HETEROCYCLES, Vol. 71, No. 2, 2007, pp. 389 - 398. © The Japan Institute of Heterocyclic Chemistry
Received, 11th October, 2006, Accepted, 15th December, 2006, Published online, 19th December, 2006. COM-06-10909

EFFICIENT METHOD FOR THE SYNTHESIS OF DIBENZO[*b,f*]THIEPIN-10-ONES UNDER MILD CONDITIONS

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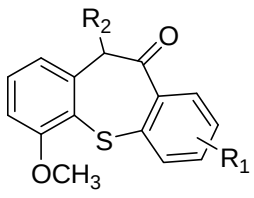
Abstract – A mild and efficient method to synthesize dibenzo[*b,f*]thiepin-10-one derivatives was achieved, with key steps of PPE mediated cyclization of seven-member ring and selective ketone α bromination with $CuBr_2$. Reaction of α alkylation and arylation of ketones were also optimized to finish the synthesis with good overall yield.

INTRODUCTION

During the past decades, the tricyclic system of dibenzo[*b,f*]thiepin-10-ones has been the object of intense investigation by medicinal chemists and organic chemists in search of compounds that exhibit clinically relevant neurotropic and psychotropic activities.[1-4] Most recently, drug discovery efforts have been directed toward the identification of novel dibenzo[*b,f*]thiepins as atypical neuroleptic drugs.[5-8] Our laboratory has focused on the computer-aided design and synthesis of novel compounds that target CNS receptors,[9-11] thus herein we report an efficient and convergent synthesis of substituted dibenzo[*b,f*]thiepin-10-ones (Figure 1) as potential novel therapeutics.

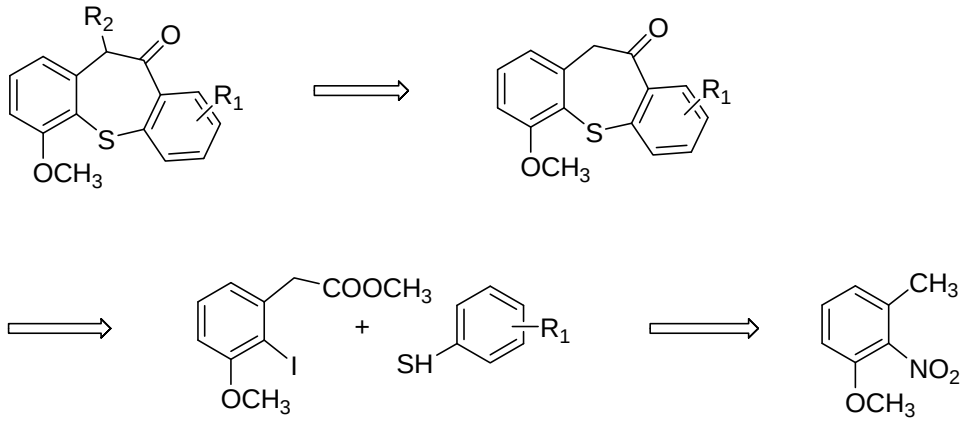
Figure 1



RESULTS AND DISCUSSION

Although there are different methods to synthesize these compounds,[1-4] thus far cyclization of the seven-membered ring has been the key step has been the most practical method for parallel synthesis. From retro-analysis depicted in Scheme 1, 3-methyl-2-nitroanisole (**1**) was selected as starting material.

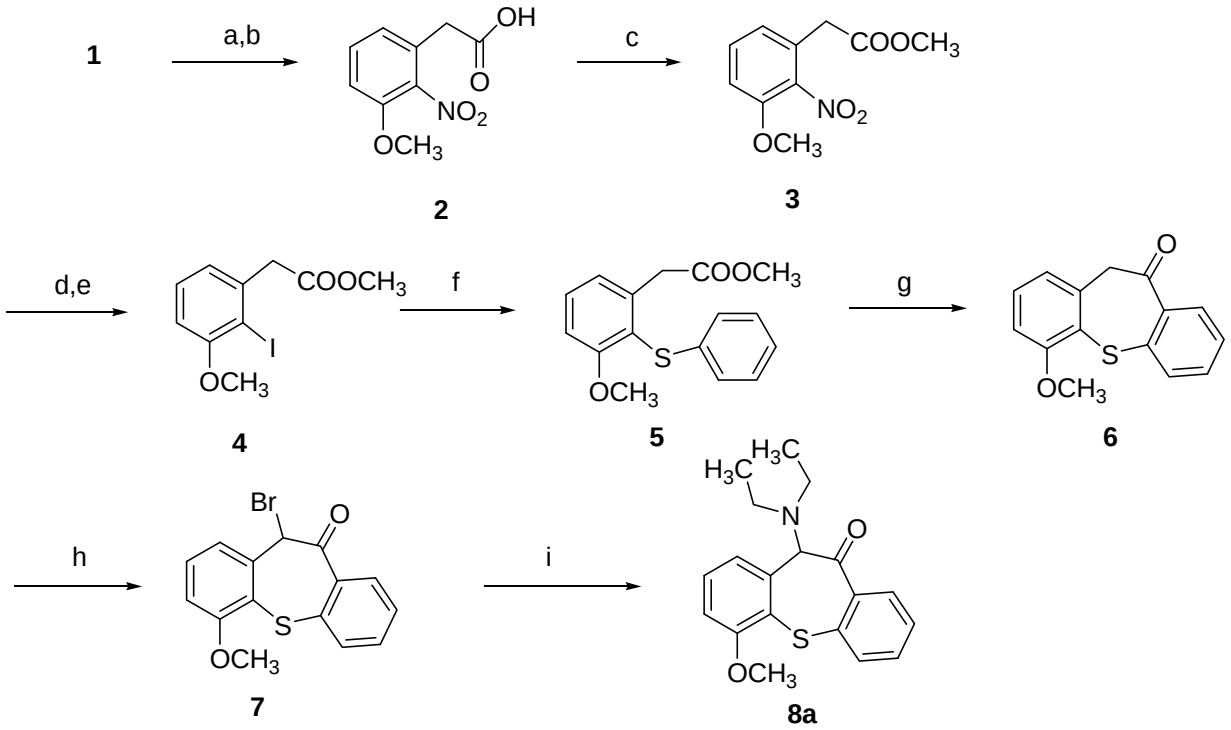
Scheme 1



1

Reissert indole synthesis was applied to prepare the ketoacid,[12] which was then oxidized to **2** by hydrogen peroxide in one pot.[13] The overall yield was 60% after recrystallization from ethyl acetate and hexane. With protection of acid, iodide (**4**) was successfully prepared in 70% yield from **3**. In order to optimize the synthesis of **5**, various catalyst systems were screened for the metal-catalyzed coupling of iodides with aryl thioethers.[14-15] During these experiments, Venkataraman's chemistry was found to proceed easily and to provide high yields.[14] With compound (**5)** in hand, we then pursued a mild and efficient method to cyclize the seven-membered ring. We investigated a variety of reagents, such as polyphosphoric acid (PPA), CH_3SO_3H, $TiCl_4$ and CF_3SO_3H; however, the yields were only moderate and many side products were observed. Although the combination of trifluoroacetic anhydride with BF_3 can generate product in moderate yield,[16] we sought a method that would be amenable to parallel synthesis and scale-up under mild conditions using a more efficient reagent cyclization. By refluxing PPA with P_2O_5 in ether and chloroform following standard procedures,[17] we serendipitously obtained the product ethyl polyphosphate ester (PPE) which led to a clean and quantitative conversion.[18-19] PPE is miscible with chloroform, and the cyclization reaction usually finished within 3-5 hours at room temperature with simple stirring. It is worth noting that the polyphosphoric acid trimethylsilyl ester (PPSE), a commercially available alternative to PPE that has been widely employed for the synthesis of heterocycles, failed to give any product under the same conditions.[20-22]

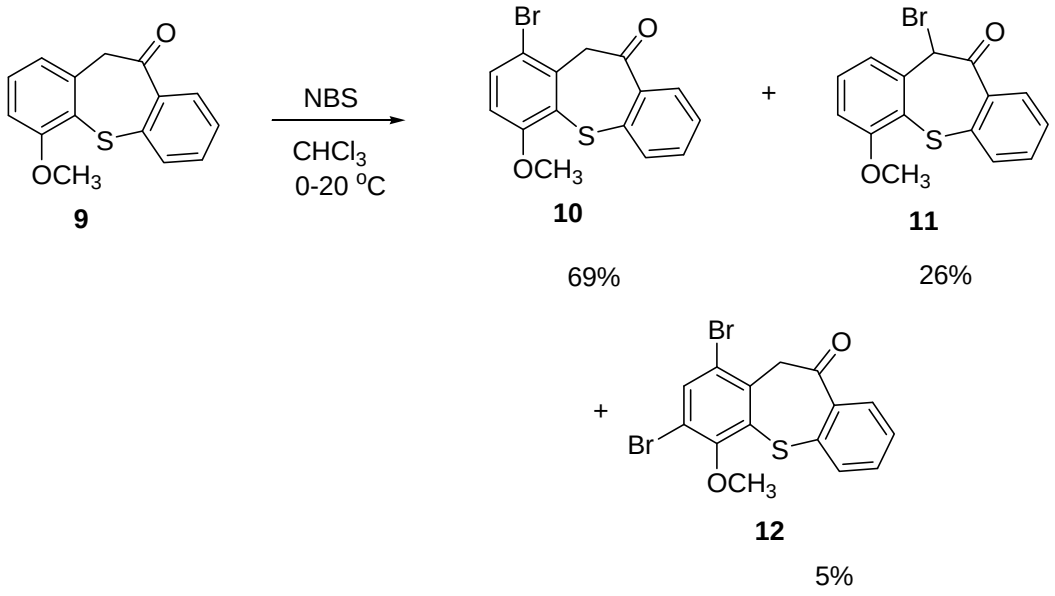
Scheme 2



Reagents and Conditions: a) diethyl oxalate, NaH, DMF-20-0°C; b) H_2O_2, rt, 60% for two steps; c) CH_2N_2, Et_2O, rt, 100%; d) H_2, Pd/C, 40°C; e) $NaNO_2$, HCl, CuI, -5°C-rt, 70% for two steps; f) CuI, NaO*t*-Bu, Neocuproine, 110°C, 95%; g) PPE, rt, 100%; h) $CuBr_2$, EtOAc, $CHCl_3$, reflux, 100%; i) $TiCl_4$, diethylamine, $CHCl_3$, 50°C, 82%.

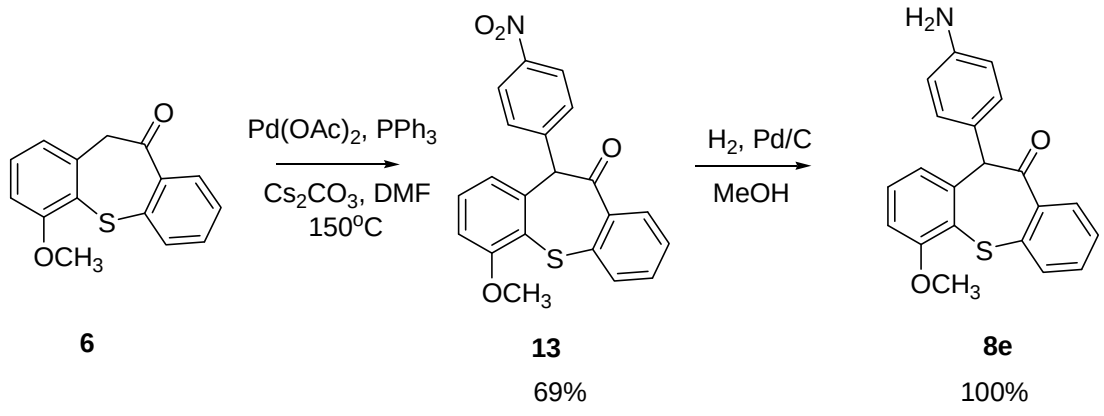
The α bromination of ketone (**7)** was expected to be straightforward with common brominating reagents, such as bromine, NBS, etc. Unfortunately, we encountered difficulty obtaining **7** from **6** and, in most cases, an aromatic bromide resulted as the main product. Only 26% prospective product was detected by GC-MS, and the isomers are difficult to isolate by chromatography (Figure 3). The appearance of the aromatic bromide is likely due to the electron-donating effect of the methoxyl group which would induce Br^+ to attack the electron-rich aromatic ring over the α position of the ketone. After an extensive literature search, $CuBr_2$ was selected as the reagent of choice for our synthesis.[23] Our subsequent experiments demonstrated that this choice was fortunate. By refluxing in 1:1 (v/v) ethyl acetate and chloroform for 5 hours, **7** was obtained in 100% yield as the sole product. After a simple filtration to remove CuBr formed in the reaction, **7** was available for the next step without need for further purification.

Scheme 3



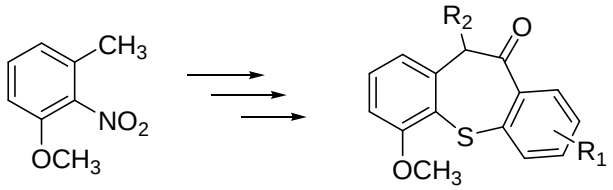
An initial attempt to reflux **7** with diethylamine in chloroform gave a mixture of decomposed unknown structures instead of **8**, as shown by GC-MS. We then exploited a Lewis-acid catalyzed reaction to finish the total synthesis of **8**.[24] By using $TiCl_4$ as catalyst, amination of **7** finished successfully within 5 hours at 50°C with a yield of 82% after purification. Meanwhile, another series of dibenzo[*b*,*f*]thiepin-10-ones where R = *p*-aromatic anilines were predicted active as CNS therapeutics by our Computer-Aided Molecular Design (CAMD). The chemistry we applied to synthesize these compounds was α-arylation of the ketone (**6**) (Figure 4). Buchwald and Hartwig's group have pioneered the successful development of this chemistry in recent years for a variety of ligands.[25] However, the conditions for these methods are often difficult to follow. In our synthesis, the method developed by Dominguez's lab was found to be most practical.[26] Compound (**8e**) was obtained in 69% yield from **6** with $Pd(OAc)_2$ as catalyst Adopting this strategy, we synthesized six dibenzo[*b*,*f*]thiepin-10-one derivatives (Table 1) in good overall yields.

Scheme 4

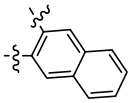
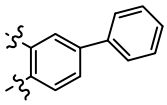
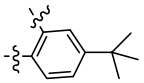
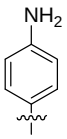
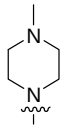


Preliminary in vitro studies indicate that **8e** exhibits moderate binding affinity to selected CNS targets. Structure optimization and molecular modeling studies will be pursued to enhance binding affinity and selectivity.

Table 1: Synthesis of dibenzo[*b*,*f*]thiepin-10-ones (**8**) from 3-methyl-2-nitroanisole (**1**)



1 **8**

No.	R_1	R_2	Total Yield (%)[a]
8a			30
8b			28
8c			33
8d			30
8e			25
8f			30

a: isolated yield of analytically pure products

In summary, we have demonstrated an efficient method to synthesize a series of dibenzo[*b*,*f*]thiepin-10-one derivatives. The reaction steps are mild, clean, and suitable for library synthesis and scale-up development. The present method offers a new avenue for large-scale chemical synthesis of a new family of therapeutic agents.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 400 MHz on Varian Gemini-400 spectrometer, in deuterated chloroform ($CDCl_3$) or DMSO (DMSO-d_6) solution at room temperature, using TMS (0.00 ppm) as internal standards and were reported in parts per million (ppm). ^{13}C NMR spectra were recorded on a Varian Gemini 100 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet;

t, triplet; q, quartet; m, multiplet; w, wide. Coupling constants, *J*, are reported (Hz). Analytical Thin Layer Chromatography (TLC) was performed on pre-coated plastic backed plates purchased from Aldrich (silica gel 60 F254; 0.25mm thickness). Flash column chromatography was conducted with silica gel 60 (230-400 mesh) from Natland Co. MS and MS-MS were conducted on a Finnigan LCQ DUO Mass Spectrum (Thermo Quest Co.) Gas chromatographic analyses were performed on a Hewlett-Packard 6890 GC-MS instrument with a FID detector using 25 m × 0.20 mm capillary column with cross-linked methylsiloxane as a stationary phase.

All reactions were carried out with anhydrous solvents in oven-dried and argon-charged glassware. All anhydrous solvents except as mentioned were freshly distilled and stored in 4Å molecular sieves. All solvents used in workup, extraction procedures, recrystallization process and chromatography were used as received from commercial supplier without further purification. All reagents were purchased from Aldrich Chemical Company.

Procedure for the synthesis of dibenzo[*b,f*]thiepin-10-ones (8a-8f): synthesis of 8a as example.

Methyl-2-(3-methoxylphenyl) acetate (3): Sodium hydride (150 mg, 95%) was suspended in DMF (15mL) and cooled to 0^{o}C. Anisole (**1**) (510 mg, 3.0 mmol) was added in small portions to yield a green solution. 10 min later, the solution was heated to rt. Ethyl oxalate (450 μL, 3.3 mmol) was slowly added, and the solution was stirred overnight. The DMF was largely evaporated, and the residue was dissolved in 2.5N NaOH (20 mL). The solution was cooled to 0^{o}C by ice and H_2O_2 (5.0 mL, 30% solution) was added dropwise to control the temperature below 5^{o}C. The resulting basic solution was acidified by adding concentrated HCl solution dropwise until pH< 2. The mixture was left overnight, and the solid was filtered to dryness under air to obtain 2-(3-methoxylphenyl)acetic acid (**2**) as an off-white solid, yield 80%. The acid (**2**) was dissolved in Et_2O (20 mL) and CH_2N_2 in Et_2O was added dropwise with stirring until a consistent yellow color appeared. Several drops of AcOH were added to quench excess CH_2N_2, and solution was concentrated to yield **3** as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ3.66 (s, 2H), 3.69 (s, 3H), 3.89 (s, 3H), 6.93 (d, *J* = 7.52 Hz, 2H), 6.98-7.04 (m, 2H), 7.07(d, *J* = 6.0 Hz, 1H), 7.14-7.20 (m, 2H), 7.39 (t, *J* = 7.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 40.7, 49.6, 56.2, 114.5, 119.4, 125.7, 137.2, 140.6, 156.8, 173.5. MS (ESI) = 226.4 (M^{+}+1).Anal. Calcd for $C_{10}H_{11}NO_5$: C 53.33, H 4.92, N 6.22. Found: C 53.31, H 4.95, N 6.27.

Methyl 2-(2-iodo-3-methoxylphenyl) acetate (4): Compound **3** (2.25 g, 10.0 mmol) and Pd/C (220 mg, 10%) were added to MeOH (100 mL). After degassing, the mixture was hydrogenated with a hydrogen balloon at 45^{o}C. 5 h later, TLC indicated the reaction was finished. Pd/C was filtered and the solution was concentrated to give amine as only product. The amine was dissolved in HCl solution (50 mL, 10%) and cooled to 0-5^{o}C. $NaNO_2$ (779 mg, 11.0 mmol), which was dissolved in water (5 mL), was added dropwise carefully to control the temperature below 5^{o}C. KI (16.6 g, 0.1 mol) was dissolved in water (20 mL) and

added slowly into above solution, and stirred overnight. $CHCl_3$ (50 mL) was added to extract the product. After drying and concentrating, the product was purified by chromatography to get **4** in 70% yield as white crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ3.71 (s, 3H), 3.74 (s, 2H), 3.75 (s, 2H), 6.73 (d, *J* = 7.0 Hz, 1H), 6.91 (d, *J* = 6.7 Hz, 1H), 7.23-7.29(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.1, 49.6, 54.2, 71.2, 115.3, 121.4, 127.7, 135.2, 146.8, 154.3, 172.4. MS (ESI) = 307.3 (M^++1).Anal. Calcd for $C_{10}H_{11}IO_3$: C 39.24, H 3.62, I 41.46. Found: C 39.21, H 3.59, I 41.48.

Methyl (2-(3-methoxyl-2-nitrophenyl) acetate (5): In a 50 mL flask, neocuprine (4.5 mg, 0.02 mmol), CuI (7.7 mg, 0.04 mmol) and toluene (5 mL) were introduced and the system was purged by argon. NaO*t*-Bu (29 mg, 90.3 mmol), thiophenol L (45 μ, 0.45 mmol) and **4** (0.2 mmol) were added in sequence. The mixture was refluxed overnight and then cooled to rt. $CHCl_3$ (10 mL) was added dropwise, and solid was removed by filtration. The product, which is yellow solid, was purified by chromatography using EtOAc and hexane (1:4) as eluent. Yield was 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ3.55 (s, 3H), 3.78 (s, 3H), 3.91 (s, 2H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.98-7.02 (m, 2H), 7.07 (d, *J* = 6.2 Hz, 1H), 7.14-7.19 (m, 3H), 7.39 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7, 51.6, 55.8, 112.9, 117.3, 121.4, 127.7, 130.6, 131.2, 133.8, 135.2, 138.9, 162.3, 172.4. MS (ESI) = 288.3 (M^++1).Anal. Calcd for $C_{16}H_{16}O_3S$: C 66.64, H 5.59, S 11.12. Found: C 66.59, H 5.62, S 11.10.

4-Methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (6): Methyl ester (**4**) (1.45 g, 5.0 mmol) was dissolved in MeOH(10 mL) and NaOH (10 mL, 1.0 N)was added. The mixture was refluxed overnight and cooled to rt. MeOH was evaporated, and concentrated HCl was slowly added dropwise to acidified to pH < 2. The solid was filtered and dried under vacuum. The acid was dissolved in $CHCl_3$ (20 mL) and PPE (10 mL) was added to generate a brown solution. The solution was stirred 5 hr at rt and TLC indicated the reaction was complete. Water was added to quench excess PPE, and $CHCl_3$ layer was dried and concentrated to yield **6** as yellow crystal in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ3.89 (s, 3H), 4.36 (s, 2H), 6.80 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 12.3 Hz, 2H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.7, 56.5, 98.2, 105.6, 114.6, 126.9, 130.3, 131.6, 131.7, 132.7, 136.7, 141.0, 141.5, 159.7, 162.7, 191.8. MS (ESI) = 257.1 (M^++1).Anal. Calcd for $C_{15}H_{12}O_2S$: C 70.29, H 4.72, S 12.51. Found: C 70.31, H 4.75, S 12.49.

11-(Diethylamino)-4-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (8a): Compound **6** (1.28 g, 5.0 mmol) was dissolved in $CHCl_3$ (10 mL) and EtOAc (10 mL). After $CuBr_2$ (2.2 g, 10.0 mmol) was added, the system was purged by argon. The mixture was refluxed overnight and cooled to rt. The solid was filtered and the solvents evaporated to give the bromide **7** as a light green solid. The bromide was dissolved in dry benzene (25 mL) and $TiCl_4$ (1.1 equiv., 1.0 M in CH_2Cl_2) was added dropwise. Diethylamine (4.0 equiv.) was added dropwise at rt, and the solution refluxed overnight. Water (20 mL) was added dropwise to

quench reaction, and the organic layer was dried and concentrated. The final compound (**8a**) was purified by chromatography to get **8a** in yield of 82% as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (t, J = 6.8 Hz, 6H), 2.43 (m, J = 7.5 Hz, 4H), 3.89 (s, 3H),4.66 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 10.3 Hz, 2H), 7.30 (t, J = 7.1 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.5, 46.4, 51.4, 55.8, 98.5, 105.4, 114.8, 127.3, 131.1, 131.4, 131.6, 132.1, 136.4, 149.6, 140.9, 159.4, 162.1, 198.5. MS (ESI) = 328.3 (M^++1).Anal. Calcd for $C_{19}H_{21}NO_2S$: C 69.69, H 6.46, N 4.28, S 9.79. Found: C 69.73, H 6.42, N 4.26, S 9.81.

13-(Diethylamino)-4-methoxyl-13H-5-thia-benzo[4,5]cyclohepta[1,2-*b*]naphthalen-12-one (8b): Synthesized same as **8a** with yield of 80%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 6.8 Hz, 6H), 2.41 (dd, J = 7.0, 7.5 Hz, 4H), 3.91 (s, 3H),4.27 (s, 1H), 6.82 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 7.1 Hz, 1H), 7.26 (s, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 5.8 Hz, 1H), 7.58 (t, J = 6.5 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.80 (dd, J = 3.3, 8.3 Hz, 2H), 8.85 (d, J = 9.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 45.9, 53.4, 67.9, 98.5, 113.2, 117.8, 125.1, 126.5, 126.8, 127.3, 127.5, 128.6, 128.9, 132.8, 134.4, 134.8, 137.4, 139.1, 161.3, 198.7. MS (ESI) = 378.5 (M^++1).Anal. Calcd for $C_{23}H_{23}NO_2S$: C 73.18, H 6.14, N 3.71, S 8.49. Found: C 73.18, H 6.11, N 3.73, S 8.52.

11-(Diethylamino)-4-methoxyl-8-phenyldibenzo[*b,f*]thiepin-10(11*H*)-one (8c): Synthesized same as **8a** with yield of 85%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 6.9 Hz, 6H), 2.41 (dd, J = 7.2, 6.9 Hz, 4H), 3.91 (s, 3H),4.40 (s, 1H), 6.82 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 7.26-7.46 (m, 5H), 7.58 (d, J = 5.3 Hz, 2H), 7.63 (d, J = 13.5 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 8.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 46.3, 55.6, 68.9, 115.2, 117.8, 123.1, 127.5, 128.3, 128.9, 129.5, 130.2, 131.9, 132.7, 135.8, 136.2, 137.4, 138.1, 138.9, 160.7, 198.1. MS (ESI) = 404.5 (M^++1).Anal. Calcd for $C_{25}H_{25}NO_2S$: C 74.41, H 6.24, N 3.47, S 7.95. Found: C 74.45, H 6.23, N 3.45, S 7.90.

11-(Diethylamino)-8-*tert*-butyl-4-methoxyl-8-phenyldibenzo[*b,f*]thiepin-10(11*H*)-one (8d): Synthesized same as **8a** with yield of 83%, yellow solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 6.5 Hz, 6H), 1.30 (s, 9H), 2.41 (m, 4H), 3.88 (s, 3H),4.37 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 8.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 30.9, 41.2, 46.7, 54.8, 68.9, 113.7, 117.3, 125.7, 126.3, 127.3, 127.5, 128.6, 132.8, 134.4, 139.4, 146.9, 160.3, 198.1. MS (ESI) = 383.3 (M^++1).Anal. Calcd for $C_{23}H_{29}NO_2S$: C 72.02, H 7.62, N 3.65, S 8.36. Found: C 72.07, H 7.58, N 3.63, S 8.31.

11-(4-Aminophenyl)-4-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (8e): $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), Cs_2CO_3 (1.63 g, 5.0 mmol), PPh_3 (42.0 mg, 0.16 mmol), ketone (**6**) (580 mg, 2.0 mmol), and 4-nitro-1-bromobenzene (808.0 mg, 4.0 mmol) were added to dry degassed DMF (30 mL) at rt. The flask was purged with argon. The resultant stirred suspension was heated to 150^{o}C for 2 hr.

After cooling, HCl (60 mL, 1.4 M) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl, dried over anhydrous $MgSO_4$ and evaporated in vacuum to give a residue that was purified by flash chromatography on silica gel to obtain **13** as yellow solid, yield 69%. The nitro compound (**13**) and Pd/C (10%, w/w) were added to MeOH(50 mL) and hydrogenated under hydrogen at 45°C. 5 hr later, Pd/C was filtered and MeOH was evaporated to obtain **8e** in 100% yield as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 2H), 3.84 (s, 3H), 5.99 (s, 1H), 6.49 (s, 1H), 6.56 (d, *J* = 8.2 Hz, 2H), 6.77 (s, 1H), 6.80 (t, *J* = 5.1 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.15 (m, 2H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.7, 55.9, 98.2, 105.6, 114.6, 116.8,. 126.9, 129.0, 130.3, 131.6, 131.7, 132.7, 136.7, 141.0, 141.5, 142.5, 159.6, 162.4, 191.8. MS (ESI) = 348.2 (M^++1). Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03; S, 9.23. Found: C, 72.56; H, 4.98; N, 4.06; S, 9.21.

4-Methoxy-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*]thiepin-10(11*H*)-one (8f): Synthesized same as **8a** with yield of 83%, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11 (s, 3H), 2.41-2.47 (m, 8H), 3.78 (s, 3H), 5.05 (s, 1H), 6.36 (d, *J* = 6.8 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 7.26-7.30 (m, 2H), 7.42 (d, *J* = 5.5 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.9, 50.4, 55.4, 55.9, 68.6, . 112.9, 116.7, 123.8, 127.7, 128.3, 128.9, 130.2, 132.8, 133.4, 136.4, 138.9, 161.2, 196.5. MS (ESI) = 355.3 (M^++1). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05. Found: C, 67.70; H, 6.29; N, 7.87; S, 9.08.

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