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Selective Access to *N*-aryl or *N*-alkyl Derivatives of Isoindolo[2,1-b][2,4]benzo(or thieno)diazepines

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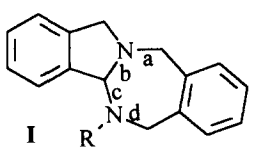
Abstract: *N*-alkyl isoindolo[2,1-b][2,4]benzodiazepines **15c** were synthesized *via* an intramolecular *N*-acyliminium ion-amide reaction, *N*-aryl derivatives **8c** were obtained from an intramolecular acylation of amino acids **6c** in acetic anhydride. A generalization of these methodologies is given in the synthesis of the thiophenic analogues **15d** and **8d**. © 1998 Elsevier Science Ltd. All rights reserved.

Benzodiazepines are widely expanded in the literature since many of them have potent biological activities. Nevertheless [2,4]benzodiazepines are little explored and only few reports exist about [2,4]benzodiazepines connected at the [b] position to an isoindole ring as in structure **I**.



I

One[1,2] synthesis involved the condensation of 2-formylbenzoic acid with *o*-di(aminomethyl)benzene. Another[3] consisted of an intramolecular aza-Wittig reaction of the 2-(phthalimidomethyl)azidomethylbenzene and recently[4] the condensation of an amidine with a difunctional electrophile gave isoindolo[2,1-b][2,4]benzodiazepine **I** derivatives. In connection with our studies on the synthesis of heterocyclic structures[5-8] with pharmacological potential we wish to report herein two general approaches to the heterocyclic system **I** *via* *N*-acyliminium intermediates. It has been demonstrated[9,10] that an *N*-acyliminium ion could react with a tertiary amine to give a quaternary aminoalkylamide salt or a biscarbamate when reacted with a carbamate. Based on this work, we tried a reaction with acetamide and we obtained the expected bisamides **2a,b** from the known hydroxylactams **1a,b**[7] in a quantitative yield. Unfortunately when they were treated with phosphorus oxychloride[11] (Scheme 1) or formaldehyde and formic acid[12] no cyclized product was observed, but complete degradation occurred.

Thus, we investigated another route (route A) for the synthesis of compounds related to **I**. During the course of our work we have shown[13] that dibenzo[a,f]indolizinedione did not give [2,4]benzodiazepine *via* a Schmidt reaction of the ketone function or a Beckmann rearrangement of the corresponding oxime. On the other

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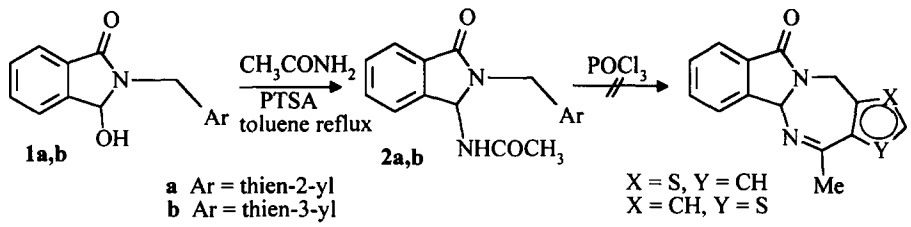
hand, since we reported[14] an easy synthesis of 3-amino-*N*-aryl(or arylmethyl)phthalimides we wished to extend this methodology to form the requisite amino derivatives **6c,d** as precursors of [2,4]benzo(or thieno)diazepines **8c,d** (Scheme 2).



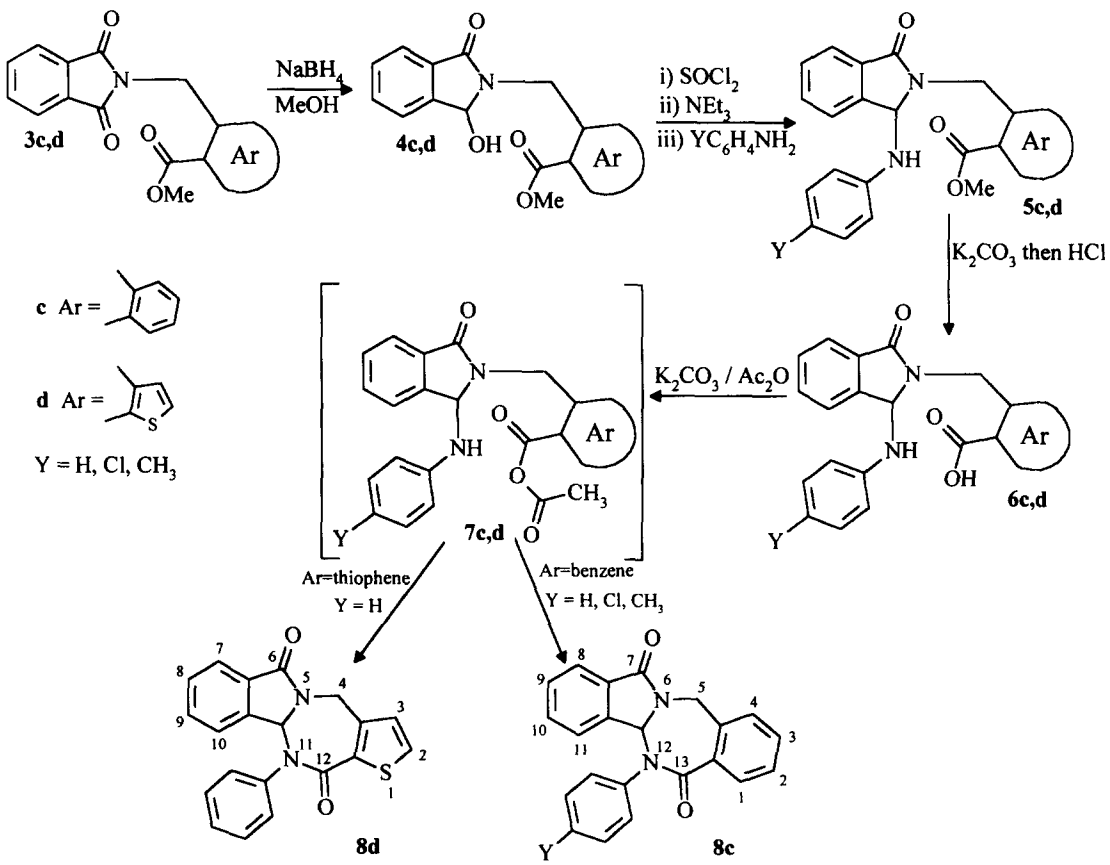
Scheme 1

The starting arylmethylphthalimide **3c** was prepared *via* the alkylation of phthalimide with methyl *o*-bromomethylbenzoate in dimethylformamide using potassium carbonate as the base. The alkylated phthalimide **3c** was selectively reduced with sodium borohydride to give the hydroxyisoindolone **4c** in excellent yield (96%). We recently reported that a hydroxylactam led to the amino derivative when treated successively with thionyl chloride and ammonia *via* a chlorolactam and the corresponding *N*-acyliminium ion[14]. Although ethyl glycinate did not react with the chlorolactam in these conditions, we tested arylamines (aniline, *p*-toluidine, *p*-chloroaniline) which provided the expected amino derivatives **5c** (Y = H, Me, Cl) in excellent yields (more than 90%). These conditions are better than those (PTSA + amide) used above for **2a,b**. Saponification of these esters with potassium carbonate gave the corresponding carboxylic acid derivatives **6c** in good yields (74-81%). Intramolecular condensation of the secondary amine function with either the ester or the acid function under classical conditions did not give the cyclized bisamides **8c** (Y = H, Me, Cl). Since these functions did not react we prepared a better leaving group being -O-COMe in the mixed anhydride intermediate **7c**. Thus, when acids **6c** (Y = H, Me, Cl) were treated with potassium carbonate in refluxing acetic anhydride, they directly gave the *N*-aryl[2,4]benzodiazepines **8c** (Y = H, Me, Cl) in satisfactory yields of 68 to 72%. No trace of the possible *N*-acetylated compound was detected in the reaction mixture. On the other hand the use of a more basic amine such as alkylamine (methyl or butylamine) in place of arylamine did not give the amino esters similar to **5c**. Nevertheless, ammonia gave the expected amino ester but the corresponding amino acid (similar to **6c**) could not be isolated as a pure product in a sufficient yield to follow this way so that a better route B (Scheme 3) was investigated.

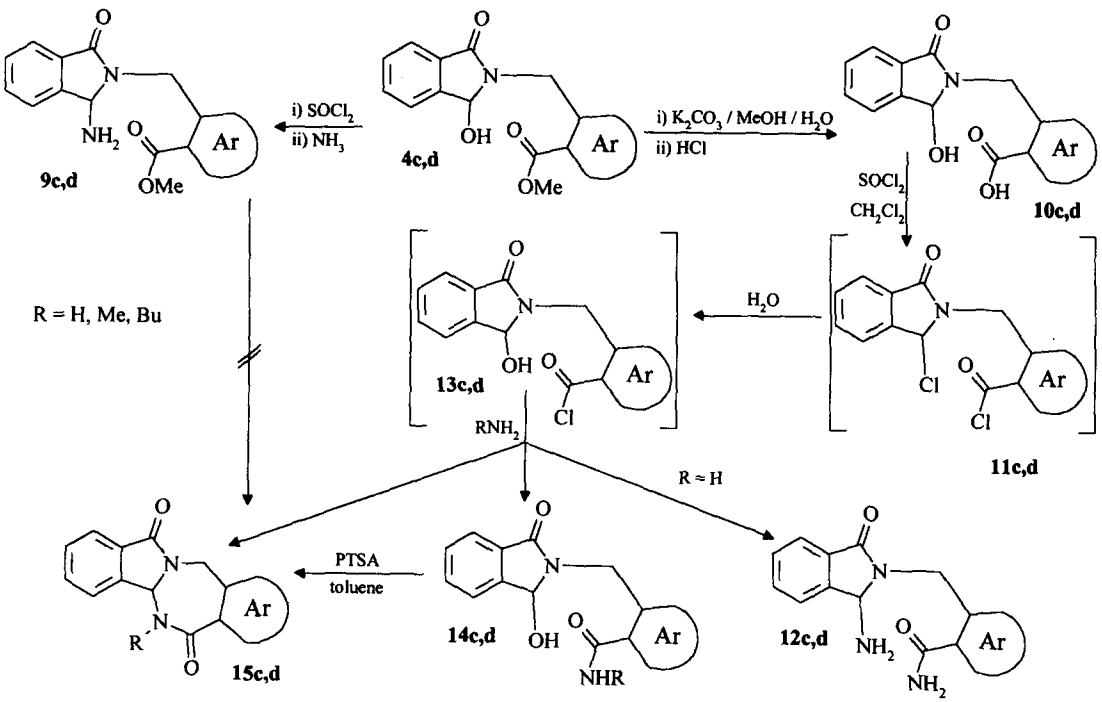
A generalization of pathway A started from the thiophene derivative **3d**[15]. Reduction of this latter species followed by reaction with aniline furnished the amino ester **5d** (Y = H, 96%). Saponification of **5d** (89%) followed by a treatment with acetic anhydride produced the isoindolo[2,1-b]thieno[2,3-e][2,4]diazepine **8d** (76%).

Our second approach (route B) to synthesize [2,4]benzodiazepines is reported in Scheme 3. Amination of **4c,d** ($SOCl_2$, NH_3) was effected in good yields (77-82%), but unfortunately cyclization of the resulting amino esters **9c,d** did not occur under various conditions. Then, the amidation reaction leading to compounds **2a,b** was investigated in an intramolecular process with the aromatic ring bearing the amide function as in **14c,d**. Since reaction of ammonia or an amine (aniline, butylamine) with the ester **4c** did not give the amides **14c**[16] we attempted a one pot cyclization by treatment of hydroxylactam-acid **10c** obtained by saponification with

potassium carbonate of the corresponding ester **4c** in excellent yield (90%) with successively thionyl chloride, water and ammonia or an amine. In our conditions the acyl chloride function was less reactive towards water than the chlorolactam and could give the intermediate **13c**. In this manner four compounds were isolated. The recovered starting acid **10c** (13%) was first separated from the mixture by a selective extraction (NaOH). Afterwards the aminolactam-amide **12c** (15%) was extracted using an acidic solution (HCl). The resulting mixture **15c** and **14c** was treated with *p*-toluenesulfonic acid (in a similar manner as described above for **2a,b**) to give the expected [2,4]benzodiazepine **15c** (R = H) in a 60% yield calculated from **10c**. As mentioned above, in the acidic medium an *N*-acyliminium ion was generated which reacted with the amide function fixed on the aromatic ring to give the cyclized product **15c** (R = H). Similar reactions conducted with amines as butylamine or methylamine gave the corresponding *N*-alkylated [2,4]benzodiazepines **15c** (R = Me, Bu) without formation of **12** but unfortunately aniline or other aromatic amines (*p*-toluidine, *p*-chloroaniline) gave a poor quantity of the expected *N*-aryl[2,4]benzodiazepines **8c** (Y = H, Me, Cl) with other products, not separable and not identifiable. This result could be due to the formation of the arylamine-amide similar to **12** as the major product and we have to consider the facile reaction of the arylamine with the *N*-acyliminium ion generated in situ as in route A.



Scheme 2 (route A)



Scheme 3 (route B)

Nevertheless, this method has been successfully extended to the preparation of heterocyclic ring fused [2,4]diazepines by employing the heterocyclic hydroxylactam-acid **10d** in place of the benzene derivative **10c**, as demonstrated by the synthesis of **15d** (R = H, Bu, Me) from the thiophene hydroxylactam-ester **4d**.

In conclusion, we have presented an efficient synthesis of isoindolo[2,1-b][2,4]benzodiazepines. Selective access to *N*-aryl derivatives consisted of an intramolecular acylation of an amino acid as the key step, whereas selective access to *N*-alkyl derivatives consisted of an intramolecular *N*-acyliminium ion-amide reaction. The generalization of these methodologies have been demonstrated using thiophene as aromatic ring leading to the new thieno[2',3':5,6][1,3]diazepino[2,1-a]isoindole system (diazepine analog of **I**).

Experimental

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuterochloroform solution and chemical shifts (δ) are expressed in ppm relative to internal TMS. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M^{t}. S^{t}. Aignan, France. Compounds **1a,b**[7], **3d**[15], **15c** (R = H, Me, Bu)[16] were synthesized according to our previous work.

Synthesis of bisamides 2a,b: general procedure.

Hydroxylactams **1a,b** (2.45 g, 10 mmol), a catalytic amount of *p*-toluenesulfonic acid, acetamide (0.59 g, 10 mmol) and toluene were heated to reflux for 2 days. The solution was cooled, washed with a sodium hydrogen carbonate solution, dried and concentrated under reduced pressure. The residue was recrystallized from ethanol.

2,3-Dihydro-3-(N-acetamido)-2-(thien-2-ylmethyl)-1*H*-isoindol-1-one (2a).

This compound was prepared from **1a**. Yield 100%; mp: 199°C; IR: 3288 (NH), 1678 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.06 (s, 3H, CH_3), 4.56 (d, J = 15 Hz, 1H, NCH_2), 4.79 (d, J = 15 Hz, 1H, NCH_2), 6.21 (d, J = 10 Hz, 1H, NH), 6.54 (d, J = 10 Hz, 1H, CH), 6.89 (dd, J = 5 and 4 Hz, 1H, $H_{thiophene}$), 7.08 (d, J = 4 Hz, 1H, $H_{thiophene}$), 7.16 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.36-7.58 (m, 3H, H_{arom}), 7.66 (d, J = 7 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.86; H, 4.85; N, 9.64.

2,3-Dihydro-3-(N-acetamido)-2-(thien-3-ylmethyl)-1*H*-isoindol-1-one (2b).

This compound was prepared from **1b**. Yield 100%; mp 189°C; IR: 3249 (NH), 1671 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3), 4.31 (d, J = 15 Hz, 1H, NCH_2), 4.61 (d, J = 15 Hz, 1H, NCH_2), 6.33 (d, J = 10 Hz, 1H, NH), 6.48 (d, J = 10 Hz, 1H, CH), 7.00-7.70 (m, 7H, $4H_{arom}+3H_{thiophene}$).

2-(2-Methoxycarbonylbenzyl)phthalimide (3c).

A mixture of phthalimide (33 g, 224 mmol), methyl 2-bromomethylbenzoate (34.6 g, 151 mmol), anhydrous potassium carbonate (15.5 g, 112 mmol) and dry dimethylformamide (100 ml) was heated at reflux with stirring for 4 hours. After cooling, the mixture was poured into water, then the precipitate was washed with water and dried. The solid was triturated with dichloromethane and the insoluble excess of phthalimide was removed by filtration. The solution was evaporated and the ester **3c** was recrystallized from ethanol. Yield 65%; mp: 150°C; IR: 1715 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 7.15 (d, J = 8 Hz, 1H, H_{arom}), 7.22-7.46 (m, 2H, H_{arom}), 7.67-7.79 (m, 2H, H_{arom}), 7.80-7.92 (m, 2H, H_{arom}), 7.97 (d, J = 8 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.81; H, 4.49; N, 4.78.

2,3-Dihydro-3-hydroxy-2-(2-methoxycarbonylbenzyl)-1*H*-isoindol-1-one (4c).

To a mixture of **3c** (4 mmol) in dry methanol (40 ml) at 10-20°C was added sodium borohydride (0.9 g, 24 mmol) by portions. To this mixture were added 5 drops of ethanolic hydrochloric acid solution (prepared from 9 drops of concentrated hydrochloric acid in 15 ml of ethanol) at regular intervals (10 min). The reaction was monitored by TLC (dichloromethane-acetone 9/1). When starting product had disappeared (30 min), the excess of sodium borohydride was decomposed by addition of cold water (15 ml) and 10% hydrochloric acid. Sodium hydrogen carbonate was added and the solvent was evaporated. The residue was triturated with water and the hydroxylactam **4c** was separated by filtration, washed with water, dried and recrystallized from ethanol. Yield 96%; mp: 171°C; IR: 3327 (OH), 1716 (C=0), 1674 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.96 (s, 3H, CH_3), 4.87 (d, J = 15 Hz, 1H, CH_2), 5.16 (d, J = 15 Hz, 1H, CH_2), 5.18 (d, J = 6 Hz, 1H, OH), 5.75 (d, J = 6 Hz, 1H, CH), 7.30 (t, J = 8 Hz, 1H, H_{arom}), 7.40-7.57 (m, 4H, H_{arom}) , 7.60 (d, J = 8 Hz, 1H, H_{arom}), 7.78 (d, J = 6 Hz, 1H, H_{arom}), 7.86 (d, J = 8 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.32; H, 5.16; N, 4.64.

2,3-Dihydro-3-hydroxy-2-[(2-(methoxycarbonyl)thien-3-yl)methyl]-1*H*-isoindol-1-one (4d).

This compound was prepared with the same procedure, starting from phthalimide **3d**. Yield 94%; mp: 178°C; IR: 3388 (OH), 1680 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3), 4.94 (d, J = 14 Hz, 1H, CH_2), 4.95 (d, J = 6 Hz, 1H, OH), 5.18 (d, J = 14 Hz, 1H, CH_2), 5.74 (d, J = 6 Hz, 1H, CH), 7.23 (d, J = 5 Hz, 1H, $H_{thiophene}$),

7.44 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.43-7.58 (m, 3H, H_{arom}), 7.78 (d, J = 7 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.40; H, 4.32; N, 4.62. Found: C, 58.98; H, 4.18; N, 4.53.

Preparation of aminolactams 5c,d (Y = H, Me, Cl): general procedure.

Hydroxylactams **4c,d** (10 mmol) and thionyl chloride (1 ml, 15 mmol) were stirred in dry dichloromethane for 30 min. Triethylamine (2 ml) was added and the solution was stirred for 5 min. Aromatic amine (10 mmol) was added and stirring was continued for 1 hour. The solution was washed with water, dried, then concentrated under reduced pressure. The solid was recrystallized from ethanol.

2,3-Dihydro-3-anilino-2-(2-methoxycarbonylbenzyl)-1*H*-isoindol-1-one (5c Y = H).

This compound was prepared from **4c** and aniline. Yield 98%; mp 120°C; IR: 3289 (NH), 1725 (C=0), 1684 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.51 (s, 1H, NH), 3.78 (s, 3H, CH_3), 4.92 (d, J = 16 Hz, 1H, NCH_2), 5.24 (d, J = 16 Hz, 1H, NCH_2), 5.86 (s, 1H, CH), 6.32 (d, J = 8 Hz, 2H, H_{Ph}), 6.69 (t, J = 7 Hz, 1H, H_{Ph}), 6.99 (t, J = 8 Hz, 2H, H_{Ph}), 7.25-7.34 (m, 1H, H_{arom}), 7.35-7.44 (m, 2H, H_{arom}), 7.47-7.59 (m, 3H, H_{arom}), 7.86 (d, J = 7 Hz, 1H, H_{arom}), 7.87-7.97 (m, 1H, H_{arom}). Anal. Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.02; H, 5.47; N, 7.59.

2,3-Dihydro-3-(4-methylanilino)-2-(2-methoxycarbonylbenzyl)-1*H*-isoindol-1-one (5c Y = Me).

This compound was prepared from **4c** and *p*-toluidine. Yield 96%; mp 210°C; IR: 3290 (NH), 1724 (C=0), 1683 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 3.80 (m, 1H, NH), 4.90 (d, J = 16 Hz, 1H, NCH_2), 5.23 (d, J = 16 Hz, 1H, NCH_2), 5.81 (s, 1H, CH), 6.26 (d, J = 8 Hz, 2H, H_{tolyl}), 6.79 (d, J = 8 Hz, 2H, H_{tolyl}), 7.24-7.33 (m, 1H, H_{arom}), 7.35-7.44 (m, 2H, H_{arom}), 7.49-7.57 (m, 3H, H_{arom}), 7.82-7.94 (m, 2H, H_{arom}). Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 7.25; N, 8.09. Found: C, 74.22; H, 7.20; N, 8.02.

3-(4-Chloro)anilino)-2,3-dihydro-2-(2-methoxycarbonylbenzyl)-1*H*-isoindol-1-one (5c Y = Cl).

This compound was prepared from **4c** and *p*-chloroaniline. Yield 95%; mp 193°C; IR: 3290 (NH), 1725 (C=0), 1685 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H, CH_3), 4.88 (d, J = 16 Hz, 1H, NCH_2), 5.16 (d, J = 16 Hz, 1H, NCH_2), 5.80 (s, 1H, CH), 6.21 (d, J = 8 Hz, 2H, $H_{chlorophenyl}$), 6.91 (d, J = 8 Hz, 2H, $H_{chlorophenyl}$), 7.25-7.33 (m, 1H, H_{arom}), 7.33-7.43 (m, 2H, H_{arom}), 7.43-7.58 (m, 3H, H_{arom}), 7.81-7.92 (m, 2H, H_{arom}). Anal. Calcd. for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89. Found: C, 67.74; H, 4.65; N, 6.82.

2,3-Dihydro-3-anilino-2-[(2-(methoxycarbonyl)thien-3-yl)methyl]-1*H*-isoindol-1-one (5d Y = H).

This compound was prepared from **4d** and aniline. Yield 96%; mp 177°C; IR: 3303 (NH), 1709 (C=0), 1678 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.77 (s, 3H, CH_3), 4.73 (d, J = 9 Hz, 1H, NH), 4.95 (d, J = 16 Hz, 1H, NCH_2), 5.06 (d, J = 16 Hz, 1H, NCH_2), 5.81 (d, J = 9 Hz, 1H, CH), 6.36 (d, J = 7 Hz, 2H, H_{Ph}), 6.69 (t, J = 7 Hz, 1H, H_{Ph}), 6.90-7.10 (m, 3H, $2H_{Ph}$+$H_{thiophene}$), 7.35 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.40-7.55 (m, 3H, H_{arom}), 7.80-7.90 (m, 1H, H_{arom}).

Formation of acids 6c,d (Y = H, Me, Cl): general procedure.

Acids **5c,d** (5 mmol), potassium carbonate (1.4 g, 10 mmol), water (10 ml) and methanol (40 ml) were stirred under reflux for 2 hours. The solution was concentrated under reduced pressure. Water and dichloromethane were added and the organic layer was discarded. The aqueous layer was washed with dichloromethane and acidified with hydrochloric acid (10%) to pH = 2. Compound **6** was extracted with dichloromethane several times. After removal of the solvent, the residue was recrystallized from acetone to give pure **6**.

2,3-Dihydro-3-anilino-2-(2-carboxybenzyl)-1*H*-isoindol-1-one (6c Y = H).

Yield 76%; mp 224°C; IR: 3455 (OH), 3289 (NH), 1700 (C=0), 1683 (C=0) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.37 (s, 1H, OH), 4.78 (d, J = 18 Hz, 1H, NCH_2), 5.09 (d, J = 18 Hz, 1H, NCH_2), 6.15 (d, J = 9 Hz, 1H, CH), 6.43 (d, J = 8 Hz, 2H, H_{Ph}), 6.46-6.61 (m, 2H, NH+H_{Ph}), 6.93 (t, J = 8 Hz, 2H, H_{Ph}), 7.18 (d, J = 8 Hz, 1H, H_{arom}), 7.34 (t, J = 8 Hz, 1H, H_{arom}), 7.40-7.72 (m, 4H, H_{arom}), 7.80 (d, J = 7 Hz, 1H, H_{arom}), 7.89 (d, J = 8 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.59; H, 5.00; N, 7.87.

2,3-Dihydro-3-(4-methylanilino)-2-(2-carboxybenzyl)-1*H*-isoindol-1-one (6c Y = Me).

Yield 81%; mp 236°C; IR: 3456 (OH), 3294 (NH), 1697 (C=0), 1682 (C=0) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.08 (s, 3H, CH_3), 3.30 (s, 1H, OH), 4.77 (d, J = 18 Hz, 1H, NCH_2), 5.08 (d, J = 18 Hz, 1H, NCH_2), 6.08 (d, J = 9 Hz, 1H, CH), 6.33 (d, J = 8 Hz, 2H, H_{tolyl}), 6.39 (d, J = 8 Hz, 1H, NH), 6.74 (d, J = 8 Hz, 2H, H_{tolyl}), 7.17 (d, J = 7 Hz, 1H, H_{arom}), 6.79 (t, J = 7 Hz, 1H, H_{arom}), 7.41-7.71 (m, 4H, H_{arom}), 7.79 (d, J = 7 Hz, 1H, H_{arom}), 7.89 (d, J = 8 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.02; H, 5.45; N, 7.42.

3-(4-Chloroanilino)-2,3-dihydro-2-(2-carboxybenzyl)-1*H*-isoindol-1-one (6c Y = Cl).

Yield 74%; mp 224°C; IR: 3456 (OH), 3296 (NH), 1696 (C=0), 1681 (C=0) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.35 (s, 1H, OH), 4.79 (d, J = 18 Hz, 1H, NCH_2), 5.09 (d, J = 18 Hz, 1H, NCH_2), 6.18 (d, J = 9 Hz, 1H, CH), 6.45 (d, J = 8 Hz, 2H, $H_{chlorophenyl}$), 6.75 (d, J = 9 Hz, 1H, NH), 6.96 (d, J = 8 Hz, 2H, $H_{chlorophenyl}$), 7.33 (t, J = 8 Hz, 1H, H_{arom}), 7.47 (t, J = 8 Hz, 1H, H_{arom}), 7.52-7.72 (m, 3H, H_{arom}), 7.81 (d, J = 6 Hz, 1H, H_{arom}), 7.88 (d, J = 8 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{22}H_{17}ClN_2O_3$: C, 67.26; H, 4.36; N, 7.13. Found: C, 67.03; H, 4.29; N, 7.16.

2,3-Dihydro-3-anilino-2-[(2-(carboxy)thien-3-yl)methyl]-1*H*-isoindol-1-one (6d Y = H).

Yield 89%; mp: 213°C; IR: 3476 (OH), 3303 (NH), 1663 (C=0), 1694 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.82 (d, J = 17 Hz, 1H, NCH_2), 4.98 (d, J = 17 Hz, 1H, NCH_2), 6.17 (s, 1H, OH), 6.40-6.65 (m, 4H, H_{arom}+$H_{thiophene}$), 6.85-7.05 (m, 3H, H_{arom}+NCH), 7.45-7.70 (m, 4H, H_{arom}+$H_{thiophene}$), 7.79 (d, J = 6 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69. Found: C, 65.82; H, 4.43; N, 7.72.

Preparation of amino-esters 9c,d : general procedure.

A solution of ammonia in dichloromethane was prepared by extraction of 400 ml of concentrated aqueous ammonia solution with 400 ml of dichloromethane. The aqueous layer was kept in the separatory funnel for later use and the solution of ammonia in dichloromethane was dried over magnesium sulfate and filtered.

Hydroxylactams **4c,d** (10 mmol) and thionyl chloride (1.5 ml, 21 mmol) were stirred in dry dichloromethane until all solid had disappeared, then the reaction was continued for 30 min. This solution was poured into the previous solution of ammonia in dichloromethane and the mixture was stirred for 10 min. The solution was transferred into the separatory funnel containing the previous aqueous ammonia, then the mixture was made more basic with addition of sodium hydroxide solution. The organic layer was decanted then extracted twice with 5% HCl solution. The aqueous solutions were combined, washed with dichloromethane, made basic with sodium hydroxide solution then extracted twice with dichloromethane. The combination of organic layers was dried and evaporated. The solid was recrystallized from ethanol.

3-Amino-2,3-dihydro-2-[2-(methoxycarbonyl)benzyl]-1*H*-isoindol-1-one (9c).

Yield 77%; mp 142°C; IR: 3387 (NH), 1715 (C=O), 1682 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.98 (s, 2H, NH_2), 3.93 (s, 3H, CH_3), 5.07 (d, J = 15 Hz, NCH_2), 5.18 (s, 1H, CH), 5.21 (d, J = 15 Hz, 2H, NCH_2), 7.24-7.63 (m, 6H, H_{arom}), 7.79 (d, J = 8 Hz, 1H, H_{arom}), 7.89 (d, J = 8 Hz, 1H, H_{arom}).

3-Amino-2,3-dihydro-2-[(2-(methoxycarbonyl)thien-3-yl)methyl]-1*H*-isoindol-1-one (9d).

Yield 82%; mp 125°C; IR: 3399 (NH), 1698 (C=O), 1682 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H, CH_3), 5.05 (s, 1H, CH), 5.08 (s, 2H, NCH_2), 7.15 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.30-7.60 (m, 4H, $3H_{arom}+H_{thiophene}$), 7.72 (d, J = 7 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 60.05; H, 4.60; N, 9.21.

Formation of acids 10c,d : general procedure

In a similar manner as described for the synthesis of **6c,d**, esters **4c,d** afforded acids **10c,d**.

2,3-Dihydro-3-hydroxy-2-(2-carboxybenzyl)-1*H*-isoindol-1-one (10c).

Yield 90%; mp 175°C; IR: 3342 (OH), 3210 (OH), 1685 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.38 (s, 1H, OH), 4.93 (d, J = 17 Hz, 1H, NCH_2), 5.07 (d, J = 17 Hz, 1H, NCH_2), 5.79 (s, 1H, CH), 7.16 (d, J = 8 Hz, 1H, H_{arom}), 7.35 (t, J = 7 Hz, 1H, H_{arom}), 7.45 (d, J = 8 Hz, 1H, H_{arom}), 7.49-7.77 (m, 4H, H_{arom}), 7.90 (d, J = 8 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.36; H, 4.38; N, 9.96.

2,3-Dihydro-3-hydroxy-2-[(2-(carboxy)thien-3-yl)methyl]-1*H*-isoindol-1-one (10d).

Yield 92%; mp 175°C; IR: 3422 (OH), 3210 (OH), 1671 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.90 (d, J = 17 Hz, 1H, NCH_2), 5.00 (d, J = 17 Hz, 1H, NCH_2), 5.80 (s, 1H, CH), 6.70 (s, 1H, OH), 6.91 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.45-7.80 (m, 5H, $4H_{arom}+H_{thiophene}$).

Preparation of diazepines 8c,d (Y = H, Me, Cl) from acids 6c,d (Y = H, Me, Cl): general procedure.

Acid **6** (3 mmol) and potassium carbonate (0.62 g, 4.5 mmol), were stirred in acetic anhydride (20 ml) for 30 min at room temperature, then for 2 days at reflux. The solvent was evaporated under high vacuum. The solid was chromatographed on silica gel, eluting with dichloromethane. Diazepines **8** were recrystallized from ethanol.

5,11$_b$-Dihydro-12-phenylisoindolo[2,1-b][2,4]benzodiazepine-7,13-dione (8c Y = H).

Yield 68%; mp: 233°C; IR: 1683 (C=O), 1617 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.69 (d, J = 14 Hz, 1H, H_5), 5.21 (d, J = 14 Hz, 1H, H_5), 6.16 (s, 1H, H_{11b}), 6.92-7.06 (m, 3H, H_{arom}), 7.06-7.35 (m, 5H, H_{arom}), 7.35-7.47 (m, 1H, H_{arom}), 7.47-7.59 (m, 2H, H_{arom}), 7.70 (d, J = 7 Hz, 1H, H_{arom}), 7.89-8.01 (m, 1H, H_{arom}); ^{13}C NMR: δ 44.2 (CH_2), 71.5 (CH), 123.2 (CH), 124.6 (CH), 127.6 (CH), 128.0 (2CH), 128.6 (2CH), 128.9 (CH), 129.0 (CH), 129.3 (CH), 130.0 (CH), 131.2 (CH), 131.8 (C), 132.1 (CH), 133.1 (C), 135.5 (C), 137.6 (C), 137.9 (C), 165.2 (CO), 170.2 (CO). Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.51; H, 4.70; N, 8.03.

5,11$_b$-Dihydro-12-(4-methylphenyl)-isoindolo[2,1-b][2,4]benzodiazepine-7,13-dione (8c Y = Me).

Yield 72%; mp: 228°C; IR: 1683 (C=O), 1616 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 4.71 (d, J = 14 Hz, 1H, H_5), 5.23 (d, J = 14 Hz, 1H, H_5), 6.16 (s, 1H, H_{11b}), 6.87 (d, J = 9 Hz, 2H, H_{tolyl}), 6.96 (d, J = 9 Hz, 2H, H_{tolyl}), 7.06 (d, J = 7 Hz, 1H, H_{arom}), 7.19-7.47 (m, 3H, H_{arom}), 7.49-7.59 (m, 2H, H_{arom}), 7.72 (d, J = 7 Hz, 1H, H_{arom}), 7.91-8.01 (m, 1H, H_{arom}); ^{13}C NMR: δ 20.9 (CH_3), 44.1 (CH_2), 71.7 (CH), 123.4 (CH), 124.7 (CH), 127.8 (2CH), 129.0 (CH), 129.2 (CH), 129.4 (2CH+CH), 130.1 (CH), 131.4 (CH), 131.9 (C), 132.3 (CH), 133.1 (C), 134.9 (C), 135.6 (C), 137.6 (C), 138.0 (C), 165.6 (CO), 170.7 (CO). Anal. Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.65; H, 5.02; N, 7.65.

12-(4-Chlorophenyl)-5,11$_b$-dihydroisoindolo[2,1-b][2,4]benzodiazepine-7,13-dione (8c Y = Cl).

Yield 71%; mp: >270°C; IR: 1687 (C=O), 1661 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.65 (d, J = 15 Hz, 1H, H_5), 5.20 (d, J = 15 Hz, 1H, H_5), 6.14 (s, 1H, H_{11b}), 6.92 (d, J = 9 Hz, 2H, $H_{chlorophenyl}$), 7.00 (d, J = 7 Hz, 1H, H_{arom}),

7.11 (d, J = 9 Hz, 2H, $H_{chlorophenyl}$), 7.20-7.45 (m, 3H, H_{arom}), 7.49-7.59 (m, 2H, H_{arom}), 7.71 (d, J = 7 Hz, 1H, H_{arom}), 7.87-7.98 (m, 1H, H_{arom}); ^{13}C NMR: δ 44.3 (CH_2), 71.6 (CH), 123.7 (CH), 124.6 (CH), 129.0 (2CH), 129.2 (CH), 129.3 (CH), 129.4 (2CH), 129.8 (CH), 130.2 (CH), 131.7 (CH), 132.0 (C), 132.5 (CH), 133.4 (C), 133.5 (C), 135.5 (C), 136.3 (C), 137.8 (C), 165.3 (CO), 170.4 (CO). Anal. Calcd. for $C_{22}H_{15}ClN_2O_2$: C, 70.50; H, 4.03; N, 7.47. Found: C, 70.15; H, 3.91; N, 7.32.

4,10b-Dihydro-11-phenylthieno[2',3':5,6][1,3]diazepino[2,1-a]isoindole-6,12-dione (8d).

Yield 76%; mp: >270°C; IR: 1689 (C=O), 1652 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.75 (d, J = 15 Hz, 1H, H_4), 5.28 (d, J = 15 Hz, 1H, H_4), 6.49 (s, 1H, H_{10b}), 6.90-7.40 (m, 9H, H_{arom}+H_3), 7.61 (d, J = 5 Hz, 1H, H_2), 7.71 (d, J = 7 Hz, 1H, H_7); ^{13}C NMR: δ 41.2 (CH_2), 71.9 (CH), 123.1 (CH), 124.8 (CH), 127.6 (CH), 128.1 (2CH), 128.4 (2CH+CH), 129.3 (CH), 131.3 (CH), 131.6 (CH), 132.8 (C), 135.7 (C), 137.4 (C), 137.7 (C), 138.3 (C), 164.5 (CO), 166.2 (CO). Anal. Calcd. for $C_{20}H_{14}N_2O_2S$: C, 69.35; H, 4.07; N, 8.09. Found: C, 68.95; H, 3.65; N, 8.19.

Preparation of diazepines 15c,d from acids 10c,d.

The hydroxylactam-acid **10** (2.83 g, 10 mmol) and thionyl chloride (2 ml) were refluxed in dry dichloromethane during one hour. The solution was cooled, then water (approx. 5 ml) was added. After strong stirring for 10 min, concentrated ammonia (approx. 20 ml for **15c,d R = H**) or 30% aqueous methylamine (approx. 20 ml for **15c,d R = Me**) or pure butylamine (1 ml for **15c,d R = Bu**) was added. The mixture was stirred for 30 min then was poured in 10% aqueous sodium hydroxide. The organic layer was washed successively with 10% hydrochloric acid, saturated sodium hydrogen carbonate, water then was dried and concentrated. The residue was heated to reflux in toluene (Dean-Stark apparatus) with a catalytic amount of para-toluenesulfonic acid for two days. After cooling, the solution was washed with saturated sodium hydrogen carbonate then with water and was dried and concentrated. Recrystallization (chloroform for **15c,d R = H**, ethanol for the other diazepines) furnished the corresponding diazepines.

4,10$_b$-Dihydrothieno[2',3':5,6][1,3]diazepino[2,1-a]isoindole-6,12-dione (15d R = H).

Yield 57%; mp >270°C; IR: 3182 (NH), 1717 (C=0), 1651 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.99 (s, 2H, H_4), 6.00 (d, J = 5 Hz, 1H, H_{10b}), 6.52 (d, J = 5 Hz, 1H, NH), 7.05 (d, J = 5 Hz, 1H, H_3), 7.51-7.71 (m, 4H, $H_{2,8,9,10}$), 7.89 (d, J = 8 Hz, 1H, H_7); ^{13}C NMR: δ 43.2 (CH_2), 66.4 (CH), 122.5 (CH), 124.6 (CH), 129.3 (CH), 129.7 (CH), 131.7 (CH), 131.9 (C), 132.1 (CH), 134.8 (C), 138.4 (C), 140.8 (C), 164.4 (CO), 166.8 (CO). Anal. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.36; H, 3.74; N, 10.31.

4,10$_b$-Dihydro-11-methylthieno[2',3':5,6][1,3]diazepino[2,1-a]isoindole-6,12-dione (15d R = Me).

Yield 62%; mp 237°C; IR: 1694 (C=0), 1652 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H, CH_3), 4.50 (d, J = 15 Hz, 1H, H_4), 5.13 (d, J = 15 Hz, 1H, H_4), 6.21 (s, 1H, H_{10b}), 7.00 (d, J = 5 Hz, 1H, H_3), 7.42-7.68 (m, 4H, $H_{2,8,9,10}$), 7.88 (d, J = 6 Hz, 1H, H_7); ^{13}C NMR: δ 31.2 (CH_3), 41.2 (CH_2), 71.3 (CH), 124.1 (CH), 124.4 (CH), 128.4 (CH), 130.2 (CH), 131.1 (CH), 131.9 (CH), 133.5 (C), 135.9 (CH), 137.3 (C), 138.1 (C), 166.1 (CO), 166.2 (CO). Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.69; H, 4.40; N, 9.75.

11-Butyl-4,10$_b$-dihydrothieno[2',3':5,6][1,3]diazepino[2,1-a]isoindole-6,12-dione (15d R = Bu).

Yield 76%; mp 225°C; IR: 1689 (C=0), 1637 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.63 (t, J = 7 Hz, 3H, CH_3), 0.89-1.33 (m, 4H, CH_2-CH_2), 2.86-3.06 (m, 1H, NCH_2), 3.90-4.11 (m, 1H, NCH_2), 4.45 (d, J = 15 Hz, 1H, H_4), 5.00 (d, J = 15 Hz, 1H, H_4), 6.21 (s, 1H, H_{10b}), 6.99 (d, J = 5 Hz, 1H, H_3), 7.44-7.68 (m, 4H, $H_{2,8,9,10}$), 7.88 (d, J = 6 Hz, 1H, H_7); ^{13}C NMR: δ 13.3 (CH_3), 19.7 (CH_2), 31.5 (CH_2), 40.8 (CH_2), 43.4 (CH_2), 71.4 (CH), 123.9

(CH), 124.6 (CH), 128.2 (CH), 130.1 (CH), 131.0 (CH), 131.7 (CH), 133.7 (C), 136.3 (C), 137.1 (C), 137.8 (C), 165.5 (CO), 165.8 (CO). Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.63; H, 5.64; N, 8.85.

By-products 12c,d.

These compounds were extracted during the washing of the mixture of **12c-14c-15c R = H** (or **12d-14d-15d R = H**) with 10% hydrochloric acid solution. This solution was basified with 10% aqueous sodium hydroxide and **12c,d** were isolated by extraction with dichloromethane. Compounds **12c,d** were recrystallized from ethanol.

3-Amino-2,3-dihydro-2-[2-(carboxamido)benzyl]-1*H*-isoindol-1-one (12c).

This compound was isolated as a solid, mp 192°C; IR: 3365 (NH), 3207 (NH), 1686 (C=0), 1655 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.80 (d, J = 15 Hz, 1H, NCH_2), 5.08 (d, J = 15 Hz, 1H, NCH_2), 5.22 (s, 1H, CH), 5.84 (s, 2H, NH_2), 6.56 (s, 2H, NH_2), 7.22-7.62 (m, 7H, H_{arom}), 7.80 (d, J = 7 Hz, 1H, H_{arom}). Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.09; H, 5.41; N, 14.86.

3-Amino-2,3-dihydro-2-[(2-(carboxamido)thien-3-yl)methyl]-1*H*-isoindol-1-one (12d).

This compound was isolated as a solid, mp 164°C; IR: 3356 (NH), 3212 (NH), 1682 (C=0), 1661 (C=0) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.84 (s, 4H, $2NH_2$), 4.96 (d, J = 15 Hz, 1H, NCH_2), 5.15 (d, J = 15 Hz, 1H, NCH_2), 5.21 (s, 1H, CH), 7.18 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.32 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.39-7.61 (m, 3H, H_{arom}), 7.78 (d, J = 7 Hz, 1H, H_{arom}).

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