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FACILE SYNTHESIS OF NOVEL IMIDAZO[2,1-*b*]THIAZOLE LINKED SCHIFF'S BASES: POTENTIAL SYNTHON FOR β-LACTAMS

Preety Saini,[1] Shamsher S. Bari,[1] Bimal K. Banik,[2] and Aman Bhalla[1*]

[1]*Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh 160014, India*
[2]*Community Health Systems of South Texas; 3135 South Sugar Road, Edinburg, Texas, 78539, USA*
E-mail: amanbhalla@pu.ac.in

ABSTRACT
A simple and efficient synthesis of novel imidazo[2,1-*b*]thiazole linked Schiff's bases **3a-e** is described. Vilsmeier-Haack formylation of 3,6-diphenylimidazo[2,1-*b*]thiazole **1** is achieved to afford novel 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde **2**. The compound **2** upon treatment with appropriately substituted primary amines furnishes 3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl Schiff's bases **3a-e** in good yield. The imidazo[2,1-*b*]thiazole linked Schiff's bases **3a-e** are potential synthons for the synthesis of amino acids, metal complexes and biologically active β-lactams. The structure elucidation of all the newly synthesized compounds is carried out using FT-IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis (CHN).

KEYWORDS
Schiff's bases, imidazole, thiazole, imidazole[2,1-*b*]thiazole, heterocycles, β-lactams.

INTRODUCTION
Heterocycles have constituted one of the largest areas of research in organic chemistry and are of great significance because their structural subunits exist in many natural products such as vitamins, hormones and antibiotics[i,ii]. They have received considerable attention in the design of biologically active molecules[iii,iv] and as useful synthons in advanced synthetic organic chemistry[v,vi]. Construction of natural product-like compounds with privileged scaffolds that are prone to display different biological activities is in great demand. Therefore, the design and development of strategies, toward new heterocyclic molecules of biological potency continues to be a major focus in contemporary synthetic chemistry in recent years.
Both monocyclic and bicyclic aromatic heterocycles such as imidazole, thiazole, thiadiazole, oxazole, oxadiazole, quinazoline, indole, benzimidazole, imidazo[2,1-*b*]thiazole, purine pyrido[4,3-*d*]pyrimidine, thiazolo[5,4-*d*]pyrimidine, thiazolo[4,5-*d*]pyrimidine, oxazolo[5,4-

d]pyrimidine and thieno[2,3-*d*]pyrimidines are renowned pharmacophores in drug discovery and have maintained the interest of researchers due to their unique structures that lead to several applications in different areas of pharmaceutical and agrochemical research and more recently, in material science[vii]. Nitrogen- and/or sulfur-containing organic aromatic heterocycles result in significant changes in the cyclic molecular structure due to the availability of unshared pairs of electrons and the difference in electronegativity between heteroatom and carbon, therefore nitrogen- and/or sulfur-containing heterocyclic compounds viz. thiazole, indazole and imidazole display physicochemical characteristics and quite different reactivity from the parent hydrocarbons[vii].

Among these privileged scaffolds, the imidazole and thiazole moieties are abundant in natural heterocycles and act as the functional core in the structures of a wide range of naturally occurring molecules and exhibit diverse biological activities[viii,ix]. The imidazole moiety fused with thiazole ring (i.e. imidazo[1,2-*b*]thiazole) is an important hetero-fused bicyclic aromatic molecule, which is found to be a key structural unit in many natural products and synthetic drugs with a wide range of biological activities; for example, tetramisole (**I**) (as anthelmintic), 3-methyl-5,6-diarylimidazo[2,1-*b*]benzothiazoles (**II**), 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles (**III**), ^{11}C-labeled imidazo[2,1-*b*]benzothiazoles (**IV**) (as antibiotic) and recently discovered drug (**V**) (as a SIRT1 enzyme activator) (**Figure 1**)[x,xi].

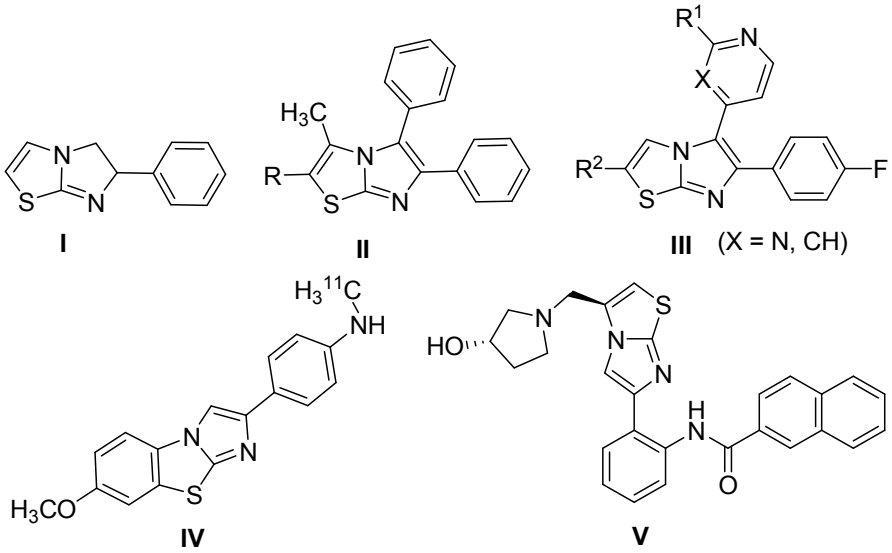


Figure 1: Bioactive imidazo[2,1-*b*]thiazole heterocycles

Schiff's bases constitute an important class of organic compounds due to their flexibility and structural similarities with natural biological molecules[xii]. The novel imidazo[2,1-*b*]thiazole linked Schiff bases **3a-e** have two imino groups and therefore, are interesting substrates to study the Staudinger cycloaddition reaction for the preparation of unique β-lactams.

Our research group has been extensively engaged in synthetic β-lactam chemistry and their precursors[xiii] such as 3-thio/seleno-β-lactams and their Lewis acid mediated functionalization, stereoselective *cis*- and *trans*-alkoxy-β-lactams, spirocyclic-β-lactams, α-keto-β-lactams, bicyclic-β-lactams, novel 4-pyrazolyl-β-lactams and (*E*)- and (*Z*)-3-allylidene-β-lactams. In a continuation of the above studies and considering the wide spectrum of biological activities associated with imidazole, thiazole and imidazo[2,1-*b*]thiazole heterocycle, we describe herein the synthesis and characterization of novel imidazo[2,1-*b*]thiazole linked Schiff's bases.

EXPERIMENTAL: Melting points were determined in an open capillary on melting point apparatus (Perfit GSI-MP-3) and are uncorrected. Fourier transform infrared spectra were recorded on a Thermo scientific Nicolet iS50 (FT-IR) spectrophotometer (υ_{max} in cm^{-1}). ^1H (300 MHz) and ^1H (400 MHz) NMR spectra were recorded on JEOL AL 300 (300 MHz) and BRUKER AVANCE II 400 (400 MHz) spectrometer. Chemical shifts are given in ppm relative to Me_4Si as an internal standard (δ = 0 ppm) for ^1H NMR, $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectra. The elemental analysis (C, H, N) were determined on a Flash 2000 Organic elemental analyzer. Column chromatography was performed using Merck Silica Gel (60–120 mesh) using ethyl acetate-hexanes (10:90) as an eluant system. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F254 aluminium plates with visualization under UV light.

The syntheses and reactions of novel compounds were carried out under dry and deoxygenated nitrogen atmospheres. Phosphorus oxychloride (Merck), calcium chloride (Qualigen), alumina (Merck) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. *N,N*-dimethylformamide was dried and distilled over anhydrous calcium chloride ($CaCl_2$) and alumina. Dichloromethane was dried and distilled over phosphorus pentoxide (P_2O_5) immediately before use.

The starting material 3,6-diphenylimidazo[2,1-*b*]thiazole **1** was prepared following a method reported in literature[xiv].

Synthesis of 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde 2

To the Vilsmeier-Haack reagent, prepared by dropwise addition of $POCl_3$ (1.5 ml) to DMF (5 ml) at 0^oC, 3,6-diphenylimidazo[2,1-*b*]thiazole (0.01 mole) was added in small aliquots at a time with swirling. The solution was kept at room temperature for 30 min and then heated at 70-80^oC for 3 h. The precipitated solid obtained after pouring onto ice cold water was filtered, dried, purified by column chromatography using ethyl acetate-hexanes (10:90) as eluant and further purified by recrystallization from a mixture of methylene chloride and hexanes to give **2** (0.62 g, 60%) as a yellow crystalline solid, mp 103^oC; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.73 (s, 1H, Imd-H), 7.10-7.76 (m, 10H, Ar-H), 9.51 (s, 1H, CHO) ppm; FT-IR ν_{max} 1652 (C=O) cm^{-1}. (Found C 70.96; H 3.94; N 9.13 $C_{18}H_{12}N_2OS$ requires C 71.03; H 3.97; N 9.20 %).

Typical procedure for the synthesis of Schiff's bases 3a-e

Equimolar solution of an appropriate primary amine and 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde in the presence of molecular sieves (4 Å) in dry methylene chloride (15 ml) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered to remove the molecular sieves and the filtrate was concentrated in *vacuo* to give the crude product which was purified by crystallization from a mixture of methylene chloride and hexanes to yield **3a-e**.

(21*E*)-4-Methyl-N-((3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl)methylene)benzenamine [(3a) 70%] was isolated as yellow crystalline solid; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 1H, CH_3), 6.62 (s, 1H, Imd-H), 6.73-7.75 (m, 14H, Ar-H), 8.26 (s, 1H, =CH) ppm; FT-IR ν_{max} 1648 (C=N) cm^{-1}. (Found C 76.26; H 4.81; N 10.62; $C_{25}H_{19}N_3S$ requires C 76.31; H 4.87; N 10.68 %).

(21*E*)-4-Methoxy-N-((3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl)methylene)benzenamine [(3b) 73%] was isolated as yellow crystalline solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 1H, OCH_3), 6.70 (s, 1H, Imd-H), 7.25-7.75 (m, 14H, Ar-H), 8.28 (s, 1H, =CH) ppm; FT-IR ν_{max} 1656 (C=N) cm^{-1}. (Found C 73.24; H 4.60; N 10.61; $C_{25}H_{19}N_3OS$ requires C 73.32; H 4.68; N 10.68 %).

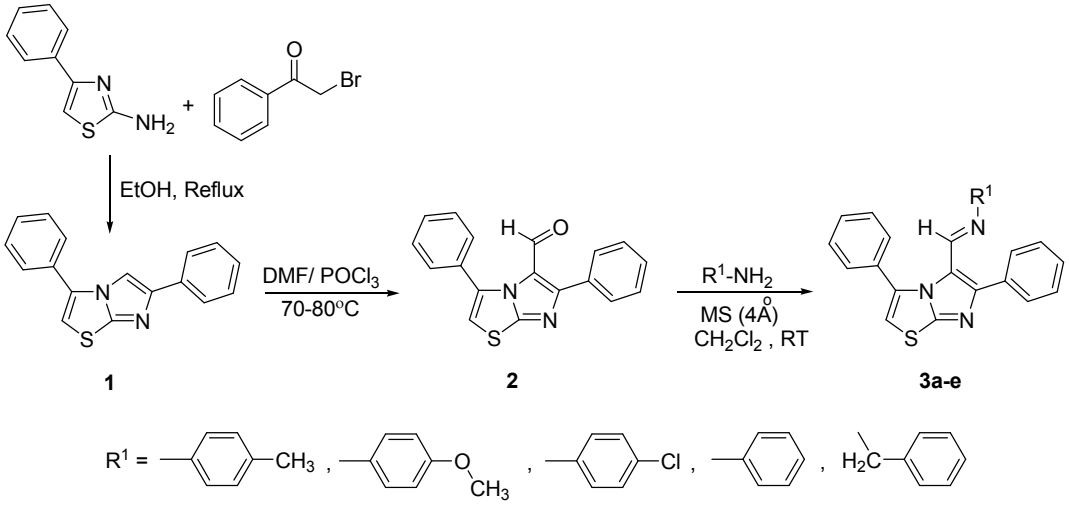
(6*E*)-4-Chloro-N-((3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl)methylene)benzenamine [(3c) 68%] was isolated as yellow crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H, Imd-H), 6.61-7.84 (m, 14H, Ar-H), 8.42 (s, 1H, =CH) ppm; FT-IR ν_{max} 1654 (C=N) cm^{-1}. (Found C 69.60; H 3.90; N 10.11; $C_{24}H_{16}ClN_3S$ requires C 69.64; H 3.90; N 10.15 %).

(21*E*)-N-((3,6-Diphenylimidazo[2,1-*b*]thiazol-5-yl)methylene)benzenamine [(3d) 65%] was isolated as yellow crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H, Imd-H), 6.81-8.03 (m, 16H, Ar-H and =CH) ppm; FT-IR ν_{max} 1644 (C=N) cm^{-1}. (Found C 75.86; H 4.48; N 10.92; $C_{24}H_{17}N_3S$ requires C 75.96; H 4.52; N 11.07 %).

(1*E*)-Phenyl-N-((3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl)methylene)methanamine [(3e) 67%] was isolated as yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 1H, CH_2), 6.69 (s, 1H, Imd-H), 6.96-7.85 (m, 15H, Ar-H), 8.17 (s, 1H, =CH) ppm; FT-IR ν_{max} 1657 (C=N) cm^{-1}. (Found C 75.97; H 4.80; N 10.62; $C_{25}H_{19}N_3S$ requires C 76.13; H 4.87; N 10.68 %).

RESULTS AND DISCUSSION

The starting substrate 3,6-diphenylimidazo[2,1-*b*]thiazole **1** was prepared by the cyclization of 4-phenylthiazol-2-amine with 2-bromo-phenylethanone in absolute ethanol following a reported procedure[xiv] (**Scheme 1**).



Scheme 1: Synthesis of furnished 3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl Schiff's bases

The canonical structures (**1A-1C**) of bicyclic molecule **1** show the delocalization of π electrons only in the imidazole ring and an almost localized double bond in the thiazole ring (**Figure 2**). Among these three canonical structures (**1A-1C**), the structure **1A** has an electronegative nitrogen atom bearing negative charge and is higher in energy than that of structures **1B** and **1C** due to the significant electrostatic repulsions between π-electrons and the lone pair of the nitrogen atom. Further, out of the structures **1B** and **1C**, the structure **1C**

is less favoured due to accumulation of negative charge adjacent to a heteroatom with lone pair of electrons. Therefore, the structure **1B** is the most likely and has been considered to be the maximum contributing structure for the pseudoaromatic behavior of imidazole moiety in the 3,6-diphenylimidazo[2,1-*b*]thiazole molecule.

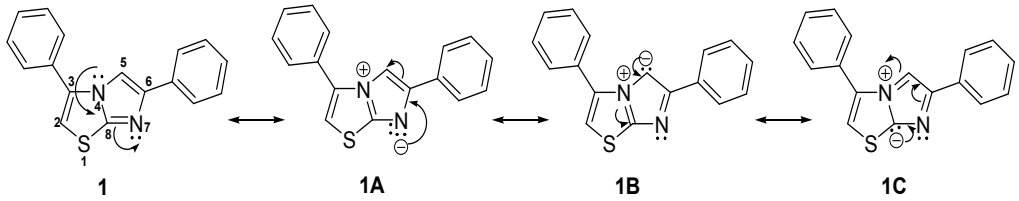
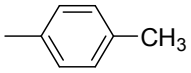
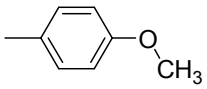
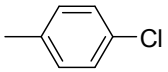
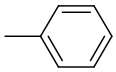
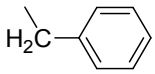


Figure 2: Canonical structures (**1A-1C**) of 3,6-diphenylimidazo[2,1-*b*]thiazole

Therefore, electrophilic formyl group introduction to 3,6-diphenylimidazo[2,1-*b*]thiazole **1** using the Vilsmeier-Haack reagent (DMF/$POCl_3$) occurred preferentially at *C*-5 position (**Figure 2**) to afford novel 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde **2** (**Scheme 1**). The crude compound **2** was purified by column chromatography using ethyl acetate-hexanes (10:90) as eluant and further recrystallized from a mixture of methylene chloride and hexanes to give the yellow crystalline solid **2** in 60% yield. The structure of **2** was established by spectroscopy (FT-IR, ^{1}H and ^{13}C NMR) and elemental analysis (CHN).

Initially, 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde **2** upon condensation with 4-methyl aniline (R^1 = -$C_6H_4(CH_3$-4)) using molecular sieves (4Å) in dichloromethane furnished (21*E*)-4-methyl-N-((3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl)methylene)benzenamine **3a** (**Scheme 1, Table 1**, entry 1). This reaction was found to be general with different primary amines. Finally, following the same reaction conditions, the condensation of aldehyde **2** with different primary amines furnished a novel series of 3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl Schiff's bases in moderate to good yield (**Table 1,** entries 2-5).

Table 1: Synthesis of 3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl Schiff's bases **3a-e**

Entry	R^1	Schiff's base **3**	Yield (%)[a]
1.		**3a**	70
2.		**3b**	73
3.		**3c**	68
4.		**3d**	65
5.		**3e**	67

[a]Yield of pure, isolated product with correct analytical and spectral data

The structures of **3a-e** were characterized by FT-IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis (CHN). The synthesized 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde **2** and 3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl Schiff's bases **3a-e** were obtained as stable solids and were air and moisture stable, soluble in solvents like dichloromethane, chloroform, ethyl acetate, ethanol and methanol.

CONCLUSION

To summarize, the significance of present work lies in the availability of starting materials, simplicity of reaction steps and good yield of products. The structure elucidation of newly synthesized 3,6-diphenylimidazo[2,1-*b*]thiazole-5-carbaldehyde **2** and 3,6-diphenylimidazo[2,1-*b*]thiazol-5-yl Schiff's bases **3a-e** was carried out by FT-IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis (CHN). Due to the dynamic biological potential of hybrid imidazo[2,1-*b*]thiazole moiety, the novel Schiff's bases **3a-e** have been already submitted for the potential biological evaluation. The novel imidazo[2,1-*b*]thiazole linked Schiff bases **3a-e** are interesting substrates to study Staudinger cycloaddition reaction for the preparation of unique β-lactams due to the presence of two imino groups. The transformation of these novel Schiff's bases **3a-e** into β-lactams is underway in our laboratory.

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