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Review Article

A REVIEW ON CHROMONES – BIOLOGICALLY ACTIVE PHARMACOPHORES

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ABSTRACT

Oxygen containing heterocycles are abundantly found in nature. Flavone, isoflavones, flavanones, catechins, anthocyanins are some phytoconstituents collectively grouped as flavonoids and isoflavonoids. Chemically, they are categorized as chromenes, chromenones, dihydrofurobenzofurans, chromanochromanones, benzofurochromans, xanthones and amphipyrones. Chromones (4*H*-Benzopyran-4-ones) are the heterocyclic compounds with benzopyron network with substituated keto group on pyron ring. It is an isomer of coumarin. Chromone nucleus is recognised as pharmacophore having a number of biological activities such as anticancer, antiviral, antifungal, antimicrobial, antioxidant, antidepressant, antiobesity. These derivatives also possess enzymetic inhibition properties towards different systems such as oxidoreductase, kinase, lipoxygenase and cycloxygenase. Chromone moiety is obtained from number of sources such as plants, marine and synthetic sources. These are khellin, aloesin, kaemferol, hormothamnione, asperginone and flavopiridol. So, this chromone nucleus find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems.

Keywords: Chromones, Anticancer, Antibacterial, Flavone, Antioxidants.

INTRODUCTION

Chromone (1) word is derived from the Greek word chroma, meaning 'color', which indicates that many chromone derivatives exhibits a broad variation of colors[1]. Chromone (1) moiety forms the important component of pharmacophores of a number of biologically active molecules having synthetic or natural origin and many of them have useful medicinal applications[2]. Chromones are the hetrocyclic compounds with benzopyron network with substituted keto group on pyron ring. Chromone is an isomer of coumarin. Chromone derivatives have a number of biological activities such as anticancer[3-6], antihypertensive[3], antiviral, antifungal, antimicrobial, antioxidant, antidepressant, antiobesity. These derivatives

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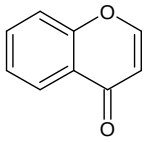
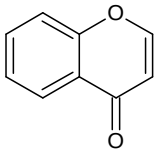
also possess enzymetic inhibition properties towards different systems such as oxidoreductase, kinase, lipoxygenase and cycloxygenase.



1

CHEMISTRY OF CHROMONE NUCLEUS

Chromones (1) are heterocyclic compounds with the benzo-γ-pyron network. It is a derivative of benzopyron with a substituted keto group on the pyron ring[7]. Benzofused analogues of the pyron and pyrilliumcations are the ring system of several important groups of natural products. These systems[8] are chromone (1), coumarin (2), benzyopriliumcations (3).



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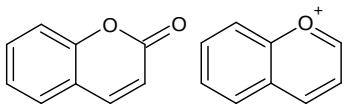
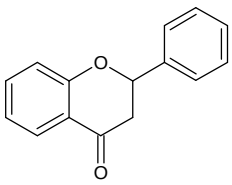


2 **3**

Many flavones (4), isoflavones (5), chalchones (6), neoflavones (7) and their glycosides have been also reported[9].



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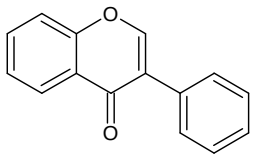

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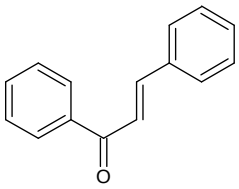

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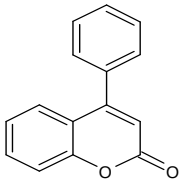
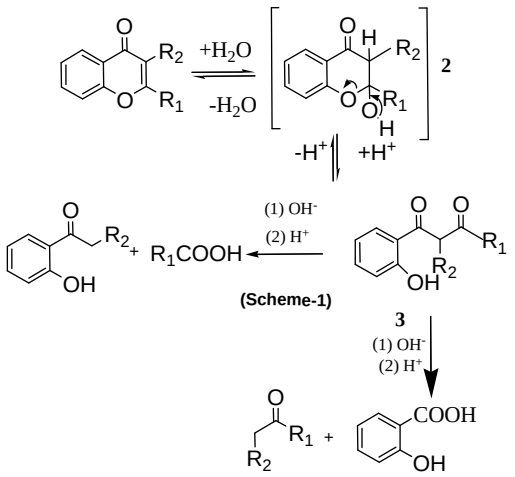


7

Attack on C-2 and C-3 Position

- Protonation and alkylation occurs on oxygen of the chromonemoeity. Electrophilic attack takes place at the deactivated pyran 4-one ring in the C-3 position of chromone[8].
- Toward neucleophiles, the chromone system behaves as Michael accepter. In general neucoleophillic attack occurs at C-2, and addition is accompanied by ring transformation[10]. For instance, aqueous alkali leads to base-induced water addition **(2)**, and subsequent cleavage of the 4-pyrone ring gives rise to 2-hydroxy-phenyl-1,3-diketones (**3) (Scheme-1).**



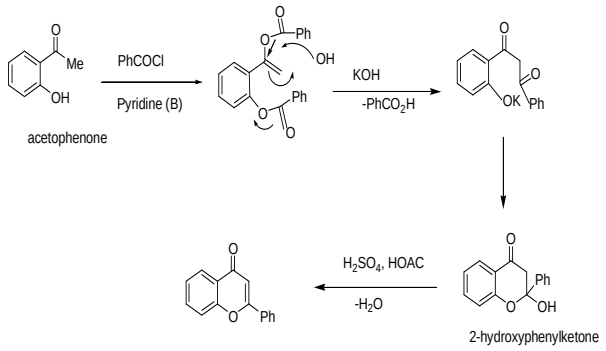
Synthesis

I. The reaction of acetophenones with substituted amide, typically N,N-dimethyl formamide (DMF) with phosphorous oxy chloride ($POCl_3$) leads to the formation of 3-Formylchromones via vilsmeier–Haack reaction[10]. The active agent is the substituted chloroiminium ion that is formed by the reaction of DMF and $POCl_3$. This chloroiminium ion then attacks the electron rich arene to give the corresponding aromatic ketone or aldehyde[11].

(Scheme-2) Synthesis of 3-formyl chromone via vilsmeier – Haack reaction

A signature feature of chromone-3-carboxaldehyde is the facile opening of γ–pyrone ring via attack of nucleophiles at the highly electron deficient C-2 position. However, not every nucleophile is capable of ring opening or even nucleophilic addition at C-2 position. It has been found that certain substituents at position 3, particularly those which are in conjugation with the C-2, C-3 double bond not only have an effect on the electrophilicity of the C-2 carbon atom, but also favor the nucleophilic addition into the C-2, C-3 double bond[12].

II. 2, 3-substituted chromones can be synthesised from salicylic acid derivatives and from 2-hydroxyphenyl ketones (Scheme-II). 3-substituted chromones can be synthesised via the condensation of the enolate of 2-hydroxyphenyl ketone and ethyl formate. Synthesis of 2- and 3-substituted chromones normally start from 2-hydroxyphenyl ketones. In the first of two examples, a route to flavone is shown in Scheme I using 2-hydroxyacetophenone-(2-hydroxyphenylethanone) and benzoyl chloride as staring materials. Initially, the phenolic group of the acetophenone is *o*-acylated by benzoyl chloride, using pyridine as a base (a Schotten-Baumann type reaction). Under these conditions, the *o*-benzoyl derivative immediately enolises and is *o*-acylated again to yield a dibenzoate. Without isolation, this product is cyclised by treatment with aqueous potassium hydroxide to yield 2-hydroxy-2,3-dihydroflavone. Dehydration to flavone is then affected by the action of glacial acetic acid containing sulphuric acid[13,14].

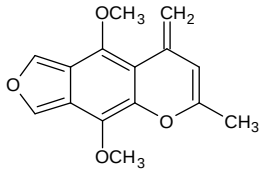


(**Scheme -3)** synthesis of 2- substituted chromones

CHROMONE- BIOLOGICALLY ACTIVE PHARMACOPHORE

AS DIURETIC

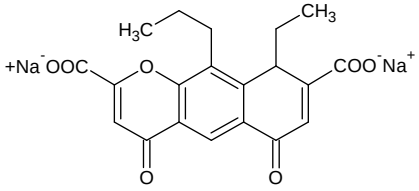
Khellin (8) is a furanohromone, extracted from the seeds of plant *Ammivisnaga*. It is a first chromone in clinical practice and it has been used as a diuretic to relieve renal colic[15]. It has been used successfully to treat vitiligo by topical application and causes vasodilation (widening of blood vessels)



8

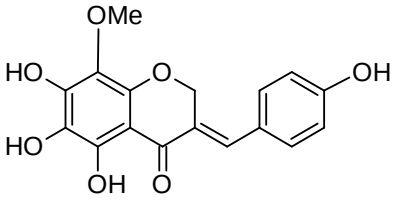
AS ANTI-INFLAMMATORY AGENT

Nedocromil sodium (9) is used for the treatment of asthma and has anti-inflammatory activity. It acts by inhibiting activation of inflammatory cells including neutrophils, eosinophils, macrophages, monocytes, mast cells, platelets[16].



9

Homoisoflavanones (10) and their structurally related compound (11) have been reported for their antimicrobial as well as anti-inflammatory activity against COX-1 enzyme[17].



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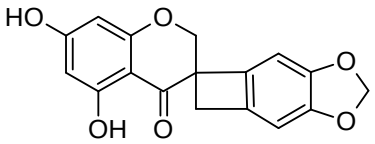
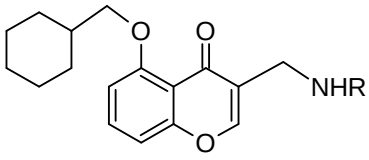
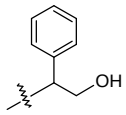
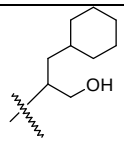
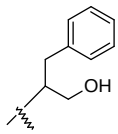
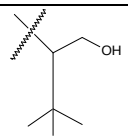


11

A series of novel Hydroxyalkyl-aminomethylchromone analogs (12a-d) have been evaluated as inhibitors of interleukin-5 (IL-5). (12d**)** has emerged as the most active analog. These compounds are used in treatment of inflammatory disease such as arithritis, psoriasis, asthma[18].

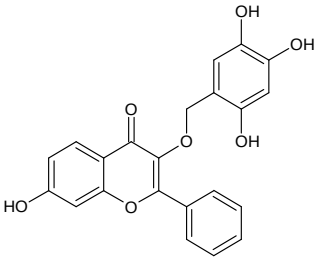


(12a-d)

Compound	R
a.	
b.	
c.	
d.	

AS ANTICANCER AGENT

Epigallaocathechingall at (13), Apigenin (14), MST-199 (15) are the telomerase inhibiters, used as anticancer agents. Telomerase protect the ends of chromosomes and their stability as well as length are regulated by telomerase enzyme which is a ribonucleoprotein responsible for adding telomere repeats to 3'-ends[19,20].



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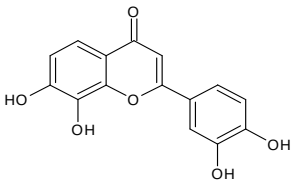

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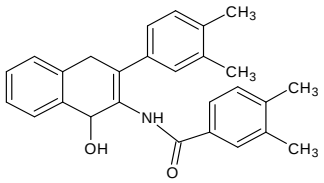
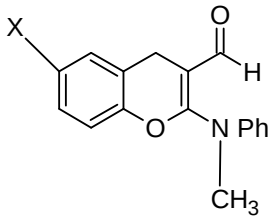


15

2-(*N*-methylanilino)-3-formylchromones (16) have been reported for their anticancer activities against breast cancer, leukemia and prostate cancer[21].

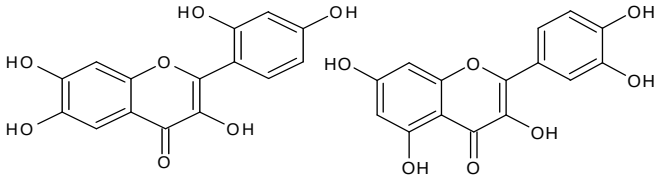


16

X = H ,Cl

AS PROTEIN TYROSINE PHOSPHATASE INHIBITOR

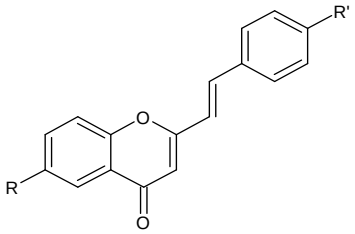
Quercetin (17) and Morin (18) are the natural flavanoids that inhibits the cyclic AMP phosphodiesteraes[22].These also possess anti-inflammatory, antioxidant and hepatoprotective activities.



17 **18**

AS ANTIVIRAL AGENT

2-Styrylchromones (19a-d) are the chromone derivatives that are used as antiviral agents. These compounds possess the anti-rhinovirus activity against Human *rhino* virus (HRVs)[23].



(19a-d)

19a R=R'=H

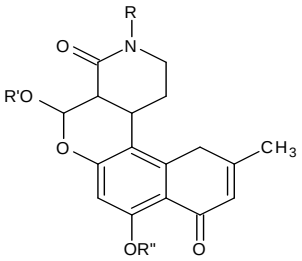
19b R=H, R'=Cl

19c R=H, R'=CH_3

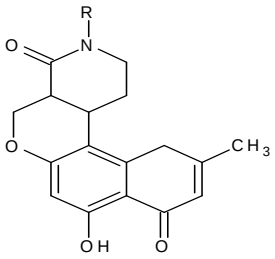
19d R=H, R'=OCH_3

Schammannificine I (20a-b) have inhibitory effect on HIV-I *reverse transcriptaes* enzyme.

It binds irreversibily and prevent the virus binding to the cell and prevent the infection[24]. It is a natural alkaloid and extracted from the rootbark of *Schumanniophytonproblematicum*.



(20a)

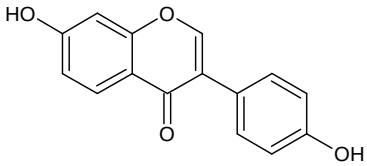


(20b)

	R	R'	R''
(20a)	**CH_3**	**H**	**H**
(20b)	**H**	**H**	**CH_3**

AS ANTIOXIDANT AGENT

Quercetin (17) Daidzein (21) and Noringenin (22) are used as antioxidant agents. Quercetin is a natural flavonoid and obtained from red wine. It exhibits antioxidant activity against free radical, asthma, cancer and various heart diseases[25]. Daidzein (21) is an isoflavone and Noringenin (22) is a flavanone and these exhibit antioxidant activity[26,27].



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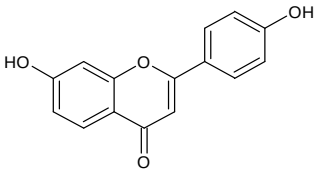
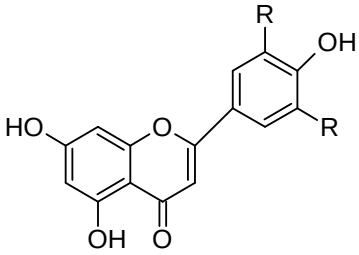


22

(C_6-C_3-C_6) Flavonoids (23) are naturally occurring polyphenols known to exhibit antioxidant property[28].

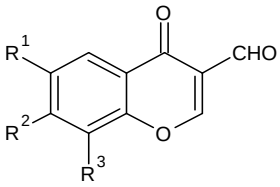


23

R = H, CH_3, OH

AS ANTI *H.pyroli* AGENT

A series of chromonederivatives FC (24-34) are screened against *H.pyroli* and shows potent anti *H. Pyroli* activity[29] and are used in the treatment of gastritis, peptic ulcer and stomach cancer.

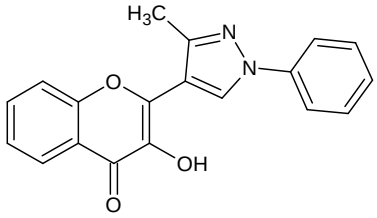


(24-34)

Compd.	R_1	R_2	R_3
24	CH_3	H	H
25	H	HH	
26	i-Pr	H	H
27	CH_3O	H	H
28	NO_2	H	H
29	F	H	H
30	Cl	H	H
31	Br	H	H
32	Cl	CH_3	H
33	Cl	H	H
34	Br	H	Br

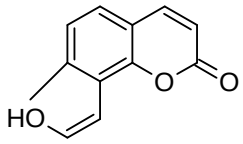
AS ANTIFUNGAL AGENT

3-Hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromone**(35),** derivatives are used as antifungal agents. They act by interferring in the mycelia growth of fungi[30].



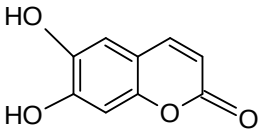
35

Angelicin (36), a naturally occurring furanocoumarin shows antifungal activity against *Candida albicans, Cryptococcus neoformans and Aspergillus niger*[31].



36

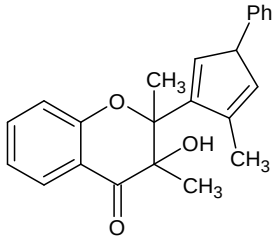
Esculetin (37) a coumarin derivative shows antifungal activity against *Cryptococcus neoformans and Saccharomyces cerevisiae*[32].



37

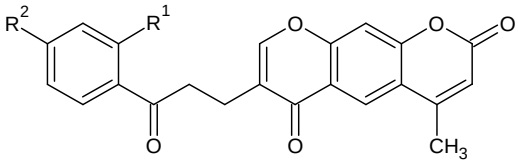
AS ANTIBACTERIAL AGENT

Seven 2,3-Dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromones (38) are active against three gram +ve bacteria *S. Aureus , S. Epidermidis , B. Pumilus*and two gram –ve bacteria *S. Typhi , P. Aeruginosa*[33].



38

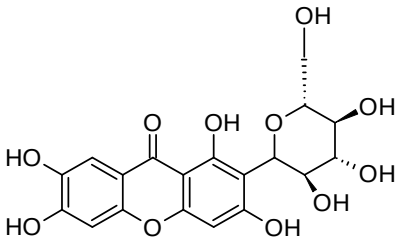
The chalcone (39a-b) analoges of chromone-4-ones(pyrano[3,2-g]chromone-8-carbaldehyde, have been found promising antibacterial agents. These compounds are also effective against different gram positive bacteria (*Bacillus subtilis & Staphylococcus aureus*) and gram negative bacteria (*Eshcherichia coli, Pseudomonus aeruginosa*)[34].



(39a-b)

	R_1	R_2
(39a)	H	H
(39b)	OH	OH

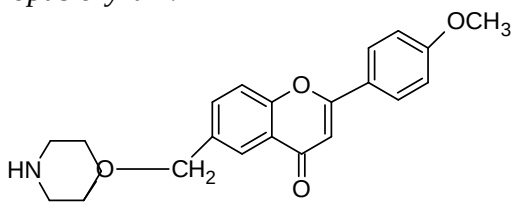
Magniferin (40) contains the 3-Hydroxy-2-(4'-Methyl benzoyl)chromone and this chromone is evaluated for their antibacterial activity against *Salmonella typhimurium, Streptococcus mutans, Pseudomonas aeruginosa, and Escherichia coli*[35].



40

A series of 6-Aminomethyl-2-aryl-1-benzopyran-4-one derivatives (41) have been evaluated for their antibacterial activity against

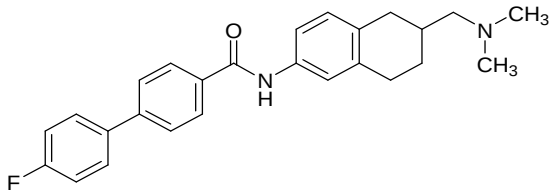
Penicillin citrum, Escherichia coli and Rhizopus oryza[36].



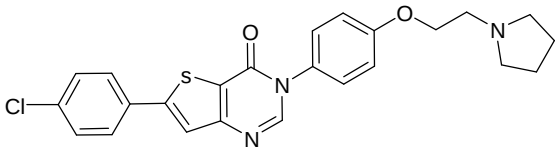
41

AS ANTIOBESITY AGENT

T-226296 (42) and GW3430 (43) are used in treatment of anxiety and depression. These are the MCHIR antagonists[37].



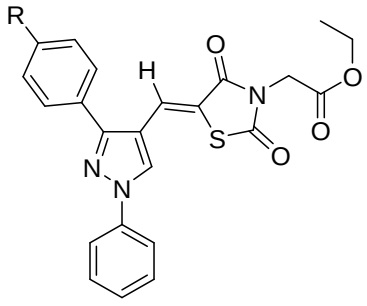
42



43

AS BOTH ANTIBACTERIAL AND ANTIFUNGAL AGENT

New Pyrazolyl-2,4-thiazolidinediones (44a-h), shows antimicrobial and antifungal activity. These compounds are active against two gram positive bacterial strains, *Staphylococcus aureus, Bacillus subtilis* and two gram negative bacterial strains, *Escherchia coli*, *Pseudomonas aeruginosa* and two fungal strains, *Aspergillusniger*, *A. flavus*[38].

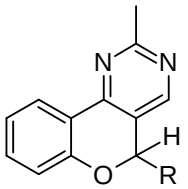


(44a-h)

Compound	R
44a.	H
44b.	OMe
44c.	F
44d.	OH
44e.	Me
44f.	Cl
44g.	Br
44h.	NO_2

AS ANTIPLATELETAGENT

New Polycyclic Pyrimidine derivatives (45a-f) have been screened as antiplatelet agents and proven as potent as acetylsalicylic acid against arachidonic acid – stimulated aggregation[39].

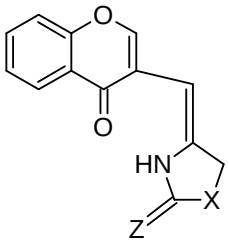


(45a-f)

Compound	R
a.	Isopropylamino
b.	t-Butylamino
c.	piperidino
d.	Cyclopropylamino
e.	morpholino
f.	pyrrolidino

AS ANTISPASMODIC AGENTS

2,4-Thiazolidenedione (46) are the chromones which are used as antispasmodic agent, in the treatment of angina pectoris and as anti-diabetic agent that improve peripheral insulin resistance in type- II diabetic patients respectively[40].



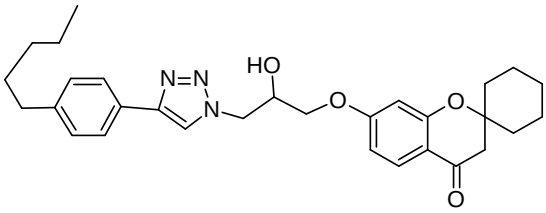
46

X = S, NH, NMe, NEt

Z = O, S

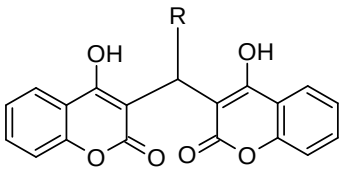
AS ANTITUBERCULOSIS AGENTS

A series of new novel 1,2,3-Triazole fused spirochromone (47) conjugate has been prepared and evaluated *invitro* against *Mycobacterium tuberculosis*, that inhibits growth[41].



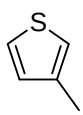
47

4-Hydroxy-3-[(4-hydroxy-2-Oxo-2H-3-chromen-yl)(3-thienyl)methyl]-2H-2-Chromenone (48) is found to be the most active agent against *Mycobacterium tuberculosis*[42].



48

R =



CONCLUSION

As from the literature, it is confirmed that chromone nucleus is having a number of pharmacological activities and is a very active biological pharmacophore, so, this nucleus find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems. In recent years, 3-formylchromones have attracted considerable attention as highly reactive compounds, which can serve as the starting materials in synthesis of a whole series of heterocycles with useful properties due to three strong electrophilic centres (carbon atoms C-2 and C-4 of the chromone system and formyl group).

CONFLICTS OF INTEREST

All authors have none to declare.

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