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Design, Synthesis and Evaluation of Novel Thiopyrimidine-Glucuronide Compounds with Promising Biological Activities

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Asian Journal of Organic & Medicinal Chemistry

Volume: 7 Year: 2022
Issue: 3 Month: July–September
pp: 239–244
DOI: https://doi.org/10.14233/ajomc.2022.AJOMC-P397

Received: 5 July 2022
Accepted: 23 July 2022
Published: 30 July 2022

ABSTRACT

3-Methyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazoles (**2a-n**) were obtained from *N*-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-3-arylprop-2-enamides (**1a-n**) and thiourea. Products (**2a-n**) oxidized with $KMnO_4$ to afford 5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazole-3-carboxylic acids (**3a-n**). Reaction of **3a-n** with D-gluconic acid and pyridine yielded β-D-glucuronosyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazol-3-carboxylates (**4a-n**). The present synthesis featured the formation of dihydropyrimidine skeleton through ring closure of key intermediates and installation of pyrimidine ring with amino group. The structures of all the newly synthesized compounds were characterized by analytical data, IR, ^{1}H NMR and mass spectrometry.

KEYWORDS

1,2-Benzisoxazoles, Thiopyrimidines, β-D-Glucuronides.

INTRODUCTION

The β-D-glucuronides are the conjugation products of aglycone possessing carboxylic group with glucuronic acid and formation of glucuronides is the principal conjugation reaction in the body. The same pathway is used by many drugs that contain hydroxyl, amino, carboxyl, thiol and phenolic groups. Glucuronidation is considered to be a detoxification process or a defense mechanism that helps removal of unwanted substances including endogenous substances *e.g.*, bilirubin, drugs *e.g.*, SN-38 and other xenobiotics *e.g.*, environ-mental toxins from the human body. Compounds with relatively low molecular weights are almost completely excreted from urine, whereas those with high molecular weights are eliminated almost entirely in bile. It is important pharmacophore in the field of medicinal chemistry and possesses range of biologically activities such as polar and chemically reactive metabolites [1]. They form covalent adduct with protein, generating increasing interest as potential hypersensitive mediator and profound effect on drug metabolism [2-6].

Heterocyclic compounds, bearing pyrimidine scaffold, are known for exhibiting interesting biological activities, such as bactericidal, fungicidal, anti-amoebic, antioxidant, anticancer and anti-inflammatory agents [7,8]. Some of the pyrimidine and fused heterocyclic pyrimidine derivatives have provided to be active antiviral and analgesic activities. Recently, we have

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found that certain substituted pyrimidine and their heterocyclic derivatives show antimicrobial and antitumor activities. Pyrimidine derivatives have been well known in medicinal chemistry for their therapeutic applications. One possible reason for their activity is due to the presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids [9,10].

Thiopyrimidine derivatives show wide range of biological activities, which include integral part of the genetic material *viz.* DNA and RNA, calcium channel blockers, therapeutic agents and analgesic activities. Thiopyrimidine moiety present in large number of important compounds such as agrochemicals or antimicrobial agents and alkaloids [11-14]. 1,2-Benzisoxazole derivatives shows antidepressant, hypertensive, anticonvulsant, antifungal, anti-inflammatory, analgesic, sedative and tuberculostearic properties. It has been reported that 1,2-benzisoxazoles is antiepileptic drug, can show pronounced protective impacts against transient focal cerebral ischemia in rats and decreased oxidative stress. 1,2-Benzisoxazole derivatives shows protective effects of neurotoxicity, it improve therapeutic effects and used as potential systems for the treatment of acute spinal cord injury [15-19]. Based on the above reports, herein the synthesis of some novel thiopyrimidine containing D-gluconic acid derivatives is reported.

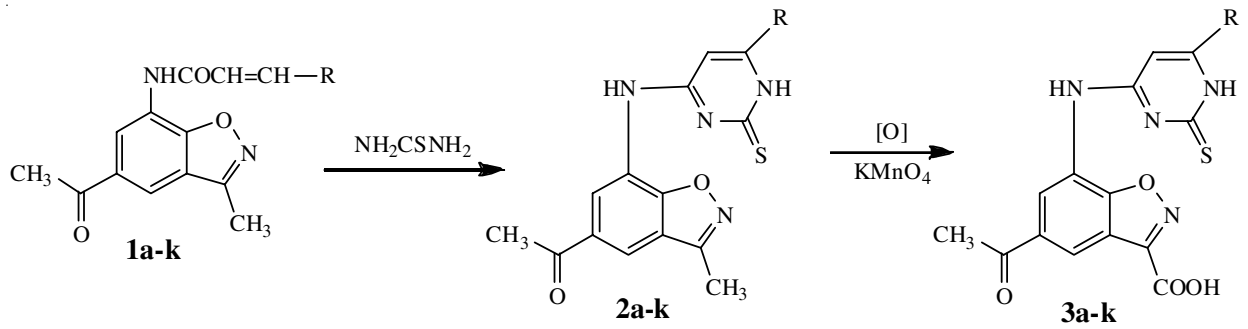
EXPERIMENTAL

All chemicals used in present work were synthetic grade and used without further purification. Elemental analysis and spectral data were done at CDRI, Lucknow. Infrared spectra were recorded in KBr disc on Shimadzu FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC-300F (300 MHz) instrument with TMS as internal standard and chemical shift reported in (δ) or ppm values. Mass spectra were analyzed in JEOL SX 102/DA-6000 mass spectrometer. Purity of synthesized compounds were checked by TLC on silica gel plates.

3-Methyl-5-acetyl-7-[(2-sulfanylidene-6-phenyl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazole (2a): Compounds **1a-k** have been synthesized as previously described [20,21]. Mixture of *N*-(5-acetyl-3-methyl-1,2-benzisoxazol-7-yl)-3-phenylprop-2-enamide (**1a**, 0.01 mol, 3.76 g), thiourea (0.76 g), ethanol and KOH (0.5 g) was refluxed for 5 h. Obtained product was cooled, acidified with HCl and poured on cold water. The solid was filtered, washed with water, dried and crystallized from alcohol (yield 2.3 g, 61%), m.p.: 117 ºC. IR (KBr, ν_{max}, cm^{-1}): 1720 (C=O ketone), 2592 (C-SH *str.*), 3144 (N-H *str.*), 1222 (C-O-N *str.* vibration in isoxazole ring), 1563 (C=N), 3404 (N-H), 3010 (Ar-H), 2940 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 7.4-8.4 (m, aromatic), 4.0 (s, SH), 6.2-7.7 (9H, m, aromatic); FAB-MS: M^+ 376, 300, 286, 190, 175 and 148. Similarly, 3-methyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazoles (**2b-n**) were synthesized (**Scheme-I**, Table-1).

Spectral data

Compound 2b: Yield 2.1 g, 53.7%, m.p.: 112 ºC. IR (KBr, ν_{max}, cm^{-1}): 1724 (C=O ketone), 2593 (C-SH *str.*), 3142 (N-H



Scheme-I

TABLE-1
PHYSICAL CHARACTERISTICS OF 3-METHYL-5-ACETYL-7-[(2-SULFANYLIDENE-6-ARYL-1,2-DIHYDROPYRIMIDIN-4-YL)-AMINO]-1,2-BENZISOXAZOLES (**2a-n**)

Compd.	R	m.f.	m.w.	m.p. (°C)	R_f value	Elemental analysis (%): Calcd. (Found)		
						C	H	N
2a	C_6H_5	$C_{20}H_{16}N_4O_2S$	376.4	117	0.25	63.81 (63.80)	4.28 (4.26)	14.88 (14.86)
2b	*o*-OHC_6H_4	$C_{20}H_{16}N_4O_3S$	392.4	112	0.31	61.21 (61.20)	4.11 (4.11)	14.28 (14.27)
2c	*p*-OHC_6H_4	$C_{20}H_{16}N_4O_3S$	392.4	109	0.29	61.21 (61.21)	4.11 (4.10)	14.28 (14.28)
2d	2,4-$(OH)_2C_6H_3$	$C_{20}H_{16}N_4O_4S$	408.4	113	0.32	58.81 (58.78)	3.95 (3.93)	13.72 (13.70)
2e	*p*-OH-*m*-$OCH_3C_6H_3$	$C_{21}H_{18}N_4O_4S$	422.4	109	0.30	59.70 (59.67)	4.29 (4.26)	13.26 (13.26)
2f	*o*-ClC_6H_4	$C_{20}H_{15}ClN_4O_2S$	410.8	114	0.27	58.46 (58.42)	3.68 (3.66)	13.64 (13.63)
2g	*p*-ClC_6H_4	$C_{20}H_{15}ClN_4O_2S$	410.8	112	0.30	58.46 (58.45)	3.68 (3.65)	13.64 (13.62)
2h	*o*-$NO_2C_6H_4$	$C_{20}H_{15}N_5O_4S$	421.4	117	0.28	57.00 (57.00)	3.59 (3.58)	16.62 (16.60)
2i	*m*-$NO_2C_6H_4$	$C_{20}H_{15}N_5O_4S$	421.4	114	0.30	57.00 (56.97)	3.59 (3.59)	16.62 (16.61)
2j	*p*-$N(CH_3)_2C_6H_4$	$C_{22}H_{21}N_5O_2S$	419.4	108	0.31	62.99 (62.90)	5.05 (5.00)	16.69 (16.67)
2k	*p*-$OCH_3C_6H_4$	$C_{21}H_{18}N_4O_3S$	406.4	102	0.32	62.05 (62.00)	4.46 (4.44)	13.78 (13.78)
2l	2-C_5H_4N	$C_{19}H_{15}N_5O_2S$	377.4	110	0.28	60.46 (60.41)	4.01 (4.00)	18.56 (18.54)
2m	4-C_5H_4N	$C_{19}H_{15}N_5O_2S$	377.4	109	0.32	60.46 (60.44)	4.01 (4.01)	18.56 (18.55)
2n	3-C_4H_3O	$C_{18}H_{14}N_4O_3S$	366.3	99	0.28	59.01 (59.00)	3.85 (3.83)	15.29 (15.25)

str.), 1223 (C-O-N *str.* vibration in isoxazole ring), 1562 (C=N), 3404 (N-H), 3012 (Ar-H), 3450 (OH peak), 2941 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 6.77-7.26 (m, aromatic), 4.1 (s, SH), 5.0 (C-OH, aromatic), 4.0 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 392, 376, 300, 286, 258, 190, 175 and 133.

Compound 2d: Yield 2.5 g, 61.2%, m.p.: 113 ºC. IR (KBr, ν_{max}, cm^{-1}): 1720 (C=O ketone), 2590 (C-S *str.*), 3140 (N-H *str.*), 1221 (C-O-N *str.* vibration in isoxazole ring), 1565 (C=N), 3410 (N-H), 3012 (Ar-H), 3452 and 3448 (two OH peak), 2943 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 7.06-7.22 (m, aromatic), 4.3 (s, SH), 5.0 (two C-OH, aromatic), 4.0 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 408, *m/z* 392, 376, 394, 366, 301, 286, 258, 190, 176 and 133.

Compound 2e: Yield 2.6 g, 61.6%, m.p.: 109 ºC. IR (KBr, ν_{max}, cm^{-1}): 1730 (C=O ketone), 2585 (C-SH *str.*), 3142 (N-H *str.*), 1218 (C-O-N *str.* vibration in isoxazole ring), 1562 (C=N), 3414 (N-H), 3010 (Ar-H), 3450 (OH peak), 2850 (O-CH_3), 2941 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 3.7 (O-CH_3), 6.4-7.2 (m, aromatic), 4.4 (s, SH), 5.0 (C-OH, aromatic), 4.0 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ *m/z* 422, 406, 392, 364, 376, 300, 270, 286, 258, 191, 176 and 132.

Compound 2g: Yield 2.2 g, 53.6%, m.p.: 112 ºC. IR (KBr, ν_{max}, cm^{-1}): 1748 (C=O ketone), 2590 (C-SH *str.*), 3140 (N-H *str.*), 1218 (C-O-N *str.* vibration in isoxazole ring), 1565 (C=N), 3410 (N-H), 3012 (Ar-H), 3430 (OH peak), 836 (aromatic C-Cl), 2948 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.3 and 2.5 (two CH_3), 7.0 (C-Cl), 7.0-7.2 (m, aromatic), 4.2 (s, SH), 4.0 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 410, 396, 380, 376, 368, 300, 286, 258, 244, 190, 175, 161 and 133.

Compound 2i: Yield 2.4 g, 57.0%, m.p.: 114 ºC. IR (KBr, ν_{max}, cm^{-1}): 1750 (C=O ketone), 2592 (C-SH *str.*), 3138 (N-H *str.*), 1220 (C-O-N isoxazole ring), 1560 (C=N), 3412 (N-H), 3010 (Ar-H), 1478 (NO_2 group), 2948 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.4 (CH_3), 7.4 (C-NO_2), 7.0-8.2 (m, aromatic), 4.0 (s, SH), 4.0 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 421, 376, 62, 334, 300, 270, 258, 190, 176 and 148.

Compound 2j: Yield 2.5 g, 59.6%, m.p.: 108 ºC. IR (KBr, ν_{max}, cm^{-1}): 1710 (C=O ketone), 2590 (C-SH *str.*), 3130 (N-H *str.*), 1228 (C-O-N isoxazole ring), 1564 (C=N), 3416 (N-H), 3020 (Ar-H), 3410 and 3348 (two aniline peak), 2898 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.1 (CH_3), 6.5 (C-N=), 6.5-7.2 (m, aromatic), 4.2 (s, SH), 4.1 (C-NH, aromatic), 2.2 (NH, amine); FAB-MS: M^+ 419, 393, 376, 377, 349, 300, 286, 258, 192, 175 and 176.

Compound 2k: Yield 2.4 g, 59.1%, m.p. 111 ºC. IR (KBr, ν_{max}, cm^{-1}): 1780 (C=O ketone), 2850 (O-CH_3), 2573 (C-SH *str.*), 3132 (N-H *str.*), 1228 (C-O-N isoxazole ring), 1560 (C=N), 3424 (N-H), 3024 (Ar-H), 3412 and 3120 (ter. amine-NH), 2890 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.5 and 3.7 (two CH_3), 6.5 (C-N=), 6.7-7.6 (m, aromatic), 4.1 (s, SH), 4.0 (C-NH, aromatic), 2.0 (NH, amine), 7.4 (=N pyridine); FAB-MS: M^+ 406, 392, 376, 364, 300, 190, 176, 148, 176, 175 and 134.

5-Acetyl-7-[(2-sulfanylidene-6-phenyl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazole-3-carboxylic acid (3a): Reaction of 3-methyl-5-acetyl-7-[(2-sulfanylidene-6-phenyl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazole (**2a**, 0.01mol, 3.76 g), sodium carbonate (1.5 g), $KMnO_4$ (1.5 g) and water was refluxed for 4 h and acidified with dil. H_2SO_4. Excess MnO_2 was removed by sodium metabisulphite, filtered, washed and crystallized with distilled water and product was found to be soluble in dilute $NaHCO_3$ with effervescences. Various, 5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)-amino]-1,2-benzisoxazole-3-carboxylic acids (**3b-n**) were also synthesized in a similar manner.

Spectral data

Compound 3a: Yield 2.6 g, 64.0%, m.p. 103 ºC.IR (KBr, ν_{max}, cm^{-1}): 3468 (OH peak), 1714 and 1670 (two C=O ketones), 2564 (C-SH *str.*), 1363 (C=N *tert*. amine), 1224 (C-O-N *str.*); ^{1}H NMR: δ 10.2 (s, COOH), 4.1 (s, Ar-SH), 6.2-7.8 (m, 9H, aromatic); FAB-MS of the compound showed a molecular ion peak at *m/z* 407 $[C_{20}H_{14}N_4O_4S+H]^+$, *m/z* 362, 330, 288, 220 and 119.

Compound 3b: (Yield 2.3 g, 54.5%), m.p. 114 ºC. IR (KBr, ν_{max}, cm^{-1}): 1685 and 1720 (two C=O), 2594 (C-SH *str.*), 3146 (N-H *str.*), 1221 (C-O-N *str.* vibration in isoxazole ring), 1561 (C=N), 3401 (N-H), 3014 (Ar-H), 3442 (OH peak), 2943 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 6.6-7.2 (m, aromatic), 4.2 (s, SH), 11.0 (carboxylic acid), 5.1 (C-OH, aromatic), 4.2 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 422, 406, 380, 378, 330, 288, 286, 220, 205, 178 and 176.

Compound 3d: Yield 2.6 g, 59.3%, m.p. 111 ºC. IR (KBr, ν_{max}, cm^{-1}): 1680 and 1732 (two C=O), 2586 (C-SH *str.*), 3135 (N-H *str.*), 1214 (C-O-N *str.* vibration in isoxazole ring), 1560 (C=N), 3424 (N-H), 3010 (Ar-H), 3450 and 3432 (two OH peak), 2942 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 6.1-7.2 (m, aromatic), 4.3 (s, SH), 11.0 (carboxylic acid), 5.0 (two C-OH, aromatic), 4.2 (C-NH, aromatic), 2.1 (NH, amine); FAB-MS: M^+ *m/z* 438, 422, 406, 396, 394, 380, 378, 330, 300, 288, 286, 220, 205, 178, 163 and 161.

Compound 3e: (Yield 2.8 g, 61.9%), m.p.: 118 ºC. IR (KBr, ν_{max}, cm^{-1}): 1694 and 1746 (two C=O), 2852 (O-CH_3), 2580 (C-SH *str.*), 3136 (N-H *str.*), 1220 (C-O-N *str.* in isoxazole ring), 1564 (C=N), 3410 (N-H), 3016 (Ar-H), 3424 (OH peak), 2946 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 11.0 (carboxylic acid), signal at δ 2.2 (s, 3H, CH_3), 3.6 (O-CH_3), 6.2-7.6 (m, aromatic), 4.4 (s, SH), 5.2 (C-OH, aromatic), 4.0 (C-NH, aromatic), 2.2 (NH, amine); FAB-MS: M^+ 452, 436, 422, 410, 408, 406, 330, 300, 288, 286, 220, 205, 178, 176, 163 and 161.

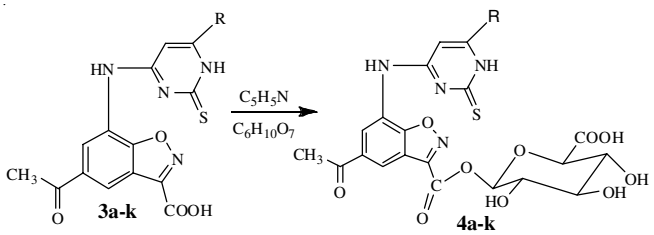
Compound 3g: Yield 2.8 g, 63.6%, m.p.: 120 ºC. IR (KBr, ν_{max}, cm^{-1}): 1680 and 1740 (two C=O), 2572 (C-SH *str.*), 3144 (N-H *str.*), 1218 (C-O-N *str.* in isoxazole ring), 1566 (C=N), 3392 (N-H), 3014 (Ar-H), 3433 (OH peak), 798 (aromatic C-Cl), 2952 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.4 (CH_3), 6.8 (C-Cl), 7.0-7.7 (m, aromatic), 4.0 (s, SH), 4.0 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 440, 406, 380, 378, 330, 300, 288, 286, 258, 220, 205, 178, 176 and 134.

Compound 3i: Yield 2.4 g, 52.8%, m.p.: 117 ºC. IR (KBr, ν_{max}, cm^{-1}): 1696 and 1758 (two C=O groups), 2585 (C-SH *str.*), 3138 (N-H *str.*), 1226 (C-O-N isoxazole ring), 1564 (C=N), 3414 (N-H), 3014 (Ar-H), 10.8 (COOH group), 1480 (NO_2 group), 2944 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.4 (CH_3), 7.6 (C-NO_2), 6.2-7.8 (m, aromatic), 4.0 (s, SH), 3.8 (C-NH, aromatic), 2.0 (NH, amine); FAB-MS: M^+ 451, 421, 409, 406, 330, 288, 270, 244 and 190.

Compound 3j: Yield 2.8 g, 62.3%, m.p. 110 ºC. IR (KBr, ν_{max}, cm^{-1}): 1698 and 1742 (two C=O groups), 2605 (C-SH *str.*), 3110 (N-H *str.*), 1251 (C-O-N isoxazole ring), 1566 (C=N), 3412 (N-H), 3028 (Ar-H), 3408 and 3342 (two aniline peak), 2892 (methyl C-H); ^{1}H NMR ($CDCl_3$): signal at δ 2.2 and 2.8 (two CH_3), 10.9 (COOH group), 6.6 (C-N=), 6.5-7.2 (m, aromatic), 4.6 (s, SH), 4.2 (C-NH, aromatic), 2.2 (NH, amine); FAB-MS: M^+ 449, 435, 421, 407, 405, 377, 349, 330, 286, 220, 205, 178, 176 and 121.

Compound 3k: Yield 2.5 g, 57.3%, m.p. 117 ºC. IR (KBr, ν_{max}, cm^{-1}): 1984 and 1782 (two C=O groups), 2574 (C-SH *str.*), 2850 (O-CH_3), 3133 (N-H *str.*), 1230 (C-O-N isoxazole ring), 1564 (C=N), 3414 (N-H), 3020 (Ar-H), 3410 and 3122 (*tert*. amine-NH), 2892 (methyl C-H); ^{1}H NMR ($CDCl_3$): δ 2.0 (CH_3), 6.4 (C-N=), 11.0 (COOH), 3.7 (O-C), 6.2-7.8 (m, aromatic), 4.0 (s, SH), 4.6 (C-NH, aromatic), 2.1 (NH, amine), 7.2 (=N pyridine); FAB-MS: M^+ 436, 422, 406, 380, 378, 330, 233, 220, 176 and 175.

β-D-Glucuronosyl-5-acetyl-7-[(2-sulfanylidene-6-phenyl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazol-3-carboxylates (4a): Mixture of 5-acetyl-7-[(2-sulfanylidene-6-phenyl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benziso-xazole-3-carboxylic acid (**3a**) (0.01 mol, 4.06 g), pyridine (5 mL) and glucuronic acid (1.94 g) was added in portion with constant stirring and kept for 18 h. Reaction mixture was poured onto ice, the product was filtered and washed with distilled water. Others, β-D-glucuronosyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazol-3-carboxylates (**4a-n**) were also synthesized in the similar manner and gave satisfactory C, H and N analysis (**Scheme-II**, Table-2).



R = a; C_6H_5 h; *o*-$NO_2C_6H_4$
b; *o*-OHC_6H_4 i; *m*-$NO_2C_6H_4$
c; *p*-OHC_6H_4 j; *p*-*N* $(CH_3)_2C_6H_4$
d; 2,4-$(OH)_2C_6H_3$ k; *p*-$OCH_3C_6H_4$
e; *p*-OH-*m*-OCH_3 C_6H_3 l; 2-C_5H_4N
f; *o*-ClC_6H_4 m; 4-C_5H_4N
g; *p*-ClC_6H_4 n; 3-C_4H_3O

Scheme-II

Spectral data

Compound 4a: (yield 2.8 g, 48.1%). FAB-MS: M^+ 582, base peak *m/z* 406 (due to loss of glucuronic acid moiety), 376, 330, 220, 190 and 175.

Compound 4b: Yield 3.1 g, 51.8%. FAB-MS: M^+ 598, *m/z* 582, 506, 422 (base peak due to loss of glucuronic acid moiety), 396, 381, 354, 339, 190, 178 and 175.

Compound 4d: Yield 2.9 g, 47.2%. FAB-MS: M^+ 614, 598, 582, 572, 506, 438 (base peak due to loss of glucuronic acid moiety), 396, 394, 354, 381, 352, 320, 300, 288, 244, 221, 205 and 178.

Compound 4e: Yield 3.2 g, 50.9%. FAB-MS: M^+ 628, 612, 598, 586, 506, 452 (base peak due to loss of glucuronic acid moiety), 408, 396, 381, 354, 339, 288, 286, 222, 178, 176 and 163.

Compound 4g: Yield 3.4 g, 55.1%. FAB-MS: M^+ 616, 582, 540, 506, 574, 464, 440 (base peak due to loss of glucuronic acid moiety), 398, 396, 381, 354, 339, 220, 178, 176 and 163.

Compound 4i: Yield 3.0 g, 47.8%. FAB-MS: M^+ 627, 585, 506, 451 (base peak due to loss of glucuronic acid moiety), 582, 540, 406, 409, 396, 381, 365, 320, 244 and 178.

Compound 4j: Yield 3.7 g, 59.2%. FAB-MS: M^+ 625, 611, 583, 597, 582, 449 (base peak due to loss of glucuronic acid moiety), 421, 407, 405, 406, 396, 381, 377, 354, 330, 286, 220, 178, 176 and 162.

Compound 4k: Yield 3.8 g, 62.0%. FAB-MS: M^+ 612, 598, 582, 570, 436 (base peak due to loss of glucuronic acid moiety), 406, 394, 392, 364, 362, 330, 320, 286, 244, 220, 178 and 175.

RESULTS AND DISCUSSION

Thiopyrimidine derivatives were synthesized in appropriate yields (**Schemes I** and **II**) and compounds were confirmed through elemental and spectral analysis. The starting comp-

TABLE-2
PHYSICAL CHARACTERISTICS OF β-D-GLUCURONOSYL-5-ACETYL-7-[(2-SULFANYLIDENE-6-ARYL-1,2-DIHYDROPYRIMIDIN-4-YL)-AMINO]-1,2-BENZISOXAZOL-3-CARBOXYLATES (**4a-n**)

Compd.	R	m.f.	m.w.	$[\alpha]_D^{25}$ (°)	R_f value	Elemental analysis (%): Calcd. (Found)		
						C	H	N
4a	C_6H_5	$C_{26}H_{22}N_4O_{10}S$	582.5	+40.1	0.32	53.61 (53.61)	3.81 (3.80)	9.62 (9.59)
4b	*o*-OHC_6H_4	$C_{26}H_{22}N_4O_{11}S$	598.5	+42.3	0.30	52.17 (52.16)	3.70 (3.68)	9.36 (9.35)
4c	*p*-OHC_6H_4	$C_{26}H_{22}N_4O_{11}S$	598.5	+40.2	0.26	52.17 (52.13)	3.70 (3.67)	9.36 (9.36)
4d	2,4-$(OH)_2C_6H_3$	$C_{26}H_{22}N_4O_{12}S$	614.5	+37.3	0.31	50.82 (50.80)	3.61 (3.60)	9.12 (9.08)
4e	*p*-OH-*m*-$OCH_3C_6H_3$	$C_{27}H_{24}N_4O_{12}S$	628.5	+41.4	0.31	51.59 (51.57)	3.85 (3.84)	8.91 (8.89)
4f	*o*-ClC_6H_4	$C_{26}H_{21}ClN_4O_{10}S$	616.9	+33.8	0.28	50.61 (50.60)	3 .43(3.40)	9.08 (9.06)
4g	*p*-ClC_6H_4	$C_{26}H_{21}ClN_4O_{10}S$	616.9	+38.2	0.30	50.61 (50.58)	3 .43(3.41)	9.08 (9.07)
4h	*o*-$NO_2C_6H_4$	$C_{26}H_{21}N_5O_{12}S$	627.5	+43.3	0.24	49.76 (48.80)	3.37 (3.36)	11.16 (11.13)
4i	*m*-$NO_2C_6H_4$	$C_{26}H_{21}N_5O_{12}S$	627.5	+44.1	0.30	49.76 (49.58)	3.37 (3.34)	11.16 (11.15)
4j	*p*-*N*$(CH_3)_2C_6H_4$	$C_{28}H_{27}N_5O_{10}S$	625.6	+42.3	0.32	53.76 (53.74)	4.35 (4.32)	11.19 (10.98)
4k	*p*-$OCH_3C_6H_4$	$C_{27}H_{24}N_4O_{11}S$	612.5	+36.6	0.26	52.94 (52.92)	3.95 (3.91)	9.15 (9.15)
4l	2-C_5H_4N	$C_{25}H_{21}N_5O_{10}S$	583.5	+38.7	0.30	51.46 (51.37)	3.63 (3.60)	12.00 (11.91)
4m	4-C_5H_4N	$C_{25}H_{21}N_5O_{10}S$	583.5	+40.1	0.28	51.46 (51.39)	3.63 (3.63)	12.00 (11.98)
4n	3-C_4H_3O	$C_{24}H_{20}N_4O_{11}S$	572.5	+34.8	0.31	50.35 (50.30)	3.52 (3.51)	9.79 (9.80)

ounds *N*-(5-acetyl-3-methyl-1,2-benzoxazol-7-yl)-3-arylprop-2-enamides (**1a-n**) cyclized with thiourea and alcoholic KOH yielded 3-methyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazoles (**2a-n**). Oxidation of 3-methyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazoles (**2a-n**) with $KMnO_4$ and sodium carbonate to form 5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)-amino]-1,2-benzisoxazole-3-carboxylic acids (**3a-n**). Titled compounds β-D-glucuronosyl-5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazol-3-carboxylates (**4a-n**) were synthesized by the glucuronidation of 5-acetyl-7-[(2-sulfanylidene-6-aryl-1,2-dihydropyrimidin-4-yl)amino]-1,2-benzisoxazole-3-carboxylic acids (**3a-n**) with glucuronic acid and pyridine. The structure of compounds (**2a-n, 3a-n** and **4a-n**) were successfully eludicated by FT-IR, ^{1}H NMR and FAB-MS spectral results.

Antimicrobial activities: Synthesized compounds (**4a-k**) were tested for their antibacterial activities by using the cup plate method against *S. aureus* and *E. coli* at concentration of 150 µg/mL in DMF. The screening results showed excellent (13-16 mm growth), moderate (9-12 mm growth) and inactive (below 8 mm) against both organisms. The antifungal activity of compounds was evaluated by the using above same cup-plate procedure against *Aspergillus niger* and *Candida albicans* at a concentration 100 µm/mL in DMF. The screening results showed excellent (22-28 mm growth), moderate (15-21 mm growth) and poor (11-14 mm growth) against both organisms. Norfloxacin 100 µg/mL used as standard against *E. coli* and *S. aureus* diameter of zone of inhibition is 20. Griseofulvin 100µm/mL used as standard against *A. niger* and *C. albicans* diameter of zone of inhibition is 32 (Table-3).

TABLE-3
ANTIMICROBIAL ACTIVITIES OF COMPOUNDS (**4a-n**)

Compd.	Diameter of inhibition zone (mm)			
	Bacterial strains		Fungal strain	
	E. coli	*S. aureus*	*A. niger*	*C. albicans*
4a	14	16	–	22
4b	13	12	20	26
4c	15	15	19	–
4d	16	16	24	17
4e	–	12	22	20
4f	16	14	18	–
4g	14	–	23	22
4h	–	14	21	28
4i	–	10	–	23
4j	16	15	20	19
4k	13	10	19	24
4l	14	14	–	18
4m	16	16	–	20
4n	15	–	27	16

Conclusion

The novel thiopyrimidine containing D-gluconic acid derivatives have been synthesized and characterized sucessfully using IR, ^{1}H NMR mass spectra and elemental analysis. The synthesized compounds showed pharmaceutical activity with specified mechanism of action and have unique biological applications.

ACKNOWLEDGEMENTS

The author would like to thank Director, CDRI, Lucknow for running the IR, NMR and mass samples. Author is thankful to Head, Department of Chemistry, RTM, Nagpur University, Nagpur and Principal, Jawaharlal Nehru Arts, Commerce and Science College, Wadi, Nagpur for continuous support and encouragement to perform research work.

REFERENCES

1. B.C. Sallustio, L. Sabordo, A.M. Evans and R.L. Nation, Hepatic Disposition of Electrophilic Acyl Glucuronide Conjugates, *Curr. Drug Metab.*, **1**, 163 (2000); https://doi.org/10.2174/1389200003339153
2. A.V. Stachulski, T.A. Baillie, B.K. Park, R.S. Obach, D.K. Dalvie, D.P. Williams, A. Srivastava, S.L. Regan, D.J. Antoine, C.E.P. Goldring, A.J.L. Chia, N.R. Kitteringham, L.E. Randle, H. Callan, J.L. Castrejon, J. Farrell, D.J. Naisbitt and M.S. Lennard, *Med. Res. Rev.*, **33**, 985 (2013); https://doi.org/10.1002/med.21273
3. G. Yang, S. Ge, R. Singh, S. Basu, K. Shatzer, M. Zen, J. Liu, Y. Tu, C. Zhang, J. Wei, J. Shi, L. Zhu, Z. Liu, Y. Wang, S. Gao and M. Hu, Glucuronidation: Driving Factors and Their Impact on Glucuronide Disposition, *Drug Metab. Rev.*, **23**, 19 (2017); https://doi.org/10.1080/03602532.2017.1293682
4. P. Zia-Amirhosseini, H. Spahn-Langguth and L.Z. Benet, Bioactivation by Glucuronide-Conjugate Formation, *Adv. Pharmacol.*, **27**, 385 (1994); https://doi.org/10.1016/S1054-3589(08)61040-6
5. H.S. Langguth and L.Z. Benet, Acyl Glucuronides Revisited: Is the Glucuronidation Proces a Toxification as Well as a Detoxification Mechanism?, *Drug Metab. Rev.*, **24**, 5 (1992); https://doi.org/10.3109/03602539208996289
6. M.J. Bailey and R.G. Dickinson, Chemical and Immunochemical Comparison of Protein Adduct Formation of Four Carboxylate Drugs in Rat Liver and Plasma, *Chem. Res. Toxicol.*, **9**, 659 (1996); https://doi.org/10.1021/tx960017o
7. W.S. El-Serwy, H.S. Mohamed, W.S. El-Serwy, N.A. Mohamed, E.M.M. Kassem, K. Mahmoud and E.S. Nossier, Thiopyrimidine-5-carbonitrile Derivatives as VEGFR-2 Inhibitors: Synthesis, Anticancer Evaluation, Molecular Docking, ADME Predictions and QSAR Studies, *ChemistrySelect*, **5**, 15243 (2020); https://doi.org/10.1002/slct.202002566
8. B.A. Babgi, J.H. Alsayari, B. Davaasuren, A.H. Emwas, M. Jaremko, M.H. Abdellattif and M.A. Hussien, Synthesis, Structural Studies and Anticancer Properties of [CuBr(PPh_3)$_2$(4,6-Dimethyl-2-thiopyrimidine-κS], *Crystals*, **11**, 688 (2021); https://doi.org/10.3390/cryst11060688
9. 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
10. U.W. Hawas, M.A. Al-Omar, A.G.E. Amr and A.E.-F.G. Hammam, Synthesis of Some Thiopyrimidine and Thiazolopyrimidines Starting from 2,6-Dibenzylidene-3-Methylcyclohexanone and its Antimicrobial Activities, *Arab. J. Chem.*, **5**, 509 (2012); https://doi.org/10.1016/j.arabjc.2010.09.019
11. H.G. Garg and C. Prakash, Potential Antidiabetics. 7. N^1-(β-Hydroxybenzylmethyl)-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones and N^1-(β-Hydroxybenzylmethyl)-3-methyl-4-arylazo-5-methyl- or -phenylpyrazoles, *J. Med. Chem.*, **14**, 175 (1971); https://doi.org/10.1021/jm00284a028
12. C.J. Shishoo, U.S. Pathak, I.S. Rathod and K.S. Jain, Synthesis and Pharmacological Evaluation of Some Novel 5-Aryl-6-arylamine-1-phenylpyrazolo[3,4-d]pyrimidin-4(5*H*)-ones as Analgesic and Anti-inflammatory Agents, *Indian J. Chem.*, **38B**, 684 (1999).
13. P.F. Lamie and J.N. Philoppes, 2-Thiopyrimidine/Chalcone Hybrids: Design, Synthesis, ADMET Prediction, and Anticancer Evaluation as STAT3/STAT5a Inhibitors, *J. Enzym. Inhib. Med. Chem.*, **44**, 377 (2014); https://doi.org/10.1016/j.ijantimicag.2014.06.001

14. O.Y. Voskoboynik, O.S. Kolomoets, G.G. Berest, I.S. Nosulenko, Y.V. Martynenko and S.I. Kovalenko, Preparation and Biological Properties of 2-Thio-containing Pyrimidines and their Condensed Analogs, *Chem. Heterocycl. Compd*., **53**, 256 (2017); https://doi.org/10.1007/s10593-017-2048-2
15. Y.S. Zhao, M. Zhang and Q. Li, Protective Effects of 1,2-Benzisoxazole-3-methanesulfonamide (zonisamide)-Loaded Polymeric Micelles against Neurotoxicity in Spinal Cord: *in vitro*, *J. Drug Deliv. Sci. Technol.*, **62**, 102311 (2021); https://doi.org/10.1016/j.jddst.2020.102311
16. Y.-S. Zhao, M. Zhang and Q. Li, Protective Effects of 1,2-Benzisoxazole-3-methanesulfonamide (Zonisamide)-Loaded Polymeric Micelles Against Neurotoxicity in Spinal Cord: *in vitro*, *J. Drug Deliv. Sci. Technol*., **62**, 102311 (2021); https://doi.org/10.1016/j.jddst.2020.102311
17. K.P. Rakesh, C.S. Shantharam, M.B. Sridhara, H.M. Manukumar and H.-L. Qin, Benzisoxazole: A Privileged Scaffold for Medicinal Chemistry, *Med. Chem. Commun.*, **8**, 2023 (2017); https://doi.org/10.1039/c7md00449d
18. S.S. Kumari, K.S.R. Krishna Mohan Rao and N.V. Sbba Rao, Isoxazolo (7,8-*d*)Flavones, *Proc. Indian Acad. Sci.*, **77A**, 149 (1973); https://doi.org/10.1007/BF03048406
19. J.C. Saunders and W.R.N. Williamson, Potential Antiinflammatory Compounds. 2. Acidic Antiinflammatory 1,2-Benzisoxazoles, *J. Med. Chem.*, **22**, 1554 (1979); https://doi.org/10.1021/jm00198a026
20. S.V.K. Archana, R. Chandra and A. Kumar, Synthesis of Potential Quinazolinonyl Pyrazolines and Quinazolinyl Isoxazolines as Anticonvulsant Agents, *Indian J. Chem.*, **41B**, 2371 (2002).
21. R.K. Wanare, Y.V. Punatkar and R.M. Jugade, Synthesis, Glucosylation and Polarographic Studies of Benzofused Pyrimidine Derivatives, *Asian J. Org. Med. Chem.*, **6**, 230 (2021); https://doi.org/10.14233/ajomc.2021.ajomc-p328