



Review Article

Pyrazole and 2-Pyrazoline Derivatives: Potential Anti-Inflammatory and Analgesic Agents

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ABSTRACT

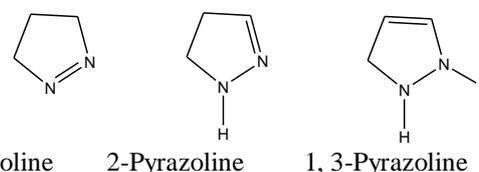
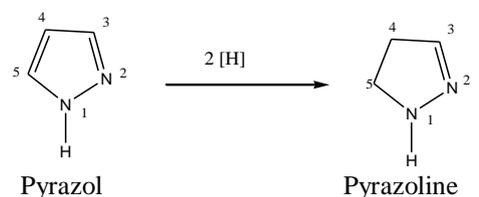
The search for new analgesic and anti-inflammatory agents are gaining lots of attraction because of their importance in management of acute pain and inflammation as well as their utility in early phases of many serious disorders like Alzheimer's dementia, cancer, heart vascular disease etc. In literature pyrazole and 2-pyrazoline derivatives are reported to possess interesting profile of analgesic and anti-inflammatory activity. As well as number pyrazole derivatives have already found their application as NSAIDs clinically. In this review article it has been tried to collate the reported work by many researchers on the pyrazole and 2-pyrazoline derivatives as analgesic and anti-inflammatory agents. The overview of various reported pyrazole and 2-pyrazoline derivatives claims that they are potentially active as analgesic and anti-inflammatory agents.

KEY WORDS: Pyrazole, 2-pyrazoline, analgesic, anti-inflammatory

INTRODUCTION

Non-steroidal anti-inflammatory drugs find the most clinical importance in the management of inflammation, pain and fever¹. These drugs exert anti-inflammatory activity and relieve inflammation associated pain by the interacting and inhibiting the enzymatic activity² leading to the inhibition of prostaglandins. Design and development of NSAIDs with enhanced safety profile is still a necessity and challenge for the pharmaceutical industry. Moreover NSAIDs are getting lot of attraction because of their utility in early phases of many serious disorders like Alzheimer's dementia, cancer, heart vascular disease etc.

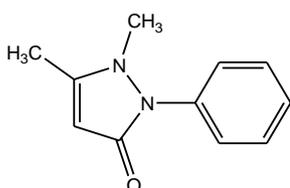
Pyrazole is a five membered heterocyclic compound containing two nitrogen atoms in adjacent position and contains two endocyclic double bonds. Pyrazoline is dihydropyrazole possessing only one endocyclic double bond. Depending on the position of the double bond three forms of pyrazoline are possible. These are 1-pyrazoline, 2-pyrazoline and 1, 3-pyrazoline³. Among all the pyrazolines, 2-pyrazoline has gained attraction and is frequently studied one⁴.



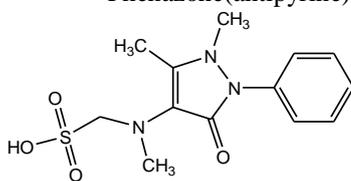
Pyrazole and 2-pyrazoline are reported to possess wide range of biological activities in literature such as anti-microbial, anti-mycobacterial, antiameobic, analgesic, anti-inflammatory, anti-convulsant, anti-depressant, hypotensive, cytotoxic, anticancer, anti-oxidant, ACE inhibitory etc. Among them analgesic and anti-inflammatory are also of most important.

Many pyrazole derivatives has already found their application as NSAIDs clinically⁵ such

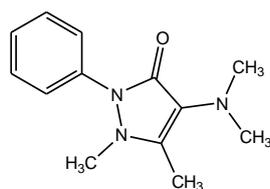
as Antipyrine or phenazone (analgesic and antipyretic), Metamizole or Dipyrone (analgesic and antipyretic), Aminopyrine or aminophenazone (anti-inflammatory, antipyretic and analgesic), Phenylbutazone or bute (Anti-inflammatory, antipyretic mainly used in Osteoarthritis, Rheumatoid arthritis, Spondylitis, Reiter's disease), Sulfinpyrazone (Chronic gout), Oxyphenbutazone (antipyretic, analgesic, anti-inflammatory, mild uricosuric).



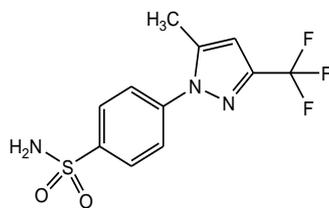
Phenazone(antipyrine)



Metamizole (dipyrone)

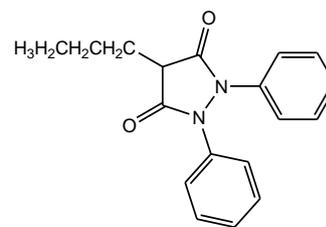


Aminophenazone

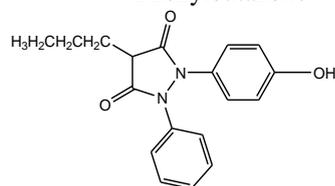


Celecoxib

In this review article some of the pyrazole and 2-pyrazoline derivatives are represented which are reported to possess analgesic and anti-inflammatory activity by many researchers.



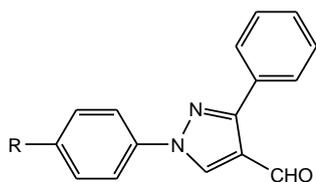
Phenylbutazone



Oxyphenbutazone

PYRAZOLE AND 2-PYRAZOLINE DERIVATIVES POSSESSING ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES

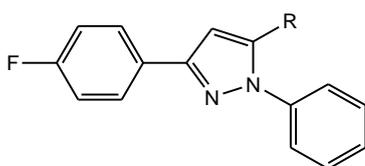
PanneerSelvam T *et.al.*⁶ synthesized a series of 1-(4-substitutedphenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde has been synthesized and tested for their anti-inflammatory and analgesic activities. The heterocycles, 1-(4-substitutedphenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde were synthesized by the reaction of acetophenone with substituted phenyl hydrazine in the presence of vilsmeier-haack reagent. The synthesized compounds were evaluated for their analgesic activity by benzoquinone induced writhing in Adult Swiss Webster mice. The synthesized compounds had shown significant analgesic activity at doses of 50 and 100 mg kg⁻¹. Compounds 4b, 4c and 4d exhibited higher analgesic activity ranging from 68 to 98 % at dose of 100 mg kg⁻¹ than reference drug flufenamic acid at dose level of 20 mg kg⁻¹ and protection of these compounds ranged from 30 to 62 % at a dose level of 50 mg kg⁻¹. But none of the tested them showed activity at doses of 25 and 5 mg kg⁻¹. Compounds were evaluated for their anti-inflammatory activity by Carrageenan induced paw edema in albino rats. None of the compounds showed anti-inflammatory activity at doses level of 3 and 5 mg kg⁻¹, while compounds, 4c, 4d had exhibited remarkable anti-inflammatory activity ranging from 35 to 69 % at a dose of 50 mg kg⁻¹ and from 54 to 78 % at a dose of 100 mg kg⁻¹. Most potent compound was found to be 4c with anti-inflammatory activity of 78 % at a dose of 100 mg kg⁻¹ and 69 % at a dose of 50 mg kg⁻¹, respectively. Among the synthesized compounds those who were substituted by electron-withdrawing (-Br, -Cl and -F) groups had show enhanced biological activity.



4(a-e)

R= -H, -Br, -Cl, -F, -NHCOCH₃

Bole SB *et.al.*⁷ reported a series of N-phenyl-5-substituted-aryl-3-p-(fluorophenyl) pyrazoles were synthesized by cyclization of 4-fluoroacetophenone with various benzaldehydes to give 4-fluoro phenyl phenylstyryl ketone followed by treating with phenyl hydrazine. They were evaluated for their *in-vivo* and *in-silico* anti-inflammatory activity. Inhibition of protein denaturation was evaluated according to the method of Eias and Rao. Carrageenan induced paw edema method was used to evaluate their *in-vivo* anti-inflammatory activity. They were subjected for their molecular docking studies. The anti-inflammatory activity of the synthesized compounds (250 mg/kg, p.o.) ranged from 30-47% which is much less than the standard indomethacin (10 mg/kg, p.o.) which showed 97% inhibition. The inhibition of BSA denaturation did not co-relate with the anti-inflammatory activity. Among the pyrazole derivatives 5b and 5e exhibited minimal docking energy and maximal hydrogen bonds. It can be highlighted that minimum binding energy of compounds with the target protein made this molecules good inhibitors of inflammation.

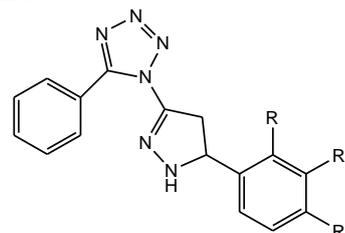


5(a-e)

R= 5a=-C₆H₅, 5b= 4-OH, 3-OCH₃C₆H₅,
5c= 4-ClC₆H₅, 5d= 4-N(CH₃)₂C₆H₅,
5e= 2-NO₂C₆H₅

Mohite PB *et.al.*⁸ synthesized eight different derivatives of substituted 5-phenyl-1-(5-substituted phenyl) -4,5-dihydro-1H-pyrazol-3-yl)-1H-tetrazole (4a-h) by reacting the chalcones with hydrazine hydrate in the presence of glacial acetic acid. The synthesized compounds were evaluated for their analgesic activity by hot plate and acetic acid induced writhing method in Swiss Albino mice and anti-inflammatory activity by

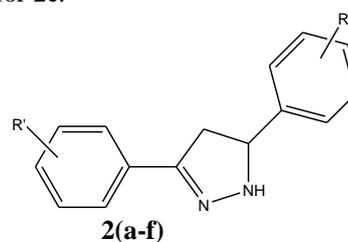
Carrageenan induced rat paw edema model. All the synthesized compounds exhibited analgesic activity at 25 mg/kg on both models. Introduction of chloro, nitro group, hydroxyl, bromo group, dimethylamino group, methyl group, methoxyl group had shown almost equivalent analgesic activity as that of Ibuprofen. On hot plate method analgesic activity of 4c, 4f and 4e were found to be superior compared to other compounds. On considering their anti-inflammatory activity analogs with a p-Methoxy phenyl group in R (4e) showed equal to that exhibited by the standard paracetamol.



4(a-h)

Comp.	R	R ¹	R ²
4a	H	H	H
4b	H	Cl	H
4c	H	H	Cl
4d	H	H	Br
4e	H	H	OCH ₃
4f	H	H	OH
4h	H	H	N(CH ₃) ₂
4g	H	H	NO ₂

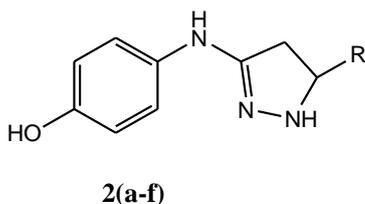
Velmurugan V *et.al.*⁹ reacted substituted acetophenones with substituted aromatic aldehydes to obtain chalcone derivatives by Claisen-Schmidt reaction which on treatment with hydrazine hydrate resulted in 3, 5-disubstituted pyrazoline derivatives. The synthesized compounds were screened for their analgesic activity by acetic acid induced writhing and tail-flick method in Wistar albino mice. The results obtained by tailflick method had shown that compound 2b and 2e has good activity and 2c has moderate activity. The results from acetic-acid induced writhing model had shown good analgesic activity for 2b and 2e and moderate activity for 2c.



2(a-f)

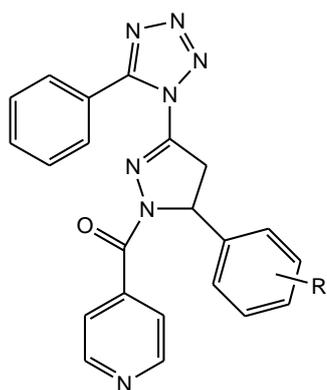
R¹ = 2,6-dihydroxy, p-Cl, 2-Br, p-F
R² = 3-ethoxy-4-hydroxy, 2-OH, p-(CH₃)₂NH₂

Sahu SK *et.al.*¹⁰ synthesized a series of 4-(5'-substituted aryl-4', 5'-dihydropyrazole-3'-yl-amino) phenols (2a-f) by treating substituted aryl-N-chalconyl amino phenols with hydrazine hydrate. The compounds were investigated for analgesic activity by Glassman's analgesic model and anti-inflammatory activity by Carrageenan induced paw edema method in rat model. Observed increased in analgesic and anti-inflammatory activity can be attributed to the presence of 2-OH, 4-NO₂, 4-Cl in the phenyl group in position 5 of the pyrazoline ring of synthesized compounds.



R= -C₆H₅, 2-furyl, 4-NO₂C₆H₄, 4-OCH₃C₆H₄,
2-OHC₆H₄, 4-ClC₆H₄

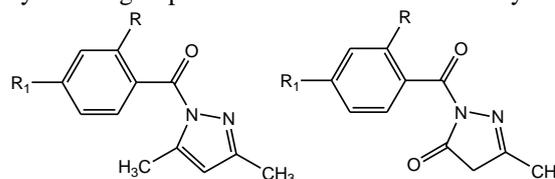
Mohite PB *et.al.*¹¹ synthesized 5-(4-chlorophenyl)-3-(5-phenyl-1H-tetrazol-1-yl)-4,5-dihydro-1H-pyrazol-1-yl(pyridin-4-yl)methanone and screened their in-vitro anti-inflammatory activity. Results revealed that all compounds had inhibited the denaturation of albumin in comparison with control. 4a and 4e inhibited the denaturation of albumin to 68.33% and 70.00% respectively. 4b, 4c and 4d inhibited the denaturation by 54.16%, 65.00% and 62.50% respectively.



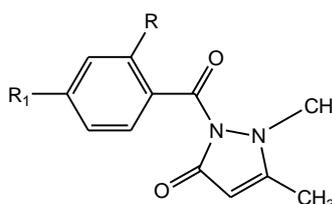
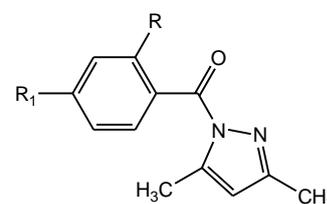
R= -H, 2-Cl, 4-Cl, 4-Br, 4-OCH₃, 4-NO₂,
4-(CH₃)₂N, 4-CH₃

Pathak D *et.al.*¹² synthesized some novel new substituted 3,5- dimethyl pyrazole (4a-c), 3-methyl pyrazol-5-onederivatives (5a-c), 3-Methyl-1-(substituted phenyl) pyrazol-5-ones (7a-b) and 2,3-dimethyl-1-(substitutedphenyl)pyrazol-5-ones

(8a-b). Synthesized compounds were investigated for in vivo anti-inflammatory and analgesic activity by Carrageenan-induced paw edema in rat model and acetic acid induced writhing method Swiss mice model respectively. 4a, 4b, 4c, 8a and 8b were found to possess significant anti-inflammatory activity. Same compounds were screened for analgesic activity and were found to be effective analgesics. Presence of two methyl groups i.e; electron donating at position 3 and 5 increase the activities. The presence of hydroxyl or nitro at *p*-position retains the activities due to increase in the electron density of the compounds. When the methyl group present at 5th position was replaced by an oxo group it led to decrease in the activity.



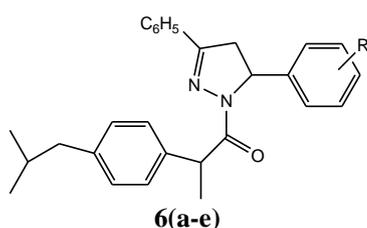
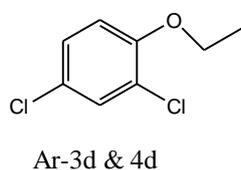
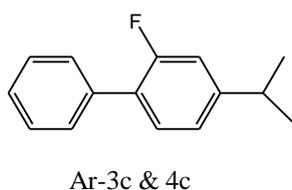
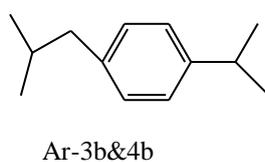
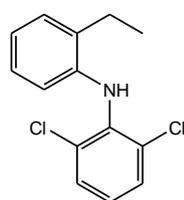
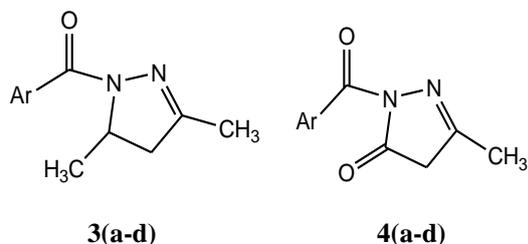
4a= 5a= R=R₁=H
4b=5b= R=OH, R₁=H
4c= 5c= R=H, R₁=OH



7a=8a=R=H, R₁=NO₂
7b= 8b=R=NO₂, R₁=H

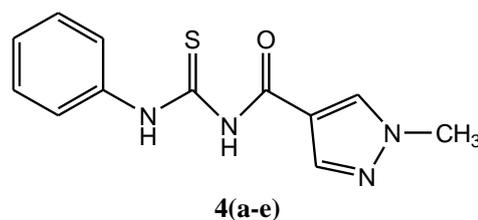
Amir M *et.al.*¹³ synthesized a series of 3,5-dimethyl pyrazoles (3a-d), 3-methyl pyrazol-5-ones (4a-d) derivatives of diclofenac, ibuprofen, flubiprofen and 2,4-dichlorophenoxy acetic acid and substituted pyrazoline derivatives (6a-e) of ibuprofen. They were evaluated for their analgesic, anti-inflammatory, lipid peroxidation and ulcerogenic activities. Compound 3a-d which possess were found to exhibit significant anti-

inflammatory activity ranging from 70.73-86.47% in carrageenan induced model. 4a-d showed reduction in activity. 6b, 6d, 6e exhibited 73.26, 76.92 and 74.35 reduction in edema. 3a-c and 6b were evaluated for their analgesic activity by acetic acid induced writhing in mice and were found to possess analgesic activity ranging from 44.05-79.12%.



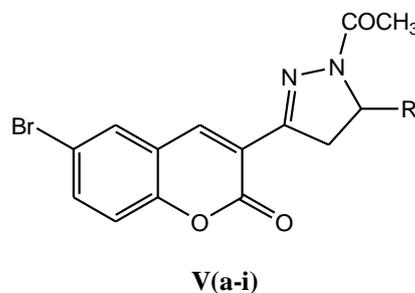
R=a:4-OCH₃; b:2-OH; c:3-OCH₃,4-OH; d: 3-Cl; e: 3,4,5-tri-OCH₃

Nitulescu GM *et.al.*¹⁴ synthesized some new N-(1-methyl-1H-pyrazole-4-carbonyl)-thiourea derivatives and evaluated their analgesic activity by acetic acid induced writhing in mice. No significant analgesic activity was observed. 4a exhibited highest analgesic activity among the synthesized derivatives.



R=a: -H, b:3-C₂H₅, c:2-Cl, d:4-Cl, e:3-I

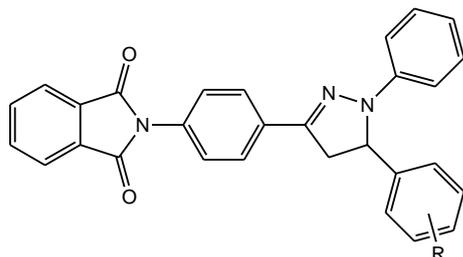
Reddy PK *et.al.*¹⁵ synthesized 6-Bromo-3-Pyrazolyl coumarins (Va-i) and evaluated their anti-inflammatory activity. The resulted compounds at dose of 100 mg/kg exhibited significant anti-inflammatory activity in rat model. The compounds Vc, Vf, Vb, Ve, Vi, Va, Vg, Vd and Vh exhibited significant inhibition when compared with standard indomethacin in Carrageenan induced rat hind paw edema model. The substitution of the phenyl ring at 5th position of pyrazoline nucleus exhibited significant anti-inflammatory activity.



R=a:-C₆H₅, b:4-F-C₆H₄-, c:3-NO₂-C₆H₄-, d:2-NO₂-C₆H₄-, e:2-Cl-C₆H₄-, f:4-OHC₆H₄-, g:4-OCH₃-C₆H₄-, h:4-N(CH₃)₂-C₆H₄-, i:3-Cl-C₆H₄

Deodhar MN *et.al.*¹⁶ synthesized ten 2-(4-(1-Phenyl-5-(substituted phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) isoindoline-1,3-dione and investigated their analgesic and anti-inflammatory activity. Except compound 3b all exhibited good anti-inflammatory activity in Carrageenan induced paw edema method, whereas compounds 3d, 3h and 3j exhibited good analgesic activity in acetic acid induced writhings in mice. 3a having a *p*-chloro substitution on the phenyl ring was found to be the most active anti-inflammatory agent.

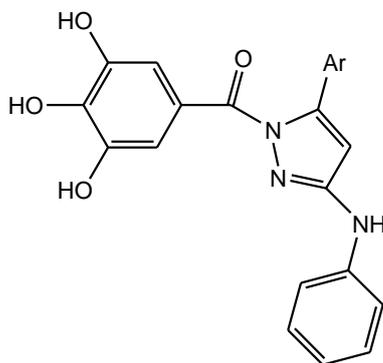
Compound 3j having *m*-bromo substitution on the phenyl ring was most active analgesic agent.



3(a-j)

R= a: *p*-Cl, b: *o*-Cl, c: *m*-Cl, d: *o*-NO₂, e: *p*-NO₂, f: *p*-OCH₃, g: 3,4,5-(OCH₃)₃, h: H, i: *p*-Br, j: *m*-Br

Arunkumar S *et.al.*¹⁷ synthesized a series of [5-substituted-3-(phenylamino)-1*H*-pyrazol-1-yl] (3,4,5-trihydroxyphenyl)-methanone (4a-j). The compounds were tested for *in vivo* anti-inflammatory activity by the Carrageenan induced paw edema method. It was reported that compounds (4b), (4e) and (4j) exhibited good anti-inflammatory activity with the percentage inhibition of 55.60, 55.89 and 55.60 respectively.

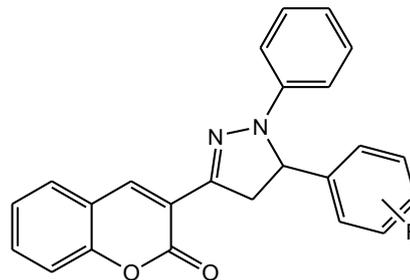


4(a-j)

Ar= a: C₆H₅, b: 4-(OCH₃)-C₆H₄, c: 2-NO₂-C₆H₄, d: 3-NO₂-C₆H₄, e: 2-Cl-C₆H₄, f: 4-Cl-C₆H₄, g: 2-OH-C₆H₄, h: 3-OH-C₆H₄, i: 4-N(CH₃)₂-C₆H₄, j: 3,4,6-(OCH₃)₃-C₆H₂

Khode S *et.al.*¹⁸ synthesized a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines (3a-l) were synthesized by reaction of various substituted 3-aryl-1-(3-coumarinyl) propan-1-ones with phenyl hydrazine in presence of hot pyridine. Compounds 3d, e, i and j were reported to have significant anti-inflammatory activity in acute inflammation such as carrageenan induced paw edema in rat model. While compounds 3d and 3e exhibited considerable activity in chronic inflammation such as adjuvant-induced arthritis when compared with standard diclofenac. Compounds 3e (59%) and 3j (55%) showed

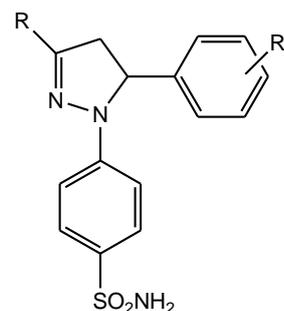
comparable analgesic activity to that of standard drug acetyl salicylic acid (67%) in peripheral analgesic activity model.



3(a-l)

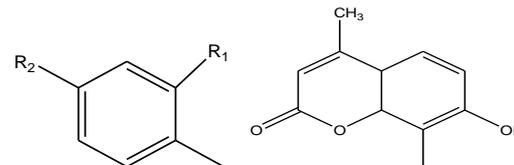
Ar =a: -C₆H₅; b: 4-OMe-C₆H₄-; c: -CH=CH-C₆H₅; d: 4-Cl-C₆H₄; e: 2,4-(Cl)₂-C₆H₃; f: 4-NMe₂-C₆H₄; g: 3-NO₂-C₆H₄; h: 4-Me-C₆H₄; i: 3-OMe-C₆H₄; j: 4-F-C₆H₄; k: 2-NO₂-C₆H₄; l: 4-OH-C₆H₄

Rathish IG *et.al.*¹⁹ synthesized nineteen 2-pyrazoline having benzenesulfonamide derivatives by condensing chalcones with 4-hydrazinonbenzenesulfonamide hydrochloride. The compounds were evaluated at a dose of 20 mg/kg for their anti-inflammatory activity by carrageenan induced rat paw edema model. Compounds 3k and 3l were found to have more active anti-inflammatory than celecoxib throughout the study (at 3h and 5 h). While the compounds 3m and 3n had shown more potent anti-inflammatory activity than celecoxib at 5 h. They were found to devoid of ulcerogenic potential when administered orally at dose of 60 mg/kg.



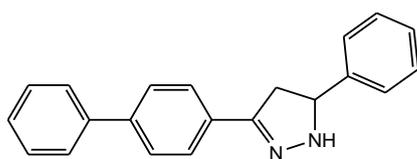
3(a-s)

R=

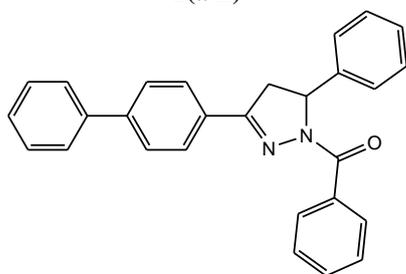


R₁= -OH, -OCH₃; R₂=-H, -OCH₃; R₃=-4-OCH₃, 3,4-(OCH₃)₂, 2-Cl, 4-Cl, 3-OH etc.

Amir M *et al.*²⁰ synthesized and of a series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (2a-h) and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (3a-h) by condensing chalcones with hydrazine hydrate in solvent system ethanol and DMF and evaluated the analgesic and anti-inflammatory activity. The compounds showed anti-inflammatory activity ranging from 28.06% to 82.45% at 4h, whereas standard drug flurbiprofen showed 80.29% inhibition after 4 h. The anti-inflammatory activity results showed that compounds possessing 4-methyl (2e) and 2,4,6-trimethoxy group (2h) on the phenyl ring at C-5 of pyrazoline nucleus possess highest activity (82.45%) which is greater than the standard drug flurbiprofen. Benzoylation of 2e resulted in sharp decrease of anti-inflammatory activity 31.57% (3e), while benzoylation of compound 2h had shown slight decrease in anti-inflammatory activity 75.38% (3h). The compounds 2e, 2h, and 3h showing better anti-inflammatory activity were screened for their analgesic activity. They had shown analgesic activity ranging from 28.60% to 72.90%, while standard flurbiprofen had shown 69.50% inhibition. Compound 2e showing highest anti-inflammatory activity also showed highest analgesic activity 72.90%. But compound 2h showed sharp decrease in analgesic activity (28.60%), although it had shown high anti-inflammatory activity (82.45%). The compound 3h showed moderate analgesic activity (43.20%). The maximum reduction in ulcerogenic activity (0.500 ± 0.00) was found with 2e having 4-methylphenyl group at position 5 of pyrazoline ring at an equimolar oral dose relative to 30 mg/kg flurbiprofen.



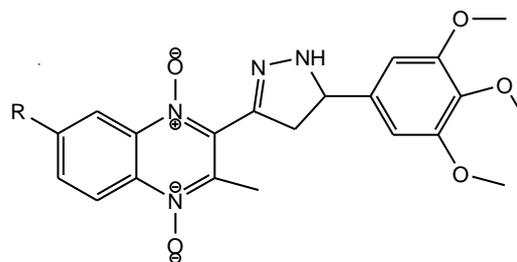
2(a-h)



3(a-h)

R = a : H; b : 2-Cl; c : 4-Cl; d : 4-N(CH₃)₂; e : 4CH₃; f : 4-OCH₃; g : 3,4-(OCH₃)₂; h : 2,4,6-(OCH₃)₃

Burguete A *et al.*²¹ synthesized 4,5-dihydro-(1H)-pyrazole analogues of 3-phenyl-1-(1,4-di-N-oxide quinoxalin-2-yl)-2-propen-1-one and screened their anti-inflammatory activity by carrageenan induced rat paw edema model. 5a exhibited 24.3% inhibition and 5b exhibited 23.4% inhibition of edema. 5a, and 5b were also evaluated for inhibition of soybean lipoxygenase LOX by the UV absorbance based enzyme assay. Perusal of % inhibition values or IC₅₀ values of 5a was found to be 67.3%.



5(a-c)

5a: R=H; 5b: R=F; 5c: R=CH₃O

CONCLUSION

The article has high lightened that pyrazole and 2-pyrazoline derivatives as potential analgesic and anti-inflammatory agents. Further research and optimization of these compounds may result in highly effective compounds with minimal side effects.

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