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A FACILE SYNTHESIS OF 5,6-DIHYDRO-4*H*-PYRROLO[3,4-*d*]THIAZOLE AND OTHER PYRROLIDINE-FUSED AROMATIC RING SYSTEMS *VIA* ONE-STEP CYCLIZATION FROM DIOLS

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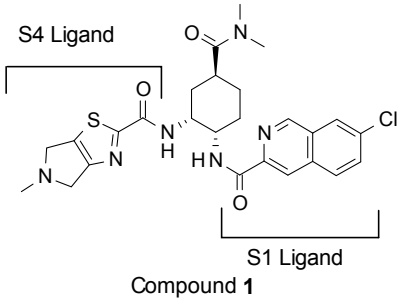
Abstract – A facile synthetic method of 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]thiazole, which is a subunit of a potent factor Xa (fXa) inhibitor was developed. This new approach employs one-step cyclization from a diol and can be applied to the syntheses of other pyrrolidine-fused aromatic ring sytems.

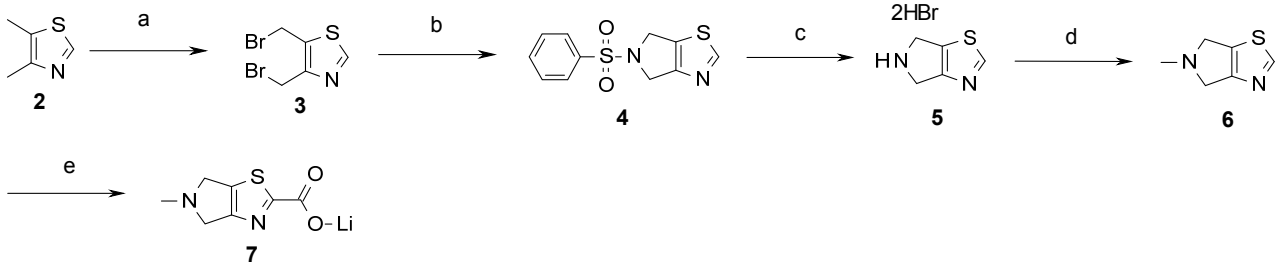
We previously reported an orally active potent fXa inhibitor, compound **1**.[1] During the course of the discovery of compound **1**, we found that 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]thiazole moiety is an excellent subunit for the S4 binding site in terms of activity, solubility, and pharmacokinetics.



Compound **1**

Figure 1

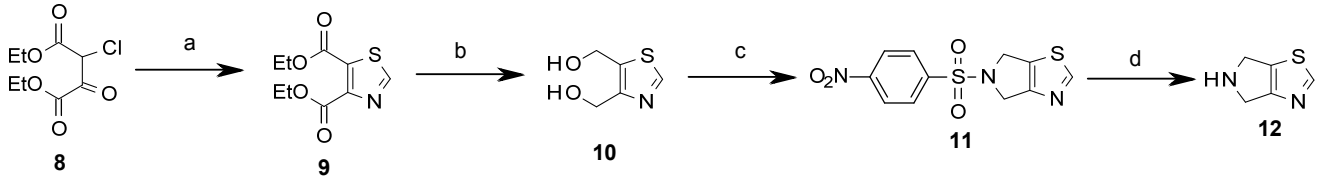
This subunit was synthesized according to Scheme 1. However, this route possesses the following problems:



Scheme 1. Reagents and conditions: (a) AIBN, NBS, CCl_4, reflux, 31%; (b) NaH, benzenesulfonamide, DMF, rt, 13%; (c) 47% HBr aq., PhOH, reflux, 60%; (d) HCHOaq., Et_3N, AcOH, $NaBH(OAc)_3$, CH_2Cl_2, rt, 86%; (e) i) *tert*-BuLi, THF, Ar, -78 to 0 °C; ii) CO_2 gas, -78 °C, quant.

First, the selectivity of the dibromination of **2** was poor, producing an isomer of dibromide, a tribromide, and a tetrabromide apart from the desired dibromide **3**, resulting in the low yield of compound **3** (around 30%).[2] Second, the stability of compound **3** was low and it decomposed upon concentration. Third, the yield of cyclization using benzenesulfonamide was crucially low (13%). Finally, the removal of the benzenesulfonyl group requires harsh conditions, such as refluxing in a HBr aqueous solution. We started exploration of alternative synthetic routes to overcome these problems.

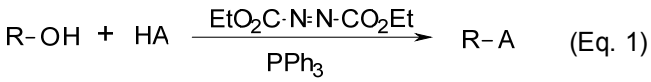
We set a diol **10** as a key intermediate instead of the unstable dibromide **3** and developed a cyclization reaction from a diol utilizing the Mitsunobu reaction (Scheme 2). In this paper, this new efficient synthetic route and the scope and limitations of the cyclization reaction will be discussed.



Scheme 2. Reagents and conditions: (a) thioformamide, rt, 59%; (b) $LiBH_4$, THF, MeOH, rt, 62%; (c) 4-nitrobenzenesulfonamide, CMBP, THF, toluene, 80 °C, 58%; (d) PS-thiophenol, THF, MeOH, rt, 73%.

Ester **9** was synthesized according to the literature with slight modifications.[3] The reduction of ester **9** using $LiBH_4$ gave the key intermediate **10**, which turned out to be a stable solid unlike dibromide **3**. The formation of a 5-membered ring from a diol usually requires conversion of the diol to a corresponding dihalide or disulfonate which is then substituted by a nucleophile. We tried one-step cyclization from a

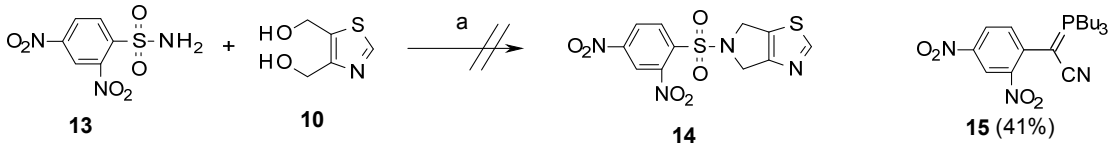
diol employing the Mitsunobu reaction,[4,5] which is one of the most frequently used reactions to substitute an alcohol by a nucleophile. It is well known that the pKa of the HA component is important to make this reaction proceed smoothly (Eq. 1).[4,5]



(Eq. 1)

Therefore, 4-nitrobenzenesulfonamide was chosen as a nucleophile instead of benzenesulfonamide. 4-Nitrobenzenesulfonamide also possesses another desirable feature, the ease of its removal under mild conditions.[6] However, it should be noted that conventional Mitsunobu reagents, like diethyl azodicarboxylate (DEAD) and PPh_3, react with sulfonamide to produce *N*-sulfonylphospha-λ^5-azene.[7] Therefore, we adopted one of the phosphorane reagents, cyanomethylenetributylphosphorane (CMBP),[8] with which sulfonamide can be used as a nucleophile. Another concern was the possibility of intramolecular ether formation.[9,10] As it turned out, the intermolecular substitution of sulfonamide, which led to the formation of a pyrrolidine ring, proceeded in good yield. The undesired ether product was not observed, and in addition, compound **11** was obtained as a practically pure solid simply by filtration without column chromatography. The removal of the 4-nitrobenzenesulfonyl group proceeded in good yield at room temperature with PS-thiophenol resin, which was selected because of its easy work-up.

Assuming that the yield of the cyclization can be improved by increasing the acidity of sulfonamide, we employed 2,4-dinitrobenzenesulfonamide **13** as a nucleophile (Scheme 3).

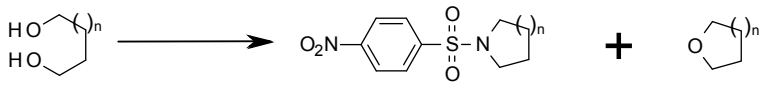


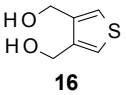
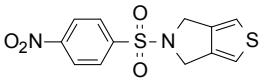
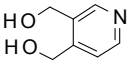
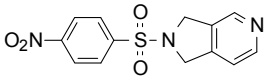
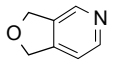
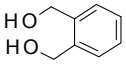
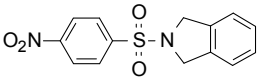
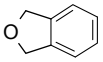
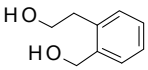
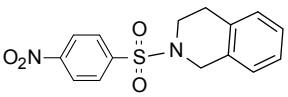
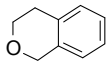
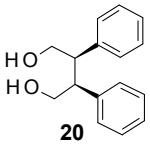
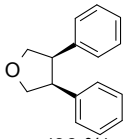
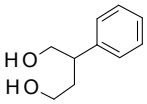
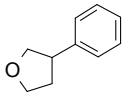
Scheme 3. Reagents and conditions: (a) CMBP, THF, toluene, 80 °C

However, sulfonamide **13** reacted with CMBP producing the undesired compound **15** and cyclized product **14** was not obtained.

We then examined the scope and limitations of the one-step cyclization, and the results of the reaction using various diols as the substrates are summarized in Table 1.

Table 1. The reactions of diols with 4-nitrobenzenesulfonamide[a]



entry	substrate	product	
1	 **16**	 **22** (45%)	-
2[b]	 **17**	 **23** (56%)	 **26** (2%)
3	 **18**	 **24** (54%)	 **27** (6%)
4	 **19**	 **25** (44%)	 **28** (36 %)
5	 **20**	-	 **29** (96 %)
6	 **21**	-	 **30** (93 %)

a) Reagents and conditions: 4-nitrobenzenesulfonamide (1.0 eq.), CMBP (3.8 eq.), THF, toluene, 80 °C. b) CMBP (4.8 eq.) was used.

In regards to the aromatic ring moiety, 5-membered or 6-membered aromatic rings other than thiazole were also applicable for this reaction. Those substrates predominantly gave the desired pyrrolidine derivatives (entries 1-3). In the 1,5-diol derivative, a comparable amount of ether compound was produced along with the piperidine product (entry 4). When there was no aromatic ring between the two hydroxyl groups, ether ring formation proceeded almost quantitatively (entries 5, 6).

We assume the reason for this result is as follows: When there are sp^2 carbons between two hydroxyl groups like in substrates **16-18**, it is difficult for the reaction centers to come in close proximity, so the intramolecular ether formation is slow. Therefore, it is possible for a sulfonamide to react with an alcohol and the resultant intermediate then reacts with another alcohol intramolecularly. On the other hand, when

the carbon chain is prolonged to make a 6-membered ring (like substrate **19**), the two reaction centers can come closer even though there are sp^2 carbons. Thus, the intramolecular ether formation competes with the desired sulfonamide substitution. When there are only sp^3 carbons between the two hydroxyl groups, intramolecular ether formation proceeds smoothly.

From the results of Table 1, this one-step cyclization from a diol is considered to be suitable for the synthesis of a pyrrolidine ring fused to an aromatic ring system.

In summary, we have developed an improved synthetic route for 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]thiazole moiety, which is a subunit of a potent fXa inhibitor. During the course of this study, the one-step cyclization from a diol utilizing the Mitsunobu reaction was established. In this new route, we have achieved 1) improvement of the yield, 2) circumvention of the unstable intermediate, 3) avoidance of harsh reaction conditions, and 4) easy purification. The one-step pyrrolidine ring formation from a diol is applicable to the syntheses of other pyrrolidine-fused aromatic ring systems and is expected to be a useful tool in organic synthesis.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification. Melting points were determined on a METLER TOLEDO FP81HT and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-EX-400 spectrometer and ^{13}C NMR spectra were recorded on a JEOL JNM-ECP400, JNM-ECA500, or BRUKER AVENCEIII 500 spectrometer using tetramethylsilane as an internal standard. FAB mass spectra were recorded on a JEOL JMS-700 spectrometer. ESI mass spectra were recorded on a SCIEX API-150EX spectrometer or WATERS Xevo-QTOFMS spectrometer. CI mass spectra were recorded on a JEOL JMS-T100GC spectrometer. IR spectra were recorded on a JASCO FT/IR-6100 typeA. Column chromatography was performed with a Pulif-Pack (SI, NH, or DIOL) purchased from Shoko scientific. Thin-layer chromatography (TLC) was performed on Merck TLC silica gel 60 F_{254}, HPTLC silica gel 60 NH_2 F_{254S}, or Fuji Silysia Chemical Ltd. TLC plates DIOL.

Diethyl thiazole-4,5-dicarboxylate (9) : To diethyl 2-chloro-3-oxo-butanedioate (purity 95%, 2.87 g, 12.2 mmol) was added thioformamide (purity 92%, 2.25 g, 33.9 mmol). The mixture was stirred for 30 min (The reaction was exothermic). The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution. The water layer was extracted with CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed (SI, EtOAc/hexane = 1/2) to give the title compound (1.64 g, 7.15 mmol, 59%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, J = 7.4 Hz, 3H), 1.42 (t, J = 7.4 Hz, 3H), 4.39 (q, J = 7.4 Hz, 2H), 4.47 (q, J = 7.4 Hz, 2H), 8.85 (s, 1H). MS (ESI) *m/z*: 230 $(M + H)^+$.

[5-(Hydroxymethyl)thiazol-4-yl]methanol (10) : To a solution of compound **9** (1.24 g, 5.39 mmol) in THF (36 mL) and MeOH (18 mL) was added $LiBH_4$ (939 mg, 43.1 mmol) in portions. After stirring for 1 h at room temperature, the reaction mixture was cooled to 0 °C and acetone was slowly added. The solvent was evaporated and the residue was chromatographed (DIOL, MeOH/CH_2Cl_2 = 1/9) to give the title compound (487 mg, 3.35 mmol, 62%) as a colorless solid. mp 105 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.53 (d, J = 5.6 Hz, 2H), 4.74 (d, J = 5.6 Hz, 2H), 5.09 (t, J = 5.6 Hz, 1H), 5.55 (t, J = 5.6 Hz, 1H), 8.88 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 55.1, 57.3, 136.6, 151.2, 151.5. IR (KBr) ν: 3340, 3104, 2814, 1414, 1248, 1007 cm^{-1}. MS (CI) *m/z*: 146 $(M + H)^+$. HRMS (CI) Calcd for $C_5H_8NO_2S$: 146.0276. Found: 146.0275.

General Procedure for the cyclization reaction.

5-(4-Nitrophenyl)sulfonyl-4,6-dihydropyrrolo[3,4-*d*]thiazole (11) : A mixture of compound **10** (145 mg, 1.00 mmol), 4-nitrobenzenesulfonamide (202 mg, 1.00 mmol), and cyanomethylenetributylphosphorane (CMBP) (purity 95%, 965 mg, 3.80 mmol) in THF (13.3 mL) and toluene (6.7 mL) was stirred at 80 °C for 2.5 h under nitrogen atmosphere. The solvent was evaporated and to the residue were added hexane and EtOAc. The resultant precipitate was collected by filtration to give the title compound (182 mg, 0.585 mmol, 58%) as a pale brown solid. mp 228 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.59-4.61 (m, 2H), 4.69-4.71 (m, 2H), 8.15-8.19 (m, 2H), 8.38-8.42 (m, 2H), 9.04 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ:49.6, 50.0, 124.8, 127.8, 128.9, 141.6, 150.0, 154.7, 159.7. IR (KBr) ν: 3102, 2880, 1520, 1346, 1314, 1163, 1105 cm^{-1}. MS (ESI) *m/z*: 312 $(M + H)^+$. HRMS (ESI) Calcd for $C_{11}H_{10}N_3O_4S_2$: 312.0113. Found: 312.0101. Anal. Calcd for $C_{11}H_9N_3O_4S_2$: C, 42.44; H, 2.91; N, 13.50; S, 20.60. Found: C, 42.75; H, 3.21; N, 13.21; S, 20.50.

5,6-Dihydro-4*H*-pyrrolo[3,4-*d*]thiazole (12) : To a suspension of compound **11** (200 mg, 0.642 mmol) in THF (10 mL) and MeOH (10 mL) were added PS-thiophenol resin (1.41 g, 1.93 mmol, 1.37 mmol/g) and Cs_2CO_3 (417 mg, 1.28 mmol). The reaction mixture was shaken for 18 h at room temperature. The reaction mixture was filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and the residue was chromatographed (SI, MeOH/CH_2Cl_2 = 1/5) to give the title compound (59 mg, 0.47 mmol, 73 %) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (s, 1H), 4.19 (t, J = 3.0 Hz, 2H), 4.29 (t, J = 3.0 Hz, 2H), 8.74 (s, 1H). MS (ESI) *m/z*: 127 $(M + H)^+$. **HCl salt of (12)** : a pale yellow solid. ^{1}H-NMR (CD_3OD) δ: 4.54 (s, 2H), 4.70 (s, 2H), 9.08 (s, 1H). ^{13}C-NMR (CD_3OD) δ: 47.7, 48.7, 130.1, 156.0, 163.0. IR (KBr) ν: 3031, 2672, 2551, 2394, 1936, 1596, 1392, 1165 cm^{-1}. MS (ESI) *m/z*: 127 $(M + H)^+$. HRMS (ESI) Calcd for $C_5H_7N_2S$: 127.0330. Found: 127.0333. Anal. Calcd for $C_5H_6N_2S{\cdot}2HCl{\cdot}1/8H_2O$: C, 29.82.; H, 4.13; N, 13.91; Cl, 35.21; S, 15.92. Found: C, 29.53.; H, 4.00; N, 13.52; Cl, 35.24; S, 16.31.

(2,4-Dinitrophenyl)(tributyl-λ^5-phosphanylidene)acetonitrile (15) : a wine-red solid. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, J = 7.3 Hz, 9H), 1.43-1.60 (m, 12H), 2.07-2.14 (m, 6H), 7.54 (d, J = 9.7 Hz, 1H), 8.01-8.04 (m, 1H), 8.85 (d, J = 2.4 Hz, 1H). MS (ESI) *m/z*: 408 $(M + H)^+$.

[4-(Hydroxymethyl)-3-thienyl]methanol (16) : Thiophene-3,4-dicarboxylic acid (1.38 g, 8.00 mmol), 1-hydroxybenzotriazole (HOBt) (216 mg, 1.60 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (4.60 g, 24.0 mmol) were dissolved in MeOH (30 mL) and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was partitioned between AcOEt and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed (SI, MeOH/CH_2Cl_2 = 1/19) to give dimethyl thiophene-3,4-dicarboxylate (363 mg, 1.81 mmol, 23%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 6H), 7.86 (s, 2H). MS (ESI) *m/z*: 201 $(M + H)^+$.

To a solution of dimethyl thiophene-3,4-dicarboxylate (327 mg, 1.63 mmol) in CH_2Cl_2 (20 mL) was added a solution of diisobutylaluminum hydride (1.0M in toluene, 8.2 mL, 8.2 mmol) at 0 °C. After stirring for 5 min at 0 °C, potassium sodium (+)-tartrate tetrahydrate (2.76 g, 9.78 mmol) was added. The mixture was stirred for 30 min at room temperature. MeOH (10 mL) and H_2O (1 mL) were then added to the mixture. The resultant precipitate was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed (DIOL, MeOH/CH_2Cl_2 = 3/97) to give the title compound (183 mg, 1.27 mmol, 78%) as a pale yellow solid. ^{1}H-NMR (acetone-d_6) δ: 4.32 (t, J = 5.4 Hz, 2H), 4.62 (d, J = 5.4 Hz, 4H), 7.28 (s, 2H). MS (CI): 127 $(M – OH)^+$.

[3-(Hydroxymethyl)-4-pyridyl]methanol (17) : To a solution of diethyl pyridine-3,4-dicarboxylate (1.00 g, 4.48 mmol) in CH_2Cl_2 (30 mL) was added a solution of diisobutylaluminum hydride (1.0M in toluene, 22.4 mL, 22.4 mmol) at 0 °C. After stirring for 10 min at 0 °C, potassium sodium (+)-tartrate tetrahydrate (7.59 g, 26.9 mmol) was added. The mixture was stirred overnight at room temperature. MeOH (10 mL) and H_2O (1 mL) were then added to the mixture. The mixture was concentrated *in vacuo* and the residue was chromatographed (DIOL, MeOH/CH_2Cl_2 = 8/92) to give the title compound (135 mg, 0.970 mmol, 22%) as a pale yellow solid. ^{1}H-NMR (CD_3OD) δ: 4.67 (s, 2H), 4.77 (s, 2H), 7.57 (d, J = 5.4 Hz, 1H), 8.42-8.46 (m, 2H). MS (ESI) *m/z*: 140 $(M + H)^+$. HRMS (ESI) Calcd for $C_7H_{10}NO_2$: 140.0712. Found: 140.0712.

2-[2-(Hydroxymethyl)phenyl]ethanol (19) : To a solution of homophthalic acid (1.80 g, 10.0 mmol) in THF (40 mL) was added a solution of BH_3·THF (0.95M in THF, 18.7 mL, 17.8 mmol). After stirring for 2 h at room temperature, a solution of BH_3·THF (0.95M in THF, 18.7 mL, 17.8 mmol) was added again. After stirring for 6.5 h, water was slowly added to the reaction mixture at 0 °C. The reaction mixture was partitioned between AcOEt and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed (SI, MeOH/CH_2Cl_2 = 1/19) to give the title compound (1.11 g, 7.29 mmol, 82%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.92 (t, J = 5.7 Hz, 2H), 3.85 (t, J = 5.7 Hz, 2H), 4.61 (s, 2H), 7.20-7.24 (m, 2H), 7.26-7.32 (m, 2H). MS (CI): 135 $(M – OH)^+$.

***cis*-2,3-Diphenylbutane-1,4-diol (20)** : To a suspension of $LiAlH_4$ (610 mg, 14.8 mmol) in THF (15 mL) was added a solution of *meso*-2,3-diphenylsuccinic acid (1.00 g, 3.70 mmol) in THF (15 mL). After stirring for 1 h at room temperature, the reaction mixture was refluxed for 4 h. The reaction mixture was cooled to 0 °C and water was slowly added. Et_2O and 1N-NaOH aqueous solutions were added and the organic layer was separated. The water layer was extracted with Et_2O and the combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed (SI, $MeOH/CH_2Cl_2$ = 1/19) to give the title compound (318 mg, 1.31 mmol, 35%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (dd, *J* = 7.9, 4.8 Hz, 2H), 3.10-3.14 (m, 2H), 3.50-3.63 (m, 4H), 7.28-7.43 (m, 10H). MS (ESI) *m/z*: 243 $(M + H)^+$.

2-Phenylbutane-1,4-diol (21) : This compound was prepared according to the literature.[11]

5-(4-Nitrophenyl)sulfonyl-4,6-dihydrothieno[3,4-*c*]pyrrole (22) : a pale yellow solid. mp 190 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.40 (s, 4H), 7.20 (s, 2H), 8.12-8.16 (m, 2H), 8.38-8.42 (m, 2H). ^{13}C-NMR (DMSO-d_6) δ: 48.8, 116.2, 124.7, 128.6, 139.2, 141.5, 150.0. IR (KBr) ν: 3115, 2870, 1544, 1350, 1313, 1161, 1098 cm^{-1}. MS (ESI) *m/z*: 311 $(M + H)^+$. HRMS (ESI) Calcd for $C_{12}H_{11}N_2O_4S_2$: 311.0160. Found: 311.0164. Anal. Calcd for $C_{12}H_{10}N_2O_4S_2$: C, 46.44; H, 3.25; N, 9.03; S, 20.66. Found: C, 46.36; H, 3.27; N, 8.94; S, 20.37.

2-(4-Nitrophenyl)sulfonyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (23) : a pale yellow solid. mp 205 °C (decomp.). ^{1}H-NMR (DMSO-d_6) δ: 4.69-4.70 (m, 4H), 7.32 (d, *J* = 5.4 Hz, 1H), 8.12-8.16 (m, 2H), 8.37-8.41 (m, 2H), 8.43 (d, *J* = 5.4 Hz, 1H), 8.49 (s, 1H) . ^{13}C-NMR (DMSO-d_6) δ: 51.7, 53.1, 118.1, 124.7, 128.9, 132.1, 141.3, 144.3, 144.9, 148.2, 150.0. IR (KBr) ν: 3110, 2866, 1607, 1543, 1351, 1162, 1097 cm^{-1}. MS (ESI) *m/z*: 306 $(M + H)^+$. HRMS (ESI) Calcd for $C_{13}H_{12}N_3O_4S$: 306.0549. Found: 306.0547.Anal. Calcd for $C_{13}H_{11}N_3O_4S \cdot 1/10H_2O$: C, 50.84; H, 3.68; N, 13.68; S, 10.44. Found: C, 51.17; H, 3.78; N, 13.30; S, 10.56.

2-(4-Nitrophenyl)sulfonylisoindoline (24) : a pale gray solid. mp 233 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.64 (s, 4H), 7.25 (s, 4H), 8.13-8.16 (m, 2H), 8.38-8.42 (m, 2H). ^{13}C-NMR (DMSO-d_6) δ: 53.4, 122.7, 124.7, 127.6, 128.9, 135.4, 141.4, 150.0. IR (KBr) ν: 3108, 2867, 1531, 1346, 1314, 1169, 1114 cm^{-1}. MS (FAB) *m/z*: 305 $(M + H)^+$. HRMS (ESI) Calcd for $C_{14}H_{13}N_2O_4S$: 305.0596. Found: 305.0599. Anal. Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.25; H, 3.97; N, 9.21; S, 10.54. Found: C, 55.28; H, 4.02; N, 9.12; S, 10.77.

2-(4-Nitrophenyl)sulfonyl-3,4-dihydro-1*H*-isoquinoline (25) : a pale yellow solid. mp 178 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.86 (t, *J* = 6.0 Hz, 2H), 3.40 (t, *J* = 6.0 Hz, 2H), 4.29 (s, 2H), 7.10-7.16 (m, 4H), 8.08-8.12 (m, 2H), 8.40-8.43 (m, 2H). ^{13}C-NMR (DMSO-d_6) δ: 27.8, 43.4, 46.9, 124.6, 126.1, 126.3, 126.6, 128.6, 128.9, 131.2, 132.8, 141.7, 149.9. IR (KBr) ν: 3113, 2868, 1529, 1351, 1311, 1163, 1093 cm^{-1}. MS (ESI) *m/z*: 319 $(M + H)^+$. HRMS (ESI) Calcd for $C_{15}H_{15}N_2O_4S$: 319.0753. Found: 319.0753. Anal. Calcd for

$C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; S, 10.07. Found: C, 56.43; H, 4.50; N, 8.75; S, 9.84.

1,3-Dihydrofuro[3,4-*c*]pyridine (26) : a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 5.11 (s, 2H), 5.16 (s, 2H), 7.22 (d, *J* = 5.1 Hz, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.55 (s, 1H). MS (CI) *m/z*: 122 $(M + H)^+$. HRMS (CI) Calcd for C_7H_8NO: 122.0606. Found: 122.0606.

1,3-Dihydroisobenzofuran (27) : a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 5.12 (s, 4H), 7.22-7.28 (m, 4H). MS (CI) *m/z*: 121 $(M + H)^+$. HRMS (CI) Calcd for C_8H_9O: 121.0653. Found: 121.0655.

Isochromane (28) : a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (t, *J* = 6.0 Hz, 2H), 3.98 (t, *J* = 6.0 Hz, 2H), 4.78 (s, 2H), 6.93-7.03 (m, 1H), 7.09-7.18 (m, 3H). MS (CI) *m/z*: 135 $(M + H)^+$. HRMS (CI) Calcd for $C_9H_{11}O$: 135.0810. Found: 135.0808.

***cis*-3,4-Diphenyltetrahydrofuran (29)** : a colorless solid. mp 86 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.70-3.76 (m, 2H), 4.22-4.34 (m, 4H), 6.84-6.88 (m, 4H), 7.08-7.12 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ: 50.7, 72.6, 126.4, 127.9, 128.6, 138.6. IR (KBr) ν: 3026, 2934, 2878, 1496, 1451, 1163, 1058 cm^{-1}. MS (CI) *m/z*: 225 $(M + H)^+$. HRMS (CI) Calcd for $C_{16}H_{17}O$: 225.1279. Found: 225.1274. Anal. Calcd for $C_{16}H_{16}O \cdot 2/3H_2O$: C, 81.32; H, 7.39. Found: C, 81.37; H, 7.36.

3-Phenyltetrahydrofuran (30) : a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.97-2.06 (m, 1H), 2.32-2.41 (m, 1H), 3.40 (quint, *J* = 7.8 Hz, 1H), 3.73 (t, *J* = 7.8 Hz, 1H), 3.92 (q, *J* = 7.8 Hz, 1H), 4.07 (td, *J* = 8.5, 4.2 Hz, 1H), 4.14 (t, *J* = 7.8 Hz, 1H), 7.20-7.34 (m, 5H). MS (CI) *m/z*: 149 $(M + H)^+$.

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