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AN EFFICIENT SYNTHESIS OF NOVEL BENZOTHIAZOLYLPYRAZOLE SUBSTITUTED IMINES: VERSATILE SYNTHONS FOR HETEROCYCLES

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ABSTRACT
An efficient synthesis of novel benzothiazolylpyrazole substitutedimines**5a-e** is described. The substrate i.e. benzothiazolylpyrazolecarbaldehydes**4a-c** were prepared via $POCl_3$-DMF mediated cyclization-formylation of benzothiazolylhydrazones**3a-b**. The target product i.e. benzothiazolylpyrazole substituted imines **5a-e**were synthesized in excellent yields by the reaction betweenbenzothiazolylpyrazolecarbaldehydes**4a-c**and various aromatic/aliphatic amines. All the novel compounds were characterized using various spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (CHN).

KEYWORDS
Imines, benzothiazole, pyrazole, β-lactams, thiazolidinone.

INTRODUCTION
Heterocyclic compounds are widely dispersed in nature and are essential to life in multiple ways.Nitrogen followed by oxygen and sulphur containing heterocycles are most abundant in nature. The importance of heterocyclic rings is due to their abundance in various natural products, vitamins, co-enzymes, DNA, RNA, porphyrins and also in plant products viz. alkaloids.The heterocyclic compounds exhibits wide range of biological activities such as antimicrobial, anticancer, antimalarial and anti-inflammatory[i]. In the modern era, chemistry and biology of heterocyclic compounds has emerged as an important branch of research in agrochemical, pharmaceutical and medicinal field. Therefore, significant attention has been paid in order to develop novel and efficient strategies to synthesize novel heterocycles.
Benzothiazole and pyrazoleheterocycles are well known for their diverse biological applications(**Figure 1**)[ii,iii].Benzothiazoles have also found use in other fields of research such as dyes and polymer chemistry[iv,v]whereaspyrazole derivatives have been successfully utilized in agricultural activities, supramolecular chemistry, polymer products, food and cosmetics industries[vi,vii].

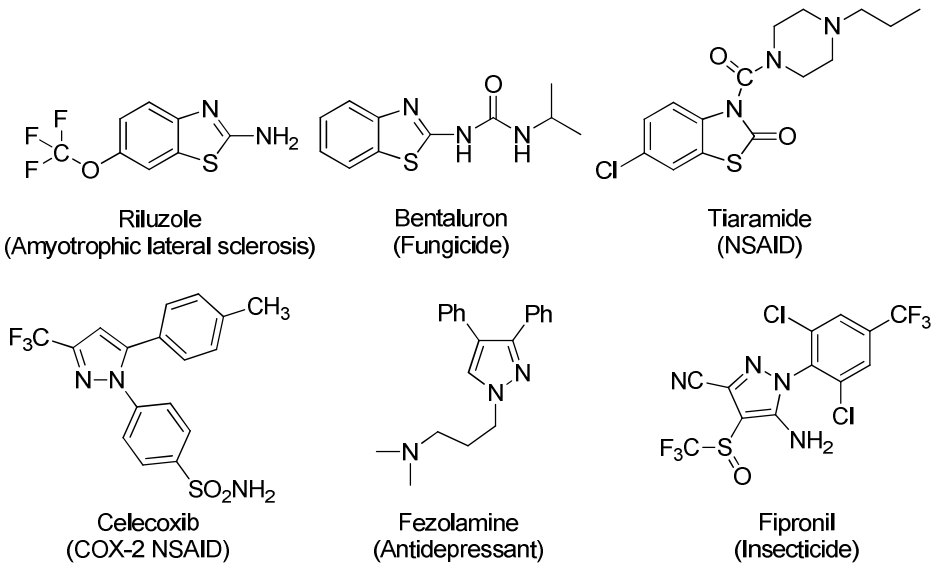


Figure 1: Biologically active benzothiazole and pyrazole derivatives.

One of the major areas of organic chemistry research is synthesis of new chemical entities (NCEs) which that can be transformed in order to give different types of heterocyclic molecules having high end applications. Imines or Schiff's bases are one of the most important and highly applicable groups of chemical compounds in organic chemistry. In addition to their biological potential,[viii] imines are widely used in various fields viz. chemosensors and coordination chemistry[ix]. Moreover, imines are an important synthons for other biologically active molecules such as β-lactams and thiazolidinones[x,xi].

Till now, our research group has been actively engaged in synthesis, characterization and applications of novel β-lactamheterocycles and their precursors[xii,xiii]and our ongoing interest in chemicaland biological applications of functionalized heterocyclic synthonshasprovoked us to investigate a novel class of benzothiazolylpyrazolesubstitutedimine derivatives which will serve as versatile synthons for heterocycles.

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), ^{13}C (75 MHz) NMR spectra were recorded on JEOL AL 300 (300 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 recorded on Flash 2000 Organic elemental analyzer. Column chromatography was performed using Merck Silica Gel (60–120 mesh) using ethyl acetate-hexanes as an eluant system. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F254 aluminium plates with visualization under UV light.

Phosphorus oxychloride (Merck), triethylamine (Qualigen), hydrazine hydrate (Qualigen) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Dimethylformamide and dichloromethane were dried and distilled over anhydrous calcium chloride ($CaCl_2$) and phosphorus pentoxide (P_2O_5) respectively. Toluene was distilled under N_2 from sodium-benzophenone immediately before use.

Starting materials 2-aminobenzothiazoles **1** and 2-hydrazinobenzothiazoles **2** were prepared following the methods described in literature[xiv,xv].

General procedure for the synthesis of benzothiazolehydrazones 3a-c
Benzothiazolehydrazone**3a-c** were prepared using reported methodology[xiv,xv] and the spectroscopic data of **3a**has been reported in the cited references.

6-Chloro-2-[2-(1'-phenylethylidene)hydrazinyl]benzo[*d*]thiazole[**(3b)** 73%] was isolated as crystalline solid, mp 175–176 °C; FT-IR (neat): 1302, 1369, 1416, 1445, 1491, 1547, 1563, 1592, 1626, 2922, 3064, 3455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ2.31 (s, 3H, C*H*$_3$), 7.14-7.77 (m, 8H, Ar*H*), 9.87 (br s, 1H, N*H*). (Found C 59.35; H 3.94; N 13.76; $C_{15}H_{12}ClN_3S$ requires C 59.70; H 4.01; N 13.92 %).

6-Methoxy-2-[2-(1'-*p*-tolylethylidene)hydrazinyl]benzo[*d*]thiazole[**(3c)** 80%]was isolated as crystalline solid, mp 165–166 °C; FT-IR (neat): 1343, 1431, 1459, 1509, 1557, 1577, 1606, 2933, 2988, 3076, 3448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ 2.11 (s, 3H, C*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 7.25-7.84 (m, 7H, Ar*H*), 9.28 (br s, 1H, N*H*). (Found C 65.22; H 5.39; N 13.36; $C_{17}H_{17}N_3OS$ requires C 65.57; H 5.50; N 13.49 %).

General procedure for the synthesis of benzothiazolylpyrazolecarbaldehyde 4a-c
Benzothiazolylpyrazolecarbaldehyde**4a-c** were prepared using reported methodology[xiv,xv]and the spectroscopic data of **4a**has been reported in the cited references.

1-(6'-chlorobenzo[*d*]thiazol-2'-yl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde[**(4b)**71%]was isolated as crystalline solid, mp 166–167 °C; FT-IR (neat): 1677 (CHO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ7.43-7.78 (m, 8H, Ar*H*), 8.96 (s, 1H, =C*H*), 10.02 (s, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$)δ121.4, 123.7, 127.8, 128.8, 129.0, 129.9, 131.4, 132.5, 184.0.(Found C 59.75; H 2.88; N 12.26; $C_{17}H_{10}ClN_3OS$ requires C 60.09; H 2.97; N 12.37 %).

1-(6'-Methoxybenzo[*d*]thiazol-2'-yl)-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde [**(4c)** 76%] was isolated as crystalline solid, mp 176–177 °C; FT-IR (neat): 1672 (CHO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ2.35 (s, 3H, C*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 6.96-7.72 (m, 7H, Ar*H*), 8.87 (s, 1H, =C*H*), 9.96 (s, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$)δ21.4, 55.7, 104.4, 115.9, 123.2, 123.4, 127.6, 128.9, 129.4, 132.0, 135.0, 139.8, 144.9, 155.3, 156.6, 157.9, 184.2.(Found C 65.09; H 4.23; N 11.91; $C_{19}H_{15}N_3O_2S$ requires C 65.31; H 4.33; N 12.03 %).

General procedure for the synthesis of Schiff's bases 5a-e
Solution of aromatic amine (10 mmol) and benzothiazolylpyrazolecarbaldehyde**4a-c**(10 mmol) in the presence of molecular sieves (4 Å) in dry methylene chloride (30 mL) was stirred at room temperature. Progress of the reaction was monitored by TLC. After the completion, reaction mixture was filtered and solvent was evaporated to yield crude product **5** which was purified by recrystallization from a mixture of methylene chloride and hexane.

***N*-[{1-(6'-Methoxybenzo[*d*]thiazol-2'-yl)-3-phenyl-1*H*-pyrazol-4-yl}methylene]-4-methoxybenzenamine** [**(5a)**76%] was isolated as yellowish solid, mp 181–182 °C; FT-IR (neat): 1437, 1472, 1499, 1548, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ3.73 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 6.49-7.69 (m, 12H, Ar*H*), 8.39 (s, 1H, =C*H*), 8.99 (s, 1H, N=C*H*);^{13}C NMR (75 MHz, $CDCl_3$)δ55.3, 55.6, 104.5, 114.4, 115.6, 121.9, 122.1, 123.4, 128.2, 128.7, 129.0, 134.9, 145.4, 149.1, 154.8, 157.7. (Found C 67.87; H 4.35; N 12.56; $C_{25}H_{20}N_4O_2S$ requires C 68.16; H 4.58; N 12.72 %).

***N*-[{1-(6'-Methoxybenzo[*d*]thiazol-2'-yl)-3-phenyl-1*H*-pyrazol-4-yl}methylene]-1-phenylmethanamine** [**(5b)**93%] was isolated as pale yellow solid, mp 139–140 °C; FT-IR (neat): 1382, 1466, 1541, 1597, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H, OC*H*$_3$), 4.78 (s, 2H, C*H*$_2$N), 7.03-7.78 (m, 13H, Ar*H*), 8.43 (s, 1H, =C*H*), 8.97 (s, 1H, N=C*H*);^{13}C NMR (75 MHz, $CDCl_3$) δ55.7, 65.4, 104.5, 115.5, 123.1, 123.2, 127.0, 127.4, 127.8, 128.1, 128.4, 128.7, 129.0, 131.4, 134.6, 134.7, 139.1, 139.2, 145.1, 153.4, 154.4, 157.3, 157.5. (Found C 70.41; H 4.62; N 13.02; $C_{25}H_{20}N_4OS$ requires C 70.73; H 4.75; N 13.20).

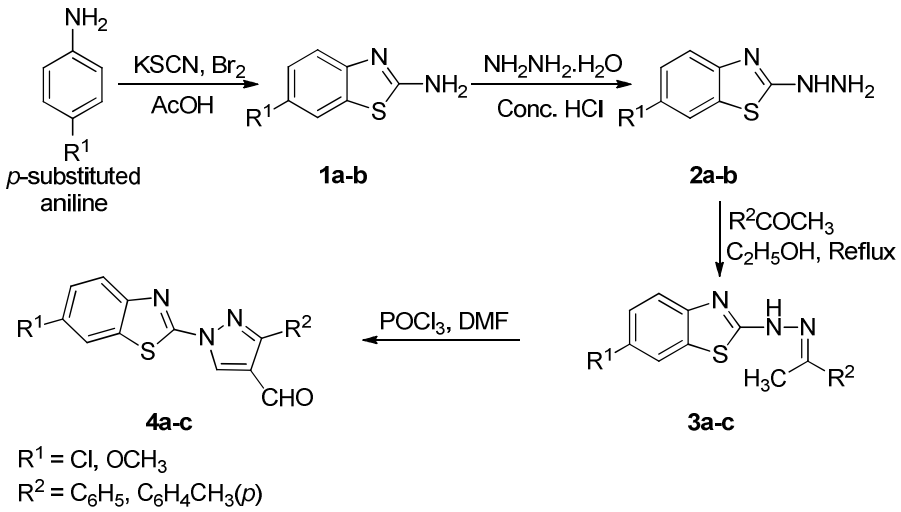
***N*-[{1-(6'-Methoxybenzo[*d*]thiazol-2'-yl)-3-phenyl-1*H*-pyrazol-4-yl}methylene]-2-methylpropan-1-amine** [**(5c)** 73%] was isolated as yellowish solid, mp 118–119 °C; FT-IR (neat): 1429, 1544, 1606, 1654, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ0.89 (s, 3H, C*H*$_3$), 0.91 (s, 3H, C*H*$_3$), 1.88 (m, 1H, C*H*), 3.30 (d, *J* = 6.6 Hz, 2H, NC*H*$_2$), 3.79 (s, 3H, OC*H*$_3$), 6.94-7.69 (m, 8H, Ar*H*), 8.19 (s, 1H, =C*H*), 8.83 (s, 1H, N=C*H*);^{13}C NMR (75 MHz, $CDCl_3$) δ20.8, 29.8, 55.6, 70.3, 104.5, 115.5, 121.3, 123.3, 128.1, 128.6, 128.9, 131.8, 134.8, 145.3, 152.1, 154.2, 157.6. (Found C 67.37; H 5.56; N 14.21; $C_{22}H_{22}N_4OS$ requires C 67.67; H 5.68; N 14.35).

***N*-[{1-(6'-Chlorobenzo[*d*]thiazol-2'-yl)-3-phenyl-1*H*-pyrazol-4-yl}methylene]-4-methoxybenzenamine** [**(5d)**76%] was isolated as yellowish solid, mp 180–181 °C; FT-IR (neat): 1447, 1501, 1551, 1595, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ3.74 (s, 3H, OC*H*$_3$), 6.77-7.73 (m, 12H, Ar*H*), 8.40 (s, 1H, =C*H*), 9.00 (s, 1H, N=C*H*);^{13}C NMR (75 MHz, $CDCl_3$) δ55.3, 114.4, 121.3, 122.2, 122.4, 123.5, 127.4, 128.4, 128.8, 129.0, 129.3, 130.9, 131.4, 134.8, 144.8, 148.9, 149.7, 158.5. (Found C 64.46; H 3.73; N 12.42; $C_{24}H_{17}ClN_4OS$ requires C 64.79; H 3.85; N 12.59).

***N*-[{1-(6'-Methoxybenzo[*d*]thiazol-2'-yl)-3-*p*-tolyl-1*H*-pyrazol-4-yl}methylene]-4-methoxybenzenamine** [**(5e)**85%] was isolated as yellowish solid, mp 152–153 °C; FT-IR (neat): 1437, 1472, 1501, 1548, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ2.36 (s, 3H, C*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 6.77-7.69 (m, 11H, Ar*H*), 8.38 (s, 1H, =C*H*), 8.96 (s, 1H, N=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.5, 55.3, 55.6, 104.5, 114.4, 115.5, 121.8, 122.1, 123.3, 128.1, 128.8, 128.9, 129.4, 134.9, 138.8, 145.1, 145.4, 149.4, 157.6, 158.4. (Found C 68.32; H 4.69; N 12.21; $C_{26}H_{22}N_4O_2S$ requires C 68.70; H 4.88; N 12.33).

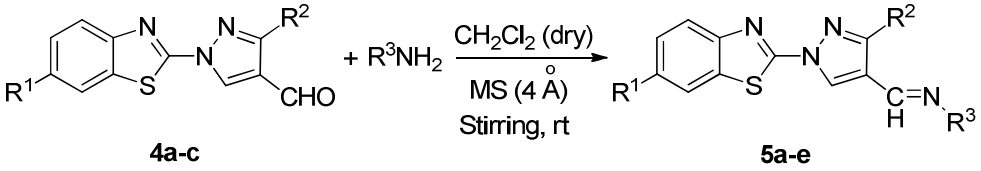
RESULTS AND DISCUSSION

Starting substrate, 2-hydrazinobenzothiazoles **2a-b** were prepared by cyclization of appropriately substituted anilines using potassium thiocyanate and bromine followed by nucleophilic substitution of amino group using hydrazine hydrate.[xiv,xv]1-(Benzo[*d*]thiazol-2'-yl)-1*H*-pyrazole-4-carbaldehydes **4a-c** were prepared via Vilsmeier-Haack reaction of various hydrazones**3a-c** which in turn were prepared via condensation of **2a-b** with various acetophenones using reported methodology (Scheme 1).[xiv,xv]



Scheme 1: Synthesis of benzothiazolylpyrazolecarbaldehydes**4a-c.**

The next step was to utilize benzothiazolylpyrazolecarbaldehydes**4a-c** for the synthesis of novel benzothiazolylpyrazole substituted imines **5a-e**. Initial studies were carried out by treatment of an equimolar amount of benzothiazolylpyrazolecarbaldehydes**4a** with *p*-anisidine in dry methylene chloride in the presence of molecular sieves at room temperature (Scheme 2). The progress of the reaction was monitored by TLC. After the completion of reaction, reaction mixture was filtered, solvent was removed under reduced pressure and the crude product was purified by recrystallization. The pure product was identified as 4-methoxy-*N*-{(1-(6-methoxybenzo[*d*]thiazol-2-yl)-3-phenyl-1*H*-pyrazol-4-yl)methylene}aniline **5a** (Table 1, entry 1) on the basis of various spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis). The reaction was found to be general for other aromatic/aliphatic amines as well as benzothiazolylpyrazolecarbaldehydes having different substitutions and furnished novel benzothiazolylpyrazole substituted imines **5b-e** summarized in Table 1 (entries 2-5).



Scheme 2: Synthesis of Schiff's bases **5a-e.**

Table 1: Synthesis of benzothiazolylpyrazole substituted imines**5a-e**

Entry	Substrate**4**	R^1	R^2	R^3	Imines**5**	Yield (%)[a]
1	**4a**	-OCH_3	-C_6H_5	-$C_6H_4OCH_3$(*p*)	**5a**	76
2	**4a**	-OCH_3	-C_6H_5	-$CH_2C_6H_5$	**5b**	93
3	**4a**	-OCH_3	-C_6H_5	-C_4H_9(*iso*)	**5c**	73
4	**4b**	-Cl	-C_6H_5	-$C_6H_4OCH_3$(*p*)	**5d**	76
5	**4c**	-OCH_3	-$C_6H_4CH_3$(*p*)	-$C_6H_4OCH_3$(*p*)	**5e**	85

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

All these newly synthesized imines (**5a-e**) were purified by recrystallization using a mixture of methylene chloride and hexane.Thestructural characterization of novel compounds were established on the basis of various spectroscopic techniques (FT-IR, NMR)andelemental analysis(CHN).Thenovel benzothiazolylpyrazole substituted imines**5a-e**are air- and moisture-

stable, soluble in solvents such as dichloromethane, chloroform, acetone, toluene and ethyl acetate.

CONCLUSIONS

In conclusion, we have successfully synthesized a novel series of benzothiazolylpyrazole substituted imines**5a-e** as potential synthonsin excellent yields. The structures of all the novel compounds were established on the basis of various spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. Due to the dynamic biological potential of heterocycles, novel imineshave been submitted for molecular docking and*in-vitro*evaluationfor potential biological activities. Moreover, transformation of these imines into β-lactam and thiazolidinone derivatives is currently in progress.

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