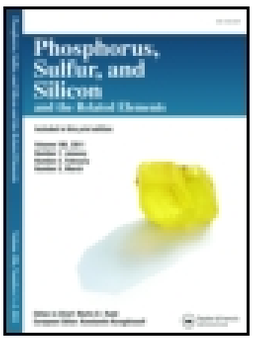

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Synthesis of novel 3-[(2*R**)-2-[(2*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl]-2-hydroxyethyl]-urea/thiourea derivatives and evaluation of their antimicrobial activities

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ABSTRACT

A new series of biologically active 3-[(2*R**)-2-[(2*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl]-2-hydroxyethyl]-urea/thiourea derivatives (**1**) have been designed and synthesized in four steps from 6-fluoro-3,4-dihydro-2-(oxiran-2-yl)-2*H*-chromene (**2**). The structures of newly synthesized compounds (**1a–j**) were confirmed by ^{1}H, ^{13}C NMR, and HRMS. The major advantages of the present article include the development of an efficient eluent system for good separation of diastereomers (**2a** and **2b**) with high yields and synthesis of (*R**)-2-(benzylamino)-1-((*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl)ethanol (**3**) in high yields (87%) from epoxide **(2a)** through new reaction conditions. The synthesized compounds (**1a–j**) exhibited moderate to excellent antimicrobial activities against both bacterial strains (gram + Ve and gram –Ve strains) and fungal strains. Among the tested compounds, promising lead compounds were identified (compounds **1a** and **1d** against bacterial strains and compound **1h** and **1j** against fungal strains) and their antimicrobial activities are comparable with the reference standard.

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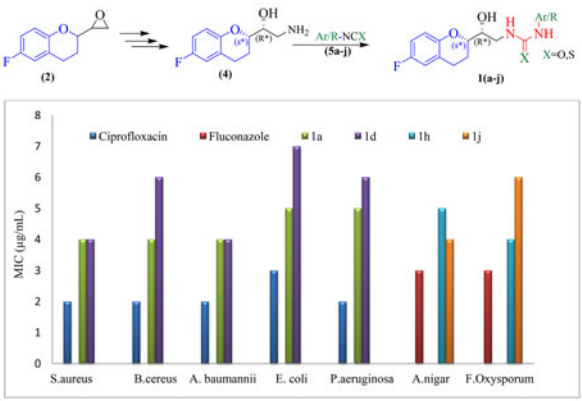
KEYWORDS
Chromane; nebivolol intermediate; urea and thiourea derivatives; antimicrobial activity

GRAPHICAL ABSTRACT



Introduction

Antibiotics usage in modern medicine has become more abundant, after their discovery, in numerous crucial surgeries and treatments. The consequences of their higher utility leads to antibiotic resistance, and in turn into one of the major problems faced in public health throughout the world.[1,2] Thus, there is an increasing and constant demand for the discovery and development of new antimicrobial drug candidates with a novel mechanism of action.[3,4] The design and development of new antimicrobial agents (effective against either bacterial or fungal strains which have developed resistance) are possible to achieve by alteration of the structural feature of existing antimicrobial agents or design of new drug candidates by combining two or more pharmacophores.[5,6] By keeping these factors in mind, our attention turned toward bioactive chromane, chromanone skeleton and urea/thiourea moieties as they possess potential biological activities. The chromane and chromanone skeleton was found in natural products (epigallocatechin gallate and vitamin E), some pharmaceuticals and other biologically active compounds as shown in Figure 1; for example, Nebivolol hydrochloride,[7] Repinotan[8] Fidarestat[9] and 2-

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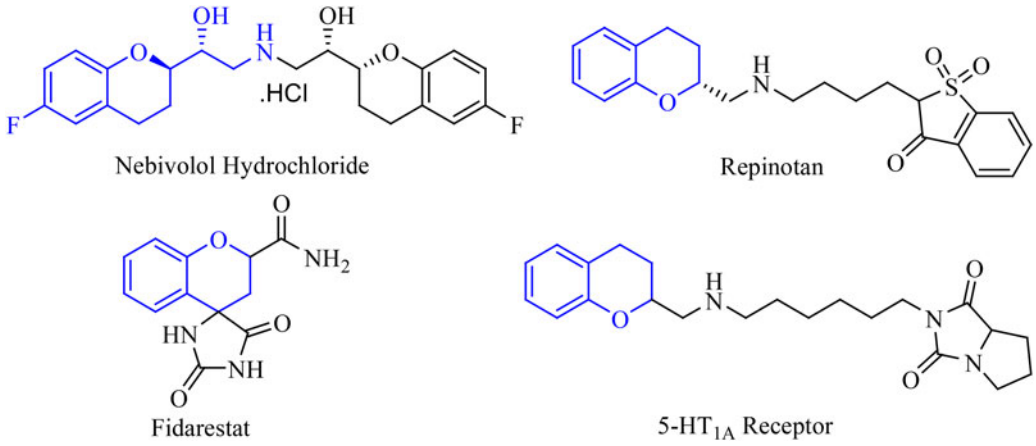
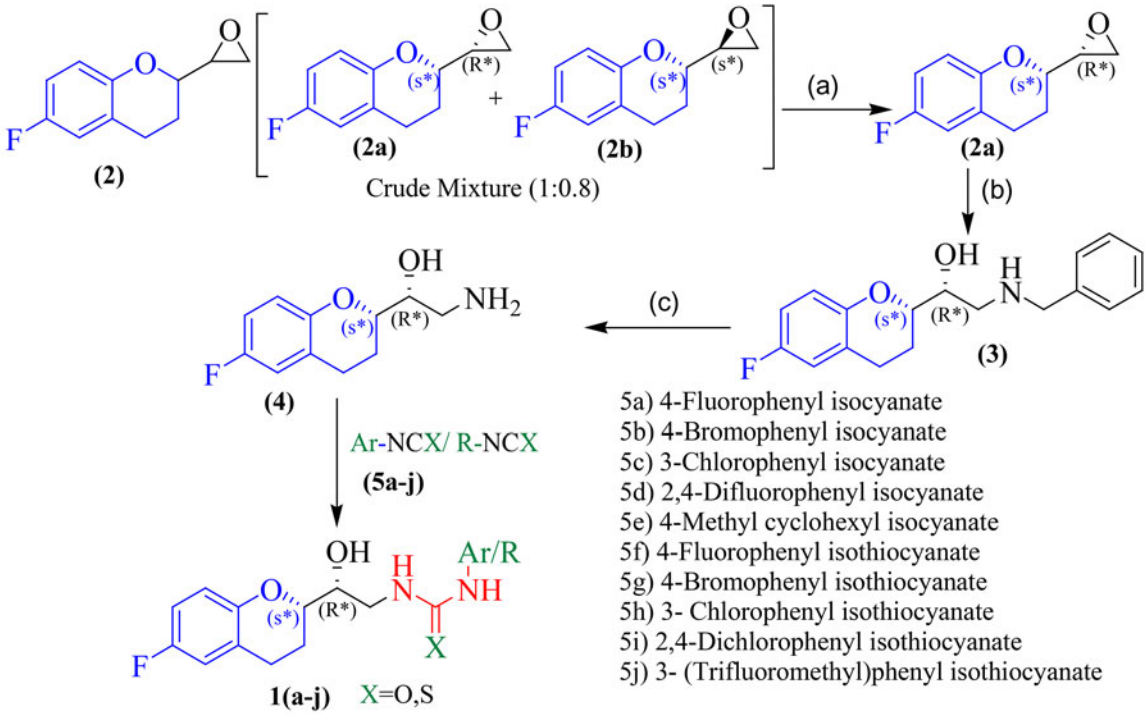


Figure 1. Biologically active chromane derivatives.



Reaction conditions: a) Column separation using 2-5% ethyl acetate in n-hexane eluent, 45%; b) Benzylamine, IPA, 80-85 °C, 87%; c) Ammonium formate, methanol, 10Pd/C, 20-30 °C, 90%, and d) THF, Et_3N, 60-65 °C, 70–85%.

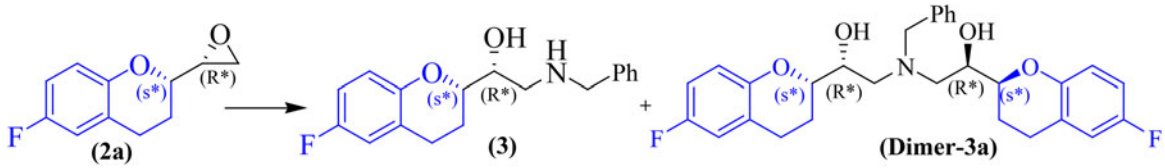
Scheme 1. Synthetic scheme for the preparation of title urea and thiourea derivatives.
Reaction conditions: (a) Column separation using 2–5% ethyl acetate in n-hexane eluent, 45%; (b) Benzylamine, IPA, 80–85 °C, 87%; (c) Ammonium formate, methanol, 10Pd/C, 20–30 °C, 90%, and (d) THF, Et_3N, 60–65 °C, 70–85%.

{6-[(3,4-dihydro-2*H*-chromen-2-yl-methyl)amino]hexyl} tetrahydro-1*H*-pyrrolo[1,2-*c*] imidazole-1,3(2*H*)-dione.[10]

Molecules with a chromane moiety and fluorine atom substitution can attain various chemical and biological properties.[11] For example, it is well known that the presence of a fluorine atom in the chemical structure of a drug can enhance the distribution of the drug, drug clearance, and extent of drug metabolism.[12] We anticipate that the combination of fluorine-substituted chromanes with urea/thiourea would enhance the biological activity of presently designed molecules (**1a–j**).

Nebivolol hydrochloride (*S**, *R**, *R**, *R**) is a well-known antihypertensive drug and it is a racemic compound, formed by the reaction of both (*S**, *R**) and (*R**, *R**) 2-amino-6-fluorochroman-2-yl)ethanol (**4**) where compound **4** was synthesized from 6-fluoro-3,4-dihydro-2-(oxiran-2-yl)-2*H*-chromene (**2**).[13]

An extensive literature search revealed that the molecules with chromane moiety[14–16] and urea/thiourea[17–19] functionalities exhibit excellent antimicrobial and anti cancer[20] activities. Recently, it was reported that the combination of chromane with urea and thiourea derivatives displayed good



Scheme 2. Synthetic scheme for the preparation of compound **3**.

Table 1. Separation of (**2a**) from the diastereomeric compound (**2**) by column chromatography[a].

Entry	Eluent	Yield[b] (%)
1	Toluene (100%)	25
2	EtOAc (100%)	20
3	DCM (100%)	15
4	n-Hexane (100%)	26
5	2 % EtOAc in hexane	40
6	5% EtOAc in hexane	35
7[c]	2% to 5% EtOAc in hexane	45

[a]**Column separation conditions:** eluent, stationary phase: silica gel-100-200 mesh at 20–30 °C.
[b]Isolated yield.
[c]Concentration of EtOAc increase from 2% to 5% gradually.

Table 2. Screening of various solvents for preparation of compound (**3**).

Entry	Solvent	Temp'(°C)	Time (h)	Yield[b](%)
1	Methanol	25–30	**24**	10
2	Methanol	60–65	**4**	30
3	Ethanol	60–65	**4**	40
4	IPA	80–85	**5**	45
5	ACN	80–85	**4**	28
6	DMF	80–85	**3**	20
7	DMSO	80–85	**3**	24
8	Toluene	80–85	**24**	5

Reaction conditions: Compound **2a** (10.0 mmol), benzylamine (12.0 mmol) in solvent (5 vol.) at 80–85 °C.
[b]Isolated yield.

antimicrobial activities.[21,22] Hence, we have planned to design and synthesize a new series of molecules comprised of both the chromane skeleton and urea/thiourea moieties.

Results and discussion

Chemistry

Herein, we report the synthesis of 3-[(2*R**)-2-[(2*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl)-2-hydroxyethyl]-urea/thiourea derivatives (**1a–j**) starting from a commercially available diastereomeric mixture (**2a** and **2b** in 1:0.8 ratio, respectively) of 6-fluoro-3,4-dihydro-2-(oxiran-2-yl)-2*H*-chromene (**2**) as shown in Scheme 1. The *in-vitro* antimicrobial activity studies of synthesized compounds (**1a–j**) were also reported.

At the outset, the diastereomeric mixture of compound (**2**) 6-fluoro-3,4-dihydro-2-(oxiran-2-yl)-2*H*-chromene was resolved by column chromatography.[13] The resulting desired racemic compound (**2a**) of epoxide was treated with benzylamine to obtain (*R**)-2-(benzylamino)-1-((*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl)ethanol (**3**). The resulting compound **3** was debenzylated using 10% palladium on carbon with ammonium formate as a hydrogen source to afford (*S**)-2-amino-1-((*R**)-6-fluorochroman-2-yl)ethanol (**4**). Further, compound **4** was treated with various isocyanates (**5a–e**) and isothiocyanate (**5f–j**) in the presence of triethylamine in THF to afford the target molecules (**1a–j**) in good to moderate yields.

Separation of diastereomer by column chromatography

Several asymmetric methods were reported for the synthesis of amino alcohol (**4**) as a racemic and enantiomerically enriched compound in the literature. [23,24] But, the major disadvantages associated with these methods include the number of chemical steps, low conversion and low reported yields. Hence, our attention turned toward finding a more robust and cost-effective process. Along this line, we found there are reports for resolving a diastereomeric mixture using column chromatography.[13] The reported method was adopted to separate a diastereomeric mixture (**2**) using toluene alone. However, low yield (25%) of single diastereomer was obtained (entry 1, Table 1). Hence, our attention turned toward the utilization of other solvents or mixture of solvents for efficient separation.

In place of toluene, other single solvents, both polar and non-polar, were screened such as ethyl acetate, dichloromethane, and n-hexane. Compound (**2a**) was obtained in the yields of 20%, 15%, and 32%, respectively (entries 2, 3, and 4). Therefore, we attempted to use a mixture of solvents of n-hexane and ethyl acetate. The isocratic elution with ethyl acetate (2%) in hexane was applied and obtained a 40% yield of compound **2a** (entry 5). With ethyl acetate (5%) in hexane, the desired diastereomer was obtained in 35% yield (entry 6). Alternatively, when gradient elution was applied using ethyl acetate (2–5%) in hexane and desired diastereomer in good yield 45% was obtained.

Epoxide ring opening with benzylamine

The ring opening of epoxide compound **2a** was carried out by the reaction of compound **2a** with benzylamine (1.2 equiv.) in methanol at room temperature to prepare compound **3** as shown in Scheme 2. The desired compound **3** was obtained in low yield (10%) (entry 1, Table 2) as substrate **2a** was found unreacted at room temperature. The same reaction was carried out at reflux temperature and the yield of desired compound **3** was improved slightly (30%) (entry 2, Table 2). In this condition, the compound **3** was obtained in low yield even though, the substrate **2a** was consumed completely due to formation of undesired dimer compound **3a** (Scheme 2). To suppress the formation of undesired compound **3a**, the same reaction was screened in various solvents and the obtained results were presented in Table 2. The study revealed that the reaction proceeded well and provide moderate yields of compounds in the presence

Table 3. Screening of benzylamine equivalents for the synthesis of compound **3**[a].

Entry	Reagent	equiv.	Temp (°C)	Yield[b](%)
1	Benzylamine	2.0	80–85	47
2	Benzylamine	5.0	80–85	55
3	Benzylamine	8.0	80–85	65
4	Benzylamine	10.0	80–85	64
5	Benzylamine[c]	8.0	80–85	87

[a]**Reaction conditions:** Compound **2a** (10.0 mmol), in IPA (5 vol) at 80–85 °C.
[b]Isolated yield.
[c]Addition of compound **2a** to Benzylamine.

of polar protic solvents such as ethanol and isopropyl alcohol (entries 3 and 4, Table 2). The same reaction provided low yields in presence of polar aprotic solvents, for example, acetonitrile, DMF and DMSO afforded 28%, 20%, and 24% yields of compound 3, respectively (entries 5–7). The same reaction was unsuccessful in toluene because of poor solubility of reactants (entry 8). The study disclosed that isopropyl alcohol afforded good yield of desired compound **3** as well as control the formation of undesired compound **3a**.

To further improve the yield, the effect of mole equivalents of benzylamine was studied on the course of the reaction. Accordingly, the reaction was carried out in isopropyl alcohol using different equivalents of benzylamine at 80–85 °C, for example at 2.0, 5.0, 8.0, and 10.0 equiv. of benzylamine to obtained 47%, 55%, 65%, and 64% of compound **3** respectively (entries 1–4, Table 3). The study revealed that 8.0 equiv of benzylamine offered 65% yield (entry 3). To improve the yield further, the mode of addition of benzylamine was studied. The compound **2a** was added dropwise to benzylamine at 80–85 °C and observed minimum formation of the dimer (4–5%) and the yield was dramatically increased to 87% (entry 5). The study disclosed that the addition of **2a** to benzylamine at 80–85 °C offered an excellent yield.

Synthesis of (S*)-2-amino-1-((R*)-6-fluorochroman-2-yl)ethanol (4)

The debenzylation of compound **(3)** to prepare amino alcohol **4** was carried out using the literature process and the results were reproduced.[25] The yield of compound **4** was good (90%).

Synthesis of 3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-chromen-2-yl]-2-hydroxy ethyl]-urea/thiourea derivatives (1a–j)

Initially, the synthesis of target compound 3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-chromen-2-yl]-2-hydroxy ethyl]-1-(4-fluorophenyl) urea (**1a**) was carried out by the reaction of compound **4** with substrate **5a** in toluene at room temperature and the desired compound **1a** was obtained in low yield 6%. The same reaction at 60–65 °C temperature provided 17% of compound **1a** (entry 1, Table 4). It may be due to the insolubility of compound **4** in toluene. To increase the yield further, various solvents were studied, for example, THF, ACN, EtOH, DMF, DMSO, DMAc and obtained 80%, 61%, 44%, 52%, 61%, and 49%, isolated yields of compound **1a** respectively (entries 2–7, Table 4) at 60–65 °C. The study disclosed that THF is the best solvent for maximum conversion and formation of compound **1a** (entry 2, Table 4). The same reaction in THF at room temperature offered low yield 38% even on prolonged reaction time. With the help of the above-optimized reaction conditions, the other desired compounds (**1b–j**) were synthesized by the reaction of compound **4** with substrates (**5b–j**) as shown in Table 5.

Table 4. Optimization of reaction conditions for the synthesis of compound **1a**.

Entry	Solvent	Time (h)	Temp (°C)	Product	Yield[b](%)
1	Toluene	24	60–65	**1a**	17
2	THF	5	60–65	**1a**	80
3	ACN	10	60–65	**1a**	61
4	EtOH	24	60–65	**1a**	44
5	DMF	3	60–65	**1a**	52
6	DMSO	3	60–65	**1a**	61
7	DMAc	2.5	60–65	**1a**	49

[a]**Reaction conditions:** Compound **4** (10.0 mmol), compound **5a** (12.0 mmol), Et_3N (12.0 mmol) in solvent (6 vol.) at 60–65 °C.
[b]Isolated yields.

Spectroscopic data

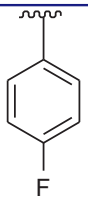
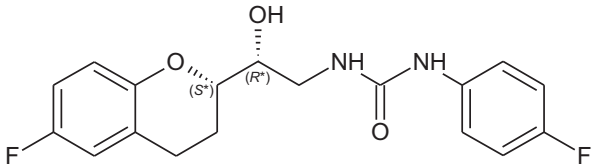
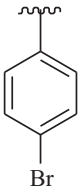
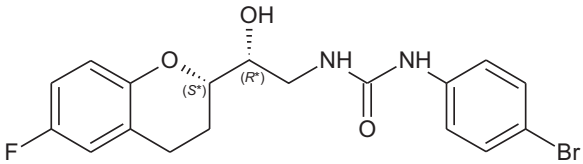
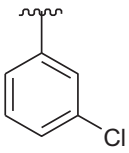
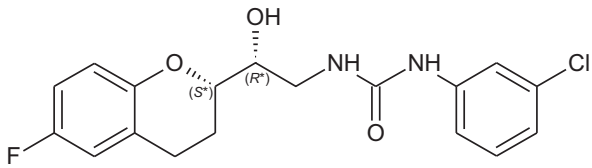
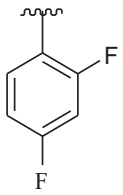
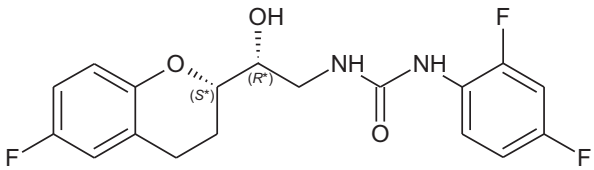
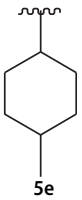
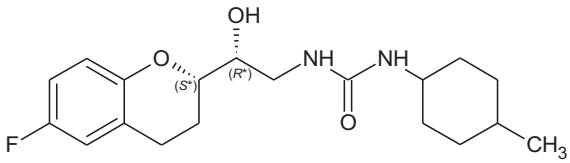
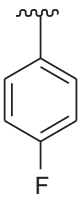
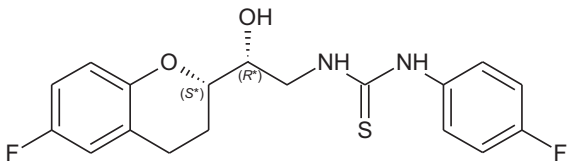
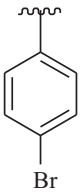
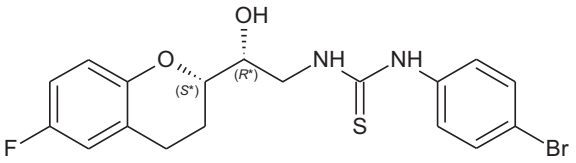
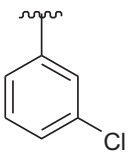
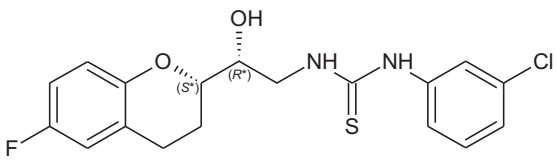
The structures of the synthesized compounds (**1a–j**) were characterized and confirmed their structures using by FT-IR, ^1H, ^{13}C-NMR and HRMS data. For structure elucidation, 1-(4-bromophenyl)-3-[(2*R**)-2-[(2*S**)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]urea (**1b**) was selected and discussed.

The characteristic absorption bands in the region of 3406, 3312, 1675, 1535, and 1017 cm^{-1} of IR spectra are mainly attributed due to the presence of –OH, –NH, C = O, C = C, and C–O functionalities respectively. In ^1H NMR spectra, the chemical shift value in the region of δ_H 8.77 as singlet indicated the presence of –NH proton attached to urea functionality. The chemical shift value at δ_H 5.35 as a broad singlet indicated the presence of –OH proton, Moreover, the aromatic protons based on the structural orientation, resonated in the range of δ_H 6.75–7.39. Chemical shift value δ_H 1.67, 2.10, 2.74, 3.06, 3.51 and 3.80 multiplets confirmed presence the eight aliphatic protons. The signal δ_C 155.16 in 13C NMR spectra has attributed the carbon attached to a urea carbonyl group. The doublet peaks at δ_C 157.04 and 154.70 with a coupling constant 234 Hz confirmed the presence of the –CF group. Chemical shifts in the region of δ_C 22.33–77.06 are correlated with five aliphatic carbons and other aromatic carbons are observed in the range of δ_C 112.12–150.53. The mass value found in HRMS m/z 409.0540 in positive mode was evident to in the structural characterization of compound **1b**.

Antibacterial activity

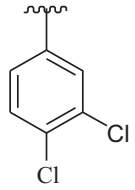
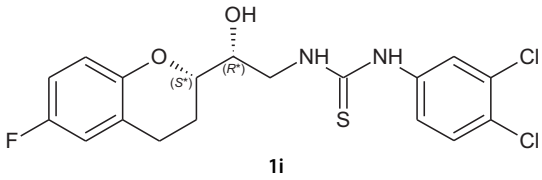
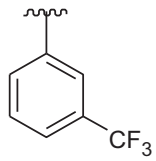
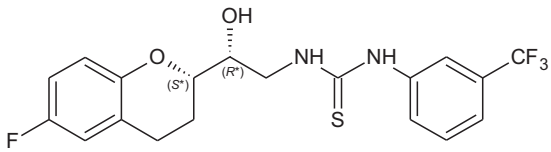
The newly synthesized urea/thiourea derivatives (**1a–j**) were screened for their antibacterial activity against both Gram + Ve bacterial strains, *Staphylococcus aureus* (ATCC-19433), *Bacillus cereus* (ATCC-11778) and Gram –Ve bacterial strains, *Acinetobacter baumannii* (ATCC-19606),

Table 5. Synthesis of 3-[(2*R**)-2-[(2*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl]-2-hydroxyethyl]-urea/thiourea derivatives (**1a–j**).[a]

Entry	Compound 5 R	X	Time (h)	Product	Yield[b] (%)
1	 **5a**	O	5	 **1a**	87
2	 **5b**	O	4	 **1b**	82
3	 **5c**	O	6	 **1c**	75
4	 **5d**	O	6	 **1d**	79
5	 **5e**	O	5	 **1e**	70
6	 **5f**	S	5	 **1f**	81
7	 **5g**	S	4	 **1g**	79
8	 **5h**	S	5	 **1h**	82

(*continued*)

Table 5. Continued.

Entry	Compound 5 R	X	Time (h)	Product	Yield[b] (%)
9	 **5i**	S	7	 **1i**	75
10	 **5j**	S	6	 **1j**	72

[a]**Reaction conditions:** Compound **4** (10.0 mmol), isocyanate (**5a–e**)/isothiocyanate (**5f–j**) (12.0 mmol), Et_3N (12.0 mmol) in THF (6 vol) at 60–65 °C.

Escherichia coli (ATCC-25922), and Pseudomonas aeruginosa (ATCC-27853) using agar disc diffusion method[26,27] at two different concentrations 50 μg/mL and 100 μg/mL. The antibacterial activity of DMSO against the test microorganisms was investigated and was found to be nil. Most of the tested compounds (**1a–j**) exhibited promising activity against *S. aureus*, *P. aeruginosa*, *K. pneumonia*, *A. baumannii*, and *E. coli*.

It was found that the urea-based compounds with 4-fluorophenyl (**1a**) and 2,4-difluorophenyl (**1d**) substitution exhibited excellent antibacterial activity against all the tested bacterial strains. The same other urea-based compounds, for example, compound **1b**, **1c**, and **1e** showed low activity as shown in Tables S1 and S2 (Supplemental Materials).

Interestingly, the thiourea-based compound with 4-fluorophenyl (**1f**) substitution exhibited moderate antibacterial activity against all the tested bacterial strains. Interestingly, the other thiourea based compounds **1g**, **1h**, **1i,** and **1j** with –Cl, –Br, and $-CF_3$ substitution exhibited very low activity against all the tested bacterial strains.

The antibacterial activity studies revealed that the urea-based fluoro substituted (*S**)-2-amino-1-((*R**)-6-fluoro chroman-2-yl)ethanol derivatives (**1a** and **1d**) showed excellent antibacterial activity which is comparable with standard ciprofloxacin drug as presented in Figure S1 (Supplemental Materials).

Antifungal activity

The synthesized compounds (**1a–j**) were tested to evaluate their antifungal activity against various fungal strains, *Aspergillus niger* (MTCC-1881), *Fusarium oxysporum* (MTCC-1755) and *Aspergillus foetidus* (NCIM-505) using two-fold dilution method[28] at two different concentrations of 50 μg/mL and 100 μg/mL. Among the tested compounds, the thiourea based compound (**1h**) with chloro substitution and the compound (**1j**) with trifluoromethyl substitution on phenyl ring at meta position exhibited excellent antifungal activity against *A. niger*, *F. oxysporum*, and *A. foetidus*. All other compounds displayed inferior activity as shown in Table S3 (Supplemental Materials) and Figure S2 (Supplemental Materials).

The structure-activity relationship (SAR) studies of the synthesized compounds revealed that the presence of electron withdrawing group, for example, fluoro substitution on phenyl ring (**1a, 1d**) of urea-based (*S**)-2-amino-1-((*R**)-6-fluorochroman-2-yl)ethanol derivatives exhibited excellent antibacterial activity. Interestingly, the compounds with –Cl (**1h**) and trifluoromethyl (**1j**) substitution on phenyl ring at meta position displayed good antifungal activity.

The minimum inhibitory concentration of lead compounds (**1a**, **1d, 1h**, and **1j**) was reported in Table S4 (Supplemental Materials) and Figure S3 (Supplemental Materials).

Experimental

Materials and methods

The solvents and reagents were obtained from commercial sources and were used without any purification. Nuclear magnetic resonance (NMR) spectra of the synthesized compounds were recorded on Ascend Bruker 400 (Bruker, Fallanden, Switzerland) instrument and operated at 400 MHz for ^{1}H NMR and 100 MHz for 13C NMR using $CDCl_3$, DMSO–d_6 solvents and tetramethylsilane (TMS) as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), qd (quartet of doublets), t (triplet), and m (multiplet) as well as brs (broad singlet). The ^{1}H chemical shift values were reported on δ scale in ppm relative to TMS ($\delta = 0.00$ ppm) and the ^{13}C chemical shift values were reported relative to DMSO–d_6 ($\delta = 39.5$ ppm). The ESI/MS experiments were performed on a Velos Pro Ion Trap mass spectrometer from Thermo Scientific San Jose, CA, USA) and HRMS spectra were recorded on Q-Exactive benchtop Orbitrap mass spectrometer (Thermo Scientific). The Supplemental Materials contains characterization data for the previously reported compounds, in addition to selected ^{1}H and ^{13}C NMR and High Resolution Mass spectra for products 1 (Figures S4–S58).

Disc diffusion method for antimicrobial activity

The bacteria were cultured with 0.5 mL containing 1×10^7 CFU/mL in nutrient broth spread on nutrient agar medium in agar plates. The nutrient agar medium was prepared and sterilized in an autoclave at 120 °C for 15–20 min and then stored at room temperature, 20 mL of agar medium was added to each agar plates and allowed for solidification. The bacterial lawn culture was made using a sterile cotton swab for uniform growth. Ciprofloxacin was used as standard and soluble in DMSO, whereas, DMSO was used as a solvent for test compounds at a concentration of 1.0 mg/mL. The DMSO was used as a negative control. To test the activity of compounds, wells were made in the media with the help of a metallic border with centers at least 6.0 mm. The tested solutions were introduced aseptically through micropipette into the wells in the agar plates and incubated at 37 °C for 24 h, and the process was repeated thrice. The inhibition zone of microbial growth was appeared at around the wells in each agar plate. The bacterial growth of the tested compounds was determined by measuring the diameter of zone inhibition (mm) around the wells. The activity of each compound was compared with standard antibiotic ciprofloxacin.

The sabouraud dextrose agar (Himedia) was used as a medium for the test of fungal activity, and the fungi strains were incubated for three days at 30 °C. The culture was spread on Sabouraud dextrose agar using sterile glass spreader for the uniform distribution of inoculums. The incubated Fungi spore suspension contain approximately $1–2 \times 10^6$ CFU/mL population. After solidification of media, respective fungal spore suspensions were transferred to well plates. The 1 mg of the test compounds were dissolved in 1 mL of DMSO. The DMSO was used as a negative control. The wells were made in the media with the help of a sterile metallic borer with centers at least 6.0 mm. Prepared tested solutions were introduced into the wells and immediately incubated at 30 °C for 72 h. After the incubation time, antifungal activity was evaluated by measuring the diameter of zone inhibition (mm) around the wells. The activity of each compound was compared with fluconazole as a standard.

Separation of 2a from compound 2 by column chromatography

The diastereomeric mixture (*R**, *S** and *R**, *R**) of compound **2** was separated by using column chromatography with silica gel (eluent: n-hexane followed by 2–5% ethyl acetate in n-hexane) to obtained enantiomeric mixture (*R**, *S**) of compound **2a.** The enantiomeric mixture (*R**, S*) of compound **2a** was eluted first. The fraction was collected and the solvent was evaporated to get compound **2a**.

Synthesis (*R)-2-(benzylamino)-1-((*S**)-6-fluoro-3,4-dihydro-2*H*-chromen-2-yl)ethanol (3).** In a three–neck round bottom flask, a solution of benzylamine (44.17 g, 0.412 mol) in isopropyl alcohol (40 mL) was taken at 20–30 °C. The temperature of the reaction mixture was heated to 80–85 °C. At this temperature, A solution of (*S**)-6-fluoro-2-((*R**)-oxiran-2-yl)chroman **2a** (10 g, 0.0514 mol) in isopropyl alcohol 10 mL was added dropwise over 50–60 min. and stirred for 4 h. The reaction progress was monitored by TLC, upon completion of the reaction, the mass was cooled to 20–30 °C and stirred at the same temperature for 3 h. The solid was filtered, washed with IPA (10 mL), and vacuum-pump dried for 30 min. The compound was dried in a hot air oven at 50 °C for 6 h, dry weight: 13.5 g, yield: 87.0%.

Synthesis of 3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxy ethyl]-urea/thiourea (general method)

A mixture of (*S**)-2-Amino-1-((*R**)-6-fluorochroman-2-yl)ethanol **4** and TEA in THF (20 mL) was taken in a three-neck round bottom flask at 20–30 °C. The isocyanate **5a–j** was added to the reaction mixture at 20–30 °C and stirred for 10 min. The temperature of the reaction mass was raised to 50–60 °C and stirred at the same temperature for 4–7 h. After completion of the reaction on TLC, the reaction mass was cooled to 20–30 °C. The solvent was evaporated under vacuum at below 50 °C, to the crude residue, diisopropyl ether (36 mL) was added and kept under stirring for 30 minutes. The solid was filtered and washed with diisopropyl ether (12 mL) The obtained solid was dried under vacuum 50–55 °C for 4 h.

3-[(2R*)-2-[(2S*)-6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]-1-(4-fluorophenyl)urea (1a)

Yield: 86.5%, White crystalline solid, m.p.: 187.9–188.3 °C. IR (KBr, υ, cm^{-1}): 3360, 3253, 1674, 1614, 1573, 1508, 1263, 1222, 1056, 835. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (*J*, Hz):1.64–1.74 (1H, m, H-3a); 2.09–2.13 (1H, m, H-3b); 2.74–2.78 (2H, m, H-4a, 4b); 3.04–3.1 (1H, m, H-13a); 3.51–3.62 (2H, m, H-13b, H-2); 3.80–3.84 (1H, m, H-11); 5.34 (1H, d, $J = 5.6$, −OH); 6.18 (1H, t, $J = 4.8$, H-14, −NH); 6.75 (1H, dd, $J = 4.8$, 4.8H-7); 6.87–6.93 (2H, m, H-8, 10); 7.04 (2H, t, $J = 8.0$, H-19, 21); 7.35–7.39 (2H, m, H-18, 22); 8.65 (1H, s, H-16, -NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.33 (C-4); 23.85 (C-3); 42.22 (C-13); 70.93 (C-11); 77.09 (C-2); 113.75–113.52 (d, $J = 22.0$, C-8); 115.10 (d, $J = 17.0$, C-19, 21); 115.32, (d, $J = 17.0$, C-21); 117.39 (d, $J = 8.0$, C-10); 119.0 (d, $J = 7.0$, C-22); 123.83 (d, $J = 7.0$, C-5); 136.90 (d, $J = 2.0$, C-17); 150.55 (d, $J = 2.0$, C-6); 155.66 (C-15),157.06,154.72 (d, $J = 234.0$, C-9), 158.01, 155.44 (d, $J = 257.0$, C-20); 155.66 (C-9). HRMS (FAB) Calc: $C_{18}H_{18}F_2N_2O_3$: 348.1285; Found m/z 349.1354 $[M+H]^+$ and 371.1171 $[M+Na]^+$.

1-(4-Bromophenyl)-3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]urea (1b)

Yield: 82%, White crystalline solid, m.p.: 192.6–194.1 °C. IR (KBr, υ, cm^{-1}): 3406, 3312, 1675, 1594, 1535, 1492, 1212, 1017, 835. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (*J*, Hz): 1.67–1.72 (1H, m, H-3a); 2.10–2.13 (1H, m, H-3b); 2.74-2.78 (2H, m, H-4a, 4b); 3.06–3.11 (1H, m, H-13a); 3.51–3.62 (2H, m, H-13b, 2; 3.80–3.85 (1H, m, H-11); 5.35 (1H, d,

$J = 5.6$, OH); 6.23–6.26 (1H, t, $J = 4.8$, H-14, −NH); 6.75 (1H, dd, H-7); 6.86 − 6.93 (2H, m, H-8,10); 7.34 − 7.39 (4H, m, H-18, 19, 21, 22); 8.77 (1H, s, H-16, −NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (J, Hz): 22.33 (C-4); 23.82 (C-3); 42.17 (C-13); 70.84 (C-11); 77.06 (C-2); 112.12 (C-20); 113.61 (d, $J = 23.0$, C-8); 115.28 (d, $J = 22.0$, C-10); 117.38 (d, $J = 8.0$, C-7); 119.40, (C-18,22); 123.81 (d, $J = 7.0$, C-5); 131.37, (C-19,21); 139.94 (C-17); 150.53 (C-6); 157.04,154.70 (d, $J = 234.0$, C-9); 155.16 (C-15). HRMS (FAB) Calc: $C_{18}H_{18}BrFN_2O_3$: 408.0485; Found m/z 409.0540 $[M + H]^+$.

1-(3-Chlorophenyl)-3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl] urea (1c)

Yield: 75%, White crystalline solid, m.p.: 175.5–175.2 °C. IR (KBr, υ, cm^{-1}): 3358, 3290, 1678, 1595, 1562, 1213, 1082, 856, 684. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (J, Hz): 1.67–1.72 (1H, m, H-3a); 2.10–2.14 (1H, m, H-3b); 2.75–2.78 (2H, m, H-4a, 4b); 3.06–3.12 (1H, m, H-13a); 3.34–3.62 (2H, m, H-2,13b); 3.81–3.85 (1H, m, H-11); 5.35 (1H, d, $J = 5.6$, −OH); 6.27–6.30 (1H, t, $J = 5.2$, H-14, −NH); 6.74–6.76 (1H, m, H-20); 6.78–6.93 (3H, m, H-7, 10, 21); 7.15 (1H, d, $J = 8.0$, H-8); 7.22 (1H, t, $J = 8.0$ Hz, H-22); 7.67 (1H, s, H-18); 8.85 (1H, s, H-16, −NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (J, Hz): 22.32 (C-4); 23.81(C-3); 42.15 (C-13); 70.79 (C-11); 77.04 (C-2); 113.60 (d, $J = 23.0$, C-8); 115.26 (d, $J = 22.0$, C-10); 115.83 (C-22); 116.82 (C-18); 117.36 (d, $J = 8.0$, C-7); 120.54 (C-20); 123.79 (d, $J = 8.0$, C-5); 130.24 (C-21); 133.12 (C-19); 142.05 (C-17); 150.40 (d, $J = 2.0$, C-6); 155.07 (C-15); 157.03,154.70 (d, $J = 233.0$, C-9). HRMS (FAB) Calc: $C_{18}H_{18}ClF_2N_2O_3$: 364.0990; Found m/z 365.10567$[M + H]^+$ and 387.08740 $[M + Na]^+$.

1-(2,4-Difluorophenyl)-3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]urea (1d)

Yield: 79%, White crystalline solid, m.p.: 184.2–185.9 °C. IR (KBr, υ, cm^{-1}): 3356, 1658, 1573, 1494, 1219, 962, 854. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (J, Hz): 1.69–1.70 (1H, m, H-3a); 2.11-2.14 (1H, m, H-3b); 2.75–2.78 (2H, m, H-4a, 4b); 3.07–3.10 (1H, m, H-13a); 3.55–3.60 (2H, m, H-2,13b); 3.81–3.84 (1H, m, H-11); 5.35 (d, $J = 5.6$, 1H,-OH); 6.71–6,77 (2H, m, H-14, -NH, 19); 6.86–6.93 (2H, m, H-7,21); 6.95–6.99 (1H, m, H-10); 7.19–7.25 (1H, m, H-8); 8.05–8.11 (1H, m, H-22); 8.44 (1H, s, H-16, -NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (J, Hz): 22.35 (C-4); 23.80(C-3); 42.20 (C-13); 70.83 (C-11); 76.98 (C-2); 103.48 (dd, $J = 24.0$, 24.0, C-19); 110.76 (dd, $J = 18.0$, 3.0, C-21); 113.60 (d, $J = 22.0$, C-8); 115.26 (d, $J = 22.0$, C-10); 117.36 (d, $J = 8.0$, C-7); 121.20 (d, $J = 6.0$, C-22); 123.79 (d, $J = 7.0$, C-5); 124.94 (dd, $J = 8.0$, 3.0, C-17); 150.51 (C-6); 155.11 (C-15); 157.03,154.69 (d, $J = 234.0$, C-9); 152.74, 150.31, 152.61, 150.19 (dd, $J = 243.0$, 12, C-18); 157.32, 154.93, 157.20, 154.82 (dd, $J = 239.0$, 12.0, C-20). HRMS (FAB) Calc: $C_{18}H_{18}F_3N_2O_3$: 366.1191; Found m/z 367.1221 $[M + H]^+$.

3-[(2R*)-2-[(2S*)-6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]-1-(4-methylcyclohexyl) urea (1e)

Yield: 70%, White crystalline solid, m.p.: 170.4–171.1 °C. IR (KBr, υ, cm^{-1}): 3354, 2926, 1614, 1577, 1492, 1215. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (J, Hz): 0.84 (3H d, $J = 6.0$, H-23); 0.91–1.04 (4H, m, H-19, 21); 1.26 (1H, m, H-20); 1.60–1.67 (3H, m, 18, 3a); 1.75–1.78 (2H, m, H-22); 2.06 (1H, m, H-3b); 2.72–2.73 (2H, m, H-4a, 4b); 2.96–2.98 (1H, m, H-13a); 3.22–3.24 (1H, m, H-17); 3.40–3.41 (1H, m, 13b); 3.50–3.51 (1H, m, H-2); 3.75–3.78 (1H, m, H-11); 5.33 (1H, d, $J = 5.2$, OH); 5.79–5.82 (1H, m, H-14, −NH), 5.89–5.91(1H, d, $J = 8.0$, H-16) 6.71–6.75 (1H, m, H-7), 6.86–6.92 (2H, m, H-8,10). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (J, Hz): 22.16 (C-23), 23.81(C-4), 31.49 (C-3), 33.28 (C-19,21), 33.69 (C-18, 22), 42.50 (C-13), 48.25 (C-17), 71.50 (C-11), 77.01 (C-2), 113.55 (d, $J = 23.0$, C-8), 115.24 (d, $J = 22.0$, C-10), 117.32 (d, $J = 8.0$, C-7), 123.80 (d, $J = 8.0$, C-5), 150.57 (C-6), 156.98,154.64 (d, $J = 234.0$, C-9), 157.91 (C-15). HRMS (FAB) Calc: $C_{19}H_{27}FN_2O_3$: 350.2006; Found m/z 351.20725 $[M + H]^+$ and 373.18885 $[M + Na]^+$.

3-[(2R*)-2-[(2S*)-6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]-1-(4-fluorophenyl)thiourea (1f)

Yield: 81%, White crystalline solid, m.p.: 139.5–139.8 °C. IR (KBr, υ, cm^{-1}): 3323, 3226, 3055, 1546, 1510, 1492, 1219, 1143, 1058, 835, 677. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (J, Hz): 1.66–1.76 (1H, m, H-3a); 2.09–2.12 (1H, m, H-3b); 2.76-2.83 (2H, m, H-4a, 4b); 3.33–3.45 (1H, m, H-2); 3.77–3.88 (2H, m, H-13a, 13b); 3.95 (1H, broad s, H-11); 5.39 (1H, s, OH); 6.71–6.74 (1H, m, H-7); 6.85–6,93 (2H, m, H-8, 10); 7.15 (2H, t, $J = 8.8$, H-19, 21); 7.43-7.46 (2H, m, H-18, 22); 7.66 (1H, brs s, H-14, NH), 9.65 (1H, s, H-16, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (J, Hz): 22.18 (C-4); 23.82 (C-3); 46.93 (C-13); 70.02 (C-11); 77.31 (C-2); 113.60 (d, $J = 23.0$, C-8); 115.28 (d, $J = 22.0$, C-10); 115.14 (d, $J = 22.0$, C-19,21); 117.39 (d, $J = 8.0$, C-7); 123.82 (C-5); 125.36 (C-18, 22); 135.65 (C-17); 150.53 (C-6); 157.05, 154.72 (d, $J = 233.0$, C-9); 160.07, 157.67 (d, $J = 240.0$, C-20); 180.93 (C-15). HRMS (FAB) Calc: $C_{18}H_{18}F_2N_2O_2S$:364.1057; Found m/z 365.1076 $[M + H]^+$.

1-(4-Bromophenyl)-3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]thiourea (1g)

Yield: 79%, White crystalline solid, m.p.: 140.1–141.7 °C. IR (KBr, υ, cm^{-1}): 3223, 3012, 1629, 1591, 1562, 1492, 1211, 777. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (J, Hz):1.67–1.77 (1H, m, H-3a); 2.10–2.13 (1H, m, H-3b); 2.76–2.83 (2H, brs, H-4a, 4b); 3.42–3.45 (1H, m, H-2); 3.81–3.88 (2H, m, H-13a,13b); 4.036 (1H, brs, H-11); 5.43 (1H,-s, OH); 6.72–6.75 (1H, m, H-7); 6.86–6,93 (2H, m, H-8,10); 7.25–7.26 (2H, s, H-19, 21); 7.38 (1H, brs, H-14, -NH); 7.87(brs, 1H, H-18); 7.93 (brs, 1H, H-22); 9.83 (1H, s, H-16, −NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (J, Hz): 22.21 (C-4); 23.82 (C-3); 46.83 (C-13); 69.86 (C-11); 77.26 (C-2); 113.61 (d, $J = 23.0$, C-8); 115.27 (d, $J = 23.0$, C-

10); 117.40 (d, $J = 8.0$, C-7); 121.03 (C-20); 123.80 (d, $J = 7.0$, C-5); 124.60 (C-18); 126.28 (C-22); 130.38 (C-19,21); 141.28 (C-17); 150.50 (C-6); 154.72; 157.06,154.72 (d, $J = 234.0$, C-9); 180.44 (C-15). HRMS (FAB) Calc: $C_{18}H_{18}BrFN_2O_2S$:424.0256; Found m/z 425.03248 $[M + H]^+$.

1-(3-Chlorophenyl)-3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl] thiourea (1h)

Yield: 82%, White crystalline solid, m.p.: 156.6–157.0 °C. IR (KBr, υ, cm^{-1}): 3327, 3282, 1552, 1496, 1317, 1170, 1058, 933, 813, 700. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (*J*, Hz): 1.67–1.77 (1H, m, H-3a); 2.10–2.13 (1H, m, H-3b); 2.73–2.84 (2H, m, H-4a, 4b); 3.41–3.47 (1H, m, H-2); 3.78–3.81 (1H, m, H-13a); 3.82–3.9 (1H, m, H-113b); 3.95 (1H, brs, H-11); 5.43 (1H, s, OH); 6.72–6.86 (1H, m, H-20); 6.86–6,94 (2H, m, H-7,10); 7.11–7.14 (1H, d, 21); 7.30–7.37 (2H, m, H-8, 18); 7.81(1H, brs, H-22); 7.87 (1H, brs, −NH); 9.83 (1H, s, H-16, −NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.22 (C-4); 23.81 (C-3); 46.83 (C-13); 69.87 (C-11); 77.25 (C-2); 1113.61 (d, $J = 22.0$, C-8); 115.27 (d, $J = 22.0$, C-10); 117.40 (d, $J = 8.0$, C-7); 120.71 (C-21); 121.73 (C-18); 123.39 (C-20); 123.80 (d, $J = 7.0$, C-5); 130.09 (C-22); 132.59 (C-19); 141.14 (C-17); 150.50 (C-6); 157.06, 154.72 (d, $J = 234.0$, C-9); 180.45 (C-15). HRMS (FAB) Calc: $C_{18}H_{18}ClFN_2O_2S$: 380.0762; Found m/z 381.08315 $[M + H]^+$ and 403.06486 $[M + Na]^+$.

1-(3,4-Dichlorophenyl)-3-[(2R*)-2-[(2S*)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]thiourea (1i)

Yield: 75%, White crystalline solid, m.p.: 114.9–115.4 °C. IR (KBr, υ, cm^{-1}): 3271, 1593, 1492, 1215, 1138, 1029, 929, 810. ^{1}H NMR (400 MHz; DMSO-d_6), δ, ppm (*J*, Hz): 1.60–1.77 (1H, m, H-3a); 2.10–2.18 (1H, m, H-3b); 2.77 (2H, brs, H-4a, 4b); 3.42–3.45 (1H, m, H-2); 3.81-3.86 (1H, m, H-13a); 3.88-3.89 (1H, m, H-113b); 3.95 (1H, brs, H-11); 5.43 (1H, s, OH); 6.73-6.76 (1H, m, H-7); 6.87–6,93 (2H, m, H-10, 22); 7.42 (1H, d, $J = 8.0$, H-8); 7.54 (1H, d, $J = 8.0$, H-21); 7.95 (1H, brs, H-18); 8.03 (1H, brs, −NH); 9.83 (1H, s, H-16, −NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.22 (C-4); 23.82 (C-3); 46.84 (C-13); 69.83 (C-11); 77.23 (C-2); 113.62 (d, $J = 23.0$, C-8); 115.29 (d, $J = 22.0$, C-10); 117.41 (d, $J = 8.0$, C-7); 122.25 (C-22); 123.39 (C-18); 123.80 (d, $J = 7.0$, C-5); 125.16 (C-21), 130.21, (C-20); 130.47 (C-19), 139.86 (C-17), 150.50 (C-6); 157.07,154.73 (d, $J = 234.0$, C-9); 180.43 (C-15). HRMS (FAB) Calc: $C_{18}H_{18}Cl_2FN_2O_2S$: 414.0372; Found m/z 415.0399 $[M + H]^+$.

3-[(2R*)-2-[(2S*)-6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2-hydroxyethyl]-1-[3-(trifluoromethyl) phenyl]thiourea (1j)

Yield: 72%, White crystalline solid, m.p.: 134.8–135.3 °C. IR(KBr, υ, cm^{-1}): 3223 1631, 1593, 1568, 1492, 1211, 779. ^{1}H NMR spectrum, (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 1.68-1.78 (1H, m, H-3a); 2.1 − 2.14 (1H, m, H-3b); 2.78-2.84 (2H, m, H-4a, 4b); 3.43 − 3.49 (1H, m, H-2); 3.73 − 3.82 (1H, m, H-13a); 3.87 − 3.91 (1H, m, H-13b); 3.97 (1H, brs, H-11); 5.45 (1H, s, −OH), 6.73 − 6.76 (1H, m, H-7); 6.86 − 6,94 (2H, m, H-8,10); 7.41 (d, $J = 8.0$, 1H, H-20); 77.53 (1H, t, $J = 7.6$, H-21); 7.70 (1H, d, $J = 8.0$, H-18); 7.94 (1H, brs, H-18); 8.10 (1H, brs, H-14, -NH); 9.65 (1H, s, H-16, -NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.24 (C-4); 23.83 (C-3); 46.81 (C-13); 69.87 (C-11); 77.24 (C-2); 113.75–113.52 (d, $J = 23.0$, C-8); 115.30 (d, $J = 22.0$, C-10); 117.42 (d, $J = 8.0$, C-7); 118.37 (C-20); 119.93 (C-18); 125.46, 122.75, (d, $J = 271.0$, C-9); 123.81 (d, $J = 7.0$, C-5); 125.86 (C-21); 129.15,128.17 (q, $J = 38.0$, 36.0, C-23); 129.61 (22); 140.57 (C-17); 150.52-150.51 (d, $J = 1.2$, C-6); 157.08, 154.74 (d, $J = 234.0$, C-9); 180.64 (C-15). HRMS (FAB) Calc: $C_{19}H_{18}F_4N_2O_2S$: 414.1025; Found m/z 415.10931 $[M + H]^+$ and 437.09115 $[M + Na]^+$.

Conclusion

We have synthesized a new series of 3-[(2*R**)-2-[(2*S**)-6-fluoro-3,4-dihydro-2*H*-1-chromen-2-yl]-2-hydroxyethyl]-urea/thiourea derivatives (**1a–j**) starting from 6-fluoro-2-(oxiran-2-yl)chroman (**2**) in high yields (80–90%). The structures of the synthesized compounds were confirmed by FT-IR, NMR (^{1}H, 13C) and HRMS data. Among the synthesized molecules, the urea-based fluoro substituted compounds (**1a, 1d**) showed outstanding antibacterial activity against both Gram + Ve, Gram –Ve bacterial strains and the thiourea based –Cl, $-CF_3$ substituted compounds **1h** and **1j** showed excellent antifungal activity against fungal strains. The present work helped in addition to a new library of biologically active molecules to the heterocyclic chemistry domain. The identified promising lead compounds (**1a**, **1d**, and **1h**) are useful for further studies in the development of new antimicrobial agents in drug discovery and development programs. The screening of anticancer activities of the present molecules is under progress.

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Disclosure statement

The author declared no conflict of interest.

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