Taylor & Francis
Taylor & Francis Group

Natural Product Research
Formerly Natural Product Letters

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

Non-ulcerogenic pyrazolyl 2-hydroxychalcones and pyrazolylpyrazolines derived from naturally existing furochromone (khellin): semi-synthesis, docking study and anti-inflammatory activity

Fatma Abd El-Fattah Ragab, Yassin Mohammed Nissan, M. Alaraby Salem, Mamdouh Moawad Ali & Ahmed Abbass Mohamed Abdelrahman Selim

To cite this article: Fatma Abd El-Fattah Ragab, Yassin Mohammed Nissan, M. Alaraby Salem, Mamdouh Moawad Ali & Ahmed Abbass Mohamed Abdelrahman Selim (2021): Non-ulcerogenic pyrazolyl 2-hydroxychalcones and pyrazolylpyrazolines derived from naturally existing furochromone (khellin): semi-synthesis, docking study and anti-inflammatory activity, Natural Product Research, DOI: 10.1080/14786419.2021.1907383

To link to this article: https://doi.org/10.1080/14786419.2021.1907383

NATURAL PRODUCT RESEARCH
https://doi.org/10.1080/14786419.2021.1907383

Taylor & Francis
Taylor & Francis Group

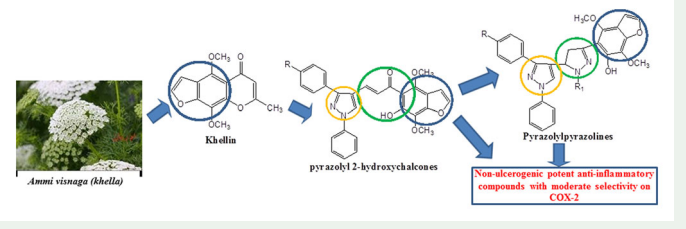
Non-ulcerogenic pyrazolyl 2-hydroxychalcones and pyrazolylpyrazolines derived from naturally existing furochromone (khellin): semi-synthesis, docking study and anti-inflammatory activity

Fatma Abd El-Fattah Ragab[a], Yassin Mohammed Nissan[a,b], M. Alaraby Salem[b,c], Mamdouh Moawad Ali[d] and Ahmed Abbass Mohamed Abdelrahman Selim[e]

[a]Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt; [b]Pharmaceutical Chemistry Department, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), Giza, Egypt; [c]School of Life and Medical Sciences, University of Hertfordshire hosted by Global Academic Foundation, New Administrative Capital, Cairo, Egypt; [d]Biochemistry Department, Genetic Engineering and Biotechnology Research Division, National Research Centre, Giza, Egypt; [e]Medicinal and Aromatic Plants Department, Desert Research Centre, Cairo, Egypt

ABSTRACT

Novel pyrazolyl 2-hydroxychalcone derivatives **3a–e** and pyrazolylpyrazoline derivatives **4a–e** and **5a–j** derived from the naturally existing furochromone (Khellin) were synthesized and evaluated for their *in vivo* anti-inflammatory activity. Most of the synthesized compounds showed better or comparable activity to that of Diclofenac as reference drug. Twelve compounds were evaluated for their ulcerogenic potential and exhibited no ulcerogenic effect. In addition compounds **3c**, **5c** and **5h** as examples showed PGE_2 inhibition % 88.86, 65.87 and 44.06, respectively and TNFα inhibition % 48.62, 31.11 and 16.02, respectively in rat serum samples. Compounds **3c**, **5c**, **5h** and Celecoxib were subjected to *in vitro* COX-1 and COX-2 inhibition assay, showed selectivity index 45.04, 102.04, 131.58 and 185.18, respectively. The computational finding supported those of *in vitro*, where the pyrazolylpyrazolines interacted with the COX-2 enzyme in a similar orientation to that of Celecoxib, while chlacones were found to exhibit similar orientation to that of Diclofenac.



ARTICLE HISTORY

Received 23 January 2021
Accepted 19 March 2021

KEYWORDS

Pyrazole; pyrazolylpyrazoline; khellin; anti-inflammatory

CONTACT Fatma Abd El-Fattah Ragab fatmarag@hotmail.com; Ahmed Abbass Mohamed Abdelrahman Selim ahmed-abbass-10@hotmail.com

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14786419.2021.1907383.

1. Introduction

Despite their side effects non-steroidal anti-inflammatory drugs have been extensively used to treat inflammation and increase pain threshold (Day and Graham 2013). These side effects (renal malfunction, delayed labour and mainly gastric irritation that may lead to peptic or duodenal ulcer) were mainly attributed to the inhibition of cyclooxygenase-1 enzyme (COX-1), a constitutive isoform with no definite role in inflammation process (Matsui et al. 2011). On the contrary, the second isoform of cyclooxygenase enzyme (COX-2), an inducible isoform, was recognized as the key enzyme in synthesis of prostaglandins (PGs) inflammatory mediators with a major role in inflammation process (Forey and Yonida 2002). Discovering selective COX-2 inhibitors was considered a breakthrough to control inflammation without suffering from these side effects (Forey and Yonida 2002). However, two selective COX-2 inhibitors (Rofecoxib and Valdecoxib) were withdrawn due to their serious cardiotoxicity (Back et al. 2012). Explanation of these side effects depends on the fact that selective COX-2 inhibitors may disturb the balance between prostacyclin (PGI_2) and thromboxane (TxA_2) towards TxA_2 which may lead to coronary artery disease, heart attack and stroke (Back et al. 2012). Therefore, seeking for mildly selective COX-2 inhibitors is still a goal for medicinal chemists in order to control inflammation without suffering from COX-1 inhibition side effect (peptic ulcer) or selective COX-2 inhibition side effect (cardiotoxicity).

In the other hand, for millennia medicinal plants have been a valuable source of therapeutic agents and still many of today's drugs are plant-derived natural products or their derivatives (Kinghorn et al. 2011). It has been estimated that approximately over half of the pharmaceuticals in clinical use today are derived from natural products (Newman and Cragg 2012). In the past decades, pharmaceutical industry focused mainly on libraries of synthetic compounds as drug discovery source, they are comparably easy to produce and resupply and demonstrate good compatibility with established high throughput screening (HTS) platforms (David et al. 2015). However, at the same time there has been a declining in the number of new drugs reaching the market (Scannell et al. 2012), which rising and renewed scientific interest in drug discovery from natural sources despite of its known challenges (Kingston 2011).

Ammi visnaga (khella) is a widely distributed ancient egyption medicinal plant, the furochromone khellin **I** (major constituent of *ammi visnaga* seeds) has been used to treat a variety of diseases including renal colic, kidney stones, coronary diseases, bronchial asthma, vitilligo and psoriasis (Günaydin and Beyazit 2004; Badr et al. 2015; Khalil et al. 2020). The existence of benzofuran moiety in khellin encourages the medicinal chemist to use it as synthone in the search for new anti-inflammatory agents, as benzofuran containing structures were reported to possess anti-inflammatory activity (Deshpande et al. 2012; Ragab et al. 2020) and exhibited promising gastro-protective effect (Ragab et al. 2007; Hassan and Soliman 2010; Ragab et al. 2020). Furthermore, the existence of pyrazole moiety in several anti-inflammatory agents especially, the well-known selective COX-2 inhibitor (Celecoxib) (Penning et al. 1997) encouraged many researchers to develop anti-inflammatory agents with pyrazole scaffold carrying a vicinal diaryl substitution pattern which thought to be responsible for the selectivity of Celecoxib (Ren et al. 2018). Several semisynthetic derivatives of khellin containing pyrazole scaffold have been semi-synthesized and showed good anti-inflammatory

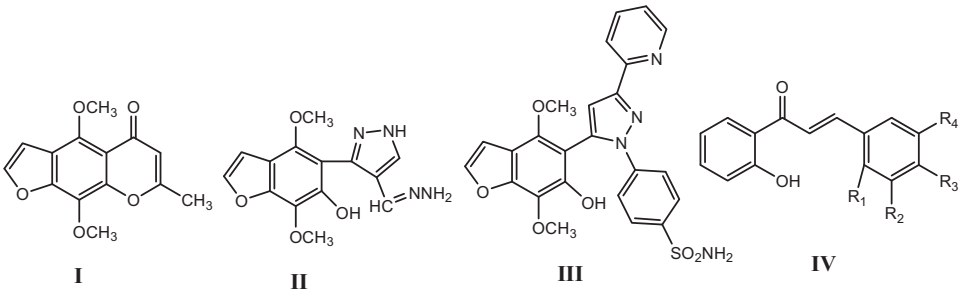


Figure 1. Khellin, pyrazolyl khellin derivatives and 2-hydroxychalcone as anti-inflammatory agents.

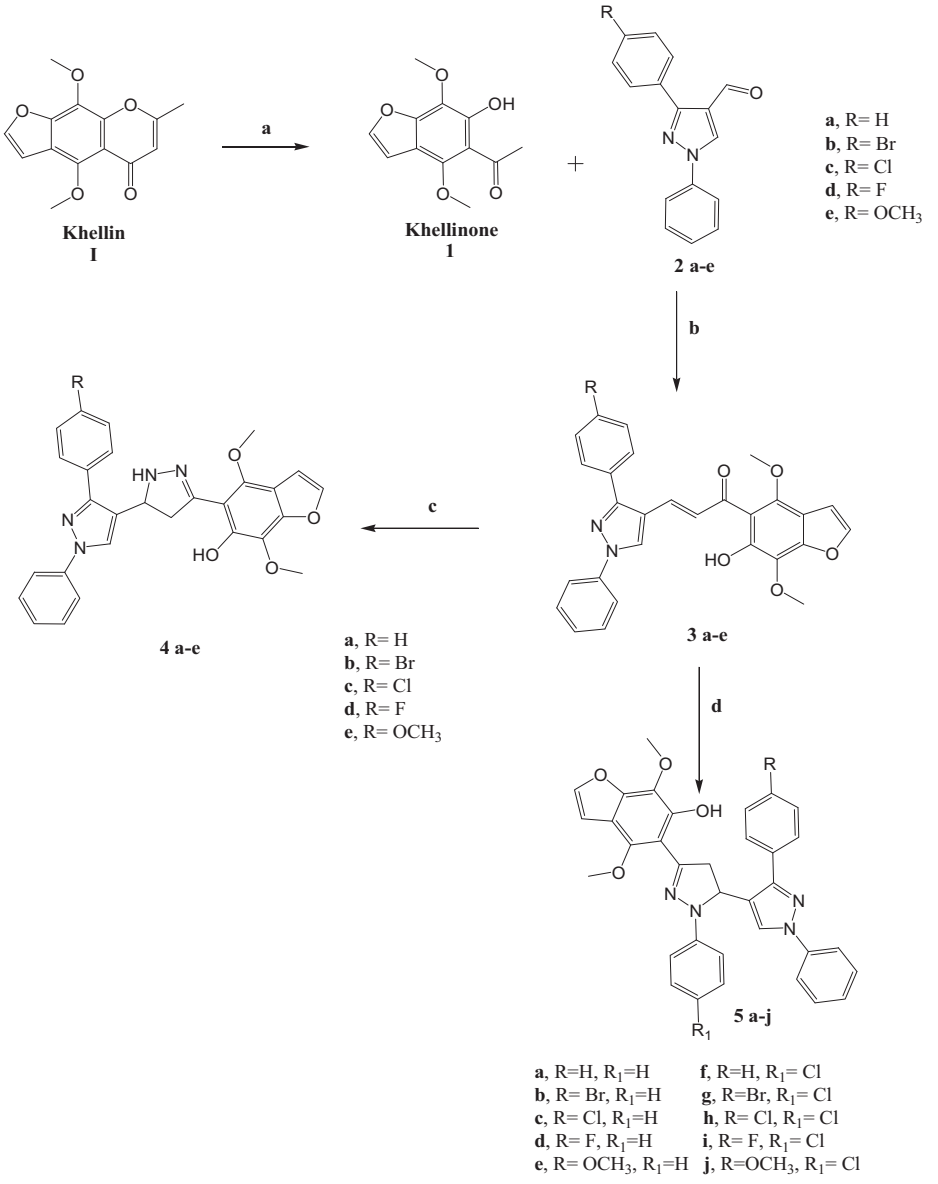
properties **II** and **III** (Figure 1) (Ragab et al. 1992; Hassan et al. 2014). Chalcones are a group of plant-derived polyphenolic compounds belonging to the flavonoids family, chalcones either natural or synthetic have been reported to exhibit diverse biological activity including anti-inflammatory activity (Singh et al. 2014). 2-hydroxychalcones **IV** have demonstrated anti-inflammatory activity with strong inhibition of prostagalndins (PGs) the main inflammatory mediators, presenting promising candidates in the search for potent anti-inflammatory agents (Figure 1) (Dao-Tran et al. 2009).

Motivated by the above information the present investigation deals with the semi-synthesis of pyrazolyl 2-hydroxychalcones **3a–e** derived from naturally occurring furochromone khellin to be tested as anti-inflammatory agents. As pyrazoline nucleus is present as a core in a variety of leading drugs as phenazone (antipyrine) and metamizole, which possess anti-inflammatory, antipyretic and analgesic activity (Elattar and Fadda 2016). The synthesized chalcones **3a–e** are used to construct the corresponding pyrazolylpyrazoline derivatives **4a–e** and **5a–j** hoping that these compounds containing the three active anti-inflammatory motifs pyrazole, pyrazoline and hydroxybenzofuranyl may exhibit enhanced anti-inflammatory activity, also in **5a–j** the pyrazoline nucleus is disubstituted with vicinal aryl rings (substituted pyrazole and phenyl) hoping to increase COX-2 selectivity. The most active compounds were evaluated for their ulcerogenic effect. Compounds **3c**, **5c** and **5h** as examples were subjected to *in vitro* COX-1 and COX-2 inhibition activity as well as their ability to inhibit PGE_2 and TNFα in rat serum samples. Furthermore, docking study on the active site of COX-2 enzyme was conducted for all compounds.

2. Results and discussion

2.1. Chemistry

The pyran ring of khellin **I** was subjected to alkaline hydrolysis with KOH to reveal kellinone **1** which was confirmed by its melting point 95 °C (Spath and Gruber 1938). On the other hand, 1,3-diarylpyrazol-4-carboxaldehydes **2a–e** were prepared through Vilsemier-Haack reaction, the structures of the formed products were confirmed on the basis of spectral analyses as well as their melting points (Yogi et al. 2015). Khellinone **1** was further subjected to Claisen-Schmidt condensation with pyrazol-4-carboxaldehyde derivatives **2a–e** to give the pyrazolyl 2-hydroxychalcones **3a–e**, respectively (Figure 2). The structures of compounds **3a–e** were confirmed on the



Solvents and Reagents: a: H_2O, 5%KOH; b: ethanol, NaOH; c: ethanol, hydrazine hydrate
d: ethanol, phenylhydrazine hydrochloride or 4-chlorophenylhydrazine hydrochloride

Figure 2. Scheme for semi-synthesis of compounds **3a–e**, **4a–e** and **5a–j**.

basis of spectral and elemental analyses. ^{1}H NMR spectra of compounds **3a–e** revealed beside other peaks two new doublets assigned to the two olefinic protons of α and β unsaturated ketones confirming chalcones formation (Figures S1–S13). For example ^{1}H NMR spectra of compound **3c** showed the presence of two doublet at 7.06 and 7.29 ppm corresponding to (-CO-CH = CH) $J = 15.89$, 15.90 Hz indicating the trans configuration (Figures S7–S9). The pyrazolylpyrazoline derivatives **4a–e** and **5a–j** were obtained by reacting chalcones **3a–e** with hydrazine hydrate, phenylhydrazine

hydrochloride or 4-chlorophenylhydrazine hydrochloride, respectively (Figure 2). The structures of pyazolylpyrazoline derivatives were confirmed on the basis of spectral and elemental analyses. ^{1}H NMR spectra of compounds **4a–e** and **5a–j** revealed two doublet of doublet assigned to two protons of C_4 pyrazoline ring and a triple doublet or doublet of doublet assigned to one proton of C_5 pyrazoline ring (Figures S14–S59). For example ^{1}H NMR spectra of compounds **5c** revealed beside other peaks three doublet of doublet at 3.47 ppm $J = 7.76$, 18.03 Hz, 4.22 ppm $J = 11.99$, 18.04 Hz and 5.51 ppm $J = 7.78$, 11.95 Hz corresponding to two protons of C_4 pyrazoline and one proton of C_5 pyrazoline, respectively and the disappearance of the two doublet corresponding to (-CO-CH = CH) (Figures S36–S38), while ^{13}C NMR revealed beside other peaks the appearance of two aliphatic carbon peak at 46.75 ppm and 55.03 ppm corresponding to C_4 and C_5 of pyrazoline, respectively (Figure S39), the mechanism of formation of **4a–e** and **5a–j** illustrated in Figure S60.

2.2. Biological screening

2.2.1. In vivo anti-inflammatory activity

All the newly synthesized compounds **3a–e**, **4a–e** and **5a–j** have been evaluated for their *in vivo* anti-inflammatory activity using carrageenan-induced paw edema in rats model (50 mg/kg interperitoneal dose) (Winter et al. 1962). The protocol of animal experiments was approved by ethical committee. The results of the anti-inflammatory activity revealed that all the tested compounds showed good activity with a percentage inhibition of rat paw edema after four hours ranged from 66.02–95.24% (Table S1). It was also noticed that all of the tested compounds showed higher inhibition than Diclofenac (21.25%) after one hour interval except compounds **4d** and **5f** which showed nearly equal percentage inhibition, while after four hours interval twelve compounds were still more active than Diclofenac (84.20%). Concerning chalcone derivatives **3a–e** this series showed excellent anti-inflammatory activity with percentage inhibition ranged from 73.67–92.72% after four hours, four derivatives were superior in activity than Diclofenac. It was obvious that the nature of substituent at the 3rd position of the pyrazole nucleus influenced the activity. The 4-chlorophenyl derivative **3c** exhibited the greatest activity. Conversion of **3a–e** to the corresponding pyrazolylpyrazolines **4a–e** with unsubstituted N^1 pyrazoline also showed good anti-inflammatory activity although less than the chalcone series with percentage inhibition after four hours ranged from 66.02 to 87.75% but still two compounds **4c** and **4e** possessed superior activity than Diclofenac. Again the nature of substituent at the 3rd position of the pyrazole nucleus affected the activity. The most active compound was **4c** with its 4-chlorophenyl substituent. While conversion of **3a–e** to the corresponding pyrazolylpyrazolines **5a–e** with N^1 pyrazoline substituted with phenyl moiety showed better activity than the previous series **4a–e** and equal or better activity than its chalcones **3a–e**. The percentage of inhibition after four hours ranged from 80.29–95.24%. Four compounds revealed improved activity than Diclofenac. The derivative **5c** with 4-chlorophenyl moiety at the 3rd position of the pyrazole nucleus showed the most superior activity. Pyrazolylpyrazolines **5f–j** carrying 4-chlorophenyl substituent at N^1 pyrazoline exhibited decreased activity than those with N^1 phenyl substituent **5a–e** with

percentage inhibition after four hours ranged from 77.31–94.92%. Two compounds **5h** and **5j** were more active than Diclofenac. Again the most active compound was the 4-chlorophenyl substituted derivative **5h**.

From this study we concluded that in the pyrazolylpyrazoline derivatives both substitutions at 3rd position of the pyrazole and N^1 position of the pyrazoline affected the anti-inflammatory activity, the best substituents were 4-chlorophenyl in the pyrazole and phenyl in the pyrazoline moieties. The best member was **5c**, with percentage inhibition 95.24%. While in chalcones substitution at 3rd position of the pyrazole affected the anti-inflammatory activity, again the best substituents were 4-chlorophenyl in the pyrazole nucleus. The best member was **3c** with percentage inhibition 92.72%. Replacement of the 4-chlorophenyl moiety substitutions at 3rd position of the pyrazole with its isostere 4-bromophenyl moiety decreased the activity, while the 4-fluorophenyl derivatives showed marked decrease in the anti-inflammatory activity than the 4-chlorophenyl or 4-bromophenyl derivatives.

2.2.2. Ulcerogenic effect

The ulcerogenic potential of the **3a–c, 3e, 4c, 4e, 5a–c, 5e, 5h and 5j** with reference to Diclofenac (in an oral dose 100 mg/kg/day) was evaluated (Hassan et al. 2014). The results revealed that the twelve tested compounds exhibited no ulcerogenic effect. In the contrary, Diclofenac showed marked ulcerogenic effect (ulcer index 40 ± 2.21). These results greatly supported our main objective to avoid gastric insult caused by COX-1 inhibition.

2.2.3. Evaluation of PGE_2 inhibition in rat serum samples

The PGE_2 concentration in rat serum samples for the three most active compounds **3c, 5c, 5h** and Diclofenac were assayed and the percentages of PGE_2 inhibition were calculated. Two compounds **3c** and **5c** were superior in activity than Diclofenac (45.49%) with percentage inhibition 88.86 and 65.87%, respectively, while the derivative **5h** was nearly equal to Diclofenac with percentage inhibition 44.06% (Table S2).

2.2.4. Evaluation of TNFα inhibition in rat serum samples

The Tumor necrosis factor alpha (TNFα) concentration for compounds **3c, 5c, 5h** and Diclofenac were assayed and the percentages of TNFα inhibition were calculated. Again two compounds **3c** and **5c** were more active than Diclofenac (19.43%) with percentage inhibition of 48.62 and 31.11%, respectively, while the derivative **5h** were slightly less than Diclofenac with 16.02% (Table S2).

2.2.5. In vitro COX-1 and COX-2 inhibition assay

Compounds **3c**, **5c**, **5h** and Celecoxib have been screened for their inhibitory activity of COX-1 and COX-2 isozymes using an ovine-COX-1/COX-2 assay kit (Hassan et al. 2014). All the tested compounds showed no inhibitory effect on COX-1 up to 50 μM. Moreover, compounds **3c, 5c, 5h** and Celecoxib showed *in vitro* COX-2 inhibitory activity with IC_{50} 1.11, 0.49, 0.38 and 0.27 μM, respectively. Pyrazolyl 2-hydroxychalcone **3c** (SI 45.04) and pyrazolylpyrazoline derivatives **5c** and **5h** (SI 102.04 and 131.58, respectively) showed less selectivity against COX-2 than Celecoxib (SI 185.18) (Table

S3). These results mean that our compounds may have lower or absent cardiovascular side effects due to its mild selectivity on COX-2.

2.3. Docking study

The structure of the COX-2 enzyme differs from that of COX-1 enzyme in the volume of the active site. The active site of COX-2 possesses an additional binding pocket, which is thought to be responsible for the selectivity of selective COX-2 inhibitors (Blobaum and Marnett 2007). In order to elucidate the mechanism of selectivity shown by compounds **3c**, **5c** and **5h**, compounds **3a–e**, **4a–e**, **5a–j**, Diclofenac and Celecoxib were docked into the active site of COX-2 enzyme PDB code: 3LN1 (Wang et al. 2010) using Maestro 11.4 (Schrödinger Release 2017-4: Maestro; Schrödinger, LLC: New York, NY, USA, 2017) (Table S4 and Figures S61-S71). The computational finding supported those of *in vitro*, where the pyrazolylpyrazoline derivatives were found to exhibit high probability (high number of pose for the same compound) to interact with the active site in a similar orientation to that of Celecoxib by fitting one of its aromatic rings in the same additional pocket the Celecoxib fit its N^1-phenyl pyrazole and forming bonds with some of the amino acids Celecoxib binds to (Arg 106, Arg 499, Phe 504, Gln 178 and Ser 339) (Figures S64, S66 and S68). While chlacone derivatives were found to exhibit high probability to orientate similarly to the non-selective COX inhibitor Diclofenac (Figures S70 and S71).

3. Conclusion

New pyrazolyl 2-hydroxychalcones **3a–e**, and pyrazolylpyrazolines **4a–e** and **5a–j** were semi-synthesized and showed good *in vivo* anti-inflammatory activity with a percentage inhibition of rat paw edema after four hours ranged from 66.02–95.24%. Twelve compounds were still more active than Diclofenac (84.20%) after four hour interval. Concerning chalcone derivatives **3a–e** the best compound was **3c** with percentage inhibition 92.72%, while for pyrazolylpyrazoline derivatives **5a–j** the best compounds were **5c** and **5h** 95.24 and 94.92%, respectively. Twelve compounds were evaluated for their ulcerogenic potential and exhibited no ulcerogenic effect. In addition compounds **3c**, **5c** and **5h** as examples showed PGE_2 inhibition % 88.86, 65.87 and 44.06, respectively and TNFα inhibition % 48.62, 31.11 and 16.02, respectively in rat serum samples. Moreover compounds **3c**, **5c**, **5h** and Celecoxib were subjected to *in vitro* COX-1 and COX-2 inhibition assay and showed selectivity index 45.04, 102.04, 131.58 and 185.18, respectively. The docking study supported those of *in vitro*, where the pyrazolylpyrazolines interacted with the COX-2 enzyme in a similar orientation to that of Celecoxib, while chlacones were found to exhibit similar orientation to that of Diclofenac. So our study suggest that these classes of compounds may be able to control inflammation without suffering from COX-1 inhibition side effect (peptic ulcer) or selective COX-2 inhibition side effect (cardiotoxicity) due to its safety on stomach mucosa and its moderate selectivity against COX-2 enzyme.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

Back M, Yin L, Ingelsson E. 2012. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nationwide cohort study after the withdrawal of rofecoxib. Eur Heart J. 33(15):1928–1933.

Badr JM, Hadad GM, Nahriry K, Hassanean HA. 2015. Validated HPLC method for simultaneous estimation of khellol glucoside, khellin and visnagin in Ammi visnaga L. fruits and pharmaceutical preparations. Nat Prod Res. 29(7):593–601.

Blobaum AL, Marnett LJ. 2007. Structural and functional basis of cyclooxygenase inhibition. J Med Chem. 50(7):1425–1441.

Dao-Tran T, Park H, Kim HP, Ecker GF, Thai KM. 2009. Inhibitory activity of prostaglandin E2 production by the synthetic 2′-hydroxychalcone analogues: synthesis and SAR study. Bioorg Med Chem Lett. 19(6):1650–1653.

David B, Wolfender JL, Dias DA. 2015. The pharmaceutical industry and natural products: historical status and new trends. Phytochem Rev. 14(2):299–315.

Day RO, Graham GG. 2013. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ. 346:f3195.

Deshpande R, Bhagawan Raju M, Parameshwar S, Shanth Kumar SM, Appalaraju S, Manjunath S, Yelagatti SM. 2012. Microwave-assisted synthesis and pharmacological activity of pyrazolyl benzofuran deravatives. Chemistry. 2(3):115–120.

Elattar KM, Fadda AA. 2016. Chemistry of antipyrine. Synth Commun. 46(19):1567–1594.

Forey A, Yonida M. 2002. Treating acute gouty arthritis with selective COX 2 inhibitors. BMJ. 325(7371):980–981.

Günaydin K, Beyazit N. 2004. The chemical investigations on the ripe fruits of Ammi visnaga (Lam.) lamarck growing in turkey. Nat Prod Res. 18(2):169–175.

Hassan GS, Abou-Seri SM, Kamel G, Ali MM. 2014. Celecoxib analogs bearing benzofuran moiety as cyclooxygenase-2 inhibitors: design, synthesis and evaluation as potential anti-inflammatory agents. Eur J Med Chem. 76:482–493.

Hassan GS, Soliman GA. 2010. Design, synthesis and anti-ulcerogenic effect of some of furo-salicylic acid derivatives on acetic acid-induced ulcerative colitis. Eur J Med Chem. 45(9):4104–4112.

Khalil N, Bishr M, Desouky S, Salama O. 2020. *Ammi visnaga* L., a potential medicinal plant: a review. Molecules. 25(2):301–318.

Kinghorn AD, Pan L, Fletcher JN, Chai H. 2011. The relevance of higher plants in lead compound discovery programs. J Nat Prod. 74(6):1539–1555.

Kingston DG. 2011. Modern natural products drug discovery and its relevance to biodiversity conservation. J Nat Prod. 74(3):496–511.

Matsui H, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I. 2011. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. J Clin Biochem Nutr. 48(2):107–111.

Newman DJ, Cragg GM. 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod. 75(3):311–335.

Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, et al. 1997. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3- (trifluoromethyl)-1 H-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). J Med Chem. 40(9):1347–1365.

Ragab FA, El-Said MK, Kenawy SAK. 1992. Synthesis and pharmacological activities of certain new pyrazole and chromone derivatives. Egypt J Pharm Sci. 33:83–97.

Ragab FA, Hassan GS, Yossef HA, Hashem HA. 2007. Synthesis of 6- and 9-alkylaminomethyl furoflavones as gastroprotective agents. Eur J Med Chem. 42(8):1117–1127.

Ragab FA, Mohammed EI, Abdel Jaleel GA, Selim AAMA, Nissan YM. 2020. Synthesis of hydroxybenzofuranyl-pyrazolyl and Hydroxyphenyl-pyrazolyl chalcones and their corresponding pyrazoline derivatives as COX inhibitors, anti-inflammatory and gastroprotective agents. Chem Pharm Bull (Tokyo). 68(8):742–752.

Ren S-Z, Wang Z-C, Zhu X-H, Zhu D, Li Z, Shen F-Q, Duan Y-T, Cao H, Zhao J, Zhu H-L. 2018. Design and biological evaluation of novel hybrids of 1, 5-diarylpyrazole and chrysin for selective COX-2 inhibition. Bioorg Med Chem. 26(14):4264–4275.

Scannell JW, Blanckley A, Boldon H, Warrington B. 2012. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov. 11(3):191–200.

Singh P, Anand A, Kumar V. 2014. Recent developments in biological activities of chalcones: a mini review. Eur J Med Chem. 85:758–777.

Spath E, Gruber W. 1938. Die konstitution des kellins (aus ammi visnaga) 1.Mitteil uber natur-liche chromone. Ber Dtsch Chem Ges A/B. 71(1):106–113.

Wang JL, Limburg D, Graneto MJ, Springer J, Hamper JR, Liao S, Pawlitz JL, Kurumbail RG, Maziasz T, Talley JJ, et al. 2010. The novel benzopyran class of selective cyclooxygenase-2 inhibitors. Part 2: the second clinical candidate having a shorter and favorable human half-life. Bioorg Med Chem Lett. 20(23):7159–7163.

Winter CA, Risley EA, Nuss GW. 1962. Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. Proc Soc Exp Biol Med. 111:544–547.

Yogi P, Ashid M, Hussain N, Khanam R, Khan S, Joshi A. 2015. Synthesis of pyrazoles via Vilsmeier Haack reaction and their pyrazolone, thiazolidinedione derivative: a comparative study of conventional and microwave routes. Iran J Org Chem. 7(2):1515–1522.