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Different Protective Effects of Trimetazidine against Renal Ischemia/Reperfusion Injury in Rats

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Abstract: Ischemia/Reperfusion (I/R) injury during kidney transplantation is a major clinical problem which leads to delayed graft function or even graft rejection. Therefore, the aim of the present study was to explore the possible protective effects of trimetazidine, an anti-ischemic agent, against experimentally-induced renal I/R injury in rats. Ischemia was induced by bilateral clamping of renal pedicles for 45 min followed by 24 h of reperfusion. Trimetazidine (10 mg/kg) was orally administered twice daily for 14successive days before induction of ischemia. At the end of the reperfusion period (24 h), blood and renal tissue samples were collected for biochemical and histopathological examination. Trimetazidine showed nephroprotective effects as evidenced by significant decrease in blood urea nitrogen and serum creatinine levels as well as renal content of tumor necrosis factor-a, malondialdehyde and myeloperoxidase. In addition, trimetazidine replenished renal content of adenosine triphosphate and glutathione that was confirmed by the improvement in histopathological features. The current study demonstrated the nephroprotective effects of trimetazidine against renal I/R injury, which might be mediated through its anti-ischemic, anti-inflammatory or antioxidant activities.

Keywords: Anti-inflammatory, anti-ischemic, antioxidant, renal ischemia/reperfusion, trimetazidine

Bioorg Chem. 2015 Dec;63:13-23. doi: 10.1016/j.bioorg.2015.09.002. Epub 2015 Sep 8.

1-(4-Methane(amino)sulfonylphenyl)-3-(4-substituted-phenyl)-5-(4-trifluoromethylphenyl)-1H-2-pyrazolines/pyrazoles as potentialanti-inflammatory agents.

Abdellatif KR[1], Elshemy HA[2], Azoz AA[3].

Abstract

2-Pyrazolins 14a-l and pyrazoles 15a-l were designed as celecoxib analogs for the evaluation of their in vitro COX-1/COX-2 inhibitory activity and the in vivo anti-inflammatory activity. Compounds 14i, 15a, 15d and 15f were the most COX-2 selective derivatives (S.I.=5.93, 6.08, 5.03 and 5.27 respectively) while the pyrazoline derivatives 14g and 14i exhibited the highest AI activity (ED50=190.5 and 160.1μmol/kg po, respectively).

KEYWORDS:

Anti-inflammatory activity; Celecoxib analogs; Cyclooxygenase-2; Pyrazole; Pyrazoline

J Enzyme Inhib Med Chem. 2016;31(sup2):6-12. Epub 2016 May 22.

Synthesis, cyclooxygenase inhibition, anti-inflammatoryevaluation and ulcerogenic liability of new 1-phenylpyrazolo[3,4-d]pyrimidine derivatives.

Bakr RB[1], Azouz AA[2], Abdellatif KR[1].

Abstract

A new group of 1-phenylpyrazolo[3,4-d]pyrimidine derivatives 14a-d-21 were synthesized from 2-(6-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy)acetohydrazide (12). All the synthesized compounds were evaluated for their cyclooxygenase (COX) inhibition, anti-inflammatory activity and ulcerogenic liability. All the target compounds were more potential in inhibiting COX-2 than COX-1. Compounds having pyrazolyl moiety in a hybrid structure with pyrazolo[3,4-d]pyrimidine scaffold (14a-d, 16 and 17) showed higher edema inhibitionpercentage activities (34-68%) and the 5-aminopyrazole derivative (14c, ED_{50} = 87.9 µmol/kg) was the most potent one > celecoxib (ED_{50} = 91.9 µmol/kg). While, the in vivo potent compounds (14a-d, 16, 17 and 21) caused variable ulceration effect (ulcer index = 0.33-4.0) comparable to that of celecoxib (ulcer index = 0.33), the pyrazol-3-one derivative (16) and the acetohydrazide (21) were the least ulcerogenic derivatives showing the same ulcerogenicpotential of celecoxib.

KEYWORDS:

Anti-inflammatory; cyclooxygenase inhibition; pyrazolo [3,4-d] pyrimidine

Arch Pharm (Weinheim). 2016 Oct;349(10):801-807. doi: 10.1002/ardp.201600145. Epub 2016 Sep 7.

Synthesis, Cyclooxygenase Inhibition, Anti-InflammatoryEvaluation, and Ulcerogenic Liability of New 1,3,5-Triarylpyrazoline Derivatives Possessing a Methanesulfonylpharmacophore.

Abdellatif KR[1], Fadaly WA[2], Azouz AA[3].

Abstract

A new series of 1,3,5-triarylpyrazolines 13a-l was synthesized and all prepared compounds were evaluated for their in vitro COX-1/COX-2 inhibitory activity and in vivo anti-inflammatoryactivity. All test compounds were more selective for the COX-2 isozyme and showed good in vivo anti-inflammatory activity. Compound 13h was the most COX-2 selective compound (COX-2 selectivity index (SI) = 10.23) and the most potent anti-inflammatory derivative (ED_{50} = 60.1 μmol/kg) in comparison with celecoxib (COX-2 SI = 9.29 and ED_{50} = 81.4 μmol/kg). All screened compounds were less ulcerogenic (ulcer indexes (UI) = 0.33-1.33) than aspirin (UI = 2.33) and comparable to celecoxib (UI = 0.33).

KEYWORDS:

1,3,5-Triarylpyrazoline; Anti-inflammatory; Cyclooxygenase-2 inhibitors; Pyrazoline

Future Med Chem. 2017 Oct;9(16):1899-1912. doi: 10.4155/fmc-2017-0115. Epub 2017 Oct 27.

Discovery of a COX-2 selective inhibitor hit with anti-inflammatory activity and gastric ulcer protective effect.

Abdelgawad MA[1,2], Bakr RB[1,2], El-Gendy AO[3], Kamel GM[4], Azouz AA[5], Bukhari SNA[2].

Abstract

AIM:

A novel series of 2-arylimino-5-arylidenethiazolidin-4-ones 12a-n were synthesized and all the target compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. Materials & methods: All the target compounds were evaluated for their COX inhibition by enzyme immunoassay kit and in vivo anti-inflammatoryactivity.

RESULTS:

Tested compounds were found more potent inhibitors of COX-2 (IC_{50} = 0.54-3.14 µM) than COX-1 (IC_{50} = 4.97-11.52 µM). The ulcerogenic liability of compounds 12(d, e, f, h, k, m) was performed and showed gastric safety more than or comparable to celecoxib.

CONCLUSION:

In addition, docking study of the most potent and selective compound 12h into COX-2 active site revealed that this target compound assumed interactions and binding pattern similar to that of as a cocrystallized ligand bromocelecoxib (S-58).

KEYWORDS:

COX-2; anti-inflammatory; inhibition; thiazolidinone

J Enzyme Inhib Med Chem. 2017 Dec;32(1):805-820. doi: 10.1080/14756366.2017.1326110.

Novel tetrazole and cyanamide derivatives as inhibitors o f cyclooxygenase-2 enzyme: design, synthesis, anti-inflammatoryevaluation, ulcerogenic liability and docking study.

Lamie PF[1], Philoppes JN[1], Azouz AA[2], Safwat NM[3].

Abstract

Nineteen new compounds containing tetrazole and/or cyanamide moiety have been designed and synthesised. Their structures were confirmed using spectroscopic methods and elemental analyses. Anti-inflammatory activity for all the synthesised compounds was evaluated in vivo. The most active compounds 4c, 5a, 5d-f, 8a and b and 9a and b were further investigated for their ulcerogenic liability and analgesic activity. Pyrazoline derivatives 9b and 8b bearing trimethoxyphenyl part and SO_2NH_2 or SO_2Me pharmacophore showed equal or nearly the same ulcerogenic liability (UI: 0.5, 0.75, respectively), to celecoxib (UI: 0.50). Most of tested compounds showed potent central and/or peripheral analgesic activities. Histopathological investigations were done to evaluate test compounds effect on rat's gastric tissue. The obtained results were in consistent with the in vitro data on COX evaluation. Docking studywas also done for all the target compounds inside COX-2-active site.

KEYWORDS:

Tetrazole; anti-inflammatory; cyanamide; histopathology; ulcerogenicity

Eur J Med Chem. 2017 Feb 15;127:10-21. doi: 10.1016/j.ejmech.2016.12.030. Epub 2016 Dec 23.

Synthesis, anti-inflammatory, cyclooxygenases inhibitionsassays and histopathological study of poly-substituted 1,3,5-triazines: Confirmation of regiospecific pyrazole cyclization by HMBC.

Elshemy HAH[1], Abdelall EKA[2], Azouz AA[3], Moawad A[4], Ali WAM[5], Safwat NM[6].

Abstract

Three novel triazines series were prepared. These series are pyrazolines (4a and 4b), pyrazoles (6a, 6b and 8a-d) and isoxazoles (7a and 7b). Such series were designed as COX-2 inhibitors. All compounds were characterized by using spectroscopic methods and elemental analysis. Regarding COX-2, compounds 5b, 4a and 3b were the most active with IC_{50} in the range of 0.55-0.87 μM. Most of synthesized compounds were relatively more potent to celecoxib (0.78 μM), diclofenac (2.94 μM) and indomethacin (7.24 μM). A molecular modeling study was performed for the most active compounds. Histopathological evaluation also was done to estimate the safety of compounds. Finally, structure elucidation of pyrazole 8 was studied by 2D NMR.

KEYWORDS:

Anti-inflammatory activity; COX-2 inhibitors; Enaminone; HMBC; Histopathology; S-Triazines

Bioorg Med Chem Lett. 2018 Feb 15;28(4):839. doi: 10.1016/j.bmcl.2018.01.024. Epub 2018 Jan 31.

Corrigendum to "Synthesis and biological evaluations of new nitric oxide-anti-inflammatory drug hybrids" [Bioorg Med Chem Lett (2017) 4358-4369].

Abdelall EKA[1], Abdelhamid AO[2], Azouz AA[3].

Erratum for

Synthesis and biological evaluations of new nitric oxide-anti-inflammatory drug hybrids. [Bioorg Med Chem Lett. 2017]

Abstract

Three novel series of nitroso derivatives (11-15), isoxazolopyrazoles (17a-c) and isoxazolo[3,4-d]pyridazines (18a-c) were prepared from the hydroxyimoyl chloride 10. In vitro COX1\2 inhibition activities were evaluated, both of 17b and 18a proved a promising inhibitory activity with IC_{50}=1.12, 0.78μM in sequent. Carrageenan induced Paw edema, ulcer liability, nitric oxide (NO) release and histopathological study were determined. Most of the prepared compounds showed excellent activities. Reactions of 2-aminopyridine and enaminone with hydroxyimoyl chloride 10 were investigated and proved by 2D NMR. Molecular docking for most active compounds was operated giving a hint for compound-receptor interactions.

KEYWORDS:

1,3-Dipolar cycloaddition; 2D NMR, Anti-inflammatory; Diarylpyrazoles; Hydroximoylchloride; Nitric oxide donor

Bioorg Chem. 2018 Apr;77:339-348. doi: 10.1016/j.bioorg.2018.01.028. Epub 2018 Jan 31.

Novel pyrimidine-pyridine hybrids: Synthesis, cyclooxygenaseinhibition, anti-inflammatory activity and ulcerogenic liability.

Abdelgawad MA[1], Bakr RB[2], Azouz AA[3].

Abstract

Some derivatives containing pyrido[2,3-d:6,5d']dipyrimidine-4,5-diones (9a-f), tetrahydropyrido[2,3-d]pyrimidine-6-carbonitriles (11a-c) and 6-(4-acetylphenyl)-2-thioxo-2,3,5,6,7,8-hexahydro-1H-pyrimido[4,5-d]pyrimidin-4-one (12) were synthesized from 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (8). The anti-inflammatory effect of these candidates was determined and the ulcer indices were calculated for active compounds. 7-Amino-5-(3,4,5-trimethoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carbonitrile (11c) exhibited better edema inhibition than celecoxib. Moreover, compounds 9b, 9d and 11c revealed better COX-2 inhibitory activity in a range (IC_{50} = 0.25-0.89 μM) than celecoxib (IC_{50} = 1.11 μM). Regarding ulcerogenic liability, all of the compounds under the study were less ulcerogenic than indomethacin. Molecular docking studies had been carried on active candidates 9d and 11c to explore action mode of these candidates as leads for discovering other anti-inflammatory agents.

KEYWORDS:

Anti-inflammatory activity; Cox isoforms; Pyridine derivatives; Pyrimidine derivatives; Ulcerogenic studies

Bioorg Chem. 2018 Aug;78:103-114. doi: 10.1016/j.bioorg.2018.03.011. Epub 2018 Mar 8.

Design, synthesis, analgesic, anti-inflammatory activity of novelpyrazolones possessing am inosulfonyl pharmacophore as inhibitors of COX-2/5-LOX enzymes: Histopathological and docking studies.

Abdelgawad MA[1], Labib MB[2], Ali WAM[3], Kamel G[4], Azouz AA[5], El-Nahass ES[6].

Abstract

A series of newly synthesized 4-aryl-hydrazonopyrazolones were designed and their structures were confirmed by spectral and elemental analyses. All synthesized compounds were evaluated for their in vitro COXs, 5-LOX inhibition, in vivo analgesic and anti-inflammatory activities. Compounds 5d, 5f and 5i were found to be the most potent COX-2/5-LOX inhibitors with superior COX-2 selectivity index values (SI = 5.29-5.69) to reference standard celecoxib (SI = 3.52). Four compounds; 5b, 5c, 5d and 5f showed excellent anti-inflammatory activity (% edema inhibition = 72.72-54.54%) and perfect ED_{50} values (ED_{50} = 0.044-0.104 mmol/kg) relative to celecoxib (ED_{50} = 0.032 mmol/kg). To explore the most active compounds, ulcerogenic effect on stomach in comparison with indomethacin and celecoxib in addition to histopathological investigations were performed. Compound 5f showed better gastric profile (UI = 2.33) than celecoxib (UI = 3.00). Also, 5f caused 50% increase in thermal pain threshold close to reference drug indomethacin (53.13%). Docking study of all the target compounds into COX-2 and 5-LOX active sites was performed to rational their anti-inflammatory activities.

KEYWORDS:

5-LOX; Analgesic; Anti-inflammatory; COX-2; Pyrazolone

Life Sci. 2018 Aug 15;207:50-60. doi: 10.1016/j.lfs.2018.05.048. Epub 2018 May 28.

Targeting Keap-1/Nrf-2 pathway and cytoglobin as a potentialprotective mechanism of diosmin and pentoxif ylline againstcholestatic liver cirrhosis.

Ali FEM[1], Bakr AG[2], Abo-Youssef AM[3], Azouz AA[3], Hemeida RAM[2].

Abstract

AIM:

The effects of diosmin (DS), pentoxifylline (PTX) and their combination on inflammatory response, oxidant/antioxidant balance, cytoglobin and cirrhotic reaction during bile duct ligation (BDL) were investigated and explored.

MAIN METHODS:

Fifty adult male Wistar albino rats were randomly allocated to five groups as following, sham: received vehicle only, BDL: subjected to common BDL without treatment, BDL plus DS: received 100 mg/kg/day orally, BDL plus PTX: received 50 mg/kg/day orally, BDL plus DS plus PTX: received DS and PTX in the same manner. The test period lasted 28 days, liver tissues and blood samples were collected to investigate biochemical markers (liver function biomarkers, oxidative stress markers, and antifibrotic markers), mRNA expression of Nrf-2, Keap-1, NF-κB-p65 and p38-MAPK by real-time PCR, protein expression of cytoglobin and NF-κB-p65 by western blot and iNOS and eNOS by immunohistochemistry. Histopathological study was performed to confirm our results.

KEY FINDINGS:

Chronic BDL induced a significant alteration in liver functions, oxidative stress and fibrotic markers. Furthermore, unfavorable effects on gene and protein expression were observed after BDL. Histopathological findings of this group showed parallel effects. DS, PTX and their combination treatment significantly ameliorated the disturbance that occurred due to BDL. Similar findings were observed in liver histopathology.

SIGNIFICANCE:

DS and PTX could mitigate liver cirrhosis through modulation of Keap-1/Nrf-2/GSH and NF-κB-p65/p38-MAPK signaling pathways. In addition, we demonstrated that the hepatoprotective effect of DS and PTX is mediated by up-regulation of cytoglobin with inhibition of fibrotic reaction.

KEYWORDS:

Bile duct ligation; Cytoglobin; Diosmin; Keap-1/Nrf-2; Pentoxifylline

Food Chem Toxicol. 2018 Oct;120:294-304. doi: 10.1016/j.fct.2018.07.027. Epub 2018 Jul 17.

Hepatoprotective effects of diosmin and/or sildenafil against cholestatic liver cirrhosis: The role of Keap-1/Nrf-2 and P_{38}-MAPK/NF-κB/iNOS signaling pathway.

Ali FEM[1], Azouz AA[2], Bakr AG[3], Abo-Youssef AM[2], Hemeida RAM[3].

Abstract

The present study was designed to investigate the potential protective effects of diosmin (DS) and/or sildenafil against bile duct ligation (BDL). In order to achieve this goal, BDL was performed to induce liver cirrhosis, DS (100 mg/kg/day, p.o.) and sildenafil (10 mg/kg, twice daily, p.o.) were administrated alone or in combination 24 h after the surgical operation and lasted for 4 weeks. Liver function biomarkers, fibrotic markers, oxidative stress markers, mRNA expression of NF-κB-p65, P_{38}-MAPK, Nrf-2, and Keap-1, as well as protein expression of cytoglobin, NF-κB-p65, Nrf-2, iNOS and eNOS were investigated concomitantly with histopathological study. The results revealed that, 4 weeks of BDL induced a significant alteration in liver functions, fibrotic and oxidative stress markers. Furthermore, up-regulation of NF-κB-p65, P_{38}-MAPK, Keap-1 and iNOS concomitantly with down-regulation of Nrf-2, cytoglobin and eNOS expressions were observed after BDL. DS and/or sildenafil treatment significantly alleviated the disturbance induced by BDL. These findings were further supported by the improvement in histopathological features. Additionally, co-administration of DS and sildenafil were found to significantly improved liver defects due to BDL as compared to the individual drugs. It can be concluded that, DS and sildenafil exhibit hepatoprotective effectsthrough modulation of Keap-1/Nrf-2 and P_{38}-MAPK/NF-κB/iNOS pathway.

KEYWORDS:

Cholestatic liver cirrhosis; Diosmin; Keap-1/Nrf-2; P(38)-MAPK/NF-κB/iNOS; Sildenafil