+ for $C_{22}H_{20}N_2O_3S$ 393.1273; found 393.1289.

1-[5-(3,5-Bis-trifluoromethyl-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18e**).

The title product was prepared in 33% yield as a yellow solid according to the procedure described for compound **18a** using (3,5-bis-trifluoromethyl-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.7 – 7.4 (m, 8H), 3.6 – 3.5 (m, 4H), 2.7 – 2.6 (m, 4H); MS (m/z): 499 (MH^+), 497 (MH); HRMS: calc'd MH^+ for $C_{23}H_{16}F_6N_2O_2S$ 499.0915; found 499.0914.

1-[5-(4-Nitro-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18f**).

The title product was prepared in 47% yield as a yellow solid according to the procedure described for compound **18a** using (4-nitro-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.6 – 6.9 (m, 9H), 3.3 – 3.2 (m, 4H), 2.7 – 2.6 (m, 4H); MS (m/z): 408 (MH^+), 407 (MH^-); HRMS: calc'd MH^+ for $C_{21}H_{17}N_3O_4S$ 408.1018; found 408.1024.

1-[5-(3-Methoxy-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18g**).

The title product was prepared in 73% yield according to the procedure described for compound **18a** using [5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-(3-methoxy-phenyl)-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.7 (m, 2H), 7.5 – 7.1 (m, 9H), 3.5 – 3.4 (m, 4H), 2.7 – 2.6 (m, 4H); MS (m/z): 393 (MH^+), 391 (MH^-); HRMS: calc'd MH^+ for $C_{22}H_{20}N_2O_3S$ 393.1273; found 393.1280.

1-[5-(3-Bromo-benzoyl)-3-pyridin-4-yl-thiophen-2-yl]-piperidin-4-one (**18h**).

The title product was prepared in 71% yield according to the procedure described for compound **18a** using (3-bromo-phenyl)-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-methanone as starting material. ^{1}H NMR ($CDCl_3$) δ 8.7 – 8.6 (m, 2H), 7.9 – 7.4 (m, 7H), 3.4 – 3.3 (m, 4H), 2.7 – 2.6 (m, 2H); MS (m/z): 441 (MH^+), 439 (MH^-); HRMS: calc'd MH^+ for $C_{21}H_{17}BrN_2O_2S$ 441.0272; found 441.0263.

Anal. Calc'd for $C_{21}H_{17}BrN_zO_2S$: C, 57.15; H, 3.88; N, 6.35. Found , C, 57.48; H, 3.93; N, 5.97.

1-(5-Propionyl-3-pyridin-4-yl-thiophen-2-yl)-piperidin-4-one (**18i**).

The title product was prepared in 60% yield as a white solid according to the procedure described for compound **18a** using 1-[5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-pyridin-4-yl-thiophen-2-yl]-propan-1-one as starting material. ^{1}H NMR ($CDCl_3$) δ 8.7 – 8.6 (m, 2H), 7.6 – 7.5 (m, 2H), 3.5 – 3.4 (m, 4H), 3.0 – 2.9 (m, 2H), 2.6 – 2.5 (m, 2H), 1.3 – 1.2 (m, 3H); MS (m/z): 315 (MH^+), 313 (MH^-); HRMS: calc'd MH^+ for $C_{17}H_{18}N_2O_2S$ 315.1167; found 315.1171.

Anal. Calc'd for $C_{17}H_{18}N_2O_2S$, C, 64.94; H, 5.77; N, 8.91. Found , C, 64.16; H, 5.77; N, 8.52.

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