*New Heterocyclic Syntheses from Pyridinethiones: an Efficient Route for the Syntheses of Some Novel Azo Derivatives of Thieno[2,3-*b*]pyridine as Potential Anti-bacterial and Anti-cancer Agents*

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RESUMEN

Se sintetizan derivados del sistema heterocíclico 3-(pirrol-1-il)tieno[2,3-*b*]piridina 5 y 6 con diversos sustituyentes en la posición 2. Algunos de estos productos se usan para preparar diversos anillos heterocíclicos que contienen nitrógeno u oxígeno en la posición mencionada. Se investigan las configuraciones electrónicas de productos seleccionados empleando el método de orbitales moleculares semiempírico AM1. Se observan variaciones considerables en la magnitud i en la orientación del momento dipolar. Además, se investiga la estabilidad relativa de las estructuras bajo condiciones fisiológicas calculando el componente electrostático de la energía libre de solvatación. La serie sintetizada muestra energías libres de solvatación favorables, dentro del margen de –30 a –23 kcal/mol. La alta polaridad y los cambios favorables de energía libre de solvatación en condiciones fisiológicas sugieren que la sustitución en la posición 2 podría incrementar la actividad biológica de los derivados de 3-(pirrol-1-il)tieno[2,3-*b*]piridina.

Palabras clave: **Tienopiridinas. 1,3-Cetoenamina. Hidrólisis. Acoplamiento. AM1. Energía libre de solvatación. Momento dipolar.**

SUMMARY

Derivatives of a heterocyclic system 3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine 5 and 6 carrying various substituents in the position 2 were synthesized. Some of these products were used to build up a variety of nitrogen- and/or oxygen-containing heterocyclic rings in that position. The electronic configurations of selected products were investigated using the AM1 semi-emperical molecular orbital method. Considerable variations in the magnitude and orientation of the dipole moment were observed. Further, the relative stability of the structures was investigated at physiological conditions *via* calculation of the electrostatic component of the solvation free energy. The synthesized series showed favourable solvation free energies which were within the range from –30 to –23 kcal/mol. The high polarity and favourable solvation free energy changes at physiological conditions suggest that substitution in the position 2 could enhance the biological activity of the 3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine derivatives.

Key words: **Thienopyridines. 1,3-Ketoenamine. Hydrolysis. Coupling. AM1. Solvation free energy. Dipole moment.**

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RESUM

Es sintetitzen derivats del sistema heterocíclic 3-(pirrol-1-il)tieno[2,3-*b*]piridina 5 i 6 amb diversos substituents a la posició 2. Alguns d'aquests productes s'empren per a preparar diversos anells heterocíclics que contenen nitrogen o oxigen en la posició esmentada. S'investiguen les configuracions electròniques de productes seleccionats emprant el mètode d'orbitals moleculars semiempíric AM1. S'observen variacions considerables en la magnitud i l'orientació del moment dipolar. A més, s'investiga l'estabilitat relativa de les estructures sota condicions fisiològiques calculant el component electrostàtic de l'energia lliure de solvatació. La sèrie sintetitzada mostra energies lliures de solvatació favorables, dins el marge de –30 a –23 kcal/mol. L'alta polaritat i els canvis favorables d'energia lliure de solvatació en condicions fisiològiques suggereixen que la substitució en la posició 2 podria incrementar l'activitat biològica dels derivats de 3-(pirrol-1-il)tieno[2,3-*b*]piridina.

Mots clau: **Tienopiridines. 1,3-Cetoenamina. Hidròlisi. Acoblament. AM1. Energia lliure de solvatació. Moment dipolar.**

INTRODUCTION

In the last few years, 3-cyanopyridine-2-(1*H*)-thiones have attracted great attention from many researchers due to their unusual properties and possibilities for use as synthons for preparing novel biologically active substances[1-4]. For example, 4,6-diaryl-3-cyanopyridine-2-(1*H*)-thiones are used for the synthesis of antioxidants, biocides, dyes, and other practically valuable substances[5-7]. Additionally, a wide range of biological activities has been attributed to thienopyridines. In particular, derivatives of the thieno[2,3-*b*]pyridine nucleus have significant biological importance. They show anti-bacterial[8, 9], anti-cancer[10], and anti-inflammatory[11, 12] activities. Others have been reported to be used as lipoxygenases inhibitors[13]. On the other hand, pyrrole and its derivatives also constitute an important family of compounds due to their applications as pharmaceuticals, such as fungicides, antibiotics[14-17], nonsteriodal anti-inflammatory drugs (NSAIDS)[18-20], cholesterol-reducing drugs[21], and anti-tumor agents[22, 23]. In conjunction with an ongoing program aimed at developing efficient syntheses of functionally substituted heteroaromatics utilizing readily obtainable inexpensive starting materials[24-26], it seemed therefore relevant to design and synthesize a series of novel 3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine derivatives as potential bioactive molecules. This approach was also stimulated by the assumption that the introduction of biologically active heterocycles in the 2-position of thieno[2,3-*b*]pyridine moiety may lead to compounds of general and analytical biological significance.

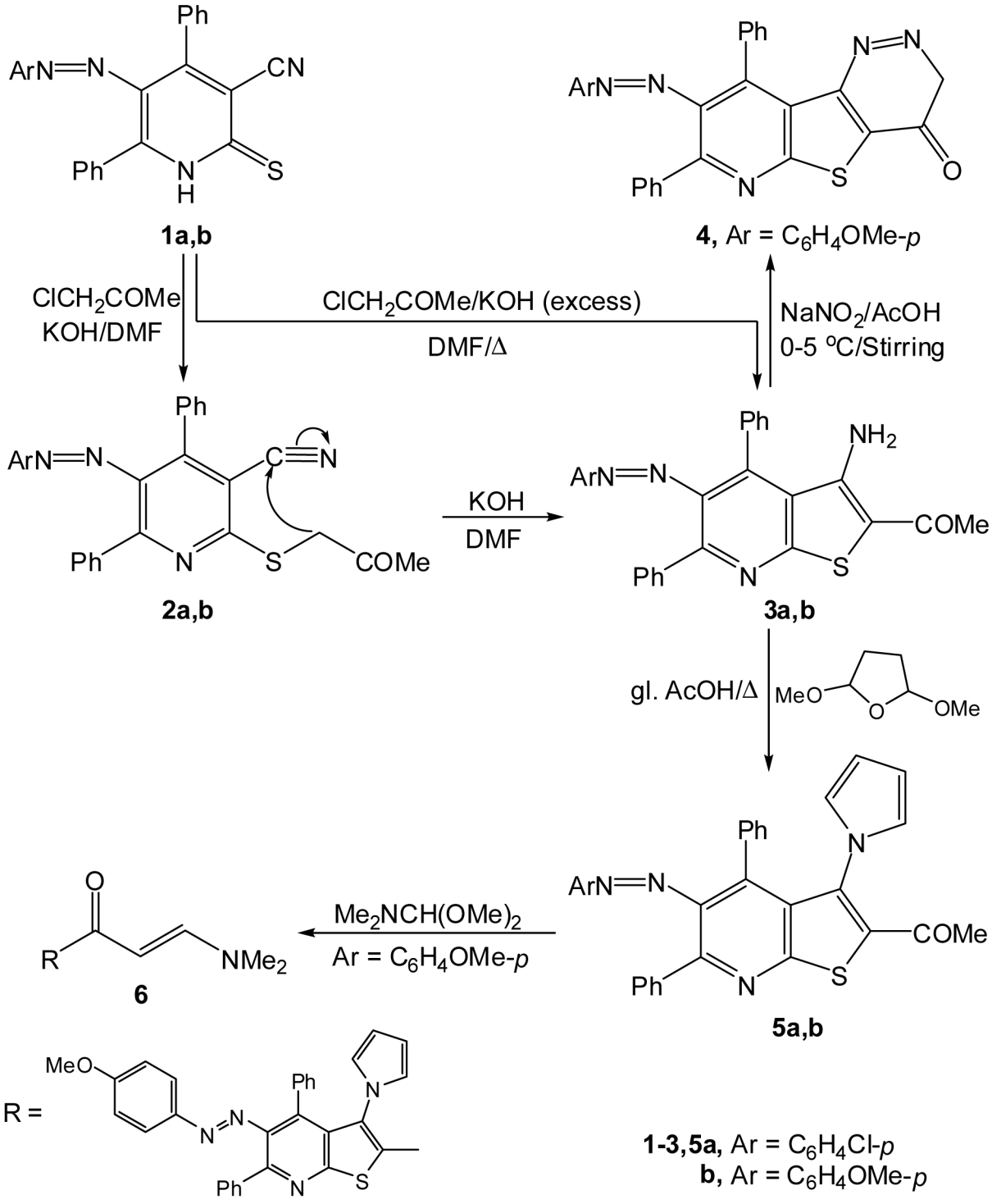
RESULTS AND DISCUSSION

In our recent review[27], we presented the chemistry of α-haloketones and their utility in heterocyclic synthesis. In the present study, we have extended the utility of an appropriate α-haloketone, namely; chloroacetone, in the synthesis of aminoketones **3a,b** as new key precursors for this study. Thus, *S*-alkylation of pyridinethione derivative **1a**[28, 29] (Ar = C_6H_4Cl-*p*) with chloroacetone was carried out in the presence of alkali. *S*-Acetylmethylthiopyridine **2** was the product from reaction of an equimolar ratio of **1a**, chloroacetone, and potassium hydroxide. When compound **2** was heated in dimethylformamide (DMF) in the presence of alkali (*Thorpe-Ziegler* conditions), it cyclized into the corresponding 2-acetyl-3-aminothienopyridine **3a**. Alternatively, compound **3a** may also be obtained in one step from the same starting materials without isolation of the intermediate product by using a two-fold excess of potassium hydroxide. Better yield of the required product was obtained in this case. Likewise, it has been found that pyridinethione derivative **1b**[28, 29] (Ar = C_6H_4OMe-*p*) could react with chloroacetone, in DMF in the presence of excess potassium hydroxide, to afford the bicyclic product **3b**. Obviously, this reaction occurred, in this case, through the intermediacy of **2b** (Scheme 1). The thieno[2,3-*b*]pyridine structure **3** was suggested for those reaction products on the bases of their molecular formulae and on their spectral data. Compound **3a**, as a representative example, indicated in its IR spectrum the disappearance of the absorption band characteristic for cyano group and the presence of two absorption bands due to symmetric and asymmetric stretching frequencies of primary amine at 3415 and 3275 cm^{-1} and another band at 1645 cm^{-1} corresponding to carbonyl group. Its ^1H NMR spectrum exhibited a singlet integrating for 3-protons at δ2.61 ppm attributable to acetyl group, as well as a singlet integrating for 2-protons at δ8.20 ppm assigned to the NH_2 group, besides the expected multiplet signal for the aromatic protons. Moreover, its ^{13}C NMR spectrum was also in accordance with the proposed structure (see Experimental section for details).

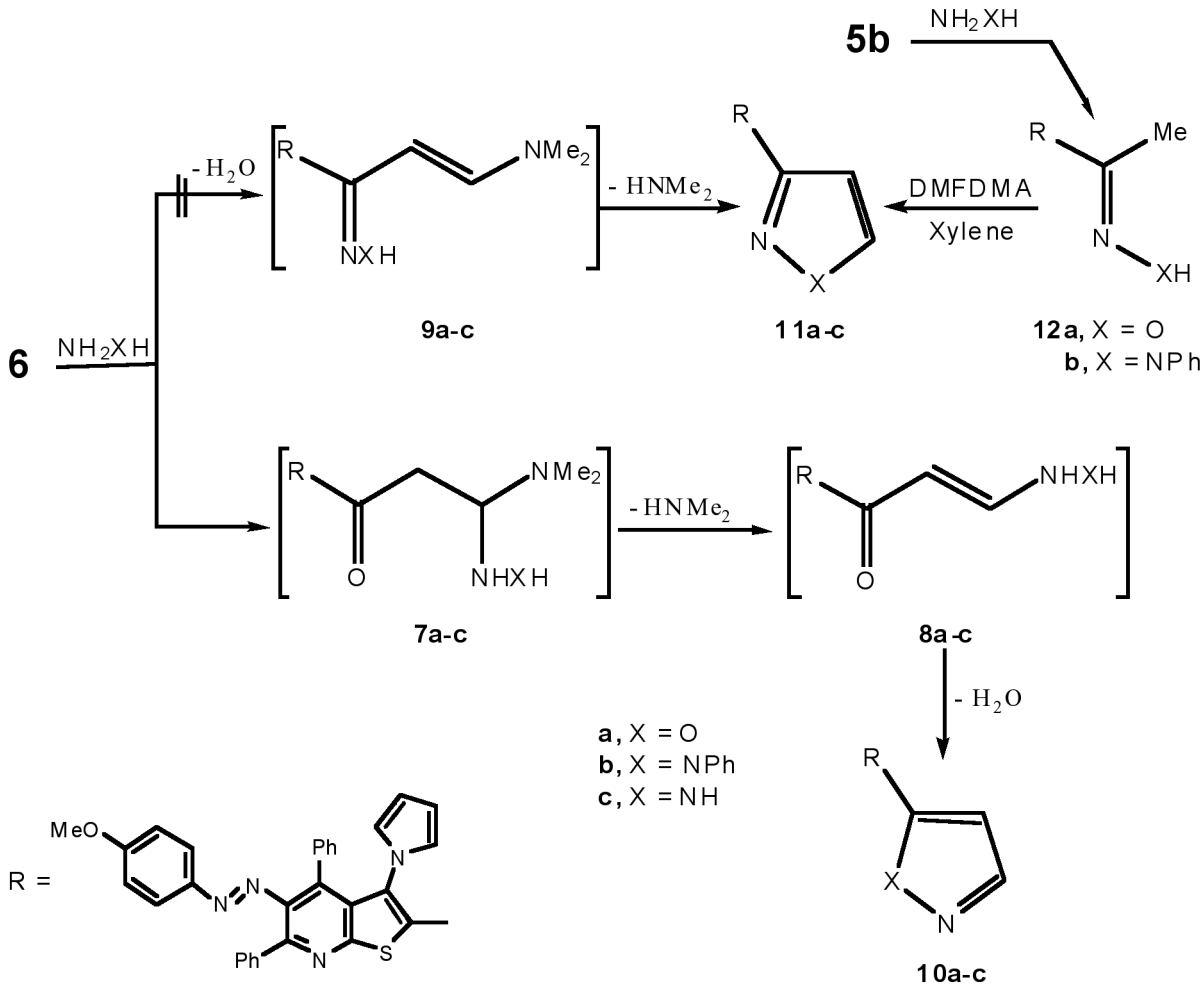
The reactivity of enaminoacetyl moiety in **3b** was demonstrated by its treatment with nitrous acid to produce a tricyclic product of molecular formula $C_{28}H_{19}N_5O_2S$ (M/Z = 489) which could be formulated as the thienopyridopyridazinone derivative **4**, according to elemental analysis and spectral data. The IR spectrum of this product showed the presence of pyridazinone-CO (1704 cm^{-1}) group while its ^1H NMR spectrum revealed the absence of NH_2 signal and the presence of a singlet signal for pyridazinone-CH_2. In accordance with literature[30], β-enaminocarbonyl compounds **3a,b** were easily condensed with 2,5-dimethoxytetrahydrofuran, in boiling acetic acid, to give the respective pyrrolyl ketones **5a,b** (Scheme 1). The analytical and spectroscopic (IR and NMR) data of the products **5a,b** are consistent with their structural assignments (see Experimental section for details).

In spite of the rich chemistry with pyridinethiones[31-34], it is surprisingly that there is no report, to the best of our knowledge, on the formation of enaminones using pyridinethiones as starting materials. In this regards, the reactivity and synthetic potentials of the acetyl derivative **5b** for the formation of an enaminone was explored by its interaction with little excess (1:1.2 mole) of dimethylformamide dimethylacetal (DMFDMA). This reaction led to the formation of a bicyclic product of molecular formula $C_{35}H_{29}N_5O_2S$ (*M/Z* = 583), whose structure was based on correct elemental analysis and spectroscopic data studies. Thus, its IR spectrum revealed the presence of the absorption band characteristic for CO group at 1652 cm^{-1}. Also, its ^1H NMR spectrum exhibited, besides the expected signals, a singlet signal at δ2.98 (6H) ppm due to the dimethylamino group as well as two doublets at δ5.75 (1H) and δ8.40 (1H) ppm with a *J* value of 14 Hz which can be only attributed to *trans* olefinic protons. Furthermore, its ^{13}C NMR spectrum was also in agreement with the proposed structure. All these data indicate that the reaction product could be formulated as the 3-(dimethylamino)-1-(thieno[2,3-*b*]pyridinyl)propenone structure **6**. To our knowledge, this is the first reported formation of an β-enaminoketone from a pyridinethione.

The versatility of the 1,3-ketoenamine **6** was proved by studying its reactivity towards each of nitrogen nucleophiles and nitrogen electrophiles as well (Scheme 2 & 3). Interestingly, this enaminone has been utilized as a starting material for preparing the targeted isoxazole and pyrazole ring systems (Scheme 2). Thus, treatment of that β-


1a,b
4, Ar = C6H4OMe-p
ClCH2COMe
KOH/DMF
ClCH2COMe/KOH (excess)
DMF/Δ
NaNO2/AcOH
0-5 °C/Stirring
2a,b
KOH
DMF
3a,b
gl. AcOH/Δ
MeO
OMe
Me2NCH(OMe)2
Ar = C6H4OMe-p
6
5a,b
R =
1-3,5a, Ar = C6H4Cl-p
b, Ar = C6H4OMe-p

Scheme 1

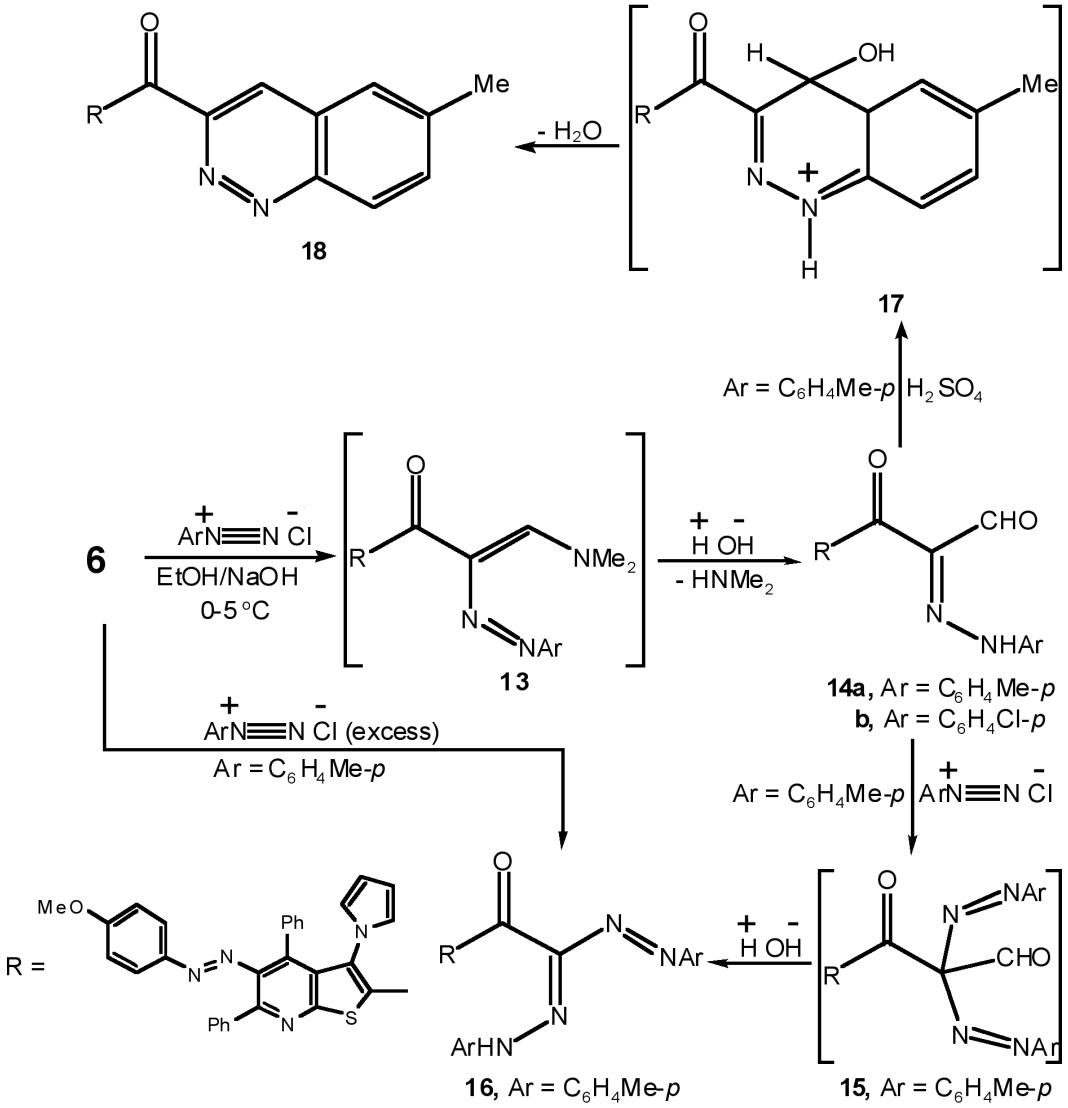


Scheme 2

ketoenamine **6** with hydroxylamine hydrochloride, in the presence of sodium acetate in ethanol, furnished a cyclic product that may be formulated as **10a** or **11a**. In order to establish the structure of that product, the acetyl derivative **5b** was allowed to react with hydroxylamine hydrochloride and subsequent treatment of the formed oxime **12a** with DMFDMA. The product of this sequence of reactions proved to be different from that of the reaction of **6** with hydroxylamine hydrochloride. Thus, the isoxazole structure **10a** could be established for that product. By analogy with hydroxylamine, compound **6** also reacted with phenylhydrazine to yield a product of addition and dimethylamine elimination. Again, the pyrazole structure **10b** was established for that product based on the non-identity of reaction of **6** with phenylhydrazine with a sample of **11b**, prepared *via* initial condensation of **5b** with phenylhydrazine and subsequent reaction of the formed phenylhydrazone **12b** with DMFDMA. The synthesis was expanded to include the preparation of a new pyrazole derivative **10c** by reaction of compound **6** with hydrazine hydrate. It can thus be stated that the reaction of **6** with hydroxylamine hydrochloride, phenylhydrazine, or hydrazine hydrate proceeded by initial addition of the unsubstituted hydroxylamine or hydrazine nitrogen to the activated double bond of **6** to form the non-isolable acyclic adducts **7a-c** followed by elimination of a dimethylamine molecule to give the acyclic intermediates **8a-c**. The latter underwent intramolecular condensation to yield the final products **10a-c**, respectively, whereas compounds **11a,b** arose by the alternate route, *i.e.* condensation of **12a,b** with DMFDMA (Scheme 2). Elucidation of the proposed structure of the latter products was established on the basis of elemental analyses and spectral background in each case. No absorption bands for CO groups in the IR spectra of **10a-c**, indicating the formation of a cyclic structure, in each case. Additionally, their ^{1}H NMR spectra revealed the complete absence of dimethylamino group, while they revealed only the presence of signals for methoxy, pyrrole-CH, isoxazole-CH or pyrazole-CH and aromatic protons (see Experimental section for details). The above reactions of the 1,3-ketoenamine **6** with various nitrogen nucleophiles open up a facile and convenient route to a variety of isoxazoles and pyrazoles, that are otherwise difficult to access, and seem to be of interest as potential bioactive molecules.

The reactivity of the ketoenamine **6** towards some nitrogen electrophiles was also examined. It has been found that incorporation of the cinnoline moiety into thienopyridine structure was achieved by converting of the enaminone **6** into its corresponding acyclic hydrazonal **14a** followed by cyclization of the latter with sufuric acid. Thus, typical for our recent reported behaviour of enamines towards aromatic diazonium salts[26, 35], compound **6** was coupled with an equimolar amount of *p*-tolyldiazonium

chloride or its *p*-chloro analogue, yielding products of coupling and hydrolysis of the dimethylamine moiety. Thus, the acyclic β-ketoaldehyde structure **14** could be established for those products based on their ^{1}H NMR spectra. In case of **14a**, ^{1}H NMR spectrum showed the appearance of the formyl group at δ 10.02 ppm and the hydrazone hydrogen proton at δ 14.20 ppm. Formation of **14a,b** was assumed to be formed by coupling at C-2' of the α,β-unsaturated ketone **6** with diazonium ion followed by hydrolysis of the substituent at 3-position into the formyl group by the action of the aqueous base existing in the medium. *p*-Tolylhydrazone derivative **14a** seemed to be a useful candidate for further chemical transformations. Thus, it further coupled with *p*-tolylbenzenediazonium chloride salt, yielding the bisazo compound **16** *via* the intermediacy of **15**. The structure of the isolated formazan **16** was further proved by an alternative synthesis. Thus, it could be successfully obtained *via* an independent one step route involving the coupling of **6** with excess *p*-tolylbenzenediazonium chloride in DMF at 0-5 °C. Compound **16** prepared by this route was found to be identical in all respects (mp, mixed mp and IR data) to that prepared as described before. Closure of the cinnoline ring was carried out by condensation of the arylhydrazonal **14a** with concentrated sulfuric acid to give, similar to our earlier report on arylhydrazonals[35], the corresponding cinnoline derivative **18**. A proposed mechanism for the formation of **18** involved a nucleophilic attack by the aromatic ring of the hydrazone moiety on the formyl carbonyl carbon, affording the intermediate **17** followed by elimination of a water molecule to give the final product **18** (Scheme 3). The analytical and spectral data obtained for **18** were in agreement with the assigned structure. A Band of CO group appeared in its IR spectrum, while its ^{1}H NMR spectrum confirmed the presence of CH_3 and OCH_3 functions, in addition of the aromatic protons, in their proper positions (see Experimental section for details). This reaction represents an easy access to 3-aroylcinnoline **18**. Notably, a literature survey revealed that benzopyridazine analogues are biologically interesting candidates[36], especially as antibacterial[37] and anxiolytic[38] agents. Work along the expansion of such synthetic approach is now in progress. A discussion of the biological results will be the subject of a future publication.



Scheme 3

Conformational flexibility and relative stability at physiological conditions

Due to the importance of the thieno[2,3-*b*]pyridines in terms of their established biological activities, it's been necessary to understand quantitatively the effect of different substituents on the electronic properties of the synthesized series. This has been investigated via calculation of the electronic distribution of the structures using the AM1 level of theory[39, 40] (see Energetics).

The molecular structure is by no means a still-life image. The thienopyridine structure is a common moiety throughout the series with a multitude of rotameric states due to free rotation of the phenyl and the *p*-methoxyphenylazo substituents. These single-bond rotations are interdependent and correlated due to the closeness and bulkiness of the substituents and thereby the rotameric states of the two phenyl rings are very much dependent on the rotameric state of the intervening *p*-methoxyphenylazo group. Therefore, we decided to map the dihedral energy profile of the *p*-methoxyphenylazo substituent for each member in the series by incrementing the C1-C2-N=N dihedral in 10-degree steps (Figure 1). The energy profiles indicate that the structures span two minima that are less than 0.5 kcal/mol apart with an energy barrier that is less than 2.5 kcal/mol. Therefore, at room temperature, a state of equilibrium exists where the

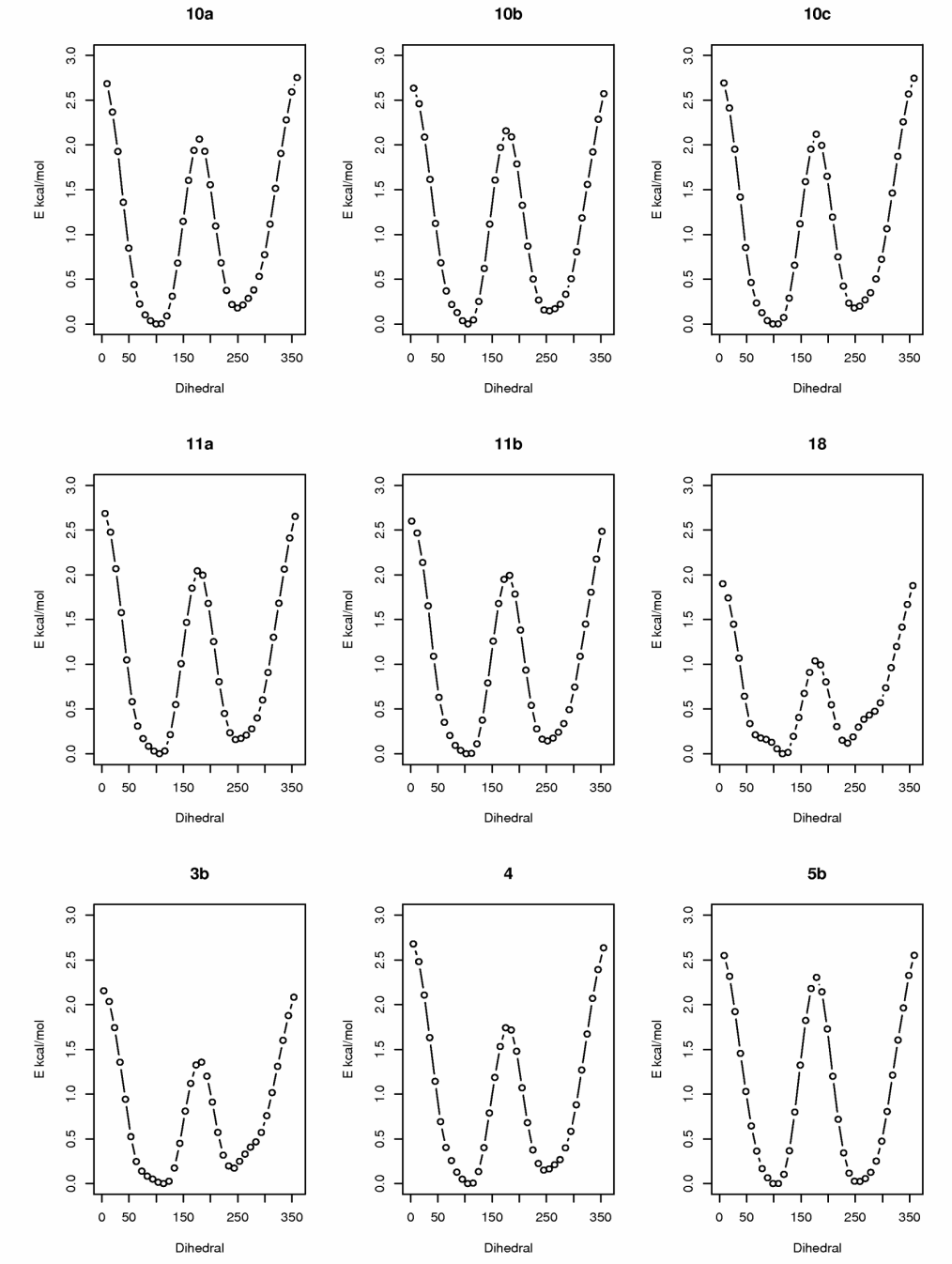


Figure 1. Energy profiles of the C-C-N=N dihedral rotation for the nine thieno[2,3-*b*]pyridine derivatives based on applying constraints at incremental dihedral steps of 10 degrees and relaxation of the free degrees of freedom by geometry optimization using the AM1 semiemperical model.

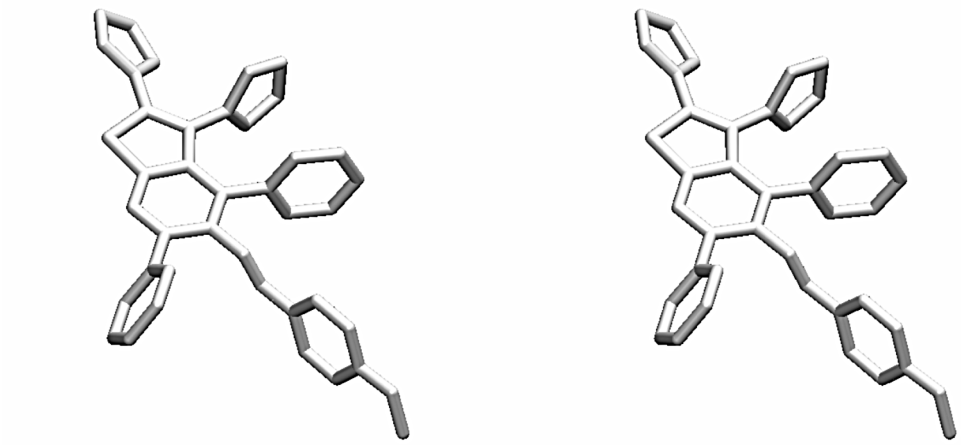


Figure 2. Cross-eyed stereo view of the energy-minimized geometry of **11a**-structure using the AM1. Hamiltonian at a restricted Hartree-Fock (RHF) self-consistent field level. For the sake of clarity, hydrogen atoms are not shown.

p-methoxyphenylazo group is equally likely to exist in two rotameric states. Moreover, the low energy barriers between the two minima indicate that intermediate states have significant contribution to the equilibrium ensemble. Importantly, the electronic properties of the ensemble of the rotameric states does not span a significant range of variation (data not shown); *e.g.* the direction of the dipole moment lies within ± 10º from the most stable structure. Therefore, we decided to focus only on the lowest energy; *i.e.* the most stable conformer for each structure in the series. It is interesting to note that a common feature of the lowest energy structures is the stacking of the substituents in a direction which is almost perpendicular to the thieno[2,3-*b*]pyridine moiety (Figure 2). Such stacking confers stability on the molecular structures whilst its degree is primordial for their relative stability. This is a reminiscent of the role of base-pair stacking in DNA structures[41, 42].

However, given that the biological system is the native environment for *in vivo* studies of putative drug candidates, the calculations have been supplemented by computation of the solvation free energy (ΔG_{solv}) of each of the series members *via* solving the Poisson-Boltzmann equation[43] at physiological conditions (0.15 M NaCl and 310 K). Inspection of Table I reveals that the whole series shows favourable free energies of solvation that are within the range from –30 to –23 kcal/mol with the **3b** structure being the least stabilized. It is quite evident thereby that substitution in the 2-position enhances the stability of the thieno[2,3-*b*]pyridine derivatives at physiological conditions. The trend in stability due to solvation under these conditions is also closely matched by decrease in the magnitude of the dipole moment whilst the **3b** structure having the largest dipole moment (Table I). Moreover, the variation in the magnitude of the dipole moments is accompanied by noticeable

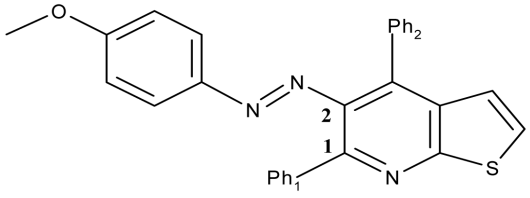


TABLE I

The conformational parameters and energetics of the lowest energy conformers of thieno[2,3-*b*]pyridine derivatives.

Structure	Dihedrals			ΔG_{solv} [kcal/mol]	Dipole Moment [Debye]	IP‡ [Hartree]	HOMO-LUMO gap [Hartree]
	C1-C2-N=N	Ph_1	Ph_2				
11b	102.0	-117.8	85.6	-31.152	1.978	0.313	0.280
18	116.0	-117.4	92.4	-29.380	4.644	0.284	0.245
10c	98.2	-117.7	91.1	-28.340	4.773	0.317	0.276
10b	105.5	-116.7	75.9	-27.957	4.398	0.315	0.279
11a	105.8	-117.1	85.1	-26.725	5.017	0.320	0.279
5b	98.6	-116.3	73.4	-26.530	5.010	0.315	0.276
10a	99.5	-117.8	92.8	-25.634	5.500	0.323	0.274
4	104.9	-116.9	74.6	-25.325	3.909	0.323	0.271
3b	113.4	-117.1	99.3	-23.915	7.216	0.297	0.267

‡ IP: The Ionization Potential

change in its direction (Figure 3) which indicates appreciable redistribution of charge over the molecular skeleton due to substitution. This could have drastic consequences on the mode of binding of this series of structures to putative receptor sites, which is the subject of an ongoing study. On the other hand, the ionisation potential and the HOMO-LUMO energy gap do not show significant variation due to substitution in the 2-position which implies a limited effect of the current substitution scheme on charge transfer reactions.

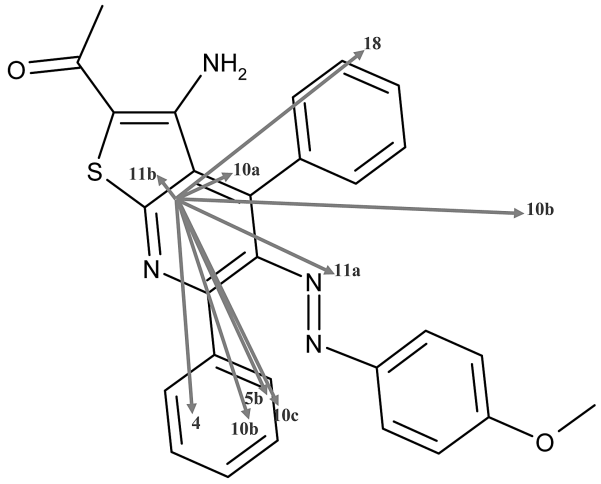


Figure 3. Variation of the magnitude and direction of the dipole moment of thieno[2,3-*b*]pyridine derivatives. For the sake of clarity, the dipole moment vectors were translated to the centre of mass of the thieno[2,3-*b*]pyridine moiety.

CONCLUSION

In conclusion, we have demonstrated the potential uses of 2-acetyl derivative **5b** and enaminone **6** as new versatile building blocks for the preparation of a variety of pharmaceutically important arylazo derivatives of 3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine, for which we might expect a wide spectrum of bioresponses, especially as anti-bacterial and anti-cancer agents.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. EI mass spectra were recorded on a Finnigan MAT SSQ 710 at 70 eV. Compounds **1a,b** were prepared following the published procedure[28, 29].

Synthesis of 2-Acetylmethylthio-5-[(4-chlorophenyl) diazenyl]-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (2)

Chloroacetone (0.005 mol) was added to a stirred suspension of pyridinethione **1a** (0.005 mol), in dimethylformamide (20 ml) in the presence of potassium hydroxide (0.005 mol). The reaction mixture was kept for 2 h at room temperature under stirring and then diluted with cold water (~ 20 ml). The precipitate was filtered off, washed with water, dried and recrystallized from EtOH to give the mercapto derivative **2** (0.75 g; 31%). Mp 120-122 ºC; IR (ν/cm^{-1}) = 3055 (CH aromatic), 2226 (CN), 1710 (C=O ketone); ^{1}H NMR δ_H = 2.36 (s, 3H, $COCH_3$), 6.03 (s, 2H, SCH_2), 7.35-7.97 (m, 14H, $2C_6H_5$, C_6H_4); $C_{27}H_{19}ClN_4OS$ (482.984): Calcd: C, 67.14; H, 3.97; Cl, 7.34; N, 11.60; S, 6.64; Found: C, 66.87; H, 4.02; Cl, 7.12; N, 11.35; S, 6.40.

General Procedure for the Synthesis of 5-(Aryldiazenyl)-2-acetyl-3-amino-4,6-diphenylthieno[2,3-*b*]pyridines 3a,b

Method (A) for compounds 3a,b

To a solution of either pyridinethione **1a** or **1b** (0.005 mol) in dimethylformamide (25 ml), potassium hydroxide (0.01 mol) and chloroacetone (0.005 mol) were added. The reaction mixture was refluxed with stirring for 1 h and then allowed to stand at room temperature overnight under stirring. The reaction mixture was then diluted with cold water and the resulting precipitate, in each case, was removed by filtration, dried and recrystallized from the proper solvents to give the enaminoketones **3a** (1.28 g; 53%) and **3b** (1.34 g; 56%), respectively.

2-Acetyl-3-amino-5-[(4-chlorophenyl)diazenyl]-4,6-diphenylthieno[2,3-*b*]pyridine (3a)

Mp 211-213 ºC (DMF/H_2O); IR (ν/cm^{-1}) = 3415, 3275 (NH_2), 3036 (CH aromatic), 1645 (C = O with H-bonding), 1614 (C=N); ^{1}H NMR δ_H = 2.61 (s, 3H, $COCH_3$), 7.41-7.89 (m, 14H, $2C_6H_5$, C_6H_4), 8.20 (s, br, 2H, NH_2, D_2O-exchangeable); ^{13}C NMR δ_C = 27.3 (CH_3), 122.8, 125.4, 126.1, 126.5, 127.0, 127.4, 128.1, 128.4, 128.9, 129.5, 130.4, 134.2, 137.9, 138.9, 142.5, 143.6, 144.8, 150.5, 158.1 (aromatic-C), 191.8 (C=O); $C_{27}H_{19}ClN_4OS$ (482.984): Calcd: C, 67.14; H, 3.97; Cl, 7.34; N, 11.60; S, 6.64; Found: C, 66.91; H, 3.73; Cl, 7.21; N, 11.47; S, 6.51.

2-Acetyl-3-amino-5-[(4-methoxyphenyl)diazenyl]-4,6-diphenylthieno[2,3-b]pyridine (3b)

Mp 190-191 °C (1,4-dioxane); IR (ν/cm^{-1}) = 3421, 3286 (NH_2), 3040 (CH aromatic), 1645 (C=O with H-bonding), 1618 (C=N); ^{1}H NMR δ_H = 2.49 (s, 3H, $COCH_3$), 3.91 (s, 3H, OCH_3), 7.11-7.82 (m, 14H, $2C_6H_5$, C_6H_4), 7.99 (s, br, 2H, NH_2, D_2O-exchangeable); MS: *m/z* (%) = 478 (M^+, 17%); $C_{28}H_{22}N_4O_2S$ (478.565): Calcd: C, 70.27; H, 4.63; N, 11.71; S, 6.70; Found: C, 70.03; H, 4.48; N, 11.47; S, 6.61.

Method (B) for compound 3a

Potassium hydroxide (0.005 mol) was added to compound **2** (0.005 mol) in dimethylformamide (20-25 ml), the mixture was refluxed with stirring for 30 min and then diluted with cold water (~ 20 ml). The precipitate formed was filtered off and recrystallized from aqeuous ethanol to give a solid product (0.97 g; 40%) that was found to be identical in all aspects (mp, mixed mp, and IR data) to authentic sample of **3a** obtained by method A.

Synthesis of 8-[(4-Methoxyphenyl)diazenyl]-7,9-diphenylpyrido[3',2':4,5]thieno[3,2-*c*]pyridazin-4(3*H*)-one (4)

A sample of sodium nitrite (0.005 mol) dissolved in water (5 ml) was added dropwise with stirring to an ice-cold solution (0-5 ºC) of **3b** (0.003 mol) in acetic acid (30 ml). After the completion of addition, the reaction mixture was stirred for 1 h and then left overnight at room temperature. The solid obtained was isolated by filtration, dried and recrystallized from EtOH to give the corresponding tricyclic product **4** (0.72 g; 49%). Mp 161-162 ºC; IR (ν/cm^{-1}) = 3065 (CH aromatic), 1704 (C=O ring), 1622 (C=N); ^{1}H NMR δ_H = 3.80 (s, 3H, OCH_3), 4.88 (s, 2H, pyridazinone-CH_2), 7.27-7.85 (m, 14H, $2C_6H_5$, C_6H_4); MS: *m/z* (%) = 489 (M^+, 22%); $C_{28}H_{19}N_5O_2S$ (489.548): Calcd: C, 68.70; H, 3.91; N, 14.31; S, 6.55; Found: C, 68.53; H, 3.82; N, 14.13; S, 6.40.

General Procedure for the Synthesis of 5-(Aryldiazenyl)-2-acetyl-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*] pyridines 5a,b

A mixture of either enaminoketone **3a** or **3b** (0.005 mol) and dimethoxytetrahydrofuran (0.005 mol), in glacial acetic acid (30 ml), was boiled under reflux for 1 h. The solvent was distilled off under reduced pressure and the residual products were triturated with water, whereupon the solid that formed, in each case, was collected by filtration and recrystallized from the appropriate solvent to give the corresponding pyrrol-1-yl derivatives **5a** (1.28 g; 48%) and **5b** (1.45 g; 55%), respectively.

2-Acetyl-5-[(4-chlorophenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine (5a)

Mp 148-149 ºC (MeOH); IR (ν/cm^{-1}) = 3042 (CH aromatic), 1681 (C=O ketone), 1617 (C=N); ^{1}H NMR δ_H = 2.57 (s, 3H, $COCH_3$), 6.29 (m, 2H, 3'-H, 4'-H pyrrole), 7.10 (m, 2H, 2'-H, 5'-H pyrrole), 7.47-7.92 (m, 14H, $2C_6H_5$, C_6H_4); ^{13}C NMR δ = 26.9 (CH_3), 107.8, 119.0 (pyrrole-C), 125.1, 125.6, 126.3, 126.8, 127.1, 127.6, 128.2, 128.6, 129.0, 129.3, 130.1, 133.9, 138.1, 139.4, 142.9, 143.3, 144.7, 150.7, 158.5 (aromatic-C), 191.2 (C=O); $C_{31}H_{21}ClN_4OS$ (533.043): Calcd: C, 69.85; H, 3.97; Cl, 6.65; N, 10.51; S, 6.02; Found: C, 69.57; H, 3.85; Cl, 6.51; N, 10.39; S, 5.88.

2-Acetyl-5-[(4-methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine (5b)

Mp 127-128 ºC (MeOH/H_2O); IR (ν/cm^{-1}) = 3037 (CH aromatic), 1681 (C=O ketone), 1613 (C=N); ^{1}H NMR δ_H = 2.44 (s, 3H, $COCH_3$), 3.86 (s, 3H, OCH_3), 6.37 (m, 2H, 3'-H, 4'-H pyrrole), 7.02 (m, 2H, 2'-H, 5'-H pyrrole), 7.33-7.79 (m, 14H, $2C_6H_5$, C_6H_4); MS: *m/z* (%) = 528 (M^+, 18%); $C_{32}H_{24}N_4O_2S$ (528.624): Calcd: C, 72.71; H, 4.58; N, 10.60; S, 6.07; Found: C, 72.51; H, 4.33; N, 10.38; S, 5.90.

Synthesis of 3-(Dimethylamino)-1-{5-[(4-methoxyphenyl) diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*] pyridin-2-yl}prop-2-en-1-one (6)

A mixture of **5b** (0.005 mol) and DMFDMA (0.006 mol) was refluxed in xylene (30 ml) for 12 h. The solvent was removed by evaporation under *vacuo*. The solid formed was filtered off, dried and recrystallized from EtOH to give the enaminone **6** (1.52 g; 52%). Mp 172 ºC; IR (ν/cm^{-1}) = 3050 (CH aromatic), 1652 (C=O ketone), 1616 (C=N); ^{1}H NMR δ_H = 2.98 (s, 6H, $2NCH_3$), 3.96 (s, 3H, OCH_3), 5.75 (d, 1H, *J* = 14 Hz, vinyl H-2), 6.22 (m, 2H, 3'-H, 4'-H pyrrole), 6.93 (m, 2H, 2'-H, 5'-H pyrrole), 7.20-7.71 (m, 14H, $2C_6H_5$, C_6H_4), 8.40 (d, 1H, *J* = 14 Hz, vinyl H-3); ^{13}C NMR δ_C = 45.2 [$N(CH_3)_2$], 56.3 (OCH_3), 93.0 (olefinic-*C*=C-N), 108.2, 118.7 (pyrrole-C), 113.5, 120.7, 125.7, 126.9, 127.0, 127.5, 128.3, 128.7, 129.0, 129.4, 129.9, 137.6, 139.8, 142.3, 143.6, 144.5, 149.9, 154.7 (olefinic-C=*C*-N), 159.6, 164.2 (*C*-OCH_3), 180.8 (C=O); MS: m/*z* (%) = 583 (M^+, 21%); $C_{35}H_{29}N_5O_2S$ (583.702): Calcd: C, 72.02; H, 5.01; N, 12.00; S, 5.49; Found: C, 71.76; H, 4.84; N, 11.79; S, 5.39.

Synthesis of 2-(Isoxazol-5-yl)-5-[(4-methoxyphenyl) diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*] pyridine (10a)

Compound **6** (0.005 mol) was mixed with hydroxylamine hydrochloride (0.006 mol), in ethanol (30 ml) containing anhydrous sodium acetate (0.5 g). The mixture was heated at reflux for 6 h, allowed to cool at room temperature and then diluted with cold water. The solid that separated was filtered off, washed with water, dried and recrystallized from 1,4-dioxane to give **10a** (1.61 g; 58%). Mp 197-199 ºC; IR (ν/cm^{-1}) = 3063 (CH aromatic), 1614 (C=N); ^{1}H NMR δ_H = 3.96 (s, 3H, OCH_3), 6.47 (m, 2H, 3'-H, 4'-H pyrrole), 6.94 (m, 2H, 2'-H, 5'-H pyrrole), 6.98 (d, 1H, *J* = 2 Hz, 4-H isoxazole), 7.32-8.00 (m, 14H, $2C_6H_5$, C_6H_4), 8.39 (d, 1H, *J* = 2 Hz, 3-H isoxazole); $C_{33}H_{23}N_5O_2S$ (553.633): Calcd: C, 71.59; H, 4.19; N, 12.65; S, 5.79; Found: C, 71.36; H, 4.04; N, 12.47; S, 5.81.

General Procedure for the Synthesis of 2-(1-Substituted-1*H*-pyrazol-5-yl)-5-[(4-methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridines 10b,c

To a solution of enaminone **6** (0.005 mol), in absolute ethanol (30 ml), either hydrazine hydrate (1 ml, 0.02 mol) or phenylhydrazine (0.75 ml, 0.0076 mol) were added. The reaction mixture was heated at reflux for 4 h, left to cool at room temperature and then poured over cold water. The solid products that separated were isolated by filtration, washed with ethanol, dried and recrystallized from the proper solvents to give **10b** (1.38 g; 44%) and **10c** (1.41 g; 51%), respectively.

5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-2-(1-phenyl-1*H*-pyrazol-5-yl)-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine (10b)

Mp 205-206 ºC (EtOH/H_2O); IR (ν/cm^{-1}) = 3056 (CH aromatic), 1620 (C=N); ^{1}H NMR δ_H = 3.77 (s, 3H, OCH_3), 6.40 (m, 2H, 3'-H, 4'-H pyrrole), 6.79 (d, 1H, *J* = 2 Hz, 4-H pyrazole), 7.03 (m, 2H, 2'-H, 5'-H pyrrole), 7.28-7.82 (m, 19H, $3C_6H_5$, C_6H_4), 7.85 (d, 1H, *J* = 2 Hz, 3-H pyrazole); MS: *m/z* (%) = 628 (M^+, 25%); $C_{39}H_{28}N_6OS$ (628.744): Calcd: C, 74.50; H, 4.49; N, 13.37; S, 5.10; Found: C, 74.36; H, 4.26; N, 13.11; S, 4.88.

5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-2-(1*H*-pyrazol-5-yl)-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine (10c)

Mp 183-185 ºC (AcOH); IR (ν/cm^{-1}) = 3241 (NH), 3045 (CH aromatic), 1612 (C=N); ^{1}H NMR δ_H = 3.89 (s, 3H, OCH_3), 5.90 (d, 1H, *J* = 2 Hz, 4-H pyrazole), 6.28 (m, 2H, 3'-H, 4'-H pyrrole), 7.12 (m, 2H, 2'-H, 5'-H pyrrole), 7.21-7.97 (m, 14H, $2C_6H_5$, C_6H_4), 8.22 (d, 1H, *J* = 2 Hz, 3-H pyrazole), 13.06 (s, br, 1H, NH, D_2O-exchangeable); $C_{33}H_{24}N_6OS$ (552.648): Calcd: C, 71.72; H, 4.38; N, 15.21; S, 5.80; Found: C, 71.61; H, 4.21; N, 14.96; S, 5.59.

Synthesis of 1-{5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl} ethanone oxime (12a)

A mixture of **5b** (0.002 mol) and hydroxylamine hydrochloride (0.0024 mol), in pyridine (20 ml), was refluxed for 6 h. The solvent was removed and the residue was diluted with ethanol, neutralized with dilute hydrochloric acid, and when cooled, a solid was deposited. This solid was collected by filtration and recrystallized from 1,4-dioxane to give **12a** (0.66 g; 61%). Mp 141-142 ºC; IR (ν/cm^{-1}) = 3455 (OH), 3047 (CH aromatic), 1614 (C=N); ^{1}H NMR δ_H = 2.57 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.38 (m, 2H, 3'-H, 4'-H pyrrole), 6.94 (m, 2H, 2'-H, 5'-H pyrrole), 7.14-7.85 (m, 14H, $2C_6H_5$, C_6H_4), 11.20 (s, 1H, OH, D_2O-exchangeable); $C_{32}H_{25}N_5O_2S$ (543.638): Calcd: C, 70.70; H, 4.64; N, 12.88; S, 5.90; Found: C, 70.44; H, 4.42; N, 12.73; S, 5.75.

Synthesis of 5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-2-[1-(2-phenylhydrazono)ethyl]-3-(1*H*-pyrrol-1-yl) thieno[2,3-*b*]pyridine (12b)

A mixture of the acetyl derivative **5b** (0.002 mol) and phenylhydrazine (0.0024 mol), in absolute ethanol (30 ml)

containing a few drops of acetic acid, was refluxed for 6 h. The reaction mixture was then cooled and poured onto cold water. The solid product obtained was collected by filtration and recrystallized from EtOH/H_2O (1:1) to give **12b** (0.80 g; 65%). Mp 98 ºC; IR (ν/cm^{-1}) = 3210 (NH), 3042 (CH aromatic), 1615 (C=N); ^{1}H NMR δ_H = 2.20 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.26 (m, 2H, 3'-H, 4'-H pyrrole), 7.16 (m, 2H, 2'-H, 5'-H pyrrole), 7.20-8.09 (m, 19H, $3C_6H_5$, C_6H_4), 10.82 (s, 1H, NH, D_2O-exchangeable); $C_{38}H_{30}N_6OS$ (618.749): Calcd: C, 73.76; H, 4.89; N, 13.58; S, 5.18; Found: C, 73.60; H, 4.68; N, 13.44; S, 4.97.

General Procedure for the Synthesis of 2-Heterocyclyl-5-[(4-methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridines 11a,b

A mixture of either **12a** or **12b** (0.0025 mol) and DMFDMA (0.003 mol) was refluxed in xylene (20 ml) for 18 h. The solid obtained on evaporating excess solvent under *vacuo* was collected by filtration and recrystallized from the appropriate solvents to give **11a** (0.97 g; 70%) and **11b** (0.99 g; 63%), respectively.

3-{5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl}isoxazole (11a)

Mp 230-232 ºC (1,4-dioxane); IR (ν/cm^{-1}) = 3049 (CH aromatic), 1616 (C=N); ^{1}H NMR δ_H = 3.81 (s, 3H, OCH_3), 6.23 (m, 2H, 3'-H, 4'-H pyrrole), 6.99 (m, 2H, 2'-H, 5'-H pyrrole), 7.18 (d, 1H, *J* = 3 Hz, 4-H isoxazole), 7.24-7.95 (m, 14H, $2C_6H_5$, C_6H_4), 8.92 (d, 1H, *J* = 3 Hz, 5-H isoxazole); ^{13}C NMR δ_C = 55.9 (OCH_3), 104.2 (isoxazole-C_4), 108.5, 118.9 (pyrrole-C), 114.0, 121.2, 124.3, 126.7, 127.1, 127.6, 128.3, 128.6, 129.3, 129.7, 130.1, 137.5, 138.3, 140.1, 142.9, 144.2, 149.7, 150.1 (aromatic-C), 150.5 (isoxazole-C_3), 159.1 (isoxazole-C_5), 163.9 (C-OCH_3); $C_{33}H_{23}N_5O_2S$ (553.633): Calcd: C, 71.59; H, 4.19; N, 12.65; S, 5.79; Found: C, 71.44; H, 3.98; N, 12.53; S, 5.58.

5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-2-(1-phenyl-1*H*-pyrazol-3-yl)-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine (11b)

Mp 251-253 ºC (DMF); IR (ν/cm^{-1}) = 3060 (CH aromatic), 1619 (C=N); ^{1}H NMR δ_H = 3.84 (s, 3H, OCH_3), 6.31 (m, 2H, 3'-H, 4'-H pyrrole), 6.81 (d, 1H, *J* = 3 Hz, 4-H pyrazole), 7.17 (m, 2H, 2'-H, 5'-H pyrrole), 7.23-7.88 (m, 19H, $3C_6H_5$, C_6H_4), 7.93 (d, 1H, *J* = 3 Hz, 5-H pyrazole); $C_{39}H_{28}N_6OS$ (628.744): Calcd: C, 74.50; H, 4.49; N, 13.37; S, 5.10; Found: C, 74.25; H, 4.32; N, 13.28; S, 4.91.

General Procedure for the Synthesis of 2-(2-Arylhydrazono)-3-{5-[(4-methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl}-3-oxopropanals 14a,b

A solution of enaminone **6** (0.005 mol), in ethanol (50 ml) containing sodium hydroxide (0.8 g), was refluxed for 15 min and the solution was then cooled to 0-5 ºC with stirring. The reaction mixture was then treated gradually with a cold solution of the appropriate aryldiazonium chloride salt (0.005 mol) [prepared by adding a cold solution (0-5 ºC) of sodium nitrite (0.005 mol, 0.35 g into 5 ml water) to a cold solution (0-5 ºC) of the corresponding arylamine hydrochloride (0.005 mol of arylamine in 2.5 ml concentrated hydrochloric acid) with continuous stirring at 0-5 ºC]. The mixture was then stirred at room temperature for an additional 2 h. The precipitated product, in each case, separated upon dilution with cold water (30 ml) was filtered off, washed with water several times, dried, and recrystallized from EtOH to give **14a** (1.69 g; 50%) and **14b** (1.46 g; 42%), respectively.

3-{5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl}-3-oxo-2-(2-*p*-tolylhydrazono)propanal (14a)

Mp 155-156 ºC; IR (ν/cm^{-1}) = 3432 (NH), 3041 (CH aromatic), 1662 (C=O aldehyde), 1637 (C=O ketone), 1615 (C=N); ^{1}H NMR δ_H = 2.28 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.40 (m, 2H, 3'-H, 4'-H pyrrole), 7.07 (m, 2H, 2'-H, 5'-H pyrrole), 7.25-7.99 (m, 18H, $2C_6H_5$, $2C_6H_4$), 10.02 (s, 1H, CHO), 14.20 (s, br, 1H, NH hydrazone, D_2O-exchangeable); MS: *m/z* (%) = 674 (M^+, 16%); $C_{40}H_{30}N_6O_3S$ (674.770): Calcd: C, 71.20; H, 4.48; N, 12.45; S, 4.75; Found: C, 70.93; H, 4.33; N, 12.24; S, 4.60.

2-[2-(4-Chlorophenyl)hydrazono]-3-{5-[(4-methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl}-3-oxopropanal (14b)

Mp 243-245 ºC; IR (ν/cm^{-1}) = 3441 (NH), 3033 (CH aromatic), 1667 (C=O aldehyde), 1640 (C=O ketone), 1618 (C=N); ^{1}H NMR δ_H = 3.90 (s, 3H, OCH_3), 6.26 (m, 2H, 3'-H, 4'-H pyrrole), 7.24 (m, 2H, 2'-H, 5'-H pyrrole), 7.30-8.02 (m, 18H, $2C_6H_5$, $2C_6H_4$), 10.08 (s, 1H, CHO), 13.83 (s, br, 1H, NH hydrazone, D_2O-exchangeable); $C_{39}H_{27}ClN_6O_3S$ (695.188): Calcd: C, 67.38; H, 3.91; Cl, 5.10; N, 12.09; S, 4.61; Found: C, 67.24; H, 3.72; Cl, 4.94; N, 11.86; S, 4.55.

Synthesis of 3-{5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carbonyl}-1,5-di*p*-tolylformazan (16)

Method A

To a stirred solution of hydrazonal **14a** (0.002 mol) at 0-5 ºC, in ethanol (30 ml) containing sodium hydroxide (0.3 g), *p*-toluenediazonium chloride salt (0.002 mol) [prepared from the corresponding *p*-toluidine (0.002 mol) and the appropriate quantities of concentrated hydrochloric acid and sodium nitrite] was added dropwise while cooling at 0-5 ºC and stirring. After addition of the diazonium salt, the reaction mixture was then stirred at room temperature for an additional 2 h. The precipitated product, separated upon dilution with cold water (30 ml), was filtered off, washed with water several times, dried, and recrystallized from DMF/EtOH (1:2) to give the corresponding formazan **16** (0.90 g; 59%). Mp 266-268 ºC; IR (ν/cm^{-1}) = 3390 (NH), 3052 (CH aromatic), 1651 (C=O with H-bonding between O and NH), 1616 (C=N); ^{1}H NMR δ_H = 2.27 (s, 6H, $2CH_3$), 3.94 (s, 3H, OCH_3), 6.33 (m, 2H, 3'-H, 4'-H pyrrole), 6.90 (m, 2H, 2'-H, 5'-H pyrrole), 6.95-8.11 (m, 22H, $2C_6H_5$, $3C_6H_4$), 12.15 (s, br, 1H, NH hydrazone, D_2O-exchangeable); MS: *m/z* (%) = 764 (M^+, 23%); $C_{46}H_{36}N_8O_2S$ (764.895): Calcd: C, 72.23; H, 4.74; N, 14.65; S, 4.19; Found: C, 71.97; H, 4.60; N, 14.46; S, 4.01.

Method B

A cold solution (0-5 ºC) of *p*-toluenediazonium chloride salt (0.005 mol) was prepared by addition of a cold solution (0-5 ºC) of sodium nitrite (0.005 mol) in water (5 ml) to a solution of *p*-toluidine (0.005 mol) in concentrated hydrochloric acid (2.5 ml) at 0-5 ºC with vigorous stirring. The resulting solution of the diazonium salt was added dropwise with continuous stirring to a cold solution (0-5 ºC) of enaminone **6** (0.0025 mol) in DMF (30 ml) containing sodium hydroxide (0.8 g). The mixture was kept at room temperature for 2 h under stirring. The precipitate formed was washed with water, collected by filtration, and recrystallized from

DMF/EtOH (1:2) to give a solid product (1.17 g; 61%) identical to that described in method A.

Synthesis of 3-{5-[(4-Methoxyphenyl)diazenyl]-4,6-diphenyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carbonyl}-6-methylcinnoline (18)

A sample of hydrazonal **14a** (1 g), in concentrated sulfuric acid (15 ml), was heated at reflux for 15 min and then allowed to cool. Under stirring, the reaction mixture was poured over iced water. The separated solid product was collected by filtration, washed with water, dried and recrystallized from EtOH to give the cinnoline derivative **18** (0.55 g; 57%). Mp 275-276 ºC; IR (ν/cm^{-1}) = 3058 (CH aromatic), 1662 (C=O ketone), 1619 (C=N); ^{1}H NMR δ_H = 2.30 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.29 (m, 2H, 3'-H, 4'-H pyrrole), 7.01 (m, 2H, 2'-H, 5'-H pyrrole), 7.26-8.31 (m, 17H, $2C_6H_5$, C_6H_4, 5-H, 7-H, 8-H cinnoline), 8.92 (s, 1H, 4-H cinnoline); ^{13}C NMR δ_C = 22.8 (CH_3), 55.6 (OCH_3), 108.0, 119.2 (pyrrole-C), 113.8, 120.9, 122.1, 124.5, 125.7, 126.8, 127.0, 127.3, 127.9, 128.2, 128.5, 128.9, 129.5, 130.2, 130.7, 133.0, 137.3, 138.7, 140.8, 142.5, 143.3, 144.7, 147.2, 149.9, 154.5, 160.1 (aromatic-C), 163.5 (*C*-OCH_3), 185.2 (C=O); MS: *m/z* (%) = 656 (M^+, 19%); $C_{40}H_{28}N_6O_2S$ (656.754): Calcd: C, 73.15; H, 4.30; N, 12.80; S, 4.88; Found: C, 72.92; H, 4.21; N, 12.58; S, 4.72.

Energetics

Molecular orbital geometry optimizations were performed using the semi-empirical Austin Model (AM1) Hamiltonian at a restricted Hartree-Fock (RHF) self-consistent field level within the GAMESS package[44]. A gradient tolerance of 10^{-4} Hartree Å^{-1} was used throughout. The rotational energy profiles were obtained by constraining the C1-C2-N=N dihedral to discreet values while the rest of the degrees of freedom were subjected to full geometry optimization.
The electrostatic component of the solvation free energy (ΔA_{solv}) was calculated by solving the Poisson-Boltzmann (PB) equation[45] for the geometry optimized structures using the APBS package[46]. The ΔA_{solv} values were obtained from the difference between the electrostatic potential computed in bulk solvent (salt concentration = 0.15 M, relative dielectric permitivity = 80) and the electrostatic potential calculated in vacuum (salt concentration = 0.0 M, relative dielectric permitivity = 1.0) at 310 K. In order to increase the accurecy of the calculations, the focusing technique[47] was used where three focussing stages were carried out. A final grid spacing of 0.3 Å was used and the relative dielectric permitivity within the structures was set to 1. The solute-solvent boundary was constructed from the solvent accessible surface using a solvent probe radius of 1.4 Å.

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