ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2016, *61*(10), 755-761

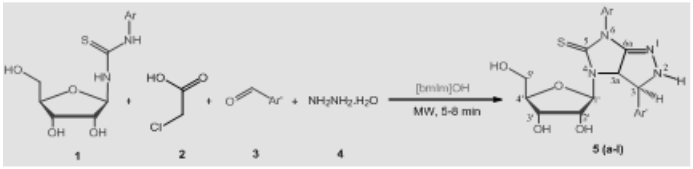
[bmIm]OH CATALYSED FOUR COMPONENT ONE-POT SYNTHESIS OF IMIDAZO[4,5-C]PYRAZOLE-2-THIONE-*N*-NUCLEOSIDES

Vishal SRIVASTAVA,[a] Pravin K. SINGH,[b] Surabhi SINHA[c] and Praveen P. SINGH[*c]

[a] Department of Chemistry, United College of Engineering & Management, Naini, Allahabad - 211010, India
[b]Food Analysis and Research Lab, Centre of Food Technology, University of Allahabad, Allahabad – 211002, India
[c]Department of Chemistry, United College of Engineering & Research, Naini, Allahabad - 211010, India

Received November 17, 2015

A basic ionic liquid, 1-butyl-3-methyl imidazolium hydroxide [bmIm]OH has been used as an efficient catalyst for the novel synthesis of pyrazoloimidazole-2-thione-*N*-nucleosides by one-pot four component condensation reaction of aryl ribosylthiourea, chloroacetic acid, aromatic aldehyde and hydrazine hydrate at room temperature.



INTRODUCTION

Pyrazole derivatives are well-known and important *N*-containing five-membered heterocyclic compounds and have occupied a unique position in the design and synthesis of novel biologically active agents. The pyrazole motif makes up the core structure of numerous biologically active compounds. Many substituted pyrazole derivatives are acknowledged to possess a wide range of bioactivities such as antimicrobial[1] (Sulphaphenazole), antifungal[2] (Sedaxane, Penflufen), anti-inflammatory[3] (Celecoxib, lonazolac) and antitumor[4] (Tozasertib, Barasertib) activities. With growing application on their synthesis and bioactivity, chemists and biologists in recent years have directed considerable attention on the research of pyrazole derivatives.

The chemistry of imidazoles has also attracted more attention during recent years due to their reactivity and novel biological activities. The incorporation of the imidazole nucleus, a biologically accepted pharmacophore in medicinal compounds, has made it versatile heterocyclic nucleus possessing wide spectrum of pharmacological properties[5-6] (Enilconazole, Fluconazole, Thiabendazole). Most important of these are 2-thioxo-imidazolidinones which exhibit antiviral particularly anti HIV activity.[7-8] The studies on the influence of the structure on the activity have shown that by fusing one heterocyclic moiety with another, in most cases the pharmacological profile was enhanced many folds than any one of the heterocyclic moiety.[9]

Recently, ionic liquids have emerged as very potential green alternatives to the volatile and hazardous organic solvents and have been used as efficient and recyclable reaction media for a variety of organic reactions.[10] Green organic synthesis has attracted many researchers and thus has considerable awareness of applications of environmentally benign reaction media such as of ionic liquids as solvent,[11] catalysts,[12] and reagents.[13] Recently, basic functionalized and task specific ionic liquids such as [bmIm]OH (Fig. 1) have been extensively applied in different organic reactions.

* Corresponding author: ppsingh23@gmail.com

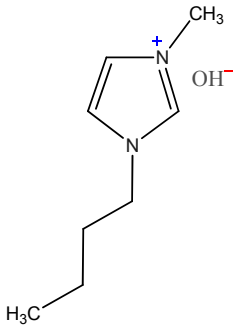


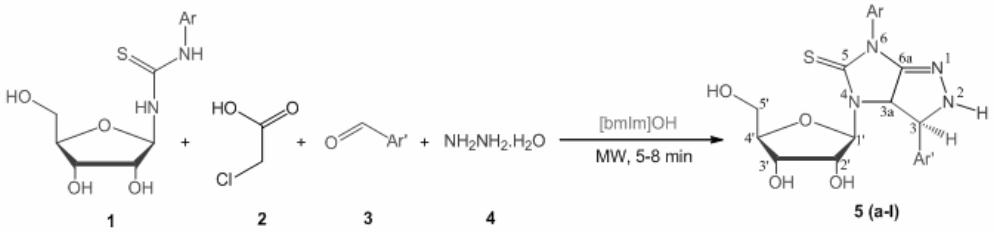
Fig. 1.

The application of the molecular diversity technique to drug discovery is a multidisciplinary effort ranging from computational chemistry to engineering to organic synthesis to molecular biology. The main objective of the work described here is to provide an account of one aspect of molecular diversity based drug discovery viz. the development of a general synthetic strategy for the generation of nucleoside analogues for screening of lead molecules for novel assays in the archives a chemicals amassed through organic synthesis.[14]

Encouraged by above reports and as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds[15-19] as well as in pursuing of our work on new solvent-free cyclisation processes we developed a regioselective, novel, [bmIm]OH catalysed, synthesis of hitherto unknown pyrazoloimidazol-2-thione *N*-nucleosides (Scheme 1). The key element in our approach is the utilization of α-haloacid as a bifunctional building block whose application to the construction of various heterocycles of chemical and biological interest is well documented.[20-21] Interestingly it is the first example of [bmIm]OH catalysed synthesis of pyrazoloimidazol-2-thione *N*-nucleosides.

RESULTS AND DISCUSSION

The synthetic pathway for preparation of the target compounds is shown in Scheme 1. The reaction scheme includes [bmIm]OH catalysed four component, one-pot, synthesis of pyrazoloimidazol-2-thione *N*-nucleoside with aryl ribosylthiourea **1** and chloroacetic acid **2**, followed by cyclocondensation with aromatic aldehyde **3** and hydrazine hydrate **4** at room temperature. In synthetic pathway, aryl ribosylthiourea reacts with chloroacetic acid to form intermediate compound **I**, which after dehydration leads to intermediate compound **II**. Further, compound **II** via nucleophilic attack on substituted benzylidenehydrazine gave the desired target compounds **5(a-l)**. The ionic liquid [bmIm]OH was prepared according to a standard procedure.[22-23]



Compound	Ar	Ar'	Yield (%)
5a	C_6H_5	C_6H_5	90
5b	C_6H_5	4-Cl-C_6H_4	82
5c	C_6H_5	4-HO- C_6H_4	91
5d	C_6H_5	4-MeO- C_6H_4	94
5e	C_6H_5	2-NO_2- C_6H_4	84
5f	C_6H_5	3-MeO, 4-HO-C_6H_3	96
5g	4-Me- C_6H_4	C_6H_5	92
5h	4-Me- C_6H_4	4-Cl-C_6H_4	83
5i	4-Me- C_6H_4	4-HO- C_6H_4	93
5j	4-Me- C_6H_4	4-MeO- C_6H_4	95
5k	4-Me- C_6H_4	2-NO_2- C_6H_4	86
5l	4-Me- C_6H_4	3-MeO, 4-HO-C_6H_3	97

Scheme 1.

Table 1

Optimization of catalyst

Entry	Catalyst (mmol%)	Time (min)	Yield of Product (%)[a]
1	0	215	No reaction
2	1	46	60
3	3	30	80
4	5	25	92,92,91[b]
5	10	25	92

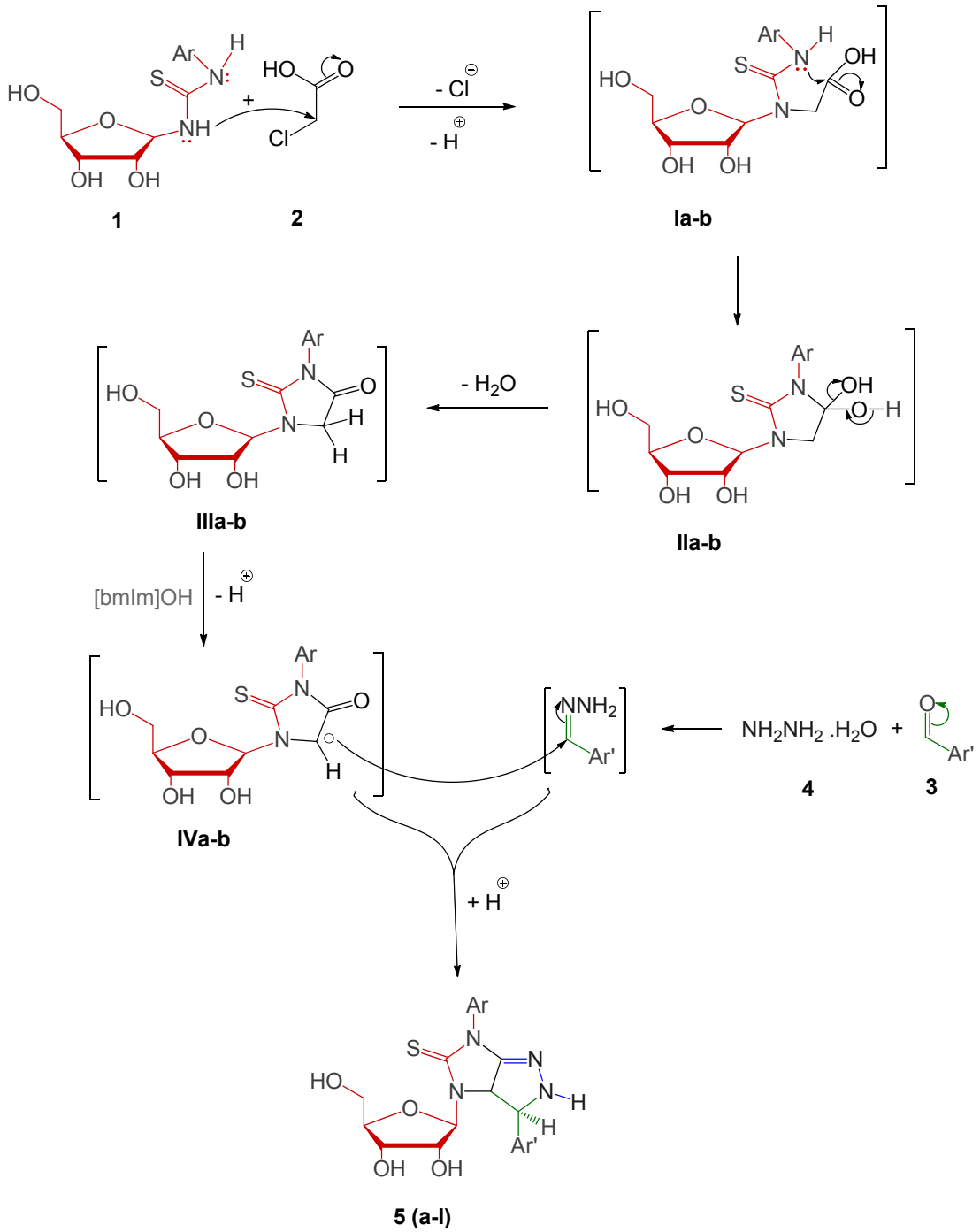
Conditions: substituted/unsubstituted aryl ribosylthiourea **1** (1 mmol), chloroacetic acid **2** (1 mmol), aromatic aldehyde **3**(0.01 mol) Ar = C_6H_5 / 4-Me- C_6H_4, Ar' = C_6H_5 / 4-Cl- C_6H_4/ 4-OH- C_6H_4/ 4-OMe- C_6H_4/ 2-NO_2- C_6H_4/ 3-MeO, 4-HO-C_6H_3, hydrazine hydrate **4** (1 mmol) and [bmIm]OH (5 mmol%),
[a] Yield of isolated product
[b] Catalyst was used three times

Encouraged by these results, we further investigated the effect of the catalyst on the reaction and found that there is significant reduction in time along with excellent increment in yield on using [bmIm]OH as a catalyst. We performed the reaction using different molar concentration of catalyst (Table 1), carefully studied its effect on the yield of isolated product and found that on using 1, 3, 5, 10 mmol% of [bmIm]OH, the yield was 60%, 80%, 92% and 92%, respectively. Further increase in catalyst concentration did not lead to significant enhancement in the yield therefore we decided to use only 5 mmol% of the catalyst for the best result. Only 5 mmol% of [bmIm]OH gives products in very excellent yield within very short time. Therefore we are able to say that this methodology follows several principles of green chemistry. Further it found that without catalyst the reaction did not proceed. The ionic liquid can be reused without any significant loss of activity.

The synthesis is regioselective and regioselectivity obtained in cyclocondensation of arylribosylthiourea with chloroacetic acid was due to difference in nucleophilicity of –NH-Sugar and –NHAr groups. Additional delocalisation of electrons on aromatic ring in –NHAr makes it a poor nucleophile and hence –NH-Sugar group by nucleophilic substitution of α-halogen of $ClCH_2COOH$ resulted an intermediate (**Ia-b**) (Scheme 2). Structure of (**Ia-b**) was supported by IR and ^{1}H NMR spectral analysis. Absorption bands in the region of 3300-3350 cm^{-1} for N-H, 3050 cm^{-1} for aromatic C-H, 1690 cm^{-1} for C=O, 1620 cm^{-1} for C=C, 1600, 1500, 1468 cm^{-1} for aromatic C-C, 1200 cm^{-1} for C=S and 1180 cm^{-1} for C-N stretching in IR spectra and signals at δ 7.2 - 7.4 as multiplet for aromatic protons, δ 4.80 as singlet for vinylic proton of benzylideno group and δ 2.1 - 2.5 as singlet for –NH- proton in ^{1}H NMR spectra were indicative of the synthesis of compounds **5a-l**. Doublets at δ 3.58-3.60 and at δ 4.10-4.12 due to 3a-CH and 3-CH respectively and multiplets at δ 6.25-7.40 due to aromatic protons in ^{1}H NMR spectra of **(5a-l)** showed the pyrazoloimidazol-2-thione nucleus. Multiplets in the region at δ 3.65-3.80 due to four sugar protons as well as doublets at δ 4.96 due to anomeric proton and broad singlet at δ 2.00 exchangeable with D_2O due to three –OH group were indicative of *β*-D-ribofuranosyl moiety in **(5a-l)**. In ^{13}C NMR spectral analysis in the region δ 108-165 for aromatic carbons and at δ 165-175 for C=S and C=O carbons and at δ 61-178 for sugar carbons supported that all synthesized compounds have pyrazoloimidazolidin-2-thione *N*-ribofuranosidic skeleton.

EXPERIMENTAL

Melting points were determined by open glass capillary method and are uncorrected. The chemical ribosylthiourea has been prepared by standard procedure[24] and remaining chemicals used were reagent grade (Sigma Aldrich) and were used as received. The completion of reactions was monitored by TLC (n-hexane–AcOEt, 7:3, Merk silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer in KBr. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400^{o}C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in $CDCl_3$ using TMS as an internal reference (chemical shift in δ, ppm). Mass spectra were recorded on JEOL SX-102 (FAB) mass spectrophotometer at 6 kV and 10 mA with an accelerating voltage of 10 kV. Elemental analyses were carried out using a Coleman automatic C, H, N analyser.



Scheme 2 – Proposed mechanism for the synthesis of Pyrazoloimidazol-2-thione *N*-nucleoside using [bmIm]OH as a catalyst.

*4-[β-D-Ribofuranosyl]-3,6-diphenyl-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione)***(5a-l)**

Substituted/unsubstituted aryl ribosylthiourea **1** (1 mmol), chloroacetic acid **2** (0.0945g), and [bmIm]OH (5 mmol%) was taken in 50 mL round bottom flask and stirred for 5 min then aromatic aldehyde **3** (1 mmol) and hydrazine hydrate **4** (50 ml) was added to this mixture. The reaction mixture was stirred for 20 min. at room temperature. Completion of the reaction was monitored by TLC. The product was extracted with ethyl acetate (3 × 10 mL). The organic layer was concentrated under reduced pressure and the residue obtained was triturated with cold methanol and purified by flash column chromatography on silica gel (eluent n-hexane–AcOEt, 4:1) to obtained analytically pure **5a-l**.

Intermediate Ia: IR spectrum, ν, cm^{-1}: 1335, 1455, 1580, 3135, 3345, ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.35-4.40(2H, s, -NCH_2); 6.81-6.91 (1H, m, 4″ArH); 7.15-7.25 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.65-7.75 (2H, dd, *J* = 3.1 Hz, *J* = 2.5 Hz, 2″, 6″ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm:54.8; 61.6; 71.5; 73.5; 87.9; 106.7; 126.5; 128.4; 129.0; 138.5; 173.1; 182.3. Mass spectrum, *m/z:* 342

$[M]^+$. Found, %: C 49.09; H 5.25; N 8.15. $C_{14}H_{18}N_2O_6S$. Calculated, %: C 49.11; H 5.30; N 8.18.

Intermediate Ib: IR spectrum, ν, cm^{-1}: 1345, 1460, 1583, 3139, 3350, ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.30-2.35 (3H, s, -CH_3), 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.35-4.40 (2H, s, -NCH_2); 6.35-6.40 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.95-7.00 (2H, dd, *J* = 3.1 Hz, *J* = 2.4 Hz, 3″, 5″ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 54.8; 61.6; 71.5; 73.5; 87.9; 106.7; 126.4; 129.3; 135.5; 137.2; 173.1; 182.3. Mass spectrum, *m/z:* 356 $[M]^+$. Found, %: C 50.53; H 5.64; N 7.82. $C_{15}H_{20}N_2O_6S$. Calculated, %: C 50.55; H 5.66; N 7.86.

4-[β-D-Ribofuranosyl]-3,6-diphenyl-2,3a,4,6-tetrahydroimidazo[4,5-c]pyrazole-5(3H)-thione(**5a**): mp 110-112ºC. IR spectrum, ν, cm^{-1}: 1340, 1442, 1468, 1584, 3050, 3127, 3345 , ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* = 3.2 Hz, *J* = 4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 6.25-6.30 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.35-6.45 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH); 6.48-6.59 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4‴ ArH); 6.81-6.91 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.20-7.29 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.35-7.45 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 126.7; 126.9; 128.4; 128.5; 129.0; 133.0; 133.9; 143.5; 157.0; 180.9. Mass spectrum, *m/z:* 426 $[M]^+$. Found, %: C 59.12; H 5.16; N 13.11. $C_{21}H_{22}N_4O_4S$. Calculated, %: C 59.14; H 5.20; N 13.14.

3-(4-chlorophenyl)-4-[β-D-Ribofuranosyl]-6-phenyl-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione (**5b):** m.p. : 120-123ºC. IR spectrum, ν, cm^{-1}: 1360, 1442, 1469, 1588, 3052, 3150, 3349, ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 6.25-6.30 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.81-6.91 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.20-7.29 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.40-7.44 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH); 7.45-7.50 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 127.2; 128.4; 128.6; 129.0; 132.3; 133.0; 133.9; 141.6; 157.0; 180.9. Mass spectrum, *m/z:* 460 $[M]^+$. Found %: C, 54.68: H, 4.56; N, 12.12. $C_{21}H_{21}ClN_4O_4S$. Calculated, %: C, 54.72: H, 4.59: N, 12.16.

4-[β-D-Ribofuranosyl]-3-(4-hydroxyphenyl)-6-phenyl-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione (**5c):** m.p.: 116-119ºC. IR spectrum, ν, cm^{-1}: 1350, 1449, 1470, 1595, 3054, 3145, 3345, 3400, ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 5.35 (1H, s, ArOH); 6.25-6.30 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.81-6.91 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4″ArH); 6.92-6.99 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH);7.05 (1H, d, *J* =4.2 Hz, -NH); 7.10-7.18 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH); 7.20-7.29 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 115.7; 127.0; 128.4; 129.0; 133.0; 136.1; 157.0; 180.9. Mass spectrum, *m/z:* 442 $[M]^+$. Found %: C, 56.99: H, 4.98; N, 12.63. $C_{21}H_{22}N_4O_5S$. Calculated, %: C, 57.00: H, 5.01: N, 12.66.

4-[β-D-Ribofuranosyl]-3-(4-methoxyphenyl)-6-phenyl-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione (**5d):** m.p. : 115-118ºC. IR spectrum, ν, cm^{-1}: 1355, 1455, 1465, 1588, 3048, 3156, 3350, ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.90 (3H, s, -OCH_3); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 5.35 (1H, s, ArOH); 6.25-6.30 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.81-6.91 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4″ArH); 6.92-6.99 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH);7.05 (1H, d, *J* =4.2 Hz, -NH); 7.12-7.19 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH); 7.20-7.29 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 55.8; 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 114.1; 126.6; 129.0; 128.4; 133.0; 133.9; 135.8; 157.0; 158.6; 180.9. Mass spectrum, *m/z:* 442 $[M]^+$. Found %: C, 57.85: H, 5.28; N, 12.23. $C_{22}H_{24}N_4O_5S$. Calculated, %: C, 57.88: H, 5.30: N, 12.27.

4-[β-D-Ribofuranosyl]-3-(2-nitrophenyl)-6-phenyl-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione (**5e):** m.p. : 118-121ºC. IR spectrum, ν, cm^{-1}: 1365, 1472, 1475, 1593, 3055, 3159, 3355, 3400, ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 6.25-6.30 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 7.58-7.62 (1H, d, *J* = 3.1 Hz, 6‴ArH); 7.45-7.55 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4‴ ArH); 6.81-6.91 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.20-7.29 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.90-8.05 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 51.3; 58.3; 61.6; 71.5; 73.8; 87.9; 104.9; 124.7; 127.6; 127.8; 128.4; 129.0; 133.0; 133.9; 134.6; 137.5; 147.2; 157.0; 180.9. Mass spectrum, *m/z:* 471 $[M]^+$. Found %: C, 53.49: H, 4.45; N, 14.81. $C_{21}H_{21}N_5O_6S$. Calculated, %: C, 53.50: H, 4.49: N, 14.85.

4-[β-D-Ribofuranosyl]-3-(4-hydroxy-3-methoxyphenyl)-6-phenyl-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione (**5f):** m.p.: 125-128ºC. IR spectrum, ν, cm^{-1}: 1375, 1445, 1468, 1530, 1585, 3049, 3156, 3358, 3400, ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.90 (3H, s, -OCH_3); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 5.35 (1H, s, ArOH); 6.25-6.30 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.81-6.91 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4″ArH); 6.93-6.99 (1H, d, *J* = 3.1 Hz, 5‴ArH);7.05 (1H, d, *J* =4.2 Hz, -NH); 7.07-7.16 (2H, d, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH); 7.20-7.29 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 56.1; 56.2; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 110.2; 119.3; 128.4; 129.0; 133.0; 133.9; 137.1; 146.7; 147.3; 157.0; 180.9. Mass spectrum, *m/z:* 472 $[M]^+$. Found %: C, 55.90: H, 5.10; N, 11.84. $C_{22}H_{24}N_4O_6S$. Calculated, %: C, 55.92: H, 5.12: N, 11.86.

4-[β-D-Ribofuranosyl]-3-phenyl-6-(p-tolyl)-2,3,3a,4-tetrahydroimidazo[4,5-c]pyrazole-5(6H)-thione (**5g**)**:** m.p. : 114-117ºC. IR spectrum, ν, cm^{-1}: 1341, 1440, 1466, 1581, 3048, 3121, 3334, ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.35 (3H, s,-CH_3); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 6.05-6.10 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.35-6.45 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH); 6.90-6.98 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.20-7.27 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4‴ ArH); 7.35-7.45 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 126.7; 126.9; 128.4; 128.5; 126.7; 129.3; 130.9; 133.4; 143.5; 157.0; 180.9. Mass spectrum, *m/z:* 440 $[M]^+$. Found %: C, 59.94: H, 5.45; N, 12.70. $C_{22}H_{24}N_4O_4S$. Calculated, %: C, 59.98: H, 5.49: N, 12.72.

3-(4-chlorophenyl)-4-[β-D-Ribofuranosyl]-6-(p-tolyl)-2,3,3a,4-tetrahydroimidazo[4,5-c] pyrazole-5(6H)-thione (**5h**)**:** m.p. : 124-127ºC. IR spectrum, ν, cm^{-1}: 1356, 1440, 1468, 1585, 3051, 3147, 3345, ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.35 (3H, s,-CH_3); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 6.05-6.10 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.90-6.98 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.20-7.27 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4‴ ArH); 7.40-7.44 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH); 7.45-7.50 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 127.2; 128.4; 128.6; 126.7; 129.3; 130.9; 132.3; 133.4; 137.2; 141.6; 157.0; 180.9. Mass spectrum, *m/z:* 474 $[M]^+$. Found %: C, 55.60: H, 4.86; N, 11.77. $C_{22}H_{23}ClN_4O_4S$. Calculated, %: C, 55.63: H, 4.88: N, 11.80.

4-[β-D-Ribofuranosyl]-3-(4-hydroxyphenyl)-6-(p-tolyl)-2,3,3a,4tetrahydroimidazo[4,5-c] pyrazole-5(6H)-thione (**5i**)**:** m.p. : 122-125ºC. IR spectrum, ν, cm^{-1}: 1355, 1445, 1464, 1590, 3045, 3141, 3338, 3403, ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.35 (3H, s,-CH_3); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.90 (3H, s, -OCH_3); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 5.35 (1H, s, ArOH); 6.05-6.10 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.90-6.98 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.20-7.27 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4‴ ArH); 6.92-6.99 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH); 7.12-7.19 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH);. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 55.8; 55.9; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 114.1; 126.6; 129.3; 130.9; 133.4; 135.8; 137.2; 158.6; 157.0; 180.9. Mass spectrum, *m/z:* 456 $[M]^+$. Found %: C, 57.85: H, 5.28; N, 12.25. $C_{22}H_{24}N_4O_5S$. Calculated, %: C, 57.88: H, 5.30: N, 12.27.

4-[β-D-Ribofuranosyl]-3-(4-methoxyphenyl)-6-(p-tolyl)-2,3,3a,4-tetrahydroimidazo[4,5-c] pyrazole-5(6H)-thione (**5j**)**:** m.p. : 124-127ºC. IR spectrum, ν, cm^{-1}: 1358, 1485, 1464, 1578, 3045, 3166, 3338,^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.35 (3H, s,-CH_3); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 5.35 (1H, s, ArOH); 6.05-6.10 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.90-6.98 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.07-7.16 (2H, d, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 56.1; 56.2; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 110.2; 115.4; 119.3; 129.3; 130.9; 133.4; 137.1; 137.2; 146.7; 147.3; 157.0; 180.9. Mass spectrum, *m/z:* 486 $[M]^+$. Found %: C, 56.76: H, 5.35; N, 11.50. $C_{23}H_{26}N_4O_6S$. Calculated, %: C, 56.78: H, 5.39: N, 11.52.

4-[β-D-Ribofuranosyl]-3-(2-nitrophenyl)-6-(p-tolyl)-2,3,3a,4-tetrahydroimidazo[4,5-c] pyrazole-5(6H)-thione (**5k**)**:** m.p. : 130-133ºC. IR spectrum, ν, cm^{-1}: 1360, 1465, 1469, 1590, 3051, 3165, 3343, 3420, ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.35 (3H, s,-CH_3); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 5.35 (1H, s, ArOH); 6.05-6.10 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.90-6.98 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.45-7.55 (1H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 4‴ ArH); 7.58-7.62 (1H, d, *J* = 3.1 Hz, 6‴ArH);7.90-8.05 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3‴, 5‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 51.3; 58.3; 61.6; 71.5; 73.8; 87.9; 104.9; 124.7; 127.6; 127.8; 129.3; 130.9; 133.4; 134.6; 137.2; 137.5; 147.2; 157.0; 180.9. Mass spectrum, *m/z:* 485 $[M]^+$. Found %: C, 54.40: H, 4.75; N, 14.40. $C_{22}H_{23}N_5O_6S$. Calculated, %: C, 54.42: H, 4.77: N, 14.42.

4-[β-D-Ribofuranosyl]-3-(4-hydroxy-3-methoxyphenyl)-6-(p-tolyl)-2,3,3a,4tetrahydroimidazo [4,5-c]pyrazole-5(6H)-thione (**5l**)**:** m.p. : 131-134ºC. IR spectrum, ν, cm^{-1}: 1379, 1442, 1462, 1520, 1574, 3043, 3160, 3351, 3410,^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.00 (3H, brs, 3×OH, exchangeable with D_2O); 2.35 (3H, s,-CH_3); 3.58 (1H, d, *J* = 3.2 Hz, 3a-CH); 3.65–3.88 (4H, m, 2', 3'-CH, 5'-CH_2); 3.90 (3H, s, -OCH_3);3.92-4.05 (1H, m, 4'-CH); 4.10 (1H, dd, *J* =3.2 Hz, *J* =4.2 Hz, 3-CH); 4.96 (1H, d, *J* =4.2 Hz, 1'-CH); 6.05-6.10 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 2″, 6″ArH); 6.90-6.98 (2H, dd, *J* = 3.1 Hz, *J* = 2.7 Hz, 3″, 5″ArH); 6.93-6.99 (1H, d, *J* = 3.1 Hz, 5‴ArH); 7.05 (1H, d, *J* =4.2 Hz, -NH); 7.07-7.16 (2H, d, *J* = 3.1 Hz, *J* = 2.7 Hz, 2‴, 6‴ArH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 56.1; 56.2; 59.3; 61.6; 71.5; 73.8; 87.9; 104.9; 110.2; 115.4; 119.3; 129.3; 130.9; 133.4; 137.1; 137.2; 146.7; 147.3; 157.0; 180.9. Mass spectrum, *m/z:* 486 $[M]^+$. Found %: C, 56.76: H, 5.35; N, 11.50. $C_{23}H_{26}N_4O_6S$. Calculated, %: C, 56.78: H, 5.39: N, 11.52.

CONCLUSION

In conclusion, we have reported herein, basic ionic liquid catalysed novel synthesis of pyrazoloimidazole-2-thione *N*-nucleosides by one-pot four component condensation of aryl ribosylthiourea, chloroacetic acid, aromatic aldehyde and hydrazine hydrate under solvent-free

conditions at room temperature. The reaction is stereoselective. Only one disteriomer has been obtained in the reaction. Although the resulting product could have been formed as diastereomeric pair we could not separate product into diastereomers. It seems that *cis*-isomers, if formed, probably isomerised into more stable *trans* form. This method includes marked improvements regarding to operational simplicity, reaction time, environmentally benign protocol, easily and reusable basic ionic liquid, avoiding hazardous organic solvents and toxic catalysts, which fulfil basic need of green chemistry.

Acknowledgements: We sincerely thank SAIF, CDRI, Lucknow and IISc Banglaore for providing microanalyses and spectra.

REFERENCES

1. A. M. Farag, A. S. Mayhoub, S. E. Barakat and A. H. Bayomi, *Bioorg. Med. Chem.*, **2008**, *16*, 4569.
2. M. S. Karthikeyan, B. S. Holla and N. S. Kumari, *Eur. J. Med. Chem.*, **2007**, *42*, 30.
3. N. Gokhan-Kelekci, S. Yabanoglu, E. Kupeli, U. Salgin, O. Ozgen, G. Ucar, E. Yesilada, E. Kendi, A. Yesilada and A. A. Bilgin, *Bioorg. Med. Chem.*, **2007**, *15*, 5775.
4. L. Ronghui, C. George, Y. Yang, J. C. Peter, L. Shengjian, L. Yanhua and A. Mary, *Bioorg Med. Chem. Lett.*, **2007**, *17*, 4557.
5. F. Franchetti, S. Marchetti, L. Capellacci, J. A. Yalowitz, H. N. Jayaram, B. M. Goldstein and M. Grifantini, *Bioorg Med. Chem. Lett.*, **2001**, *11*, 67.
6. A. M. Agh-Atabay, B. Dulger and F. Gucin, *Eur. J. Med. Chem.*, **2003**, *38*, 875.
7. A. Rosario, J. I. Andres, M. T. Lopez, F. G. Heras, R. Herranz, B. Alarcon and L. Carrasco, *J. Med. Chem.*, **1985**, *28*, 834.
8. D. P. C. Mc Gee, J. C. Martin, D. F. Smee and J. P. H. Verheyden, *Nucleosides and Nucleotides*, **1990**, *9*, 815.
9. M. Pierrot, B. Garrigus, J. Fifani, Eessasi Em and B. Djerrari, *Indian J. Chem.*, **2003**, *42B*, 2820.
10. D. G. Gu, S. J. Ji, Z. Q. Jiang, M. F. Zhou and T. P. Loh, *Synlett*, **2005**, 959.
11. S. Choudhury, R. S. Mohan and J. L. Sott, *Tetrahedron*, **2007**, *63*, 2393.
12. K. Quiao and C. Yakoyama, *Chem. Lett.*, **2004**, *33*, 472.
13. S. K. Singh, P. Gupta, S. Dugginei and B. Kundu, *Synlett*, **2003**, 2147.
14. M. Nuss John, C. Desai Manoj, N. Zuckermann Ronald, R. Singh and S. Sharadha, *Pure & Appl. Chem.*, **1997**, *69*, 447.
15. V. Srivastava, P. K. Singh and P. P. Singh, *Chem. Heterocyclic Comp.*, **2014**, *50*, 573.
16. I. R. Siddiqui, P. K. Singh, J. Singh and J. Singh, *J. Chem. Res.*, **2004**, *8*, 554.
17. I. R. Siddiqui, P. K. Singh, J. Singh and J. Singh, *Indian J. Chem.*, **2005**, *44B*, 2102.
18. I. R. Siddiqui, P. K. Singh, V. Srivastava and J. Singh, *Indian J. Chem.*, **2005**, *44B*, 2178.
19. V. Srivastava, P. K. Singh and P. P. Singh, *Croat. Chem. Acta*, **2014**, *87*, 91.
20. N. N Farshori, M. R. Banday, A. Ahmad, A. U. Khan and A. Rauf, *Indian J. Chem.* **2011**, *50B*, 605.
21. F. Chadegani, F. Darviche and S. Balalaie, *Int. J.Org. Chem.*, **2012**, *2*, 31.
22. J. M. Xu, C. Qian, B. K. Liu, Q. Wu and X. F. Lin, *Tetrahedron*, **2007**, *63*, 986.
23. B. C. Ranu and S. Banerjee, *Org. Lett*., **2005**, *7*, 3049.
24. I. R. Siddiqui, V. Srivastava and P. K. Singh, *Nucleosides, Nucleotides and Nucleic Acids*, **2008**, 27, 992.