Asian Pub. Corp.

www.asianpubs.org

ARTICLE

A Novel and Facile Synthesis of Thiopyrimidines and *O*-Glucosides

Rajendra Krushnaji Wanare✉

Asian Journal of Organic & Medicinal Chemistry

Volume: 4 Year: 2019
Issue: 2 Month: April–June
pp: 65–69
DOI: https://doi.org/10.14233/ajomc.2019.AJOMC-P161

Received: 27 November 2018
Accepted: 24 March 2019
Published: 29 June 2019

ABSTRACT

Reaction of 3-methyl-5-(3'-aryl prop-2'-enoyl)-1,2-benzisoxazole (**1a-j**) with thiourea and alcoholic solution of KOH afforded 3-methyl-5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazoles (**2a-j**). Oxidation of products **2a-j** using alkaline $KMnO_4$ solution produces 5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acids (**3a-j**). Condensation of products **3a-j** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGBr), the glucosylating agent synthesized 3-(2,3,4,6-tetra-*O*-acetyl-3-acetyl-β-D-glucopyranosyl)-5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazoles (**4a-j**). Subsequent deacetylation of compounds **4a-j** were carried out with CH_3ONa furnishes β-D-glucopyranosyl-5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylates (**5a-j**). All the synthesized compounds were analyzed by elemental analysis (C, H and N), FT-IR, ^1H NMR and mass spectral data. Most of the prepared compounds were analyzed their antibacterial and antifungal activities by cup-plate method. The present approach offers several advantages such as shorter reaction times, cleaner reactions, good yields, low-cost reagent and mild reaction conditions.

KEYWORDS

Thiopyrimidines, 1,2-Benzisoxazoles, TAGBr, Glycosylation, *O*-Glucosides.

INTRODUCTION

Various thiopyrimidines have been synthesized by a facile and efficient method and showed good anti-inflammatory, analgesic, analgesic, protein kinase and inhibitory activities [1,2]. Its derivatives attracted organic chemists due to their biological and chemotherapeutic importance and related fused heterocycles are important classes of heterocyclic compounds that exhibit a broad spectrum of biological importance such as anticancer, antiviral, antibacterial, antioxidant, anxiolytic, antidepressant and analgesic that are well documented in the literature [3-8]. Glucosides are normally water soluble and optically active compounds. *O*-Glucosides are the acetals of alcohols or phenols and are widely distributed in nature in plants and animals. The main function of *O*-glucosides is to serve as a handle of pharmacophoric group for recognition of the structure by target cells. It also helps in the interaction of organic molecules to enter into the membrane glycoprotein and finally entering the cell cytoplasm of target cells and has been the subject of considerable interest in carbohydrate

Author affiliations:

Department of Chemistry, Jawaharlal Nehru Arts Commerce & Science College, Wadi, Nagpur-440023, India

✉To whom correspondence to be addressed:

E-mail: rajwanare@rediffmail.com

Available online at: http://ajomc.asianpubs.org

chemistry because many carbohydrates exhibit very interesting biological activities like anti-inflammatory, analgesic, antipyretic, antioxidant, antihyperglycemic, antitumor and inhibitor of metabolic processes [9-12]. The interesting stable family of glucoside derivatives shows potential antimalarial activities and carbohydrate moiety enhances the water and lipid solubility of the pharmacophoric group and major active molecule is the aglycone, which is responsible for its biological and pharmacological activities [13,14]. In preceding papers [15], the synthesis of a series of novel chalcones, pyrazole and carboxylic acid derivatives with *O*-glucoside moiety are described. In this respect, an important role is played by thiopyrimidine nucleus known to possess various physiological activities. This stimulated us to synthesize a series of thiopyrimidine derivatives, which are reported in this paper along with their physicochemical characterization and study of their potential as biological activities.

EXPERIMENTAL

All chemicals which have been used were of reagent grade and used as provided directly unless otherwise stated. All melting points were measured by Veego-Precision (VMD-D) melting point apparatus and are uncorrected. The mass spectra were recorded under ESI mode on Thermo Finnigan (Model-LCQ Advantage MAX) mass spectrometer. Infrared spectra were investigated (KBr) by means of a Perkin Elmer 1650 spectrophotometer. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) of prepared compounds was carried out on 300 MHz NMR spectrometer at 25 °C and chemical shifts were expressed as ppm (δ values) with respect to TMS as internal standard.

Procedure for synthesis of thiopyrimidines and *O*-glucosides

3-Methyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole (2a): 3-Methyl-5-(3'-phenyl prop-2'-enoyl)-1,2-benzisoxazole (**1a**) (0.01 mol, 2.63 g), thiourea (0.76 g), ethyl alcohol (20 mL) and KOH (0.5 g) was refluxed on water bath for 5 h. It was cooled and acidified with dilute HCl (1.0 mL) and was poured on ice-cold water (75 mL). The yellow solid compound 3-methyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole (**2a**) obtained was filtered, washed with cold distilled water (150 mL), dried and crystallized with aq. alcohol (yield 2.0 g, 76 %), m.p. 131 °C. Purity of compound was checked on TLC plate using iodine vapour as visualizing agent (R_f = 0.29). It did not give any colour with conc. H_2SO_4. Similarly, 3-methyl-5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazoles (**2a-j**) were prepared and compounds gave satisfactory C, H and N analysis (Table-1).

5-(4'-Phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acid (3a): Mixture of 3-methyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole (**2a**) (0.01 mol, 3.19 g), sodium carbonate (1.5 g), $KMnO_4$ (1.5 g) and distilled water (100 mL) was refluxed under water bath for 4 h, until the purple colour of the permanganate has disappeared. It was acidified with dil. H_2SO_4, the excess manganese dioxide was removed by metabisulphite (0.1 g), filtered, washed and crystallized with distilled water produces 5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**) (yield 1.4 g, 43.88 %), m.p. 103 °C. Purity of compound was checked on TLC plate using iodine vapour as visualizing agent (R_f = 0.24). It was found to be soluble in dil. $NaHCO_3$ with effervescences. Similarly, various 5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acids (**3a-j**) were synthesized and gave satisfactory C, H and N analysis.

β-D-Glucopyranosyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylates (5a)

Glucosylation: To a solution of 5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**) (0.01 mol, 3.49 g) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGBr, 3 g) in dichloromethane was added tetrabutylammonium bromide (0.32 g) with stirring at 5 °C. Sodium hydroxide (10 %, 10 mL) was added to it drop wise over a period of 30 min and the reaction mixture further stirred for 24 h. The organic layer of 3-(2,3,4,6-tetra-*O*-acetyl-4'-*O*-β-D-glucosidoxyphenyl)-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole (**4a**) was separated, washed with water, 5 % dil $NaHCO_3$ and again with water and dried.

Deacetylation: 3-(2,3,4,6-Tetra-*O*-acetyl-4'-*O*-β-D-glucosidoxyphenyl)-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole (**4a**) in absolute methanol (26 mL) was added (1.5 mL) of 0.5 % of sodium methoxide solution and kept at room temperature for 50 min. The reaction mixture was neutralized with ion exchange resin (Amberlite IR 120), filters and dried. A semi-solid mass β-D-glucopyranosyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylates (**5a**) so obtained was purified on a column of silica gel and crystallized from ethanol as brown syrupy compound was obtained (2.0 g, 57.3 %). The obtained product was found to be optically active and the specific rotation $[\alpha]_D^{25}$ in water was found to be +50.2°. Following the same procedure, β-D-glucopyranosyl-

TABLE-1
PHYSICO-CHEMICAL DATA OF THE SYNTHESIZED COMPOUNDS (**2a-j**)

Compd.	R	m.f.	m.w.	R_f value	Elemental analysis (%): Found (calcd.)		
					C	H	N
2a	C_6H_5	$C_{18}H_{13}N_3OS$	319	0.29	67.68 (67.69)	4.09 (4.10)	13.15 (13.16)
2b	*o*-OHC_6H_4	$C_{18}H_{13}N_3O_2S$	335	0.36	64.45 (64.46)	3.90 (3.91)	12.92 (12.94)
2c	2,4-$(OH)_2C_6H_3$	$C_{18}H_{13}N_3O_3S$	351	0.24	61.50 (61.53)	3.70 (3.73)	11.95 (11.96)
2d	*p*-OH-*m*-$OCH_3C_6H_3$	$C_{19}H_{15}N_3O_3S$	365	0.34	62.43 (62.45)	4.14 (4.14)	11.49 (11.50)
2e	*o*-ClC_6H_4	$C_{18}H_{12}N_3OSCl$	353	0.30	61.08 (61.10)	3.41 (3.42)	11.87 (11.88)
2f	*m*-$NO_2C_6H_4$	$C_{18}H_{12}N_4O_3S$	364	0.23	59.35 (59.33)	3.33 (3.32)	15.36 (15.38)
2g	4-C_5H_4N	$C_{17}H_{12}N_4OS$	320	0.28	63.71 (63.73)	3.75 (3.78)	17.46 (17.49)
2h	3-C_4H_3O	$C_{16}H_{11}N_3O_2S$	309	0.40	62.10 (62.12)	3.55 (3.58)	13.57 (13.58)
2i	3-C_8H_5N	$C_{20}H_{14}N_4OS$	358	0.29	67.00 (67.02)	3.94 (3.94)	15.62 (15.63)
2j	*p*-*N*$(CH_3)_2C_6H_4$	$C_{20}H_{18}N_4OS$	362	0.27	66.27 (66.28)	5.05 (5.01)	15.47 (15.46)

5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylates (**5a-o**) were prepared and gave satisfactory C, H and N analysis (Table-2).

Spectral data for selected compounds

3-Methyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole (2a): Yield 76.0 %, m.p. 131 °C, FT-IR (KBr, ν_{max}, cm^{-1}): 2592 (C-SH str.), 3007 (C-H str. $-CH_3$), 1622 (C=N), 3144 (N-H str.) 1222 (C-O-N str. In isoxazole ring), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, $-CH_3$), 4.0 (s, Ar-SH), 6.2-7.7 (9H, m, aromatic protons), 2.0 (s, –NH), 6.3 (s, isoxazole ring), 5.6 (s, –CH, pyrimidine ring) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) 122.1-164.2 (benzisoxazole), 99 (s, isoxazole), 15.9 (s, $-CH_3$), 128.9-131.2 (m, benzene), 164.5 (C=N, imine in thiopyrimidine), 180 (C=S, thioamide); Calculated for $C_{18}H_{13}N_3OS$, MS (*m/z*): found 319 (M^+), base peak found at *m/z* 187 $[C_{10}H_7N_2S]^+$, *m/z* 304 $[C_{17}H_{10}N_3OS]^+$, *m/z* 286 $[C_{18}H_{12}N_3O]^+$, *m/z* 242 $[C_{12}H_8N_3OS]^+$, *m/z* 132 $[C_8H_6NO]^+$.

5-(4'-Phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acid (3a): Yield 43.88 %, m.p. 103 °C, FT-IR (KBr, ν_{max}, cm^{-1}): 3468 (br. –OH peak), 1714 (C=O), 2563 (C-SH str), 1362 (C=N ter. amine), 1222 (C-O-N str. in isoxazole ring), 903 (=N-O str), 3007 (C-H str.); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.9 (s, –OH carboxylic acid), 4.1 (s, Ar-SH), 6.2-7.7 (9H, m, aromatic proton), 2.0 (–NH, amine), 6.2 (s, 1H, isoxazole ring, C_4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) 147 (benzisoxazole), 122-124 (C-H, benzisoxazole), 98.6 and 146 (C-H, isoxazole), 180 (thioamide), 167 (s, –COOH), 164 (imine), 128-131 (m, benzene); Calculated for $C_{18}H_{11}N_3O_3S$, MS (*m/z*): found 350 (M^+), base peak found at *m/z* 187 $[C_{10}H_7N_2S]^+$, *m/z* 316 $[C_{18}H_{10}N_3O_3]^+$, *m/z* 304 $[C_{17}H_{10}N_3OS]^+$, *m/z* 272 $[C_{12}H_6N_3O_3S]^+$, *m/z* 162 $[C_8H_4NO_3]^+$.

β-D-Glucopyranosyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylate (5a): Yield 57.3 %, $[\alpha]_D^{25}$ + 50.2; FT-IR (KBr, ν_{max}, cm^{-1}): 3295 (br, –OH peak of carbohydrate moiety), 1745 (C=O), 2563 (C-SH), 1423 (C=N ter. amine), 3000 (Ar-H str), 1092 (C-O-C, ester linkage), 1361 (C-O), 1580 (isoxazole ring), 1223 (ring str. vibration in isoxazole ring); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.0-8.0 (m, 9H aromatic), 3.5-6.2 (4H, sugar moiety) ppm. The PMR spectrum displayed no signals of acetyl protons, signal due to protons of the carbohydrate hydroxyl group were not observed in the spectrum because of the fast exchange of all non-hydrogen bonded –COOH groups; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) 147.1 (benzisoxazole), 122-129 (C-H, benzisoxazole), 98.5 and 144 (C-H, isoxazole), 180.4 (thioamide), 167.9 (s, –COOH), 164.5 (imine), 129-133 (m, benzene); Calculated for $C_{25}H_{21}N_3O_8S$, MS (*m/z*): 511, found 511 (M^+), base peak found at *m/z* 350 $[C_{18}H_{13}N_3O_3S]^+$, *m/z* 317 $[C_{18}H_{10}N_3O_3+H]^+$, *m/z* 304 $[C_{17}H_{10}N_3OS]^+$, *m/z* 272 $[C_{12}H_6N_3O_3S]^+$, *m/z* 187 $[C_{10}H_7N_2S]^+$.

Antimicrobial activity: The obtained product were tested for their antibacterial activities by using cup-plate method against *Bacillus subtilis* (Gram-positive) and *Escherichia coli* (Gram-negative) at concentration of 100 µg/mL in DMF. Pure norfloxacin was used as standard antibiotic for the comparison of the results. The sterilized Muller-Hinton agar medium 50 mL was inoculated with test organism and poured into petri-dishes. Then four holes of 6 mm were completely filled with different test solution. The plates were then incubated for 24 h at 37 °C and zones of inhibitions were measured. Same procedure was adopted for pure norflaxacin and the corresponding zone diameters were compared.

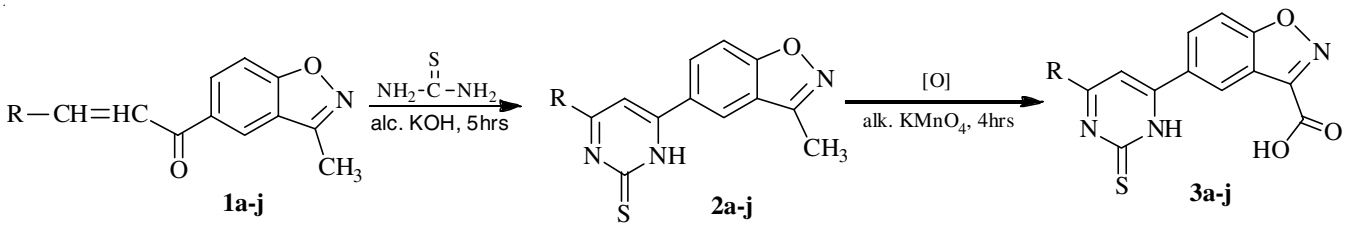
Antifungal activity: The antifungal activity of newly synthesized compounds was analyzed by using above similar method against *Aspergillus niger* and *Candida albicans* at concentration 100 µm/mL in DMF. The plates were incubated for 8 days at 37 °C. The zones of inhibitions were measured. A commercial fungicides gresiofulvin was tested under similar condition with a view of comparing the results.

RESULTS AND DISCUSSION

Mixture of 3-methyl-5-(3'-phenyl prop-2'-enoyl)-1,2-benzisoxazole **(1a)**, thiourea, ethyl alcohol and KOH was refluxed for 5 h, cyclization take place to form 3-methyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole **(2a)**. Oxidation of product **(2a)** with alkaline $KMnO_4$ solution produced 5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acid **(3a)**. In view of pronounced biological and pharmacological significance of glucosides, β-D-glucopyranosyl-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylate **(5a)** have been synthesized by the glucosylation of 5-(4'-Phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylic acid **(3a)** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGBr) in CH_2Cl_2 and sodium hydroxide in the presence of tetrabutyl ammonium bromide (PTC) and followed by deacetylation of 3-(2,3,4,6-tetra-*O*-acetyl-4'-*O*-β-D-glucosidoxyphenyl)-5-(4'-phenyl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole **(4a)** using methanol and sodium methoxide solution. Followed by the same above methods, the synthesis

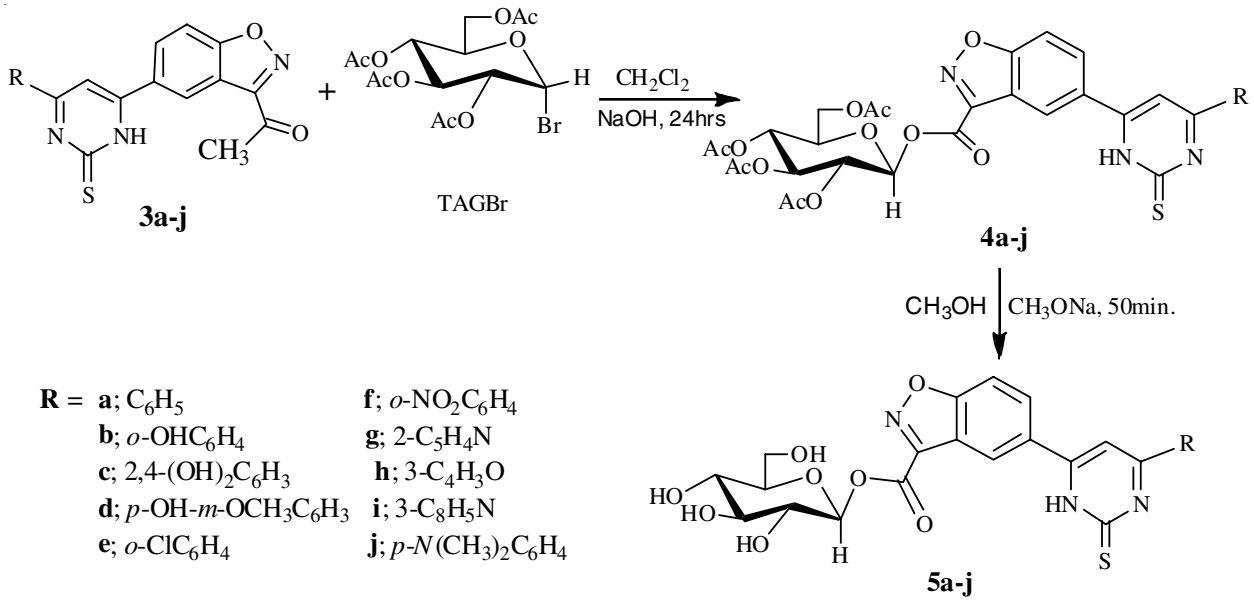
TABLE-2
PHYSICO-CHEMICAL DATA OF THE SYNTHESIZED COMPOUNDS (**5a-j**)

Compd.	R	m.f.	$[\alpha]_D^{25}$ (°)	R_f value	Elemental analysis (%): Found (calcd.)		
					C	H	N
5a	C_6H_5	$C_{24}H_{21}N_3O_8S$	+50.2	0.19	56.01 (56.35)	3.60 (4.14)	7.14 (8.22)
5b	*o*-OHC_6H_4	$C_{24}H_{21}N_3O_9S$	+51.0	0.25	54.10 (54.65)	4.12 (4.01)	7.25 (7.97)
5c	2,4-$(OH)_2C_6H_3$	$C_{24}H_{21}N_3O_{10}S$	+51.5	0.14	53.00 (53.04)	3.90 (3.89)	7.53 (7.73)
5d	*p*-OH-*m*-$OCH_3C_6H_3$	$C_{25}H_{23}N_3O_{10}S$	+50.2	0.20	52.98 (53.86)	4.11 (4.16)	7.39 (7.54)
5e	*p*-ClC_6H_4	$C_{24}H_{20}N_3O_8SCl$	+51.9	0.19	51.98 (52.80)	3.68 (3.69)	7.70 (7.70)
5f	*m*-$NO_2C_6H_4$	$C_{24}H_{20}N_4O_{10}S$	+52.4	0.27	51.51 (51.80)	3.29 (3.62)	9.78 (10.07)
5g	4-C_5H_4N	$C_{24}H_{20}N_4O_8S$	+48.8	0.29	53.45 (53.90)	3.47 (3.93)	10.83 (10.93)
5h	3-C_4H_3O	$C_{22}H_{19}N_3O_9S$	+47.5	0.21	52.68 (52.69)	3.80 (3.82)	8.36 (8.38)
5i	3-C_8H_5N	$C_{26}H_{22}N_4O_8S$	+55.0	0.31	56.70 (56.72)	4.00 (4.03)	10.20 (10.18)
5j	*p*-$N(CH_3)_2C_6H_4$	$C_{26}H_{26}N_4O_8S$	+55.1	0.24	56.34 (56.31)	4.72 (4.73)	10.15 (10.10)



R = **a**; C_6H_5 **f**; *o*-$NO_2C_6H_4$
b; *o*-OHC_6H_4 **g**; 2-C_5H_4N
c; 2,4-$(OH)_2C_6H_3$ **h**; 3-C_4H_3O
d; *p*-OH-*m*-$OCH_3C_6H_3$ **i**; 3-C_8H_5N
e; *o*-ClC_6H_4 **j**; *p*-$N(CH_3)_2C_6H_4$

Scheme-I



R = **a**; C_6H_5 **f**; *o*-$NO_2C_6H_4$
b; *o*-OHC_6H_4 **g**; 2-C_5H_4N
c; 2,4-$(OH)_2C_6H_3$ **h**; 3-C_4H_3O
d; *p*-OH-*m*-$OCH_3C_6H_3$ **i**; 3-C_8H_5N
e; *o*-ClC_6H_4 **j**; *p*-$N(CH_3)_2C_6H_4$

Scheme-II

of thiopyrimidine, carboxylic acids and *O*-glucosides are discussed in detail (**Schemes I & II** and Tables 1 & 2). Advantages of followed methods are that the reagents are non-toxic, readily available and stable under the reaction conditions.

Conclusion

The reported *O*-glucosylation methodology is an alternate pathway for *O*-glucosylation of heterocyclic moieties. Moreover, this novel and facile methodology will open insights in understanding *O*-glucosylation reactions of structurally rigid and multifunctional heterocyclic molecules. β-D-Glucopyranosyl-5-(4'-aryl-2'-thiopyrimidin-6'-yl)-1,2-benzisoxazole-3-carboxylates **(5a-j)** were prepared and evaluated for *in vitro* antibacterial activity against *Escherichia coli* and *Bacillus subtilis* strain as well as for antifungal activity against *Candida allbicans* and *Aspergilus niger* strain using cup-plate method. Most of *O*-glucosides show excellent results against bacterial and fungal strains (Table-3). The structures of the compounds

TABLE-3
ANTIMICROBIAL SCREENING OF SOME β-D-GLUCOPYRANOSYL-5-(4'-ARYL-2'-THIOPYRIMIDIN-6'-YL)-1,2-BENZISOXAZOLE-3-CARBOXYLATES (**5a-j**)

Compounds	Antibacterial activity		Antifungal activity	
	E. coli	*B. subtilis*	*C. albicans*	*A. niger*
5a	++	Inactive	++	+++
5b	+	++	+	+++
5c	+	++	Inactive	+
5d	+++	---	++	++
5e	++	+++	+	+++
5f	---	++	++	+++
5g	+++	++	+++	++

+++ = Excellent active, ++ = Moderately active, and + = Less active.

have been assigned on the basis of FT-IR spectra, ^{1}H NMR, ^{13}C NMR, FAB-MS, optical activity and elemental analysis.

ACKNOWLEDGEMENTS

The author is sincerely thankful to the Head, RSIC, CDRI, Lucknow, India for providing the spectral data of synthesized compounds; Head, Department of Chemistry, Rashtrasant Tukadoji Maharaj, Nagpur University, Nagpur and Principal, Jawaharlal Nehru Arts, Commerce and Science College, Wadi, Nagpur for providing necessary facilities.

REFERENCES

1. S.M. Sondhi, R.N. Goyal, A.M. Lahoti, N. Singh, R. Shukla and R. Raghubir, Synthesis and Biological Evaluation of 2-Thiopyrimidine Derivatives, *Bioorg. Med. Chem.*, **13**, 3185 (2005); https://doi.org/10.1016/j.bmc.2005.02.047.
2. S.A. Luzhnova, A.G. Tyrkov, N.M. Gabitova and E.A. Yurtaeva, Synthesis and Antimicrobial Activity of 5-(Arylmethylidene)-2,4,6-Pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-Triones, *Pharm. Chem. J.*, **52**, 506 (2018); https://doi.org/10.1007/s11094-018-1849-7.
3. K.M. Amin, M.M. Hanna, H.E. Abo-Youssef and R.F. George, Synthesis, Analgesic and Anti-Inflammatory Activities Evaluation of Some Bi-, Tri- and Tetracyclic Condensed Pyrimidines, *Eur. J. Med. Chem.*, **44**, 4572 (2009); https://doi.org/10.1016/j.ejmech.2009.06.028.
4. J.M. Quintela, C. Peinador, L. González, I. Devesa, M.L. Ferrándiz, M.J. Alcaraz and R. Riguera, 6-Dimethylamino 1H-Pyrazolo[3,4-*d*]-pyrimidine Derivatives as New Inhibitors of Inflammatory Mediators in Intact Cells, *Bioorg. Med. Chem.*, **11**, 863 (2003); https://doi.org/10.1016/S0968-0896(02)00562-X.
5. J.P. Zhou, Y.W. Ding, H.B. Zhang, L. Xu and Y. Dai, Synthesis and Anti-Inflammatory Activity of Imidazo[1,2-*a*]pyrimidine Derivatives, *Chin. Chem. Lett.*, **19**, 669 (2008); https://doi.org/10.1016/j.cclet.2008.04.020.
6. H.S. Choi, Z. Wang, W. Richmond, X. He, K. Yang, T. Jiang, D. Karanewsky, X. Gu, V. Zhou, Y. Liu, J. Che, C.C. Lee, J. Caldwell, T. Kanazawa, I. Umemura, N. Matsuura, O. Ohmori, T. Honda, N. Gray and Y. He, Design and Synthesis of 7*H*-pyrrolo[2,3-*d*]pyrimidines as Focal Adhesion Kinase Inhibitors. Part 2, *Bioorg. Med. Chem. Lett.*, **16**, 2689 (2006); https://doi.org/10.1016/j.bmcl.2006.02.032.
7. I. Devesa, M.J. Alcaraz, R. Riguera and M.L. Ferrándiz, A New Pyrazolo Pyrimidine Derivative Inhibitor of Cyclooxygenase-2 with Anti-Angiogenic Activity, *Eur. J. Pharmacol.*, **488**, 225 (2004); https://doi.org/10.1016/j.ejphar.2004.02.015.
8. S. Baluja, N. Kacchadia and S. Chanda, Thiopyrimidine Derivatives: Synthesis and Antibacterial Activity, *Pharm. Chem. J.*, **46**, 117 (2012); https://doi.org/10.1007/s11094-012-0744-x.
9. J.-E.Igarashi and M. Sunagawa, Structural Analysis by NMR of Antitumor Drug-DNA Complexes: 9-Aminoanthracycline (SM-5887), *Bioorg. Med. Chem. Lett*., **2**, 2923 (1995); https://doi.org/10.1016/0960-894X(95)00505-N.
10. H. Rudiger, H.-C. Siebert, D. Solis, J. Jimenez-Barbero, A. Romero, C.-W. Lieth, T. Diaz-Maurino and H.-J. Gabius, Medicinal Chemistry Based on the Sugar Code: Fundamentals of Lectinology and Experimental Strategies with Lectins as Targets, *Curr. Med. Chem.*, **7**, 389 (2000); https://doi.org/10.2174/0929867003375164.
11. M.I. Nassar, E.-S.A. Aboutabl, D.M. Eskander, M.H. Grace1, E.-D.A. El-Khrisy and A.A. Sleem, Flavonoid Glycosides and Pharmacological Activity of *Amphilophium paniculatum*, *Pharmacogn. Res.*, **5**, 17 (2013); https://doi.org/10.4103/0974-8490.105643.
12. B.G. Davis, Recent Developments in Glycoconjugates, *J. Chem. Soc. Perkin Trans. I*, 3215 (1999); https://doi.org/10.1039/a809773i.
13. B. Szechner, B. Grzeszczyk, B. Furman and M. Chmielewski, Glycosyl Hydroperoxides, *J. Carbohydr. Chem.*, **37**, 104 (2018); https://doi.org/10.1080/07328303.2018.1438453.
14. P.S. Wharton and R.L. Nicholson, Temporal Synthesis and Radiolabelling of the Sorghum 3-Deoxyanthocyanidin Phytoalexins and the Anthocyanin, Cyanidin 3-Dimalonyl glucoside, *Res. New Phytol.*, **145**, 457 (2000); https://doi.org/10.1046/j.1469-8137.2000.00600.x.
15. R.K. Wanare, Highly Efficient Multistep Synthesis of Isoxazoles and their Glucosides, *Asian J. Org. Med. Chem.*, **2**, 130 (2017); https://doi.org/10.14233/ajomc.2017.AJOMC-P75.