Scientific paper

Generation of a Structurally Diverse Library through Alkylation and Ring Closure Reactions Using 3-Dimethylamino-1-(thiophen-2-yl)propan-1-one Hydrochloride*

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Abstract

3-Dimethylamino-1-(thiophen-2-yl)propan-1-one hydrochloride (**2**), a ketonic Mannich base derived from 2-acetylthiophene, was used as a starting material in different types of alkylation and ring closure reactions with a view to generate a structurally diverse library of compounds. Compound **2** reacts with *S*-alkylated dithiocarbamic acid salts and aryl mercaptans to produce dithiocarbamates and thioethers, respectively. The dimethylamino moiety in compound **2** was exchanged with various aliphatic secondary and aromatic primary and secondary amines, whereas monocyclic *NH*-azoles such as pyrazole, imidazole, 1,2,4-triazole, and tetrazole were *N*-alkylated by compound **2**. Ketones, pyrrole and indoles have been the substrates subjected to *C*-alkylation reactions by compound **2**. Ring closure reactions of compound **2** with a suitable bifunctional nucleophile yielded pyrazolines, pyridines, 2,3-dihydro-1,5-1*H*-benzodiazepines, 2,3-dihydro-1,5-1*H*-benzothiazepine, pyrimido[1,2-*a*]benzimidazole and 4-hydroxypiperidine derivatives.

Keywords: Ketonic Mannich base, alkylation, amine exchange, cyclization.

1. Introduction

The chemistry of Mannich bases has drawn a great deal of attention owing to the high synthetic potential and the outstanding applications of this class of compounds.[2–4] Two of the most remarkable features of the chemistry of Mannich bases are undoubtedly their ability to alkylate miscellaneous substrates, and to participate in a large variety of ring closure reactions leading to numerous types of carbocyclic and heterocyclic compounds. Our steady interest in the chemistry of Mannich bases has been illustrated over the years by a series of papers exploring the ability of these compounds to produce an array of structurally diverse chemical entities, some of them being difficult to obtain otherwise.[5–9] The present study aims at creating a structurally diverse library of compounds starting from a ketonic Mannich base of 2-acetylthiophene, namely 3-dimethylamino-1-(thiophen-2-yl)propan-1-one hydrochloride (**2**), through the replacement of the easily leaving dimethylamino group by various nucleophiles. Also, several cyclizations of the aforementioned Mannich base with bifunctional nucleophiles to 5-, 6- and 7-membered nitrogen-containing heterocycles have been investigated.

2. Results and Discussion

The ketonic Mannich base hydrochloride **2**, a key intermediate in the synthesis of antidepressant duloxetine,[10] is conveniently obtained by the direct aminomethylation of 2-acetylthiophene (**1**) under the conditions of the classical Mannich reaction (substrate, paraformaldehyde, dimethylamine hydrochloride) with very good yields and in high purity. Therefore, no advantage can be expected from the use of a more expensive preformed aminomethylation reagent[11] or a microwave-assisted variant of the Mannich reaction.[12]

The replacement of the dialkylamino moiety in Mannich bases by nucleophiles can be performed either

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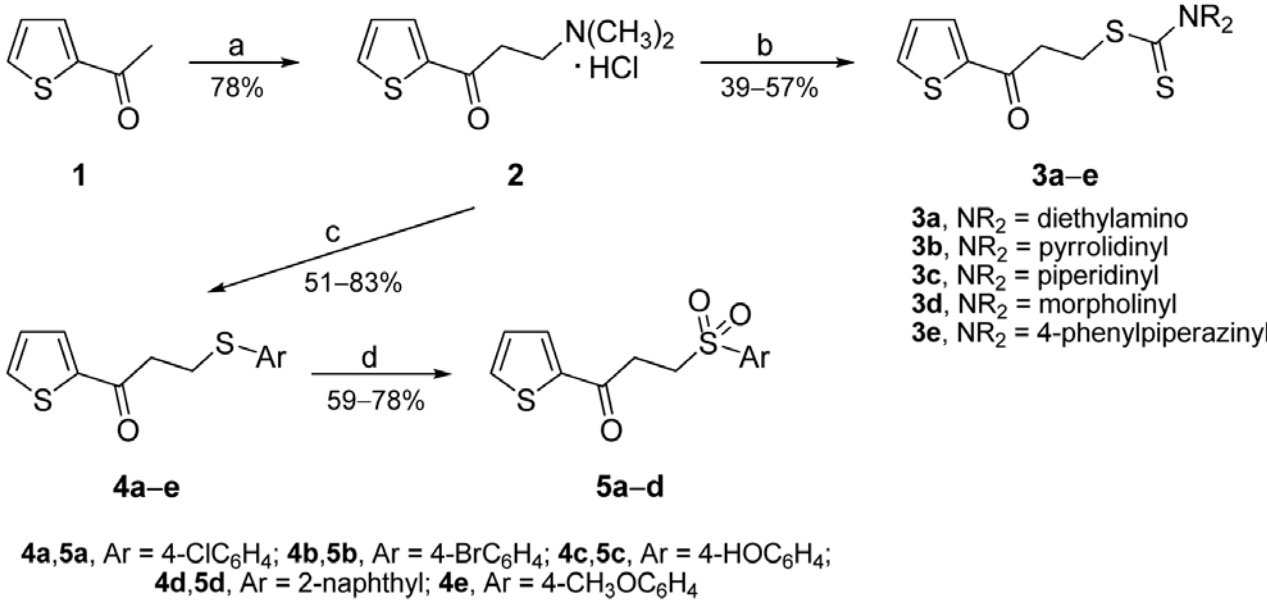
by using the free base in an aprotic medium (such as toluene), or by employing the corresponding hydrochloride (or the methiodide) in a protic solvent or a mixture of protic solvents.[13] The latter method has been preferred in this study, owing to the fact that Mannich base **2** is already available as a hydrochloride, and because this approach allows the use of more environmentally friendly solvents. Briefly, Mannich base **2** was reacted with the nucleophile either in water (in the case of water-soluble compounds) or in a mixture of ethanol–water (in the case of compounds that are not soluble in water). The advantage of this methodology is that the reaction mixture is homogeneous, as both reactants are dissolved in the medium at the beginning of the reaction. In addition, the less soluble reaction product separates at the end of the procedure and, in most cases, can be easily isolated by filtration. As far as the reaction mechanism is concerned, the exchange of the dialkylamino moiety in ketonic Mannich bases with arylamines has been shown to proceed by a substitution as well as by an elimination-addition mechanism,[14] whereas the replacement of the dialkylamino moiety with thiols takes place solely through an elimination-addition mechanism.[15]

The replacement of the amine moiety in Mannich base **2** by sulfur nucleophiles proceeds particularly well under these conditions. For example, the *S*-alkylation of several carbamodithioic acids (either as Na or K salts, or as ammonium salts with the secondary amine from which the acid was derived) takes place at room temperature to afford esters **3**, a class of compounds that have been shown to exhibit anticholinergic,[16,17] antihistaminic,[18,19] antifungal,[20,21] and antimicrobial[22,23] properties (Scheme 1). The yields of the isolated reaction products are very good, but substantial loss is incurred by recrystallization. The structures proposed for thioesters **3** are confirmed by their NMR spectra. It is worth mentioning that the protons in the methylene groups adjacent to the nitrogen atom are magnetically non-equivalent. A similar behavior has been recently reported for other carbamodithioates,[24] and can be tentatively explained by the existence of a rotation barrier around the thioxo-to-nitrogen bond arisen from the overlap between the nitrogen lone pair orbital and the thiocarbonyl π system.

The replacement of the dimethylamine group in Mannich base **2** by aryl mercaptans leads to thioethers **4** (Scheme 1). Owing to the limited solubility of aryl mercaptans in water, the reaction is best conducted in an ethanol–water mixture. Upon cooling of the reaction mixture, sulfides **4a**–**d** initially separate as heavy oils, which turn into solids upon further cooling in an ice bath and can be isolated by filtration. Thioether **4e** derived from 4-methoxybenzenethiol did not solidify even after having been kept overnight in a refrigerator, and was finally separated by the removal of the supernatant with a pipette. Compounds **4** were purified by crystallization from small volumes of ethanol, in which they are quite soluble. With the exception of thioether **4d**, which has been supposedly obtained through a different method,[23] but whose reported lower melting point makes either its identity or its purity questionable, all other sulfides **4** are novel and have been fully characterized by NMR.

In connection with their synthesis, the oxidation of thioethers **4** with an excess of *m*-chloroperoxybenzoic acid in chloroform at room temperature has been also examined (Scheme 1). Under these conditions, the sole reaction products are the corresponding sulfones **5**, as proven



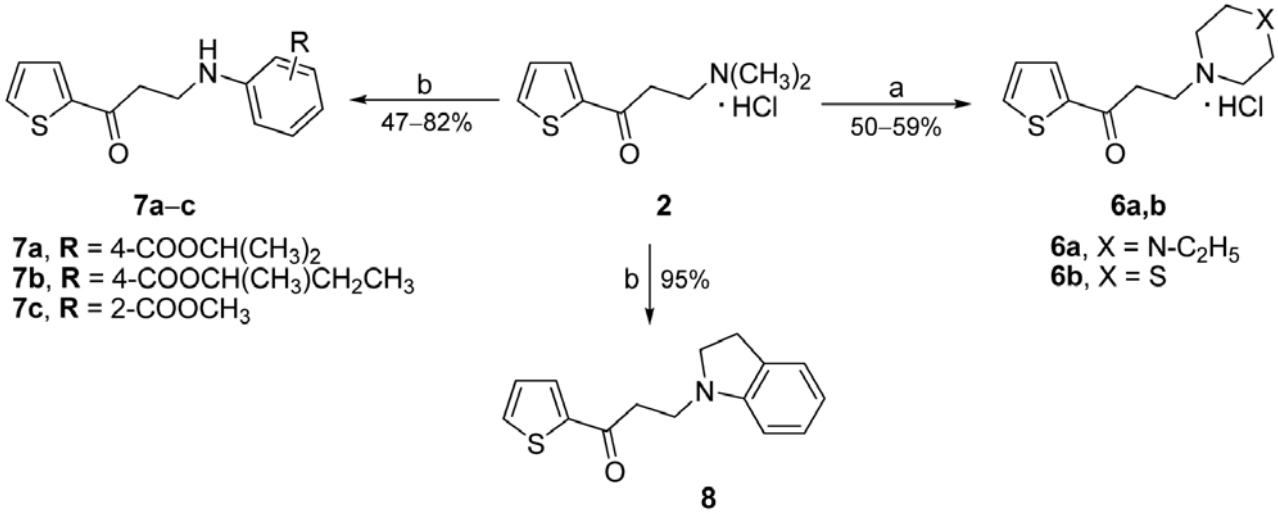
Scheme 1. *S*-Alkylation of dithiocarbamic acid salts and aryl mercaptans with Mannich base **2**, and oxidation of thioethers **4** to sulfones **5**. Reagents and conditions: (a) paraformaldehyde, dimethylamine hydrochloride, 37% HCl, ethanol, reflux, 8 h; (b) dithiocarbamic acid salts, water, rt, 24 h; (c) aryl mercaptan, ethanol–water (1:1, v/v), reflux, 1 h; (d) 3-chloroperoxybenzoic acid, chloroform, rt, 24 h.

by their correct elemental analysis. No trace of the starting material or by-products such as the related sulfoxide could be evidenced by TLC or NMR analysis of the reaction mixture that has been processed by thoroughly washing with saturated $NaHCO_3$.

The replacement of the dimethylamino moiety in Mannich base **2** by nitrogen nucleophiles has been also investigated. First, a procedure representing a valuable tool for the indirect preparation of Mannich bases, namely the amine exchange with aliphatic or aromatic amines, was explored. This method proves helpful in the case of aliphatic amines that are less common, or aliphatic amines that are usually commercially available as free bases, not as their hydrochlorides, which are the typical amine reagents in the direct aminomethylation of ketones. Despite recent progress in the direct aminomethylation of ketones using aromatic amines,[25–29] transamination remains an attractive alternative for the preparation of Mannich bases having aromatic amine moieties. The reaction is best conducted in water with amines that are miscible with water, such as pyrrolidine[30] or piperazine.[31] However, for the transamination of Mannich bases with amines that are less miscible with water, a mixture of ethanol and water in various proportions is a more appropriate solvent.[32–34]

The water-miscible 1-ethylpiperazine and thiomorpholine were selected as amine reagent in a transamination reaction with Mannich base **2** due to their high pharmacological potential;[35,36] the process led to the synthesis of novel amino ketones **6a** and **6b**, respectively. As shown previously,[31] reaction times as long as 18 to 24 h are critical for high yields of transamination product. Also, long reaction time appears to be an important factor in lowering the content of the free base of the starting Mannich base hydrochloride in the isolated crude reaction product,[30] an undesired by-product which is most likely formed through the extraction of HCl from the initial Mannich base hydrochloride by the amine used in transamination. The isolated amino ketones **6a** and **6b** were transformed into their hydrochlorides upon treatment with an excess of ethereal HCl, and purified by recrystallization to constant melting point (two recrystallizations usually suffice). Compound **6a** containing piperazine as amine moiety has been characterized as a dihydrochloride, as suggested by its proton spectrum taken in d_6-DMSO (data not shown), in which a broad singlet integrating for almost 2 protons and exchangeable with deuterium was observed at 11.9 ppm.

On the other hand, the transamination of the dimethylamino moiety in Mannich base **2** in a water–ethanol mixture was illustrated by the use of several primary and secondary aromatic amines. First, derivatives of pharmacologically relevant 4-aminobenzoic acid,[37] namely isopropyl and isobutyl 4-aminobenzoate, led only to moderate yields of compounds **7a** and **7b**, respectively. However, transamination product **7c** was obtained in excellent yield from methyl anthranilate when the reaction time was extended to 4 h and the composition of the reaction medium was modified. Also, indoline was used as an example of a secondary aromatic amine in the amine exchange reaction with Mannich base **2**; it afforded quantitatively the transamination product **8**, which could be isolated in high purity through a simple extraction from the reaction mixture. In compounds **7a–c**, the nitrogen proton gives a triplet at 4.6 ppm for compounds **7a** and **7b**, which can be found at a higher δ value (7.9 ppm) in the case of compound **7c**. The presence of this signal in the proton spectra of compounds **7** rules out the bis-*N*-alkylation of the initial arylamine. A HMBC NMR experiment allowed the assignment of the triplets at 2.96 and 3.41 ppm to the protons in the methylene groups of the indoline residue in compound **8**, whereas the methylene groups in the 2-thienoylethyl moiety in the same compound are responsible for the triplets at 3.19 and 3.58 ppm.

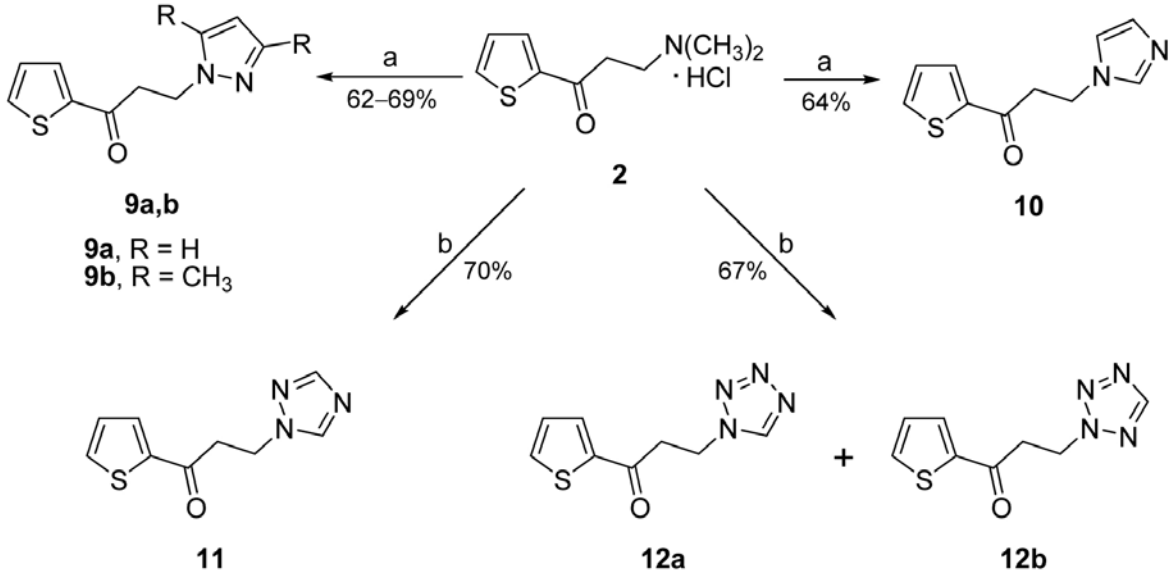


Scheme 2. *N*-Alkylation of water-soluble aliphatic secondary amines and aromatic primary and secondary amines with Mannich base **2**. Reagents and conditions: (a) aliphatic secondary amine, water, rt, 24 h; (b) aromatic amine, ethanol–water, reflux, 1–4 h.

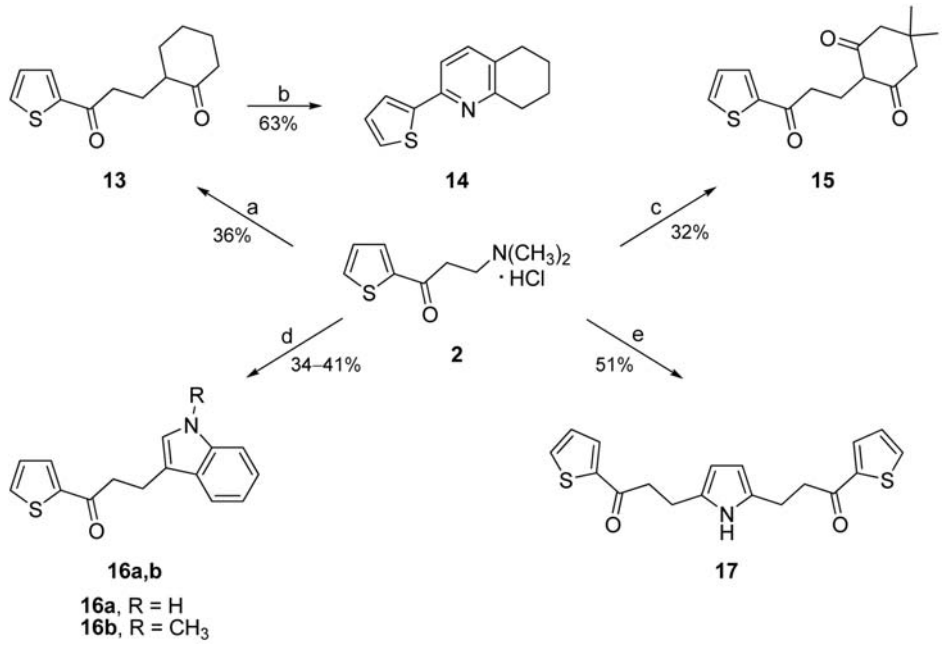
NH-Azoles are another class of compounds that can be used as nitrogen nucleophiles in *N*-alkylation reactions with Mannich bases.[38] The *N*-alkylation of pyrazole, 3,5-dimethylpyrazole and imidazole with Mannich base **2** in water at reflux temperature for 1 h gave reasonable yields of compounds **9a**, **9b** and **10** (Scheme 3). After a failed attempt to replace the dimethylamine group in Mannich base **2** with a 1,2,4-triazolyl moiety in the same manner, toluene was found to be a better solvent for the *N*-alkylation of both 1*H*-1,2,4-triazole and tetrazole with Mannich base **2**. Heating Mannich base **2** and 1*H*-1,2,4-triazole in toluene at reflux temperature for 7 h led to practically pure N^1-alkylated triazole **11** in good yields. Under the same conditions, tetrazole afforded a mixture of N^1- and N^2-alkylated tetrazoles **12a** (major component) and **12b** (minor component), respectively, which were separated by flash column chromatography. The correct number of protons in the azole ring confirms that the alkylation with Mannich base **2** occurred at N^1. The two singlets at 7.9 and 8.2 ppm in the proton NMR spectrum of compound **11** indicate the existence of two magnetically non-equivalent protons in the triazole ring, which proves that the alkylation with Mannich base **2** took place at N^1 rather than at N^4. In the cases of tetrazoles **12**, the correct structure for each of the regioisomers **12a** and **12b** was assigned using both NOESY and HMBC techniques. The difference in the chemical shift values for the proton in the azole ring of these two regioisomers (9.2 ppm for **12a** and 8.5 ppm for **12b**) is a characteristic that could help discriminate between an N^1-substituted tetrazole and an N^2-substituted tetrazole. The δ value for the carbon atom of the methylene group adjacent to the tetrazole ring, which is higher for **12b** compared to **12a**, could also be used as a characteristic to distinguish between these regioisomers in their mixtures.

Ketonic Mannich bases have been known to *C*-alkylate organic compounds having a *CH*-acidic group which is activated either by a neighbouring functional group or by the presence of a heteroatom in a heterocycle. Ketones[39] (or their enamines[40]) and 1,3-diketones[41] have been known to react with ketonic Mannich bases at elevated temperature to yield 1,5-diketones and triketones, respectively. *C*-Alkylation of these ketones with ketonic Mannich bases takes place at the carbon atom α to the carbonyl function, or at C^2 in the case of 1,3-diketones. The reaction of Mannich base **2** with 1-pyrrolidinocyclohexene in dioxane afforded a modest yield of compound **13**, which was transformed into the quinoline derivative **14** upon treatment with hydroxylamine hydrochloride (Scheme 4). On the other hand, triketone **15** was obtained through the *C*-alkylation of dimedone with Mannich base **2** in the presence of triethylamine at 160 °C. The lack of a signal in the aliphatic region of the ^{1}H NMR spectrum for the proton at C^2 in the dimedone moiety of compound **15**, and the broad singlet at approximately 10 ppm suggest that triketone **15** exists in enol form in solution. This observation is fully supported by the ^{13}C NMR spectrum of this compound, in which the chemical shift values for the carbon atoms at position 1 and 2 of the dimedone residue in compound **15** are typical for carbon atoms that are part of an enol system.

A few examples are available in the literature regarding the *C*-alkylation of heterocycles. For example, pyrrole and its benzo-fused derivative, indole, have been shown to react with ketonic Mannich bases,[38] either as a hydrochloride in a mixture of ethanol and water, or as a free base in toluene. Similar yields of reaction products have been obtained under both sets of conditions. Pyrrole has been bis-*C*-alkylated at positions 2 and 5, whereas in-



Scheme 3. *N*-Alkylation of monocyclic *NH*-azoles with Mannich base **2**. Reagents and conditions: (a) *NH*-azole, water, reflux, 1 h; (b) *NH*-azole, toluene, reflux, 7 h.

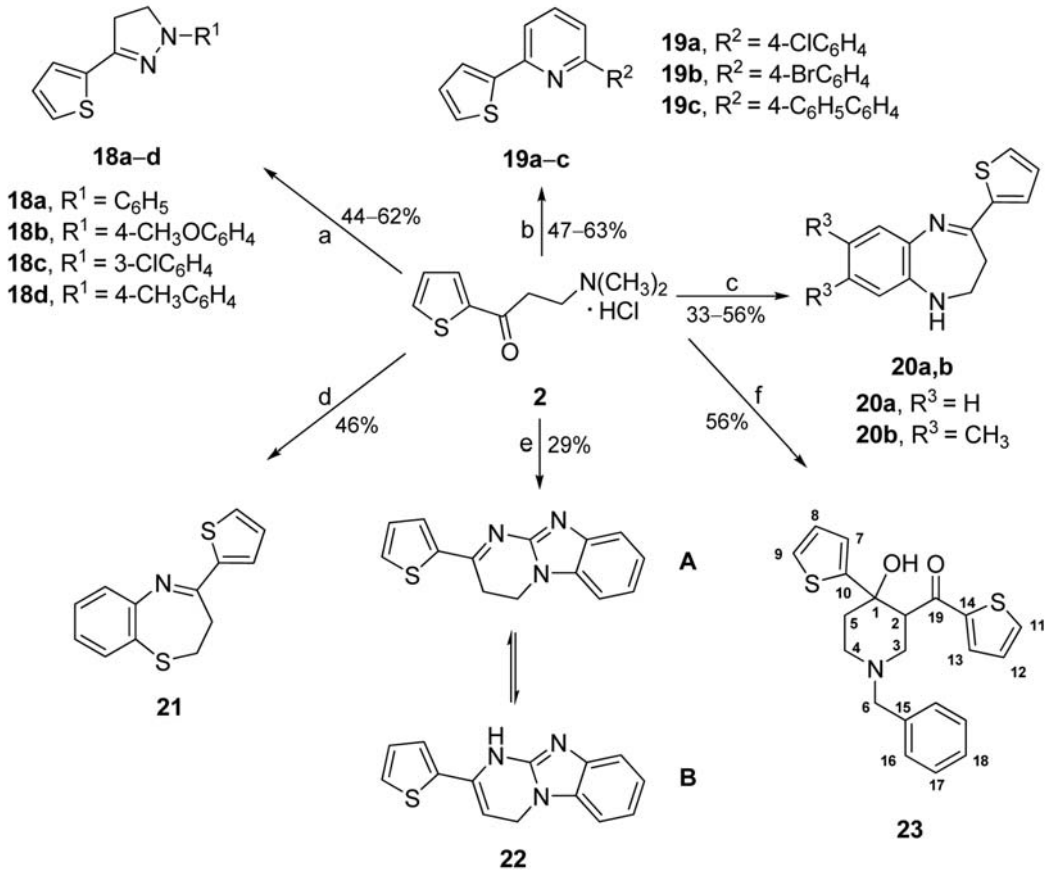


Scheme 4. *C*-Alkylation of ketones, indoles and pyrrole with Mannich base **2**. Reagents and conditions: (a) 1-pyrrolidinocyclohexene, dioxane, reflux, 18 h, then water, reflux, 1 h; (b) hydroxylamine hydrochloride, ethanol, reflux, 3 h; (c) 5,5-dimethyl-1,3-cyclohexanedione, triethylamine, 160 °C, 15 min; (d) indoles, ethanol–water (1:1 v/v), 4 h; e) pyrrole, water, reflux, 4 h.

dole has been *C*-alkylated at position 3.[38] The reaction of Mannich base **2** with indole and 1-methylindole in ethanol–water at reflux temperature afforded C^3-alkylated indoles **16a** and **16b**, respectively, in modest yields (Scheme 4). The use of pyrrole as a substrate in the *C*-alkylation with Mannich base **2** led to the 2,5-disubstituted pyrrole **17**. The broad singlet at 8 ppm corresponding to the proton of the nitrogen atom in the indole derivative **16a** proves that nitrogen did not undergo alkylation. The doublet at 5.6 ppm in the proton NMR spectrum of compound **17** in correlation with the absence of any signals attributable to other protons in the pyrrole moiety provides evidence that the *C*-alkylation of pyrrole with Mannich base **2** took place at positions 2 and 5, and the broad singlet in the off-set confirms that no alkylation occurred at nitrogen.

Cyclization of different types of Mannich bases leads to a large variety of carbocycles and heterocycles.[2–4] In particular, the ring closure reactions of ketonic Mannich bases have earned well-deserved attention, as proven by the reviews dedicated to this particular topic.[42,43] A general type of ring closure reaction of ketonic Mannich bases involves the elimination of the easily leaving dialkylammonium halide group, a process that generates a highly reactive alkyl (or aryl) vinyl ketone as an intermediate. In the presence of the suitable bifunctional nucleophile, this α, β-unsaturated ketone leads to cyclic structures. The ring closure with the elimination of the dialkylamino group from ketonic Mannich bases is exemplified by the reaction with hydrazines.[44–47] Upon treatment with phenylhydrazine (or with substituted phenylhydrazine hydrochlorides in the presence of NaOH), Mannich base **2** generated a series of 1-(substituted)phenyl-3-(2-thiophen-2-yl)-4,5-dihydro-1*H*-pyrazoles **18a–d** (Scheme 5). The first stage in the synthesis of pyrazolines **18** from Mannich base **2** is the formation of the corresponding phenylhydrazones, followed by the elimination of the dimethylamino group and subsequent ring closure. This mechanism is supported experimentally by the isolation of the intermediate phenylhydrazones in some cases.[48,49] The analysis of the ^{1}H and ^{13}C NMR spectra of compounds **18** further validates the proposed structure (see Supporting Information).

Ketonic Mannich bases have been shown to generate pyridines in a reaction with *N*-phenacylpyridinium halides and ammonium acetate.[50] The methylene group adjacent to the protonated nitrogen in these pyridiunium salts is highly reactive, which makes it susceptible to Michael type additions with α,β-unsaturated ketones, such as alkyl (or aryl) vinyl ketones which could be produced *in situ* by the cleavage of the dialkylammonium group from ketonic Mannich bases. The resulting 1,5-diketones close the pyridine ring in the presence of ammonium acetate as a source of nitrogen. The use of ketonic Mannich bases as acceptors in the Michael addition leads to 2,6-disubstituted pyridines, some of which have been shown to exhibit moderate cytotoxicity against several human cancer cell lines.[51] The reaction of Mannich base **2** with *N*-phenacylpyridinium bromides and ammonium acetate in acetic acid yielded three novel 2-(substituted aryl)-6-(thiophen-2-yl)pyridines **19a–c** in moderate to good yields (Scheme 5). It should be noted that an attempt to perform



Scheme 5. Ring closure reaction with Mannich base **2**. Reagents and conditions: (a) phenylhydrazine, NaOH, ethanol–water (2:3, v/v), reflux, 3 h; (b) 1-(aroylmethyl)pyridinium bromide, CH_3COONH_4, acetic acid, reflux 6 h; (c) 1,2-diaminobenzene, ethanol, reflux 30 min; (d) 2-aminobenzenethiol, toluene, reflux, 7 h; (e) 2-aminobenzimidazole, 2-propanol, reflux, 1 h; (f) benzylamine, water, rt, 24 h.

the reaction in ethanol as reported by Korean researchers[51] failed to give the desired pyridines.

The cyclocondensation of ketonic Mannich bases with bifunctional nucleophiles such as 1,2-diamines or 1,2-mercaptoamines provides an entry to seven-membered heterocycles. Aliphatic 1,2-diamines (e.g., ethylenediamine)[52,53] and 1,2-mercaptoamines such as cysteamine,[52] or aromatic 1,2-diamines,[54–56] heteroaromatic 1,2-diamines[57–60] and 2-aminothiophenols[61–63] can act as bifunctional nucleophiles in the synthesis of 1,4-diazepines, 1,4-thiazepines and their annelated congeners. 2,3-Dihydro-1*H*-1,5-benzodiazepines **20** were obtained in moderate yields when Mannich base **2** and *ortho*-phenylenediamines were heated in ethanol at reflux temperature for a short period of time (Scheme 5). 4-(Thiophen-2-yl)-2,3-dihydrobenzo[*b*]-1,4-thiazepine (**21**) was also synthesized in moderate yield through the reaction of Mannich base **2** with 2-aminobenzenethiol in toluene at reflux temperature. A comparison between the δ values of the protons and carbon atoms in the methylene groups that were recorded for structures similar to compound **20** supports the 2,3-dihydro-1*H*-1,5-benzodiazepine structure for these compounds.[7,54] The cyclic structure is confirmed by the absence in the ^{13}C NMR spectra of compounds **20** and **21** of a signal at 190–200 ppm that could be attributed to the carbon atom of the carbonyl function, and by the presence of a signal at 160–165 ppm that is typical for the carbon atom in the imine function in compounds **20** and **21**.[54]

The use of 2-aminobenzimidazole as a bifunctional nucleophile in the reaction with ketonic Mannich base **2** afforded dihydropyrimido[1,2-*a*]benzimidazole **22** in modest yield (Scheme 5). Orlov *et al.*[64] have shown that structures similar to that of compound **22** exist in solution as a mixture of 3,4-dihydro form **A** and 1,4-dihydro form **B** owing to the imine-enamine tautomerism of dihydropyrimido[1,2-*a*]benzimidazoles. The tautomeric forms of compound **22** can be easily evidenced in the ^1H NMR spectra due to their different pattern for the signals of the protons in the pyrimidine ring. The four protons in the two methylene groups of the imine 3,4-dihydro form **A** appear in the proton NMR spectrum as two triplets at approximately 3.4 and 4.4 ppm. On the other hand, the system of peaks comprising a doublet at 4.8 ppm integrating for two protons at C^3 and a triplet at 5.3 ppm integrating for one proton at C^4, in conjunction with the broad singlet at about 9.8 ppm integrating for one proton of the *NH* moiety, ac-

counts for the protons in the pyrimidine ring of the enamine 1,4-dihydro form **B**. The ratio between the tautomeric forms **A** and **B** in the analytical sample of compound **22**, as calculated from the proton NMR spectrum, is approximately 9 to 1. This finding is in contrast to the data presented by Russian researchers,[64] who reported the enamine form **B** as the major tautomer (or even as the only tautomer) to have been evidenced in the dihydropyrimido[1,2-*a*]benzimidazoles derived from ketonic Mannich bases that were described in their paper.

The reaction of Mannich base **2** with an equimolar amount of benzylamine in water at room temperature for 24 h was also investigated. The TLC analysis of the crude reaction product showed that it contained one major reaction product along with several by-products. Two recrystallizations from ethanol afforded a pure sample of compound **23** as the major reaction products (Scheme 5). An attempt to isolate other reaction products from the residue obtained after the removal of ethanol from the mother liquors failed to yield pure compounds. The analysis of the proton NMR data showed that compound **23** was neither the product of mono-*N*-alkylation, nor the product of bis-*N*-alkylation of benzylamine with Mannich base **2.** An extensive NMR analysis that included DEPT and correlation spectroscopy experiments (COSY, HMQC and HMBC) finally allowed the assignment of a 4-hydroxypiperidine structure to compound **23**. The structure proposed for compound **23** was also confirmed by high resolution mass spectroscopy. Similar structures have been previously obtained in modest yield by direct aminomethylation using aliphatic primary amine hydrochlorides,[65–67] or by the base-catalyzed intramolecular aldol condensation of ketonic bis-Mannich bases derived from primary alkylamines.[68,69] Compound **23** was most likely obtained through a sequence of reactions comprising the sequential bis-*N*-alkylation of benzylamine with ketonic Mannich bases **2**, followed by the ring closure of the resulting bis-Mannich base catalyzed by the excess of benzylamine. The detailed assignment of all of the signals in the NMR spectra to the protons and carbon atoms in the structure of compound **23**, according to their numbering in Scheme 5, was accomplished by correlating the data obtained through exhaustive NMR analysis.

3. Experimental

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Analytical thin-layer chromatography was performed on glass-backed Merck precoated silica gel 60 F_{254} plates, and the compounds were visualized by UV illumination (254 nm). Flash column chromatography was performed on Merck silica gel (230–400 mesh, 60 Å). Elemental analysis was conducted in-house, on a PerkinElmer 2400 Series II CHNS/O system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to $CDCl_3$ (δ = 77.16 ppm) or d_6-DMSO (δ = 39.52 ppm).

The dithiocarbamic acid salts required for the synthesis of dithiocarbamates **3** were prepared from the corresponding amine and CS_2 in the presence of a base. Specifically, dithiocarbamic acid salts derived from pyrrolidine, piperidine and morpholine were synthesized by gradually treating an ice-cold mixture of secondary amine and water (1:1 v/v) with CS_2, according to a reported procedure.[70] The synthesis of potassium 4-phenylpiperazine-1-carbodithioate by heating a mixture of secondary amine, CS_2 and KOH in ethanol at reflux temperature was performed according to a published procedure.[19] The reaction between phenacyl bromide (1 eq) and pyridine (1.5 eq) in a mixture of ethanol-ethyl acetate (1:1, v/v) at room temperature for 2 days yielded the 1-(aroylmethyl)pyridinium bromides required for the synthesis of pyridines **19**. Isopropyl 4-aminobenzoate and isobutyl 4-aminobenzoate were purchased from TCI Europe, whereas 1-(biphenyl-4-yl)-2-bromoethanone was obtained from Alfa Aesar. All other reagents were available from Sigma-Aldrich, and were used without prior purification.

The analytical and spectral data for the synthesized compounds can be found in the Supporting Information for this article, which is available as an electronic file on the WWW under http://acta.chem-soc.si or from the author.

General procedure for the synthesis of *S*-(3-oxo-3-(thiophen-2-yl)propyl) dithiocarbamates 3a–e. The salt of a dithiocarbamic acid (6 mmol) was dissolved in water (100 mL) and filtered. The solution was added with good stirring to a solution of compound **2** (1.1 g, 5 mmol) in water (20 mL). The reaction mixture was stirred at room temperature for 24 h, and then the precipitate was filtered, washed thoroughly with water and recrystallized.

General procedure for the synthesis of 3-(substituted aryl)thio-3-(thiophen-2-yl)-1-propanones 4a–e. The solution of compound **2** (1.1 g, 5 mmol) and aryl mercaptan (5 mmol) in a mixture of ethanol–water (16 mL, 1:1 v/v) was heated at reflux temperature for 1 h, and then it was cooled in an ice bath. The solid that separated was filtered, washed with a cold mixture of ethanol–water (5 mL, 1:1 v/v), and air-dried. In the case of compound **4e**, the supernatant was removed with a pipette to give a thick oil.

General procedure for the synthesis of 3-(substituted aryl)sulphonyl-3-(thiophen-2-yl)-1-propanones 5a–d. A solution of 3-(substituted aryl)thio-3-(thiophen-2-yl)-1-propanones **4** (2 mmol) in chloroform (20 mL) was treated with 3-chloroperbenzoic acid (990 mg, 4.3 mmol, 2.15 equiv, 75% purity), and the mixture was stirred at room temperature for 24 h. The mixture was then diluted with

dichloromethane (30 mL), washed with saturated $NaHCO_3$ (4 × 25 mL) and water (30 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue.

3-(4-Ethylpiperazin-1-yl)-1-(thiophen-2-yl)-1-propanone dihydrochloride (6a). A mixture of compound **2** (1.1 g, 5 mmol) and 1-ethylpiperazine (570 mg, 5 mmol) in water (15 mL) was stirred at room temperature for 24 h. The mixture was then extracted with ethyl acetate (2 × 15 mL), the combined organic phases were washed with water (15 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent afforded a thick oil, which was dissolved in acetone (10 mL) and treated with an excess of ethereal HCl. The solid was filtered and recrystallized twice from methanol.

3-(Thiomorpholin-4-yl)-1-(thiophen-2-yl)-1-propanone hydrochloride (6b). This compound was prepared starting from of compound **2** (1.1 g, 5 mmol) and thiomorpholine (515 mg, 5 mmol) by a procedure analogous to that used to synthesize **6a**.

Isopropyl 4-(3-oxo-3-(thiophen-2-yl)propylamino)benzoate (7a). A mixture of compound **2** (1.1 g, 5 mmol) and isopropyl 4-aminobenzoate (895 mg, 5 mmol) in ethanol–water (6 mL, 1:1 v/v) was heated at reflux temperature for 1 h. The reaction mixture was then cooled in an ice bath, and the solid that separated was filtered, air-dried, and recrystallized.

Isobutyl 4-(3-oxo-3-(thiophen-2-yl)propylamino)benzoate (7b). This compound was prepared starting from of compound **2** (1.1 g, 5 mmol) and isobutyl 4-aminobenzoate (965 mg, 5 mmol) by a procedure analogous to that used to synthesize **7a**.

Methyl 2-(3-oxo-3-(thiophen-2-yl)propylamino)benzoate (7c). A mixture of compound **2** (1.1 g, 5 mmol) and methyl 2-aminobenzoate (755 mg, 5 mmol) in ethanol–water (8 mL, 1:3 v/v) was heated at reflux temperature for 4 h. The reaction mixture was then cooled in an ice bath, and the solid that separated was filtered, air-dried, and recrystallized.

3-(Indolin-1-yl)-1-(thiophen-2-yl)-1-propanone (8). A mixture of compound **2** (1.1 g, 5 mmol) and indoline (600 mg, 5 mmol) in ethanol–water (6 mL, 1:2 v/v) was heated at reflux temperature for 1 h. The heavy oil that separated on cooling in an ice bath was extracted with ethyl acetate (2 × 15 mL), the combined organic phase was washed with water (15 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the title compound, practically pure by ^{1}H NMR.

3-(1*H*-Pyrazol-1-yl)-1-(thiophen-2-yl)propan-1-one (9a). A mixture of compound **2** (659 mg, 3 mmol) and 1*H*-pyrazole (204 mg, 3 mmol) in water (10 mL) was heated at reflux temperature for 1 h. The solid that separated upon cooling in an ice bath was filtered, air-dried, and recrystallized.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-1-(thiophen-2-yl)-1-propanone (9b). This compound was prepared starting from of compound **2** (659 mg, 3 mmol) and 3,5-dimethyl-1*H*-pyrazole (288 mg, 3 mmol) by a procedure analogous to that used to synthesize **9a**.

3-(1*H*-Imidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (10). A mixture of compound **2** (659 mg, 3 mmol) and 1*H*-imidazole (204 mg, 3 mmol) in water (10 mL) was heated at reflux temperature for 1 h. The reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with water (15 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Flash chromatography of the residue (silica gel, ethyl acetate–methanol 9:1 v/v) afforded the title compound.

1-(Thiophen-2-yl)-3-(1*H*-1,2,4-triazol-1-yl)-1-propanone (11). A mixture of compound **2** (659 mg, 3 mmol) and 1*H*-1,2,4-triazole (414 mg, 6 mmol) in toluene (18 mL) was heated at reflux temperature for 7 h. The solvent was then removed under reduced pressure, and the residue was partitioned between water (30 mL) and ethyl acetate (15 mL). The aqueous phase was further extracted with ethyl acetate (15 mL), the combined organic phase was washed with water (15 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue that was purified by flash column chromatography (silica gel, ethyl acetate–hexanes 4:1 v/v) to give the title compound.

3-(1*H*-Tetrazol-1-yl)-1-(thiophen-2-yl)-1-propanone (12a) and 3-(2*H*-tetrazol-2-yl)-1-(thiophen-2-yl)-1-propanone (12b). These compounds were prepared starting from of compound **2** (659 mg, 3 mmol) and 1*H*-tetrazole (420 mg, 6 mmol) by a procedure analogous to that used to synthesize compound **11**. Flash column chromatography of the residue (silica gel, hexanes–ethyl acetate 1:1 v/v) afforded first regioisomer **12b**. Further elution with hexanes–ethyl acetate 1:2 (v/v) yielded the regioisomer **12a**.

2-(3-Oxo-3-(thiophen-2-yl)propyl)cyclohexanone (13). A mixture of compound **2** (2.2 g, 10 mmol) and 1-pyrrolidinocyclohexene (1.51 g, 10 mmol) in dioxan (10 mL) was refluxed for 18 h, then water (3 mL) was added, and the mixture was refluxed for 1 h, cooled to room temperature and diluted with water (10 mL). The mixture was then extracted with ethyl acetate (4 × 30 mL), the combined organic phase was washed with dilute HCl (10 mL), water (40 mL), and brine (15 mL), and dried over anhy-

drous Na_2SO_4. The solvent was removed under reduced pressure to afford a brown oil from which the title compound was separated by flash column chromatography (silica gel, hexanes–ethyl acetate 5:1 v/v).

2-(Thiophen-2-yl)-5,6,7,8-tetrahydroquinoline (14). A mixture of diketone **13** (802 mg, 3.4 mmol) and hydroxylamine hydrochloride (237 mg, 3.4 mmol) in ethanol (5 mL) was heated at reflux temperature for 3 h, and then the cooled solution was brought to pH 7 by addition of saturated Na_2CO_3. The mixture was diluted with water to a volume of 100 mL, and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with water (25 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give an orange oil that was subjected to flash column chromatography (silica gel, toluene).

5,5-Dimethyl-2-(3-oxo-3-(thiophen-2-yl)propyl)-1,3-cyclohexanedione (15). A mixture of compound **2** (878 mg, 4 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1120 mg, 8 mmol) and triethylamine (606 mg, 6 mmol) were heated at 160 °C for 15 min. The reaction mixture was partitioned between ethyl acetate (15 mL) and water (15 mL), and the aqueous phase was further extracted with ethyl acetate (15 mL). The combined organic phase was washed with water (20 mL) and brine (10 mL), and then the solvent was removed under reduced pressure to yield an orange solid that was recrystallized.

3-(1*H*-Indol-3-yl)-1-(thiophen-2-yl)-1-propanone (16a). A mixture of compound **2** (878 mg, 4 mmol) and indole (468 mg, 4 mmol) in ethanol–water (10 mL, 1:1 v/v) was heated at reflux temperature for 4 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with water (15 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue that was purified by flash column chromatography (silica gel, hexanes–ethyl acetate 6:1 v/v).

3-(1-Methyl-1*H*-indol-3-yl)-1-(thiophen-2-yl)-1-propanone (16b). This compound was prepared starting from of compound **2** (1.1 g, 5 mmol) and 1-methylindole (655 mg, 5 mmol) by a procedure analogous to that used to synthesize **16a**. Flash column chromatography (silica gel, hexanes–ethyl acetate 14:1 v/v, then hexanes–ethyl acetate 9:1 v/v) afforded the title compound.

3-(5-(3-Oxo-3-(thiophen-2-yl)propyl)-1*H*-pyrrol-2-yl)-1-(thiophen-2-yl)-1-propanone (17). A mixture of compound **2** (878 mg, 4 mmol) and pyrrole (134 mg, 2 mmol) in water (15 mL) was heated at reflux temperature for 4 h. The solid that separated upon refrigeration was filtered and recrystallized.

General procedure for the synthesis of 1-aryl-3-(thiophen-2-yl)pyrazolines 18a–d. To a solution of sodium hydroxide (240 mg (6 mmol) if phenylhydrazine was used; 480 mg (12 mmol) if a substituted phenylhydrazine hydrochloride was used) in 40% aqueous ethanol (10 mL), compound **2** (658 mg, 3 mmol) and phenylhydrazine (either as free base or as hydrochloride) was added. The mixture was heated at reflux temperature for 3 h, then it was slowly cooled to room temperature and refrigerated overnight. The separated solid was filtered, washed with a little 40% aqueous alcohol, and air-dried.

General procedure for the synthesis of 2-aryl-6-(thiophen-2-yl)pyridines 19a–c. A mixture of compound **2** (658 mg, 3 mmol), 1-(2-aryl-2-oxoethyl)pyridinium bromide (3 mmol), and ammonium acetate (3 g, 39 mmol) in glacial acetic acid (7 mL) was heated at reflux temperature for 6 h. The mixture was then diluted with water (30 mL), and the solid that separated was filtered, washed thoroughly with water and air-dried.

4-(Thiophen-2-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (20a). A mixture of compound **2** (1.1 g, 5 mmol) and 1,2-diaminobenzene (540 mg, 5 mmol) in ethanol (7 mL) was heated at reflux temperature for 30 min. The mixture was refrigerated overnight, and then the separated solid was filtered and recrystallized.

7,8-Dimethyl-4-(thiophen-2-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (20b). This compound was prepared starting from of compound **2** (1.1 g, 5 mmol) and 4,5-dimethyl-1,2-diaminobenzene (680 mg, 5 mmol) by a procedure analogous to that used to synthesize **20a**.

4-(Thiophen-2-yl)-2,3-dihydrobenzo[b]-1,4-thiazepine (21). A mixture of compound **2** (1.1 g, 5 mmol) and 2-aminobenzenethiol (625 mg, 5 mmol) in toluene (20 mL) was heated at reflux temperature for 7 h, while the water resulted from the reaction was being removed as an azeotrope by using a Dean-Stark trap. The solvent was then removed under reduced pressure, the residue was partitioned between water water (30 mL) and ethyl acetate (30 mL), and the organic phase was washed sequentially with 5% NaOH (10 mL), water (15 mL), and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure to give a brown oil. Flash column chromatography (silica gel, hexanes–ethyl acetate 4:1 v/v) afforded the title compound.

2-(Thiophen-2-yl)-3,4-dihydro-pyrimido[1,2-*a*]benzimidazole (tautomer A) and 2-(thiophen-2-yl)-1,4-dihydro-pyrimido[1,2-*a*]benzimidazole (tautomer B) (22). A mixture of compound **2** (658 mg, 3 mmoles) and 2-aminobenzimidazole (400 mg, 3 mmoles) in 2-propanol (10 mL) was heated at reflux temperature for 1 h. The crystals

that separated by refrigerating the reaction mixture were filtered and recrystallized.

1-Benzyl-4-hydroxy-4-(thiophen-2-yl)piperidin-3-yl thiophen-2-yl methanone (23). To a solution of compound 2 (1.1 g, 5 mmoles) in water (15 mL), a solution of benzylamine (535 mg, 5 mmoles) in water (5 mL) was added dropwise under efficient stirring at room temperature. The initially clear reaction mixture soon became turbid, and then small droplets of a heavy colorless oil separated gradually and turned into a semisolid. After 24 h, the supernatant was removed with a pipette, the residue in the reaction flask was sequentially washed with water (20 mL) and 95% ethanol (5 mL) to yield a colorless solid (910 mg). Two recrystallizations from absolute ethanol afforded colorless crystals.

4. Conclusions

The behavior of 3-dimethylamino-1-(thiophen-2-yl)propan-1-one hydrochloride (**2**), a ketonic Mannich base derived from 2-acetylthiophene, in selected alkylation and ring closure reactions has been investigated. Compound **2** racts with *S*-alkylated dithiocarbamic acid salts and aryl mercaptans smoothly. Primary and secondary aliphatic and aromatic amines, as well as monocyclic *NH*-azoles, were *N*-alkylated by compounds **2.** *C*-Alkylation of monoketones, 1,3-diketones, indoles and pyrrole by compound **2** was also successful. Ring closure reactions of compound **2** afforded pyrazolines, pyridines, 2,3-dihydro-1,5-1*H*-benzodiazepines, 2,3-dihydro-1,5-1*H*-benzothiazepine, pyrimido[1,2-*a*]benzimidazole and 4-hydroxypiperidine derivatives. The significant versatility of this ketonic Mannich base has allowed the synthesis of a large variety of organic compounds using mostly simple and facile one-step approaches. The flexibility and the broad scope of these synthetic applications may be employed in generating structurally diverse libraries of compounds for drug discovery.

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Povzetek

3-Dimetilamino-1-(tiophen-2-il)propan-1-on hidroklorid (**2**), poznan tudi kot keto-Mannichva baza, smo pripravili iz 2-acetiltiofena in jo uporabili kot izhodno spojino v različnih reakcijah alkiliranja in v reakcijah sinteze obročnih sistemov, z namenom priprave strukturno raznolike knjižnice spojin. Tako pri reakciji spojine **2** s soljo S-alkilirane ditiokarbamske kisline in aril merkaptanov nastanejo ditiokarbamati in tioetri. Nadalje smo dimetilamino skupino v spojini **2** zamenjali z različnimi alifatskimi sekundarnimi ter aromatskimi primarnimi in sekundarnimi amini, medtem ko monociklične *NH*-azole, kot je pirazol, imidazol, 1,2,4-triazol in tetrazol, lahko *N*-alkiliramo s spojino **2**. Z istim substratom smo izvedli tudi reakcijo C-alkiliranja na različnih ketonih, pirolu in indolih. Prav tako lahko z reakcijo ciklizacije spojine **2** s primernim bifunkcionalnim nukleofilom pripravimo različne derivate pirazolina, piridina, 2,3-dihydro-1,5-1*H*-benzodiazepina, 2,3-dihydro-1,5-1*H*-benzotiazepina, pyrimido[1,2-*a*]benzimidazola in 4-hidroksipiperidina.

Supplementary Material

Generation of a Structurally Diverse Library through Alkylation and Ring Closure Reactions Using 3-Dimethylamino-1-(thiophen-2-yl)propan-1-one Hydrochloride

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Analytical and spectral data of the synthesized compounds

***S*-(3-Oxo-3-(thiophen-2-yl)propyl)-*N*,*N*-diethylcarbamodithioate (3a)**. Colorless crystals (775 mg, 54%), mp 48–49 °C (ethanol); ^{1}H hNMR ($CDCl_3$): δ 1.27 (t, J = 6.8 Hz, 6H), 3.44 (t, J = 6.4 Hz, 2H), 3.65–3.75 (m, 4H), 4.03 (q, J = 6.4 Hz, 2H), 7.13 (t, J = 4.0 Hz, 1H), 7.64 (d, J = 4.4 Hz, 1H), 7.79 (d, J = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.9, 12.8, 31.1, 39.2, 47.2, 50.1, 128.2, 132.4, 133.9, 144.1, 191.4, 196.9; Anal. Calcd. for $C_{12}H_{17}NOS_3$: C 50.14, H 5.96, N 4.87. Found: C 50.39, H 6.19, N 4.62.

***S*-(3-Oxo-3-(thiophen-2-yl)propyl)-pyrrolidine-1-carbodithioate (3b)**. Colorless crystals (810 mg, 57%), mp 82–83 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.94–2.10 (m, 4H), 3.45 (t, J = 6.4 Hz, 2H), 3.63 (t, J = 6.4 Hz, 2H), 3.70 (t, J = 6.4 Hz, 2H), 3.93 (t, J = 6.4 Hz, 2H), 7.13 (br s, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.79 (d, J = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.7, 26.5, 31.0, 39.0, 51.1, 55.5, 128.3, 132.5, 134.0, 143.9, 191.4, 196.3; Anal. Calcd. for $C_{12}H_{15}NOS_3$: C 50.49, H 5.30, N 4.91. Found: C 50.73, H 5.48, N 4.74.

***S*-(3-Oxo-3-(thiophen-2-yl)propyl)-piperidine-1-carbodithioate (3c)**. Colorless crystals (760 mg, 51%), mp 80–81 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.62–1.76 (m, 6H), 3.45 (t, J = 6.8 Hz, 2H), 3.71 (t, J = 6.8 Hz, 2H), 3.86 (br s, 2H), 4.29 (br s, 2H), 7.12 (dd, J = 4.0 and 4.8 Hz, 1H), 7.63 (dd, J = 0.8 and 4.8 Hz, 1H), 7.79 (dd, J = 0.8 and 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, δ): δ 24.4, 25.6, 26.0, 31.1, 39.3, 51.4, 53.0, 128.3, 132.5, 133.9, 144.0, 191.5, 195.4; Anal. Calcd. for $C_{13}H_{17}NOS_3$: C 52.14, H 5.72, N 4.68. Found: C 52.41, H 5.87, N 4.57.

***S*-(3-Oxo-3-(thiophen-2-yl)propyl)-morpholine-4-carbodithioate (3d)**. Colorless crystals (590 mg, 39%), mp 107–108 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.44 (t, J = 6.4 Hz, 2H), 3.68–3.81 (m, 6H), 3.92 (br s, 2H), 4.32 (br s, 2H), 7.12 (dd, J = 4.0 and 4.8 Hz, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.77 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 30.9, 39.0, 50.6, 51.3, 66.3, 128.3, 132.5, 134.1, 143.9, 191.2, 197.4; Anal. Calcd. for $C_{12}H_{15}NO_2S_3$: C 47.81, H 5.02, N 4.65. Found: C 48.08, H 5.17, N 4.48.

***S*-(3-Oxo-3-(thiophen-2-yl)propyl)-4-phenylpiperazine-1-carbodithioate (3e)**. Colorless crystals (980 mg, 52%), mp 120–121 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.29 (br s, 4H), 3.47 (t, J = 6.4 Hz, 2H), 3.75 (t, J = 6.4 Hz, 2H), 4.09 (br s, 2H), 4.50 (br s, 2H), 6.87–6.97 (m, 3H), 7.13 (br s, 1H), 7.29 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 4.4 Hz, 1H), 7.78 (d, J = 2.8 Hz, 1H); Anal. Calcd. for $C_{18}H_{20}N_2OS_3$: C 57.41, H 5.35, N 7.44. Found: C 57.25, H 5.49, N 7.30.

3-(4-Chlorophenylthio)-1-(thiophen-2-yl)-1-propanone (4a). Colorless crystals (860 mg, 61%), mp 90–91 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.18–3.24 (m, 2H), 3.27–3.33 (m, 2H), 7.12 (dd, J = 4.0 and 4.8 Hz, 1H), 7.24–7.33 (m, 4H), 7.63–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 28.7, 39.0, 128.3, 129.3, 131.2, 132.2, 132.6, 134.2, 134.4, 143.9, 190.8; Anal. Calcd. for $C_{13}H_{11}ClOS_2$: C 55.21, H 3.92. Found C 55.40, H 4.07.

3-(4-Bromophenylthio)-1-(thiophen-2-yl)-1-propanone (4b). Colorless crystals (915 mg, 56%), mp 103–104 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.19–3.25 (m, 2H), 3.27–3.33 (m, 2H), 7.12 (dd, J = 4.0 and 4.8 Hz, 1H), 7.20–7.26 (m, 2H), 7.39–7.45 (m, 2H), 7.65 (d, J = 0.8 Hz, 1H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 28.3, 38.9, 120.4, 128.3, 131.2, 132.2 (2 × C), 134.2, 135.0, 143.8, 190.8; Anal. Calcd. for $C_{13}H_{11}BrOS_2$: C 47.71, H 3.39. Found C 47.52, H 3.53.

3-(4-Hydroxyphenylthio)-1-(thiophen-2-yl)-1-propanone (4c). Colorless crystals (925 mg, 70%), mp 109–110 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.13–3.23 (m, 4H), 5.68 (br s, 1H), 6.77–6.83 (m, 2H), 7.10 (dd, J = 4.0 and

4.8 Hz, 1H), 7.29–7.35 (m, 2H), 7.63–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 30.6, 39.3, 116.4, 125.6, 128.3, 132.4, 134.1, 134.3, 143.9, 155.6, 191.7; Anal. Calcd. for $C_{13}H_{12}O_2S_2$: C 59.06, H 4.58. Found C 58.89, H 4.72.

3-(Naphthalen-2-ylthio)-1-(thiophen-2-yl)-1-propanone (4d). Colorless crystals (1235 mg, 83%), mp 88–89 °C (ethanol) (lit.[1] mp 78 °C); ^{1}H NMR ($CDCl_3$): δ 3.25–3.31 (m, 2H), 3.39–3.45 (m, 2H), 7.09 (dd, J = 4.0 and 4.8 Hz, 1H), 7.42–7.51 (m, 3H), 7.62–7.65 (m, 2H), 7.73–7.82 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 28.3, 39.1, 126.0, 126.8, 127.3, 127.7 (2 × C), 127.9, 128.2, 128.8, 132.1, 132.2, 133.2, 133.9, 134.1, 144.0, 191.1; Anal. Calcd. for $C_{17}H_{14}OS_2$: C 68.42, H 4.73. Found C 68.30, H 4.85.

3-(4-Methoxyphenylthio)-1-(thiophen-2-yl)-1-propanone (4e). Colorless crystals (710 mg, 51%), mp 49–50 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.13–3.23 (m, 4H), 6.83–6.88 (m 2H), 7.11 (dd, J = 4.0 and 4.8 Hz, 1H), 7.35–7.41 (m, 2H), 7.63 (s, 1H), 7.64 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 30.5, 39.3, 55.5, 114.8, 125.6, 128.2, 132.1, 133.8, 134.0, 144.1, 159.4, 191.3; Anal. Calcd. for $C_{14}H_{14}O_2S_2$: C 60.40, H 5.07. Found C 60.21, H 4.89.

3-(4-Chlorophenylsulphonyl)-1-(thiophen-2-yl)-1-propanone (5a). Off-white crystals (405 mg, 64%), mp 108–109 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.39–3.46 (m, 2H), 3.52–3.59 (m, 2H), 7.15 (dd, J = 4.0 and 4.8 Hz, 1H), 7.50–7.57 (m, 2H), 7.68 (dd, J = 1.2 and 4.8 Hz, 1H), 7.74 (dd, J = 1.2 and 4.0 Hz, 1H), 7.84–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 31.9, 51.1, 128.5, 129.7, 129.9, 132.7, 134.8, 137.6, 141.0, 142.8, 188.1; Anal. Calcd. for $C_{13}H_{11}ClO_3S_2$: C 49.60, H 3.52. Found C 49.84, H 3.71.

3-(4-Bromophenylsulphonyl)-1-(thiophen-2-yl)-1-propanone (5b). Off-white crystals (465 mg, 65%), mp 117–118 °C; ^{1}H NMR ($CDCl_3$): δ 3.39–3.46 (m, 2H), 3.52–3.59 (m, 2H), 7.15 (dd, J = 4.0 and 5.2 Hz, 1H), 7.67–7.73 (m, 3H), 7.74 (dd, J = 1.2 and 4.0 Hz, 1H), 7.76–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 31.8, 51.0, 128.5, 129.6, 129.7, 132.8, 133.0, 134.8, 138.0, 142.8, 188.1; Anal. Calcd. for $C_{13}H_{11}BrO_3S_2$: C 43.46, H 3.09. Found C 43.69, H 3.26.

3-(4-Hydroxyphenylsulphonyl)-1-(thiophen-2-yl)-1-propanone (5c). Off-white crystals (350 mg, 59%), mp 136–137 °C (ethanol–hexanes); ^{1}H NMR (d_6-DMSO): δ 3.30 (t, J = 7.2 Hz, 2H), 3.55 (t, J = 7.2 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 7.23 (dd, J = 4.0 and 4.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.98 (dd, J = 0.8 and 4.0 Hz, 1H), 8.01 (dd, J = 0.8 and 4.8 Hz, 1H), 10.60 (s, 1H); ^{13}C NMR (d_6-DMSO): δ 31.9, 50.3, 115.8, 128.5, 128.8, 130.2, 133.7, 135.2, 142.7, 162.2, 188.7; Anal. Calcd. for $C_{13}H_{12}O_4S_2$: C 52.69, H 4.08. Found C 52.86, H 4.20.

3-(Naphthalen-2-ylsulphonyl)-1-(thiophen-2-yl)-1-propanone (5d). Off-white crystals (515 mg, 78%), mp 133–134 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.42–3.50 (m, 2H), 3.59–3.67 (m, 2H), 7.12 (dd, J = 4.0 and 4.8 Hz, 1H), 7.59–7.71 (m, 3H), 7.72 (d, J = 3.6 Hz, 1H), 7.90 (dd, J = 2.0 and 8.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 32.1, 51.0, 122.7, 128.0, 128.2, 128.4, 129.6 (2 × C), 130.0, 130.1, 132.3, 132.7, 134.7, 135.5, 135.8, 142.9, 188.3; Anal. Calcd. for $C_{13}H_{12}O_4S_2$: C 61.79, H 4.27. Found C 61.98, H 4.40.

3-(4-Ethylpiperazin-1-yl)-1-(thiophen-2-yl)-1-propanone dihydrochloride (6a). Colorless crystals (815 mg, 50%), mp 209–211 °C (methanol); ^{1}H NMR (D_2O): δ 1.40 (t, J = 7.2 Hz, 3H), 3.41 (q, J = 7.2 Hz, 2H), 3.70 (t, J = 6.0 Hz, 2H), 3.77 (t, J = 6.0 Hz, 2H), 3.45–4.27 (br s, 8H), 7.30 (dd, J = 4.0 and 4.8 Hz, 1H), 7.98 (dd, J = 1.0 and 4.8 Hz, 1H), 8.02 (dd, J = 1.0 and 4.0 Hz, 1H); ^{13}C NMR (D_2O): δ 8.9, 33.4, 48.3, 49.4, 52.2, 52.8, 129.4, 135.4, 136.8, 141.8, 191.9; Anal. Calcd. for $C_{13}H_{22}Cl_2N_2OS$: C 48.00, H 6.82, N 8.61. Found: C 48.25, H 7.03, N 8.40.

3-(Thiomorpholin-4-yl)-1-(thiophen-2-yl)-1-propanone hydrochloride (6b). Pinkish crystals (820 mg, 59%), mp 197–198 °C (methanol); ^{1}H NMR (d_6-DMSO): δ 2.83 (d, J = 13.2 Hz, 2H), 3.10–3.29 (m, 4H), 3.35–3.49 (m, 2H), 3.65 (t, J = 7.4 Hz, 2H), 3.75 (d, J = 12.0 Hz, 2H), 7.30 (dd, J = 3.6 and 4.8 Hz, 1H), 8.05 (dd, J = 1.2 and 4.0 Hz, 1H), 8.07 (dd, J = 1.2 and 4.8 Hz, 1H), 11.39 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 23.8, 32.7, 51.3, 52.9, 128.7, 133.8, 135.3, 142.7, 189.4; Anal. Calcd. for $C_{11}H_{16}ClNOS_2$: C 47.55, H 5.80, N 5.04. Found: C 47.39, H 5.96, N 5.20.

Isopropyl 4-(3-oxo-3-(thiophen-2-yl)propylamino)benzoate (7a). Colorless crystals (745 mg, 47%), mp 140–141 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.32 (d, J = 6.4 Hz, 6H), 3.22 (t, J = 6.0 Hz, 2H), 3.65 (dd, J = 6.0 and 12.4 Hz, 2H), 4.61 (t, J = 6.0 Hz, 1H), 5.13–5.26 (m, 1H), 6.57 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 3.6 and 4.8 Hz, 1H), 7.65 (dd, J = 0.8 and 4.8 Hz, 1H), 7.69 (dd, J = 0.8 and 3.6 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 22.2, 38.3, 38.5, 67.5, 111.7, 119.7, 128.4, 131.7, 132.4, 134.2, 144.0, 151.4, 166.4, 191.8; Anal. Calcd. for $C_{17}H_{19}NO_3S$: C 64.33, H 6.03, N 4.41. Found: C 64.11, H 5.82, N 4.60.

Isobutyl 4-(3-oxo-3-(thiophen-2-yl)propylamino)benzoate (7b). Colorless crystals (960 mg, 58%), mp 152–153 °C (methanol); ^{1}H NMR ($CDCl_3$): δ 1.00 (d, J = 6.8 Hz, 6H), 1.97–2.12 (m, 1H), 3.22 (t, J = 6.0 Hz, 2H), 3.66 (dd, J = 6.0 and 12.4 Hz, 2H), 4.04 (d, J = 6.4 Hz, 2H), 4.63 (t, J = 5.6 Hz, 1H), 6.58 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 3.6 and 4.8 Hz, 1H), 7.65 (dd, J = 1.2 and 4.8 Hz, 1H), 7.69 (dd, J = 1.2 and 3.6 Hz, 1H), 7.87 (d, J = 8.8

Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 19.4, 28.1, 38.3, 38.5, 70.5, 111.7, 119.2, 128.4, 131.7, 132.4, 134.2, 144.0, 151.5, 166.9, 191.8; Anal. Calcd. for $C_{18}H_{21}NO_3S$: C 65.23, H 6.39, N 4.23. Found: C 65.05, H 6.21, N 4.07.

Methyl 2-(3-oxo-3-(thiophen-2-yl)propylamino)benzoate (7c). Colorless crystals (1185 mg, 82%), mp 116–117 °C (2-propanol); ^{1}H NMR ($CDCl_3$): δ 3.27 (t, J = 6.8 Hz, 2H), 3.70 (dd, J = 6.8 and 13.2 Hz, 2H), 3.84 (s, 3H), 6.57–6.65 (m, 1H), 6.77 (d, J = 8.8 Hz, 1H), 7.12 (dd, J = 4.0 and 4.8 Hz, 1H), 7.34–7.42 (m, 1H), 7.64 (dd, J = 1.0 and 4.8 Hz, 1H), 7.71 (dd, J = 1.0 and 4.0 Hz, 1H), 7.87 (t, J = 6.4 Hz, 1H), 7.90 (dd, J = 1.6 and 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 38.1, 38.9, 51.6, 110.5, 111.2, 115.0, 128.3, 131.9, 132.2, 134.0, 134.8, 144.2, 150.8, 169.1, 191.3; Anal. Calcd. for $C_{15}H_{15}NO_3S$: C 62.26, H 5.23, N 4.84. Found: C 62.44, H 5.04, N 5.03.

3-(Indolin-1-yl)-1-(thiophen-2-yl)-1-propanone (8). Golden oil (1220 mg, 95%), R_f 0.25 (hexanes–ethyl acetate 6:1 v/v); ^{1}H NMR ($CDCl_3$): δ 2.96 (t, J = 8.4 Hz, 2H), 3.19 (t, J = 7.2 Hz, 2H), 3.41 (t, J = 8.4 Hz, 2H), 3.58 (t, J = 7.2 Hz, 2H), 6.54 (d, J = 8.0 Hz, 1H), 6.66 (t, J = 7.4 Hz, 1H), 7.04–7.12 (m, 2H), 7.13 (dd, J = 4.0 and 4.8 Hz, 1H), 7.65 (dd, J = 1.0 and 4.8 Hz, 1H), 7.73 (dd, J = 1.0 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 28.7, 36.8, 44.5, 53.3, 107.0, 117.8, 124.6, 127.5, 128.3, 130.1, 132.2, 134.0, 144.4, 151.8, 192.0; Anal. Calcd. for $C_{15}H_{15}NOS$: C 70.01, H 5.87, N 5.44. Found: C 69.68, H 6.19, N 5.16.

3-(1*H*-Pyrazol-1-yl)-1-(thiophen-2-yl)-1-propanone (9a). Colorless needles (765 mg, 62%), mp 54–55 °C (cyclohexane), R_f = 0.28 (hexanes–ethyl acetate 2:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.51 (t, J = 6.6 Hz, 2H), 4.57 (t, J = 6.6 Hz, 2H), 6.18 (t, J = 2.0 Hz, 1H), 7.09 (dd, J = 4.0 and 4.8 Hz, 1H), 7.44–7.51 (m, 2H), 7.63 (dd, J = 0.8 and 4.8 Hz, 1H), 7.68 (dd, J = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 39.5, 46.7, 105.4, 128.3, 130.2, 132.5, 134.3, 139.8, 143.7, 190.3; Anal. Calcd. for $C_{10}H_{10}N_2OS$: C 58.23, H 4.89, N 13.58. Found: C 58.41, H 5.05, N 13.34.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-1-(thiophen-2-yl)-1-propanone (9b). Colorless crystals (485 mg, 69%), mp 46–47 °C (*n*-hexane), R_f = 0.16 (hexanes–ethyl acetate 4:1 v/v); ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 2.27 (s, 3H), 3.49 (t, J = 6.8 Hz, 2H), 4.36 (t, J = 6.8 Hz, 2H), 5.73 (s, 1H), 7.10 (dd, J = 0.8 and 4.0 Hz, 1H), 7.63 (d, J = 4.8 Hz, 1H), 7.70 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.1, 13.6, 39.5, 43.1, 104.9, 128.3, 132.5, 134.2, 139.4, 143.9, 147.9, 190.8; Anal. Calcd. for $C_{12}H_{14}N_2OS$: C 61.51, H 6.02, N 11.96. Found: C 61.73, H 5.81, N 12.19.

3-(1*H*-Imidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (10). Colorless flakes (395 mg, 64%), mp 74–75 °C, R_f = 0.19 (ethyl acetate–methanol 9:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.36 (t, J = 6.4 Hz, 2H), 4.40 (t, J = 6.4 Hz, 2H), 6.95 (s, 1H), 7.01 (s, 1H), 7.11 (dd, J = 4.0 and 4.8 Hz, 1H), 7.54 (s, 1H), 7.63–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 40.6, 41.5, 119.2, 128.4, 129.7, 132.4, 134.6, 137.5, 143.4, 189.4; Anal. Calcd. for $C_{10}H_{10}N_2OS$: C 58.23, H 4.89, N 13.58. Found: C 58.37, H 4.75, N 13.72.

1-(Thiophen-2-yl)-3-(1*H*-1,2,4-triazol-1-yl)-1-propanone (11). Yellowish solid (435 mg, 70%), mp 57–58 °C, R_f = 0.26 (ethyl acetate–hexanes 4:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.51 (t, J = 6.2 Hz, 2H), 4.62 (t, J = 6.2 Hz, 2H), 7.11 (dd, J = 3.6 and 5.0 Hz, 1H), 7.65 (dd, J = 1.2 and 5.0 Hz, 1H), 7.69 (dd, J = 1.2 and 3.6 Hz, 1H), 7.89 (s, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 38.6, 44.1, 128.5, 132.6, 134.6, 143.3, 144.1, 152.2, 189.4; Anal. Calcd. for $C_9H_9N_3OS$: C 52.16, H 4.38, N 20.27. Found: C 52.40, H 4.62, N 20.04.

3-(1*H*-Tetrazol-1-yl)-1-(thiophen-2-yl)-1-propanone (12a). Off-white solid (280 mg, 45%), mp 112–113 °C, R_f 0.20 (hexanes–ethyl acetate 1:1 v/v); ^{1}H NMR (CD_3OD): δ 3.73 (t, J = 6.4 Hz, 2H), 4.89 (t, J = 6.4 Hz, 2H), 7.19 (dd, J = 4.0 and 5.2 Hz, 1H), 7.85 (dd, J = 1.2 and 4.8 Hz, 1H), 7.90 (dd, J = 1.2 and 4.0 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (CD_3OD): δ 39.0, 44.3, 129.6, 134.5, 135.9, 144.2, 145.4, 191.1; Anal. Calcd. for $C_8H_8N_4OS$: C 46.14, H 3.87, N 26.90. Found: C 46.29, H 4.06, N 26.75.

3-(2*H*-Tetrazol-2-yl)-1-(thiophen-2-yl)-1-propanone (12b). Off-white solid (190 mg, 31%), mp 86–87 °C, R_f 0.57 (hexanes–ethyl acetate 1:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.72 (t, J = 7.0 Hz, 2H), 5.09 (t, J = 7.0 Hz, 2H), 7.15 (dd, J = 3.8 and 5.0 Hz, 1H), 7.69 (dd, J = 1.2 and 5.0 Hz, 1H), 7.75 (dd, J = 1.2 and 3.8 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 37.8, 47.9, 128.5, 132.7, 134.8, 143.0, 153.0, 188.3; Anal. Calcd. for $C_8H_8N_4OS$: C 46.14, H 3.87, N 26.90. Found: C 46.33, H 4.03, N 27.09.

2-(3-Oxo-3-(thiophen-2-yl)propyl)cyclohexanone (13). Yellow solid (850 mg, 36%), mp 45–46 °C (lit.[2] mp 50–51 °C), R_f 0.48 (hexanes–ethyl acetate 5:1 v/v); ^{1}H NMR ($CDCl_3$): δ 1.34–1.50 (m, 1H), 1.61–1.76 (m, 3H), 1.81–1.92 (m, 1H), 2.00–2.13 (m, 3H), 2.24–2.35 (m, 1H), 2.35–2.49 (m, 2H), 2.84–2.96 (m, 1H), 2.98–3.10 (m, 1H), 7.11 (dd, J = 4.0 and 4.8 Hz, 1H), 7.60 (dd, J = 1.2 and 4.8 Hz, 1H), 7.76 (dd, J = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.0, 25.2, 28.3, 34.7, 37.2, 42.4, 50.0, 128.2, 132.2, 133.6, 144.4, 193.4, 213.2; Anal. Calcd. for $C_{13}H_{16}O_2S$: C 66.07, H 6.82. Found: C 65.76, H 7.02.

2-(Thiophen-2-yl)-5,6,7,8-tetrahydroquinoline (14). Light yellow oil (460 mg, 63%), R_f 0.47 (toluene); ^{1}H NMR ($CDCl_3$): 1.77–1.95 (m, 4H), 2.76 (t, J = 6.4 Hz, 2H), 2.94 (t, J = 6.4 Hz, 2H), 7.08 (dd, J = 3.6 and 4.8 Hz, 1H), 7.32 (dd, J = 1.2 and 4.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.51 (dd, J = 1.2 and 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.9, 23.3, 28.8, 32.8, 116.4,

123.9, 126.7, 127.9, 130.8, 137.4, 145.6, 149.9, 157.4; Anal. Calcd. for $C_{13}H_{13}NS$: C 72.52, H 6.09, N 6.51. Found: C 72.25, H 6.40, N 6.28.

5,5-Dimethyl-2-(3-oxo-3-(thiophen-2-yl)propyl)-1,3-cyclohexanedione (15). Yellow crystals (355 mg, 32%), mp 165–166 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 6H), 2.19 (br s, 2H), 3.32 (br s, 2H), 2.64 (t, J = 5.4 Hz, 2H), 3.21–3.28 (m, 2H), 7.14 (dd, J = 4.0 and 4.8 Hz, 1H), 7.69 (dd, J = 1.0 and 4.8 Hz, 1H), 7.78 (dd, J = 1.0 and 4.0 Hz, 1H), 9.77 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.4, 28.4, 31.6, 39.0, 43.0, 50.7, 113.6, 128.6, 133.7, 135.1, 142.8, 171.9, 197.1, 198.7; Anal. Calcd. for $C_{15}H_{18}O_3S$: C 64.72, H 6.52. Found: C 64.47, H 6.79.

3-(1*H*-Indol-3-yl)-1-(thiophen-2-yl)-1-propanone (16a). Colorless solid (345 mg, 34%), mp 114–115 °C (lit.[3] mp 105 °C), R_f 0.15 (hexanes–ethyl acetate 6:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.21–3.27 (m, 2H), 3.30–3.36 (m, 2H), 7.04 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 3.6 and 4.8 Hz, 1H), 7.12–7.24 (m, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 1.2 and 4.8 Hz, 1H), 7.63–7.67 (m, 1H), 7.68 (dd, J = 1.2 and 3.6 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.2, 40.2, 111.3, 115.3, 118.8, 119.5, 121.8, 122.2, 127.3, 128.2, 132.0, 133.6, 136.4, 144.5, 193.0; Anal. Calcd. for $C_{15}H_{13}NOS$: C 70.56, H 5.13, N 5.49. Found: C 70.32, H 5.31, N 5.68.

3-(1-Methyl-1*H*-indol-3-yl)-1-(thiophen-2-yl)-1-propanone (16b). Colorless solid (550 mg, 41%), mp 87–88 °C, R_f 0.35 (hexanes–ethyl acetate 9:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.20–3.27 (m, 2H), 3.29–3.35 (m, 2H), 3.74 (s, 3H), 6.92 (s, 1H), 7.08–7.18 (m, 2H), 7.21–7.28 (m, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 1.0 and 5.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 1.0 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.0, 32.7, 40.5, 109.4, 113.8, 118.9, 121.7, 126.7, 127.7, 128.2, 131.9, 133.5, 137.2, 144.5, 192.9; Anal. Calcd. for $C_{16}H_{15}NOS$: C 71.34, H 5.61, N 5.20. Found: C 71.12, H 5.39, N 5.37.

3-(5-(3-Oxo-3-(thiophen-2-yl)propyl)-1*H*-pyrrol-2-yl)-1-(thiophen-2-yl)-1-propanone (17). Yellow crystals (350 mg, 51%), mp 158–159 °C (ethyl acetate) (lit.[4] mp 158–160 °C); ^{1}H NMR (d_6-DMSO): δ 2.82 (t, J = 7.6 Hz, 4H), 3.24 (t, J = 7.6 Hz, 4H), 5.61 (d, J = 2.4 Hz, 2H), 7.24 (dd, J = 4.0 and 4.8 Hz, 2H), 7.96–8.01 (m, 4H), 10.37 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 22.2, 38.6, 104.3, 128.7, 129.2, 133.2, 134.7, 143.8, 192.4; Anal. Calcd. for $C_{18}H_{17}N_2O_2S$: C 62.94, H 4.99, N 4.08. Found: C 63.19, H 5.11, N 4.23.

1-Phenyl-3-(thiophen-2-yl)-4,5-dihydropyrazole (18a). Recrystallization of the solid obtained from compound **2** and phenylhydrazine from ethanol gave bright yellow crystals (370 mg, 54%), mp 100–101 °C (lit.[5] mp 100–101 °C); ^{1}H NMR ($CDCl_3$): δ 3.25 (t, J = 10.4 Hz, 2H), 3.88 (t, J = 10.4 Hz, 2H), 6.83–6.90 (m, 1H), 7.04 (dd, J=3.6 and 4.8 Hz, 1H), 7.09–7.15 (m, 3H), 7.27–7.34 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 33.0, 48.5, 113.2, 119.3, 125.9, 126.5, 127.4, 129.2, 137.0, 145.2, 145.8; Anal. Calcd. for $C_{13}H_{12}N_2S$: C 68.39, H 5.30, N 12.27. Found: C 68.63, H 5.19, N 12.05.

1-(4-Methoxyphenyl-3-(thiophen-2-yl)-4,5-dihydropyrazole (18b). Recrystallization of the solid obtained from compound **2** and 4-methoxyphenylhydrazine hydrochloride from ethanol gave yellow crystals (395 mg, 51%), mp 146–147 °C; ^{1}H NMR (d_6-DMSO): δ 3.25 (t, J = 10.4 Hz, 2H), 3.70 (s, 3H), 3.80 (t, J = 10.4 Hz, 2H), 6.84–6.91 (m, 2H), 6.96–7.03 (m, 2H), 7.10 (dd, J = 3.6 and 4.8 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.56 (d, J = 4.8 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 32.6, 49.3, 55.3, 114.0, 114.5, 126.7, 126.9, 127.7, 136.2, 140.2, 145.3, 152.8; Anal. Calcd. for $C_{14}H_{14}N_2OS$: C 65.09, H 5.46, N 10.84. Found: C 64.88, H 5.61, N 10.98.

1-(3-Chlorophenyl-3-(thiophen-2-yl)-4,5-dihydropyrazole (18c). Recrystallization of the solid obtained from compound **2** and 3-chlorophenylhydrazine hydrochloride from ethanol gave dark yellow crystals (345 mg, 44%), mp 99–100 °C; ^{1}H NMR ($CDCl_3$): δ 3.27 (t, J = 10.4 Hz, 2H), 3.86 (t, J = 10.4 Hz, 2H), 6.77–6.83 (m, 1H), 6.90–6.96 (m, 1H), 7.04 (dd, J = 3.6 and 5.2 Hz, 1H), 7.10 (t, J = 2.4 Hz, 1H), 7.13 (dd, J = 0.8 and 3.6 Hz, 1H), 7.18 (t, J = 8.4 Hz, 1H), 7.33 (dd, J = 1.2 and 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 33.1, 48.2, 111.1, 113.0, 119.0, 126.4, 127.0, 127.5, 130.2, 135.0, 136.5, 146.0, 146.6; Anal. Calcd. for $C_{13}H_{11}ClN_2S$: C 59.42, H 4.22, N 10.66. Found: C 59.68, H 4.49, N 10.37.

1-(4-Methylphenyl-3-(thiophen-2-yl)-4,5-dihydropyrazole (18d). Recrystallization of the solid obtained from compound **2** and 4-tolylhydrazine hydrochloride from ethanol gave yellow crystals (450 mg, 62%), mp 106–107 °C; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 3.24 (t, J = 10.4 Hz, 2H), 3.86 (t, J = 10.4 Hz, 2H), 6.99–7.06 (m, 3H), 7.07–7.14 (m, 3H), 7.29 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.7, 33.1, 49.0, 113.3, 125.7, 126.3, 127.4, 128.6, 129.7, 137.2, 143.9, 144.7; Anal. Calcd. for $C_{14}H_{14}N_2S$: C 69.39, H 5.82, N 11.56. Found: C 69.24, H 6.02, N 11.71.

2-(4-Chlorophenyl)-6-(thiophen-2-yl)pyridine (19a). Light brown crystals (505 mg, 62%), mp 88–89 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 7.13 (dd, J = 3.8 and 5.0 Hz, 1H), 7.42 (dd, J = 1.0 and 5.0 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.54–7.61 (m, 2H), 7.65 (dd, J = 1.0 and 3.8 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 8.06 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 117.3, 118.1, 124.8, 127.9, 128.1, 128.3, 129.0, 135.3, 137.5, 137.7, 145.4, 152.5, 155.6; Anal. Calcd. for $C_{15}H_{10}ClNS$: C 66.29, H 3.71, N 5.15. Found: C 66.47, H 3.93, N 5.00.

2-(4-Bromophenyl)-6-(thiophen-2-yl)pyridine (19b). Greyish crystals (595 mg, 63%), mp 105–106 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 7.13 (dd, J = 3.6 and 5.2 Hz, 1H), 7.42 (dd, J = 1.0 and 5.2 Hz, 1H), 7.54–7.67 (m, 5H), 7.74 (t, J = 7.8 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 117.4, 118.1, 123.7, 124.8, 127.9, 128.1, 128.6, 132.0, 137.7, 137.9, 145.3, 152.5, 155.6; Anal. Calcd. for $C_{15}H_{10}BrNS$: C 56.97, H 3.19, N 4.43. Found: C 57.21, H 3.37, N 4.20.

2-(4-Biphenyl-1-yl)-6-(thiophen-2-yl)pyridine (19c). Tan crystals (440 mg, 47%), mp 172–173 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.15 (dd, J = 4.0 and 5.2 Hz, 1H), 7.37–7.45 (m, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.63–7.80 (m, 7H), 8.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 117.1, 118.3, 124.7, 127.2, 127.4, 127.5, 127.6, 127.8, 128.1, 129.0, 137.5, 138.0, 140.8, 142.0, 145.6, 152.4, 156.4; Anal. Calcd. for $C_{21}H_{15}NS$: C 80.48, H 4.82, N 4.47. Found: C 80.25, H 5.04, N 4.59.

4-(Thiophen-2-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (20a). Yellow crystals (375 mg, 33%), mp 109–110 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.07 (t, J = 5.6 Hz, 2H), 3.79 (t, J = 5.6 Hz, 2H), 3.83 (br s, 1H), 6.70 (dd, J = 1.2 and 8.0 Hz, 1H), 6.87–6.93 (m, 1H), 6.96–7.03 (m, 1H), 7.07 (dd, J = 3.6 Hz and 4.8 Hz, 1H), 7.35 (dd, J = 1.2 and 8.0 Hz, 1H), 7.39 (dd, J = 1.2 and 4.0 Hz, 1H), 7.43 (dd, J = 1.0 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 33.7, 50.5, 119.6, 120.6, 127.1, 127.7, 128.1, 130.4, 131.6, 136.9, 141.4, 147.8, 162.1; Anal. Calcd. for $C_{13}H_{12}N_2S$: C 68.39, H 5.30, N 12.27. Found: C 68.13, H 5.52, N 12.04.

7,8-Dimethyl-4-(thiophen-2-yl)-2,3-dihydro-1*H*-1,5-benzodiazepine (20b). Orange leaflets (715 mg, 56%), mp 151–152 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 2.20 (s, 3H), 3.04 (t, J = 5.6 Hz, 2H), 3.71 (t, J = 5.6 Hz, 3H), 6.49 (s, 1H), 7.06 (dd, J = 4.0 and 5.2 Hz, 1H), 7.15 (s, 1H), 7.30 (dd, J = 1.2 and 4.0 Hz, 1H), 7.41 (dd, J = 1.2 and 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.6, 19.4, 33.8, 49.8, 120.2, 126.8, 127.6, 128.5, 129.6, 132.3, 134.4, 135.5, 138.9, 148.0, 160.6; Anal. Calcd. for $C_{15}H_{16}N_2S$: C 70.27, H 6.29, N 10.93. Found: C 70.06, H 6.04, N 11.17.

4-(Thiophen-2-yl)-2,3-dihydrobenzo[*b*]-1,4-thiazepine (21). Yellow oil (565 mg, 46%), R_f 0.59 (hexanes–ethyl acetate 4:1 v/v); ^{1}H NMR ($CDCl_3$): δ 2.97 (t, J = 6.8 Hz, 2H), 3.66 (t, J = 6.8 Hz, 2H), 7.02–7.09 (m, 1H), 7.12 (dd, J = 4.0 and 5.2 Hz, 1H), 7.21 (dd, J = 1.2 and 8.0 Hz, 1H), 7.35–7.42 (m, 1H), 7.49–7.57 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 30.5, 41.4, 123.8, 125.1, 125.5, 127.9, 128.7, 129.7, 131.2, 134.9, 145.0, 152.5, 165.8; Anal. Calcd. for $C_{13}H_{11}NS_2$: C 63.64, H 4.52, N 5.71. Found: C 63.87, H 4.26, N 5.54.

2-(Thiophen-2-yl)-3,4-dihydro-pyrimido[1,2-*a*]benzimidazole (tautomer A) and 2-(thiophen-2-yl)-1,4-dihydro-pyrimido[1,2-*a*]benzimidazole (tautomer B) (22). Yellow crystals (220 mg, 29%), mp 229–231 °C (ethanol); ^{1}H NMR (d_6-DMSO): δ 3.38 (t, J = 7.6 Hz, 2H) 4.36 (t, J = 7.6 Hz, 2H) 4.84 (d, J = 3.2 Hz, 2H) 5.29 (t, J = 3.2 Hz, 1H), 7.01–7.36 (m, 3H), 7.45–7.62 (m, 2H), 7.93–8.00 (m, 2H), 9.84 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 24.5, 36.9, 41.3, 91.2, 108.2, 109.5, 115.7, 118.9, 119.5, 121.4, 122.6, 124.5, 125.7, 127.7, 128.7, 132.3, 132.6, 133.2, 133.6, 137.6, 142.3, 143.3, 147.6, 150.8, 165.8 (for both tautomers); Anal. Calcd. for $C_{14}H_{11}N_3S$: C 66.38, H 4.38, N 16.59. Found: C 66.07, H 4.65, N 16.24.

1-Benzyl-4-hydroxy-4-(thiophen-2-yl)piperidin-3-yl thiophen-2-yl methanone (23). Colorless crystals (535 mg, 56%), mp 152–153 °C (ethanol); ^{1}H NMR (d_6-DMSO): δ 1.77 (d, J = 13.6 Hz, 1H, H_5), 2.05 (dt, J = 4.0 and 12.8 Hz, 1H, H_5), 2.49–2.59 (m, 1H, H_4), 2.60–2.76 (m, 2H, H_3 and H_4), 2.81 (dd, J = 2.8 and 10.8 Hz, 1H, H_3), 3.61 (s, 2H, H_6), 4.18 (dd, J = 3.2 and 11.2 Hz, 1H, H_2), 5.41 (s, 1H, OH), 6.83 (dd, J = 3.6 and 4.8 Hz, H_7), 7.08 (d, J = 3.6 Hz, 1H, H_8), 7.13 (dd, J = 4.0 and 4.8 Hz, 1H, H_{12}), 7.20 (d, J = 4.8 Hz, 1H, H_9), 7.21–7.28 (m, 1H, H_{18}), 7.29–7.39 (m, 4H, H_{16} and H_{17}), 7.93 (d, J = 3.6 Hz, 1H, H_{13}), 7.96 (d, J = 4.8 Hz, 1H, H_{11}); ^{13}C NMR (d_6-DMSO): δ 40.1 (C_5), 48.1 (C_4), 51.9 (C_3), 52.5 (C_2), 61.4 (C_6), 71.9 (C_1), 122.1 (C_8), 123.8 (C_9), 126.9 (C_7 and C_{18}), 128.1 (C_{17}), 128.8 (C_{12} and C_{16}), 134.4 (C_{13}), 136.3 (C_{11}), 138.0 (C_{15}), 143.5 (C_{14}), 153.6 (C_{10}), 195.2 (C_{19}); HRMS (EI) Calcd for $C_{21}H_{21}NO_2S_2$: 383.1014 (M^+). Found: 383.1009; Anal. Calcd. for $C_{21}H_{21}NO_2S_2$: C 65.76, H 5.52, N 3.65. Found: C 65.50, H 5.68, N 3.53.

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