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Synthesis and pharmacological evaluation of 6-hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene)chroman-2-carbohydrazide derivatives as antimicrobial agents

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ABSTRACT

The synthesis and antimicrobial activity of 7 new 6-hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene) chroman-2-carbohydrazide derivatives (4-10) were reported against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Salmonella Typhi, Vibrio cholera, Candida albicans and Aspergillus niger. Some of the tested compounds were showing activity against several of the microorganisms. In particular, compounds 6 and 7 were found to be of potent activity against bacterial strain, Escherichia coli *(15 mm) and compound 4 and 5 against fungal strain, Candida albicans (16 mm) at a concentration of 100 µg/ml. The highest MIC of 12.5 µg/ml was shown by compound 7 against E. coli.*

Keywords: Agar well diffusion method, Isatin, Serial tube dilution method.

INTRODUCTION

There is a growing incidence of drug resistance to infectious diseases caused by bacteria and fungi, which represents a serious medical problem. Bacteria and fungi release a variety of toxins or destructive enzymes which can damage the tissue. Therefore, there is an urgent need to develop new antimicrobial agents to treat these infectious diseases. The heterocyclic compounds containing oxygen are now a day's consider as very much interesting due of their physico-chemical properties relevant as far as design of new drugs is concerned. The published data showed that chroman is one of the most effective, newly emerging class of heterocyclic molecules, associated with a broad range of biological activities as anti-breast cancer agents [1], insulin release process inhibitors [2], neuroprotective [3], antioxidant [4], etc.

Many chroman derivatives show antimicrobial activities [5-8] (Frolova *et al*., 2011; Kidwai *et al*., 2005; Tahtaou *et al*., 2010; Lago *et al*., 2004). In quest for biologically more potent antimicrobial compounds, we envisioned synthesizing a new series of 6-Hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene)chroman-2-carbohydrazide derivatives (4-10) by reacting 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide with different substituted isatins and studied their antimicrobial activity.

EXPERIMENTAL SECTION

All commercial chemicals were purchased from Sigma-Aldrich and Spectrochem. Thin layer chromatography was performed on E Merck silica gel GF-254 precoated plates (Merck, Darmstadt, Germany) and the identification was done with UV light and spraying with charring solution followed by heating. Melting points were determined in open glass capillaries and are uncorrected. NMR spectra were recorded on JEOL ECX-500 spectrometer in DMSO-d_6 and $CDCl_3$ at 400 and 500 MHz for ^{1}H NMR. The chemical shifts were recorded in (δ,ppm) relative to TMS as an internal standard. The mass spectra were recorded with a Waters-Q-Tof Premier-HAB213 spectrometer and Microscopic II triple Quadrupole mass spectrometer using EI and the *m/z* values are indicated in Dalton. The IR spectra (KBr) were recorded on a Bruker FT/IR Vector 22 spectrophotometer.

Synthesis of 6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid methyl ester (Trolox, 1): A 100 ml three-neck flask was equipped with heating mantle, reflux condenser, and stirrer and charged with 15.9 ml (0.150 mol) of methyl methacrylate, 0.9 g (30 mmol) of paraformaldehyde, 0.48 g (3.6 mmol) of dibutylamine and 4.5 ml of acetic acid. This mixture was stirred at room temperature and 4.56 g (30 mmol) of trimethylhydroquinone were added. This mixture was stirred under reflux for 20 h. The resulting dark mixture (solid was present) was cooled to 0-5^{0}C and filtered (methanol wash) to give 3.07 g (39% yield) light tan solid. This material was recrystallized from methanol [the hot solution being filtered to remove traces of insoluble poly(methyl methactylate)] gave white prisms.

Synthesis of 6-Substituted-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (2): Compound 1 (1 mmol) and 80% hydrazine hydrate (5 mmol) in 10 ml ethanol were refluxed at 80 ^{0}C for 10 h. While the reaction completed, the ethanol was evaporated. The separated solid was filtered, washed with water and dried to obtain slight white solid. Yeild: 60%; ^{1}HNMR (500MHz, DMSO-d^6, ppm): 8.47 (s,1H,OH), 7.43 (s,1H,-NH), 4.19 (s,2H,NH_2), 2.52-2.49 (m,1H), 2.40-2.37 (m,1H), 2.20-2.15 (m,1H), 2.04 (s,3H), 2.02 (s,3H), 1.94 (s,3H), 1.68-1.63 (m,1H), 1.35 (s,3H).

General procedure for the synthesis of 6-Hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene)chroman-2-carbohydrazide derivatives (4-10): The compounds were prepared through condensation reaction between **2** (1 mmol) and **3** (1 mmol) in 10 ml acetic acid under reflux at 120˚C for 4-6 h. Then 20 ml distilled water was added into the reaction media. The compounds were filtered and recrystallized in ethanol.

6-hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene)-3,4-dihydro-2H-chromene-2-carbohydrazide (4): Yield: Yellow solid (74%); MP: 240˚C; IR (KBr, ν, cm^{-1}): 3426 (NH), 3227 (OH), 1694 (CO); ^{1}H NMR (500MHz, DMSO-d^6, ppm): 11.28 (s,1H,-NH), 7.54 (s,1H,OH), 7.51-7.49 (d,1H), 7.42-7.38 (t,1H), 7.10-7.05 (m,2H), 3.33-3.27 (m,1H), 2.59-2.54 (m,1H), 2.28-2.25 (m,1H), 2.21 (s,3H), 2.05 (s,3H), 1.96 (s,3H), 1.86-1.81 (m,1H), 1.47 (s,3H); HR-MS: 394.1700 $(M+H)^+$,calcd. 394.1766.

6-hydroxy-2,5,7,8-tetramethyl-N'-(1-methyl-2-oxoindolin-3-ylidene)-3,4-dihydro-2H-chromene-2-carbohydrazide (5): Yield: Yellow solid (72%), MP: 237˚C; IR (KBr, ν, cm-1): 3406 (NH), 3261 (OH), 1683 (CO); ^{1}H NMR (500MHz, DMSO-d^6, ppm): 7.54 (s,1H,OH), 7.51-7.49 (d,1H), 7.42-7.38 (t,1H), 7.10-7.05 (m,2H), 3.33-3.27 (m,1H), 3.13 (s,3H), 2.59-2.54 (m,1H), 2.28-2.25 (m,1H), 2.21 (s,3H), 2.05 (s,3H), 1.96 (s,3H), 1.86-1.81 (m,1H), 1.47 (s,3H); HR-MS: 408.1926 $(M+H)^+$, calcd. 408.4702.

N'-(5-chloro-2-oxoindolin-3-ylidene)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (6): Yield: Light Yellow solid (87%), MP: 255˚C; IR (KBr, ν, cm-1): 3598 (NH), 3151 (OH), 1680 (CO); ^{1}H NMR (500MHz, DMSO-d^6, ppm): 11.28 (s,1H,-NH), 7.53 (s,1H,OH), 7.45-7.44 (d,1H), 7.36-7.34 (dd,1H), 6.88-6.87 (d,1H), 3.43-3.37 (m,1H), 2.60-2.54 (m,1H), 2.29-2.24 (m,1H), 2.17 (s,3H), 2.03 (s,3H), 1.96 (s,3H), 1.86-1.80 (m,1H), 1.47 (s,3H); HR-MS: 450.1377 $(M+H)^+$, calcd. 450.1196.

N'-(5-bromo-2-oxoindolin-3-ylidene)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (7): Yield: Yellow solid (56%), MP: 260˚C; IR (KBr, ν, cm-1): 3594 (NH), 3149 (OH), 1680 (CO); ^{1}H NMR (500MHz, DMSO-d^6, ppm): 11.29 (s,1H,-NH), 7.55 (s,1H,OH), 7.53 (s,1H), 7.48-7.47 (d,1H), 6.83-6.82 (d,1H), 3.43-3.37 (m,1H), 2.60-2.54 (m,1H), 2.29-2.24 (m,1H), 2.17 (s,3H), 2.03 (s,3H), 1.96 (s,3H), 1.86-1.80 (m,1H), 1.47 (s,3H); HR-MS: 494.0690 $(M+Na)^+$, calcd. 494.0691.

N'-(6-chloro-2-oxoindolin-3-ylidene)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (8): Yield: Yellow solid (57%), MP: 290˚C; IR (KBr, ν, cm-1): 3443 (NH), 3141 (OH), 1678 (CO); ^{1}H NMR (500MHz, DMSO-d^6, ppm): 11.20 (s,1H,-NH), 7.54 (s,1H,OH), 7.30-7.28 (dd,1H), 7.18-7.14 (m,1H), 6.87-6.85 (dd,1H), 3.30-3.28 (m,1H), 2.60-2.54 (m,1H), 2.29-2.24 (m,1H), 2.17 (s,3H), 2.03 (s,3H), 1.96 (s,3H), 1.85-1.80 (m,1H), 1.47 (s,3H); HR-MS: 428.1372 $(M+H)^+$, calcd. 428.1377.

N'-(5-fluoro-2-oxoindolin-3-ylidene)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (9): Yield: Yellow solid (51%),MP: 290˚C; IR (KBr, ν, cm-1): 3566 (NH), 3206 (OH), 1686 (CO); ^{1}H NMR (500MHz, DMSO-d^6, ppm): 11.18 (s,1H,-NH), 7.52 (s,1H,OH), 7.30-7.28 (dd,1H), 7.18-7.14 (m,1H), 6.87-6.85 (dd,1H), 2.59-2.54 (m,1H), 2.50-2.42 (m,1H), 2.29-2.24 (m,1H), 2.18 (s,3H), 2.04 (s,3H), 1.96 (s,3H), 1.86-1.80 (m,1H), 1.47 (s,3H); HR-MS: 412.1681 $(M+H)^+$, calcd. 412.1672.

N'-(6-chloro-1-methyl-2-oxoindolin-3-ylidene)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (10): Yield: Yellow solid (59%), MP: 257˚C; ^{1}H NMR (500MHz, DMSO-d^6, ppm): 7.54 (s,1H,OH), 7.474-7.471 (d,1H), 7.46-7.44 (dd,1H), 7.11-7.10 (d,1H), 3.33-3.27 (m,1H), 3.12 (s,3H), 2.60-2.54 (m,1H), 2.29-2.24 (m,1H), 2.20 (s,3H), 2.04 (s,3H), 1.96 (s,3H), 1.87-1.81 (m,1H), 1.47 (s,3H); HR-MS: 442.1537 $(M+H)^+$, calcd. 442.1530.

Antimicrobial Activity

For the determination of antimicrobial activities Agar-well diffusion and Serial tube dilution methods were employed for the synthesized compounds [11].

Test microorganisms

All the tested bacterial strains (*Escherichia coli* MTCC 118, *Salmonella Typhi* MTCC 3216, *Bacillus subtilis* MTCC 3053, *Klebsiella pneumonia* MTCC 4031, *Pseudomonas aeruginosa* MTCC 4673, *Staphylococcus aureus* MTCC 3160 *and Vibrio cholera* MTCC 3906) and fungal strains (*Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 281) used in this study were obtained from the Department of Microbiology, Birla Institute of Technology, Mesra, Ranchi, India. Muller-Hinton Agar (MHA) and Sabouraud's Dextrose Agar (SDA) media were used for bacteria and fungi, respectively. Freshly prepared media were sterilized by autoclaving at 15 lb/psi pressure for 15 minutes. Bacterial and fungal cultures of test organisms were maintained at refrigerated conditions on Nutrient agar slants.

Antibacterial and antifungal screening by Agar well diffusion method

Seven compounds (4-10) were tested for *in vitro* antimicrobial activity. The synthesized compounds and standard drugs (Azithromycin and fluconazole) were dissolved in DMSO and were tested for antimicrobial activity at varying level of concentrations of 50 μg/ml and 100 μg/ml. Approximately 30 ml of agar media was poured into sterile Petri plates and transferred 0.5 ml of test microorganisms. The plates were allowed to dry. Wells were bored into the plates with a sterile cork borer (5.0 mm diameter). Each well received 0.l ml of the test compound and standard drug in the concentrations of 50 μg/ml and 100 μg/ml. These plates were then incubated at 37˚C for 24 h for bacterial strains and 48 h for fungal strains. After incubation, the resulting inhibition zone (IZ) was recorded. DMSO was used as a negative control and showed no antimicrobial activity.

Antibacterial and antifungal screening by Serial tube dilution method

The compounds which were found active in above antimicrobial screening by Agar well diffusion method, were again diluted to obtain 100, 50, 25, 12.5, 6, 25, and 3.125 μg /ml concentrations. DMSO was used as a vehicle to obtain the desired concentration of synthesized compounds and standard drugs. Approximately 10 ml of nutrient broth was poured into sterile test tubes and transferred 0.5 ml of test microorganisms. The tubes were then put for incubation at 37˚C for 24 h for bacterial strains and 48 h for fungal strains. The highest dilution (lowest concentration) preventing the appearance of turbidity was considered as MIC (μg/ml).

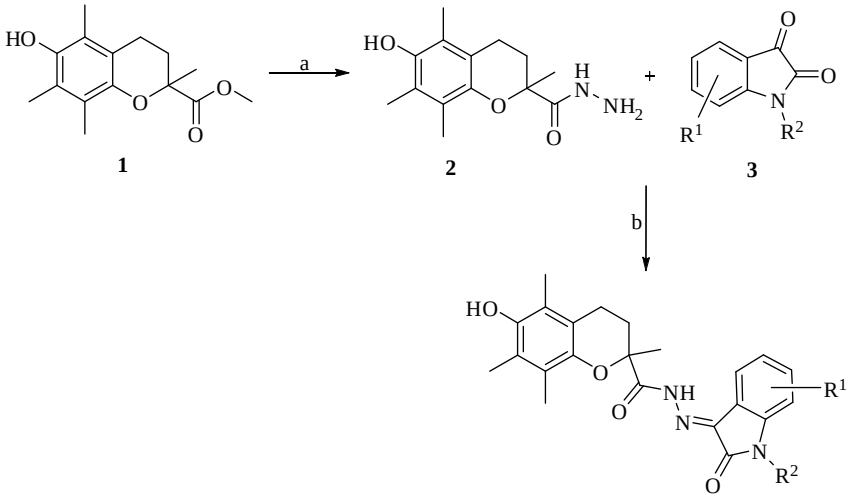
RESULTS AND DISCUSSION

Chemistry

6-Hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene)chroman-2-carbohydrazide derivatives (4-10) described in this study were prepared as depicted in Scheme 1. Trolox (1) was prepared by the reaction of methyl methacrylate, paraformaldehyde and dibutylamine in acetic acid [9]. The esteric carboxylate group of trolox undergo

nucleophilic attack by hydrazine molecule resulting in 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (2) [10]. The condensation between compound 2 and different substituted isatins resulted in target compounds (4-10). The properties of these newly synthesized compounds (4-10) were shown in Table 1.

The synthesized compounds were characterized by FT-IR, ^{1}H-NMR, Mass spectroscopy and melting point analysis. Compounds (4-10) were confirmed by its IR spectrum which showed the presence of characteristic strong absorption band at 1678-1694 of carbonyl group (-CO, strech) and a broad absorption band at 3141-3261 of hydroxy group (-OH, strech). In ^{1}H NMR, the amide group (-$CONH_2$) was observed as a singlet at δ 11.18-11.29 ppm. The presence of a hydroxy group (-OH) was confirmed by the sharp singlet at δ 7.53-7.55 ppm. The mass spectra showed $(M+H)^+$ and $(M+Na^+)^+$ (m/z) peaks respectively confirming their purity and molecular weight. The R_f value of all synthesized compounds was calculated in ethyl acetate (EtOAc) and hexane (40:60) and ranges between 0.4-0.7. The analytical data were fully consistent with the proposed structures.



Scheme 1. Synthetic pathway for compounds 4-10. (a) $NH_2NH_2.H_2O$, C_2H_5OH, reflux, 10 hrs (b) C_2H_5OH, CH_3COOH, reflux, 4-6 hrs

Table 1. Some properties of the compounds (4-10)

Compd	R^1	R^2	Time (hrs)	Yield (%)*	MP (˚C)	Mol. formula	Mol. weight	Rf
4	H	H	4	74	240	$C_{22}H_{23}N_3O_4$	393.44	0.7
5	H	CH_3	6	72	237	$C_{23}H_{25}N_3O_4$	407.46	0.7
6	5-Cl	H	6	87	255	$C_{22}H_{22}N_3O_4Cl$	427.88	0.6
7	5-Br	H	6	56	260	$C_{22}H_{22}N_3O_4Br$	472.33	0.4
8	6-Cl	H	5	57	290	$C_{22}H_{22}N_3O_4Cl$	427.88	0.5
9	5-F	H	4	51	290	$C_{22}H_{22}N_3O_4F$	411.43	0.4
10	5-Cl	CH_3	5	59	257	$C_{23}H_{24}N_3O_4Cl$	441.91	0.5

**Yield refers to pure products after recrystallization.*

Antimicrobial Activity

All synthesized compounds were preliminary evaluated for their *in vitro* antimicrobial activity by the Agar well diffusion and serial tube dilution method [11]. Antimicrobial activity was measured against tested microorganisms (*Escherichia coli* MTCC 118, *Salmonella Typhi* MTCC 3216, *Bacillus subtilis* MTCC 3053, *Klebsiella pneumonia* MTCC 4031, *Pseudomonas aeruginosa* MTCC 4673, *Staphylococcus aureus* MTCC 3160, *Vibrio cholera* MTCC 3906, *Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 281). Standard antibacterial drug, azithromycin and antifungal drug, fluconazole were used to compare the antibacterial and antifungal activities shown by tested compounds. Screening results are summarized in Table 2 and Table 3.

The zone of inhibition (ZI) was measured at 50 µg/ml and 100 µg/ml concentrations against above said microorganisms. The protocols were summarized in Table 2. All compounds showed antibacterial activity against the growth of tested Gram-positive and Gram-negative bacterial strains with the diameters of zone inhibition ranging between 2 to 15 mm and five compounds (4, 5, 6, 7, 10) showed antifungal activity against *C. albicans* with the diameters of zone inhibition ranging between 9 to 16 mm. None of the screened compound showed significant

activity against fungal strain, *A. niger*. It was shown that compounds had elevated antimicrobial activity against *E. coli* and *C. albicans* than against other microorganisms. The most potent antibacterial activity was exhibited by compounds 6 and 7 (15 mm) against *E. coli*, at the concentration of 100 µg/ml. The highest antifungal effect was obtained in the cases of compounds 4 and 5 (16 mm), against *C. albicans*. Compounds 6 and 7 showed more favourable antimicrobial activities against all bacterial strain except *S. aureus* and this may be attributed to the presence of electron withdrawing groups (Cl and Br) in the compounds. Compound 6f showed antimicrobial activity only against *S. typhii*. The compounds 6 and 8 displayed differences in activity due to the presence of chloro group at different positions. These results were compared with standard antimicrobial drugs azithromycin and fluconazole. The compounds showed less activity than the given standard antibacterial drug ciprofloxacin against all bacteria. Interestingly all the compounds showed higher antifungal activity than the standard drug fluconazole against *C. albicans*.

The minimum inhibitory concentration (MIC) of the compounds was recorded by serial tube dilution method at concentrations of 100, 50, 25, 12.5, 6.25, 3.125 µg/ml against microorganisms which showed ZI. The lowest concentration, which showed no turbidity, was considered as MIC for each compound. The results of the MIC determinations have been presented in Table 3. The MIC values of compounds ranged 50 or 100 µg/ml against gram positive bacteria. Compounds 6 and 7 displayed moderate MIC of 50 µg/ml against *B. subtilis* whereas compounds 4 and 5 showed MIC of 100 µg/ml against *S. aureus*. However, in case of gram negative bacteria, MIC of compounds ranged between 12.5 to 100 µg/ml. The highest MIC of 12.5 µg/ml was shown by compound 7 against *E. coli*. Compounds 6 and 9 exhibited MIC of 25 µg/ml against *E. coli* and *S. typhii*. All the newly synthesized compounds showed high activity against gram negative bacteria as compared to gram positive bacteria. The MICs were also evaluated for all the synthesized compounds 4a-c and 6a-q against *C. albicans*. The highest antifungal activity was displayed by compound 5 (MIC 12.5 µg/ml) whereas compounds 4 and 6 showed moderate antifungal activity at MIC of 25 µg/ml. It was found that compounds exhibited less or similar MIC as compare to standard drug azithromycin and while all compounds possessed less antifngal activity than fluconazole.

From above discussion, it can be concluded that the presence of electron withdrawing substituents (chloro, bromo and fluoro) in the aromatic ring of isatin moiety of compounds enhance antibacterial activity.

Table 2: Results of antibacterial and antifungal screening of compounds

Comp (µg/ml)	Zone of Inhibition (mm)																	
	Bacterial Strain														Fungal Strain			
	E. coli		*S. typhii*		*B. subtilis*		*K. pneumonia*		*P. aurogenosa*		*S. aureus*		*V. cholera*		*C. albicans*		*A. niger*	
	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100
4	-	-	-	-	-	-	-	6.5	-	-	-	5	6	-	14.5	16	-	-
5	-	-	-	-	-	-	-	-	-	-	-	6	6	-	14	16	-	-
6	14	15	10	7	7	8	2.5	2.5	6	5	-	-	2	5	9	9	-	-
7	12	15	8	7	7	7	2	-	6	5	-	-	5	4	9	9.5	-	-
8	-	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	8	11	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	8	9	-	-	-	-	-	-	-	-	-	-	-	-	9.5	10	-	-
Azithromycin	25	27	25	28	15	15	12	12	35	35	15	15	35	35				
Fluconazole															2	2	-	-

**Dash indicates no inhibition*

Table 3. MICs* for the most potent compounds against certain microorganisms

Compound (µg/ml)	MIC (µg/ml)							
	E. coli	*S. typhii*	*B. subtilis*	*K. pneumonia*	*P. aurogenosa*	*S. aureus*	*V. cholera*	*C. albicans*
4	-	-	-	100	-	100	50	25
5	-	-	-	-	-	100	50	12.5
6	25	25	50	50	50	-	50	25
7	12.5	50	50	50	50	-	50	50
8	100	-	-	-	-	-	-	-
9	50	25	-	-	-	-	-	-
10	50	-	-	-	-	-	-	50
Azithromycin	6.25	6.25	12.5	12.5	6.25	12.5	6.25	
Fluconazole								12.5

***** *The minimum concentration of a compound that inhibits the growth of tested microorganisms.*

CONCLUSION

A series of new 6-hydroxy-2,5,7,8-tetramethyl-N'-(2-oxoindolin-3-ylidene)chroman-2-carbohydrazide derivatives (4-10) were synthesized with moderate to higher yields. The *in vitro* antimicrobial activity of these compounds was also determined by Agar well diffusion and serial dilution methods and compared with standard drugs. In general, most of the compounds synthesized during the present work exhibited promising activity against all tested bacteria and fungi except *Aspergillus niger*. The present work adds new data in the relationship with chroman and isatin and their anti-breast cancer and antimicrobial activities.

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