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Computational evaluation and experimental verification of antibacterial and antioxidant activity of 7-hydroxy-3-pyrazolyl-4H-chromen-4-ones and their O-glucosides: identification of pharmacophore sites

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ORIGINAL RESEARCH

Computational evaluation and experimental verification of antibacterial and antioxidant activity of 7-hydroxy-3-pyrazolyl-4*H*-chromen-4-ones and their *o*-glucosides: identification of pharmacophore sites

Javed Sheikh · Kishor Hatzade · Ammar Bader · Usama Shaheen · Thomas Sander · Taibi Ben Hadda

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Abstract This paper reports the computational evaluation and experimental verification of 7-hydroxy-3-(1-phenyl-3-aryl-1*H*-pyrazol-5-yl)-4*H*-chromen-4-ones **3** and their *o*-β-D-glucopyranosides **5** for their antimicrobial and antioxidant activity. The prepared compounds were tested against various Gram-positive and Gram-negative bacteria species. Some of the synthesized compounds have shown potential antimicrobial and antioxidant activity. This POM bioinformatic study could greatly help to pharmacomodulate the potential antibiotics and antioxidants.

Keywords Chromones · Pyrazoles · *o*-β-D-Glucosides · Virtual screening · Petra, Osiris, and molinspiration (POM) · Chemoinformatics

Introduction

Flavonoids constitute one of the most active classes of compounds possessing diverse pharmacological and microbial activity (Billeret *et al.*, 1993; Cingolani *et al.*, 1969). The widespread flavonoids act as various functional secondary metabolites in plants. Literature survey reveals that chromones show anticancer (Atassi *et al.*, 1985; Birt *et al.*, 2001; López-Lázaro, 2002; Pouget *et al.*, 2001; Zheng *et al.*, 2003), anti-HIV (Yu *et al.*, 2004), and antioxidant properties (Burda and Oleszek, 2001; Rackova *et al.*, 2005). Pyrazoles are quite popular in the field of medicine and agro chemistry. A number of pyrazole derivatives have been reported to possess interesting biological activities like anti-inflammatory (Bernard *et al.*, 1986), antimicrobial and antiprotozoal (Bochis *et al.*, 1986). In addition, pyrazole is found widely as a core structure in a large variety of compounds that exhibit important biological activity (Pevarello *et al.*, 2005). Many organic compounds containing carbohydrate exhibit a wide variety of biological and therapeutic properties (Dwek, 1996). Another group of carbohydrate exhibiting potential therapeutic uses is nucleoside analogs. Nucleosides are also glycosides that occur in nucleic acids. Several O-, N-, and C-glycosides have been isolated from other natural sources (The Merck Index, 1989). These compounds have a wide range of biological relevance including antibacterial, antifungal, antiviral, and antitumoral activities. As a result, the formation of the glycosidic linkage continues to be a predominant theme in carbohydrate chemistry (Boons, 1996). Carbohydrates play important roles in a variety of biological processes, such as signaling, cell–cell communications, molecular and cellular targeting (Sears and Wong, 1999).

In view of these pertinent observations and in continuation to our work (Ingle *et al.*, 2007) on chromone-based heterocycles, it was considered to synthesize chemical entities incorporating three active pharmacophores namely chromone, pyrazole, and glucose moiety in a single molecular framework so as to get biologically active

J. Sheikh (✉) · K. Hatzade
Department of Chemistry, Dhote Bandhu Science College, Gondia 441614, India
e-mail: sheikhchemie@gmail.com

A. Bader · U. Shaheen
Department of Pharmacognosy, Faculty of Pharmacy, Umm Al-Qura University, Mecca 21955, Saudi Arabia

T. Sander
Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, 4123 Allschwil, Switzerland

T. Ben Hadda
Laboratoire Chimie Matériaux, FSO, Université Mohammed 1ER, 6000 Oujda, Morocco
e-mail: taibi.ben.hadda@gmail.com

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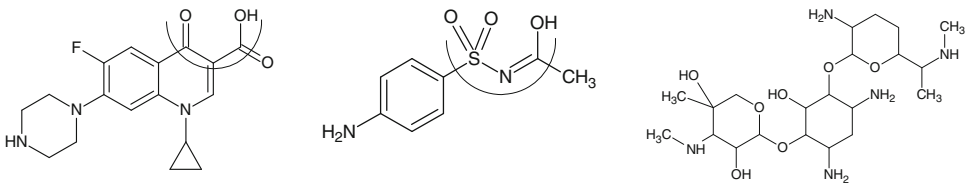
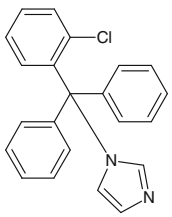
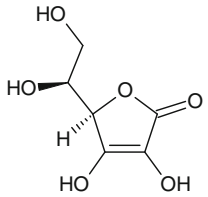


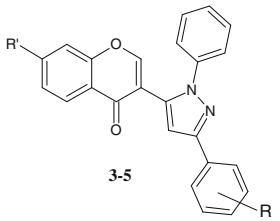
Ciprofloxacin
(Antibacterial agent)

Sulphacetamide
(Antibacterial agent)

Gentamycin
(antifungal agent)







Clotrimazole
(antifungal agent)

ascorbic Acid
(anti-oxidant agent)

3a-3i & **5a-5i**
(POM analyzed compounds)

Fig. 1 Structures of standard drugs and POM analyzed **3a–3i** and **5a–5i** compounds

compounds (Hatzade *et al.*, 2008). Herein, we report the computational evaluation of chromones/pyrazoles glucoside using Petra/Osiris/Molinspiration (POM) approach and their experimental verification (Fig. 1).

Results and discussion

Synthesis of compounds **3–5**

7-Hydoxy-3-formyl chromen-4*H*-one **1** on condensation with substituted acetophenones in the presence of piperidine in dry alcohol affords 7-hydroxy-3-(3-oxo-3-arylprop-1-enyl)-4*H*-chromen-4-ones **2** which on cyclization with phenyl hydrazine hydrochloride leads to the formation of 7-hydroxy-3-(1-phenyl-3-aryl-1*H*-pyrazol-5-yl)-4*H*-chromen-4-ones **3**. 7-*o*-β-D-Glucopyranosyloxy-3-(1-phenyl-3-aryl-1*H*-pyrazol-5-yl)-4*H*-chromen-4-ones **5** have been synthesized by the reaction of 2,3,4,6-tetra-*o*-acetyl-α-D-glucopyranosyl bromide with potassium salt of **3** followed by deacetylation with $Zn(CH_3COO)_2$ in absolute methanol. All the compounds described have been previously prepared and well characterized by NMR, Mass and IR spectroscopic methods (Hatzade *et al.*, 2008) (Scheme 1).

Biological activity

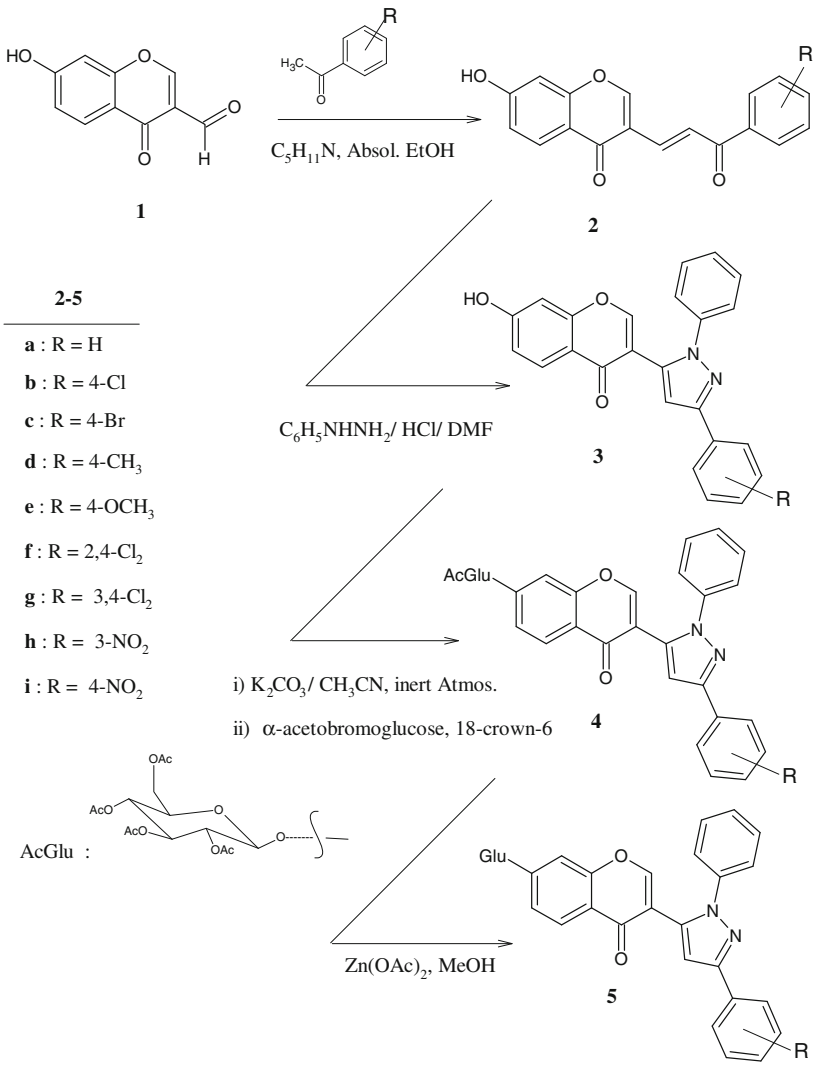
Compounds **3a–3i** and **5a–5i** were evaluated for various biological screening programs. The various screening programs carried out includes the in vitro antibacterial activity against *Escherichia coli, Klebisilla aerogens, Staphyllococcus aureus*, and *Bacillus substilis* and in vitro antifungal activity against *A. niger* and *C. albicans* fungi using the cup plate diffusion method (Vagdevi *et al.*, 2001) by measuring the inhibition zones in mm. The comparative studies of the aglycones and glucosides have been observed by using standard ciprofloxacin, sulfacetamide for bacteria and gentamycin, clotrimazole (100 μg/mL) for fungi. The test compounds were dissolved in DMSO at a concentration of 100 μg/mL. Most of the compounds exhibited mild to moderate antibacterial activity as well as antifungal activity against all the microbes tested (Table 1). Similarly in vitro free radical scavenging activities of glucosides were evaluated by DPPH assay method and most of the compounds were found to be active at 1 mg/mL concentration. Percentage scavenging of DPPH radical was calculated using the formula:

$$\% \text{ Scavenging of DPPH} = [(\text{Control} - \text{Test})/\text{Control}] \times 100.$$

Theoretical calculations of molecular properties of **3a–3i** and **5a–5i**

The aqueous and/or ethanol extraction of flavonoids have often been used in traditional medicine, and also have, therefore, been studied for their antitumor, antioxidant, antiviral, anti-algal, antimicrobial, cytotoxic, and anti-inflammatory, significant hepatoprotective and cardiovascular activity without any criteria of selection.

In continuation of our first POM analyses (Ben Hadda *et al.*, 2012), on Natural Flavonoids (Fig. 2), as potential antibacterial/antiviral drugs, the present study furnishes an overview of the 20 synthetic flavonoids and antifungal/antibacterial activity of their metabolite species. Here, on the basis of POM analyses, a simple, economic, quick and



Scheme 1 Synthetic protocol for compounds **3–5** (Hatzade *et al.*, 2008)

efficient bioinformatic platform, it now becomes easy and possible to predict and optimize the flavonoids bioactivity.

Petra calculations

During the past 15 years, our group investigated the potential pharmacophores of various heterocycles for their possible antiviral and/or antibacterial activity and verified them further with Petra/Osiris/Molinspiration (POM) analyses (Chohan *et al.*, 2010; Jarrahpour *et al.*, 2010, 2011; Masand *et al.*, 2012; Parvez *et al.*, 2010a, b; Rauf *et al.*, 2011; Sheikh *et al.*, 2011; Sheikh and Hadda, 2012). On the basis of the new findings, we can conclude that series **3a–3i** and **5a–5i** engage in opening/closing of B ring showing that **3–5** act as prodrugs and, in the presence of bacteria, can furnish active metabolites bearing keto and two hydroxyl groups containing a potential antibacterial/antiviral/antifungal O,O,O-pharmacophore site (Fig. 3).

For antibacterial activity, the compound should possess ($X^{\delta-}$–$Y^{\delta+}$) pharmacophore site and also it was hypothesized that the difference in charge between *X* and *Y* of the same dipolar pharmacophoric site should facilitate the inhibition of bacteria more than viruses. In contrast to antibacterial agent, the antiviral drug should have ($X^{\delta-}$–$Y^{\delta-}$) pharmacophore site with respect of some architectural parameters (dihedral angle = 0–10° and distance d*x*−*y* = 3–3.5 A°) (Chohan *et al.*, 2010; Jarrahpour *et al.*, 2010, 2011; Masand *et al.*, 2012; Parvez *et al.*, 2010a, b; Rauf *et al.*, 2011; Sheikh *et al.*, 2011; Sheikh and Hadda, 2012). POM analyses confirm the existence of a combined antibacterial/antifungal pharmacophore site (Fig. 4).

Osiris calculations

The remarkably well-behaved mutagenicity of divers synthetic molecules classified in database of Celeron Company of Swiss can be used to quantify the role played by various

Table 1 Antimicrobial and antioxidant activity of compounds **3a–i** and **5a–i**

Zone of inhibition (mm) (Activity index)[std]							% Inhibition
Sr. No.	Antibacterial activity				Antifungal activity		Antioxidant activity
	Gram-positive		Gram-negative		*C. albicans*	*A. niger*	
	S. aureus	*B. substilis*	*E. coli*	*K. aerogens*			DPPH
3a	20 (0.58)[a] (0.65)[b]	17 (0.59)[a] (0.65)[b]	17 (0.49)[a] (0.59)[b]	22 (1.00)[a] (1.04)[b]	30 (1.43)[a] (1.30)[b]	19 (0.76)[a] (0.79)[b]	86.56 (0.88)[a]
3b	21 (0.62)[a] (0.68)[b]	19 (0.66)[a] (0.73)[b]	19 (0.54)[a] (0.66)[b]	19 (0.86)[a] (0.90)[b]	27 (1.29)[a] (1.17)[b]	20 (0.80)[a] (0.83)[b]	88.73 (0.90)[a]
3c	20 (0.58)[a] (0.65)[b]	19 (0.66)[a] (0.73)[b]	22 (0.63)[a] (0.76)[b]	20 (0.91)[a] (0.95)[b]	23 (1.09)[a] (1.00)[b]	16 (0.64)[a] (0.66)[b]	86.10 (0.86)[a]
3d	21 (0.62)[a] (0.68)[b]	18 (0.62)[a] (0.69)[b]	17 (0.49)[a] (0.59)[b]	17 (0.77)[a] (0.81)[b]	23 (1.09)[a] (1.00)[b]	18 (0.72)[a] (0.75)[b]	79.87 (0.81)[a]
3e	24 (0.71)[a] (0.77)[b]	20 (0.69)[a] (0.77)[b]	20 (0.57)[a] (0.69)[b]	19 (0.86)[a] (0.90)[b]	25 (1.19)[a] (1.07)[b]	20 (0.80)[a] (0.83)[b]	80.56 (0.87)[a]
3f	23 (0.68)[a] (0.74)[b]	17 (0.59)[a] (0.65)[b]	21 (0.60)[a] (0.72)[b]	24 (1.09)[a] (1.14)[b]	23 (1.09)[a] (1.00)[b]	22 (0.88)[a] (0.92)[b]	86.13 (0.86)[a]
3g	23 (0.68)[a] (0.74)[b]	22 (0.76)[a] (0.85)[b]	20 (0.57)[a] (0.69)[b]	22 (1.00)[a] (1.04)[b]	29 (1.38)[a] (1.26)[b]	19 (0.76)[a] (0.79)[b]	85.56 (0.87)[a]
3h	22 (0.65)[a] (0.71)[b]	18 (0.62)[a] (0.69)[b]	16 (0.46)[a] (0.55)[b]	17 (0.77)[a] (0.81)[b]	19 (0.90)[a] (0.83)[b]	16 (0.64)[a] (0.66)[b]	88.75 (0.90)[a]
3i	25 (0.74)[a] (0.81)[b]	20 (0.69)[a] (0.77)[b]	21 (0.60)[a] (0.72)[b]	19 (0.86)[a] (0.90)[b]	20 (0.95)[a] (0.87)[b]	20 (0.80)[a] (0.83)[b]	86.45 (0.88)[a]
5a	28 (0.82)[a] (0.90)[b]	20 (0.69)[a] (0.77)[b]	18 (0.51)[a] (0.62)[b]	24 (1.09)[a] (1.14)[b]	34 (1.62)[a] (1.48)[b]	21 (0.84)[a] (0.88)[b]	88.68 (0.90)[a]
5b	26 (0.76)[a] (0.84)[b]	18 (0.62)[a] (0.69)[b]	20 (0.57)[a] (0.69)[b]	20 (0.91)[a] (0.95)[b]	29 (1.38)[a] (1.26)[b]	21 (0.84)[a] (0.88)[b]	90.76 (0.93)[a]
5c	22 (0.65)[a] (0.71)[b]	22 (0.76)[a] (0.85)[b]	24 (0.69)[a] (0.83)[b]	22 (1.00)[a] (1.04)[b]	22 (1.04)[a] (0.96)[b]	18 (0.72)[a] (0.75)[b]	87.19 (0.89)[a]
5d	25 (0.74)[a] (0.81)[b]	21 (0.72)[a] (0.81)[b]	18 (0.51)[a] (0.62)[b]	19 (0.86)[a] (0.90)[b]	25 (1.19)[a] (1.09)[b]	19 (0.76)[a] (0.79)[b]	80.57 (0.82)[a]
5e	31 (0.91)[a] (1.00)[b]	24 (0.83)[a] (0.92)[b]	22 (0.63)[a] (0.76)[b]	22 (1.00)[a] (1.04)[b]	27 (1.29)[a] (1.17)[b]	22 (0.88)[a] (0.92)[b]	82.45 (0.84)[a]
5f	33 (0.97)[a] (1.06)[b]	22 (0.76)[a] (0.85)[b]	20 (0.57)[a] (0.69)[b]	27 (1.23)[a] (1.29)[b]	25 (1.19)[a] (1.07)[b]	23 (0.92)[a] (0.96)[b]	88.73 (0.90)[a]
5g	30 (0.88)[a] (0.97)[b]	27 (0.93)[a] (1.04)[b]	19 (0.54)[a] (0.66)[b]	24 (1.09)[a] (1.14)[b]	30 (1.43)[a] (1.30)[b]	22 (0.88)[a] (0.92)[b]	86.12 (0.88)[a]
5h	25 (0.74)[a] (0.81)[b]	19 (0.66)[a] (0.73)[b]	17 (0.49)[a] (0.59)[b]	17 (0.77)[a] (0.81)[b]	20 (0.95)[a] (0.87)[b]	16 (0.64)[a] (0.66)[b]	91.65 (0.93)[a]
5i	31 (0.91)[a] (1.00)[b]	23 (0.79)[a] (0.88)[b]	23 (0.66)[a] (0.79)[b]	20 (0.91)[a] (0.95)[b]	23 (1.09)[a] (1.00)[b]	21 (0.84)[a] (0.88)[b]	86.56 (0.88)[a]
Std. 1	34	29	35	22	21	25	98.03
Std. 2	31	26	29	21	23	24	

(Activity index) = Inhibition zone of the sample/Inhibition zone of the standard. For antibacterial activity: Std. 1 = ciprofloxacin and Std. 2 = sulfacetamide, For antifungal activity: Std. 1 = gentamycin and Std. 2 = clotrimazole. For antioxidant activity: Std. 1 = ascorbic Acid

[a] Activity index against Std. 1

[b] Activity index against Std. 2

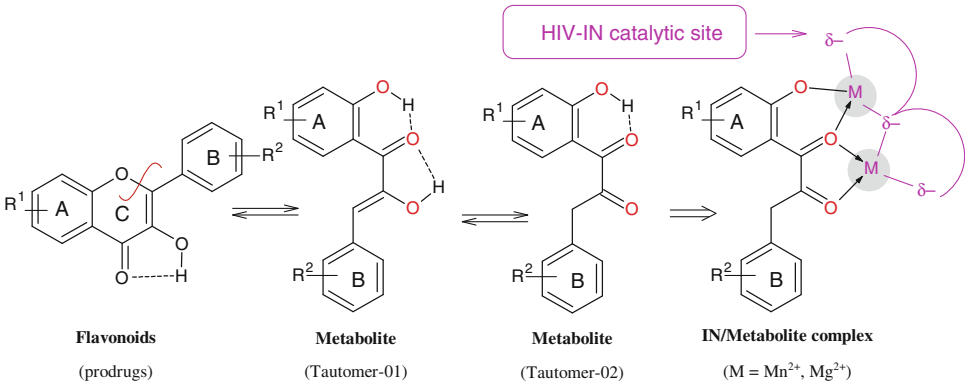


Fig. 2 Opening of C ring of prodrug (Flavonoids) followed by a conformational rearrangement. The formation of tautomeric forms is crucial in the orientation/preparation of hypothetical anti-HIV-IN O,O,O-pharmacophore site (Marchand *et al.*, 2006)

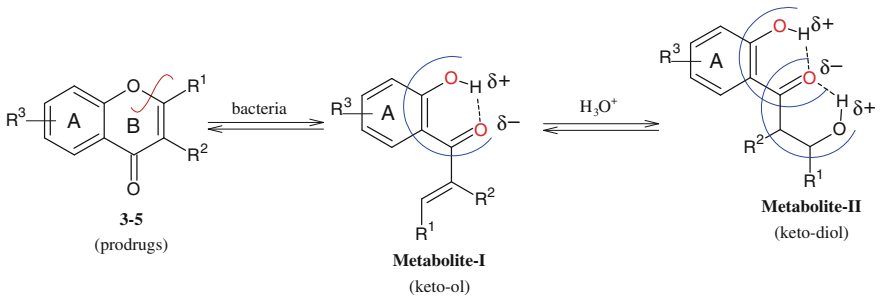


Fig. 3 Plausible mechanism for opening of C ring of prodrugs **3–5** followed by the regeneration of bioactive metabolites **3′–5′** bearing O,O,O-pharmacophore

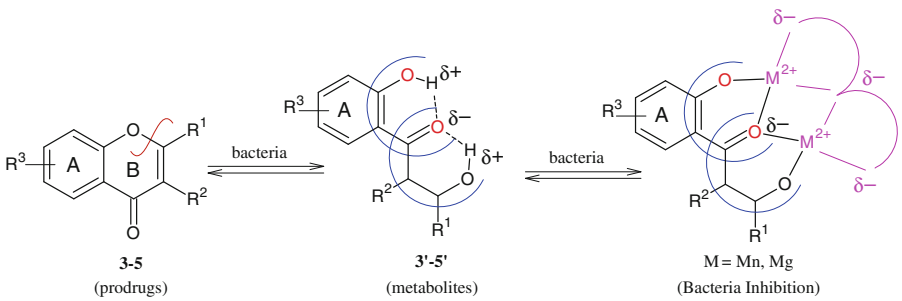


Fig. 4 Structure of dual antibacterial/antifungal pharmacophore site of prodrugs **3–5**

organic groups in promoting or interfering with the way a drug can associate with DNA. The Osiris calculations are tabulated in Tables 2 and 3. Toxicity risks (mutagenicity, tumorogenicity, irritation, reproduction) and physico-chemical properties (CLogP, solubility, drug-likeness, and drug-score) of prodrugs **3–5** and their metabolites **3′–5′** were calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. From the data evaluated in Tables 2 and 3 it is obvious that, majority of structures are supposed to be non-mutagenic, non-irritating with no reproductive effects when run through the mutagenicity assessment system in comparison with the standard drug. Low hydrophilicities and, therefore, high log *P* values may cause poor absorption or permeation. It has been shown that for compounds to have a reasonable probability of good absorption, their log *P* value must not be greater than 5.0. On this basis, all the prodrugs **3–5** and their metabolites **3′–5′** possessed log *P* values in the acceptable range.

The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and, therefore, the general aim is to avoid poorly soluble compounds. Our estimated log *S* value is a unit stripped logarithm (base 10) of a compound's solubility in mol/L. There are more than 80 % of the drugs in the market that have an (estimated) log *S* value greater than −4. In case of compounds **3–5** and **3′–5′**, values of log *S* are around (−4)−(−5). Further, Tables 2 and 3 show drug-likeness of compounds **3–5** and **3′–5′** which is in the comparable zone with that of standard drugs used for comparison. The reported compounds **3–5** and **3′–5′** (except **3h**, **5h**, **3h′**, and **5h′**) showed no toxicity risk and have good drug-score as compared with the two standard drugs used.

Table 2 Osiris calculations of compounds **3a–3i** and **5a–5i**

Compd.	MW	Toxicity risk				Osiris calculations			
		MUT	TUMO	IRRI	REP	CLP	*S*	D-L	D-S
3a	380					3.51	−4.86	−0.83	0.41
3b	414					4.12	−5.59	0.26	0.39
3c	458					4.21	−5.69	−2.63	0.24
3d	394					3.83	−5.20	−2.06	0.32
3e	410					3.41	−4.87	−0.31	0.44
3f	448					4.74	−6.33	0.44	0.31
3g	448					4.74	−6.33	−046	0.27
3h	425					3.38	−5.32	−5.93	0.22
3i	425					3.38	−5.32	−10.80	0.28
5a	542					1.40	−4.74	−3.89	0.27
5b	576					2.01	−5.48	−3.01	0.23
5c	620					2.10	−5.58	−5.60	0.20
5d	556					1.72	−5.09	−5.04	0.24
5e	572					1.30	−4.76	−3.32	0.26
5f	610					2.63	−6.21	−2.90	0.19
5g	610					2.63	−6.21	−3.57	0.18
5h	587					1.27	−5.20	−8.81	0.18
5i	587					1.27	−5.20	−13.82	0.23
Ciprof	330					1.63	−3.42	2.33	0.65
Sulpha	214					0.17	−1.53	5.46	0.35
Genta	477					−4.03	−1.18	4.88	0.77
Clotri	344					4.97	−7.72	−0.10	0.28
Ascorb	176					−2.23	−0.35	0.02	0.44

MUT mutagenic, *TUMO* tumorigenic, *IRRI* irritant, *REP* reproductive effective, *CLP* CLogP, *S* solubility, *DL* druglikness, *DS* drug-score, *Ciprof* ciprofloxacin, *Sulpha* sulfacetamide, *Genta* gentamycin, *Clotri* clotrimazole, *Ascorb* ascorbic acid

Molinspiration calculations

This method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the corresponding methodology as a sum of fragment contributions (Chohan *et al.*, 2010; Jarrahpour *et al.*, 2010, 2011; Parvez *et al.*, 2010a, b; Rauf *et al.*, 2011; Sheikh

Table 3 Osiris calculations of compounds **3a′**–**3i′** and **5a′**–**5i′** resulting from opening of ring B of flavonoids/prodrugs **3a**–**3i** and **5a**–**5i**

Compd.	MW	Toxicity risk				Osiris calculations			
		MUT	TUMO	IRRI	REP	CLP	*S*	D-L	D-S
3a′	400					3.02	−4.24	0.56	0.57
3b′	434					3.64	−4.98	1.67	0.53
3c′	478					3.72	−5.08	−1.26	0.32
3d′	414					3.34	−4.59	−0.70	0.43
3e′	430					2.92	−4.26	1.06	0.59
3f′	468					4.25	−5.71	1.95	0.41
3g′	468					4.25	−5.71	0.93	0.38
3h′	445					2.89	−4.70	−4.57	0.25
3i′	445					2.89	−4.70	−9.54	0.31
5a′	561					0.91	−4.13	−2.61	0.30
5b′	596					1.53	−4.86	−1.73	0.27
5c′	640					1.61	−4.96	−4.33	0.22
5d′	576					1.23	−4.47	−3.77	0.26
5e′	592					0.81	−4.15	−2.05	0.29
5f′	630					2.14	−5.60	−1.61	0.23
5g′	630					2.14	−5.6	−2.29	0.21
5h′	607					0.78	−4.59	−7.57	0.19
5i′	605					1.42	−5.05	−11.15	0.13

MUT mutagenic, *TUMO* tumorigenic, *IRRI* irritant, *REP* reproductive effective, *CLP* CLogP, *S* solubility, *DL* druglikness, *DS* drug-score

Table 4 Molinspiration calculations of compounds **3a**–**3i** and **5a**–**5i**

Compd.	R	Molinspiration calculations					Drug-likeness					
		TPSA	NONI	NV	nrotb	VOL	GPCR	ICM	KI	NRL	PI	EI
3a	H	68	1	0	3	332	−0.14	−0.58	−0.06	−0.03	−0.67	−0.03
3b	4-Cl	68	1	0	3	346	−0.14	−0.57	−0.08	−0.05	−0.69	−0.06
3c	4-Br	68	1	1	3	350	−0.22	−0.62	−0.10	−0.13	−0.75	−0.09
3d	4-CH_3	68	1	0	3	349	−0.17	−0.63	−0.10	−0.06	−0.70	−0.08
3e	4-OCH_3	77	1	0	4	358	−0.17	−0.59	−0.08	−0.05	−0.67	−0.07
3f	2,5-Cl_2	68	1	1	3	359	−0.10	−0.54	−0.06	−0.04	−0.65	−0.08
3g	3,5-Cl_2	68	1	1	3	359	−0.13	−0.55	−0.07	−0.03	−0.68	−0.05
3h	3-NO_2	114	1	0	4	355	−0.25	−0.58	−0.15	−0.11	−0.73	−0.11
3i	4-NO_2	114	1	0	4	355	−0.25	−0.57	−0.17	−0.12	−0.73	−0.12
5a	H	147	4	1	6	464	−0.06	−0.64	−0.15	−0.13	−0.43	0.08
5b	4-Cl	147	4	1	6	478	−0.08	−0.71	−0.20	−0.20	−0.45	0.01
5c	4-Br	147	4	1	6	482	−0.14	−0.75	−0.22	−0.25	−0.50	−0.01
5d	4-CH_3	147	4	1	6	481	−0.11	−0.75	−0.22	−0.20	−0.46	−0.01
5e	4-OCH_3	157	4	2	7	490	−0.12	−0.81	−0.25	−0.26	−0.44	−0.04
5f	2,5-Cl_2	147	4	1	6	491	−0.09	−0.78	−0.25	−0.25	−0.43	−0.06
5g	3,5-Cl_2	147	4	1	6	491	−0.10	−0.79	−0.25	−0.24	−0.45	−0.04
5h	3-NO_2	199	4	2	7	483	−0.27	−0.93	−0.40	−0.36	−0.51	−0.27
5i	4-NO_2	199	4	2	7	483	−0.27	−0.93	−0.42	−0.37	−0.51	−0.28
Std. 1	–	70	2	0	3	290	0.36	0.09	−0.05	0.01	0.14	0.18
Std. 2	–	89	3	0	2	175	−0.46	−0.48	−0.70	−1.28	−0.36	−0.12
Std. 3	–	200	11	2	7	451	0.34	0.19	0.18	−0.06	0.66	0.46
Std. 4	–	18	0	1	4	310	0.17	0.30	0.14	−0.21	−0.13	0.42

TPSA total polar surface area, *VOL* volume, *ONI* OH–NH interaction, *NV* number of violation, *GPCR* GPCR ligand, *ICM* ion channel modulator, *KI* kinase inhibitor, *NRL* nuclear receptor ligand, *Std. 1* ciprofloxacin, *Std. 2* sulfacetamide, *Std. 3* gentamycin, *Std. 4* clotrimazole

Table 5 Molinspiration calculations of compounds **3a′–3i′** and **5a′–5i′** resulting from opening of ring B of flavonoids/prodrugs **3a–3i** and **5a–5i**, respectively

Compd.	R	Molinspiration calculations					Drug-likeness					
		TPSA	NONI	NV	nrotb	VOL	GPCR	ICM	KI	NRL	PI	EI
3a′	H	96	3	0	6	356	0.02	−0.21	−0.06	0.21	−0.17	0.06
3b′	4-Cl	96	3	0	6	370	0.02	−0.21	−0.08	0.18	−0.20	0.03
3c′	4-Br	96	3	0	6	374	−0.06	−0.27	−0.01	0.11	−0.26	−0.01
3d′	4-CH_3	96	3	0	6	372	−0.01	−0.26	−0.10	0.18	−0.22	0.01
3e′	4-OCH_3	105	3	0	7	382	−0.01	−0.25	−0.09	0.17	−0.20	0.02
3f′	2,5-Cl_2	96	3	0	6	383	0.05	−0.20	−0.06	0.18	−0.18	0.00
3g′	3,5-Cl_2	96	3	0	6	383	0.03	−0.21	−0.07	0.20	−0.21	0.03
3h′	3-NO_2	141	3	0	7	379	−0.10	−0.24	−0.15	0.11	−0.28	−0.03
3i′	4-NO_2	141	3	0	7	379	−0.10	−0.24	−0.17	0.10	−0.27	−0.04
5a′	H	175	6	3	9	488	0.03	−0.44	−0.20	0.00	−0.10	0.09
5b′	4-Cl	175	6	3	9	502	0.00	−0.52	−0.26	−0.07	−0.12	0.01
5c′	4-Br	174	6	3	9	506	−0.06	−0.56	−0.28	−0.13	−0.17	−0.01
5d′	4-CH_3	175	6	3	9	505	−0.03	−0.56	−0.28	−0.08	−0.13	−0.00
5e′	4-OCH_3	184	6	3	10	514	−0.06	−0.64	−0.32	−0.16	−0.13	−0.06
5f′	2,5-Cl_2	175	6	3	9	515	−0.02	−0.61	−0.32	−0.14	−0.12	−0.08
5g′	3,5-Cl_2	175	6	3	9	515	−0.04	−0.62	−0.32	−0.153	−0.14	−0.05
5h′	3-NO_2	221	6	3	10	511	−0.18	−0.75	−0.46	−0.28	−0.21	−0.18
5i′	4-NO_2	221	6	3	10	512	−0.18	−0.75	−0.48	−0.28	−0.21	−0.19
Std. 1	–	70	2	0	3	290	0.36	0.09	−0.05	0.01	0.14	0.18
Std. 2	–	89	3	0	2	175	−0.46	−0.48	−0.70	−1.28	−0.36	−0.12
Std. 3	–	200	11	2	7	451	0.34	0.19	0.18	−0.06	0.66	0.46
Std. 4	–	18	0	1	4	310	0.17	0.30	0.14	−0.21	−0.13	0.42
Std. 5	–	107	4	0	2	140	−0.53	−0.24	−1.01	−1.01	−0.81	0.20

TPSA total polar surface area, *VOL* volume, *ONI* OH–NH interaction, *NV* number of violation, *GPCR* GPCR ligand, *ICM* ion channel modulator, *KI* kinase inhibitor, *NRL* nuclear receptor ligand, *Std. 1* ciprofloxacin, *Std. 2* sulfacetamide, *Std. 3* gentamycin, *Std. 4* clotrimazole, *Std. 5* ascorbic acid

et al., 2011; Sheikh and Hadda, 2012). O-centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood–brain barrier penetration. CLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Tables 4 and 5).

Conclusion

The tested compounds are flavonoid analogs substituted at different positions and were virtually evaluated by POM for their in vitro antimicrobial activity against the pathogen bacteria. The preliminary structure–activity relationship (SAR) analysis suggested that the introduction of appropriate di-substituted pyrazole ring into position 3 of chromen-4-one ring enhanced antibacterial activities of these compounds.

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