Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(20):175-181
(http://derpharmachemica.com/archive.html)

Green synthesis of saccharin substituted urea and thiourea derivatives and their antimicrobial evaluation

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ABSTRACT

A series of saccharin substituted urea and thiourea derivatives has been synthesized by reaction of differently substituted ureas and thioureas with saccharin under microwave irradiations using water as a non-toxic, non-flammable green solvent. The structure of the synthesized compounds has been confirmed by IR, ^{1}H NMR, mass and elemental analysis. The synthesized compounds have been evaluated for their antimicrobial activity against different bacterial and fungal strains using micro broth dilution assay. The compounds are further screened for drug likeliness and In silico ADMET analysis.

Keywords: Urea, thiourea, saccharin, antimicrobial evaluation

INRODUCTION

Saccharin, a derivative of 1,2- benzisothiazole is a versatile heterocyclic compound known over many years as artificial sweetening agent [1] and is frequently used to enhance the taste and solubility of many pharmaceutical drugs [2]. Several saccharin derivatives exhibited diverse chemotherapeutic activities such as antibacterial [3], antifungal [4], anxiolytic [5], anticancer [6], anti-inflammatory [7], analgesic [8], antioxidant [9], α-1A adrenergic receptor antagonists [10], herbicidal [11] and peptidomimetic [12]. Various potent inhibitors containing saccharin as key structural element are reported such as tyrosinase inhibitor [13], serine protease inhibitor [14], human leucocyte elastase inhibitor [15], aldehyde dehydrogenase inhibitor [16], histone deacetylase inhibitor [17], human mast cell tryptase inhibitor [18] and cathepsin-G and proteinase 3 inhibitor [19]. Some saccharin derivatives act as antidote of metal poisoning [20], pharmacophore of bioactive compounds [21] and CNS active drug [22].

Ureas and thioureas are important organic compounds present in a number of naturally occurring compounds and have numerous applications in medicinal chemistry, laboratories, industries, automobiles, agrochemicals and in chemical transformations. Several urea and thiourea derivatives are known to possess a wide range of pharmaceutical applications as antibacterial [23], cytotoxic [24], anti-inflammatory [25], anti-diabetic [26], anti-melanoma [27], antiviral [28], antioxidant [29], antifungal [30], inhibitors of influenza virus neuraminidase [31] analgesic [32], diuretics [33] and peptidomimetic [34].

In recent times, antimicrobial drug resistance emerges as a global threat, which leads to an ever increasing demand for developing and designing novel and more effective chemotherapeutic agents. Diverse pharmaceutical profile of saccharin, urea and thiourea derivatives prompted us to explore the reaction of different ureas and thioureas with saccharin and to envisage the antimicrobial properties of the synthesized compounds.

MATERIAL AND METHODS

Melting points were determined in open capillaries and are uncorrected. The reactions were carried out in a Samsung microwave oven operating between 80-800 W, Model No. CE745G. All reagents were purchased from

Sigma-Aldrich and used without further purification. The reactions were examined by analytical thin layer chromatography (TLC) performed on glass plates precoated with silica gel G as supplied by Sisco Research Laboratories (SRL). Elemental analyses were recorded on a Thermo Scientific (FLASH 2000) CHN Elemental Analyser. IR spectra were recorded in the region 4000-400 cm^{-1} on a FT Infra-Red Spectrometer Model Nicolet IS50 (Thermo Scientific) with KBr pellets. ^{1}H-NMR spectra in DMSO-d_6 solution were recorded on Bruker Avance Π 400 MHz Spectrometer. The chemical shifts were in parts per million (ppm) downfield from Tetramethylsilane (TMS) which was used as internal standard. The Mass spectra were recorded on Thermo Scientific TSQ 8000 Gas chromatograph-Mass Spectrometer.

Synthesis of 1,1,3-Trioxo-1, 3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid amide (3a):
Saccharin (0.183 g, 1mmol) and urea (0.06 g, 1mmol) were taken in a 10 mL Pyrex beaker and thoroughly mixed with the addition of 2-3 drops of water and then exposed to microwave irradiations at 480 W. The progress of the reaction was monitored by TLC (CCl_4: Ethylacetate/ 3:1) after interval of every 10 sec. The reaction was found to be completed in 5 min. The reaction mixture was diluted with water and the solid thus separated out was filtered, washed with water and recrystallized from ethanol to give 1,1,3-Trioxo-1, 3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid amide in 84 % yield.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid amide (3a):
M.P. 235 °C; Anal. Calc. for $C_8H_6N_2O_4S$ (226): C, 42.48; H, 2.65; N, 12.38; Found: C, 41.01; H, 2.91; N, 12.18 %; FT IR (KBr, υ in cm^{-1}): 3341 (N-H), 3092 (C-H_{Ar}), 1677 (C=O), 1588 (N-H_{bend}), 1431 (C-N), 1337 (S=O_{asy}), 1174 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.93 (br, 2H, NH_2); 8.23-7.81 (m, 4H, Ar-H); GC-MS (m/z): 226 (M^+), 228 (M+2), 182, 120, 103, 76, 60.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid methylamide (3b):
M.P. 230 °C; Anal. Calc. for $C_9H_8N_2O_4S$ (240): C, 45.00; H, 3.33; N, 11.66; S, 13.33; Found: C, 45.78; H, 3.68; N, 11.69; S, 13.49 %; FT IR (KBr, υ in cm^{-1}): 3366 (N-H), 3098 (C-H_{Ar}), 1632 (C=O), 1589 (N-H_{bend}), 1406 (C-N), 1342 (S=O_{asy}), 1158 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.43 (br, 1H, NH); 8.14-7.79 (m, 4H, Ar-H); 3.06 (s, 3H, CH_3); GC-MS (m/z): 240 (M^+), 242 (M+2), 182, 140, 120, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid ethylamide (3c):
M.P. 222 °C; Anal. Calc. for $C_{10}H_{10}N_2O_4S$ (254): C, 47.24; H, 3.94; N, 11.02; S, 12.59; Found: C, 45.71; H, 3.56; N, 10.86; S, 12.79 %; FT IR (KBr, υ in cm^{-1}): 3339 (N-H), 3099 (C-H_{Ar}), 1625 (C=O), 1587 (N-H_{bend}), 1461 (C-N), 1337 (S=O_{asy}), 1156 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.39 (br, 1H, NH); 8.20-7.75 (m, 4H, Ar-H); 3.19-2.74 (m, 5H, -C_2H_5); GC-MS (m/z): 254 (M^+), 256 (M+2), 182, 140, 120, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid butylamide (3d):
M.P. 195 °C; Anal. Calc. for $C_{12}H_{14}N_2O_4S$ (282): C, 51.06; H, 4.96; N, 9.92; Found: C, 52.85; H, 4.69; N, 10.68 %; FT IR (KBr, υ in cm^{-1}): 3421 (N-H), 3071 (C-H_{Ar}), 1706 (C=O), 1606 (N-H_{bend}), 1406 (C-N), 1300 (S=O_{asy}), 1158 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.20 (br, 1H, NH); 7.99-7.51 (m, 4H, Ar-H); 1.69-1.32 (m, 9H, -C_4H_9); GC-MS (m/z): 282 (M^+), 284 (M+2), 226, 182, 120, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid trimethylsilylamide (3e):
M. P. 243 °C**;** Anal. Calc. for $C_{11}H_{14}N_2O_4SSi$ (298): C, 44.29; H, 4.69; N, 9.39; S, 10.73; Found: C, 42.12; H, 4.09; N, 10.45; S, 10. 49 %; FT IR (KBr, υ in cm^{-1}): 3342 (N-H), 3096 (C-H_{Ar}), 1710 (C=O), 1584 (N-H_{bend}), 1400 (C-N), 1338 (S=O_{asy}), 1163 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.87 (br, 1H, NH); 8.09-7.76 (m, 4H, Ar-H); GC-MS (m/z): 298 (M^+), 300 (M+2), 182, 140, 120, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid cyclohexylamide (3f):
M.P. 245 °C; Anal. Calc. for $C_{14}H_{16}N_2O_4S$ (308): C, 54.54; H, 5.19; N, 9.09; S, 10.38; Found: C, 54.48; H, 5.15; N, 9.06; S, 10.66 %; FT IR (KBr, υ in cm^{-1}): 3352 (N-H), 3090 (C-H_{Ar}), 1667 (C=O), 1580 (N-H_{bend}), 1414 (C-N), 1385 (S=O_{asy}), 1168 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.13 (s, 1H, NH); 8.52-7.91 (m, 4H, Ar-H); 3.42 (s, 1H, Cyclohexyl-H); 1.31-1.10 (m, 10 H, Cyclohexyl-H); GC-MS (m/z): 308 (M^+), 310 (M+2), 182, 140, 126, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carbothioic acid amide (3g):
M.P. 223 °C; Anal. Calc. for $C_8H_6N_2O_3S_2$ (242): C, 39.66; H, 2.48; N, 11.57; S, 26.44; Found: C, 38.47; H, 2.77; N, 12.34; S, 25.79 %; FT IR (KBr, υ in cm^{-1}): 3396 (N-H), 3070 (C-H_{Ar}), 1654 (C=O), 1585 (N-H_{bend}), 1458 (C=S), 1394 (C-N), 1339 (S=O_{asy}), 1149 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.03-7.48 (m, 4H, Ar-H); 6.98 (br, 2H, NH_2); GC-MS (m/z): 242 (M^+), 244 (M+2), 182, 140, 120, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazole-2-carbothioic acid methylamide (3h):
M.P. 190 °C; Anal. Calc. for $C_9H_8N_2O_3S_2$ (256): C, 42.18; H, 3.12; N, 10.93; S, 25.00; Found: C, 42.79; H, 3.62; N, 11.30; S, 23.49 %; FT IR (KBr, υ in cm^{-1}): 3364 (N-H), 3029 (C-H_{Ar}), 1634 (C=O), 1590 (N-H_{bend}), 1460 (C=S), 1406 (C-N), 1345 (S=O_{asy}), 1158 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.36 (br, 1H, NH); 8.18-7.48 (m, 4H, Ar-H); 3.08 (s, 3H, CH_3); GC-MS (m/z): 256 (M^+), 258 (M+2), 182, 140, 120, 103, 92, 76, 62.

1,1,3-Trioxo-1,3-dihydro-1λ^6-benzo[d]isothiazol-2-carbothioic acid ethylamide (3i):
M.P. 207 °C; Anal. Calc. for $C_{10}H_{10}N_2O_3S_2$ (270): C, 44.44; H, 3.70; N, 10.37; S, 23.70; Found: C, 44.47; H, 3.76; N, 9.86; S, 23.49 %; FT IR (KBr, υ in cm^{-1}): 3349 (N-H), 3165 (C-H_{Ar}), 2818 (C-H), 1707 (C=O), 1583 (N-H_{bend}), 1460 (C=S), 1405 (C-N), 1337 (S=O_{asy}), 1165 (S=O_{sym}); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.14 (br, 1H, NH); 7.92-7.70 (m, 4H, Ar-H); 1.31-1.00 (m, 5H, -C_2H_5); GC-MS (m/z): 270 (M^+), 272 (M+2), 242, 218, 182, 163, 123, 103, 92, 76.

Antibacterial Activity
The synthesized compounds (**3a-i**) were evaluated for their antibacterial activity against two gram positive bacteria *Staphylococcus aureus* (MTCC 3160), *Bacillus cereus* (MTCC 10085) and two gram negative bacteria *Escherichia coli* (MTCC 433) and *Salmonella enterica* (MTCC 27853). Luria broth obtained from Himedia Chemicals Laboratories, India was used as nutrient medium for the bacterial strains and the compounds were dissolved in DMSO for preparing stock solutions. Ciprofloxacin was used as standard anti-bacterial drug. Modified Resazurin Micro broth Dilution Assay [35] was used for determing the MIC values of standard drug and the synthesized compounds.

Antifungal Activity
The synthesized compounds (**3a-i**) were evaluated for their antifungal activity against two fungal strains *Aspergillus fumigatus* (ITCC 4517) and *Aspergillus niger* (ITCC 5405) by modified Micro broth Dilution Assay [36]. The standard drug used for antifungal assessment was fluconazole. The fungal species cultures were grown on Sabouraud Dextrose (SD) agar at 37 ^{o}C until sporulation occurs, normally for 4-5 days.

***In Silico* ADMET analysis**
With the growing awareness towards high throughput screening and combinatorial chemistry, the synthesized compounds were further screened for their drug likeliness and pharmacokinetics in human body i.e. absorption, distribution, metabolism, excretion and toxicity (ADMET). Using Molinspiration software, a number of different physicochemical properties of the title compounds were evaluated such as polar surface area, molecular weight, Milog P (partition coefficient), number of heavy atoms, volume, number of rotable bonds and number of hydrogen bond donors and acceptors. These physicochemical properties were examined according Lipinski's rule [37], Veber filter [38] and Ghose filter [39] to provide an insight about the suitability of a chemical compound to act as an orally active drug in human beings.

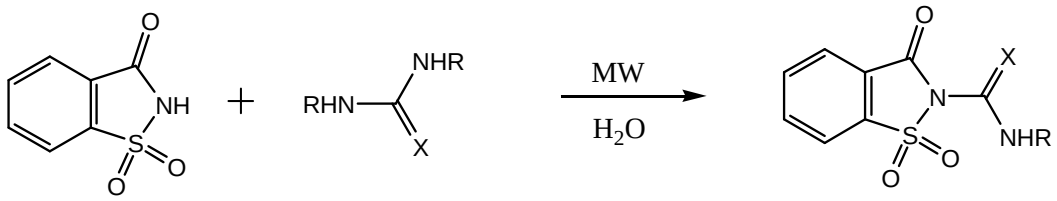
Lipinski's rule of five
- Molecular mass must be less than 500 daltons.
- Calculated octanol-water partition coefficient (log P) must be less than 5.
- Number of hydrogen bond donors must be less than 5.
- Number of hydrogen bond acceptor must be less than 10.
- Number of violations must be equal to or less than 1.

Veber Filter
- Rotatable bond count must be less than or equal to 10
- Polar surface area (PSA) must be less than or equal to 140 Å^2.

Ghose Filter
- Total number of atoms must be in range 20 to 70.
- Molecular weight must be in range 160 to 480 daltons.
- Molar refractivity should be in range 40-130 m^3 mol^{-1}

RESULTS AND DISCUSSION

In the present work, various saccharin substituted urea and thiourea derivatives were synthesized by reaction of diverse ureas and thioureas with saccharin using water as a solvent under microwave irradiations **Scheme 1**.



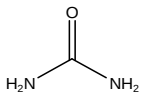
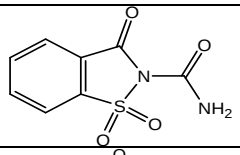
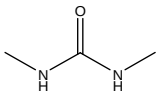
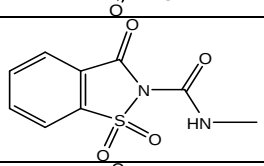
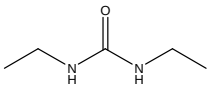
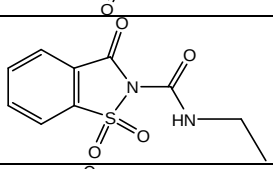
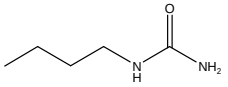
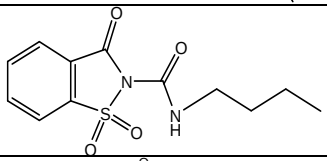
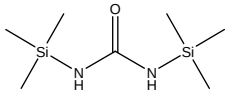
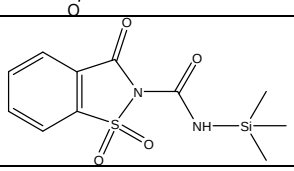
Saccharin (**1**) Ureas/Thioureas (**2a-i**) Saccharin substituted ureas and thioureas (**3a-i**)

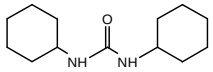
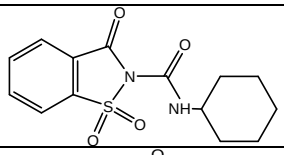
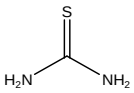
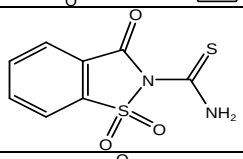
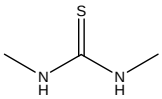
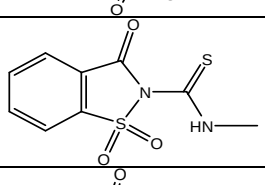
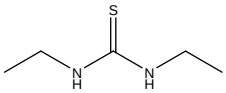
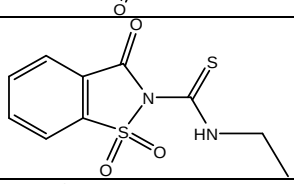
X= O, S
R= H, Alkyl, cyclohexyl, trimethylsilyl

Scheme 1

In a typical reaction, an equimolar amount of urea and saccharin was thoroughly mixed by adding few drops of water and then subjected to microwave irradiations at 480 W. The progress of reaction was monitored by TLC using carbon tetrachloride and ethylacetate as eluent (3:1). The reaction was found to be completed in 5 min and the product was obtained by simply adding water to the reaction mixture. The product thus obtained in 84 % yield with melting point 235 °C, exhibited in its IR a band in the region 3341 for N-H stretching, 3092 for aromatic C-H stretching, 1677 for C=O stretching, 1588 for N-H bending, 1431 for C-N stretching, 1337 for S=O asymmetric stretching, 1174 for S=O symmetric stretching. In the ^{1}H NMR spectra, the compound exhibited a singlet at δ 8.93 due to two NH_2 protons, a multiple at δ 8.23-7.81 due to four aromatic protons. In the Mass spectra, the molecular ion peaks was found at m/z 226 and the base ion peak was found at m/z 182. Corresponding peaks were also noticed at m/z values of 120, 103, 76 and 60. The elemental analyses data was also found to be in agreement with the proposed structure of the synthesized compound i.e. 1,1,3-Trioxo-1, 3-dihydro-1λ^6-benzo[d]isothiazole-2-carboxylic acid amide. Similar procedure was also extended for the synthesis of different saccharin substituted urea and thiourea derivatives in excellent yields **Table 1**. Further, the IR, ^{1}H NMR, mass and elemental analyses data of the synthesized compounds was in good agreement with the proposed structures.

Table 1 Synthesis of saccharin substituted urea and thiourea derivatives in the presence of water under MW irradiations

Entry	Reactants	Product	Time (min)	Yield[a] (%)
3a			5	84
3b			5	82
3c			4	81
3d			6	81
3e			14	84

3f			14	80
3g			5	89
3h			4	83
3i			4	82

[a]*Yields are of pure product isolated*

Antimicrobial Evaluation:

All the compounds (**3a-i**) exhibited moderate to good antibacterial activity against different bacterial strains. Compound **3b** displayed significant activity against gram negative bacterial strains *E. coli* and *S. enteric*. Compound **3d** displayed significant activity against gram positive bacterial strains *S. aureus and B. cereus*. Compounds **3c, 3f, 3g, 3h** and **3i** have displayed moderate to good antibacterial activity against both gram positive and gram negative bacterial strains.

Antifungal activity data of compounds (**3a-i**) revealed that the compound **3b, 3c, 3g, 3h** and **3i** displayed good antifungal activity against A. *fumigates* and A. *niger* as compared to the other compounds. Results are gathered in **Table 2**.

Table 2 Antimicrobial evaluation [MIC (mg/ml)] of saccharin substituted urea and thiourea derivatives

Entry	Gram positive bacteria		Gram negative bacteria		Fungi	
	S. aureus	*B. cereus*	*E. coli*	*S. enterica*	*A. fumigatus*	*A. niger*
	MTCC 3160	MTCC 10085	MTCC 433	MTCC 27853	ITCC 4517	ITCC 5405
3a	20	10	20	20	20	20
3b	10	10	5	5	10	10
3c	5	10	10	10	10	10
3d	5	5	10	10	20	20
3e	20	20	20	20	20	20
3f	20	20	10	10	20	20
3g	10	10	20	20	10	10
3h	10	10	10	10	10	10
3i	5	10	10	10	10	10
Fluconazole	-	-	-	-	125 µg/mL	62.5µg/mL
Ciprofloxacin	62.5µg/mL	125µg/mL	125µg/mL	125µg/mL	-	-

***In Silico* ADMET Analysis:**

All the synthesized saccharin-urea/thiourea derivatives were further evaluated for *In Silico* ADMET analysis in combination with Lipinski's rule, Veber filter and Ghose filter. As the compound **3e** does not shows any significant antibacterial or antifungal activity so it is excluded from this study. In the calculated physicochemical properties, all the compounds have molecular weight in the range of 226.21 to 308.36 daltons and log P value in the range of -0.25 to 2.03. A molecular weight of less than 500 daltons and log P of less than 5 is a measure of lipophilic character of the compound and predicts its intestinal absorption and transcellular transport. TPSA of all the compounds is less than 140 $Å^2$ and it is a measure of hydrogen bonding potential of the compounds. Number of rotable bonds in all the compounds lies below 10 and it is a parameter of molecular flexibility. Further TPSA of less than equal to 140 $Å^2$ and number of rotable bonds less than equal to 10 signifies good oral bioavailability of drug. Number of hydrogen donor and acceptor is a parameter for checking good absorption and permeability of the drug across the cell membrane. High TPSA in combination with low Log P value is a measure of low toxicity of the compound. Hence all the compounds examined possess significant drug likeliness scores and the results are summarized in **Table 3**.

Table 3 Calculated molecular properties and topology analysis of saccharin substituted urea and thiourea derivatives

Entry	miLogP	TPSA	nAtoms	n ON	n OHNH	n violation	n rotb.	Volume	MW
3a	-0.25	97.55	15	6	2	0	0	166.67	226.21
3b	0.12	83.55	16	6	1	0	0	184.35	240.24
3c	0.50	83.55	17	6	1	0	1	201.15	254.27
3d	1.56	83.55	19	6	1	0	3	234.75	282.32
3f	2.03	83.55	21	6	1	0	1	257.78	308.36
3g	0.29	80.47	15	5	2	0	1	175.55	242.28
3h	0.66	66.48	16	5	1	0	2	193.22	256.31
3i	1.04	66.48	17	5	1	0	3	210.03	270.33

CONCLUSION

Saccharin substituted urea and thiourea derivatives were synthesized with excellent yield in environmentally affable conditions using water as a solvent under microwave irradiations. Further, the synthesized compounds were examined for their antibacterial, antifungal activities and *In silico* ADMET analysis. The compounds displayed moderate to good antimicrobial activity and significant drug likeliness scores.

Acknowledgements
Authors are grateful to M. D. University, Rohtak, India for providing research facilities. The authors are also thankful to RSIC-SAIF, Punjab University, Chandigarh, India for spectral and elemental analysis of compounds.

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